Pembrolizumab Versus Investigator's Choice of Paclitaxel, Docetaxel, or Vinflunine in Recurrent Advanced Urothelial Cancer: 5-Year Follow-Up From the Phase 3 KEYNOTE-045 Trial

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Background

- Survival rates are low for patients with metastatic urothelial carcinoma (UC) after disease progression with platinum-based chemotherapy (platinum-resistant or platinum-refractory UC), but use of immune checkpoint inhibitors as second-line therapy shows improved outcomes[1]
- The PD-1 inhibitor pembrolizumab is the only second-line therapy recommended for use after platinum-based chemotherapy, based on the highest level of evidence (category 1)[1]
- KEYNOTE-045 (NCT02256436) was an open-label, phase 3 trial to compare the safety and efficacy of pembrolizumab monotherapy with that of chemotherapy in patients with advanced UC that progressed after platinum-based chemotherapy[2]
  - Prior results from KEYNOTE-045 showed pembrolizumab significantly prolonged overall survival (OS) with a lower rate of adverse events (AEs) than with chemotherapy,[2] and these benefits were maintained after 2 years[3] and 3 years[4] of follow-up

Objective

- To compare the efficacy and safety of pembrolizumab monotherapy with that of chemotherapy as second-line therapy in patients with advanced UC, with up to 5 years of follow-up after the last patient was randomly assigned to treatment

Methods

Figure 1. Study Design

Key Eligibility Criteria
- UC of the renal pelvis, ureter, bladder, or urethra
- Predominantly transitional cell histology
- PD after 1-2 lines of platinum-based chemotherapy or recurrence <12 months after perioperative platinum-based therapy
- ECOG PS 0-2
- Measurable disease per RECIST v1.1
- Tumor sample for biomarker assessment

Stratification Factors
- ECOG PS (0 or 1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 months)

R (1:1)
N = 542

n = 270 → **Pembrolizumab 200 mg IV Q3W up to 2 years**

n = 272 → **Paclitaxel 175 mg/m² Q3W or Docetaxel 75 mg/m² Q3W or Vinflunine 320 mg/m² Q3W**

- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded independent central review

CPS, combined positive score; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; IV, intravenous; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization.
[a]In total ITT population and in patients with a CPS ≥10. CPS is the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

- Analysis populations
  - Efficacy: all patients randomly assigned to receive treatment (ITT)
  - Safety: all randomly assigned patients who received ≥1 dose of study treatment (all patients as treated [APaT])
- Statistical analysis
  - PFS, OS, and DOR were estimated using the Kaplan-Meier method, as previously described[2]
  - Differences in ORR were calculated using the stratified Miettinen and Nurminen method[2,5]

Results

- Median time from randomization to database cutoff of October 1, 2020: 62.9 months (range, 58.6-70.9 months)

Figure 2. Patient Disposition

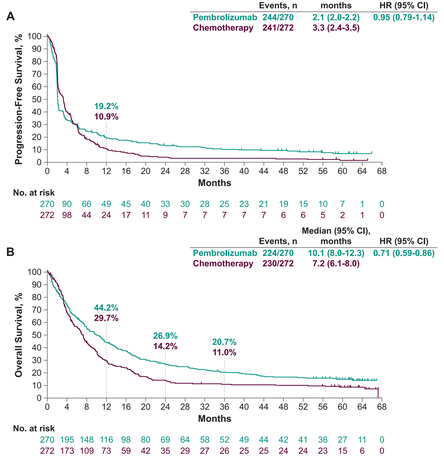
542 patients randomly assigned

Pembrolizumab 270 assigned	Chemotherapy 272 assigned	ITT (*efficacy population*)
266 treated	255 treated	APaT (*safety population*)
• 0 ongoing • 25 completed 2 years • 241 discontinued – 191 PD[a] – 29 AE – 11 CR – 6 physician decision – 3 withdrawal of consent – 1 protocol violation	• 0 ongoing • 0 completed 2 years[b] • 255 discontinued – 159 PD[a] – 36 AE – 1 CR – 28 physician decision – 29 withdrawal of consent – 2 excluded medication	

CR, complete response.
[a]Includes clinical PD.
[b]Time on chemotherapy was not limited.

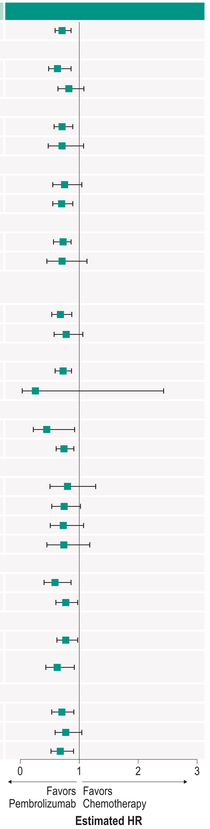
Efficacy

Figure 3. Kaplan-Meier Estimates of (A) Progression-Free Survival and (B) Overall Survival (ITT)



HR, hazard ratio.

