CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125527Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	March 4, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	STN BL 125527
Applicant Name	Bristol Myers Squibb
Date of Submission	December 22, 2014
PDUFA Goal Date	June 22, 2015
Proprietary Name / Established (USAN) Name	Opdivo injection/ nivolumab
Dosage Forms / Strength	Injection, for intravenous use/ 40-mg and 100-mg vials
Proposed Indication(s)	"treatment of advanced squamous non-small cell lung cancer (NSCLC) (b) (4)"
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Meredith Libeg
Medical & Statistical Joint Review	Dickran Kazandjian, Sean Khozin, & Lijun Zhang
Clinical Pharmacology Review	Xianhua W. Cao & Hongshan Li
OPDP Consult Review	Nicholas Senior

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion

Division Director Summary Review

1. Introduction

Opdivo (nivolumab; Bristol Myers Squibb), a monoclonal antibody that binds to and blocks the activity of the programmed death receptor-1 (PD-1), was approved on December 22, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication was approved under accelerated approval based on tumor response rate and durability of response, [ORR 32% (95% CI: 23, 41)], with 34% (13/ 38) tumor responses lasting more than 6 months.

This Type 9 BLA supports the approval of expanded labeling claims for nivolumab for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. The basis for approval of this application is demonstration of superior overall survival in patients receiving second-line treatment for the squamous subtype of non-small cell lung cancer (SQ NSCLC) in a randomized, open-label trial, Study CA209017. Because of the striking efficacy results, FDA encouraged Bristol Myers Squibb to submit partial results of the CA209017 study (characterizing the study population and survival results only) and relied on safety data in a single-arm trial, Study CA209063, to provide the primary data characterizing adverse reactions and the pharmacokinetic profile of nivolumab in SQ NSCLC.

Study CA209017 was a randomized (1:1), open-label trial designed to compare the safety and efficacy of nivolumab 3 mg/kg intravenously every 2 weeks with docetaxel 75 mg/m^2 intravenously every 3 weeks that enrolled 272 patients with SQ NSCLC who had experienced disease progression following a platinum-based doublet chemotherapy regimen. The primary study objective was overall survival.

Among the 272 patients enrolled, 135 patients were randomized to nivolumab and 137 were randomized to docetaxel. The study population was predominantly White (93%) and male (76%) with a median age of 63 years and an ECOG PS of 1 in 76% of the study population. The data monitoring committee recommended termination of the trial following the results of a protocol-specified interim analysis which demonstrated a statistically significant improvement in overall survival for the nivolumab arm compared with docetaxel [Hazard Ratio (HR) 0.59 (95% confidence interval (CI): 0.44, 0.79); p=0.00025]; the median survival was 9.2 months for the nivolumab arm and 6 months for the docetaxel arm. The magnitude of the treatment effect (3.2 month increase in median OS) is larger than that observed for any active- or placebo-controlled trial for the second-line treatment of NSCLC; based on the KM curves, the effect at the median may under-represent the magnitude of the treatment effect at later time-points.

This Type 9 BLA also contained supportive evidence of anti-tumor activity observed in a single-arm, multinational, multicenter trial (Study CA209063) enrolling 117 patients with

metastatic squamous NSCLC who had progressed after receiving a platinum-based therapy and at least one additional systemic regimen. All patients received nivolumab 3 mg/kg intravenously every 2 weeks. The overall response rate (ORR), as determined by an independent review committee (IRC) according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), was 15% (95% CI: 9, 22); all 17 responding patients achieved partial responses. The median duration of response has not been reached, with 10 of the 17 responses durable for 6 months or longer.

Safety data in this Type 9 BLA relied on data supporting the original approval of nivolumab and safety data obtained in Study CA209063. The adverse reaction profile in patients with NSCLC was consistent with that observed in patients with melanoma. The most common (≥20%) adverse reactions observed in patients with advanced squamous non-small cell lung cancer, based on the results of Study 209063 were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. The most common (≥5%) grade 3 and 4 adverse drug reactions observed in patients with NSCLC were dyspnea, fatigue, and musculoskeletal pain. Immune-mediated adverse drug reactions (immune-mediated pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism) occurred at a similar incidence to that observed in patients with melanoma, with the exception of a higher incidence of immune-mediated pneumonitis in patients with NSCLC than in those with melanoma.

The clinical, statistical, and clinical pharmacology review teams all recommended approval of this application. The benefits of nivolumab on overall survival are robust and clinically meaningful; the risks of immune-mediated organ toxicity, which can be mitigated by, or reversed in many cases, with dose interruption or termination of nivolumab along with high-dose corticosteroid therapy, are acceptable in light of the observed benefits in this patient population that has no satisfactory alternative therapy. The major issues considered during review of this application was whether the survival results from Study CA209017 could be reviewed independently of the complete clinical study result and, related to this issue, whether there was sufficient safety data in patients with NSCLC to make a risk:benefit determination using results from Study CA209063.

