Clinical Cancer Research

U.S. FDA Approval Summary: Nivolumab for Treatment of Unresectable or Metastatic Melanoma Following Progression on Ipilimumab

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Abstract

On December 22, 2014, the FDA granted accelerated approval to nivolumab (OPDIVO; Bristol-Myers Squibb) for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Approval was based on a clinically meaningful, durable objective response rate (ORR) in a noncomparative analysis of 120 patients who received 3 mg/kg of nivolumab intravenously every 2 weeks with at least 6-month follow-up in an ongoing, randomized, open-label, active-controlled clinical trial. The ORR as assessed by a blinded independent review committee per RECIST v1.1 was 31.7% (95% confidence interval, 23.5–40.8). Ongoing responses were observed in 87% of responding patients, ranging from 2.6+ to 10+ months. In 13 patients, the response duration was 6 months or longer. The risks of nivolumab, including clinically significant immune-mediated adverse reactions (imARs), were assessed in 268 patients who received at least one dose of nivolumab. The FDA review considered whether the ORR and durations of responses were reasonably likely to predict clinical benefit, the adequacy of the safety database, and systematic approaches to the identification, description, and patient management for imARs in product labeling. *Clin Cancer Res; 23(14); 3484–8. ©2017 AACR.*

Introduction

Melanoma is the fifth leading cancer type in men and the seventh leading cancer type in women, with an estimated 76,380 new cases and 10,130 deaths due to melanoma expected in 2016 (1). Five-year survival rates for regional and distant stage melanomas are 63% and 17%, respectively (2). Mutations in the *B-Raf* proto-oncogene (BRAF) have been reported in 41% to 55% of metastatic melanomas (3). At the time nivolumab was approved, FDA-approved therapies for the treatment of BRAF V600 mutation–positive metastatic melanoma included the BRAF inhibitors vemurafenib and dabrafenib, the MEK inhibitor trametinib, and concurrent dabrafenib and trametinib. For the treatment of unresectable or metastatic melanoma irrespective of BRAF V600 mutation status, FDA-approved therapies included dacarbazine, aldesleukin, and the CTLA-4 inhibitor ipilimumab. FDA-approved therapies for use in patients with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, included dacarbazine, aldesleukin, and pembrolizumab; the latter, a programmed cell death 1 (PD-1) inhibitor, received accelerated approval in 2014 in the same indication based on an objective response rate (ORR) of 24% [95% confidence interval (CI), 15–34], with 86% of patients with ongoing responses and durations ranging from 1.4+ to 8.5+ months (4).

The PD-1 receptor binds to two ligands, PD-L1 and PD-L2, which are expressed constitutively on antigen-presenting cells and can be upregulated in a variety of normal tissues, including tumor cells and the surrounding stroma, leading to immune suppression (5). Upregulation of these receptors contributes to the immune system's inability to reject tumor cells, primarily through inhibition of tumor cell apoptosis and cytotoxic T-cell activity.

Nivolumab [OPDIVO; Bristol-Myers Squibb (BMS)] is an IgG4 kappa human monoclonal antibody that targets the PD-1 receptor. It binds to PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby releasing PD-1 pathway–mediated inhibition of immune responses, including the antitumor immune response.

This article summarizes the FDA review of the clinical trials submitted to support the initial approval of nivolumab, the issues considered, and the basis for approval.

Chemistry

Nivolumab consists of two identical heavy chains (440 amino acids each) and two identical kappa light chains (214 amino acids

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each), which are linked through interchain disulfide bonds and have a calculated molecular mass of 146 kDa. Nivolumab is produced by bioreactor fermentation of a recombinant cell line derived from a Chinese Hamster Ovary (CHO) host cell line. The product is supplied as a 40 mg/4 mL and a 100 mg/10 mL sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow solution in single-dose vial.

Nonclinical Pharmacology and Toxicology

Nivolumab bound to PD-1 in humans and cynomolgus monkeys to a similar extent but did not bind to PD-1 in rodents or rabbits. Therefore, antitumor activity was demonstrated using a surrogate anti-mouse PD-1 monoclonal antibody. In multiple murine syngeneic tumors models, tumor-bearing animals treated with the surrogate antibody at circulating concentrations of 4 to 5 nmol/L showed delayed tumor progression and/or complete tumor regression as compared with controls.

The toxicity of nivolumab was assessed in 4- and 13-week studies in cynomolgus monkeys at up to 42 times the recommended clinical exposure based on AUC. Toxicity was limited to a diffuse pattern of inflammatory infiltration, and no specific target organs of toxicity were identified.

