The Oncologist®

Clinical Trial Results

A Phase I/II Open-Label Study of Nivolumab in Previously Treated Advanced or Recurrent Nasopharyngeal Carcinoma and Other Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02593786
- **Sponsor:** Bristol-Myers Squibb Pharmaceuticals Ltd.
- **Principal Investigator:** Li Zhang
- **IRB Approved:** Yes

Lessons Learned

- Nivolumab treatment at doses of 3 mg/kg once every 2 weeks (Q2W), 240 mg Q2W, and 360 mg once every 3 weeks was well tolerated in the Chinese population, with no new safety signals identified.
- Comparison of intensive pharmacokinetic profiles of nivolumab at 3 mg/kg Q2W in Chinese versus global populations revealed no ethnic differences of nivolumab treatment.
- Nivolumab shows promising preliminary antitumor activity in nasopharyngeal carcinoma.

Abstract

Background. This phase I/II study investigated the safety and pharmacokinetics (PK) of nivolumab (anti-programmed cell death-1 monoclonal antibody) in Chinese patients with nasopharyngeal carcinoma (NPC) and other solid tumors.

Methods. A dose evaluation phase (3 mg/kg once every 2 weeks [Q2W]) was followed by a cohort expansion phase (3 mg/kg Q2W or flat doses of 240 mg Q2W or 360 mg once every 3 weeks).

Results. In the dose evaluation phase, 8/8 patients completed one cycle with no dose-limiting toxicities. At data cutoff, 46/51 patients were evaluable for safety (all cohorts). Treatment-related adverse events (TRAEs) occurred in 35 (76%) patients and were primarily grade 1–2; one patient (3 mg/kg Q2W) discontinued because of study drug toxicity. Intensive PK profiles at 3 mg/kg, 240 mg, and 360 mg were well characterized at single and multiple doses of nivolumab. An objective response was determined in six (6/46) patients, four (4/32) of whom had NPC tumors.

Conclusion. Nivolumab monotherapy at 3 mg/kg and flat doses of 240 mg and 360 mg were well tolerated in this Chinese patient population, with PK profiles at 3 mg/kg being similar to those of global patients. Preliminary efficacy results showed promising antitumor activity of nivolumab in advanced NPC. ***The Oncologist*** 2019;24:891–e431

Discussion

Nivolumab is a human monoclonal antibody that targets the programmed cell death-1 receptor. Nivolumab has been approved for the treatment of various types of cancer in >60 countries, and numerous clinical trials are ongoing. Although

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Table 1. Summary of treatment-related adverse events and serious adverse events

Adverse events	Nivolumab 3 mg/kg (*n* = 15)			Nivolumab 240 mg (*n* = 20)			Nivolumab 360 mg (*n* = 11)			All patients (*n* = 46)			NPC (*n* = 32)		
	Any grade	Grade 3–4	Grade 5	Any grade	Grade 3–4	Grade 5	Any grade	Grade 3–4	Grade 5	Any grade	Grade 3–4	Grade 5	Any grade	Grade 3–4	Grade 5
Total TRAEs, *n* (%)	12 (80)	1 (7)	0	14 (70)	1 (5)	0	9 (82)	0	0	35 (76)	2 (4)	0	22 (69)	1 (3)	0
TRAEs leading to discontinuation, *n* (%)	1 (7)[a]	0	0	0	0	0	0	0	0	1 (2)[a]	0	0	0	0	0
TRAEs occurring in ≥10%[b], *n* (%)															
Hypothyroidism	2 (13)			5 (25)			6 (55)			13 (28)			11 (34)		
Rash	5 (33)			2 (10)			4 (36)			11 (24)			8 (25)		
Malaise	2 (13)			5 (25)						7 (15)					
Fatigue	3 (20)									5 (11)			4 (13)		
Decreased appetite	3 (20)			2 (10)						5 (11)					
Increased alanine aminotransferase	2 (13)			2 (10)						5 (11)					
Increased aspartate aminotransferase				2 (10)											
Pyrexia				2 (10)			2 (18)								
Chest discomfort							2 (18)								
Diarrhea	2 (13)														
Nausea				2 (10)											
Proteinuria				2 (10)											
Dizziness				2 (10)											
Total treatment-related SAEs, *n* (%)	1 (7)	0	0	1 (5)	1 (5)	0	0	0	0	2 (4)	1 (2)	0	1 (3)	1 (3)	0

[a]Pancreatitis and cerebellar hemorrhage of indeterminate grade that occurred in one patient in the 3 mg/kg cohort.
[b]Data for TRAEs (any grade) occurring in ≥10% of patients per treatment cohort or patient group.
Abbreviations: NPC, nasopharyngeal carcinoma; SAE, serious adverse event; TRAE, treatment-related adverse event.

Table 2. Summary of pharmacokinetic parameters of nivolumab treatment (3 mg/kg, once every 2 weeks) in Chinese and global patient populations

PK parameter[b]	Chinese patients		Global patients[a]	
	Cycle 1, Day 1 (*n* = 15)	Cycle 3, Day 1 (*n* = 7)	Cycle 1, Day 1 (*n* = 13)	Cycle 3, Day 1[c] (*n* = 7)
C_{max}, μg/mL	57 (18)	132 (17)	61 (26)	132 (20)
T_{max}, hours	4.0 (0.5–4.0)	8.0 (4.0–48.2)	2.1 (0.8–8.0)	4.0 (1.0–8.0)
AUC_{tau}, hours × μg/mL	8,732 (24)	30,824 (21)	8,786 (23)	30,640 (18)
$t_{1/2\text{-effective}}$, hours	—	566 (24)	—	661 (202)

