Safety profile of nivolumab administered as 30-minute infusion:

Analysis of data from CheckMate 153

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Abstract

Purpose Nivolumab has been administered using a 60-minute infusion time. Reducing this time to 30 minutes would benefit both patients and infusion facilities. This analysis compared the safety of 30- and 60-minute infusions of nivolumab in patients with previously treated advanced non-small cell lung cancer.

Methods CheckMate 153 is an open-label, phase 3b/4, predominantly community-based study ongoing in the United States and Canada. Patients with stage IIIB/IV disease with progression/recurrence after at least one prior systemic therapy received nivolumab 3 mg/kg every 2 weeks over 30 or 60 minutes for 1 year or until disease progression. The primary outcome overall was to estimate the incidence of grade 3–5 treatment-related select adverse events; a retrospective objective was to estimate the incidence of hypersensitivity/infusion-related reactions (IRRs) with the 30-minute infusion. Exploratory pharmacokinetic analyses were performed using a population pharmacokinetics model.

Results Of 1420 patients enrolled, 369 received only 30-minute infusions and 368 received only 60-minute infusions. Similar frequencies of hypersensitivity/IRRs were noted in patients receiving 30-minute (2% [*n* = 8]) and 60-minute (2% [*n* = 7]) infusions. Grade 3–4 treatment-related hypersensitivity/IRRs led to treatment discontinuation in < 1% of patients in each group; < 1% of patients in each group received systemic corticosteroids. Hypersensitivity/IRRs were managed by dosing interruptions, with minimal impact on total dose received. Nivolumab pharmacokinetics were predicted to be similar in the two groups.

Conclusions Nivolumab infused over 30 minutes had a comparable safety profile to the 60-minute infusion, including a low incidence of IRRs.

ABSTRACT WORD COUNT: 248 (limit 150–250 words)

Introduction

Nivolumab is a fully human programmed death-1 (PD-1) checkpoint inhibitor antibody that is approved in the United States for the treatment of metastatic non-small cell lung cancer (NSCLC), unresectable or metastatic melanoma, advanced renal cell carcinoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, classical Hodgkin lymphoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, and hepatocellular carcinoma; approvals were based on results of phase 2 and phase 3 clinical trials [1–10].

In clinical studies across tumor types, a 60-minute infusion time has been used to administer nivolumab. Severe infusion reactions have been rare with nivolumab (occurring in < 1% of patients) and are managed by using relevant safety algorithms (eg, treatment discontinuation) [10]. Reducing the infusion time of 3 mg/kg of nivolumab to 30 minutes would provide potential benefits to both patients and treatment facilities. Because the mean elimination half-life of nivolumab monotherapy is 25 days [10], shortening the infusion period to 30 minutes would not be expected to affect the pharmacokinetics of treatment. Reductions in infusion times have been demonstrated to be feasible and safe for other therapeutic antibodies in clinical trials [11–14], supporting investigation of shorter infusions of nivolumab.

The phase 3b/4 study CheckMate 153 (NCT02066636) is an ongoing, predominantly community-based study evaluating the safety of nivolumab monotherapy in patients with advanced or metastatic NSCLC with disease progression or recurrence after at least one prior therapy regimen. The study was launched in April 2014 and was initially designed to administer nivolumab over 60 minutes. The protocol was amended in December 2014 to evaluate the incidence of infusion reactions when nivolumab is administered over 30 minutes. The purpose of this retrospective analysis is to compare the safety profiles associated with the 30-minute

versus 60-minute intravenous infusion times in patients who received nivolumab with either time exclusively.

