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Post hoc analysis of pembrolizumab efficacy in potentially platinum-ineligible patients with advanced urothelial carcinoma enrolled in KEYNOTE-052 and LEAP-011

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[a]At the time the study was conducted.

Background

- Platinum-based chemotherapy is a recommended first-line therapy for advanced urothelial carcinoma (UC), but many patients are ineligible because of medical comorbidities[1]
  - There is no standard definition of platinum ineligibility, so treatment decisions are currently made based on clinical judgment[1,2]
- KEYNOTE-052 (NCT02335424) was a phase 2 trial of first-line pembrolizumab monotherapy in patients with advanced UC who were ineligible for cisplatin-based chemotherapy, which included patients who were potentially ineligible for any platinum-based chemotherapy[3-5]
  - After a median follow-up of 56.3 months, the objective response rate (ORR) was 28.9% (95% CI, 24.3-33.8)[5]
  - Median overall survival (OS) was 11.3 months (95% CI, 9.7-13.1), and median duration of response (DOR) was 33.4 months (range, 1.4+ to 60.7+)[5]
- Based on the results of KEYNOTE-052, first-line pembrolizumab monotherapy is now a standard-of-care option for platinum-ineligible patients with advanced UC in the United States[6] and for cisplatin-ineligible patients with PD-L1 combined positive score (CPS) ≥10 in Europe[7]
- LEAP-011 (NCT03898180) is a phase 3 randomized trial of first-line pembrolizumab + lenvatinib versus pembrolizumab + placebo in patients with advanced UC who were considered potentially ineligible for platinum-based chemotherapy[8]
  - The benefit-to-risk ratio for pembrolizumab + lenvatinib was not considered positive, and enrollment was stopped based on the recommendation of an external data monitoring committee
  - ORR was 28.9% (95% CI, 23.3-35.1) and DOR was 19.3 months (range, 1.4+ to 21.9+) in the pembrolizumab + placebo arm
  - Median OS was 12.9 months (95% CI, 9.8-17.8)

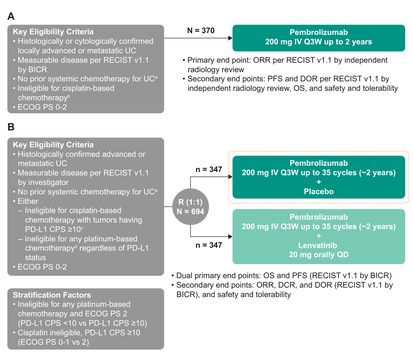
Objective

- To evaluate the efficacy of pembrolizumab monotherapy in UC based on the definition of platinum ineligibility

Methods

- This post hoc analysis of KEYNOTE-052 and LEAP-011 included an extensive search of the literature to identify criteria commonly used by clinicians for identifying patients who may be intolerant to or at higher risk of toxicity with platinum-based chemotherapy ("potentially platinum ineligible")[1,2]
  - Eastern Cooperative Oncology Group performance status (ECOG PS) 2
  - Renal dysfunction (defined as glomerular filtration rate <60 mL/min)
  - Visceral disease
  - Age ≥80 years
- Subgroups of patients with combinations of these criteria were evaluated
  - ECOG PS 2
  - ECOG PS 2 + age ≥80 years
  - ECOG PS 2 + renal dysfunction
  - ECOG PS 2 + visceral disease
  - Age ≥80 years + renal dysfunction
  - Visceral disease + age ≥80 years
  - Visceral disease + renal dysfunction
- Patients from KEYNOTE-052 and from the pembrolizumab + placebo arm of LEAP-011 were pooled for this analysis

Figure 1. Study design of (A) KEYNOTE-052[3,4] and (B) LEAP-011[8]



BICR, blinded independent central review; DCR, disease control rate; IV, intravenously; PFS, progression-free survival; Q3W, every 3 weeks; QD, daily; R, randomization.

[a]Patients who received adjuvant/neoadjuvant platinum-based chemotherapy before or after radical cystectomy and experienced recurrence >12 months after completion were eligible to participate.
[b]Defined as at least 1 of the following: ECOG PS 2, creatinine clearance (CrCl) ≥30 to <60 mL/min, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) grade ≥2 audiometric hearing loss, CTCAE v4.0 grade ≥2 peripheral neuropathy, or New York Heart Association class III or greater heart failure.
[c]CPS was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.
[d]Defined as ECOG PS 2 and at least 1 of the following: documented visceral metastatic disease, CrCl ≥30 to ≤60 mL/min, CTCAE v4.0 grade ≥2 audiometric hearing loss, CTCAE v4.0 grade ≥2 peripheral neuropathy, or other reason identified on the case report form.

