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Original Article

Impact of Prior Chemotherapy on Response to Second-line Pembrolizumab in Urothelial Cancer: Exploratory Analysis of the Phase 3 KEYNOTE-045 Trial

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Abstract

Background and objective: Until recently, the standard first-line treatment for advanced urothelial carcinoma (UC) was platinum-based combination chemotherapy followed by avelumab maintenance therapy for patients without progressive disease (PD). For patients with advanced UC who experience PD or recurrence, standard-of-care treatment is pembrolizumab monotherapy based on the phase 3 KEYNOTE-045 study. This post hoc analysis of the KEYNOTE-045 study evaluated the efficacy of pembrolizumab compared with chemotherapy by the best response to prior platinum-based chemotherapy.

Methods: Patients with advanced UC that progressed or recurred after first-line platinum-based chemotherapy were randomly assigned 1:1 to receive either pembrolizumab 200 mg every 3 wk (Q3W) for ≤ 2 yr or investigator's choice of chemotherapy (paclitaxel [175 mg/m²], docetaxel [75 mg/m²], or vinflunine [320 mg/m²], each Q3W).

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Urothelial carcinoma

Endpoints included overall survival (OS) from the initiation of the last treatment prior to death, objective response rate (ORR), and duration of response (DOR) as per Response Evaluation Criteria in Solid Tumors version 1.1 from the date of the first response.

Key findings and limitations: An objective response to pembrolizumab was observed in all groups in terms of a prior response to first-line platinum-based chemotherapy. Median OS, ORR, and median DOR were numerically greater with pembrolizumab than with chemotherapy across subgroups. Patients with PD as the best response to prior platinum-based chemotherapy had the poorest OS outcomes. Limitations include a lack of formal hypothesis testing.

Conclusions and clinical implications: When compared with chemotherapy, prolonged OS and durable responses to second-line pembrolizumab were observed independently of the response to or type of prior platinum-based chemotherapy. These findings further support pembrolizumab as second-line treatment for advanced UC.

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ADVANCING PRACTICE

What does this study add?

Based on findings from the phase 3 KEYNOTE-045 study, pembrolizumab monotherapy is standard-of-care treatment for patients with advanced urothelial carcinoma (UC) who experience disease progression during or disease recurrence after first-line platinum-based chemotherapy. This post hoc analysis of the KEYNOTE-045 study showed benefit from second-line pembrolizumab treatment independent of how the disease responded to or the type of initial platinum-based chemotherapy received. These findings further support pembrolizumab as a second-line treatment for advanced UC following disease progression during or disease recurrence after first-line platinum-based chemotherapy.

Clinical Relevance

We have witnessed a significant and rapid expansion of options for treating metastatic urothelial carcinoma, from platinum-based cytotoxic chemotherapy to checkpoint inhibitor monotherapy, antibody drug conjugates, and targeted therapies. In the setting of this expanded field of options, the calculus regarding optimal treatment selection and sequencing for an individual is complicated, and we have limited data to guide prediction of optimal strategies at the individual level. In this post hoc analysis of the results of the phase 3 KEYNOTE-045 trial, which led to approval of pembrolizumab monotherapy as second-line therapy for advanced urothelial carcinoma, the authors evaluated whether prior depth of response to platinum-based chemotherapy or the specific chemotherapeutic agent previously used were associated with the efficacy (primary endpoint: overall survival; secondary endpoints: objective response rate, and duration of response) of second-line pembrolizumab monotherapy. In these secondary analyses, the authors observed that response to pembrolizumab monotherapy in the second-line setting was observed regardless of response to or type of prior platinum-based chemotherapy in patients with advanced UC, underscoring its broad efficacy in the second-line setting. Associate Editor: Sarah P Psutka.

Patient Summary

In this report, we looked at whether the efficacy of second-line pembrolizumab compared with chemotherapy varied across subgroups of patients with advanced urothelial carcinoma, based on their prior response to first-line platinum-based chemotherapy or the platinum agent used. We found that patients with advanced urothelial carcinoma whose disease progressed or recurred after treatment with platinum-based chemotherapy benefited from pembrolizumab treatment independently of how their disease responded to or the type of initial platinum-based chemotherapy. Based on these findings, we conclude that the benefit from second-line pembrolizumab was greater than that with an additional course of chemotherapy in all patient groups in terms of a prior response to first-line platinum-based chemotherapy.