Materials and methods

Patients

Patients aged 18 years or older with histologically or cytologically confirmed stage IIIB or IV NSCLC and disease progression or recurrence after treatment with at least one prior systemic regimen for advanced, metastatic disease were eligible for enrollment. Measurable disease confirmed radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was required. Testing for *EGFR* mutations and *ALK* rearrangements was also required for patients with non-squamous histology. Patients with tumors that were positive for these aberrations and who had disease progression after first-line tyrosine kinase inhibitor treatment were eligible to enroll. Eligible patients also had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and adequate hematologic, hepatic, and renal function. Patients with treated central nervous system metastases that had been stable for ≥ 2 weeks were eligible, provided that they did not require corticosteroids or were on a stable or decreasing daily dose of ≤ 10 mg of prednisone (or equivalent). Exclusion criteria included a history of interstitial lung disease, autoimmune disease, conditions requiring immunosuppressive doses of systemic corticosteroids, previous anti–PD-1 or anti–programmed death-ligand 1 (PD-L1) therapy, or previous malignancy within 2 years of study entry.

This study was conducted in accordance with Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol was approved by the

institutional review board or independent ethics committee at each participating center. All patients provided written, informed consent prior to enrollment.

Study design and treatment

In this open-label, phase 3b/4 safety study, nivolumab was administered at a dose of 3 mg/kg every 2 weeks by intravenous infusion until disease progression or unacceptable toxicity. Patients who were still on treatment at 1 year were randomized either to continue receiving nivolumab (until disease progression, unacceptable toxicity, or withdrawal of consent) or to discontinue treatment, with the possibility of resuming treatment upon disease progression. An amendment to the protocol (dated December 17, 2014) changed the nivolumab infusion time from 60 minutes to 30 minutes. Patients who were receiving nivolumab over 60 minutes at the time of the amendment were switched to the 30-minute infusion. Only those patients who received the 30-minute or 60-minute infusions exclusively (ie, patients who initiated treatment after the amendment was implemented or who discontinued treatment prior to the amendment, respectively) were included in the infusion substudy (**Fig. 1**); the safety analysis of this sub-study is reported.

The primary endpoint of the study as a whole was the incidence of treatment-related select adverse events (AEs) of grades 3–5. Secondary endpoints included the incidence of any AEs of grades 3–5, the proportion of patients who received immunomodulating agents to treat these AEs, and the duration of this treatment. Exploratory assessments included overall safety and tolerability, efficacy, patient-reported outcomes, pharmacokinetics, and immunogenicity. The results of the overall study will be reported separately. The primary objective of this study was to estimate the incidence of high-grade treatment-related select AEs in patients with advanced or metastatic NSCLC whose disease had progressed during or after at least one prior systemic therapy and who were subsequently treated with nivolumab monotherapy. An

exploratory objective was to estimate the incidence of hypersensitivity/infusion-related reactions (IRRs) with nivolumab administered as a 30-minute infusion.

Assessments

Safety assessments and laboratory tests were performed at screening, the first day of each 2-week cycle, within 30 days of the last dose (last dose prior to randomization for patients who were randomized to discontinue treatment after 1 year), approximately 70 days after the first follow-up visit, and until treatment-related AEs were resolved (if lasting > 100 days). AEs were summarized by worst grade per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, by system organ class, and by Medical Dictionary for Regulatory Activities preferred term. Select AEs were defined as events with a potential immunologic mechanism; these may involve pulmonary, gastrointestinal, hepatic, renal, endocrine, dermatologic, or hypersensitivity/IRR events and require more frequent monitoring and/or immunosuppressant treatment.

Pharmacokinetics

Pharmacokinetic profiles of nivolumab administered at a dose of 3 mg/kg as 30-minute and 60-minute infusions were simulated using a previously developed population pharmacokinetics model [15]. Maximum nivolumab serum concentrations (C_{max}) were compared at first dose and at steady state.

Results

Patients

Between April 16, 2014 and July 4, 2016 (data cutoff date), 1420 patients were enrolled and treated, among whom 737 received a single type of infusion (30-minute: 369 patients; 60-

minute: 368 patients; **Table 1**; **Fig. 1**). The remaining 683 patients received 60-minute infusions initially and 30-minute infusions subsequent to the protocol amendment; this patient group was not included in the infusion time analysis. The study was ongoing at the time of the database lock, at which time, 52 patients (14%) in the 30-minute infusion group continued to receive treatment and all 368 patients (100%) in the 60-minute infusion group had discontinued treatment.

