CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125554 Supplement Number: 0 NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2 PDUFA Goal Date: 3/30/15 Stamp Date: 7/30/2014

Proprietary Name: OPDIVO

Established/Generic Name: Nivolumab

Dosage Form: Injection for Intravenous Infusion

Applicant/Sponsor: Bristol-Myers Squibb Company

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed△
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

;heck pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

.re the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

:heck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

.dditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

MID-CYCLE COMMUNICATION

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351 of the Public Health Service Act for Opdivo (nivolumab) Injection for Intravenous Infusion.

We also refer to the teleconference between representatives of your firm and the FDA on November 3, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time:	Monday, November 3, 2014; 1:00 PM – 2:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue (Teleconference)
Application Number:	BLA 125554
Product Name:	Proposed name: Opdivo (nivolumab) Injection for Intravenous Infusion
Applicant Name:	Bristol-Myers Squibb Company
Meeting Chair:	Marc Theoret, M.D.
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Chuk, M.D.	Medical Officer, DOP2
Dow-Chung Chi	Medical Officer, DOP2
Sirisha Mushti, Ph.D.	Biometrics Reviewer, OBV
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCPV
Xianhua Cao, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Liang Zhao, Ph.D.	Pharmacometrics Team leader, DCPV
Hongshan Li, Ph.D.	Pharmacometrics Reviewer, DCPV
Laurie Graham, M.S.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, DMA
Joel Welch, Ph.D.	CMC Reviewer, DMA
Patricia Hughes, Ph.D.	Team Leader, Biotechnology Manufacturing Assessment Branch (BMAB)
Bo Chi, Ph.D.	Drug Substance Reviewer, BMAB
Steven Fong, Ph.D.	Drug Product Reviewer, BMAB
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Shawna Weis, Ph.D.	Pharmacology/Toxicology Reviewer, DHOT
Carolyn Yancey, M.D.	Medical Officer, OSE, DRISK
Miriam Dinatale, D.O.	Medical Officer, Maternal Health
Sharon Mills, B.S.N., R.N., C.C.R.P.	Patient Labeling Reviewer, DMMP
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)	Independent Assessor
	Independent Assessor

APPLICANT ATTENDEES

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Todd Bunch, Ph.D.	Group Director, Drug Safety Evaluation
Marybeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Manish Gupta, Ph.D., F.C.P.	Director, Clinical Pharmacology and Pharmacometrics
Brendan Hughes Ph.D.	Vice-President, Manufacturing Sciences and Technology, Biologics Development and Manufacturing
Helen Liu, M.D.	Director, Global Pharmacovigilance and Epidemiology
Fouad Namouni, M.D.	Vice President, Development Lead
Christina Smith, D.Phil.	Vice President, Global Development, Nivolumab Filing and Dossier Strategy
Amy Straub, Ph.D.	Director, Biopharma Project Management
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, MD, Ph.D.	Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research - Oncology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology
Pradip Ghosh-Dastidar	Associate Director, Global Regulatory Sciences, CMC
Annie Sturgess	Executive Director, Global Regulatory Sciences, CMC
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

FDA noted that no significant issues have been identified; however, if significant issues arise, FDA will ensure that BMS is notified immediately, preferably via a teleconference.

3.0 INFORMATION REQUESTS

FDA noted there was only one outstanding information request, but that this information was not expected from BMS until Thursday, November 6, 2014. FDA expressed there will be additional chemistry, manufacturing, and controls (CMC) information requests anticipated to be sent in the next week. Furthermore, additional requests may be forthcoming as the team continues to perform their review of the application. BMS acknowledged FDA's statement and no further discussion occurred during the meeting.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

FDA noted a formal REMS is not planned for this application. Additionally, FDA notified BMS that the pregnancy category proposed in the package insert will be modified to Category (b) (4) based on the available data both in the application and on the overall product class. BMS acknowledged FDA's statement and no future discussion occurred during the meeting.

5.0 ADVISORY COMMITTEE MEETING

FDA noted an Advisory Committee meeting is not planned for this application. No further discussion occurred during the meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for **December 5, 2014**. We intend to send the briefing package to you approximately 2 days in advance of the meeting depending on the review of the application. If these timelines change, we will communicate updates to you during the course of review.

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 22, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 22, 2014, approximately 10:00 a.m. to approximately 10:15 a.m.

FDA Participants:

Marc Theoret, M.D.	Clinical Team Leader, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Susan Martindale	Associate Director, Global Labeling Operations
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology
Christina Smith, D.Phil.	Vice President, Global Development, Nivolumab Filing and Dossier Strategy
Todd Rider	Associate Director, Global Biometric Sciences.

This was an FDA-initiated teleconference (TCON) to discuss the current package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to discuss and obtain agreement on the FDA proposed changes for the package insert.

Attachments:

1. FDA Proposed Labeling of December 22, 2014

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 19, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 19, 2014, approximately 4:15 p.m. to approximately 4:30 p.m.

FDA Participants:

Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Susan Martindale	Associate Director, Global Labeling Operations
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences
Fouad Namouni, M.D.	Vice President, Development Lead
Todd Rider	Associate Director, Global Biometric Sciences.

This was an FDA-initiated teleconference (TCON) to discuss the current package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to obtain further clarification and information on the patients treated with corticosteroids and the details surrounding the action taken with the study drug, resolution and outcome of the patients so that the information is accurately reflected in the proposed package insert, specifically Sections 2 and 5. Based on the information received in response to the December 5, 2014, teleconference, FDA and BMS both provided detailed explanations for their proposals to these sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 17, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 17, 2014, approximately 1:30 p.m. to approximately 4:00 p.m.

FDA Participants:

Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Susan Martindale	Associate Director, Global Labeling Operations
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences
Fouad Namouni, M.D.	Vice President, Development Lead
Todd Rider	Associate Director, Global Biometric Sciences.

This was an FDA-initiated teleconference (TCON) to discuss the current package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to obtain further clarification and information on the patients treated with corticosteroids and the details surrounding the action taken with the study drug, resolution and outcome of the patients so that the

information is accurately reflected in the proposed package insert, specifically Sections 2 and 5. Based on the information received in response to the December 5, 2014, teleconference, FDA and BMS both provided detailed explanations for their proposals to these sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

Attachments:

1. FDA Proposed Labeling of December 17, 2014

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 15, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 15, 2014, 2:00 p.m. to approximately 3:30 p.m.

FDA Participants:

Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Susan Martindale	Associate Director, Global Labeling Operations
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences

This was an FDA-initiated teleconference (TCON) to further discuss the current package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to obtain further clarification and information on the patients treated with corticosteroids and the details surrounding the action taken with the study drug, resolution and outcome of the patients so that the information is accurately reflected in the proposed package insert, specifically Sections 2 and 5. Based on the information received in response to the December 5, 2014, teleconference, FDA further informed BMS of the approach taken for each of the subsections to Section 5 of the package insert. Additionally, FDA and BMS both provided detailed explanations for their proposals to these sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 12, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 12, 2014, 4:00 p.m. to approximately 5:00 p.m.

FDA Participants:

Patricia Keegan, M.D	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
MaryBeth Frosco	Director, Global Regulatory Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research

This was an FDA-initiated teleconference (TCON) as a follow-up to the December 5, 2014 discussion and to further discuss the current package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to obtain further clarification and more information on the patients treated with corticosteroids and the details surrounding the action taken with the study drug, resolution and outcome of the patients so that the information is accurately reflected in the proposed package insert, specifically Sections 2 and 5. Based on the information received in response to the December 5, 2014, teleconference, FDA informed BMS of the approach taken for each of the subsections to Section 5 of the package insert. Additionally, FDA and BMS both provided detailed explanations for their proposals to these sections; and FDA noted what would and would not be acceptable for inclusion in the package insert. FDA agreed to provide BMS with a proposed version of the package insert on December 13 or

14, 2014, and requested a potential call with BMS on Monday, December 15, 2014. In advance of the proposed December 15, 2014 teleconference, FDA also requested BMS provide a revised version of the proposed package insert that incorporates all text that is agreeable to BMS or provides a counterproposal with rationale for discussion at the proposed December 15, 2014 teleconference. BMS agreed this was acceptable.

Items Requiring FDA's Follow-up:

1. Provide FDA Proposed Labeling
2. Schedule Teleconference for Monday, December 15, 2014

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MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 19, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

We have reviewed your December 11, 2014, responses to our CMC requests for information. Based on our review, the CMC review team has the following additional information.

CMC Comments:

1. The protocol for the qualification of new working cell banks (WCBs) should be submitted as a prior approval supplement (PAS) to your BLA as you have agreed. Please note the following when making this PAS submission:

   Agency experience indicates that an assessment of at least three lots of Drug Substance (DS) manufactured at full scale with a new WCB is necessary to confirm product quality is comparable to material manufactured with the current WCB. We recommend that you provide in the PAS any available data from material manufactured at full scale with the proposed working cell bank. This data should be compared to historical results from the current working cell bank.

   If you are going to rely upon data from small scale models to support qualification of a new working cell bank, you should provide additional information, such as:

   - A justification for the quality attributes and process performance attributes included in the working cell bank qualification protocol.

- A justification for excluding (b) (4) manufacturing and relying on product quality data from the harvest. For example, you should provide summary information to support that (b) (4) manufacturing and storage of DS are unlikely to result in product quality differences between DS manufactured with the current and new working cell banks.
- Information, and a justification, on the specific acceptance criteria that will be used during qualification.
- A justification for the use of the small scale models, rather than the full scale process. This should include comparison, and a statistical evaluation, of the small scale models compared to the full scale commercial process.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/19/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Friday, December 19, 2014 10:07 PM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Labeling Edits (12.19.14)

Importance: High

Hi Kathy,

Please find attached FDA's next round of proposed edits to the Nivolumab PI relating to your original BLA application (BLA 125554) submitted on July 30, 2014.

Please review our edits and comments to determine if you are in agreement. If you have modifications to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. Lastly, when making edits to the label, please update formatting as necessary.

Please provide a response as soon as possible via email and followed by an official submission to the BLA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
12/19/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Thursday, December 18, 2014 8:10 AM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Edits to Label (2/18/14)

Importance: High

Hi Kathy,
As per the discussion yesterday, please find below the FDA proposal language noted in the specific section of the warning and precautions to the Nivolumab PI relating to your original BLA application (BLA 125554) submitted on July 30, 2014.

Section 5.1 (Paragraph 2):

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range 25 days – 3.5 months). In (b) (4) patients, pneumonitis was diagnosed after discontinuation of OPDIVO for other reasons, and the remaining (b) (4) patients with Grade 2 pneumonitis had interruption of OPDIVO. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with Grade 2 pneumonitis that completely resolved (defined as xxxxx) and OPDIVO was restarted without recurrence of pneumonitis.

Section 5.3 (after the sentence: The time to onset was 97, 113, and 86 days after initiation of OPDIVO.)

In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4-15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved with continuation of corticosteroids in two of three patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

Section 5.4 (Paragraph 1):

In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. (b) %). Grade 2 or 3 immune-mediated nephritis or renal dysfunction (defined as ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) occurred in 0.7% (2/268) of patients at 3.5 and 6 months after OPDIVO initiation, respectively. OPDIVO was discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents) (b) (4)

Section 5.5 (Paragraph 1 and 2) – Please also add the information about the hypothyroidism as discussed during the t-con

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days - 11.7 months).

Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. The median time to onset in OPDIVO-treated patients was 1.6 months (range: 0 - 3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

In addition, please make the following additional modifications to the nivolumab PI:

1) Section 5.4, incidence of creatinine elevations in the chemotherapy group changes from (b) (4) % to 9%.

   Revise sentence to: "In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. **9**%)."

2) Table 2, delete (b) (4) from Table 2 as it no longer meets criteria for inclusion.

Should you have any questions, please don't hesitate to contact me.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 5, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 5, 2014, 11:30 a.m. to 12:30 p.m.

FDA Participants:

Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Chuk, M.D.	Medical Officer, DOP2
Kun He, Ph.D.	Biometrics Team Leader, OBV
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCPV
Xianhua Cao, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Joel Welch, Ph.D.	CMC Reviewer, DMA
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Miriam Dinatale, D.O.	Medical Officer, Maternal Health
Sharon Mills, B.S.N., R.N., C.C.R.P.	Patient Labeling Reviewer, DMMP
Jibril Abdus-Samad, Pharm.D.	Labeling Reviewer, DMA
Nick Senior, Pharm.D., J.D.	Regulatory Review Officer, OPDP
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety
Sciences Susan Martindale	Associate Director, Global Labeling Operations
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology

This was an FDA-initiated teleconference (TCON) to discuss FDA proposed edits of December 3, 2014, to the package insert in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to review the current label with BMS. In advance of the meeting, BMS provided a version of the label containing only notes for sections to be discussed during the meeting – BMS made no embedded revisions to the label. These sections included: Highlights, Sections 2, Section 5, Section 6, and Section 14. FDA and BMS both provided explanations for their proposals; and FDA noted what would and would not be acceptable for inclusion in the package insert.

Attachments:

- BMS Version of the Label received on December 4, 2014, with comments to be discussed during the meeting.

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MEREDITH LIBEG
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 2, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Labeling

Date and Time of Teleconference: December 2, 2014, 12:00 p.m. to 12:30 p.m.

FDA Participants:

Patricia Keegan, M.D.	Division Director, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Meredith Chuk, M.D.	Medical Officer, DOP2
Meredith Libeg	Regulatory Health Project Manager

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Helen Liu, M.D.	Director, Global Pharmacovigilance and Epidemiology
Susan Martindale	Associate Director, Global Labeling Operations
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology

This was an FDA-initiated teleconference (TCON) to discuss the clinical aspects contained in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status, specifically Sections 2 and 5 to the proposed package insert.

Details of the discussion are provided below.

Summary of the TCON:

FDA thanked BMS for agreeing to the meeting and noted that the goal of the meeting was to obtain clarification and additional information on the patients treated with corticosteroids and the details surrounding the action taken with the study drug, resolution and outcome of the patients so that the information is accurately reflected in the proposed package insert, specifically Sections 2 and 5. In advance of the meeting, FDA provided a table for discussion highlighting examples of the issues encountered. FDA noted that the table was for internal use and was being provided for referencing only to aid in the discussion. BMS acknowledged FDA's concerns and agreed to provide additional information for each category of Section 5 in order to help explain and address the FDA's concern and aid in reaching agreement to the proposed language.

Items Requiring BMS' Follow-up:

1. Provide additional detailed information on corticosteroid use and details surrounding the action taken with the study drug, resolution and outcome of the patients in the specific categories in Section 5 of the proposed package insert.

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/s/

MEREDITH LIBEG
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 16, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Labeling Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information relating to the proposed package insert received via email communication on Monday, December 15, 2014. Please provide your response as a formal submission to the BLA by Monday, December 16, 2014, or sooner if possible.

Section 5.1:

1. **BMS**
   - Proposal of December 15, 2014: "The median time to onset for the six cases was xx months (range xx - x); (b) (4)
   - Comment of December 15, 2014: "Editorial changes proposed to address resolution in all six patients."

   FDA
   - Proposal Edit of December 16, 2014: "The median time to onset for the six cases was (b) (4) months (range (b) (4)); (b) (4)
   - Comment of December 16, 2014: "Inserted median time to onset and range. Information not in dataset since only colitis in patient 27-37152 is recorded. Time to onset taken from the narrative."

Section 5.3:

2. **BMS**
   - Proposal of December 15, 2014: "Liver tests improved within (b) (4) days of initiation of corticosteroids"
   - Comment of December 15, 2014: "BMS is providing, per FDA's comment. (b) (4)

   FDA
   - Proposal of December 16, 2014: "Liver tests improved within (b) (4) days of initiation of corticosteroids."
   - Comment of December 16, 2014: (b) (4)

Section 5.4:

3. **BMS**
   - Proposal of December 15, 2014: (b) (4)
   - Comment of December 15, 2014: "BMS is providing, per FDA's comment. (b) (4)

   FDA
   - Comment of December 16, 2014: " (b) (4)

Section 6.1:

4. **BMS**
   - Proposal of December 15, 2014: "The study population characteristics in the OPDIVO group vs. the chemotherapy group were: (b) (4) male; median age of (b) (4) years"
   - Comment of December 15, 2014: "The percentages reflect all treated patients found in response to Information Request dated 12/3/2014."

FDA

- Comment of December 16, 2014: "Calculated as (b) (4) years from datasets. We cannot locate the information; provide the SDN."

5. **BMS**

- Proposal of December 15, 2014: (b) (4)

- Comment of December 15, 2014: "The percentages reflect all treated patients found in response to Information Request dated 12/3/2014."

FDA

- Comment of December 16, 2014: "Calculated as (b) (4) from datasets. We cannot locate the information; provide the SDN."

6. **BMS**

- Proposal of December 15, 2014: "Grade 3 and 4 adverse reactions occurred in (b) (4) of patients receiving OPDIVO (b) (4)

FDA

- Proposal of December 16, 2014: "Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO (b) (4)

- Comment of December 16, 2014: "The percentages BMS has inserted are ARs occurring 30 days after the last dose of drug. The percentages FDA has inserted is based on ARs occurring up to 100 days after the last dose of the drug."

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/16/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Friday, December 19, 2014 10:07 PM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Labeling Edits (12.19.14)

Importance: High

Hi Kathy,

Please find attached FDA's next round of proposed edits to the Nivolumab PI relating to your original BLA application (BLA 125554) submitted on July 30, 2014.

Please review our edits and comments to determine if you are in agreement. If you have modifications to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. Lastly, when making edits to the label, please update formatting as necessary.

Please provide a response as soon as possible via email and followed by an official submission to the BLA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
12/19/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Sunday, December 14, 2014 9:39 PM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Labeling Edits (12.14.14)

Importance: High

Hi Kathy,

Please find attached FDA's next round of proposed edits to the Nivolumab PI relating to your original BLA application (BLA 125554) submitted on July 30, 2014.

Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. Lastly, when making edits to the label, please update formatting as necessary.

As discussed at the late cycle meeting on Friday, December 12, 2014, we would like to propose a meeting for Monday, December 15, 2014 from 2 to 3 PM to discuss the proposed edits and try to reach agreement on sections of the label.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
12/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Chemistry, Manufacturing, and Controls

Date and Time of Teleconference: December 3, 2014, 12:00 p.m. to 12:30 p.m.

FDA Participants:

Laurie Graham, M.S.	CMC Team Leader
Joel Welch, Ph.D.	CMC Reviewer
Monica Hughes, M.S.	Chief, Project Management Staff
Meredith Libeg	Regulatory Health Project Manager

Sponsor Participants:

Pradip Ghosh-Dastidar, Ph.D.	Associate Director, Global Regulatory - CMC
Kathleen Munster	Director, Biologics Quality
Diane Petitti	Vice President, Head of Global Biologics Quality
Annie Sturgess	Executive Director, Global Regulatory Sciences -CMC
Peter F. Moesta	Senior Vice President, Biologics Manufacturing and Process Development
E. Morrey Atkinson	Vice President, Biologics Development
Brendan Hughes	Vice President, Manufacturing Sciences and Technology
Nancy Barbour	Vice-President, Drug Product Science and Technology Biologics Quality
Thomas Gervais.	Group Leader, Manufacturing Sciences and Technology
Mark Moyer	Vice President, Global Regulatory Sciences - Oncology Analytical Development
Kathleen O'Donnell	Director, Global Regulatory Sciences
Jonathan Basch	Associate Director, Analytical Development
Tony Mazzeo	Sr. Principal Scientist, Pharmaceutical Development – Stability
Rajesh Gandhi	Director, (b) (4)
MaryBeth Frosco	Director, Global Regulatory Sciences

This was an FDA-initiated teleconference (TCON) to discuss the chemistry, manufacturing, and controls (CMC) aspects contained in the submission dated July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

On November 25, 2014, FDA issued a CMC information request related to drug substance and drug product specifications; and BMS provided responses via electronic mail (email) communication on December 2, 2014, and followed with a formal submission to the BLA. The call was conducted to discuss BMS' responses and reach agreement on specifications. Details of the discussion are provided below.

Summary of the TCON:

FDA thanked BMS for their responses to the information request and asked BMS to acknowledge the comments for which FDA and BMS are in agreement. BMS confirmed agreement to Comments 1c, 2, and 3 from the November 25, 2014, information request. As a result, FDA and BMS discussed Comments 1a, 1b, 1d during the meeting in order to reach agreement.

Comment 1a, the (b) (4) test:
FDA proposed BMS to tighten the drug product release specifications (b) (4) (b) (4) (b) (4) Additionally, FDA proposed BMS to tighten the drug substance release specifications (b) (4) (b) (4).

BMS acknowledged FDA's proposal. However, BMS requested to reevaluate the data internally and get back to FDA with agreement to the proposal or provide a counterproposal by close of business on Thursday, December 4, 2014. FDA agreed this was acceptable.

Comment 1b, the non-reduced CE-SDS test:
FDA proposed BMS to tighten drug substance and drug product criteria (b) (4) (b) (4) FDA requested confirmation that non-reduced CE-SDS was part of on-going stability program, which BMS confirmed. Additionally, FDA noted that in order to improve reproducibility for the reduced CE-SDS method, FDA will be proposing a PMC.

BMS acknowledged FDA's proposal, and agreed this appeared to be acceptable. However, BMS requested to reevaluate the data internally and get back to FDA with agreement to the proposal or provide a counterproposal by close of business on Thursday, December 4, 2014. FDA agreed this was acceptable. Additionally, BMS acknowledged FDA's proposal to the PMC, and agreed this appeared to be acceptable and would await additional information to confirm the PMC.

Comment 1d, sub-visible particle testing:
FDA noted that compendial limits for this test (USP <788>) are not appropriate and drastic changes in sub-visible particle testing may reflect changes in product quality that are not controlled by the use of an in-line filter during administration. FDA proposed BMS revise the acceptance criteria for DP release and shelf life specifications to be consistent with clinical experience for nivolumab.

BMS acknowledged FDA′s concern, and queried if FDA would be open to allowing BMS using alert limits and hard specification at this point. FDA restated that the acceptance criteria for the DP specifications should still be tightened. Based on the FDA's feedback, BMS requested to get back to FDA with revised specifications by close of business on Thursday, December 4, 2014. FDA agreed this was acceptable.

Items Requiring BMS' Follow-up:

1. Provide agreement to the proposal or providing a counterproposal for the (b) (4) test by close of business on Thursday, December 4, 2014.

2. Provide agreement to the proposal or providing a counterproposal for the non-reduced CE-SDS test by close of business on Thursday, December 4, 2014.

3. Provide a proposal for the sub-visible particle testing by close of business on Thursday, December 4, 2014.

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/s/

MEREDITH LIBEG
12/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 10, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Based on our review, the CMC review team has the following additional requests for information. Please provide your responses via email communication by Thursday, December 11, 2014, and follow with a formal submission to the BLA.

CMC Comments:

1. Please confirm that the establishment and qualification of a new working cell bank will include the submission of a comparability protocol as a prior approval supplement.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 9, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Nonclinical Labeling Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Nonclinical Reviewer has the following request for information relating to the proposed package insert received via email communication on Monday, December 8, 2014. Please provide your response as a formal submission to the BLA by Tuesday, December 9, 2014, or sooner if possible.

Nonclinical Comments:

1. Please provide a rational for the proposed durations of contraception for both males and females added to the label.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 9, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Tuesday, December 9, 2014, or sooner if possible.

Clinical Comments:

1. Provide an explanation for the difference in estimates of some adverse events between Tables 2.2-1 and LSQ.3.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 8, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Tuesday, December 9, 2014, or sooner if possible.

Clinical Comments:

1. Provide a narrative for patient CA209037-16-37662 with increased lipase/amylase.

2. For all patients with increased lipase / amylase:
   - Indicate the reason for checking the lipase / amylase levels.
   - Provide imaging results ruling out pancreatitis.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 8, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Memorandum relating to Clinical Review Comments and Information Request dated December 2, 2014

Background:

On December 2, 2014, FDA initiated a request for information relating to Clinical aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the Clinical information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the Clinical information request dated December 2, 2014, BMS sought clarification, specifically relating to FDA request number 2. This request for clarification was received on December 2, 2014, via email from Kathleen O'Donnell of BMS.

FDA comment #2 of December 2, 2014: "Please confirm that AVAL variable in the ADEF.xpt dataset is DOR in days and the discrepancy between this value and the response duration in weeks listed in Appendix 5.2.2 for patients CA209003-5-140, CA209003-5-210, CA209003-5-210 (2nd occurrence), CA209003-7-139, CA209003-7-143, CA209003-1-215, CA209003-12-148, and CA209003-3-138 as in the following table:"

Patient ID	Sponsor-assessed DOR from CRF (changed to months)	Duration of Response (months)
Nivolumab 0.1 mg/kg		
CA209003-5-140	18.4+	11.1+
Nivolumab 0.3 mg/kg		
CA209003-5-210	15.7+	10.2+
CA209003-5-210	21.4+	15.2+
CA209003-7-139	20.5+	14.8+
CA209003-7-143	20.7	15+
Nivolumab 1 mg/kg		
CA209003-1-215	15.6+	10+
CA209003-12-148	19.4+	14.8+
CA209003-3-138	16.7	7.5

BMS request for clarification of December 2, 2014: "We have noted in the table provided by the FDA, that the 2nd listing of pt CA209003-210, should actually be CA209003-7-129 based on the our assessed DOR from the CRF and the Duration of response results listed in the table.

PT ID	Sponsor assessed DOR from CRF (changed to months)	Duration of Response (months)
Nivolumab 0.3 mg/kg		
CA209003-5-210	15.7+	10.2+
CA209003-5-210	21.4+	15.2+

Can you provide clarification on this, and if FDA agrees that the patient above is CA209003-7-129, then confirm if Question 3 should be further clarified based on the new patient ID?"

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on December 2, 2014:

FDA clarification December 2, 2014: You are correct. It appears the patient number was transcribed incorrectly. Additionally, we still would like an explanation for the discrepancy in timing.

Upon receipt of the FDA clarification December 2, 2014, BMS sought additional clarification. This request for clarification was received on December 2, 2014, via email from Kathleen O'Donnell of BMS.

BMS request for clarification of December 2, 2014: "Confirm we will provide an explanation for this new patient and also then apply an NA to question 3 since it no longer applies – this new patient was not re-treated. Do you agree?"

Upon receipt of the request for additional clarification, FDA discussed internally and provided the following clarification to BMS via email on December 3, 2014:

FDA clarification December 3, 2014: Please confirm if any patients who were counted as responders were retreated as allowed by the protocol.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe via email and followed with a formal submission to the BLA.

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/s/

MEREDITH LIBEG
12/08/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Monday, December 08, 2014 9:39 AM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Language for Section 8 to the PI

Importance: High

Hi Kathy,
As discussed at last week's meeting, please find the FDA proposed Section 8 as a result of the new Pregnancy and Lactation Labeling Rule that published last week.

8.1 Pregnancy

Risk Summary:

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPVIDO are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown, however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data:

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on, neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk, instruct women to discontinue breastfeeding during treatment with OPDIVO.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least (b) (4) months following the last dose of OPDIVO.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35%patients were 65 years or older and 40 (15%) were 75 years or older.

8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

Should you have any questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
12/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 5, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Friday, December 5, 2014.

Clinical Comments:

1. Clarify the location of Table 2 of the label in the BLA submission.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 5, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

We have reviewed your December 1 and December 3, 2014, responses to our CMC requests for information. Based on our review, the CMC review team has the following additional requests for information. Please provide your responses via email communication by Friday, December 5, 2014, and follow with a formal submission to the BLA.

CMC Comments:

1. We do not agree that implementation of annual testing of your primary reference standard can wait until a new working reference standard has been qualified and implemented. Update your reference standard testing strategy to include immediate implementation of annual testing for the primary reference standard.

2. Regarding your specification test for (b) (4) we accept your proposal for drug substance (DS) and drug product (DP) release criteria and drug substance stability criteria. However, we consider your DP stability specification for (b) (4) to be too broad and not reflective of your clinical experience. Please acknowledge your intent to revise criteria for (b) (4) to NMT (b) (4) and (b) (4) to NLT (b) (4)

3. We accept your proposed acceptance criteria for drug product sub-visible particle testing.

Additionally, we remind you that appropriate sections of the BLA need to be updated to reflect all agreements and commitments made to date.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 5, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Proposed PMC/PMR Language

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Please see FDA's post-marketing requirement and post-marking commitment proposal. Please provide your responses via email communication by Monday, December 8, 2014.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

Confirmatory Trial(s) For Nivolumab:

1. Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

   Final Protocol Submission:
   Trial Completion Date:
   Final Report Submission:

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Drug Substance Specification Assessment:

2. To re-evaluate nivolumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

Drug Product Specification Assessment:

Final Report Submission:

3. To re-evaluate nivolumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

Final Report Submission:

Improvements To Methods Assessment (HCP Assay):

4. To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the nivolumab drug substance release program. The analytical procedure, validation report, proposed specification acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.

Final Report Submission:

Improvements To Methods Assessment (CE-SDS Method):

5. To optimize and re-validate a non-reduced CE-SDS method that has improved reproducibility. The analytical procedure, validation report, any proposed changes to specification acceptance criteria, and the data used to set the proposed acceptance criteria will be provided in the final study report

   Final Report Submission:

MICROBIOLOGY (CMC)

Improvements To Endotoxin Limits (Drug Substance):

6. Re-evaluate and tighten the endotoxin limits for the following in-process samples: (b) (4) Re-evaluate and tighten the endotoxin limits for the following additional samples: (b) (4)

   Final Report Submission:

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf.
- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 4, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Friday, December 5, 2014.

Clinical Comments:

1. We have reviewed your responses to our December 3, 2014, clinical information request. Based on the information contained in the response, provide the following data regarding the 4 melanoma patients who had an objective response and later had disease progression who initiated dosing in retreatment phase of trial CA 209003 (CA209003-3-138, CA209003-4-1315, CA209003-7-1309, and CA209003-1-2316) as noted under response to Question 3:
   - First dose and last dose of nivolumab initial treatment
   - Date of initial response and subsequent PD
   - Dates of retreatment
   - Response assessment to retreatment with dates

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
12/04/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Wednesday, December 03, 2014 3:51 PM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Proposed Labeling Edits (12.3.14)

Importance: High

Hi Kathy,

Please find attached FDA's first round of proposed edits to the Nivolumab PI relating to your original BLA application (BLA 125554) submitted on July 30, 2014.

As noted in yesterday's teleconference, FDA has not completed Sections 2 and 5. These sections will be updated/revised as discussed and agreed in the teleconference. Please review our edits and comments to the other sections and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. Lastly, when making edits to the label, please update formatting as necessary.

Please submit the updated labeling via email by COB on **Thursday, December 4, 2014.**

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Wednesday, December 3, 2014.

Clinical Comments:

1. In patient CA209037-101-37645, the narrative mentions "post-operative inability to wrinkle the left forehead" on Day 32. Clarify the time and details of the surgery referred to in the narrative.

2. For patient CA209037-50-37189, you state "The investigator confirmed that the patient had rapid progression of his liver metastasis" (Response to 9/17/2014 FDA IR). Provide radiology and/or laboratory reports to confirm disease progression.

3. For patient CA209037-67-37526, you state "the patient was also found to have progressive disease" (Response to 9/17/2014 FDA IR). Provide radiology and/or laboratory reports to confirm disease progression.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Thursday, December 4, 2014, or sooner if possible.

CMC Comments:

1. Clarify if the incoming [redacted] (b) (4) are received with a bioburden limit and state what the limit is. Provide a justification if there is no bioburden limit. Amend Module 3.2.P.3.5.2.4 accordingly.

2. Clarify whether the [redacted] (b) (4) descriptions presented in Module 3.2.P.3.5.2.5 are specific for Nivolumab manufacture, or represent [redacted] (b) (4) Amend Module 3.2.P.3.5.2.5 as necessary

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Memorandum relating to Clinical Review Comments and Information Request dated November 3, 2014

Background:

On November 3, 2014, FDA initiated a request for information relating to clinical aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the clinical information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the of the clinical information request dated November 3, 2014, BMS sought clarification, specifically relating to FDA request number 1 and 6. This request for clarification was received on November 4, 2014, and November 5, 2014, via email from Kathleen O'Donnell of BMS.

FDA comment #1 of November 3, 2014

- FDA comment #1 of November 3, 2014: "Provide a narrative summary based on the data submitted, in patients with immune-mediated adverse events to determine the time to onset of immune-mediated adverse events (AEs), duration of AEs, action taken with the drug, outcome, and type/amount/duration of steroid treatment for each AE including pneumonitis, colitis, hepatitis, adrenal insufficiency, skin rash, renal failure/nephritis, hypothyroidism, hyperthyroidism, and hypersensitivity/infusion reactions to inform prescribers in product labeling of appropriate management of side effects to promote the safe and effective use of nivolumab.

  When providing the numerical estimate of the risk, include immune-mediated AEs irrespective of causality. In accordance with the serious adverse event (SAE) collection and reporting requirements in Protocol CA209037, include SAEs that occur up to 100 days following the last dose of study treatment. When providing information related to the outcome of an AE, consider the event as ongoing if the patient died with symptoms still present."

- BMS request for clarification of November 4, 2014, to FDA comment #1: Can you clarify the above request?

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on November 4, 2014:

- FDA clarification of November 4, 2014, to FDA, comment #1: please include nonserious AEs up to 30 days and serious and significant AEs (include non-fatal SAEs, immune-mediated SAEs), up to 100 days.

Upon receipt of the FDA's response of November 4, 2014, BMS requested additional clarification on November 5, 2014, via email from Kathleen O'Donnell of BMS:

- BMS request for clarification of November 5, 2014, to FDA comment #1: FDA requested a narrative summary for patients with immune-mediated AEs for the following AEs: pneumonitis, colitis, hepatitis, adrenal insufficiency, skin rash, renal failure/nephritis, hypothyroidism, hyperthyroidism and hypersensitivity/infusion reactions, irrespective of causality. We can agree to this approach, however BMS requests clarification on which specific preferred terms to include under each category, recognizing that the scope should be limited because inclusion of a broader set of terms in an all-causality analysis would capture events due to non-immune mediated etiologies, such as disease progression, and would therefore hinder the interpretation of the data by the prescribing physician.

  Please note in formulating our initial response, the preliminary search of the Preferred Term "hepatitis", there are no events in study CA209037. However, there is a case of hepatotoxicity. BMS seeks FDA's recommendation regarding how best to produce a clinically meaningful analysis of immune-mediated AEs regardless of causality and requests clarification on which specific preferred terms to include under each category.

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on November 5, 2014:

- FDA clarification of November 5, 2014, to FDA, comment #1: We clarify that the final labeling will not have broad categories, but will have specific AEs. Please include at least the following specific AE terms in the narrative summary and any other terms which is significant based on your review of data and as defined in the Select AE category: Pneumonitis / interstitial lung disease; Colitis / diarrhea; hepatitis to include all preferred terms that would encompass those most likely to reflect hepatotoxicity and potential drug-induced liver injury; Renal failure and nephritis; hypothyroidism and hyperthyroidism; thyroiditis; adrenal insufficiency; and pancreatitis. Include the preferred terms identified in the analyses. Please revise the numerical estimate of risk based on these preferred terms which occurred up to 100 days after the last dose of study therapy, and include both the nivolumab arm (N=268) and the investigator's choice arm (N=102), regardless of causality. Attribution is not a reliable assessment of causality and the comparison to a control arm would help inform the prescribers of the immune-mediated AEs observed with nivolumab vs. chemotherapy.

FDA comment #6 of November 3, 2014

- FDA comment #6 of November 3, 2014: "Please confirm the status of subject 066 with regards to study treatment: DX.xpt states continued therapy, Appendix 5.2 states subject received subsequent therapy and CRF is unclear. Please note if any biopsy results from the surgical resection of small bowel on 10/21/13 is available and if the resected lesion was the new lesion found of scan of 9/27/13 as noted by the investigator."

- BMS request for clarification of November 4, 2014, to FDA comment #6: "Can we confirm that the subject referred to in Q6, is subject 50-37006 and not 066?"

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on November 4, 2014:

- FDA clarification of November 4, 2014, to FDA, comment #6: This was a typographical error and should be subject 50-37006.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe via email and followed with a formal submission to the IND.

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MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 17, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Clinical and Statistical Dataset Meeting

Date and Time of Teleconference: October 17, 2014, 9:30 a.m. to 10:00 a.m.

FDA Participants:

Maitreyee Hazarika, M.D.	Clinical Reviewer
Meredith Chuk, M.D.	Clinical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Randall H. White, Ph.D.	Director, Project Management
Aimee Bergey-Reilly	Associate Director, Data Operations
Georgia Kollia, Ph.D.	Associate Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Katie Medici	Manager, Global Dossier Management
Todd Rider	Associate Director, Statistical Programming Manager
Ian Waxman, M.D.	Director, Global Clinical Research - Oncology
Lihui Deng	Technical Manager, Global Biometric Sciences
Rebecca Drain	Associate Director, Global Dossier Management
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology

This was an FDA-initiated teleconference (TCON) to discuss the clinical and statistical aspects of the datasets submitted on July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on July 30, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification. Information that required BMS' follow-up internally in order to address the question/inquiry, are captured below and responses will be provided via email communication to FDA; and followed by BMS' formal submission to the BLA.

Items Requiring BMS' Follow-up:

1. Please clarify the number of subjects treated at 3 mg/kg for nivolumab monotherapy.

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/s/

MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Memorandum relating to Clinical Review Comments and Information Request dated October 31, 2014

Background:

On October 31, 2014, FDA initiated a request for information relating to clinical aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the clinical information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the of the clinical information request dated October 31, 2014, BMS sought clarification, specifically relating to FDA request number 9. This request for clarification was received on November 3, 2014, via email from Kathleen O'Donnell of BMS.

FDA comment of October 31, 2014:
"Provide narratives for the following patients:

- CA209037-2-37512
- CA209037-39-37514
- CC209037-98-37510
- CA209037-27-37089
- CA209037-77-37118
- CA209037-69-37106
- CA209037-73-37163
- CA209037-25-37223
- CA209037-37-37134
- CA209037-47-37184"

BMS request for clarification of November 3, 2014: FDA requested a narrative for subject 39-37514. We do not have 39-37514 in our database. Nor does 37514 exist for another site. We do have a patient 39-37154. Can you confirm that the narrative is requested for 39-37154?

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on November 3, 2014:

FDA clarification of November 3, 2014: The narrative request is for patient CA209037-39-37154.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe via email and followed with a formal submission to the IND.

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/s/

MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Memorandum relating to Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request dated October 28, 2014

Background:

On October 28, 2014, FDA initiated a request for information relating to CMC aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the CMC information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the CMC information request dated October 28, 2014, BMS sought clarification, specifically relating to FDA request number 1 and 2. This request for clarification was received on October 30, 2014, via email from Kathleen O'Donnell of BMS.

FDA comment #1 of October 28, 2014: "We note that you have included both critical process parameters and process parameters in section 3.2.S.2.4. Provide confirmation that these parameters are both considered regulatory commitments. We recommend that these process parameters be listed or described in 3.2.S.2.2."

FDA comment #2 of October 28, 2014: "We note that 3.2.S.2.4 includes the use of critical performance attributes and performance attributes. As with item #1, provide confirmation that these are all considered regulatory commitments."

BMS request for clarification of October 30, 2014:

1. BMS confirms that the information presented in 3.2.S.2.4 on critical process parameters and process parameters are considered regulatory commitments. Any changes to these parameters will be reported following the filing category as required by FDAs guidance(s).

2. Clarification is requested regarding the recommendation that the process parameters also be listed or described in 3.2.S.2.2. BMS is proposing to maintain the sections as currently formatted in the BLA. Alternatively, to comply with the FDA recommendation, the exact information on the process parameters that is currently in 3.2.S.2.4 can be added into 3.2.S.2.2. The information in either section would be assessed equally for reporting changes as required by FDA guidance(s).

BMS requests FDA feedback to maintain the current BLA format for these sections or to add the exact information that is currently in 3.2.S.2.4 into section 3.2.S.2.2.

