

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761041Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

NDA/BLA#: BLA 761041 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Division of Oncology PDUFA Goal Date: 10/19/16 Stamp Date: 2/19/2016
Products 1 (DOP1)

Proprietary Name: Tecentrig

Established/Generic Name: atezolizumab

Dosage Form: Liquid Single-Use Vial, 1200 mg/20mL (60 mg/mL)

Applicant/Sponsor: Genentech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) N/A
(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): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Non-Small Cell Lung Cancer (NSCLC)

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 ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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).

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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)

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 ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	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?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAKAR M WAHBY
03/30/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 761041	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Tecentriq [®] Established/Proper Name: atezolizumab Dosage Form: Injection		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Sakar Wahby, PharmD		Division: Division of Oncology Products 1 (DOP1)
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 19, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> Received
❖ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)**

- 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 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> 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 <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 10/18/2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 2/19/2016
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 2/19/2016
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 7/8/2016
❖ Proprietary Name	Acceptability letter issued 3/8/2016 Review dated 3/4/2016
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 3/22/16 DMEPA: <input checked="" type="checkbox"/> Review 6/23/2016; Memo 7/15/2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 10/4/2016 (DMPP); 9/28/2016 (DRISK) OPDP: <input checked="" type="checkbox"/> 10/5/2016 SEALD: <input type="checkbox"/> None N/A CSS: <input type="checkbox"/> None N/A Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Filing Review 3/25/2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>4/20/2016</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Granted: 1/28/2015
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	1/13/2015
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	N/A
❖ 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, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	3/30/2016; 4/28/2016(2); 5/6/2016(2); 6/27/2016; 6/28/2016; 6/30/2016; 7/6/2016; 7/7/2016(2); 7/8/2016; 7/11/2016; 7/12/2016; 8/4/2016; 8/5/2016; 8/26/2016; 8/29/2016; 9/8/2016; 9/9/2016; 9/19/2016; 9/20/2016; 9/21/2016; 9/27/2016; 9/28/2016; 9/29/2016; 10/3/2016; 10/4/2016; 10/5/2016
❖ 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)	4/8/2016
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	Pre-BLA meeting 11/10/2015
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	EOP2 meeting 10/22/2013
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 7/21/2016
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/17/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/12/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 10/13/2016
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	6/9/2016 10/14/2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review dated 10/14/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 9/28/2016
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 9/30/2016 7/29/2016 7/25/2016
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	9/28/2016; 4/8/2016

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	9/28/2016; 4/5/2016
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Filing review 3/21/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done <i>N/A</i>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, October 07, 2016 10:51 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI
Attachments: 10-7-16 Tecentriq FDA revised PI.docx

Importance: High

Dear Nitzan,

In reference to BLA 761041, please see attached the FDA revised label, please submit WORD and PDF copy of your Final Agreed Upon Label **by COB, Monday, October 10, 2016.**

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Nitzan Sternheim [<mailto:sternheim.nitzan@gene.com>]
Sent: Thursday, October 06, 2016 11:59 PM
To: Wahby, Sakar
Cc: Nitzan Sternheim
Subject: Re: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI with FDA Revisions

Dear Sakar,

Per our separate email conversation, please find attached Genentech's revisions to Section 5.6 in the attached USPI and a document detailing our rationale for the changes. These documents were submitted to BLA 761041 earlier today.

Best regards,
Nitzan

On Wed, Oct 5, 2016 at 11:36 AM, Nitzan Sternheim <nitzans@gene.com> wrote:
Dear Sakar,

I confirm receipt of your email.

Best regards,

Nitzan

On Wed, Oct 5, 2016 at 11:05 AM, Wahby, Sakar <Sakar.Wahby@fda.hhs.gov> wrote:

Dear Nitzan,

Please see the attached MS Word document of Genentech's USPI for Tecentriq (atezolizumab) for BLA 761041, with FDA comments and revisions. Please submit WORD and PDF copy of your Final Agreed Upon Label

by COB, Thursday, October 6, 2016. Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): [240-402-5364](tel:240-402-5364)

(F): [301-796-9845](tel:301-796-9845)

--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Mobile (b) (6) | Fax [\(650\) 467-1844](tel:650-467-1844) | sternheim.nitzan@gene.com

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Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Mobile [REDACTED]^{(b) (6)} | Fax (650) 467-1844 | sternheim.nitzan@gene.com

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/s/

SAKAR M WAHBY
10/07/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, October 05, 2016 2:36 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/PMR/PMC

Importance: High

Dear Nitzan,

In reference to your response to FDA draft PMR and PMC for BLA 761041 dated October 5, 2016, and in reference to your request for FDA input regarding your interpretation of FDA requested analyses in PMR 1, please find the Agency's response below:

FDA Response:

PMR: The FDA concur with your interpretation of the FDA requested analyses described in PMR 1; (GNE interpretation submitted to BLA 761041 on October 5, 2016).

PMC: The FDA finds your edits to PMC description acceptable.

Please contact me if you have any questions, and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Nitzan Sternheim [<mailto:sternheim.nitzan@gene.com>]
Sent: Wednesday, October 05, 2016 11:29 AM
To: Wahby, Sakar
Cc: Nitzan Sternheim
Subject: Re: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/PMR/PMC

Dear Sakar,

Please find attached Genentech's response to FDA's draft PMR and PMC. It will be formally submitted to BLA 761041 later today.

Best regards,

Nitzan

On Thu, Sep 29, 2016 at 11:36 AM, Nitzan Sternheim <nitzans@gene.com> wrote:
Dear Sakar,

I confirm receipt of your email, and will provide our response per your request.

Best regards,
Nitzan

On Thu, Sep 29, 2016 at 10:34 AM, Wahby, Sakar <Sakar.Wahby@fda.hhs.gov> wrote:

Dear Nitzan,

In reference to BLA 761041, please find below the current text for PMR and PMC implementation:

1) Text for a PMR that we will be requiring. This is being shared as a courtesy only. Please provide feedback on the feasibility of the completion date only.

PMR Description: Conduct a randomized trial that will characterize the incidence, severity and response to treatment of Tecentriq™ induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

PMR Schedule Milestones: Final Report Submission: 03/2017

2) Current text for a PMC:

PMC Description: Submit the final report and datasets for clinical trial entitled “A Phase III, Multicenter, Randomized Study of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy” [OAK (GO28915)].

PMC Schedule Milestones: Final Report Submission: 03/2017

Please respond with your commitment to conduct this PMC. If you make any changes, please use track changes. Your response needs to be in the following format:

“We commit to submit the final report and datasets for clinical trial entitled “A Phase III, Multicenter, Randomized Study of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy” [OAK (GO28915)] by March, 2017”

Please provide your responses **by 12:00 pm EST., Wednesday, October 5, 2016.** Please provide by 1) email to facilitate review 2) formal submission to the BLA .

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): [240-402-5364](tel:240-402-5364)

(F): [301-796-9845](tel:301-796-9845)

--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Mobile [REDACTED] ^{(b) (6)} | Fax (650) 467-1844 | sternheim.nitzan@gene.com

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--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Mobile [REDACTED] ^{(b) (6)} | Fax (650) 467-1844 | sternheim.nitzan@gene.com

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/s/

SAKAR M WAHBY
10/05/2016

From: Wahby, Sakar
To: ["Nitzan Sternheim"](#)
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI with FDA Revisions
Date: Wednesday, October 05, 2016 2:05:00 PM
Attachments: [10-5-16 Tecentriq FDA revised PI.docx](#)
Importance: High

Dear Nitzan,

Please see the attached MS Word document of Genentech's USPI for Tecentriq (atezolizumab) for BLA 761041, with FDA comments and revisions. Please submit WORD and PDF copy of your Final Agreed Upon Label

by COB, Thursday, October 6, 2016. Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

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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/

SAKAR M WAHBY
10/05/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, October 04, 2016 5:06 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/Med Guide with FDA Revisions
Attachments: 10-4-16 Tecentriq FDA revised Medication Guide.doc
Importance: High

Dear Nitzan,

Please see the attached MS Word document of Genentech's Medication Guide for Tecentriq (atezolizumab) for BLA 761041, with FDA comments and revisions. We ask that Genentech review and return to us your comments/revisions of the Medication Guide (combined with the USPI document) **by 12:00 pm EST., Wednesday, October 5, 2016.** Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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(P): 240-402-5364
(F): 301-796-9845

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/s/

SAKAR M WAHBY
10/04/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, October 04, 2016 3:47 PM
To: 'Nitzan Sternheim'
Subject: RE: BLA 761041: Question about PMR 1 description

Importance: High

Dear Nitzan,

In reference to your request for clarification regarding PMR 1 scope and timing, please find the FDA Response below:

FDA Response:

For PMR 1, the FDA is requesting an analysis of all immune-mediated adverse reactions, including immune-mediated pneumonitis.

Please let me know if you have any questions, and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Nitzan Sternheim [<mailto:sternheim.nitzan@gene.com>]
Sent: Tuesday, October 04, 2016 1:09 PM
To: Wahby, Sakar
Subject: BLA 761041: Question about PMR 1 description

Dear Sakar,

Genentech is ready to agree to PMR 1 scope and timing, but wanted to get more clarity on the specific analyses that FDA is requesting. Per the PMR description:

Conduct a randomized trial that will characterize the incidence, severity and response to treatment of Tecentriq™ induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

Is FDA requesting an analysis of all immune-mediated adverse reactions, including immune-mediated pneumonitis, or an analysis of immune-mediated pneumonitis only?

Best regards,
Nitzan

--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program
Management | Genentech, Inc. | Mobile (b) (6) | Fax (650) 467-1844 | sternheim.nitzan@gene.com

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SAKAR M WAHBY
10/04/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Monday, October 03, 2016 1:38 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI with FDA Revisions
Attachments: 10-3-16 Tecentriq FDA revised PI.docx

Importance: High

Dear Nitzan,

Please see the attached MS Word document of Genentech's USPI for Tecentriq™ (atezolizumab) for BLA 761041, with DOP1 comments and revisions. We ask that Genentech review and return to us your comments/revisions of the USPI **by 12:00 pm EST., Wednesday, October 5, 2016.** Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
10/03/2016

Wahby, Sakar

From: Nitzan Sternheim <sternheim.nitzan@gene.com>
Sent: Wednesday, September 28, 2016 10:27 AM
To: Wahby, Sakar
Cc: Nitzan Sternheim
Subject: Re: BLA 761041/OAK Study/Financial Certification and Disclosure

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Orange Category

Dear Sakar,

We have not submitted the Financial Certification and Disclosure for Study OAK, and will work to submit it as soon as possible to the BLA.

Best regards,
Nitzan

On Wed, Sep 28, 2016 at 6:20 AM, Wahby, Sakar <Sakar.Wahby@fda.hhs.gov> wrote:

Dear Nitzan,

In reference to BLA 761041, in your recent submissions containing OAK Study reports received on September 16, 2016, and September 20, 2016, I'm unable to find "Financial Certification and Disclosure" for OAK Study. If you have submitted it already can you point me to where I can find it in the modules submitted, if you haven't submitted it yet, please submit it ASAP formally to the application.

Feel free to contact me if have any questions.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): [240-402-5364](tel:240-402-5364)

(F): [301-796-9845](tel:301-796-9845)

--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Mobile (b) (6) | Fax (650) 467-1844 | sternheim.nitzan@gene.com

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SAKAR M WAHBY
09/30/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, September 29, 2016 1:34 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/PMR/PMC

Importance: High

Dear Nitzan,

In reference to BLA 761041, please find below the current text for PMR and PMC implementation:

1) Text for a PMR that we will be requiring. This is being shared as a courtesy only. Please provide feedback on the feasibility of the completion date only.

PMR Description: Conduct a randomized trial that will characterize the incidence, severity and response to treatment of Tecentriq™ induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

PMR Schedule Milestones: Final Report Submission: 03/2017

2) Current text for a PMC:

PMC Description: Submit the final report and datasets for clinical trial entitled “A Phase III, Multicenter, Randomized Study of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy” [OAK (GO28915)].

PMC Schedule Milestones: Final Report Submission: 03/2017

Please respond with your commitment to conduct this PMC. If you make any changes, please use track changes. Your response needs to be in the following format:

“We commit to submit the final report and datasets for clinical trial entitled “A Phase III, Multicenter, Randomized Study of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy” [OAK (GO28915)] by March, 2017”

Please provide your responses **by 12:00 pm EST., Wednesday, October 5, 2016**. Please provide by 1) email to facilitate review 2) formal submission to the BLA .

Thank you,
Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

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/s/

SAKAR M WAHBY
09/29/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, September 28, 2016 2:54 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI with FDA Revisions
Attachments: 9-28-16 Tecentriq FDA revised PI.docx

Importance: High

Dear Nitzan,

Please see the attached MS Word document of Genentech's USPI for Tecentriq™ (atezolizumab) for BLA 761041, with DOP1 comments and revisions. We ask that Genentech review and return to us your comments/revisions of the USPI **by 12:00 pm, Friday, September 30, 2016.** Feel free to contact me if you have any questions and kindly confirm the receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
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SAKAR M WAHBY
09/28/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, September 27, 2016 8:53 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request:

- 1) Please submit a formal timeline outlining anticipated submission of full efficacy and safety data from study OAK, including relevant datasets and CSR.**

Please respond by 12 pm EST., on Wednesday, September 28, 2016. Feel free to contact me if you have any questions and kindly confirm the receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
09/27/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, September 21, 2016 10:30 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR-Advice

Importance: High

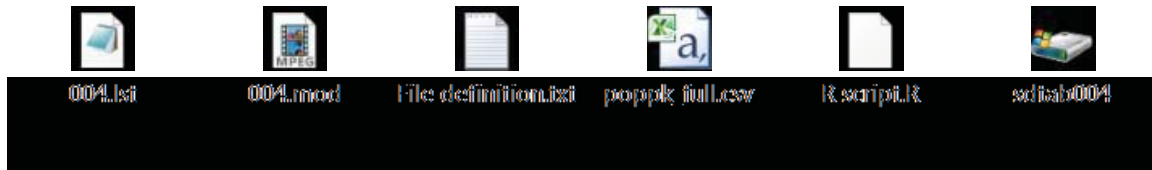
Dear Nitzan,

In reference to BLA 761041, and in reference to Genentech's RESPONSE #4 submitted to BLA 761041 on September 14, 2016 (listed below), in response to FDA proposed label changes submitted to Genentech on September 8, 2016, please note the attached files provided to Genentech by the FDA Pharmacometrics team:

COMPANY RESPONSE

The Sponsor acknowledges FDA revisions to Section 12.3 of the USPI, as shown above. The Sponsor requests the opportunity to review the model input and output files (i.e. NONMEM dataset, control file, list file and table of posthoc parameter estimates, as well as any post-processing scripts) associated with the estimated reduction in CL as stated in the proposed revision "mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 17.1% (40.6%)."

