

Clinical Benefit-Risk Assessment of Nivolumab 240 mg Every 2 Weeks in Chinese Patients With Advanced and Metastatic Solid Tumors

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Abstract

Nivolumab 240 mg every 2 weeks is approved in China by the National Medical Product Agency for squamous cell carcinoma of the head and neck and gastric cancer, based on population pharmacokinetic (PPK) analyses and benefit-risk assessment of safety/efficacy in solid tumors, including Chinese and global populations. The aim of this assessment was to investigate exposure and risk for adverse events (AEs) with flat dosing compared with weight-based dosing. Nivolumab 240-mg and 3-mg/kg every-2-week exposures in Chinese patients were simulated using PPK modeling, and AEs in Chinese and pooled global populations were compared by dosing regimen, exposure, and weight. The 10-mg/kg every-2-week regimen was included because it is known to be well tolerated. Predicted nivolumab exposure in Chinese patients receiving 240 mg every 2 weeks was ~25% higher versus 3 mg/kg every 2 weeks, but ~60% lower versus 10 mg/kg every 2 weeks. Grade 3/4 AE incidence in Chinese patients receiving nivolumab 3 mg/kg every 2 weeks was similar with 240-mg every-2-week dosing and with patients from global populations treated with 3 or 10 mg/kg every 2 weeks. There was no trend toward increased AE incidence with high versus low nivolumab exposure or in global patients of varying body weight receiving 3 or 10 mg/kg every 2 weeks. Objective response rates were similar in Chinese and global patients with squamous and nonsquamous NSCLC. Results showed that benefit-risk profiles with nivolumab 240 mg every 2 weeks were similar to those of the 3-mg/kg every-2-week regimen in Chinese patients and global populations, providing an alternative treatment option to Chinese patients.

Keywords

China, flat dosing, nivolumab, population pharmacokinetics, solid tumors

In clinical trials, nivolumab 3 mg/kg every 2 weeks demonstrated an overall survival benefit over standard of care across multiple tumor types.^{1–5} Most monoclonal antibodies, including immune checkpoint inhibitors, have been dosed based on body weight, assuming that this may potentially reduce interpatient variability in exposure and clinical response.^{6,7} A major concern with flat dosing is that weight might influence the safety profile, although efficacy is not expected to be reduced, given higher exposure with flat dosing.^{6,8} Monoclonal antibody clearance rises with increasing body weight, yet the increment is less than proportional.⁹ Therefore, patients with higher body weight tend to have higher exposure with weight-based dosing because of less than proportional increases in clearance with increasing body weight. Conversely, flat dosing results in decreased exposure as weight increases.⁷ Exposure variability associated with flat dosing may be acceptable, as many monoclonal antibodies have selective modes of action with wide therapeutic indexes.

The fully human immunoglobulin G4 monoclonal antibody nivolumab has a wide therapeutic index, as

evidenced by efficacy in many malignancies and favorable safety profiles at doses from 0.1 to 10 mg/kg every 2 weeks in early-phase, dose-ranging studies.^{10,11} Similarly, nivolumab population pharmacokinetic (PPK) and exposure-response (E-R) analyses revealed linear pharmacokinetics (PK) with dose-proportional exposure and relatively flat E-R relationships for efficacy and safety across doses from 0.1 to 10 mg/kg and 240 mg every 2 weeks.^{6,12} There were no clinically meaningful relationships between body weight or exposure

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quartiles and frequency or severity of adverse events (AEs).⁶ Together, these data suggest that benefit-risk profiles for nivolumab 3 mg/kg and 240 mg every 2 weeks would be similar, despite potentially increased exposure variability with flat dosing.^{6,12} Potential benefits of transitioning to flat dosing include improved ease of use and administration and reduced health care burden, dose-calculation errors, and waste.^{6,13} Nivolumab 240 mg every 2 weeks is approved for multiple indications in the United States,¹⁴ European Union,¹⁵ and Japan.¹⁶ Approvals were based on PPK and E-R analyses demonstrating comparable exposure, safety, and efficacy of 240 mg with 3 mg/kg every 2 weeks and on an acceptable safety profile of 10 mg/kg every 2 weeks.^{6,12,17}

The Chinese National Medical Product Agency (NMPA) approved nivolumab 3 mg/kg every 2 weeks for patients with non-small cell lung cancer (NSCLC) on June 15, 2018, based on CheckMate 077 and 078.¹⁸ CheckMate 077 investigated nivolumab 3 mg/kg and 240 mg every 2 weeks in Chinese patients with previously treated advanced or recurrent solid tumors.¹⁹ On September 29, 2019, the NMPA announced approval of nivolumab 240 mg every 2 weeks for squamous cell carcinoma of the head and neck.²⁰ On March 16, 2020, the NMPA approved nivolumab 240 mg every 2 weeks for third-line or later gastric cancer.²¹ For Chinese patients, a potential challenge associated with a flat dosing regimen of 240 mg every 2 weeks is the higher exposure because of lower average body weight of the Asian populations (58 kg) versus European and North American populations (71 and 81 kg, respectively).²² Thus, the association of lower body weight with increased exposure and potentially associated safety risks may be more relevant for Chinese patients compared with Western populations.²³ However, the efficacy is not expected to be reduced given higher exposure with flat dosing.^{6,8}

