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Clinical Trial Results

Phase I Pharmacokinetic Study of Nivolumab in Korean Patients with Advanced Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT02261285 (ONO-4538-13) and NCT02261298 (ONO-4538-14)
- **Sponsor(s)**: Ono Pharmaceutical Co., Ltd.
- **Principal Investigator**: Yung-Jue Bang
- **IRB Approved**: Yes

Lessons Learned

- This pharmacokinetic study of nivolumab showed that there is little ethnic difference in the handling of nivolumab.
- Nivolumab was well tolerated in Korean patients.

Abstrct

Background. This phase I study of nivolumab, an anti-programmed cell death-1 (anti-PD-1) monoclonal antibody, investigated the pharmacokinetics and safety of nivolumab in Korean patients with advanced solid tumors. Findings were compared with results from Japan and the U.S.

Materials and Methods. In this two-part study, patients received a single dose of nivolumab (1, 3, and 10 mg/kg; ONO-4538-13) and were followed up for 3 weeks. Those who met the required criteria proceeded to the second part (ONO-4538-14), and received the same dose as in part one every 2 weeks.

Results. Six patients per dose level were enrolled ($n = 18$). The mean elimination half-life of nivolumab among the groups ranged from 15.0 to 19.1 days. The maximum serum concentration and area under serum concentration–time curve increased almost dose-proportionally at doses from 1 to 10 mg/kg. Adverse drug reactions (ADRs; mostly grade $\leq$2) were reported in seven patients (38.9%). ADRs grade $\geq$3 occurred in one patient (5.6%; pneumonitis). Three patients (16.7%) developed ADRs related to thyroid dysfunction.

Conclusion. The pharmacokinetic parameters of nivolumab were similar among patients from Korea, Japan, and the U.S. The safety profile was consistent with findings from previous studies. ***The Oncologist*** 2018;23:155–e17

Discussion

Nivolumab is a fully human immunoglobulin G4 anti-PD-1 monoclonal antibody approved in Korea for the treatment of melanoma and non-small cell lung cancer. The U.S. Food and Drug Administration (FDA) has approved it for treatment of several tumor types and more trials are ongoing.

Several phase I studies in the U.S. and Japan have shown that nivolumab was well tolerated at different doses. Although more widespread use of nivolumab is expected for other tumor types, no studies on the pharmacokinetics (PK) of nivolumab in Korean patients have been conducted.

This multicenter, open-label, phase I study was conducted to investigate PK and safety in Korean patients with solid tumors and to compare the PK of nivolumab between Koreans and other ethnic groups. We enrolled patients with advanced solid tumors who were refractory or intolerant to standard therapy or for whom no appropriate treatment was available. Among the 18 patients enrolled in ONO-4538-13, 2 could not proceed to the second part because of disease progression. All patients were included in the safety analysis set and PK-evaluable population.

The maximum serum concentration and area under serum concentration–time curve increased almost dose-proportionally

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Table 1. Summary statistics of pharmacokinetic parameters (C_{max} and AUC_{21day}) of nivolumab after a single intravenous infusion over approximately 60 minutes at doses of 1, 3, and 10 mg/kg in 3 regions

	C_{max} (μg/mL) Geometric mean [coefficient of variation] (patients, *n*)			AUC_{21day} (μg × h/mL) Geometric mean [coefficient of variation] (patients, *n*)		
Dose	**United States[a]**	**Japan[a]**	**Korea**	**United States[a]**	**Japan[a]**	**Korea**
1 mg/kg	16.0 [32.1%] (6)	24.1 [18.5%] (3)	25.7 [16.5%] (6)	2,641 [49%] (6)	4,927 [12%] (3)	5,040 [19%] (6)
3 mg/kg	60.0 [27.6%] (5)	68.1 [15.9%] (5)	61.2 [34.9%] (6)	9,832 [33%] (5)	11,561 [36%] (5)	12,100 [17%] (6)
10 mg/kg	196.3 [19.5%] (21)	189.2 [18.8%] (6)	232.0 [27.5%] (6)	34,405 [29%] (21)	43,436 [16%] (6)	35,500 [37%] (5)

[a]From reference [2].
Abbreviations: AUC_{21day}, areas under serum concentration–time curve from day 0 to day 21 (last measurement); C_{max}, maximum serum concentration.

at doses from 1 to 10 mg/kg. When PK parameters of nivolumab were compared among studies in Korea, Japan (ONO-4538-01), and the U.S. (CA209-001), they overlapped and showed similar distributions (Table 1). No new safety issues were raised in this study. With respect to efficacy, no complete or partial response was observed, and stable disease was shown in two patients. Owing to the limited sample size, the data are not sufficient to draw conclusions on efficacy.

