Geographical Differences in the Management and Outcomes of Patients With Advanced Urothelial Carcinoma Treated With Pembrolizumab After Progression on Platinum-Based Chemotherapy: Results From ARON-2 Study

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ABSTRACT

PURPOSE Our investigation assessed the impact of geographical disparities in the treatment of patients with advanced urothelial cancer (aUC) included in the international, real-world ARON-2 trial.

PATIENTS AND METHODS The study population comprised 1,137 patients with aUC treated with pembrolizumab for relapsed or progressive disease after platinum-based chemotherapy (PBC) at 63 institutions in 19 countries. Patients were divided into three geographical areas: Europe (area 1: 791 patients), the United States (area 2: 156 patients), and Asia (area 3: 190 patients). Clinicopathologic and treatment data were extracted from medical records. The primary end points were to identify differences in patient and treatment characteristics and to assess overall survival (OS) and progression-free survival (PFS) between the three areas.

RESULTS There were differences in patient characteristics: more patients age 70 years and older in area 1; more patients with BMI ≥25 kg/m², squamous histotype, and T1 neoplasia at diagnosis in area 2; and more pure urothelial carcinoma in area 3. There were differences in treatment characteristics: Bacillus Calmette-Guérin instillations and primary tumor surgery were more common in area 1; neoadjuvant and adjuvant PBC, third-line therapies, and specifically enfortumab vedotin (EV) were less common in area 1. Median OS (mOS) from pembrolizumab initiation was 13.0 months in area 1, 29.1 months in area 2 and 13.2 months in area 3 ($P < .001$), and median PFS was 4.8 months, 5.2 months, and 3.8 months, respectively ($P = .002$). In patients receiving EV after progression to PBC and pembrolizumab, mOS was 44.1 months in area 1, 31.7 months in area 2, and 23.8 months in area 3 ($P = .267$).

CONCLUSION Real-world data suggest that facilitating and extending access to targeted therapies for patients with aUC in different geographical areas worldwide may lead to a consistent and widespread survival increase.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

The expansion of therapeutic armamentaria for patients with advanced urothelial carcinoma (aUC) has highlighted disparities in access to care across different regions of the world,[1,2] leading to different treatment strategies and possibly also to different oncologic outcomes.

Hasan et al[3] reported that several factors are associated with a reduced probability of receiving direct cancer therapies for early-stage urothelial cancer: treatment at a nonacademic center, older age, female sex, Hispanic origin, Black race, lower income, and residence in rural areas. The probability of receiving therapies for muscle-invasive, locally advanced, and metastatic disease was found to be

CONTEXT

Key Objective

Does the adoption of different treatment strategies for advanced urothelial carcinoma (aUC) in different countries around the world affect survival outcomes?

Knowledge Generated

In the international real-world ARON-2 study evaluating 1,137 patients treated with pembrolizumab for recurrent or progressive aUC after platinum-based therapy, consistent differences were observed in three different geographical areas (area 1: Europe, area 2: United States, area 3: Asia). These differences were observed in both patient and treatment characteristics and affected overall survival. The approval and reimbursement process for innovative treatments has been subject to significant delays, resulting in inequitable distribution and affecting survival.

Relevance

By intervening in the factors that influence survival and accelerating the approval of innovative drugs in different countries around the world, we will be able to improve prevention and treatment strategies and increase the survival of patients with aUC.

lower for women, older patients, and patients of black ethnicity.[3]

Moreover, the availability of innovative therapeutic agents for aUC varies widely worldwide.[1,2] Significant obstacles persist with respect to access to these therapeutic options in regions including Africa, the Middle East, India, and the Far East. In other countries, although these pharmaceutical products have received approval from the relevant regulatory authorities, the reimbursement processes for these therapies have yet to be finalized or will take a long time.[4] These critical issues affect the availability of the anti–PD-1 inhibitor pembrolizumab as a first-choice treatment option after disease progression following platinum-based chemotherapy (PBC), on the basis of the results of the Keynote-045 trial,[5,6] and even more so the accessibility of drugs for subsequent lines of therapy. The regulatory process for the approval/reimbursement of enfortumab vedotin (EV), a drug-conjugated antibody targeting nectin-4, has been severely delayed in some countries,[4] despite its accelerated approval by the US Food and Drug Administration in 2021 for patients with aUC after PBC and an immune checkpoint inhibitor, on the basis of the phase III EV-301 trial.[7,8]

To date, few large-scale studies examining clinical practice models have focused on aUC. Recently, data from 4,817 patients with aUC reported in 11 geographic SEER registries in the United States were analyzed.[9] Significant regional disparities in overall mortality were observed, with variations attributable to patient, tumor, and treatment characteristics.

The ARON-2 study (ClinicalTrials.gov identifier: NCT05290038)[10-16] was a multicenter, international, retrospective study designed to collect global real-world data on the efficacy of pembrolizumab in patients relapsing or progressing after PBC.