Files provided to Genentech by the FDA Pharmacometrics team for clarification purposes:



BEST AVAILABLE
COPY

Please let me know if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
09/21/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, September 20, 2016 6:12 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Review teams:

Regarding OAK dataset ASLOS-

- 1. We notice what appear to be inconsistencies between the dataset columns “IC” and “TC” and their mapping to the TC/IC categorization columns (TCIC4GRP, TC3IC3, TC2IC2, and TC1IC1 columns) based on IC and TC cutoffs used in the scoring criteria.**
- 2. There are many seeming inconsistencies between the eventual categorization in the “IC” column and the initial categorization in column ICLVL1.**
- 3. We noticed similar inconsistencies in patients being listed as “UNKNOWN” in some groupings (e.g. TC3IC3 column) but assigned to a group for other categories (e.g. TC2IC2 column) (USUBJIDs: GO28915-264903-431021, GO28915-265971-413046, GO28915-265976-413016, GO28915-266739-431072, GO28915-263631-431173, GO28915-263893-431183, GO28915-265989-407010, GO28915-266735-411030, GO28915-272326-431170).**

Please explain if the scores in the IC and TC columns were the ones used to group patients, why these scores do not seem to map to the groupings, and the inconsistencies between the IC and ICLVL1 columns.

Please respond by COB, Thursday, September 22, 2016. Kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
09/20/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Monday, September 19, 2016 12:32 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Statistics team:

- 1) Please submit a SAS dataset with region information (US vs. Non-US) for individual patients of study OAK by September 21, 2016.**

Kindly confirm the receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
09/19/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, September 09, 2016 3:10 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR
Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Statistics team:

- 1) Please submit all versions of protocol and SAP for study OAK with a summary of changes for each amendment by September 19, 2016.**

Kindly confirm the receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
09/09/2016

From: Tilley, Amy
To: [Nitzan Sternheim \(sternheim.nitzan@gene.com\)](mailto:Nitzan.Sternheim@gene.com)
Cc: [Wahby, Sakar](#)
Bcc: [Khozin, Sean \(FDA\)](#)
Subject: BLA 761041 Tecentriq - FDA Revised PI
Date: Thursday, September 08, 2016 1:01:00 PM
Attachments: [9-7-16 Tecentriq GNE Proposed \(2\).docx](#)
Importance: High

Nitzan,

On behalf of my colleague, Sakar Wahby, attached is the FDA revised PI for Genentech's review. FDA would appreciate Genentech's labeling revisions incorporating data from OAK before Sept 19, 2016, if possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1
CDER | FDA 10903 New Hampshire Avenue | Room 2108 | Silver Spring,
MD 20993 📞 📠 301.796.3994 | F 301.796.9845 | amy.tilley@fda.hhs.gov

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AMY R TILLEY
09/08/2016



BLA 761041

MID-CYCLE COMMUNICATION

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Tecentriq™ (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial.

We also refer to the teleconference between representatives of your firm and the FDA on July 21, 2016. 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 Sakar Wahby, Regulatory Project Manager at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Sean Khozin, MD
Cross Discipline Team Leader
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: July 21, 2016, 1:00 PM- 2:00 PM
Application Number: 761041
Product Name: Tecentriq™ (atezolizumab) Infusion
Indication: Locally advanced or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq
Applicant Name: Genentech, Inc.
Meeting Chair: Sean Khozin, MD, Cross Discipline Team Leader
Meeting Recorder: Sakar Wahby, PharmD, Regulatory Project Manager

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Sean Khozin, MD, Cross Discipline Team Leader, DOP2
Chana Weinstock, MD, Clinical Reviewer, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Statistics Team Leader, DBV
Lijun Zhang, PhD, Statistics Reviewer, DBV
Kimberly Ringgold, PhD, Pharmacology/Toxicology Reviewer, DHOT
Eunice Lee, PhD, Branch Chief, MPCB/DMGP/OIR/CDRH
Shyam Kalavar, MPH, CT (ASCP), Scientific Reviewer, MPCB/DMGP/OIR/CDRH
Chao Liu, PhD, Biometrics Reviewer, OCP
Qi Liu, PhD, Clinical Pharmacology Team Leader, OCP
Wentao Fu, PhD, Clinical Pharmacology Reviewer, OCP
Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist, CDER/OSE/OPE
Sakar Wahby, PharmD, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES

Zach Boyd, Senior Manager, Companion Diagnostics
Nick Bruno, Associate Group Director, PD Regulatory
Andrew Chia, PharmD, Program Manager, PD Regulatory
Sandhya Girish, PhD, Global Head Oncology, Clinical Pharmacology
Pei He, PhD, Statistical Scientist, Biostatistics
Conny Irl, PhD, Senior Director, Biostatistics
Marcin Kowanetz, PhD, Senior Scientist, Oncology Biomaker Development
Cathrine Leonowens, PhD, Scientist, Clinical Pharmacology

Flavia Di Nucci, MD, Senior Safety Scientist, PD Safety Risk Management
Sush Patel, PhD, Lifecycle Leader, Global Product Strategy
Alan Sandler, MD, Group Medical Director, PD Clinical Oncology
Nitzan Sternheim, PhD, Program Director, PD Regulatory
Daniel Waterkamp, MD, PhD, Senior Medical Director, PD Clinical Oncology
Ying Yuen, MA, Project Lead, Statistical Programming & Analysis

Eastern Research Group Attendees:

Christopher A. Sese, Eastern Research Group, Inc.

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

We have identified the following significant review issues.

- Please provide an update on the timeframe anticipated for submission of the topline results from the OAK clinical study.
- FDA considers the updated overall survival analysis in Study G028753 to be exploratory. Therefore, for labeling purposes, no p values based on the updated analyses can be used.

Meeting discussion:

- Genentech will share the high-level results from the first stage of Genentech's review of OAK topline results (primary efficacy and demographics/baseline) with the Agency by the end of August, 2016.
- Genentech will share the high-level results from the second stage of Genentech's review of OAK study (OAK safety and secondary efficacy) with the Agency by early September, 2016.
- Genentech will submit OAK study primary efficacy datasets to the FDA by September 19, 2016.
- Genentech will submit the OAK study safety data and CSR datasets to the FDA at a later point, following action on BLA 761041.

- Genentech inquired if the Agency will be providing comments on the revised USPI for Tecentriq™ submitted to the Agency on June 15, 2016 prior to the submission of the OAK study topline results. The FDA is planning on submitting comments on the revised USPI dated June 15, 2016 in early September, 2016.

2.0 INFORMATION REQUESTS

Pharmacometrics:

- Pharmacometrics information request dated July 6, 2016, with a response due July 29, 2016.

Meeting discussion:

- Genentech will provide their response to the outstanding Pharmacometrics information request dated July 6, 2016 by the due date of July 29, 2016.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

All major safety concerns can be addressed through review of the submission and the responses to our information requests. A REMS will not be required.

Meeting discussion:

None.

4.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

Meeting discussion:

None.

5.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is currently planned for September 21, 2016. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is October 19, 2016.

Meeting discussion:

- Genentech inquired if in light of the OAK study data planned to be submitted by September, 19, 2016, will the Agency keep the Late Cycle meeting scheduled for September 21, 2106. The FDA responded that the date of the Late Cycle meeting will stay the same taking into consideration that results from Genentech's first review of the OAK study will be shared with the Agency by late August, 2016. Updates regarding scheduling of the late cycle meeting will be communicated to Genentech during the course of the review.

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/s/

SEAN N KHOZIN
08/29/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, August 26, 2016 12:56 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/USPI with FDA Revisions/Comments
Attachments: 8-25-16 Tecentriq FDA revised PI(1).docx
Importance: High

Dear Nitzan,

Please see the attached MS Word document of Genentech's USPI for Tecentriq® (atezolizumab) for BLA 761041, with DOP1 comments and revisions. We ask that Genentech review and return to us your comments/revisions of the USPI by COB, Monday, September 5, 2016. We ask that you don't submit your comments/revisions to Section 14 of the USPI until after review of the OAK Study results as the content of Section 14 may change based on the results of OAK Study.

Feel free to contact me if you have any questions and kindly confirm the receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
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/s/

SAKAR M WAHBY
08/26/2016



BLA 761041

MID-CYCLE COMMUNICATION

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Tecentriq™ (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial.

We also refer to the teleconference between representatives of your firm and the FDA on July 21, 2016. 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 Sakar Wahby, Regulatory Project Manager at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Sean Khozin, MD
Cross Discipline Team Leader
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: July 21, 2016, 1:00 PM- 2:00 PM
Application Number: 761041
Product Name: Tecentriq™ (atezolizumab) Infusion
Indication: Locally advanced or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq
Applicant Name: Genentech, Inc.
Meeting Chair: Sean Khozin, MD, Cross Discipline Team Leader
Meeting Recorder: Sakar Wahby, PharmD, Regulatory Project Manager

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Sean Khozin, MD, Cross Discipline Team Leader, DOP2
Chana Weinstock, MD, Clinical Reviewer, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Statistics Team Leader, DBV
Lijun Zhang, PhD, Statistics Reviewer, DBV
Kimberly Ringgold, PhD, Pharmacology/Toxicology Reviewer, DHOT
Eunice Lee, PhD, Branch Chief, MPCB/DMGP/OIR/CDRH
Shyam Kalavar, MPH, CT (ASCP), Scientific Reviewer, MPCB/DMGP/OIR/CDRH
Chao Liu, PhD, Biometrics Reviewer, OCP
Qi Liu, PhD, Clinical Pharmacology Team Leader, OCP
Wentao Fu, PhD, Clinical Pharmacology Reviewer, OCP
Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist, CDER/OSE/OPE
Sakar Wahby, PharmD, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES

Zach Boyd, Senior Manager, Companion Diagnostics
Nick Bruno, Associate Group Director, PD Regulatory
Andrew Chia, PharmD, Program Manager, PD Regulatory
Sandhya Girish, PhD, Global Head Oncology, Clinical Pharmacology
Pei He, PhD, Statistical Scientist, Biostatistics
Conny Irl, PhD, Senior Director, Biostatistics
Marcin Kowanz, PhD, Senior Scientist, Oncology Biomarker Development
Cathrine Leonowens, PhD, Scientist, Clinical Pharmacology

Flavia Di Nucci, MD, Senior Safety Scientist, PD Safety Risk Management
Sush Patel, PhD, Lifecycle Leader, Global Product Strategy
Alan Sandler, MD, Group Medical Director, PD Clinical Oncology
Nitzan Sternheim, PhD, Program Director, PD Regulatory
Daniel Waterkamp, MD, PhD, Senior Medical Director, PD Clinical Oncology
Ying Yuen, MA, Project Lead, Statistical Programming & Analysis

Eastern Research Group Attendees:

Christopher A. Sese, Eastern Research Group, Inc.

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

We have identified the following significant review issues.

- Please provide an update on the timeframe anticipated for submission of the topline results from the OAK clinical study.
- FDA considers the updated overall survival analysis in Study G028753 to be exploratory. Therefore, for labeling purposes, no p values based on the updated analyses can be used.

Meeting discussion:

- Genentech will submit OAK study topline results to the FDA by September 19, 2016.
- Genentech stated that they will be looking at the OAK study results in two stages. Genentech will share the topline results from the first stage of Genentech's review of OAK topline results with the Agency by the end of August, 2016. The OAK study safety data and CSR data sets will be submitted to the Agency by September 19, 2016.

- Genentech inquired if the Agency will be providing comments on the revised USPI for Tecentriq™ submitted to the Agency on June 15, 2016 prior to the submission of the OAK study topline results. The FDA is planning on submitting comments on the revised USPI dated June 15, 2016 in early September, 2016.

2.0 INFORMATION REQUESTS

Pharmacometrics:

- Pharmacometrics information request dated July 6, 2016, with a response due July 29, 2016.

Meeting discussion:

- Genentech will provide their response to the outstanding Pharmacometrics information request dated July 6, 2016 by the due date of July 29, 2016.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

All major safety concerns can be addressed through review of the submission and the responses to our information requests. A REMS will not be required.

Meeting discussion:

None.

4.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

Meeting discussion:

None.

5.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is currently planned for September 21, 2016. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is October 19, 2016.

Meeting discussion:

- Genentech inquired if in light of the OAK study data planned to be submitted by September, 19, 2016, will the Agency keep the Late Cycle meeting scheduled for September 21, 2106. The FDA responded that the date of the Late Cycle meeting will stay the same taking into consideration that results from Genentech's first review of the OAK study will be shared with the Agency by late August, 2016. Updates regarding scheduling of the late cycle meeting will be communicated to Genentech during the course of the review.

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/s/

SEAN N KHOZIN
08/19/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, August 05, 2016 9:51 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1) Provide a narrative for FIR patient 182110 with detail regarding his events of primary hypogonadism and hypothyroidism including laboratory values.**

Please respond by COB, Wednesday, August 10, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): 240-402-5364

(F): 301-796-9845

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/s/

SAKAR M WAHBY
08/05/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, August 04, 2016 1:27 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1) Please provide a narrative for BIRCH subject 307017 with additional details regarding patients event of elevated transaminases and bilirubin.**

Please respond by COB, Tuesday, August 9, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

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(F): 301-796-9845

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/s/

SAKAR M WAHBY
08/04/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, July 12, 2016 2:17 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1) Regarding the ARS dataset submitted as part of the 150-event analysis, patient 259306-213111 was initially considered a confirmed responder with a PR listed as occurring at the 5/12/14, 12 week assessment. This was later changed to a best overall response of PD in the later datasets (180 event and 200 event) since the patient actually had a new lesion at that date (seen in the later versions of dataset TR) and should not have been considered a confirmed RECIST responder. Using the 150-death data, the docetaxel arm appears to have 22 responders. This number drops to 21 at the subsequent time analyses. Please clarify the discrepancy between the initial and subsequent classifications of the best overall response of this patient.**

Please respond by 12:00 pm EST., Wednesday, July 20, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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/s/

SAKAR M WAHBY
07/12/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Monday, July 11, 2016 8:26 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1. Please provide a narrative for POPLAR patient 305006 with details regarding hemolysis and administration of corticosteroids.**

Please respond by COB, Friday, July 15, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

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/s/

SAKAR M WAHBY
07/11/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, July 08, 2016 11:27 AM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, please note the following information request from the Clinical and Stats teams:

- 1) In reference to protocol G028753, we note that the data cutoff for the 150 death event analysis occurred at the end of January 2015. Additionally, the IMC meeting to discuss the results of the OS analysis based on 150 events was held on Feb 6, 2015. We also note that the first protocol amendment to add 3 more months of follow up, corresponding to approximately 180 death events, was dated February 24, 2015. Please clarify whether the results of the 150 event analysis was known before the protocol amendment was initiated. In addition, provide applicable documentation to support your claim that the analysis based on 180 events is the pre specified final analysis.**

Please respond by 12:00 pm EST, on Monday, July 11, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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/s/

SAKAR M WAHBY
07/08/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, July 07, 2016 1:23 PM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1) **Please provide a narrative for patients 307004 and 305065 from BIRCH regarding the episode of dyspnea requiring corticosteroid treatment.**
- 2) **Please provide a narrative for patient 305056 from BIRCH regarding the episode of respiratory failure requiring corticosteroid treatment.**

Please respond by COB, Tuesday, July 12, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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SAKAR M WAHBY
07/07/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, July 07, 2016 8:21 AM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, please note the following information request from DMEPA and Product Quality team:

- 1) Please submit to BLA 761041 the container labels and carton labeling that was approved for BLA 761034 (final version submitted to BLA 761034 on April 20, 2016) for Tecentriq™ (atezolizumab).**

Please respond by COB, Wednesday, July 20, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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/s/

SAKAR M WAHBY
07/07/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, July 06, 2016 12:06 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR
Attachments: 001.lst; 002.lst

Importance: High

Dear Nitzan,

In reference to BLA 761041, the Pharmacometrics team has the following information request, **please respond by COB, Friday, July 29, 2016.**

Pharmacometrics IR:

Time-Dependent Clearance of Atezolizumab:

Reference is made to Atezolizumab population pharmacokinetics analysis final model for report titled "*1066935: Pharmacokinetics of Atezolizumab (PD-L1 inhibitor) Administered as a Single Agent in Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies (Based on Studies PCD4989g and JO28944)*" and "*1067735: Pharmacokinetics of Atezolizumab (PD-L1 inhibitor) in Patients with Non-Small Cell Lung Cancer (Based on Study GO28754, Study GO28625, Study GO28753)*" dated 2/19/2016. FDA updated sponsor's final model by incorporating the data from Study GO28754, 28625, 28753 (Mod#1). FDA's analysis suggested that in NSCLC patients, atezolizumab's clearance is time dependent as shown in Figure 1 (see attached lst output file for more details, Mod#2). The magnitude of clearance change over time appears to be correlated with disease progression and shown in **Figure 2**. For Atezolizumab BLA761041, reconsider the population pharmacokinetics analyses by describing the time-varying PK and update the label if needed.

