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ORIGINAL ARTICLE

Efficacy and safety of pembrolizumab in patients with advanced urothelial carcinoma deemed potentially ineligible for platinum-containing chemotherapy: Post hoc analysis of KEYNOTE-052 and LEAP-011

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Abstract

Background: First-line pembrolizumab monotherapy is a standard of care for platinum-ineligible patients with advanced urothelial carcinoma (UC). No global standardized definition of platinum ineligibility exists. This study aimed to evaluate the efficacy and safety of pembrolizumab monotherapy in patients with UC who met various criteria for platinum ineligibility.

Methods: Patients from KEYNOTE-052 and LEAP-011 deemed potentially platinum ineligible were pooled for this post hoc exploratory analysis as follows: group 1: Eastern Cooperative Oncology Group performance status (ECOG PS) 2; group 2: ECOG PS 2 and age ≥80 years, renal dysfunction, or visceral disease; and group 3: any two other factors regardless of ECOG PS. Patients received pembrolizumab 200 mg intravenously every 3 weeks. End points included objective response rate (ORR), progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded independent central review, overall survival (OS), and safety.

Results: A total of 612 patients treated with pembrolizumab from KEYNOTE-052 (n = 370) and LEAP-011 (n = 242) were included; the median (range) follow-up was 56.3 months (51.2–65.3 months) and 12.8 months (0.2–25.1 months), respectively. For group 1, ORR was 26.2%, median PFS was 2.7 months, and median OS was 10.1 months. For group 2, ORR ranged from 23.5% to 33.3%, median PFS

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ranged from 2.1 to 4.4 months, and median OS ranged from 9.1 to 10.1 months. For group 3, ORR ranged from 25.7% to 27.9%, median PFS ranged from 2.1 to 2.8 months, and median OS ranged from 9.0 to 10.6 months. Treatment-related adverse event rates were consistent across groups.

Conclusions: Frontline pembrolizumab has consistent antitumor activity and safety in patients with advanced UC categorized as potentially ineligible for platinum-based chemotherapy, regardless of the variable definitions of platinum ineligibility used.

KEYWORDS
advanced urothelial carcinoma, bladder cancer, immunotherapy, pembrolizumab, platinum ineligibility

INTRODUCTION

Approximately 30%–50% of patients with advanced urothelial carcinoma (UC) are ineligible to receive cisplatin-based chemotherapy because of baseline characteristics such as advanced age, renal dysfunction, poor performance status, and other medical comorbidities.[1,2] Although numerous patients in this population can still receive carboplatin-based treatment, many are deemed ineligible for any cytotoxic platinum-based chemotherapy by their treating physicians.[3,4] Because no global, standardized guidance to determine platinum ineligibility exists, treatment decisions are based on individual clinical judgment of patients' baseline characteristics. Before the advent of immunotherapy, patients ineligible to receive any platinum-based chemotherapy were typically considered candidates for best supportive care/hospice and had a dismal prognosis.[5,6]

In the phase 2 KEYNOTE-052 trial, first-line pembrolizumab monotherapy was found to demonstrate antitumor activity and acceptable tolerability in patients with advanced or metastatic UC and in patients ineligible for cisplatin-based chemotherapy or any platinum-containing chemotherapy.[7] Long-term follow-up of up to 5 years continued to show durable responses to pembrolizumab.[8,9] On the basis of results from KEYNOTE-052, first-line pembrolizumab monotherapy became a standard-of-care option for platinum-ineligible patients with advanced UC in the United States.[8,10] This approval was further expanded in Europe for the subgroup of cisplatin-ineligible patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of ≥10.[11]

In the phase 3 LEAP-011 trial, first-line pembrolizumab plus lenvatinib versus pembrolizumab plus placebo was investigated in patients with advanced UC who were ineligible for cisplatin-based chemotherapy.[12] Although enrollment was stopped because of the unfavorable benefit-to-risk ratio for the pembrolizumab plus lenvatinib combination, benefits of pembrolizumab monotherapy continued to be observed in platinum-ineligible patients with advanced UC.[12] This trial provided a relevant, randomized population to further investigate the application of pembrolizumab monotherapy in the frontline setting.

Given the challenge of defining reproducible platinum ineligibility, determining whether pembrolizumab (Food and Drug Administration approved in this patient population) shows a consistent efficacy and safety profile regardless of the different criteria used to define platinum ineligibility is relevant. This exploratory post hoc analysis of a pooled population of patients from KEYNOTE-052 and LEAP-011 characterizes the efficacy of pembrolizumab monotherapy in frontline UC on the basis of several different definitions of platinum ineligibility.

MATERIALS AND METHODS

Patients and treatment

KEYNOTE-052 (NCT02335424) was a single-arm, open-label, phase 2 trial of first-line pembrolizumab monotherapy in patients with histologically/cytologically confirmed locally advanced or metastatic UC who had not previously received systemic therapy for advanced UC, were ineligible for cisplatin-based chemotherapy, had measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients were ineligible for cisplatin-based chemotherapy if they met at least one of the following criteria: an ECOG PS of 2, creatinine clearance of 30–60 mL/min, grade ≥2 audiometric hearing loss, grade ≥2 peripheral neuropathy, or New York Heart Association (NYHA) class III heart failure. Eligible patients received pembrolizumab 200 mg intravenously (iv) every 3 weeks until documented progression, unacceptable toxicity, withdrawal of consent, investigator decision to discontinue therapy, or completion of 2 years of pembrolizumab treatment. Detailed study design and trial methods have been previously published.[7]

