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ORIGINAL ARTICLE

Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select *FGFR* alterations: cohort 2 of the randomized phase III THOR trial☆

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Background: Erdafitinib is an oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor approved to treat locally advanced/metastatic urothelial carcinoma (mUC) in patients with susceptible *FGFR3/2* alterations (*FGFRalt*) who progressed after platinum-containing chemotherapy. *FGFR*-altered tumours are enriched in luminal 1 subtype and may have limited clinical benefit from anti—programmed death-(ligand) 1 [PD-(L)1] treatment. This cohort in the randomized, open-label phase III THOR study assessed erdafitinib versus pembrolizumab in anti—PD-(L)1-naive patients with mUC.

Patients and methods: Patients ≥18 years with unresectable advanced/mUC, with select *FGFRalt*, disease progression on one prior treatment, and who were anti—PD-(L)1-naive were randomized 1 : 1 to receive erdafitinib 8 mg once daily with pharmacodynamically guided uptitration to 9 mg or pembrolizumab 200 mg every 3 weeks. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety.

Results: The intent-to-treat population (median follow-up 33 months) comprised 175 and 176 patients in the erdafitinib and pembrolizumab arms, respectively. There was no statistically significant difference in OS between erdafitinib and pembrolizumab [median 10.9 versus 11.1 months, respectively; hazard ratio (HR) 1.18; 95% confidence interval (CI) 0.92-1.51; $P = 0.18$]. Median PFS for erdafitinib and pembrolizumab was 4.4 and 2.7 months, respectively (HR 0.88; 95% CI 0.70-1.10). ORR was 40.0% and 21.6% (relative risk 1.85; 95% CI 1.32-2.59) and median duration of response was 4.3 and 14.4 months for erdafitinib and pembrolizumab, respectively. 64.7% and 50.9% of patients in the erdafitinib and pembrolizumab arms had ≥1 grade 3-4 adverse events (AEs); 5 (2.9%) and 12 (6.9%) patients, respectively, had AEs that led to death.

Conclusions: Erdafitinib and pembrolizumab had similar median OS in this anti—PD-(L)1-naive, *FGFR*-altered mUC population. Outcomes with pembrolizumab were better than assumed and aligned with previous reports in non—*FGFR*-altered populations. Safety results were consistent with the known profiles for erdafitinib and pembrolizumab in this patient population.

Key words: erdafitinib, pembrolizumab, metastatic urothelial cancer, FGFR, overall survival, safety

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INTRODUCTION

Despite recent advances in systemic therapy, surgically unresectable or metastatic urothelial cancer remains incurable and associated with significant morbidity; 5-year survival rates remain <10%.[1] Systemic therapy remains the standard in the first-line setting for metastatic urothelial cancer.[2] For patients eligible to receive cisplatin, cisplatin-based combination regimens such as cisplatin—gemcitabine or dose-dense methotrexate—vinblastine—doxorubicin—cisplatin (DDMVAC) are preferred. For patients ineligible for first-line cisplatin-based regimens, combination therapy with carboplatin—gemcitabine is an alternative, but is associated with generally inferior outcomes.[3,4] Development of immune checkpoint inhibitors and maintenance avelumab has expanded options in first and subsequent lines. In the first-line setting, these agents represent, where available, a preferred option for patients ineligible for any platinum-based chemotherapy and are also standard as maintenance after platinum-based chemotherapy. In the second-line setting, treatment with pembrolizumab led to significantly longer median overall survival (OS) compared with chemotherapy.[5,6] However, only 21% of patients had a confirmed response to pembrolizumab.[6] There is a clear unmet need for improved treatment options for patients after progression on first-line chemotherapy.

Fibroblast growth factor receptor (*FGFR*) alterations are observed in ∼20% of advanced or metastatic urothelial cancer of the bladder (∼36% in upper tract urothelial cancer) and may function as oncogenic drivers. Tumours with *FGFR* alterations are enriched in luminal 1 subtype, which have shown a low likelihood of response to anti—programmed death-(ligand)1 [PD-(L)1].[7,8] Erdafitinib is an oral selective pan-*FGFR* tyrosine kinase inhibitor. In the single-arm, phase II BLC2001 trial (NCT02365597), erdafitinib showed clinical benefit in adult patients with locally advanced or metastatic urothelial cancer with susceptible *FGFR3/2* alterations who had progressed after platinum-containing chemotherapy.[9,10] Erdafitinib treatment led to an overall response rate of 40%, a median PFS of 5.5 months, and a median OS of 11.3 months.[10] Erdafitinib was granted approval in the United States (accelerated) and several other countries to treat locally advanced or metastatic urothelial carcinoma (mUC) in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy on the basis of this trial.[11] THOR is a confirmatory, randomized phase III study in patients with mUC with two independently designed and analysed cohorts: in cohort 1, erdafitinib showed superior OS compared with investigator's choice of chemotherapy (median OS 12.1 versus 7.8 months, respectively) in patients who had previously received an anti—PD-(L)1 agent.[12] In cohort 2, we assessed whether erdafitinib improved survival over pembrolizumab in patients with *FGFR*-altered mUC whose disease progressed after one prior line of systemic therapy, excluding anti—PD-(L)1 agents.

PATIENTS AND METHODS

Study design and oversight

This ongoing study was conducted in 168 sites in 24 countries/territories in North America, South America, Europe, Oceania, and Asia. It was designed by the sponsor, Janssen Research & Development, with input from the protocol steering committee. Review boards at all participating institutions approved the study, which was conducted in accordance with the current Good Clinical Practice guidelines of the International Council for Harmonisation, applicable regulatory and country-specific requirements, and the principles of the Declaration of Helsinki. The protocol, amendments, informed consent form, investigator brochure, and all other relevant documents were approved by the respective Independent Ethics Committee/Institutional Review Board. All patients provided written informed consent.

An independent data monitoring committee was commissioned to review safety data after at least 60 patients were enrolled and every 6 months afterwards, with a review of one pre-planned interim analysis to assess both efficacy and futility. Case report form data were captured via data entry by study centre personnel in a sponsor database system.