Figure 1 shows the diagnostic plot Comparison between sponsor's final model and FDA's analysis using the time-dependent PPK model.

Figure 1: Diagnostic Plot Comparison between Stationary Pharmacokinetics (Left Panels) and Time-Dependent Pharmacokinetics (Right Panels) of Atezolizumab

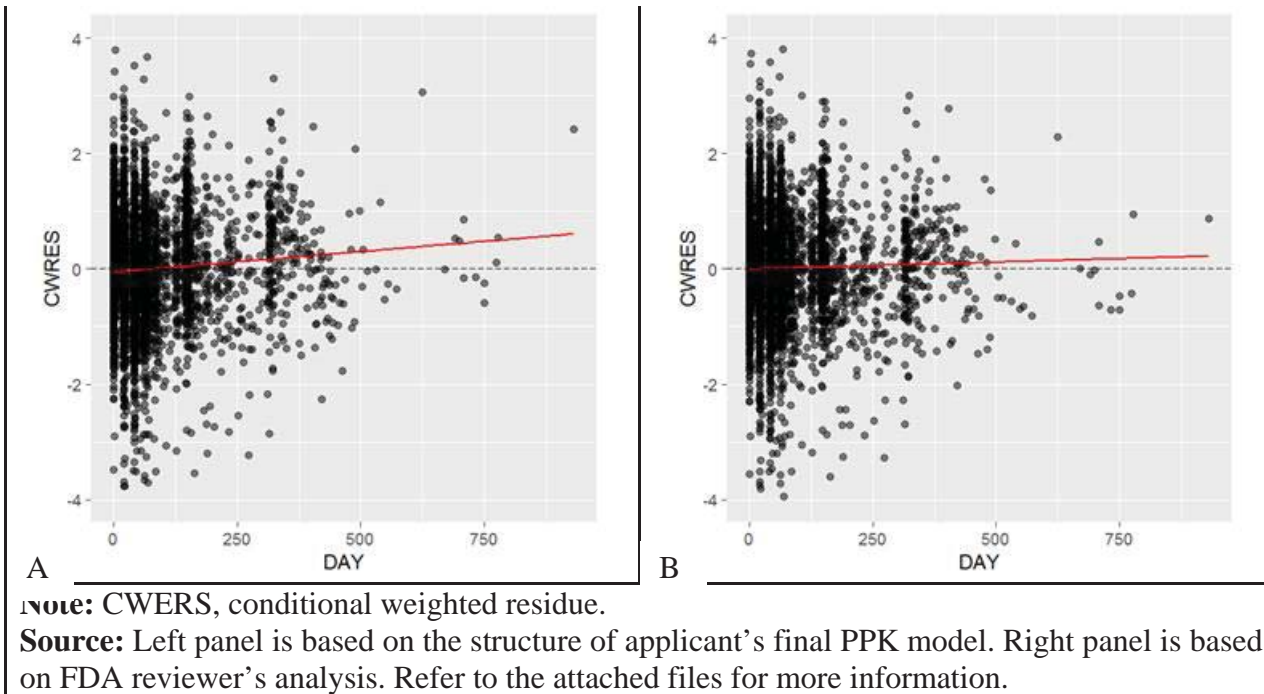
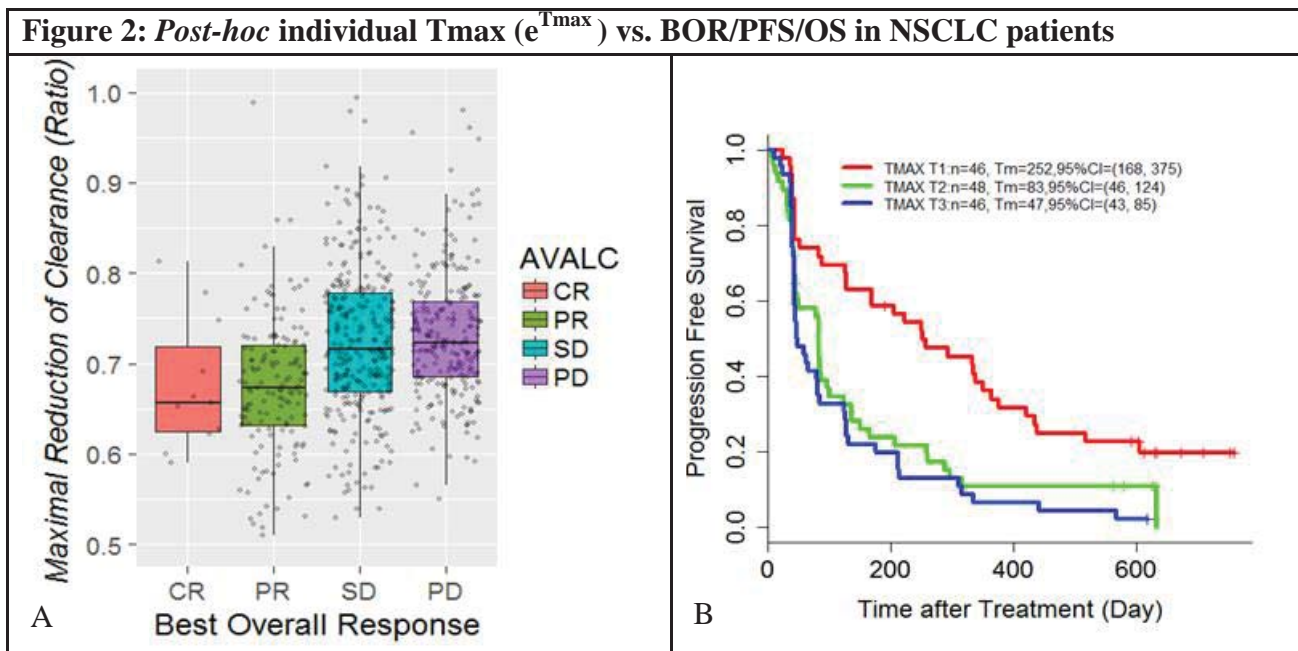
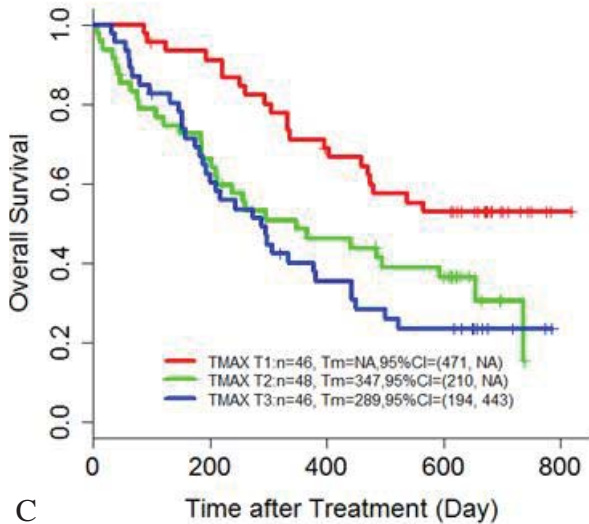


Figure 2 shows the clearance change based on FDA's analysis using the time-dependent PPK model.

These steps are used for generating the plot:

1. From NONMEM output of the time-dependent modeling analysis, extract the Tmax post-hoc estimate for each individual subject (Mod002).
2. Analyze the *post-hoc* Tmax versus various efficacy endpoints





C

Source: FDA reviewer's analysis. Refer to the attached files for more information.

2A, data based on Study PCD4989g , GO28754, GO28625 and GO28753

2B, C: data from GO28753

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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SAKAR M WAHBY
07/06/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, June 30, 2016 12:18 PM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, the Clinical team has the following information request:

- 1) **Provide additional details regarding the pneumopathy reported for Patient 202002. Include any relevant clinical history/exam, imaging, or other studies.**
- 2) **Provide additional detail regarding the intestinal perforation reported for Patient 211004. Include data from the patient's laparotomy and pathologic review including whether there was evidence of ulceration or other corticosteroid-related changes. Indicate the last date of corticosteroid use or whether this was continued until perforation. Provide additional data regarding the assessment of diverticulitis on Day 83 including any treatment received and the outcome.**
- 3) **Please provide a narrative for Patient 202005.**

Please respond by COB, Monday, July 11, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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SAKAR M WAHBY
06/30/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, June 28, 2016 4:21 PM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, please note the following information request from the Clinical team:

- 1) Please indicate if there is a treatment beyond progression flag for patients on the Atezolizumab arm on study POPLAR, and in which dataset it is found.

Please respond by COB, Thursday, June 30, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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/s/

SAKAR M WAHBY
06/28/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Monday, June 27, 2016 11:16 AM
To: Andrew Chia
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Andrew,

In reference to BLA 761041, the Clinical Pharmacology team has the following information request:

1) Please provide update on Table 17 below in the Summary of Clinical Pharmacology (section 2.7.2) using results from cutoff date 12/01/2015. Please also provide data for PD-L1 expression subgroups and corresponding efficacy outcomes for both ATA-Negative and ATA-Positive groups.

Table 17 POPLAR: Impact of ATA on OS, PFS and ORR (Atezolizumab Arm)

	ATA-Negative (n = 62)	ATA-Positive (n = 73)
OS		
Patients with event (%)	28 (45.2%)	41 (56.2%)
Median duration of Survival (months)	NE	13.0
95% CI	(11.0, NE)	(8.5, 16.4)
PFS		
Patients with event (%)	52 (83.9%)	63 (86.3%)
Median duration of PFS (months)	2.7	4.1
95% CI	(1.5, 4.2)	(2.7, 5.7)
Best confirmed response ^a		
Responders (n)	6	15
Non-responders (n)	56	58
ORR	9.7%	20.5%
95% CI for ORR	(3.6, 19.9)	(12.0, 31.6)

ATA = anti-therapeutic antibody; CI = confidence interval; ORR = overall response rate;
OS = overall survival; NE = not evaluable; PFS = progression free survival.

^a Based on objective response evaluable population where an ATA sample was available. Best confirmed response rate was the objective response rate.

Please respond by COB, Thursday, June 30, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

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SAKAR M WAHBY
06/27/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, May 06, 2016 6:40 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, please find the following information request from our Clinical Team:

- 1) Please provide a dataset for protocol deviations, both major and minor, by each subject for Study GO28753.

Please respond by COB, Thursday, May 12, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
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SAKAR M WAHBY
05/06/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, May 06, 2016 1:50 PM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR- Time Sensitive
Importance: High

Dear Nitzan,

In reference to BLA 761041, please find the following information request from our Clinical Team, **please respond by COB, TODAY, May 6, 2016:**

Please provide the phone number and e-mail address for the sites associated with the following investigators:

- 1) Dr. Louis Fehrenbacher
Kaiser Permanente-Vallejo
975 Sereno Drive
Vallejo, CA

- 2) Dr. Aleksandra Szczesna
MAZOWIECKIE CENTRUM LECZENIA CHOROBY PLUC I GRUZYLCY;
ODDZIAŁ III, III Oddział Choroby Pluc z, pododdziałem Onkologicznym;
ul. Reymonta 83/91, 05- 400, Otwock,
POLAND

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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/s/

SAKAR M WAHBY
05/06/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, April 28, 2016 4:06 PM
To: 'Andrew Chia'
Cc: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Chia,

In reference to BLA 761041, the STATs team has the following information request regarding **BLA761041 POPLAR Study**:

- 1) Please submit IMC meeting minutes for all interim efficacy analyses.
- 2) Following the intent-to-treat principle, the primary efficacy analysis should be conducted using stratification data collected at the time of randomization. Please perform the primary OS analysis in the ITT population stratified by stratification data obtained from IxRS.

Please respond by COB, Thursday, May 12, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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/s/

SAKAR M WAHBY
04/28/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, April 28, 2016 3:38 PM
To: Andrew Chia
Cc: 'Nitzan Sternheim'
Subject: RE: BLA 761041: Question regarding label merging with atezolizumab mUC USPI

Importance: High

Dear Chia,

In reference to BLA 761041, also in reference to your question submitted on April 28, 2016 regarding label merging with atezolizumab mUC USPI, please find the following comments from our Clinical Team:

The datasets used were alb.xpt for each trial. Only patients who had both a TSH at baseline and at least one at follow-up were included. TSH was considered elevated if:

- a) It had increased from baseline (i.e. PCHG > 0)
- b) It was higher than the listed reference value (i.e. LBNRIND = HIGH)

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
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From: Nitzan Sternheim [<mailto:sternheim.nitzan@gene.com>]
Sent: Thursday, April 28, 2016 1:02 AM
To: Wahby, Sakar
Cc: Andrew Chia
Subject: BLA 761041: Question regarding label merging with atezolizumab mUC USPI

Dear Sakar,

We are working on updating the draft NSCLC USPI and implementing FDA feedback on the mUC USPI. In mUC USPI Section 5.4 Immune-Related Endocrinopathies, subsection Thyroid Disorders, the analyses provided by FDA for thyroid stimulating hormone elevation and decrease include 131 patients. Can you please clarify the data source and methodology used to generate this number?

I will be on vacation Thursday and Friday of this week, so please direct any communications to Andrew Chia, cc'd here, and include me. I'll be back on Monday.

Best regards,
Nitzan

--

Nitzan Sternheim, PhD | Regulatory Program Director, Product Development Regulatory - Program Management | Genentech, Inc. | Work (650) 467-2002 | Mobile (b) (6) | Fax (650) 467-1844 | sternheim.nitzan@gene.com

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

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/s/

SAKAR M WAHBY
04/28/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 29, 2016

Application Number: BLA 761041

Product Name: Tecentriq™ (atezolizumab)

Sponsor/Applicant Name: Genentech, Inc.