In September 2016, the FDA approved a flat dosage regimen for nivolumab (240 mg every 2 weeks). According to a previous report, the overall exposure at a 240 mg flat dose (every 2 weeks) was similar to that at a dose of 3 mg/kg (every 2 weeks) based on simulations in a population PK model. Our study suggests that the flat dose regimen of nivolumab can also be used in Korean patients and that nivolumab can be used safely in this population.

Trial Information

Disease	Advanced cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study - 1	Phase I
Type of Study - 2	Phase I pharmacokinetic study
Primary Endpoint	PK outcome: maximum serum concentration (C_{max}), time to reach C_{max}, area under the serum concentration–time curve, and elimination half-life
Secondary Endpoint	Safety

Additional Details of Endpoints or Study Design
The primary objective of the ONO-4538-13 study was to investigate the pharmacokinetics of nivolumab in Korean patients with solid tumors; the secondary objective was to investigate the safety of nivolumab. The objective of the ONO-4538-14 study was to investigate the safety, pharmacokinetics, and efficacy of nivolumab in Korean patients.

Investigator's Analysis	Drug tolerable, efficacy indeterminant

Drug Information for Phase I Control

Drug 1	
Generic/Working Name	Nivolumab/ONO-4538
Trade Name	Opdivo
Company Name	Ono Pharmaceutical Co., Ltd.
Drug Type	Antibody
Drug Class	Immune therapy
Dose	1 milligram (mg) per kilogram (kg), 3 mg/kg, and 10 mg/kg
Route	Intravenous

Schedule of Administration
In the treatment phase of ONO-4538-13, patients were assigned to treatment groups (1, 3, or 10 mg/kg of nivolumab) and a single dose of nivolumab was administered in order of increasing nivolumab doses (six patients per dose level). Nivolumab was administered as an intravenous infusion over approximately 60 minutes. To evaluate the pharmacokinetic profile of a single dose of nivolumab, each patient was observed for 3 weeks without further administration of nivolumab. In the ONO-4538-14, the same dose of nivolumab that was used in ONO-4538-13 was administered with a 2-week dosing interval (on days 1, 15, and 29 of each cycle), and a 6-week interval was regarded as one cycle of nivolumab treatment.

Patient Characteristics for Phase I Control	
Number of Patients, Male	8
Number of Patients, Female	10
Stage	Korean patients with advanced or recurrent solid tumors who were refractory or intolerant to standard therapy or for whom no appropriate treatment was available
Age	Median (range): 56 (27–84)
Number of Prior Systemic Therapies	Median (range): 4 (0–6)
Performance Status: ECOG	0 — 8 1 — 10 2 — 0 3 — 0 Unknown — 0
Other	Patient characteristics are shown in Table 2

Primary Assessment Method for Phase I Control	
Title	Total patient population
Number of Patients Screened	21
Number of Patients Enrolled	18
Number of Patients Evaluable for Toxicity	18
Number of Patients Evaluated for Efficacy	18
Evaluation Method	Response Evaluation Criteria In Solid Tumors 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 0$ (0%)
Response Assessment SD	$n = 2$ (11.1%)
Response Assessment PD	$n = 12$ (66.7%)
Response Assessment OTHER	$n = 4$ (22.2%)
(Median) Duration Assessments PFS	62.5 days, confidence interval: 58.0–122.0

Phase I Control Adverse Events							
	All Dose Levels, All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Investigations - Increased blood thyroid-stimulating hormone	94%	6%	0%	0%	0%	0%	6%
Immune system disorders - Hypersensitivity	94%	0%	6%	0%	0%	0%	6%
Endocrine disorders - Thyroiditis	89%	0%	11%	0%	0%	0%	11%
Anorexia	94%	6%	0%	0%	0%	0%	6%
Pneumonitis	89%	6%	0%	6%	0%	0%	11%
Fever	94%	6%	0%	0%	0%	0%	6%
Chills	94%	0%	6%	0%	0%	0%	6%
Eye pain	94%	6%	0%	0%	0%	0%	6%

Incidence of adverse drug reactions by worst Common Terminology Criteria for Adverse Events grade (safety analysis set).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Event	
Name	Pneumonitis
Grade	3
Attribution	Probable

One patient in the 3 mg/kg group developed grade 3 pneumonitis. This was the only serious adverse event that was considered to be related to nivolumab treatment in this study and was relieved after systemic steroid therapy.