Patients

Eligible patients were aged ≥18 years with metastatic or surgically unresectable urothelial cancer and select *FGFR3/2* alterations (mutations/fusions), an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, adequate organ function, progression on one prior line of systemic therapy, and were naive to anti—PD-(L)1 therapy. Molecular eligibility was evaluated using central laboratory screening or by local historical test results (from tissue or blood). Tumours were required to have one or more of the following *FGFR3* gene mutations: R248C, S249C, G370C, or Y373C; or one or more of the following fusions (translocations): *FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3_V1*, *FGFR3-TACC3_V3,* or *FGFR3-BAIAP2L1.*

Treatment

Patients were randomized 1 : 1 to receive oral erdafitinib (8 mg per day with pharmacodynamically guided uptitration to 9 mg on day 14) or pembrolizumab 200 mg as a 30-min infusion once every 3 weeks until disease progression, intolerable toxicity, withdrawal of consent, or decision by the investigator to discontinue treatment. Randomization was stratified according to ECOG performance status score (0 or 1 versus 2), disease distribution [presence versus absence of visceral (lung, liver, or bone) metastases], and region (North America versus the European Union versus the rest of the world).

Endpoints

The primary endpoint was OS, defined as the time from randomization to death due to any cause. Secondary

endpoints included investigator-assessed PFS (defined as the time from randomization to investigator-assessed disease progression based on RECIST v1.1 or death), objective response rate (ORR) (defined as the proportion of patients who achieved complete or partial response as assessed by RECIST v1.1 by investigator assessment), duration of response (DOR) (defined as the duration from the date of initial documentation of an overall response of complete or partial response to first documented evidence of progressive disease or death), and safety.

Assessments

Imaging was carried out every 6 weeks for the first 6 months and then every 12 weeks for the next 6 months and beyond, and assessment of response was by investigator based on RECIST v1.1. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Ophthalmologic examination at baseline included an Amsler grid test, optical coherence tomography scan (OCT), and ophthalmologic evaluation. An Amsler grid test was conducted at every cycle. Repeat OCT was done as clinically indicated based on the Amsler grid test or clinical assessment.

Statistical analysis

The study was designed to enrol ∼350 patients, with the final analysis planned for when ∼264 deaths had occurred. For sample size calculation purposes, a median OS of 7.24 months was assumed for pembrolizumab, and a median OS of 10.5 months was assumed for erdafitinib. Assuming a 46% improvement in median OS for the erdafitinib arm versus the chemotherapy arm, the study had at least 85% power to detect a hazard ratio (HR) of 0.69 at a statistical significance level of 5% (two-sided), with one interim analysis at ∼65% information fraction (∼172 deaths) and a final analysis. For the interim analysis, superiority and futility were assessed using O'Brien-Fleming boundaries. The stopping boundaries were implemented by the Lan-DeMets spending function to control the type I error at a 0.05 significance level overall. Cohort 2 may have been stopped for futility if the HR observed at the interim analysis was $\geq$1.0, taking into consideration the totality of the data. The study was not stopped at the interim analysis and continued to the final analysis. A two-sided significance level of 0.0460 was used for this final analysis after adjusting for the interim analysis. Key secondary endpoints were part of a hierarchical testing strategy to strongly control the overall family-wise Type I error rate at 0.05 (two-sided). Per the trial design, since the primary endpoint was not met, formal testing of the secondary endpoints was not done and consequently, all *P*-values reported for these endpoints are nominal.

Efficacy analyses used the intention-to-treat (ITT) population, comprising all patients randomized. Safety analyses used the safety population, comprising all randomized patients who received $\geq$1 dose of study treatment. The Kaplan—Meier method was used to summarize the distribution of OS and PFS for each treatment arm; treatment arms were compared with a stratified log-rank test. A stratified Cox proportional hazards model, with treatment as the sole independent variable, was used to estimate HR with a 95% confidence interval (CI) to summarize the magnitude of the benefit of erdafitinib relative to chemotherapy. The distribution of objective response between treatment groups was compared using the Cochran—Mantel—Haenszel method, including an estimate of the relative risk with 95% CI.

RESULTS

Patients

A total of 8733 patients were centrally screened for molecular eligibility in the THOR trial (cohorts 1 and 2); 8396 had tumour samples available with any test results; 7293 had valid central laboratory test results. Of patients with valid central test results, 1212 had *FGFR* alterations (positivity rate, 16.6%; Figure 1A and Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.003). The first patient was enrolled in cohort 2 on 26 April 2018. The clinical cut-off for this analysis was 15 January 2023. 351 patients were randomized in cohort 2, 175 to the erdafitinib arm and 176 to the pembrolizumab arm (Figure 1B). Among the five patients randomized but not treated, three discontinued the study before the start of treatment due to death. The two remaining patients continued in survival follow-up; one was not treated due to refusal to receive study treatment and the other patient did not receive study treatment due to anaemia. As of the data cut-off, 324 (erdafitinib, $n = 164$; pembrolizumab, $n = 160$) of the 346 treated patients had discontinued treatment. 80.9% of patients had *FGFR* mutations, 17.1% had *FGFR* fusions, and 2.0% had both *FGFR* mutations and fusions (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.003). All patients had at least one *FGFR3* alteration; one patient also had an *FGFR2* alteration. The *FGFR3*-S249C mutation was the most prevalent *FGFR* alteration (46.4%), followed by the *FGFR3*-Y373C mutation (19.4%) and *FGFR3-TACC3_V1* fusion (12.0%) (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.003). The demographic and clinical characteristics of the patients at baseline were balanced across the erdafitinib and pembrolizumab treatment arms (Table 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.10.003). The majority of patients (90.6%) with PD-L1 results had low PD-L1 expression [combined positive score $<$10 (Dako PD-L1 IHC 22C3 assay, Labcorp)], with baseline PD-L1 expression not reported in 9.2% of patients due to insufficient tumour availability. In both treatment arms, most patients (98.3%) had prior treatment with platinum-based chemotherapy, with cisplatin being the most common.