Figure 4. Overall Survival by Patient Subgroups



	n/N	HR (95% CI)
Overall	454/542	0.71 (0.59-0.86)
Age		
<65 years	207/230	0.64 (0.48-0.86)
≥65 years	247/312	0.83 (0.64-1.08)
Prior platinum therapy		
Cisplatin	340/413	0.71 (0.57-0.89)
Carboplatin	111/126	0.71 (0.47-1.07)
Liver metastases		
Present	169/186	0.76 (0.55-1.04)
Not present	285/356	0.70 (0.55-0.89)
Hemoglobin		
≥10 g/dL	363/444	0.70 (0.56-0.86)
<10 g/dL	83/87	0.71 (0.45-1.13)
Time from most recent chemotherapy		
≥3 months	276/365	0.68 (0.53-0.87)
<3 months	178/207	0.78 (0.57-1.06)
ECOG PS		
0 or 1	439/526	0.72 (0.59-0.87)
2	6/7	0.25 (0.03-2.43)
Visceral disease		
Lymph node only	44/65	0.45 (0.22-0.92)
Visceral disease	410/476	0.74 (0.61-0.91)
Risk score		
0	71/99	0.80 (0.50-1.28)
1	157/194	0.74 (0.53-1.02)
2	132/146	0.73 (0.51-1.07)
3 or 4	84/90	0.73 (0.45-1.18)
PD-L1 CPS		
≥10	132/164	0.59 (0.40-0.86)
<10	310/362	0.77 (0.61-0.97)
Histology		
Transitional cell	325/385	0.77 (0.62-0.97)
Mixed transitional/ nontransitional	127/155	0.63 (0.43-0.92)
Chemotherapy choice		
Paclitaxel	300/350	0.70 (0.53-0.91)
Docetaxel	288/350	0.78 (0.59-1.04)
Vinflunine	297/353	0.68 (0.52-0.90)

Table 1. Confirmed Objective Response Rate per RECIST v1.1 by Central Radiology Assessment

	Pembrolizumab ITT n = 270	Chemotherapy ITT n = 272
ORR, % (95% CI)	21.9 (17.1-27.3)	11.0 (7.6-15.4)
Best response, n (%)		
CR	27 (10.0)	8 (2.9)
PR	32 (11.9)	22 (8.1)
SD	47 (17.4)	92 (33.8)
PD	129 (47.8)	90 (33.1)
NA[a]	31 (11.5)	51 (18.8)
NE[b]	4 (1.5)	9 (3.3)

NA, no assessment; NE, not evaluable; PR, partial response; SD, stable disease.
[a]Patients had postbaseline imaging, and best overall response was NE per RECIST v1.1.
[b]Patients had no postbaseline imaging.

Figure 5. Kaplan-Meier Estimates of Duration of Response (ITT)

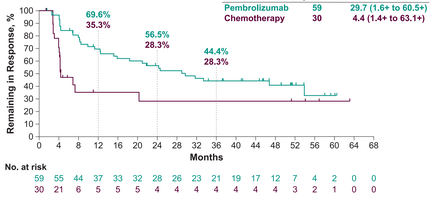
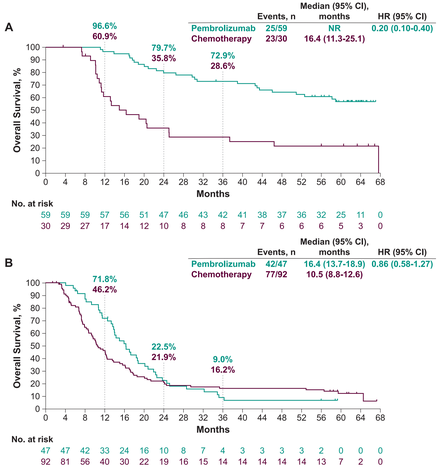


Figure 6. Overall Survival by Best Response for Patients With (A) Complete Response/Partial Response and (B) Stable Disease



NR, not reached.

Safety
- Safety was consistent with that of previously reported results[2-4]

Conclusions

- After at least 5 years of follow-up, pembrolizumab monotherapy continued to show improved OS, ORR, and DOR compared with investigator's choice of chemotherapy in patients with advanced platinum-resistant or platinum-refractory UC
  - OS: 10.1 months versus 7.2 months
  - ORR: 21.9% versus 11.0%
  - DOR: 29.7 months versus 4.4 months
- Safety was consistent with that of previous reports
- These data are consistent with the primary analysis and with the 2- and 3-year follow-up analyses[2-4] that led to the approval of pembrolizumab for treatment of advanced platinum-resistant or platinum-refractory UC irrespective of PD-L1 status

References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): bladder cancer (Version 3.2021). April 22, 2021. Accessed May 2, 2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
2. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.
3. Fradet Y et al. *Ann Oncol*. 2019;30:970-976.
4. Necchi A et al. *Ann Oncol*. 2019;30(suppl_5):V366-V367.
5. Miettinen O, Nurminen M. *Stat Med*. 1985;4:213-226.

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