LEAP-011 (NCT03898180) was a randomized, double-blind, multicenter, phase 3 trial of first-line pembrolizumab plus lenvatinib compared with pembrolizumab plus placebo in cisplatin-ineligible patients whose tumors expressed a PD-L1 CPS of ≥10 and in patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status.[12] Eligible patients had a histologically/cytologically confirmed diagnosis of advanced or metastatic UC, had measurable disease per RECIST v1.1 by the investigator, received no prior systemic chemotherapy for UC, and had an ECOG PS of 0–2. The criteria

used to determine cisplatin ineligibility in LEAP-011 included having a tumor with a PD-L1 CPS of ≥10 and one or more of the following: an ECOG PS of 2, creatinine clearance of ≥30–≤60 mL/min, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0), grade ≥2 audiometric hearing loss, or NCI CTCAE v4.0 grade ≥2 peripheral neuropathy. Contributing criteria for ineligibility of any platinum-based chemotherapy included having an ECOG PS of 2 and one or more of the following frequently associated characteristics: documented visceral metastatic disease, creatinine clearance of ≥30–≤60 mL/min, NCI CTCAE v4.0 grade ≥2 audiometric hearing loss, NCI CTCAE v4.0 grade ≥2 peripheral neuropathy, or other reasons identified on the case report form. Although an ECOG PS of 2 is not sufficient to define platinum ineligibility by itself, it was part of the definition of platinum ineligibility in LEAP-011[12] and a main factor for cisplatin ineligibility in KEYNOTE-052 (32% of patients were cisplatin ineligible because of an ECOG PS of 2),[7] and therefore was investigated in group 1 as a key single contributing criterion. Patients were randomly assigned 1:1 to receive pembrolizumab 200 mg iv every 3 weeks for up to 35 cycles (approximately 2 years) plus oral lenvatinib 20 mg once daily or pembrolizumab 200 mg iv every 3 weeks for up to 35 cycles plus placebo until progression according to RECIST v1.1, intolerable toxicity, or physician or patient decision to withdraw from the study. Detailed study design and trial methods have been previously published.[12]

Both trials were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The protocols and their amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent before the intervention.

Assessments and end points

On-study imaging in KEYNOTE-052 was performed 9 weeks after the first dose of study treatment, every 6 weeks for the first 12 months, and then every 12 weeks thereafter. Tumor response was assessed per RECIST v1.1 by blinded independent central review. Imaging in LEAP-011 occurred at week 6, every 6 weeks until week 24, every 9 weeks through week 60, and then every 12 weeks thereafter. Tumor response was assessed per RECIST v1.1 by blinded independent central review. Adverse events (AEs) were monitored throughout both trials and for 30 days after the end of study treatment (90 days for serious AEs), and graded according to NCI CTCAE v4.0.

Post hoc analysis

An extensive literature search of clinical trial results, guidelines, and real-world data was performed to identify key criteria commonly used to predict higher risk of toxicity with, or intolerance of, platinum-based chemotherapy. The full list of contributing criteria for platinum ineligibility is provided in Table S1. Criteria were separated into four groups; group 1: ECOG PS 2 only; group 2: ECOG PS 2 and one other factor (age ≥80 years, renal dysfunction [defined as a glomerular filtration rate of <60 mL/min], visceral disease, any neuropathy, or any NYHA heart failure); group 3: any two factors (age ≥80 years, renal dysfunction, visceral disease, any neuropathy, or any NYHA heart failure) regardless of ECOG PS score; and group 4: any grade ≥2 comorbidity (defined as grade ≥2 hearing loss, grade ≥2 neuropathy, or NYHA class III+). Patients treated with pembrolizumab monotherapy from KEYNOTE-052 and LEAP-011 who were potentially platinum ineligible on the basis of these criteria were pooled for this post hoc analysis. On the basis of the available patient numbers for each group (Table S1), the following baseline characteristics were evaluated in this analysis: group 1: ECOG PS 2 only; group 2: patients with an ECOG PS of 2 and one other factor (age ≥80 years, renal dysfunction, or visceral disease); and group 3: patients with any two factors (age ≥80 years, renal dysfunction, or visceral disease) regardless of ECOG PS score.

The efficacy population from KEYNOTE-052 consisted of all enrolled patients who received at least one dose of the study treatment and had measurable disease at baseline, and the efficacy population from LEAP-011 consisted of all randomly assigned patients. The safety population from both studies consisted of all patients who received at least one dose of the study treatment. End points evaluated included objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), overall survival (OS), progression-free survival (PFS), and safety. PFS, OS, DOR, and 95% CIs were estimated via the Kaplan–Meier method. CIs for ORR were assessed via the exact binomial CI method.

RESULTS

Patients

A total of 612 patients treated with pembrolizumab were included in this analysis (370 patients in KEYNOTE-052; 242 patients in LEAP-011 [80% of patients in the pembrolizumab arm of LEAP-011 were ineligible for all platinum agents]).[12] The median time from enrollment to the database cutoff of September 26, 2020, in KEYNOTE-052 was 56.3 months (range, 51.2–65.3 months). The median time from randomization to the database cutoff of July 26, 2021, in LEAP-011 was 12.8 months (range, 0.2–25.1 months). Of the 612 patients, 355 (58.0%) had an ECOG PS of 2 and were assigned to group 1. In group 2, 87 patients had an ECOG PS of 2 and were aged ≥80 years; 176 patients had both an ECOG PS of 2 and renal dysfunction; and 285 patients had both an ECOG PS of 2 and visceral disease. In group 3, 111 patients were aged ≥80 years and had renal dysfunction, 116 had visceral disease and were aged ≥80 years, and 308 had both visceral disease and renal dysfunction (307 were included in the efficacy population).