In this paper, we investigate whether geographical differences in patient and tumor characteristics, as well as in treatment strategies, may cause discrepancies in the outcome of patients with aUC across the participating countries of the ARON-2 study.

PATIENTS AND METHODS

Study Population

The study population consisted of patients age 18 years and older with a cytologic and/or histologic confirmed diagnosis of recurrent or progressing aUC after PBC and treated with pembrolizumab between January 1, 2016, and April 1, 2024. A total of 63 institutes in 19 countries around the globe participated in the ARON-2 study.

The case series included patients who had progressed on first-line PBC or relapsed within <1 year of completing neoadjuvant/adjuvant chemotherapy.

All consecutive patients included had a known date on age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), neutrophil-to-lymphocyte ratio (NLR), BMI and concomitant drugs before pembrolizumab administration, primary tumor location (upper urinary tract *v* lower urinary tract [LTUC]), tumor histology and stage at diagnosis, type and timing of surgery, timing and setting (neoadjuvant *v* adjuvant *v* metastatic) of previous PBC, timing of metastatic disease (synchronous *v* metachronous), metastasis sites, magnitude and duration of response to immunotherapy, and date of last follow-up or death.

Clinical data were extracted from the patients' medical records at each center. Pathologic information was extracted from pathology reports for clinical use. Response to pembrolizumab was assessed by radiologists at each institution referring to the RECIST version 1.1.[17] A routine blood count was used to determine NLR, which was calculated as the number of neutrophils divided by the number of lymphocytes. BMI was calculated as weight in kilograms divided by height in meters squared. The WHO recommendations[18] were used for classification of normal weight (BMI = 18.5-24.9), overweight (BMI = 25-29.9), and obesity (BMI ≥30).

The unavailability of any of the above information was an exclusion criterion from this study.

Study End Points

The primary objectives were (1) to assess geographical differences in patient and tumor characteristics and treatment strategies; and (2) to assess discrepancies in progression-free survival (PFS) and overall survival (OS) across the different countries.

Disease response to treatment was classified into one of four categories according to RECIST 1.1: complete response, partial response (PR), stable disease, or progressive disease. The overall response rate was calculated from the sum of the complete response and PR.

OS was calculated from the start of pembrolizumab to death from any cause. PFS was calculated from the first pembrolizumab administration to documented disease progression or death from any cause, whichever occurred first. Patients who had not progressed, died, or were lost to follow-up at the time of analysis were censored at the last follow-up visit.

Statistical Analysis

The Kaplan-Meier method with Rothman's 95% CIs was used to estimate survival curves for OS and PFS. Comparisons between survival curves were performed using the log-rank test. Landmark analysis was performed designating 6, 12, and 24 months as the time points during follow-up period to reduce potential biases related to the follow-up time. Cox proportional hazards models were used to compare multivariable effects on patients' survival and to calculate hazard ratios and 95% CIs.

To assess the potential differences between geographical areas in Table 1, Fisher's exact test was performed to assess statistically significant associations between dual categorical variables, and chi-square test for multiple categorical variables. The level of significance was set to 0.05, and all *P* values were two-sided.

The statistical analyses were performed using the MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Ethics Approval

The study protocol was approved on September 28, 2023, by the ethical committee of the coordinating center (Marche Region—Italy—No. 2022 39/7875, Study Protocol ARON 2 Study; ClinicalTrials.gov identifier: NCT05290038) and by the institutional review boards of participating centers.

Consent to Participate

The informed consent with subsequent analysis of the follow-up data was obtained from all participants.

Consent for Publication

All authors have approved the manuscript for publication.

RESULTS

Descriptive Characteristics

The ARON-2 data set included 1,137 patients treated with pembrolizumab for recurrent or progressive aUC after PBC. The median age at initial diagnosis was 70 years (range, 26-95 years); 74% of patients were male and 26% female. BMI was ≥25 kg/m² in 504 patients (44%).

According to TNM stage, 67% of included patients had T3-T4 tumors at first diagnosis. Seven hundred and sixty-seven patients (67%) had localized disease at onset, while 370 patients (33%) had locally advanced disease or synchronous metastases. LTUC was predominant (73%). Tumor histology was pure urothelial carcinoma (UC) in 79% of patients included.

According to number of metastatic sites, patients were distributed as follows: 48% had one metastatic site and 52% had at least two metastatic sites.

Differences in Patient Characteristics Across Different Geographical Areas

We stratified 1,137 patients into three different geographical areas: area 1 comprises patients from Europe, area 2 from the United States, and area 3 from Asia (Fig 1). The number of patients included by geographic area ranged from 791 in area 1 (69%) to 156 in area 2 (14%) and 190 in area 3 (17%; Data Supplement, Table S1). The Data Supplement (Table S1) details the number of patients included in the study from each participating country.