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on October 31, 2014:

FDA clarification of October31, 2014: We'd prefer the latter, the direct addition of 3.2.S.2.4 into section 3.2.S.2.2.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe via email and followed with a formal submission to the BLA.

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/s/

MEREDITH LIBEG
12/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 2, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Wednesday, December 3, 2014, or sooner if possible.

Clinical Comments:

As a follow-up to your responses to the Clinical Information Request from November 26, 2014, we have the following additional requests for information:

1. Please clarify the response classification for patient MDX1106-03-5-225. This patient is listed as a responder in the CSR and response to IRs; however, is listed as having a best response of SD in dataset ADEF.xpt.

2. Please confirm that AVAL variable in the ADEF.xpt dataset is DOR in days and the discrepancy between this value and the response duration in weeks listed in Appendix 5.2.2 for patients CA209003-5-140, CA209003-5-210, CA209003-5-210 (2nd occurrence), CA209003-7-139, CA209003-7-143, CA209003-1-215, CA209003-12-148, and CA209003-3-138 as in the following table:

Patient ID	Sponsor-assessed DOR from CRF (changed to months)	Duration of Response (months)
Nivolumab 0.1 mg/kg		
CA209003-5-140	18.4+	11.1+
Nivolumab 0.3 mg/kg		
CA209003-5-210	15.7+	10.2+
CA209003-5-210	21.4+	15.2+
CA209003-7-139	20.5+	14.8+
CA209003-7-143	20.7	15+
Nivolumab 1 mg/kg		
CA209003-1-215	15.6+	10+
CA209003-12-148	19.4+	14.8+
CA209003-3-138	16.7	7.5

3. Confirm if patient CA209003-5-210 was re-treated with nivolumab, the timing of the retreatment and responses, and if they were the only responder retreated in this study.

4. For the patients on trial CA209003 listed as having an ongoing response, please clarify:
   - Why patient CA209003-10-103 is listed as having an ongoing response but has PD listed as reason for study discontinuation.
   - Why patient CA209003-11-1324 is listed as having an ongoing response but the reason for off study is listed as patient withdrew consent and the CRF states that the patient will no longer be followed.
   - The reason for study drug discontinuation listed as "other" for patient CA209003-10-2314.

5. Please provide a breakdown by patient number for the patients considered as ongoing responders for trials CA209037 and CA209003 that lead to the statements that 95% of patients in trial CA209037 and 57% of patients in trial CA209003 had ongoing responses at the time of data-cutoff. It is unclear that the censoring rules for PFS and calculation of DOR should be used in the calculation of percent of ongoing responders. (e.g. the 3 patients on trial CA209037 who received subsequent therapy following PD should be considered as having an event).

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 2, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Tuesday, December 2, 2014, or sooner if possible.

Clinical Comments:

1. Clarify that patient CA209037-27-37152 received corticosteroids for Grade 3 pneumonitis. Clarify the location of the information in the datasets.

2. Provide an analysis of corticosteroid use in the patients with increased amylase and increased lipase.

3. Clarify whether adrenal insufficiency in patient CA209037-27-37089 increased from baseline as the adverse event is identified as treatment emergent in the dataset.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 1, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Monday, December 1, 2014, or sooner if possible.

Clinical Comments:

1. Please provide the number of ipilimumab doses received by patients in the treated ORR population for Trial CA209037.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
12/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 29, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Monday, December 1, 2014, or sooner if possible.

Clinical Comments:

1. Provide the narrative for the death of patient CA209037-110-37543 treated in the investigator's choice group.

2. For patient CA209037-30-37309, provide the day and date the patient started treatment with nivolumab. Clarify the reason(s) the patient received hydrocortisone and prednisone treatment during the trial.

3. Provide a detailed description and time course of signs, symptoms, evaluation, and treatments administered (if any) leading to the death for patient CA209037-28-37383. Include details after his discharge from the hospital on (b) (6)

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 26, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Tuesday, December 2, 2014, or sooner if possible.

Clinical Comments:

1. Provide details on how you calculated the ongoing responses for patients in the nivolumab and investigator's choice arm on trial CA209037.

2. Supply a similar analysis for the melanoma patients treated with doses at or below 3mg/kg on trial CA209003.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 26, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 28, 2014, or sooner if possible.

Clinical Comments:

1. Provide details on the treatment of hyperthyroidism in the eight patients in the nivolumab arm and the outcome of hyperthyroidism in these patients.

2. Clarify what is meant by 'resolution' of hypothyroidism and hyperthyroidism.

3. Provide the narrative for the patient with the hematological malignancy who died of pneumonitis.

4. Clarify how pancreatitis was diagnosed in patient CA209037-43-37239.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 25, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Tuesday, December 2, 2014, or sooner if possible.

CMC Comments:

1. Regarding your specifications, we require the following additional information to evaluate your proposed acceptance criteria:
    a. For your [redacted] (b) (4) test, we do not agree that [redacted] (b) (4) [redacted] (b) (4) as their impact on PK does not appear to have been fully considered [redacted] (b) (4) Provide additional data which summarizes clinical experience to date for drug product with respect to [redacted] (b) (4)
    b. For the non-reduced CE-SDS test, provide additional data which summarizes clinical experience to date with respect to purity levels observed for drug product.
    c. For the host cell protein content in drug substance, we acknowledge that clinical experience includes [redacted] (b) (4) drug substance. Provide additional information regarding how manufacturing consistency will be demonstrated for [redacted] (b) (4) drug substance with respect to host cell protein given your proposed specification limit.
    d. For sub-visible particle testing included in DP specifications, acceptance criteria should be based on available clinical experience. Provide summary clinical experience information along with proposed revised acceptance criteria.

2. For drug substance and drug product release and stability specifications:
   a. For the potency ELISA, we recommend acceptance criteria of (b) (4).
   b. For the cell-based bioassay, we recommend acceptance criteria of (b) (4).
   c. For (b) (4)-HPLC assay, we recommend acceptance criteria of NMT (b) (4) for (b) (4) and NMT (b) (4) for (b) (4)

3. For drug product specifications, we recommend that you revise your criterion for (b) (4) visible particles to (b) (4).

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 21, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 28, 2014, or sooner if possible.

CMC Comments:

1. Please update Section 3.2.S.2.4 of the BLA to include the [redacted] (b) (4) bioburden acceptance criteria of [redacted] (b) (4) for the production [redacted] (b) (4) on day [redacted] (b) (4)

2. Please commit as a post-market commitment to re-evaluate and tighten the following endotoxin limits when more endotoxin data are available:
[redacted] (b) (4)

3. Please clarify the difference between [redacted] (b) (4) (b) (4)

(b) (4)

10. Please confirm that procedures are in place to conduct the DS endotoxin release test within (b) (4)

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 20, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Wednesday, November 26, 2014, or sooner if possible.

CMC Comments:

Drug Substance

(b) (4)

(b) (4)

[redacted]

Drug Product

8. Update the stability table in section 3.2.P.8.3 to include the [redacted] (b) (4) potency result at long-term storage conditions for batch 2J71008.

9. For the drug product stability studies described in the BLA, clarify if any samples are stored or tested at the Lonza Portsmouth facility. If so, update section 3.2.P.3.1 to include this information.

10. 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information to confirm that identity testing of both nivolumab 100 mg/10 mL and 40 mg/4 mL meets this CFR requirement.

11. Table 3.2.P.5.4.1-1 notes that three PPQ lots each of the 40 mg/4 mL and 100 mg/10 mL drug product presentations are currently in an ongoing stability program. (b) (4) Provide a summary of stability results for PPQ batches.

12. Your ongoing stability programs in section 3.2.P.8 do not include an assessment of polysorbate 80 or (b) (4) Provide additional data or justification to demonstrate that polysorbate 80 (b) (4) of nivolumab injection.

13. It is noted in section 3.2.P.2.4 Container Closure System that the leachables/extractables study is scheduled to complete (b) (4) of testing, but only (b) (4) months of data are available. Update 3.2.P.8.2 to include a commitment to complete this testing post licensure.

14. In your filter validation studies (section 3.2.P.3.5.2.6) you identified (b) (4) as leachate by (b) (4) Provide additional information regarding the potential levels observed, and a toxicology assessment demonstrating these levels result in no safety concern.

15. Regarding Shipping Qualification (3.2.P.3.5.3), additional information is required to assess the adequacy of this program.

    a. Provide additional detail on the (b) (4) of nivolumab drug product and the (b) (4) performed during shipment.

    b. Provide product quality referenced in this section that demonstrates that there is no product quality impact observed during shipment.

16. Testing for (b) (4) visible particles was not performed in your registration stability program. Provide additional information to support the conclusion that drug product will remain within specification for (b) (4) visible particles throughout the shelf life of the product.

17. The drug product specifications allow for the presence of particulates in the appearance and the (b) (4) visible particle tests. Provide any additional information available describing the characterization of the particulates present in drug product at release or on stability.

18. Additional process parameters should be included to ensure sufficient control of the DP manufacturing process. Specifically update sections 3.2.P.3.3.2.1 Manufacturing Process Description of (b) (4) Solution for Dilution, 3.2.P.3.3.2.2 Manufacturing Process Description of Nivolumab Injection, and 3.2.P.3.4, Description of Critical Steps and (b) (4) Description of Manufacturing Process and Process Controls with the parameter ranges described within Table 3.2.P.2.3-12 as inclusion of information in the pharmaceutical development section (3.2.P.2) only is not sufficient. In addition, confirm Agency understanding that these parameters reflect regulatory commitments post-licensure.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 20, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Monday, November 24, 2014, or sooner if possible.

Clinical Comments:

1. Provide an assessment of the occurrence of rhabdomyolysis, transverse myelitis, diabetes, diabetic ketoacidosis and hypogonadism, including the incidence, toxicity grade, dose of drug at which the AE occurred, time to onset, treatment, management, and outcome in the safety database of nivolumab used as a single agent.

2. Provide narratives for the three patients with hypophysitis reported in the BMS safety database.

3. Provide narratives for the following patients with details related to adrenal insufficiency,:
   a. CA209037-25-37223
   b. CA209037-27-37089
   c. CA209037-86-37198

4. Provide narratives for the following patients with details related to hyperglycemia/ diabetes:
   a. CA209037-16-37063
   b. CA209037-16-37413
   c. CA209037-16-37611
   d. CA209037-17-37259
   e. CA209037-20-37098

f. CA209037-72-37643
g. CA209037-87-37488

5. Clarify how the time to resolution of the select specific AEs were calculated.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 18, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Thursday, November 20, 2014, or sooner if possible.

Clinical Comments:

1. With regards to study discontinuation in the treated ORR population:
   a. for the 25 patients in the nivolumab arm and 13 patients in the investigator's choice arm who have death as a reason for study discontinuation, please confirm cause of death.
   b. for the 7 patients on the nivolumab arm and 3 patients in the investigator's choice arm who have "other" listed as a reason for study discontinuation, please provide further explanation for "other."

2. Please clarify if patients in the ORR population were replaced if they were lost to follow up or came off study for toxicity before the 6 month cut off for the primary analysis (Per the CSR: ORR Population=All randomized subjects to either treatment group with at least 6 months of follow-up at the time of the ORR analysis, which occurred when the first 120 nivolumab-treated subjects had a minimum of 6 months of follow-up).

3. For patients censored for ORR due to patient receiving additional anti-cancer therapy prior to the first scan in the nivolumab and investigators choice group (CA209037-2-37016, CA209037-13-37161, CA209037-27-37252,CA209037-51-37023, CA209037-62-37153 and CA209037-10-37168, CA209037-38-37185, CA209037-51-37011, CA209037-62-37224, CA209037-42-37212, CA209037-50-37262,

CA209037-86-37198)), please provide reasons for starting other therapies (i.e., toxicity of study therapy, progression, etc.).

4. For patient CA209037-51-37023, please describe the reason that this patient was not evaluable by the IRRC.

5. For patients CA209037-77-37272 and CA209037-28-37020, please describe the nature and timing of the clinical progression described by the investigator. Also please clarify reason for PD as assessed by investigator for patient 020 as CSR states clinical progression (Table 7.2.2-1) and response to FDA request dated November 3, 2014 states radiographic progression.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/18/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Thursday, November 13, 2014 10:48 AM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - Risk Management Plan

Hi Kathy,
We note that in your risk management plan included in your July 30, 2014 original BLA submission, you have proposed the following safety education materials: (b) (4) 3) Medication Guide, and 4) Patient Alert Card. Your risk management plan also notes (b) (4) As we indicated at the mid-cycle sponsor communication, a REMS is not needed at this time; therefore, we considered these documents to be promotional materials. These documents should be submitted to the BLA in accordance with the timelines and regulations for promotional materials.

Should you have any questions, please don't hesitate to contact me; and kindly confirm receipt.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
11/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 12, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Monday, November 17, 2014, or sooner if possible.

Clinical Comments:

1. Provide a narrative for the following patient to include the onset, duration, management and outcome of urticaria: CA209037-61-37367.

2. Provide a narrative for the following patient to include the actions taken, management and outcome of chills: CA209037-69-37207.

3. In the All Treated Population in the ADAE.xpt dataset, age is missing for 45 patients. Clarify that the Tables provided in the CA209037 CSR with summaries of the subgroup analysis for age, gender, and race include these patients. If not, provide updated tables.

4. Provide one summary table each for age, gender, and race in the All Treated Population (N=370) comparing all AEs, all SAEs, all AEs leading to discontinuation, Grade 3-4 AEs, and Select AEs in the nivolumab arm and investigator's choice arm.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 27, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Sponsor Face-To-Face/Teleconference – Clinical and Statistical Dataset Meeting

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Date and Time of Face-To-Face/Teleconference: August 27, 2014, 1:30 p.m. to 3:00 p.m.

FDA Participants:

Marc Theoret, M.D.	Clinical Team Leader
Meredith Chuk, M.D.	Clinical Reviewer
Maitreyee Hazarika, M.D.	Clinical Reviewer
Sirisha Mushti, Ph.D.	Statistical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants (Present in Person):

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Rebecca L Drain	Associate Director, Global Dossier Management
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology
Christina Smith, D.Phil.	Vice President, Global Development, Nivolumab Filing and Dossier Strategy
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research

Sponsor Participants (Present via Teleconference):

Aimee Bergey-Reilly	Associate Director, Data Operations
Dana P. Grimaldi, M.B.A.	Associate Director, Documentation Lead for Nivolumab
Georgia Kollia, Ph.D.	Associate Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Katie Medici	Manager, Global Dossier Management
Todd Rider	Associate Director, Statistical Programming Manager
Amit Roy	Group Director: Clinical Pharmacology and Pharmacometrics
Ian Waxman, M.D.	Director, Global Clinical Research - Oncology
Yan Zhang	Technical Manager, Global Biometric Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology

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This was an FDA-initiated Face-to-Face to discuss the clinical and statistical aspects of the datasets submitted on July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. Due to the timing of the meeting, several BMS participants joined via teleconference.

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on July 30, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification. Information that required BMS' follow-up internally in order to address the question/inquiry, are captured below and responses will be provided via email communication to FDA; and followed by BMS' formal submission to the BLA.

Items Requiring BMS' Follow-up:

1. In the data conformance summary (SDTM reviewer's guide), Warnings related to duplicate records were reported for TR and TU SDTM datasets. Clarify what are these duplicates and how these were handled in the analysis?

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/s/

MEREDITH LIBEG
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 15, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Clinical and Statistical Dataset Meeting

Date and Time of Teleconference: September 15, 2014, 10:00 a.m. to 10:30 a.m.

FDA Participants:

Maitreyee Hazarika, M.D.	Clinical Reviewer
Sirisha Mushti, Ph.D.	Statistical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Aimee Bergey-Reilly	Associate Director, Data Operations
Georgia Kollia, Ph.D.	Associate Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Katie Medici	Manager, Global Dossier Management
Todd Rider	Associate Director, Statistical Programming Manager
Ian Waxman, M.D.	Director, Global Clinical Research - Oncology
Lihui Deng	Technical Manager, Global Biometric Sciences
Marianne Federici	Director, Dossier Management
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology

This was an FDA-initiated teleconference (TCON) to discuss the clinical and statistical aspects of the datasets submitted on July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on July 30, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification. Information that required BMS' follow-up internally in order to address the question/inquiry, are captured below and responses will be provided via email communication to FDA; and followed by BMS' formal submission to the BLA.

Items Requiring BMS' Follow-up:

1. Not applicable for this meeting.

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/s/

MEREDITH LIBEG
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 7, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Monday, November 17, 2014, or sooner if possible.

CMC Comments:

1. Please provide the bioburden sample volumes for the (b) (4) (b) (4) The bioburden acceptance criteria should be expressed as CFU/sample volume tested. Update the BLA accordingly. Clarify if additional bioburden samples are taken from the (b) (4)

2. The endotoxin acceptance criteria (b) (4) for the (b) (4) and (b) (4) Please tighten the acceptance criteria based on manufacturing capability and product quality impact.

3. The bioburden acceptance criteria (b) (4) for (b) (4) Please justify the bioburden acceptance criteria or alternatively, tighten the acceptance criteria based on manufacturing capability.

4. Provide a diagram indicating all the bioburden and endotoxin sampling locations in relation to the locations of the 0.2 µm filters and the (b) (4). The bioburden samples should be taken prior to 0.2 µm filtration and at the end of the (b) (4)

5. Please explain the difference in sampling locations between the microbiology samples (bioburden and endotoxin) for (b) (4)

6. The endotoxin acceptance criterion (b) (4) Please tighten the acceptance criteria based on manufacturing capability and product quality impact.

7. Please clarify if the filter (b) (4) is a 0.2 µm filter.

8. Please tighten the (b) (4) endotoxin acceptance criterion for the (b) (4) based on manufacturing capability.

9. The endotoxin acceptance criteria of (b) (4) for both the (b) (4) Please tighten the acceptance criteria according to manufacturing capability.

10. Please establish endotoxin limits for all the (b) (4) used for nivolumab drug stubstance (DS) manufacturing that are microbially growth promoting. Provide the endotoxin limits. Clarify if the (b) (4) are tested for endotoxin prior to use.

11. In the case of (b) (4) If so, how long will be the hold time? Clarify if the bioburden and endotoxin level in the (b) (4) Specify the bioburden and endotoxin limits.

12. In the case of (b) (4) If so, how long will be the hold time? Clarify if the bioburden and endotoxin level in the (b) (4) Specify the bioburden and endotoxin limits.

13. Please clarify if all the bioburden and endotoxin samples taken during the (b) (4)

14. The hold times of the (b) (4) Please clarify if all the (b) (4)

15. One of the PPQ lots 352504 had endotoxin level of (b) (4) Please explain the sources of the endotoxin. Clarify if investigations were conducted for the (b) (4) results.

16. With regard to Table 3.2.S.2.5.5.7-5, (b) (4) endotoxin data (b) (4) . With the exception of < LOQ results, the exact endotoxin level should be provided. In addition, for the same table, explain why the endotoxin data (b) (4) provided in (b) (4) Lonza document (b) (4) was not used.

17. Please tighten the bioburden specification to (b) (4) for the (b) (4) drug substance stored at (b) (4)

18. Please include bioburden and endotoxin monitoring of the (b) (4) Provide the bioburden and endotoxin limits for the study. In addition, provide the bioburden and endotoxin limits for the (b) (4)

(b) (4)

20. Please provide summary data from the endotoxin (b) (4) In addition, provide the (b) (4) and summary data for the qualification the formulated (b) (4) DS endotoxin sample for the (b) (4) method demonstrating the suitability of the test method.

21. The qualification of the [redacted] (b) (4) samples for the endotoxin test used samples from [redacted] (b) (4) [redacted] (b) (4) have different [redacted] (b) (4). It is not clear if the [redacted] (b) (4) samples have the same impurities and can represent the [redacted] (b) (4) samples in the endotoxin qualification study. Please provide qualification data of the [redacted] (b) (4) sample for the endotoxin test.

22. Please clarify if sample [redacted] (b) (4) described in bioburden qualification repor [redacted] (b) (4) is equivalent to the [redacted] (b) (4) drug substance sample. If the samples are not equivalent, provide qualification data of the [redacted] (b) (4) drug substance sample for the bioburden test. Data provided in report [redacted] (b) (4) used [redacted] (b) (4) samples, which may not be representative of the [redacted] (b) (4) samples. In addition, provide qualification data of the [redacted] (b) (4) sample for the bioburden test.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 7, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Wednesday, November 12, 2014, or sooner if possible.

Clinical Comments:

1. Provide narratives for the following patients, including outcomes of the increased lipase and amylase AEs:
   - CA209037-110-37507
   - CA209037-16-37662
   - CA209037-17-37259
   - CA209037-39-37154
   - CA209037-71-37105
   - CA209037-72-37584
   - CA209037-77-37079
   - CA209037-77-37337

2. For patient CA209037-43-37239, clarify that the laboratory test result of amylase of 509 U/L constitutes Grade 3 and not Grade 1.

3. Provide narratives for the following patients, including age and outcome of the cardiac AEs:
   - CA209037-17-37259
   - CA209037-62-37251
   - CA209037-71-37105
   - CA209037-87-37487

4. Provide additional information on the management of atrial fibrillation and outcome at the time of death for the following patients:
   - CA209027-16-37413
   - CA209037-16-37419

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 12, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Clinical and Statistical Dataset Meeting

Date and Time of Teleconference: September 12, 2014, 9:30 a.m. to 10:00 a.m.

FDA Participants:

Meredith Chuk, M.D.	Clinical Reviewer
Maitreyee Hazarika, M.D.	Clinical Reviewer
Sirisha Mushti, Ph.D.	Statistical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research
Aimee Bergey-Reilly	Associate Director, Data Operations
Georgia Kollia, Ph.D.	Associate Director, Global Biometric Sciences
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Katie Medici	Manager, Global Dossier Management
Todd Rider	Associate Director, Statistical Programming Manager
Ian Waxman, M.D.	Director, Global Clinical Research - Oncology
Lihui Deng	Technical Manager, Global Biometric Sciences
Marianne Federici	Director, Dossier Management

This was an FDA-initiated teleconference (TCON) to discuss the clinical and statistical aspects of the datasets submitted on July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on July 30, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification. Information that required BMS' follow-up internally in order to address the question/inquiry, are captured below and responses will be provided via email communication to FDA; and followed by BMS' formal submission to the BLA.

Items Requiring BMS' Follow-up:

1. Clarify the definition of the nivolumab cumulative dose and provide example of the derivation for a specific subject?

2. Provide code that enables merging of Adverse Events that were treated with Immune Modulating medications?

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/s/

MEREDITH LIBEG
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 6, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC review team has the following request for information. Please provide your response as a formal submission to the BLA by Wednesday, November 12, 2014, or sooner if possible.

CMC Comments:

1. Clarify the [redacted] (b) (4) (b) (4)

2. Regarding the biological qualification data presented in the tables and modules listed below, indicate the media and growth conditions used for [redacted] (b) (4) (b) (4)

2 Pages Withheld in Full as B4(CCI/TS) Immediately Following this Page

(b) (4)

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
11/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 7, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**

Memorandum relating to Clinical Review Comments and Information Request dated September 17, 2014

Background:

On September 17, 2014, FDA initiated a request for information relating to clinical aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the clinical information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the clinical information request dated September 17, 2014, BMS sought clarification, specifically relating to FDA request number 17. This request for clarification was received on September 18, 2014 via email from Kathleen O'Donnell of BMS.

FDA comment of September 17, 2014: "In Module 5.3.5.1, provide a PDF with a list of all CRFs by patient ID number with links to individual CRFs."

BMS request for clarification of September 18, 2014: Can FDA confirm that as noted in question 17, "In Module 5.3.5.1, provide a PDF with a list of all CRFs by patient ID number with links to individual CRFs," that this request is for study CA209037 only.

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on September 18, 2014:

FDA clarification of September 18, 2014: This request is for study CA209037 only.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe.

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/s/

MEREDITH LIBEG
11/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 5, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Memorandum relating to Clinical Review Comments and Information Request dated September 17, 2014

Background:

On September 17, 2014, FDA initiated a request for information relating to clinical aspects contained in submission dated July 30, 2014, via email communication in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab). Upon receipt of the of the clinical information request, BMS requested clarification. This memorandum provides information regarding the request for clarification and the final result of that request.

Clarification Request:

Upon receipt of the of the clinical information request dated September 17, 2014, BMS sought clarification, specifically relating to FDA request number 17. This request for clarification was received on September 18, 2014 via email from Kathleen O'Donnell of BMS.

FDA comment of September 17, 2014: "In Module 5.3.5.1, provide a PDF with a list of all CRFs by patient ID number with links to individual CRFs."

BMS request for clarification of September 18, 2014: Can FDA confirm that as noted in question 17, "In Module 5.3.5.1, provide a PDF with a list of all CRFs by patient ID number with links to individual CRFs," that this request is for study CA209037 only.

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to BMS via email on September 18, 2014:

FDA clarification of September 18, 2014: This request is for study CA209037 only.

Conclusion:

BMS concluded that the clarification was clear and agreed to address the request for information in the requested timeframe via email and followed with a formal submission to the BLA.

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/s/

MEREDITH LIBEG
11/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 4, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Statistical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Statistical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 7, 2014, or sooner if possible.

Statistical Comments:

1. Please provide the SAS code used to generate the event chart in CSR "Figure 7.2.1.2-2: Event Chart for Tumor Response and Progression per IRRC, Duration of Therapy, and Death - Subjects with Response Among the ORR Population."

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
11/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 15, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125554 – Bristol-Myers Squibb Company (BMS)**
Sponsor Teleconference – Chemistry, Manufacturing, and Controls

Date and Time of Teleconference: September 15, 2014, 9:00 a.m. to 9:30 a.m.

FDA Participants:

Marc Theoret, M.D.	Medical Team Leader
Meredith Chuk, M.D.	Medical Reviewer
Maitreyee Hazarika, M.D.	Clinical Reviewer
Sirisha Mushti, Ph.D.	Statistical Reviewer
Dow-Chung Chi, M.D.	Medical Officer
Laurie Graham, Ph.D.	CMC Team Leader
Joel Welch, Ph.D.	CMC Reviewer
Patricia Hughes, Ph.D.	CMC Consumer Safety Officer
Meredith Libeg	Regulatory Health Project Manager

Sponsor Participants:

Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology
Pradip Ghosh-Dastidar, Ph.D.	Associate Director, Global Regulatory - CMC
Mark Rosolowsky, Ph.D.	Vice President, Global Regulatory - CMC
Thomas Gervais, Ph.D.	Group Leader, Manufacturing Sciences and Technology
Edward M. Atkinson, Ph.D.	Vice President, Biologics Development
Jonathan Basch, MS.	Associate Director, Analytical Development
Tony Mazzeo, Ph.D.	Sr. Principal Scientist, Pharmaceutical Development Stability
Rajesh Gandhi, Ph.D.	Director, (b) (4)
Nancy Barbour, Ph.D.	Vice President, Drug Product Science and Technology
Brett Budis, Ph.D.	Director, Biologics Quality
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology

This was an FDA-initiated teleconference (TCON) to discuss the chemistry, manufacturing, and controls (CMC) information submitted on July 30, 2014, in support of the pending BLA 125554 for Opdivo (proposed proprietary name) (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

Summary of the TCON:

FDA and BMS discussed the manufacturing and testing facilities sites included in the original BLA submitted on July 30, 2014. Specifically, the FDA requested clarification on the activities performed at the Lonza, Porrino, Spain facility site. FDA noted that this facility does not have an inspectional history with the FDA. FDA continued by stating that if this site is required to be included in the pending BLA (e.g. the site performs activities different from the other facilities included in the

pending BLA) an inspection of the facility would be needed for the pending BLA. A possible alternative to an FDA facility inspection would be the use of an inspection report from the European counterparts to the FDA, but only if the authorities holding the report make it available to the FDA, which is not always the case. Lastly, if the Lonza, Porrino, Spain site is not required, BMS can elect to withdraw this site from the pending BLA, and file a future CMC supplement to the application requesting the addition of the site. BMS indicated that it is their understanding that the Porrino, Spain site is an alternative testing site to the Portsmouth, New Hampshire, U.S. site; however, they will follow-up with Lonza to confirm this information. Following receipt of information from Lonza, BMS would discuss with the FDA the appropriate actions to be taken for the Porrino, Spain site. FDA found this approach to be acceptable.

Items Requiring BMS' Follow-up:

1. Provide additional information on the activities and testing performed at the Lonza, Porrino, Spain site.

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/s/

MEREDITH LIBEG
11/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 7, 2014, or sooner if possible.

Clinical Comments:

1. Provide a narrative summary based on the data submitted, in patients with immune-mediated adverse events to determine the time to onset of immune-mediated adverse events (AEs), duration of AEs, action taken with the drug, outcome, and type/amount/duration of steroid treatment for each AE including pneumonitis, colitis, hepatitis, adrenal insufficiency, skin rash, renal failure/nephritis, hypothyroidism, hyperthyroidism, and hypersensitivity/infusion reactions to inform prescribers in product labeling of appropriate management of side effects to promote the safe and effective use of nivolumab.

   When providing the numerical estimate of the risk, include immune-mediated AEs irrespective of causality. In accordance with the serious adverse event (SAE) collection and reporting requirements in Protocol CA209037, include SAEs that occur up to 100 days following the last dose of study treatment. When providing information related to the outcome of an AE, consider the event as ongoing if the patient died with symptoms still present.

2. Provide an assessment of the occurrence of hypophysitis, hypopituitarism, and myasthenia gravis, including the incidence, toxicity grade, dose of drug at which the AE occurred, time to onset, treatment, management, and outcome in the safety database of nivolumab used as a single agent.

3. As additional information to what is found in Appendix 5.9, please submit a table in pdf and .xpt or excel format for the 10 patients treated beyond progression referenced in CSR Section 7.2.2 who were stated to have target lesion reduction of >30% compared to baseline after RECIST progression that includes the following:
   a. Date of investigator-assessed progression and basis of progression (radiographic or clinical)
   b. Date of investigator-assessed >30% reduction in target lesions and time to this reduction from first detection of PD by investigator
   c. Best overall response (BOR) and date by investigator
   d. First/last dose date and indicate if patient remains on therapy
   e. Duration of treatment beyond investigator assessed-progression and number of doses of nivolumab
   f. Dates of imaging and measurements of all lesions, target and non-target by investigator and corresponding response (CR, PR, SD, PD, NE) at each timepoint
   g. Date of subsequent therapy, nature of the therapy and indicate which lesion was treated if subsequent therapy was locally directed (radiation, surgery)
   h. Confirmed BOR by central review and date of CBOR
   i. Dates of imaging and measurements of all lesions, target and non-target by central review and corresponding response at each timepoint (include both reviewers and note if case was adjudicated and, if so, with which reader the adjudicator agreed)

   Please also confirm if there were any patients not treated according to the protocol given the provisions in Section 4.3.9 that states that "subjects should discontinue therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target and new measurable lesions.)"

4. For trial CA209003, please provide a:
   a. Table for summary of best response similar to CSR table 7.3.1-1 for all patients treated with nivolumab doses equal to or less than 3mg/kg.
   b. Table of duration of response by patient for responders treated with nivolumab doses equal to or less than 3mg/kg as per tables in Appendix 5.1, 5.2, and 5.3 of CA209037 CSR.

5. For Trial CA209037, please provide demographics and baseline characteristics as per CSR table 5.3-1 and 2 and associated tables for patients in the ORR treated population for both nivolumab and investigator's choice.

6. Please confirm the status of subject 066 with regards to study treatment: DX.xpt states continued therapy, Appendix 5.2 states subject received subsequent therapy and CRF is unclear. Please note if any biopsy results from the surgical resection of small bowel on 10/21/13 is available and if the resected lesion was the new lesion found of scan of 9/27/13 as noted by the investigator.

7. Please confirm the treatment and disease status of patient 142. Datasets refer to subsequent therapy which is not listed in the CRF. By investigator, patient had PD with new lung lesion 10/11/13 and by IRRC patient listed as PR, but investigator BOR was SD.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
11/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 31, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Thursday, November 6, 2014, or sooner if possible.

Clinical Comments:

1. Clarify that among the all treated safety population, 12 patients had no adverse events reported and are not included in the ADAE dataset.

2. CA209037-35-37047 is reported to have discontinued nivolumab because he is "experiencing some toxicity." However, the AEs leading to discontinuation are not recorded in the dataset. Provide the AEs with toxicity grades due to which the patient requested discontinuation from the study.

3. Provide a detailed description and time course of signs, symptoms, evaluation including laboratory and radiologic reports, and treatments administered (if any) leading to the sudden death for patient CA209037-30-37309.

4. For patients CA209037-14-37211, CA209037-28-37383 and CA209037-9-37286, provide radiology reports that confirm that the patients had disease progression.

5. Provide an adverse event table and analysis of adverse events for the patients who continued treatment on nivolumab after disease progression.

6. Provide the outcomes of colitis and diarrhea for the following patients, which are not provided in the dataset ADAE.xpt. Consider the event as ongoing if the patient died with the AE.
   - CA209037-15-37264
   - CA209037-8-37075

7. Provide the outcomes of the hepatic adverse events for the following patients, which are not provided in the dataset ADAE.xpt. Consider the event as ongoing if the patient died with the AE.
   - CA209037-1-37214
   - CA209037-16-37419
   - CA209037-20-37098
   - CA209037-41-37354
   - CA209037-57-37445
   - CA209037-63-37270
   - CA209037-77-37142
   - CA209037-90-37625

8. Provide the end day for the hepatic adverse event in the following patients, which are not provided in the dataset ADAE.xpt.
   - CA209037-11-37648
   - CA209037-1-37214
   - CA209037-16-37419 (ALT increased)
   - CA209037-16-37419 (AST increased)
   - CA209037-41-37354
   - CA209037-63-37270
   - CA209037-90-37625

9. Provide narratives for the following patients:
   - CA209037-2-37512
   - CA209037-39-37514
   - CC209037-98-37510
   - CA209037-27-37089
   - CA209037-77-37118
   - CA209037-69-37106
   - CA209037-73-37163
   - CA209037-25-37223
   - CA209037-37-37134
   - CA209037-47-37184

10. Clarify whether a treatment-emergent flag is included in the AE datasets.

11. Provide the outcomes of the pneumonitis adverse events for the following patients, which are not provided in the dataset ADAE.xpt. Consider the event as ongoing if the patient died with the AE.
    - CA209037-15-37264
    - CA209037-50-37235
    - CA209037-61-37367
    - CA209037-90-37547

12. Provide the end day for the pneumonitis event in the following patients, which are not provided in the dataset ADAE.xpt.
    - CA209037-50-37235
    - CA209037-61-37367
    - CA209037-90-37547

13. Provide the outcomes of the adrenal insufficiency adverse events for the following patients, which are not provided in the dataset ADAE.xpt. Consider the event as ongoing if the patient died with the AE.
    - CA209037-25-37223
    - CA209037-47-37184

14. Provide the end day for the adrenal insufficiency event in the following patient, which is not provided in the dataset ADAE.xpt.
    - CA209037-47-37184

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
10/31/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125554/0

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

ATTENTION: Kathleen O'Donnell
Director, US Liaison-Oncology

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351(a) of the Public Health Service Act for Nivolumab, 100 mg/10 mL and 40 mg/4 mL.

We also refer to your August 29, 2014, correspondence, received August 29, 2014, requesting review of your proposed proprietary name, Opdivo.

We have completed our review of the proposed proprietary name, Opdivo, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your August 29, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Meredith Libeg, Regulatory Project Manager in the Office of New Drugs, at (301) 796-7121.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

FRANCES G FAHNBULLEH
10/28/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
10/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 28, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our CMC Review team has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 7, 2014, or sooner if possible.

Comments:

1. We note that you have included both critical process parameters and process parameters in section 3.2.S.2.4. Provide confirmation that these parameters are both considered regulatory commitments. We recommend that these process parameters be listed or described in 3.2.S.2.2.

2. We note that 3.2.S.2.4 includes the use of critical performance attributes and performance attributes. As with item #1, provide confirmation that these are all considered regulatory commitments.

3. Provide a raw and consumable material risk assessment for both drug substance (DS) and drug product (DP) manufacturing. This should include the criteria being used to determine the raw materials that need to be either measured in DS or assessed for clearance by the manufacturing process during performance qualification. For the identified higher risk materials, provide a toxicological assessment on the levels in DS.

4. Provide the toxicological assessments performed for the DS and DP extractable/leachable studies referenced in the BLA.

5. Provide a justification for the assays included in the DS shipping qualification studies. For example, we note that potency assays were not included.

6. Provide clarification as to whether there are concurrent (b) (4) protocols. Provide a justification for the assays included in the (b) (4) studies included in the BLA.

7. Provide clarification on why the master cell bank and end of production cell bank testing included the use of different assays for the detection of retroviruses (b) (4)

8. Provide clarification on whether MAP testing was ever performed on the master cell bank.

9. The criteria being used in the concurrent (b) (4) lifetime studies seem unusually broad considering the results obtained in the (b) (4) lifetime studies. Provide a justification for the selection of these acceptance criteria.

10. Provide a justification for the parameters included in the concurrent (b) (4) lifetime studies as being those most impacted by (b) (4) use. (b) (4) (b) (4) (b) (4)

11. It is noted that (b) (4) (b) (4)

12. Regarding you re-evaluation of the MCB and WCB, provide the following information:
    a. The parameters and criteria used to establish the stability of MCB and WCB. (b) (4)

13. As you state, the variability of the non-reduced CE-SDS method makes interpretation of stability data difficult. Additionally, we have the following observations regarding this method:

    [redacted] (b) (4)

    Provide an assessment for the [redacted] (b) (4) profile differences observed between [redacted] (b) (4) drug substance.

14. Provide a summary of the verification activities performed to demonstrate the suitability of compendial methods.

15. Regarding your [redacted] (b) (4) studies, provide the following information:

    [redacted] (b) (4)

16. Provide data or justification that drug substance manufactured using cumulative proposed hold times [redacted] (b) (4) will result in drug substance of an adequate quality.

17. Regarding your qualification of reference standard, provide the protocol for establishing a new working reference standard. Additionally, provide details regarding your plans to establish a new primary reference standard.

18. Regarding your analytical methods, provide additional detail for each, including specifying the following:
    a. The number of samples analyzed for each run
    b. Numerical system suitability criteria

19. We note that your control for the limit of [redacted] (b) (4)

20. Your [redacted] (b) (4)

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
10/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 28, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Container Labels and Carton Labeling Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Container Labels and Carton Labeling review team has the following request for information. Please provide your response as a formal submission to the BLA by Friday, November 7, 2014, or sooner if possible.

General Comments for the Vial:

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP) standard [USPC Official 8/1/2014 - 11/30/2014, USP 37/NF 32, <1> Injections/General Requirements] that went into effect on December 1, 2010. We refer you to the following address: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf.

2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

3. Provide justification for additional overfill in the 40 mg/4 mL vial. This vial contains (b) (4) overfill, however USPC 8/1/2014 - 11/30/2014, USP 37/NF 32, General Chapters: <1151> Pharmaceutical Dosage Forms recommends (b) (4) overfill.

Vial Container Label:

4. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.

5. Revise the strength statement to emphasize the strength per total volume in the vial is more prominent than the strength per mL. Unbold the strength per mL statement.[1]

   For example, change:

   100 mg/10 mL
   (10 mg/mL)

   To appear as:

   100 mg/10 mL
   (10 mg/mL)

6. Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t), 21 CFR 610.60(a)(2), and 21 CFR 610.61(b). Thus, the manufacturer name, address, and license number should match the Applicant on your 356h form. Additionally, include your US License Number on your 356h form.

   Based on the currently submitted 356h forms, the manufacturer address is:
   Bristol-Myers Squibb Company
   Wallingford CT 06492 USA

Carton Labeling:

7. See B1, B2, and B3.

8. Remove bolding from "providing xx mg of nivolumab per 10 mL," from the list of ingredients on the side panel.

9. Revise the statement of ingredients to comply with USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients such that the names of the inactive ingredients are in alphabetical order in the following format: inactive ingredient (amount). For example:

   Contents: One single-use vial providing 40 mg nivolumab per 4 mL, mannitol (30 mg/mL), pentetic acid... and Sterile Water for Injection, USP.