A pooled PPK analysis of data from global studies showed that the time-averaged steady-state exposure of nivolumab 240 mg was consistent with 3 mg/kg every 2 weeks across multiple tumor types.²⁴ In addition, the overall benefit-risk analysis demonstrated that exposures, safety, and efficacy of 240 mg relative to 3 mg/kg every 2 weeks were similar across body weights, exposure quartiles, and tumor types in global populations.⁶ A PPK analysis developed for Chinese patients demonstrated similar linear and dose-proportional PK of nivolumab with time-dependent clearance in both Chinese and non-Asian patients.¹⁹ In this model, Asian race and tumor type did not have a clinically meaningful impact on clearance together with other covariates, including baseline body weight, estimated glomerular filtration rate, Eastern Cooperative Oncology Group performance status, and sex.¹⁹

Here, we report the totality of benefit-risk assessment of 240 mg every 2 weeks for Chinese patients, thus providing additional nivolumab treatment options to health care providers and patients. We compared exposures of nivolumab 240 mg and 3 mg/kg every 2 weeks in Chinese patients with advanced and metastatic solid tumors. Importantly, we conducted extensive safety analyses with a pooled global population from 7 studies and a Chinese population from 2 studies, thus supporting the alternative dosing of 240 mg every 2 weeks for Chinese patients. We also compared clinical efficacy in Chinese patients with the pooled global population.

Methods

Analyses included predicted exposures calculated from individual PK parameters determined from a previously developed PPK model¹⁹ and clinical safety and efficacy data (Table 1) and predicted exposures calculated from individual PK parameters determined from a previously developed PPK model¹⁹ and observed concentrations. The PPK model was developed using data from Chinese patients enrolled in CheckMate 077 and 078 and data from global patients in CheckMate 001, 003, 017, 057, and 063.¹⁹

Comparison of Nivolumab Exposures

The final PPK model developed for Chinese patients¹⁹ was used to simulate nivolumab PK, predict exposures for Chinese patients receiving nivolumab 240 mg or 3 mg/kg every 2 weeks (CheckMate 077 and 078) and patients from a pooled global population receiving 10 mg/kg every 2 weeks (CheckMate 001 and 003; Table 1), and compare exposures between Chinese and global populations. Predicted summary measures of exposure were obtained for each patient for whom maximum a posteriori individual Bayesian estimates of PK parameters were available. The summary measures included time-averaged concentration (C_{avg1}), trough concentration (C_{min1}), and peak concentration (C_{max1}), all during the first dosing interval, and steady-state time-averaged concentration (C_{avgss}), trough concentration (C_{minss}), and peak concentration (C_{maxss}).

Comparison of Subgroup Safety Profiles

Safety analyses included the incidence of all-cause AEs, serious AEs (SAEs), immune-mediated AEs (IMAEs), and AEs leading to discontinuation (AEs-DC). Safety profiles in Chinese patients receiving nivolumab 240 mg every 2 weeks (CheckMate 077) were compared with Chinese patients receiving 3 mg/kg every 2 weeks (CheckMate 077 and 078) and with global populations receiving 3 or 10 mg/kg every 2 weeks (CheckMate 003, 017, 037, 057, 063, 066, and 067; Table 1).

Safety profiles were also compared using a high versus low exposure threshold (32.4 $\mu\text{g/mL}$) calculated