Subject: Potential review and approval paths for BLA 761041 for Non-Small Cell Lung Cancer

FDA Participants

Geoffrey Kim, MD, Director, Division of Oncology Products 1 (DOP1)

Sean Khozin, MD, Medical Officer, DOP2

Chana Weinstock, MD, Medical Officer, DOP1

Daniel Suzman, MD, Medical Officer, DOP1

Sakar Wahby, PharmD, Regulatory Project Manager, DOP1

Alice Kacuba, RN, MSN, GWCPM, RAC, Chief, Project Management Staff

Sponsor Participants

Cathie Ahearn, MBA, Lifecycle Team Leader, Global Product Strategy Oncology

Nicholas Bruno, Associate Group Director, Product Development Regulatory

Cornelia Irl, PhD, Senior Director, Biostatistics

Alan Sandler, MD, Group Medical Director, Product Development Clinical Oncology

Nitzan Sternheim, PhD, Program Director, Product Development Regulatory

Nathan Winslow, Global Franchise Head, Product Development Regulatory

1.0 BACKGROUND:

BLA 761041 is submitted to the Agency on February 19, 2016 proposing approval of Tecentriq™ (atezolizumab) for the indication of NSCLC. The FDA is conducting an expedited review timeline for BLA 761041. Genentech, Inc. requested a teleconference with the FDA to discuss potential review and approval paths for atezolizumab in NSCLC (BLA 761041). BLA 761034 from Genentech, Inc. is still pending with the Agency for the indication of locally advanced or metastatic urothelial carcinoma (mUC). The Action Goal date for BLA 761034 is May 18, 2016.

2.0 DISCUSSION:

Genentech, Inc. inquired about the implication of an expedited review timeline for BLA 761041 (based on the BIRCH 2L+TC3 population) and the timing for submission of top-line results from the OAK study which is anticipated by Genentech, Inc. to be available mid-September 2016.

Dr. Geoffrey Kim, Director of the Division of Oncology Products 1 at the FDA stated that the regulatory landscape for NSCLC is changing rapidly and the FDA is conducting an expedited review of the submitted data to BLA 761041 based on the BIRCH 2L+TC3 population.

Dr. Kim further explained that:

- The path for full approval requires positive results from the OAK study data and the timing of when Genentech, Inc. estimates it will be available; the BLA amendment would be a major amendment and extends the PDUFA review clock of BLA 761041.
- The path to accelerated approval would be to submit the OAK top-line results and updated labeling in an efficacy supplement post approval of BLA 761041.

Genentech, Inc. referred to the November 10, 2015 Pre-BLA meeting conducted between the Agency and Genentech Inc., during which the FDA agreed on reviewing OAK top-line results 30 days prior to the PDUFA date for BLA 761041. Meeting minutes dated November 16, 2015, see Question 2a.

Dr. Kim replied that the strategy of expedited approval of BLA 761041 based on the currently submitted BIRCH 2L+TC3 population and the proposed submission of OAK study data as a sBLA to BLA 761041 post approval, will mitigate regulatory risks taken of the changing landscape. This pathway will not slow down the submission of Oak OS data nor the action on the Oak OS data.

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/s/

SAKAR M WAHBY
04/08/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, March 30, 2016 8:12 AM
To: 'Nitzan Sternheim'
Subject: FDA Communication, BLA 761041/Tecentriq (atezolizumab)/IR

Importance: High

Dear Nitzan,

In reference to BLA 761041, submitted on February 19, 2016, the STATs team has the following information request regarding **BLA761041 BIRCH Study**:

Provide the SAS program used to derive the response status from raw data (target lesion measurements, non-target status, and new lesion status at each assessment) following RECIST v1.1 based on investigator and IRF assessments. This program should be stand-alone (i.e., no macros) so that it can be run on FDA computers. Please also submit an output dataset (one record per patient per tumor assessment) including the following data:

- Patient ID, Randomized arm, Visit number, Visit name, Visit date, Baseline target lesion SLD, Target lesion SLD at this visit, % change of SLD from baseline, Nadir SLD value, % change of SLD from nadir, Non-target lesion response status at this visit, New lesion (yes/no) at this visit, Response status at this visit, Best overall response, Evaluator (Investigator or IRF)

Please respond by COB, Friday, April 15, 2016.

Feel free to contact me with any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

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/s/

SAKAR M WAHBY
03/30/2016



BLA 761041

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Biologics License Application (BLA) dated February 19, 2016, received February 19, 2016, submitted under section 351(a) of the Public Health Service Act for Tecentriq™ (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial.

We also refer to your amendments dated March 9, 2016, and March 16, 2016.

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**. Therefore, the user fee goal date is October 19, 2016. 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>).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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 by July 15, 2016. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling

and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is May 17, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI). Please include a horizontal line separating these two sections from one another.
2. White space should be present before each major heading in Highlights (HL). Please insert the necessary white space.
3. Your product has FDA-approved patient labeling (Medication Guide), therefore please change the patient counseling information statement in Highlights to read: "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide".

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 25, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the 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.

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, as required by 21 CFR 601.45, 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), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Sakar Wahby, Regulatory Project Manager, at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GEOFFREY S KIM
03/29/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761041

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Nitzan Sternheim, Ph.D.
Regulatory Project Management

Dear Dr. Sternheim:

Please refer to your Biologics License Application (BLA) dated February 19, 2016, received February 19, 2016, submitted under section 351(a) of the Public Health Service Act for Atezolizumab, 60 mg/mL.

We also refer to your February 19, 2016, correspondence, received February 19, 2016, requesting review of your proposed proprietary name, Tecentriq.

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

If any of the proposed product characteristics as stated in your February 19, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Sakar Wahby, Regulatory Project Manager in the Office of New Drugs, at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/08/2016



BLA 761041

BLA ACKNOWLEDGMENT

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

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: Tecentriq® (atezolizumab)

Date of Application: February 19, 2016

Date of Receipt: February 19, 2016

Our Reference Number: BLA 761041

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 19, 2016, in accordance with 21 CFR 601.2(a).

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 content and format requirements of revised 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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 761041** submitted on February 19, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 1
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 Sakar Wahby, Regulatory Project Manager, at (240) 402-5364 or email at sakar.wahby@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sakar Wahby, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

SAKAR M WAHBY
02/26/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION			
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Sakar Wahby, PharmD Regulatory Project Manager OND/OHOP/DOP1 Phone: 240-402-5364			
REQUEST DATE: February 25, 2016		NDA/BLA NO.: BLA 761041	TYPE OF DOCUMENTS: NEW BLA Application		
NAME OF DRUG: TECENTRIQ (atezolizumab)	PRIORITY CONSIDERATION: Priority Review	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) TBD		
SPONSOR: Genentech, Inc.		PDUFA Date: October 19, 2016			
TYPE OF LABEL TO REVIEW					
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: EDR Location: \\CDSESUB1\evsprod\BLA761041\761041.enx					
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.					
COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request review of the PPI for this new pending 505b2 NDA. Filing/Planning Meeting: March 22, 2016 Mid-Cycle Meeting: TBS Labeling Meetings: TBS Wrap-Up Meeting: TBS					
SIGNATURE OF REQUESTER Sakar Wahby					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL (BLAs Only) <input type="checkbox"/>		

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/s/

SAKAR M WAHBY
02/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning
meeting****

TO:
CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Sakar Wahby, PharmD
Regulatory Project Manager
OND/OHOP/DOP1
Phone: 240-402-5364

REQUEST DATE:
February 25, 2016

IND NO.

NDA/BLA NO.
BLA 761041

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)
NEW BLA Application

NAME OF DRUG:
TECENTRIQ (atezolizumab)

PRIORITY CONSIDERATION:
Priority Review

CLASSIFICATION OF DRUG
Oncology

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up
meeting)
TBD

NAME OF FIRM:
Genentech, Inc.

PDUFA Date: October 19, 2016

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
 PATIENT PACKAGE INSERT (PPI)
 CARTON/CONTAINER LABELING
 MEDICATION GUIDE
 INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
 IND
 EFFICACY SUPPLEMENT
 SAFETY SUPPLEMENT
 LABELING SUPPLEMENT
 PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
 LABELING REVISION

For OSE USE ONLY

- REMS

EDR link to submission:

EDR Location: <\\CDSESUB1\evsprod\BLA761041\761041.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request review of labeling for this alcohol-free 505b2 NDA.

Filing Meeting: March 22, 2016
Mid-Cycle Meeting: TBS
Labeling Meetings: TBS
Wrap-Up Meeting: PDUFA Date: October 19, 2016

SIGNATURE OF REQUESTER

12/15/2014

Reference ID: 3892767

Sakar Wahby	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/

SAKAR M WAHBY
02/25/2016



IND 117296/Pre-BLA 761041

GRANT ROLLING REVIEW

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Investigational New Drug Application (IND) 117296 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and please refer to the Pre-BLA 761041 meeting held between the FDA and Genentech, Inc. on November 10, 2015 for Atezolizumab (MPDL3280A).

We also refer to your November 13, 2015, request for rolling submission and review of portions of your planned Biologics License Application (BLA) for Atezolizumab (MPDL3280A) which was designated as a breakthrough therapy for the treatment of patients with PD-L1-positive NSCLC with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

We have reviewed and accept your request and plan for submitting portions of the proposed application.

If the breakthrough therapy designation for Atezolizumab (MPDL3280A) for PD-L1-positive NSCLC with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive is rescinded, submission of portions of the BLA will not be permitted under this program.

For further information regarding breakthrough therapy designations, please refer to the FDA *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*¹.

If you have any questions, contact Sakar Wahby, Regulatory Project Manager, at (240) 402-5364.

Sincerely,
{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

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/s/

GEOFFREY S KIM
11/25/2015



IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to the meeting between representatives of your firm and the FDA on November 10, 2015. The purpose of the meeting was to discuss and for Sponsor to obtain feedback on the acceptability of the results from the pivotal Study BIRCH and supporting Studies, GO28753 (POPLAR), GO28625 (FIR), and PCD4989g to form the basis of a BLA for MPDL3280A for the treatment of patients with Non-Small Cell Lung Cancer (NSCLC). We also refer to your November 2, 2015, correspondence, proposing to explore a path for MPDL3280A for accelerated approval in 2L+ TC3 Non-Small Cell Lung Cancer.

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 (240) 402-5364 or email me at sakar.wahby@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sakar Wahby, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Sean Khozin, MD
Medical Officer
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: November 10, 2015, 11:30 am – 1:00 pm (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 117296
Product Name: Atezolizumab (MPDL3280A)
Indication: Non-Small Cell Lung Cancer (NSCLC)
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Sean Khozin, MD
Meeting Recorder: Sakar Wahby, PharmD

FDA ATTENDEES

Geoffrey Kim, MD, Director, Division of Oncology Products 1 (DOP1)
Gideon Blumenthal, MD, Clinical Team Leader, DOP2
Sean Khozin, MD, Medical Officer, DOP2
Chana Weinstock, MD, Medical Officer, DOP1
Michael Brave, MD, Medical Officer, DOP1
Harpreet Singh, MD, Medical Officer, DOP1
Shenghui Tang, PhD, Statistics Team Leader, DBV
Lijun Zhang, PhD, Statistics Reviewer, DBV
Tiffany Ricks, PhD, Pharmacology/Toxicology Reviewer, DHOT
Reena Philip, PhD, Director, DMGP/OIR/CDRH
Eunice Lee, PhD, Branch Chief, MPCB/DMGP/OIR/CDRH
Shyam Kalavar, MPH, CT (ASCP), Scientific Reviewer, MPCB/DMGP/OIR/CDRH
Chao Liu, PhD, Biometrics Reviewer, OCP
Qi Liu, PhD, Clinical Pharmacology Team Leader, OCP
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Susan Jenney, MS, Safety Project Manager, DOP1
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SPONSOR ATTENDEES

Cathi Ahearn, MBA, Lifecycle Team Leader, Global Product Strategy Oncology
Dietmar Berger, MD, Senior Vice President, Clinical Hematology/Oncology

Nicholas Bruno, Associate Group Director, Product Development Regulatory
Andrew Chia, PharmD, Program Manager, Product Development Regulatory
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Pei He, PhD, Statistical Scientist, Biostatistics
Marcin Kowanetz, PhD, Senior Scientist, Oncology Biomarker Development
Zhengrong Li, PhD, Senior Statistical Scientist, Biostatistics
Simonetta Mocchi, MD, PhD, Medical Director, Product Development Clinical Oncology
Hina Patel, PharmD, Principal Safety Scientist, Safety Science
Alan Sandler, MD, Group Medical Director, Product Development Clinical Oncology
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Jing Yi, PhD, Associate Director, Biostatistics
Julie Engel, PhD, Regulatory Affairs, Ventana Medical Systems

1.0 BACKGROUND

The purpose of this Type B pre-BLA meeting is to discuss a planned BLA submission by Genentech to the FDA of Atezolizumab (MPDL3280A; RO5541267), IND 117296. The proposed indication for the planned BLA would be for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are selected by PD-L1 status, as determined by an FDA-approved test, after failure of (b) (4) platinum-containing chemotherapy regimen. The BLA will be based on the results from the pivotal Study GO28754 (BIRCH), entitled, "A Phase II, Multicenter, Single-Arm Study of Atezolizumab in Patients with PD-L1-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer." Supportive safety and efficacy data from studies GO28753 (POPLAR), GO28625 (FIR), and PCD4989g (NSCLC cohort) will also be provided by the Sponsor in the BLA; cross-reference will also be made to the module 3 and 4 data submitted in support of the BLA submission for Atezolizumab in metastatic urothelial bladder cancer.

Regulatory History

On April 11, 2011, Genentech submitted an IND (IND 111271) for MPDL3280A for the treatment of locally advanced and metastatic malignancies. The IND-enabling trial was protocol PCD4989g entitled "A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies".

On February 12, 2015, a meeting was held to discuss the clinical data from the Study PDC4989g and their proposed clinical development plan for MPDL3280A in for the treatment of patients with PD-L1-selected locally advanced or metastatic NSCLC that had progressed during or after standard platinum-based chemotherapy. FDA stated that for the clinical program to be considered for accelerated approval (AA) based on durable objective responses, Study G028754

(BIRCH) would need to include patients with unmet medical need with NSCLC.

On March 26, 2013, Genentech submitted IND 117296 for the investigational product MPDL3280A for the treatment of NSCLC with four ongoing studies enrolling 2L + NSCLC patients and six planned ongoing studies enrolling 1L NSCLC patients.

On September 22, 2013, Genentech submitted a preliminary breakthrough therapy designation (BTD) for MPDL3280A in 2L/3L NSCLC in patients on the basis of interim data from the POPLAR study.

On October 22, 2013, a meeting was held to discuss the acceptability of the protocols and Statistical Analysis Plans (SAPs) for BIRCH and Study G028915 (OAK) in order to support accelerated and regular approval, respectively for MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC. FDA stated that the proposed modifications to the protocols and analysis plans for BIRCH and OAK appeared acceptable provided that the changes made were entirely based on external data and that the Genentech remain blinded to the results of BIRCH and OAK.