Statistical analysis

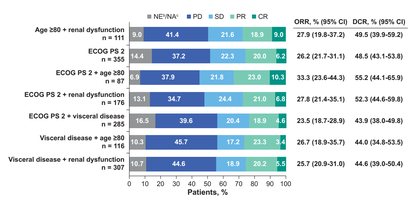
- The database cutoff dates for KEYNOTE-052 and LEAP-011 were September 26, 2020, and July 26, 2021, respectively
- In KEYNOTE-052, efficacy and safety were analyzed in all patients who received ≥1 dose of study treatment (all patients as treated)
- In LEAP-011, efficacy was analyzed in all randomly assigned patients (intention-to-treat) and safety was analyzed in all patients as treated
- PFS, OS, and DOR medians and 95% CIs were estimated using the Kaplan-Meier method
- ORR and the corresponding 95% CIs were assessed using the binomial exact confidence interval method

Results

- This pooled analysis included patients treated with pembrolizumab monotherapy from KEYNOTE-052 (N = 370) and pembrolizumab + placebo from LEAP-011 (n = 242) who met at least 1 of the potential criteria for platinum ineligibility
- Median time from enrollment to database cutoff was 56.3 months (range, 51.2-65.3) in KEYNOTE-052
- Median time from randomization to death or database cutoff was 7.0 months (range, 0.2-25.0) in the pembrolizumab + placebo arm of LEAP-011

Efficacy

Figure 2. ORR, DCR, and best response by platinum ineligibility criteria[a]



CR, complete response; NE/NA, nonevaluable/no assessment; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Values may not sum to 100 because of rounding.
[b]Includes patients with insufficient data for assessment of response per RECIST v1.1.
[c]Includes patients without postbaseline assessment on the data cutoff date.

Table 1. DOR by platinum ineligibility criteria

	Age ≥80 y + renal dysfunction n = 111	ECOG PS 2 n = 355	ECOG PS 2 + age ≥80 y n = 87	ECOG PS 2 + renal dysfunction n = 176	ECOG PS 2 + visceral disease n = 285	Visceral disease + age ≥80 y n = 116	Visceral disease + renal dysfunction n = 307
DOR, median (range), months	19.3 (1.4+ to 57.3+)	30.1 (1.4+ to 56.4+)	33.4 (1.4+ to 51.5+)	14.5 (1.4+ to 51.5+)	25.9 (2.7+ to 56.4+)	12.5 (2.8 to 51.5+)	19.3 (1.4+ to 54.2+)
Response lasting ≥48 months	27.8%	33.4%	28.6%	27.5%	33.8%	12.3%	30.7%

Figure 3. Kaplan-Meier estimates of (A) OS and (B) PFS for patients with ECOG PS 2

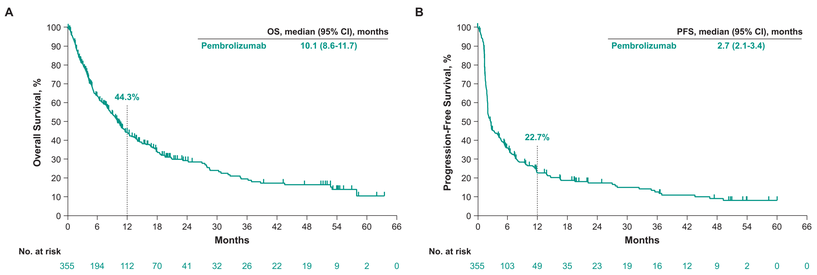


Figure 4. Kaplan-Meier estimates of (A) OS and (B) PFS for patients with ECOG PS 2 and visceral disease

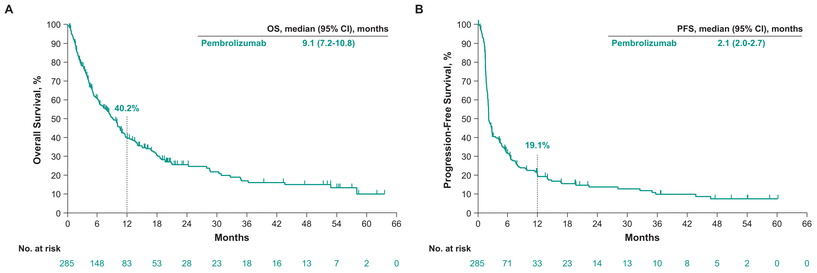


Figure 5. Kaplan-Meier estimates of (A) OS and (B) PFS for patients with visceral disease and renal dysfunction