Efficacy

Group 1

ORR for group 1 was 26.2% (95% CI, 21.7%–31.1%), and DCR was 48.5% (95% CI, 43.1%–53.8%) (Figure 1; Table S2). Median TTR in patients with a confirmed response was 2.1 months (range, 1.2–7.8 months) (Figure 2A). Median DOR was 30.1 months (range, 1.4+ to 56.4+ months); 33.4% of patients had a response lasting at least 48 months (Figure 2A). Median PFS was 2.7 months (range, 2.1–3.4 months), with a 12-month PFS rate of 22.7% (Figure 3A). Median OS was 10.1 months (range, 8.6–11.7 months), with a 12-month OS rate of 44.3% (Figure 4A).

Group 2

ORR was from 23.5% (95% CI, 18.7%–28.9%) to 33.3% (95% CI, 23.6%–44.3%), and DCR was from 43.9% (95% CI, 38.0%–49.8%) to 55.2% (95% CI, 44.1%–65.9%) (Figure 1; Table S2). Median TTR was similar within group 2 and ranged from 2.0 to 2.1 months (Figure 2B). Median DOR was from 14.5 months (range, 1.4+ to 51.5+ months) to 33.4 months (range, 1.4+ to 51.5+ months); the proportion of patients with a response lasting at least 48 months ranged from 27.5% to 33.8% (Figure 2B). Median PFS ranged from 2.1 months (95% CI, 2.0–2.7 months) to 4.4 months (95% CI, 2.1–7.8 months), and the 12-month PFS rate ranged from 19.1% to 27.8% (Figure 3B). Median OS ranged from 9.1 months (95% CI, 7.2–10.8 months) to 10.1 months (95% CI, 8.6–13.8 months), and the 12-month OS rate ranged from 40.2% to 45.2% (Figure 4B).

Group 3

ORR was similar within group 3 and ranged from 25.7% (95% CI, 20.9%–31.0%) to 27.9% (95% CI, 19.8%–37.2%), and DCR was from 44.0% (95% CI, 34.8%–53.5%) to 49.5% (95% CI, 39.9%–59.2%) (Figure 1; Table S2). Median TTR was 2.1 months (Figure 2C). Median DOR was from 12.5 months (range, 2.8 to 51.5+ months) to 19.3 months (range, 1.4+ to 57.3+ months). The proportion of patients with a response lasting at least 48 months ranged from 12.3% to 30.7% (Figure 2C). Median PFS was similar within group 3 and ranged from 2.1 months (95% CI, 2.0–2.8 months) to 2.8 months (95% CI, 2.1–4.5 months), and the 12-month PFS rate ranged from 19.4% to 22.9% (Figure 3C). Median OS was from 9.0 to 10.6 months (Figure 4C).

Safety

The proportion of patients experiencing any treatment-related AEs was consistent across groups (Table 1). The frequency of serious treatment-related AEs, the number of patients who died from treatment-related AEs, and the number of patients who discontinued treatment because of treatment-related AEs were similar across groups.

DISCUSSION

This exploratory post hoc analysis of KEYNOTE-052 and LEAP-011 demonstrated that pembrolizumab monotherapy provides durable responses in patients with advanced UC who are potentially ineligible

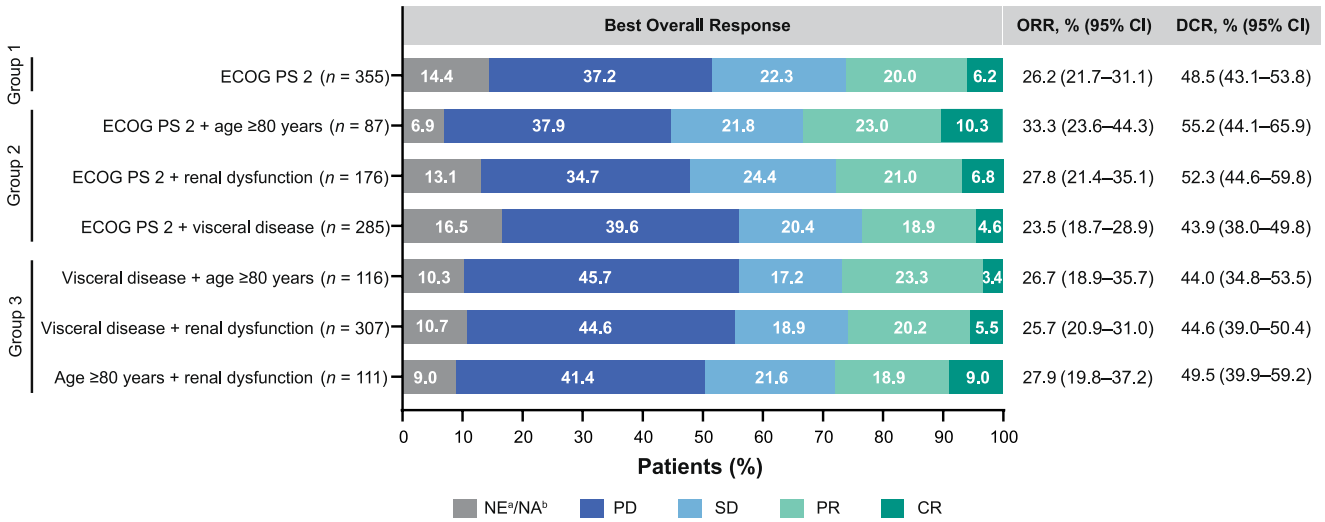

FIGURE 1 Objective response rate, disease control rate, and best overall response by different definitions of platinum ineligibility. CR indicates complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, no assessment; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. [a]Includes patients with insufficient data for assessment of response per Response Evaluation Criteria in Solid Tumors, version 1.1. [b]Includes patients without postbaseline assessment on the data cutoff date.