2. Background

Proposed indication and available therapy

The American Cancer Society estimated that there were 224,210 new cases of lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and an estimated 159,260 deaths due to lung cancer in the US in 2014.[1] The 5-year relative survival rate between 2010 and 2014 was 4.5% for patients with metastatic, non-small cell lung cancer.[2]

[1] American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014.
[2] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

Initial treatment of locally advanced/unresectable or metastatic NSCLC is platinum-doublet chemotherapy for both squamous and non-squamous NSCLC or in combination with bevacizumab or followed by maintenance chemotherapy with pemetrexed or erlotinib for non-squamous, NSCLC. Available therapy for the treatment of patients with squamous cell, non-small cell lung cancer (SQ NSCLC) with disease progression following a platinum-based doublet therapy includes the following FDA-approved drugs:

Docetaxel, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. This approval was based on the results of two randomized, controlled trials and established that docetaxel at a dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy. TAX317 compared outcomes in patients randomized to docetaxel or to best supportive care, which TAX320 compared outcomes in patients randomized to docetaxel or to investigator's choice of vinorelbine or ifosfamide. The primary endpoint was survival in both trials. The TAX317 trial showed a significant improvement in overall survival [HR 0.56 (95% CI: 0.35, 0.88); p=0.01] with a median survival of 7.5 months in the docetaxel arm and 4.6 months in the best supportive care arm. The TAX320 trial showed no significant difference in survival for patients randomized to docetaxel as compared to those randomized to investigator's choice of vinorelbine or ifosfamide.

Ramucirumab, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab. This approval was based on the results in a randomized (1:1), multinational, placebo-controlled, "add-on" trial comparing overall survival in patients randomized to docetaxel 75 mg/m^2 every 3 weeks plus ramucirumab versus docetaxel 75 mg/m^2 every 3 weeks plus matching placebo. The trial demonstrated a statistically significant improvement in overall survival [HR 0.86 (0.75, 0.98); p=0.024] with median survival times of 10.5 months and 9.1 months for the docetaxel/ramucirumab and docetaxel/placebo arms, respectively. This was supported by an improvement in progression-free survival [HR 0.76 (0.68, 0.86); p < 0.001] and a significantly higher overall response rates (23% vs. 14%; p <0.001).

Erlotinib is indicated for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. This approval was based on the results of a randomized 2:1, placebo-controlled trial conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. In this trial, 93% of patients had received prior platinum therapy and 30% had squamous histology. The trial demonstrated a statistically significant improvement in overall survival [HR 0.73 (0.61, 0.86); p<0.001 with median survival times of 6.7 months and 4.7 months for the erlotinib and placebo arms, respectively. This was supported by an improvement in progression-free survival [HR 0.59 (0.50, 0.70); p < 0.001] with median PFS times of 9.9 weeks and 7.9 weeks, respectively, and a significantly higher overall response rate (8.9% vs. 0.9%; p <0.001).

Pemetrexed is indicated as a single agent for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer after prior chemotherapy. This approval was based on the results of a multi-center, randomized (1:1), open label study conducted in 568 patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with pemetrexed with single agent docetaxel 75 mg/m^2 every 3 weeks. The study failed to demonstrate an improvement in overall survival, however based on a retrospective subgroup analysis by histology, the adjusted hazard ratio favored the pemetrexed arm for the 399 patients with non-squamous, NSCLC [HR 0.78 (0.61, 100), whereas outcomes were inferior among the 172 patients with SQ NSCLC [HR 1.56 (95% CI: 1.08, 2.26)]. This difference in treatment effect for pemetrexed based on histology, demonstrating a lack of efficacy in squamous cell histology in NSCLC, was also observed in the first-line combination study and in the maintenance study. This is the basis for the limitation of use in the USPI, stating that pemetrexed is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

Pre-Submission Regulatory History

June 28, 2006: Submission of IND 100052

September 2, 2009: Change in sponsorship of IND 100052 from Medarex to Bristol Myers Squibb; the drug product was identified as subsequently identified as BMS-936558.

December 6, 2011: EOP1/pre-P3 meeting to discuss the clinical pharmacology plan for the development of nivolumab and BMS' plan to conduct a single trial to support approval for the treatment of patients with non-small cell lung cancer (NSCLC), Study CA209017 titled "An open-label, randomized Phase 3 trial of BMS-936558 versus docetaxel in previously treated metastatic non-small cell lung cancer (NSCLC)." The proposed trial was an open-label, randomized (1:1) study comparing nivolumab with docetaxel in 720 adults with metastatic or recurrent NSCLC that has progressed during or after one prior platinum-containing chemotherapy regimen. Patients with known EGFR mutations or an ALK translocation must also have received an EGFR tyrosine kinase inhibitor or an ALK inhibitor, respectively. Randomization would be stratified by histology (squamous versus non-squamous), prior therapy (maintenance versus no maintenance), presence of driver mutation versus absence/ unknown driver mutation, and region (US/Canada versus Europe versus rest of world).

- FDA generally agreed with the patient population, primary endpoint (survival), and comparator for the proposed trial but stated that for evaluation of the safety profile, the trial should document all adverse events including serious adverse events (not only those deemed to be treatment-related) during treatment and for a minimum of 100 days following the last dose of study treatment.
- FDA advised the trial include more than one dose of nivolumab.
- FDA stated that an "add-on" design to docetaxel would also be acceptable.

February 7, 2012: Type B CMC meeting only to discuss CMC plans to obtain feedback on the comparability of Process (b) (4) and assignment of the shelf life of a new 40 mg presentation.

May 25, 2012: Type A meeting held to discuss BMS' proposal for separate clinical development programs for nivolumab in non-small cell lung cancer (NSCLC) for squamous and non-squamous histology and to discuss potential for accelerated approval regulatory pathway for squamous NSCLC. Based on preliminary results from Study CA209003, in which 3 of 6 patients with squamous NSCLC treated with nivolumab 3 mg/kg every 2 weeks and 3 of 7 patients with squamous NSCLC treated with nivolumab 10 mg/kg every 2 weeks, BMS proposed revisions to the Study CA209017 (from overall survival as the single primary endpoint to overall survival and overall response rate as co-primary endpoints) and to seek accelerated approval pathway based on demonstration of a clinically important and statistically significant improvement in ORR with nivolumab as compared to docetaxel in Study CA209017, supported by a positive trend in overall survival at interim analysis after approximately 65% of the planned deaths for the final analysis.