[a]Data for the global patient population are from the phase I CA209003 study [1].
[b]Geometric mean (% coefficient of variation [CV]) for all parameters except for T_{max} (median [range]) and $t_{1/2\text{-effective}}$ (mean [% CV] for the CheckMate 077 study and mean [SD] for the global patient data.
[c]*n* = 5 for AUC_{tau} and $t_{1/2\text{-effective}}$.
Abbreviations: —, data not available; AUC_{tau}, area under the serum concentration-time curve for a dosing interval; C_{max}, maximum serum concentration; PK, pharmacokinetic; $t_{1/2\text{-effective}}$, effective half-life calculated using the formula $\frac{\tau \cdot \ln(2)}{\ln\left[\frac{AI}{AI-1}\right]}$, where t is the dosing interval and AI is the ratio of AUC_{tau} at steady state to that at single dose; T_{max}, time taken to reach maximum concentration.

the overall efficacy, safety, and PK of nivolumab have been extensively studied, these data were established in predominantly Caucasian populations. The safety and intensive PK of nivolumab flat-dose regimens (240 mg Q2W or 360 mg once every 3 weeks) have not been assessed in Chinese patients.

This single-center, open-label, phase I/II study assessed the safety and tolerability of nivolumab in Chinese adult patients with previously treated, advanced or recurrent NPC or other solid tumors. Secondary objectives were PK, immunogenicity, and preliminary antitumor activity.

There were no new safety signals for nivolumab in Chinese patients, and safety profiles were consistent with prior clinical studies (Table 1). Of 46 evaluable patients, 35 experienced TRAEs; there were no grade 4–5 TRAEs, and only two were grade 3 (asthenia, 3 mg/kg cohort; hypochloremia, 240 mg cohort). Two serious TRAEs occurred, a grade 4 hyponatremia (240 mg cohort) and an indeterminate grade pancreatitis and cerebellar hemorrhage (3 mg/kg cohort) that led to discontinuation.

Intensive PK profiles were characterized after first nivolumab dose and at steady state in all cohorts; PK data were compared with results from global patients and revealed no ethnic sensitivity at 3 mg/kg Q2W (Table 2). At data cutoff, antidrug antibodies were detected in 1 of 41 patients tested (3 mg/kg cohort).

Among the 32 patients (70%) with NPC, the objective response rate was 13% (95% confidence interval [CI]: 4–29) and the disease control rate was 66% (95% CI: 47–81). The median follow-up duration was 7.5 months (range: 0.8–24.7 months), and median progression-free survival was 3.5 months (95% CI: 1.8–5.5).

In this pretreated group of patients with predominantly NPC, our study showed that the safety, tolerability, and PK (3 mg/kg) of nivolumab are similar in Chinese and global populations. Furthermore, promising antitumor activity of nivolumab in NPC suggests that further studies are warranted.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	≥1 prior regimen
Type of Study - 1	Phase I/II
Type of Study - 2	Dose evaluation and cohort expansion
Primary Endpoint	Safety and tolerability
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Immunogenicity
Secondary Endpoint	Efficacy
Additional Details of Endpoints or Study Design Dose evaluation and cohort expansion phases: Based on global clinical experience, a nivolumab dose of 3 mg/kg was selected for the initial 8-week dose evaluation phase. The study proceeded to the cohort expansion phase following the absence of dose-limiting toxicities in any of the treated patients. In the cohort expansion phase, three patient cohorts received differing nivolumab regimens (3 mg/kg, 240 mg, and 360 mg) until disease progression or unacceptable toxicity, for a maximum of 2 years. At the time of data analysis, a fourth expansion cohort (480 mg flat dose, once every 4 weeks [Q4W]) was active and not yet recruiting.	
Investigator's Analysis	Drug tolerable, efficacy undetermined

Drug Information	
Drug 1	
Generic/Working Name	Nivolumab
Trade Name	Opdivo
Company Name	Bristol-Myers Squibb Pharmaceuticals Ltd.
Drug Type	Antibody
Drug Class	Immune therapy
Dose	3 mg/kg, 240 mg, 360 mg
Route	IV
Schedule of Administration Dose evaluation phase: 3 mg/kg Q2W for 8 weeks. Cohort expansion phase: 3 mg/kg Q2W; or 240 mg flat dosing Q2W; 360 mg flat dosing once every 3 weeks (Q3W); 480 mg flat dosing Q4W. Note: At the time of data analysis, a fourth expansion cohort (480 mg flat dose Q4W) was active and not yet recruiting. The treatment cycles for the dose evaluation phase and 3 mg/kg Q2W and 240 mg Q2W dose expansion cohorts were 8 weeks' duration (four doses per cycle), whereas the treatment cycles for the 360 mg Q3W cohort were 3 weeks' duration (one dose per cycle).	

Dose Escalation Table

Dose level	Dose of drug: nivolumab	Number enrolled	Number evaluable for toxicity
Cohort expansion	3 mg/kg Q2W for 8-week cycle	15	15
Cohort expansion	240 mg flat dose Q3W	20	20
Cohort expansion	360 mg flat dose Q3W	11	11

Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks.

Dose Information: Evaluable Safety and PK Population

	Nivolumab 3 mg/kg, Q2W	Nivolumab 240 mg, Q2W	Nivolumab 360 mg, Q3W
n	15	20	11
Number of doses	6 (1–51)	8 (1–48)	8 (1–15)
Duration of therapy, weeks	11.7 (2.0–105.1)	16.6 (2.0–98.7)	24.1 (3.0–48.9)
Cumulative dose per subject	18.2 (3.0–152.3) mg/kg	1,920.0 (240.0–11,520.0) mg	2,880.0 (360.0–5,076.0) mg

Data are median (range).