1. Introduction

The standard first-line treatment for patients with advanced urothelial carcinoma (UC) includes platinum-based combination chemotherapy followed by maintenance

therapy with avelumab in the absence of disease progression [1–3]. Based on the findings from the KEYNOTE-045 study, pembrolizumab monotherapy is the standard-of-care treatment for patients with advanced UC who experience disease progression during or disease recurrence after

first-line platinum-based chemotherapy [1,4]. Enfortumab vedotin, an antibody-drug conjugate directed against Nectin-4, is approved for patients with advanced or metastatic UC who had previously received platinum-based chemotherapy and a programmed cell death protein 1/programmed cell death ligand 1 (PD-1/L1) inhibitor [5]. Also, sacituzumab govitecan, an antibody-drug conjugate directed against trophoblast cell surface antigen 2, has been approved for patients with advanced or metastatic UC who had previously received platinum-based chemotherapy and a PD-1/L1 inhibitor [6]. The tyrosine kinase inhibitor erdafitinib is also approved for patients with advanced or metastatic UC with alterations in the fibroblast growth factor receptor (*FGFR*) gene [7].

In the randomized, open-label, phase 3 KEYNOTE-045 trial, pembrolizumab as monotherapy versus investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) was evaluated in patients with advanced UC that progressed or recurred after first-line platinum-based chemotherapy [4,8]. Pembrolizumab was shown to demonstrate durable efficacy and a manageable safety profile versus chemotherapy. After 5 yr of follow-up, the median overall survival (OS) was 10.1 mo in the pembrolizumab group versus 7.2 mo in the chemotherapy group (hazard ratio [HR], 0.71 [95% confidence interval {CI}, 0.59–0.86]) [9].

We conducted a post hoc exploratory analysis of KEYNOTE-045 to examine whether the efficacy of second-line pembrolizumab compared with chemotherapy varied across patient subgroups based on prior response to first-line platinum-based chemotherapy or the platinum agent used.

2. Patients and methods

2.1. Study design and patients

In the randomized, open-label, phase 3 KEYNOTE-045 trial (NCT02256436), patients with advanced UC that progressed or recurred after first-line platinum-based chemotherapy were enrolled. A detailed description of the trial methodology has been published [4]. Patients aged ≥ 18 yr with histologically or cytologically confirmed UC of the renal pelvis, ureter, bladder, or urethra were eligible for enrollment. All patients had measurable disease as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), had received two or fewer prior lines of systemic chemotherapy for metastatic UC, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2. Patients must have experienced either progression after platinum-based chemotherapy for advanced disease or recurrence within ≤ 12 mo after platinum-based adjuvant or neoadjuvant chemotherapy for localized muscle-invasive disease.

The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The protocol and its amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent prior to enrollment.

2.2. Randomization, treatment, and assessments

Patients were enrolled by study investigators. The study sponsor generated the randomization allocation schedule

using a validated propriety tool, Clinical Schedule Generation System, with a block size of 2. Randomization was performed using a centralized interactive voice response system or an integrated web response system (Almac Clinical Technologies, Souderton, PA, USA) and was stratified by ECOG PS (0 or 1 vs 2), presence or absence of liver metastases, hemoglobin (≥ 10 vs < 10 g/dl), and time of completion of most recent chemotherapy (< 3 or ≥ 3 mo). Patients were randomly assigned 1:1 to receive either pembrolizumab 200 mg intravenously every 3 wk for up to 35 cycles (~ 2 yr) or investigator's choice of chemotherapy (paclitaxel [175 mg/m²], docetaxel [75 mg/m²], or vinflunine [320 mg/m²], each administered intravenously every 3 wk). Treatment continued until disease progression per RECIST v1.1, withdrawal of consent, unacceptable toxicity, decision by the investigator to discontinue study therapy, or the completion of 2 yr of pembrolizumab treatment.

The response was assessed by computed tomography (preferred) or magnetic resonance imaging as per RECIST v1.1 by a blinded independent central review (BICR) at week 9, then every 6 wk for the first year, and every 12 wk thereafter. Further details regarding the schedule of assessments have been published [4].

2.3. Endpoints and statistical analysis

The dual primary endpoints for KEYNOTE-045 were progression-free survival per RECIST v1.1 by a BICR and OS [4]. The secondary endpoints were safety and tolerability of pembrolizumab, objective response rate (ORR), and duration of response (DOR) per RECIST v1.1 by BICR from the date of the first documented complete response (CR) or partial response (PR) to disease progression or death. A detailed description of the statistical analysis methodology for the protocol-specified endpoints has been published [4]. In this post hoc analysis, OS, ORR, and DOR were evaluated by the best overall response to prior platinum-based chemotherapy before enrollment (per investigator assessment) and by whether prior chemotherapy was cisplatin or non-cisplatin based in each treatment arm. OS was defined as the time since the initiation of the most recent prestudy platinum-based chemotherapy to death due to any cause, or to the date of censoring at the time of last contact for patients who were alive or lost to follow-up. OS and DOR were estimated using the Kaplan-Meier method. OS, ORR, and DOR were evaluated in the intention-to-treat (ITT) population, defined as all patients who were randomly assigned to a treatment group. No formal statistical hypothesis testing was performed in this post hoc subgroup analysis. OS HRs and associated 95% CIs were calculated using a stratified Cox proportional hazards model and the Efron method of handling ties.