- FDA agreed that the proposal to split NSCLC development by histology was acceptable.
- FDA stated that demonstration of a statistically significant effect on objective response rate, in the absence of a detrimental effect on survival in an interim analysis would be sufficient to support a request for accelerated approval but will also depend on the magnitude of the treatment effect and the risk:benefit evaluation. The effect size for objective response rate which may support accelerated approval should be similar to that observed in the expansion cohort (i.e., approximately 50%) with a clinical important durability similar to that seen in the responding patients in the expansion cohort;
- FDA advised that Study CA209017 should incorporate a plan for an interim analysis of the objective response rate for the purpose of re-sizing the trial, given the uncertainty of the true effect size based on limited data;
- FDA advised that Study CA209017 should employ a (2:1) randomization of nivolumab to docetaxel;
- FDA advised that an additional, single-arm trial of nivolumab for the third-line treatment of patients with squamous cell NSCLC in which a clinically important rate of durable objective responses are observed may also serve to support a request for accelerated approval.

June 29, 2012:Letter granting Fast Track designation for the development program investigating nivolumab for improvement in overall survival, progression-free survival, and overall response rate, as compared to standard second-line treatment (docetaxel monotherapy), for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with disease progression during or after their first systemic therapy; (b) (4)

July 3, 2012: Submission of protocol CA209017 to IND 100052.

September 19, 2012: FDA letter responding to BMS' question regarding Study CA209017, in which FDA stated

- The magnitude of an effect on durable overall response rate intended to support a request for accelerated approval should be sufficiently high that it is likely to predict clinical benefit. We agree that response rates of approximately 50% as determined with a high degree of certainty (i.e. narrow confidence intervals around that estimate) in a setting of unmet medical need are likely to predict clinical benefit.
- Study CA209017 was sufficiently and appropriately powered as a single major efficacy trial to detect a clinically important effect on survival, however whether additional trials would be required would be contingent upon an assessment of the effect observed in Study CA209017.

October 16, 2012: Submission of protocol CA209063 to IND 100052.

July 10, 2013: FDA issued Type C meeting, Written Responses, providing general guidance on the administrative aspects of the planned BLA.

January 18, 2013: FDA letter providing comments on Study CA209063 and responding to BMS' question posed in the IND submission of October 24, 2012:

- The proposed primary efficacy endpoint in Protocol CA209003, investigator-assessed overall response rate, was not acceptable to provide evidence of substantial evidence of effectiveness in this open-label trial. If you intend to seek labeling claims based on this trial, revise the protocol to require determination of the primary efficacy endpoint of ORR as determined by an independent review committee.
- As discussed during the May 25, 2012 meeting, the effect size for objective response rate which may support accelerated approval should be similar to that observed in study CA209003 (i.e., approximately 50%) with a clinically important duration of responses, similar to that seen in the responding patients in CA209003. Please note that in the proposed study, although the sample size calculation appears to be acceptable, the assumed response rate, which may be as low as 15% based on the lower limit of the 95% confidence boundary would not be considered to be reasonably likely to predict clinical benefit.
- For US regulatory purposes, IRC-determined objective responses rates (ORR) will be considered the primary efficacy endpoint to support a regulatory action. We note that both CA209017 and CA209037 are open-labeled studies with potential for investigator bias in determining the disease progression or response. BMS should include investigator-determined ORR as a secondary endpoint in both trials with sufficient allocation of Type I error and adjustment for multiplicity because both IRC-determined ORR and investigator-determined ORR may be included in product labeling.
- For the purpose of labeling claims, the ORR would be limited to analyses of those patients with objective responses that have been confirmed.

February 5, 2013: FDA letter, which stated that in order to support a request for approval under 21 CFR 601.41, BMS must provide evidence that the overall response rate (ORR) observed in clinical studies supporting a request for accelerated approval is clinically meaningful in magnitude and in duration.

February 14, 2014: Letter amending the Fast Track designation to the development program investigating:

- durable objective responses in patients with metastatic, refractory NSCLC which has progressed following cisplatin-doublet chemotherapy and at least one additional systemic therapy;
- improved overall survival, progression-free survival, and overall response rate with nivolumab as compared to docetaxel for the second-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with disease progression during or after their first systemic therapy; and
- [redacted] (b) (4)

February 26, 2013: [redacted] (b) (4)

April 18, 2014: pre-BLA meeting for discussion of CMC issues.

April 28, 2014: pre-BLA meeting to reach agreement regarding the content and timing of a rolling submission for the BLA in June 2014 for nivolumab for the treatment of patients with advanced, squamous NSCLC with disease progression following platinum-based doublet therapy [redacted] (b) (4). BMS stated that the BLA will mainly be supported by efficacy and safety data from [redacted] (b) (4) During the meeting, FDA provided the following advice:

- Based on the data provided, FDA believes that submission of an application based on the results from [redacted] (b) (4) is premature. [redacted] (b) (4) The magnitude of an effect on durable ORR in support of accelerated approval should have a sufficiently high magnitude of effect in order to predict clinical benefit. Therefore, FDA does not agree that data from studies [redacted] (b) (4) could form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of refractory squamous NSCLC patients. If BMS elects to submit a BLA based only on this data, the application would be referred to an ODAC. FDA strongly recommends that BMS delay submission of the proposed BLA until the planned interim analysis for the ongoing CA209017 trial is conducted. It would be acceptable to initiate a rolling BLA in which the CMC, Nonclinical, and Clinical Pharmacology modules are submitted; however, the clinical module should not be provided until the completion of the planned interim analysis of study CA209017. If the data from study CA209017 demonstrates a

statistically significant robust effect on OS, FDA would work closely with BMS to expedite the submission and review of the clinical module.