Baseline demographic and clinical characteristics of patients who received 30-minute or 60-minute infusions exclusively were comparable with those of the entire patient population (**Table 1**). In the overall patient population, the majority of patients were aged < 70 years (61%), had an ECOG performance status of 0 or 1 (89%), had stage IV disease (91%), and had non-squamous tumor histology (71%) (**Table 1**). There were no notable differences in baseline characteristics between patients receiving the 30-minute and 60-minute infusions; most patients in either group were former smokers (68% and 74%, respectively) and had non-squamous tumor histology (70% and 76%, respectively). Only 12% and 13% of patients in the 30-minute and 60-minute infusion groups, respectively, had an ECOG performance status of 2.

Dose administration

Due to the protocol change approximately 9 months after the study start date, the median duration of therapy was 3.5 months (range 0–16.6 months) for patients who received the 30-minute infusion versus 1.4 months (range 0–7.3 months) for patients who received the 60-minute infusion. Patients in the 30-minute infusion group received a median of 8 doses (range 1–36 doses) of nivolumab, whereas those in the 60-minute infusion group received a median of 4 doses (range 1–16 doses). Patients who received only 60-minute infusions discontinued nivolumab prior to the amendment, allowing for a maximum possible treatment duration of approximately 9 months (the time between study initiation and implementation of the amendment). Those who received only 30-minute infusions initiated treatment after the

amendment, allowing for a maximum possible treatment duration of approximately 19 months (the time between implementation of the amendment and database lock; **Fig. 1**). The relative dose intensity was 90% to 110% in the majority of patients in both the 30-minute (80%) and 60-minute (88%) infusion groups.

Incidence of hypersensitivity/IRRs

Hypersensitivity/IRRs were infrequent and occurred at similar rates in the 30-minute and 60-minute infusion groups, the majority of which occurred during the first or second nivolumab dosing cycles. Hypersensitivity/IRRs of any cause were reported in 10 (3%) and 8 (2%) patients who received 30-minute and 60-minute infusions, respectively (**Table 2**). The majority of hypersensitivity/IRRs (8 [2%] of 10 events and 7 [2%] of 8 events in the 30-minute and 60-minute infusion groups, respectively) were considered treatment-related by the investigators. All patients who had hypersensitivity/IRR events experienced only one such event, with the exception of one patient given 30-minute infusions who experienced two events. Grade 3 hypersensitivity/IRRs were experienced by 2 patients in the 60-minute infusion group (IRR in both patients) and 2 patients in the 30-minute infusion group (bronchospasm and anaphylactic reaction [1 patient each]).

Management of hypersensitivity/IRRs

Interruptions of nivolumab dosing due to hypersensitivity/IRRs were reported in 13 patients (2%) across the two infusion groups during the study: 9 (2%) in the 30-minute and 4 (1%) in the 60-minute infusion group. One patient who received 30-minute infusions required two dose interruptions; this patient had two hypersensitivity/IRR events. The mean (SD) nivolumab dose in these patients with treatment interruptions was similar in both cohorts: 2.8 (1.0) mg/kg and 2.8 (0.3) mg/kg in the 30-minute and 60-minute infusion groups, respectively.

In the 30-minute and 60-minute infusion groups, systemic corticosteroids were administered to 3 of 10 patients and 2 of 8 patients with a hypersensitivity/IRR, respectively. Two patients in each cohort received a high-dose (≥ 40 mg) prednisone equivalent per day. None of the patients who received corticosteroids required a corticosteroid taper.

Three patients (< 1%) discontinued nivolumab treatment due to a hypersensitivity/IRR. One patient (< 1%) in the 30-minute infusion group discontinued due to a grade 3 anaphylactic reaction, and 2 patients (< 1%) in the 60-minute infusion group discontinued due to grade 3 IRRs. All of these events that led to discontinuation were considered related to treatment.