On December 5, 2014, Genentech submitted a formal request for BTD for MPDL3280A, which was granted BTD on January 28, 2015 for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1 selected with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

On December 9, 2014, a meeting was held to seek FDA guidance regarding the proposed changes to the definition of PD-L1 positivity in NSCLC and resulting modified hypothesis testing procedures for the ongoing clinical studies, OAK and BIRCH. The FDA agreed that demonstration of an ORR of large magnitude and duration in (b) (4) BIRCH with a favorable benefit-risk profile could potentially support accelerated approval of MPDL3280A in previously treated NSCLC with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

On May 12, 2015 a meeting was held to discuss plans for filing of the BLA. FDA stated that the possibility of obtaining accelerated approval remained for programs in NSCLC populations that show a substantial improvement over available therapies, which may be demonstrated if the lower bound of the 95% CI around the observed effect exceeds the upper bound of the 95% CI observed with currently available therapies. FDA stated that it would consider the POPLAR OS analysis at approximately 150 events as the final survival analysis but would review data from a later OS analysis based on approximately 180 events as well. FDA requested datasets, including on immune-related adverse events, defined as any adverse event requiring the use of systemic corticosteroids with no clear alternate etiology.

On June 26, 2015 a teleconference was held to discuss content of the proposed BLA submission, including the format of the module 5 datasets. FDA requested that the Sponsor pool AESI and immune-mediated adverse events from POPLAR, FIR, and PCD4989g (lung), which used a

90-day reporting window, and present data side-by-side with BIRCH, which used a 30-day reporting window. FDA stated the approach to cross reference Module 3 and Module 4 of the mUC BLA in the NSCLC BLA appeared acceptable but would revisit this topic at the time of the pre-BLA meeting. FDA agreed with the Sponsor's proposal to submit separate analyses conducted in the POPLAR study for the 150 deaths and 180 deaths event groups.

On August 7, 2015 the FDA provided written feedback on the Sponsor's ORR proposal, in which the FDA agreed to consider acceptance of a meta-analysis limited to patients receiving third-line treatment for non-squamous NSCLC as the basis for comparison with the current study's ORR, reiterating that the lower bound of the BIRCH 95% CI for ORR would need to demonstrate improvement over the upper bound of the 95% CI derived from the meta-analysis. FDA stated that even if the lower bound of the 95% CI for the observed ORR in BIRCH was larger than the identified ORR, the magnitude of the improvement over available therapy had to be sufficiently large with adequate duration of response to be reasonably likely to predict clinical benefit.

Clinical/Statistical

The trials intended to support the proposed BLA (originally planned for submission in February 2016) in previously treated advanced NSCLC are summarized below (Table 1). Genentech proposes to support an initial request for accelerated approval based on the results of the BIRCH trial, with supportive data from POPLAR, FIR, and PCD4989g.

Table 1 – Clinical Studies to be included in efficacy and safety summaries evaluating MPDL3280A in Proposed BLA

Study	Design	Patient Population (No. of Patients Enrolled/Treated)	Treatment and Type of IHC Assay	Primary Efficacy Endpoint	Timing of Primary Analysis
GO28754 (BIRCH) Efficacy	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n = 130) 2L (n = 255) ≥ 3L (n = 282)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥ 2L patients IUO IHC assay	IRF-assessed ORR per RECIST v1.1	Approximately 100 PD-L1 TC3 or IC3 patients in Cohort 3 with minimum 6 months follow-up
GO28753 (POPLAR) Supportive	Open-label, randomized 1:1 to MPDL3280A vs. docetaxel	All comers with 1 or 2 prior chemotherapy regimens according to stratification: 1 prior chemotherapy (n = 189) 2 prior chemotherapies (n = 98)	MPDL3280A as a fixed dose of 1200 mg IV q3w until loss of clinical benefit; docetaxel 75mg/m ² IV q3w till disease progression or intolerable toxicity IUO IHC assay	Overall survival	A total of approximately 180 deaths have been observed in the overall population
GO28625 (FIR) Supportive	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n = 31) ≥ 2L (n = 94) ≥ 2L with previously treated brain metastases (n = 13)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥ 2L patients IUO IHC assay	Investigator-assessed ORR per modified RECIST	6 months after the last patient is enrolled
PCD4989g Supportive	Multicenter, dose escalation, and expansion	All comers, enrollment ongoing a; for NSCLC cohort 1L = 15 2L = 23 3L + = 50	Weight-based dose escalation (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 15, and 20 mg/kg) and fixed 1200 mg dose, administered IV q3w up to 1 year or loss of clinical benefit Prototype IHC assay	investigator-assessed ORR per RECIST v1.1 a	Data up to 2 December 2014

1L = first-line; 2L = second-line; 3L = third-line; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; IRF = Independent Review Facility; IUO = investigational use only; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell. The primary objective of this study is to evaluate the safety and tolerability of MPDL3280A. In order to further characterize the safety of MPDL3280A and to assess biomarkers of tumor activity in different cancer types, this study was amended to increase enrollment in the expansion cohort.

The proposed criteria for PDL-1 expression assessment are presented in Table 2. This assessment takes into account PDL-1 expression on both the tumor cells (TC) and the tumor-infiltrating immune cells (IC).

Table 2. Proposed Criteria for PD-L1 Expression Assessment in Planned BLA

Description of IHC Scoring Algorithm	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering <1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between $\geq 1\%$ and <5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between $\geq 5\%$ and <10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering $\geq 10\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in <1% TCs	TC0
Presence of discernible PD-L1 staining of any intensity in $\geq 1\%$ and <5% TCs	TC1
Presence of discernible PD-L1 staining of any intensity in $\geq 5\%$ and <50% TCs	TC2
Presence of discernible PD-L1 staining of any intensity in $\geq 50\%$ TCs	TC3

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death-ligand 1; TC = tumor cell.

Trial design and results

1. BIRCH

BIRCH Trial Design

The BIRCH study is a multicenter, three-arm, parallel cohort trial of atezolizumab conducted in patients with PD-L1-positive (IHC 2+ or 3+), locally advanced or metastatic non-small cell lung cancer (NSCLC). The primary objective for this study is to evaluate the ORR of atezolizumab as assessed by an Independent Review Facility (IRF) according to RECIST v1.1. There were three cohorts studied that were defined based on extent of prior treatment:

- Cohort 1: Patients who are chemotherapy-naive (first-line treatment)
- Cohort 2: Patients who have received one prior line of platinum-based chemotherapy (second-line treatment)
- Cohort 3: Patients who have received at least 2 lines of prior therapy (a platinum-based chemotherapy and at least one additional regimen for advanced NSCLC (third or greater line

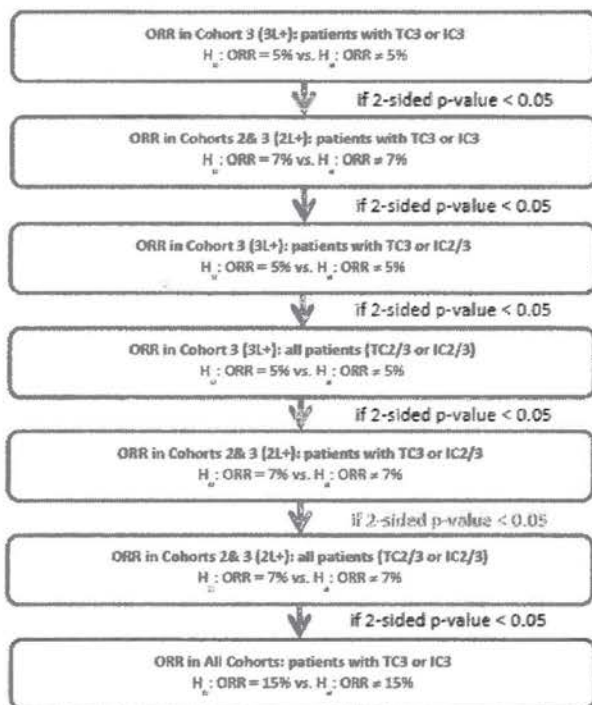
treatment).

Protocol-specified treatment in all cohorts was atezolizumab 1200 mg intravenously every three weeks (Day 1 of each 21-day cycle). Patients in Cohort 1 were to receive atezolizumab until RECIST-defined disease progression or unacceptable toxicity. Patients in Cohorts 2 and 3 were allowed to receive atezolizumab past tumor progression at the investigator's discretion as long as patients were demonstrating clinical benefit as assessed by the investigator defined as absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression.

The SAP called for a primary analysis to be performed after approximately 100 patients with PD-L1 TC3 or IC3 NSCLC in Cohort 3 have a minimum of 6 months follow-up (or have discontinued). With approximately 100 patients who are PD-L1 TC3 or IC3 enrolled in Cohort 3, there is > 99% power to detect a 25% increase in ORR from 5% to 30% in this population at the 5% two-sided significance level.

The primary efficacy analysis successively tested the IRF-assessed ORR per RECIST v1.1 in seven subpopulations using a hierarchical fixed-sequence procedure as shown in Figure 1.

Figure 1 Hierarchical Fixed-Sequence Testing Procedure for the Primary Efficacy Endpoint in BIRCH



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BIRCH Trial Results

The ORR in BIRCH in the ITT population is shown below. In Cohort 3 (3L+), the TC3 or IC3 subgroup had the highest ORR at 27.0% (95% CI: 19.1, 36.0). Additionally, the ORR in this subgroup was similar between squamous and non-squamous patients (27.0% [95% CI: 13.8, 44.1] and 26.9% [95% CI: 17.5, 38.2], respectively) DOR was evaluated in treated patients whose confirmed best overall response was a complete or partial response. As of the clinical cutoff date of 28 May 2015, 61.3% of the DOR-evaluable patients in the TC3 or IC3 subgroup of Cohort 3 (3L+) had ongoing response (i.e., no progressive disease or death). The minimum follow-up was 6 months for this subgroup, and the median DOR was 7.2 months (95% CI: 5.6, NE). OS data are not mature. The 6-month survival rate for the 3L + TC3 or IC3 subgroup was 75.1%.

**Objective Response Rates for Pre-Specified Subgroups
(Assessment by IRF per RECIST v1.1)**

Line of Therapy	PD-L1 Subgroup	ORR per IRF RECIST v1.1 Responders (%) (95% CI)
3L+ (Cohort 3)	TC3 or IC3	27.0% (31 of 115) (19.1, 36.0)
2L+ (Cohorts 2+3)	TC3 or IC3	25.3% (60 of 237) (19.9, 31.4)
3L+ (Cohort 3)	TC3 or IC2/3	18.2% (43 of 236) (13.5, 23.8)
3L- (Cohort 3)	TC2/3 or IC2/3	17.4% (44 of 253) (12.9, 22.6)
2L+ (Cohorts 2+3)	TC3 or IC2/3	17.8% (86 of 483) (14.5, 21.5)
2L+ (Cohorts 2+3)	TC2/3 or IC2/3	17.3% (90 of 520) (14.2, 20.8)
All lines (Cohorts 1+2+3)	TC3 or IC3	25.5% (77 of 302) (20.7, 30.8)

IC = tumor-infiltrating immune cell; IRF = Independent Review Facility;
ORR = objective response rate; RECIST = Response Evaluation Criteria in
Solid Tumors; TC = tumor cell.

Note: The p-value for each of the specified subgroups was < 0.0001 when
comparing observed ORR with the protocol-specified historical control.

The overall safety profile of atezolizumab in the BIRCH study was as follows: 93.6% reported AEs of any grade (64% attributable to atezolizumab), and 38.2% experienced Grade 3-4 AEs (11.2% attributable to atezolizumab). There was a 2.9% rate of grade 5 AEs, with 1 patient (0.2%) experiencing a grade 5 AE thought to be attributable to atezolizumab (pneumonia). Overall, 26.3% of patients reported an adverse event of special interest (AESI). The most frequently occurring AESIs were rash (9.1%), AST increased, hypothyroidism, and pneumonitis (3.6% each), and ALT increased (3.2%).

2. POPLAR

POPLAR Trial Design

POPLAR is a Phase II, global, multicenter, open-label, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

Male and female patients aged ≥ 18 years with ECOG performance status of 0 or 1 who had locally advanced or metastatic NSCLC and who experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy, or those who progressed within 6 months of a platinum-based adjuvant or neoadjuvant regimen. Patients were not to have received more than two prior regimens of cytotoxic chemotherapy. Tumor specimens from eligible patients were prospectively tested for PD-L1 expression on ICs and TCs using the IUO-labeled VENTANA PD-L1 (SP142) CDx assay (see Section 10.5). The study enrolled all patients whose tissue was evaluable for expression testing, regardless of PD-L1 expression status.

Eligible patients were stratified by PD-L1 IC status, by number of prior chemotherapy regimens, and by histology, and randomized 1:1 to atezolizumab or docetaxel. The study planned to enroll patients until a minimum of approximately 54 patients considered PD-L1 selected (defined by having PD-L1 status of IC2 or IC3 [IC2/3]) were enrolled. In the case that the prevalence of the PD-L1+ selected subset patients was lower than 18%, up to a maximum of approximately 300 total patients was planned to be enrolled. On the basis of enrollment trends, the study was expected to enroll 285 total patients and 55 PD-L1 IC2/3 patients.

Atezolizumab at a fixed dose of 1200 mg was administered intravenously on Day 1 of each 21-day cycle. Atezolizumab treatment continued as long as patients were experiencing clinical benefit, and patients were permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease if they were otherwise stable and deriving benefit from treatment. Docetaxel 75 mg/m² was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

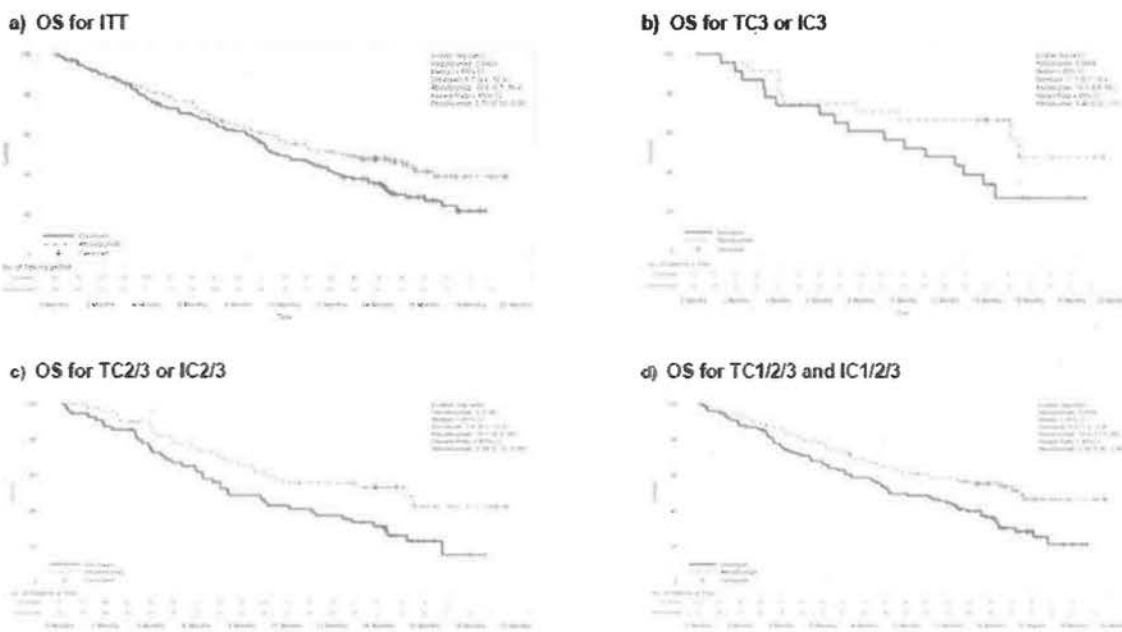
The primary efficacy outcome measure was OS. The SAP for POPLAR called for three interim OS analyses to be conducted when approximately 30, 100, and 150 events in the overall population occurred. A small alpha of 0.0001, 0.0001, and 0.001 was spent for the first, second, and third planned interim analysis of OS, respectively. For U.S. registrational purposes, the third interim analysis was considered the main efficacy analysis for this study. The primary analysis was performed when a total of approximately 180 deaths were observed in the overall population. At the primary analysis, the OS analysis was conducted at the 4.88% level of significance in four populations, with a hierarchical fixed-sequence testing procedure in the following order: 1) TC2/3 or IC2/3; 2) TC1/2/3 or IC1/2/3; 3) ITT; and 4) TC3 or IC3.

