Impact of Histology on Clinical Outcomes of Pembrolizumab Monotherapy in Patients With Advanced or Metastatic Urothelial Carcinoma in the Phase 3 KEYNOTE-045 and KEYNOTE-361 Trials

Patrizia Giannatempo,[1] Jean-Pascal Machiels,[2] Naoto Sassa,[3] Jose Angel Arranz,[4] Yasuhisa Fujii,[5] Wen-Pin Su,[6] Bhumsuk Keam,[7] Stéphane Culine,[8] Ying-Chun Shen,[9] José Muñoz Langa,[10] David Sarid,[11] Maureen Aarts,[12] Fabio Calabrò,[13] Eli Rosenbaum,[14] Blanca Homet Moreno,[15] Abhishek Bavle,[15] Jin Z. Xu,[15] Sun Young Rha[16]

Abstract

The impact of histology on outcomes in urothelial carcinoma (UC) remains unclear. This posthoc analysis evaluated patients from KEYNOTE-045 and KEYNOTE-361 with pure transitional cell carcinoma (TCC) or mixed predominant TCC. Efficacy and safety outcomes with pembrolizumab monotherapy were generally consistent for patients with advanced or metastatic UC in the KEYNOTE-045 and KEYNOTE-361 studies regardless of histology.

Introduction: A post hoc analysis of efficacy and safety outcomes with pembrolizumab monotherapy was conducted in patients with advanced or metastatic urothelial carcinoma (UC) with pure transitional cell carcinoma (TCC) or mixed predominant TCC histology enrolled in the phase 3 KEYNOTE-045 and KEYNOTE-361 studies. **Methods:** Adults with platinum-refractory advanced or metastatic UC who received pembrolizumab monotherapy in KEYNOTE-045 and adults with advanced or metastatic UC and no prior systemic chemotherapy who received pembrolizumab monotherapy in KEYNOTE-361 were analyzed separately. Pembrolizumab 200 mg was administered intravenously every 3 weeks for ≤2 years. Histology was assessed by investigator. End points included objective response rate (ORR), progression-free survival, and duration of response per RECIST v1.1 by central radiology assessment, as well as overall survival (OS) and safety. **Results:** In KEYNOTE-045, 268 patients had known histology (pure TCC: 186; mixed predominant

Abbreviations: AE, adverse event; BICR, blinded independent central review; CPS, combined positive score; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NCI, National Cancer Institute; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TCC, transitional cell carcinoma; UC, urothelial carcinoma.

[1]Genitourinary Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[2]Institut Roi Albert II, Cliniques Universitaires Saint-Luc and Pôle Oncologie, Institut de Recherche Clinique et Expérimentale, UCLouvain, Bruxelles, Belgium
[3]Aichi Medical University, Nagakute, Japan
[4]Hospital General Universitario Gregorio Marañón, Madrid, Spain
[5]Institute of Science Tokyo Hospital, Tokyo, Japan
[6]Institute of Clinical Medicine & National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[7]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea
[8]Department of Medical Oncology, AP-HP, Hôpital Saint-Louis, Paris Cité University, Paris, France
[9]National Taiwan University Hospital, Taipei, Taiwan
[10]Hospital Universitario Y Politécnico La Fe, Valencia, Spain
[11]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[12]Maastricht University Medical Centre, GROW School for Oncology and Reproduction, Maastricht, Netherlands
[13]IRCCS National Cancer Institute Regina Elena, Rome, Italy
[14]Institute of Oncology Clinical Trials Department, Rabin Medical Center, Petah Tikva, Israel
[15]Merck & Co., Inc., Rahway, NJ
[16]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea

Submitted: Sep 6, 2024; Revised: Oct 31, 2024; Accepted: Nov 11, 2024; Epub: 15 November 2024

Address for correspondence: Patrizia Giannatempo, MD, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, 1, 20133 Milan, Italy.
E-mail contact: Patrizia.Giannatempo@istitutotumori.mi.it

https://doi.org/10.1016/j.clgc.2024.102273

TCC: 82). At data cutoff (October 1, 2020), median follow up was 62.9 months (range, 59.0-70.9). For pure TCC, confirmed ORR was 21.0% (95% CI, 15.4-27.5); median OS was 9.7 months (95% CI, 7.5-11.8). For mixed predominant TCC, confirmed ORR was 24.4% (95% CI, 15.6-35.1); median OS was 11.6 months (95% CI, 7.4-16.4). In KEYNOTE-361, 307 patients had known histology (pure TCC: 280; mixed predominant TCC: 27). At data cutoff (April 29, 2020), median follow-up was 32.5 months (range, 22.0-42.3). For pure TCC, confirmed ORR was 29.3% (95% CI, 24.0-35.0); median OS was 14.8 months (95% CI, 11.8-17.9). For mixed predominant TCC, confirmed ORR was 40.7% (95% CI, 22.4-61.2); median OS was 16.2 months (95% CI, 5.5-NR). Grade 3-5 treatment-related adverse events occurred at similar rates for treated patients in both studies. **Conclusion:** In this post hoc analysis, efficacy and safety outcomes with pembrolizumab monotherapy were generally consistent for patients with advanced or metastatic UC in KEYNOTE-045 and KEYNOTE-361 studies between histology subgroups. **Clinical Trial Registration:** ClinicalTrials.gov, KEYNOTE-045 (NCT02256436) and KEYNOTE-361 (NCT02853305)

Clinical Genitourinary Cancer, Vol. 23, No. 2, 102273
Keywords: Immunotherapy, Platinum-refractory, Post hoc, PD-1 inhibitor, Transitional cell carcinoma

Introduction

Pure transitional cell carcinoma (TCC) is the predominant histology of urothelial carcinoma (UC) in Western countries.[1,2] Variant histology (also referred to as UC with divergent differentiation) is divided into urothelial and nonurothelial subtypes.[1,3] Histologic subtypes of UC include nested, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid/signet ring cell, sarcomatoid, clear cell, and mixed.[3,4] Nonurothelial variants include neuroendocrine tumors, adenocarcinoma, and pure squamous cell carcinoma.[3,4] Generally, variant histology is associated with higher-stage disease at diagnosis, increased risk of recurrence, and reduced overall survival (OS).[4,5]

Immunotherapy is a crucial part of treatment for advanced or metastatic UC.[6] Clinical trials have primarily enrolled patients with pure TCC because it is the most common type of UC histology, and the effect of histology on the efficacy of immunotherapy for patients with UC remains unclear. To explore the impact of histology on the efficacy and safety of pembrolizumab monotherapy for advanced UC, we performed a post hoc analysis using data from the pembrolizumab monotherapy arms of the phase 3 KEYNOTE-045 and KEYNOTE-361 trials to evaluate efficacy and safety by histology in patients with advanced UC. KEYNOTE-045 was a randomized, active-controlled, multisite, open-label, phase 3 clinical trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in patients with recurrent or progressive advanced or metastatic UC.[7,8] KEYNOTE-361 was a randomized, controlled, open-label, phase 3 clinical trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy alone in patients with advanced or metastatic UC. Patients in both studies were required to have TCC as the predominant histology, but both pure TCC and mixed TCC/non-TCC histologies were allowed.