Pharmacokinetics/Pharmacodynamics	
Dose of drug: Nivolumab/ONO-4538	**Number enrolled**
1 mg/kg	6
3 mg/kg	6
10 mg/kg	6

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Drug tolerable, efficacy indeterminant

This was a multicenter, open-label, phase I study conducted in five institutions in Korea. The study comprised two parts. The first part (protocol number: ONO-4538-13) was conducted to investigate the pharmacokinetics (PK), safety, and pharmacological action of nivolumab after a single dose. In the treatment phase of ONO-4538-13, patients were assigned to treatment groups (1, 3, or 10 mg/kg of nivolumab) and a single dose of nivolumab was administered in order of increasing nivolumab doses (six patients per dose level). Nivolumab was administered as an intravenous infusion over approximately 60 minutes. To evaluate the PK profile of a single dose of nivolumab, each patient was observed for 3 weeks without further administration of nivolumab. Patients who satisfied any of the following criteria in the treatment phase of ONO-4538-13 did not receive further nivolumab treatment and proceeded to the follow-up phase of ONO-4538-13: (a) progressive disease (PD) with unplanned tumor assessment according to the Response Evaluation Criteria In Solid Tumors guideline or worsening of clinical symptoms attributed to PD; (b) grade $\geq$2 interstitial lung disease; (c) eye pain or reduced visual acuity (grade $\geq$2) that did not improve to grade 1 with local treatment; (d) grade $\geq$3 bronchospasm, hypersensitivity reaction, infusion reaction, or uveitis; or (e) investigator determined that continuing to administer nivolumab was inappropriate. Only patients who did not meet any of the above criteria could proceed to the second part (ONO-4538-14) and continue nivolumab treatment.

In ONO-4538-14, the same dose of nivolumab that was used in ONO-4538-13 was administered with a 2-week dosing interval (on days 1, 15, and 29 of each cycle), and a 6-week interval was regarded as one cycle of nivolumab treatment. Patients who satisfied any of the following criteria during the treatment phase of ONO-4538-14 discontinued the nivolumab administration and proceeded to the follow-up phase: (a) confirmation of PD with planned or unplanned tumor assessment or worsening of clinical symptoms attributed to disease progression, (b–e) same criteria used in ONO-4538-13, or (f) nivolumab was not administrated within 6 weeks from the last administration because of an adverse event or other events.

In the pharmacokinetic study, serum concentrations of nivolumab were determined using the validated electrochemiluminescence method. The electrochemiluminescence assay utilizes the Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD) using a biotin-labeled capture antibody and a ruthenium-labeled detection antibody. The pharmacokinetic parameters of nivolumab (e.g., maximum serum concentration [C_{max}], time to reach C_{max}, area under the serum concentration–time curve [AUC], and elimination half-life) were calculated for each patient.

The primary objective of the ONO-4538-13 study was to investigate the pharmacokinetics of nivolumab in Korean patients with solid tumors; the secondary objective was to investigate the safety of nivolumab. The objective of the ONO-4538-14 study was to investigate the safety, pharmacokinetics, and efficacy of nivolumab in Korean patients. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). In patients who continued nivolumab treatment in the ONO-4538-14 study, antitumor activity was assessed every 6 weeks according to the Response Evaluation Criteria In Solid Tumors guideline (version 1.1). Progression-free survival was measured from the first dose of nivolumab to the first documented PD or death of any cause, whichever came earlier.

In the ONO-4538-13 study, 18 patients were enrolled from October to December 2014. The median age was 56 years (range, 27–84 years). Patient characteristics are shown in Table 2. Of the 18 patients, 17 (94.4%) completed the treatment phase in ONO-4538-13 (3 weeks after administration of the first dose of nivolumab) as planned; one patient in the 10 mg/kg group did not complete the treatment phase because of rapid disease progression. Among those enrolled in ONO-4538-13, 2 of 18 patients could not proceed to the ONO-4538-14 study because of disease progression. All 18 patients were included in the safety analysis set and pharmacokinetics-evaluable population.