POPLAR Trial Results

In the ITT population, atezolizumab had a statistically significant OS improvement over docetaxel (stratified HR of 0.73, 95% CI: 0.53, 0.99; $p = 0.040$). OS improvement favoring atezolizumab was also observed across the PD-L1 expression subgroups of TC3 or IC3 (unstratified HR of 0.49, 95% CI: 0.22, 1.07; $p = 0.068$), TC2/3 or IC2/3 (unstratified HR of 0.54, 95% CI: 0.33, 0.89; $p = 0.015$), and TC1/2/3 or IC1/2/3 (unstratified HR of 0.59, 95% CI: 0.42, 0.94; $p = 0.0050$).

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Figure 7 Kaplan-Meier OS Curves for ITT and PD-L1 Expression Subgroups in POPLAR (Clinical Cutoff 8 May 2015)



In terms of safety data, the number of patients reporting at least one adverse event was similar between docetaxel and atezolizumab (96.3% vs. 95.8%, respectively). In the atezolizumab arm, fatigue (38.7%), decreased appetite (34.5%), dyspnea (26.8%), cough (26.8%), nausea (21.8%), and constipation (20.4%) were the most common. In the docetaxel arm, fatigue (40.0%), alopecia (38.5%), nausea (33.3%), diarrhea (28.1%), cough (24.4%), constipation (23.7%), decreased appetite (20.7%), and dyspnea (20.0%) were the most common. Grades 3-4 events were reported at a higher rate in the docetaxel arm (52.6% vs. 40.1%). The Grade 5 adverse event rate (with 30-day window) was comparable between treatment arms (3.7% docetaxel and 4.2% atezolizumab). An event each of death, sepsis, and acute respiratory distress syndrome were considered related to docetaxel treatment per the investigator. Cardiac failure was the only Grade 5 adverse event considered related to atezolizumab treatment per the investigator. Serious adverse events attributed to docetaxel occurred at a higher rate than those attributed to atezolizumab (17.0% vs. 8.5%). In the atezolizumab arm, rash (9.1%), hypothyroidism (4.9%), rash maculo-papular (2.8%), and AST increased and pneumonitis (2.1% each) were the most frequently occurring Grade 1-2 AESIs; there were 3 patients (2.1%) with Grade 3-4 increases in AST.

Additional supportive studies- FIR and PCD4989g (NSCLC cohort)

Table 26 Topline Efficacy Results in Study PCD4989g and FIR by PD-L1 Diagnostic Subgroups (Efficacy-Evaluable Population)

Efficacy Endpoint	Study PCD4989g ^a			FIR ^a	
	Efficacy Evaluable (All Comer) (n=88)	TC3 or IC3 (n=22)	TC2/3 or IC2/3 (n=48)	Efficacy Evaluable (TC2/3 or IC2/3) (n=93)	TC3 or IC3 (n=38)
ORR (95% CI) ^b	22.7% (20 of 88) (14.5, 32.9)	50% (11 of 22) (28.2, 71.8)	33.3% (16 of 48) (20.4, 48.4)	16.1% (15 of 93) (9.3, 25.2)	23.7% (9 of 38) (11.4, 40.2)
Median DOR (months) (95% CI) ^b	17.3 (14.2, 24.7)	14.6 (8.7, 25.3)	17.3 (14.2, NE)	NE (10.4, NE)	NE (10.4, NE)
Patients without event	40% (8 of 20)	45.5% (5 of 11)	50.0% (8 of 16)	86.7% (13 of 15)	88.9% (8 of 9)
Median PFS (months) (95% CI) ^b	3.8 (2.6, 10.0)	7.1 (1.4, 17.3)	2.8 (1.9, 10.1)	2.7 (1.5, 3.5)	4.1 (1.5, 13.0)
Median OS (months) (95% CI)	16.5 (13.7, 22.0)	17.9 (14.5, NE)	17.9 (14.1, NE)	10.6 (5.7, NE)	NE (5.8, NE)
Patients without event	44.3% (39 of 88)	54.5% (12 of 22)	50% (24 of 48)	53.8% (50 of 93)	63.2% (24 of 38)

1L=first-line; 2L=second-line; 2L+=second-line and beyond; 3L+=third-line and beyond; IUO=investigational use only; NE=not estimable; ORR=objective response rate (confirmed); OS=overall survival; PFS=progression-free survival.

Notes: The results of Study PCD4989g are based on a clinical cutoff date of 2 December 2014. The results of FIR are based on a clinical cutoff date of 7 January 2015.

Study PCD4989g used a prototype assay to test for PD-L1 expression while FIR used the IUO assay, similar to POPLAR and BIRCH.

^a Only Cohort 2 (2L+) patients for FIR. All lines of therapy (1L, 2L, and 3L+) in Study PCD4989g.

^b ORR/DOR/PFS as assessed by investigator per RECIST v1.1.

ORR Benchmark Comparison to BIRCH primary efficacy endpoint

In the FDA’s August 7, 2015 communication with the Sponsor, the following statement was made- “FDA would accept a proposal comparing the lower bound of the 95% CI of the observed ORR in BIRCH with the upper bound of the 95% CI for the ORR derived from the meta-analysis limited to patients receiving third-line treatment for non-squamous NSCLC (NS-NSCLC). Evidence of a substantial improvement over available therapy may be demonstrated if the lower bound of the 95% CI around the observed ORR in BIRCH exceeds the upper bound of the 95% CI of ORR with nivolumab for second- or further-line treatment of squamous NSCLC or with ramucirumab plus docetaxel for second-line treatment of NS-NSCLC. Please note that even if the lower bound of the 95% CI for the observed ORR in BIRCH is larger than the ORR identified in the meta-analysis of historical studies for a specific population, the magnitude of the ORR improvement over available therapy in BIRCH must be sufficiently large with adequate duration to be reasonably likely to predict clinical benefit.”

The Sponsor submitted benchmark ORR data based on the available Nivolumab data in squamous NSCLC as well as their own meta-analysis of observational studies, in the 3L+ and 2L settings. These data are presented below:

Table 29 Benchmarks by Line of Therapy and Histology

Patient Population by Line of Therapy and Histology	ORR Benchmark Source	Patient Population Size	ORR Benchmark (95% CI)	BIRCH ORR by IRF in TC3 or IC3 (95% CI)
				Overall n=115^a 27.0% (19.1, 36.0)
3L+ squamous	CheckMate 063 (nivolumab),	117	14.5% (8.7, 22.2)	Squamous n=37^a 27.0% (13.8, 44.1)
3L+ non-squamous	Meta-analysis of observational studies ^b	495	6.8% (4.9, 9.2)	Non-squamous n=78^a 26.9% (17.5, 38.2)
				Overall n=237^c 25.3% (19.9%, 31.4%)
2L+ squamous	Pooled results of CheckMate 063 and 017 (nivolumab)	252 (117+135 ^d)	16.9% (12.5, 22.5)	Squamous n=78^c 17.9% (10.2%, 28.3%)
2L non-squamous	REVEL study (ramucirumab plus docetaxel)	465	21.9% (18.3, 26.0)	Non-squamous n=159^c 28.9% (22.0%, 36.6%)

^a These are 3L+ TC3 or IC3 ORRs.

^b This benchmark rate was derived by the Sponsor based on a meta-analysis of observational studies. The methodology, which was developed prior to the database lock of BIRCH, is described in Appendix 17.

^c These are 2L+ TC3 or IC3 ORRs.

^d Study CheckMate 017 included 135 patients in the nivolumab arm and 137 patients in the docetaxel arm.

Updated Accelerated Approval Proposal

On October 29, 2015, FDA held an informal teleconference with Genentech (b) (4)

(b) (4) based on the current landscape of available therapy for second-line treatment of patients with advanced NSCLC, including the recent traditional approval of nivolumab for second- and further-line treatment of patients with metastatic NSCLC. Genentech therefore responded with the following proposal:

“Genentech proposes a February/March 2016 submission of a BLA for atezolizumab accelerated approval in 2L+ TC3 NSCLC, with subsequent submission of the PMA Modules 3 and 4 for the Ventana PD-L1 (SP142) companion diagnostic in NSCLC.”

Genentech also proposed to modify the Phase 3 study OAK (GO28915) to conduct the primary analysis based on the 850 initially enrolled patients (the sample size specified in the original protocol), after ~595 events have occurred within this subgroup. This will provide 93.5% power to detect an OS hazard ratio of 0.73 at a two-sided alpha level of 0.02. Top-line results from this primary analysis are anticipated to be available for submission in Q3 2016, during the BIRCH BLA review. Genentech proposes to conduct secondary analyses on all patients enrolled in OAK (n=1225 patients) in Q1 2017.

In support of the updated proposed indication, Genentech provided the data analysis shown in the table below.

Data Source	Patient Population	Nivolumab Benchmark ORR (95% CI upper bound)	BIRCH Data ORR (95% CI lower bound)
CheckMate 063 + CheckMate 017	2L+ squamous	17.5% (23.6%)	<u>2L+ TC3 NSCLC</u> 32.4% (24.7%)
CheckMate 057	2L+ non-squamous	19.2% (24.2%)	

Genentech states that the ORR benefit in the 2L+ TC3 NSCLC patients was observed across supportive trials PCD4989g (50.0%, n=10), FIR (GO28625; 22.7%, n=22), and POPLAR (GO28753; 40.0%, n=15). Moreover, Genentech states that the POPLAR OS hazard ratio for this patient population is 0.36 (n=30).

FDA sent Preliminary Comments to Genentech, Inc. on November 5, 2015.

2. DISCUSSION

List of Genentech's Questions to FDA in Genentech's updated proposal dated November 2, 2015:

Question 1a:

Does FDA agree that there is a path for accelerated approval in 2L+ TC3 NSCLC?

FDA Response:

Yes. FDA agrees that the updated evidence provided by Genentech on the activity of atezolizumab in the 2L+ TC3 NSCLC population supported by the results of the supportive trials (FIR, POPLAR, and PCD4989g) in the 2L+ TC3 NSCLC population can support submission of a BLA for FDA review under the accelerated approval provisions. However, the final benefit-risk determination for atezolizumab in the 2L+ TC3 population and the

exact indication will be based on review of the data by FDA. Determination of available therapies is made at the time of BLA action.

GNE Response:

The Sponsor acknowledges the Agency's feedback and would like to discuss the impact of a potential pembrolizumab full approval on the planned atezolizumab BLA. Specifically, the Sponsor would like to understand whether the Agency would keep the BIRCH BLA open and accept the OAK top-line results in the event that pembrolizumab receives full approval in a selected 2L+ population during the BIRCH BLA review but prior to availability of OAK top-line results.

Meeting Discussion:

FDA agreed to accept the OAK topline results during the review of the proposed BLA provided that Genentech submitted the data within the PDUFA timeframe.

Question 2a:

Does FDA agree to accept OAK top-line results during the BIRCH BLA review?

FDA Response:

Yes. FDA states it's acceptable to submit topline results from OAK during the proposed BLA review.

GNE Response:

The Sponsor proposes to provide top-line results from the OAK primary analysis in September 2016. This analysis will be based on the first 850 patients enrolled, with an anticipated clinical cutoff date of July 2016 and the following estimated dates related to data availability:

- Data extraction is planned for August 2016.
- A summary document containing summary tables and explanatory text for all topline results will be submitted in September 2016.

Top-line results will include the following:

- Efficacy for the first 850 patients enrolled:
 - OS in all-comers and TC1/2/3 or IC1/2/3, TC2/3 or IC2/3, and TC3 or IC3 subgroups
- Demographics for (1) first 850 patients and (2) full ITT of 1225 patients – in all-comers and TC1/2/3 or IC1/2/3, TC2/3 or IC2/3, and TC3 or IC3 subgroups
- Topline safety for treated ITT of 1225 patients, including all adverse events, deaths, adverse events of special interest, adverse events leading to study treatment discontinuation, and serious adverse events

The Sponsor is targeting to submit the BIRCH BLA in mid-February 2016 and request Priority Review, which would result in an mid-October 2016 PDUFA date. Because the OAK results are based on an event-driven analysis, data extraction in August 2016 is a projection based on

current event rates and there is a risk that the topline results may not be available before a mid-October PDUFA date.

- I. Does FDA have any comments on the proposal for OAK topline results?

Meeting Discussion:

FDA stated that Genentech's proposed topline efficacy and demographic data for OAK is acceptable and that topline safety results will not necessarily be required based on Genentech's proposal timing for submission of the results during the BIRCH BLA review. Please also refer to FDA response to Question 1a.

- II. Does FDA require submission of datasets together with the OAK topline results?

Meeting Discussion:

Yes, FDA requires submission of datasets with the OAK topline results discussed in 2a (I). FDA stated that the required datasets do not have to be in CDISC format.

- III. Does FDA agree that submission of the OAK topline results could support full approval?

Meeting Discussion:

This is a review issue.

- IV. Is there a minimum duration of time prior to the PDUFA date when FDA must receive the summary document of OAK topline data?

Meeting Discussion:

FDA recommended submission of OAK topline results and data at least one month prior to the proposed BLA's PDUFA goal date.

- V. Does FDA have any comments on the Sponsor's proposal to request Priority Review and the timeline risk associated with topline OAK results submission?

Meeting Discussion:

FDA had no further comments.

Question 3a:

With respect to the OAK analysis, would FDA agree to an OAK primary analysis on the first 850 patients enrolled onto the study, and to conduct secondary analyses on all patients enrolled in OAK?

FDA Response:

FDA generally agreed with Genentech's proposal to modify the statistical analysis plan (SAP) in OAK to conduct the primary analysis based on the 850 initially enrolled patients and to conduct the secondary analyses on all patients enrolled in OAK (n=1225). FDA will provide further comments to Genentech upon review of the modified SAP for OAK.

FDA requested a timeline regarding the submission of the revised SAP for OAK, the final clinical module for the BLA, and the topline results from OAK.

GNE Response:

The Sponsor proposes an OAK primary analysis of OS as shown in Figure 1. Details will be provided in the SAP for the Agency's review, to be submitted in December 2015.

