EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study

Francesco Massari[a,†], *Veronica Mollica*[a,†,*], *Ondrej Fiala*[b,c], *Ugo De Giorgi*[d], *Jakub Kucharz*[e], *Maria Giuseppa Vitale*[f], *Javier Molina-Cerrillo*[g], *Gaetano Facchini*[h], *Emmanuel Seront*[i], *Edoardo Lenci*[j], *Maria T. Bourlon*[k], *Francesco Carrozza*[l], *Renate Pichler*[m], *Cristian Lolli*[d], *Zin W. Myint*[n], *Ravindran Kanesvaran*[o], *Mariangela Torniai*[p], *Pasquale Rescigno*[q], *Alfonso Gomez de Liaño*[r], *Roubini Zakopoulou*[s], *Sebastiano Buti*[t], *Camillo Porta*[u,v], *Enrique Grande*[w,‡], *Matteo Santoni*[x,‡]

[a] *Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy;* [b] *Department of Oncology and Radiotherapeutics, Faculty of Medicine and University Hospital Pilsen, Charles University, Pilsen, Czechia;* [c] *Biomedical Center, Faculty of Medicine, Charles University, Pilsen, Czechia;* [d] *Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori Dino Amadori, Meldola, Italy;* [e] *Department of Uro-oncology, Maria Sklodowska-Curie National Research Institute of Oncology Warsaw, Poland;* [f] *Division of Oncology, Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy;* [g] *Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain;* [h] *Medical Oncology Unit, SM delle Grazie Hospital, Pozzuoli, Italy;* [i] *Department of Medical Oncology, Centre Hospitalier de Jolimont, Haine Saint Paul, Belgium;* [j] *UOC Oncologia, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy;* [k] *Hematology and Oncology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico;* [l] *Oncology Unit, Santa Maria delle Croci Hospital, Department of Oncology and Hematology, AUSL Romagna, Ravenna, Italy;* [m] *Department of Urology, Medical University of Innsbruck, Innsbruck, Austria;* [n] *Markey Cancer Center, University of Kentucky, Lexington, KY, USA;* [o] *Division of Medical Oncology, National Cancer Centre Singapore, Singapore;* [p] *UOC Oncologia Medica, Ospedale A. Murri, Fermo, Italy;* [q] *Translational and Clinical Research Institute, Centre for Cancer, Newcastle University, Newcastle upon Tyne, UK;* [r] *Medical Oncology Department, CHU Insular-Materno Infantil, Las Palmas, Spain;* [s] *2nd Department of Propedeutic Internal Medicine, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece;* [t] *Medical Oncology Unit, University Hospital Parma, Parma, Italy;* [u] *Interdisciplinary Department of Medicine, Aldo Moro University of Bari, Bari, Italy;* [v] *Division of Medical Oncology, A.O.U. Consorziale Policlinico di Bari, Bari, Italy;* [w] *Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain;* [x] *Oncology Unit, Macerata Hospital, Macerata, Italy*

Article info

Article history:
Received 16 November 2023
Received in Revised form
13 February 2024
Accepted 22 March 2024

Associate Editor:
Laurence Albiges

Keywords:
ARON-1
Immunotherapy

Abstract

Background and objective: Papillary renal cell carcinoma (pRCC) is the most frequent histological subtype of non-clear cell RCC (nccRCC). Owing to the heterogeneity of nccRCC, patients are often excluded from large phase 3 trials focused on clear cell RCC, so treatment options for nccRCC remain limited. Our aim was to investigate the efficacy of first-line treatment with tyrosine kinase inhibitors (TKIs) or immuno-oncology (IO)-based combinations in patients with pRCC.

Methods: We performed a multicenter retrospective analysis of real-world data collected for patients with advanced pRCC treated in 40 centers in 12 countries as part of the ARON-1 project (NCT05287464). The primary endpoints were overall survival (OS), progression-free survival (PFS), the overall response rate (ORR), and time to second progression (PFS2). OS, PFS, and PFS2 were estimated using the Kaplan-Meier method and

† These author contributed equally to this work.
‡ These authors are joint senior authors.
* Corresponding author. Department of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italia.
E-mail address: veronica.mollica7@gmail.com (V. Mollica).