Efficacy

The median survival follow-up was 33.2 months (34.8 and 31.1 months in the erdafitinib and pembrolizumab arms,

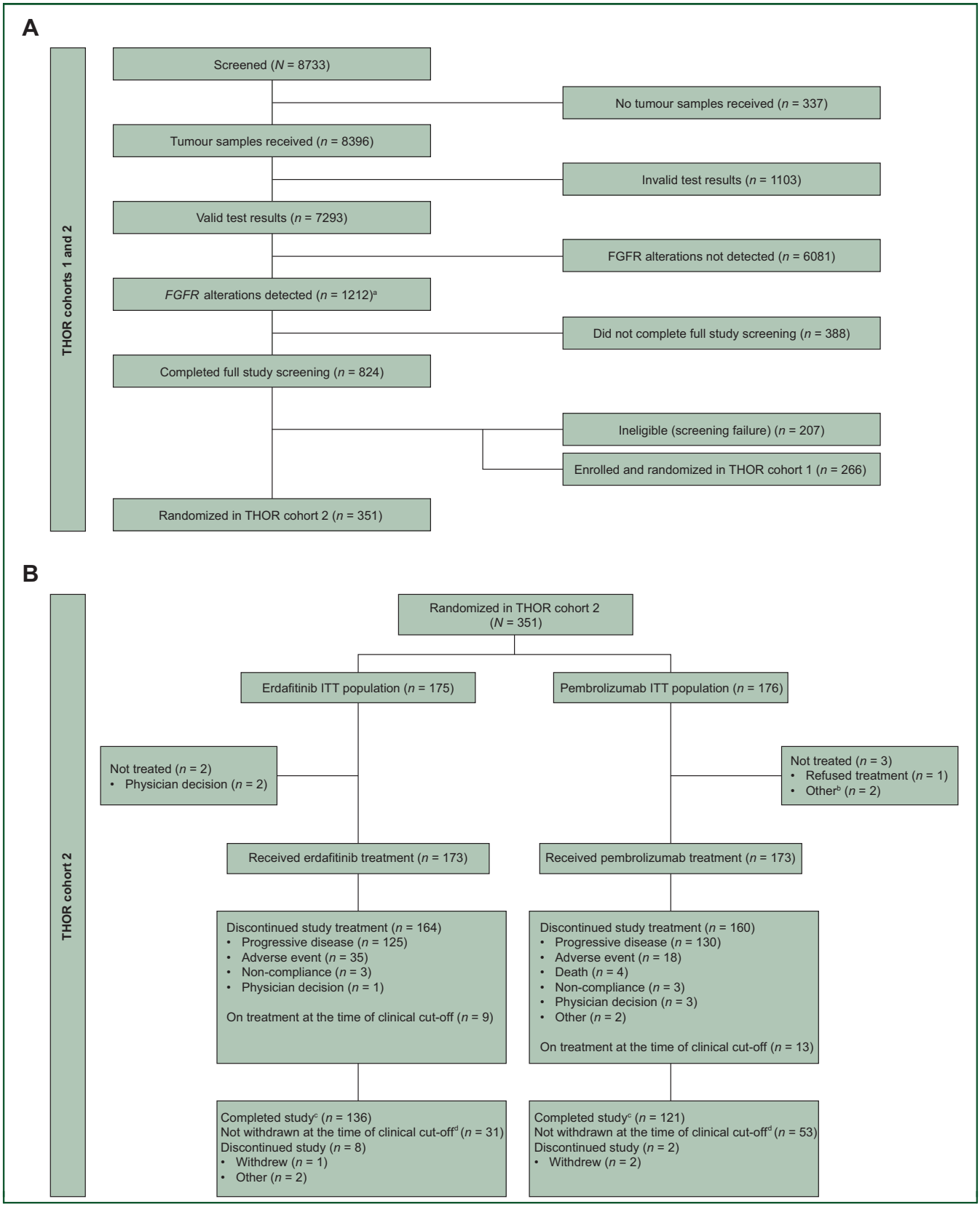

Figure 1. Patient disposition.
(A) THOR screening. (B) THOR cohort 2 patient flow.
ITT, intent-to-treat.
[a]A total of 1212 patients with any test results had *FGFR* alterations detected based on central laboratory test results, 108 on local laboratory test results, and 64 transferred from other Janssen-sponsored studies [ANNAR (NCT03955913) and NORSE (NCT03473743)]. Most patients with local laboratory test results had samples submitted to the central laboratory and patients from other Janssen-sponsored studies used the same central test as those from THOR.
[b]Patients experienced at least one adverse event after being randomized.
[c]Completed study: patients who died during the study (including patients who were randomized but not treated).
[d]Including those still on treatment and those who discontinued treatment without discontinuing the study at the time of clinical cut-off.

Table 1. Demographics and disease characteristics of the patients at baseline

Characteristic	Erdafitinib (*N* = 175)	Pembrolizumab (*N* = 176)
Median age (range), years	67 (44-86)	66 (31-87)
Age subgroup, *n* (%)		
<65	67 (38.3)	70 (39.8)
≥65	108 (61.8)	106 (60.3)
Sex, *n* (%)		
Male	142 (81.1)	132 (75.0)
Female	33 (18.9)	44 (25.0)
Race, *n* (%)		
White	95 (54.3)	111 (63.1)
Asian	37 (21.1)	36 (20.5)
Black	4 (2.3)	0
Multiple	0	1 (0.6)
Not reported	39 (22.3)	28 (15.9)
Geographic region, *n* (%)		
North America	8 (4.6)	6 (3.4)
Europe	118 (67.4)	119 (67.6)
Rest of the world	49 (28.0)	51 (29.0)
Visceral metastasis, *n* (%)		
Present[a]	118 (67.4)	133 (75.6)
Absent	57 (32.6)	43 (24.4)
ECOG PS, *n* (%)[b]		
0	90 (51.4)	90 (51.1)
1	74 (42.3)	74 (42.0)
2	11 (6.3)	12 (6.8)
Primary tumour location, *n* (%)	*n* = 175	*n* = 175
Upper tract	42 (24.0)	44 (25.1)
Lower tract	133 (76.0)	131 (74.9)
PD-(L)1 status, *n* (%)[c]	*n* = 134	*n* = 133
CPS <10	121 (90.3)	121 (91.0)
CPS ≥10	13 (9.7)	12 (9.0)
CPS <1	67 (50.0)	70 (52.6)
CPS ≥1	67 (50.0)	63 (47.4)
Creatinine clearance, ml/min		
<30	1 (0.6)	3 (1.7)
30-<60	72 (41.1)	76 (43.2)
≥60	102 (58.3)	97 (55.1)
FGFR alterations, *n* (%)		
Mutations	142 (81.1)	142 (80.7)
Fusions	30 (17.1)[d]	30 (17.0)
Mutations and fusions	3 (1.7)	4 (2.3)
Prior platinum-based chemotherapy, *n* (%)	172 (98.3)	173 (98.3)
Number of prior lines of systemic therapy	*n* = 172	*n* = 173
1	168 (97.7)	173 (100)
2	4 (2.3)	0
3	0	0
≥3	0	0