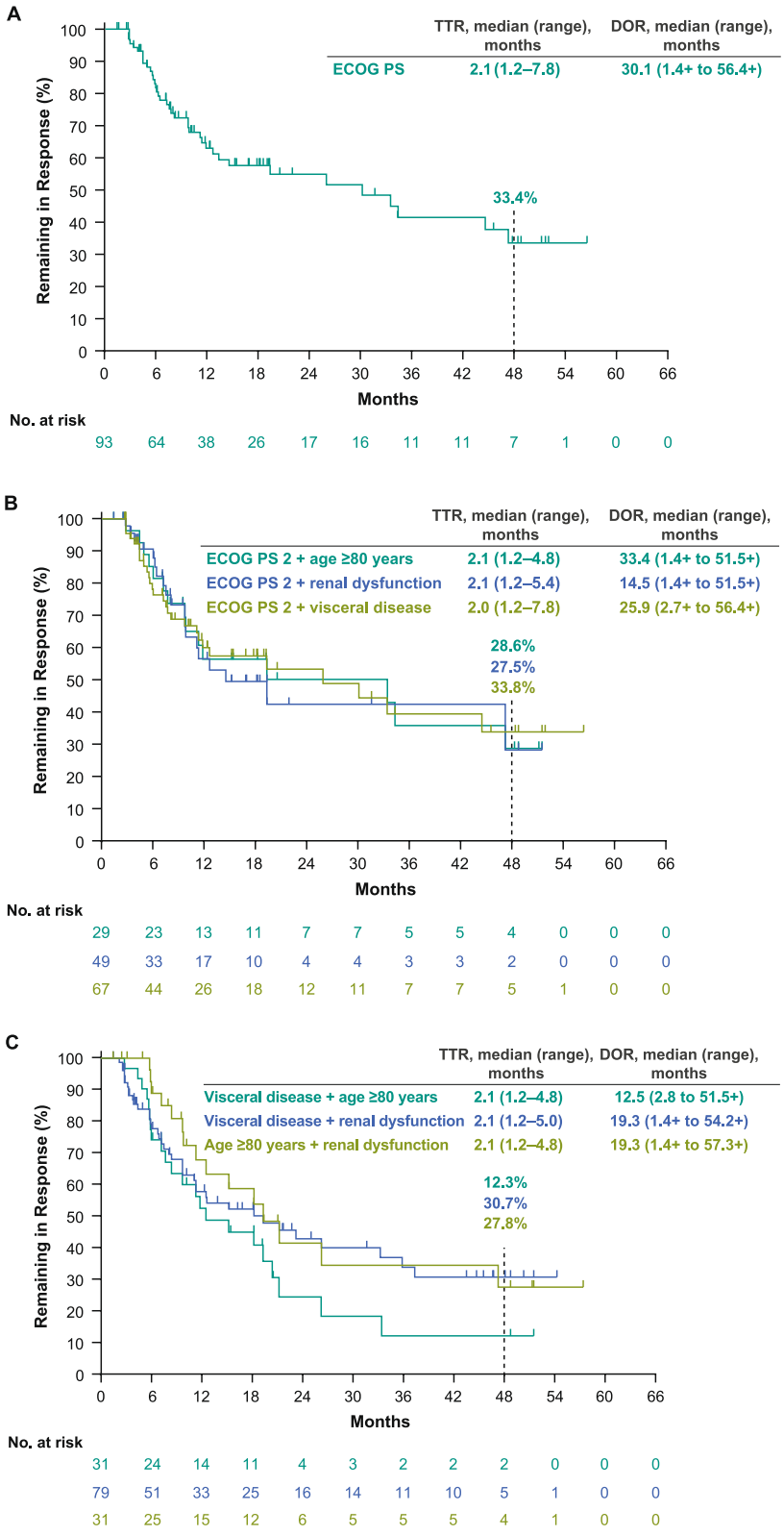

FIGURE 2 Kaplan–Meier estimates of duration of response for patients in (A) group 1, (B) group 2, and (C) group 3. DOR indicates duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; TTR, time to response.

for any platinum-based chemotherapy on the basis of different criteria of platinum ineligibility. Results from the primary analyses of KEYNOTE-052 and the pembrolizumab arm of LEAP-011 were consistent.[7,12] In the current analysis, ORR ranged from 23.5% to 33.3% among subgroups. Median OS was generally consistent among subgroups and ranged from 9.0 to 10.6 months. The proportion of patients experiencing any treatment-related AEs was consistent with the proportion of AEs reported in each respective trial.