10. To emphasize "Usual Dosage", we recommend separating the "Usual Dosage" statement from the "Administration" section (**Administration:** Administer the infusion over 60 minutes… See prescribing information for dosage and administration). This can be accomplished by creating a new section, such as "**Usual Dosage:** See prescribing information" and placing it above the "Administration" section.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.
(http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf)

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/s/

MEREDITH LIBEG
10/28/2014

FDA QUESTION 1

Additional analysis for exposure-efficacy relationship based on expanded data (MDX1106-03 + CA209037). Explore the effects of the following covariates on Exposure-ORR relationship and the Time to Overall Survival Time (TTOS):

a. Any route of steroid use (for immune-related AE)

b. Systemic use of steroid (for immune-related AE)

c. PD-L1 status

d. Prior medication (at your discretion)

e. Prior anti CTLA-4 therapy and prior benefit from anti CTLA-4 therapy if yes

f. Other covariates deemed appropriate including those that have been screened in your Population Pharmacokinetic and Exposure-Response Report (930079466 V 1.0)

g. Please include the variable of "percent change from baseline per IRC" (i.e., variable PCHGIRC in dataset ADEFTM) into your exposure-efficacy analysis dataset, which can be used for additional assessment.

BMS RESPONSE TO FDA QUESTION 1

BMS agrees to provide additional analyses of exposure-efficacy with objective response (OR) and time to overall survival (OS), with pooled data from MDX1106-03 (melanoma cohorts only) and CA209037.

However, BMS would like to note that the criteria for assessing OR was not the same in MDX1106-03 and CA209037 for the following 2 reasons: (1) MDX1106-03 and CA209037 used different tumor-response criteria (RECIST 1.0 vs. RECIST 1.1, respectively), (2) Sponsor derived OR was reported in MDX1106-03, whereas the primary endpoint in CA209037 was based upon OR adjudicated by an independent review committee (IRC).

> ***FDA Comment of October 7, 2014:*** *You may want to use study ID as a covariate or use different parameter sets for different studies at your discretion in your exposure-response analysis for OR, since OR was assessed differently for studies CA209037 and MDX1106*-03. We acknowledge that the latter approach is equivalent to running a separate analysis for each study.

Furthermore, the patient populations in the 2 studies were different: MDX1106-03 enrolled anti-CTLA4 naive subjects with multiple tumor types (including NSCLC, melanoma and RCC) whereas CA209037 enrolled prior anti-CTLA4 treated subjects with melanoma. BMS proposes to only include the melanoma subjects from MDX1106-03 in the pooled exposure-response analysis.

BMS requests the following clarification and suggests alternative analyses for the covariates assessments:

a. Any route of steroid use (for immune-related AE), **AND**

b. Systemic use of steroid (for immune-related AE)

It may not be appropriate to assess the effect of steroid use on efficacy by incorporating steroid use as a binary (yes/no) variable in the exposure-response analyses because the timing and duration of steroid use could be important considerations in assessing their effect. In particular, the timing and duration of steroid use in relation to the time of best overall response (BOR).

BMS therefore proposes to present a tabular summary of exposures and efficacy (objective response rate [ORR] and OS) by steroid use (yes/no; all routes and systemic) for the treatment of immune-related AEs, and study. For the purposes of this analysis, select drug-related AEs will be considered as immune-related AEs.

Is this proposal for a tabular summary acceptable to the FDA?

> ***FDA Response of October 7, 2014****: A tabular summary as proposed is acceptable to the FDA if the timing and duration of steroid use before BOR were not available to the majority of patients.*

c. PD-L1 status

The relationship of PD-L1 status (based on the Verified Assay) on OR has been assessed for study CA209037, and reported in the exposure-efficacy analysis submitted in support of BLA 125554. It may not be possible to perform an exposure-response analysis of PD-L1 status with the pooled data set, as PD-L1 status (Verified Assay) is not available for most melanoma subjects in MDX1106-03. Tabular summaries of ORR and OS will be provided for subjects for whom PD-L1 status (Verified Assay) is available.

Is this approach acceptable to FDA?

> ***FDA Response of October 7, 2014****: A tabular summary is acceptable to the FDA.*

d. Prior medication (at your discretion)

BMS acknowledges FDA request and will determine (depending on data availability) if prior medication can be evaluated as a covariate in exposure-efficacy analysis. Prior anti-CTLA will be assessed as a covariate (as described below).

e. Prior anti CTLA-4 therapy and prior benefit from anti CTLA-4 therapy if yes

BMS agrees to assess prior anti-CTLA4 therapy as a covariate in the exposure-response analyses, based upon study enrollment. All patients from CA209037 had prior anti CTLA-4 therapy, and none of the patients in MDX1106-03 received prior anti-CTLA4 therapy.

BMS proposes to not assess prior benefit from anti-CTLA4 therapy with the pooled analysis data set, as the subjects in MDX1106-03 did not receive anti-CTLA-4 therapy, and thus did not have the opportunity to benefit from anti-CTLA-4 therapy. However, BMS would like to note that prior benefit from anti CTLA-4 therapy was previously evaluated as a covariate in the current CA209037 exposure-efficacy analysis submitted in support of BLA 125554.

Is this approach acceptable to FDA?

FDA Response of October 7, 2014*: We suggest you combine all these categories (e.g., 0=no prior anti-CTLA-4 treatment, 1= no benefit from prior anti-CTLA-4 treatment, 2= benefit from prior anti-CTLA-4 treatment) into one variable that can enable the analysis.*

f. Other covariates deemed appropriate including those that have been screened in your Population Pharmacokinetic and Exposure-Response Report (930079466 V 1.0)

BMS agrees to evaluate the effect of selected covariates previously assessed in the exposure-efficacy response analysis submitted in support of BLA 125554, to the extent that the inclusion of these covariates is supported by the pooled data.

g. Please include the variable of "percent change from baseline per IRC" (i.e., variable PCHGIRC in dataset ADEFTM) into your exposure-efficacy analysis dataset, which can be used for additional assessment.

BMS acknowledges and agrees to provide the variable of "percent change from baseline per IRC" (i.e., variable PCHGIRC in dataset ADEFTM) into the exposure-efficacy analysis dataset.

FDA QUESTION 2

Additional analyses for exposure-AE relationships:

a. If number of events allows, provide exposure-response analyses including time to event analyses for the following adverse events: hypothyroidism, hyperthyroidism, diarrhea, colitis, increased AST and ALT, pneumonitis, nephritis, renal failure, and rash. Provide descriptive analyses otherwise.

b. Provide covariate effect analysis for any clinically meaningful exposure-AE relationships identified.

BMS RESPONSE TO FDA QUESTION 2

BMS agrees to provide additional analyses for exposure-safety relationships.

Current exposure-safety analyses in support of BLA 125554 were performed with time to first occurrence of drug-related Grade 3+ events, and time to AEs leading to discontinuation of drug/death with data from CA209037. For the requested additional adverse events, BMS proposes to examine any Grade and Grade 3+ drug-related adverse events of interest in the same study, in order to align with the previous analyses.

BMS proposes to provide descriptive statistics and graphical analysis of exposure-response for the requested AEs. Furthermore, BMS also proposes to perform a model-based time to event analysis (including covariate effects) for the requested AEs only if the drug-related Grade 3+ events exceed 20.

Is this approach acceptable to FDA?

FDA Response of October 7, 2014*: This approach is acceptable to the FDA.*

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/s/

MEREDITH LIBEG
10/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 3, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Nonclinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Nonclinical reviewer has the following request for information. Please provide your response to me via email on Monday, October 6, 2014, or sooner if possible, and follow that with a formal submission to the BLA.

Comments:

1. Please specify the molecular targets of the monoclonal antibodies, 5H1 and 4C5, which were used in Study SUV00006, entitled "An Investigative Repeat-Dose Toxicity and Efficacy Study of MDX-010, 4C5 and 5H1 in Combination with HBsAg, DNP-Ficoll and SKMel Immunostimulants Following Three Monthly Administrations."

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
10/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 1, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Pharmacology Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Pharmacology reviewer has the following request for information. They are requesting you to please conduct additional analyses. Data, (b) (4) and scripts used to generate analyses should be provided for the analyses requested. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files be submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt).

Please provide your response by **Tuesday, October 21, 2014**, or sooner if possible.

Comments:

1. Additional analysis for exposure-efficacy relationship based on expanded dat (MDX1106-03 + CA209037). Explore the effects of the following covariates on Exposure-ORR Relationship (ORR) and the Time To Overall Survival Time (TTOS):
   a. Any route of steroid use (for immune-related AE)
   b. Systemic use of steroid (for immune-related AE)
   c. PD-L1 status
   d. Prior medication (at your discretion)
   e. Prior anti CTLA-4 therapy and prior benefit from anti CTLA-4 therapy if yes
   f. Other covariates deemed appropriate including those that have been screened in your Population Pharmacokinetic and Exposure-Response Report (930079466 V 1.0)

g. Please include the variable of "percent change from baseline per IRC" (i.e., variable PCHGIRC in dataset ADEFTM) into your exposure-efficacy analysis dataset, which can be used for additional assessment.

2. Additional analyses for exposure-AE relationships:

a. If number of events allows, provide exposure-response analyses including time to event analyses for the following adverse events: hypothyroidism, hyperthyroidism, diarrhea, colitis, increased AST and ALT, pneumonitis, nephritis, renal failure, and rash. Provide descriptive analyses otherwise.

b. Provide covariate effect analysis if any clinically meaningful exposure-AE relationships identified.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
10/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351(a) of the Public Health Service Act for "Opdivo (nivolumab) Injection."

We also refer to your amendments dated August 29, 2014, September 11, 2014, September 17, 2014, and September 24, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority.** This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is March 30, 2015.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests as early as December 1, 2014, but no later than February 28, 2015. In addition, the planned date for our internal mid-cycle review meeting is October 30, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

2. Please provide Rabbit Pyrogen data from three drug product lots tested in accordance with 21CFR610.13(b).

3. Regarding the [redacted] (b) (4) product, submit the bacterial retention validation report. This report should include details on the filter integrity testing of the [redacted] (b) (4)

4. Please refer to the information request dated September 24, 2014, requesting completion of the Table entitled "Highlights of Clinical Pharmacology and Cardiac Safety."

5. Please refer to the information request dated September 25, 2014, requesting submission of all ECG waveforms related to study CA209010 to the ECG warehouse.

6. Please refer to the information request dated September 25, 2014, requesting submission of the Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with nivolumab following market approval.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

See attached draft labeling for comments concerning issues with content and format of the Full Prescribing Information. Submit revised product labeling addressing these comments within 3 weeks of the date of this letter, no later than October 17, 2014.

All labeling should be submitted in both track changes version and clean version (in Microsoft Word format), unless otherwise noted. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ATTACHMENTS: FDA Proposed Labeling Revisions

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA KEEGAN
09/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 25, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Safety Group Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Safety group has the following request for information. Please provide your response to me via email on Thursday, October 9, 2014, or sooner if possible, and follow that with a formal submission to the BLA.

Comments:

1. FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with nivolumab following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the BLA application in the appropriate module so it can be reviewed accordingly.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

ATTACHMENTS:

- FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
- FDA Guidance for Industry on E2E Pharmacovigilance Planning

44 page(s) have been withheld for FDA guidance. Refer to http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf & http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

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/s/

MEREDITH LIBEG
09/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 25, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
QT-IRT Group Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our QT-IRT group has the following request for information. They are requesting the below to be performed as soon as possible.

Comments:

1. Please submit all ECG waveforms related to study CA209010 to the ECG warehouse at www.ecgwarehouse.com.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
09/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 25, 2014

From: Meredith Libeg, B.S., Senior Regulatory Health Project Manager - CDER/OHOP/DOP2

Subject: Planning Meeting Summary Memo: Nivolumab: BLA 125554

Original BLA: BLA 125554

Product:	Proposed name: Opdivo (nivolumab) Injection for Intravenous Infusion
Submission Date:	July 30, 2014
Received Date:	July 30, 2014
Sponsor:	Bristol-Myers Squibb Company
Proposed New Indication:	Treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status

Meeting Participants:

Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Medical Team Leader (TL) and CDTL, DOP2
Meredith Chuk, M.D.	Medical Reviewer, DOP2
Maitreyee Hazarika, M.D.	Medical Reviewer, DOP2
Sirisha Mushti, Ph.D.	Biometrics Reviewer, DBV
Stacy Shord, Ph.D.	Clinical Pharmacology Acting TL, DCPV
Liang Zhao, Ph.D.	Pharmacometrics Acting TL, DPM
Hongshan Li, Ph.D.	Pharmacometrics Reviewer, DPM
Whitney Helms, Ph.D.	Pharmacology/Toxicology TL, DHOT
Shawna Weis, Ph.D.	Pharmacology/Toxicology, DHOT
Laurie Graham, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) TL, DMA
Joel Welch, Ph.D.	CMC Reviewer, DMA
Bo Chi, Ph.D.	Safety Consumer Officer, BMAB
Jibril Abdus-Samad, Pharm.D.	Director Regulatory, OBP
Monica Hughes, M.S.	Chief Project Management Staff (CPMS), DOP2
Meredith Libeg	Senior Regulatory Health Project Manager, DOP2

Discussion Items:

1. Review Status
   - Priority Review requested (accelerated approval)
   - Exclusivity Request: Orphan-Drug designation for treatment of Stage IIb to Stage IV melanoma granted on January 23, 2013
   - Claims exemptions for PREA due to Orphan-Drug Designation

2. Review of Milestone Dates:
   - Filing Action Date: Sunday, September 28, 2014
   - Deficiencies Identified Letter (Day 74 Letter): Sunday, October 12, 2014
   - PDUFA Goal Date: March 30, 2015
   - Planned Action Date: December 19, 2014

3. Review and determination of consults needed for application

4. Determination and agreement of team meetings

5. Applicant Orientation Presentation

6. Discussion on needs for ODAC meeting

Summary and Decisions from Meeting:

Decision
The review team determined ODAC was not required for this application.
Application Orientation Presentation is tentatively scheduled for Monday, September 22, 2014.
The review team agreed that a separate filing meeting would be scheduled.
The review team determined the number of internal team meetings and the duration for these meetings as one hour meeting for October 2014 only. Additional internal team meetings will be scheduled as needed.
As the review team discussed and agreed to target labeling negotiations with the sponsor to begin at end of November 2014, labeling meetings were determined to start at the beginning of November. The review team decided on between 4 and 5 labeling meetings for the application with the RPM to set a schedule of sections to be reviewed at each meeting based on disciplines as opposed to chronological order.
The review team agreed to target PMRs/PMC negotiations to begin at the end of November 2014.
The review team determined that the application will be priority review with accelerated timelines.

The review team determined that consults required for the application are as follows:

- OSI
- OSE (Other)
- OPDP
- DMPP
- Maternal Health
- OMPQ

The review team will follow-up after the meeting if the following consults are required for the application:

- SEALD
- OSE (Proprietary Naming)
- QR-IRT
- SGE or Patient Representatives

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/s/

MEREDITH LIBEG
09/24/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Wednesday, September 24, 2014 8:21 AM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Request for Information

Hi Kathy,
Please find attached a table from our QT-IRT group for your completion relating to your original BLA application (BLA 125554) submitted on July 30, 2014. We are requesting a response to the comments and request for as soon as possible.

Highlights; QTim...

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

MEREDITH LIBEG
09/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 17, 2014

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **Original BLA 125554 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo [*Proposed*] (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response to me via email on Tuesday, September 23, 2014, or sooner if possible, and follow that with a formal submission to the BLA.

Clinical Comments:

1. Provide narratives for the following patient deaths:
   - CA209037-9-37286
   - CA209037-14-37211
   - CA209037-16-37242
   - CA209037-50-37189
   - CA209037-76-37654
   - CA209037-69-37515
   - CA209037-63-37270
   - CA209037-64-37250
   - CA209037-65-37304

2. Clarify whether the AEDECOD "embolism" for patients CA209037-57-37445 and CA209037-69-37646 refers to arterial, venous or pulmonary embolism.

3. Provide a table and analysis of vital sign changes from baseline in the All Treated Safety Population in Trial CA209037.

4. Provide a table and analysis of patients who were started on steroids on study that includes the adverse event which prompted the use of steroids (including start and stop dates), toxicity severity grade, the specific steroid administered, the route of administration of steroid, the dose of steroid administered (including start and stop dates), and the duration of steroid administration.

5. Provide details surrounding the death of patient CA209037-50-37189 which describes a Grade 4 cardiac arrest on Day 26 (b) (6) 11 days after the 2nd dose of nivolumab, and also death on the same day due to disease progression in the narrative. Explain why the cardiac arrest is not attributed to the study drug.

6. Provide details regarding the adverse event of diverticular perforation which occurred in patient CA209037-36-37328. There is only one sentence in the narrative, "the event of diverticular perforation was ongoing at the time of death." Describe the time course, management and outcome with dates.

7. Provide details regarding the adverse event of embolism noted in the ADAE dataset for patient CA209037-43-37151. There is no mention of embolism in the narrative provided in the submission.

8. Provide details regarding the adverse events of increased AST and bilirubin in patient CA209037-61-37367. It is not clear from the narrative why the patient's death is not attributed to hepatotoxicity due to the 3rd dose of the study drug.

9. There is no reason provided for Patient CA209037-35-37047 discontinuing the study in the dataset ADSL. However, the reason for treatment discontinuation includes the description: "…however is now experiencing some toxicity." Provide a narrative with the details of the toxicity experienced by the patient and explain why the patient is not counted among the patients who discontinued due to study drug toxicity as it appears that the "subject request to discontinue study treatment" is related to study drug toxicity.

10. The reason for patient CA209037-40-37323 discontinuing the study is stated to be "subject withdrew consent." The narrative describes that the patient developed Grade 3 herpes zoster on Day 25 and Grade 3 post-herpetic neuralgia on Day 44. The investigator considered both serious adverse events to be related to study therapy. The patient withdrew consent on Day 46. Please explain why the patient is not counted among the patients who discontinued due to drug toxicity as it appears that the reason for the withdrawal is the study drug toxicity.

11. The reason for the patient CA209037-67-37526 discontinuing the study is described as "other" and "adverse event unrelated to study drug" in the dataset ADSL. However the reason in the narrative is "AE leading to discontinuation." The narrative also states that Grade 4 cardiac arrest occurred on Day 59, two days after the 5th dose of nivolumab and that "Study therapy was discontinued due to the event of cardiac arrest…" Please explain the discrepancy between the two and explain why the patient is not counted among the patients who discontinued due to drug toxicity as it appears that the reason for discontinuation is due to the cardiac arrest.

12. Explain the reason provided as "Other" for infusion interruptions in the following patients:
    - CA209037-101-37645: confirm that the reason as stated in the narrative is facial paresis and provide additional details
    - CA209037-2-37576: provide details on the reason: "the infusion was stopped"
    - CA209037-29-37444: provide details on the reason: "vasovagal reaction"
    - CA209037-87-37183: clarify the reason stated as: "patient went to the toilet several times"
    - CA209037-87-37487: clarify the reason stated as: "toilet"?

13. Provide the route of administration of corticosteroids in the following patients:
    - CA209037-28-37021
    - CA209037-62-37251
    - CA209037-71-37105
    - CA209037-73-37163
    - CA209037-77-37142

14. Provide a table and analysis of electrolyte changes based on laboratory data including changes in calcium, potassium, sodium and magnesium. The tables should contain the treatment emergent laboratory abnormalities by toxicity grade that exclude patients who did not have an increase in grade from baseline.

15. Provide a table and analysis for all the patients in Study CA209037 who had an increase of the QTc ≥ 501 ms and / or who had a change from baseline of > 60 ms, including the following:
    - Time to onset of QTc prolongation
    - Associated adverse events
    - Action taken with study drug and when the study drug was re-started
    - Outcome of QT prolongation

16. Provide Case Report Forms (CRFs) for the 38 patients with an objective response rate on the nivolumab arm of Study CA209037.

17. In Module 5.3.5.1, provide a PDF with a list of all CRFs by patient ID number with links to individual CRFs.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
09/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: September 11, 2014

FROM: Patricia Keegan, M.D.
Director, Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation memo

Sponsor:	Bristol-Myers Squibb Company
Product:	Opdivo (nivolumab) Injection for Intravenous Infusion
Proposed Indication:	Treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status

TO: BLA 125554

The review status of this file submitted as an Original BLA is designated to be:

☐ Standard (PDUFA V - 12 Months) ☒ Priority (PDUFA V - 8 Months)

In the original BLA submission, Bristol Myers Squibb (BMS) requested priority review designation based on their determination that the results of Study CA209037, a randomized, open-label, trial comparing the safety and anti-tumor activity of nivolumab 3mg/kg administered intravenously every 2 weeks with investigator's choice of chemotherapy (dacarbazine or carboplatin plus paclitaxel) in patients with unresectable or metastatic melanoma in patients whose melanoma had progressed following anti-CTLA-4 therapy, or for those with BRAF V600 mutation-positive melanoma, has progressive disease after both anti-CTLA-4 and BRAF inhibitor therapy.

In concur with BMS' determination that this population has a serious and life-threatening disease with no satisfactory alternative therapies. Since pembrolizumab was approved

under the provisions of 21 CFR 601.70 (accelerated approval), this does not constitute alternative therapy. Neither ipilimumab nor any BRAF-directed therapies (dabrafenib, vemurafenib, or trametinib) are indicated for this patient population. While dacarbazine and aldesleukin have broad indications, the reported response rates with both agents are relatively low (≤ 20%), with short duration of responses with dacarbazine and a high incidence of serious adverse reactions with aldesleukin, therefore neither agent is a satisfactory alternative therapy.

Study CA 209037 met the agreed-upon threshold for demonstration of a clinically important objective response rate in this patient, excluding a response rate of less than 15% based on the observed IRRC-confirmed overall response rate for the nivolumab arm of 31.7%. There were 38 IRRC-confirmed responses among 120 nivolumab-treated patients who were followed for at least 6 months; of these, four were complete responses and 34 were partial responses. The median duration of response has not been reached; among the 38 responding patients, the duration of responses ranges from 1.4+ to 10+ months.

{See appended electronic signature page}

Patricia Keegan, M.D.
Director, Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MEREDITH LIBEG
09/11/2014

PATRICIA KEEGAN
09/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

APPLICATION ORIENTATION MEETING

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

We also refer to your August 14, 2014, email correspondence agreeing to an application orientation meeting to discuss for Opdivo (nivolumab) Injection for Intravenous Infusion. Based on the statement of purpose, objectives, and proposed agenda, we will consider this an informal type C meeting. Meeting minutes will not be issued.

The meeting is scheduled as follows:

Date: Monday, September 22, 2014
Time: ~10:30 AM – 12:00 PM (ET)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 2205
Silver Spring, Maryland 20903

Tentative CDER participants:

Richard Pazdur	Joseph Gootenberg
Patricia Keegan	Marc Theoret
Meredith Chuk	Maitreyee Hazarika
Kun He	Sirisha Mushti
Hong Zhao	Stacy Shord
Ruby Leong	Xianhua Cao
Hongshan Li	Liang Zhao
Whitney Helms	Shawna Weis
Laurie Graham	Joel Welch
Karen Jones	Monica Hughes
Norma Griffin	Meredith Libeg

Please e-mail me any updates to your attendees at Meredith.Libeg@FDA.HHS.Gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Meredith Libeg 301-796-1721.

Please submit desk copies and/or slides to me at the following address:

Meredith Libeg
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2326
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Bristol-Myers Squibb Company
MEETING START DATE AND TIME	September 22, 2014 10:00 AM ET
MEETING ENDING DATE AND TIME	September 22, 2014 12:00 PM ET
PURPOSE OF MEETING	BLA Application Orientation Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	~10:00 AM ET – 10:30 AM ET (prior to the start of the meeting) WO Building 22 Room 1313 ~10:30 AM ET – 12:00 PM ET WO Building 22 Room 2205
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
	Meredith Libeg Regulatory Health Project Manager WO Building 22 Room 2326 Phone: 301-796-1721
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEREDITH LIBEG
09/09/2014

Libeg, Meredith

From: Libeg, Meredith
Sent: Tuesday, September 09, 2014 12:46 PM
To: O'Donnell, Kathleen (Kathleen.O'Donnell@bms.com)
Subject: BLA 125554 - BMS - Nivolumab - FDA Request for information

Hi Kathy,
While reviewing BLA 125554, it appears I was unable to find the location where the Trial Master Files (TMFs) are housed. Would it be possible to confirm and/or provide me the following information?

- The address where these files are housed
- Contact person's name, phone number, and email address for these files at BMS, if not you

Alternatively, can you please provide me the location where this information can be found in the application?

Additionally, can you please confirm and/or provide the following information for your IRR CRO (b) (4):

- Contact person's name, phone number, and email address

Alternatively, can you please provide me the location where this information can be found in the application?

Please provide a response via email and follow with a formal submission to the BLA.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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/s/

MEREDITH LIBEG
09/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

BLA ACKNOWLEDGEMENT

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Opdivo (nivolumab) Injection for Intravenous Infusion, 40 mg/4 ml (10 mg/mL) vial, 100 mg/10 ml (10 mg/mL) vial

Date of Application: July 30, 2014

Date of Receipt: July 30, 2014

Our Secondary Tracking Number (STN): BLA 125554

Proposed Use: For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Monica L. Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA L HUGHES
08/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We also refer to the meeting between representatives of your firm and the FDA on July 9, 2014. The purpose of the meeting was to discuss the planned BLA submission for nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in patients who have progressed on or after ipilimumab and, if BRAF mutation positive, a BRAF inhibitor regimen. The BLA will be submitted under the provisions of 21 CFR 601 Subpart E, based on demonstration of durable objective responses in Study CA209037.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Wednesday, July 9, 2014; 3:00 to 4:00 PM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1315
Application Number:	IND 115195
Product Name:	Nivolumab [BMS-936558, MDX-1106, or ONO-4538]
Indication:	Advanced [Unresectable or Metastatic] Melanoma in Patients Progressing Post Anti-Cytotoxic T-lymphocyte Antigen-4 [CTLA-4] Therapy
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Marc Theoret, M.D.
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Kun He, Ph.D.	Biometrics Reviewer, Team Leader, OBV
Sirisha Mushti, Ph.D.	Biometrics Reviewer, OBV
Nam Rahman, Ph.D.	Supervisor Pharmacologist, DCPV
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCPV
Stacy Shord, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Xianhua Cao, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Laurie Graham, M.S.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, DMA
Joel Welch, Ph.D.	CMC Reviewer, DMA
James Andrews, M.S., Ph.D.	CMC Reviewer, DMA
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Frances Fahnbulleh,	Regulatory Health Project Manager, OSE
Carolyn Yancey, M.D.	Medical Officer, OSE, DRISK
Janice Pohlman, M.D.	Lead Medical Officer, OSI
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)	Independent Assessor

SPONSOR ATTENDEES

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Dominic Labriola, Ph.D.	Vice President, Global Biometric Sciences
Amy Straub, Ph.D.	Director, Biopharma Project Management
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences
David Feltquate, M.D., Ph.D.	Executive Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Manish Gupta, Ph.D., F.C.P.	Director, Clinical Pharmacology and Pharmacometrics
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Michael Giordano, M.D.	Senior Vice President, Head of Development, Oncology & Immunology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Helen Liu, M.D.	Director, Global Pharmacovigilance and Epidemiology
Eric Masson, Pharm.D.	Executive Director, Clinical Pharmacology and Pharmacometrics
Susan Welsh, M.D.	Vice-President Medical Safety, Global Pharmacovigilance and Epidemiology
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research

1.0 BACKGROUND

Nivolumab is a monoclonal antibody directed against the Programmed Cell Death-1 (PD-1) molecule. PD-L1expression has been documented in multiple solid tumor histologies including: non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, gastric cancer, and breast cancer. Preclinical data show that blocking interactions between PD-1 and its ligands, PD-L1 or PD-L2, restores T-cell function and inhibits tumor growth in several murine models.

BMS is planning to submit a Biologics License Application (BLA) for accelerated approval for the treatment of patients with advanced (unresectable or metastatic) melanoma who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who progressed on or after a BRAF inhibitor in addition to anti-CTLA-4 therapy. BMS stated that the BLA will mainly be supported by efficacy and safety data from one study (CA209037) with data from a key supportive study (CA209003, also referred to as MDX1106-03 study).
A detailed table of contents containing the proposed components for the BLA was included in

the meeting package under Appendix 3. Additionally, a proposed draft US Package Insert to be included in the BLA submission was included in the meeting package under Appendix 2.

BMS will be seeking accelerated approval based on co-primary endpoints of ORR (noncomparative point estimation of IRC-assessed ORR in the first 120 patients treated with nivolumab with at least 6 months follow-up). A subsequent application to support potential conversion to regular approval will be based on the CA209037 co-primary endpoint of OS. The statistical analysis plan (SAP) for CA209037 is provided in Appendix 1 of the briefing document.

At the time of the BLA submission, the estimated total number of patients treated with nivolumab monotherapy at 3 mg/kg every 2 weeks across multiple studies and indications will be approximately 1879 (1356 unblinded patients and approximately 523 blinded patients randomized to nivolumab). Of the 1879 nivolumab treated patients, 285 patients from Studies CA209037 and CA209003 were treated with the proposed dosing regimen (3 mg/kg every 2 weeks) that represents the relevant safety population in the BLA.

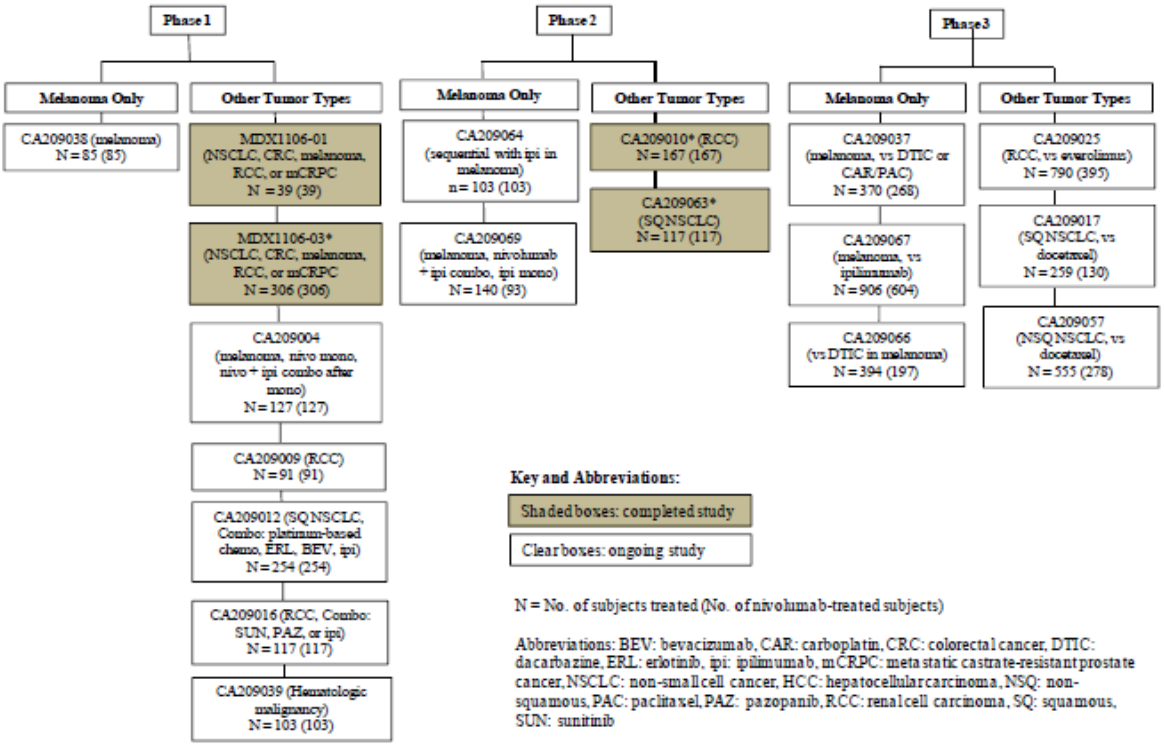
Nivolumab Development Program

Nivolumab is administered as an intravenous (IV) infusion in various schedules, either as a single agent or in combination with other antineoplastic agents. Nivolumab is in development under the following thirteen active INDs and one presubmission IND:

IND #	Indication
100052	Treatment of Advanced or Metastatic NSCLC
(b) (4)	(b) (4)
104225	Ipilimumab Combination for Treatment for Melanoma
113463	Advance Renal Cell Carcinoma (RCC)
114460	IL-21 Combination for Treatment of Solid Tumors
115195	Melanoma
(b) (4)	(b) (4)
117607	Anti-LAG-3 Combination for Treatment of Solid Tumors
(b) (4)	(b) (4)
119380	Non-Hodgkin's Lymphoma
119381	Treatment of Colorectal Cancer
119382	Treatment of Head and Neck Cancer
119590	Glioblastoma
PIND (b) (4)	(b) (4)

The nivolumab clinical development program for oncology includes the following completed or ongoing trials:

Figure 2-1: Nivolumab Clinical Development Program - BMS Sponsored Studies with Available Data In the BLA



BMS is developing, with their partner Dako North America (Dako), an immunohistochemistry (IHC) assay for the detection of PD-L1in tumor tissues as an in vitro companion diagnostic.

Regulatory History

- On February 7, 2012, a CMC only meeting was held to discuss plans to support clinical trials supporting licensure and marketing approval under the cross-referenced IND 100052.
- On June 13, 2012, BMS administratively split the indication of nivolumab monotherapy in melanoma from the existing IND 100052 into a new IND 115195. The new IND included Protocol CA209038 entitled, "An Exploratory Study of the Biologic Effects of BMS-936558 (Anti-PD-1 Monoclonal Antibody) Treatment in Subjects with Advanced Melanoma (Unresectable or Metastatic)."
- On July 13, 2012, the new IND 115195 was allowed to proceed.

- On July 17, 2012, an End of Phase 1/Pre-Phase 3 meeting was held to provide the Agency with preliminary data from the dose-finding and tolerability study (CA209003); to seek FDA's feedback on the proposed clinical development plan for treatment of advanced, unresectable, or metastatic melanoma; and to discuss the potential to obtain accelerated approval based on this development plan.
- On October 4, 2012, BMS was granted Fast Track Designation for patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.
- On October 17, 2012, BMS submitted a new Protocol CA209063 entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy."
- December 13, 2012, a CMC-only meeting was held to obtain FDA's feedback on the comparability of (b) (4) and assignment of the shelf life of a new 40 mg presentation.
- On January 23, 2013, BMS was granted Orphan Designation for the treatment of Stage IIb to Stage IV melanoma.
- On March 27, 2013, FDA issued an Advice/Information Letter providing comments relating to Protocol CA209037.
- On October 3, 2013, a Type C meeting was held under the cross-referenced IND 104225 to provide the Agency with an update on the nivolumab global registration strategy, and potential initiation of an expanded access program (EAP), for nivolumab as monotherapy in NSCLC, melanoma, and RCC and in combination with ipilimumab for melanoma. In this meeting, FDA agreed to review a proposal for an alternate timing of the final objective response rate (ORR) analysis in Study CA209037.
- On October 25, 2013, BMS submitted a proposal to "decouple" the timing of the analysis of the co-primary endpoints of ORR and OS in Study CA209037. FDA agreed with the proposal to perform an earlier analysis of ORR, but did not agree on the modification for alpha adjustment and recommended that the two-sided, alpha allocation ratio remain 0.01:0.04 for ORR and OS, respectively, as proposed in the original statistical analysis plan. FDA did not agree to accept investigator-assessed response rate for the primary analysis of ORR and recommended that BMS include investigator-determined ORR as a secondary endpoint with proper allocation of Type I error to include investigator-assessed ORR in the label. FDA did not agree that unconfirmed responses can be included when evaluating ORR.
- On January 16, 2014, FDA issued an Advice/Information Letter providing comments relating to the Protocol CA209037 and BMS' October 25, 2013, proposal.
- On February 12, 2014, BMS submitted a proposal for modification to the primary analysis of ORR in CA209037 to incorporate an analysis of the independent review committee (IRC) assessed ORR in the first 120 patients treated with nivolumab in order to seek accelerated approval. OS remains a co-primary endpoint and will serve as confirmation of clinical benefit (full approval).

- On March 17, 2014, FDA issued an Advice/Information Letter providing comments relating to the Protocol CA209037 and BMS' February 12, 2014, proposal. FDA agreed with the proposal to analyze confirmed ORR based on an independent review in 120 nivolumab-treated patients based on a minimum of 6 months follow-up for all patients to seek accelerated approval. FDA agreed with the proposed plan of using an alpha of 0.04 for the analysis of OS as a co-primary endpoint which would serve as confirmation of clinical benefit (full approval).
- On April 9, 2014, BMS submitted an Expanded Access Program Treatment Protocol CA209168 for the treatment of Nivolumab for Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma Progressing Post Prior Systemic Treatment Containing an Anti-CTLA-4 Monoclonal Antibody.
- On April 18, 2014, a pre-BLA CMC only meeting was held to obtain feedback and agreement on the contents of the BLA application and acceptability of any late components to the application.
- On May 8, 2014, new Treatment Protocol CA209168 was allowed to proceed.

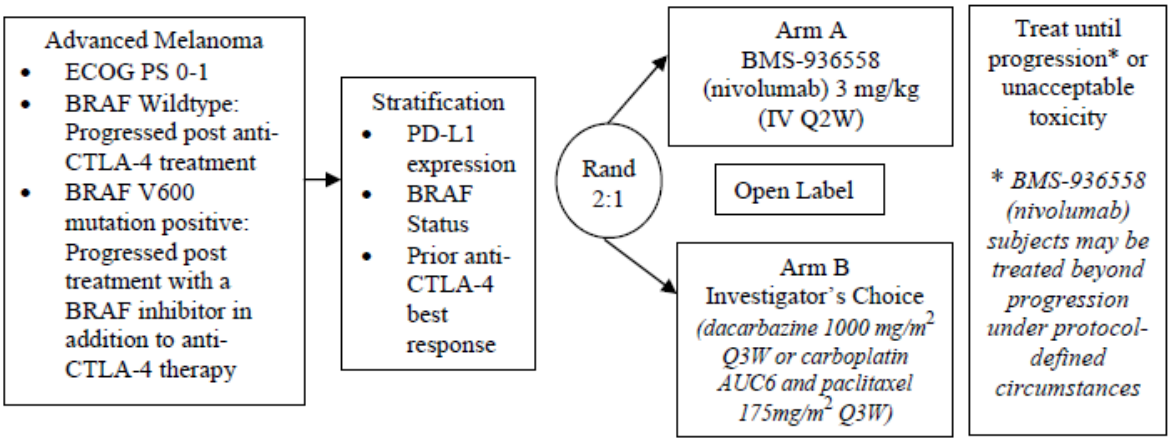
Study CA209037

Study Design:

Study CA209037 is a randomized (2:1), open-label, multinational (United States, Austria, Belgium, Brazil, Canada Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom) study to evaluate single-agent nivolumab (3 mg/kg Q2W) versus investigator's choice (dacarbazine or carboplatin and paclitaxel) in approximately 390 adult (≥ 18 years old) patients with histologically confirmed, unresectable Stage III or Stage IV melanoma who progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who also progressed on or after a BRAF inhibitor regimen. Patients were randomized in a 2:1 ratio to nivolumab or investigator's choice, respectively, in order to evaluate the co-primary endpoints of ORR and OS. Screening evaluations to determine eligibility were to occur within 28 days prior to randomization with the exception of the tumor biopsy which was permitted more than 28 days prior to randomization. However, the tumor biopsy must have been from an unresectable or metastatic site, and the patient must have had no intervening systemic therapy between the time of biopsy and randomization.