Overall safety

The incidence of treatment-related AEs was similar in the 30-minute and 60-minute infusion groups (59% and 50%, respectively; **Table 3**). The most common treatment-related AEs were fatigue (18%), diarrhea (10%), and nausea (8%) in the 30-minute infusion group, and fatigue (15%), decreased appetite (10%), and nausea (7%) in the 60-minute infusion group. The following AEs were more frequent in the 30-minute infusion group than in the 60-minute infusion group: diarrhea (10% vs 5%), hypothyroidism (6% vs 2%), hypomagnesemia (5% vs 2%), pneumonitis (5% vs 2%), pruritus (4% vs 2%), pyrexia (4% vs 2%), and rash (5% vs 2%). AEs that were more frequent in the 60-minute infusion group than in the 30-minute infusion group were decreased appetite (10% vs 7%) and anemia (4% vs 2%).

Grade 3–4 treatment-related events were reported in 12% of patients in each group (**Table 3**). The incidences of the most common treatment-related grade 3–4 events were similar in the 30-minute and 60-minute infusion groups. Grade 3–4 fatigue was reported in 3% of patients in both groups, and grade 3–4 pneumonitis was reported in 2% and 1% of patients in the 30-minute and 60-minute infusion groups, respectively. Treatment-related AEs leading to discontinuation were reported in 8% of patients in the 30-minute infusion group and 5% of patients in the 60-minute infusion group. The most frequently reported treatment-related event

leading to discontinuation was pneumonitis, reported in 2% and 1% of patients in the 30-minute and 60-minute infusion groups, respectively. One patient in the 30-minute group died due to bowel perforation that was considered related to treatment by the treating investigator.

In both infusion groups, the majority of treatment-related AEs and select AEs (those of potential immunologic etiology that frequently require intervention) were grade 1–2 (**Table 3**). Although the overall frequencies of gastrointestinal, skin, endocrine, and pulmonary treatment-related select AEs were higher in the 30-minute infusion group than in the 60-minute infusion group, most of these events were grade 1–2. The higher frequencies of grade 1–2 AEs in the 30-minute infusion group may have been due to the longer duration of exposure in that group. Notably, the frequencies of grade 3–4 treatment-related select AEs were low and similar in both infusion groups (≤ 2%).Treatment-related and select AEs reported in the two infusion groups were similar to those reported in the overall patient population (**Table 1 in Online Resource 1**).

Given that the protocol amendment that changed the infusion time from 60 to 30 minutes resulted in longer exposure in the 30-minute infusion group, exposure-adjusted incidence rates of AEs were used to account for the exposure difference (median of 8 doses in the 30-minute infusion group compared with 4 doses in the 60-minute infusion group). These analyses found a greater incidence of all-causality AEs in the 60-minute infusion group: AEs of any cause were reported at a rate of 2379 per 100 person-years of exposure (100 P-Y) in the 30-minute infusion group and 5161 per 100 P-Y in the 60-minute infusion group (**Table 2 in Online Resource 1**). Serious AEs of any cause were reported at a rate of 266 per 100 P-Y in the 30-minute infusion group and 884 per 100 P-Y in the 60-minute infusion group (**Table 3 in Online Resource 1**).

Pharmacokinetics

A previously developed population pharmacokinetics model [15] predicted similar pharmacokinetics of nivolumab in the two infusion groups. The predicted C_{max} of nivolumab was

58.5 μg/mL after the first dose and 128 μg/mL at steady state in patients in both the 30-minute and 60-minute infusion groups (**Fig. 2**).