In the ONO-4538-13 study, two deaths occurred during the follow-up period; these two deaths were caused by tumor progression and were not related to the study treatment. Table 3 shows all adverse drug reactions (ADRs; defined as nivolumab-related adverse events) that developed from the first dose of nivolumab in ONO-4538-13 until 28 days after the final dose in ONO-4538-14 (or until the start of subsequent anticancer therapy, whichever came first). No new safety issue was raised in this phase I study. ADR of grade 3 or higher occurred in only one patient (5.6%; pneumonitis) in the 3 mg/kg group; this was the only serious adverse event that was considered to be related to nivolumab treatment in this study and was relieved after systemic steroid therapy. Hormonal testing showed that three patients (16.7%) developed ADRs related to thyroid dysfunction. ADRs leading to study discontinuation occurred in two patients (grade 3 pneumonitis in the 3 mg/kg group and recurrent grade 1 pneumonitis in the 10 mg/kg group). Overall, when administered at multiple doses of 1, 3, or 10 mg/kg,

nivolumab was well tolerated and most ADRs were grade 1 or 2 in Korean patients with solid tumors. No ADRs led to death.

The efficacy evaluation in this analysis was conducted based on the tumor assessments of 18 patients in the full analysis set by the cut-off date (June 15, 2015). Among the 18 patients, 3 had no target lesions. Of the 15 patients with measurable lesions, no complete or partial response was observed; stable disease was observed in 2 patients (both with adenoid cystic carcinoma [ACC] of the salivary gland in the 1 mg/kg group and 3 mg/kg group, respectively) and PD in 12 patients. In one patient, the tumor response was not evaluable (Table 4). Three patients were still undergoing the treatment phase of ONO-4538-14 on the cut-off date. The median progression-free survival was 62.5 days (95% confidence interval, 58.0–122.0 days) in all groups. Because of the limited sample size, the data are not sufficient to draw any conclusions regarding the efficacy of nivolumab in the patient population of this study. In addition, because ACC has indolent courses in many cases, it is unclear whether the response of "stable disease" in the two cases was a result from the nivolumab effect rather than a result from indolent natural courses of ACC. Therefore, the efficacy of nivolumab in ACC should be evaluated in randomized clinical trials.

This is the first study on the pharmacokinetics of nivolumab in the Korean population. The ONO-4538-13 study was completed in December 2014, and the Ministry of Food and Drug Safety in Korea approved nivolumab for treatment of melanoma based on this study in March 2015. In a previous Japanese phase I study (ONO-4538-01; NCT00836888), repeated intravenous infusions of nivolumab (1, 3, 10, and 20 mg/kg) at 2-week intervals were well tolerated [1, 2]. In the U.S., administration of nivolumab was also well tolerated in a phase I single-dose study (CA209-001; NCT00441337) in which doses of 0.3, 1, 3, and 10 mg/kg were examined [3, 4], and in a phase I multiple-dose study (CA209-003; NCT00730639) in which doses of 0.1, 0.3, 1, 3, and 10 mg/kg at 2-week intervals were examined [5]. Based on these previous studies, 3 dose levels of nivolumab (1, 3, and 10 mg/kg) were selected in the present study. The results of pharmacokinetic analysis after a single intravenous infusion of nivolumab are shown in Figures 1–3 and Table 5. The pharmacokinetic parameters (C_{max} and AUC) of nivolumab increased almost dose-proportionally at doses ranging from 1 to 10 mg/kg (Figs. 1–3; Table 5). When the pharmacokinetic parameters of nivolumab were compared among three regions, Korea, Japan (ONO-4538-01 [1, 2]), and the U.S. (CA209-001 [3, 4]), they overlapped and showed similar distributions in these regions. The pharmacokinetic parameters for nivolumab across these regions are summarized in Table 1.