(b) (4)

As a result of this discussion, BMS stated that a revised rolling review request would be formally submitted to IND 100052.

- (b) (4)

  FDA disagreed with the proposed approach. FDA noted that in single arm studies, it is very difficult to determine accurate drug causality given the imprecision in investigator-based causality attribution. However, adverse reactions which were clearly not attributable to the drug should not be included in the table. Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event. Typical reasons to suspect causality for an event include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population, and (4) occurrence of an event typical of drug-induced adverse reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome). For serious events that are typical of drug-induced adverse reactions, the occurrence of even a single event could be a basis for inclusion in the list. When none of these reasons exist, however, an event should be excluded from the list. BMS agreed to this approach in describing adverse drug reactions in the proposed product labeling.

- FDA requested, and BMS agreed to provide datasets and a clinical study report (CSR) for Study CA209003 and the protocols, narratives, and case report forms for Studies CA209001 and CA209010 could be included as narratives and case report forms in the proposed BLA.

- Because FDA recommended a delay in the submission of the clinical module, BMS agreed to provide a revised proposal for the data cut-off date for the 90-day safety update.

- FDA agreed that BMS can submit a second BLA for the proposed indication of treatment of refractory melanoma while the initial BLA for the indication of treatment of refractory squamous NSCLC is still under review.

Regulatory History of Submission

April 30, 2014: First module received containing portions of Module 1 (FDA Form 356h, Cover Letter, Reviewer's Guide, Confidentiality Statement, Request for Submission of Portions of an Application, Investigator Brochures for Nivolumab and Ipilimumab (referenced in Nonclinical Summary Documents); portions of Module 2 (Nonclinical Overview (2.4), Nonclinical Written and Tabulated Summaries (2.6.1 - 2.6.7); and a complete Module 4.

June 20, 2014: Second module received containing additional information in Module 1 (Debarment Certification Statement for the clinical studies that support a Clinical Pharmacology review, Financial Disclosure Package for the clinical studies that support a Clinical Pharmacology review, Letters of Authorization for Drug Master File (DMF) references. Rolling Review Granted Letter, Categorical Exclusion Statement); additional portions of Module 2 (Quality summary (2.3), Clinical Pharmacology summaries (2.7.1 and 2.7.2); Module 3 (all components except for the stability update to be provided with the final module); and portions of Module 5 [Clinical Pharmacology (5.3.1.4, 5.3.3.2 and 5.3.3.5) supporting reports with datasets and CRFs for Studies MDX1106-01 (CA209001), MDX1106-03 (CA209003), and CA209010].

December 9, 2014: In response to FDA's request for clarification on the timing of the planned interim analysis of overall survival, BMS provided the following information by electronic mail (e-mail):

"BMS had a data sweep on December 1, 2014 for Study 017 (randomized study of nivolumab versus docetaxel)… the preplanned interim analysis will take place in 2014. The current plan is to lock the database on December 15, 2015… Upon review for completeness of information, [an individual within BMS] will send to you via email. These results will remain blinded to others within BMS until the external DMC meets in early January, 2015. Your review will enable you to determine if the results are sufficient to support submission of the final portion of the rolling BLA in NSCLC and BMS request that you notify [individual within BMS] of the FDA's perspective.

As discussed briefly with [FDA], the report from the independent statistical group will include: K-M of OS with HR, CI, and p-value. In addition, associated demographic information will be included: baseline stratification factors, demographic characteristics summary (age, gender, race/ethnicity, baseline disease characteristics summary (stage, histology, CNS metastases, smoking status), baseline physical measurements summary (weight, ECOG PS), and prior cancer therapy summary (number and type of therapy, best response, time from completion)."

December 18, 2014: The data monitoring committee (DMC) report containing the interim analysis of overall survival for Study CA209017 was provided by e-mail to FDA; upon receipt of the results, FDA stated that the final module for BLA 125527 should be submitted and the clinical protocol and analysis plan for CA209017, DMC report and its associated datasets should be submitted to BLA 125527 following the meeting and recommendations of the DMC and disclosure of the results to BMS staff.

December 22, 2014: Final portion received containing administrative information and proposed draft labeling in Module 1; updated summary documents in Module 2; updated stability data in Module 3, identical to the information provided in BLA 125554; and the Clinical Study Report, CRFs, and Datasets for CA209036 and interim clinical study report for Study CA209037 as supportive information to the Clinical Summary of Safety and the Summary of Clinical Pharmacology in Module 5.

January 29, 2015: The supplement was amended to include the Data Monitoring Committee (DMC) report of the interim analysis of overall survival (January 7, 2015), and the datasets supporting this analysis.

3. CMC/Device

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Pharmacometrics

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The application contained pharmacokinetic from multiple clinical studies and was identical to data package supporting BLA 125554, which supported the approval of nivolumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Therefore, no changes to the FDA-approved US Package Insert (USPI) were proposed by Bristol Myers Squibb.