3. Results

3.1. Patients

A total of 542 patients were randomly assigned to pembrolizumab ($n = 270$) or investigator's choice of chemotherapy ($n = 272$). The median time from randomization to database cutoff (October 1, 2020) was 62.9 mo (interquar-

tile range [IQR], 60.8–65.6). In the pembrolizumab arm, 73 patients (27%) had the best overall response of CR or PR, 65 patients (24%) had stable disease (SD), and 107 patients (40%) had progressive disease (PD) to prior platinum-based chemotherapy; 25 patients (9.3%) had no assessment. A total of 180 patients (67%) had received cisplatin-based treatment previously, and 90 patients (33%) had received non-cisplatin-based treatment (including one patient [0.37%] who received oxaliplatin or nedaplatin; all others received carboplatin). In the chemotherapy arm, 71 patients (26%) had a CR or PR, 70 patients (26%) had SD, and 89 patients (33%) had PD to prior platinum-based chemotherapy; 42 patients (15%) had no assessment. Among patients in the chemotherapy arm, 186 (68%) had previously received cisplatin-based treatment and 86 (32%) had previously received non-cisplatin-based treatment (including 83 patients [31%] who received carboplatin

and three patients [1.1%] who received oxaliplatin or nedaplatin).

Patient demographics and baseline disease characteristics were generally balanced between the pembrolizumab and chemotherapy arms in the subgroups of patients with the best response to prior chemotherapy of CR, PR, or SD and PD (Supplementary Tables 1 and 2). Regardless of the treatment arms, baseline disease characteristics were generally balanced between the CR, PR, or SD subgroup and the PD subgroup, except that fewer patients in the CR, PR, or SD subgroup had liver metastases, low hemoglobin (<10 g/dl), short duration (<3 mo) between completion of prior therapy and baseline, and three or four risk factors compared with patients in the PD subgroup.

The median time between stopping prior platinum-based chemotherapy and starting pembrolizumab monotherapy was 4.0 mo (IQR, 2.1–8.3) for all treated