As of February 2017, nivolumab has been approved for treatment of two types of cancer in Korea: melanoma and non-small cell lung cancer (NSCLC) [6–8]. In addition to melanoma and NSCLC, the U.S. Food and Drug Administration (FDA) has approved nivolumab for treatment of classic Hodgkin lymphoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma [9–11]. A recent study revealed that salvage treatment with nivolumab significantly improved the overall survival of pretreated patients with advanced gastric cancer compared with placebo [12]. Many clinical trials using nivolumab are currently ongoing, including combination studies. Therefore, it is clearly expected that nivolumab will become more widely used for the treatment of various cancer types. However, the fact that no objective tumor response was observed in our study was disappointing. In recent phase III trials, the response rate to nivolumab was 11%–25% in NSCLC, head and neck cancer, renal cell carcinoma, and stomach cancer [7–10, 12]. These results suggest that only a minor portion of most patients with solid tumors receive benefit from immune checkpoint inhibitors. Therefore, more studies are warranted to identify predictive markers of nivolumab efficacy in various solid tumors.

In September 2016, the FDA approved a flat dosage regimen for nivolumab (240 mg every 2 weeks). According to one report, the overall exposure with a 240 mg flat dose (every 2 weeks) was similar to that with a 3 mg/kg dose (taken every 2 weeks) based on simulations using a population pharmacokinetics model [13]. Considering the few differences in pharmacokinetic parameters between Koreans and other ethnic groups, our study also suggests that the flat dose regimen of nivolumab can be used in Korean patients.

In conclusion, the present study on the pharmacokinetics and safety of nivolumab has shown that there is little ethnic difference in the handling of nivolumab. These findings support the safe use of nivolumab in Korean patients, in accordance with the results of other clinical studies involving patients of different ethnicities.

Acknowledgments

This study was funded by Ono Pharmaceutical Co. Ltd. (Osaka, Japan) and Bristol-Myers Squibb Company. The authors thank the patients and their families, and the investigators and research staff at all study sites. The authors also thank Lourdes Briz of Edanz Medical Writing for the partial assistance in drafting part of this manuscript.

Disclosures

Keun-Wook Lee: Ono Pharmaceutical, AstraZeneca, Merck Sharp & Dohme, Merck (RF); **Dae Ho Lee**: Ministry of Food and Drug Safety (Korea), Health Insurance Review and Assessment Service (Korea), National Evidence-Based Collaborating Agency (Korea), National Cancer Control Planning Board (Korea); AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, CJ Healthcare, Eli Lilly, Merck, Merck Sharp & Dohme, Mundipharma, Novartis, Ono Pharmaceutical, Pfizer, Roche, Samyang Biopharm, ST (C/A); **Jin Hyoung Kang**:; **Joon Oh Park**: Celgene (RF); **Se Hyun Kim**:; **Yong Sang Hong**:; **Seung Tae Kim**:; **Do-Youn Oh**:; **Yung-Jue Bang**: Ono Pharmaceutical (C/A, RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

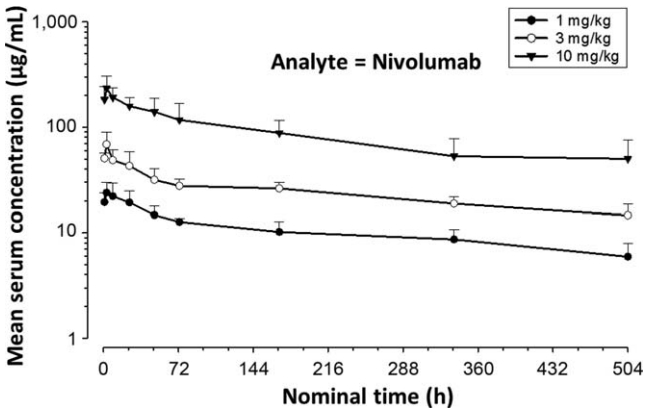

Figure 1. Pharmacokinetics of nivolumab: Mean serum concentration–time profiles of nivolumab after administration of a single intravenous infusion to Korean patients at doses of 1–10 mg/kg. Bars indicate mean ± standard deviation.