Patient Characteristics	
Number of Patients, Male	31
Number of Patients, Female	15
Stage	Advanced or recurrent
Age	Median (range): 48 (27–72)
Number of Prior Systemic Therapies	Median (range): 3 (1 to ≥4)
Performance Status: ECOG	0 — 17 1 — 29
Other	Race: Asian 100%; Complete baseline demographic and disease characteristics are presented in Table 3.
Cancer Types or Histologic Subtypes	Hepatocellular carcinoma, 2 Lung, non-small cell, 11 Nasopharyngeal carcinoma, 32 Not reported, 1

Primary Assessment Method	
Title	New assessment
Title	Total patient population
Number of Patients Screened	51
Number of Patients Enrolled	51
Number of Patients Evaluable for Toxicity	46
Number of Patients Evaluated for Efficacy	46
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 6 (13%)
Response Assessment SD	*n* = 20 (43%)
Response Assessment PD	*n* = 18 (39%)
Response Assessment OTHER	*n* = 2 (4%)
Outcome Notes	Regarding "Response Assessment OTHER," responses could not be determined for these patients.

Adverse Events

All-cause adverse events

	Grade					
All phases, all cycles	**1**	**2**	**3**	**4**	**5**	**Total**
Nivolumab 3 mg/kg (*n* = 15)						
Chest pain	13%	7%	0%	0%	0%	20%
Fatigue	20%	0%	0%	0%	0%	20%
Malaise	13%	7%	0%	0%	0%	20%
Rash	27%	7%	0%	0%	0%	33%
Decreased appetite	33%	0%	0%	0%	0%	33%
Hypoalbuminemia	7%	7%	0%	0%	0%	13%
Vomiting	27%	0%	0%	0%	0%	27%
Diarrhea	20%	0%	0%	0%	0%	20%
Abdominal discomfort	13%	0%	0%	0%	0%	13%
Constipation	13%	0%	0%	0%	0%	13%
Nausea	13%	0%	0%	0%	0%	13%
Dyspnea	7%	13%	0%	0%	0%	20%

Dizziness	27%	0%	0%	0%	0%	27%
Headache	20%	0%	0%	0%	0%	20%
Increased alanine aminotransferase	20%	0%	0%	0%	0%	20%
Decreased weight	13%	7%	0%	0%	0%	20%
Phlebitis	20%	0%	0%	0%	0%	20%
Hypertension	0%	13%	0%	0%	0%	13%
Malignant neoplasm progression	0%	0%	0%	0%	20%	20%
Cancer pain	0%	13%	0%	0%	0%	13%
Anemia	7%	7%	7%	0%	0%	20%
Hypothyroidism	0%	13%	0%	0%	0%	13%
Musculoskeletal chest pain	13%	0%	0%	0%	0%	13%
Insomnia	20%	0%	0%	0%	0%	20%
Nivolumab 240 mg (*n* = 20)						
Malaise	30%	0%	0%	0%	0%	30%
Pyrexia	10%	5%	5%	0%	0%	20%
Fatigue	15%	0%	0%	0%	0%	15%
Chills	10%	0%	0%	0%	0%	10%
Pain	10%	0%	0%	0%	0%	10%
Diarrhea	10%	5%	0%	0%	0%	15%
Constipation	10%	0%	0%	0%	0%	10%
Nausea	10%	0%	0%	0%	0%	10%
Upper respiratory tract infection	20%	10%	0%	0%	0%	30%
Pneumonia	0%	15%	5%	0%	0%	20%
Increased alanine aminotransferase	20%	0%	10%	0%	0%	30%
Increased aspartate aminotransferase	15%	5%	10%	0%	0%	30%
Increased blood bilirubin	0%	5%	10%	0%	0%	15%
Decreased blood albumin	10%	0%	0%	0%	0%	10%
Increased C-reactive protein	10%	0%	0%	0%	0%	10%
Increased granulocyte count	10%	0%	0%	0%	0%	10%
Decreased hemoglobin	10%	0%	0%	0%	0%	10%
Anemia	0%	10%	10%	0%	0%	20%
Leukocytosis	15%	0%	0%	0%	0%	15%
Thrombocytosis	10%	5%	0%	0%	0%	15%
Dizziness	25%	0%	0%	0%	0%	25%
Headache	10%	0%	0%	0%	0%	10%
Hypothyroidism	15%	15%	0%	0%	0%	30%
Hyperthyroidism	5%	5%	0%	0%	0%	10%
Hyponatremia	0%	0%	20%	5%	0%	25%
Hypochloremia	10%	0%	5%	0%	0%	15%
Decreased appetite	5%	5%	0%	0%	0%	10%
Hypoalbuminemia	0%	10%	0%	0%	0%	10%
Neck pain	10%	0%	0%	0%	0%	10%
Malignant neoplasm progression	0%	0%	0%	0%	20%	20%
Proteinuria	25%	0%	0%	0%	0%	25%
Cough	10%	0%	0%	0%	0%	10%
Rash	10%	5%	0%	0%	0%	15%
Insomnia	10%	0%	0%	0%	0%	10%
Nivolumab 360 mg (*n* = 11)						
Constipation	27%	0%	0%	0%	0%	27%
Vomiting	27%	0%	0%	0%	0%	27%
Hypothyroidism	46%	9%	0%	0%	0%	55%