TABLE 1. Clinicopathologic Features of Patients Included in the ARON-2 Study

Characteristic	Overall, No. (%)	Area 1 (Europe), No. (%)	Area 2 (United States), No. (%)	Area 3 (Asia), No. (%)	*P*
Total patients	1,137 (100)	791 (100)	156 (100)	190 (100)	—
Sex					.983
Male	839 (74)	585 (74)	114 (73)	140 (74)	
Female	298 (26)	206 (26)	42 (27)	50 (26)	
Age, years, median (IQR)					
18-49	61 (5)	44 (6)	6 (4)	11 (6)	.768
50-69	489 (43)	317 (40)	81 (52)	91 (48)	.223
≥70	587 (52)	430 (54)	69 (44)	88 (46)	.326
BMI					<.001
≥25 kg/m^2	504 (44)	365 (46)	89 (57)	50 (26)	
<25 kg/m^2	633 (56)	426 (54)	67 (43)	140 (74)	
Current or former smokers					.417
Yes	696 (61)	468 (59)	98 (63)	130 (68)	
No	441 (39)	323 (41)	58 (37)	60 (32)	
ECOG performance status					.091
0-1	957 (84)	687 (87)	128 (82)	142 (75)	
2-3	180 (16)	104 (13)	28 (18)	48 (25)	
Tumor histology					
Pure urothelial carcinoma	906 (80)	632 (80)	109 (70)	165 (87)	.012
Squamocellular variant	91 (8)	58 (7)	25 (16)	8 (4)	.009
Minor or mixed variants	140 (12)	101 (13)	22 (14)	17 (9)	.515
Primary tumor location					.352
Upper urinary tract	312 (27)	206 (26)	41 (26)	65 (34)	
Lower urinary tract	825 (73)	585 (74)	115 (74)	125 (66)	
T stage					
T1	78 (7)	34 (4)	31 (20)	13 (7)	<.001
T2	295 (26)	221 (28)	31 (20)	43 (23)	.405
T3	510 (45)	355 (45)	58 (37)	97 (51)	.136
T4	254 (22)	181 (23)	36 (23)	37 (19)	.730
Metastatic disease					.107
Synchronous	370 (33)	227 (29)	65 (42)	78 (41)	
Metachronous	767 (67)	564 (71)	91 (58)	112 (59)	
Common sites of metastasis					
Lymph nodes (nonregional)	732 (64)	520 (66)	88 (56)	124 (65)	.275
Lung	393 (35)	279 (35)	63 (40)	51 (27)	.147
Bone	326 (29)	238 (30)	38 (24)	50 (26)	.621
Liver	207 (18)	152 (19)	19 (12)	36 (19)	.309
Brain	25 (2)	12 (2)	4 (3)	9 (5)	.485
N sites ≥2	587 (52)	424 (54)	82 (53)	81 (43)	.228

Abbreviations: ECOG, Eastern Cooperative Oncology Group; T, tumor.

The rate of patients age 70 years and older was higher in area 1, registering +10% and +8% compared with areas 2 and 3, respectively. Furthermore, area 2 showed a +13% and +31% of patients with BMI ≥25 kg/m^2 compared with areas 1 and 3, respectively, while area 3 reported +12% and +7% of patients with ECOG PS ≥2 compared with areas 1 and 2, respectively (Table 1). The differences between the three groups were reported in Table 1 and were statistically significant for BMI ($P < .001$), tumor histology ($P = .012$), and T1 stage ($P < .001$).

Differences in Tumor Characteristics Across Different Geographical Areas

The rate of squamocellular differentiation was higher in area 2, while area 3 was characterized by a higher rate of