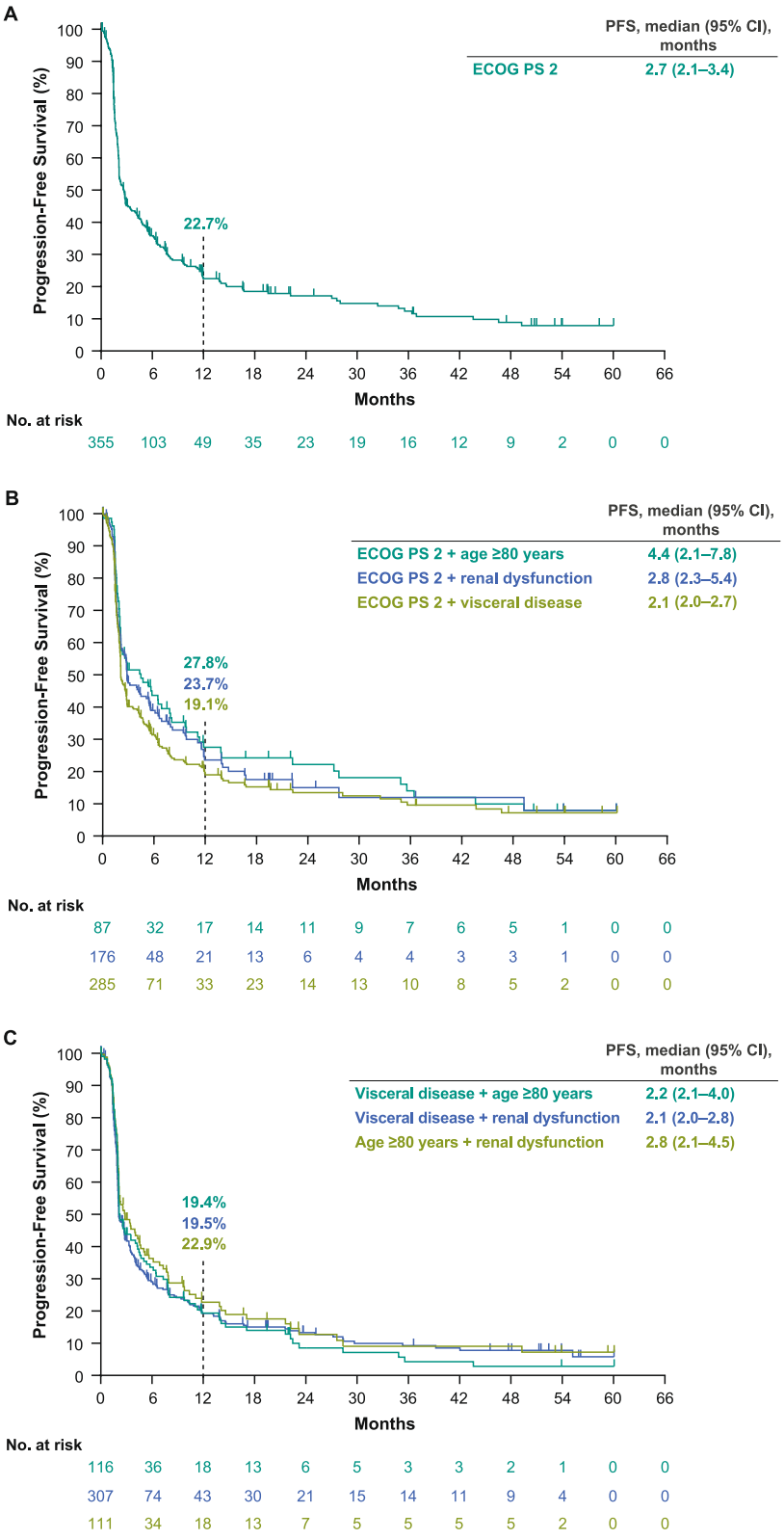

FIGURE 3 Kaplan–Meier estimates of progression-free survival for patients in (A) group 1, (B) group 2, and (C) group 3. ECOG PS indicates Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

At the time of trial development, reports describing criteria to define platinum ineligibility were limited.[13–15] However, several comparator publications are available that evaluate treatment regimens on the basis of different criteria used to define platinum ineligibility. In the randomized phase 2/3 European Organisation for Research and Treatment of Cancer 30986 trial, two carboplatin-