Figure 1:



Notes:

- Prevalence Assumption for TC1/2/3 or IC1/2/3: 65%
- FPI: March 2014
- LPI:
 - November 2014 for first 850 pts
 - April 2015 for 1225 pts
- Data maturity projected for July 2016 when 595 events are observed in the first 850 enrolled pts

Does the Agency agree with the proposed OAK primary OS testing procedure?

The following submission timeline is proposed:

Revised SAP for OAK – December 2015

Final clinical BIRCH BLA module – targeted for mid-February 2016

The following are event-driven and based on current projections:

Summary document with all topline results from OAK – targeted for September 2016

Meeting Discussion:

FDA generally agreed with OAK primary analyses of OS on the first 850 patients (595 events). FDA noted that analyses conducted beyond the proposed final analysis for the first 850 patients will be considered exploratory. FDA agreed to review the revised SAP and provide additional comments if necessary. FDA stated that Genentech can also consider conducting an interim analysis of OS and provide the topline results and the data during the proposed BIRCH BLA review with the final analysis conducted at a later time point. FDA reiterated that the revision to the statistical design of OAK and the approach for submission of the topline results and data during the BIRCH BLA review will ultimately be Genentech's decision.

CDRH Comments based on Genentech's Updated Proposal:

- 1. In order to avoid missing data or potential selection bias, the sponsor should ensure that Each enrolled patient including the first part of trial, i.e. patients who were enrolled based on IC status only (161 enrolled patients in which 159 were treated) has TC test result.**

GNE Response:

The Sponsor acknowledges the Agency's feedback, and will provide this information in the BLA and PMA. No further discussion is needed.

Meeting Discussion:

None.

2. For us to better understand the device clinical performance and distribution of test results, the sponsor should provide the following information for the second part of trial, i.e. patients who were enrolled based on TC or IC status (506 enrolled patients in which 500 were treated):

- the number of patients in each cell in the below table
- the drug efficacy in each cell in the following table for the screening population

		TC				
		0	1	2	3	
IC	0					
	1					
	2					
	3					

GNE Response:

The Sponsor acknowledges the Agency's feedback. The Sponsor proposes to provide the requested table with TC/IC distribution and ORR results for all treated patients who were enrolled after the IDE amendment. The specific TC/IC subgroups will be based on raw scores from the TC3 to IC3 stepwise reread.

Does the Agency agree with this proposal?

Meeting Discussion:

FDA agreed with that proposal and stated that Genentech clarified that all patients have both TC and IC scoring.

3. The sponsor should provide drug efficacy estimates in the TC3 and TC2 data sets and also provide drug efficacy comparison between these two data sets.

GNE Response:

The Sponsor acknowledges the Agency's feedback and proposes to provide efficacy data based on raw scores from the TC3 to IC3 stepwise reread, as follows:

- ORR by IRF will be summarized for both TC3 and TC2 patient populations.
- ORR by IRF will be summarized separately for treated patients enrolled before and after IDE amendment, as well as all treated patients enrolled into BIRCH.

Does the Agency agree with this proposal?

Meeting Discussion:

FDA agreed with Genentech's proposal.

4. The sponsor should confirm that the clinical trial assay (CTA) is the final version and is same as the market ready assay (MRA). If the CTA and the MRA are not the same, a bridging study will be needed.

GNE Response:

The Sponsor confirms that the CTA is the same as the MRA. No further discussion is needed.

Ventana will contact CDRH for additional input following the Pre-BLA meeting, as needed.

Meeting Discussion:

None.

List of Genentech's original Questions to FDA in the original Pre-BLA meeting background package dated October 9, 2015:

Question 1:

Does the Agency agree that the efficacy and safety results from the pivotal study BIRCH, [REDACTED] (b) (4), and from the supporting studies POPLAR, FIR, and Study PCD4989g (NSCLC cohort) provide sufficient clinical evidence to characterize the benefit-risk profile of atezolizumab and to form the basis of a BLA [REDACTED] (b) (4)?

FDA Response:

Please refer to FDA response to Question 1a.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 2:

Does the Agency agree that the data from BIRCH support the following indication:

Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are selected by PD-L1 status, as determined by an

FDA-approved test, after failure of (b) (4) platinum-containing chemotherapy regimen

FDA Response:

Please refer to FDA response to Question 1a. The exact indication for atezolizumab in NSCLC will be decided at the time of review.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 3:

Given the unmet medical need for patients with metastatic NSCLC (b) (4) and the data presented in BIRCH, the Sponsor plans to submit a request for Priority Review. Does the Agency have any comments?

FDA Response:

FDA agrees with Genentech submitting a request for Priority Review designation at the time of the proposed BLA submission for the updated proposed indication discussed in 2L+ TC3 NSCLC population. Please refer to FDA response to Question 1a.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion required.

Meeting Discussion:

None.

Question 4:

Given the totality of the evidence for atezolizumab in NSCLC, including the overall survival (OS) benefit observed in POPLAR, does the Agency agree that these data may support accelerated approval of atezolizumab for the treatment of 2L+ TC2/3 or IC2/3 NSCLC patients?

FDA Response:

Please refer to FDA response to Question 1a.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 5:

In light of the safety results from BIRCH, POPLAR, FIR, and Study PCD4989g (NSCLC cohort), does the Agency agree with the Sponsor's proposal of not submitting a Risk Evaluation and Mitigation Strategy (REMS) for the use of atezolizumab in the proposed indication?

FDA Response:

Based on the safety data described in the meeting package, FDA does not anticipate any REMS requirements. However, this decision will ultimately be a review issue.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 6:

Does the Agency agree with the Sponsor's plans for a rolling submission of the NSCLC BLA and for cross referencing Module 2.3, Module 3, and Module 4 of the metastatic urothelial carcinoma (mUC) BLA 761034 in the NSCLC BLA?

FDA Response:

Yes, FDA agrees with Genentech's plan for a rolling submission of the NSCLC BLA (updated proposed indication discussed in Question 1a) and for cross referencing Module 2.3, Module 3, and Module 4 of the metastatic urothelial carcinoma BLA 761034.

GNE Response:

The Sponsor acknowledges the Agency's feedback, and plans to submit a formal request for rolling submission to the IND in the week of November 9.

May the Sponsor proceed with initiation of the rolling submission shortly thereafter?

Meeting Discussion:

Yes.

Question 7:

Does the Agency agree with the dataset format for population pharmacokinetic (PK), exposure-response, and concentration QT analyses?

FDA Response:

Yes, FDA agrees that the proposed dataset format seems acceptable.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 8:

Does the Agency foresee at this time that the proposed BLA will be reviewed by the Oncologic Drugs Advisory Committee (ODAC)?

FDA Response:

The final decision will be made at the time of the proposed BLA review.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 9:

Does the Agency agree that the data from the pivotal study BIRCH is adequate to demonstrate the clinical utility of the VENTANA PD-L1 (SP142) companion diagnostic (CDx) assay in support of a Premarket Approval (PMA) submission [REDACTED] (b) (4)

?

FDA Response:

Please see CDRH Comments based on Updated Proposal listed above.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 10:

Would the Agency like to have an orientation meeting with the Sponsor after submission of the BLA to outline the major components of the BLA?

FDA Response:

Yes, FDA would like to have an orientation meeting with Genentech after submission of the BLA for atezolizumab.

GNE Response:

The Sponsor acknowledges the Agency's feedback. No further discussion is needed.

Meeting Discussion:

None.

Question 11:

Does the Agency agree with proposed content and format of the NSCLC BLA?

FDA Response:

Yes. Your proposal appears reasonable. Please provide FDA with separate datasets for patients who were treated beyond progression on the protocol.

The proposed content and format of the clinical pharmacology components appear to be acceptable.

GNE Response:

The Sponsor acknowledges the Agency's feedback and proposes to provide a flag variable in the Integrated Summary of Efficacy datasets (pooled data across 4 studies including demographics, key efficacy, and exposure) to identify patients who were treated beyond progression. Does the Agency agree with this proposal?

In addition, [REDACTED] (b) (4) the Sponsor plans to update the Summary of Clinical Efficacy (SCE) and the Summary of Clinical Safety (SCS) analyses accordingly. Specifically:

- The SCE prespecified analyses will be performed for the indicated population, 2L+ TC3 NSCLC patients.
- In addition to the analyses described in the SCS SAP (submitted 13 August 2015 as Serial No. 0293) for all treated NSCLC patients [REDACTED] (b) (4) patients, selected safety outputs will be provided for the indicated population, TC3 2L+ NSCLC. These outputs include: all adverse events, adverse events of special interest, deaths, adverse events leading to study treatment discontinuation, and serious adverse events.

Meeting Discussion:

FDA agreed with Genentech's proposal to provide a flag variable in the Integrated Summary of Efficacy dataset to identify patients treated beyond RECIST progression.

FDA also requested the following variables in the Integrated Summary of Efficacy datasets:

- 1- Reason(s) for and timing of study drug discontinuation for patients who continued therapy beyond RECIST progression.
- 2- Tumor response and timing in patients who continued therapy beyond RECIST progression.

FDA also stated that Genentech's proposal for SCE and SCS in the TC3 patient population is acceptable.

Genentech asked if FDA would accept the 90-day safety update results with no accompanying datasets. FDA states that the datasets for the 90-day safety update will not be necessary provided that there are no clinically significant unexpected adverse events.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed on the following:

BLA 761041: LATE COMPONENT – CLINICAL- FDA recommends submission of OAK topline data approximately 30 days prior to the PDUFA date of the original application

BLA 761041: CROSS REFERENCE – QUALITY SUMMARY- Module 2.3 cross referenced to Part 1 of BLA 761034

BLA 761041: CROSS REFERENCE – QUALITY - Module 3 cross referenced to Part 1 of BLA 761034

BLA 761041: CROSS REFERENCE – NONCLINICAL- Module 4 cross referenced to Part 1 of BLA 761034

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan 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. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

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](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in 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
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and

archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

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.				

Office of Scientific Investigations (OSI) Requests

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 (Item 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 Item 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 (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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).

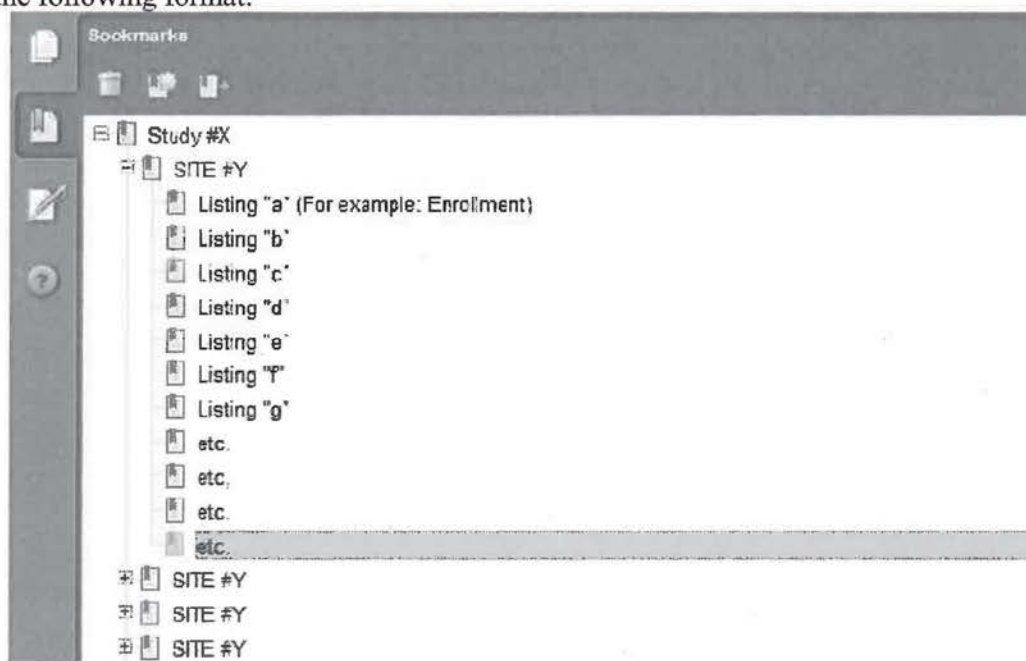
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number

- 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 NDA 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).

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:



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.

Attachment 1

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.”

DSI 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:

```
- [m5]
  - datasets
    - bimo
      - site-level
```

- 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.

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/s/

SAKAR M WAHBY
11/16/2015

SEAN N KHOZIN
11/16/2015



IND 117296

**MEETING REQUEST-
WRITTEN RESPONSES**

Genentech, Inc.
Attention: Nitzan Sternheim
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Ms. Sternheim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to your submission dated June 23, 2015, containing a Type B meeting request. The purpose of the requested meeting was to discuss the analysis of objective response rate (ORR) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of a platinum-containing regimen, which you believe provide the information needed to evaluate the clinical benefit of MPDL3280A (atezolizumab) in the context of existing therapies.

Further reference is made to our Meeting Granted letter dated July 7, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 30, 2015, background package.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Guidance/Other
Application Number: IND 117296
Product Name: atezolizumab
Indication: non-small cell lung cancer (NSCLC)
Sponsor/Applicant Name: Genentech, Inc.
Regulatory Pathway: 505(b)(1)

BACKGROUND

On June 23, 2015, Genentech submitted a meeting request to discuss the objective response rate (ORR) in patients with locally advanced or metastatic NSCLC after failure of a platinum-containing chemotherapy regimen.

MPDL3280A (atezolizumab) is a human IgG1 monoclonal antibody designed to specifically bind to the programmed cell death-1 ligand 1 (PD-L1). Genentech states that MPDL3280A is a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans.

On February 12, 2013, a preIND (pIND 117296) meeting was held to discuss the clinical data from the Study PDC4989g, "A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies" and Genentech's proposed clinical development plan, which included a plan to seek accelerated approval for MPDL3280A in for the treatment of patients with PD-L1-selected, locally advanced or metastatic, NSCLC that had progressed during or after platinum-based chemotherapy, based on the overall response rate (ORR) observed in Study GO28754 (BIRCH), a single-arm trial assessing the overall response rate and durability of response with MPDL3280A in patients with PD-L1 positive, locally advanced or metastatic NSCLC patients receiving first-, second-, or third-line or greater therapy. FDA stated that to support a request for accelerated approval (AA) based on demonstration of a clinically meaningful response rate with adequate duration determined by independent review based on RECIST version 1.1, Study GO28754 (BIRCH) must demonstrate meaningful therapeutic benefit in this population over existing treatments (e.g., ability to treat patients unresponsive to or intolerant of, available therapy, or improved patient response over available therapy).

On March 26, 2013, Genentech submitted the IND-enabling protocol for IND 117296 investigating MPDL3280A for the treatment of NSCLC.

On October 22, 2013, a meeting was held to discuss the acceptability of the statistical analysis plans (SAPs) for the BIRCH trial and Study GO28915 (OAK) in order to support accelerated and regular approval, respectively, for MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC. FDA stated that the analysis plans for BIRCH and OAK appeared generally acceptable.

On December 5, 2014, Genentech submitted a request for Breakthrough Therapy designation (BTD) for MPDL3280A for the development program in NSCLC. The BTD request was granted on January 28, 2015, for the treatment of patients with PD-L1 positive, NSCLC with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy, if EGFR- or ALK-positive.