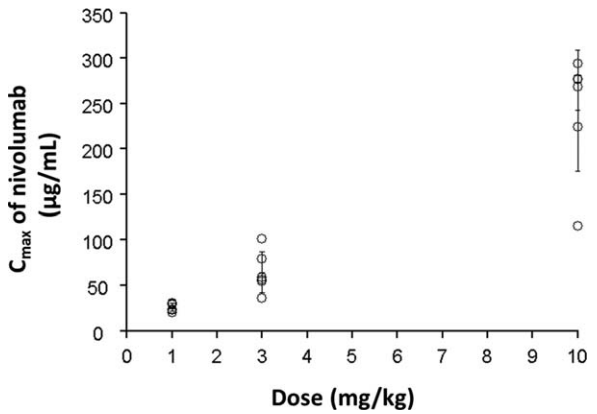

Figure 2. Pharmacokinetics of nivolumab: C_{max} of nivolumab after administration of a single intravenous infusion to Korean patients at doses of 1–10 mg/kg. Bars indicate mean ± standard deviation.

Abbreviation: C_{max}, maximum serum concentration.

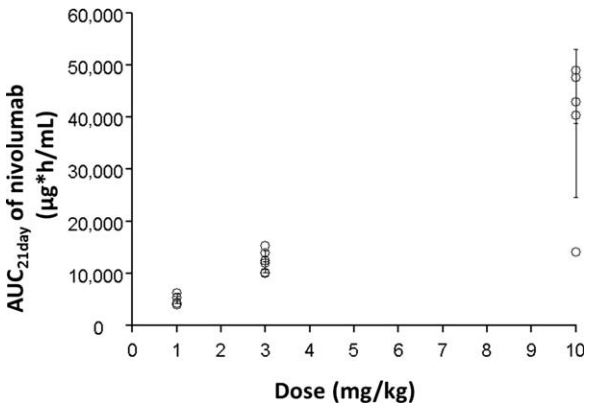

Figure 3. Pharmacokinetics of nivolumab: AUC_{21day} of nivolumab after administration of a single intravenous infusion to Korean patients at doses of 1–10 mg/kg. Bars indicate mean ± standard deviation.

Abbreviation: AUC_{21day}, areas under serum concentration–time curve from day 0 to day 21 (last measurement).

Table 2. Patient characteristics

Characteristics	1 mg/kg ($n = 6$), *n* (%)	3 mg/kg ($n = 6$), *n* (%)	10 mg/kg ($n = 6$), *n* (%)	Total ($n = 18$), *n* (%)
Sex				
Male	1 (16.7)	5 (83.3)	2 (33.3)	8 (44.4)
Female	5 (83.3)	1 (16.7)	4 (66.7)	10 (55.6)
Age (years)				
Median	44.5	63.0	52.5	56.0
Range	36–74	49–70	27–84	27–84
Performance status (ECOG)				
0	4 (66.7)	1 (16.7)	3 (50.0)	8 (44.4)
1	2 (33.3)	5 (83.3)	3 (50.0)	10 (55.6)
Type of primary cancer				
Lung cancer	—	1 (16.7)	3 (50.0)	4 (22.2)
Melanoma	3 (50.0)	—	—	3 (16.7)
Salivary gland cancer	1 (16.7)	1 (16.7)	—	2 (11.1)
Rectal cancer	—	2 (33.3)	—	2 (11.1)
Renal cell carcinoma	—	—	1 (16.7)	1 (5.6)
Pancreatic cancer	—	1 (16.7)	—	1 (5.6)
Gastric cancer	1 (16.7)	—	—	1 (5.6)
Nasal cavity cancer	—	—	1 (16.7)	1 (5.6)
Nasopharyngeal carcinoma	—	1 (16.7)	—	1 (5.6)
Colon cancer	—	—	1 (16.7)	1 (5.6)
Sarcoma	1 (16.7)	—	—	1 (5.6)
History of surgery				
Yes	6 (100.0)	5(83.3)	3 (50.0)	14 (77.8)
No	0 (0.0)	1(16.7)	3 (50.0)	4 (22.2)
History of radiotherapy				
Yes	4 (66.7)	4 (66.7)	4 (66.7)	12 (66.7)
No	2 (33.3)	2 (33.3)	2 (33.3)	6 (33.3)
History of chemotherapy				
None	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
1 regimen	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
2 regimens	2 (33.3)	1 (16.7)	2 (33.3)	5 (27.8)
3 regimens	1 (16.7)	2 (33.3)	1 (16.7)	4 (22.2)
4 regimens	0 (0.0)	1 (16.7)	2 (33.3)	3 (16.7)
5 regimens	2 (33.3)	0 (0.0)	0 (0.0)	2 (11.1)
6 regimens	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Table 3. Incidence of adverse drug reactions by worst Common Terminology Criteria for Adverse Events grade (safety analysis set)