Randomization was stratified by PD-L1 status with a verified immunohistochemistry (IHC) assay (≥ 5% vs. < 5% tumor cell membrane staining), BRAF status (wildtype vs. mutation positive), and prior anti-CTLA-4 best response (prior clinical benefit [defined as complete response, CR; partial response, PR; stable disease, SD] vs. no prior clinical benefit [progressive disease, PD]).

The study schema is shown in the following Figure:



Patients were dosed with nivolumab intravenously over 60 minutes at 3 mg/kg every 2 weeks or with investigator's choice of chemotherapy (choice of either dacarbazine dosed intravenously between 30 to 60 minutes at 1000 mg/m^2 every 3 weeks or carboplatin at an AUC of 6 dosed intravenously over 30 minutes and paclitaxel 175mg/m^2 dosed intravenously over 180 minutes every 3 weeks) until PD (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, or withdrawal of consent. Treatment was continued until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond initial RECIST v1.1-defined progression), discontinuation due to toxicity, or other protocol-defined reasons.

Radiographic assessments of tumor response were performed at Week 9 (plus or minus 7 days) and every 6 weeks after Week 9 (plus or minus 7 days) for the first year and then every 12 weeks (plus or minus 7 days) until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons. Recent tumor tissue that was formalin-fixed and paraffin-embedded (FFPE) were systematically collected for determination of baseline (pre-study) PD-L1 expression status.

The co-primary efficacy endpoints are ORR and OS.

The sample size of 390 patients for the study accounts for the co-primary efficacy endpoints: ORR (per independent review committee [IRC]) and OS with an alpha allocation of 0.1% and 4.9% respectively. Formal analyses of ORR and OS will be conducted at different timepoints with ORR being analyzed first followed by interim and final OS analyses.

The primary analysis of ORR in the nivolumab treatment group will be performed when approximately 180 treated patients (120 patients randomized and treated in the nivolumab arm and 60 patients randomized and treated in the investigator's choice arm) have a minimum follow up of 6 months. BMS states that the timing of this analysis will allow sufficient follow up for ORR to have a stable estimate, adequate safety follow up as well as information on duration of response in this population.

The final analysis of OS will be performed in the intent-to-treat (all randomized; at least 260 deaths will be required to provide approximately 90% power to detect a hazard ratio (HR) of 0.65, corresponding to a median OS of 8 months vs. 12.3 months for the investigator's choice and nivolumab groups, respectively, with an overall two-sided type I error of 4.9%. One formal OS interim analysis will be conducted when at least 169 deaths (i.e., 65% of total events) have been observed. The stopping boundaries at the interim and final OS analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

The secondary efficacy endpoints include: 1) PFS, as assessed by an IRC, to be formally assessed at the time of the OS analysis; and 2) ORR and OS correlation with PD-L1 expression by a validated IHC assay. PD-L1 expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining in a minimum of 100 evaluable tumor cells per a validated PD-L1 IHC assay (referred to as quantifiable PD-L1 expression). To evaluate the potential association between PD-L1 expression and efficacy endpoints, tumor tissues were systematically collected in all patients in CA209037, for determination of baseline PD-L1 expression status by a verified PD-L1 IHC assay using a 5% cutoff.

Analyses of safety included summaries of deaths, adverse events (AEs), serious adverse events (SAEs), select AEs, laboratory abnormalities, and immunogenicity.

Study CA209037 Results:

Based on the meeting package dated June 6, 2014, 631patients were enrolled, 405 patients were randomized, 272 to the nivolumab arm and 133 to the investigator's choice arm. The enrollment period lasted approximately 12 months (December 2012 to December 2013) with the Last Patient's First Treatment (LPFT) for ORR analysis occurred on September 10, 2013. The clinical database for the ORR analysis was locked on April 30, 2014, and the IRC database was locked on May 20, 2014. The imaging cut-off date (IRC and investigator) for this database lock was March 10, 2014, approximately 6 months after LPFT for the ORR population.

BMS states that the IRC-assessed confirmed ORR for the nivolumab arm was 31.7% (38/120) [95% confidence interval (95% CI): 23.5%, 40.8%] and 10.6% (5/47) [95% CI: 3.5%, 23.1%] in the investigator's choice arm. There were 3.3% (4/120) complete responses (CRs) in the nivolumab arm and no CRs in the investigator's choice arm. With a minimum follow-up of 6 months for all patients, the median DOR among IRC-assessed responders was not reached for the nivolumab arm.

BMS stated that the investigator-assessed confirmed ORR was 25.8% (31/120) [95% CI: 18.3%, 34.6%] comprised of 1.7% (2/120) CRs and 24.2% (29/120) PRs, in the nivolumab arm. The ORR was 10.6% (5/47) [95% CI: 3.5%, 23.1%], all PRs, in the investigator's choice arm.

The final analysis for PFS and the interim analysis of OS have not been conducted.

The following is a summary of the safety results as presented in the briefing package:

- The incidence of deaths in nivolumab- vs. investigator's choice-treated groups were 25.0% (67/268) vs. 23.5% (24/102), respectively. The majority 23.5% (63/268) vs. 22.5% (23/102) were attributed to disease progression (nivolumab-treated vs. investigator's choice-treated patients, respectively. The number of patients who died within 30 days of last dose was 10.4% (28/268) vs. 2.9% (3/102) with the majority 9.7% (26/268) vs. 2.9% (3/102) attributed to disease progression in the nivolumab- vs. investigator's choice-treated groups, respectively.
- Serious adverse events (SAE) irrespective of causality occurred in 44% of patients on the nivolumab-treated group and 22% of patients receiving investigator's choice of treatment. Serious adverse events occurring in ≥2% of patients on the nivolumab arm were malignant neoplasm progression (10.4%), abdominal pain (2%), and back pain (2%). The incidence of drug-related SAEs occurring in the nivolumab-treated group vs. investigator's choice-treated group were 6.3% vs. 9.8%, respectively. The most frequent (≥ 2 events) drug-related SAE in the nivolumab-treated group was hyperglycemia.
- The incidence of AEs leading to discontinuation regardless of causality occurring in the nivolumab-treated group vs. investigator's choice-treated group were 9.3% vs. 11.8%, respectively. The most commonly reported AE leading to discontinuation in the nivolumab-treated and the investigator's choice-treated groups were malignant neoplasm progression, 3.7% vs. 2.0%, respectively.
- Adverse events (AE) irrespective of causality occurred in 95% of patients on the nivolumab arm and 93% of patients on the investigator's choice arm, of which 35% and 43% were Grades 3-4, respectively. The most common AEs (≥ 20%) occurring on the nivolumab arm were fatigue (39% nivolumab-treated group vs. 43% for investigator's choice-treated group), nausea (24% vs. 42%), and diarrhea (20% vs. 17%). Drug-related AEs of any grade occurring in in the nivolumab vs. investigator's choice group was 67.5% vs. 79.4%, of which 9.0% vs. 31.4% were Grade 3-4.

Study MDX-1106-03 (CA209003):

Study Design:

Study CA209003 is a completed phase 1, two-part, open-label, multicenter, multidose, dose-escalation study of nivolumab in 306 patients with selected refractory and advanced malignancies. In total, 107 melanoma patients were enrolled and treated with nivolumab; 17 patients at a dose of 0.1 mg/kg, 18 patients at a dose of 0.3 mg/kg, 35 patients at a dose of 1 mg/kg, 17 patients at a dose of 3 mg/kg, and 20 patients at a dose of 10 mg/kg. Patients with melanoma must have had previous treatment in the metastatic setting but were not allowed to have received prior ipilimumab treatment. Part A was the dose-escalation phase using a traditional 3+3 design and up to 5 dosing cohorts (0.1, 0.3, 1, 3, and 10 mg/kg). Part B, the expansion phase, characterized tumor activity in different disease and dose specific cohorts:

- Melanoma: 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts
- Renal Cell Carcinoma: 10 mg/kg cohort
- Non-small cell lung cancer: 10 mg/kg cohort
- Colorectal Cancer: 10 mg/kg cohort
- Prostate Cancer: 10 mg/kg cohort

With Amendment 4, 7 additional cohorts were added:

- NSCLC: 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts
- Melanoma: 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg cohorts
- RCC: 1 mg/kg cohort

The primary endpoint was safety and tolerability and determination of maximum tolerated dose of multiple doses of nivolumab. Efficacy endpoints included ORR, durable objective responses, TTR, PFS, and OS. Tumor assessments were conducted at screening and approximately every 8 weeks thereafter. Responses were centrally assessed by the Sponsor using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0.

BMS states that a CSR was completed based on a 05-Mar-2013 database lock, and extended follow-up efficacy data (OS, PFS, and DOR) are being collected and will be provided in an addendum to the CSR based on a 17-Sep-2013 database lock which included a 3-year OS rate. BMS plans to submit data from this study to support the selection of the 3 mg/kg administered Q2W as the Phase 2/3 dose and schedule of nivolumab monotherapy across tumor types.

Study CA209003 Results:

Based on the June 6, 2014, meeting package, durable objective responses (DOR) were observed in previously treated patients with melanoma (31% across all dose levels, 41% at 3 mg/kg every 2 weeks). The median OS was 17.3 months (95% CI: 12.5, 36.7]) across all dose groups and was 20.3 months (95% CI: 7.2, -) in patients treated with 3 mg/kg. The 3-year survival rate across all dose groups was 44% (95% CI: 26, 60) and was 41% (95% CI: 31, 51) in patients treated with 3 mg/kg.

Table 3.3: Overall Efficacy Summary - Nivolumab Monotherapy in Melanoma (MDX1106-03)

	MDX1106-03	
Endpoint	**Melanoma 3 mg/kg N=17**	**Melanoma All Doses N=107**
ORR,[a] n (%) (95% CI)	7 (41.2) (18.4; 67.1)	33 (30.8) (22.3; 40.5)
DOR, Median Range (Months)[b,c]	17.5 (9.2+ - 26.5+)	22.9 (3.9+ - 26.9+)
PFS		
Median (95% CI) (Months)	9.69 (1.84, 16.43)	3.65 (1.87, 9.30)
Rate (95% CI)		
At 24 Weeks (~6 Months)	55% (28, 76)	45% (35, 54)
At 48 Weeks (~1 Year)	48% (22, 70)	38% (28, 47)
At 96 Weeks (~2 Years)	24% (6, 48)	29% (20, 39)
OS		
Median (95% CI) (Months)	20.3 (7.2, -)	17.3 (12.5, 36.7)
Rate (95% CI)		
At 24 Weeks (~6 Months)	88% (61, 97)	82% (74, 88)
At 48 Weeks (~1 Year)	65% (38, 82)	63% (53, 71)
At 96 Weeks (~2 Years)	47% (23, 68)	48% (38, 57)
At 144 Weeks (~3 Years)	41% (31, 51)	44% (26, 60)

a Confirmed PR or CR per sponsor using RECIST v1.0 criteria.

b Responses were still ongoing in 19 of the 34 responders (56%) at all doses as of the 17-Sep-2013 database lock.

c For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

Abbreviations: CR: complete response, DOR: duration of response, ORR: objective response rate, OS: overall survival, PFS: progression free survival, PR: partial response

2.0 DISCUSSION

Clinical:

1. *Background: See Pages 10 to 25 of the Briefing Document.*

Does FDA agree that results based on ORR from the pivotal study CA209037, with data from key supporting study MDX1106-03, form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of advanced (unresectable or metastatic) melanoma patients based on FDA's final assessment of benefit/risk?

FDA Response: A final analysis of independently-assessed, confirmed objective response rate (ORR) that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in confirmed ORR over available therapy— supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS at the planned interim analysis can form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of advanced (unresectable or metastatic) melanoma patients.

In addition, please provide the following in the BLA submission:

a) The topline results of the interim analyses of the overall survival (OS) and progression-free survival (PFS) at the time of the original BLA submission for FDA review. Absence of the OS and PFS results may result in a determination that the proposed application is not fileable.

BMS' Emailed Response of 7/9/14: BMS would like clarification regarding providing "results" of OS and PFS from the topline report. BMS will provide datasets and can analyze if requested.

- BMS needs specificity if BMS does an unplanned analysis with no statistical penalty. BMS proposes the following:
  - For OS we will have ITT ORR population (122/60 pts) and overall ITT (272/133 pts).
  - IRRC assessed PFS will be included in the CSR. We cannot provide IRRC PFS beyond ORR population but we can provide investigator assessed PFS overall ITT population (not cleaned).

Discussion During Meeting of 7/9/14: FDA confirmed that the unplanned analyses of PFS and OS requested by FDA will not require a statistical penalty; the proposal BMS has provided is acceptable. FDA agreed that BMS may submit the datasets and the analyses of OS and PFS from the topline report. BMS confirmed that this topline report would be submitted at the time of the initial BLA submission.

b) The number of patients treated in the US in the two arms of Study CA209037. If appropriate, based on the number of patients enrolled in the US, the BLA should contain a justification that supports the applicability of the results of CA209037 to the US population.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

c) The results of the confirmed ORR based on the intent-to-treat population (i.e., the first 120 patients enrolled and randomized to the nivolumab arm).

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

d) Identification of patients with melanoma treated with the proposed dose in Study MDX1106-01 and inclusion of such patients in the integrated summary of safety and efficacy. See FDA Response to Question 2a.

BMS' emailed responses of 7/9/14: BMS would like to confirm that there are no melanoma subjects in study MDX1106-01that have been treated at the proposed dose.

Discussion During Meeting of 7/9/14: FDA clarified that reference to the MDX1106-01 study was an error; the intended reference was to the MDX1106-03 study.

e) Evidence to support the dosage and dose interval recommended.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

f) A discussion of the relevance of PD-L1 as a prognostic or predictive biomarker in melanoma and the potential association between PD-L1 expression and efficacy endpoints in Study CA209037. Please note that this trial was not adequately designed to support claims for an indication based on the PD-L1 subgroup.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

2. *Background: This BLA will be submitted entirely in electronic format following the electronic Common Technical Document (eCTD) structure specified in International Conference on Harmonisation (ICH) M2 EWG Electronic Common Technical Document Specification v.3.2.2 dated July 2008, and utilizing the recommendations in the FDA Guidance for Industry entitled Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*

Specifications, Revision 2, dated June 2008 and ICH 21 Approved 930080783 1.0 pre-BLA Background Document (Advanced Melanoma) IND 115195 BMS-936558 Nivolumab M2 EWG The eCTD Backbone File Specification for Study Tagging Files dated June 2008. The draft BLA Table of Contents (TOC) is provided in Appendix 3 of the Briefing Document.

a) Is the proposed format and content of the BLA acceptable to FDA?

FDA Response: No. There is insufficient information in Section 2 and Appendix 3 to determine whether they include the complete contents of the BLA. Confirm that the following will be included in the BLA submission:

- An integrated summary of safety (ISS) and the integrated summary of efficacy (ISE) that includes data from Study MDX1106-03 and CA209037, since Study MDX1106-03 is intended to support Study CA209037, per 21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi) . The ISS can include the safety data from the 268 patients from Study CA209037 and 17 patients from Study MDX1106-03 treated with the proposed dosing regimen of 3 mg/kg Q2W. The ISE can include efficacy data from Study MDX1106-03 to include the patients with melanoma who received nivolumab at or below the proposed dose of 3 mg/kg. Absence of integrated data may result in a determination that the proposed application is not fileable. Confirm whether both Study CA209037 and Study MDX1106-03 used the same versions of the NCI CTCAE for the severity grading of adverse events. If Study MDX1106-01 has patients with melanoma treated with the proposed dose, include in the integrated datasets.

  BMS' emailed responses of 7/9/14: BMS would like to clarify the FDA comment on the ISS and ISE for studies CA209003 and CA209037.
  Our current plan is to present the data by study, based on the small number of pts from CA209003 (N=17 for ISS). There are study level datasets but not an integrated data set. The CTCAE is different for each study (CA209003 and CA209037).

  Discussion During Meeting of 7/9/14: BMS clarified that the safety data from the CA209037 study and from 17 patients with melanoma who received 3 mg/kg in the CA209003 study will be presented study-by-study, but not in a pooled dataset or analyses since the populations are different and the version of NCI CTCAE used to grade toxicity is different between these studies. FDA stated that BMS' proposal is acceptable for the melanoma population; however, the ISS should also include information on the safety data from all relevant studies, particularly those enrolling patients who received other dosage regimens or with other tumors types from the CA209003 study, for a complete assessment of safety. BMS agreed.

BMS stated that efficacy data in the ISE will include all 107 patients with melanoma enrolled in the CA209003 study. The data will be sufficiently detailed to indicate the dose level that patients received. FDA requested that BMS provide detailed information on the duration of response. BMS agreed.

- If BMS intends to submit data for the non-melanoma studies, CA209010 (RCC), and CA209063 (NSCLC), confirm that complete safety information from all studies in the total number of patients treated with nivolumab as single-agent will be presented as side-by-side comparisons in the BLA submission in the ISS.

  BMS' emailed responses of 7/9/14: The CSRs for studies CA209010 and CA209063 are being included to provide full disclosure for completed studies. However, since these studies are in a different patient population, BMS did not plan a side by side presentation in the ISS. In addition, Study CA209010 is included because of QTC assessment.

  Discussion During Meeting of 7/9/14: Regarding studies CA209010 and CA209063, BMS clarified that the Clinical Study Reports (CSRs) for these two studies will be included in the BLA submission since PK and QTc information to support the Clinical Pharmacology of nivolumab were obtained in these studies. Full safety data will not be provided. FDA acknowledged BMS' rationale and did not object to inclusion of the CSRs to support the pharmacokinetic assessment.

- Confirm that the BLA will include an analysis of adverse events based on all SMQs.

  BMS' emailed responses of 7/9/14: BMS will provide a verbal explanation and seek FDA clarification at the meeting.

  Discussion During Meeting of 7/9/14: BMS explained that they will provide all of the following product-specific adverse events in the BLA submission: pulmonary, renal, endocrine, liver, gastrointestinal, skin/rash, and hypersensitivity. FDA clarified that an analysis of SMQs was different from a listing of the product-specific adverse events by preferred terms, as SMQs may identify additional adverse events identified by related preferred terms. FDA requested BMS to analyze all SMQs and provide flags in the datasets. BMS agreed and stated that SMQs with no meaningful results will be identified.

- Provide variables in the adverse event datasets to identify safety information that includes extended follow-up.

BMS' emailed responses of 7/9/14: BMS would like to clarify that 'extended follow up' is defined as events occurring up to 100 days. The datasets will include a flag to identify those events that occur within 30 days and 100 days of last dose.

Discussion During Meeting of 7/9/14: FDA agreed with BMS' proposal.

- Provide the details of the imaging data sets for lesion assessment/response.

  BMS' emailed responses of 7/9/14: Can FDA please clarify what is meant by "details" of the imaging data sets?

  Discussion During Meeting of 7/9/14: BMS agreed that the datasets will include all information necessary to verify and validate the reported response rates by the investigators and IRC, including the modality used, lesion size, and identification of target lesions.

- Confirm that the BLA will contain a list of Adverse Events of Special Interest (AESIs) that will be included in the BLA. Identify and include safety issues that are known to occur with other investigational or approved agents which belong to the same class. In the BLA submission, provide the following for each identified AESI:
  - Duration of the adverse event, and degree of resolution of the adverse event.
  - Details on the action taken and dose modifications.
  - Further details for adverse events which require corticosteroid therapy.
  - Methods used to monitor for the AESIs.
  - Methods to prevent, mitigate, or manage adverse events.
  - For important adverse reactions that occur later in treatment, provide explorations of the time dependency of the reaction.

- Provide a definition of Treatment Emergent Adverse Events and confirm that the adverse event datasets in the BLA submission will include a variable (flag) to identify Treatment Emergent Adverse Events.

- Include the following information with the Financial Disclosure Form:
  - A list of clinical investigators.
  - The number of investigators who are sponsor employees (including both full-time and part-time employees).
    - The number of investigators with disclosable financial interests/arrangements.

- If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
  - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study.
  - Significant payments of other sorts.
  - Proprietary interest in the product tested held by investigator.
  - Significant equity interest held by investigator in sponsor of covered study.
- Details of the disclosable financial interests/arrangements.
- A description of the steps taken to minimize potential bias.
- The number of investigators with certification of due diligence (Form FDA 3454, box 3), and include the reason in an attachment.
- A narrative discussion on whether BMS has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data?
  - If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data).
  - If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements).

Discussion During Meeting of 7/9/14: BMS acknowledged major bullets 6 through 8 above and agreed with FDA's responses above. There was no discussion during the meeting.

From a technical standpoint (i.e., not content-related), the proposed format for the planned BLA is acceptable. However, please see additional comments below:

- 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- Please combine all study report amendments for study "MDX-1106-025-R-amendment 1-4" as a single pdf file with proper bookmarks, table of contents and hyperlinks (instead of separate pdf files for

each amendment). In the future, if sponsor has to submit amendment 5, it should be replacing amendment 1-4 pdf file. Please apply the same for other studies with more than one amendment.

- Do not provide placeholders for sections that will not be submitted (e.g. 4.2.1.2 Secondary Pharmacodynamics, N/A).

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- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in Modules 4 and 5, with the exception of Module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including Case Report Forms (CRFs). CRFs need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to the eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

Discussion During Meeting of 7/9/14: BMS acknowledged technical standpoint bullets above and agreed with FDA's response. There was no discussion during the meeting.

b) Does FDA agree that the draft TOC, which includes the contents of the application, is complete for FDA review in support of a BLA submission and potential BLA approval?

FDA Response: The draft TOC is generally acceptable but lacks sufficient detail on certain elements. Confirm that you will include the following in the BLA submission:

- Clinical Study Report and datasets for Study MDX1106-03 in Module 5.3.5 along with the datasets.
- Clinical subheadings within Modules 2.5 (Clinical Overview):
  - Module 2.5.4, Overview of Efficacy
  - Module 2.5.5, Overview of Safety
  - Module 2.5.6, Benefits and Risks Conclusions
- ISS and ISE in Module 5.3.5.3.

See also FDA Response to Question 2a.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

3. *Background: BMS submitted a preliminary proposal in the Administrative Pre-BLA briefing package on June 6, 2013 to IND 100052 (for Agency feedback. As noted in the Administrative Pre-BLA briefing package, the principles outlined in the BMS document were to apply to all future nivolumab submissions in other indications. FDA's written responses in the Type C Written Responses Only document (See Appendix 4 of the Briefing Document), provided on July 10, 2013, have been taken into account in this submission plan for the melanoma indication.*

Information about the proposed Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) package for the registrational study (CA209037) and supportive study (MDX1106-03) are provided in Section 8 of Appendix 5 of the Briefing Document.

Does FDA agree with the proposed SDTM and ADaM package for the registrational study, CA209037, and supportive study, MDX1106-03?

FDA Response: In addition to the proposed SDTM and ADAM package, provide the following in the BLA submission:

- Detailed Data Reviewer's Guides especially with regard to the algorithms used to arrive at the safety and efficacy results. Provide detailed information or algorithms to explain the exact methods used in calculating derived variables as well as ensuring that the results are traceable back to the original SDTM data elements that were used in the derivations, and can ultimately be linked back to patient Case Report Forms.
- Analysis dataset for derived best overall response data (one record per subject).
- Independent radiology- and investigator-derived tumor measurement datasets.

BMS' emailed responses of 7/9/14: Clarification - BMS will provide SDTM and ADAM datasets for the IRC and investigator data.

Discussion During Meeting of 7/9/14: FDA found BMS' proposal acceptable. Also see Discussion During Meeting under Question 2a.

4. *Background: BMS submitted a preliminary proposal in the Administrative Pre-BLA briefing package on June 6, 2013 to IND 100052 (for Agency feedback. As noted in the Administrative Pre-BLA briefing package, the principles outlined in the BMS document were to apply to all future nivolumab submissions in other indications. FDA's written responses in the Type C Written Responses Only document (See Appendix 4 of the Briefing Document), provided on July 10, 2013, have been taken into account in this submission plan for the melanoma indication.*

For the completed studies (CA209010, CA209063, CA209037, MDX1106-01, and MDX1106-03), BMS proposes to submit narratives for nivolumab treated subjects meeting the following criteria:

- *All deaths within 100 days of last dose (100 days is based on nearly 5 times the half life of 17-25 days for nivolumab), except those due to progression.*
- *Related SAEs.*
- *AEs leading to discontinuation of treatment*
- *Pregnancy*
- *Overdose*
- *Any Grade ≥ 2 Related Select AE* requiring systemic immunosuppressants to treat AE*
- *Any causality concurrent (concurrent = within 1 day) alanine transaminase (ALT) or aspartate transaminase (AST) > 3x Upper Limit of Normal (ULN) and T.Bili > 2x ULN.*
- *CRFs for all randomized/treated subjects in the completed studies CA209010, CA209037, CA209063, MDX1106-01, and MDX1106-03 for all deaths within 100 days of the last dose, all SAEs, and all AEs leading to discontinuation.*
- *No CRFs or narratives will be provided for ongoing studies. Limited summaries of safety (deaths, SAEs, and AEs leading to discontinuation) will be provided for these studies.*

a) Does the FDA agree with the proposed plans for reporting safety narratives in the completed studies?

FDA Response: In addition to the safety narratives proposed for the completed studies, provide narratives in the BLA submission for other significant adverse events judged to be of special interest.

Please ensure that narratives for patients with immune-related serious adverse events include at a minimum the following information:

- Patient age, gender, and race.
- Concomitant medications, including details of dose, route of administration, and length of administration.
- Onset of the immune-related adverse event in relation to exposure to the study drug.
- Relevant physical examination, laboratory, and radiologic findings.
- Action(s) taken with regard to nivolumab.
- Outcome of the treatment.

In addition, FDA may request that BMS submit additional narratives during the review of the BLA.

See also FDA Response to Question 2a.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

b) Does the FDA agree with this proposal for submission of CRFs?

FDA Response: In addition to the proposed CRFs, please include in the BLA submission the case report forms for the patients who discontinued due to an adverse event irrespective of causality. FDA may request that BMS submit additional case report forms during the review of the BLA.

See also FDA Responses to Question 2a.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

c) Does FDA agree with the proposed plans for limited safety summaries for ongoing studies in the BLA?

FDA Response: See FDA Responses to Question 2a.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

5. *Background: See Pages 23 to 24 of the Briefing Document.*

Does FDA agree with the BMS proposal regarding the Summary Level Clinical Site Data for CA209037 that will be provided in the nivolumab BLA?

FDA Response: See Attachment to the meeting minutes, titled "FDA Response to Question 5" containing FDA's response.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

6. *Background: See Pages 24 to 25 of the Briefing Document.*

a) The submission of the safety update at 90 days after submission of the BLA?

FDA Response: FDA requests that BMS provide a safety update 90 days from the date of BLA submission. This safety update should focus on new safety information about nivolumab that may reasonably affect the statement of

contraindications, warnings, precautions, and adverse reactions in the draft labeling and the Medication Guide.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

b) The timing of the database lock for the safety update?

FDA Response: See FDA response to Question 6a.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

7. *Background: See Pages 25 to 26 of the Briefing Document.*

Based on the preliminary study results for CA209037 and safety profile from the additional nivolumab studies, does FDA agree with the current proposed Risk Management Strategy, which includes a Medication Guide that will be part of the US product labeling and does not propose/include a Risk Evaluation and Mitigation Strategy (REMS)?

FDA Response: Since additional information regarding risks and safe product use may emerge during the review of the actual trial results in the BLA, it is premature to determine whether a Risk Evaluation and Mitigation Strategy (REMS) will be required. However, based on the available safety information in the pre-meeting briefing package, we agree that submission of a proposed REMS will not be required for filing of the BLA.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Clinical Pharmacology:

8. *Background: See Pages 27 to 30 of the Briefing Document.*

The proposed clinical pharmacology package for melanoma will include revisions to the clinical pharmacology package planned to be submitted in support of the NSCLC BLA (b) (4) **The revisions include: PPK analysis with all available data, exposure-response analysis with safety/efficacy data from CA209037, and presentation of immunogenicity data from MDX1106-03, CA209063, and CA209037. Does FDA agree with this proposal?**

FDA Response: Yes. The proposed clinical pharmacology package for melanoma appears acceptable from a clinical pharmacology perspective.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Regulatory (Preliminary Breakthrough Designation Request Advice):

9. *Background: See Attached document.*

FDA Response: Yes, as noted in the February 26, 2013, communication, BMS may submit a breakthrough designation request (BTDR) if you obtain new clinical evidence that nivolumab may demonstrate a substantial improvement over existing therapies for the treatment of patients with previously treated or untreated, unresectable or metastatic melanoma; however, the final decision on the designation will consider the opinions of the representatives from the review division within Center for Drug Evaluation and Research (CDER), the Office of New Drugs (OND), and Office of Medical Policy (OMP) within CDER.

If BMS wishes to submit a BTDR, include the following information in the official BTDR:

- Table 1 in the preliminary request for breakthrough designation of nivolumab as monotherapy does not contain adequate information concerning the durability of objective responses observed with nivolumab. Provide data on the duration of responses in a format that supports that the objective responses observed with nivolumab are durable, e.g., a swimmer plot.
- Clarify the definition of the "primary objective population" (footnote, Table 1).
- Provide the information on the stratification factor of PD-L1 as defined in Study CA209037.

BMS' emailed responses of 7/9/14: BMS plans to submit the Request for Breakthrough Designation next week.

Discussion During Meeting of 7/9/14: FDA acknowledged BMS' intentions.

Additional Comments:

Clinical:

10. Clarify why the Clinical Study Report for Study CA209063 (A Single-Arm Phase 2 Study of BMS-936558 in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens), which is not intended to support this submission is included Module 5.3.5.4.

BMS' emailed responses of 7/9/14: The CSR for CA209063 is being included to provide full disclosure for completed studies.

Discussion During Meeting of 7/9/14: BMS clarified that the CSR will be provided for full disclosure and to support clinical pharmacology review.

11. Provide a list of clinical investigators who participated in Study CA209037 and Study MDX1106-03 as an IND amendment. Include contact information (address and telephone number).

BMS' Emailed Response of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

12. **BMS' emailed responses of 7/9/14:** We propose to submit the DMC report for CA209-066 as part of the original BLA. The DMC database, which would not be in ADAM format, might be able to be provided at the time of submission or within 30 days. The completed dataset and BMS written CSR will not be completed prior to the planned submission date. BMS would like to discuss FDA's needs relative to a complete application and/or decision making.

Discussion During Meeting of 7/9/14: FDA agreed that BMS may include the DMC report for Study CA209066 in the initial BLA submission. BMS will provide a timeline for the completion of the full study report and datasets.

BMS and DOP2 reached the following agreements relating to the contents of a complete application:

- The contents of a complete application were discussed. BMS proposes to submit a complete application with no late components. Since BMS stated their intent to submit a complete application, there were no agreements for late submission of application components.
- BMS agreed to include a comprehensive and readily located list of all clinical sites and manufacturing facilities to be included or referenced in the application.
- A preliminary discussion on the need for a REMS was held; FDA stated that based on a preliminary evaluation, a REMS will not be required for filing of the BLA. However, a formal determination on the need for a REMS will be communicated to BMS during the review of the BLA.

PREA REQUIREMENTS

13. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

PRESCRIBING INFORMATION

14. In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

MANUFACTURING FACILITIES

15. To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion During Meeting of 7/9/14: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

3.0 ATTACHMENTS AND HANDOUTS

- FDA Response to Question 5
- OSI Pre-NDA/BLA Request
- Breakthrough Request Designation "Preliminary Request for Nivolumab as Monotherapy in Advanced Melanoma"

FDA Response to Question 5

FDA Response: Regarding BMS's proposal for inclusion of data elements in the summary level clinical dataset (clinsite.xpt), please see the table below for BMS's proposed data variable, the corresponding variable name as stated in the technical specifications document Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning, and Office of Scientific Investigations (OSI) comment on Sponsor's proposal. Please note, to enable use in CDER's Clinical Site Selection Tool the voluntarily submitted dataset should utilize the naming conventions and format as specified in the Draft Guidance for Industry, Providing Submissions in Electronic Format- Summary Level Clinical Site Data for CDER's Inspection Planning and the associated technical specifications Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning. Please also include a define.pdf file for the clinsite.xpt that provides a brief explanation of the content of variables, in particular for those variables that contain content that may be considered unique to your application (e.g., SCREEN, ENROLL, ENDPOINT, ENDPTYPE, TRTEFFE, TRTEFFS, SITEEFFE, SITEEFFS, CENSOR, PROTVIOL, etc.).

These recommendations are specific to the proposed submission of ORR based on an independent review in the first 120 patients treated with nivolumab with a minimum of 6 months follow-up for all patients, as has been previously agreed upon to seek accelerated approval.

Sponsor Proposal	Variable Name	Comment
IND ID	IND	
Site ID	SITEID	
Study ID	STUDY	
Treatment description	ARM	
Number of enrolled subjects at a given site.	SCREEN	Should include all consented subjects.
Number of screening failure subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Randomized Subjects at a given site.		This item would be reported as ENROLL when full study results for co-primary endpoints are reported.
Number of ORR Population Subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Subjects Randomized but not Treated at a given site	no variable	Do not include in clinsite.xpt
Number of ORR Population Subjects Randomized but not Treated at a given site.	no variable	Do not include in clinsite.xpt
Number of Treated Subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Treated Subjects among the ORR Population at a given site.	ENROLL	
Number of Subjects discontinued from treatment, among Treated	DISCONT	

Sponsor Proposal	Variable Name	Comment
Subjects as defined in the CSR, at a given site.		
Number of "relevant" protocol deviations, as defined in the SAP, among Randomized Subjects at a given site.	PROTVIOL	All significant protocol violations as defined in investigational plans (e.g., monitoring plans, SAP, etc.) should be included.
ORR, restricted to treated subjects in the ORR population, as assessed by IRRC (primary endpoint) at a given site.	ENDPOINT	When multiple endpoints are reported they should be reported separately for each treatment arm, along with all corresponding arm variables (including those described in table below that lists variables currently missing from your proposal). In the case described here in which there are two treatment arms and 3 endpoints we would then expect clinsite.xpt to contain 6 rows of data per site.
Average time to response among responders, restricted to treated subjects in the ORR population, as assessed by IRRC at a given site.	ENDPOINT	
Range of duration of response among responders (minimum, maximum), restricted to treated subjects in the ORR population, as assessed by IRRC at a given site.	ENDPOINT	
Total number of AEs regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	NSAE	
Total number of AEs leading to discontinuation regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	no variable	Do not include in clinsite.xpt
Total number of SAEs regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	SAE	
Total number of deaths in all randomized subjects at a given site.	DEATH	
Investigator's First and Last Name	FRSTNAME and LASTNAME	First and last names should be reported as separate variables in clinsite.xpt

Sponsor Proposal	Variable Name	Comment
Investigator's phone number	PHONE	
Investigator's FAX number	FAX	
Investigator's email address	EMAIL	
Investigator's mailing address	COUNTRY, STATE, CITY, POSTAL, STREET	Each address component should be reported as separate variables in clinsite.xpt
Maximum financial disclosure amount (by site) by any single investigator, and total financial disclosure amount by site.	FINLMAX, FINLDISC	Maximum disclosure by single individual and total disclosure by site should be reported as separate variables in clinsite.xpt

The following data elements appear to be missing from your proposed clinsite.xpt and should be added:

Variable Name	Variable Label	Notes or Description
STUDYTL	Study Title	Title of the study as listed in the clinical study report (limit 200 characters)
DOMAIN	Domain Abbreviation	List as DE
SPONNO	Sponsor Number	Total number of sponsors throughout the study. If there was no change in sponsor while the study was ongoing, enter "1"
SPONNAME	Sponsor Name	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).
UNDERIND	Under IND	Value should equal "Y" if study at the site was conducted under an IND and "N" if study at the site was not conducted under IND (i.e., 21 CFR 312.120 sites)
NDA	NDA Number	Not applicable in this case, enter "-1"
BLA	BLA Number	Enter if available
SUPPNUM		Not applicable in this case, enter "-1"
ENDPTYPE	Endpoint Type	Variable type of the endpoint

		(i.e. continuous, discrete, time to event, or other)
TRTEFFE	Treatment Efficacy Endpoint	Summary statistic for each endpoint by treatment arm at a given site
TRTEFFS	Treatment Efficacy Endpoint Standard Deviation	Standard Deviation of the summary statistic (TRTEFFE) for each endpoint by treatment arm at a given site
SITEEFFE	Site-Specific Treatment Effect	Site-specific treatment effect reported using the same representation as reported for the corresponding endpoint analysis
SITEEFFS	Site-Specific Treatment Effect Standard Deviation	Standard deviation of the site-specific treatment effect (SITEEFFE)
CENSOR	Censored Observations	Number of censored observations at a given site by treatment arm. If not applicable, enter "-1"
MINITIAL	Investigator Middle Initial	Middle initial of investigator, if any

OSI Pre-NDA/BLA Request

OSI Pre-NDA/BLA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Part I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Part III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

Part I. Request for general study-related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the BA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as

described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

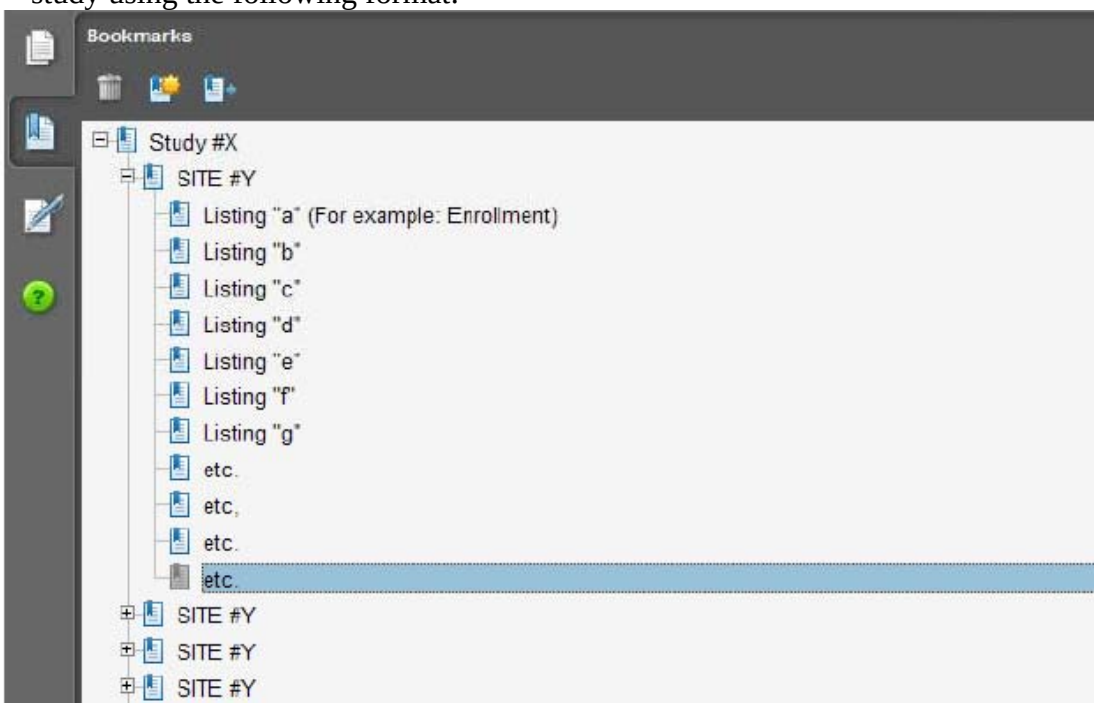
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

Part II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



Part III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Breakthrough Request Designation “Preliminary Request for Nivolumab as Monotherapy in Advanced Melanoma”

Breakthrough Request Designation:
Preliminary Request for Nivolumab as Monotherapy in Advanced Melanoma

Sponsor & IND:
Bristol-Myers Squibb (BMS); IND 115, 195

Drug/Mechanism of Action:
Nivolumab (BMS-936558/MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that targets the programmed death–1 (PD-1, cell differentiation 279 [CD279]) cell surface membrane receptor.

Indication/Disease:
Nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in subjects who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor (BRAFi) in addition to anti-CTLA-4 therapy.