Table 1. Data Summary for Exposure, Safety, and Efficacy Analyses

Measure	Patient Groups	Tumor Type	Patients, n
PPK Model ¹⁹			
Model used to predict exposures	PPK model was characterized using data from 2 predominantly Chinese studies: (CheckMate 077 [NCT02593786] and 078 [NCT02613507]) and 5 global studies (CheckMate 001 [NCT00441337], 003 [NCT00730639], 017 [NCT01642004], 057 [NCT01673867], and 063 [NCT01721759])	Solid tumors (including melanoma and NSCLC)	1200
Exposure			
Compare predicted exposure with nivolumab 240 mg every 2 weeks in Chinese patients versus nivolumab 3 mg/kg every 2 weeks in Chinese patients versus nivolumab 10 mg/kg every 2 weeks in global study patients	Data for patients treated with 10 mg/kg every 2 weeks from global studies CheckMate 001 (NCT00441337) and 003 (NCT00730639) Predicted 240-mg every-2-week data for Chinese patients treated with nivolumab 240 mg every 2 weeks (n = 20) or 3 mg/kg every 2 weeks (n = 294) from studies CheckMate 077 (NCT02593786) and 078 (NCT02613507)	Solid tumors (including melanoma and NSCLC) Solid tumors (including NSCLC)	148 314
Safety			
Safety in Chinese patients treated with 240 mg every 2 weeks or with 3 mg/kg every 2 weeks compared with global pooled study patients treated with 3 mg/kg every 2 weeks or 10 mg/kg every 2 weeks	Chinese patients treated with 3 mg/kg every 2 weeks or 240 mg every 2 weeks from study CheckMate 077 (NCT02593786) Chinese patients treated with 3 mg/kg every 2 weeks from study CheckMate 078 (NCT02613507) Global pooled population treated with 3 mg/kg every 2 weeks from CheckMate 003 (NCT00730639), 017 (NCT01642004), 037 (NCT01721746), 057 (NCT01673867), 063 (NCT01721759), 066 (NCT01721772), and 067 (NCT01844505) Global pooled population patients treated with 10 mg/kg every 2 weeks from study CheckMate 001 and 003 (NCT00730639)	2L+ NSCLC 2L NSCLC 2L+ NSCLC and melanoma Solid tumors (including 2L+ NSCLC and melanoma)	15/20 241 1375 131
Safety by low versus high nivolumab exposure	Patients treated with nivolumab 3 mg/kg every 2 weeks or 10 mg/kg every 2 weeks with exposure data available from global studies CheckMate 003 (NCT00730639, all indications), 017 (NCT01642004), 037 (NCT01721746), 057 (NCT01673867), 063 (NCT01721759), 066 (NCT01721772), and 067 (NCT01844505)	Solid tumors (including 2L+ NSCLC and melanoma)	1423
Safety of patients treated with nivolumab 3 mg/kg every 2 weeks by weight category	Patients treated with nivolumab 3 mg/kg every 2 weeks from global studies CheckMate 003 (NCT00730639), 017 (NCT01642004), 037 (NCT01721746), 057 (NCT01673867), 063 (NCT01721759), 066 (NCT01721772), and 067 (NCT01844505)	2L+ NSCLC and melanoma	1375
Safety of patients treated with nivolumab 3 mg/kg every 2 weeks by exposure quartiles	Patients treated with nivolumab 3 mg/kg every 2 weeks with exposure data available from global studies CheckMate 003 (NCT00730639), 017 (NCT01642004), 037 (NCT01721746), 057 (NCT01673867), 063 (NCT01721759), 066 (NCT01721772), and 067 (NCT01844505)	2L+ NSCLC and melanoma	1293
Efficacy			
ORR in Chinese versus global SQ/NSQ NSCLC patients treated with nivolumab 3 mg/kg every 2 weeks	Chinese population: randomized SQ/NSQ patients treated with nivolumab 3 mg/kg every 2 weeks from China from CheckMate 078 (NCT02613507) Global population: randomized patients from CheckMate 017 (NCT01642004), SQ NSCLC, and CheckMate 057 (NCT01673867), NSQ NSCLC, treated with 3 mg/kg every 2 weeks	2L NSCLC (SQ/NSQ) 2L NSCLC (SQ/NSQ)	99/143 135/292

2L, second line; 2L+, second line or later; N/A, not available; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; SQ, squamous.

Table 2. Predicted Nivolumab Exposures for Chinese Patients Versus Global Populations Treated With Weight-Based or Flat Doses

Nivolumab Exposure Parameter	Geometric Mean of Predicted Exposure, $\mu\text{g/mL}$ (CV, %) ^a			Difference in Geometric Mean, % ^b	
	Chinese 240 mg Q2W (n = 314) ^c	Chinese 3 mg/kg Q2W (n = 294) ^d	Global 10 mg/kg Q2W (n = 148) ^b	240 mg Q2W ^e versus 10 mg/kg Q2W	240 mg Q2W ^f versus 3 mg/kg Q2W
$C_{\text{min}1}$	20.7 (24.1)	16.3 (23.4)	53.6 (27.5)	-61	27
$C_{\text{max}1}$	71.2 (18.9)	56.2 (13.8)	178.0 (25.2)	-60	27
$C_{\text{avg}1}$	32.4 (18.3)	25.6 (17.5)	85.7 (22.0)	-62	27
$C_{\text{min}ss}$	78.3 (71.8)	62.0 (73.5)	206.0 (64.0)	-62	26
$C_{\text{max}ss}$	152.0 (44.7)	120.0 (44.8)	393.0 (39.6)	-61	27
$C_{\text{avg}ss}$	101.0 (58.1)	80.2 (61.5)	268.0 (52.3)	-62	26

$C_{\text{avg}1}$, time-averaged nivolumab concentration during the first dosing interval; $C_{\text{avg}ss}$, steady-state time-averaged nivolumab concentration; $C_{\text{max}1}$, peak nivolumab concentration during the first dosing interval; $C_{\text{max}ss}$, steady-state peak nivolumab concentration; $C_{\text{min}1}$, trough nivolumab concentration during the first dosing interval; $C_{\text{min}ss}$, steady-state trough nivolumab concentration; CV, geometric coefficient of variation; Q2W, every 2 weeks.