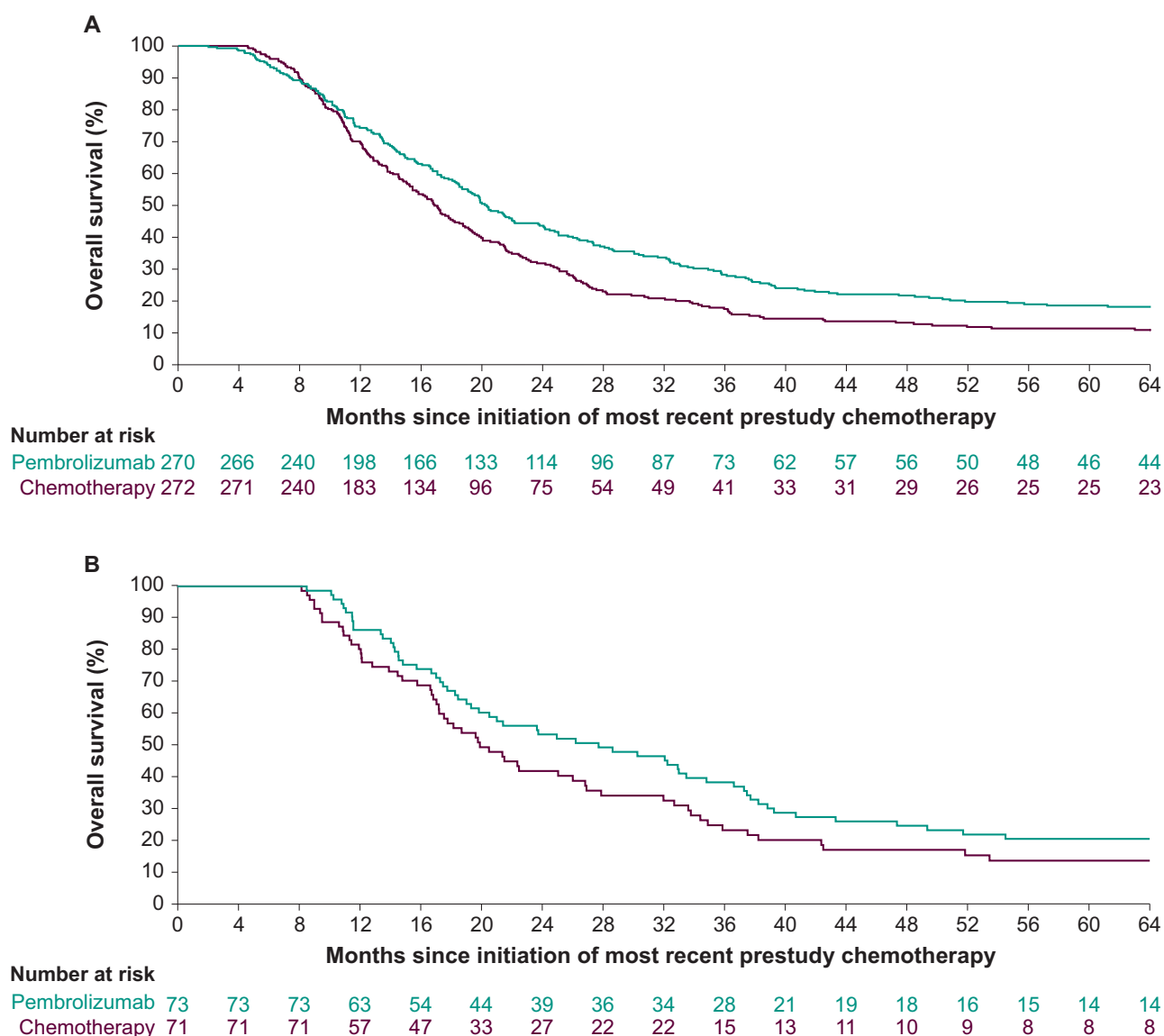


Fig. 1 – Kaplan-Meier estimates of OS since the initiation of the most recent prestudy platinum-based chemotherapy for the (A) intention-to-treat population and patients with (B) CR/PR, (C) SD, or (D) PD as the best response to prior platinum-based chemotherapy. CR = complete response; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease.