Available therapies:
There are no FDA approved therapies that have demonstrated overall survival benefit in a Phase 3 trial for patients who have progressed on or after ipilimumab and a BRAFi (for those who are BRAF V600 mutation positive).

Trial design:
CA209037 is a randomized, open-label, Phase 3 trial of nivolumab monotherapy (3mg/kg q 2W) versus investigator's choice chemotherapy (dacarbazine or carboplatin and paclitaxel) in advanced (unresectable or metastatic) melanoma in patients progressing post anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) therapy with the co-primary endpoints of objective response rate (ORR) and overall survival (OS). In the FDA advice letter dated 16-Jan-2014, FDA agreed with the BMS proposal to "decouple" the timing of the primary comparative analysis of ORR from the primary analysis of OS. FDA agreement was then received on 17-Mar-2014 for the BMS proposal to modify the study design of CA209037 to a non-comparative point estimation of independent radiology review committee (IRRC) assessed ORR (using RECIST v1.1) in the first 120 patients treated with nivolumab with at least 6 months follow-up. Confirmed OS will be analyzed when the required number of events for a planned interim analysis has occurred (169 events in the 405 randomized subjects).

Stratification in CA209037 was based on PD-L1 expression, BRAF status and prior CTLA-4 best response. Patients were treated until disease progression or unacceptable toxicity. Radiographic assessments of tumor response were performed at week 9 and then every 6 weeks for the first year, and then every 12 weeks until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons.

Breakthrough Request Justification/Preliminary clinical evidence (e.g., Response rates, duration of response, extent of prior therapies):
This Breakthrough Request is based on the efficacy and safety results from study CA209037 as summarized below.

- Baseline demographic and disease characteristics were well balanced between the nivolumab and investigator's choice arms including gender, age, baseline ECOG performance status and disease stage.
- Relevant stratification factors of the ORR population (all randomized subjects to either treatment group with at least 6 months of follow-up at the time of the ORR analysis, which occurred when the first 120 nivolumab-treated subjects had a minimum of 6 months of follow-up) were well balanced between the nivolumab and investigator's choice groups: a) BRAF mutation positive was 22.1% vs 23.3% and b) no prior anti-CTLA-4 clinical benefit (BOR of PD) was 63.9 vs 61.7%.
- All subjects received at least one prior systemic therapy in the metastatic setting. All (100%) subjects received ipilimumab in the metastatic setting in the ORR population. BRAFi received in the metastatic setting included vemurafenib (18.9% vs 18.3%) and dabrafenib (3.3% vs 3.3%) in the ORR population for the nivolumab and investigator's choice arms, respectively.
- The primary reason for treatment discontinuation as assessed by the investigator was disease progression with 43.3% (116/268) vs 60.8% (62/102) for the all treated population in the nivolumab and investigator's choice arms, respectively.
- The number of subjects discontinued in the treatment period because of study drug toxicity in the all treated population was 2.6% (7/268) vs 6.9% (7/102) in the nivolumab and investigator's choice arms, respectively.

EFFICACY

Objective response rate and duration of response results are summarized in Table 1 below.

Table 1 : Study CA209037 ORR and Duration of Response

	Nivolumab Arm % (n/N)	**Investigator's Choice Arm % (n/N)**
IRRC-assessed confirmed ORR in treated subjects among the ORR population*	31.7% (38/120) (95% CI: 23.5%, 40.8%)	10.6% (5/47) (95% CI: 3.5%, 23.1%)
IRRC-assessed confirmed best overall response (BOR) in treated subjects among the ORR population	3.3% CRs (4/120) 28.3% PRs (34/120)	10.6% PRs (5/47)
Median duration of response (DOR) among IRRC-assessed responders	Not Reached	Insufficient Follow-up^
IRRC-assessed rate of stable disease (SD) in treated subjects among the ORR population	23.3% (28/120)	34.0% (16/47)
Investigator-assessed confirmed ORR in the treated subjects among the ORR population	25.8% (31/120) (95% CI: 18.3%, 34.6%)	10.6% (5/47) (95% CI: 3.5%, 23.1%)

*Treated subjects among the ORR population (primary objective population).
^ Of the 5 responders, only 1 patient had sufficient follow-up of 3.5 months to describe the median duration of response.

SAFETY

- In the investigator's choice arm, 1 death was due to an unrelated AE (multi-organ failure). In the nivolumab arm, 2 deaths were due to unrelated AEs (cardiopulmonary arrest, sudden death due to probable pulmonary embolism), 1 death was unknown, and 1 death was attributed to study drug toxicity (hypoxia).
- The frequency of drug-related SAEs in the nivolumab vs investigator's choice arm was 6.3% vs 9.8%, of which 4.5% vs 8.8% were Grade 3-4, respectively. The most frequent drug-related SAE (≥ 2 events) in the nivolumab arm was hyperglycemia.
- The frequency of AEs leading to discontinuation regardless of causality in the nivolumab vs investigator's choice arm was 9.3% (25/268) vs 11.8% (12/102), respectively. The most commonly reported AEs leading to discontinuation in the nivolumab vs investigator's choice arm was malignant neoplasm progression 3.7% (10/268) vs 2.0% (2/102), respectively. The frequency of drug-related AEs of any grade in the nivolumab vs investigator's choice arm was 67.5% vs 79.4%, of which 9.0% vs 31.4% were Grade 3 - 4.
- The most commonly reported drug-related AE of any grade in the nivolumab vs the investigator's choice arm was fatigue (25.0% vs 34.3%). The most commonly reported Grade 3 - 4 drug-related AE for the nivolumab arm was lipase increased (1.1% vs 1.0%), respectively. The most commonly reported Grade 3-4 drug related AEs regardless of treatment group above 2% was neutropenia (0% vs 13.7%), thrombocytopenia (0% vs 5.9%), anemia (0.7% vs 4.9%), fatigue (0.7% vs 3.9%), and neutrophil count decreased (0% vs 2.9%) with all being greater in the investigator's choice arm.

CONCLUSION

Rationale for designation for breakthrough designation is supported by the ORR of 31.7% based on IRRC review using conventional (RECIST v1.1) response criteria from the first 120 nivolumab treated subjects with a minimum of 6 months follow-up in Study CA209037. These results demonstrate that nivolumab monotherapy has clinically meaningful antitumor activity in subjects in this high unmet medical need population. Confirmed responses in the reference arm (investigator's choice) are consistent with historical response rates of dacarbazine or carboplatin and paclitaxel in multiple Phase 3 studies. In addition, data from study CA209037 demonstrated an acceptable safety profile in subjects with advanced melanoma previously treated with ipilimumab and, if BRAF mutation positive, a BRAFi regimen, in the context of the observed clinical activity. The nature, frequency, and severity of drug-related AEs, SAEs, and AEs leading to discontinuation are consistent with data from a prior study in the advanced pre-treated melanoma (no prior ipilimumab) subjects. A Biologics License Application (BLA) is planned seeking accelerated approval based on ORR, with OS data from study CA209037 supporting a conversion to full approval.

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/s/

MEREDITH LIBEG
08/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We also refer to your May 19, 2014, correspondence, requesting a meeting to discuss the planned BLA submission and potential accelerated approval of nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in patients who have progressed on or after ipilimumab and, if BRAF mutation positive, a BRAF inhibitor regimen based on objective response rate and duration of response data from study CA209037.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Wednesday, July 9, 2014; 3:00 to 4:00 PM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1315
Application Number:	IND 115195
Product Name:	Nivolumab [BMS-936558, MDX-1106, or ONO-4538]
Indication:	Advanced [Unresectable or Metastatic] Melanoma in Patients Progressing Post Anti-Cytotoxic T-lymphocyte Antigen-4 [CTLA-4] Therapy
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)

FDA ATTENDEES (tentative)

Richard, Pazdur, M.D.	Director, OHOP
Patricia Keegan, M.D.	Division Director, DOP2
Joseph Gootenberg, M.D.	Deputy Division Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Kun He, Ph. D.	Biometrics Reviewer, Team Leader, OBV
Sirisha Mushti, Ph.D.	Biometrics Reviewer, OBV
Hong Zhao, Ph. D.	Clinical Pharmacology Team Leader, DCPV
Xianhua Cao, Ph. D.	Clinical Pharmacology Reviewer, DCPV
Laurie Graham, M.S.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, DMA
Joel Welch, Ph.D.	CMC Reviewer, DMA
James Andrews, M.S., Ph.D.	CMC Reviewer, DMA
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Shawna Weis, Ph.D.	Pharmacologist/Toxicologist, DHOT
Tamy Kim, M.S.	Associate Director of Regulatory Affairs, OHOP
Erik Laughner, M.S.	Regulatory Scientist, OHOP
Sue Kang,	Lead Regulatory Health Project Manager, OSE
Frances Fahnbulleh,	Regulatory Health Project Manager, OSE
Karen Jones, B.S.	Chief, Project Management Staff, DOP2

Monica L. Hughes, M.S.	Chief, Project Management Staff, DOP2
Norma Griffin, B.S.	Acting Team Leader, DOP2
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences
David Feltquate, M.D., Ph.D.	Executive Director, Global Clinical Research
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology
Manish Gupta, Ph.D., F.C.P.	Director, Clinical Pharmacology and Pharmacometrics
Joseph Lamendola, Ph.D.	Vice President, U.S. Regulatory Sciences and Regulatory Policy, Global Regulatory Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Michael Giordano, M.D.	Senior Vice President, Head of Development, Oncology & Immunology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology
Ian Waxman, M.D.	Director, Global Clinical Research
Helen Liu, M.D.	Director, Global Pharmacovigilance and Epidemiology
Eric Masson, Pharm.D.	Executive Director, Clinical Pharmacology and Pharmacometrics
Christina Smith, D.Phil.	Vice President, Global Development, Nivolumab Filing and Dossier Strategy
Susan Welsh, M.D.	Vice-President Medical Safety, Global Pharmacovigilance and Epidemiology
Arvin Yang, M.D., Ph.D.	Director, Global Clinical Research

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Wednesday, July 9, 2014; 3:00 to 4:00 PM (ET) between Bristol-Myers Squibb and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the

questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Nivolumab is a monoclonal antibody directed against the Programmed Cell Death-1 (PD-1) molecule. PD-L1expression has been documented in multiple solid tumor histologies including: non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, gastric cancer, and breast cancer. Preclinical data show that blocking interactions between PD-1 and its ligands, PD-L1 or PD-L2, restores T-cell function and inhibits tumor growth in several murine models.

BMS is planning to submit a Biologics License Application (BLA) for accelerated approval for the treatment of patients with advanced (unresectable or metastatic) melanoma who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who progressed on or after a BRAF inhibitor in addition to anti-CTLA-4 therapy. BMS stated that the BLA will mainly be supported by efficacy and safety data from one study (CA209037) with data from a key supportive study (CA209003, also referred to as MDX1106-03 study).
A detailed table of contents containing the proposed components for the BLA was included in the meeting package under Appendix 3. Additionally, a proposed draft US Package Insert to be included in the BLA submission was included in the meeting package under Appendix 2.

BMS will be seeking accelerated approval based on co-primary endpoints of ORR (noncomparative point estimation of IRC-assessed ORR in the first 120 patients treated with nivolumab with at least 6 months follow-up). A subsequent application to support potential conversion to regular approval will be based on the CA209037 co-primary endpoint of OS. The statistical analysis plan (SAP) for CA209037 is provided in Appendix 1 of the briefing document.

At the time of the BLA submission, the estimated total number of patients treated with nivolumab monotherapy at 3 mg/kg every 2 weeks across multiple studies and indications will be approximately 1879 (1356 unblinded patients and approximately 523 blinded patients randomized to nivolumab). Of the 1879 nivolumab treated patients, 285 patients from Studies CA209037 and CA209003 were treated with the proposed dosing regimen (3 mg/kg every 2 weeks) that represents the relevant safety population in the BLA.

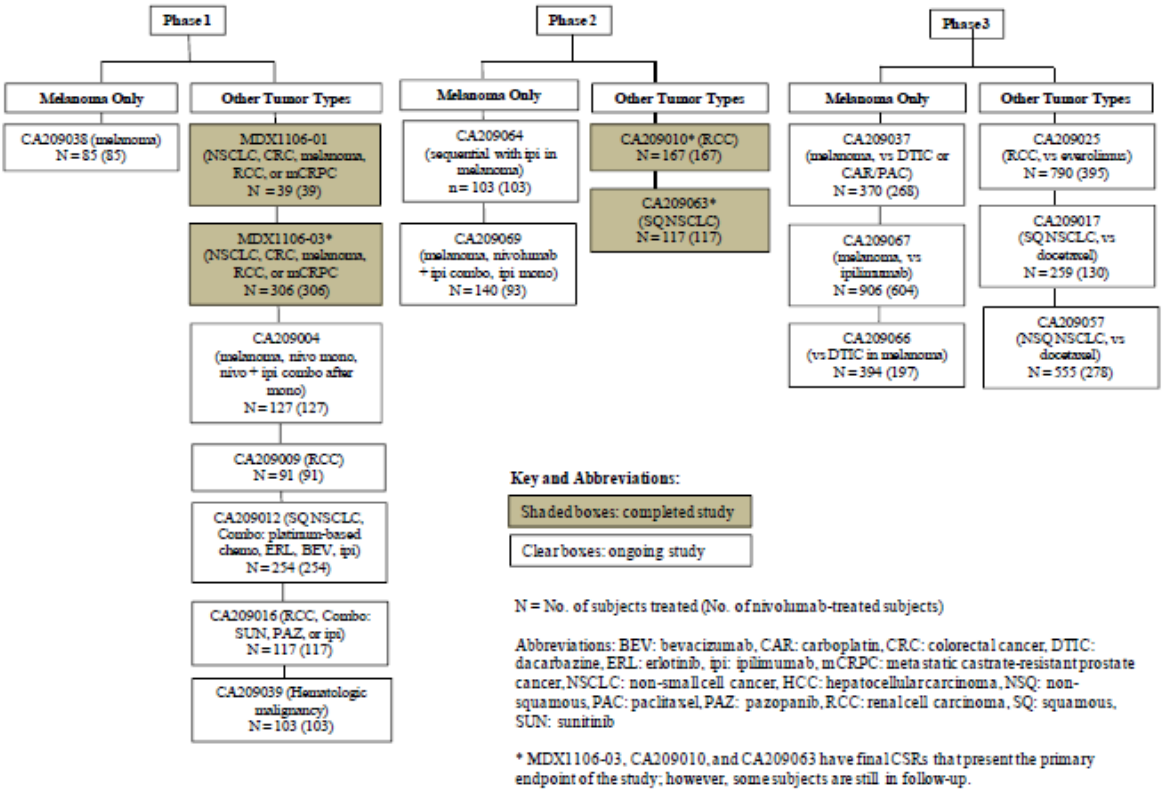
Nivolumab Development Program

Nivolumab is administered as an intravenous (IV) infusion in various schedules, either as a single agent or in combination with other antineoplastic agents. Nivolumab is in development under the following thirteen active INDs and one presubmission IND:

IND #	Indication
100052	Treatment of Advanced or Metastatic NSCLC
(b) (4)	(b) (4)
104225	Ipilimumab Combination for Treatment for Melanoma
113463	Advance Renal Cell Carcinoma (RCC)
114460	IL-21 Combination for Treatment of Solid Tumors
115195	Melanoma
(b) (4)	(b) (4)
117607	Anti-LAG-3 Combination for Treatment of Solid Tumors
(b) (4)	(b) (4)
119380	Non-Hodgkin's Lymphoma
119381	Treatment of Colorectal Cancer
119382	Treatment of Head and Neck Cancer
119590	Glioblastoma
PIND (b) (4)	(b) (4)

The nivolumab clinical development program for oncology includes the following completed or ongoing trials:

Figure 2-1: Nivolumab Clinical Development Program - BMS Sponsored Studies with Available Data In the BLA



BMS is developing, with their partner Dako North America (Dako), an immunohistochemistry (IHC) assay for the detection of PD-L1in tumor tissues as an in vitro companion diagnostic.

Regulatory History

- On February 7, 2012, a CMC only meeting was held to discuss plans to support clinical trials supporting licensure and marketing approval under the cross-referenced IND 100052.
- On June 13, 2012, BMS administratively split the indication of nivolumab monotherapy in melanoma from the existing IND 100052 into a new IND 115195. The new IND included Protocol CA209038 entitled, "An Exploratory Study of the Biologic Effects of BMS-936558 (Anti-PD-1 Monoclonal Antibody) Treatment in Subjects with Advanced Melanoma (Unresectable or Metastatic)."
- On July 13, 2012, the new IND 115195 was allowed to proceed.
- On July 17, 2012, an End of Phase 1/Pre-Phase 3 meeting was held to provide the Agency with preliminary data from the dose-finding and tolerability study (CA209003); to seek FDA's feedback on the proposed clinical development plan for treatment of advanced, unresectable, or metastatic melanoma; and to discuss the potential to obtain accelerated approval based on this development plan.
- On October 4, 2012, BMS was granted Fast Track Designation for patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.
- On October 17, 2012, BMS submitted a new Protocol CA209063 entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy."
- December 13, 2012, a CMC-only meeting was held to obtain FDA's feedback on the comparability of (b) (4) and assignment of the shelf life of a new 40 mg presentation.
- On January 23, 2013, BMS was granted Orphan Designation for the treatment of Stage IIb to Stage IV melanoma.
- On March 27, 2013, FDA issued an Advice/Information Letter providing comments relating to Protocol CA209037.
- On October 3, 2013, a Type C meeting was held under the cross-referenced IND 104225 to provide the Agency with an update on the nivolumab global registration strategy, and potential initiation of an expanded access program (EAP), for nivolumab as monotherapy in NSCLC, melanoma, and RCC and in combination with ipilimumab for melanoma. In this meeting, FDA agreed to review a proposal for an alternate timing of the final objective response rate (ORR) analysis in Study CA209037.
- On October 25, 2013, BMS submitted a proposal to "decouple" the timing of the analysis of the co-primary endpoints of ORR and OS in Study CA209037. FDA agreed with the proposal to perform an earlier analysis of ORR, but did not agree on the modification for alpha adjustment and recommended that the two-sided, alpha allocation ratio remain 0.01:0.04 for ORR and OS, respectively, as proposed in the original statistical analysis

plan. FDA did not agree to accept investigator-assessed response rate for the primary analysis of ORR and recommended that BMS include investigator-determined ORR as a secondary endpoint with proper allocation of Type I error to include investigator-assessed ORR in the label. FDA did not agree that unconfirmed responses can be included when evaluating ORR.

- On January 16, 2014, FDA issued an Advice/Information Letter providing comments relating to the Protocol CA209037 and BMS' October 25, 2013, proposal.
- On February 12, 2014, BMS submitted a proposal for modification to the primary analysis of ORR in CA209037 to incorporate an analysis of the independent review committee (IRC) assessed ORR in the first 120 patients treated with nivolumab in order to seek accelerated approval. OS remains a co-primary endpoint and will serve as confirmation of clinical benefit (full approval).
- On March 17, 2014, FDA issued an Advice/Information Letter providing comments relating to the Protocol CA209037 and BMS' February 12, 2014, proposal. FDA agreed with the proposal to analyze confirmed ORR based on an independent review in 120 nivolumab-treated patients based on a minimum of 6 months follow-up for all patients to seek accelerated approval. FDA agreed with the proposed plan of using an alpha of 0.04 for the analysis of OS as a co-primary endpoint which would serve as confirmation of clinical benefit (full approval).
- On April 9, 2014, BMS submitted an Expanded Access Program Treatment Protocol CA209168 for the treatment of Nivolumab for Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma Progressing Post Prior Systemic Treatment Containing an Anti-CTLA-4 Monoclonal Antibody.
- On April 18, 2014, a pre-BLA CMC only meeting was held to obtain feedback and agreement on the contents of the BLA application and acceptability of any late components to the application.
- On May 8, 2014, new Treatment Protocol CA209168 was allowed to proceed.

Study CA209037

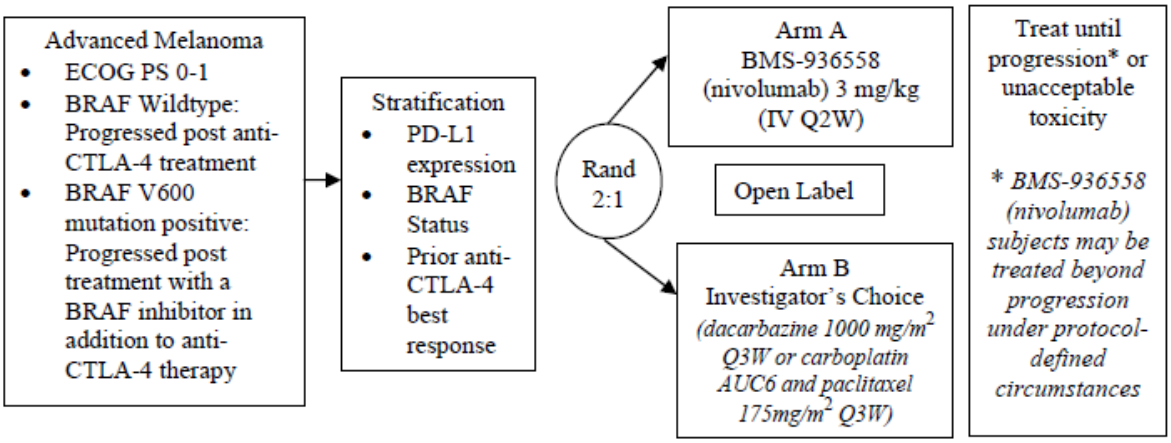
Study Design:

Study CA209037 is a randomized (2:1), open-label, multinational (United States, Austria, Belgium, Brazil, Canada Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom) study to evaluate single-agent nivolumab (3 mg/kg Q2W) versus investigator's choice (dacarbazine or carboplatin and paclitaxel) in approximately 390 adult (≥ 18 years old) patients with histologically confirmed, unresectable Stage III or Stage IV melanoma who progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who also progressed on or after a BRAF inhibitor regimen. Patients were randomized in a 2:1 ratio to nivolumab or investigator's choice, respectively, in order to evaluate the co-primary endpoints of ORR and OS. Screening evaluations to determine eligibility were to occur within 28 days prior to randomization with the exception of the tumor biopsy which was permitted more than 28 days prior to randomization. However, the tumor biopsy must have been

from an unresectable or metastatic site, and the patient must have had no intervening systemic therapy between the time of biopsy and randomization.

Randomization was stratified by PD-L1 status with a verified immunohistochemistry (IHC) assay (≥ 5% vs. < 5% tumor cell membrane staining), BRAF status (wildtype vs. mutation positive), and prior anti-CTLA-4 best response (prior clinical benefit [defined as complete response, CR; partial response, PR; stable disease, SD] vs. no prior clinical benefit [progressive disease, PD]).

The study schema is shown in the following Figure:



Patients were dosed with nivolumab intravenously over 60 minutes at 3 mg/kg every 2 weeks or with investigator's choice of chemotherapy (choice of either dacarbazine dosed intravenously between 30 to 60 minutes at 1000 mg/m^2 every 3 weeks or carboplatin at an AUC of 6 dosed intravenously over 30 minutes and paclitaxel 175mg/m^2 dosed intravenously over 180 minutes every 3 weeks) until PD (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, or withdrawal of consent. Treatment was continued until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond initial RECIST v1.1-defined progression), discontinuation due to toxicity, or other protocol-defined reasons.

Radiographic assessments of tumor response were performed at Week 9 (plus or minus 7 days) and every 6 weeks after Week 9 (plus or minus 7 days) for the first year and then every 12 weeks (plus or minus 7 days) until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression) or other protocol defined reasons. Recent tumor tissue that was formalin-fixed and paraffin-embedded (FFPE) were systematically collected for determination of baseline (pre-study) PD-L1 expression status.

The co-primary efficacy endpoints are ORR and OS.

The sample size of 390 patients for the study accounts for the co-primary efficacy endpoints: ORR (per independent review committee [IRC]) and OS with an alpha allocation of 0.1% and 4.9% respectively. Formal analyses of ORR and OS will be conducted at different timepoints with ORR being analyzed first followed by interim and final OS analyses.

The primary analysis of ORR in the nivolumab treatment group will be performed when approximately 180 treated patients (120 patients randomized and treated in the nivolumab arm and 60 patients randomized and treated in the investigator's choice arm) have a minimum follow up of 6 months. BMS states that the timing of this analysis will allow sufficient follow up for ORR to have a stable estimate, adequate safety follow up as well as information on duration of response in this population.

The final analysis of OS will be performed in the intent-to-treat (all randomized; at least 260 deaths will be required to provide approximately 90% power to detect a hazard ratio (HR) of 0.65, corresponding to a median OS of 8 months vs. 12.3 months for the investigator's choice and nivolumab groups, respectively, with an overall two-sided type I error of 4.9%. One formal OS interim analysis will be conducted when at least 169 deaths (i.e., 65% of total events) have been observed. The stopping boundaries at the interim and final OS analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

The secondary efficacy endpoints include: 1) PFS, as assessed by an IRC, to be formally assessed at the time of the OS analysis; and 2) ORR and OS correlation with PD-L1 expression by a validated IHC assay. PD-L1 expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining in a minimum of 100 evaluable tumor cells per a validated PD-L1 IHC assay (referred to as quantifiable PD-L1 expression). To evaluate the potential association between PD-L1 expression and efficacy endpoints, tumor tissues were systematically collected in all patients in CA209037, for determination of baseline PD-L1 expression status by a verified PD-L1 IHC assay using a 5% cutoff.

Analyses of safety included summaries of deaths, adverse events (AEs), serious adverse events (SAEs), select AEs, laboratory abnormalities, and immunogenicity.

Study CA209037 Results:

Based on the meeting package dated June 6, 2014, 631patients were enrolled, 405 patients were randomized, 272 to the nivolumab arm and 133 to the investigator's choice arm. The enrollment period lasted approximately 12 months (December 2012 to December 2013) with the Last Patient's First Treatment (LPFT) for ORR analysis occurred on September 10, 2013. The clinical database for the ORR analysis was locked on April 30, 2014, and the IRC database was locked on May 20, 2014. The imaging cut-off date (IRC and investigator) for this database lock was March 10, 2014, approximately 6 months after LPFT for the ORR population.

BMS states that the IRC-assessed confirmed ORR for the nivolumab arm was 31.7% (38/120) [95% confidence interval (95% CI): 23.5%, 40.8%] and 10.6% (5/47) [95% CI: 3.5%, 23.1%] in the investigator's choice arm. There were 3.3% (4/120) complete responses (CRs) in the nivolumab arm and no CRs in the investigator's choice arm. With a minimum follow-up of 6 months for all patients, the median DOR among IRC-assessed responders was not reached for the nivolumab arm.

BMS stated that the investigator-assessed confirmed ORR was 25.8% (31/120) [95% CI: 18.3%, 34.6%] comprised of 1.7% (2/120) CRs and 24.2% (29/120) PRs, in the nivolumab arm. The ORR was 10.6% (5/47) [95% CI: 3.5%, 23.1%], all PRs, in the investigator's choice arm.

The final analysis for PFS and the interim analysis of OS have not been conducted.

The following is a summary of the safety results as presented in the briefing package:

- The incidence of deaths in nivolumab- vs. investigator's choice-treated groups were 25.0% (67/268) vs. 23.5% (24/102), respectively. The majority 23.5% (63/268) vs. 22.5% (23/102) were attributed to disease progression (nivolumab-treated vs. investigator's choice-treated patients, respectively. The number of patients who died within 30 days of last dose was 10.4% (28/268) vs. 2.9% (3/102) with the majority 9.7% (26/268) vs. 2.9% (3/102) attributed to disease progression in the nivolumab- vs. investigator's choice-treated groups, respectively.
- Serious adverse events (SAE) irrespective of causality occurred in 44% of patients on the nivolumab-treated group and 22% of patients receiving investigator's choice of treatment. Serious adverse events occurring in ≥2% of patients on the nivolumab arm were malignant neoplasm progression (10.4%), abdominal pain (2%), and back pain (2%). The incidence of drug-related SAEs occurring in the nivolumab-treated group vs. investigator's choice-treated group were 6.3% vs. 9.8%, respectively. The most frequent (≥ 2 events) drug-related SAE in the nivolumab-treated group was hyperglycemia.
- The incidence of AEs leading to discontinuation regardless of causality occurring in the nivolumab-treated group vs. investigator's choice-treated group were 9.3% vs. 11.8%, respectively. The most commonly reported AE leading to discontinuation in the nivolumab-treated and the investigator's choice-treated groups were malignant neoplasm progression, 3.7% vs. 2.0%, respectively.
- Adverse events (AE) irrespective of causality occurred in 95% of patients on the nivolumab arm and 93% of patients on the investigator's choice arm, of which 35% and 43% were Grades 3-4, respectively. The most common AEs (≥ 20%) occurring on the nivolumab arm were fatigue (39% nivolumab-treated group vs. 43% for investigator's choice-treated group), nausea (24% vs. 42%), and diarrhea (20% vs. 17%). Drug-related AEs of any grade occurring in in the nivolumab vs. investigator's choice group was 67.5% vs. 79.4%, of which 9.0% vs. 31.4% were Grade 3-4.

Study MDX-1106-03 (CA209003):

Study Design:

Study CA209003 is a completed phase 1, two-part, open-label, multicenter, multidose, dose-escalation study of nivolumab in 306 patients with selected refractory and advanced malignancies. In total, 107 melanoma patients were enrolled and treated with nivolumab; 17 patients at a dose of 0.1 mg/kg, 18 patients at a dose of 0.3 mg/kg, 35 patients at a dose of 1 mg/kg, 17 patients at a dose of 3 mg/kg, and 20 patients at a dose of 10 mg/kg. Patients with melanoma must have had previous treatment in the metastatic setting but were not allowed to have received prior ipilimumab treatment. Part A was the dose-escalation phase using a traditional 3+3 design and up to 5 dosing cohorts (0.1, 0.3, 1, 3, and 10 mg/kg). Part B, the expansion phase, characterized tumor activity in different disease and dose specific cohorts:

- Melanoma: 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts
- Renal Cell Carcinoma: 10 mg/kg cohort
- Non-small cell lung cancer: 10 mg/kg cohort
- Colorectal Cancer: 10 mg/kg cohort
- Prostate Cancer: 10 mg/kg cohort

With Amendment 4, 7 additional cohorts were added:

- NSCLC: 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts
- Melanoma: 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg cohorts
- RCC: 1 mg/kg cohort

The primary endpoint was safety and tolerability and determination of maximum tolerated dose of multiple doses of nivolumab. Efficacy endpoints included ORR, durable objective responses, TTR, PFS, and OS. Tumor assessments were conducted at screening and approximately every 8 weeks thereafter. Responses were centrally assessed by the Sponsor using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0.

BMS states that a CSR was completed based on a 05-Mar-2013 database lock, and extended follow-up efficacy data (OS, PFS, and DOR) are being collected and will be provided in an addendum to the CSR based on a 17-Sep-2013 database lock which included a 3-year OS rate. BMS plans to submit data from this study to support the selection of the 3 mg/kg administered Q2W as the Phase 2/3 dose and schedule of nivolumab monotherapy across tumor types.

Study CA209003 Results:

Based on the June 6, 2014, meeting package, durable objective responses (DOR) were observed in previously treated patients with melanoma (31% across all dose levels, 41% at 3 mg/kg every 2 weeks). The median OS was 17.3 months (95% CI: 12.5, 36.7]) across all dose groups and was 20.3 months (95% CI: 7.2, -) in patients treated with 3 mg/kg. The 3-year survival rate across all dose groups was 44% (95% CI: 26, 60) and was 41% (95% CI: 31, 51) in patients treated with 3 mg/kg.

Table 3.3: Overall Efficacy Summary - Nivolumab Monotherapy in Melanoma (MDX1106-03)

	MDX1106-03	
Endpoint	**Melanoma 3 mg/kg N=17**	**Melanoma All Doses N=107**
ORR,[a] n (%) (95% CI)	7 (41.2) (18.4; 67.1)	33 (30.8) (22.3; 40.5)
DOR, Median Range (Months)[b,c]	17.5 (9.2+ - 26.5+)	22.9 (3.9+ - 26.9+)
PFS		
Median (95% CI) (Months)	9.69 (1.84, 16.43)	3.65 (1.87, 9.30)
Rate (95% CI)		
At 24 Weeks (~6 Months)	55% (28, 76)	45% (35, 54)
At 48 Weeks (~1 Year)	48% (22, 70)	38% (28, 47)
At 96 Weeks (~2 Years)	24% (6, 48)	29% (20, 39)
OS		
Median (95% CI) (Months)	20.3 (7.2, -)	17.3 (12.5, 36.7)
Rate (95% CI)		
At 24 Weeks (~6 Months)	88% (61, 97)	82% (74, 88)
At 48 Weeks (~1 Year)	65% (38, 82)	63% (53, 71)
At 96 Weeks (~2 Years)	47% (23, 68)	48% (38, 57)
At 144 Weeks (~3 Years)	41% (31, 51)	44% (26, 60)

a Confirmed PR or CR per sponsor using RECIST v1.0 criteria.

b Responses were still ongoing in 19 of the 34 responders (56%) at all doses as of the 17-Sep-2013 database lock.

c For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

Abbreviations: CR: complete response, DOR: duration of response, ORR: objective response rate, OS: overall survival, PFS: progression free survival, PR: partial response

2.0 DISCUSSION

Clinical:

1. *Background: See Pages 10 to 25 of the Briefing Document.*

Does FDA agree that results based on ORR from the pivotal study CA209037, with data from key supporting study MDX1106-03, form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of advanced

(unresectable or metastatic) melanoma patients based on FDA's final assessment of benefit/risk?

FDA Response: A final analysis of independently-assessed, confirmed objective response rate (ORR) that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in confirmed ORR over available therapy supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS at the planned interim analysis can form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of advanced (unresectable or metastatic) melanoma patients.

In addition, please provide the following in the BLA submission:

a) The topline results of the interim analyses of the overall survival (OS) and progression-free survival (PFS) at the time of the original BLA submission for FDA review. Absence of the OS and PFS results may result in a determination that the proposed application is not fileable.

b) The number of patients treated in the US in the two arms of Study CA209037. If appropriate, based on the number of patients enrolled in the US, the BLA should contain a justification that supports the applicability of the results of CA209037 to the US population.

c) The results of the confirmed ORR based on the intent-to-treat population (i.e., the first 120 patients enrolled and randomized to the nivolumab arm).

d) Identification of patients with melanoma treated with the proposed dose in Study MDX1106-01 and inclusion of such patients in the integrated summary of safety and efficacy. See FDA Response to Question 2a.

e) Evidence to support the dosage and dose interval recommended.

f) A discussion of the relevance of PD-L1 as a prognostic or predictive biomarker in melanoma and the potential association between PD-L1 expression and efficacy endpoints in Study CA209037. Please note that this trial was not adequately designed to support claims for an indication based on the PD-L1 subgroup.

2. *Background: This BLA will be submitted entirely in electronic format following the electronic Common Technical Document (eCTD) structure specified in International Conference on Harmonisation (ICH) M2 EWG Electronic Common Technical Document Specification v.3.2.2 dated July 2008, and utilizing the recommendations in the FDA Guidance for Industry entitled Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Revision 2, dated June 2008 and ICH 21 Approved 930080783 1.0 pre-BLA Background Document (Advanced Melanoma) IND 115195 BMS-936558 Nivolumab M2 EWG The eCTD Backbone File Specification for Study Tagging Files dated June 2008. The draft BLA Table of Contents (TOC) is provided in Appendix 3 of the Briefing Document.*

a) Is the proposed format and content of the BLA acceptable to FDA?

FDA Response: No. There is insufficient information in Section 2 and Appendix 3 to determine whether they include the complete contents of the BLA. Confirm that the following will be included in the BLA submission:

1. An integrated summary of safety (ISS) and the integrated summary of efficacy (ISE) that includes data from Study MDX1106-03 and CA209037, since Study MDX1106-03 is intended to support Study CA209037, per 21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi) . The ISS can include the safety data from the 268 patients from Study CA209037 and 17 patients from Study MDX1106-03 treated with the proposed dosing regimen of 3 mg/kg Q2W. The ISE can include efficacy data from Study MDX1106-03 to include the patients with melanoma who received nivolumab at or below the proposed dose of 3 mg/kg. Absence of integrated data may result in a determination that the proposed application is not fileable. Confirm whether both Study CA209037 and Study MDX1106-03 used the same versions of the NCI CTCAE for the severity grading of adverse events. If Study MDX1106-01 has patients with melanoma treated with the proposed dose, include in the integrated datasets.
2. If BMS intends to submit data for the non-melanoma studies, CA209010 (RCC), and CA209063 (NSCLC), confirm that complete safety information from all studies in the total number of patients treated with nivolumab as single-agent will be presented as side-by-side comparisons in the BLA submission in the ISS.
3. Confirm that the BLA will contain a list of Adverse Events of Special Interest (AESIs) that will be included in the BLA. Identify and include safety issues that are known to occur with other investigational or approved agents which belong to the same class. In the BLA submission, provide the following for each identified AESI:
   - Duration of the adverse event, and degree of resolution of the adverse event.
   - Details on the action taken and dose modifications.
   - Further details for adverse events which require corticosteroid therapy.
   - Methods used to monitor for the AESIs.
   - Methods to prevent, mitigate, or manage adverse events.
   - For important adverse reactions that occur later in treatment, provide explorations of the time dependency of the reaction.

4. Confirm that the BLA will include an analysis of adverse events based on all SMQs.
5. Provide a definition of Treatment Emergent Adverse Events and confirm that the adverse event datasets in the BLA submission will include a variable (flag) to identify Treatment Emergent Adverse Events.
6. Provide variables in the adverse event datasets to identify safety information that includes extended follow-up.
7. Provide the details of the imaging data sets for lesion assessment/response.
8. Include the following information with the Financial Disclosure Form:
   - A list of clinical investigators.
   - The number of investigators who are sponsor employees (including both full-time and part-time employees).
     - The number of investigators with disclosable financial interests/arrangements.
   - If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
     - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study.
     - Significant payments of other sorts.
     - Proprietary interest in the product tested held by investigator.
     - Significant equity interest held by investigator in sponsor of covered study.
   - Details of the disclosable financial interests/arrangements.
   - A description of the steps taken to minimize potential bias.
   - The number of investigators with certification of due diligence (Form FDA 3454, box 3), and include the reason in an attachment.
   - A narrative discussion on whether BMS has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data?

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data).
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements).

From a technical standpoint (i.e., not content-related), the proposed format for the planned BLA is acceptable. However, please see additional comments below:

1. 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
2. Please combine all study report amendments for study "MDX-1106-025-R-amendment 1-4" as a single pdf file with proper bookmarks, table of contents and hyperlinks (instead of separate pdf files for each amendment). In the future, if sponsor has to submit amendment 5, it should be replacing amendment 1-4 pdf file. Please apply the same for other studies with more than one amendment.
3. Do not provide placeholders for sections that will not be submitted (e.g. 4.2.1.2 Secondary Pharmacodynamics, N/A).
4. Study Tagging Files (STF) are required for submissions to the FDA when providing study information in Modules 4 and 5, with the exception of Module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including Case Report Forms (CRFs). CRFs need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to the eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

b) Does FDA agree that the draft TOC, which includes the contents of the application, is complete for FDA review in support of a BLA submission and potential BLA approval?

FDA Response: The draft TOC is generally acceptable but lacks sufficient detail on certain elements. Confirm that you will include the following in the BLA submission:

1. Clinical Study Report and datasets for Study MDX1106-03 in Module 5.3.5 along with the datasets.
2. Clinical subheadings within Modules 2.5 (Clinical Overview):
   - Module 2.5.4, Overview of Efficacy
   - Module 2.5.5, Overview of Safety
   - Module 2.5.6, Benefits and Risks Conclusions
3. ISS and ISE in Module 5.3.5.3.

See also FDA Response to Question 2a.