Pyrexia	18%	18%	0%	0%	0%	36%
Chest discomfort	18%	0%	0%	0%	0%	18%
Rash	36%	0%	0%	0%	0%	36%
Pruritus	18%	0%	0%	0%	0%	18%
Anemia	18%	9%	0%	0%	0%	27%
Granulocytosis	18%	0%	0%	0%	0%	18%
Leukocytosis	18%	0%	0%	0%	0%	18%
Leukopenia	0%	0%	18%	0%	0%	18%
Thrombocytopenia	9%	9%	0%	0%	0%	18%
Increased C-reactive protein	27%	0%	0%	0%	0%	27%
Decreased neutrophil count	9%	0%	9%	0%	0%	18%
Hypoalbuminemia	18%	0%	0%	0%	0%	18%
Proteinuria	46%	0%	0%	0%	0%	46%
Cough	9%	9%	0%	0%	0%	18%
Hemoptysis	9%	9%	0%	0%	0%	18%
Productive cough	18%	0%	0%	0%	0%	18%

Data represent percentage of all-cause adverse events occurring in ≥10% across any grade up to September 25, 2018 (database lock date for analysis of clinical data). Adverse events were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Serious Adverse Events

	Grade				
All-cause serious adverse events	**3**	**4**	**5**	**Unknown**	**Attribution**
Nivolumab 3 mg/kg (*n* = 15)					
Malignant neoplasm progression	0%	0%	20%	0%	Unrelated
Brain edema	7%	0%	0%	0%	Unrelated
Cerebellar hemorrhage	0%	0%	0%	7%	Treatment -related[a]
Pericardial effusion	7%	0%	0%	0%	Unrelated
Pancreatitis	0%	0%	0%	7%	Treatment -related[a]
Septic shock	0%	0%	7%	0%	Unrelated
Respiratory failure	0%	7%	0%	0%	Unrelated
Nivolumab 240 mg (*n* = 20)					
Malignant neoplasm progression	0%	0%	20%	0%	Unrelated
Lung infection	5%	0%	0%	0%	Unrelated
Pneumonia	5%	0%	0%	0%	Unrelated
Hypothalamo-pituitary disorder	5%	0%	0%	0%	Unrelated
Dysphagia	5%	0%	0%	0%	Unrelated
Cholestatic Jaundice	5%	0%	0%	0%	Unrelated
Hyponatremia	0%	5%	0%	0%	Treatment-related
Asphyxia	0%	0%	5%	0%	Unrelated
Nivolumab 360 mg (*n* = 12)					
Appendicitis	9%	0%	0%	0%	Unrelated
Muscular weakness	9%	0%	0%	0%	Unrelated

[a]Treatment-related pancreatitis and cerebellar hemorrhage in one patient led to discontinuation of study treatment.

Assessment, Analysis, and Discussion

Completion	Interim analysis, study ongoing (480 mg cohort recruiting)
Investigator's Assessment	Drug tolerable, efficacy undetermined

Nivolumab is a human monoclonal antibody that targets the programmed death receptor-1 (PD-1) and has been approved for the treatment of various types of cancer in ≥60 countries [2]. Early-stage clinical trials of anti-PD-1 therapies have shown promising activity in recurrent or metastatic nasopharyngeal carcinoma (NPC), a common cancer in southeast Asia and North Africa [3, 4], with objective response rates (ORRs) of 21%–34% [5–7].

The overall efficacy, safety, and pharmacokinetics (PK) of nivolumab are based on clinical data from approximately 17,600 global (predominantly Caucasian) patients [8–15]. The safety of nivolumab 3 mg/kg administered once every 2 weeks (Q2W) has been assessed in Chinese patients in the CheckMate 078 study (NCT2613507), leading to its approval for the treatment of non-small cell lung cancer in China [16]; nivolumab 240 mg Q2W is approved in the U.S. [2] and Japan [17].

This study therefore aimed to assess the safety, tolerability, and PK of nivolumab in Chinese patients with previously treated, advanced or recurrent NPC or other solid tumors. Importantly, this is the first study to assess the safety and intensive PK of 240 mg and 360 mg flat-dose regimens in Chinese patients.

This was an open-label, single-center, phase I/II study (CheckMate 077; NCT02593786) of nivolumab monotherapy. The study comprised a dose evaluation phase (3 mg/kg Q2W, 60-minute intravenous [IV] infusion) and cohort expansion phase (3 mg/kg Q2W, flat dose 240 mg Q2W and 360 mg once every 3 weeks [Q3W]; 30-minute IV infusion) and consisted of a screening period (≤28 days), a treatment period (until disease progression or intolerable toxicities), and a follow-up period (≤100 days).

Included patients were Chinese adults (aged ≥18 years), Eastern Cooperative Oncology Group Performance Status 0 or 1, with histologically or cytologically confirmed solid tumors that were clinically advanced or recurrent, who had progressed after ≥1 prior line of systemic therapy. Exclusion criteria included central nervous system metastases, prior malignancy (except for nonmelanoma or certain in situ cancers, or complete remission ≥2 years), autoimmune disease, prior immunotherapy, active tuberculosis infection, pregnancy, or immunosuppressive agent treatment.

At data cutoff, 51 patients were enrolled, of whom 46 (90%) received ≥1 dose of study treatment and were evaluable for safety (Fig. 1). Baseline patient characteristics are presented in Table 3; the median patient age was 48 years (range: 27–72 years), 67% (31) were male, and 28 (61%) had received >2 prior lines of systemic anticancer therapy. Forty-three patients (93%) had discontinued during the treatment period, mostly because of disease progression (35 patients, 76%), and only 1 patient because of study drug toxicity. Three patients (7%) discontinued because of adverse events (AEs) unrelated to nivolumab.