^a Geometric mean of predicted exposure, $\mu\text{g/mL}$ (CV, %): unit of CV is in %, unit of geometric mean is in $\mu\text{g/mL}$.

^b Represents predicted data for patients receiving 10 mg/kg Q2W from global studies CheckMate 001 and 003.

^c Predicted data for all Chinese patients in CheckMate 077 and 078 receiving nivolumab 3 mg/kg (n = 294) or 240 mg Q2W (N = 20) as if they had been dosed with 240 mg Q2W.

^d Predicted data for Chinese patients in CheckMate 077 and 078 receiving nivolumab 3 mg/kg Q2W.

^e Calculated as $([240 \text{ mg Q2W group} - 10 \text{ mg/kg group}] / 10 \text{ mg/kg group}) \times 100$.

^f Calculated as $([240 \text{ mg Q2W group} - 3 \text{ mg/kg group}] / 3 \text{ mg/kg group}) \times 100$.

from the predicted geometric mean of $C_{\text{avg}1}$ in Chinese patients with NSCLC receiving 240 mg every 2 weeks in CheckMate 077 and 078 using the PPK model.¹⁹ This threshold was then applied to the pooled global populations to compare 3- and 10-mg/kg every-2-week safety profiles between low- and high-exposure subgroups.

In addition, in patients with NSCLC or melanoma from global studies receiving second-line or later (2L+) 3 mg/kg every 2 weeks (CheckMate 003, 017, 037, 057, 063, 066, and 067), safety was assessed based on body weight (<50, ≥ 50 to <70 kg, ≥ 70 to <90, ≥ 90 to <110, and ≥ 110 kg) and $C_{\text{avg}1}$ quartiles.

Efficacy

Clinical efficacy was evaluated by investigator-assessed objective response rate (ORR) in the Chinese population with squamous/nonsquamous NSCLC (CheckMate 078; time to treatment failure [TTF] interim analysis data) and compared with patients in global studies with squamous (CheckMate 017) or nonsquamous (CheckMate 057) NSCLC receiving nivolumab 3 mg/kg every 2 weeks (Table 1).

Results

Nivolumab Exposures

In Chinese patients, the geometric means of all predicted exposure metrics with 240-mg every-2-week dosing were $\sim 25\%$ higher versus 3 mg/kg every 2 weeks, but $\sim 60\%$ lower than exposures in the global 10-mg/kg every-2-week cohort (Table 2).

Safety

Nivolumab 240 mg and 3 mg/kg every 2 weeks were well tolerated in Chinese patients with solid tumors. The incidence of grade 3/4 all-cause AEs was 10.0% in Chinese patients receiving nivolumab 240 mg every 2 weeks (CheckMate 077; n = 20) and 6.7% and 43.2% in Chinese patients receiving 3 mg/kg every 2 weeks in CheckMate 077 (n = 15) and 078 (n = 241), respectively (Table 3). It is important to note the limited patient numbers in CheckMate 077 (n = 15) when comparing results with CheckMate 078 (n = 241). The incidence of grade 3/4 all-cause AEs was numerically lower in Chinese patients versus global studies receiving nivolumab 3 mg/kg (45.5%) or 10 mg/kg every 2 weeks (50.4%).

In the global population of patients with 2L+ NSCLC or melanoma, high nivolumab $C_{\text{avg}1}$ ($\geq 32.4 \mu\text{g/mL}$) was not associated with an increased incidence of any-grade or grade 3 to 5 all-cause AEs, SAEs, or AEs-DC versus low $C_{\text{avg}1}$ (Table 4). In the body weight subgroup analyses in patients with solid tumors receiving nivolumab 3 mg/kg every 2 weeks, lower body weight was not associated with an increased incidence of any-grade or grade 3/4 AEs; patients in the <50-kg subgroup had numerically more all-cause grade 5 AEs (Table 5). In the exposure quartile analyses in patients from global studies with 2L+ NSCLC or melanoma receiving nivolumab 3 mg/kg every 2 weeks, the incidence of any-grade or grade 3 to 4 AEs was similar across quartiles (Table 6). Overall, nivolumab safety profiles in Chinese patients were similar across regimens and consistent with patients from global studies.