3. *Background: BMS submitted a preliminary proposal in the Administrative Pre-BLA briefing package on June 6, 2013 to IND 100052 (for Agency feedback. As noted in the Administrative Pre-BLA briefing package, the principles outlined in the BMS document were to apply to all future nivolumab submissions in other indications. FDA's written responses in the Type C Written Responses Only document (See Appendix 4 of the Briefing Document), provided on July 10, 2013, have been taken into account in this submission plan for the melanoma indication.*

Information about the proposed Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) package for the registrational study (CA209037) and supportive study (MDX1106-03) are provided in Section 8 of Appendix 5 of the Briefing Document.

Does FDA agree with the proposed SDTM and ADaM package for the registrational study, CA209037, and supportive study, MDX1106-03?

FDA Response: In addition to the proposed SDTM and ADAM package, provide the following in the BLA submission:

a) Detailed Data Reviewer's Guides especially with regard to the algorithms used to arrive at the safety and efficacy results. Provide detailed information or algorithms to explain the exact methods used in calculating derived variables as well as ensuring that the results are traceable back to the original SDTM data elements that were used in the derivations, and can ultimately be linked back to patient Case Report Forms.

b) Analysis dataset for derived best overall response data (one record per subject).

c) Independent radiology- and investigator-derived tumor measurement datasets.

4. *Background: BMS submitted a preliminary proposal in the Administrative Pre-BLA briefing package on June 6, 2013 to IND 100052 (for Agency feedback. As noted in the Administrative Pre-BLA briefing package, the principles outlined in the BMS document were to apply to all future nivolumab submissions in other indications. FDA's written responses in the Type C Written Responses Only document (See Appendix 4 of the*

Briefing Document), provided on July 10, 2013, have been taken into account in this submission plan for the melanoma indication.

For the completed studies (CA209010, CA209063, CA209037, MDX1106-01, and MDX1106-03), BMS proposes to submit narratives for nivolumab treated subjects meeting the following criteria:

- *All deaths within 100 days of last dose (100 days is based on nearly 5 times the half life of 17-25 days for nivolumab), except those due to progression.*
- *Related SAEs.*
- *AEs leading to discontinuation of treatment*
- *Pregnancy*
- *Overdose*
- *Any Grade ≥ 2 Related Select AE* requiring systemic immunosuppressants to treat AE*
- *Any causality concurrent (concurrent = within 1 day) alanine transaminase (ALT) or aspartate transaminase (AST) > 3x Upper Limit of Normal (ULN) and T.Bili > 2x ULN.*
- *CRFs for all randomized/treated subjects in the completed studies CA209010, CA209037, CA209063, MDX1106-01, and MDX1106-03 for all deaths within 100 days of the last dose, all SAEs, and all AEs leading to discontinuation.*
- *No CRFs or narratives will be provided for ongoing studies. Limited summaries of safety (deaths, SAEs, and AEs leading to discontinuation) will be provided for these studies.*

a) Does the FDA agree with the proposed plans for reporting safety narratives in the completed studies?

FDA Response: In addition to the safety narratives proposed for the completed studies, provide narratives in the BLA submission for other significant adverse events judged to be of special interest.

Please ensure that narratives for patients with immune-related serious adverse events include at a minimum the following information:

1. Patient age, gender, and race.
2. Concomitant medications, including details of dose, route of administration, and length of administration.
3. Onset of the immune-related adverse event in relation to exposure to the study drug.
4. Relevant physical examination, laboratory, and radiologic findings.

5. Action(s) taken with regard to nivolumab.
6. Outcome of the treatment.

In addition, FDA may request that BMS submit additional narratives during the review of the BLA.

See also FDA Response to Question 2a.

b) Does the FDA agree with this proposal for submission of CRFs?

FDA Response: In addition to the proposed CRFs, please include in the BLA submission the case report forms for the patients who discontinued due to an adverse event irrespective of causality. FDA may request that BMS submit additional case report forms during the review of the BLA.

See also FDA Response to Question 2a.

c) Does FDA agree with the proposed plans for limited safety summaries for ongoing studies in the BLA?

FDA Response: See FDA Response to Question 2a.

5. *Background: See Pages 23 to 24 of the Briefing Document.*

Does FDA agree with the BMS proposal regarding the Summary Level Clinical Site Data for CA209037 that will be provided in the nivolumab BLA?

FDA Response: Regarding BMS's proposal for inclusion of data elements in the summary level clinical dataset (clinsite.xpt), please see the table below for BMS's proposed data variable, the corresponding variable name as stated in the technical specifications document Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning, and Office of Scientific Investigations (OSI) comment on Sponsor's proposal. Please note, to enable use in CDER's Clinical Site Selection Tool the voluntarily submitted dataset should utilize the naming conventions and format as specified in the Draft Guidance for Industry, Providing Submissions in Electronic Format- Summary Level Clinical Site Data for CDER's Inspection Planning and the associated technical specifications Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning. Please also include a define.pdf file for the clinsite.xpt that provides a brief explanation of the content of variables, in particular for those variables that contain content that may be considered unique to your application (e.g., SCREEN, ENROLL, ENDPOINT, ENDPTYPE, TRTEFFE, TRTEFFS, SITEEFFE, SITEEFFS, CENSOR, PROTVIOL, etc.).

These recommendations are specific to the proposed submission of ORR based on an independent review in the first 120 patients treated with nivolumab with a minimum of 6 months follow-up for all patients, as has been previously agreed upon to seek accelerated approval.

Sponsor Proposal	Variable Name	Comment
IND ID	IND	
Site ID	SITEID	
Study ID	STUDY	
Treatment description	ARM	
Number of enrolled subjects at a given site.	SCREEN	Should include all consented subjects.
Number of screening failure subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Randomized Subjects at a given site.		This item would be reported as ENROLL when full study results for co-primary endpoints are reported.
Number of ORR Population Subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Subjects Randomized but not Treated at a given site	no variable	Do not include in clinsite.xpt
Number of ORR Population Subjects Randomized but not Treated at a given site.	no variable	Do not include in clinsite.xpt
Number of Treated Subjects at a given site.	no variable	Do not include in clinsite.xpt
Number of Treated Subjects among the ORR Population at a given site.	ENROLL	
Number of Subjects discontinued from treatment, among Treated Subjects as defined in the CSR, at a given site.	DISCONT	
Number of "relevant" protocol deviations, as defined in the SAP, among Randomized Subjects at a given site.	PROTVIOL	All significant protocol violations as defined in investigational plans (e.g., monitoring plans, SAP, etc.) should be included.
ORR, restricted to treated subjects in the ORR population, as assessed by IRRC (primary endpoint) at a given site.	ENDPOINT	When multiple endpoints are reported they should be reported separately for each treatment arm, along with all corresponding arm variables (including those described in table below
Average time to response among responders, restricted to treated subjects in the ORR population, as	ENDPOINT	

Sponsor Proposal	Variable Name	Comment
assessed by IRRC at a given site.		that lists variables currently missing from your proposal). In the case described here in which there are two treatment arms and 3 endpoints we would then expect clinsite.xpt to contain 6 rows of data per site.
Range of duration of response among responders (minimum, maximum), restricted to treated subjects in the ORR population, as assessed by IRRC at a given site.	ENDPOINT	
Total number of AEs regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	NSAE	
Total number of AEs leading to discontinuation regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	no variable	Do not include in clinsite.xpt
Total number of SAEs regardless of relationship to study drug in all treated subjects at a given site. This number includes multiple events per subject.	SAE	
Total number of deaths in all randomized subjects at a given site.	DEATH	
Investigator's First and Last Name	FRSTNAME and LASTNAME	First and last names should be reported as separate variables in clinsite.xpt
Investigator’s phone number	PHONE	
Investigator’s FAX number	FAX	
Investigator’s email address	EMAIL	
Investigator’s mailing address	COUNTRY, STATE, CITY, POSTAL, STREET	Each address component should be reported as separate variables in clinsite.xpt
Maximum financial disclosure amount (by site) by any single investigator, and total financial disclosure amount by site.	FINLMAX, FINLDISC	Maximum disclosure by single individual and total disclosure by site should be reported as separate variables in clinsite.xpt

The following data elements appear to be missing from your proposed clinsite.xpt and should be added:

Variable Name	Variable Label	Notes or Description
STUDYTL	Study Title	Title of the study as listed in the clinical study report (limit 200 characters)
DOMAIN	Domain Abbreviation	List as DE
SPONNO	Sponsor Number	Total number of sponsors throughout the study. If there was no change in sponsor while the study was ongoing, enter "1"
SPONNAME	Sponsor Name	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).
UNDERIND	Under IND	Value should equal "Y" if study at the site was conducted under an IND and "N" if study at the site was not conducted under IND (i.e., 21 CFR 312.120 sites)
NDA	NDA Number	Not applicable in this case, enter "-1"
BLA	BLA Number	Enter if available
SUPPNUM		Not applicable in this case, enter "-1"
ENDPTYPE	Endpoint Type	Variable type of the endpoint (i.e. continuous, discrete, time to event, or other)
TRTEFFE	Treatment Efficacy Endpoint	Summary statistic for each endpoint by treatment arm at a given site
TRTEFFS	Treatment Efficacy Endpoint Standard Deviation	Standard Deviation of the summary statistic (TRTEFFE) for each endpoint by treatment arm at a given site
SITEEFFE	Site-Specific Treatment Effect	Site-specific treatment effect reported using the same representation as reported for the corresponding endpoint analysis

SITEEFFS	Site-Specific Treatment Effect Standard Deviation	Standard deviation of the site-specific treatment effect (SITEEFFE)
CENSOR	Censored Observations	Number of censored observations at a given site by treatment arm. If not applicable, enter "-1"
MINITIAL	Investigator Middle Initial	Middle initial of investigator, if any

6. *Background: See Pages 24 to 25 of the Briefing Document.*

a) The submission of the safety update at 90 days after submission of the BLA?

FDA Response: FDA requests that BMS provide a safety update 90 days from the date of BLA submission. This safety update should focus on new safety information about nivolumab that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and the Medication Guide.

b) The timing of the database lock for the safety update?

FDA Response: See FDA response to Question 6a.

7. *Background: See Pages 25 to 26 of the Briefing Document.*

Based on the preliminary study results for CA209037 and safety profile from the additional nivolumab studies, does FDA agree with the current proposed Risk Management Strategy, which includes a Medication Guide that will be part of the US product labeling and does not propose/include a Risk Evaluation and Mitigation Strategy (REMS)?

FDA Response: Since additional information regarding risks and safe product use may emerge during the review of the actual trial results in the BLA, it is premature to determine whether a Risk Evaluation and Mitigation Strategy will be required. However, based on the available safety information in the premeeting briefing package, we agree that submission of a REMS will not be required for filing of the BLA.

Clinical Pharmacology:

8. *Background: See Pages 27 to 30 of the Briefing Document.*

The proposed clinical pharmacology package for melanoma will include revisions to the clinical pharmacology package planned to be submitted in support of the NSCLC BLA (b) (4) The revisions include: PPK analysis with all available data, exposure-response analysis with safety/efficacy data from CA209037, and presentation of immunogenicity data from MDX1106-03, CA209063, and CA209037. Does FDA agree with this proposal?

FDA Response: Yes. The proposed clinical pharmacology package for melanoma appears acceptable from a clinical pharmacology perspective.

Regulatory (Preliminary Breakthrough Designation Request Advice):

9. *Background: See Attached document.*

FDA Response: Yes, as noted in the February 26, 2013, communication, BMS may submit a breakthrough designation request (BTDR) if you obtain new clinical evidence that nivolumab may demonstrate a substantial improvement over existing therapies for the treatment of patients with previously treated or untreated, unresectable or metastatic melanoma; however, the final decision on the designation will consider the opinions of the representatives from the review division within Center for Drug Evaluation and Research (CDER), the Office of New Drugs (OND), and Office of Medical Policy (OMP) within CDER.

If BMS wishes to submit a BTDR, include the following information in the official BTDR:

a) Table 1 in the preliminary request for breakthrough designation of nivolumab as monotherapy does not contain adequate information concerning the durability of objective responses observed with nivolumab. Provide data on the duration of responses in a format that supports that the objective responses observed with nivolumab are durable, e.g., a swimmer plot.

b) Clarify the definition of the "primary objective population" (footnote, Table 1).

c) Provide the information on the stratification factor of PD-L1 as defined in Study CA209037.

Additional Comments:

Clinical:

10. Clarify why the Clinical Study Report for Study CA209063 (A Single-Arm Phase 2 Study of BMS-936558 in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens), which is not intended to support this submission is included Module 5.3.5.4.

11. Provide a list of clinical investigators who participated in Study CA209037 and Study MDX1106-03 as an IND amendment. Include contact information (address and telephone number).

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

12. As stated in our June 9, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

13. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

14. In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

15. To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

3.0 ATTACHMENTS AND HANDOUTS

- OSI Pre-NDA/BLA Request

OSI Pre-NDA/BLA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Part I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Part III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

Part I. Request for general study-related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the BA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as

described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

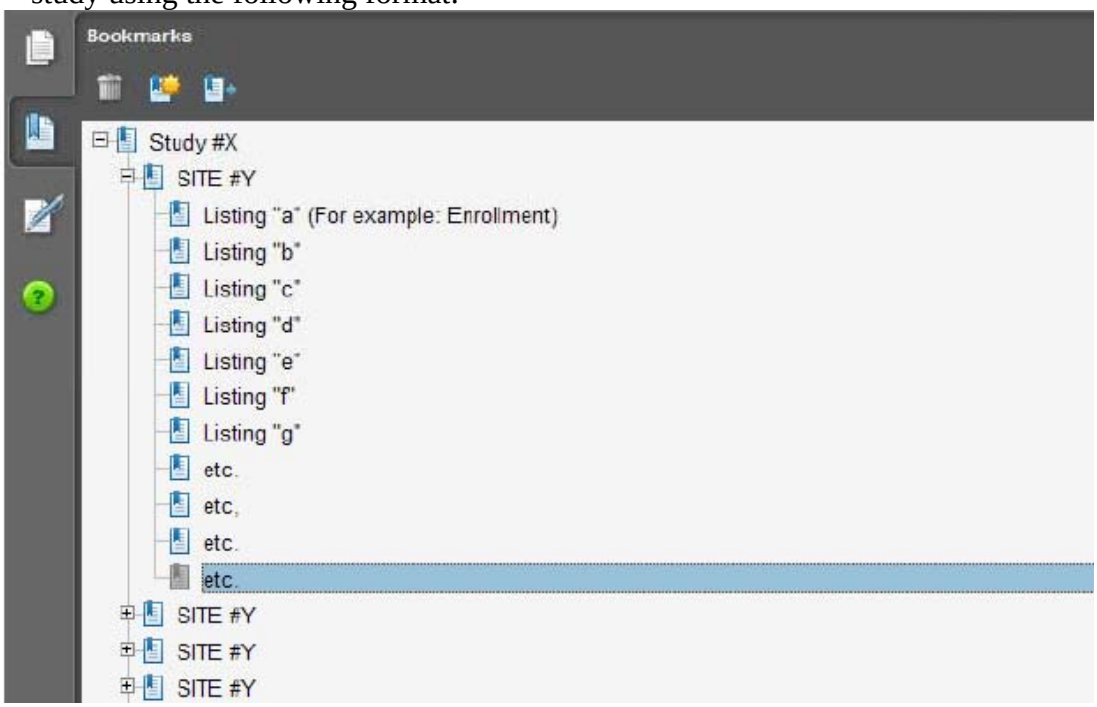
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

Part II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



Part III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEREDITH LIBEG
07/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell,

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We refer to your protocol amendment to IND 115195 dated October 17, 2012, containing the new protocol, Study CA209037, entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti CTLA-4 Therapy;" your proposal stated in the October 3, 2013, meeting conducted under IND 104225 to "decouple" the co-primary endpoints of objective response rate (ORR) and overall survival (OS) in Study CA209037; your amendment dated October 25, 2013, submitted to IND 115195 containing your proposal to decouple the co-primary endpoints of Independent Radiology Review Committee (IRRC)-assessed ORR and OS, for which an advice/information request was sent on January 16, 2014, under IND 115195; Amendment 9 of protocol CA209037 submitted to IND 115195 on January 6, 2014, which contained changes de-coupling of the co-primary endpoints of ORR and OS with an alpha allocation that was modified to 0.025 and 0.025, respectively; and your amendment dated February 13, 2014, contained a revised proposal to modifications to the primary analysis of ORR and requesting feedback on the proposal.

In the advice letter dated January 16, 2014, we agreed with your proposal to "decouple" the timing of the primary comparative analysis of ORR from the primary analysis of OS in Study CA209037; however, we recommended that the alpha allocation remain at 0.01:0.04 instead of the alpha allocation of 0.025:0.025 for ORR and OS, respectively, as modified in Amendment 9 of protocol CA209037.

In your February 13, 2014, submission, you propose to modify the design of Study CA209037 to incorporate a new analysis of ORR; in this new analysis, you propose to calculate the IRRC-assessed ORR in the first 120 patients treated with nivolumab to seek accelerated approval. The timing of this analysis will be based on a minimum of 6 months follow-up for all patients and the supporting assumptions are that a minimum of 22 responses out of 120 treated subjects (≥ 18% ORR) would need to be observed for the 99% confidence interval to rule out an ORR of

<10% based on the lower bound of the 99% confidence interval. An alternative hypothesis is that a minimum of 30 responses (≥ 25% ORR) would need to be observed to rule out an ORR of <15% based on the lower bound of the 99% confidence interval. In the proposal for the revised protocol, OS remains a co-primary endpoint and will serve as confirmation of clinical benefit. However, the proposed protocol would restore the alpha allocation to 0.01 and 0.04 for the analyses of ORR and OS, respectively.

We have the following comments and recommendations in response to your February 13, 2014, proposal submitted under IND 115195:

1. ***Sponsor Question:*** Does FDA agree with the proposed plan for analyzing the first 120 treated patients in the nivolumab arm for ORR? Would FDA consider a lower alternative number of patients for ORR based on Table 1 in the February 13, 2014, amendment?

   FDA's Response: The proposed plan to analyze confirmed ORR based on independent review in 120 nivolumab-treated patients, with the goal of excluding an overall response rate of less than 15% (based on the lower 99% confidence interval) is acceptable. However, we cannot determine whether the observed response rate of ≥25% would be considered reasonably likely to predict an effect on overall survival, in support of a request for accelerated approval. Considerations would include the magnitude of the confirmed ORR, the durability of the confirmed objective responses, and the risks of treatment. If you intend to seek accelerated approval of nivolumab based on the demonstration of durable confirmed objective responses (RECIST version 1.1), you must demonstrate an effect on ORR that, in adequate and well-controlled trial(s), is of sufficient magnitude based on the lower bounds of confidence interval and sufficient duration to be reasonably likely to predict clinical benefit.

   As stated in the End-of-Phase 2 meeting of July 17, 2012, please be advised that for a single trial to support a BLA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. For further information, please refer to the FDA Guidance for Industry, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf.

2. ***Sponsor Question:*** Does FDA agree with the proposed plan for analyzing OS?

   FDA's Response: The proposed plan of using an alpha of 0.04 for the analysis of OS is acceptable. Alternatively, BMS may consider another option of allocating 0.001 alpha for the ORR analysis in 120 patients, using a 95% confidence interval for the estimation of ORR, and allocating 0.049 alpha for the OS analysis. Please note that the analysis of

ORR should be provided as descriptive statistics only in proposed product and promotional labeling, i.e., no p-value assigned to this analysis.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  Since your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call Meredith Libeg, Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
03/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell,

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We refer to your amendment to IND 115195 dated October 17, 2012, containing the new protocol, Study CA209037, entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti CTLA-4 Therapy;" to your amendment dated October 24, 2012, requesting FDA agreement on the proposed revision in Study CA209037 to conduct the primary analysis of ORR based on investigator-assessed responses rather than Independent Review Committee (IRC) assessed responses; and to our March 27, 2013, Advice letter containing our comments and recommendations in response to your October 24, 2012, amendment.

We also refer to the October 3, 2013, Type C meeting held between FDA and BMS, conducted under IND 104225, to discuss the planned global registration strategy for nivolumab as a single agent for the treatment of advanced (unresectable or metastatic) melanoma, non-small cell lung cancer, and renal cell carcinoma and for nivolumab, in combination with ipilimumab, for the treatment of metastatic melanoma. Specifically, we refer to our request to formally submit your proposal, as stated in this meeting, to "decouple" the timing of the analysis of the co-primary endpoints of objective response rate (ORR) and overall survival (OS) in the Study CA209037 (melanoma).

Lastly, we refer to your amendment to IND 115195 dated October 25, 2013, requesting feedback on the proposal to accelerate the timing for submission of an NDA for nivolumab, as a single agent, for the treatment of metastatic melanoma following disease progression on ipilimumab treatment.

We have the following comments and recommendations in response to your October 25, 2013, amendment submitted under IND 115195:

1. BMS is proposing to modify the study design of CA209-037 to "decouple" the timing of ORR analysis from OS events in study CA209-037.

a. ***Sponsor Question:*** Does FDA agree with the proposed plan for analyzing overall response rate (ORR)?

FDA's Response: While a proposal to perform an earlier analysis of ORR is acceptable, we do not agree with the proposed change in alpha allocation to the co-primary endpoints. We recommend that the two-sided, alpha allocation ratio remains 0.01:0.04 for ORR and OS, respectively, as in the original statistical analysis plan. However, to accelerate the timing of the ORR analysis, you may consider modifying the statistical plan to provide less power to the ORR analysis since an overpowered analysis that demonstrates a statistically significant and clinically modest increase in ORR, may not provide a treatment effect that is considered likely to predict clinical benefit (and thus support a request for accelerated approval). Based on the software EAST using an alpha level of 0.01 and the assumptions proposed in the trial for analyzing ORR, there will be 90% power based on the first 271 enrolled subjects, 85% power based on the first 241 enrolled subjects, and 80% power based on the first 219 enrolled subjects. Since a test with at least 80% power is usually adequate, we recommend that the alpha allocation for analyzing ORR remains 0.01 (two-sided).

b. ***Sponsor Question:*** Does FDA agree with the proposed plan for analyzing OS?

FDA's Response: No, we do not agree based on the proposed modification for alpha adjustment. Please see our response to question 1.a.

2. ***Sponsor Question:*** In addition to the primary proposal (Questions #1a and 1b) above, the proposal listed below provides additional options for further potential optimization of the timeframe for study CA209-037. Would FDA accept Investigator-Assessed response for the primary analysis of ORR and IRC-assessed response as a sensitivity analysis?

FDA's Response: No, we do not agree. For U.S. regulatory purposes, ORR based on IRC-determined responses will be considered the primary efficacy endpoint to support a regulatory action. Since trial CA209-037 is an open-label trial, ORR based on investigator assessments has the potential for introduction of bias. As stated in our March 27, 2013, Advice letter, we recommend that you include investigator–determined ORR as a secondary endpoint with proper allocation of Type I error among all secondary endpoints in order to include investigator-assessed ORR in the label.

3. ***Sponsor Question:*** In addition to the primary proposal (Questions #1a and 1b) above, the proposal listed below provides additional options for further potential optimization of the timeframe for study CA209-037. Would FDA accept a proposal to consider both confirmed and unconfirmed responses as defined in RECIST 1.1 when evaluating ORR, with unconfirmed responses being limited to those observed at the last evaluable tumor assessment?

   FDA's Response: No, your proposal to include unconfirmed tumor responses as objective responses in the ORR is not acceptable. As stated in our March 27, 2013, Advice letter, "co-primary endpoints of ORR… would be acceptable to support accelerated approval of BMS-936558 based upon a final analysis of ORR that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in ORR supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS…[Objective tumor responses] will require confirmation at a repeat assessment to verify a minimum durability of tumor responses."

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  Since your IND is in eCTD format, you should submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. Since your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format.

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call Meredith Libeg, Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
01/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We also refer to your amendment dated October 17, 2012, containing a new protocol CA209037, entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti CTLA-4 Therapy."

Additionally, we refer to your amendment dated October 24, 2012, requesting agreement on the proposed switch from Independent Review Committee (IRC) assessment of the objective response rate (ORR) primary endpoint to investigator-assessment for both BMS-936558 proposed phase 3 pivotal studies CA209017 (squamous non-small cell lung cancer) and CA209037 (melanoma) under IND 100052 and IND 115195, respectively.

We have the following additional comments regarding study CA209037:

Clinical:

1. As stated in the July 17, 2012, Type B meeting, a trial design using co-primary endpoints of ORR and overall survival (OS) would be acceptable to support accelerated approval of BMS-936558 based upon a final analysis of ORR that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in ORR supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS at the planned interim analysis. Objective responses that are insufficiently durable and unconfirmed at repeat tumor assessments would not demonstrate a treatment effect reasonably likely to predict clinical benefit.

   Revise the protocol definition of best overall response (BOR) to state that a BOR of complete response (CR) or partial response (PR), as determined by the independent review committee, will require confirmation at a repeat assessment to verify a minimum

durability of tumor responses. We recommend that the confirmatory tumor assessment be performed no less than 4 weeks after the criteria for an objective response are first met. Longer intervals may be appropriate but must be defined in the protocol.

2. In order to minimize potential bias, we recommend that prior to subject randomization, in addition to the information listed in Section 4.2 (page 49), you require that the investigator select the choice of chemotherapy that will be administered to the patient if randomized to the chemotherapy arm. In addition, we recommend that you systematically collect this information in a format that can be verified and be used in analyses of potential sources of bias during a BLA review.

3. For the purposes of randomization stratification, we recommend that you perform centralized testing for determination of BRAF V600 mutation status. At a minimum, please systematically collect information about the test method that was used to determine BRAF V600 mutation status as well as the applicable test result (e.g., positive, negative, V600E, V600K).

4. Please ensure that the statistical analytical plan includes censoring rules and sensitivity analyses for patients who experience symptomatic deterioration in the absence of objective radiographic evidence of disease progression. We note that Section 3.4.3 does not clearly state whether patients who receive limited field palliative radiation therapy to pre-existing bone metastasis due to bone pain will be considered to have unequivocal progression of disease in the non-target lesion. In addition, administration of additional BMS-936558 doses to patients who received palliative limited field radiation to a pre-existing bone metastasis (non-target) should follow the guidelines specified in Section 4.3.9 of the protocol, Continued Treatment Beyond Progression of Disease.

5. We recommend the following additional revisions to the protocol:

   a. Clarification throughout the protocol that the randomization stratification factor "BRAF status" will be determine by the presence or absence of a BRAF V600 mutation to be consistent with the inclusion criteria that requires patients with BRAF V600 mutation-positive melanoma to have progressed following BRAF inhibitor therapy.

   b. Addition of urinalyses to the safety laboratory testing.

Statistical:

6. Please note that the significance level for the OS interim analysis to be conducted at the time of the ORR analysis should follow the O'Brien Fleming alpha spending function.

7. Please provide detailed descriptions of the timing and censoring for progression-free survival (PFS) including sensitivity analyses that consider the events in which patients have missing assessments and lost-to-follow-up in the statistical analysis plan.

Please refer to the guidance entitled, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf for more details.

8. Please provide detailed testing procedure with regard to the key secondary endpoint PFS.

We have the following response to the question contained in your October 24, 2012, submission

9. ***Sponsor Question:*** In light of the potential bias introduced by Independent Review Committee (IRC) assessment of scans for subjects treated beyond investigator-determined progression, Bristol-Myers Squibb proposes to conduct the primary analysis of the ORR co-primary endpoint based on investigator assessment, for both Study CA209017 and Study CA209037. All scans will be submitted for IRC review. Their assessments will be used to conduct sensitivity analyses. Does the agency agree with this proposal?

   FDA Response: No, we do not agree with your proposal. For U.S. regulatory purposes, IRC-determined ORR will be considered the primary efficacy endpoint to support a regulatory action. We note that both CA209017 and CA209037 are open-label studies with potential for investigator bias in determining the disease progression/response. As discussed during the July 24, 2012, Oncologic Drugs Advisory Committee, our assessment of data from multiple applications demonstrated that use of investigator-determined ORR led to an overestimation of ORR size compared to IRC-determined ORR. We recommend that you include investigator-determined ORR as a secondary endpoint in both trials with sufficient allocation of Type I error and adjustment for multiplicity because both IRC-determined ORR and investigator-determined ORR may be included in product labeling.

   Please be advised that, consistent with objective response rates provided in the labels of FDA approved products in disease settings similar to those in the proposed indications, the objective response rates for the purpose of labeling claims of BMS-936558 would be limited to analyses of those patients with objective responses that have been confirmed.

If you have any questions, contact Meredith Libeg, Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
03/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "BMS-936558."

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2012. The purpose of the meeting was to discuss the proposed Phase 3 registrational trial.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Face-to-Face Meeting
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	Thursday, December 6, 2012; 3:00 to 4:00 PM (ET)
Meeting Location:	White Oak Building 22; Room 1415
Application Number:	115195
Product Name:	BMS-936558
Indication:	Melanoma
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Suzanne Demko, P.A.-C.
Meeting Recorder:	Meredith Libeg, B.S.

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2
Suzanne Demko, P.A.-C.	Clinical Team Leader, DOP2
Marc Theoret, M.D.	Medical Officer, DOP2
Jennie Chang, PharmD	Medical Officer, DOP2
Anthony Murgo, M.D.	Associate Director of Regulatory Science, OHOP
Rosane Charlab Orbach, Ph.D.	Acting Team Leader Genomics, OCP
Christian Grimstein, Ph.D.	Genomics Reviewer, OCP
Laurie Graham, Ph.D.	CMC Reviewer, DMA
Hong Zhao, Ph. D.	Clinical Pharmacology Team Leader, DCP5, OCP
Jun Yang, Ph. D.	Clinical Pharmacology Reviewer, DCP5, OCP
Kun He, Ph. D.	Biometrics Reviewer, Team Leader, OBV
Yuan-Li Shen, Dr.P.H.	Biometrics Reviewer, OBV
Maria Chan, Ph.D.	Division Director, CDRH/OIR/DIHD
Reena Philip, Ph.D.	Deputy Division Director, CDRH/OIR/DIHD
Karen Bijwaard, M.S.	Acting Branch Chief, CDRH/OIR/DIHD/IHGB
Caryl Giuliano, Ph.D	Lead Scientific Reviewer, CDRH/OIR/DIHD/IHGB
Eunice Lee, Ph.D.	Scientific Reviewer, CDRH/OIR/DIHD/PACB
Meredith Libeg, B.S.	Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences, BMS
Renzo Canetta, M.D.	Vice President, Oncology Global Clinical Research, BMS
David Feltquate, M.D., Ph.D.	Group Director, Global Clinical Research, BMS
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences, BMS
Michael Giordano, M.D.	Senior Vice President, Head of Development, Oncology & Immunology, BMS
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology, BMS
Fouad Namouni, M.D.	Vice President, Development Lead, BMS
James F. Novotny Jr. Ph.D.	Director, Global Clinical Research/Pharmacodiagnostics, BMS
Dana M. Walker M.D., M.S.C.E.	Associate Medical Director, Global Pharmacovigilance and Epidemiology, BMS
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology, BMS
Kinnari Patel, Pharm.D.	Associate Director, U.S. Regulatory Sciences, BMS
James Simon, Ph.D.	Director, ImmunoOncology Biomarkers, BMS
Ian Waxman, M.D.	Director, Global Clinical Research, BMS
Arvin Yang, M.D.	Associated Director, Global Clinical Research, BMS
Dave Standforth	Director, PharmDx R & D, Dako North America
Xiaolei Xu	Manager, Regulatory Affairs, Dako North America

1.0 BACKGROUND

BMS-936558 is an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody administrated as an intravenous (IV) infusion. The proposed indication is for the treatment of melanoma.
On June 15, 2012, BMS filed a new administrative split Investigational New Drug Application (IND) from IND 100052. BMS-936558 is in development under the following five active INDs:

IND #	Indication
100052	Treatment of Lung Cancer
(b) (4)	(b) (4)
104225	Ipilimumab Combination Treatment
113463	Advance renal cell carcinoma (RCC)
115195	Melanoma

BMS states that preliminary data shows a signal for PD-L1 expression in melanoma as a potential predictive biomarker for BMS-936558. Therefore, BMS is developing a PD-L1 immunohistochemistry (IHC) assay with their partner Dako North America (Dako) as an *in vitro* companion diagnostic. An Investigation Device Exemption for this assay was received at FDA, CDRH, on November 1, 2012.

The BMS-936558 clinical development program in melanoma includes the following completed or ongoing trials:

Study (Status)	Design	N	Patient Population
CA209-003 (Completed)	Phase 1b, dose escalation study	305	Advanced colorectal cancer (CRC), melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and metastatic castrate-resistant prostate cancer (mCRPC) with progressive disease after 1-5 systematic therapies
CA209-004 (Ongoing)	Phase 1b, open-label, multidose, dose-escalation	57	Unresectable Stage III or Stage IV malignant melanoma
CA209-038 (Ongoing)	Exploratory, open-label	80	Unresectable or metastatic melanoma
CA209-037 (Planned)	Phase 3, open-label, randomized (2:1)	390	Unresectable or metastatic melanoma that has progressed after anti-CTLA-4 therapy and BRAF inhibitor therapy (BRAF V600E mutation-positive patients only)

CA209-066 (Planned – Non-US)	Phase 3, double-blind, randomized (1:1)	410	Previously untreated, unresectable Stage III or Stage IV BRAF-wildtype melanoma
CA209-067 (Proposed)	Phase 3, double-blind, randomized (1:1:1)	915	Previously untreated Stage III (unresectable) or Stage IV metastatic melanoma

Fast Track designation was granted on October 4, 2012, for the treatment of patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.

CA209-067

The proposed trial U.S. pivotal trial, CA209-067, is a randomized (1:1:1), double-blind, multicenter, parallel-group, active-controlled trial of BMS-936558 monotherapy or BMS-936558 combined with ipilimumab versus ipilimumab monotherapy in approximately 915 adult (≥ 18 years) subjects with previously untreated AJCC Stage III (unresectable) or Stage IV metastatic melanoma. Randomization will be stratified by PD-L1 status (positive vs. negative/indeterminate), BRAF V600 mutation status (known BRAF V600 wildtype vs. BRAF V600 mutation-positive) and AJCC M stage (M0/M1a/M1b vs. M1c). The randomization stratification factor for PD-L1 status will be considered positive if ≥ 5% out of a minimum 100 evaluable tumor cells demonstrate membrane staining by IHC.

Patients will be treated with one of the following:

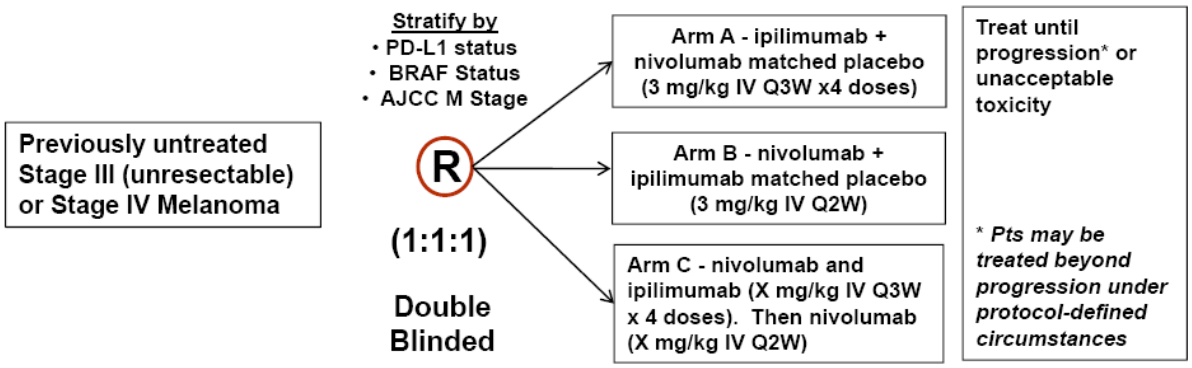
- Arm A : BMS-936558 3 mg/kg administered IV over 60 minutes every 2 weeks
- Arm B: ipilimumab 3mg/kg administered intravenously (IV) over 90 minutes every 3 weeks for a total of 4 doses
- Arm C: BMS-936558 (dose to be determined) administered IV every 3 weeks combined with ipilimumab (dose to be determined) administered IV every 3 weeks for four doses then continuing only BMS-936558 (dose to be determined) administered IV every 2 weeks

Please note: BMS plans to support the BMS-936558 dose and dose administration schedule in the final protocol based on results from trial CA209-004.

One cycle is defined as every 6 weeks.

Treatment will continue until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue.

The study schema is shown in the following Figure:



Key inclusion criteria include: (1) histological confirmation of Stage III (unresectable) or Stage IV melanoma as per the AJCC staging system; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) sufficient tumor tissue from an unresectable or metastatic site; and (4) known BRAF V600 wildtype or BRAF V600 mutation-positive melanoma.

Key exclusion criteria include: (1) prior therapy for unresectable or metastatic melanoma (prior adjuvant or neoadjuvant therapy is allowed if given in the setting of localized disease); (2) active brain metastasis or leptomeningeal metastasis; primary ocular melanoma; and (3) have active, known or suspected autoimmune disease.

The primary endpoint is overall survival (OS) as assessed by investigators every 3 months after completion of the first 2 follow-up visits after treatment discontinuation. Assuming that the median OS is 14 months in the control arm and 19.4 months in the experimental arm, a total of 460 events are needed for each treatment pairs to detect a hazard ratio of 0.72 with 90% power at a 2-sided alpha level of 2.5%. The sample size calculation also assumes a piecewise constant accrual rate (45 subjects/month during Months 1 to 2, 60 subjects/month during Months 3 to 4, 75 subjects/month during Months 5 to 6, and 90 subjects/month after Month 6). It is anticipated that it will take 40.6 months to observe the required number of deaths for the final OS analysis (12.1 months for accrual and 28.5 months for survival follow-up).

The primary analysis method will be a stratified log-rank test performed on the intent to treat (ITT) population. The Hochberg method will be used to adjust for the multiplicity for the two primary comparisons.

The final analysis will be performed when 247 deaths are observed in the control arm (instead of the pooled 460 deaths observed in the pooled arms) to maintain the power and preserve the study integrity for the 3-arm study.

BMS also states that some loss of power is expected due to non-proportional hazards, so some adjustment of the sample size may be made prior to protocol finalization.

There is no interim analysis planned for this study. However, in the case where both arms have flattening tails, the timing of the final analysis could be substantially later than the projected timeline under exponential assumptions, regardless of whether control arm deaths or pooled deaths are tracked. BMS may include an additional provision that allows the final analysis to be performed when a minimum follow-up and a pre-specified fewer number of deaths in the control arm have been observed (i.e. if 247 control events have not be observed within 29 months of the last subject randomized, the final analysis will be conducted when at least 217 control events have been observed).

Major secondary endpoints include progression-free survival (PFS) and objective response rate (ORR). The stratified log-rank tests will be used for the analysis of PFS and the Cochran-Mantel-Haenszel test will be used for best overall response (BOR). A gate-keeping method will be proposed in the up-coming SAP to adjust for multiplicity in testing the secondary endpoints.

CA209-066

Trial CA209-066 is a randomized (1:1), double-blind, multicenter trial of BMS-936558 + placebo vs. dacarbazine in approximately 410 patients with previously untreated Stage III (unresectable) or Stage IV, BRAF-wildtype melanoma. Trial CA209-066 will be conducted entirely outside of the U.S. and not under an IND. Randomization will be stratified by PD-L1 status [positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs. negative/intermediate (<5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells / tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)] and AJCC M stage (M0/M1a/M1b vs. M1c).