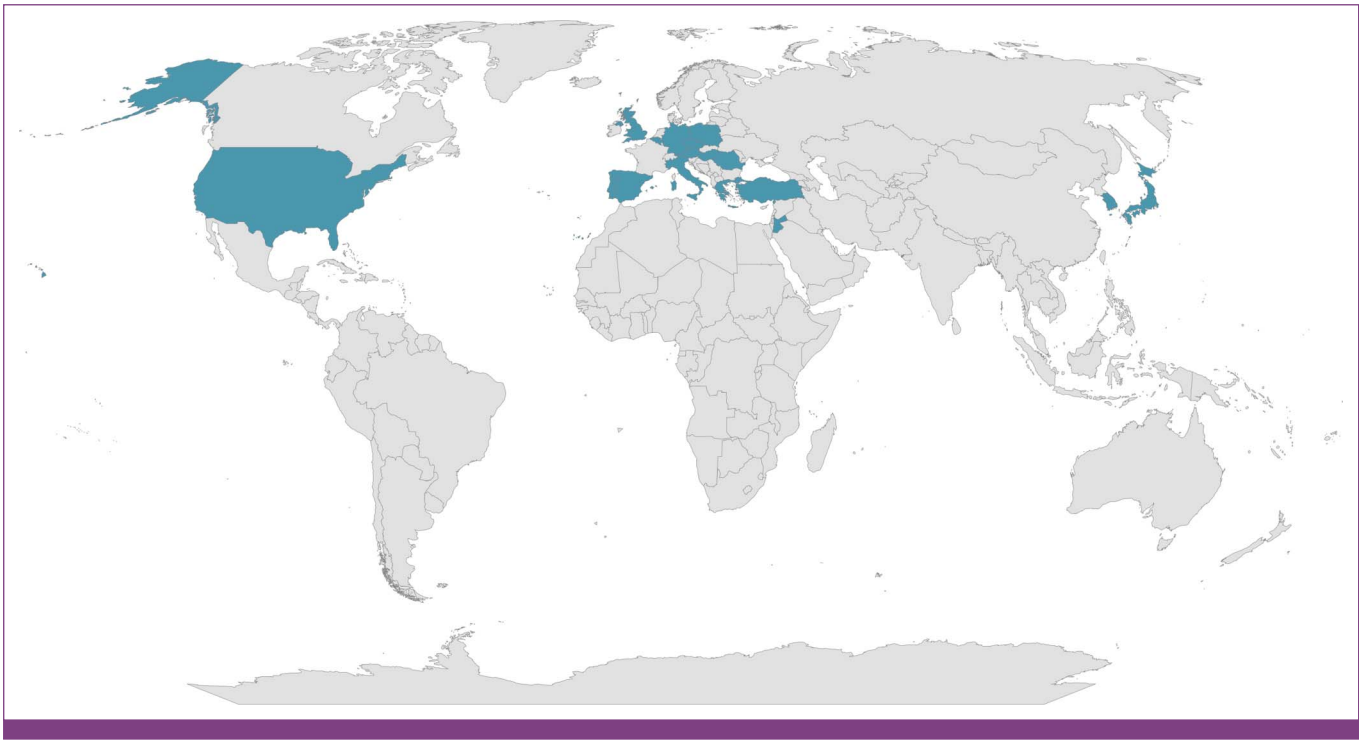

FIG 1. A visual representation of the countries included in ARON-2 project on a global map of the world.

pure UC (P = .012; Table 1). Moreover, the rate of T1 stage tumors was higher in area 2 (P < .001; Table 1), while no significant differences were found in terms of primary tumor location between the three geographical areas (P = .352; Table 1).

The proportions of patients with synchronous metastases were higher in areas 2 (42%) and 3 (41%) compared with area 1 (29%; Table 1; Fig 2). The proportion of patients with one metastatic site ranged from 46% in area 1 to 57% in area 3. No significant differences were observed between the three geographical areas in terms of site of metastases (Table 1).

Differences in Treatment Strategy Across Different Geographical Areas

A total of 736 patients underwent surgical resection of the primary tumor (508 cystectomies and 228 nephroureterectomies). In area 1, surgical resection of the primary tumor was performed in 572/791 patients (72%, 413 cystectomies

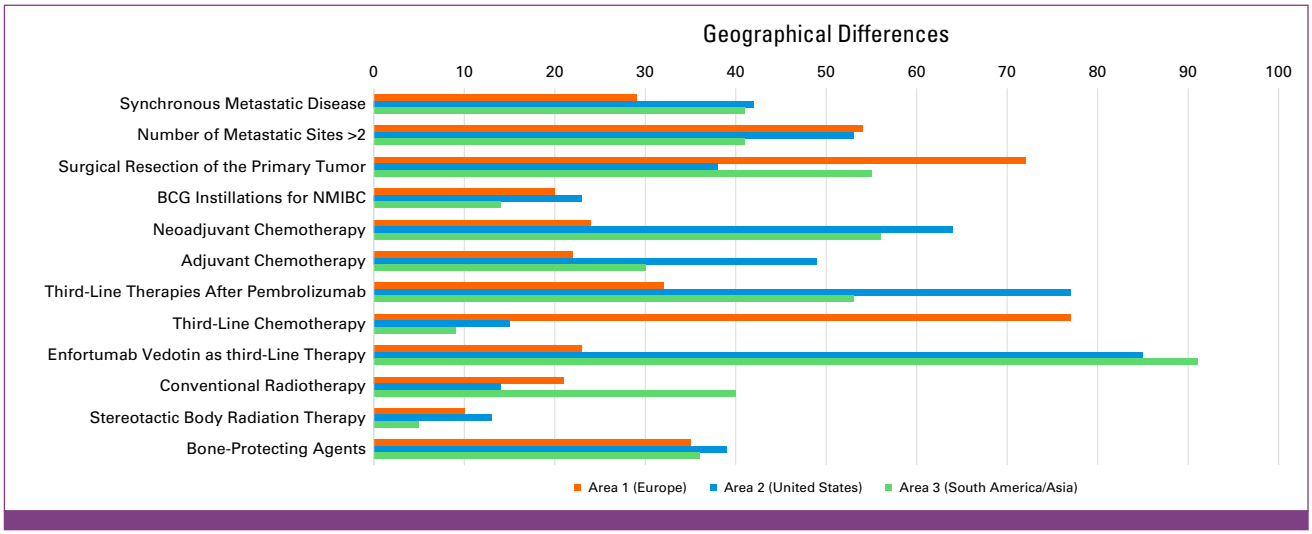

FIG 2. Clinical and pathologic geographical differences in the ARON-2 study. BCG, Bacillus Calmette-Guérin; NMIBC, non–muscle-invasive bladder cancer.