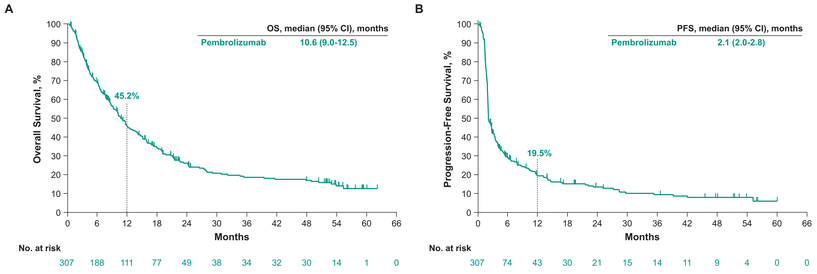


Table 2. OS and PFS by platinum ineligibility criteria

	Age ≥80 y + renal dysfunction n = 111	ECOG PS 2 n = 355	ECOG PS 2 + age ≥80 y n = 87	ECOG PS 2 + renal dysfunction n = 176	ECOG PS 2 + visceral disease n = 285	Visceral disease + age ≥80 y n = 116	Visceral disease + renal dysfunction n = 307
OS, median (95% CI), months	10.6 (6.8-12.3)	10.1 (8.6-11.7)	9.3 (6.3-12.2)	10.1 (8.6-13.8)	9.1 (7.2-10.8)	9.0 (6.1-11.3)	10.6 (9.0-12.5)
12-month OS	43.3%	44.3%	40.5%	45.2%	40.2%	35.4%	45.2%
PFS, median (95% CI), months	2.8 (2.1-4.5)	2.7 (2.1-3.4)	4.4 (2.1-7.8)	2.8 (2.3-5.4)	2.1 (2.0-2.7)	2.2 (2.1-4.0)	2.1 (2.0-2.8)
12-month PFS	22.9%	22.7%	27.8%	23.7%	19.1%	19.4%	19.5%

Safety

Table 3. Treatment-related AE summary by platinum ineligibility criteria

	Age ≥80 y + renal dysfunction n = 111	ECOG PS 2 n = 355	ECOG PS 2 + age ≥80 y n = 87	ECOG PS 2 + renal dysfunction n = 176	ECOG PS 2 + visceral disease n = 285	Visceral disease + age ≥80 y n = 116	Visceral disease + renal dysfunction n = 308	KEYNOTE-052[5] n = 370	LEAP-011[8] n = 242
Any treatment-related AEs	80 (72.1)	221 (62.3)	61 (70.1)	118 (67.0)	175 (61.4)	85 (73.3)	214 (69.5)	249 (67.3)	167 (69.0)
Grade 3-5 treatment-related AEs	25 (22.5)	81 (22.8)	17 (19.5)	50 (28.4)	60 (21.1)	26 (22.4)	77 (25.0)	78 (21.1)	66 (27.3)
Serious treatment-related AEs	12 (10.8)	34 (9.6)	10 (11.5)	18 (10.2)	24 (8.4)	14 (12.1)	33 (10.7)	43 (11.6)	24 (9.9)
Death from treatment-related AEs	2 (1.8)	1 (0.3)	1 (1.1)	1 (0.6)	0 (0)	1 (0.9)	1 (0.3)	1 (0.3)[a]	1 (0.4)[b]
Discontinued treatment because of treatment-related AEs	11 (9.9)	31 (8.7)	8 (9.2)	16 (9.1)	24 (8.4)	9 (7.8)	28 (9.1)	35 (9.5)	22 (9.1)

Values are n (%).

[a]1 patient died from myositis in addition to grade 3 thyroiditis, grade 3 hepatitis, grade 3 pneumonia, and grade 4 myocarditis.
[b]1 patient died from renal failure.

Conclusions

- In this post hoc exploratory analysis, durable responses to pembrolizumab monotherapy were observed regardless of the criteria used to define platinum ineligibility
- Median OS was generally consistent among subgroups and was similar to the overall patient population in each study

References

1. Galsky M et al. *J Clin Oncol.* 2011;29:2432-2438.
2. Gupta S et al. *J Clin Oncol.* 2022;40. Abstract 4577.
3. Balar AV et al. *Lancet Oncol.* 2017;18:1483-1492.
4. Vuky J et al. *J Clin Oncol.* 2020;38:2658-2666.
5. O'Donnell PH et al. *J Clin Oncol.* 2021;39. Abstract 4508.
6. KEYTRUDA® (pembrolizumab) injection, for intravenous use. 8/2022. Merck Sharp & Dohme, LLC: Rahway, NJ, USA; 2022.
7. Keytruda 25 mg/mL concentrate for solution for infusion (summary of product characteristics). Haarlem, Netherlands: Merck Sharp & Dohme B.V.; 2022.
8. Loriot Y et al. *J Clin Oncol.* 2022;40. Abstract 432.

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