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ORIGINAL ARTICLE

Nivolumab in patients with unresectable locally advanced or metastatic urothelial carcinoma: CheckMate 275 2-year global and Japanese patient population analyses

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Abstract

Background Nivolumab has demonstrated antitumor activity and manageable safety in the single-arm, phase II CheckMate 275 study in patients with unresectable locally advanced or metastatic platinum-resistant urothelial carcinoma. We report updated results of the global population and a subanalysis of Japanese patients from this study.

Methods Patients received nivolumab 3 mg/kg intravenously every 2 weeks until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) confirmed by blinded independent review committee (BIRC) per Response Evaluation Criteria in Solid Tumors v1.1. Secondary endpoints included progression-free survival (PFS) by BIRC and overall survival (OS). Safety was also reported. The minimum follow-up was 21 months.

Results Overall, 270 patients were treated with nivolumab globally; 23 patients were Japanese. In the global and Japanese populations, respectively, ORR per BIRC was 20.4% and 21.7%; median PFS was 1.9 (95% confidence interval [CI] 1.9–2.3) and 3.8 months (95% CI 1.9–7.2); and median OS was 8.6 (95% CI 6.1–11.3) and 21.0 months (95% CI 7.2–not reached). The most common any grade treatment-related adverse events were fatigue (18.1%) and diarrhea (12.2%) in the global population; the most common in the Japanese population were diarrhea (26.1%) and pyrexia (13.0%). Grade 3 or 4 treatment-related adverse events occurred in 61 (22.6%) and seven (30.4%) of the global and Japanese patients, respectively.

Conclusions Nivolumab continues to show antitumor activity and survival in the global population of CheckMate 275. Meaningful clinical benefit was also observed in Japanese patients. No new safety signals were identified.

Keywords Nivolumab · Metastatic urothelial carcinoma · Immunotherapy · Japanese · Immune checkpoint inhibitor

Introduction

The incidence of bladder cancer is approximately 430,000 worldwide [1, 2]. While more common in Western countries, the incidence of bladder cancer in Japan is growing [3, 4]. Most bladder tumors are urothelial carcinomas (UCs), with a minority being variant histologies [5, 6]. According to the Japanese Urological Association (JUA), the National Comprehensive Cancer Network (NCCN), and the European Society of Medical Oncology (ESMO) clinical practice guidelines, cisplatin-based combination therapies (gemcitabine plus cisplatin therapy, and methotrexate, vinblastine, Adriamycin, and cisplatin) are the recommended first-line treatment for cisplatin-eligible patients with metastatic urothelial carcinoma (mUC). JUA, NCCN, and ESMO guidelines recommend carboplatin in patients ineligible for cisplatin [7–9].

For patients with mUC, treatment options after standard first-line chemotherapy have recently expanded with the emergence of immune checkpoint inhibitors. Nivolumab and pembrolizumab are now approved as second-line treatment for patients with platinum-resistant mUC in the United States and Europe [9–12], and pembrolizumab is currently available in Japan [13]. These agents have rapidly become established as the preferred treatment in this disease setting [9].

Nivolumab is a fully human IgG4 programmed death (PD)-1 inhibitor antibody that has been associated with

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clinically meaningful response in the phase II, international, single-arm CheckMate 275 study in patients with unresectable locally advanced or metastatic platinum-resistant UC. With minimum follow-up of 6 months, the objective response rate (ORR) was 19.6% [14].

Racial and ethnic differences may impact the efficacy and safety profile of targeted cancer treatments [15, 16]. For example, in renal cell carcinoma, nivolumab treatment resulted in a higher response rate than everolimus treatment, and the difference was more pronounced in the Japanese versus global population [17]. While immunotherapies are becoming more available for the treatment of several cancer types, no studies examining immunotherapy for platinum-resistant mUC in Japanese patients have been published to date. It is, therefore, essential to better understand how immunotherapy treatments may affect patients in this population. Here, we report efficacy and safety results for CheckMate 275 overall and in the Japanese population (with a minimum follow-up of 21 months).

Patients and methods

Study design

CheckMate 275 is a phase II, single-arm trial of nivolumab monotherapy in patients with unresectable locally advanced or metastatic platinum-resistant UC [14]. Patients received nivolumab 3 mg/kg intravenous infusion over 1 h every 2 weeks until disease progression, unacceptable toxicity, or other protocol-defined reasons. Treatment beyond investigator-assessed progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [18] was permitted if the patient experienced clinical benefit and tolerated the drug. No dose modifications were permitted. Dose delays as specified in the protocol were allowed.

Patients

Eligible patients had histological or cytological evidence of metastatic or surgically unresectable UC, measurable disease per RECIST v1.1, progression or recurrence after treatment with a platinum agent, and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. PD ligand 1 (PD-L1) evaluable tumor tissue must have been provided for biomarker analysis. Key exclusion criteria included active brain metastases, prior active malignancy within the previous 3 years except for locally curable cancers that had apparently been cured, active known or suspected autoimmune disease, and conditions requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of study drug administration. Patient enrollment in Japan was planned to extend after global enrollment closed until approximately 25 treated patients were accrued or November 2015, whichever occurred first. Japanese patients who started treatment after the first treatment date of the last patient who enrolled before closure of global enrollment were not included in the initial efficacy analysis [14].