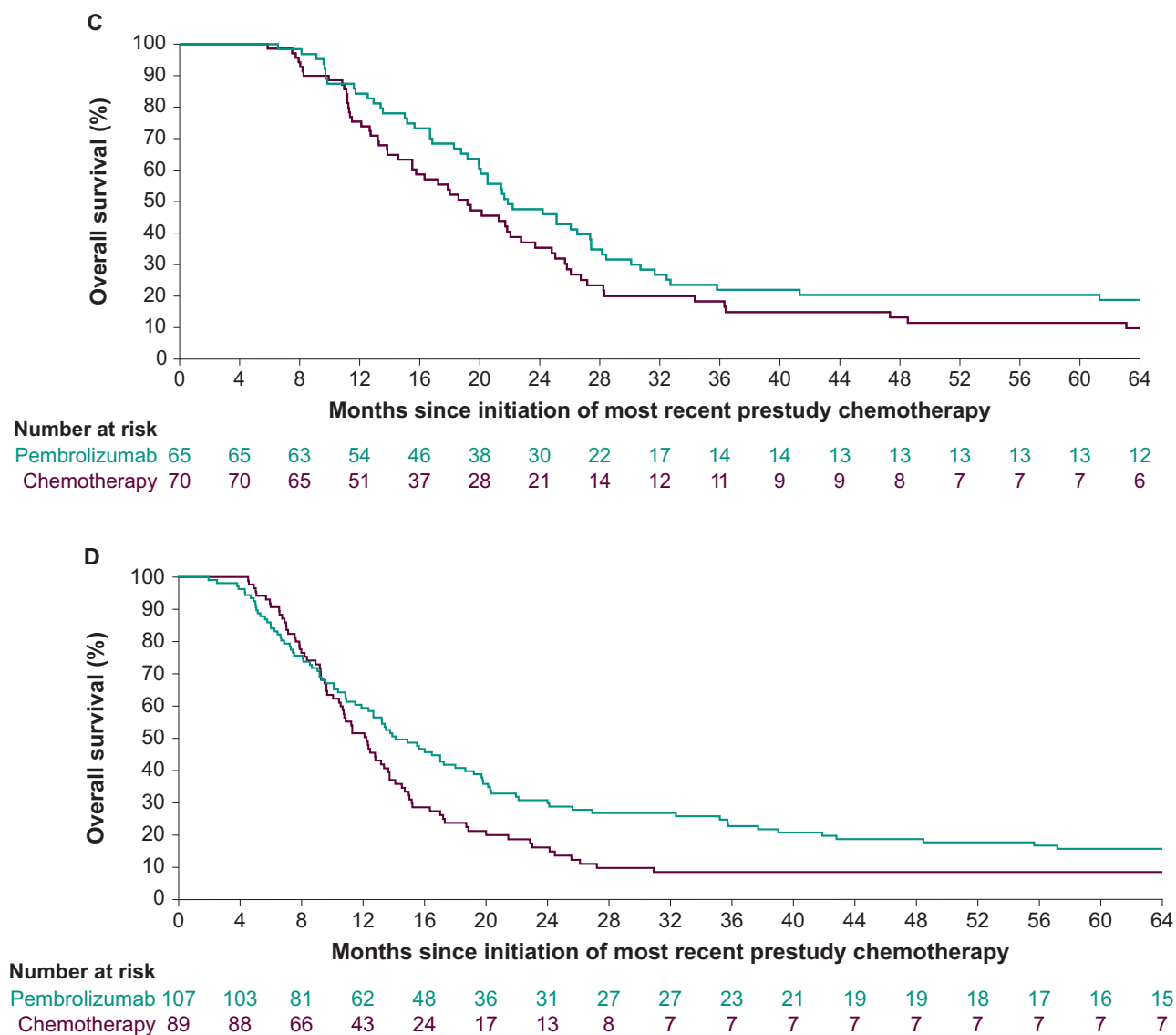


Fig. 1 (continued)

patients. The median time between stopping prior platinum-based chemotherapy and starting pembrolizumab was 6.3 mo (IQR, 3.9–9.3) for patients with CR or PR as the best response, 4.5 mo (IQR, 2.3–8.6) for patients with SD as the best response, and 2.3 mo (IQR, 1.6–4.0) for patients with PD as the best response to prior chemotherapy.

3.2. Efficacy

In the overall ITT population, 224 patients in the pembrolizumab arm and 230 in the chemotherapy arm had died at the database cutoff date. OS since the initiation of the most recent prestudy platinum-based chemotherapy favored pembrolizumab over chemotherapy (HR, 0.74; 95% CI, 0.61–0.89; median OS, 20.3 vs 16.8 mo; Fig. 1 and Supplementary Table 3); the 60-mo OS rate was 18% in the pembrolizumab arm and 11% in the chemotherapy arm. Among subgroups based on the best response to prior chemotherapy, trends for improvements in OS since the ini-

tiation of the most recent prestudy platinum-based chemotherapy with pembrolizumab versus chemotherapy was observed in patients with PD as the best response to prior chemotherapy (HR, 0.64; 95% CI, 0.46–0.89; median OS, 14.2 vs 12.2 mo; Fig. 1 and Supplementary Table 3). Similarly, trends for improvements in OS with pembrolizumab compared with chemotherapy were observed in patients with CR, PR, or SD as the best response to prior cisplatin-based chemotherapy (HR, 0.73; 95% CI, 0.52–1.02; median OS, 22.1 vs 19.1 mo; Fig. 2 and Supplementary Table 3); in patients with PD as the best response to prior cisplatin-based chemotherapy (HR, 0.64; 95% CI, 0.41–1.00; median OS, 14.2 vs 12.3 mo); and in patients with PD as the best response to prior non-cisplatin-based chemotherapy (HR, 0.51; 95% CI, 0.26–1.00; median OS, 16.6 vs 10.8 mo; Fig. 3 and Supplementary Table 3).

ORR was higher with pembrolizumab than with chemotherapy across all patient subgroups based on the