Published data in other animal models raised concerns about the toxicity of nivolumab in patients with chronic infections. For example, infection of PD-1–deficient mice with *Mycobacterium tuberculosis* resulted in a marked decrease in survival compared with similarly infected wild-type animals, which correlated with increases in both bacterial proliferation and fulminant and destructive inflammatory response in PD-1–deficient animals compared with wild-type controls (6). Because PD-1 inhibition prevents downregulation of the immune response, vaccination or antigen reexposure in patients undergoing treatment with nivolumab was also a potential safety concern. These concerns were communicated in the product labeling.

A central function of the PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Consistent with this role, nivolumab exposure during pregnancy in cynomolgus monkeys resulted in an increase in fetal and neonatal mortality within the range of clinical exposure with the approved dose. The risks of nivolumab on fetal loss and neonatal mortality were included in the product labeling.

Clinical Pharmacology

The pharmacokinetics (PK) of nivolumab was characterized in patients with various solid tumors over a dose range of 0.1 to 20 mg/kg as a single dose or as multiple doses administered every 2 weeks (Q2W) or 3 weeks (Q3W). The clearance of nivolumab increased with increasing body weight. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and the elimination half-life ($t_{1/2}$) was 26.7 days. Steady-state concentrations of nivolumab were reached by 12 weeks when administered Q2W or Q3W, and the systemic accumulation was approximately 3-fold.

Although the recommended dosage of nivolumab as a single agent for the melanoma indication has been updated to 240 mg as an intravenous infusion over 60 minutes Q2W in a subsequent application (7), the recommended dosage of nivolumab evaluated in the initial application was 3 mg/kg administered as an intravenous infusion over 60 minutes Q2W, which is supported by the response rate and safety profile observed at this dose in trial CA209037 and an apparent flat exposure–response relationship for both overall response rate and the incidence of adverse reactions. Covariates including age, sex, race, baseline lactate dehydrogenase (LDH), PD-L1 expression, renal impairment, or mild hepatic impairment have no clinically meaningful effects on nivolumab exposure. There was no evidence of altered PK or safety profile in the 24 of 281 evaluated patients (8.5%) who tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent assay.

Clinical Trial

Trial CA209037 was a randomized, open-label, active-controlled, multinational clinical trial in patients with histologically confirmed unresectable or metastatic melanoma. Eligible patients had progressed following treatment with ipilimumab or ipilimumab and a BRAF inhibitor for patients with BRAF V600 mutation–positive melanoma and were 18 years or older with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. The trial excluded patients with autoimmune disease, ocular melanoma, requirement for corticosteroids or immunosuppression, and severe ipilimumab-related adverse reactions.

Patients were randomly allocated (2:1) to receive 3 mg/kg of nivolumab intravenously Q2W or investigator's choice chemotherapy (dacarbazine 1,000 mg/m^2 Q3W or carboplatin AUC of 6 and paclitaxel 175 mg/m^2 Q3W). Randomization was stratified by PD-L1 status assessed using an investigational immunohistochemistry assay at a central laboratory (positive based on $\geq$5% tumor cell membrane staining vs. negative based on <5% tumor cell membrane staining in a minimum of 100 cells), BRAF V600 status (wild type vs. mutation positive), and best response to prior anti–CTLA-4 therapy [best overall response (complete response, CR; partial response, PR; or stable disease, SD) vs. progressive disease]. Treatment was administered until progressive disease or unacceptable toxicity. Tumor assessments were scheduled at week 9 and then every 6 weeks for the first year and every 12 weeks thereafter.

As initially designed, the two coprimary endpoints of the trial were ORR as assessed by blinded independent central review per RECIST v1.1 (8) and overall survival (OS) with an alpha allocation (two sided) of 0.1% and 4.9% to the ORR and OS analyses, respectively.

The trial was amended to perform an interim, non-comparative analysis of ORR in the first 120 patients enrolled on the nivolumab arm who had received at least one dose of nivolumab and had been followed for at least 6 months. The sample size of 120 patients for this analysis was based on the assumption that the ORR was 30%, which would exclude a response rate of 15% using the lower limit of the exact 95% CI.