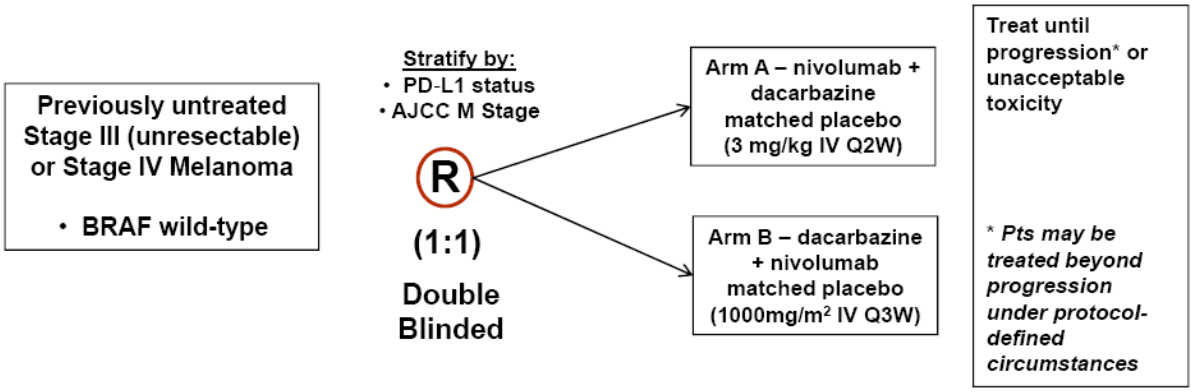
Subjects will be treated with one of the following:

- Arm A (experimental): BMS-936558 3 mg/kg IV every 2 weeks plus placebo IV every 3 weeks
- Arm B (control): dacarbazine using the standard dose and schedule (1000 mg/m^2 IV every 3 weeks) plus placebo IV every 2 weeks

One cycle was defined as every 6 weeks (i.e., 3 doses of BMS-936558; 2 doses of dacarbazine).

Treatment will continue until disease progression, unacceptable treatment-related toxicity, patient or physician decision to discontinue, or death.

The study schema is shown in the following Figure:



Key inclusion criteria include: (1) untreated, histological confirmation of unresectable Stage III or Stage IV melanoma as per AJCC staging system; (2) age ≥ 18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (4) measureable disease as per RECIST 1.1; (5) tumor tissue (acquired within 90 days prior to randomization) from an unresectable or metastatic site of disease must be provided for biomarker analyses; and (6) known BRAF wildtype as per regionally acceptable V600 mutational status testing.

Key exclusion criteria include: (1) active brain metastasis or leptomeningeal metastasis; (2) ocular melanoma; (3) active, known or suspected autoimmune disease; and (4) requirement for treatment with corticosteroids (>10 mg daily prednisone equivalent).

The primary endpoint is OS. Assuming that the median OS is 10 months in the control arm and 14.5 in the experimental arm, a total of 312 events are needed for each treatment pairs to detect a hazard ratio of 0.69 with 90% power at a 2-sided alpha level of 5%. This sample size calculation also assumes that the accrual period will be 9.5 months and the final analysis will be performed at 30 months.

The primary analysis method will be a stratified log-rank test performed on the ITT population.

Two interim analyses will be performed after 218 (70%) events for efficacy. The O'Brien-Fleming boundary method is utilized with respective alpha allocation with an alpha of 0.0148 for the interim analysis and alpha for the final analysis of 0.0455.

2.0 DISCUSSION

Clinical:

1. *Background: Slides 22 to 25 and Appendix 1 (pages 34 to 42)*

Does FDA agree with the proposed study design of CA209-067, a 3-arm Phase 3 study of nivolumab or nivolumab + ipilimumab vs ipilimumab in previously-untreated, unresectable or metastatic melanoma?

FDA Response: In general, the 3-arm design of trial CA209-067 appears acceptable. However, please ensure that the issues raised in FDA's response to Question #4 have been addressed in the final version of Protocol CA209-067 that is submitted to IND 115195.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

2. *Back ground: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

Does FDA agree with the proposed statistical analysis plan to support potential registration based on study CA209-067, including the Hochberg approach to analyzing the two primary comparisons?

FDA Response: The Hochberg approach for the two primary comparisons is acceptable.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

3. *Background: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

The analysis plan for study CA209-067 indicates that the primary analysis will be performed when a specified number of deaths has occurred in the control arm (ipilimumab monotherapy), with the deaths being tracked by an external statistical group. Does the FDA agree with this analysis plan?

FDA Response: The proposal to perform the primary analyses when a specified number of deaths have occurred in the control arm is acceptable.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

4. *Background: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

Does FDA agree in principle with pre-specifying a condition for conducting the final analysis if a minimum follow-up period after LPFV has elapsed and 247 control events have not been observed? (For example: If 247 control events have not been observed within 29 months of last subject randomized, the final analysis will be conducted when at least 217 control events have been observed).

FDA Response: Since the primary efficacy analyses are event-driven analyses, the number of events in the control arm should be pre-specified (e.g. the final OS analysis will be performed either when 247 or 217 events are reached) which does not depend on the time elapsed after the last subject randomized.

If it appears that the required number of events in the control arm will not be observed within a minimum follow-up period (e.g., 29 months after the last patient is randomized), BMS should request a meeting with FDA to discuss a specific proposal for final analysis of the study.

Discussion During 12/6/2012 Meeting: BMS proposed to revise the Data Monitoring Committee charter to include parameters and disclosures to a select group within BMS in case the expected rate of events in the control arm was not occurring, in which case, a meeting with FDA will be proposed to discuss the next steps. BMS will submit the revised charter once available. FDA stated that this approach could be acceptable; however, FDA will provide final determination upon receipt.

5. *Background: Slides 22 to 25, Appendix 1 (pages 34 to 42), and Appendix 2 (pages 43 to 50)*

Does FDA agree that the proposed study CA209-067 provides an acceptable basis for evaluation of the benefit-risk balance of nivolumab and may serve as a pivotal trial to support the potential approval of nivolumab in previous-untreated, unresectable or metastatic melanoma subjects?

FDA Response: The overall design of trial CA209-067, which specifies that the primary endpoint is overall survival, appears acceptable to provide information of safety and efficacy and support a benefit-risk analysis of BMS-936558 in the proposed indication.

Please note that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.

Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf

and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

6. *Background: Slides 22 to 27*

Study CA209-066 (nivolumab vs dacarbazine in previously-untreated, unresectable or metastatic melanoma) is being conducted to support approval of nivolumab in EU and other countries that do not have an approval for ipilimumab and/or other approved therapy in subjects with previously-untreated, unresectable or metastatic melanoma. BMS proposes to include the safety and efficacy results of CA209-066 with either study CA209-037 or CA209-067, which are designed to obtain a potential approval of nivolumab in either previously-treated or previously-untreated, unresectable or metastatic melanoma subjects. Does the FDA agree with this proposal?

FDA Response: Yes, the proposal to submit the safety and efficacy results of Protocol CA209-066 in a BLA for BMS-936558 is acceptable. Please also refer to the October 19, 2012, FDA Advice/Information Request letter in regard to the design of Protocol CA209-066.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

7. *Background: Slides 22 to 27*

Based on the timing of study CA209-067, there is a potential that nivolumab would become available for this or another indication before the time of the final OS analysis for CA209-067, and the ability to demonstrate superior OS in this study may therefore be impacted. In the case that CA209-037 or CA209-066 demonstrates superior OS, does the Agency agree to meet with BMS to discuss the potential for study design changes (e.g., the primary endpoint) for CA209-067?

FDA Response: FDA recommends that BMS request a meeting to discuss this question once the potential impact, if any, of approval BMS-936558 based on the results from CA209-037 or CA209-066 on ability to complete Protocol CA209-067 as planned, can be assessed.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Additional Comments:

Clinical:

8. Please ensure that Protocol CA209-067, which permits patients to be treated beyond progression of disease "under protocol-defined circumstances", clearly defines the minimal criteria that must be met by a patient with radiological progression of disease in order to continue to receive BMS-936558, such that the patients are not exposed to unreasonable risks. Such criteria may include the following:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression

b. No decline in ECOG performance status

c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In addition, the proposed patient population for Protocol CA209-067 includes patients for whom standard therapies exist, including FDA approved therapies that have demonstrated improved overall survival in clinical trials, thus patients should provide written informed consent in order to continue to receive BMS-936558 beyond progression of disease.

Discussion During 12/6/2012 Meeting: BMS confirmed that criteria, such as that recommended above, is a standard part of the protocols for the melanoma development program and these criteria will be incorporated into the final version of the CA209-067 Protocol. FDA finds this acceptable.

Clinical Pharmacology:

Regarding the proposed Phase 3 Trial (CA209-067):

9. Include ECG monitoring at baseline, around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment in the proposed clinical trial to capture large cardiac safety signals. This ECG monitoring plan should be included in all clinical trials until an adequate evaluation has been conducted to rule out the QT prolongation potential of BMS-936558.

Discussion During 12/6/2012 Meeting: BMS proposed to provide a global clinical pharmacology plan to address product development needs; and to discuss this plan at a future meeting with the FDA.

FDA stated that BMS should ensure that the effects on QTc are adequately addressed in the BLA submission.

10. Collect pharmacokinetic samples during the proposed clinical trial to allow for exploratory analyses of exposure-response relationships. Sparse sampling is often sufficient to perform these analyses. Clinical responses to be used in the analyses should include the clinical efficacy endpoints and toxicity outcome measures as well as any disease and/or drug response related biomarkers collected in the proposed trial.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

During the development of BMS-936558 in combination with ipilimumab:

11. Evaluate the potential for a PK interaction between BMS-936558 and ipilimumab.

Discussion During 12/6/2012 Meeting: BMS stated that an ongoing safety study of the combination will be amended to incorporate PK sampling to evaluate drug interactions between ipilimumab and BMS-936558. FDA stated that this approach is acceptable.

12. Address the additional clinical pharmacology comments conveyed during the July 16, 2012 EOP1 meeting prior to the BLA submission.

Discussion During 12/6/2012 Meeting: Please refer to Question 9 above.

Regulatory:

13. As a result of PDUFA V (the program), if a separate Chemistry, Manufacturing, and Control (CMC) pre-BLA meeting is needed, please be advised that BMS should request the 'CMC only' meeting prior to the multidisciplinary pre-BLA meeting.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

PREA PEDIATRIC STUDY PLAN

14. Please be advised that BMS must submit a Pediatric Study Plan (PSP) within 60 days of the scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that BMS plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

Discussion During 12/6/2012 Meeting: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

DATA STANDARDS FOR STUDIES

15. CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.0 ATTACHMENTS AND HANDOUTS

- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance

32 page(s) have been withheld for DOP2 Guidance . Refer to http://www.cdisc.org/fda-guidance-on-standardized-study-data & http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm271326.htm

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEREDITH LIBEG
01/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb
Attention: Kinnari Patel, PharmD, R.Ph.
Associate Director, Global Regulatory Sciences, US-Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "BMS-936558."

We also refer to your October 8, 2012, correspondence, received October 9, 2012, requesting a meeting to discuss the proposed Phase 3 registrational trial.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B Face-to-Face Meeting
Meeting Category: End-of-Phase 2

Meeting Date and Time: Thursday, December 6, 2012; 3:00 to 4:00 PM (ET)
Meeting Location: White Oak Building 22; Room 1415

Application Number: 115195
Product Name: BMS-936558
Indication: Melanoma
Sponsor/Applicant Name: Bristol-Myers Squibb (BMS)

TENTATIVE LIST OF FDA ATTENDEES:

Richard Pazdur, M.D.	Director, OODP
Patricia Keegan, M.D.	Division Director, DOP2
Joseph Gootenberg, M.D.	Deputy Division Director, DOP2
Suzanne Demko, P.A.-C.	Clinical Team Leader, DOP2
Marc Theoret, M.D.	Medical Officer, DOP2
Lee Pai-Scherf, M.D.	Medical Officer, DOP2
Anthony Murgo, M.D.	Associate Director of Regulatory Science, OHOP
Tamy Kim, Pharm.D.	Associate Director of Regulatory Affairs, OHOP
Robert Temple, M.D.	Deputy Director, Office of Drug Evaluation 1 (ODE-1)
Rosane Charlab Orbach, Ph.D.	Acting Team Leader Genomics,OCP
Christian Grimstein, Ph.D.	Genomics Reviewer, OCP
Barbara Rellahan, M.S., Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, DMA
Laurie Graham, Ph.D.	CMC Reviewer, DMA
Whitney Helms, Ph.D	Pharmacology/Toxicology Team Leader, DHOT
Shawna Weis, Ph.D.	Pharmacologist/Toxicologist, DHOT
Hong Zhao, Ph. D.	Clinical Pharmacology Team Leader, DCP5, OCP
Jun Yang, Ph. D.	Clinical Pharmacology Reviewer, DCP5, OCP
Kun He, Ph. D.	Biometrics Reviewer, Team Leader, OBV
Yuan-Li Shen, Dr.P.H.	Biometrics Reviewer, OBV
Maria Chan, Ph.D.	Division Director, CDRH/OIR/DIHD
Reena Philip, Ph.D.	Deputy Division Director, CDRH/OIR/DIHD
Karen Bijwaard, M.S.	Acting Branch Chief, CDRH/OIR/DIHD/IHGB
Robert Becker, M.D., Ph.D.	Chief Medical Officer, CDRH/OIR
Caryl Giuliano, Ph.D	Lead Scientific Reviewer, CDRH/OIR/DIHD/IHGB
Elizabeth Mansfield, Ph.D.	Director, Personalized Medicine, CDRH/OIR
Eunice Lee, Ph.D.	Scientific Reviewer, CDRH/OIR/DIHD/PACB
Dianne Spillman,	Lead Regulatory Health Project Manager, OHOP
Karen Jones, B.S.	Chief, Project Management Staff, DOP2
Meredith Libeg, B.S.	Regulatory Health Project Manager, DOP2

Norma Griffin, B.S.	Regulatory Health Project Manager, DOP2

TENTATIVE LIST OF SPONSOR ATTENDEES:

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences, BMS
Renzo Canetta, M.D.	Vice President, Oncology Global Clinical Research, BMS
David Feltquate, M.D., Ph.D.	Group Director, Global Clinical Research, BMS
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences, BMS
Michael Giordano, M.D.	Senior Vice President, Head of Development, Oncology & Immunology, BMS
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology, BMS
Fouad Namouni, M.D.	Vice President, Development Lead, BMS
James F. Novotny Jr. Ph.D.	Director, Global Clinical Research/Pharmacodiagnostics, BMS
Kathleen O'Donnell, Director	Director U.S. Regulatory Sciences – Oncology, BMS
Kinnari Patel, Pharm.D.	Associate Director, U.S. Regulatory Sciences, BMS
James Simon, Ph.D.	Director, ImmunoOncology Biomarkers, BMS
Ian Waxman, M.D.	Director, Global Clinical Research, BMS
Arvin Yang, M.D.	Associated Director, Global Clinical Research, BMS
Dave Standforth	Director, PharmDx R & D, Dako North America
Xiaolei Xu	Manager, Regulatory Affairs, Dako North America

1.0 INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Thursday, December 6, 2012; 3:00 to 4:00 PM (ET) between BMS and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions.
Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER

feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

2.0 BACKGROUND

BMS-936558 is an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody administrated as an intravenous (IV) infusion. The proposed indication is for the treatment of melanoma.
On June 15, 2012, BMS filed a new administrative split Investigational New Drug Application (IND) from IND 100052. BMS-936558 is in development under the following five active INDs:

IND #	Indication
100052	Treatment of Lung Cancer
(b) (4)	(b) (4)
104225	Ipilimumab Combination Treatment
113463	Advance renal cell carcinoma (RCC)
115195	Melanoma

BMS states that preliminary data shows a signal for PD-L1 expression in melanoma as a potential predictive biomarker for BMS-936558. Therefore, BMS is developing a PD-L1 immunohistochemistry (IHC) assay with their partner Dako North America (Dako) as an *in vitro* companion diagnostic. An Investigation Device Exemption for this assay was received at FDA, CDRH, on November 1, 2012.

The BMS-936558 clinical development program in melanoma includes the following completed or ongoing trials:

Study (Status)	Design	N	Patient Population
CA209-003 (Completed)	Phase 1b, dose escalation study	305	Advanced colorectal cancer (CRC), melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and metastatic castrate-resistant prostate cancer (mCRPC) with progressive disease after 1-5 systematic therapies
CA209-004 (Ongoing)	Phase 1b, open-label, multidose, dose-escalation	57	Unresectable Stage III or Stage IV malignant melanoma
CA209-038 (Ongoing)	Exploratory, open-label	80	Unresectable or metastatic melanoma

CA209-037 (Planned)	Phase 3, open-label, randomized (2:1)	390	Unresectable or metastatic melanoma that has progressed after anti-CTLA-4 therapy and BRAF inhibitor therapy (BRAF V600E mutation-positive patients only)
CA209-066 (Planned – Non-US)	Phase 3, double-blind, randomized (1:1)	410	Previously untreated, unresectable Stage III or Stage IV BRAF-wildtype melanoma
CA209-067 (Proposed)	Phase 3, double-blind, randomized (1:1:1)	915	Previously untreated Stage III (unresectable) or Stage IV metastatic melanoma

Fast Track designation was granted on October 4, 2012, for the treatment of patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.

CA209-067

The proposed trial U.S. pivotal trial, CA209-067, is a randomized (1:1:1), double-blind, multicenter, parallel-group, active-controlled trial of BMS-936558 monotherapy or BMS-936558 combined with ipilimumab versus ipilimumab monotherapy in approximately 915 adult (≥ 18 years) subjects with previously untreated AJCC Stage III (unresectable) or Stage IV metastatic melanoma. Randomization will be stratified by PD-L1 status (positive vs. negative/indeterminate), BRAF V600 mutation status (known BRAF V600 wildtype vs. BRAF V600 mutation-positive) and AJCC M stage (M0/M1a/M1b vs. M1c). The randomization stratification factor for PD-L1 status will be considered positive if ≥ 5% out of a minimum 100 evaluable tumor cells demonstrate membrane staining by IHC.

Patients will be treated with one of the following:

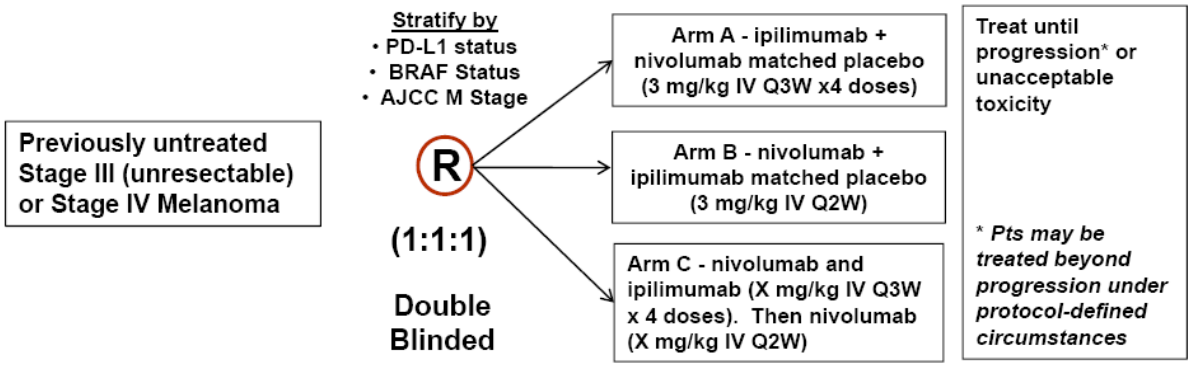
- Arm A : BMS-936558 3 mg/kg administered IV over 60 minutes every 2 weeks
- Arm B: ipilimumab 3mg/kg administered intravenously (IV) over 90 minutes every 3 weeks for a total of 4 doses
- Arm C: BMS-936558 (dose to be determined) administered IV every 3 weeks combined with ipilimumab (dose to be determined) administered IV every 3 weeks for four doses then continuing only BMS-936558 (dose to be determined) administered IV every 2 weeks

Please note: BMS plans to support the BMS-936558 dose and dose administration schedule in the final protocol based on results from trial CA209-004.

One cycle is defined as every 6 weeks.

Treatment will continue until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue.

The study schema is shown in the following Figure:



Key inclusion criteria include: (1) histological confirmation of Stage III (unresectable) or Stage IV melanoma as per AJCC staging system; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) sufficient tumor tissue from an unresectable or metastatic site; and (4) known BRAF V600 wildtype or BRAF V600 mutation-positive melanoma.

Key exclusion criteria include: (1) prior therapy for unresectable or metastatic melanoma (prior adjuvant or neoadjuvant therapy is allowed if given in the setting of localized disease); (2) active brain metastasis or leptomeningeal metastasis; primary ocular melanoma; and (3) have active, known or suspected autoimmune disease.

The primary endpoint is overall survival (OS) as assessed by investigator every 3 months after completing 2 follow-up visits after treatment discontinuation. Assuming that the median OS is 14 months in the control arm and 19.4 in the experimental arm, a total of 460 events are needed for each treatment pairs to detect a hazard ratio of 0.72 with 90% power at a 2-sided alpha level of 2.5%. The sample size calculation also assumes a piecewise constant accrual rate (45 subjects/month during Months 1 to 2, 60 subjects/month during Months 3 to 4, 75 subjects/month during Months 5 to 6, and 90 subjects/month after Month 6). It will take 40.6 months to accrual the required number of deaths for the final OS analysis (12.1 months for accrual and 28.5 months for survival follow-up).

The primary analysis will be a stratified log-rank test performed on the intent to treat (ITT) population. The Hochberg method will be used to adjust for the multiplicity for the two primary comparisons.

The final analysis will be performed when 247 deaths are observed in the control arm (instead of the pooled 460 deaths observed in the pooled arms) to maintain the power and preserve the study integrity for the 3-arm study.

BMS also states that some loss of power is expected due to non-proportional hazards, so some adjustment of the sample size may be made prior to protocol finalization.

There is no interim analysis planned for this study.

However, in the case where both arms have flattening tails, the timing of the final analysis could be substantially later than the projected timeline under exponential assumptions, regardless of whether control arm deaths or pooled deaths are tracked. BMS may include an additional provision that allows the final analysis to be performed when a minimum follow-up and a pre-specified fewer number of deaths in the control arm have been observed (i.e. if 247 control events have not be observed within 29 months of the last subject randomized, the final analysis will be conducted when at least 217 control events have been observed).

Major secondary endpoints include progression-free survival (PFS) and objective response rate (ORR). The stratified log-rank tests will be used for the analysis of PFS and the Cochran-Mantel-Haenszel test will be used for best overall response (BOR). A gate-keeping method will be proposed in the up-coming SAP to adjust for multiplicity in testing the secondary endpoints.

CA209-066

Trial CA209-066 is a randomized (1:1), double-blind, multicenter trial of BMS-936558 + dacarbazine vs. dacarbazine in approximately 410 patients with previously untreated Stage III (unresectable) or Stage IV, BRAF-wildtype melanoma. Trial CA209-066 will be conducted entirely outside of the U.S. and not under an IND. Randomization will be stratified by PD-L1 status (positive vs. negative/intermediate) and AJCC M stage (M0/M1a/M1b vs. M1c).

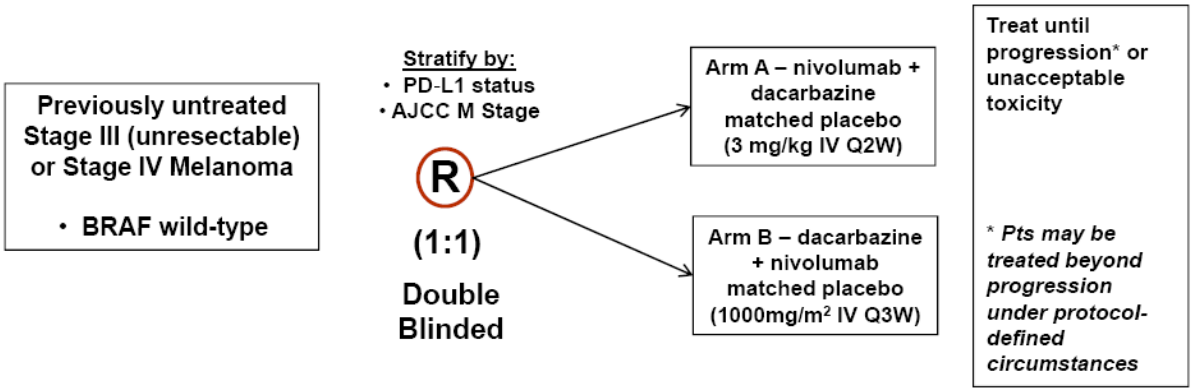
Subjects will be treated with one of the following:

- Arm A (experimental): BMS-936558 3 mg/kg IV every 2 weeks plus placebo IV every 3 weeks
- Arm B (control): dacarbazine using the standard dose and schedule (1000 mg/m^2 IV every 3 weeks) plus placebo IV every 2 weeks

One cycle was defined as every 6 weeks (i.e., 3 doses of BMS-936558; 2 doses of dacarbazine).

Treatment will continue until disease progression, unacceptable treatment-related toxicity, patient or physician decision to discontinue, or death.

The study schema is shown in the following Figure:



Key inclusion criteria include: (1) untreated, histological confirmation of unresectable Stage III or Stage IV melanoma as per AJCC staging system; (2) age ≥ 18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (4) measureable disease as per RECIST 1.1; (5) tumor tissue (acquired within 90 days prior to randomization) from an unresectable or metastatic site of disease must be provided for biomarker analyses; and (6) known BRAF wildtype as per regionally acceptable V600 mutational status testing.

Key exclusion criteria include: (1) active brain metastasis or leptomeningeal metastasis; (2) ocular melanoma; (3) active, known or suspected autoimmune disease; and (4) requirement for treatment with corticosteroids (>10 mg daily prednisone equivalent).

The primary endpoint is OS. Assuming that the median OS is 10 months in the control arm and 14.5 in the experimental arm, a total of 312 events are needed for each treatment pairs to detect a hazard ratio of 0.69 with 90% power at a 2-sided alpha level of 5%. This sample size calculation also assumes that the accrual period will be 9.5 months and the final analysis will be performed at 30 months.

The primary analysis will be a stratified log-rank test performed on the ITT population.

Two interim analyses will be performed after 218 (70%) events for efficacy. The O'Brien-Fleming boundary method is utilized with respective alpha allocations of 0.0148; the alpha for the final analysis is 0.0455.

3.0 DISCUSSION

Clinical:

1. *Background: Slides 22 to 25 and Appendix 1 (pages 34 to 42)*

Does FDA agree with the proposed study design of CA209-067, a 3-arm Phase 3 study of nivolumab or nivolumab + ipilimumab vs ipilimumab in previously-untreated, unresectable or metastatic melanoma?

FDA Response: In general, the 3-arm design of trial CA209-067 appears acceptable. However, please ensure that the issues raised in FDA's response to Question #4 have been addressed in the final version of Protocol CA209-067 that is submitted to IND 115195.

2. *Background: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

Does FDA agree with the proposed statistical analysis plan to support potential registration based on study CA209-067, including the Hochberg approach to analyzing the two primary comparisons?

FDA Response: The Hochberg approach for the two primary comparisons is acceptable.

3. *Background: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

The analysis plan for study CA209-067 indicates that the primary analysis will be performed when a specified number of deaths has occurred in the control arm (ipilimumab monotherapy), with the deaths being tracked by an external statistical group. Does the FDA agree with this analysis plan?

FDA Response: The proposal to perform the primary analyses when a specified number of deaths have occurred in the control arm is acceptable.

4. *Background: Slides 22 to 25 and Appendix 2 (pages 43 to 50)*

Does FDA agree in principle with pre-specifying a condition for conducting the final analysis if a minimum follow-up period after LPFV has elapsed and 247 control events have not been observed? (For example: If 247 control events have not been observed within 29 months of last subject randomized, the final analysis will be conducted when at least 217 control events have been observed).

FDA Response: Since the primary efficacy analyses are event-driven analyses, the number of events in the control arm should be pre-specified (e.g. the final OS analysis will be performed either when 247 or 217 events are reached) which does not depend on the time elapsed after the last subject randomized.

If it appears that the required number of events in the control arm will not be observed within a minimum follow-up period (e.g., 29 months after the last patient is randomized), BMS should request a meeting with FDA to discuss a specific proposal for final analysis of the study.

5. *Background: Slides 22 to 25, Appendix 1 (pages 34 to 42), and Appendix 2 (pages 43 to 50)*

Does FDA agree that the proposed study CA209-067 provides an acceptable basis for evaluation of the benefit-risk balance of nivolumab and may serve as a pivotal trial to support the potential approval of nivolumab in previous-untreated, unresectable or metastatic melanoma subjects?

FDA Response: The overall design of trial CA209-067, which specifies that the primary endpoint is overall survival, appears acceptable to provide information of safety and efficacy and support a benefit-risk analysis of BMS-936558 in the proposed indication.

Please note that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.

Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf

and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.

6. *Background: Slides 22 to 27*

Study CA209-066 (nivolumab vs dacarbazine in previously-untreated, unresectable or metastatic melanoma) is being conducted to support approval of nivolumab in EU and other countries that do not have an approval for ipilimumab and/or other approved therapy in subjects with previously-untreated, unresectable or metastatic melanoma. BMS proposes to include the safety and efficacy results of CA209-066 with either study CA209-037 or CA209-067, which are designed to obtain a potential approval of nivolumab in either previously-treated or previously-untreated, unresectable or metastatic melanoma subjects. Does the FDA agree with this proposal?

FDA Response: Yes, the proposal to submit the safety and efficacy results of Protocol CA209-066 in a BLA for BMS-936558 is acceptable. Please also refer to the October 19, 2012, FDA Advice/Information Request letter in regard to the design of Protocol CA209-066.

7. *Background: Slides 22 to 27*

Based on the timing of study CA209-067, there is a potential that nivolumab would become available for this or another indication before the time of the final OS analysis for CA209-067, and the ability to demonstrate superior OS in this study may therefore be impacted. In the case that CA209-037 or CA209-066 demonstrates superior OS, does the Agency agree to meet with BMS to discuss the potential for study design changes (eg, the primary endpoint) for CA209-067?

FDA Response: FDA recommends that BMS request a meeting to discuss this question once the potential impact, if any, of approval BMS-936558 based on the results from CA209-037 or CA209-066 on ability to complete Protocol CA209-067 as planned, can be assessed.

Additional Comments:

Clinical:

8. Please ensure that Protocol CA209-067, which permits patients to be treated beyond progression of disease "under protocol-defined circumstances", clearly defines the minimal criteria that must be met by a patient with radiological progression of disease in order to continue to receive BMS-936558, such that the patients are not exposed to unreasonable risks. Such criteria may include the following:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression

b. No decline in ECOG performance status

c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In addition, the proposed patient population for Protocol CA209-067 includes patients for whom standard therapies exist, including FDA approved therapies that have demonstrated improved overall survival in clinical trials, thus patients should provide written informed consent in order to continue to receive BMS-936558 beyond progression of disease.

Clinical Pharmacology:

Regarding the proposed Phase 3 Trial (CA209-067):

9. Include ECG monitoring at baseline, around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment in the proposed clinical trial to capture large cardiac safety signals. This ECG monitoring plan should be included in all clinical trials until an adequate evaluation has been conducted to rule out the QT prolongation potential of BMS-936558.

10. Collect pharmacokinetic samples during the proposed clinical trial to allow for exploratory analyses of exposure-response relationships. Sparse sampling is often sufficient to perform these analyses. Clinical responses to be used in the analyses should include the clinical efficacy endpoints and toxicity outcome measures as well as any disease and/or drug response related biomarkers collected in the proposed trial.

During the development of BMS-936558 in combination with ipilimumab:

11. Evaluate the potential for a PK interaction between BMS-936558 and ipilimumab.

12. Address the additional clinical pharmacology comments conveyed during the July 16, 2012 EOP1 meeting prior to the BLA submission.

Regulatory:

13. As a result of PDUFA V (the program), if a separate Chemistry, Manufacturing, and Control (CMC) pre-BLA meeting is needed, please be advised that BMS should request the 'CMC only' meeting prior to the multidisciplinary pre-BLA meeting.

PREA PEDIATRIC STUDY PLAN

14. Please be advised that BMS must submit a Pediatric Study Plan (PSP) within 60 days of the scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that BMS plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 ATTACHMENTS AND HANDOUTS

- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance

32 page(s) have been withheld for DOP2 Guidance . Refer to http://www.cdisc.org/fda-guidance-on-standardized-study-data & http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm271326.htm

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/s/

MEREDITH LIBEG
12/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115195

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kinnari Patel, PharmD, R.Ph.
Associate Director, Global Regulatory Sciences, US-Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "BMS-936558."

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2012. The purpose of the meeting was to discuss your Phase 1 data, proposed Phase 3 clinical study, and potential for accelerated approval regulatory pathway.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Face-to-Face Meeting
Meeting Category:	End-of-Phase 1/Pre-Phase 3
Meeting Date and Time:	Tuesday, July 17, 2012; 10:00 to 11:00 AM (ET)
Meeting Location:	White Oak Building 22; Room 1311
Application Number:	115195
Product Name:	BMS-936558
Indication:	Melanoma
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Joseph Gootenberg
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

CDER:

Patricia Keegan, M.D.	Director, DOP2/OHOP
Joseph Gootenberg, M.D.	Deputy Division Director/Clinical Team Leader, DOP2/OHOP
Marc Theoret, M.D.	Clinical Reviewer, DOP2/OHOP
Norma Griffin	Regulatory Health Project Manager, DOP2/OHOP
Meredith Libeg	Regulatory Health Project Manager, DOP2/OHOP
Jonathan Jarow, M.D.	Clinical Reviewer, DOP1/OHOP
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT/OHOP
Rosane Charlab Orbach, Ph.D.	Genomics, Acting Team Leader, OTS/OCP/Genomics
Christian Grimstein, Ph.D	Genomics Reviewer, OTS/OCP/Genomics
Kun He	Biostatistical Team Leader, DBV5/OB
Yuan Li Shen	Biostatistical Reviewer, DBV5/OB

CDRH:

Yun-Fu Hu	Associate Director for Immunology, DIHD/ OIVD
Caryl Giuliano	Immunology and Hematology Devices Reviewer, DIHD/ OIVD

SPONSOR ATTENDEES

Renzo Canetta, M.D.	Vice President, Oncology Global Clinical Research, BMS
David Feltquate, M.D., Ph.D.	Group Director, Global Clinical Research, BMS
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences, BMS
Christine Horak, Ph.D.	Senior Research Investigator II, Clinical Biomarkers - Oncology, DMCP, BMS
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology, BMS
Fouad Namouni, M.D.	Vice President, Development Lead, BMS
Kinnari Patel, Pharm.D.	Associate Director, U.S. Regulatory Sciences, BMS
James F. Novotny Jr. Ph.D.	Director, Global Clinical Research/Pharmacodiagnostics, BMS
Aparna Anderson, Ph.D.	Director, Global Biometric Sciences, BMS
Kathleen O'Donnell, Director	U.S. Regulatory Sciences, BMS
Xiaolei Xu, Ph.D.	Regulatory Affairs Manager, DAKO

1.0 MEETING OBJECTIVES

To discuss the preliminary data from the ongoing Phase 1 study CA209003 and obtain FDA input on the proposed clinical development plan for second-line metastatic melanoma.
In addition, to discuss the potential for accelerated approval regulatory pathway for metastatic melanoma.

2.0 BACKGROUND

BMS-936558 is an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody administrated as an intravenous (IV) infusion. The proposed indication is for the treatment of melanoma.
On June 15, 2012, BMS filed a new administrative split Investigational New Drug Application (IND) from IND 100052. BMS-936558 is in development under the following five active INDs:

IND #	Indication
100052	Treatment of Lung Cancer
(b) (4)	(b) (4)
104225	Ipilimumab Combination Treatment
113463	Advance renal cell carcinoma (RCC)
115195	Melanoma

BMS states that preliminary data shows a signal for PD-L1 expression in melanoma as a potential predictive biomarker for BMS-936558. Therefore, BMS is developing a PD-L1 IHC assay with their partner DAKO, and plans to submit an Investigation Device Exemption for this assay.

The BMS-936558 clinical development program in melanoma includes an ongoing phase 1 trial (CA209003) conducted under IND 100052, two phase 1 studies (CA209006 and CA209007), two phase 1b studies (CA209004 and CA 209038); and a proposed phase 3 study (CA209037). Studies CA209006, CA209007, CA209004 and CA 209038 will explore PD-L1 expression in melanoma as a potential predictive biomarker for BMS-936558.

The meeting briefing document provides preliminary results of response rates observed in trial CA209003 based on PD-L1 biomarker status. For this analysis, BMS defined PD-L1 expression positive as membranous staining in ≥ 5% tumor cells or overall score of positive for the presence of macrophages or lymphocytes in tumor. The ascertainment rate of PD-L1 biomarker status was 43% (40/93). Of these 40 patients, 34 had at least one on treatment tumor assessment for response. The objective response rates (ORR) observed with BMS-936558 administration were 26% (6/23) in the PD-L1 positive subgroup, 17% (1/6) in the PD-L1 indeterminate subgroup, 0 (0/5) in the PD-L1 negative subgroup, and 32 % (19/59) in the PD-L1 unmeasured subgroup.

The proposed trial, CA209037, is an open-label, multicenter, randomized (2:1), active-controlled study to compare BMS-936558 to chemotherapy in approximately 354 Stage III (unresectable) or Stage IV, recurrent or metastatic melanoma. Patients randomized to Arm A (n=236) will receive BMS-936558 3mg/kg dose intravenously on an every 2 week schedule.
Patients randomized to Arm B (n=118) will receive dacarbazine or carboplatin/paclitaxel as determined by the investigator. Randomization stratification factors are PD-L1 status, BRAF status, and prior ipilimumab response.

Key inclusion criteria includes: histological confirmation of Stage III (unresectable) or Stage IV melanoma; 18 years of age or older; Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 1; measurable disease at baseline by CT or MRI as per RECIST 1.1 criteria; pre-treatment fresh core or excision tumor biopsy must be provided for biomarker analyses. Subjects must consent to allow the acquisition of existing formalin-fixed paraffin-embedded (FFPE) material (block or a minimum of 10 unstained slides); have experienced RECIST 1.1 defined progression of disease (PD) during or after one and at most two prior treatment regimens for advanced melanoma; BRAF V600 wildtype patients must have PD during or following anti-CTLA-4 therapy; and BRAF V600 mutation-positive patients must have PD during or following anti-CTLA-4 and BRAF inhibitor therapy (irrespective of sequence).

Key exclusion criteria includes: active brain metastasis or leptomeningeal metastasis; primary ocular melanoma; prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel. Prior systemic therapy with one of the treatments is permitted; have active, known or suspected autoimmune disease; have a known history of select anti-CTLA-4 therapy related adverse reactions based on the CTCAE v4.0 criteria; and have received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2, (or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways except for anti-CTLA-4 therapy as described in the exclusion criterion).

BMS proposes co-primary endpoints of Objective Response Rate (ORR) and Overall Survival (OS). Proposed secondary endpoints include: evaluation of OS of BMS-936558 and dacarbazine or carboplatin/paclitaxel by PD-L1 expression; comparison of the PFS of BMS-936558 to

dacarbazine or carboplatin/paclitaxel; evaluation of duration and time to objective response in BMS-936558 and dacarbazine or carboplatin/paclitaxel; and evaluation of Health Related Quality of Life (HRQoL) between treatment groups as assessed by European Organization for Research and Treatment of Care (EORTC) QLQ-C30.

A sample size of 354 patients would provide ≥ 90% power with a two-sided type I error of 0.01 to detect an increase in the ORR from 10% in the chemotherapy arm to 30% in the BMS-936558 arm. At the time of the final OS analysis, 260 death events would provide ≥ 90% power with an overall two-sided type I error of 0.04 to detect an improvement in median OS from 8 months in the chemotherapy arm to 12.3 months in the BMS-936558 arm [hazard ratio (HR) of 0.65].

BMS plans to perform one interim OS analysis (for efficacy) at the time of the ORR analysis which is projected to occur after occurrence of approximately 195 (75%) death events. BMS proposes use of the O'Brien Fleming boundary method to allocate an alpha of 0.0145 to the interim OS analysis and an alpha of 0.0357 to the final OS analysis.