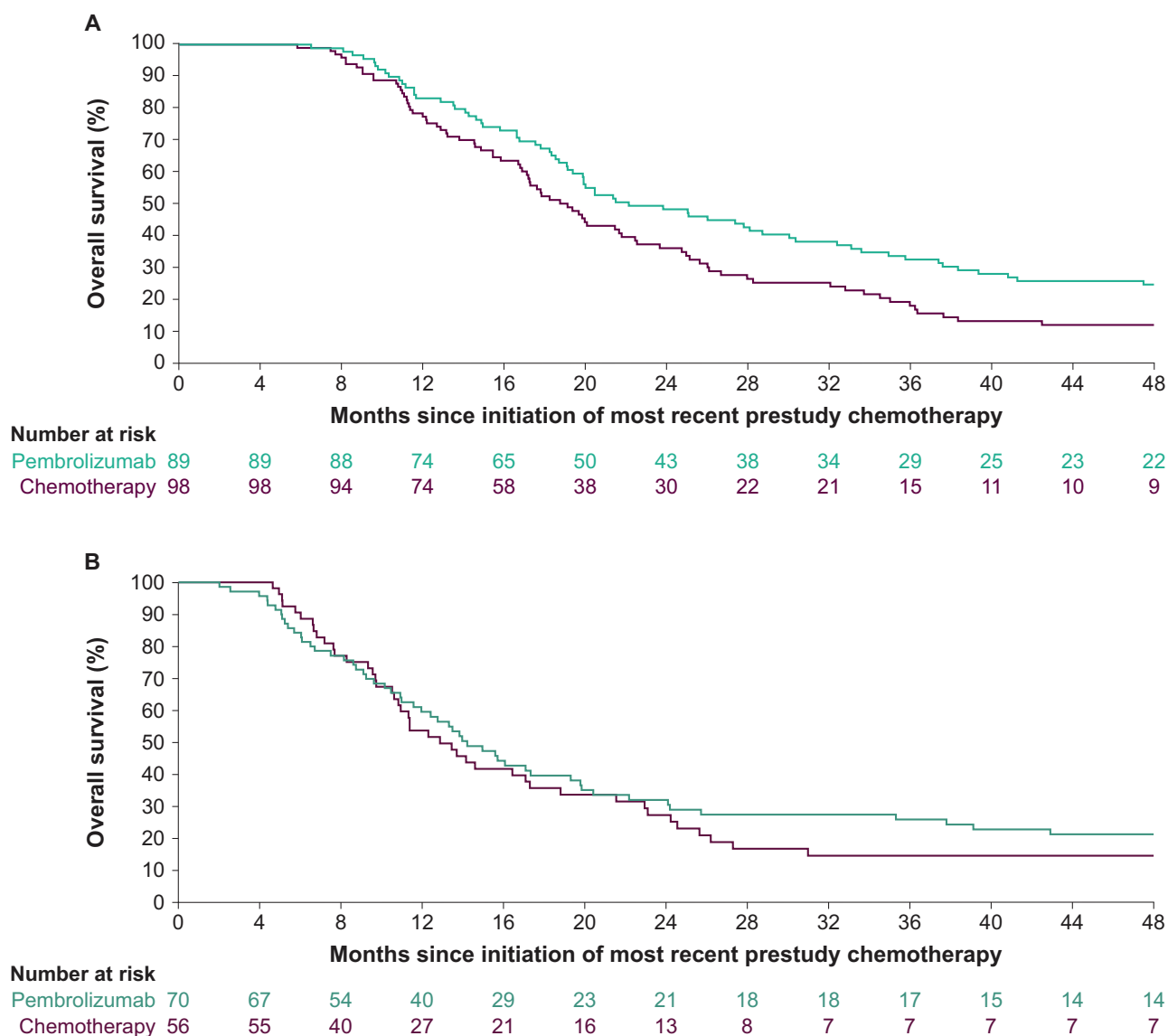


Fig. 2 – Kaplan-Meier estimates of OS since the initiation of the most recent prestudy platinum-based chemotherapy for patients with (A) CR/PR/SD or (B) PD as the best response to prior cisplatin-based chemotherapy. CR = complete response; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease.

best response to prior chemotherapy and type of prior chemotherapy (Table 1 and Supplementary Tables 4 and 5). Similarly, median DOR was numerically longer with pembrolizumab than with chemotherapy across all subgroups based on the best response to or type of prior chemotherapy (Table 2).

4. Discussion

After 5 yr of follow-up in the total ITT population, median OS since the initiation of the most recent prestudy platinum-based chemotherapy was numerically longer with pembrolizumab than with chemotherapy for all randomly assigned patients. Additionally, trends for improvements in OS with pembrolizumab versus chemotherapy were observed in patients with PD as the best response to

prior chemotherapy; in patients with CR, PR, or SD as the best response to prior cisplatin-based chemotherapy; and in patients with PD as the best response to prior cisplatin-based or non-cisplatin-based chemotherapy.

The phase 3 JAVELIN Bladder 100 trial showed that maintenance avelumab plus best supportive care significantly prolonged OS versus best supportive care alone for patients with advanced UC who did not experience disease progression on first-line chemotherapy [10]. Second-line pembrolizumab is currently recommended for patients who experience disease progression or recurrence during or after first-line therapy and are therefore ineligible for avelumab maintenance therapy [11]. In the JAVELIN Bladder 100 trial, avelumab was initiated within 3 mo of chemotherapy completion. In contrast, patients in the KEYNOTE-045 trial were retreated with pembrolizumab between 4 and 6 mo after disease progression.