Table 3. Comparison of Safety in Chinese Versus Global Patients Treated With Nivolumab Weight-Based or Flat Doses

Patients With an Event, n (%)	CheckMate 077 ^a		CheckMate 078	Global Pooled Population ^b	
	Chinese 240 mg Q2W (n = 20)	Chinese 3 mg/kg Q2W (n = 15)	Chinese 2L NSCLC 3 mg/kg Q2W (n = 241)	3 mg/kg Q2W (n = 1375)	10 mg/kg Q2W (n = 131)
All-cause AEs					
Any grade	18 (90.0)	15 (100.0)	236 (97.9)	1346 (97.9)	131 (100.0)
Grade 3/4	2 (10.0)	1 (6.7)	104 (43.2)	626 (45.5)	66 (50.4)
Grade 5	0	4 (26.7)	10 (4.1)	96 (7.0)	18 (13.7)
All-cause SAEs					
Any grade	6 (30.0)	5 (33.3)	88 (36.5)	641 (46.6)	73 (55.7)
Grade 3/4	2 (10.0)	0	50 (20.7)	435 (31.6)	49 (37.4)
All-cause AEs-DC					
Any grade	2 (10.0)	2 (13.3)	40 (16.6)	220 (16.0)	28 (21.4)
Grade 3/4	1 (5.0)	0	29 (12.0)	152 (11.1)	17 (13.0)

2L, second line; AE, adverse event; AEs-DC, adverse events leading to discontinuation; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; SAE, serious adverse event.

^aOne patient had an AE of unknown grade.

^bThe global pooled population included patients from studies CheckMate 003, 017, 037, 057, 063, 066, and 067.

Table 4. All-Cause AEs by Nivolumab Exposure for Patients Receiving Nivolumab 3 mg/kg or 10 mg/kg Every 2 Weeks

Patients With an Event, n (%)	Low C_{avg1} ^a (n = 983)	High C_{avg1} ^a (n = 440)	Total ^b (n = 1423)
All-cause AEs			
Any grade	963 (98.0)	433 (98.4)	1396 (98.1)
Grade 3/4	466 (47.4)	191 (43.4)	657 (46.2)
Grade 5	81 (8.2)	24 (5.5)	105 (7.4)
All-cause SAEs			
Any grade	485 (49.3)	185 (42.0)	670 (47.1)
Grade 3/4	328 (33.4)	132 (30.0)	460 (32.3)
All-cause AEs-DC			
Any grade	165 (16.8)	70 (15.9)	235 (16.5)
Grade 3/4	115 (11.7)	45 (10.2)	160 (11.2)

AE, adverse event; AEs-DC, adverse events leading to discontinuation; C_{avg1} , time-averaged nivolumab concentration during the first dosing interval; SAE, serious adverse event.

^aThe cutoff value of 32.4 $\mu\text{g/mL}$ was determined from the geometric mean of average concentration during the first dosing interval (C_{avg1}) predicted for Chinese patients when administered 240 mg every 2 weeks.

^bIncludes studies CheckMate 003, 017, 037, 057, 063, 066, and 067.

Efficacy

ORR with nivolumab 3 mg/kg every 2 weeks in Chinese patients from CheckMate 078 (TTF analysis population) was 22.2% for squamous and 15.4% for nonsquamous NSCLC. In global patients receiving nivolumab 3 mg/kg every 2 weeks, ORR was 20.0% for squamous and 19.2% for nonsquamous NSCLC from CheckMate 017 and 057, respectively. In addition, the 95% confidence intervals were overlapping between ORR data sets (Table 7).

Discussion

There has been a recent trend to switch programmed death-1/programmed death ligand 1 (PD-1/PD-L1)

checkpoint inhibitors from body weight-based to flat dosing or to obtain the flat-dosing label at the time of indication approval. This advancement may result from the accumulated clinical experience and understanding of safety profiles of PD-1/PD-L1 inhibitors, the lack of reaching a maximum tolerated dose in phase 1 dose-escalation studies, and PPK modeling and relatively flat E-R relationships. Model-informed strategies are innovative approaches to supporting dosing changes, as direct evidence of safety and efficacy may not be required. Per the US Food and Drug Administration E-R guidance, the totality of PPK and E-R analyses can be used to support a new dose not studied in the pivotal clinical trials.^{25,26}

The higher C_{avg1} with nivolumab 240 mg versus 3 mg/kg every 2 weeks is largely attributed to the lower average body weight (58 kg) in Asian patients versus global populations (80 kg). With higher exposure, there is concern that flat dosing could result in more AEs in Chinese patients than with body weight-based dosing. We found that nivolumab exposure in Chinese patients receiving 240 mg every 2 weeks was ~25% higher than in Chinese patients receiving 3 mg/kg every 2 weeks but was ~60% lower than in patients from global studies receiving 10 mg/kg every 2 weeks, the dose with the highest exposure during clinical development that was well tolerated.^{10,11} Of note, 10 mg/kg every 2 weeks was not administered to Chinese patients in this study. However, our previous PPK analyses demonstrated that race (Chinese or Asian versus non-Asian) was not a clinically meaningful covariate for nivolumab exposures,¹⁹ which is consistent with observations of other immuno-oncology drugs,²⁷ and there were also similar distributions of PK parameters across different races.²⁸ Even in studies in which flat dosing in an Asian population may be associated with higher exposure,

Table 5. All-Cause AEs by Weight Category in Global Patients Receiving Nivolumab 3 mg/kg Every 2 Weeks