BMS proposes that superiority in either endpoint will support the submission of a BLA for BMS-936558. Registration of BMS-936558 based on the ORR endpoint requires statistically significant ORR improvement and no evidence of detriment in OS as demonstrated in the interim OS analysis resulting in a HR point estimate of < 0.9. According to the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant treatment effects of BMS-936558 are a 10% increase in ORR (10% vs. 20%) and 2.5 month increase in OS (8 vs. 10.5 months).

3.0 DISCUSSION

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:

Clinical:

1. Does FDA agree with the proposed overall Phase 3 CA209037 study design summarized on slides 21-25 including:

a) Study population - inclusion/exclusion criteria?

FDA Response: Yes. The key inclusion and exclusion criteria appear acceptable; however, FDA notes that this is not a comprehensive listing. For example, no criteria are provided for acceptable end organ function.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

b) Prospective stratification of subjects based on PD-L1 status?

FDA Response: Yes. The proposal to stratify randomization based on PD-L1 status is acceptable. FDA acknowledges that BMS has partnered with DAKO to develop the companion *in vitro* diagnostic test kit for PD-LI. A pre-Investigational Device Exemption (IDE) meeting will be held with the Center for Devices and Radiological Health (CDRH) on July 27, 2012.

Please be aware that BMS must provide sufficient information in an amendment to the IND supporting the cutoff selected for defining PD-L1 positive/negative status prior to the initiation of the trial. Because limited preliminary data suggest that patients with PD-L1 negative tumors are less likely to benefit from BMS-936558, BMS may also consider a design that allows for early termination of the PD-L1 negative subgroup for futility.

BMS Email Response on 7/16/2012: BMS would like to discuss the cutoff for defining PD-L1 positive/negative status.

Discussion During Meeting on 7/17/2012: BMS stated that they will provide the basis for the cut-off for PD-L1 positivity in their pre-IDE package and in the IDE submission. FDA confirmed acceptability of this proposal.

c) Comparator of investigator's choice (Dacarbazine or carboplatin/paclitaxel)?

FDA Response: Based on currently available therapies for patients with unresectable or metastatic melanoma after disease progression on ipilimumab and/or BRAF inhibitors ($BRAF^{V600E}$ mutation-positive patients only), dacarbazine or paclitaxel+carboplatin are acceptable comparators for the proposed patient population.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

d) Co-primary endpoints of ORR and [OS]?

FDA Response: A trial design using co-primary endpoints of ORR and OS would be acceptable to support accelerated approval of BMS-936558 based upon a final analysis of ORR that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in ORR supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS at the planned interim analysis. However, based on the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant increase in ORR in Trial CA209307 may not be reasonably likely to predict clinical benefit. Confirmatory evidence of clinical benefit based on the final OS analysis, which demonstrates a clinically meaningful improvement in OS, would be sufficient to convert the application from accelerated to regular approval or to support regular approval.

BMS Email Response on 7/16/2012: BMS would like FDA to provide clarification on BMS's perspective on the statistical design with co-primary endpoints, relative to what may be considered clinically relevant for risk/benefit.

Discussion During Meeting on 7/17/2012: BMS acknowledged that this study is powered to detect a relatively small effect on ORR and agreed to meet with FDA to determine whether the results detected would be sufficient to support an accelerated approval.

2. The proposed CA209037 study design evaluates PD-L1 biomarker as a secondary endpoint. Should the totality of the data indicate that the PD-L1 biomarker is predictive, BMS proposes to (b) (4) Does FDA agree?

FDA Response: The meeting briefing document contains an insufficient level of detail in regard to the statistical analysis plan to provide a response to this question. To include information about PD-L1 as a predictive biomarker for BMS-936558 treatment effect in the (b) (4) based on the results of a single trial (CA209037), the trial must provide substantial evidence of effectiveness (demonstrates a statistically robust and clinically important effect on ORR or OS), a positive risk-benefit analysis, and evidence that PD-L1 is a predictive biomarker through demonstration of a statistically significant treatment interaction between PD-L1 status and treatment.

BMS should consider the following in the design and conduct of trial CA209037:

- adequate power to detect treatment effects of BMS-936558 in PD-L1 biomarker negative and positive subgroups
- type I error allocation based on hypothesis testing in multiple subgroups
- completion of analytical validation studies of the PD-L1 *in vitro* diagnostic test kit prior to initiating the trial
- alternate trial designs, including adaptive designs, to demonstrate the prognostic and/or predictive effect of the PD-L1 biomarker

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

3. Does FDA agree that the proposed development plan provides an acceptable basis for evaluation of the benefit-risk balance of BMS-936558 for metastatic unresectable melanoma?

FDA Response: Yes. The proposed development plan using overall survival, a standard endpoint to demonstrate direct clinical benefit, is sufficient to make a risk-benefit determination for full approval.

Please note that a BLA for accelerated approval of BMS-936558 based primarily on the results of study CA209037 would require demonstration of a robust effect on ORR that is of sufficient magnitude and duration to be reasonably likely to predict clinical benefit and permit a positive risk-benefit determination—a determination that may also consider available therapies for the proposed patient population at the time of a marketing application as described in 21 CFR 312.84.

Please also note that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.

Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf
and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

4. Does FDA agree that the proposed CA209037 study design with co-primary endpoints could lead to a potential accelerated approval based on ORR difference and no detriment in OS at interim and full approval if OS is significant at interim or final analysis?

FDA Response: Please see FDA responses to Questions # 1(d) and 3. Please note that based on the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant increase in ORR in Trial CA209307 may not be reasonably likely to predict clinical benefit.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Additional Comments:

Clinical:

5. The clinical experience with BMS-936558 in melanoma as presented in the briefing document appears to be mostly in patients who are naïve to treatment with ipilimumab. Please provide updated clinical information with BMS-936558 in patients with progression of disease during or following ipilimumab therapy to support the targeted 30% ORR in Trial CA209307.

BMS Email Response on 7/16/2012: The requested initial clinical experience information to address FDA comment was provided to the Agency on Friday, July 16, 2012. While we realize these were submitted to the Agency only recently, we would like to take the opportunity to review this information with you during the meeting as it provides relevant information to this second line combination development and planned first line melanoma program.

Discussion During Meeting on 7/17/2012: BMS presented slides (see attachments) and addressed the questions posed by the FDA.

6. FDA recommends collecting germline DNA from patients enrolled in BMS-93655 trials for future pharmacogenomic analysis in the event outliers are identified.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

Clinical Pharmacology:

Regarding the proposed Phase 3 Trial (CA209037), we recommend the following:

7. Evaluate the potential for a pharmacokinetics (PK) interaction between BMS-936558 and dacarbazine or carboplatin/paclitaxel in the combination therapy in the proposed Phase 3 trial or in a separate trial during the development of this combination therapy.

BMS Email Response on 7/16/2012: BMS would clarity that current Phase 3 study CA209037 is being conducted with BMS-936558 versus dacarbazine or carboplatin/paclitaxel. If we consider conducting a combination study with these agents in future, we will consider incorporating these recommendations.

Discussion During Meeting on 7/17/2012: FDA acknowledged BMS' response and had no additional comments.

8. Include electrocardiogram (ECG) monitoring at baseline, around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment in the proposed clinical trial to capture large cardiac safety signals. This ECG monitoring plan should be included in all clinical trials until an adequate evaluation has been conducted to rule out the QT prolongation potential of BMS-936558. Alternative proposals to the 'thorough QT' study including ECG collection with time matched PK sampling may be appropriate to assess BMS-936558 for its QT prolongation potential. Submit a QT evaluation plan for QT-IRT review.

Refer to the Guidance for Industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

9. Assess effect of body size, such as body weight and body surface area, on PK and Pharmacodynamic (PD) of BMS-936558 to determine the optimal dosing approach (i.e., body size-based versus fixed dosing that minimizes interpatient variability) for Phase 3 trials.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

During the development of BMS-936558, we recommend the following:

10. Characterize adequately the single/multiple dose PK and dose proportionality of BMS-936558 in the indicated patient population.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

11. Conduct population PK analyses to evaluate the effect of intrinsic and extrinsic factors on the PK of BMS-936558 in humans.

Refer to Guidance for Industry entitled "Population Pharmacokinetics" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

12. Explore the exposure-response relationships for BMS-936558 for measures of both effectiveness and toxicity.

Refer to Guidance for Industry entitled "Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

13. Develop and validate the analytical method used to determine the concentrations of BMS-936558.

Refer to the Guidance for Industry entitled "Bioanalytical Method Validation" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

14. Conduct an immunogenicity testing based on a plan taking into consideration of the following recommendations:

a) Develop and validate assays that will be used for the detection of anti-product antibodies (APA).

i. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference.
ii. The validated assay should be capable of sensitively detecting APA responses in the presence of BMS-936558 levels that are expected to be present at the time of patient sampling.
iii. An assay should also be developed that is able to delineate neutralizing APA responses.
vi. Store patient samples under appropriate storage conditions until an assay(s) is been developed.

Refer to the Guidance for Industry entitled "Assay Development for Immunogenicity Testing of Therapeutic Proteins" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf.

b) Develop immunogenicity sampling plan that capture the baseline, the early onset of the APA formation and its dynamic profile (transient or persistent) and minimize the interference from the presence of BMS-936558 in the sample.

c) Evaluate the impact of immunogenicity on PK, PD, safety/tolerability and efficacy of BMS-936558.

BMS Email Response on 7/16/2012: BMS acknowledged and agreed with FDA's comment. There was no discussion during the meeting.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Regulatory:

Discussion During Meeting on 7/17/2012: BMS asked whether a programmatic meeting including teams across DOP1 and DOP2 could be held to discuss:

- The potential effects an approval in one indication may have on ongoing trials in other indications including the possibility of alternative efficacy endpoints to support approval such as progression free survival (PSF).
- General issues pertaining to all development programs such as device development or PK studies.

FDA stated that a programmatic meeting could be held, but with regards to the first bullet, such a meeting should be scheduled after the results of the trial intended to support approval are available.

5.0 ATTACHMENTS AND HANDOUTS

- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance
- BMS Slides presented during meeting
- Meeting Participant List

41 page(s) have been withheld for DOP2 Guidance & BMS slides & Meeting Participant List. Refer to http://www.cdisc.org/fda-guidance-on-standardized-study-data-& http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm271326.htm

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEREDITH LIBEG
08/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: July 16, 2012

From: Meredith Libeg; Regulatory Health Project Manager, DOP2/OHOP/OND/CDER/FDA

Subject: Draft Responses and Comments for Bristol-Myers Squibb IND 115195 Type B; EOP2 Meeting on July 17, 2012

Meeting Type:	Type B – Face-to-Face
Meeting Category:	End-of-Phase 1 (EOP1)/Pre-Phase 3
Meeting Date and Time:	Tuesday, July 17, 2012; 10:00 to 11:00 AM (ET)
Meeting Location:	White Oak Building 22; Room 1311
IND Number:	IND 115195
Product Name:	BMS-936558
Received Briefing Package:	June 18, 2012; desk copies July 3, 2012
Sponsor Name:	Bristol-Myers Squibb
Meeting Requestor:	Kinnari Patel Associate Director; Global Regulatory Sciences, US-Oncology
Meeting Chair:	Marc Theoret, M.D.
Meeting Recorder:	Meredith Libeg

TENTATIVE LIST OF FDA ATTENDEES:

Office of New Drugs
Office of Hematology and Oncology Products
Division of Oncology Products 2

Patricia Keegan, M.D.	Division Director
Joseph Gootenberg, M.D.	Deputy Division Director/Clinical Team Leader
Marc Theoret, M.D.	Clinical Reviewer
Karen Jones	Chief Project Management Staff
Monica Hughes	Senior Regulatory Health Project Manager
Norma Griffin	Regulatory Health Project Manager
Meredith Libeg	Regulatory Health Project Manager

Office of New Drugs
Office of Hematology and Oncology Products

Anthony Murgo	Associate Director of Regulatory Science

Office of New Drugs
Office of Drug Evaluation I

Robert Temple	Deputy Director

Office of Hematology and Oncology Products
Division of Hematology, Oncology, and Toxicology

Whitney Helms	Pharmacology / Toxicology Team Leader
Andrew McDougal	Pharmacology / Toxicology Reviewer

Office of Biotechnology Products
Division of Monoclonal Antibodies

Barbara Rellahan	Product Quality Team Leader
Laurie Graham	Product Quality Reviewer

Office of Translational Sciences
Office of Clinical Pharmacology

Rosane Charlab Orbach, Ph.D.	Genomics, Acting Team Leader
Christian Grimstein, Ph.D	Genomics Reviewer

Office of Translational Sciences
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader
Jun Yang	Clinical Pharmacology Reviewer

Office of Translational Sciences
Office of Biostatistics

Kun He	Biostatistical Team Leader
Yuan Li Shen	Biostatistical Reviewer

Office of In Vitro Diagnostic Device Evaluation and Safety
Office of the Director

Robert Becker	Chief Medical Officer
Elizabeth Mansfield	Director, Personalized Medicine Staff

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Immunology and Hematology Devices

Maria Chan	Division Director
Reena Philip	Deputy Division Director
Yun-Fu Hu	Associate Director for Immunology
Caryl Giuliano	Immunology and Hematology Devices Reviewer

TENTATIVE LIST OF SPONSOR ATTENDEES:

Renzo Canetta, M.D.	Vice President, Oncology Global Clinical Research
David Feltquate, M.D., Ph.D.	Group Director, Global Clinical Research
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences
Michael Giordano, M.D.	Senior Vice President, Head of Development, Oncology & Immunology
Christine Horak, Ph.D.	Senior Research Investigator II, Clinical Biomarkers - Oncology, DMCP
Joseph Lamendola, Ph.D.	Vice President, U.S. Regulatory Sciences and Regulatory Relations & Policy
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, M.D.	Vice President, Development Lead
Kinnari Patel, Pharm.D.	Associate Director, U.S. Regulatory Sciences

Background:

On June 18, 2012, Bristol-Myers Squibb (BMS) requested a Type A EOP2 meeting for BMS-936558. Included in this meeting request was the meeting package; however, the meeting was granted as a Type B EOP2 meeting. The desk copies of the meeting package were received on July 3, 2012.

BMS-936558 is an anti-Programmed Cell Death-1 (PD-1) monoclonal antibody administrated as an intravenous (IV) infusion. The proposed indication is for the treatment of melanoma.

On June 15, 2012, BMS filed a new administrative split Investigational New Drug Application (IND) from IND 100052. BMS-936558 is in development under the following five active INDs:

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Key inclusion criteria includes: histological confirmation of Stage III (unresectable) or Stage IV melanoma; 18 years of age or older; Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 1; measurable disease at baseline by CT or MRI as per RECIST 1.1 criteria; pre-treatment fresh core or excision tumor biopsy must be provided for biomarker analyses. Subjects must consent to allow the acquisition of existing formalin-fixed paraffin-

embedded (FFPE) material (block or a minimum of 10 unstained slides); have experienced RECIST 1.1 defined progression of disease (PD) during or after one and at most two prior treatment regimens for advanced melanoma; BRAF V600 wildtype patients must have PD during or following anti-CTLA-4 therapy; and BRAF V600 mutation-positive patients must have PD during or following anti-CTLA-4 and BRAF inhibitor therapy (irrespective of sequence).

Key exclusion criteria includes: active brain metastasis or leptomeningeal metastasis; primary ocular melanoma; prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel. Prior systemic therapy with one of the treatments is permitted; have active, known or suspected autoimmune disease; have a known history of select anti-CTLA-4 therapy related adverse reactions based on the CTCAE v4.0 criteria; and have received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2, (or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways except for anti-CTLA-4 therapy as described in the exclusion criterion).

BMS proposes co-primary endpoints of Objective Response Rate (ORR) and Overall Survival (OS). Proposed secondary endpoints include: evaluation of OS of BMS-936558 and dacarbazine or carboplatin/paclitaxel by PD-L1 expression; comparison of the PFS of BMS-936558 to dacarbazine or carboplatin/paclitaxel; evaluation of duration and time to objective response in BMS-936558 and dacarbazine or carboplatin/paclitaxel; and evaluation of Health Related Quality of Life (HRQoL) between treatment groups as assessed by European Organization for Research and Treatment of Care (EORTC) QLQ-C30.

A sample size of 354 patients would provide ≥ 90% power with a two-sided type I error of 0.01 to detect an increase in the ORR from 10% in the chemotherapy arm to 30% in the BMS-936558 arm. At the time of the final OS analysis, 260 death events would provide ≥ 90% power with an overall two-sided type I error of 0.04 to detect an improvement in median OS from 8 months in the chemotherapy arm to 12.3 months in the BMS-936558 arm [hazard ratio (HR) of 0.65].

BMS plans to perform one interim OS analysis (for efficacy) at the time of the ORR analysis which is projected to occur after occurrence of approximately 195 (75%) death events. BMS proposes use of the O'Brien Fleming boundary method to allocate an alpha of 0.0145 to the interim OS analysis and an alpha of 0.0357 to the final OS analysis.

BMS proposes that superiority in either endpoint will support the submission of a BLA for BMS-936558. Registration of BMS-936558 based on the ORR endpoint requires statistically significant ORR improvement and no evidence of detriment in OS as demonstrated in the interim OS analysis resulting in a HR point estimate of < 0.9. According to the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant treatment effects of BMS-936558 are a 10% increase in ORR (10% vs. 20%) and 2.5 month increase in OS (8 vs. 10.5 months).

Meeting Purpose: The purpose of the meeting is for BMS to provide the preliminary data from the ongoing Phase 1 study CA209003 and obtain FDA input on the proposed clinical development plan for second-line metastatic melanoma. In addition, BMS would like to discuss the potential for accelerated approval regulatory pathway for metastatic melanoma.

Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Tuesday, July 17, 2012, between BMS and the Division of Oncology Products 2. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

At the end of the meeting, key discussion points, agreements, clarifications, and action items will be summarized. We request that you take the responsibility for summarizing what you have heard at the meeting. This will help ensure that there is mutual understanding of the advice given and meeting outcomes and actions.

These draft comments were sent to BMS on July 16, 2012.

Sponsor Submitted Questions and FDA Response:

Clinical:

1. Does FDA agree with the proposed overall Phase 3 CA209037 study design summarized on slides 21-25 including:

a) Study population - inclusion/exclusion criteria?

FDA Response: Yes. The key inclusion and exclusion criteria appear acceptable; however, FDA notes that this is not a comprehensive listing. For example, no criteria are provided for acceptable end organ function.

b) Prospective stratification of subjects based on PD-L1 status?

FDA Response: Yes. The proposal to stratify randomization based on PD-L1 status is acceptable. FDA acknowledges that BMS has partnered with DAKO to develop the companion *in vitro* diagnostic test kit for PD-LI. A pre-Investigational Device Exemption (IDE) meeting will be held with the Center for Devices and Radiological Health (CDRH) on July 27, 2012.

Please be aware that BMS must provide sufficient information in an amendment to the IND supporting the cutoff selected for defining PD-L1 positive/negative status prior to the initiation of the trial. FDA has not completed its review of the pre-IDE meeting package. Because limited preliminary data suggest that patients with PD-L1 negative tumors are less likely to benefit from BMS-936558, BMS may also consider a design that allows for early termination of the PD-L1 negative subgroup for futility.

c) Comparator of investigator's choice (Dacarbazine or carboplatin/paclitaxel)?

FDA Response: Based on currently available therapies for patients with unresectable or metastatic melanoma after disease progression on ipilimumab and/or BRAF inhibitors ($BRAF^{V600E}$ mutation-positive patients only), dacarbazine or paclitaxel+carboplatin are acceptable comparators for the proposed patient population.

d) Co-primary endpoints of ORR and [OS]?

FDA Response: A trial design using co-primary endpoints of ORR and OS would be acceptable to support accelerated approval of BMS-936558 based upon a final analysis of ORR that demonstrates an effect that is reasonably likely to predict clinical benefit—i.e., a substantial improvement in ORR supported by clinically meaningful response durations in the absence of evidence for a detrimental effect on OS at the planned interim analysis. However, based on the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant increase in ORR in Trial CA209307 may not be reasonably likely to predict clinical benefit. Confirmatory evidence of clinical benefit based on the final OS analysis, which demonstrates a clinically meaningful improvement in OS, would be sufficient to convert the application from accelerated to regular approval or to support regular approval.

**2. The proposed CA209037 study design evaluates PD-L1 biomarker as a secondary endpoint. Should the totality of the data indicate that the PD-L1 biomarker is predictive, BMS proposes to (b) (4)
Does FDA agree?**

FDA Response: The meeting briefing document contains an insufficient level of detail in regard to the statistical analysis plan to provide a response to this question. To include information about PD-L1 as a predictive biomarker for BMS-936558 treatment effect in the (b) (4) based on the results of a single trial (CA209037), the trial must provide substantial evidence of effectiveness (demonstrates a statistically robust and clinically important effect on ORR or OS), a positive risk-benefit analysis, and evidence that PD-L1 is a predictive biomarker through demonstration of a statistically significant treatment interaction between PD-L1 status and treatment.

BMS should consider the following in the design and conduct of trial CA209037:

- adequate power to detect treatment effects of BMS-936558 in PD-L1 biomarker negative and positive subgroups
- type I error allocation based on hypothesis testing in multiple subgroups
- completion of analytical validation studies of the PD-L1 *in vitro* diagnostic test kit prior to initiating the trial
- alternate trial designs, including adaptive designs, to demonstrate the prognostic and/or predictive effect of the PD-L1 biomarker

3. Does FDA agree that the proposed development plan provides an acceptable basis for evaluation of the benefit-risk balance of BMS-936558 for metastatic unresectable melanoma?

FDA Response: Yes. The proposed development plan using overall survival, a standard endpoint to demonstrate direct clinical benefit, is sufficient to make a risk-benefit determination for full approval.

Please note that a BLA for accelerated approval of BMS-936558 based primarily on the results of study CA209037 would require demonstration of a robust effect on ORR that is of sufficient magnitude and duration to be reasonably likely to predict clinical benefit and permit a positive risk-benefit determination—a determination that may also consider available therapies for the proposed patient population at the time of a marketing application as described in 21 CFR 312.84.

Please also note that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf
and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

4. Does FDA agree that the proposed CA209037 study design with co-primary endpoints could lead to a potential accelerated approval based on ORR difference and no detriment in OS at interim and full approval if OS is significant at interim or final analysis?

FDA Response: Please see FDA responses to Questions # 1(d) and 3. Please note that based on the statistical assumptions provided in the briefing document, the minimally detectable, statistically significant increase in ORR in Trial CA209307 may not be reasonably likely to predict clinical benefit.

Additional Comments:

Clinical:

5. The clinical experience with BMS-936558 in melanoma as presented in the briefing document appears to be mostly in patients who are naïve to treatment with ipilimumab. Please provide updated clinical information with BMS-936558 in patients with progression of disease during or following ipilimumab therapy to support the targeted 30% ORR in Trial CA209307.

6. FDA recommends collecting germline DNA from patients enrolled in BMS-93655 trials for future pharmacogenomic analysis in the event outliers are identified.

Clinical Pharmacology:

Regarding the proposed Phase 3 Trial (CA209037), we recommend the following:

7. Evaluate the potential for a pharmacokinetics (PK) interaction between BMS-936558 and dacarbazine or carboplatin/paclitaxel in the combination therapy in the proposed Phase 3 trial or in a separate trial during the development of this combination therapy.

8. Include electrocardiogram (ECG) monitoring at baseline, around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment in the proposed clinical trial to capture large cardiac safety signals. This ECG monitoring plan should be included in all clinical trials until an adequate evaluation has been conducted to rule out the QT prolongation potential of BMS-936558. Alternative proposals to the 'thorough QT' study including ECG collection with time matched PK sampling may be appropriate to assess BMS-936558 for its QT prolongation potential. Submit a QT evaluation plan for QT-IRT review.

Refer to the Guidance for Industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

9. Assess effect of body size, such as body weight and body surface area, on PK and Pharmacodynamic (PD) of BMS-936558 to determine the optimal dosing approach (i.e., body size-based versus fixed dosing that minimizes interpatient variability) for Phase 3 trials.

During the development of BMS-936558, we recommend the following:

10. Characterize adequately the single/multiple dose PK and dose proportionality of BMS-936558 in the indicated patient population.

11. Conduct population PK analyses to evaluate the effect of intrinsic and extrinsic factors on the PK of BMS-936558 in humans.

Refer to Guidance for Industry entitled "Population Pharmacokinetics" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf.

12. Explore the exposure-response relationships for BMS-936558 for measures of both effectiveness and toxicity.

Refer to Guidance for Industry entitled "Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

13. Develop and validate the analytical method used to determine the concentrations of BMS-936558.

Refer to the Guidance for Industry entitled "Bioanalytical Method Validation" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf.

14. Conduct an immunogenicity testing based on a plan taking into consideration of the following recommendations:

a. Develop and validate assays that will be used for the detection of anti-product antibodies (APA).

   i. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference.
   ii. The validated assay should be capable of sensitively detecting APA responses in the presence of BMS-936558 levels that are expected to be present at the time of patient sampling.
   iii. An assay should also be developed that is able to delineate neutralizing APA responses.
   vi. Store patient samples under appropriate storage conditions until an assay(s) is been developed.

   Refer to the Guidance for Industry entitled "Assay Development for Immunogenicity Testing of Therapeutic Proteins" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf.

b. Develop immunogenicity sampling plan that capture the baseline, the early onset of the APA formation and its dynamic profile (transient or persistent) and minimize the interference from the presence of BMS-936558 in the sample.

c. Evaluate the impact of immunogenicity on PK, PD, safety/tolerability and efficacy of BMS-936558.

ATTACHMENTS:

- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance

32 page(s) have been withheld for DOP2 Guidance . Refer to http://www.cdisc.org/fda-guidance-on-standardized-study-data & http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm271326.htm

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/s/

MEREDITH LIBEG
07/16/2012

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554

LATE-CYCLE MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351 of the Public Health Service Act for Opdivo (nivolumab) Injection for Intravenous Infusion.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 12, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time:	Friday, December 12, 2014; 10:00 AM – 11:00 AM (ET)
Meeting Location:	10903 New Hampshire Avenue (Teleconference)
Application Number:	BLA 125554
Product Name:	Proposed name: Opdivo (nivolumab) Injection for Intravenous Infusion
Applicant Name:	Bristol-Myers Squibb Company
Meeting Chair:	Marc Theoret, M.D.
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Richard Pazdur, M.D.	Director, OHOP
Patricia Keegan, M.D.	Director, DOP2
Marc Theoret, M.D.	Clinical Team Leader, DOP2
Maitreyee Hazarika, M.D.	Medical Officer, DOP2
Sirisha Mushti, Ph.D.	Biometrics Reviewer, OBV
Xianhua Cao, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Liang Zhao, Ph.D.	Pharmacometrics Team leader, DCPV
Hongshan Li, Ph.D.	Pharmacometrics Reviewer, DCPV
Laurie Graham, M.S.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, DMA
Joel Welch, Ph.D.	CMC Reviewer, DMA
Patricia Hughes, Ph.D.	Team Leader, Biotechnology Manufacturing Assessment Branch (BMAB)
Bo Chi, Ph.D.	Drug Substance Reviewer, BMAB
Steven Fong, Ph.D.	Drug Product Reviewer, BMAB
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Carolyn Yancey, M.D.	Medical Officer, OSE, DRISK
Miriam Dinatale, D.O.	Medical Officer, Maternal Health
Sharon Mills, B.S.N., R.N., C.C.R.P.	Patient Labeling Reviewer, DMMP
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)	Independent Assessor

APPLICANT ATTENDEES

Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Kathleen O'Donnell	Director U.S. Regulatory Sciences - Oncology

Randall H. White, Ph.D.	Director, Project Management
Arvin Yang, MD, Ph.D.	Director, Global Clinical Research
Alexandre Lambert, Ph.D.	Principal Biostatistician, Global Biometric Sciences
Ian Waxman, M.D.	Director, Global Clinical Research - Oncology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology
Pradip Ghosh-Dastidar	Associate Director, Global Regulatory Sciences, CMC
Annie Sturgess	Executive Director, Global Regulatory Sciences, CMC
Mark Rosolowsky	Vice President, Global Regulatory Sciences, CMC
MaryBeth Frosco	Director, Global Regulatory Sciences
Michael Giordano, M.D.	Sr. Vice President, Head of Development, Oncology & Immunology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory and Safety Sciences
Susan Martindale	Associate Director, Global Labeling Operations
Manish Gupta	Director, Clinical Pharmacology & Pharmacometrics

1.0 BACKGROUND

- BLA 125554/0 was submitted on July 30, 2014 for Opdivo (nivolumab) Injection for Intravenous Infusion.
- Proposed indication(s): For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status
- PDUFA goal date: March 30, 2015
- FDA issued a Background Package in preparation for this meeting on December 12, 2014.

2.0 DISCUSSION

LCM AGENDA

1. Introductory Comments:
   - Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues:
   - Determination of final labeling

     Discussion During Meeting of 12/12/14: FDA apprised BMS that the proposed package insert is currently being revised internally based on the additional clinical information provided by BMS via electronic (email) communication in response to the December 2, 2014, teleconference. FDA is targeting to provide a revised proposed package insert to BMS either today, Friday, December 12, 2014, or over

the weekend (December 13 or 14, 2014), and will be requesting a quick turnaround for BMS' proposed edits. Furthermore, FDA proposed to hold a meeting (teleconference) with BMS on Monday, December 15, 2014, in order to reach agreement on sections of the package insert and to discuss BMS' responses and counterproposals, if any. BMS acknowledged FDA's statement and agreed to provide a quick turnaround on the proposed package insert and to the proposed meeting on December 15, 2014.

BMS questioned if following the proposed December 15, 2014 labeling meeting it would be acceptable to begin the printing process for the labels. FDA stated any printing performed by BMS prior to an official action on the pending application is at BMS' risk. BMS acknowledged and agreed that it would be at their own risk.

- Obtaining result of inspection of imaging CRO

  Discussion During Meeting of 12/12/14: FDA informed BMS that the inspection of the imaging CRO has been completed. BMS acknowledged FDA's statement and no further discussion occurred during the meeting.

3. Additional Applicant Data

- Timing of submission of launch materials including risk management materials

  Discussion During Meeting of 12/12/14: FDA queried if the launch materials has been formally submitted to the Office of Professional Drug Promotion (OPDP). BMS stated the materials will be submitted in the very near future, but timing will be dependent on the finalization of the package insert. BMS continued by asking if FDA could comment on the timing of the review of the materials once submitted to OPDP, specifically the timing of the press release. FDA noted that no one was in attendance from OPDP at the meeting; therefore, the team will provide a sponsor following the meeting. BMS acknowledged FDA's responses and no further discussion occurred during the meeting.

4. Information Requests

- Clinical information to support labeling

  Discussion During Meeting of 12/12/14: See Discussion During Meeting under Item 2 above (Discussion of Substantive Review Issues).

5. Discussion of Upcoming Advisory Committee Meeting

Discussion During Meeting of 12/12/14: BMS acknowledged FDA's statement in the Late Cycle Package that an Advisory Committee is not planned for this BLA. There was no discussion during the meeting.

6. REMS or Other Risk Management Actions

Discussion During Meeting of 12/12/14: BMS acknowledged FDA's statement in the Late Cycle Package. There was no discussion during the meeting.

7. Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC)

Discussion During Meeting of 12/12/14: FDA thanked BMS for their responses to the proposed PMR and PMCs relating to the pending BLA application; however, FDA proposed that BMS change the proposed final report submission milestone for the accelerated approval (subpart E) PMR to reflect the timing of the overall survival (OS) results of the CA209037 Study in order to provide flexibility in fulfilling the requirement. Additionally, FDA stated that if BMS elects to submit the CA209066 Study as the confirmatory study to fulfill the requirement as proposed, and if FDA agrees this study fulfills the PMR, FDA would require as a PMC the final OS results for the CA209037 Study. BMS acknowledged FDA's response and agreed to these proposals. Furthermore, BMS stated the final report submission milestone for the CA209037 Study is December 2016.

8. Major Labeling Issues

Discussion During Meeting of 12/12/14: See Discussion During Meeting under Item 2 above (Discussion of Substantive Review Issues).

9. Review Plans

Discussion During Meeting of 12/12/14: FDA informed BMS that aspects of the review of the pending BLA application are still under review and will continue. There was no further discussion at the meeting.

On December 10, 2014, the FDA Chemistry, Manufacturing, and Controls (CMC) Team issued review comments and information request to BMS on the pending original BLA application relating to establishment and qualification of a new working cell bank. In response to that request for information, BMS asked for clarification on December 11, 2014, via email communication, and if it would be acceptable to provide information on the new working cell bank now without impacting the overall review of

the pending original BLA application. During the meeting, FDA provided preliminary advice that BMS should not submit the new working cell bank information to the pending BLA as FDA will not review nor approve this information during the current review clock. Instead, BMS should submit this information as Prior Approval Supplement. FDA stated a formal response to BMS' December 11, 2014 request for clarification will be communicated to BMS.

10. Wrap-up and Action Items

- FDA to provide revised package insert to BMS and schedule a meeting to discuss.
- FDA to follow-up with OPDP on the timing of review for the press release once submitted by BMS.
- FDA to provide the official response to BMS' CMC December 11, 2014, request for clarification.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

MEREDITH LIBEG
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA

LATE CYCLE MEETING
BACKGROUND PACKAGE

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) dated July 30, 2014, received July 30, 2014, submitted under section 351 of the Public Health Service Act for Opdivo (nivolumab) Injection for Intravenous Infusion.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 12, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	Friday, December 12, 2014; 10:00 AM – 11:00 AM (ET)
Meeting Location:	10903 New Hampshire Avenue (Teleconference)
Application Number:	BLA 125554
Product Name:	Proposed name: Opdivo (nivolumab) Injection for Intravenous Infusion
Indication:	For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status
Sponsor/Applicant Name:	Bristol-Myers Squibb Company

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- Determination of final labeling
- Obtaining result of inspection of imaging CRO

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
   - Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 5 minutes
   - Each issue as noted above will be introduced by FDA and followed by a discussion.

3. Additional Applicant Data – 5 minutes (Applicant)
   - Timing of submission of launch materials including risk management materials

4. Information Requests – 5 minutes
   - Clinical information to support labeling

5. Major labeling issues – 30 minutes

6. Review Plans – 5 minutes

7. Wrap-up and Action Items – 5 minutes

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/s/

MEREDITH LIBEG
12/12/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125554	NDA Supplement # BLA Supplement # N/A	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Opdivo Injection for Intravenous Infusion Established/Proper Name: Nivolumab Dosage Form: Injection for Intravenous Infusion		Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):
RPM: Meredith Libeg		Division: DOP2

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is March 30, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ Received Journal Article and Press Release received as of 12/18/14 by OPDP
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other - ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 12/22/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included BMS Proposed: 10/17/14 Original BMS Proposed: 7/30/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (Attached to Package Insert)
• Original applicant-proposed labeling	☒ Included (Attached to Package Insert)
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter: 10/29/14 Final Review: 10/24/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 9/19/14 DMEPA: ☐ None 10/22/14 DMPP/PLT (DRISK): ☐ None 12/16/14 OPDP: ☐ None 12/16/14 SEALD: ☐ None 10/9/14 CSS: ☒ None Other: ☐ None Maternal Health: 12/12/14 OBP: 11/20/14
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	9/26/14 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: ***Orphan designation granted***	***Orphan designation granted***
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Labeling T-Con 7: 12/22/14 (Uploaded 1/6/15) Labeling 6: 12/19/14 Labeling T-Con 6: 12/19/14 (Uploaded 1/6/15) CMC IR: 12/19/14 Labeling 5: 12/18/14 Labeling T-Con 5: 12/17/14 (Uploaded 1/6/15) Labeling 4: 12/16/14 Labeling T-Con 4: 12/15/14 (Uploaded 1/6/15) Labeling 3: 12/14/14 Labeling T-Con 3: 12/12/14 (Uploaded 1/6/15) CMC IR: 12/9/14 Labeling Nonclinical IR: 12/9/14 Clinical IR: 12/9/14 Clinical IR: 12/8/14 Labeling 2: 12/8/14 Labeling T-Con 2: 12/5/14 (Uploaded 12/18/14) PMR/PMC Doc: 12/5/14 Clinical IR: 12/5/14 CMC IR: 12/5/14 Clinical IR: 12/4/14 Labeling 1: 12/3/14 Clinical IR: 12/3/14 CMC IR: 12/3/14 T-Con Memo:12/3/14 Labeling T-Con 1: 12/3/14 (Uploaded 12/18/14) Clinical IR: 12/2/14 Clinical IR: 12/2/14 Clinical IR: 12/1/14 Clinical IR: 11/29/14 Clinical IR: 11/26/14 Clinical IR: 11/26/14 CMC IR: 11/25/14 CMC IR: 11/21/14 CMC IR: 11/20/14 Clinical IR: 11/20/14 Clinical IR: 11/18/14 DRISK IR: 11/13/14 Clinical IR: 11/12/14

	CMC IR: 11/7/14 Clinical IR: 11/7/14 CMC IR: 11/6/14 Stats IR: 11/4/14 Clinical IR: 11/3/14 Clinical IR: 10/31/14 Labeling/CMC IR: 10/28/14 CMC IR: 10/28/14 T-Con Memo:10/1/14 Clin Pharm IR: 10/7/14 NC IR: 10/3/14 Clin Pharm IR: 10/1/14 **Filing Letter: 9/26/14** Safety IR: 9/25/14 QT-IRT IR: 9/25/14 QT-IRT IR: 9/24/14 Clinical IR: 9/17/14 T-Con Memo: 9/15/14 T-Con Memo: 9/15/14 T-Con Memo: 9/12/14 **AOM Letter: 9/9/14** OSI IR: 9/9/14 T-Con Memo: 8/27/14 **Ack Letter: 8/12/14**
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Clinical IR MTF: 12/8/14 Clinical IR MTF: 12/3/14 Clinical IR MTF: 12/3/14 CMC IR MTF: 12/3/14 Clinical IR MTF: 11/5/14 Planning MTF: 8/25/14 (uploaded 9/24/14)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/9/14
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12/6/12
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 11/3/14
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A Late Cycle Minutes: 12/12/14 Late Cycle Package: 12/12/14
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	IND 115195 AI Letter: 3/17/14 IND 115195 AI Letter: 1/16/14 IND 115195 AI Letter: 3/27/13 EOP1/Pre-Phase 3 Mtg: 7/17/12

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None Final Review: 12/21/14
Division Director Summary Review *(indicate date for each review)*	☐ None Final Review: 12/19/14 Designation MTF: 9/11/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Final review: 12/22/14
PMR/PMC Development Templates *(indicate total number)*	☐ None PMR (Clinical): 12/12/14 PMC (CMC): 12/15/14 PMC (CMC - Micro): 12/19/14
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Final Review (Addendum): Concurred: 12/22/14 Final Review: Concurred - See Clinical review: 12/7/14
• Clinical review(s) *(indicate date for each review)*	Final Review (Addendum):

	12/20/14 Final Review: 12/7/14 Filing Review: 9/22/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Final review: See Clinical Review: 12/7/14 (Page 146 to 149)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT-IRT Final Review: 10/20/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☐ None TL Concurred: 12/5/14 Final review: 12/4/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Final review: 12/11/14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review Final Review: Concurred - See Stats review: 12/5/14
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Final Review: Concurred - See Stats review: 12/5/14
Statistical Review(s) *(indicate date for each review)*	☐ None Final review: 12/5/14 Filing Review: 9/11/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Final Review: Concurred - See Clin Pharm review: 12/5/14
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Final review: 12/5/14 Filing Review: 9/19/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review Final Review: 12/4/14
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review Final Review: 12/4/14
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Final review: 12/4/14 Filing Review: 9/11/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review Final Review: Concurred – See OBP executive review 12/12/14
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review Final Review: 12/12/14
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Final review: 12/5/14 Filing Review: 9/22/14
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Drug Product review: 12/5/14 Drug Substance review: 12/5/14 Final Review DMF review: 12/4/14 Filing Review: 9/10/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Quality Review 12/5/14 (See Section entitled, "Summary of Quality Assessments")
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done