Discussion

To date, nivolumab has been administered in clinical trials using an infusion time of 60 minutes [10]. The results of this novel analysis indicate that nivolumab dosed at 3 mg/kg can be safely infused over a 30-minute period in patients with previously treated NSCLC. Overall, no new safety concerns were noted with 30-minute infusions of nivolumab. The incidences of hypersensitivity/IRRs (of any cause or treatment-related) were low and similar in both the 30-minute and 60-minute infusion groups and, in general, comparable to the incidence observed in phase 3 studies of nivolumab in patients with previously treated NSCLC (CheckMate 017 and CheckMate 057) [1,2]. Hypersensitivity/IRRs were generally manageable using dosing interruptions; the impact on the nivolumab dose received was modest (the relative dose intensity was 90% to 110% in the majority of patients in both infusion groups).

IRRs are a known concern associated with the administration of therapeutic monoclonal antibodies [16,17]. When IRRs are mild or moderate, management may involve extending the rate of infusion [13,17]. For this reason, longer infusion times are generally chosen when new therapeutic antibodies are developed clinically. Indeed, the current findings potentially support a practice-changing infusion strategy. A shorter infusion time for administration of nivolumab would reduce the patient burden of lengthy infusions and result in operational and cost efficiencies for clinics and treatment centers.

Two possible limitations of this analysis include selection bias in the 60-minute infusion group, which over-represented patients who experienced disease progression and/or tolerated treatment poorly, and a greater number of nivolumab doses and longer duration of treatment in the 30-minute infusion group. Both of these limitations can be attributed to the design of the

sub-study and the timing of the protocol amendment. As the sub-study included only patients who received either 60-minute or 30-minute infusions exclusively, the 60-minute infusion group comprised patients who discontinued treatment due to disease progression or toxicity prior to the implementation of the protocol amendment (approximately 9 months from the start of the study), while the 30-minute infusion group comprised patients who enrolled after the protocol amendment (approximately 19 months prior to the date of the database lock), some of whom were still receiving treatment at the time of the database lock.

Exposure-adjusted safety analyses performed to address this potential time bias showed that incidence rates of AEs and serious AEs were lower in the 30-minute infusion group than in the 60-minute infusion group. In addition, even without adjustment for exposure time, IRR rates remained comparable in the two infusion groups. Together, these results suggest that the overall safety profile of the 30-minute nivolumab infusion remained comparable to that of the 60-minute infusion. Furthermore, because the pharmacokinetic exposure distribution was shown to be similar with the 240-mg flat dose and the 3-mg/kg dose within the body weight range of a simulated population in a pharmacokinetic modeling analysis [18], safety is expected to be similar between 30-minute infusions of the 240-mg flat dose and the 3-mg/kg dose.

In conclusion, nivolumab at 3 mg/kg can be safely infused over 30 minutes, with a low incidence of IRRs. The overall safety profile of 30-minute nivolumab infusions was comparable to that of 60-minute nivolumab infusions and was consistent with the well-characterized safety profile of nivolumab in prior clinical trials.

Compliance With Ethical Standards:

Conflict of Interest Disclosures Dr Waterhouse has participated in speakers' bureau for Genentech, Eli Lilly, Celgene, and Bristol-Myers Squibb, where he also served in a consulting and/or an advisory role. Dr Horn has served in a consulting and/or an advisory role for