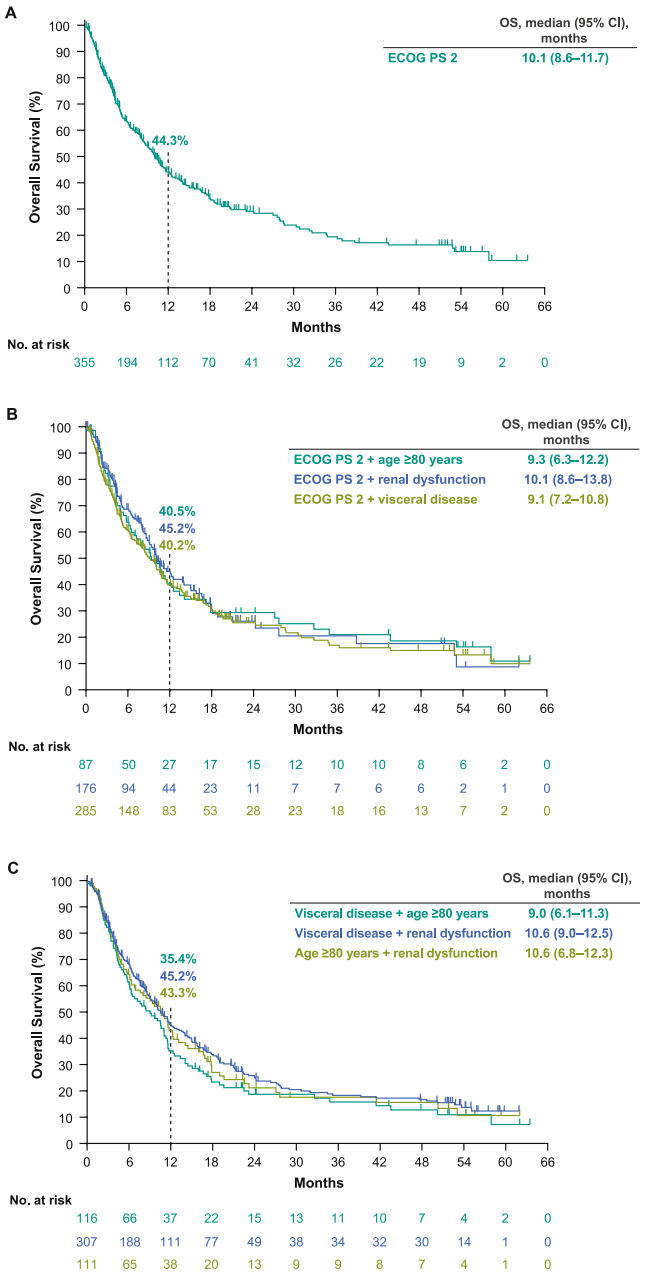

FIGURE 4 Kaplan–Meier estimates of overall survival for patients in (A) group 1, (B) group 2, and (C) group 3. ECOG PS indicates Eastern Cooperative Oncology Group performance status; OS, overall survival.

based regimens were evaluated in a cisplatin-ineligible population defined as having renal dysfunction (a glomerular filtration rate of >30–<60 mL/min) and a World Health Organization PS of 2.[16] Median OS was 8.1 months in the methotrexate/carboplatin/vinblastine arm and 9.3 months in the gemcitabine/carboplatin arm.[16] The proportion of patients with confirmed responses was 21.0% and 36.1%, respectively.[16] In the phase 2 BAYOU trial of durvalumab in combination with olaparib in platinum-ineligible patients with unresectable, stage IV UC, platinum ineligibility was defined as (1) being unfit for carboplatin-based chemotherapy in the opinion of the investigator, and (2) meeting one of the following criteria: a creatinine clearance of <60 mL/min as calculated by the Cockcroft–Gault equation; NCI CTCAE v4.03 grade ≥2 audiometric hearing loss (25 dB in two consecutive wave ranges); NCI CTCAE v4.03 grade ≥2 peripheral neuropathy; NYHA class III heart failure; or an ECOG PS of 2.[6] In the durvalumab plus olaparib group, median PFS was 4.2 months and median OS was 10.2 months; in the durvalumab plus placebo group, median PFS was 3.5 months and median OS was 10.7 months.[6] More patients in the durvalumab plus olaparib group achieved objective responses (n = 22; 28.2%) compared with those in the durvalumab plus placebo group (n = 14; 18.4%).[6]

A retrospective analysis was conducted evaluating the clinical outcomes of first-line PD-1/L1 inhibitors in patients with advanced UC who were considered platinum ineligible.[17] Criteria used to define platinum ineligibility included a creatinine clearance of <30 mL/min and ECOG PS of 3, creatinine clearance of 30–59 mL/min and ECOG PS of 2, and older adults and/or patients with comorbidities. ORR was 27.9%, and median OS was 10.4 months (95% CI, 32–80 months).[17] In a multicenter retrospective study, a prognostic model was developed to determine OS in patients with advanced UC treated with a first-line immune checkpoint inhibitor on the basis of a stepwise, hypothesis-driven approach.[18] An ECOG PS of ≥2, neutrophil:lymphocyte ratio of >5, albumin of <3.5 g/dL, and liver metastasis were identified as negative prognostic factors.[18] Another retrospective study aimed to demonstrate a correlation between performance status and OS in patients with advanced UC receiving an immune checkpoint inhibitor.[19] Median OS was higher in patients with an ECOG PS of 0–1 (median, 15.2 months) compared with an ECOG PS of ≥2 (7.2 months) (hazard ratio, 0.62; p = .01) in the first line but not in subsequent lines of treatment.[19] ORR was similar among performance status scores in each line of treatment.[19] In a subgroup analysis of cisplatin-ineligible older patients with advanced UC in KEYNOTE-052, subgroups were analyzed on the basis of patients aged ≥65 years, ≥75 years, ≥65 years with an ECOG PS of 2, and ≥75 years with an ECOG PS of 2.[20] ORR and complete and partial response rates were similar across subgroups.[20]

Enfortumab vedotin (EV) in combination with pembrolizumab was granted approval as a first-line treatment for patients with advanced UC who are ineligible for cisplatin-containing chemotherapy on the basis of results from the phase 1b/2 EV-103 and phase 3 EV-302 trials.[10,21] In cohort K of EV-103, patients were considered ineligible for cisplatin-based chemotherapy on the basis of at least one of the following: a glomerular filtration rate of ≥30–<60 mL/min, grade 2 hearing loss, ECOG PS of 2, or NYHA class III heart failure. Confirmed ORR was 64.5% (95% CI, 52.7%–75.1%) in patients treated with EV plus pembrolizumab and 45.2% (95% CI, 33.5%–57.3%) with EV alone.[21]

The approval of EV plus pembrolizumab was expanded to patients regardless of cisplatin ineligibility on the basis of the phase 3 EV-302 trial.[10,22] Significant improvements in both PFS and OS were demonstrated in patients treated with EV plus pembrolizumab compared with platinum-based chemotherapy. In the overall population, median PFS was 12.5 months (95% CI, 10.4–16.6 months) in patients treated with EV plus pembrolizumab versus 6.3 months

TABLE 1 Treatment-related adverse event summary by different definitions of platinum ineligibility.