Endpoints and assessments

The primary endpoint was ORR per blinded independent review committee (BIRC) assessments by RECIST v1.1, defined as the proportion of patients with a confirmed complete or partial response. Time to response and duration of response were estimated for patients with confirmed complete or partial response. Secondary endpoints included progression-free survival (PFS) per BIRC, overall survival (OS), and ORR per investigator review. Efficacy outcomes by PD-L1 expression are not included in this report.

Tumor assessments (per RECIST v1.1) were performed using computed tomography or magnetic resonance imaging every 8 weeks from the date of first dose up to 48 weeks, followed by every 12 weeks, until disease progression or treatment discontinuation. Images were submitted to an imaging core lab for blinded independent review. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0) and were documented for a minimum of 100 days after the last dose. Incidence of treatment-related select AEs (defined as AEs that may be immune mediated, differ from those caused by non-immunotherapies, may require immunosuppression for management, and whose early recognition may mitigate severe toxicity) was also evaluated.

Health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the three-level EuroQoL EQ-5D-3L, and the visual analog scale (VAS). All assessments were performed at baseline (after enrollment but before nivolumab dosing on day 1), every fourth cycle up to 48 weeks, and every sixth cycle thereafter until treatment discontinuation. HRQoL assessments were also collected at follow-up visits. HRQoL results for the Japanese population are not reported due to the small sample size.

Statistical analysis

Full details of the statistical analyses were previously published [14]. ORR is summarized by a binomial response rate and its corresponding two-sided 95% exact confidence interval (CI) using the Clopper–Pearson method. Time to response was analyzed using summary statistics. Duration of response, PFS, and OS were estimated using Kaplan–Meier techniques. EORTC QLQ-C30 scores were transformed to a 0–100 metric such that higher values represent a higher

response level. A clinically meaningful change in score was 10 points [19]. EQ-5D VAS scores also ranged from 0–100, with 0 being the worst health state imaginable and 100 being the best health state imaginable. A clinically meaningful change in score was 7 points [20].

Ethics statement

This study was approved by the ethics committee or institutional review boards of the participating institutions and conducted according to Good Clinical Practice guidelines per the International Conference on Harmonisation. All patients provided written informed consent based on Declaration of Helsinki principles.

Results

Patients

A total of 270 patients were enrolled and treated with nivolumab in CheckMate 275 globally, including 23 Japanese patients [14]. The minimum follow-up was 21 months. At the data cutoff (October 2017), 24 (8.9%) patients in the global population were continuing treatment, including two (8.7%) Japanese patients. In the global population, the most common reasons for treatment discontinuation were disease progression ($n=162$, 60.0%) and AEs unrelated to treatment ($n=36$, 13.3%). In the Japanese population, the most common reasons for discontinuation were disease progression ($n=13$, 56.5%) and study drug toxicity ($n=6$, 26.1%). Baseline demographic and clinical characteristics of the global and Japanese populations are shown in Table 1. The majority of patients were male in both the global ($n=211$, 78.1%) and Japanese ($n=19$, 82.6%) populations. The median age was 66 years in the global population and 63 years in the Japanese population. At baseline, there were 227 (84.1%) and 20 (87.0%) patients with visceral metastases in the global and Japanese populations, respectively. Prior systemic therapy in the metastatic setting was received by 71.5% of patients in the global population and 91.3% of patients in the Japanese population.

Efficacy

In the global population, objective response (95% CI) per BIRC was 20.4% (15.7–25.7) (Table 2). Responses per BIRC included 17 (6.3%) complete responses and 38 (14.1%) partial responses (Fig. 1, Table 2); stable disease was reported in an additional 57 (21.1%) patients (Table 2). Of the 55 responders, 40 (72.7%) had responses lasting ≥ 6 months and 30 (54.5%) had responses lasting ≥ 12 months (Fig. 2). Median time to response was 1.9 months (range 1.6–13.8).

Table 1 Baseline demographic and clinical characteristics

Characteristic	Global population ($n=270$)	Japanese population ($n=23$)
Median age (range), years	66 (38–90)	63 (44–79)
Age category, years		
< 65	122 (45.2)	13 (56.5)
≥ 65	148 (54.8)	10 (43.5)
Sex		
Male	211 (78.1)	19 (82.6)
Female	59 (21.9)	4 (17.4)
Race		
White	231 (85.6)	0
Asian	30 (11.1)	23 (100)
Other	9 (3.3)	0
ECOG performance status		
0	145 (53.7)	16 (69.6)
≥ 1[a]	125 (46.3)	7 (30.4)
Baseline metastases		
Liver	75 (27.8)	3 (13.0)
Visceral[b]	227 (84.1)	20 (87.0)
Lymph node only	43 (15.9)	3 (13.0)
Central nervous system	1 (0.4)	0
Baseline hemoglobin, g/dl		
< 10	48 (17.8)	7 (30.4)
≥ 10	222 (82.2)	16 (69.6)
Previous systemic therapy		
Adjuvant	83 (30.7)	4 (17.4)
Neoadjuvant	60 (22.2)	8 (34.8)
Metastatic	193 (71.5)	21 (91.3)