Genentech, Merck, Bristol-Myers Squibb, Boehringer Ingelheim, XCovery, and Bayer; she received research funding from a^2 Pharmaceutical; and she disclosed a financial relationship with Biodesix. Dr Reynolds has reported stock or ownership interest in Gilead; he has served in a consulting and/or an advisory role for, and received travel, accommodations, expenses, and honoraria from, Eli Lilly, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, and AstraZeneca; he has participated in a speakers' bureau for Eli Lilly, Boehringer Ingelheim, Genentech, and AstraZeneca. Dr Spigel has served in a consulting and/or an advisory role for Novartis and Genentech; he has received travel, accommodations, and expenses from Novartis, Genentech, and Pfizer. Dr Chandler has served in a consulting and/or an advisory role for, and received travel, accommodations, and expenses from, Bristol-Myers Squibb, Janssen, and Caris Life Sciences. Dr Mekhail has participated in a speakers' bureau for, and received research funding and honoraria from, Bristol-Myers Squibb. Dr Mohamed has served in a consulting and/or an advisory role for, and has participated in a speakers' bureau for, Eli Lilly, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, and Merck. Dr Creelan has participated in a speakers' bureau for, and has received travel, accommodations, and expenses from, Bristol-Myers Squibb and AstraZeneca; he has received research funding and honoraria from Boehringer Ingelheim. Dr. Blankstein has no financial relationships to disclose. Dr Nikolinakos has served in a consulting and/or an advisory role for Eli Lilly, Boehringer Ingelheim, and Exelixis; he has participated in a speakers' bureau for Boehringer Ingelheim. Dr McCleod has no financial relationships to disclose. Mr Li has been employed by and owns stock in Bristol-Myers Squibb Company. Dr Oukessou has been employed by and owns stock in Bristol-Myers Squibb Company. Dr Agrawal has been employed by and owns stock in Bristol-Myers Squibb Company. Dr Aanur has been employed by and owns stock in Bristol-Myers Squibb Company. No others disclosures were reported.

Research involving Human Participants or Animals or Ethical Standards/Approval All procedures performed in studies involving human participants were in accordance with the

ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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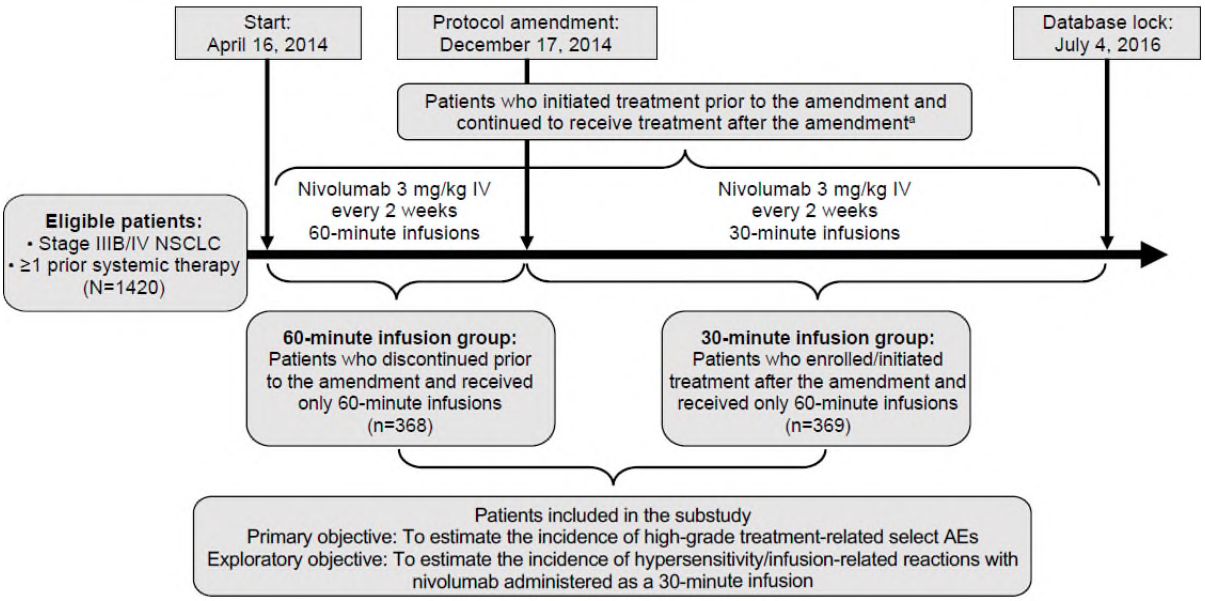