Results

At the time of review, the trial was fully accrued. Of the 120 nivolumab-treated patients included in the interim analysis, 65% were male, with a median age of 58 years; 98% were Caucasian; and 58% and 42% had a baseline ECOG performance status of 0 or 1, respectively. Disease characteristics included BRAF V600 mutation–positive melanoma (22%), elevated LDH (56%), M1c disease (76%), history of brain

Table 1. Response rate and duration of response in patients treated with nivolumab

	Nivolumab (*N* = 120)	Investigator's choice (*N* = 47)
cORR, *n* (%)	38 (31.7)	5 (10.6)
95% CI	(23.5–40.8)	(3.5–23.1)
CR, *n* (%)	4 (3.3)	0
PR, *n* (%)	34 (28.3)	5 (10.6)
Median duration of response, months (range)	Not reached (2.6+ to 10+)	3.6 (1.3+ to 3.6)
Response ongoing (%)	87	40

Abbreviation: cORR, confirmed objective response rate.

metastases (18%), and two or more prior therapies (68%). PD-L1 status was positive in 46% of patients. All patients received prior therapy with ipilimumab, and 37% of patients had a reported best response of CR, PR, or SD with ipilimumab. All of the patients with BRAF mutations had also received a BRAF inhibitor.

Efficacy

Efficacy results are summarized in Table 1. The confirmed ORR in the nivolumab group was 31.7% (95% CI, 23.5–40.8). Of the 38 patients with an objective response, 4 patients (3.3%) had a CR and 34 (28.3%) had a PR. The median duration of response (DoR) was not reached. Responses were ongoing in 33 responding patients (87%) at the time of submission of the application, with DoR ranging from 2.6+ to 10+ months. There were 13 patients with ongoing responses of 6 months or longer.

The ORR in patients who were PD-L1 positive was 43.6% (95% CI, 30.3–57.7) and 20.3% (95% CI, 11.3–33.6) in patients who were PD-L1 negative or indeterminate. The ORR in patients with BRAF V600 mutation–positive melanoma was 23.1% (95% CI, 9.0–43.6) and 34.0% (95% CI, 24.6–44.5) in BRAF wild-type melanoma. The ORR in patients with prior response to ipilimumab was 30.0% (95% CI, 16.6–46.5).

Supportive evidence for the observed magnitude and better characterization of the DoR duration was obtained from a subset of 87 patients with unresectable or metastatic melanoma enrolled in a dose-finding, activity-estimating trial. In these 87 patients, the investigator-assessed ORR was 33.3% (95% CI, 23.6–44.3), and the median DoR was 22.9 months (range, 4.2–26.6+ months).

Safety

The safety population included 268 patients who received at least one dose of nivolumab.

For context, adverse events (AE) occurring in the control arm in patients who received at least one dose of dacarbazine ($n = 45$) or carboplatin/paclitaxel ($n = 57$) were also reviewed. This safety database was supplemented with information on serious adverse drug reactions observed in 175 patients with various solid tumors who received nivolumab at doses ranging from 0.1 to 3 mg/kg in a dose-finding, activity-estimating trial.

The median DoR to nivolumab was 5.3 months (range, 1 day–13.8+ months). Among the 268 patients treated with nivolumab, 64 (24%) patients received nivolumab for greater than 6 months, and 8 patients (3%) received nivolumab for greater than 1 year.

Serious AEs, defined as those that resulted in or prolonged hospitalization, required urgent medical intervention, or resulted in death, occurred in 41% of patients treated with nivolumab. The NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and 4 AEs occurred in 42% of patients. Nivolumab was discontinued for AEs in 9% of patients, and 26% had a dosing delay due to an AE. The most common AEs (occurring in at least 20% of patients) were

Table 2. Adverse reactions reported in ≥10% of patients treated with nivolumab

	Nivolumab (*N* = 268)		Investigator's choice (*N* = 102)	
Adverse reaction	**All grades, *n* (%)**	**Grades 3–4, *n* (%)**	**All grades, *n* (%)**	**Grades 3–4, *n* (%)**
General disorders and administration site conditions				
Fatigue	104 (39)	4 (2)	44 (43)	5 (5)
Pyrexia	35 (13)	0	10 (10)	1 (1)
Edema peripheral	28 (10)	0	5 (5)	0
Gastrointestinal disorders				
Nausea	64 (24)	3 (1)	43 (42)	2 (2)
Diarrhea	54 (20)	2 (0.7)	17 (17)	2 (2)
Vomiting	37 (14)	6 (2)	24 (24)	2 (2)
Constipation	35 (13)	2 (0.7)	20 (20)	1 (1)
Abdominal pain	30 (11)	9 (3)	7 (7)	0
Skin and subcutaneous tissue disorders				
Pruritus	51 (19)	0	4 (4)	0
Rash	32 (11)	1 (0.4)	5 (5)	0
Blood and lymphatic system disorders				
Anemia	42 (16)	12 (5)	28 (28)	8 (8)
Respiratory, thoracic, and mediastinal disorders				
Cough	41 (15)	0	5 (5)	0
Dyspnea	41 (15)	3 (1)	15 (15)	2 (2)
Metabolism and nutrition disorders				
Decreased appetite	39 (15)	0	18 (17)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	35 (13)	0	15 (15)	2 (2)
Nervous system disorders				
Headache	30 (11)	2 (0.7)	11 (11)	0

NOTE: Toxicity was graded per NCI CTCAE v4.0.

fatigue, nausea, and diarrhea. Table 2 summarizes the AEs that occurred in at least 10% of nivolumab-treated patients and provides the incidence of AEs in the control arm for context.