In this type 9 BLA (125527), data obtained in Study CA209063 was used to evaluate the pharmacokinetics and tolerability of the proposed dosage regimen of nivolumab 3 mg/kg as an intravenous infusion over 60 minutes were used to evaluate pharmacokinetic relationships in patients with NSCLC to support the proposed indication. As with melanoma, the clinical pharmacology reviewer concluded that exposure-response (E-R) relationship based on data obtained in Study CA209063 was "flat" for both safety and efficacy. However given the very modest response rate observed in Study 209063, assessment of the E-R relationship for efficacy is inadequate. This should be re-assessed in the analysis of Study CA209017 when the complete clinical study report and datasets are submitted under the requested post-marketing commitment and the post-marketing requirement to submit the efficacy and safety data, respectively, from Study CA209017.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

As discussed in Section 2 of this summary review, the development program for nivolumab in NSCLC included multiple studies, including:

- a multi-part, multiple parallel cohort, dose-finding and activity estimating trial (Study CA209003), which included a cohort in patients with non-small cell lung cancer (NSCLC) who were treated at nivolumab administered at doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg;
- a single arm, multicenter activity estimating trial in patients with squamous cell NSCLC (SC NSCLC) - Study CA209063; and
- a randomized, hypothesis-testing trial to demonstrate superior overall survival for nivolumab as compared to docetaxel in the second-line treatment of patients with SQ NSCLC – Study CA209017.

Major Efficacy Trial

Study CA209017, entitled "An Open-label Randomized Phase III Trial of Nivolumab versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)."

Key eligibility criteria: Adults with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen (as defined in Study CA209063). Patients were required to have ECOG PS ≤1, measurable disease per RECIST on CT or MRI, and a formalin-fixed tumor tissue block was required for biomarker evaluation. Clinically stable patients with treated brain metastases were eligible. Patients with autoimmune disease, symptomatic interstitial lung disease, a condition requiring systemic immunosuppression, untreated brain metastases, or prior exposure to an anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA4 antibody were ineligible.

Patients were equally allocated to the two treatment arms. Randomization was stratified by prior paclitaxel exposure (yes vs. no) and region (US vs. Europe vs. the rest of the world (ROW)).

Treatment plan

- Arm 1: nivolumab 3 mg/kg intravenously over 60 minutes every 2 weeks
- Arm 2: docetaxel 75 mg/m2 intravenously every 3 weeks

Treatment continued until disease progression or unacceptable toxicity. In addition, treatment beyond investigator-assessed RECIST 1.1-defined progression could be considered with approval of the BMS medical monitor for patients receiving clinical benefit as determined by the investigator, who did not require imminent intervention to prevent serious complications, who did not have rapid disease progression, had stable performance status and signed written informed consent acknowledging the investigational nature of this approach. Patients randomized to docetaxel were permitted to receive nivolumab in an extension phase of this trial.

The primary objective was to compare overall survival between the two treatment arms. Secondary objectives included comparison of ORR and PFS between the two arms; evaluation of whether PD-L1 expression is a predictive biomarker for survival, ORR, or PFS; and

evaluation of the proportion of patients with disease-related symptoms, as measured by LCSS, improvement at study week 12 in both arms.

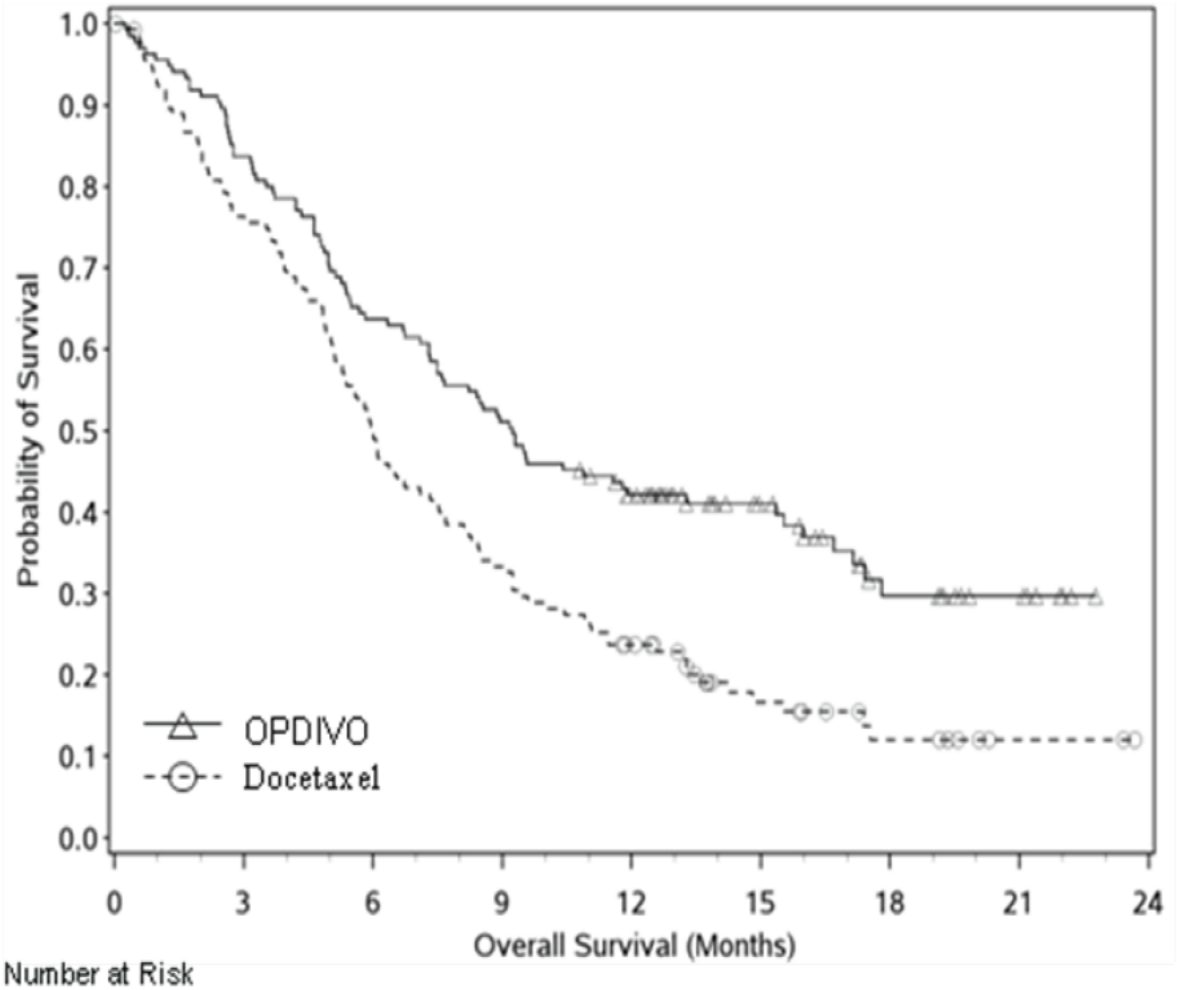
The final analysis of OS will be conducted when at least 231 deaths had been observed among 272 randomized subjects. Given the observed accrual and the survival assumptions, it is expected that the duration of the study from start of randomization to final analysis will be approximately 38 months. One formal interim analysis for superiority of OS is planned after 196 deaths (85% of deaths required for final analysis) had been observed. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses (overall alpha=0.05). If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order: ORR then PFS.