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed death-(ligand) 1.
[a]Visceral metastases in lung, liver, and bone.
[b]Scores on the ECOG scale range from 0 (no disability) to 5 (death).
[c]Based on patients with available data.
[d]Inclusive of one patient with *FGFR2-BICC1* and *FGFR3-TACC3_V1* fusions.

respectively). At final analysis, a total of 257 deaths had occurred (136 and 121 in the erdafitinib and pembrolizumab arms, respectively). The median OS for the ITT population was 10.9 months in the erdafitinib arm (95% CI 9.2-12.6 months) and 11.1 months in the pembrolizumab arm (95% CI 9.7-13.6 months), corresponding to an HR of 1.18 (Figure 2A). Based on these final results, a statistically significant difference between erdafitinib and pembrolizumab was not established. The estimated percentage of patients alive at 6 and 12 months was 77% (95% CI 70% to 83%) and 46% (95% CI 39% to 54%) in the erdafitinib arm versus 69% (95% CI 61% to 75%) and 48% (95% CI 41% to 56%) in the pembrolizumab arm, respectively. The HR for OS across clinically relevant subgroups, including age, *FGFR* alteration type, PD-L1 expression, and visceral liver, bone, and lung metastases (Figure 2B) was consistent with that for the overall ITT population. As the OS curves crossed, violating the proportional hazards assumption, an exploratory analysis was conducted to measure the OS benefit of erdafitinib relative to pembrolizumab within specified time periods. The analysis demonstrated that there was an initial trend toward survival benefit in the erdafitinib arm and in later follow-up, survival favored pembrolizumab (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.10.003).

Median PFS was 4.4 months (95% CI 4.1-5.5 months) in the erdafitinib arm versus and 2.7 months (95% CI 1.6-3.0 months) in the pembrolizumab arm (HR 0.88; 95% CI 0.70-1.10) (Figure 3A). The ORR by investigator assessment was 40.0% in the erdafitinib arm [11 patients (6.3%) with complete response; 59 (33.7%) with partial response] and 21.6% in the pembrolizumab arm [8 (4.5%) with complete response; 30 (17.0%) with partial response] [relative risk (RR) 1.85; 95% CI 1.32-2.59] (Figure 3B). The median DOR was 4.3 months (95% CI 3.7-6.9 months) in the erdafitinib arm and 14.4 months (95% CI 7.4-27.8 months) in the pembrolizumab arm (HR 2.88; 95% CI 1.78-4.67 months). The HR for PFS and RR for ORR observed across subgroups, including age, *FGFR* alteration type, PD-L1 expression, and visceral liver, bone, and lung metastases (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.003) were consistent with those observed for the overall ITT population. The disease control rate was 75.4% in the erdafitinib arm and 51.7% in the pembrolizumab arm (RR 1.45; 95% CI 1.23-1.72). The confirmed ORR by investigator assessment (≥2 consecutive assessments) was 29.1% in the erdafitinib arm and 20.5% in the pembrolizumab arm (RR 1.42; 95% CI 0.98-2.06).

Subsequent anticancer therapy was received by 89 patients (50.9%) in the erdafitinib arm and 69 (39.2%) in the pembrolizumab arm (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.10.003). 37.1% of patients in the erdafitinib arm and 6.3% of patients in the pembrolizumab arm received a checkpoint inhibitor as subsequent therapy, and 0.5% and 8.5% of patients, respectively, received an FGFR inhibitor. Thirty-nine patients (22.5%) in the erdafitinib arm and 67 patients (38.7%) in the pembrolizumab arm had an initial response assessment of disease progression and continued treatment until confirmed on a subsequent scan.

Safety

The safety population comprised 173 patients in the erdafitinib arm and 173 patients in the pembrolizumab arm who received ≥1 dose of study treatment. The median duration of exposure was 4.6 months (range, 0.1-43.4 months) with erdafitinib and 3.5 months (0.03-50.5 months) with

pembrolizumab. In the erdafitinib group, 142 (82%) patients had dose uptitration from 8 to 9 mg, and 105 (60.7%) of 173 patients maintained a dose ≥8 mg.

AEs of any cause occurred in 100% of patients in the erdafitinib arm and 96.5% of patients in the pembrolizumab arm (Table 2). The most common treatment-emergent AEs of any grade were hyperphosphataemia (77.5%), diarrhoea (53.2%), and stomatitis (47.4%) in the erdafitinib arm and anaemia (25.4%), asthenia (22.0%), constipation (21.4%), and urinary tract infection (20.8%) in the pembrolizumab arm (Table 3) (most frequent treatment-related AEs are provided in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.10.003). The most frequent (≥5%) grade ≥3 treatment-emergent AEs in the erdafitinib group were palmoplantar erythrodysaesthesia syndrome (9.2%), stomatitis (9.2%), onycholysis (5.8%), and hyponatraemia (8.1%); the most frequent treatment-emergent grade 3-4 AEs in the pembrolizumab arm were anaemia (8.7%) and urinary tract infection (5.2%) (Table 3) (most frequent treatment-related grade 3-4 AEs are provided in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.10.003). One hundred and twelve (64.7%) patients in the erdafitinib arm and 88 (50.9%) patients in the pembrolizumab arm experienced at least one grade 3-4 treatment-emergent AE. Overall, 69 (39.9%) patients in the erdafitinib group and 80 (46.2%) patients in the pembrolizumab group experienced serious treatment-emergent AEs.