At data cutoff, median (range) duration of treatment was 11.7 (2.0–105.1) weeks for the 3 mg/kg cohort, 16.6 (2.0–98.7) weeks for the 240 mg cohort, and 24.1 (3.0–48.9) weeks for the 360 mg cohort. The median (range) cumulative dose per subject were 1,920.0 (240.0–11,520.0) mg and 2,880.0 (360.0–5,076.0) mg for the 240 mg and 360 mg cohorts, respectively, and 18.2 (3.0–152.3) mg/kg in the 3 mg/kg cohort.

No dose-limiting toxicities were observed during the dose evaluation phase (n = 8) or dose expansion phase. Incidence of treatment-related adverse events (TRAEs) was similar across cohorts (Table 1). Overall, no new safety signals were identified, with safety profiles consistent with prior global studies and in line with a phase III study in Chinese patients (NCT02613507) [8–16, 18–20]. There were two grade ≥3 TRAEs: one grade 3 asthenia in the 3 mg/kg cohort and one grade 3 hypochloremia in the 240 mg cohort. Treatment-related serious adverse events were a grade 4 hyponatremia (240 mg cohort) and pancreatitis and cerebellar hemorrhage of indeterminate grade (one patient, 3 mg/kg cohort) that led to discontinuation of treatment. There were no incidences of death associated with nivolumab.

In terms of all-cause AEs, incidence of hypothyroidism was 30% in the 240 mg cohort (three patients each experienced a grade 1 or 2 event) and 55% in the 360 mg cohort (five patients with a grade 1 event and one patient with a grade 2 event) compared with no such reported events in the 3 mg/kg cohort. This most likely reflects the increased proportions of patients with NPC in the flat-dosing cohorts who had received prior radiotherapy.

Intensive PK profiles of nivolumab were characterized following a single dose (Cycle 1, Day 1) and multiple doses (3 mg/kg and 240 mg: Cycle 3, Day 1; 360 mg: Cycle 6, Day 1). Single-dose nivolumab resulted in rank-order differences in the mean serum concentration versus time profiles, with the highest mean concentrations observed for the 360 mg Q3W flat dose, followed by the 240 mg Q2W flat dose and the 3 mg/kg Q2W dose (Fig. 2A). PK parameters were assessed via noncompartmental analysis and showed similar rank-order relationships for the geometric mean area under the serum concentration-time curve for a dosing interval (AUC_{tau}), maximum serum concentration and concentration at the end of the dosing interval (Table 4).

Steady state was reached by approximately Cycle 3 (Week 17: 3 mg/kg and 240 mg flat dose) or Cycle 6 (Week 16: 360 mg flat dose; Fig. 2C). At steady state, the mean serum nivolumab concentration profiles over time were similar between the flat-dose cohorts and appeared lower for the 3 mg/kg cohort (Fig. 2B). The geometric mean AUC_{tau} for the 360 mg flat-dose cohort was approximately 41% and 72% higher than for the 240 mg flat-dose and 3 mg/kg cohorts, respectively. However, when normalized by dosing interval, the AUC_{tau} values were comparable, indicating that the different dosing regimens yielded comparable average concentrations at steady state. The mean effective half-life varied between cohorts (521–752 hours, or 21.7–31.3 days) but was within ±5 days of the mean elimination half-life of 25 days reported previously [2].

At 3 mg/kg, nivolumab exposure in Chinese patients was similar to that of patients in a global phase I study (NCT00730639), as demonstrated by a cross-study comparison (Table 2) [1]. These data are also in agreement with a recent phase I study of nivolumab in advanced solid tumors in Korean patients, in which PK data were shown to be comparable to U.S. and Japanese populations [21].

Immunogenicity was assessed via antidrug antibody (ADA) status (Table 5). Of 41 evaluable patients, only 1 patient (3 mg/kg cohort) was ADA positive after treatment. None of the patients were persistently ADA positive or neutralizing antibody positive.

Preliminary antitumor activity was assessed for patients with NPC tumors and for patients with all other solid tumors. Of 32 patients with NPC, 15 (47%) had a reduction in tumor burden from baseline following nivolumab treatment (Fig. 3). Four patients (13%) achieved a partial response (two patients each, 3 mg/kg and 240 mg cohorts), and 17 (53%) had stable disease. The ORR and disease control rate (DCR) in this patient group were 13% (95% confidence interval [CI]: 4–29) and 66% (95% CI: 47–81), respectively (Table 6; Fig. 4). Patients with other solid tumor types achieved an ORR of 14% and a DCR of 36%.

The median (range) follow-up duration for patients with NPC was 7.5 (0.8–24.7) months, with six patients (19%) having received nivolumab treatment for >1 year. Median progression-free survival (PFS) was 3.5 months (95% CI: 1.8–5.5 months), and median overall survival (OS) was not reached. The 3-month PFS and OS rates were 64.2% (95% CI: 44.7–78.4) and 87.5% (95% CI: 70.0–95.1), respectively.

This study confirms the safety profile of nivolumab at 3 mg/kg in Chinese patients and is the first to report tolerability at flat doses of 240 mg and 360 mg in this population. Additionally, these data indicate that the PK of nivolumab monotherapy are ethnically insensitive. In this population of pretreated patients with advanced or recurrent disease, preliminary antitumor responses in NPC are encouraging; confirmation is required in a larger patient population.