All items are expressed as *n* (%) unless otherwise noted

[a]One patient in the global population had ECOG performance status of 3

[b]Not visceral if patient had lymph-node-only lesions, or lesions located in bladder, ureter, urethra, and renal pelvis only

Table 2 Best overall response per BIRC

	Global population ($n=270$)	Japanese population ($n=23$)
Objective response, *n* (%)	55 (20.4)	5 (21.7)
95% CI	15.7–25.7	7.5–43.7
Best overall response, *n* (%)		
Complete response	17 (6.3)	1 (4.3)
Partial response	38 (14.1)	4 (17.4)
Stable disease	57 (21.1)	10 (43.5)
Progressive disease	112 (41.5)	5 (21.7)
Not evaluable	46 (17.0)	3 (13.0)

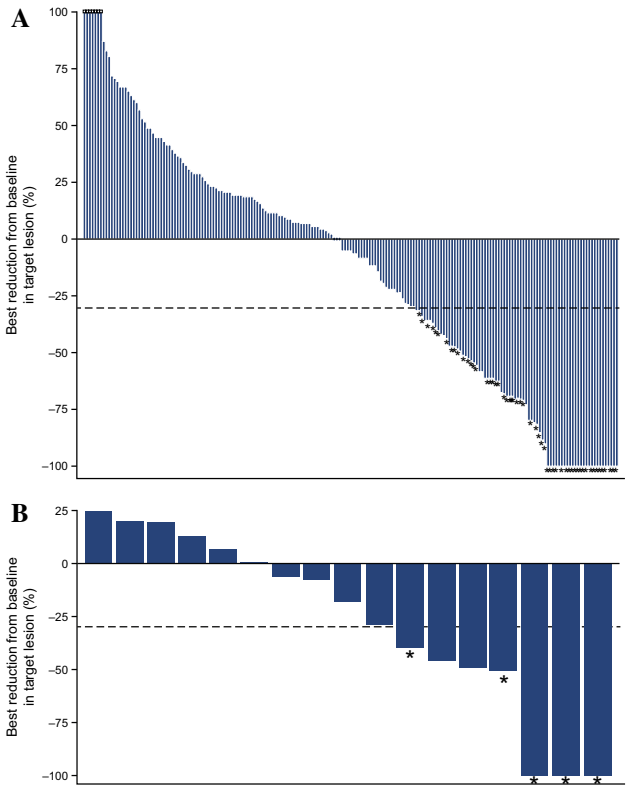

Fig. 1 Tumor burden reduction from baseline in target lesion. **a** Global population, **b** Japanese population. *Denotes responders per RECIST v1.1, confirmation of response required. Squares denote percentage change truncated to 100%

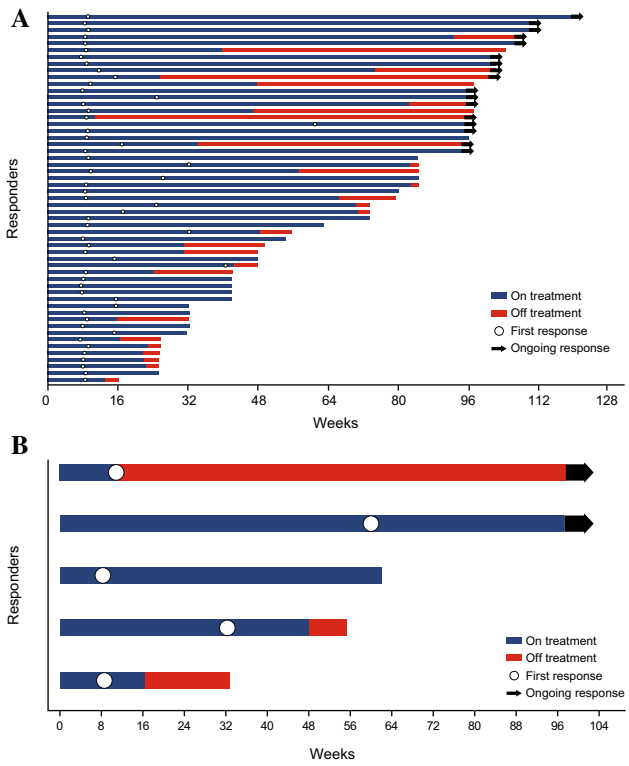

Fig. 2 Time to and duration of response. **a** Global population, **b** Japanese population

The median duration of response was 17.7 months (95% CI 11.5–22.0); 17 (30.9%) patients had an ongoing response at the time of the current analysis. Median PFS per BIRC was 1.9 months (95% CI 1.9–2.3; Fig. 3); the 12- and 24-month PFS rates were 17.5% (95% CI 13.2–22.4) and 7.9% (95% CI 4.4–12.8), respectively. Median OS was 8.6 months (95% CI 6.1–11.3; Fig. 4); the 12- and 24-month OS rates were 40.3% (95% CI 34.4–46.2) and 29.4% (95% CI 23.9–35.1), respectively.