Materials and Methods

Study Design, Patients, and Treatment

Detailed methodology for KEYNOTE-045 has been described elsewhere.[7,9] Briefly, eligible patients were adults aged ≥18 years with locally advanced/unresectable or metastatic UC of the renal pelvis, ureter, bladder, or urethra with TCC as the predominant histology (either pure or mixed). Eligible patients had disease progression or recurrence within 12 months after first-line or perioperative platinum-based chemotherapy treatment, had measurable disease per RECIST v1.1, and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2. Patients were randomly assigned (1:1) to receive pembrolizumab 200 mg intravenously (IV) every 3 weeks or investigator's choice of chemotherapy until disease progression per RECIST v1.1 by investigator, unacceptable toxicity, withdrawal of consent, investigator decision, or completion of 2 years of pembrolizumab.

Detailed methodology for KEYNOTE-361 has also been described elsewhere.[10] Briefly, eligible patients were adults aged ≥18 years with unresectable locally advanced or metastatic UC of the renal pelvis, ureter, bladder, or urethra with TCC as the predominant histology (either pure or mixed). Eligible patients had no previous systemic chemotherapy for advanced or metastatic UC, had measurable disease per RECIST v1.1 blinded independent central review (BICR), and an ECOG PS score of 0-2. Enrolled patients were randomly assigned (1:1:1) to receive pembrolizumab 200 mg IV every 3 weeks, pembrolizumab plus platinum-based chemotherapy, or platinum-based chemotherapy alone until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, investigator decision, or completion of 2 years of pembrolizumab. Sex, race, and ethnicity were self-reported.

Both trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Approval of the protocols and their amendments were granted by the appropriate institutional review board or ethics committee at each participating institution. All patients provided written informed consent prior to enrollment.

Outcomes and Assessments

End points for this post hoc analysis were objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1 by BICR, as well as OS and safety with pembrolizumab monotherapy across histology subgroups in

KEYNOTE-045 and KEYNOTE-361. Efficacy end points were analyzed in the intention-to-treat population (all randomly assigned patients), and safety was analyzed in the all-patients-as-treated population (all randomly assigned patients who received ≥1 dose of treatment) in the pembrolizumab monotherapy arms of the 2 studies. UC histology was assessed by the investigator at enrollment.

Tumor imaging by computed tomography or magnetic resonance imaging occurred every 12 weeks in KEYNOTE-045 and every 9 weeks from randomization for the first 54 weeks, then every 12 weeks thereafter in KEYNOTE-361. Adverse events (AEs) were monitored for up to 30 days after treatment cessation or discontinuation (90 days for serious AEs) and graded in severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.

Statistical Analysis

Differences in ORR and their 95% CIs were compared using the stratified Miettinen and Nurminen method. DOR, OS, and PFS were estimated using the nonparametric Kaplan-Meier method and were summarized descriptively. No formal hypothesis testing was performed. The data cutoff date was October 1, 2020, for KEYNOTE-045 and April 29, 2020, for KEYNOTE-361.

A sensitivity analysis was conducted to evaluate the impact of histology subgroup on OS and PFS, controlling for major prognostic factors. Cox proportional hazards models were used to examine the hazard ratio between the two histology subgroups in terms of OS and PFS, adjusting for major prognostic factors, including sites of metastasis and ECOG PS. The analysis for KEYNOTE-045 used liver metastases, ECOG PS, visceral disease, brain metastases, prior platinum therapy, prior cystectomy or nephrectomy, time from last prior chemotherapy, site of primary tumor, baseline hemoglobin level, PD-L1 CPS status, risk score, and metastatic staging as prognostic factors. The analysis for KEYNOTE-361 used liver metastases, ECOG PS, visceral disease, site of primary tumor, PD-L1 CPS status, actual cisplatin versus carboplatin usage, and metastatic staging as prognostic factors.

Results

The present analysis includes 268 patients from the pembrolizumab monotherapy group of KEYNOTE-045 (pure TCC: 186; mixed predominant TCC: 82), and 307 patients from the pembrolizumab monotherapy group of KEYNOTE-361 (pure TCC: 280; mixed predominant TCC: 27) who had known histology status. Baseline characteristics were similar between histologies for both studies, although the percentage of patients with programmed cell death ligand 1 combined positive score ≥10 tumors was numerically higher in the mixed predominant subgroup (Table 1). Furthermore, more patients in KEYNOTE-045 had liver metastases than in KEYNOTE-361. The median follow-up (defined as time from randomization to data cutoff) was 62.9 months (range, 59.0-70.9) for KEYNOTE-045 and 32.5 months (range, 22.0-42.3) for KEYNOTE-361. For KEYNOTE-045, 25 patients with pure TCC (n = 18; 9.8%) and mixed predominant TCC (n = 7; 8.6%) had completed 35 cycles of pembrolizumab; the rest had discontinued therapy (Figure 1). For KEYNOTE-361, 46 patients with pure TCC (n = 41; 14.8%) and mixed predominant TCC (n = 5; 18.5%) had completed 35 cycles of pembrolizumab; the rest had discontinued therapy. The most common reason for discontinuation in both studies was progressive disease (n = 163 [61.7%] in KEYNOTE-045; n = 174 [57.2%] in KEYNOTE-361).

In KEYNOTE-045, confirmed ORR per RECIST v1.1 by BICR was 21.0% for patients with pure TCC and 24.4% for patients with mixed predominant TCC (Table 2). The median DOR was 19.7 months (range, 1.6+ to 60.5+) for pure TCC and was not reached (range, 2.8+ to 60.1+ months) for mixed predominant TCC (Table 2). The median OS was 9.7 months (95% CI, 7.5-11.8) for pure TCC and 11.6 months (95% CI, 7.4-16.4) for mixed predominant TCC; 24-month rates were 25.2% and 31.5%, respectively (Figure 2A). The median PFS was 2.1 months (95% CI, 2.0-2.2) for pure TCC and 2.1 months (95% CI, 2.0-3.5) for mixed predominant TCC in KEYNOTE-045; 24-month rates were 11.0% and 18.9%, respectively (Figure 3A).

In KEYNOTE-361, confirmed ORR was 29.3% for patients with pure TCC and 40.7% for patients with mixed predominant TCC (Table 2). The median DOR in KEYNOTE-361 was 28.2 months (range, 2.1+ to 36.1+) for pure TCC and was not reached (range, 4.0+ to 30.4+ months) for mixed predominant TCC (Table 2). The median OS was 14.8 months (95% CI, 11.8-17.9) for pure TCC and 16.2 months (95% CI, 5.5 to not reached) for mixed predominant TCC in KEYNOTE-361; 24-month rates were 36.8% and 44.4%, respectively (Figure 2B). The median PFS was 3.9 months (95% CI, 2.3-5.5) for pure TCC and 2.2 months (95% CI, 2.1-18.0) in KEYNOTE-361; 24-month rates were 15.9% and 24.2%, respectively (Figure 3B).

A sensitivity analysis adjusted for major prognostic factors (eg, ECOG PS) showed that histology did not impact efficacy in terms of OS and PFS in either KEYNOTE-045 or KEYNOTE-361 (Table S1).

A total of 264 of the 268 patients with TCC (pure TCC: 183; mixed predominant TCC: 81) in KEYNOTE-045 and 304 of the 307 patients with TCC (pure TCC: 277; mixed predominant TCC: 27) in KEYNOTE-361 received at least 1 dose of pembrolizumab monotherapy. In KEYNOTE-045, the median number of pembrolizumab cycles for patients with pure TCC and mixed predominant TCC was 6 (range, 1-36) for both groups. Treatment-related AEs occurred in 120 patients (65.6%) with pure TCC and 45 patients (55.6%) with mixed predominant TCC (Table 3; Table S2). Grade 3-5 treatment-related AEs occurred in 31 patients (16.9%) with pure TCC and 14 patients (17.3%) with mixed predominant TCC. One patient with pure TCC and 3 patients with mixed predominant TCC died from treatment-related AEs (pure TCC: cause of death not specified; mixed predominant TCC: 1 patient each died due to malignant neoplasm progression, urinary tract obstruction, and pneumonitis).

In KEYNOTE-361, the median number pembrolizumab cycles was 7 (range 1-35) for patients with pure TCC and 9 (range, 1-35) for patients with mixed predominant TCC. There were 180 patients (65.0%) with pure TCC and 21 patients (77.8%)

Table 1 Baseline Characteristics

	KEYNOTE-045		KEYNOTE-361	
	Pure TCC *n* = 186	Mixed predominant TCC *n* = 82	Pure TCC *n* = 280	Mixed predominant TCC *n* = 27
Age, median (range), years	67 (39-88)	68 (39-81)	68 (29-87)	70 (34-89)
Sex				
Male	140 (75.3)	58 (70.7)	209 (74.6)	19 (70.4)
Female	46 (24.7)	24 (29.3)	71 (25.4)	8 (29.6)
PD-L1 CPS				
<10	139 (74.7)	46 (56.1)	140 (50.0)	7 (25.9)
≥10	40 (21.5)	33 (40.2)	140 (50.0)	20 (74.1)
Missing	7 (3.8)	3 (3.7)	0	0
ECOG PS				
0	84 (45.2)	35 (42.7)	124 (44.3)	10 (37.0)
1	96 (51.6)	45 (54.9)	134 (47.9)	14 (51.9)
2	2 (1.1)	1 (1.2)	22 (7.9)	3 (11.1)
Missing	4 (2.2)	1 (1.2)	0	0
Primary tumor location				
Upper tract	19 (10.2)	19 (23.2)	60 (21.4)	5 (18.5)
Lower tract[a]	167 (89.8)	63 (76.8)	220 (78.6)	22 (81.5)
Prior platinum therapy				
Cisplatin	139 (74.7)	58 (70.7)	NA	NA
Carboplatin	46 (24.7)	24 (29.3)	NA	NA
Other[b]	1 (0.5)	0	NA	NA
Choice of cisplatin or carboplatin[c]				
Cisplatin	NA	NA	124 (44.3)	13 (48.1)
Carboplatin	NA	NA	156 (55.7)	14 (51.9)
Liver metastases				
Absent	123 (66.1)	55 (67.1)	220 (78.6)	22 (81.5)
Present	63 (33.9)	27 (32.9)	60 (21.4)	5 (18.5)
Prior cystectomy/nephrectomy	44 (23.7)	14 (17.1)	NA	NA
Prior adjuvant or neoadjuvant platinum-based chemotherapy	25 (13.4)	5 (6.1)	24 (8.6)	5 (18.5)

Abbreviations: CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; PD-L1 = programmed cell death ligand 1; TCC = transitional cell carcinoma. Data are *n* (%) unless otherwise indicated.
[a] Includes bladder and urethra.
[b] Oxaliplatin or nedaplatin.
[c] Per protocol, investigators in KEYNOTE-361 were required to choose a platinum therapy for patients before randomization in the event the patient was randomly assigned to one of the treatment arms receiving chemotherapy[10]; no patients included in the present analysis received cisplatin or carboplatin as study treatment.

with mixed predominant TCC who experienced a treatment-related AE (Table 3; Table S3). Grade 3-5 treatment-related AEs occurred in 48 patients (17.3%) with pure TCC and 5 patients (18.5%) with mixed predominant TCC. Two patients with pure TCC died from treatment-related AEs (1 patient each due to cardiac failure and malignant neoplasm progression); no deaths occurred in patients with mixed predominant TCC.

Immune-mediated AEs and infusion reactions occurred in 34 patients (18.6%) with pure TCC and 18 patients (22.2%) with mixed predominant TCC from KEYNOTE-045 (Table 3; Table S2; Table S3). Grade 3-5 immune-mediated AEs occurred in 11 patients (6.0%) with pure TCC and 5 patients (6.2%) with mixed predominant TCC. One death (pneumonitis) occurred in a patient with mixed predominant TCC in KEYNOTE-045. In KEYNOTE-361, 59 patients (21.3%) with pure TCC and 11 patients (40.7%) with mixed predominant TCC experienced immune-mediated AEs and infusion reactions (Table 3; Table S2; Table S3). Grade 3-5 immune-mediated AEs occurred in 20 patients (7.2%) with pure TCC; none occurred in patients with mixed predominant TCC. No patients from KEYNOTE-361 died from immune-mediated AEs.

Discussion

Post hoc analysis from the KEYNOTE-045 and KEYNOTE-361 studies showed benefit with pembrolizumab monotherapy in patients with advanced UC regardless of histology. The ORR, DOR,

Figure 1 Patient disposition. Abbreviations: AE = adverse event; CR = complete response; PD = progressive disease; TCC = transitional cell carcinoma. [a]Physician decision ($n = 4$), protocol violation ($n = 1$), and patient withdrawal ($n = 1$). [b]Physician decision ($n = 2$) and patient withdrawal ($n = 2$). [c]Excluded medication ($n = 1$), noncompliance with study drug ($n = 1$), and nonstudy anticancer therapy ($n = 1$).

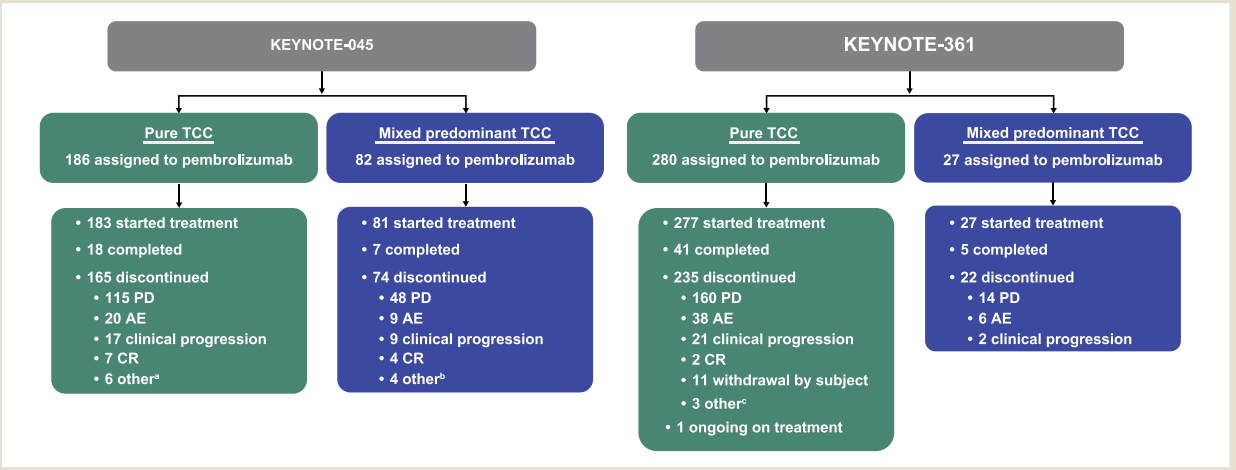


Table 2 Best Overall Response and Duration of Response per RECIST v1.1 in KEYNOTE-045 and KEYNOTE-361

	KEYNOTE-045		KEYNOTE-361	
	Pure TCC $n = 186$	Mixed predominant TCC $n = 82$	Pure TCC $n = 280$	Mixed predominant TCC $n = 27$
ORR (CR + PR), % (95% CI)	21.0 (15.4-27.5)	24.4 (15.6-35.1)	29.3 (24.0-35.0)	40.7 (22.4-61.2)
DCR (CR + PR + SD), % (95% CI)	36.0 (29.1-43.4)	46.3 (35.3-57.7)	47.1 (41.2-53.2)	48.1 (28.7-68.1)
Best overall response, *n* (%)				
CR	17 (9.1)	10 (12.2)	29 (10.4)	5 (18.5)
PR	22 (11.8)	10 (12.2)	53 (18.9)	6 (22.2)
SD	28 (15.1)	18 (22.0)	50 (17.9)	2 (7.4)
PD	96 (51.6)	32 (39.0)	107 (38.2)	11 (40.7)
Non-CR/non-PD[a]	0	0	8 (2.9)	0
Not evaluable	4 (2.2)[b]	0	7 (2.5)[c]	0
No assessment[d]	19 (10.2)	12 (14.6)	26 (9.3)	3 (11.1)
Time to response, median (range), months	2.1 (1.9-6.0)	2.1 (1.4-6.3)	2.1 (1.2-8.3)	2.2 (1.9-8.2)
DOR, median (range), months	19.7 (1.6+ to 60.5+)	NR (2.8+ to 60.1+)	28.2 (2.1+ to 36.1+)	NR (4.0+ to 30.4+)
Response ≥24 months, %	47.4	76.5	50.0	60.0

Abbreviations: CR = complete response; DCR = disease control rate; DOR = duration of response; NR = not reached; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; TCC = transitional cell carcinoma.
"+" indicates there was no progressive disease by the time of the last disease assessment.
[a] Defined as persistence of ≥1 nontarget lesions and/or maintenance of tumor marker level above the normal limits.
[b] Patients had postbaseline imaging, and the best objective response was determined to be not evaluable per RECIST v1.1.
[c] Patients with insufficient data for assessment of response per RECIST v1.1.
[d] Patients had no postbaseline imaging.

and OS were generally consistent between histology subgroups within each study, although the small sample size for some subgroups limits the interpretation of these findings. Safety was consistent with previous reports of pembrolizumab in patients with UC regardless of histology.

The ORR observed in this analysis was consistent with several other studies evaluating the efficacy of immunotherapy by histology for patients with UC, although making cross-trial comparisons is difficult because definitions of variant histology differ between studies.[11-13] Mixed results from retrospective studies assessing the effectiveness of immune checkpoint inhibitor monotherapy in patients with pure UC and variant UC have been reported. A multicenter retrospective analysis of 755 patients with advanced UC who received pembrolizumab treatment at 59 medical centers

Table 3 Summary of Adverse Events for KEYNOTE-045 and KEYNOTE-361

	KEYNOTE-045		KEYNOTE-361	
	Pure TCC $n = 183$	Mixed predominant TCC $n = 81$	Pure TCC $n = 277$	Mixed predominant TCC $n = 27$
Any-cause AEs	171 (93.4)	77 (95.1)	264 (95.3)	27 (100.0)
Grade 3-5	104 (56.8)	43 (53.1)	175 (63.2)	17 (63.0)
Serious	78 (42.6)	27 (33.3)	132 (47.7)	14 (51.9)
Led to discontinuation of treatment	20 (10.9)	8 (9.9)	42 (15.2)	6 (22.2)
Led to death	9 (4.9)	4 (4.9)	25 (9.0)	1 (3.7)
Treatment-related AEs	120 (65.6)	45 (55.6)	180 (65.0)	21 (77.8)
Grade 3-5	31 (16.9)	14 (17.3)	48 (17.3)	5 (18.5)
Serious	23 (12.6)	11 (13.6)	35 (12.6)	3 (11.1)
Led to discontinuation of treatment	12 (6.6)	7 (8.6)	20 (7.2)	5 (18.5)
Led to death	1 (0.5)[a]	3 (3.7)[b]	2 (0.7)[c]	0
Immune-mediated AEs and infusion reactions	34 (18.6)	18 (22.2)	59 (21.3)	11 (40.7)
Grade 3-5	11 (6.0)	5 (6.2)	20 (7.2)	0
Led to death	0	1 (1.2)[d]	0	0

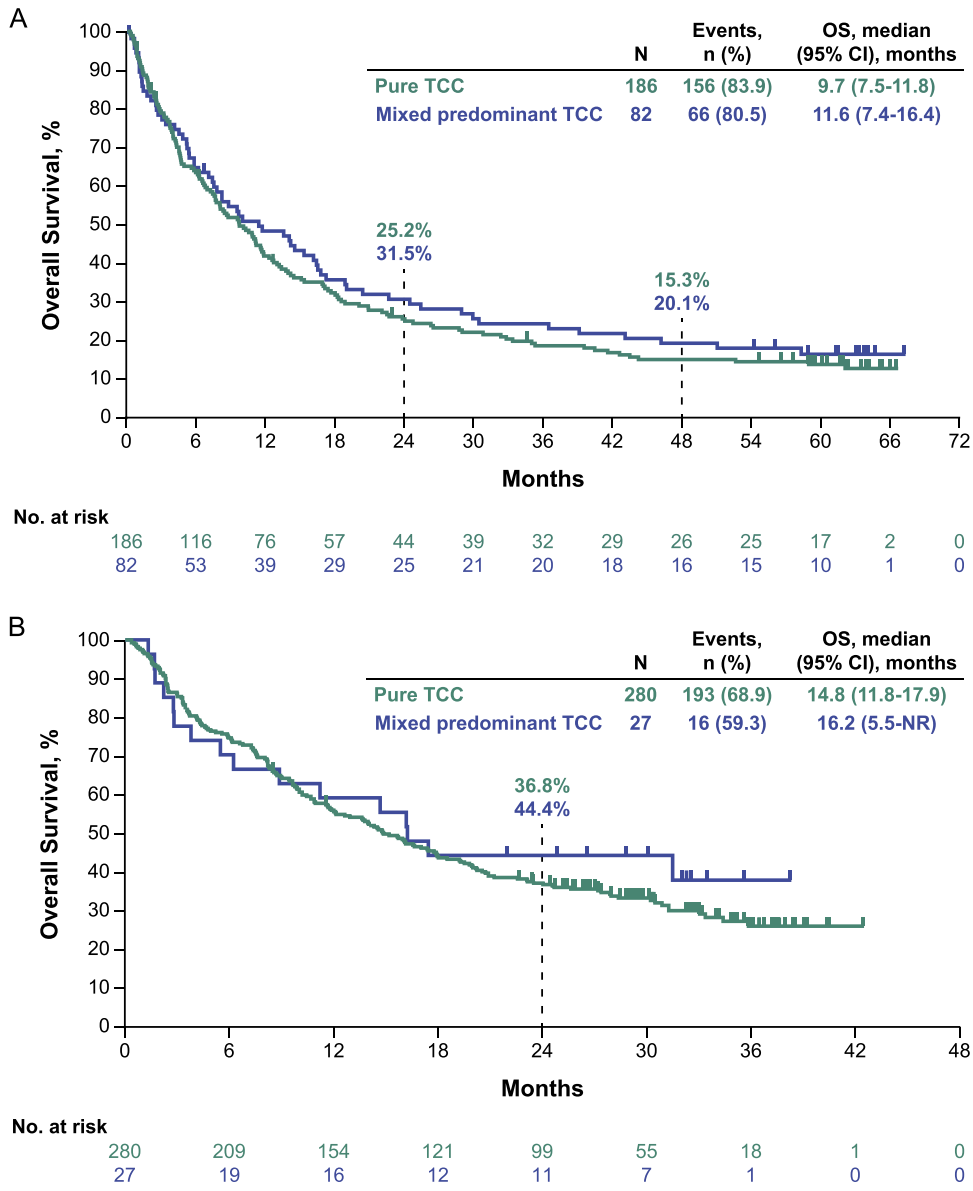
Abbreviations: AE = adverse events; TCC = transitional cell carcinoma.
[a] One patient due to unspecified cause of death.
[b] One patient each due to malignant neoplasm progression, urinary tract obstruction, and pneumonitis.
[c] One patient each due to cardiac failure and malignant neoplasm progression.
[d] One patient due to pneumonitis.