Five (2.9%) and 12 (6.9%) patients in the erdafitinib and pembrolizumab arms, respectively, had treatment-emergent AEs that led to death (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.10.003). No treatment-related AEs leading to death occurred in the erdafitinib arm, and three occurred in the pembrolizumab arm (respiratory failure, $n = 1$; pulmonary embolism, $n = 1$; urinary tract infection, $n = 1$).

AEs of any cause led to treatment discontinuation in 33 (19.1%) and 19 (11.0%) patients in the erdafitinib and pembrolizumab arms, respectively (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.10.003). More treatment-related AEs led to treatment discontinuation in the erdafitinib arm compared with the pembrolizumab arm (15.0% versus 4.6%).

Any-grade central serous retinopathy occurred in 39 (22.5%) patients receiving erdafitinib, and at grade 3 in 2 (1.2%) patients, with no grade 4 events. In 24 (62%) of 39 patients with central serous retinopathy of any grade, events were resolved by the clinical cut-off date; of those with ongoing events, 10 of 15 (67%) were grade 1.

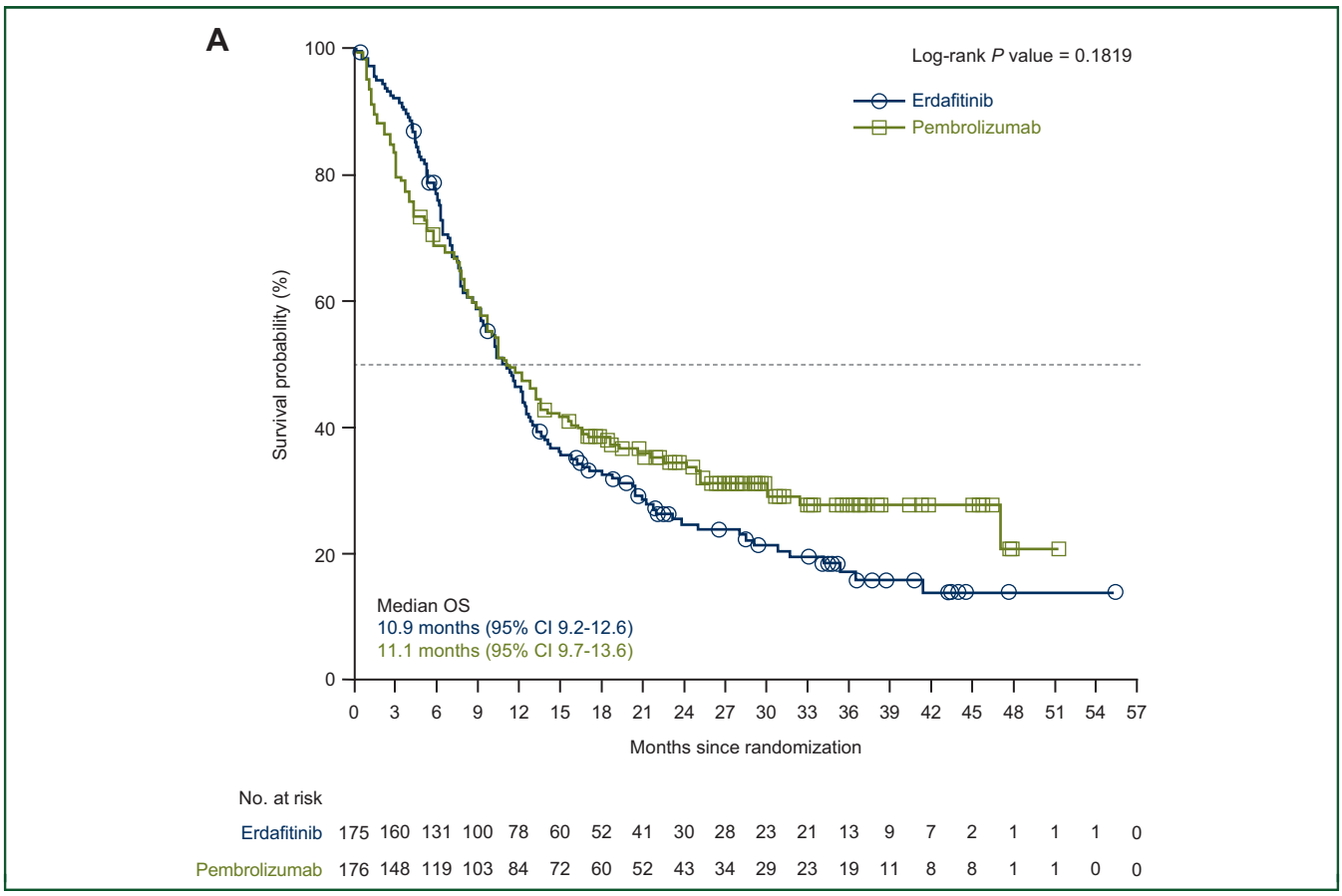

Figure 2. Overall survival.
(A) Kaplan–Meier estimate of overall survival in the erdafitinib group versus the pembrolizumab group. (B) Overall survival in subgroups of patients. The vertical dotted line represents the hazard ratio for the overall population for comparison purposes.
CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD-L1, programmed death-ligand 1.