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Disclosures

Amol Tendolkar: Bristol-Myers Squibb (E, OI); **Lu Chen:** Bristol-Myers Squibb (E); **Dong Xu:** Bristol-Myers Squibb (E); **Jennifer Sheng:** Bristol-Myers Squibb (E, OI); **Li Zhang:** Hengrui Medicine Co. Ltd., Eli Lilly, Novartis, Roche, Bristol-Myers Squibb (RF). The other authors indicated no financial relationships.

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Figures and Tables

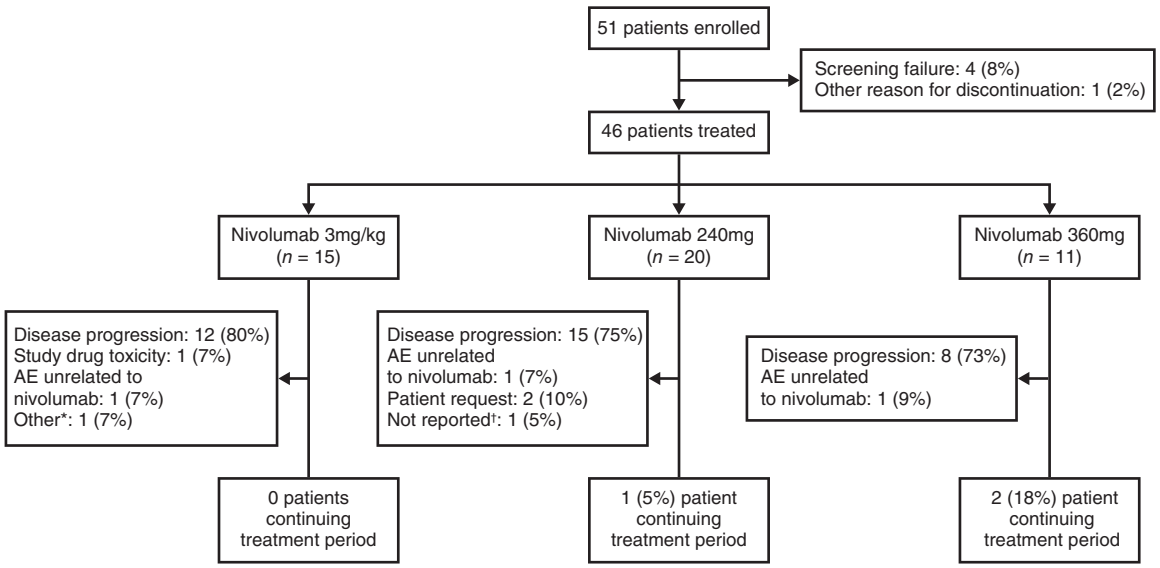

Figure 1. Patient disposition flow chart. *Death due to septic shock considered unrelated to the study drug. †Treatment status unconfirmed at the time of database lock.
Abbreviation: AE, adverse event.

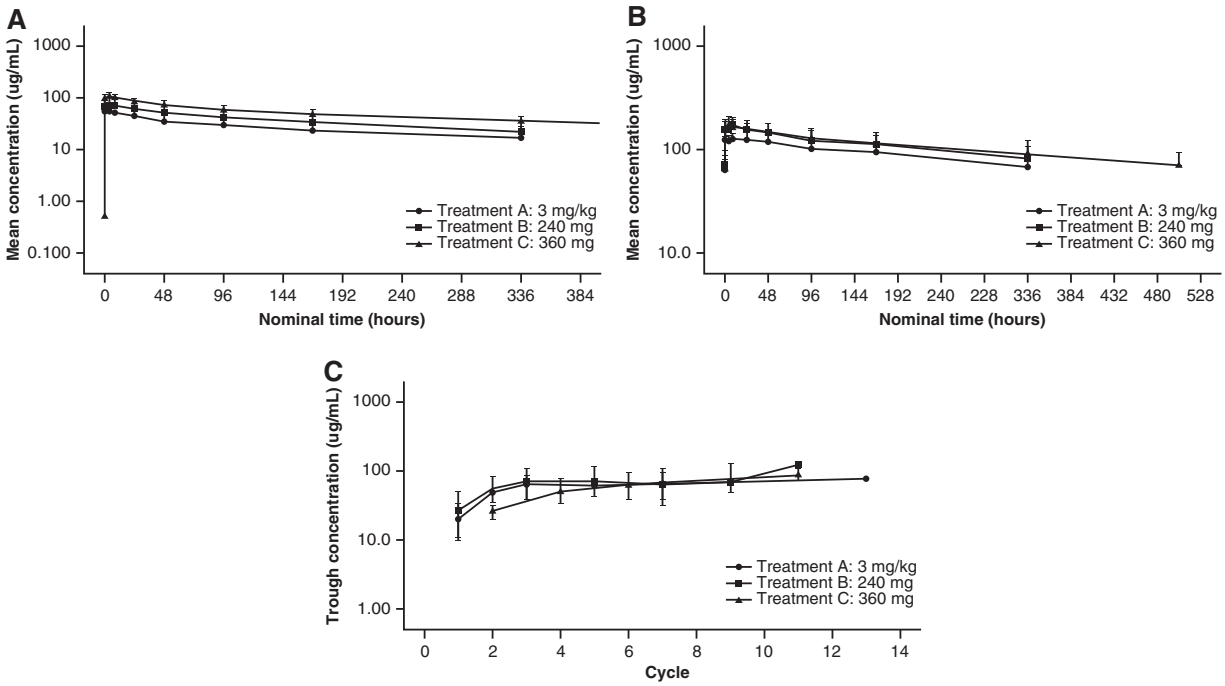

Figure 2. Pharmacokinetics of nivolumab. **(A):** Mean serum concentration-time profiles of nivolumab after single-dose administration. **(B):** Mean serum concentration-time profiles of nivolumab at steady state. **(C):** Geometric mean trough concentration profiles of nivolumab. For all figures: A, 3 mg/kg; B, 240 mg; C, 360 mg. Logarithmic scale. Bars indicate SD.