In the Japanese population, objective response per BIRC was achieved in five (21.7%; 95% CI 7.5–43.7) of 23 patients. One (4.3%) patient had a complete response and four (17.4%) patients had a partial response; 10 (43.5%) patients had stable disease (Table 2). Median time to response was 2.0 months (range 1.9–13.8). Median duration of response was 12.2 months (95% CI 5.1–not reached [NR]). Of the five patients who responded to treatment, two (40.0%) had an ongoing response at the time of the analysis (Fig. 2). Three patients had a response lasting ≥6 months, and of these, two had a response lasting ≥12 months (Figs. 2, 5). Most patients showed reduction in tumor burden from baseline (Fig. 1). Median PFS was 3.8 months (95% CI 1.9–7.2; Fig. 3). The 12-month PFS rate was 21.7% (95% CI 7.9–39.9) and the 18-month PFS rate was 13.0% (95% CI 3.3–29.7). Median OS was 21.0 months (95% CI 7.2–NR; Fig. 4). The 12- and 24-month OS rates were 59.3% (95% CI 36.2–76.4) and 48.3% (95% CI 25.9–67.6), respectively.

Safety

Patients in the global population received a median (range) of 7.0 (1–65) doses and a median (range) cumulative dose of 21.1 mg/kg (3.0–192.5) of nivolumab. In the global population, any grade treatment-related AEs occurred in 68.9% of treated patients; the most common were fatigue ($n=49$, 18.1%), diarrhea ($n=33$, 12.2%), and pruritus ($n=31$, 11.5%; Table 3). Grade 3 or 4 treatment-related AEs occurred in 22.6% of treated patients; the most common were increased lipase ($n=10$, 3.7%), increased amylase ($n=8$, 3.0%), and diarrhea ($n=7$, 2.6%). Three grade 5 treatment-related AEs were reported (one case each of pneumonitis, respiratory failure, and circulatory collapse). Treatment discontinuation occurred in 8.1% ($n=22$) of patients due to any grade AEs and in 5.6% ($n=15$) of patients due to grade ≥3 AEs.

Treatment-related select AEs of any grade included skin ($n=61$, 22.6%), endocrine (adrenal disorder [$n=4$, 1.5%], diabetes [$n=1$; 0.4%], pituitary disorder [$n=2$, 0.7%], and