B

	Erdafitinib Event/N	Erdafitinib Median	Pembrolizumab Event/N	Pembrolizumab Median	Hazard ratio (95% CI)
Overall	136/175	10.9	121/176	11.1	1.16 (0.91-1.48)
Age group					
<65 years	48/67	11.7	43/70	12.9	1.13 (0.75-1.71)
≥65 years	88/108	10.4	78/106	10.8	1.17 (0.86-1.59)
Sex					
Female	22/33	13.9	28/44	10.6	0.95 (0.54-1.65)
Male	114/142	10.3	93/132	11.1	1.20 (0.91-1.57)
Race					
Asian	25/37	18.0	20/36	15.8	1.44 (0.80-2.60)
White	75/95	10.8	81/111	9.1	0.96 (0.70-1.31)
Other	36/43	8.3	20/29	19.4	1.64 (0.94-2.84)
Ethnicity					
Hispanic or Latino	5/5	7.9	4/5	9.7	1.40 (0.37-5.30)
Not Hispanic or Latino	96/126	11.5	94/139	10.6	1.10 (0.83-1.47)
Not reported	35/44	10.3	23/32	15.1	1.29 (0.76-2.20)
***FGFR* alteration type**					
Translocation	22/30	12.3	20/30	11.7	1.13 (0.61-2.07)
Mutation	112/142	10.5	98/142	11.1	1.18 (0.90-1.54)
PD-L1 CPS status					
≥1	49/67	12.6	40/63	10.8	1.10 (0.72-1.67)
<1	56/67	10.8	54/70	10.5	1.05 (0.72-1.53)
≥10	10/13	12.4	8/12	9.1	0.87 (0.34-2.22)
<10	95/121	11.4	86/121	10.6	1.08 (0.80-1.44)
Region					
North America	7/8	12.8	5/6	11.8	1.12 (0.35-3.61)
Europe	94/118	10.0	85/119	10.6	1.09 (0.81-1.46)
Rest of the world	35/49	12.6	31/51	13.6	1.39 (0.85-2.27)
Baseline ECOG PS					
0-1	125/164	11.7	109/163	12.3	1.16 (0.90-1.50)
2	11/11	4.9	12/13	2.7	1.47 (0.59-3.64)
Baseline haemoglobin level					
<10 g/dl	23/25	6.5	25/32	4.6	1.32 (0.74-2.36)
≥10 g/dl	113/150	12.4	96/144	12.9	1.15 (0.88-1.52)
Baseline creatinine clearance					
30 to <60 ml/min	55/72	11.7	55/76	11.6	1.11 (0.76-1.61)
≥60 ml/min	81/102	10.4	63/97	11.6	1.27 (0.91-1.76)
Visceral metastases					
Yes	104/129	9.7	90/126	10.5	1.15 (0.87-1.52)
No	32/46	19.3	31/50	14.2	1.14 (0.70-1.88)
Bone metastasis					
Yes	46/51	9.7	45/54	5.9	0.84 (0.56-1.27)
No	90/124	11.6	76/122	15.8	1.31 (0.97-1.79)
Liver metastasis					
Yes	37/42	6.5	38/42	4.7	0.93 (0.59-1.46)
No	99/133	12.6	83/134	15.0	1.26 (0.94-1.69)
Lung metastasis					
Yes	58/76	10.0	57/84	13.2	1.33 (0.92-1.92)
No	78/99	12.3	64/92	10.3	1.04 (0.75-1.45)
Primary tumour location					
Upper tract	34/42	11.5	26/44	12.9	1.52 (0.91-2.54)
Lower tract	102/133	10.8	94/131	11.0	1.07 (0.81-1.42)

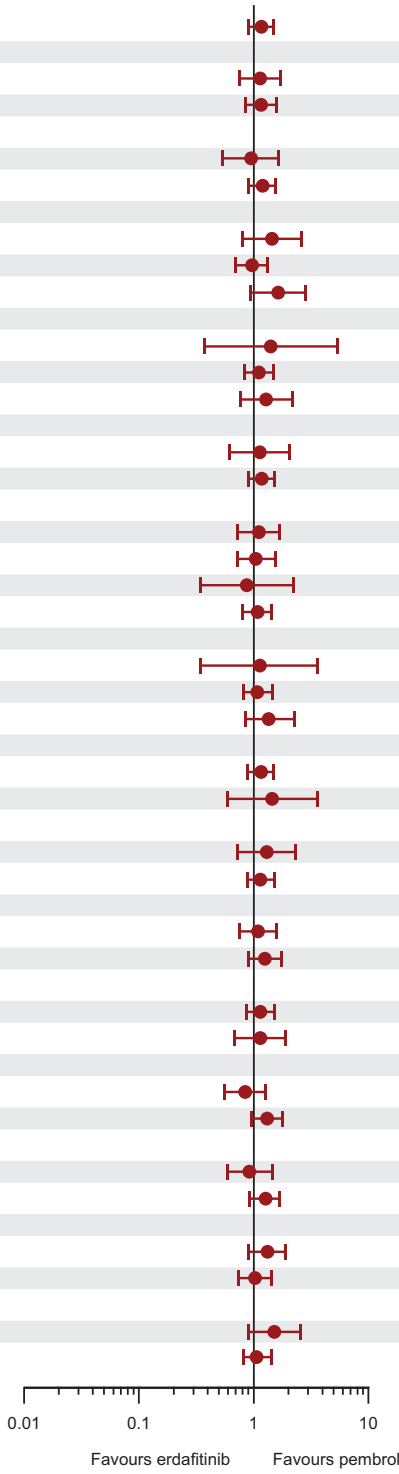

Figure 2. Continued.

Additional grade 3-4 AEs of interest based on the known safety profile of erdafitinib included nail disorders (13.9%) and skin disorders (11.6%) (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.10.003).

DISCUSSION

Erdafitinib was not superior to pembrolizumab in this anti–PD-(L)1-naive mUC patient population with *FGFR* alterations, with an OS of 10.9 months, PFS of 4.4 months, and ORR of 40%. However, pembrolizumab was more active than