	Group 1, No. (%)	Group 2, No. (%)			Group 3, No. (%)				
	ECOG PS 2 (n = 355)	ECOG PS 2 + age ≥80 years (n = 87)	ECOG PS 2 + renal dysfunction (n = 176)	ECOG PS 2 + visceral disease (n = 285)	Visceral disease + age ≥80 years (n = 116)	Visceral disease + renal dysfunction (n = 308)	Age ≥80 years + renal dysfunction (n = 111)	KEYNOTE-052[9] (n = 370), No. (%)	LEAP-011[12] (n = 242), No. (%)
Any treatment-related AEs	221 (62.3)	61 (70.1)	118 (67.0)	175 (61.4)	85 (73.3)	214 (69.5)	80 (72.1)	249 (67.3)	167 (69.0)
Grade 3–5 treatment-related AEs	81 (22.8)	17 (19.5)	50 (28.4)	60 (21.1)	26 (22.4)	77 (25.0)	25 (22.5)	78 (21.1)	66 (27.3)
Serious treatment-related AEs	34 (9.6)	10 (11.5)	18 (10.2)	24 (8.4)	14 (12.1)	33 (10.7)	12 (10.8)	43 (11.6)	24 (9.9)
Death from treatment-related AEs	1 (0.3)	1 (1.1)	1 (0.6)	0 (0)	1 (0.9)	1 (0.3)	2 (1.8)	1 (0.3)[a]	1 (0.4)[b]
Discontinued treatment because of treatment-related AEs	31 (8.7)	8 (9.2)	16 (9.1)	24 (8.4)	9 (7.8)	28 (9.1)	11 (9.9)	35 (9.5)	22 (9.1)

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]One patient died from myositis in addition to grade 3 thyroiditis, grade 3 hepatitis, grade 3 pneumonia, and grade 4 myocarditis.

[b]One patient died from renal failure.

(95% CI, 6.2–6.5 months) with chemotherapy.[22] Median OS was 31.5 months (25.4 months to not reached) in patients treated with EV plus pembrolizumab versus 16.1 months (95% CI, 13.9–18.3 months) with chemotherapy.[22] Consistent results were observed in subgroups defined by cisplatin eligibility status. Median PFS was 14.6 months in cisplatin-eligible patients and 10.6 months in cisplatin-ineligible patients treated with EV plus pembrolizumab; median OS was 31.5 months and not yet reached, respectively.[22]

In EV-302, patients with ongoing grade ≥2 sensory or motor neuropathy were excluded from enrollment.[22] Although the definition of platinum ineligibility in KEYNOTE-052 and LEAP-011 included grade ≥2 sensory or motor neuropathy, none of the patients in the current analysis had grade ≥2 neuropathy as a reason for platinum ineligibility.

In a recent study, 60 genitourinary medical oncologists were surveyed to determine a consensus definition for platinum ineligibility in advanced UC.[23] The survey included the following clinical parameters: an ECOG PS of ≥2 or ≥3; a creatinine clearance ranging from <10 to <30 mL/min or other; grade ≥2 or ≥3 peripheral neuropathy or other; NYHA class II–IV or none; and a creatinine clearance in patients with an ECOG PS of 2 ranging from <10 to <60 mL/min. On the basis of compiled results from the survey, any patient with metastatic UC meeting at least one of the following criteria should be considered platinum ineligible: an ECOG PS of ≥3, creatinine clearance of <30 mL/min, grade ≥2 peripheral neuropathy, NYHA class III or IV, or a combination of an ECOG PS of 2 and creatinine clearance of <30 mL/min.[23] Appropriately, chronologic age by itself was rejected as a criterion in determining platinum ineligibility, just as it was when cisplatin ineligibility was previously defined by a consensus working group.[1,23] Highly relevant is that our group 2 definition is very similar to the consensus definition derived by Gupta et al.,[23] whereas our group 1 definition was not adopted by the consensus group. Moreover, Gupta et al. acknowledged that other combinations of baseline factors may also define a patient as unfit for platinum-based chemotherapy, and our data from the present analysis indeed suggest that possibility and further provide prospective evidence that pembrolizumab monotherapy is likely to provide clinically meaningful activity across such varied definitions or categorizations, almost all of which may be used when treating patients in real-world practice.

Limitations of our current study include the nature of post hoc exploratory analysis, possible heterogeneity of the population, relatively shorter follow-up of LEAP-011, as well as selection bias and unmeasured confounding. The approval of EV in combination with pembrolizumab in the first-line setting (regardless of cisplatin eligibility) could alter the decision calculus around treatment options for patients who are platinum ineligible. Although the vast majority of patients are anticipated to be eligible to receive EV plus pembrolizumab, a subset of patients who are deemed ineligible for platinum-based chemotherapy and EV plus pembrolizumab may still benefit from pembrolizumab monotherapy. Furthermore, the generalizability of the data from this analysis to other treatment options in patient populations such as those who have received adjuvant nivolumab after radical cystectomy or pembrolizumab monotherapy for

non–muscle-invasive bladder cancer is unknown. Additionally, patients who are considered ineligible for platinum-based chemotherapy in the context of clinical trials are still relatively fit compared with patients in general practice who are ineligible for platinum-based chemotherapy, such as those with an ECOG PS of 2 and/or certain medical comorbidities. These patients are often excluded from or ineligible for clinical trials, and therefore it is unclear whether findings from this analysis would be generalizable to these patient populations in general practice.