and 158 nephrectomies), while the rates were significantly lower ($P < .001$; Fig 2) in area 2 (38%, 33 cystectomies and 27 nephrectomies) and area 3 (55%, 62 cystectomies and 43 nephrectomies).

Bacillus Calmette-Guérin (BCG) instillations for non–muscle-invasive bladder cancer (NMIBC) were administered in 120/584 patients (20%) with LTUC in area 1, 27/115 patients (23%) in area 2, and 18/125 patients (14%) in area 3 ($P = .256$; Fig 2).

Neoadjuvant PBC was administered in 140/572 patients (24%) in area 1, 39/61 patients (64%) in area 2, and 59/105 patients (56%) in area 3 ($P < .001$; Fig 2). Adjuvant PBC was administered in 123/572 (22%), 30/61 (49%), and 31/105 (30%), respectively ($P < .001$; Fig 2).

Eight hundred and thirty-two patients (73%) progressed to pembrolizumab after PBC, 70% (550 patients) in area 1, 80% (125 patients) in area 2, and 82% (156 patients) in area 3. A total of 344 patients (41%) received a third-line systemic treatment after progression to pembrolizumab: 200 patients received chemotherapy and 144 received EV. The complete list of third-line therapies by geographical area is reported in the Data Supplement (Table S2).

In area 1, 176/550 patients who progressed to pembrolizumab (32%) received third-line therapies, while the rate was higher in the other two geographical areas, being 77% in area 2 and 46% in area 3 ($P < .001$). The distribution of third-line treatments is reported in Figure 2 and the Data Supplement (Table S2).

In area 1, 245 patients (31%) received radiotherapy, of whom 167 (21%) received conventional radiotherapy (CRT) and 78 (10%) stereotactic body radiotherapy (SBRT). In area 2, 42 patients (27%) received radiotherapy, of whom 22 (14%) received CRT and 20 (13%) received SBRT. In area 3, 86 patients (45%) received radiotherapy, of whom 76 (40%) received CRT and 10 (5%) received SBRT. The difference between the three areas was not statistically significant ($P = .190$; Fig 2).

Among patients with bone metastases, bone-protecting agents were administered in 82/238 patients (35%) in area 1, in 15/38 (39%) in area 2, and 18/50 (36%) in area 3 ($P = .830$; Fig 2).

Differences in Overall Mortality Across Different Geographical Areas

The median follow-up time from first pembrolizumab administration was 17.0 months (95% CI, 15.2 to 88.7) in the overall population, 15.6 months (95% CI, 14.0 to 17.3) in area 1, 22.5 months (95% CI, 15.2 to 88.7) in area 2, and 19.8 months (95% CI, 16.3 to 62.8) in area 3.

The median OS (mOS) from starting pembrolizumab was 15.3 months (95% CI, 13.4 to 91.0) overall, 13.0 months (95% CI, 10.7 to 86.9) in area 1, 29.1 months (95% CI, 18.5 to 48.6) in area 2, and 13.2 months (95% CI, 10.9 to 19.6) in area 3 ($P < .001$; Fig 3). The 2-year OS rate was 34% in area 1, 54% in area 2, and 32% in area 3 ($P = .002$). The difference in terms of mOS was statistically significant at the 6-month landmark analysis, while no differences were found at 12 and 24 months (Data Supplement, Table S3).

The median PFS from the initiation of pembrolizumab therapy was 4.7 months (95% CI, 4.1 to 70.7) in the overall population, 4.8 months (95% CI, 4.1 to 57.7) in area 1,