Results

The clinical trial completed enrollment in December 2013. A total of 272 patients were enrolled with 135 randomized to nivolumab and 137 randomized to docetaxel. Across the study population, the median age was 63 years, of whom 44% were ≥65 years of age and 11% were ≥75 years of age. The trial participants were predominantly white (93%) and male (76%), with an ECOG performance status of 0 (24%) or 1 (76%) at study entry.

At a pre-specified interim analysis, conducted after 199 deaths (86% of the planned events for the final survival analysis), the boundary was crossed and the trial was terminated at the recommendation of the data monitoring committee. The study demonstrated a clinically important and statistically robust improvement in overall survival [HR 0.59 (95% CI: 0.44, 0.79); p=0.00025]. The median survival times were 9.2 months in the nivolumab arm and 6.0 months in the docetaxel arm. The Kaplan-Meier curves (abstracted from the USPI) are provided below.

Kaplan-Meier Curves for Survival in Study CA209017



Number at Risk								
OPDIVO								
135	113	86	69	52	31	15	7	0
Docetaxel								
137	103	68	45	30	14	7	2	0

Exploratory subgroup analyses of overall survival by gender, race, age, ECOG PS and stratification variables demonstrate consistent treatment effects except where the subgroup size was very small (31 patients enrolled at non-US, non-EU sites). (b) (4)

[redacted]

Supportive Efficacy Trial

Study CA209063 entitled "A Single-Arm Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens"

Study Design: single-arm study in which all patients received nivolumab 3 mg/kg as an intravenous infusion every 2 weeks until disease progression or discontinuation of beyond progression (if the patient was receiving clinical benefit as determined by the investigator, did not require imminent intervention to prevent serious complications, did not have rapid disease progression, had stable performance status and signed written informed consent acknowledging the investigational nature of this approach), discontinuation due to toxicity (including failure of recovery from toxicity within 6 weeks of suspending nivolumab), withdrawal of consent, or death.

Key inclusion criteria: Histologically- or cytologically-documented, Stage IIIB or Stage IV, squamous cell, NSCLC; disease progression or recurrence after both a platinum doublet based chemotherapy and at least one additional line of systemic therapy. Maintenance therapy following platinum doublet- based chemotherapy is not considered as a separate line of therapy. Prior platinum-containing adjuvant, neoadjuvant or definitive chemo-radiotherapy given for locally advanced disease is considered first- line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy; Measurable disease by CT or MRI per RECIST 1.1 criteria; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Assessment of PD-L1 tumor status was not required and not an eligibility criterion.

Key exclusion criteria: Active CNS metastases or carcinomatous meningitis, active, known or suspected autoimmune disease, any condition requiring systemic treatment steroids or other immunosuppressive medications within 14 days of first dose of study, prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), and a history of interstitial lung disease.

The primary endpoint was overall response rate (ORR) as assessed by an independent radiology review committee (IRC) using RECIST 1.1 criteria, with confirmation of response is required and should occur no sooner than 6 weeks after prior tumor assessment. Key secondary endpoints were IRC-determined duration of response, investigator-assessed ORR and duration of response per RECIST 1.1. The planned sample size of 100 patients was selected to provide 95% confidence intervals around potential observed response rates ranging from 10% to 50%. The protocol stated that at an observed ORR of 15%, the lower bound of the 95% CI compares favorably to historical response rates in refractory non-adenocarcinoma of 4.1% and 6.7% for erlotinib and gefitinib, respectively, and < 2% for chemotherapy;

Results

The study was initiated November 16, 2012, with last patient visit on January 22, 2014, and a database lock of August 15, 2014. A total of 117 patients were enrolled at 27 sites in 4

countries (United States, France, Germany, and Italy) and all received at least one dose of nivolumab. The median age was 65 years and 50% were ≥65 years of age. The study population were predominantly white (85%), male (73%), had Stage IV disease (94%), and an ECOG PS of 1 (78%). All patients received two or more prior systemic treatments, with 44% having received three prior regimens and 21% having received ≥ four prior systemic regimens. The IRC-determined overall response rate was 15% (95% CI: 9, 22); there were no complete responses and 17 partial responses. The median duration of response has not been reached, as only four patients have progressed following initial response. Thirteen patients have ongoing responses ranging from 1.9+ to 11.5+ months in duration; of these, 10 patients have ongoing responses lasting 6 months or longer.