System organ class Preferred term	1 mg/kg ($n = 6$), n (%)				3 mg/kg ($n = 6$), n (%)				10 mg/kg ($n = 6$), n (%)				Total ($n = 18$), n (%)			
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Endocrine disorders																
Thyroiditis[a]	—	2 (33.3)	—	—	—	—	—	—	—	—	—	—	—	2 (11.1)	—	—
Eye disorders																
Eye pain	1 (16.7)	—	—	—	—	—	—	—	—	—	—	—	1 (5.6)	—	—	—
General disorders and administration site conditions																
Chills	—	—	—	—	—	—	—	—	—	1 (16.7)	—	—	—	1 (5.6)	—	—
Pyrexia	—	—	—	—	—	—	—	—	1 (16.7)	—	—	—	1 (5.6)	—	—	—
Immune system disorders																
Hypersensitivity	—	—	—	—	—	1 (16.7)	—	—	—	—	—	—	—	1 (5.6)	—	—
Investigations																
Increased blood TSH	—	—	—	—	1 (16.7)	—	—	—	—	—	—	—	1 (5.6)	—	—	—
Metabolism and nutrition disorders																
Decreased appetite	—	—	—	—	1 (16.7)	—	—	—	—	—	—	—	1 (5.6)	—	—	—
Respiratory, thoracic, and mediastinal disorders																
Pneumonitis	—	—	—	—	—	—	1 (16.7)	—	1 (16.7)	—	—	—	1 (5.6)	—	1 (5.6)	—

G1 = grade 1 (mild); G2 = grade 2 (moderate); G3 = grade 3 (severe); G4 = grade 4 (life-threatening or disabling). No treatment-related deaths occurred.

[a]Thyroiditis and autoimmune thyroiditis were observed in one patient each. Both were classified into one category (thyroiditis) in this table.

Abbreviations: —, 0 (0.0); TSH, thyroid-stimulating hormone.

Table 4. Best overall response

Best overall response	1 mg/kg ($n = 6$)	3 mg/kg ($n = 6$)	10 mg/kg ($n = 6$)	Total ($n = 18$)
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Progressive disease	3 (50.0)	5 (83.3)	4 (66.7)	12 (66.7)
Not evaluable	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Without target lesion	1 (16.7)	0 (0.0)	2 (33.3)	3 (16.7)

Data are presented as *n* (%).

Table 5. Summary statistics of pharmacokinetic parameters of nivolumab after a single intravenous infusion to Korean patients with advanced or recurrent solid tumors at doses of 1, 3, and 10 mg/kg

	Nivolumab dose		
Pharmacokinetic parameters	**1 mg/kg ($n = 6$)**	**3 mg/kg ($n = 6$)**	**10 mg/kg ($n = 6$)**
C_{max} (μg/mL)	26.0 ± 4.29	64.3 ± 22.5	242.0 ± 66.7
T_{max} (h)	3.02 (1.07–9.00)	3.00 (1.00–8.78)	2.99 (1.00–8.62)
AUC_{21day} (μg × h/mL)	5,110 ± 952	12,200 ± 2,060	38,700 ± 14,200[a]
AUC_{inf} (μg × h/mL)	9,180 ± 3,140	22,800 ± 10,000	68,100 ± 34,700[a]
$T_{1/2}$ (days)	18.3 ± 6.97	19.1 ± 10.0	15.0 ± 7.86[a]
Clearance (mL/h/kg)	0.123 ± 0.0493	0.149 ± 0.0493	0.214 ± 0.181[a]
V_{ss} (mL/kg)	66.4 ± 10.6	86.0 ± 18.5	91.1 ± 55.5[a]

Data are presented as mean ± standard deviation or median (range).
[a]n = 5; one patient who did not complete the treatment phase of ONO-4538-13 was not included in the calculations of summary statistics.
Abbreviations: AUC_{21day}, area under serum concentration–time curve from day 0 to day 21 (last measurement); AUC_{inf}, area under serum concentration–time curve extrapolated to infinity; C_{max}, maximum serum concentration; h, hours; $T_{1/2}$, elimination half-life; T_{max}, time to reach C_{max}; V_{ss}, steady-state volume of distribution.