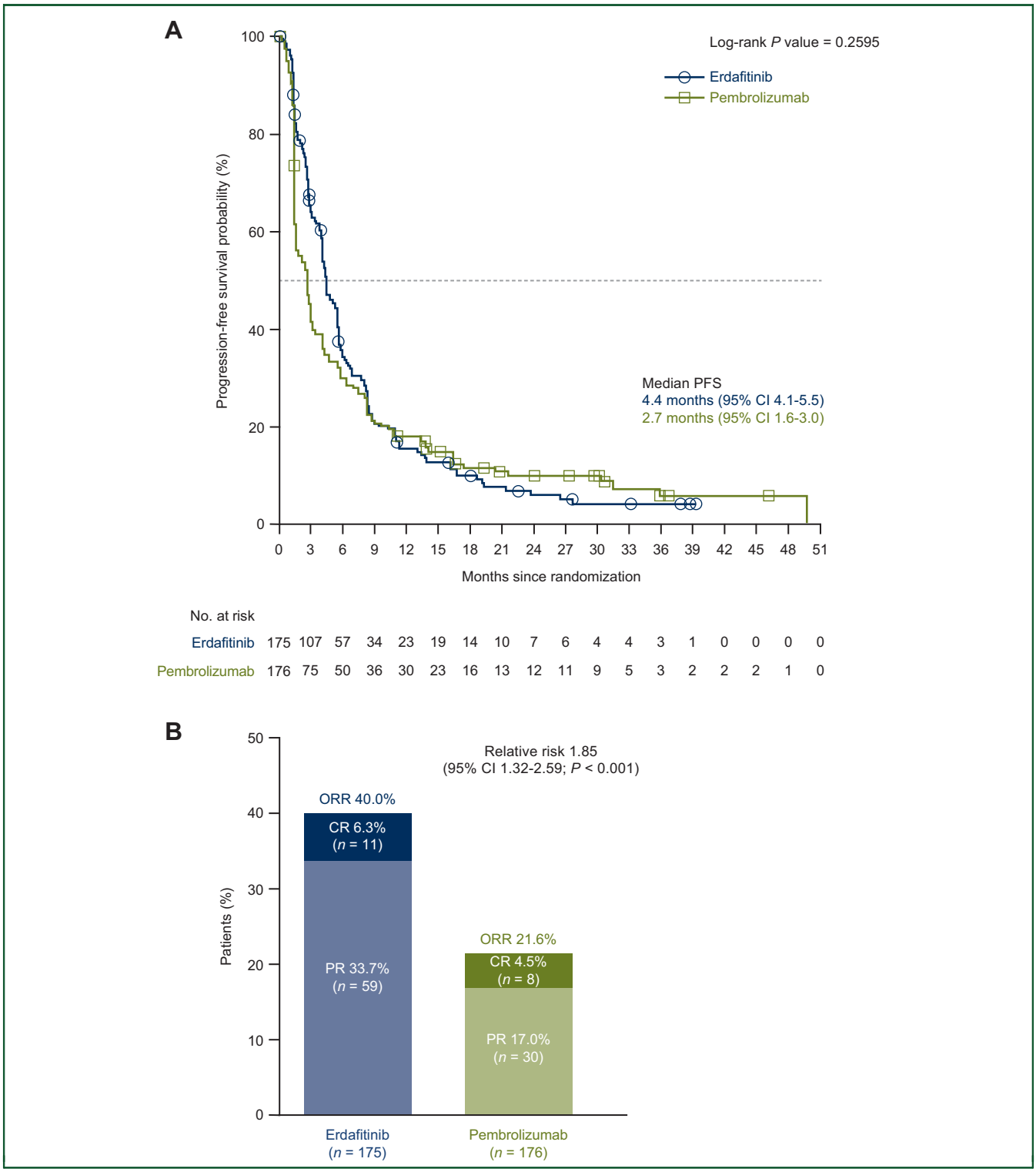

Figure 3. Secondary endpoints.
(A) Kaplan—Meier estimate of PFS in the erdafitinib group versus the pembrolizumab group. (B) ORR in the erdafitinib group versus the pembrolizumab group. Relative risk, 95% CI, and *P* value are estimated using the Cochran—Mantel—Haenszel (CMH) test with ECOG PS (0 or 1 versus 2) as stratification factor. Estimates provide nominal *P*, due to primary endpoint not being met.
CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

assumed at study design in a PD-L1—low population; consequently, the primary endpoint was not met as erdafitinib did not demonstrate superiority over pembrolizumab. Although patients treated with erdafitinib had a higher ORR, they did not have longer PFS and had a shorter DOR when compared with patients treated with pembrolizumab.

A trend towards OS benefit in the erdafitinib group compared to the pembrolizumab group was observed

Table 2. Overall safety summary

Patients with events, *n* (%)	Erdafitinib (*N* = 173)	Pembrolizumab (*N* = 173)
AEs	173 (100)	167 (96.5)
Treatment-related[a]	169 (97.7)	105 (60.7)
Grade 3-4 AEs	112 (64.7)	88 (50.9)
Treatment-related[a]	75 (43.4)	21 (12.1)
Serious AEs	69 (39.9)	80 (46.2)
Treatment-related[a]	23 (13.3)	18 (10.4)
AEs leading to death	5 (2.9)	12 (6.9)
Treatment-related[a]	0	3 (1.7)
AEs leading to treatment discontinuation	33 (19.1)	19 (11.0)
Treatment-related[a]	26 (15.0)	8 (4.6)

AE, adverse event.
[a]An AE was categorized as related if assessed by the investigator as possibly, probably, or very likely related to the study agent.