Patients With an Event, n (%)	Weight Category (kg)					Total ^a (n = 1375)
	<50 (n = 47)	≥50 to <70 (n = 428)	≥70 to <90 (n = 602)	≥90 to <110 (n = 232)	≥110 (n = 66)	
All-cause AEs						
Any grade	47 (100.0)	415 (97.0)	589 (97.8)	229 (98.7)	66 (100.0)	1346 (97.9)
Grade 3/4 ^b	21 (44.7)	194 (45.3)	276 (45.8)	104 (44.8)	31 (47.0)	626 (45.5)
Grade 5 ^b	7 (14.9)	28 (6.5)	44 (7.3)	14 (6.0)	3 (4.5)	96 (7.0)
All-cause SAEs						
Any grade	28 (59.6)	203 (47.4)	270 (44.9)	105 (45.3)	35 (53.0)	641 (46.6)
Grade 3/4 ^b	13 (27.7)	144 (33.6)	182 (30.2)	71 (30.6)	25 (37.9)	435 (31.6)
All-cause AEs-DC						
Any grade	8 (17.0)	65 (15.2)	95 (15.8)	41 (17.7)	11 (16.7)	220 (16.0)
Grade 3/4 ^b	5 (10.6)	46 (10.7)	67 (11.1)	28 (12.1)	6 (9.1)	152 (11.1)

AE, adverse event; AEs-DC, adverse events leading to discontinuation; CI, confidence interval; CTC, Common Terminology Criteria; SAE, serious adverse event.

^aIncludes studies CheckMate 003, 017, 037, 057, 063, 066, and 067.

^bWorst CTC Grade.

Table 6. All-Cause AEs by C_{avg1} Quartiles^a for Global Patients Receiving Nivolumab 3 mg/kg Every 2 Weeks

Patients With an Event, n (%)	Nivolumab C_{avg1} Quartile				Total ^b (n = 1293)
	Q1 <24.6 $\mu\text{g/mL}$ (n = 328)	Q2 ≥24.6 to <28 $\mu\text{g/mL}$ (n = 321)	Q3 ≥28 to <32.1 $\mu\text{g/mL}$ (n = 319)	Q4 ≥32.1 $\mu\text{g/mL}$ (n = 325)	
All-cause AEs					
Any grade	323 (98.5)	313 (97.5)	312 (97.8)	318 (97.8)	1266 (97.9)
Grade 3/4	165 (50.3)	147 (45.8)	145 (45.5)	135 (41.5)	592 (45.8)
Grade 5	40 (12.2)	26 (8.1)	15 (4.7)	6 (1.8)	87 (6.7)
All-cause SAEs					
Any grade	192 (58.5)	147 (45.8)	139 (43.6)	120 (36.9)	598 (46.2)
Grade 3/4	123 (37.5)	104 (32.4)	96 (30.1)	89 (27.4)	412 (31.9)
All-cause AEs-DC					
Any grade	58 (17.7)	54 (16.8)	49 (15.4)	46 (14.2)	207 (16.0)
Grade 3/4	47 (14.3)	34 (10.6)	30 (9.4)	32 (9.8)	143 (11.1)

AE, adverse event; AEs-DC, adverse events leading to discontinuation; C_{avg1} , time-averaged nivolumab concentration during the first dosing interval; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; SAE, serious adverse event.

^aSubgroup analyses of safety were performed based on quartiles of time-averaged serum concentration during the first dosing interval (C_{avg1}) predicted from the population pharmacokinetics model and were restricted to patients with exposure data in the global studies.

^bIncludes studies CheckMate 003, 017, 037, 057, 063, 066, and 067.

there may not be a significant impact on safety. In a Japanese population, exposure of nivolumab 240 mg every 2 weeks was 37% higher versus 3 mg/kg every 2 weeks; however, predicted safety profiles between doses differed by <2% across tumors for AEs-DC, AEs grade 3+, and IMAEs grade 2+.²⁹

CheckMate 078 demonstrated similar safety in Chinese and global populations receiving 3 mg/kg every 2 weeks. Therefore, safety in Chinese patients was expected to be similar to that in global populations receiving 10 mg/kg every 2 weeks. Despite higher exposure in Chinese patients, the 240-mg every-2-week regimen is expected to be well tolerated. Safety of the 240-mg every-2-week dose in Chinese patients was supported by results from CheckMate 077, in which

both nivolumab 240 mg and 3 mg/kg every 2 weeks were well tolerated in Chinese patients, with no new safety signals or increased occurrence of AEs. With evidence of similar safety profiles between Chinese and global populations, high versus low exposures were compared in global populations of patients with 2L+ NSCLC or melanoma. In the global population, high C_{avg1} was not associated with an increased incidence of AEs versus low C_{avg1} , similar to results showing no significant association between nivolumab C_{avg1} and AEs in patients with squamous/nonsquamous NSCLC.¹²

A review of nivolumab safety by body weight revealed similar safety in global populations with similar body weight (≥50 to 70 kg) to the average weight of Chinese patients (57-66 kg), as well as to higher