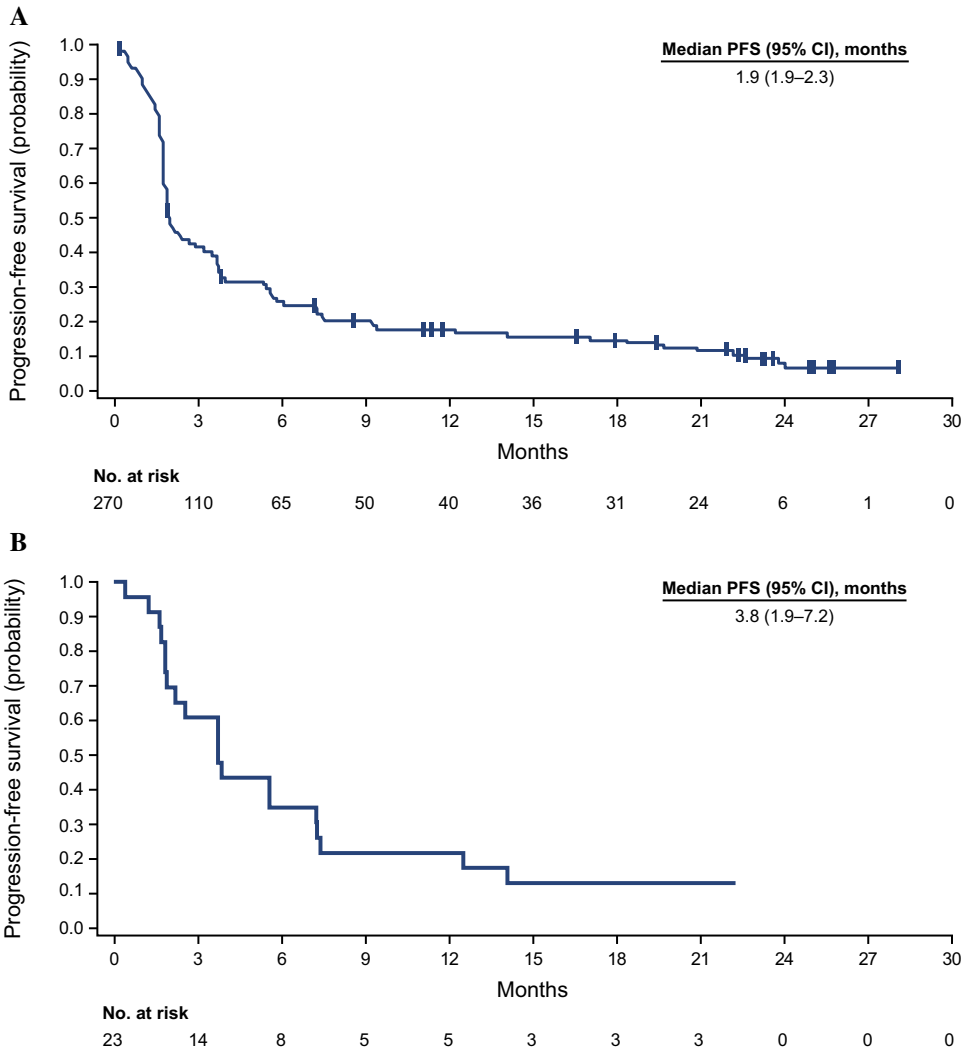

Fig. 3 Kaplan–Meier estimate of PFS **a** Global population, **b** Japanese population

thyroid disorder [*n* = 39, 14.4%]), gastrointestinal (*n* = 34, 12.6%), hepatic (*n* = 13, 4.8%), pulmonary (*n* = 13, 4.8%), and renal (*n* = 6, 2.2%) AEs (Table 4). Grade 3–5 treatment-related select AEs included skin (*n* = 8, 3.0%), gastrointestinal (*n* = 8, 3.0%), hepatic (*n* = 6, 2.2%), endocrine (adrenal disorder [*n* = 2, 0.7%] and pituitary disorder [*n* = 1, 0.4%]), pulmonary (*n* = 5, 1.9%), and renal (*n* = 1, 0.4%). Among the patients who experienced immune-related AEs, 43.6% received immune-modulating therapies, which were mainly dermatological (*n* = 19, 16.2%) and systemic (*n* = 39, 33.3%).

Japanese patients received a median (range) of 9 (1–51) doses and a median (range) cumulative dose of 27.0 mg/kg (3.0–153.4) of nivolumab. Any grade treatment-related AEs occurred in 19 (82.6%) of Japanese patients; the most common any grade treatment-related AEs were diarrhea (26.1%) and pyrexia (13.0%) (Table 3). Grade 3 or 4 treatment-related AEs occurred in seven (30.4%) Japanese patients; grade 3 or 4 treatment-related AEs were diarrhea, pemphigoid, rash, hyperkalemia, hyponatremia, lymphopenia (each occurring in one patient), and increased amylase (in two patients) (Table 3). One Japanese patient died due to study drug toxicity (grade 5 treatment-related respiratory failure).

In the Japanese population, treatment-related select AEs included skin (*n* = 6, 26.1%), endocrine (adrenal disorder [*n* = 1, 4.3%] and thyroid disorder [*n* = 3, 13.0%]), gastrointestinal (*n* = 6, 26.1%), and pulmonary (*n* = 3, 13.0%; Table 4). There were four grade 3 treatment-related select AEs (two skin, one gastrointestinal, and one pulmonary). There were no grade 4 or grade 5 treatment-related select AEs reported in this population. For the management of treatment-related select AEs, concomitant immune-modulating medications, mainly dermatological (*n* = 6, 37.5%) and systemic (*n* = 7, 43.8%) corticosteroids, were used (for any grade treatment-related select AEs: *n* = 10, 62.5%; for grade 3–5 treatment-related select AEs: *n* = 3, 75.0%).