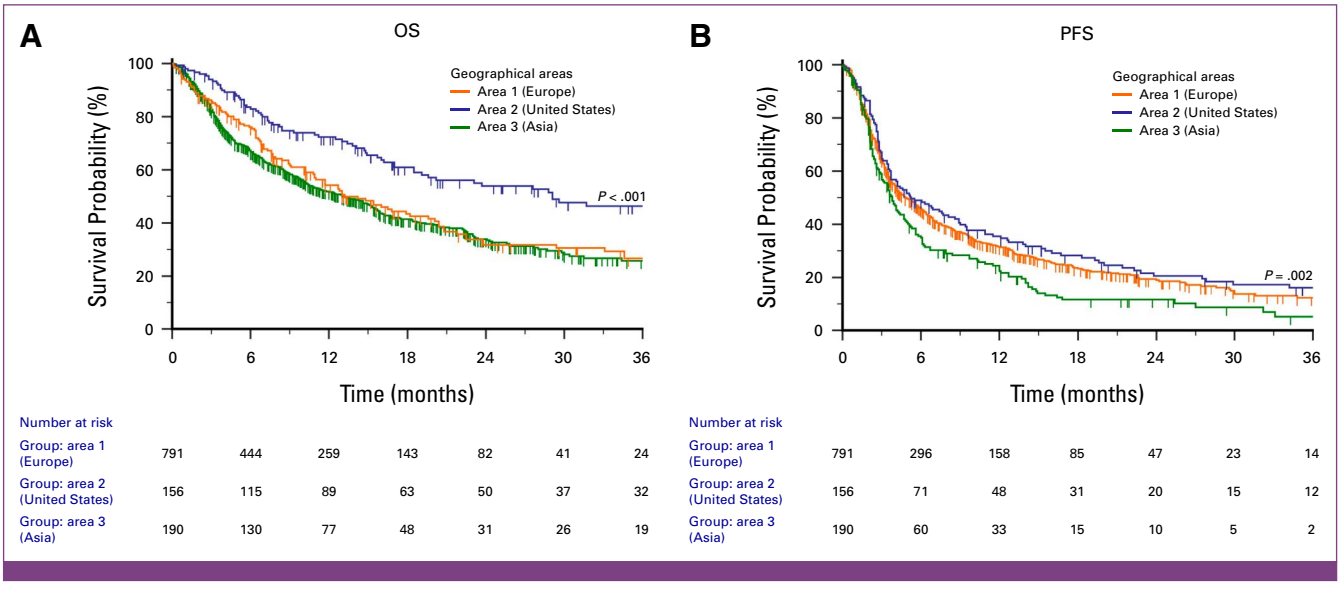

FIG 3. (A) OS and (B) PFS in patients treated with pembrolizumab for advanced UC stratified by geographical areas. OS, overall survival; PFS, progression-free survival; UC, urothelial carcinoma.

5.2 months (95% CI, 3.7 to 70.7) in area 2, and 3.8 months (95% CI, 3.0 to 47.7) in area 3 (P = .002; Fig 3). The 1-year PFS rate was 32% in area 1, 36% in area 2, and 25% in area 3 (P = .098).

In the elderly population (age ≥70 years), mOS was longer in area 2 (29.1 months; 95% CI, 19.6 to 78.8 *v* 11.4 months; 95% CI, 8.9 to 14.0 in area 1 and 16.0 months; 95% CI, 8.9 to 20.8 in area 3; P < .001; Data Supplement, Fig S1). In the overall population, mOS was lower in females compared with males (11.7 months; 95% CI, 8.4 to 14.1 *v* 15.9 months; 95% CI, 14.8 to 18.5; P = .006). In area 1, mOS was 8.5 months (95% CI, 6.4 to 12.4) in females and 14.9 months (95% CI, 12.3 to 86.9) in males (P = .013; Data Supplement, Fig S2). In area 2, mOS was 19.6 months (95% CI, 13.4 to 31.7) in females and 44.8 months (95% CI, 19.1 to 65.7) in males (P = .110; Data Supplement, Fig S2). In area 3, mOS was 12.7 months (95% CI, 6.8 to 20.8) in females and 15.4 months (95% CI, 10.2 to 20.4) in males (P = .697; Data Supplement, Fig S2).

We further analyzed the impact of third-line treatments on patient outcomes. The mOS from the start of pembrolizumab administration in patients who received chemotherapy as successive therapy was 14.6 months (95% CI, 13.0 to 15.8) in the overall study population, being 14.9 months (95% CI, 13.0 to 15.8), not reached (95% CI, not reached to not reached), and 13.2 months (95% CI, 7.9 to 16.8) in areas 1, 2, and 3, respectively (P = .408; Fig 4). Conversely, the mOS in patients who subsequently received EV was 36.1 months (95% CI, 27.6 to 91.0) in the overall study population, 44.1 months (95% CI, 25.6 to 86.9) in area 1, 31.7 months (95% CI, 23.1 to 51.5) in area 2, and 23.8 months (95% CI, 20.4 to 49.8) in area 3 (P = .267, Fig 4). By contrast, the mOS in the subgroup of patients who did not receive any third-