Based on its mechanism of action, adverse reactions of nivolumab arise from the same release of PD-1 pathway–mediated inhibition of immune responses that is responsible for efficacy, resulting in autoimmune disease. Thus, the toxicity profile of nivolumab includes immune-mediated adverse reactions (imAR), which requires treatment with high-dose corticosteroids or immunosuppressive medications and can be fatal. The overall incidence of imARs is 59% (158/268). Grade 3 or 4 imARs occurred in 7% of patients. The most common imARs, occurring in more than 2% of patients, were pneumonitis, colitis, hepatitis, hypothyroidism, hyperthyroidism, nephritis, rash, pruritus, dermatitis, and vitiligo. Other imARs observed at a lower frequency were pancreatitis, autoimmune thyroiditis, adrenal insufficiency, uveitis, autoimmune neuropathy, demyelination, hypophysitis, and facial and abducens nerve paresis.

Discussion

Accelerated approval of nivolumab was based on demonstration of a clinically meaningful ORR with prolonged DoR in an interim analysis of an open-label, randomized, active-controlled trial in patients with treatment-refractory unresectable or metastatic melanoma, a patient population with an extremely poor prognosis, with an estimated 5-year survival rate of less than 20%.

Trial CA209037 was designed to demonstrate superior survival and response rates for nivolumab over the chemotherapy arm, with the final analysis of ORR to occur at the time of the interim analysis of OS. To expedite the development of nivolumab for this refractory population, the FDA agreed to the modification of the protocol, to conduct an early assessment of antitumor activity (i.e., ORR). Based on these results, the FDA stated that this non-comparative analysis of ORR would provide sufficient information to evaluate the treatment effect of nivolumab under the provisions of accelerated approval. In doing so, the FDA considered the historically low response rates with dacarbazine and aldesleukin and the toxicity of these therapies, and the prolonged DoR observed with nivolumab. In addition, exploratory analyses of ORR demonstrated responses in all patient subgroups based on stratification factors, although any association of response to BRAF V600 mutation status, PD-L1 expression status, and prior ipilimumab benefit is unclear, as the statistical design of the trial was not adequate to answer the question. Furthermore, as the population enrolled in trial CA209037 had received and progressed on ipilimumab, and on BRAF inhibitors if they had BRAF mutation–positive melanoma, no reasonably safe therapy existed for these patients. Thus, the magnitude and durability of the ORR were determined by the FDA to be reasonably likely to predict clinical benefit (i.e., an improvement in OS) and to provide a meaningful advantage over available therapy in this serious and life-threatening condition, thus meeting the legal criteria for accelerated approval. As a condition of this accelerated approval, BMS was required to conduct trial(s) verifying the clinical benefit of nivolumab in adults with unresectable or metastatic melanoma.

The major review issue was identification and description in the product labeling of imARs. This was complicated by the absence of case definitions of imARs in the clinical protocol and incomplete capture of data on the identification and management of imARs. The size of the safety database was adequate to detect toxicities occurring at an incidence of $\leq 1.5\%$; however, more data were available on the risks of serious adverse reactions, and thus were sufficient for the treatment of a serious and life-threatening condition. In contrast, the short duration of exposure was problematic, as responding patients were expected to have longer exposure than could be adequately characterized by trial CA209037, such that only the serious adverse reactions resulting from longer exposure were adequately characterized. This would not have been sufficient in a patient population with a better prognosis. For the purposes of description of imARs in product labeling, the FDA in conjunction with BMS developed and applied the following retrospective definition: adverse reactions with no other etiology and that required treatment with corticosteroids or other immunosuppressive medications. This approach to characterization of safety was informed by prior experience with ipilimumab and appeared to capture serious adverse reactions. This definition was not useful in assessing less severe adverse reactions, as comparisons of toxicity to the active-control arm of trial CA209037 were difficult to interpret as the mechanisms of toxicity clearly differ between chemotherapy and nivolumab. However, this approach allowed an assessment of medical and other interventions taken by investigators and their outcomes in the management of imARs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Deputy Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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