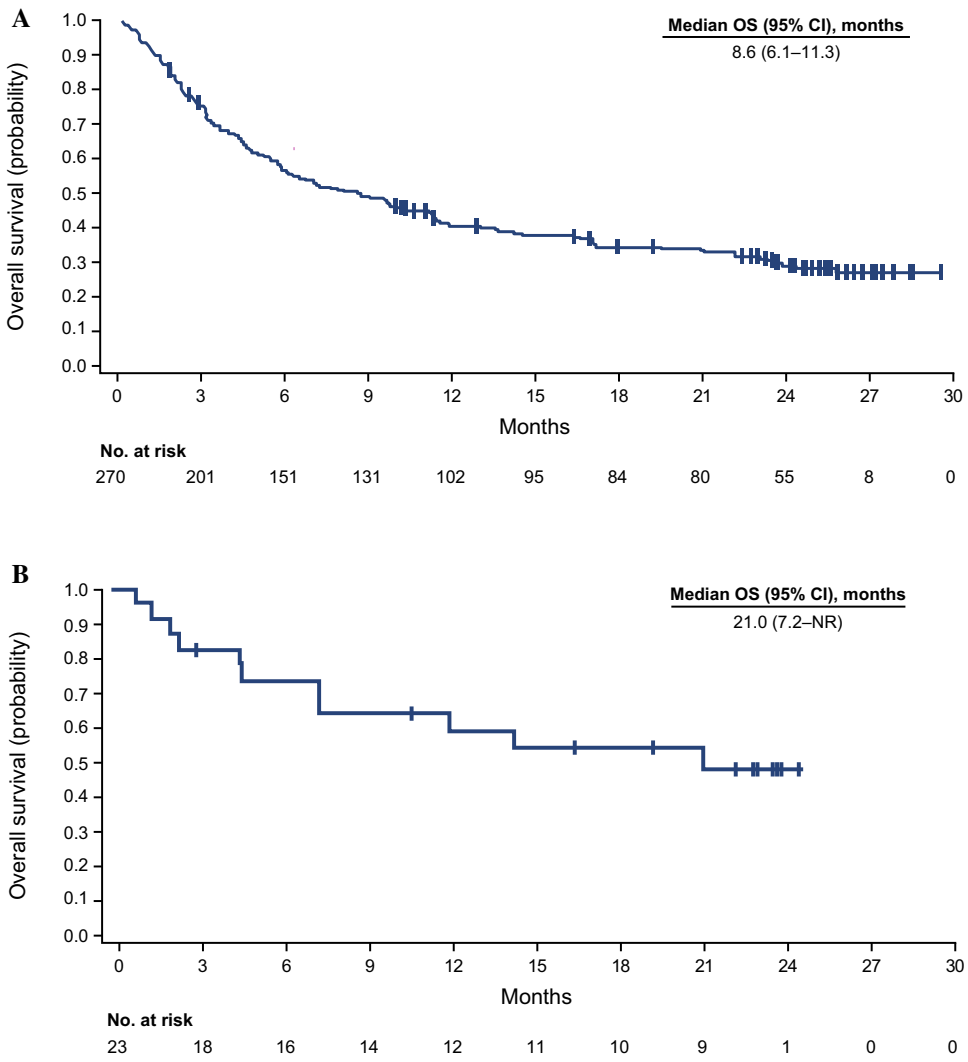

Fig. 4 Kaplan–Meier estimate of OS. **a** Global population, **b** Japanese population

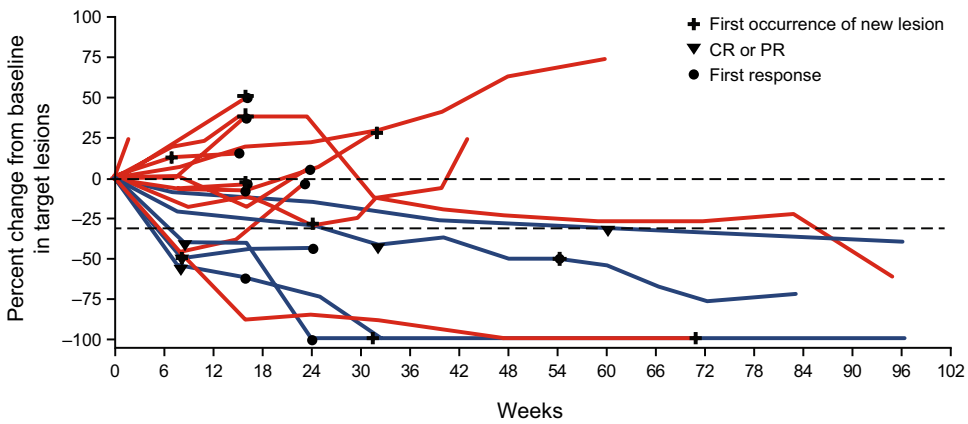

Fig. 5 Change in tumor burden over time in the Japanese population. Only patients with target lesion at baseline and at least one on-treatment tumor assessment are included. Responders are shown in blue and non-responders are shown in red. *CR* complete response, *PR* partial response

Subsequent therapy

In the overall global population, 62 (23.0%) patients received subsequent therapy. Subsequent systemic therapy was received by 37 (13.7%) patients, which was predominantly chemotherapy ($n = 35$, 13.0%); the most common chemotherapy was gemcitabine ($n = 18$, 6.7%). Six (2.2%) patients received subsequent anti-PD-1/PD-L1 immunotherapy. In

Table 3 Treatment-related AEs occurring in ≥ 5% of patients

	Global population ($n=270$)		Japanese population ($n=23$)	
	Any grade	Grade 3–4[a]	Any grade	Grade 3–4
Any treatment-related AE, *n* (%)	186 (68.9)	61 (22.6)	19 (82.6)	7 (30.4)
Fatigue	49 (18.1)	5 (1.9)	1 (4.3)	0
Diarrhea	33 (12.2)	7 (2.6)	6 (26.1)	1 (4.3)
Pruritus	31 (11.5)	0	2 (8.7)	0
Hypothyroidism	23 (8.5)	0	2 (8.7)	0
Pyrexia	17 (6.3)	1 (0.4)	3 (13.0)	0
Increased amylase	12 (4.4)	8 (3.0)	2 (8.7)	2 (8.7)
Increased lipase	12 (4.4)	10 (3.7)	0	0
Pneumonitis	12 (4.4)	3 (1.1)	2 (8.7)	0
Hyperthyroidism	11 (4.1)	0	2 (8.7)	0
Stomatitis	5 (1.9)	1 (0.4)	2 (8.7)	0
Malaise	3 (1.1)	0	2 (8.7)	0