Table 3. Treatment-emergent adverse events

Adverse event, any grade, *n* (%)[a,b]	Erdafitinib (*N* = 173)		Pembrolizumab (*N* = 173)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hyperphosphataemia	134 (77.5)	1 (0.6)	2 (1.2)	0
Diarrhoea	92 (53.2)	8 (4.6)	24 (13.9)	0
Stomatitis	82 (47.4)	16 (9.2)	6 (3.5)	0
Dry mouth	63 (36.4)	1 (0.6)	8 (4.6)	0
Decreased appetite	59 (34.1)	5 (2.9)	21 (12.1)	2 (1.2)
Anaemia	50 (28.9)	5 (2.9)	44 (25.4)	15 (8.7)
Asthenia	48 (27.7)	8 (4.6)	38 (22.0)	5 (2.9)
Dry skin	43 (24.9)	3 (1.7)	9 (5.2)	0
Dysgeusia	42 (24.3)	0	1 (0.6)	0
Onycholysis	42 (24.3)	10 (5.8)	0	0
Constipation	40 (23.1)	1 (0.6)	37 (21.4)	2 (1.2)
PPE syndrome	38 (22.0)	16 (9.2)	0	0
Alopecia	31 (17.9)	2 (1.2)	1 (0.6)	0
Fatigue	29 (16.8)	5 (2.9)	25 (14.5)	5 (2.9)
Nail discoloration	29 (16.8)	4 (2.3)	0	0
ALT increased	28 (16.2)	3 (1.7)	13 (7.5)	0
AST increased	28 (16.2)	2 (1.2)	14 (8.1)	4 (2.3)
Nausea	28 (16.2)	2 (1.2)	18 (10.4)	0
Weight decreased	28 (16.2)	4 (2.3)	7 (4.0)	0
Blood creatinine increased	27 (15.6)	0	13 (7.5)	1 (0.6)
Vomiting	25 (14.5)	2 (1.2)	8 (4.6)	1 (0.6)
Hyponatraemia	24 (13.9)	14 (8.1)	4 (2.3)	1 (0.6)
Haematuria	23 (13.3)	3 (1.7)	21 (12.1)	7 (4.0)
Urinary tract infection	23 (13.3)	8 (4.6)	36 (20.8)	9 (5.2)
Dry eye	22 (12.7)	1 (0.6)	2 (1.2)	0
Abdominal pain	21 (12.1)	3 (1.7)	10 (5.8)	1 (0.6)
Arthralgia	21 (12.1)	0	14 (8.1)	0
Back pain	20 (11.6)	3 (1.7)	22 (12.7)	2 (1.2)
Nail dystrophy	20 (11.6)	3 (1.7)	0	0
Epistaxis	19 (11.0)	0	1 (0.6)	0
Pain in extremity	19 (11.0)	2 (1.2)	9 (5.2)	2 (1.2)
Peripheral oedema	15 (8.7)	0	19 (11.0)	0
Pyrexia	12 (6.9)	0	22 (12.7)	0
Pruritis	7 (4.0)	0	24 (13.9)	1 (0.6)
Hypothyroidism	0	0	19 (11.0)	0
Intestinal obstruction	10 (5.8)	5 (2.9)	1 (0.6)	1 (0.6)
General physical health deterioration	6 (3.5)	4 (2.3)	5 (2.9)	4 (2.3)
Acute kidney injury	8 (4.6)	4 (2.3)	9 (5.2)	3 (1.7)
Dyspnoea	10 (5.8)	4 (2.3)	9 (5.2)	3 (1.7)
Onychomadesis	15 (8.7)	4 (2.3)	0	0
Pneumonia	3 (1.7)	1 (0.6)	7 (4.0)	5 (2.9)
Hypercalcaemia	7 (4.0)	1 (0.6)	9 (5.2)	4 (2.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysaesthesia.
[a]Treatment-related adverse events by preferred term are listed if events of any grade occurred in ≥10% of patients in either treatment group or if events of grade 3-4 occurred in ≥2% of patients.
[b]Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the patient with the worst toxicity was used.

initially, while OS favoured the pembrolizumab group for patients surviving beyond the first 11 months. This suggests that the overall non-significant trend towards OS benefit in the pembrolizumab group may be attributable to differences in the survival distribution later in the study and long DOR to pembrolizumab in a subset of patients.

Prior studies have demonstrated that *FGFR*-altered tumours with the luminal 1 subtype are enriched for low T-cell infiltration. As such, the study hypothesis was that pembrolizumab would have limited clinical activity in patients with *FGFR*-altered mUC. For sample size calculation purposes, we hypothesised a median OS with pembrolizumab of 7.24 months and a median OS for erdafitinib of 10.5 months. As such, these estimates formed the basis of the sample size estimations for the current THOR cohort 2 trial. Accordingly, results from this final analysis demonstrated that erdafitinib clinical benefit was aligned with expectations based on prior results, whereas the pembrolizumab outcomes were better than anticipated and similar to those reported for patient populations unselected for *FGFR* alterations.

Aligned with prior reports showing an inverse relationship of PD-(L)1 expression and *FGFR* alterations, most enrolled patients (91%) in the current study had low PD-(L)1 expression. However, the lower PD-(L)1 expression was not associated with worse outcomes with pembrolizumab, with the median OS surpassing the hypothesized 7.2 months. Rather, the 11.1-month median OS was comparable to that observed in KEYNOTE-045, with a median OS of 10.3 months in patients not enriched for *FGFR* alterations receiving pembrolizumab as second-line therapy for advanced urothelial carcinoma.[5,13] The observed efficacy of pembrolizumab in this predominantly PD-L1—low population highlights the challenges of using PD-L1 expression as a predictive biomarker.[14]

Erdafitinib with treatment interruptions or dose modifications had a manageable tolerability profile compared with pembrolizumab. Approximately 65% of patients in the erdafitinib arm and 51% of patients in the pembrolizumab arm experienced at least one grade 3-4 treatment-emergent AE. Although grade 3-4 treatment-related AEs that led to treatment discontinuation were more frequently reported with erdafitinib than with pembrolizumab, most AEs were manageable with treatment interruptions and dose modifications and were generally not life-threatening. Treatment-related AEs were consistent with the FGFR inhibitor class, including hyperphosphataemia, skin and nail toxicities, and central serous retinopathy. There were treatment-related AEs that led to three deaths in the pembrolizumab arm and none that led to death in the erdafitinib arm. Treatment-emergent AEs with an outcome

of death were reported in 5 (2.9%) patients in the erdafitinib arm and 12 (6.9%) patients in the pembrolizumab arm. The tolerability profile of pembrolizumab was consistent with its known safety profile.

In cohort 2, the median OS of 10.9 months in the erdafitinib arm [without prior anti—PD-(L)1 treatment] was shorter than the 12.1-month median OS observed in cohort 1 in patients previously treated with prior anti—PD-(L)1 treatment.[12] This was observed despite a sizable proportion of patients who received subsequent immunotherapy after erdafitinib (37% of patients in the erdafitinib group) than FGFR inhibitor therapy after pembrolizumab (8.5%). In addition, the majority (97.7%) of patients in the erdafitinib arm and all patients in the pembrolizumab arm had received one prior line of systemic therapy. It was our expectation that patients would have improved median OS with erdafitinib in the second-line setting in cohort 2 compared with cohort 1[12] after one to two lines of prior systemic treatment. Based on this observation, further studies may be needed to elucidate the biological mechanisms and better understand optimal sequencing in patients with mUC.

In conclusion, patients treated with erdafitinib or pembrolizumab had similar median OS in this anti—PD-(L)1-naive, *FGFR*-altered mUC population.

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DATA SHARING

Janssen Pharmaceutical Companies of Johnson & Johnson's data sharing policy is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for study data access can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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