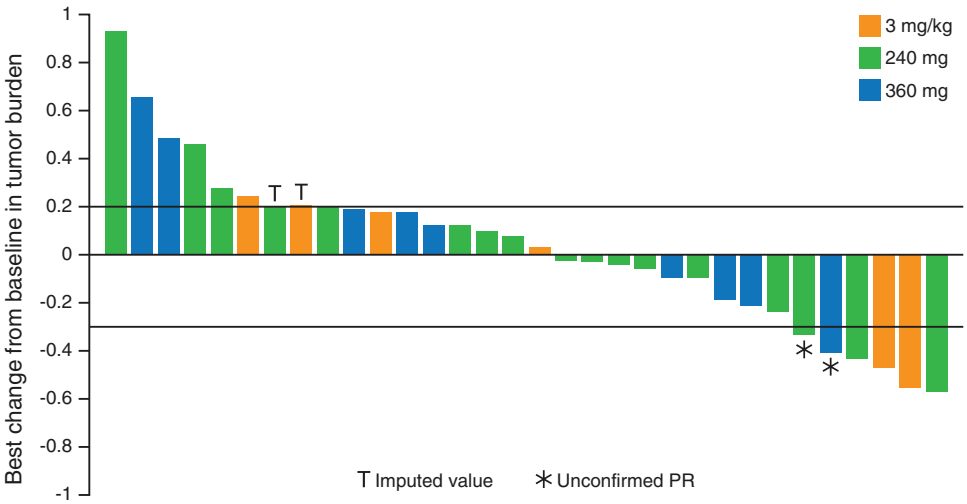

Figure 3. Waterfall plot of best reduction from baseline in target lesions for patients with nasopharyngeal carcinoma.
Abbreviation: PR, partial response.

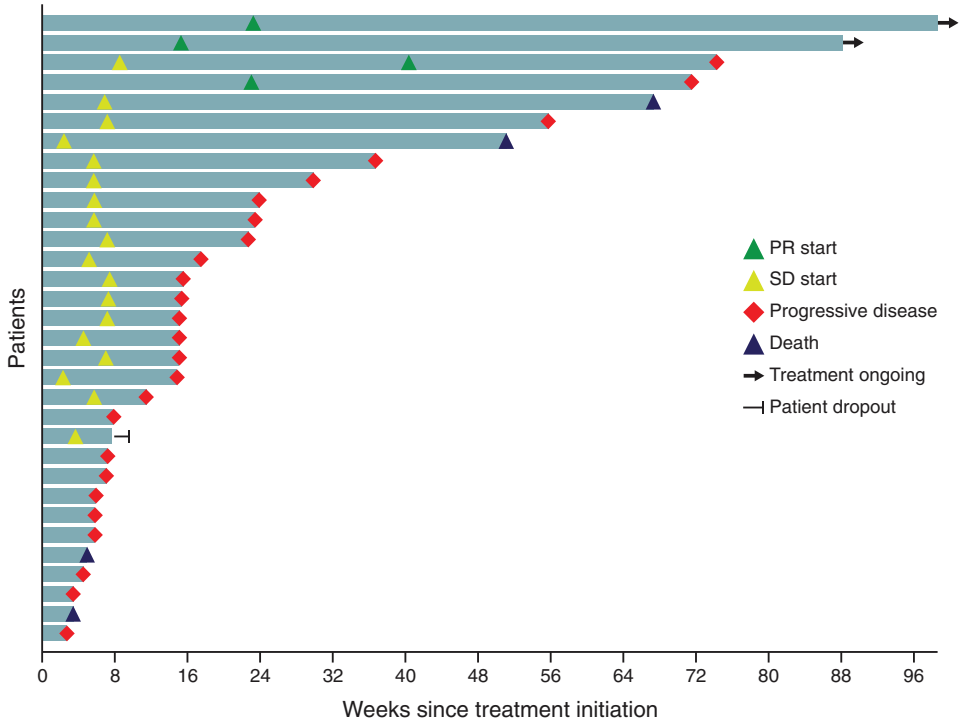

Figure 4. Tumor swimmer plot for the subpopulation of patients with nasopharyngeal carcinoma.
Abbreviations: PR, partial response; SD, stable disease.

Table 3. Baseline patient characteristics and prior cancer therapy

Characteristics, *n* (%)	Nivolumab 3 mg/kg (*n* = 15)	Nivolumab 240 mg (*n* = 20)	Nivolumab 360 mg (*n* = 11)	Total (*n* = 46)
Male	11 (73)	13 (65)	7 (64)	31 (67)
Age, median (range), years	52 (27–59)	45 (29– 60)	53 (30–72)	48 (27–72)
ECOG status				
0	8 (53)	5 (25)	4 (36)	17 (37)
1	7 (47)	15 (75)	7 (64)	29 (63)
Tumor type				
NSCLC	9 (60)	1 (5)	1 (9)	11 (24)
NPC	6 (40)	17 (85)	9 (82)	32 (70)
HCC		2 (10)		2 (4)
Not reported			1 (9)	1 (2)
Weight, median (range), kg	57.5 (44.9–73.6)	62.3 (36.2–78.4)	59.0 (37.0–69.7)	59.7 (36.2–78.4)
Prior surgery				
Yes	15 (100)	20 (100)	2 (18)	37 (80)
No	0	0	9 (82)	9 (20)
Prior radiotherapy				
Yes	10 (67)	17 (85)	11 (100)	38 (83)
No	5 (33)	3 (15)	0	8 (17)
Prior systemic therapy, number of regimens				
1	0	4 (20)	0	4 (9)
2	5 (33)	3 (15)	6 (55)	14 (30)
3	1 (7)	6 (30)	2 (18)	9 (20)
≥4	9 (60)	7 (35)	3 (27)	19 (41)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer.