Table 7. Nivolumab Efficacy in Patients With NSCLC Treated With Nivolumab 3 mg/kg Every 2 Weeks or Docetaxel

	CheckMate 078 (Chinese TTF Population, SQ NSCLC)		CheckMate 017 (All Randomized, SQ NSCLC)		CheckMate 078 (Chinese TTF Population, NSQ NSCLC)		CheckMate 057 (All Randomized, NSQ NSCLC)	
	Nivolumab (n = 99)	Docetaxel (n = 50)	Nivolumab (n = 135)	Docetaxel (n = 137)	Nivolumab (n = 143)	Docetaxel (n = 71)	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR ^a (95%CI)	22.2 (14.5-31.7)	0.0 (0.0-7.1)	20.0 (13.6-27.7)	8.8 (4.6-14.8)	15.4 (9.9-22.4)	7.0 (2.3-15.7)	19.2 (14.8-24.2)	12.4 (8.8-16.8)
Responders, n	22	0	27	12	22	5	56	36

CI, confidence interval; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; SQ, squamous; TTF, time to treatment failure.

^aInvestigator-assessed.

body weight groups. In subgroup analyses of safety by body weight and exposure quartiles in global patients with solid tumors receiving nivolumab 3 mg/kg every 2 weeks, lower body weight and higher exposure were not associated with increased AEs. Importantly, safety was generally consistent in Chinese patients receiving nivolumab 3 mg/kg every 2 weeks (CheckMate 078) and global patients receiving 3 or 10 mg/kg every 2 weeks (CheckMate 017 and 057).

The consistency of various safety subgroup analyses between and within Chinese and global populations and safety experience with nivolumab at doses from 0.1 to 10 mg/kg every 2 weeks in global populations provided confidence that the 240-mg every-2-week regimen would be safe and tolerable in the Chinese population. Previous E-R safety and efficacy relationships in global studies were relatively flat over exposures from 0.1 to 10 mg/kg every 2 weeks, indicating a wide therapeutic margin that was comparable across tumor types.^{6,10,30} The benefit-risk profiles for nivolumab 240 mg and 3 mg/kg every 2 weeks were also predicted to be similar based on safety and efficacy findings. From an efficacy perspective, ORR was comparable in Chinese and global populations with squamous/nonsquamous NSCLC receiving nivolumab 3 mg/kg every 2 weeks. Given the similarity between Chinese and global populations, E-R efficacy and safety analyses were not conducted specifically for Chinese patients.

A limitation of our study was the small number (n = 20) of Chinese patients receiving nivolumab 240 mg every 2 weeks in the all-cause AE analysis. In addition, a limitation of the assessment between 3 mg/kg and 240 mg every 2 weeks was that it was not conducted in the context of a randomized study; however, it was guided and informed by well-characterized E-R analyses. Another limitation is lack of direct data/analyses of nivolumab safety at doses from 0.1 to 10 mg/kg in Chinese patients.

CheckMate 078 provided evidence of the clinical benefit of nivolumab in Chinese patients. Based on our results, we predict that safety in Chinese patients

with higher nivolumab exposure is comparable to that observed in a global patient population. In addition, given the tolerability of nivolumab 10 mg/kg every 2 weeks in the global population, nivolumab 240 mg every 2 weeks is expected to be well tolerated in Chinese patients.

The nivolumab flat-dosing regimen provides a new treatment option that is potentially more convenient for both patients and health care providers. The recent NMPA approvals of nivolumab flat-dosing regimens across indications reflect a commitment in China to improving physician and patient experiences while receiving nivolumab therapy. In addition, nivolumab PK generally seems to demonstrate tolerability regardless of a patient's race, as similar exposures have been reported for Chinese, non-Chinese Asian, and non-Asian patients. This suggests that the conclusions about benefit-risk with nivolumab flat dosing in this study could be more broadly applicable to both Chinese and non-Chinese populations. In addition, nivolumab PK is similar in Chinese and non-Chinese Asian patients, suggesting the nivolumab flat-dosing option is tolerable regardless of a patient's race.

Conclusions

Based on PPK modeling for exposures, extensive safety subgroup analyses, and efficacy comparison, the benefit-risk profile of nivolumab 240 mg every 2 weeks is anticipated to be similar to 3 mg/kg every 2 weeks in Chinese patients with solid tumors, which was the scientific and clinical basis for NMPA approval of 240 mg every 2 weeks in China. Nivolumab 240 mg every 2 weeks represents an alternative dosing option, along with 3 mg/kg every 2 weeks, providing convenience and flexibility for Chinese health care providers and patients.

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Conflicts of Interest

All authors are employees of and hold stock and/or other ownership interests in Bristol Myers Squibb.