Fig. 1 Study design of the CheckMate 153 infusion safety analysis

IV intravenous; *NSCLC* non-small cell lung cancer
[a]Patients who were responding to therapy at the time of the December 2014 amendment and who received both 60-minute and 30-minute infusions (*n* = 683) were not included in the substudy

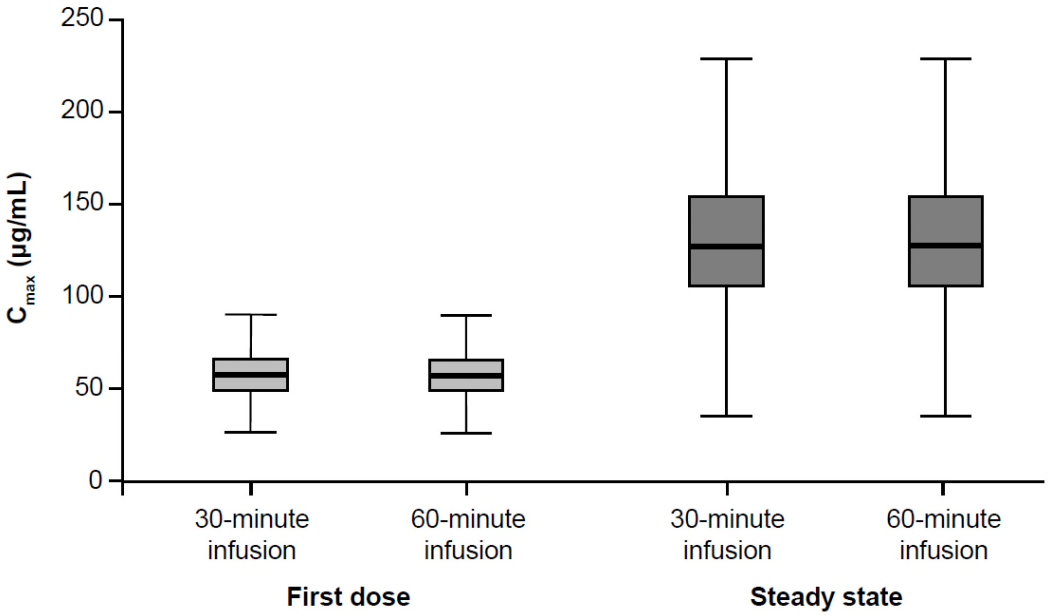

Fig. 2 Model-predicted C_{max} after the first dose and at steady state by infusion time. Box plots show mean values and 25%/75% quartiles. Whiskers above and below the box indicate 1.5 times the interquartile range
C_{max} maximal nivolumab plasma concentration

Table 1 Baseline patient characteristics

Characteristic	30-minute infusion (*n* = 369)	60-minute infusion (*n* = 368)	All patients (*N* = 1420)
Age, year, median (range)	68 (29–87)	67 (33–91)	67 (29–93)
≥ 70	155 (42)	146 (40)	556 (39)
Sex, *n* (%)			
Male	192 (52)	213 (58)	764 (54)
Female	177 (48)	155 (42)	656 (46)
ECOG PS, *n* (%)			
0 or 1	320 (87)	316 (86)	1267 (89)
2	44 (12)	47 (13)	126 (9)
Not reported	5 (1)	5 (1)	27 (2)
Smoking status, *n* (%)			
Never	54 (15)	41 (11)	182 (13)
Current	63 (17)	53 (14)	223 (16)
Former	251 (68)	273 (74)	1006 (71)
Not reported/unknown	1 (< 1)	1 (< 1)	9 (1)
Disease stage, *n* (%)			
IIIB	34 (9)	17 (5)	116 (8)
IV	334 (91)	334 (93)	1290 (91)
Not reported	1 (< 1)	7 (2)	14 (1)
Tumor histology, *n* (%)			
Non-squamous	260 (70)	279 (76)	1005 (71)
Squamous	108 (29)	82 (22)	402 (28)
Not reported	1 (< 1)	7 (2)	13 (1)
Brain metastases, *n* (%)			
Yes	2 (1)	10 (3)	21 (1)
No	365 (99)	356 (97)	1377 (97)
Unknown	2 (1)	2 (1)	22 (2)
Number of prior therapies, *n* (%)			
1	143 (39)	144 (39)	542 (38)
2	94 (25)	98 (27)	403 (28)
≥ 3	125 (34)	121 (33)	449 (32)
Not reported	7 (2)	5 (1)	26 (2)