Table 4. Summary pharmacokinetic parameters of nivolumab

	Nivolumab 3 mg/kg		Nivolumab 240 mg		Nivolumab 360 mg	
PK parameter[a]	Cycle 1, Day 1 (*n* = 15)	Cycle 3, Day 1 (*n* = 7)	Cycle 1, Day 1 (*n* = 20)	Cycle 3, Day 1 (*n* = 9)	Cycle 1, Day 1 (*n* = 11)	Cycle 6, Day 1 (*n* = 7)
C_{max}, μg/mL	57 (18)	132 (17)	78 (18)	172 (14)	108 (21)	165 (24)
T_{max}, hours	4.0 (0.5–4.0)	8.0 (4.0–48.2)	4.0 (0.5–8.0)	8.0 (4.0–48.0)	4.0 (4.0–8.0)	8.0 (0.5–24.1)
AUC_{tau}, hours × μg/mL	8,732 (24)	30,824 (21)	12,112 (24)	37,794 (22)	23,567 (17), *n* = 10	53,162 (40)
Css-avg, μg/mL	—	92.7 (20)	—	110.9 (23)	—	98.6 (28)
C_{tau}, μg/mL	16 (26), *n* = 13	65 (27), *n* = 6	20 (30), *n* = 18	78 (31), *n* = 8	26 (17), *n* = 10	66 (35), *n* = 6
$t_{1/2\text{-effective}}$, hours	—	566 (24)	—	521 (22)	—	752 (56)
C_{trough}, μg/mL	—	62 (24)	—	62 (39)	—	62 (35)

[a]Geometric mean (% coefficient of variation [CV]) for all parameters except for T_{max} (median [range]) and $t_{1/2\text{-effective}}$ (mean [% CV]).
Abbreviations: AUC_{tau}, area under the serum concentration-time curve in one dosing interval; C_{max}, maximum serum concentration; Css-avg, average concentration over a dosing interval, calculated at steady state; C_{trough}, observed trough concentration; C_{tau}, concentration at the end of the dosing interval; PK, pharmacokinetic; $t_{1/2\text{-effective}}$, effective half-life calculated using the formula $\frac{\tau \cdot \ln(2)}{\ln\left[\frac{AI}{AI-1}\right]}$, where t is the dosing interval and AI is the ratio of AUC_{tau} at steady state to that at single dose; T_{max}, time taken to reach maximum concentration.

Table 5. Nivolumab treatment immunogenicity

ADA status, *n* (%)	Nivolumab 3 mg/kg (*n* = 13)	Nivolumab 240 mg (*n* = 18)	Nivolumab 360 mg (*n* = 10)	Total (*n* = 41)
ADA positive[a]	1 (8)	0	0	1 (2)
PP[b]	0	0	0	0
Not PP–last sample positive[c]	1 (8)	0	0	1 (2)
Other positive[d]	0	0	0	0
Neutralizing positive[e]	0	0	0	0
ADA negative	12 (92)	18 (100)	10 (100)	40 (98)

[a]At least one ADA-positive (ADA+) sample relative to baseline after treatment initiation.
[b]ADA+ samples at ≥2 consecutive timepoints.
[c]Not PP, but ADA+ during the last sampling.
[d]Not PP, some ADA+, with the last sampling being negative.
[e]At least one ADA+ sample with neutralizing antibodies detected after baseline. Data shown are for patients with baseline ADA data and at least one post-baseline ADA assessment.
Abbreviations: ADA, antidrug antibody; PP, persistent positive.

Table 6. Antitumor responses

	Nivolumab 3 mg/kg		Nivolumab 240 mg		Nivolumab 360 mg		Total	
Antitumor response	**NPC (*n* = 6)**	**Other (*n* = 9)**	**NPC (*n* = 17)**	**Other (*n* = 3)**	**NPC (*n* = 9)**	**Other (*n* = 2)**	**NPC (*n* = 32)**	**Other (*n* = 14)**
Best overall response, *n* (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	2 (33)	1 (11)	2 (12)	0	0	1 (50)	4 (13)	2 (14)
Stable disease	1 (17)	1 (11)	10 (59)	2 (67)	6 (67)	0	17 (53)	3 (21)
Progressive disease	2 (33)	7 (78)	4 (24)	1 (33)	3 (33)	1 (50)	9 (28)	9 (64)
Undetermined	1 (17)	0	1 (6)	0	0	0	2 (6)	0
Objective response rate[a], *n* (% [95% CI])[b]	2 (33)	1 (11)	2 (12 [2–36])	0	0	1 (50)	4 (13 [4–29])	2 (14)
Disease control rate[c], *n* (% [95% CI])[b]	3 (50)	2 (22)	12 (71 [44–90])	2 (67)	6 (67)	1 (50)	21 (66 [47–81])	5 (36)

[a]The proportion of patients whose best overall response is either a complete response or a partial response.
[b]Confidence intervals were computed for cohorts of 10 patients or more only.
[c]The proportion of patients with a complete response, with a partial response, or who achieved stable disease.
Abbreviations: CI, confidence interval; NPC, nasopharyngeal carcinoma.