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Data Availability Statement

Bristol Myers Squibb's policy on data sharing can be found at: <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

References

- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.
- Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.
- Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.
- Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.
- Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. *Ann Oncol*. 2017;28(8):2002-2008.
- Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. *Clin Pharmacokinet*. 2012;51(2):119-135.
- Osawa M, Hasegawa M, Bello A, Roy A, Hruska MW. Population pharmacokinetics analysis of nivolumab in Asian and non-Asian patients with gastric and gastro-esophageal junction cancers. *Cancer Chemother Pharmacol*. 2019;83(4):705-715.
- Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):58-66.
- Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *J Immunother Cancer*. 2016;4:72.
- Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
- Feng Y, Wang X, Bajaj G, et al. Nivolumab exposure-response analyses of efficacy and safety in previously treated squamous or nonsquamous non-small cell lung cancer. *Clin Cancer Res*. 2017;23(18):5394-5405.
- Mathijssen RH, de Jong FA, Loos WJ, van der Bol JM, Verweij J, Sparreboom A. Flat-fixed dosing versus body surface area based dosing of anticancer drugs in adults: does it make a difference? *Oncologist*. 2007;12(8):913-923.
- Bristol-Myers Squibb Company. OPDIVO® (nivolumab) [package insert]. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Updated December 2020. Accessed February 9, 2021.
- Bristol-Myers Squibb Company. OPDIVO® (nivolumab) [SmPC]. <https://www.medicines.org.uk/emc/product/6888/smcp>. Updated December 2020. Accessed February 9, 2021.
- ONO Pharmaceutical Co. Opdivo approved for supplemental applications for expanded indications of malignant pleural mesothelioma and adjuvant treatment of melanoma, change in dosage and administration (D&A) of single dosing regimen, and expanded indication of renal cell carcinoma in Opdivo and Yervoy combination therapy 2018. https://www.onopharma.com/sites/default/files/en/news/press/sm_cn180821.pdf. Accessed February 9, 2021.
- US Food and Drug Administration. Modification of the dosage regimen for nivolumab 2016. <https://www.fda.gov/drugs/resources-information-approved-drugs/modification-dosage-regimen-nivolumab>. Accessed February 9, 2021.
- ONO Pharmaceutical Co. China National Drug Administration approves country's first immuno-oncology agent, Opdivo (nivolumab injection), for previously treated non-small cell lung cancer (NSCLC) 2018. <https://news.bms.com/press-release/corporatefinancialnews/china-national-drug-administration-approves-countrys-first-imm>. Accessed February 9, 2021.
- Zhang J, Cai J, Bello A, Roy A, Sheng J. Model-based population pharmacokinetic analysis of nivolumab in Chinese patients with previously treated advanced solid tumors, including non-small cell lung cancer. *J Clin Pharm*. 2019;59(10):1415-1424.
- Chinese National Medical Product Agency. National Medical Products Newsletter 2020. <http://www.chinadaily.com.cn/specials/nmpanewsletter202001.pdf>. Accessed February 9, 2021.
- Huang J. Bristol-Myers' Opdivo approved to treat gastric cancer in China. *S&P Global Market Intelligence*. 2020. <https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/bristol-myers-opdivo-approved-to-treat-gastric-cancer-in-china-57590260#:~:text=Bristol%2DMyers%20Squibb%20Co.,gastric%20cancer%20available%20in%20China>. Accessed February 9, 2021.
- Walpole SC, Prieto-Merino D, Edwards P, Cleland J, Stevens G, Roberts I. The weight of nations: an estimation of adult human biomass. *BMC Public Health*. 2012;12:439.
- Bajaj G, Gupta M, Wang HH, et al. Challenges and opportunities with oncology drug development in China. *Clin Pharmacol Ther*. 2019;105(2):363-375.
- Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;29(11):2208-2213.
- Bi Y, Liu J, Furmanski B, Zhao H, et al. Model-informed drug development approach supporting approval of the 4-week (Q4W) dosing schedule for nivolumab (Opdivo) across multiple indications: a regulatory perspective. *Ann Oncol*. 2019;30(4):644-651.
- US Food and Drug Administration. Guidance for industry: exposure-response relationships—study design, data analysis, and regulatory applications 2003. <https://www.fda.gov/media/71277/download>. Accessed February 9, 2021.

27. Zhou L, Higashimori M, Shen K, et al. Oncology therapy drugs in China, Japan, and the United States: pharmacokinetic characteristics, dose regimens, and development strategies. *Clin Pharmacol Ther.* 2019;105(6):1303-1320.
28. Lee KW, Lee DH, Kang JH, et al. Phase I pharmacokinetic study of nivolumab in Korean patients with advanced solid tumors. *Oncologist.* 2018;23(2):155-e17.
29. Bei D, Osawa M, Uemura S, et al. Benefit-risk assessment of nivolumab 240 mg flat dose relative to 3 mg/kg Q2W regimen in Japanese patients with advanced cancers. *Cancer Sci.* 2020;111(2):528-535.
30. Wang X, Feng Y, Bajaj G, et al. Quantitative characterization of the exposure-response relationship for cancer immunotherapy: a case study of nivolumab in patients with advanced melanoma. *CPT Pharmacometrics Syst Pharmacol.* 2017;6(1):40-48.