[a]Three grade 5 treatment-related AEs were reported (1 case each of pneumonitis, respiratory failure, and circulatory collapse)

Table 4 Treatment-related select AEs

Treatment-related select AEs by organ system[a] *n* (%)	Global population ($n=270$)		Japanese population ($n=23$)	
	Any grade	Grade 3–4[b]	Any grade	Grade 3–4[c]
Skin	61 (22.6)	8 (3.0)	6 (26.1)	2 (8.7)
Endocrine				
Adrenal disorder	4 (1.5)	2 (0.7)	1 (4.3)	0
Diabetes	1 (0.4)	0	0	0
Pituitary disorder	2 (0.7)	1 (0.4)	0	0
Thyroid disorder	39 (14.4)	0	3 (13.0)	0
Gastrointestinal	34 (12.6)	8 (3.0)	6 (26.1)	1 (4.3)
Pulmonary	13 (4.8)	4 (1.5)	3 (13.0)[d]	1 (4.3)
Hepatic	13 (4.8)	6 (2.2)	0	0
Renal	6 (2.2)	1 (0.4)	0	0

[a]Defined as AEs that may be immune mediated, differ from those caused by non-immunotherapies, may require immunosuppression for management, and whose early recognition may mitigate severe toxicity

[b]One grade 5 pulmonary select AE occurred in all treated patients

[c]No grade 5 treatment-related select AEs were observed in the Japanese population

[d]One grade 1 pneumonitis, 1 grade 2 pneumonitis, and 1 grade 3 interstitial lung disease

addition, 27 (10.0%) patients received subsequent radiotherapy and 10 (3.7%) others received subsequent surgery.

There were eight (34.8%) Japanese patients who received any subsequent therapy. Of these, six (26.1%) patients received subsequent chemotherapy, three (13.0%) received subsequent radiotherapy, and two (8.7%) received subsequent surgery. The most common chemotherapy was gemcitabine ($n=4$, 17.4%).

Health-related quality of life

In the global population, EORTC QLQ-C30 and EQ-5D-3L completion rates were high at baseline (97% for both) and stayed generally high through week 109 for patients on treatment (range 65–90). Overall, quality of life scores as measured by change from baseline remained stable in QLQ-C30, with improvements seen in fatigue (week 97), dyspnea (weeks 33, 109), appetite loss (weeks 33, 61, 97, 109), and constipation (week 109). Treated patients reported clinically meaningful improvement in EQ-5D-3L (week 49) and the VAS (weeks 25–41, 109). After adjusting for differences over time, only the VAS remained clinically meaningful. Interpretation of HRQoL results in the Japanese population was precluded by the small number of patients.

Discussion

With extended follow-up of 21 months, efficacy outcomes in the global population of CheckMate 275 were sustained in terms of ORR, PFS, and OS relative to previous analyses (with minimum follow-up of 6 and 8 months) [14, 21]. Notably, durable responses were reported, with an additional 11 complete responses achieved since initially reported with minimum follow-up of 6 months [14]. Median duration of response in the global study population (17.7 months) was also longer than reported at the last analysis with minimum follow-up of 8 months (10.4 months) [21]. The safety profile of nivolumab was manageable, and HRQoL was maintained from baseline through end of treatment.

Consistent with the results of the global population, meaningful clinical benefit was observed with nivolumab treatment in Japanese patients with unresectable locally advanced or metastatic platinum-resistant UC in this analysis [14]. Durable responses were observed and the ORR of 21.7% was comparable to that observed in the global population (20.4%). However, the median PFS of 3.8 months in the Japanese population was longer than that observed in the global population (1.9 months) as was the median OS of 21.0 months in the Japanese population (compared with 8.6 months in the global population).

No new safety signals were identified in the Japanese population compared with the global population, although certain AEs occurred in a greater proportion of the Japanese population. These included diarrhea, pyrexia, hyperthyroidism, increased amylase, malaise, and stomatitis. In contrast, AEs that were less common in the Japanese population were fatigue, decreased appetite, rash, and nausea. Grade 3 or

4 treatment-related AEs occurred with similar frequency in the Japanese and global populations. The frequency of treatment-related select AEs was generally similar in the Japanese population compared with the global population, with the exception of gastrointestinal and pulmonary treatment-related select AEs, which were more common in the Japanese population.

The differences observed in efficacy and safety between the populations may possibly be related to differences in the clinical characteristics of Japanese patients, including better performance status and differences in prior therapies [17]. In CheckMate 275, a higher proportion of Japanese patients than patients in the global population received prior therapy in the neoadjuvant setting (34.8% vs 22.2%) and the metastatic setting (91.3% vs 71.5%). In addition, differences in clinicians' experience with immunotherapy amongst the populations could have contributed to the safety profiles observed as management of AEs can be improved with greater familiarity with these treatments [22].