There were a limited number of patients identified by the applicant in which "immune-related" responses were identified. None of these patients had a clinically meaningful reduction in tumor and, based on this experience, there is no evidence supporting the clinical benefit of nivolumab treatment beyond disease progression in this patient population.

The clinical reviewers conducted a number of exploratory analyses, including assessment of overall survival based on presence/absence of objective tumor response and assessment of survival of varying degrees of PD-L1 expression in tumor specimens as determined by an investigational assay. I note that these exploratory analyses evaluate for correlations but are not hypothesis-testing evaluations. For multiple reasons, the results of these analyses are not considered substantial evidence of effectiveness (b) (4) In addition, the "responder analysis" is considered flawed analysis (b) (4)

8. Safety

Size of the database:
This application relied on FDA's prior findings of safety supporting initial approval of nivolumab in melanoma, which included assessment of all adverse events in the randomized (2:1) clinical trial comparing the safety and efficacy of nivolumab with dacarbazine for the treatment of recurrent/refractory melanoma, which included 268 patients who received one or more doses of nivolumab at doses of 3 mg/kg every 2 weeks and reports of clinically significant adverse reactions received across an open-label dose-finding and activity estimating trial enrolling n=306 who received nivolumab at doses of 0.1 to 10 mg/kg every 2 weeks. This safety database was supplemented by safety data obtained in Study CA209063, consisting of adverse events identified in 117 patients with SC NSCLC with disease progression following platinum-based chemotherapy. Given the serious nature of the disease with an anticipated 5-year survival rate of 4.5%, the comprehensive safety data in 385 patients enrolled in Studies 209063 and the randomized trial in melanoma, supplemented by reports of clinically significant adverse events in an additional 306 patients, the safety database was of adequate size to detect adverse reactions occurring in 1% of patients and it is acceptable to form a basis for a risk determination in the indicated population.

Major safety concerns related to labeling
In general, major safety concerns in this patient population (SC NSCLC) were similar to that observed in patients with recurrent/refractory melanoma. The exceptions to this general rule were that there was a higher incidence and severity of immune-mediated pneumonitis among patients with SC NSCLC than those with melanoma [6% (7 of 117 patients)] as compared to 3.4% incidence in patients with recurrent/refractory melanoma. There were five of 117 patients with Grade 3 pneumonitis in Study CA209063 as compared to one of 268 patients in the randomized trial in melanoma patients. In addition, there was less information regarding re-challenge in patients with SQ NSCLC following resolution of pneumonitis. In the absence of data, the recommendations for re-challenge remain the same in the USPI and will be monitored closely in post-marketing reports as well as in the results of Study CA209017.

As compared to patients with melanoma, the incidence of renal insufficiency based on elevated serum creatinine was higher in patients with SQ NSCLC as compared to patients with melanoma (22% vs. 13%). This difference may be a result of prior treatment with platinum-based chemotherapy in all patients with SQ NSCLC, which did not occur in patients with melanoma. The rates of immune-mediated renal dysfunction appeared similar (0.9% and 2.2%) for patients with SQ NSCLC and melanoma, respectively.

In contrast, the incidence of elevated liver tests appeared to be higher for patients with melanoma than in those with SQ NSCLC; however, there were insufficient numbers of patients enrolled in Study CA209063 to determine whether there are differences in the incidence of immune-mediated hepatitis.

The USPI was modified to include incidence information and clinical outcomes on cases of immune-mediated pneumonitis, colitis, renal dysfunction, hyper- and hypothyroidism. In addition, Section 5.6 was modified to include the following new immune-mediated adverse reactions identified in Study CA209063: uveitis, pancreatitis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis.

Common ($\geq$ 20%) adverse events observed in Study CA209063 were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. Cough, rash, and edema were also observed in patients with melanoma at a rate higher than background, however only the incidence of rash occurred in >20% of patients with melanoma. As compared to those with melanoma, the incidence of fatigue, dyspnea, musculoskeletal pain, nausea, and constipation appeared commonly in patients with SQ NSCLC. The results of Study CA209017, an internally controlled trial, should allow identification of adverse drug reactions which are occurring above the background rate in the control arm.

Postmarketing data
Nivolumab was approved for marketing on December 22, 2014 and there is no post-marketing information contained in this supplement.

REMS
I concur with the recommendations of the clinical review team that a REMS is not required to ensure safe use of nivolumab in the indicated patient population.

PMRs and PMCs
The supplement will be approved with the following post-marketing requirement, which will provide greater clarity on the absolute risks and clinical course of the following immune-mediated adverse reactions of nivolumab. The PMR trial should be randomized to allow detection of adverse drugs reactions occurring above background rates in this symptomatic population (only 25% of patients had an ECOG PS of 0 in Study CA209017) and will provide a larger database to identify uncommon toxicities and characterize clinical outcomes.

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

9. Advisory Committee Meeting

This efficacy supplement was not referred to an FDA advisory committee because: this biologic is not the first in its class; the clinical trial design is acceptable; the application did not raise significant safety or efficacy issues; and the application did not raise significant public health questions on the role of the biologic in the treatment of NSCLC.