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Table 2 Summary of hypersensitivity/IRRs by infusion time

	30-minute infusion (*n* = 369)				60-minute infusion (*n* = 368)			
	Any grade		Grade 3–4		Any grade		Grade 3–4	
Hypersensitivity/IRRs[a]	AC	TR[b]	AC	TR[b]	AC	TR[b]	AC	TR[b]
Total patients with an event, *n* (%)	10 (3)	8 (2)	2 (1)	1 (< 1)	8 (2)	7 (2)	2 (1)	2 (1)
Hypersensitivity	4 (1)	4 (1)	0	0	1 (< 1)	0	0	0
IRR	4 (1)	3 (1)	0	0	6 (2)	6 (2)	2 (1)	2 (1)
Anaphylaxis	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0	0	0	0
Bronchospasm	1 (< 1)	0	1 (< 1)	0	1 (< 1)	1 (< 1)	0	0
Hypersensitivity/IRRs leading to discontinuation, *n* (%)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (1)	2 (1)	2 (1)	2 (1)

AC any cause, *IRR* infusion-related reaction, *TR* treatment-related
[a]Reported between first dose and 30 days after last dose of nivolumab
[b]As assessed by the investigator

Table 3 Treatment-related and select AEs by infusion time

	30-minute infusion (*n* = 369)		60-minute infusion (*n* = 368)	
	Any grade[a]	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, *n* (%)[b]				
Any AE	219 (59)	45 (12)	185 (50)	45 (12)
Fatigue	66 (18)	11 (3)	56 (15)	10 (3)
Diarrhea	37 (10)	3 (1)	17 (5)	3 (1)
Nausea	29 (8)	1 (< 1)	26 (7)	0
Decreased appetite	27 (7)	0	35 (10)	1 (< 1)
Hypothyroidism	22 (6)	0	7 (2)	0
Rash	18 (5)	2 (1)	7 (2)	0
Arthralgia	17 (5)	0	12 (3)	1 (< 1)
Hypomagnesemia	17 (5)	0	9 (2)	0
Pneumonitis	17 (5)	6 (2)	6 (2)	3 (1)
Pruritus	14 (4)	0	6 (2)	0
Pyrexia	13 (4)	0	7 (2)	0
Asthenia	12 (3)	1 (< 1)	7 (2)	1 (< 1)
Dyspnea	11 (3)	1 (< 1)	13 (4)	3 (1)
Anemia	9 (2)	2 (1)	15 (4)	3 (1)
Vomiting	9 (2)	0	11 (3)	0
Constipation	7 (2)	1 (< 1)	11 (3)	0
Treatment-related select AEs by category, *n* (%)				
Gastrointestinal	39 (11)	7 (2)	19 (5)	4 (1)
Skin	42 (11)	3 (1)	26 (7)	3 (1)
Endocrine	37 (10)	0	16 (4)	1 (< 1)
Hepatic	14 (4)	6 (2)	17 (5)	4 (1)
Renal	7 (2)	1 (< 1)	2 (< 1)	0
Pulmonary	17 (5)	6 (2)	6 (2)	3 (1)
Hypersensitivity/IRR	8 (2)	1 (< 1)	7 (2)	2 (< 1)

AE adverse event, *IRR* infusion-related reaction

[a]One case of grade 5 bowel perforation that was considered related to treatment was reported after the database lock

[b]Reported between first dose and 30 days after last dose of nivolumab in ≥ 3% of patients in either group