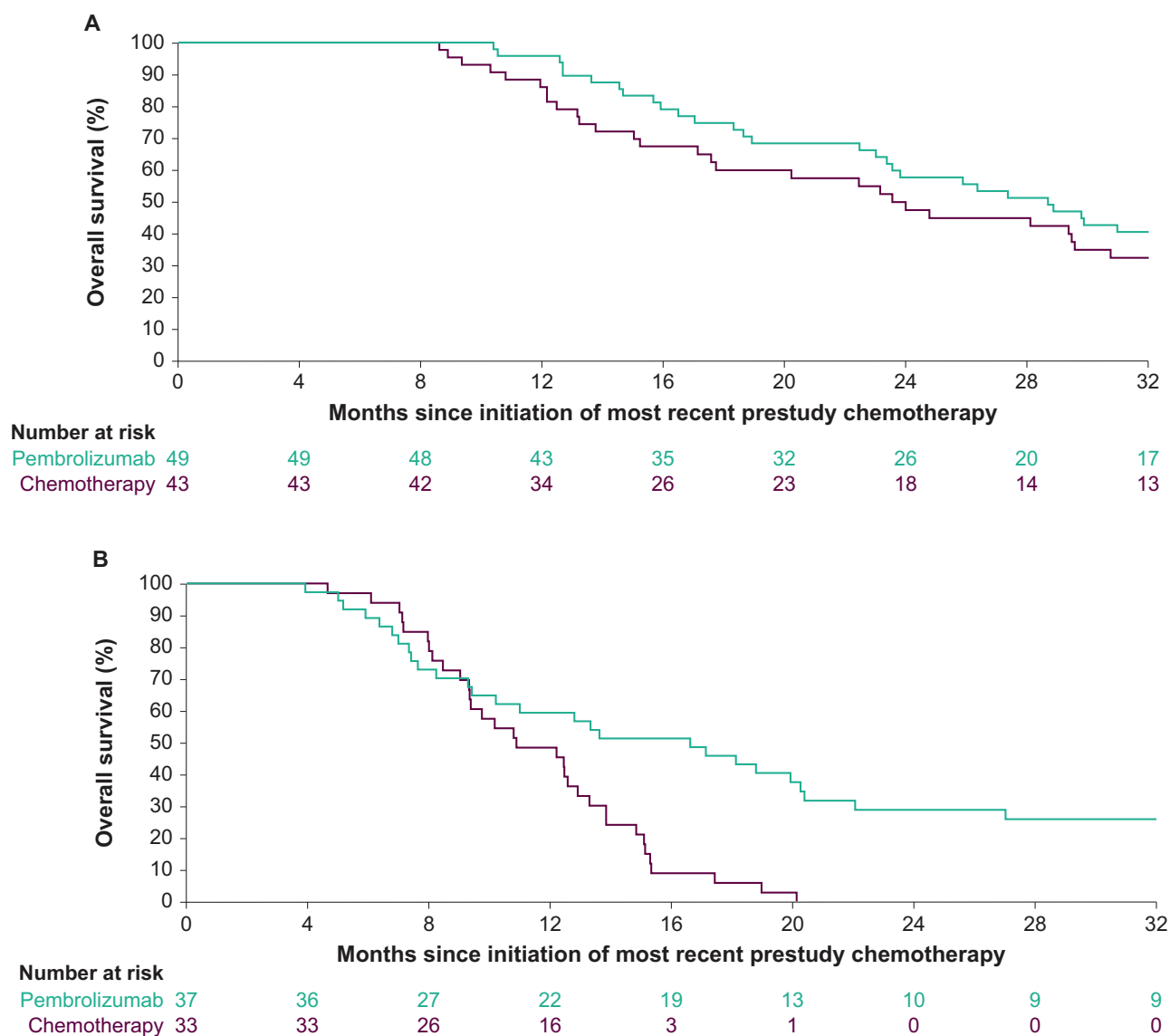


Fig. 3 – Kaplan-Meier estimates of OS since the initiation of the most recent prestudy platinum-based chemotherapy for patients with (A) CR/PR/SD or (B) PD as the best response to prior non-cisplatin-based chemotherapy. CR = complete response; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease.

Evidence shows that cytotoxic chemotherapy agents can stimulate the immune system [12]. Our results suggest that patients without an objective response to prior chemotherapy experienced a clinical benefit from second-line pembrolizumab therapy, making pembrolizumab an optimal second-line treatment for patients with progression or recurrence on or after first-line chemotherapy.

The significant improvement in OS with second-line pembrolizumab compared with chemotherapy in the overall population of KEYNOTE-045 is a strength of this analysis [4]. A limitation of the present study is the post hoc nature of this analysis, which leaves the analysis at a risk of bias and confounding because the benefit of randomization may not be retained in the subgroups. Other limitations include modest sample size and that responses to prior chemotherapy were based on investigator assessment and therefore were not reconciled by the sponsor using imaging data.

5. Conclusions

In this post hoc analysis of KEYNOTE-045, a response to pembrolizumab monotherapy was observed in all groups in terms of a response to or the type of prior platinum-based chemotherapy in patients with advanced UC. Furthermore, OS and DOR were numerically longer with pembrolizumab than with chemotherapy across subgroups based on the best response to prior chemotherapy. Although patients with PD as the best response to prior platinum-based chemotherapy had poorer overall outcomes than those with an objective response or SD as the best response, these patients still benefitted from pembrolizumab treatment over additional chemotherapy. The present analysis further supports the use of pembrolizumab as second-line treatment for advanced UC.