In summary, ORR and survival of frontline pembrolizumab monotherapy were clinically meaningful and generally consistent across groups of patients with advanced UC categorized as potentially ineligible for platinum-based chemotherapy, regardless of the variable definitions used. Results from this exploratory post hoc analysis suggest that pembrolizumab monotherapy remains a feasible and effective treatment option in patients ineligible for platinum-based chemotherapy and support its use in select patients with advanced/unresectable UC in the frontline setting.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc (Rahway, New Jersey, USA) (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses

and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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REFERENCES

1. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. *J Clin Oncol*. 2011;29(17):2432-2438. doi:10.1200/jco.2011.34.8433
2. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer*. 2006;107(3):506-513. doi:10.1002/cncr.22031
3. Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol*. 2012;23(2):406-410. doi:10.1093/annonc/mdr156
4. Sonpavde G, Galsky MD, Latini D, Chen GJ. Cisplatin-ineligible and chemotherapy-ineligible patients should be the focus of new drug development in patients with advanced bladder cancer. *Clin Genitourin Cancer*. 2014;12(2):71-73. doi:10.1016/j.clgc.2013.11.016
5. Bellmunt J, Valderrama BP. *Treatment of metastatic urothelial cancer of the bladder and urinary tract*. UpToDate Inc. Accessed March 15, 2023. https://www.uptodate.com/contents/treatment-of-metastatic-urothelial-cancer-of-the-bladder-and-urinary-tract/print#H1272429025
6. Rosenberg JE, Park SH, Kozlov V, et al. Durvalumab plus olaparib in previously untreated, platinum-ineligible patients with metastatic urothelial carcinoma: a multicenter, randomized, phase II trial (BAYOU). *J Clin Oncol*. 2023;41(1):43-53. doi:10.1200/jco.22.00205
7. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(11):1483-1492. doi:10.1016/s1470-2045(17)30616-2
8. Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. *J Clin Oncol*. 2020;38(23):2658-2666. doi:10.1200/JCO.19.01213
9. Balar AV, Castellano DE, Grivas P, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Ann Oncol*. 2023;34(3):289-299. doi:10.1016/j.annonc.2022.11.012
10. *KEYTRUDA® (Pembrolizumab) Injection, for Intravenous Use*. Merck & Co Inc. Accessed October 11, 2024. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
11. *KEYTRUDA 25 mg/mL Concentrate for Solution for Infusion*. Merck Sharp & Dohme BV. https://www.medicines.org.uk/emc/product/2498/smpc
12. Matsubara N, de Wit R, Balar AV, et al. Pembrolizumab with or without lenvatinib as first-line therapy for patients with advanced urothelial carcinoma (LEAP-011): a phase 3, randomized, double-blind trial. *Eur Urol*. 2024;85(3):229-238. doi:10.1016/j.eururo.2023.08.012
13. Bamias A, Lainakis G, Kastritis E, et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. *Oncology*. 2007;73(5-6):290-297. doi:10.1159/000132394
14. Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Saito T. Clinical results for bladder cancer treated by radiotherapy without concurrent standard chemotherapy. *Anticancer Res*. 2016;36(10):5519-5525. doi:10.21873/anticanres.11134
15. Vaishampayan U. Systemic therapy of advanced urothelial cancer. *Curr Treat Options Oncol*. 2009;10(3-4):256-266. doi:10.1007/s11864-009-0101-9
16. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012;30(2):191-199. doi:10.1200/jco.2011.37.3571
17. Pond GR, Agarwal A, Ornstein M, et al. Clinical outcomes of platinum-ineligible patients with advanced urothelial carcinoma treated with first-line PD1/L1 inhibitors. *Clin Genitourin Cancer*. 2021;19(5):425-433. doi:10.1016/j.clgc.2021.04.008
18. Khaki AR, Li A, Diamantopoulos LN, et al. A new prognostic model in patients with advanced urothelial carcinoma treated with first-line immune checkpoint inhibitors. *Eur Urol Oncol*. 2021;4(3):464-472. doi:10.1016/j.euo.2020.12.006
19. Khaki AR, Li A, Diamantopoulos LN, et al. Impact of performance status on treatment outcomes: a real-world study of advanced urothelial cancer treated with immune checkpoint inhibitors. *Cancer*. 2020;126(6):1208-1216. doi:10.1002/cncr.32645
20. Grivas P, Plimack ER, Balar AV, et al. Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer (KEYNOTE-052): outcomes in older patients by age and performance status. *Eur Urol Oncol*. 2020;3(3):351-359. doi:10.1016/j.euo.2020.02.009
21. O'Donnell PH, Milowsky MI, Petrylak DP, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. *J Clin Oncol*. 2023;41(25):4107-4117. doi:10.1200/jco.22.02887
22. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390(10):875-888. doi:10.1056/NEJMoa2312117
23. Gupta S, Bellmunt J, Plimack ER, et al. Defining "platinum-ineligible" patients with metastatic urothelial cancer (mUC). *J Clin Oncol*. 2022;40(suppl 16):4577. doi:10.1200/JCO.2022.40.16_suppl.4577

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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