To our knowledge, this is the first report of the efficacy and safety of nivolumab in Japanese patients with previously treated mUC. However, subanalyses of Japanese patients from phase III clinical trials of immunotherapeutic agents in other cancers have reported safety and efficacy consistent with those observed in the respective global study populations [17, 23]. In an analysis of Japanese patients from the phase III CheckMate 025 study of nivolumab versus everolimus in patients with previously treated renal cell carcinoma, OS with nivolumab was reported to be longer and ORR with nivolumab was greater than in the global population, and grade 3 or 4 treatment-related AEs were less common in Japanese patients [17].

In Japan, chemotherapy in the second-line setting for mUC is most commonly paclitaxel-based single agents or combination regimens [13]. Single-agent second-line taxane chemotherapy is associated with a median PFS of 2–4 months and median OS of 6–9 months [24]. In a retrospective study, OS (median, 9.0 vs 6.0 months) and PFS (median, 4.0 vs 2.4 months) were improved with combination chemotherapy ($n = 261$) compared with single-agent taxane chemotherapy ($n = 109$) ($P < 0.001$ for differences in OS and PFS) [24]. The efficacy observed with nivolumab in Japanese patients with previously treated mUC, along with the manageable safety profile, suggests that nivolumab may be a potential treatment option in these patients.

One of the limitations of this study is the small number of Japanese patients included in the analysis. This likely contributed to the differences in efficacy and safety observed between the Japanese and global populations. In addition, the small number of Japanese patients precluded a detailed analysis of outcomes by PD-L1 expression status and HRQoL data, as was previously completed for the global population [14].

In conclusion, these CheckMate 275 data support longer term use of nivolumab monotherapy in patients with unresectable locally advanced or metastatic platinum-resistant UC including in the Japanese population. Following these results, studies are underway to evaluate combination immunotherapies. The CheckMate 032 study has already shown promising efficacy of nivolumab in combination with ipilimumab in patients with advanced or metastatic platinum-resistant UC [25] and the CheckMate 901 trial will further evaluate the combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks up to four doses, followed by nivolumab 480 mg every 4 weeks versus chemotherapy in patients with previously untreated mUC (NCT03036098). Future global controlled studies enrolling more patients or studies exclusively enrolling Japanese patients will be necessary to better understand the efficacy and safety of immune checkpoint inhibitors in individual patient populations.

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Compliance with ethical standards

Conflict of interest Chikara Ohyama, Takahiro Kojima, Yoshio Naya, Takamitsu Inoue, and Shinichi Hisasue declare having no conflict of interest. Tsunenori Kondo has received honoraria from ONO Pharmaceutical and Pfizer. Yoshihiko Tomita declares an advisory role for Novartis, Taiho Pharmaceutical, and ONO Pharmaceutical, received honoraria from Astellas, ONO Pharmaceutical, Pfizer, Sonafi Aventis, and Bristol-Myers Squibb, and received research funding from Astellas, AstraZeneca, Pfizer, and ONO Pharmaceutical. Masatoshi Eto received honoraria from ONO Pharmaceutical and Bristol-Myers Squibb, and research funding from ONO Pharmaceutical. Hirotsugu Uemura received honoraria from Bayer, AstraZeneca, Takeda, Astellas, Sanofi, Janssen, MSD, Bristol-Myers Squibb, and Pfizer, and received research funding from AstraZeneca, Janssen, Takeda, Astellas, Sanofi, Taiho, ONO Pharmaceutical, and Pfizer. Wataru Obara received honoraria from Bristol-Myers Squibb and research funding from Bristol-Myers Squibb. Eiji Kikuchi received honoraria from ONO Pharmaceutical, Kissei Pharmaceutical, ASKA Pharmaceutical, Nippon Shinyaku Taiho, Takeda, MSD, Pfizer, AstraZeneca, Astellas, and Chugai, and received research funding from MSD, Nippon Kayaku, Astellas, ONO Pharmaceutical, Chugai, Takeda, Taiho, and AstraZeneca. Padmanee Sharma owns stock in Jounce, Neon, Constellation, Oncolytics, BioAtla, Forty-Seven, Apricity, Polaris, Marker Therapeutics, Codiak, ImaginAb, and Hummingbird, reports an advisory role in Constellation, Jounce, Neon, BioAtla, Pieris, Oncolytics, Merck, Forty-Seven, Polaris, Apricity, Marker Therapeutics, Codiak, ImaginAb, Hummingbird, and owns a patent licensed to Jounce. Matthew D. Galsky received research funding from Bristol-Myers Squibb, Genentech, AstraZeneca, and Merck. Arlene Siefker-Radtke reports an advisory role for Nektar Therapeutics, Janssen Biotech, Bavarian Nordic, Merck Sharp and Dohme, and Seattle Genetics, and research

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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