Table 1 – ORR to study treatment by best response to prior chemotherapy and type of prior chemotherapy

Population	Pembrolizumab		Chemotherapy
<i>Best response to prior chemotherapy</i>			
Patients with CR or PR, <i>n</i>	73		71
ORR, %	25		17
ORR difference ^a , % (95% CI)		7.8 (−5.7 to 21)	
Patients with SD, <i>n</i>	65		70
ORR, %	19		5.7
ORR difference ^a , % (95% CI)		13 (1.9–25)	
Patients with PD, <i>n</i>	107		89
ORR, %	20		11
ORR difference ^a , % (95% CI)		8.4 (−2.0 to 19)	
<i>Best response to type of prior chemotherapy</i>			
Patients with CR, PD, or SD to prior cisplatin-based chemotherapy, <i>n</i>	89		98
ORR, %	25		12
ORR difference ^a , % (95% CI)		13 (1.4–24)	
Patients with PD to prior cisplatin-based chemotherapy, <i>n</i>	70		56
ORR, %	23		11
ORR difference ^a , % (95% CI)		12 (−1.4 to 25)	
Patients with CR, PD, or SD to prior non-cisplatin-based chemotherapy, <i>n</i>	49		43
ORR, %	16		9.3
ORR difference ^a , % (95% CI)		7.0 (−7.6 to 21)	
Patients with PD to prior non-cisplatin-based chemotherapy, <i>n</i>	37		33
ORR, %	14		12
ORR difference ^a , % (95% CI)		1.4 (−16 to 18)	

CI = confidence interval; CR = complete response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

^a ORR with pembrolizumab minus ORR with chemotherapy.**Table 2 – DOR from the date of first documented objective response to study treatment by response to prior chemotherapy**

Population	Pembrolizumab	Chemotherapy
<i>Patients with CR or PR as best response to prior chemotherapy</i>		
Responders, <i>n/N</i>	18/73	12/71
DOR (mo), median (IQR)	24.6 (6.9–NR)	4.3 (2.9–NR)
Patients with ≥48-mo response duration, ^a %	31	32
<i>Patients with SD as best response to prior chemotherapy</i>		
Responders, <i>n/N</i>	12/65	4/70
DOR (mo), median (IQR)	33.4 (12.5–46.8)	4.3 (4.2–NR)
Patients with ≥48-mo response duration, ^a %	23	NE
<i>Patients with PD as best response to prior chemotherapy</i>		
Responders, <i>n/N</i>	21/107	10/89
DOR (mo), median (IQR)	NR (9.9–NR)	6.9 (4.0–20.3)
Patients with ≥48-mo response duration, ^a %	57	22
<i>Patients with CR, PR, or SD as best response to prior cisplatin-based chemotherapy</i>		
Responders, <i>n/N</i>	22/89	12/98
DOR (mo), median (IQR)	12.5 (8.0–NR)	4.4 (4.2–NR)
Patients with ≥48-mo response duration, ^a %	26	40
<i>Patients with PD as best response to prior cisplatin-based chemotherapy</i>		
Responders, <i>n/N</i>	16/70	6/56
DOR (mo), median (IQR)	NR (19.7–NR)	20.3 (6.9–NR)
Patients with ≥48-mo response duration, ^a %	69	28
<i>Patients with CR, PR, or SD as best response to prior non-cisplatin-based chemotherapy</i>		
Responders, <i>n/N</i>	8/49	4/43
DOR (mo), median (IQR)	31.7 (24.6–NR)	3.6 (2.9–4.3)
Patients with ≥48-mo response duration, ^a %	NE	0.0
<i>Patients with PD as best response to prior non-cisplatin-based chemotherapy</i>		
Responders, <i>n/N</i>	5/37	4/33
DOR (mo), median (IQR)	9.9 (8.3–24.3)	3.1 (2.9–NR)
Patients with ≥48-mo response duration, ^a %	20	NE

CR = complete response; DOR = duration of response; IQR = interquartile range; NE = not estimable; NR = not reached; PD = progressive disease; PR = partial response; SD = stable disease.

^a From the Kaplan-Meier method for censored data.

Selected data from this manuscript were previously presented at the 2022 European Society of Medical Oncology (ESMO) annual meeting held on September 9–13, 2022, in Paris, France.

Author contributions: Ronald de Wit had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Wit, Gerritsen, Choueiri, Imai, Bellmunt.

Acquisition of data: de Wit, Vaughn, Fradet, Fong, Climent, Gurney, Quinn, Culine, Sternberg, Homet Moreno, Bellmunt, Lee.

Analysis and interpretation of data: de Wit, Vaughn, Climent, Necchi, Petrylak, Gerritsen, Quinn, Culine, Sternberg, Bajorin, Choueiri, Xu, Imai, Homet Moreno, Bellmunt.

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Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eururo.2024.07.015>.

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