10. Pediatrics

Bristol Myers Squibb submitted a request for a full waiver of pediatric studies for the proposed indication. The request was reviewed by the PeRC on February 11, 2015, and was granted.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name: Not applicable for this Type 9 BLA.

- Physician labeling
  - Indications and Usage: the proposed indication was modified to replace (b) (4) " with the more specific phrase "progression on or after platinum-based chemotherapy" to reflect the patient population studied.
  - Dosage and Administration: editorial changes only (replaced " (b) (4) with "resolved."
  - Warnings and Precautions: Sections 5.1, 5.2, 5.3, 5.4, 5.5 were amended to include information on the incidence of these immune-mediated adverse reactions in patients with NSCLC, based on the 117 patients enrolled on Study CA209063. Section 5.6 was updated to include the following new autoimmune phenomenon

identified in Study CA209063: uveitis, pancreatitis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis.

- Adverse Reactions: This section was updated to provide separate headings under the Clinical Trials subsection to set off adverse reactions in studies enrolling patients with melanoma from adverse reactions in studies enrolling patients with SQ NSCLC; information on the source of safety information was moved to the beginning of the Clinical Trials subsection (6.1); adverse event information was provided for all events occurring in ≥ 10% of patients for any adverse event NCI or ≥5% per-patient incidence for Grades 3-4 adverse events regardless of investigator attribution, since investigator attribution may be flawed and consistent with FDA labeling practices for single arm trials. The adverse event data from Study CA209063 will be replaced with data from Study CA209017, when the PMR is submitted.
- Use in Specific Populations, Geriatric Use (8.5): updated to reflect the number and proportion of elderly patients enrolled in Study CA209063. This will be updated when the PMC for the final study report for Study CA209017 is submitted.
- Clinical Studies: Created subsections (14.1 and 14.2) for melanoma and NSCLC clinical studies, respectively. (b) (4) this data may be removed. With regard to the description of the studies in 14.2, FDA removed (b) (4) FDA removed (b) (4) FDA also removed statements (b) (4) In addition, (b) (4) were removed and the KM curve for overall survival was added to the labeling.

- Carton and immediate container labels: Not applicable for this supplement; the applicant did not propose changes to the FDA-approved carton/container labeling.

- Patient labeling/Medication guide:
  Modification to approved patient labeling were made to incorporate information on the new indication and common side effects noted in SQ NSCLC as a result of approval of this new indication. A Medication Guide was not deemed necessary to ensure safe use of nivolumab for this new indication.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

  Approval is granted based on demonstration of a clinically important and statistically robust improvement over available therapy (docetaxel) and acceptable risks in this population with a life-threatening condition and no satisfactory alternative therapy. There were an estimated 224,210 new cases of lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and an estimated 159,260 deaths due to lung cancer in the US in 2014. The 5-year year relative survival rate between 2010 and 2014 was 4.5% for patients with metastatic, non-small cell lung cancer, despite the availability of FDA-approved drugs for the first-line treatment (platinum-doublet chemotherapy) and for the second-line treatment (docetaxel as a single agent or in combination with ramucirumab) for this disease.

  Study CA209017 demonstrated a clinically large and statistically robust improvement in overall survival [HR 0.59 (95% CI: 0.44, 0.79); p=0.00025] over single agent docetaxel based on a planned interim analysis. The median survival was 9.2 months for the nivolumab arm and 6 months for the docetaxel arm. The magnitude of the treatment effect (3.2 month increase in median OS) is larger than that observed for any active- or placebo-controlled trial for the second-line treatment of NSCLC; based on the KM curves, the effect at the median may under-represent the magnitude of the treatment effect at later time-points. The most common (≥20%) adverse reactions observed in patients with advanced squamous non-small cell lung cancer, based on the results of Study 209063 were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. The most common (≥5%) grade 3 and 4 adverse drug reactions observed in patients with NSCLC were dyspnea, fatigue, and musculoskeletal pain. Immune-mediated adverse drug reactions (immune-mediated pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism) occurred at a similar incidence to that observed in patients with melanoma, with the exception of a higher incidence of immune-mediated pneumonitis in patients with NSCLC than in those with melanoma.

  The benefits of nivolumab on overall survival are robust and clinical meaningful; the risks of immune-mediated organ toxicity, which can be mitigated by, or reversed in many cases, with dose interruption or termination of nivolumab along with high-dose corticosteroid therapy, are acceptable in light of the observed benefits in this patient population that has no satisfactory alternative therapy.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  I concur with the recommendations of the clinical review team that a REMS is not required to ensure safe use of nivolumab in the indicated patient population. No new safety signals were identified in this application which alters the risk profile and the risk profile is acceptable in the indicated patient population, which has no satisfactory alternative therapy.

- Recommendation for other Postmarketing Requirements and Commitments

  Post-marketing requirement:
  The supplement will be approved with the following post-marketing requirement, which will provide greater clarity on the absolute risks and clinical course of the following immune-mediated adverse reactions of nivolumab. The PMR trial should be randomized to allow detection of adverse drugs reactions occurring above background rates in this symptomatic population (only 25% of patients had an ECOG PS of 0 in Study CA209017) and will provide a larger database to identify uncommon toxicities and characterize clinical outcomes.

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

  Post-marketing commitment:
  The supplement will be approved with the following agreed-upon, post-marketing commitment, which will provide additional information on the other treatment effects of nivolumab in this patient population, including progression-free survival and durability of objective tumor responses.

  - Submit the final report and efficacy datasets for the open-label randomized trial of nivolumab versus docetaxel in patients with previously treated advanced squamous non-small cell lung cancer.

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/s/

PATRICIA KEEGAN
03/04/2015