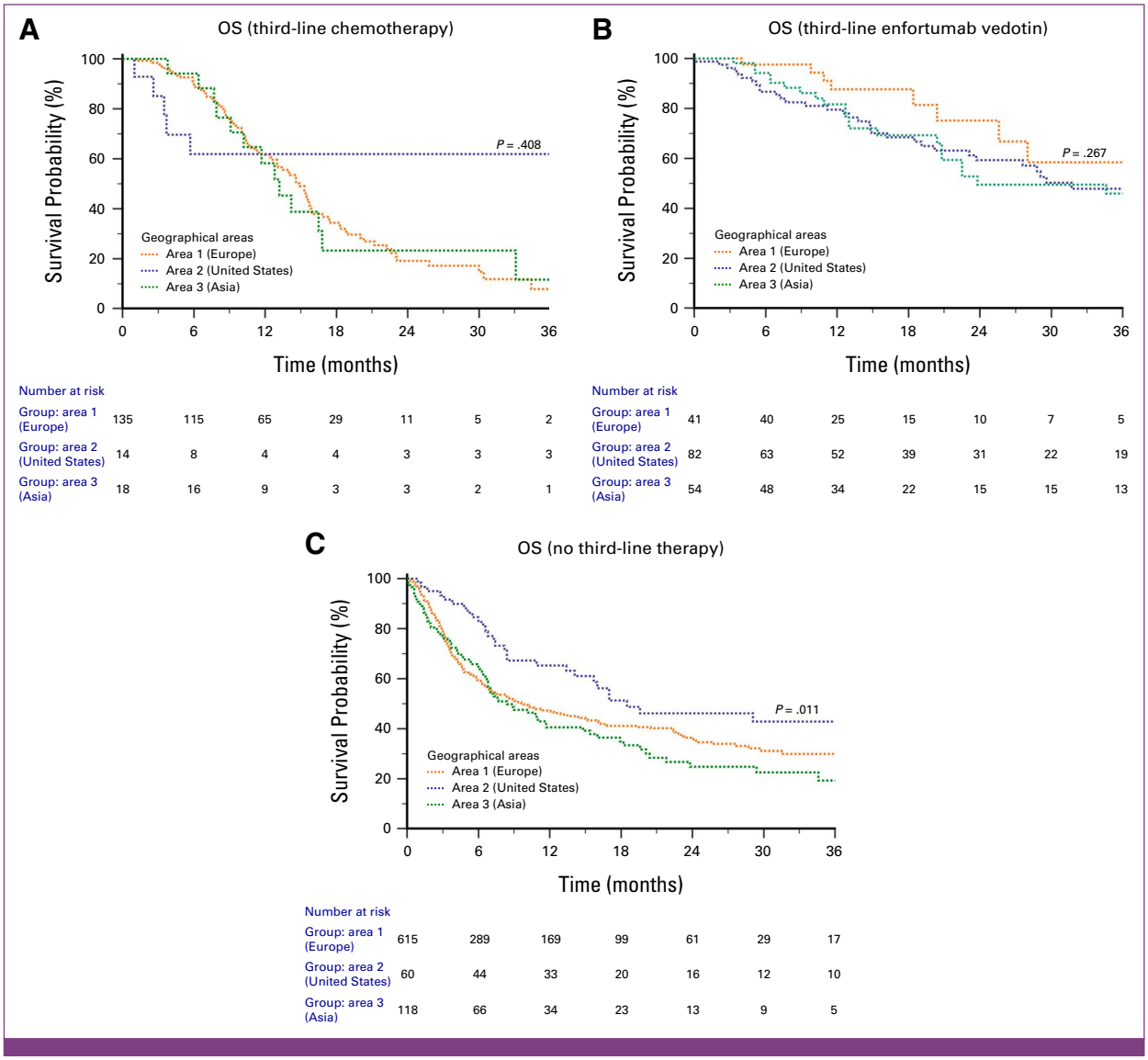

FIG 4. OS in patients with UC stratified by third-line therapy: (A) third-line chemotherapy, (B) third-line enfortumab vedotin, and (C) no third-line therapy. OS, overall survival; UC, urothelial carcinoma.

line treatment was 10.2 months (95% CI, 8.4 to 78.8), 9.7 months (95% CI, 7.4 to 13.3) in area 1, 18.5 months (95% CI, 13.4 to 78.8) in area 2, and 8.4 months (95% CI, 6.7 to 14.8) in area 3 (P = .011; Fig 4).

DISCUSSION

Geographical differences in patient, tumor, and treatment characteristics, and their potential correlation with oncologic outcomes, have not been described in registered clinical trials. We therefore investigated these differences in our international real-world series, ARON-2, to identify prognostic indicators and corrective steps for clinical practice.