On May 12, 2015, Genentech held a Type B meeting with FDA to discuss whether the results from the BIRCH trial, supported by the results of the POPLAR, FIR, and Study PCD4989g studies, would support the filing of a Biologic License Application (BLA) seeking approval under the provisions of 21 CFR 610 Subpart E (accelerated approval (AA)) for the treatment of patients with previously treated NSCLC. FDA acknowledged previous statements in the December 9, 2014, meeting minutes, that demonstration of ORR of large magnitude and duration in BIRCH that provides substantial evidence of an effect (ORR), such that it is reasonably likely to predict clinical benefit, with a favorable benefit-risk profile can potentially support accelerated approval of MPDL3280A. Evidence of a substantial improvement over available therapy may be demonstrated if the lower bound of the 95% CI around the observed treatment effect exceeds the upper bound of the 95% CI of observed effect with nivolumab for the second-line treatment of squamous NSCLC, with ramucirumab plus docetaxel for second-line treatment of non-squamous NSCLC or with available therapy for third line NSCLC.

Genentech plans to submit a BLA in the first quarter of 2016 to support the accelerated approval of MPDL3280A (atezolizumab) based primarily on the results of the BIRCH trial. In order to demonstrate that MDPL3280A provides an advance over available therapy, Genentech will demonstrate that the observed response rate among the # (47.5%) patients who received only one prior line of therapy and the # (52.5%) patients who received two or more prior lines of therapy enrolled in the BIRCH trial if the lower limit of the 95% confidence interval for ORR in these subgroups exceeds the observed response rate (calculated to be 11.5% and 8.4%, respectively) for the estimated historical response rate with available therapy. The meeting background package summarizes the approach taken to determine the historical response rates for each subgroup (one prior therapy vs. two or more prior lines of therapy) observed in clinical and observational trials in meta-analyses, employing a weighted analysis adjusting for the prevalence of patients with squamous and non-squamous NSCLC in the BIRCH trial. These meta-analyses are identified in the briefing package as the "benchmark assessment".

Genentech selected the following studies for the meta-analyses:

Observational Studies and Clinical Trials Conducted with Recently Approved Products included in Benchmark Assessment

Data Source	Study Setting and Design	Study Period	No. of Patients	Key Patient Characteristics	Top 3L Treatment	ORR and 95% CI*
Girard et al. 2009	Observational study at single institution in France	2000–2006	173	All 3L 64% with ACA 70% with metastatic	36% gemcitabine 24% TKIs 18% docetaxel	5.8% (10/173) 95% CI: 2.8%, 10.4%
Massarelli et al. 2003	Observational study at two institutions in France and US	1993–2000	43	3L/4L 44% with ACA 81% in Stage IV	18% gemcitabine 18% methotrexate/5-fluorouracil/adriamycin/mitomycin 12% vinorelbine	2.3% (1/43) 95% CI: 0%, 12.3%
Younes et al. 2011 ^b	Observational study at single institution in Brazil	1990–2008	170	3L/4L 33% with ACA 100% in Stage IV	Not reported	7.3% (13/176) 95% CI: 3.9%, 12.1%
Zietemann and Duell 2011	Observational study at single institution in Germany	2003–2007	100	All 3L 74% with ACA 87% in Stage IV	28% erlotinib 20% docetaxel 14% gefitinib 13% gemcitabine	8.0% (8/100) 95% CI: 3.5%, 15.2%
Ramucirumab REVEL study in USPI and Garon et al. 2014 ^c	Multicenter study in 26 countries	2010–2014	628	All 2L 25% squamous	Not applicable	22.9% (144/628) 95% CI: 19.7%, 26.4%
Nintedanib in SmPC and Reck et al. 2014	211 centers in 27 countries	2008–2013	322	All 2L ACA	Not applicable	4.7% (15/322) 95% CI: 2.6%, 7.8%

Data Source	Study Setting and Design	Study Period	No. of Patients	Key Patient Characteristics	Top 3L Treatment	ORR and 95% CI*
Nivolumab CheckMate 063 in USPI and Rizvi et al. 2015	27 sites in 4 countries	2012–2014	117	100% squamous 35% 3L, 44% 4L, 21% 5L+	Not applicable	14.5% (17/117) 95% CI: 8.7%, 22.2%
Nivolumab CheckMate 017 in Spigel et al. 2015	106 sites in 20 countries	2012–2014	136	All 2L squamous	Not applicable	20.0% (27/136) 95% CI: 13.6%, 27.8%
Nivolumab CheckMate 057 in Paz-Ares et al. 2015	117 sites in 22 countries	2012–2015	292	88% 2L, 12% 3L 100% non-squamous	Not applicable	19.2% (56/292) 95% CI: 14.8%, 24.2%

2L=second-line; 3L=third-line; 4L=fourth-line; 5L=fifth-line; ACA = adenocarcinoma, SmPC = summary of product characteristics; TKI=tyrosine kinase inhibitor; USPI=United States Prescribing Information.

* 95% CI is derived by the Sponsor using the Clopper-Pearson method.

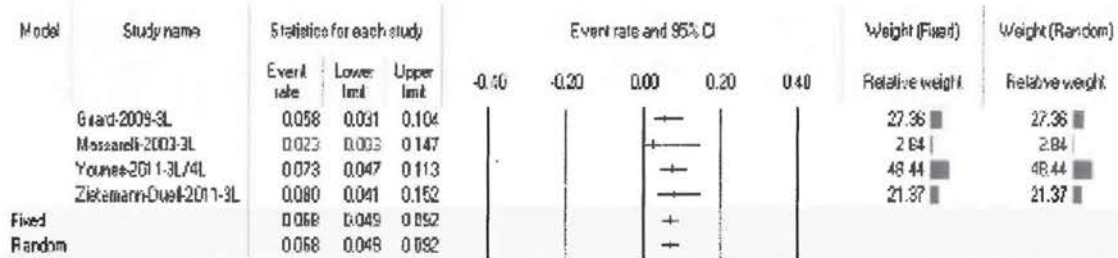
^b The Younes et al. paper provided the number of 4L patients but did not report response rate in this subgroup.

^c REVEL study (Garon et al. 2014) had an ORR of 26.8% (42/157; 95% CI: 20.0%, 34.4%) for squamous and 21.8% (102/465; 95% CI: 15.3%, 26.0%) for non-squamous.

The ORR in population who had received 2 or more lines of prior therapy (3L+) for squamous NSCLC in the nivolumab CheckMate 063 study is 14.5% [95% CI: 8.7%, 22.2%]. In order to estimate the ORR in the population who had received 2 or more lines of prior therapy third-line treatment for treatment of non-squamous NSCLC patient population, the meta-analysis was

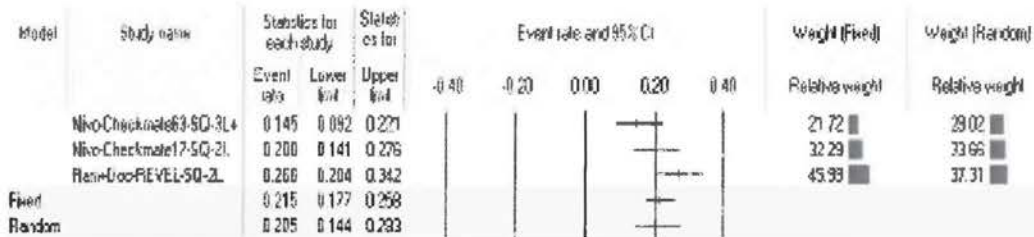
conducted using results of observational studies in patients with squamous or non-squamous NSCLC who had received 2 or more lines of prior therapy.

Results of Meta-Analysis in 3L+ Non-Squamous NSCLC

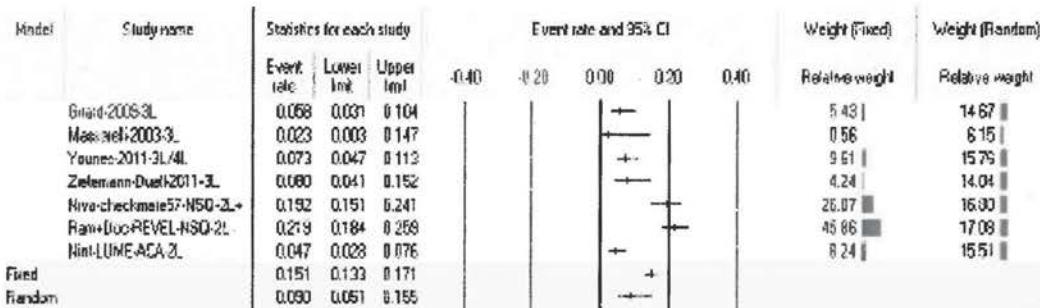


Utilizing weighted averages for the prevalence of patients with squamous and non-squamous NSCLC enrolled in the BIRCH trial (28% squamous and 72% non-squamous), the estimated historical ORR with approved drugs for treatment patients with NSCLC who have received 2 or more lines of prior therapy was estimated to be 8.4% [95% CI: 6.5%, 10.9%].

Results of Meta-Analysis in 2L+ Squamous NSCLC



Results of Meta-Analysis in 2L+ Non-Squamous NSCLC



Using estimates from the random-effects model by histology type and the observed prevalence of squamous and non-squamous NSCLC among patients enrolled in BIRCH, the weighted estimate of for the historical ORR among patients with NSCLC who received one prior line of therapy was estimated to be 11.5% [95% CI: 7.6%, 17.0%].

OBJECTIVES

- To seek and obtain FDA feedback on the historical ORR assessment for the proposed BLA.

QUESTION AND RESPONSE

1. Does the Agency agree with the Sponsor's analyses for the historical ORR estimations in 2L + 3L + NSCLC patients?

FDA response: FDA does not accept the proposed approach for establishing an advance over available therapy using the lower bound of 99.5% CI of the observed ORR in the BIRCH trial for the pooled population (both squamous and non-squamous NSCLC) compared with the meta-analysis determined point estimate of ORR for a pooled population of patients with NSCLC. FDA would accept a proposal comparing the lower bound of the 95% CI of the observed ORR in BIRCH with the upper bound of the 95% CI for the ORR derived from the meta-analysis limited to patients receiving third-line treatment for non-squamous NSCLC (NS-NSCLC).

Evidence of a substantial improvement over available therapy may be demonstrated if the lower bound of the 95% CI around the observed ORR in BIRCH exceeds the upper bound of the 95% CI of ORR with nivolumab for second- or further-line treatment of squamous NSCLC or with ramucirumab plus docetaxel for second-line treatment of NS-NSCLC.

Please note that even if the lower bound of the 95% CI for the observed ORR in BIRCH is larger than the ORR identified in the meta-analysis of historical studies for a specific population, the magnitude of the ORR improvement over available therapy in BIRCH must be sufficiently large with adequate duration to be reasonably likely to predict clinical benefit.

PREA REQUIREMENTS

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.

FDA acknowledges receipt of Genentech's Agreed Initial Pediatric Study Plan (iPSP) submitted on February 6, 2015 and also refers to FDA's letter, dated May 8, 2015, confirming FDA's agreement with the iPSP. This fulfills Genentech's requirements at this stage of development to reach an Agreed iPSP with the Agency, as required by FDASIA for products that would trigger PREA at the time of BLA submission.

DATA STANDARDS FOR STUDIES

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>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm).

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/s/

GINA M DAVIS
08/07/2015



IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Sternheim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to the teleconference between representatives of your firm and the FDA on June 26, 2015. The purpose of the meeting was to obtain preliminary advice regarding the proposed content and format of a planned Biologics License Application (BLA) for MPDL3280A for the proposed indication of "The treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is PD-L1 selected, as determined by an FDA-approved test, after failure of a platinum-containing chemotherapy regimen".

A copy of the official minutes of the teleconference 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) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior 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: B
Meeting Category: Breakthrough Therapy Designation – Guidance
Meeting Date and Time: June 26, 2015 from 2:30 PM – 3:30 PM (Teleconference)
Application Number: 117296
Product Name: MPDL3280A
Indication: For the treatment of non-small cell lung cancer (NSCLC)
Sponsor/Applicant Name: Genentech, Inc.

FDA ATTENDEES

Office of Hematology and Oncology Products

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director, DOP 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Sean Khozin, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Office of Clinical Pharmacology

Division of Clinical Pharmacology V (DCP V)

Jean Fourie-Zirkelbach, Ph.D., Acting Clinical Pharmacology Team Lead, DCP V
Stacy Shord, Pharm.D., Clinical Pharmacology Reviewer, DCP V

Office of Biostatistics

Division of Biostatistics V (DB V)

Janet Jiang, Ph.D., Statistical Reviewer, DB V
Kun He, Ph.D., Statistical Team Leader, DB V

Office of Surveillance and Epidemiology

Division of Risk Management (DRISK)

Naomi Redd, PharmD., Team Lead, DRISK
Mona Patel, PharmD., Reviewer, DRISK

Safety Regulatory Project Management

Latonia Ford, RN, BSN, Project Manager

SPONSOR ATTENDEES

Cathi Ahearn, MBA Lifecycle Team Leader, Global Product Strategy Oncology
Nicholas Bruno, Associate Group Director, Product Development Regulatory
Daniel Chen, MD, PhD Group Director, Product Development Clinical Oncology
Andrew Chia, PharmD Post-Doctoral Fellow, Product Development Regulatory
Marcin Kowanetz, PhD Scientist, Oncology Biomarker Development
Zhengrong Li, PhD Senior Statistical Scientist, Biostatistics
Chris McKenna, MS Manager, Statistical Programming and Analysis
Simonetta Mocchi, MD, PhD Medical Director, Product Development Clinical Oncology
Hina Patel, PharmD Principal Safety Scientist, Safety Science
Graham Ross, M.D., Clinical Science Leader, Product Development Clinical Oncology
Alan Sandler, MD Principal Medical Director, Product Development Clinical Oncology
Yijing Shen, PhD Statistical Scientist, Biostatistics
Nitzan Sternheim, PhD Regulatory Program Director, Product Development Regulatory
Mark Stroh, PhD Senior Scientist, Clinical Pharmacology
Jing Yi, PhD Principal Statistical Scientist, Biostatistics
Ying Yuen, MA Senior Statistical Programmer Analyst, Statistical Programming
and Analysis

BACKGROUND

On April 3, 2015, Genentech submitted a meeting request to obtain preliminary advice on the content and format of the proposed BLA for the investigational product MPDL3280A for the following proposed indication:

for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is PD-L1 selected, as determined by an FDA-approved test, after failure of a platinum-containing chemotherapy regimen.

MPDL3280A is a human IgG1 monoclonal antibody (mAb) produced by recombinant DNA technology in Chinese hamster ovary cells. Two drug processes were used during clinical development. The PCD4989g, FIR, and POPLAR studies used clinical trial material generated from the "Phase 1" process, while the BIRCH study used clinical trial material generated from the "Phase 3" process.

Genentech states that MPDL3280A binds to the human programmed death ligand 1 (PD-L1), thus inhibiting its interaction with its receptors, PD-1 and B7.1.

Regulatory History

On April 11, 2011, Genentech submitted IND 111271 for MPDL3280A for of locally advanced and metastatic malignancies. The IND-enabling trial was Protocol PCD4989g entitled "A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies."