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Pembrolizumab as First-line Therapy in Cisplatin-ineligible Advanced Urothelial Cancer (KEYNOTE-052): Outcomes in Older Patients by Age and Performance Status

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Abstract

Background: Patients with treatment-naive advanced urothelial cancer (UC) ineligible for cisplatin-based chemotherapy are typically older and have comorbidities, representing a difficult-to-treat population.

Objective: To evaluate the safety and antitumor activity of first-line pembrolizumab in subgroups of cisplatin-ineligible older patients (aged ≥65 and ≥75 yr) with advanced UC in KEYNOTE-052 (NCT02335424), including those with poor performance status (Eastern Cooperative Oncology Group performance status score 2 [ECOG PS2]).

Design, setting, and participants: Patients were cisplatin ineligible, had treatment-naive, histologically/cytologically confirmed, locally advanced/metastatic UC with measurable disease (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), and had ECOG PS0–2. Patient subgroups analyzed were aged ≥65 yr (n = 302), ≥75 yr (n = 179), ≥65 yr with ECOG PS2 (≥65 yr + ECOG PS2; n = 119), and ≥75 yr + ECOG PS2 (n = 78).

Intervention: All patients received pembrolizumab 200 mg intravenously every 3 wk until confirmed progression, intolerable toxicity, patient withdrawal, or 24 mo of therapy.

Outcome measurements and statistical analysis: The primary endpoint was objective response rate (ORR) as per RECIST v1.1. The key secondary endpoints were overall survival (OS), duration of response (DOR), and safety.

Results and limitations: ORRs for the ≥65 yr, ≥75 yr, ≥65 yr + ECOG PS2, and ≥75 yr + ECOG PS2 subgroups were 29%, 27%, 29%, and 31%, respectively; rates of complete and partial responses were similar across subgroups (9%, 5%, 6%, and 6%, and 20%, 22%, 23%, and 24%, respectively). Median DOR and OS were also consistent across the ≥65 yr and ≥65 yr + ECOG PS2 subgroups and the ≥75 yr and ≥75 yr + ECOG PS2 subgroups. Study limitations included open-label design, lack of a comparator group, and nature of post hoc exploratory analysis.

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Conclusions: The clinical benefit of pembrolizumab in advanced UC appeared to be consistent regardless of age and/or poor performance status.

Patient summary: This study looked at whether older age and poorer performance status affect how well patients with previously untreated advanced urothelial cancer ineligible for standard-of-care treatment respond to pembrolizumab. Outcomes with pembrolizumab were not affected by older age or poorer performance status, making it an effective option.

1. Introduction

Urothelial cancers (UCs) comprise a range of tumors arising from the urinary tract, including the bladder, which accounts for >90% of all urothelial tumors in the USA and Europe [1]. Bladder cancer ranks 10th in the world regarding incidence, with >500 000 cases estimated to have been diagnosed in 2018 [2]. Diagnosis peaks after age 70 yr, and approximately 20% of patients are older than 80 yr [3].

Approximately half of patients with newly diagnosed, advanced UC are ineligible for first-line cisplatin-based combination chemotherapy, in part because of age-related decline in performance status and the presence of medical comorbidities that can impact treatment-related toxicity [3–5]. Indeed, one criterion used to establish eligibility for cisplatin-based therapy is Eastern Cooperative Oncology Group performance status (ECOG PS) <2 [4]. Comorbidities in older patients include renal function impairment (chronic kidney disease with creatinine clearance level <50–60 ml/min), grade ≥2 hearing loss or neuropathy, and New York Heart Association (NYHA) class III–IV cardiac failure [4,6–8]. Treatment of UC in older patients may also be affected by potential interactions among drugs used to treat comorbidities and chemotherapy [7]. Survival with non–cisplatin-based therapies is usually short, with median progression-free (PFS) and overall (OS) survival of 4–5 and 8–10 mo, respectively [7].

Clinical benefit has been noted with gemcitabine plus carboplatin (GCa) as a first-line treatment; alternatives include gemcitabine or carboplatin monotherapy and gemcitabine plus paclitaxel [7,9]. However, shorter OS and severe toxicity in patients with both poor performance status and renal impairment (estimated glomerular filtration rate <60 ml/min) compared with those who had only one of these factors were reported with GCa [10]. Moreover, chemotherapy is not administered to approximately 20–52% of patients with UC, including those with advanced disease, because of the presence of comorbidities, poor overall health status, and concerns regarding chemotherapy-associated toxicities [3,9,11]; these untreated patients generally fare worse than those who receive chemotherapy and usually pursue only best supportive and palliative care [3]. The good tolerability profile of checkpoint inhibitors represents a new opportunity for therapeutic intervention in older patients who are chemotherapy ineligible.

Immune checkpoint blockade (anti–programmed death 1 [PD-1]/anti–programmed death ligand 1 [PD-L1]/anti-cytotoxic T-lymphocyte–associated protein 4) has demonstrated efficacy for a variety of malignancies, including UC [12,13]. The PD-1 inhibitor pembrolizumab is approved in the USA and Europe as first-line therapy for cisplatin-ineligible patients with UC, based on available efficacy and safety data from the open-label, single-arm, phase 2 KEYNOTE-052 trial (ClinicalTrials.gov, NCT02335424) evaluating the efficacy and safety of first-line pembrolizumab in cisplatin-ineligible patients with advanced UC [14–16]. A 2018 revision of these approvals for first-line pembrolizumab limited its use to cisplatin-ineligible patients with tumors exhibiting high PD-1 expression based on the companion assay (22C3; Agilent Technologies, Carpinteria, CA, USA) or patients ineligible for any platinum (cisplatin or carboplatin)-containing chemotherapy regardless of PD-L1 status [14,15]. These revisions are based on an early interim analysis that found that survival was shorter in patients with advanced UC and tumors with low PD-L1 expression who received pembrolizumab than in those who received chemotherapy alone in an ongoing phase III trial (KEYNOTE-361, ClinicalTrials.gov, NCT02853305) [17].

In KEYNOTE-052, first-line treatment of 370 patients with pembrolizumab yielded an objective response rate (ORR) of 29%, with 33 (9%) complete responses (CRs) and 73 (20%) partial responses (PRs) across the entire trial population [18]. Responses were usually rapid and durable, and pembrolizumab was well tolerated overall. It was hypothesized that pembrolizumab activity and tolerability are independent of age and performance status. An exploratory post hoc analysis of KEYNOTE-052 was conducted to evaluate the antitumor activity and safety of pembrolizumab in the subgroup of cisplatin-ineligible patients who were considered older (aged ≥65 and ≥75 yr) and/or had poor performance status (ie, ECOG PS2).

2. Patients and methods

2.1. Study design and patient population

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines, and in compliance with local and institutional regulations. All patients provided written informed consent to participate. Study design and methods are described in detail elsewhere [16]. In brief, adults with treatment-naive, histologically/cytologically confirmed, locally advanced (unresectable) or metastatic UC of the renal pelvis, ureter, bladder, or urethra, who were ineligible for cisplatin-based chemotherapy, had centrally confirmed measurable disease (as per Response Evaluation Criteria in Solid

Tumors version 1.1 [RECIST v1.1]), and had ECOG PS 0–2 were enrolled. Cisplatin ineligibility was defined by having one or more of the following factors: ECOG PS2, creatinine clearance level 30–59 ml/min, grade ≥2 neuropathy/hearing loss, or NYHA class III heart failure.

2.2. Treatment and assessments

All enrolled patients were administered pembrolizumab 200 mg intravenously every 3 wk until documented disease progression, intolerable toxicity, physician/patient decision to withdraw, or completion of 24 mo of treatment. Tumor response was assessed by computed tomography or magnetic resonance imaging at 9 wk after the first dose of pembrolizumab, every 6 wk thereafter for the 1st year, and then every 12 wk through year 2.

PD-L1 expression (assessed using the PD-L1 IHC 22C3 pharmDx assay; Agilent Technologies) was determined using combined positive score (CPS; number of PD-L1–positive cells [tumor cells, lymphocytes, and macrophages]/total number of tumor cells × 100). A CPS cutoff of 10 was used to define tumors expressing PD-L1 and was validated by determining the ORR among all subsequently enrolled patients with CPS ≥ 10 (referred to as the validation set) [16,19].

Safety was assessed by reporting adverse events (AEs) using Common Terminology Criteria for Adverse Events, version 4.0. AEs and serious AEs (SAEs) were monitored throughout the study and for 30 and 90 d, respectively, after the last dose.

2.3. Study endpoints

The primary endpoint was the ORR as per RECIST v1.1 by an independent central imaging review. Secondary efficacy endpoints were duration of response (DOR), OS, and PFS as per RECIST v1.1 by an independent central imaging review. The primary safety objective was characterization of the safety and tolerability of pembrolizumab, which was achieved by AE reporting, and included SAEs, fatal AEs, and immune-mediated AEs.

2.4. Statistical analysis

Data for the following patient subgroups were analyzed: age ≥65 yr (≥65yr), age ≥75 yr (≥75 yr), age ≥65 yr with ECOG PS2 (≥65 yr + ECOG PS2), and age ≥75 yr with ECOG PS2 (≥75 yr + ECOG PS2). ORR was summarized using point estimates with 95% confidence intervals (CIs) based on the binomial exact method. Secondary efficacy endpoints were evaluated using the Kaplan-Meier method to estimate summary statistics, including medians. Data cutoff date for these analyses was September 26, 2018.

3. Results

3.1. Baseline patient characteristics

Median follow-up for all trial patients was 11.4 mo (range, 0.1–41.2 mo). Of 370 patients, 302 (82%) were aged ≥65 yr, 179 (48%) were aged ≥75 yr, 119 (32%) were aged ≥65 yr with ECOG PS2, and 78 (21%) were aged ≥75 yr with ECOG PS2. Baseline patient characteristics were generally comparable across groups (Table 1).

3.2. Efficacy

ORRs were 29%, 27%, 29%, and 31% for the ≥65 yr, ≥75 yr, ≥65 yr + ECOG PS2, and ≥75 yr + ECOG PS2 subgroups, respectively (Table 2). The best response of CR was achieved by 9%, 5%, 6%, and 6%, respectively, and that of PR was achieved by 20%, 22%, 23%, and 24%, respectively. A supportive analysis of responses in patients aged ≥85 yr (n = 40) yielded an ORR of 28% (11 PRs). The ORRs among patients with a tumor CPS of ≥10 were 52% (32/62), 50% (17/34), 52% (17/33), and 55% (12/22) for the ≥65 yr, ≥75 yr, ≥65 yr + ECOG PS2, and ≥75 yr + ECOG PS2 subgroups, respectively (Fig. 1). For patients who were <65 yr of age (n = 68) and those who were <65 yr of age with ECOG PS 2 (n = 37), ORRs were 29% and 19%, respectively.

Median time to response was similar among all subgroups (median, 2.1 mo overall). Median DOR was 30.1 mo for both the ≥65 yr and the ≥65 yr + ECOG PS2 subgroup, 12.5 mo for the ≥75 yr subgroup, and 11.8 mo for the ≥75 yr + ECOG PS2 subgroup (Table 2). Proportions of patients who maintained response for ≥24 mo were 53% and 51% for the ≥65 yr and ≥65 yr + ECOG PS2 subgroups, respectively, and 35% and 45% for the ≥75 yr and ≥75 yr + ECOG PS2 subgroups, respectively. Findings for patients with CPS ≥ 10 were similar (median time to response, 2.1 mo overall; median DOR was not reached for all but the ≥75 yr + ECOG PS2 subgroup, in which it was 13 mo; Supplementary Table 1). For responders who were <65 yr of age (n = 20) and those who were <65 yr of age with ECOG PS 2 (n = 7), median (range) DOR was 18.1 (1.4+ to 31.9+), which was not reached (5.6 to 26.3+), respectively. Similar proportions of patients in each subgroup experienced a reduction in tumor size from baseline: 59% of the ≥65 yr, 58% of the ≥75 yr, 60% of the ≥65 yr + ECOG PS2, and 57% of the ≥75yr + ECOG PS2 subgroup (Fig. 2).

Median PFS was 2.3 mo for the ≥65 yr subgroup and 2.1 mo for the other three subgroups (Table 3). PFS rates at 6 mo in the ≥65 yr, ≥75 yr, ≥65 yr + ECOG PS2, and ≥75 yr + ECOG PS2 subgroups were 34%, 31%, 33%, and 31%, respectively. For patients who were <65 yr of age (n = 68) and were <65 yr of age with ECOG PS 2 (n = 37), median (95% CI) PFS was 2.2 (2.0–31.9+) and 2.1 (1.9–3.6) mo, respectively. Median (95% CI) OS was 11.0 (9.5–12.5), 9.7 (7.8–11.5), 8.7 (5.2–10.6), and 8.2 (4.4–10.8) mo, respectively, and OS rates at 24 mo were 29%, 21%, 24%, and 23%, respectively. In patients with CPS ≥ 10, median OS was 16.6 mo (95% CI, 11.5–27.6) in ≥65 yr, 13.6 mo (95% CI, 10.0–27.6) in ≥65 yr + ECOG PS2, 11.5 mo (95% CI, 5.8–17.1) in ≥75 yr, and 10.6 mo (95% CI, 4.4–27.0) in ≥75 yr + ECOG PS2 patients. The same pattern was observed for the OS rates at 24 mo (Supplementary Table 1). For patients who were <65 yr of age (n = 68) and those who were <65 yr of age with ECOG PS 2 (n = 37), median (95% CI) OS was 15.7 (6.9–24.2) and 14.1 (5.2–24.2), respectively.

Table 1 – Patient baseline characteristics and study disposition.

Characteristic	Age subgroups		Age/ECOG PS2 subgroups	
	Age ≥65 yr (*n* = 302)	Age ≥75 yr (*n* = 179)	Age ≥65 yr + ECOG PS2 (*n* = 119)	Age ≥75 yr + ECOG PS2 (*n* = 78)
Baseline characteristics				
Age (yr), median (range)	76 (65–94)	81 (75–94)	78 (65–91)	81 (75–91)
Sex (men), *n* (%)	230 (76)	137 (77)	93 (78)	57 (73)
ECOG PS, *n* (%)				
0 or 1	183 (61)	101 (56)	0	0
2	119 (39)	78 (44)	119 (100)	78 (100)
3	0	0	0	0
Upper tract primary tumor[a], *n* (%)	57 (19)	27 (15)	23 (19)	14 (18)
Metastasis location[b], *n* (%)				
Visceral disease	257 (85)	154 (86)	98 (82)	64 (82)
Lymph node disease only	41 (14)	21 (12)	19 (16)	12 (15)
Liver metastases, *n* (%)	65 (22)	43 (24)	30 (25)	22 (28)
Hemoglobin <10 g/dl, *n* (%)	31 (10)	21 (12)	15 (13)	11 (14)
Prior chemotherapy, *n* (%)	54 (18)	27 (15)	22 (19)	10 (13)
Reasons for cisplatin ineligibility, *n* (%)				
Renal dysfunction	154 (51)	90 (50)	9 (8)	7 (9)
ECOG PS2	87 (29)	54 (30)	81 (68)	49 (63)
ECOG PS2 + renal dysfunction	31 (10)	22 (12)	27 (23)	20 (26)
Other[c]	30 (10)	13 (7)	2 (2)	2 (3)
Study disposition				
Completed, *n* (%)	34 (11)	8 (5)	12 (10)	5 (6)
Discontinued, *n* (%)	268 (89)	171 (96)	107 (90)	73 (94)
Adverse event	50 (17)	34 (19)	22 (19)	15 (19)
Clinical progression	36 (12)	22 (12)	15 (13)	9 (12)
Complete response	11 (4)	7 (4)	5 (4)	4 (5)
Physician decision	10 (3)	8 (5)	5 (4)	4 (5)
Progressive disease	142 (47)	89 (50)	51 (43)	36 (46)
Withdrawal by patient	18 (6)	11 (6)	8 (7)	5 (6)
Noncompliance with study drug	1 (<1)	0	1 (1)	0
Treatment ongoing, *n* (%)	0	0	0	0

ECOG PS = Eastern Cooperative Oncology Group performance status.
[a] Unknown for one patient.
[b] Unknown for four patients.
[c] Other reasons include New York Heart Association Class III heart failure, grade ≥2 peripheral neuropathy, and grade ≥2 hearing loss.

Table 2 – Best confirmed objective response and response duration based on RECIST v1.1 per central imaging.

	Age subgroups		Age/ECOG PS2 subgroups	
	Age ≥65 yr (*n* = 302)	Age ≥75 yr (*n* = 179)	Age ≥65 yr + ECOG PS2 (*n* = 119)	Age ≥75 yr + ECOG PS2 (*n* = 78)
Objective response rate, *n* (%)	86 (29)	48 (27)	34 (29)	24 (31)
Complete response	27 (9)	9 (5)	7 (6)	5 (6)
Partial response	59 (20)	39 (22)	27 (23)	19 (24)
Stable disease	56 (19)	32 (18)	17 (14)	10 (13)
Progressive disease	125 (41)	78 (44)	48 (40)	34 (44)
Not evaluable	9 (3)	6 (3)	5 (4)	4 (5)
No assessment	26 (9)	15 (8)	15 (13)	6 (8)
Time to response (mo)[a], median (range)	2.1 (1.3–9.0)	2.1 (1.3–4.7)	2.1 (1.3–5.0)	2.1 (1.3–4.7)
Duration of response (mo)[a,b], median (range)	30.1 (1.6+ to 35.9+)	12.5 (1.6+ to 33.4+)	30.1 (1.6+ to 34.3+)	11.8 (1.6+ to 33.4+)
Proportion of patients with responses lasting ≥24 mo (%)[a,b]	53	35	51	45

ECOG PS2 = Eastern Cooperative Oncology Group performance status 2; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
[a] In patients achieving complete or partial responses only.
[b] Based on the Kaplan-Meier method.

3.3. *Safety*

Treatment-related AEs (TRAEs) of any grade were reported by 210 (70%), 125 (71%), 72 (61%), and 50 (64%) of the ≥65 yr, ≥75 yr, ≥65 yr + ECOG PS2, and ≥75 yr + ECOG PS2 subgroups, respectively (Table 4). Rates of grade 3–5 TRAEs were 22%, 20%, 19%, and 17%, respectively. The most common TRAEs were similar between the subgroups, with both fatigue and pruritus occurring in ≥10% of patients in any subgroup. Other TRAEs occurring in ≥10% of patients

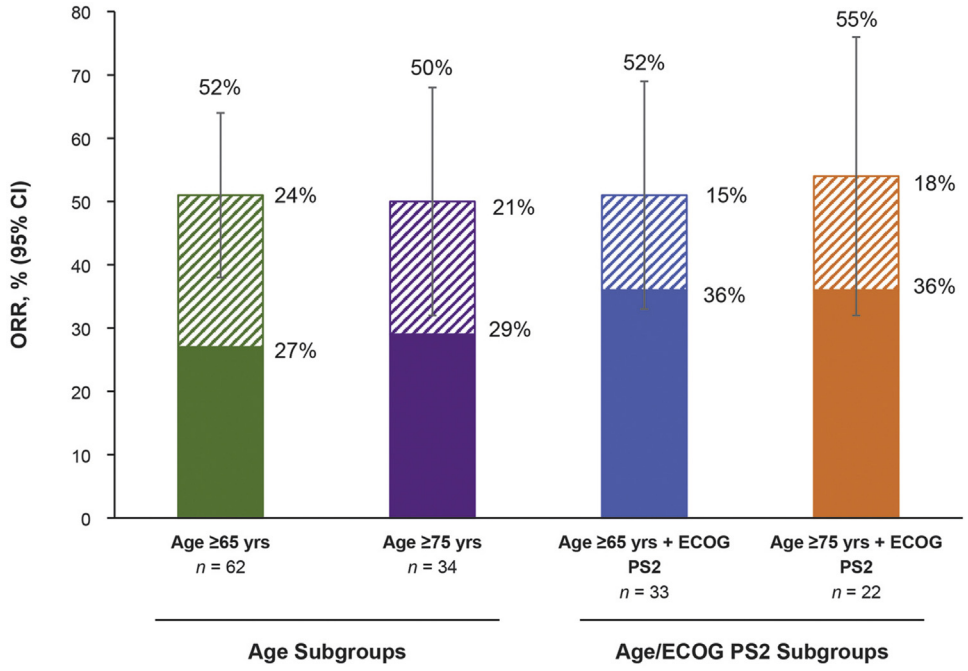

Fig. 1 – Objective response rate as per RECIST v1.1 by central imaging review in patients with CPS ≥ 10 (validation set) for each of the patient subgroups. The striped bar represents CR, while the solid bar represents PR. CI = confidence interval; CPS = combined positive score; CR = complete response; ECOG PS2 = Eastern Cooperative Oncology Group performance status 2; ORR = objective response rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

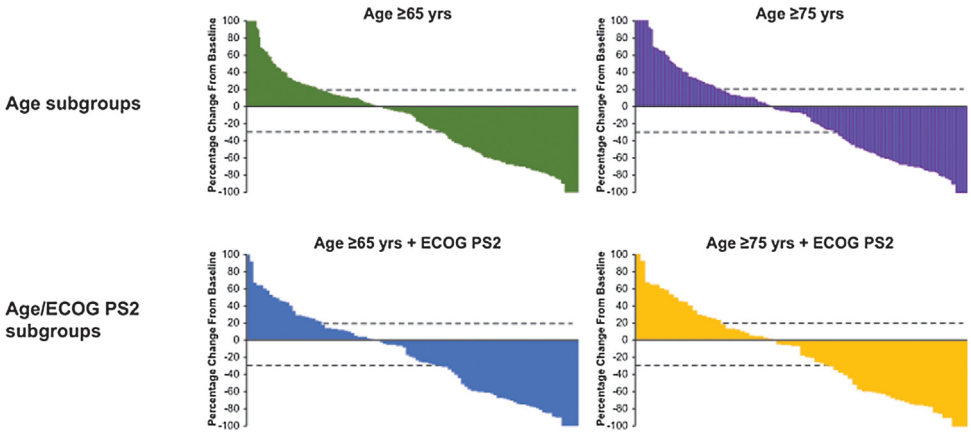

Fig. 2 – Best percentage change from baseline in the sum of the longest diameters of target lesions as per RECIST v1.1 by a central imaging review in the subgroups of patients aged ≥65 yr (*n* = 270), ≥75 yr (*n* = 158), ≥65 yr with ECOG PS2 (*n* = 102), and ≥75 yr with ECOG PS2 (*n* = 70). Dotted lines correspond to patients with a 20% increase in tumor burden and a 30% decrease in tumor burden. ECOG PS2 = Eastern Cooperative Oncology Group performance status 2; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

were decreased appetite, hypothyroidism, and rash in the ≥65 yr group and decreased appetite in the ≥75 yr group. Treatment-related SAEs ranged from 9% to 12% across the four subgroups. Rates of study discontinuations attributable to a TRAE or a treatment-related SAE were also consistent among subgroups (8–10% and 3–5%, respectively). Four grade 4 treatment-related AEs (myocarditis, asthenia, decreased appetite, and hypercalcemia) occurred in two patients who were ≥75 yr old but did not have ECOG PS 2. Only one death was considered attributable to pembrolizumab (myositis in a patient aged ≥75 yr but not with ECOG PS2). Only three immune-mediated AEs occurred in >2% of patients (across subgroups): hyperthyroidism, hypothyroidism, and pneumonitis (Table 4). Hepatitis and pruritus were also observed in >2% of patients in the ≥75 yr and ≥75 yr + ECOG PS2 subgroups, respectively. Hypothyroidism occurred in 11% of the ≥65 yr, 7% of the ≥75 yr, 5% of the ≥65 yr + ECOG PS2, and 8% of the ≥75 yr + ECOG PS2

Table 3 – Summary of PFS and OS according to age and age/ECOG PS2 subgroups.

Survival	Age subgroups		Age/ECOG PS2 subgroups	
	Age ≥65 yr (n = 302)	Age ≥75 yr (n = 179)	Age ≥65 yr + ECOG PS 2 (n = 119)	Age ≥75 yr + ECOG PS 2 (n = 78)
PFS[a], mo (95% CI)				
Median	2.3 (2.1–3.4)	2.1 (2.0–3.4)	2.1 (2.0–3.5)	2.1 (2.0–4.7)
PFS rate at 6 mo	33.6 (28.3–39.0)	31.3 (24.6–38.1)	32.8 (24.5–41.2)	30.8 (20.9–41.1)
PFS rate at 12 mo	22.2 (17.7–27.1)	17.7 (12.5–23.6)	20.0 (13.3–27.6)	18.9 (11.1–28.3)
OS[a], mo (95% CI)				
Median	11.0 (9.5–12.5)	9.7 (7.8–11.5)	8.7 (5.2–10.6)	8.2 (4.4–10.8)
OS rate at 12 mo	45.6 (39.9–51.1)	39.1 (32.0–46.2)	36.6 (28.0–45.2)	35.9 (25.5–46.4)
OS rate at 18 mo	34.9 (29.6–40.3)	25.7 (19.6–32.3)	27.2 (19.6–35.5)	26.9 (17.7–37.0)
OS rate at 24 mo	28.9 (23.9–34.1)	21.2 (15.5–27.4)	23.8 (16.6–31.8)	23.0 (14.4–32.8)

CI = confidence interval; ECOG PS2 = Eastern Cooperative Oncology Group performance status 2; OS = overall survival; PFS = progression-free survival.
[a] From the product-limit (Kaplan-Meier) method for censored data.

subgroups. The rate of pneumonitis—at 5%, 6%, 7%, and 6%, respectively—was similar across the four subgroups.

4. Discussion

Patients with advanced UC who are ineligible for cisplatin-based therapy and, in particular, those who are older and/or have poor performance status represent a population for whom systemic chemotherapy may be challenging and palliative care is often recommended instead [3,4]. In this population, chemotherapeutic alternatives to cisplatin-based chemotherapy tend to be associated with higher levels of toxicity, lower response rates, and inferior outcomes [10,20,21]. In the first-line setting, median OS was 7–10 mo with GCa, 13 mo with paclitaxel + gemcitabine, and 8 mo with single-agent gemcitabine; toxicity was particularly problematic with combination therapies, such as GCa and gemcitabine + paclitaxel [4,7,20].

This exploratory post hoc analysis of KEYNOTE-052 demonstrated that pembrolizumab displays meaningful antitumor activity in the subset of cisplatin-ineligible patients with locally advanced (unresectable) or metastatic UC who are considered senior (aged ≥65 or ≥75 yr), including those with poor functional status (ie, ECOG PS2). Overall, neither age nor poor performance status appeared to have had an impact on the efficacy of pembrolizumab in this patient population; this lack of impact of age or poor performance status is also clinically relevant for patients who cannot tolerate any chemotherapy. ORR was 27–31% across the four subgroups, with 5–9% and 20–24% of the subgroups achieving CR and PR, respectively; in patients ≥85 yr (n = 40), the ORR was 28%. The data in these subgroups were comparable with those of the overall population [18]; in addition, given that most patients were aged ≥65 yr (82%), these patients appeared to be driving the results in the overall population. Percentages of patients with a response at ≥24 mo ranged from 35% to 53% across the four subgroups, whereas median DOR, PFS, OS, and overall efficacy were comparable with those in the original analysis of the entire population [18].

Under-representation and under-reporting of older patients in clinical trials render direct comparison with other studies problematic; the National Cancer Institute, along with several agencies and organizations, strongly recommends equal access to clinical trials regardless of age [5]. Pembrolizumab (indirectly) compares well with historical data with chemotherapy in the aged, poorly functioning population with advanced UC. Median OS was 11.3 mo with pembrolizumab (KEYNOTE-052 trial) and 9.3 mo with carboplatin/gemcitabine in the overall population in an earlier trial [10], but response duration appeared higher in a phase 2 international study of gemcitabine and paclitaxel (time to disease progression, 7.6 mo) [20]. However, comparisons among trials should always be interpreted with great caution because of selection, confounding, and other possible biases.

Although both GCa and methotrexate/carboplatin/vinblastine (M-CAVI) conferred antitumor activity in cisplatin-ineligible patients with advanced UC (N = 238), severe toxicity (defined as treatment-related death, grade 4 thrombocytopenia with bleeding, grade 3 or 4 renal toxicity, neutropenic fever, and mucositis) was experienced by 9.3% of patients receiving GCa and 21.2% receiving M-CAVI [10]. The current analysis demonstrates that pembrolizumab appears to be well tolerated, and its safety profile in these patient subsets, including more senior patients with poor performance status, was similar to that of the total trial population [18]. The data corroborate findings from the KEYNOTE 045 trial that showed higher tolerability and favorable patient-reported outcomes with pembrolizumab over cytotoxic chemotherapy in the platinum-refractory setting [22,23]. Additional information in this population will be available from the ongoing KEYNOTE-361 trial in which pembrolizumab, with or without platinum-based chemotherapy, is compared with platinum-based chemotherapy for advanced UC in the first-line setting (NCT02853305).

Study limitations include the exploratory nature of the subset analyses, open-label study design, and lack of a comparator arm (single-arm phase 2). The similarity in outcomes between the overall study population and the

Table 4 – Summary of TRAEs and list of TRAEs at any grade occurring in ≥5% of patients.

	Age subgroups		Age/ECOG PS2 subgroups	
	Age ≥65 yr (*n* = 302)	Age ≥75 yr (*n* = 179)	Age ≥65 yr + ECOG PS2 (*n* = 119)	Age ≥75 yr + ECOG PS2 (*n* = 78)
AE summary, *n* (%)				
TRAE, any grade	210 (70)	125 (70)	72 (61)	50 (64)
TRAE, grades 3–5	66 (22)	36 (20)	23 (19)	13 (17)
Serious TRAEs	34 (11)	21 (12)	13 (11)	7 (9)
Immune-mediated AE [a]	78 (26)	39 (22)	23 (19)	18 (23)
Discontinuations because of a TRAE	28 (9)	17 (10)	10 (8)	6 (8)
Discontinuations because of a serious TRAE	12 (4)	9 (5)	4 (3)	2 (3)
Deaths because of a TRAE	1 (<1)	1 (<1)	0	0
TRAEs (any grade) occurring in ≥5% of patients in any subgroup, *n* (%)				
Fatigue	57 (19)	32 (18)	12 (10)	8 (10)
Pruritus	56 (19)	33 (18)	15 (13)	12 (15)
Rash	35 (12)	16 (9)	9 (8)	6 (8)
Decreased appetite	35 (12)	23 (13)	9 (8)	7 (9)
Hypothyroidism	30 (10)	11 (6)	6 (5)	6 (8)
Diarrhea	28 (9)	13 (7)	11 (9)	6 (8)
Nausea	25 (8)	11 (6)	8 (7)	3 (4)
Asthenia	14 (5)	9 (5)	8 (7)	5 (6)
ALT level increased	13 (4)	9 (5)	3 (3)	3 (4)
AST level increased	14 (5)	11 (6)	4 (3)	4 (5)
Pneumonitis	14 (5)	9 (5)	7 (6)	4 (5)
Pyrexia	11 (4)	6 (3)	6 (5)	3 (4)
Dysgeusia	11 (4)	7 (4)	4 (3)	4 (5)
TRAEs (grades 3–5) occurring in ≥2 patients in any subgroup, *n* (%)				
All	66 (22)	36 (20)	23 (19)	13 (17)
Myocarditis	2 (1)	2 (1)	1 (1)	1 (1)
Colitis	4 (1)	1 (1)	0	0
Diarrhea	3 (1)	1 (1)	2 (2)	1 (1)
Asthenia	3 (1)	2 (1)	2 (2)	1 (1)
Fatigue	8 (3)	6 (3)	2 (2)	1 (1)
Autoimmune hepatitis	2 (1)	1 (1)	1 (1)	1 (1)
Hepatitis	5 (2)	4 (2)	1 (1)	1 (1)
ALT level increased	2 (1)	2 (1)	0	0
AST level increased	4 (1)	4 (2)	1 (1)	1 (1)
ALP level increased	6 (2)	3 (2)	2 (2)	1 (1)
Decreased appetite	2 (1)	2 (1)	1 (1)	1 (1)
Dehydration	2 (1)	0	1 (1)	0
Hyperglycemia	2 (1)	1 (1)	0	0
Type 1 diabetes mellitus	2 (1)	1 (1)	0	0
Muscular weakness	4 (1)	3 (2)	1 (1)	1 (1)
Pneumonitis	4 (1)	2 (1)	3 (3)	1 (1)
Pruritus	2 (1)	2 (1)	2 (2)	2 (3)
Immune-mediated AEs (any grade) occurring in ≥2% of patients in any subgroup, *n* (%)				
Hypothyroidism	34 (11)	13 (7)	6 (5)	6 (8)
Pneumonitis	15 (5)	10 (6)	8 (7)	5 (6)
Hyperthyroidism	10 (3)	7 (4)	3 (3)	3 (4)
Pruritus	2 (1)	2 (1)	2 (2)	2 (3)
Hepatitis	5 (2)	4 (2)	1 (1)	1 (1)

AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group performance status; TRAE = treatment-related adverse event.
[a] AEs of potentially drug-related immunologic causes reported regardless of attribution by the investigator.

elderly subgroup was predictable, given that the majority of patients enrolled in this study were aged ≥65 yr (*n* = 302, 82%). These caveats can be addressed further in the ongoing KEYNOTE-361 (NCT02853305) trial.

5. Conclusions

Results from this subgroup analysis of older cisplatin-ineligible patients with advanced UC with or without poor performance status suggest that first-line pembrolizumab elicits clinically meaningful and durable responses consistent with those of the overall study population. No new safety signals were identified, consistent with prior reports. Pembrolizumab represents an established treatment option for patients with advanced UC who may not tolerate any platinum-based chemotherapy and are usually treated with best supportive care only.

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Analysis and interpretation of data: Grivas, Plimack, Balar, Bellmunt, Bajorin, Castellano, de Wit, Hahn, Ellison, Frenkl, Godwin, Vuky.
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Petros Grivas: Investigation, Writing - original draft, Writing - review & editing. **Elizabeth R. Plimack:** Investigation, Resources, Writing - original draft, Writing - review & editing. **Arjun V. Balar:** Investigation, Resources, Writing - review & editing. **Daniel Castellano:** Investigation, Resources, Writing - review & editing. **Peter H. O'Donnell:** Investigation, Resources, Writing - review & editing. **Joaquim Bellmunt:** Conceptualization, Investigation, Resources, Writing - review & editing. **Thomas Powles:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Noah M. Hahn:** Conceptualization, Investigation, Resources, Writing - original draft, Writing - review & editing. **Ronald de Wit:** Conceptualization, Investigation, Resources, Writing - review & editing. **Dean F. Bajorin:** Investigation, Resources, Writing - original draft, Writing - review & editing. **Misoo C. Ellison:** Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing. **Tara L. Frenkl:** Investigation, Writing - original draft, Writing - review & editing. **James L. Godwin:** Investigation, Writing - review & editing. **Jacqueline Vuky:** Investigation, Writing - review & editing.

Appendix A. Supplementary data

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