in Japan reported consistent ORR and OS between histology groups.[14] Conversely, a retrospective analysis of 103 patients with advanced UC from 6 institutions who received pembrolizumab after platinum-based chemotherapy reported higher ORR for patients who had variant UC compared with patients with pure UC, but no significant differences were noted in PFS or OS.[15] Another retrospective analysis of 168 patients with advanced UC who received pembrolizumab after platinum-based chemotherapy in 11 institutions in Japan showed patients with basal-type UC had significantly shorter PFS and cancer-specific survival rates than those with pure UC.[16] A retrospective analysis of checkpoint inhibitor therapies in 142 patients with metastatic UC at 2 medical centers in Taiwan (pembrolizumab, nivolumab, avelumab, durvalumab, and atezolizumab) reported similar ORR values for pure UC versus variant UC. PFS and OS were also similar between histology groups, but subgroup analysis indicated improved OS in a first-line setting for patients with pure UC.[17] A separate retrospective analysis of the same checkpoint inhibitors in 519 patients with advanced UC at 18 medical centers reported similar ORR values between histologies.[18]

A population-based study based on SEER data showed that overall survival for patients with metastatic urothelial carcinoma was better with contemporary treatments (2017-2020) compared with historical treatments (2000-2016), but the magnitude of this benefit with contemporary treatments was higher for patients with metastatic bladder cancer with urothelial carcinoma histology (overall mortality HR, 0.68 [95% CI, 0.60-0.76]; $P < .001$) compared with patients with histology other than urothelial carcinoma (overall mortality HR, 0.81 [95% CI, 0.66-1.01]; $P = .06$).[19]

However, comparisons of efficacy of treatment regimens for UC with variant histology are limited by differences across studies in eligibility criteria based on histology, differences in histology options made available to investigators in data collection forms for different trials, variations in the diagnosis of variant histology by different investigators both within a trial and across different trials, and the lack of central confirmation of the histopathologic diagnosis for most trials. The EV-302 (enfortumab vedotin + pembrolizumab vs. platinum chemotherapy) and JAVELIN-100 (maintenance avelumab vs. best supportive care for patients with stable disease or better after platinum chemotherapy) phase 3 trials allowed variant and mixed histology and did not mandate that the urothelial carcinoma needed to be predominant.[20,21] This contrasts with the KEYNOTE-045, KEYNOTE-361, and CheckMate-901 (nivolumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine) phase 3 studies which also allowed variant and mixed histology but did require that the urothelial carcinoma component be predominant.[7,10,22] The histologic subtypes reported for participants who received enfortumab vedotin + pembrolizumab in the EV-302 study included urothelial carcinoma (85.7%), urothelial carcinoma, mixed types (11.3%), variant urothelial carcinoma only (0.9%), and unknown (2%).[20] In the CheckMate-901 study for participants who received nivolumab + cisplatin + gemcitabine, the reported histologic subtypes of urothelial carcinoma had either no variants (49.3%), or had adenocarcinoma, squamous cell carcinoma, micropapillary, or other histology (total 50%). Histology was not reported for 0.7% of participants.[22] To our knowledge, subgroup analysis based on histology has not been reported for the EV-302 and CheckMate-901 trials. On the experimental arm of the JAVELIN-100 trial (maintenance avelumab), the histology reported was urothelial carcinoma for 87.4% of participants and urothelial carcinoma with squamous, glandular, or variant differentiation for 12.6% of participants.[21,23] In a post hoc exploratory analysis, for participants with a histologic subtype component, OS and PFS were longer with avelumab maintenance compared with best supportive care (stratified HR [95% CI] for OS: 0.74 [0.44-1.24] and PFS:

Figure 2 Kaplan-Meier estimates of OS for (A) KEYNOTE-045 and (B) KEYNOTE-361. Abbreviations: NR = not reached; OS = overall survival; TCC = transitional cell carcinoma.



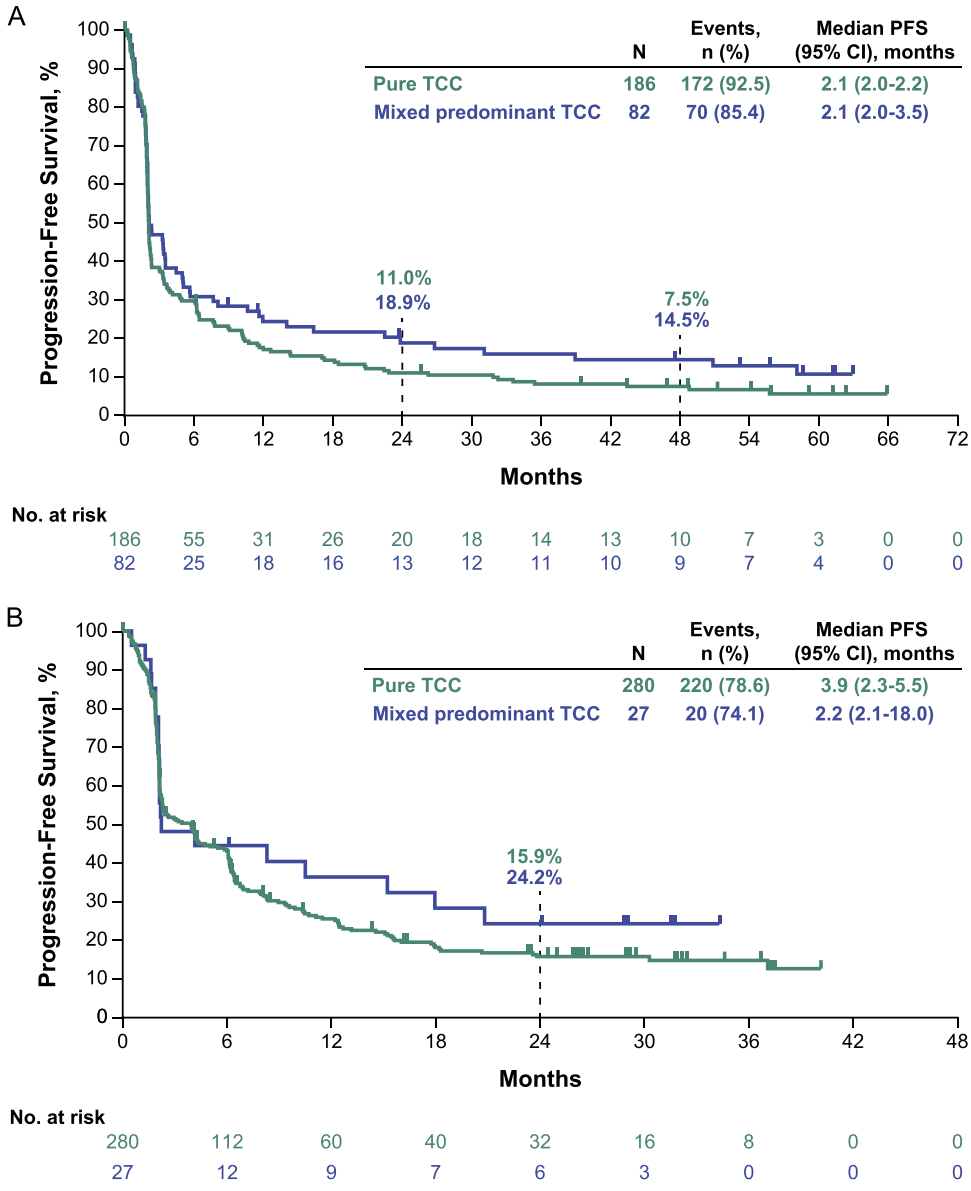
0.52 [0.33-0.83]).[23] Further studies are needed to better characterize the efficacy of the various treatment regimens for different variant histologic types of urothelial cancer.