Our analyses revealed significant geographical differences in patient and tumor characteristics between ARON-2 countries. The area 2 population exhibited distinctive clinical and histologic characteristics. The percentage of patients with a BMI ≥25 kg/m² was significantly higher (+13% and +31% more patients than in areas 1 and 3), consistent with US anthropometric data.[19] A higher percentage of squamous cell carcinoma was also identified in area 2, which may be due to more accurate identification and reporting of variant histologies associated with pure urothelial carcinoma by US pathologists.[20] In addition, 20% of patients had T1 cancer at the time of diagnosis, supporting the previously documented observation that US individuals have more direct access to preventive services (including urinary tract cancer screening) and are therefore more likely to be diagnosed at an earlier stage of disease.[21,22]

Furthermore, geographical differences were identified in the treatment strategy previously used for the NMIBC and perioperative setting within the ARON-2 study population (Fig 2). The administration of intravesical instillations of BCG was more prevalent in areas 1 and 2 (20% and 23%, respectively) than in area 3 (14%), although the overall rate remained low in part due to the recent worldwide shortage of BCG availability,[23] which may have contributed to the high recurrence rates.[24] These data may explain the larger size (T3: 51%) at diagnosis of neoplasms in the Asian patients (Table 1). Although the proportion of patients undergoing surgical resection of the primary tumor was significantly higher in area 1 (72%) than in area 2 (38%) or area 3 (55%), there is a significant disparity in the lower proportion of patients receiving neoadjuvant/adjuvant chemotherapy in area 1 compared with the other areas. Area 1 exhibited the lowest rates of these interventions, particularly in comparison with area 2. This finding may reflect more effective multidisciplinary management of patients with UC in the United States and Asia.[25,26] However, the utilization of perioperative therapeutic strategies is anticipated to rise in the near future, on the basis of the most recent clinical evidence.[27,28]

It is noteworthy that a high percentage of patients (43% of the overall population) received subsequent therapy after progression to PBC and pembrolizumab (area 1: 32%, area 2: 77%, area 3: 46%). These rates exceed those reported in recently published treatment models[29,30] and testify to a continuous and substantial improvement in aUC management worldwide. Compared with other regions, the percentage of European patients receiving third-line EV therapy (23% EV, 70% CT) is much lower (area 2: 85% EV, 12% CT; area 3: 76% EV, 9% CT). The significant delay in the approval/reimbursement of EV in several countries (Data Supplement, Table S4) has denied a significant proportion of patients the opportunity to receive an innovative drug that has been demonstrated to improve OS compared with conventional regimens.

mOS from pembrolizumab initiation in the overall population (mOS, 15.3 months) and in the three different geographical areas (area 1: 13.0 months, area 2: 29.1 months; area 3: 13.2 months) were longer than in the pivotal trial[4,5] and other real-world case series.[31,32] For patients receiving EV after pembrolizumab, mOS was 36.1 months overall, 44.1 months in area 1, 31.7 months in area 2, and 23.8 months in area 3 (Fig 4). Our results are consistent with other recent retrospective analyses[33,34] and further confirm the favorable efficacy outcomes of pivotal trial[6,7] in real-world clinical practice. The differences that we found among North America, Europe, and Asia in terms of OS and PFS are in line with the results of a pooled meta-analysis published in 2021, showing 33%, 28%, and 26% of OS benefit and 42%, 39%, and 13% of PFS benefit in these three geographical areas, respectively. This variability reflects a series of factors including inherent geographical, ethnic, and lifestyle differences.[35]

In our case series, mOS was significantly lower in women and older patients (Data Supplement, Figs S1 and S2) across three geographical regions. This is consistent with other literature data, despite the absence of a robust rationale to support it.[22,36] These disparities highlight the crucial need to implement the enrollment of women and older patients in clinical and genomic studies, particularly when evaluating prognostic and predictive biomarkers that can guide therapeutic approaches.

To limit disparities and ensure effective therapies for as many patients with aUC as possible, it may be beneficial to extend inclusion in clinical trials to less developed countries and more vulnerable patients, as well as conducting large-scale expanded-access programs for innovative treatments. Furthermore, local research could contribute to the expansion of knowledge on aUC in different geographical areas, thereby fostering the adoption of standardized treatment strategies appropriate for different patient subgroups and compatible with the limited resources of developing countries.[37]

To the best of our knowledge, this is the first analysis to explore the geographical differences in treatment approaches and outcomes in a large international population of patients with aUC.

The main limitations of our work are as follows: (1) the retrospective nature of data collection and consequent

imprecision, particularly in cancer classification/staging and response assessment; (2) the limited information on patients' race, genetic factors, and lifestyle; (3) the lack of information on patients' socioeconomic status, place of residence, and the availability of health care and other factors that influence treatment and, consequently, survival outcomes; (4) the limited number of countries worldwide; (5) the difference in number of patients included in the three geographical areas and from each country; and (6) the delay in the approval/reimbursement of innovative agents in several countries.

Although our results are not exactly representative of the entire global population and are restricted to the specific study population, they are certainly a topic of reflection for health care professionals, patients, and stakeholders at the national and international levels. A more comprehensive grasp of the interrelationship between patient/treatment characteristics and UC incidence/mortality will facilitate the formulation of more efficacious strategic plans for the prevention of this malignancy and the design of more appropriate treatment strategies in different regions of the world.

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DATA SHARING STATEMENT

The data sets generated and/or analyzed during the current study are not publicly available because of patient data security but are available from the last author on reasonable request.

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