Limitations of this exploratory analysis included the different therapy settings of KEYNOTE-045 (second-line treatment) and KEYNOTE-361 (first-line treatment), the smaller sample size of the mixed predominant TCC subgroup, the smaller proportion of patients with upper tract UC, and the absence of central review of investigator-assessed histologic diagnosis. In addition, the limited data available to classify subgroups by the type of mixed histology meant that the impact of the percentage of each component (eg, minor urothelial or pure variant histology) was unclear.

Conclusion

Efficacy was generally consistent between patients with pure TCC histology and mixed predominant TCC histology in the pembrolizumab monotherapy arms of both KEYNOTE-045 and KEYNOTE-361. The safety profile of pembrolizumab was consistent with previous reports, with no substantial differences observed between histologic types of urothelial cancer. The results of this

Figure 3 Kaplan-Meier estimates of PFS for (A) KEYNOTE-045 and (B) KEYNOTE-361. Abbreviations: PFS = progression-free survival; TCC = transitional cell carcinoma.



exploratory analysis support the use of pembrolizumab monotherapy as a treatment option for patients with advanced UC regardless of TCC histology.

Clinical Practice Points

- **What is known about this subject?**
  The most common histological subtype of urothelial carcinoma is pure transitional cell carcinoma (TCC). Other variants are associated with higher-stage disease at diagnosis, increased risk of recurrence, and reduced overall survival. Immune checkpoint inhibitors are a crucial treatment for bladder cancer, but it is not yet clear how variant UC histology might impact the efficacy of these agents because clinical trials have primarily enrolled patients with pure TCC. We performed a post hoc analysis using data from the pembrolizumab monotherapy arms of the phase 3 KEYNOTE-045 and KEYNOTE-361 trials to evaluate efficacy and safety by histology in patients with advanced UC.
- **What are the new findings?**
  In KEYNOTE-045, for pure TCC the confirmed ORR was 21.0% (95% CI, 15.4-27.5) and median OS was 9.7 months (95% CI, 7.5-11.8). For mixed predominant TCC, the confirmed ORR was 24.4% (95% CI, 15.6-35.1) and median OS was 11.6 months (95% CI, 7.4-16.4). In KEYNOTE-361, for pure

TCC the confirmed ORR was 29.3% (95% CI, 24.0-35.0) and median OS was 14.8 months (95% CI, 11.8-17.9). For mixed predominant TCC, confirmed ORR was 40.7% (95% CI, 22.4-61.2) and median OS was 16.2 months (95% CI, 5.5-not reached). The safety profile of pembrolizumab was consistent with previous reports with no substantial differences observed between histologies.

- **How might it affect clinical practice in the future?**
  The results of this exploratory analysis support the use of pembrolizumab monotherapy as a treatment option for patients with advanced UC regardless of TCC histology.

Prior Presentation

The data in this manuscript were presented in part at the 2023 ASCO Annual Meeting, June 2-6, 2023.

Availability of Data and Material

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, 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 (available at: 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 the 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.

Disclosure

Patrizia Giannatempo has received personal fees for consulting from Astellas, Janssen, Merck & Co., Inc., MSD, and Pfizer; has received honoraria from Astellas, Janssen, Merck & Co., Inc., and MSD; has received payment for expert testimony from Astellas; and has received travel support for meeting attendance from Merck & Co., Inc. and Pfizer.

Jean-Pascal Machiels has received institutional support for advisory board participation from ALX Oncology, Astellas, Bayer, Boerhinger, Bristol Myers Squibb, Cue Biopharma, CureVac, eTheRNA, F-Star, Genmab, GSK, Incyte, iTEOS, IPSEN, Merck Serono, Merus, MSD, NEKTAR, Novartis, Pfizer, Roche, and Seagen; and has received travel support for meeting attendance from Amgen, Bristol Myers Squibb, Gilead, Merck Serono, MSD, Pfizer, and Sanofi.

Naoto Sassa, Wen-Pin Su, Ying-Chun Shen, and Eli Rosenbaum have nothing to disclose.

Jose Angel Arranz has received personal fees for advisory board participation from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Merck & Co., Inc., MSD, Novartis, and Pfizer; has received honoraria from Astellas, Bristol Myers Squibb, and Ipsen; and has received travel support from Bristol Myers Squibb and Merck & Co., Inc.

Yasuhisa Fujii has received honoraria from Merck & Co., Inc., MSD, and Ono.

Bhumsuk Keam has received grants from AstraZeneca, MSD Oncology, and Ono Pharmaceutical; and has received personal fees for consulting from Celid, Handok, ImmuneOncia, MSD Oncology, NeoImmuneTec, and Trialinformatics; and has received honoraria from Merck & Co., Inc. and MSD Oncology.

Stéphane Culine received personal fees for consulting from Astellas, Bayer, Bristol Myers Squibb, Ipsen, Janssen, Merck & Co., Inc., MSD, and Takéda and travel support from Astellas, Astra-Zeneca, Chugaï, and Janssen.

José Muñoz Langa has received nonfinancial support for meeting attendance from AstraZeneca, GSK, and MSD.

David Sarid has received consulting fees and honoraria for lectures or presentations from MSD.

Maureen Aarts has received personal fees for advisory board participation from Amgen, Astellas, Bayer, Bristol Myers Squibb, Merck-Pfizer, MSD, Novartis, Pierre Fabre, and Sanofi; has received honoraria and travel support from Ismar Health NV; and has received institutional research grants from Merck-Pfizer.

Fabio Calabrò has received travel support from Novartis; and has participated in data safety monitoring boards or advisor boards for Astellas, AstraZeneca, Ipsen, Johnson & Johnson, MSD, Novartis, and Pfizer.
Blanca Homet Moreno, Abhishek Bavle, and Jin Z. Xu are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and own stock in Merck & Co., Inc., Rahway, NJ, USA.

Sun Young Rha has received institutional research grants from ABLBIO, ALX Oncology, Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, BeiGene, Bold Therapeutics, Daiichi Sankyo, Eisai, Ipsen, Leap Therapeutics, Macrogenics, MedPacto, Merck KGaA, Merck Sharpe and Dohme, MSD, Ono Pharmaceutical, Pfizer, Seagen, Taiho Pharmaceutical, and Zymeworks; has received consulting fees from Indivumed and LG Biochem; has received honoraria from Amgen, Astellas, Daiichi Sankyo, Eisai, Ipsen, Lilly, MSD, and Sanofi; and has participated in data safety monitoring boards or advisory boards for Amgen, Arcus, and Toray.

CRediT authorship contribution statement

Patrizia Giannatempo: Writing – review & editing, Investigation. **Jean-Pascal Machiels:** Writing – review & editing, Investigation, Formal analysis. **Naoto Sassa:** Writing – review & editing, Investigation, Formal analysis. **Jose Angel Arranz:** Writing – review & editing, Investigation, Formal analysis. **Yasuhisa Fujii:** Writing – review & editing, Investigation, Formal analysis. **Wen-Pin Su:** Writing – review & editing, Investigation. **Bhumsuk Keam:** Writing – review & editing, Investigation. **Stéphane Culine:** Writing – review & editing, Investigation, Formal analysis. **Ying-Chun Shen:** Writing – review & editing, Investigation. **José Muñoz Langa:** Writing – review & editing, Investigation, Formal analysis. **David Sarid:** Writing – review & editing, Investigation. **Maureen Aarts:** Writing – review & editing, Resources, Formal analysis. **Fabio Calabrò:** Writing – review & editing, Investigation, Formal analysis. **Eli Rosenbaum:** Writing – review & editing, Formal analysis. **Blanca Homet Moreno:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Abhishek Bavle:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Jin Z. Xu:** Writing – review & editing, Formal analysis. **Sun Young Rha:** Writing – review & editing, Investigation, Formal analysis.

Acknowledgments

The authors thank the patients and their families and caregivers, all primary investigators, and site personnel for participating in the KEYNOTE studies. Medical writing and/or editorial assistance was provided by Bresler Swanepoel, PhD, Shane Walton, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The research and preparation of the manuscript were supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The study funder had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured that data were collected according to the protocol. All authors reviewed the final version of the manuscript to be submitted and agree with its content and submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2024.102273.

References

1. Rogers CG, Palapattu GS, Shariat SF, et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. *J Urol*. 2006;175:2048–2053 discussion 53.
2. Al-Husseini MJ, Kunbaz A, Saad AM, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in the USA: a SEER-based analysis. *BMC Cancer*. 2019;19:46.
3. Processali T, Diminutto A, Cerruto MA, Antonelli A. The impact of histological variants on bladder cancer outcomes. *AME Medical Journal*. 2020;5:4.
4. Black AJ, Black PC. Variant histology in bladder cancer: diagnostic and clinical implications. *Transl Cancer Res*. 2020;9:6565–6575.
5. Wright JL, Black PC, Brown GA, et al. Differences in survival among patients with sarcomatoid carcinoma, carcinosarcoma and urothelial carcinoma of the bladder. *J Urol*. 2007;178:2302–2306 discussion 7.
6. Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33:244–258.
7. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015–1026.
8. 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;34:289–299.
9. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann Oncol*. 2019;30:970–976.
10. Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:931–945.
11. Sternberg CN, Loriot Y, James N, et al. Primary results from SAUL, a multinational single-arm safety study of Atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. *Eur Urol*. 2019;76:73–81.
12. McGregor BA, Campbell MT, Xie W, et al. Results of a multicenter, phase 2 study of nivolumab and ipilimumab for patients with advanced rare genitourinary malignancies. *Cancer*. 2021;127:840–849.
13. Hoffman-Censits J, Pal S, Kaiser C, Ding B, Bellmunt J. Atezolizumab in patients with renal insufficiency and mixed variant histology: analyses from an expanded access program in platinum-treated locally advanced or metastatic urothelial carcinoma. *J Immunother Cancer*. 2020;8:e000419.
14. Kobayashi M, Narita S, Matsui Y, et al. Impact of histological variants on outcomes in patients with urothelial carcinoma treated with pembrolizumab: a propensity score matching analysis. *BJU Int*. 2022;130:226–234.
15. Minato A, Furubayashi N, Harada M, et al. Efficacy of Pembrolizumab in patients with variant urothelial carcinoma: a multicenter retrospective study. *Clin Genitourin Cancer*. 2022;20(499):e1–e8.
16. Inoue S, Sassa N, Kawanishi H, et al. Impact of histological variants on clinical responses to Pembrolizumab in patients with metastatic urothelial cancer. *Anticancer Res*. 2022;42:3627–3636.
17. Tsai TH, Su PJ, Huang SY, et al. The prognostic significance of histologic variant on survival outcomes in patients with metastatic urothelial carcinoma receiving immune checkpoint inhibitor therapy. *BMC Cancer*. 2023;23:871.
18. Miller NJ, Khaki AR, Diamantopoulos LN, et al. Histological subtypes and response to PD-1/PD-L1 blockade in advanced urothelial cancer: a retrospective study. *J Urol*. 2020;204:63–70.
19. Di Bello F, Siech C, Jannello LMI, et al. Contemporary survival in metastatic bladder cancer patients: a population-based study. *Int J Cancer*. 2024;55:1762–1768.
20. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390:875–888.
21. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383:1218–1230.
22. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma. *N Engl J Med*. 2023;389:1778–1789.
23. Loriot Y, Gupta S, Powles T, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC): long-term outcomes from the JAVELIN Bladder 100 trial in patients (pts) with histological subtypes. *J Clin Oncol*. 2024;42:4567.