https://doi.org/10.1016/j.euo.2024.03.011

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

Immuno-oncology combinations
Papillary renal cell carcinoma
Survival
Tyrosine kinase inhibitors

results were compared between the treatment groups using a log-rank test. Univariate and multivariable analyses were carried out using Cox proportional-hazard models.
Key findings and limitations: We included 200 patients with metastatic pRCC, of whom 73 were treated with IO-based combinations and 127 with TKIs. Median OS was 22.5 mo in the TKI group 28.8 mo in the IO group ($p = 0.081$). Median PFS was 6.4 mo in the TKI group and 17.4 mo in the IO group ($p < 0.001$). The ORR was higher in the IO group than in the TKI group (41% vs 27%; $p = 0.037$).
Conclusions and clinical implications: Our results show that IO-based combinations have superior efficacy outcomes to TKIs for first-line treatment of metastatic pRCC.
Patient summary: The ARON-1 project collects clinical data for patients with kidney cancer treated in multiple centers worldwide to assess outcomes in the real-world setting. We analyzed data for patients with metastatic kidney cancer of a specific subtype to evaluate the efficacy of different first-line treatments. Patients treated with immune-based combinations had better outcomes than patients treated with tyrosine kinase inhibitors.

1. Introduction

Kidney cancer is a heterogeneous disease, consisting of clear cell renal cell carcinoma (ccRCC) in the majority of cases (~75%) and non-clear cell histologies (nccRCC) in the remaining 25% [1]. The term *non-clear cell* covers a wide range of different histological subtypes with diverse prognoses, clinical behaviors, and treatment responses. Papillary RCC (pRCC) is the most frequent nccRCC subtype, accounting for approximately 15% of all RCC cases, followed by chromophobe RCC. The World Health Organization 2022 classification included several changes to the definitions for nccRCC histological subtypes [2]. The historic division of pRCC into type I and type II was eliminated on the basis of evidence that the two subtypes have a single origin and represent low- to high-grade progression from one form to the other [3–5].

Considering the rarity of nccRCC subtypes, they are usually not included in phase 3 trials, and treatment strategies are mostly based on evidence from phase 2 or retrospective studies [6]. Historically, the cornerstone of treatment has long been tyrosine kinase inhibitors (TKIs) or mTOR inhibitors [1,6]. More recently, the phase 2 SWOG 1500 trial [7] enrolled patients with pRCC and demonstrated that cabozantinib resulted in superior progression-free survival (PFS) in comparison to sunitinib, the previous standard of care for metastatic disease (median PFS 9.0 mo with cabozantinib vs 5.6 mo with sunitinib; $p = 0.019$).

Phase 2 and 3 prospective trials and several retrospective studies have investigated the role of immune checkpoint inhibitors (ICIs), either given as monotherapy (pembrolizumab in the phase 2 KEYNOTE-427 trial [8] and nivolumab in the phase 3b/4 CheckMate 374 study [9]), or in combination with TKIs [10–13], in patients with metastatic nccRCC, mainly represented by pRCC; this choice was related to the pivotal role of ICIs, especially immuno-oncology (IO)-based combinations, in ccRCC treatment [14,15]. For nccRCC, promising results have been achieved with the combination of atezolizumab + cabozantinib (phase 1b, COSMIC-021) [10], pembrolizumab + lenvatinib (phase 1, KEYNOTE-B61) [11], nivolumab + cabozantinib (phase 2) [12], and nivolumab + ipilimumab (phase 3b/4, CheckMate 920) [13]. Furthermore, the combination of pembrolizumab + axitinib is currently being evaluated in the phase 2 PAXIPEM trial (NCT05096390) in patients with untreated pRCC.

ARON-1 (NCT05287464) is a project that involves analysis of real-world data for patients with metastatic RCC in multiple centers around the world [16–19]. We performed a multicenter retrospective real-world analysis of treatments outcomes for patients with pRCC who received first-line treatment with TKIs or IO-based combinations in 40 centers in 12 countries included in the ARON-1 project.

2. Patients and methods

2.1. Study population

We retrospectively collected data for patients aged ≥18 yr with a histologically confirmed diagnosis of pRCC and histologically or radiologically confirmed metastatic disease. Patients in all three International Metastatic RCC Database Consortium (IMDC) risk groups (including good risk) who were treated with a first-line TKI-IO or IO-IO combination or with a TKI alone between January 1, 2016 and July 1, 2023 in 40 centers in 12 countries were eligible for inclusion.

We retrospectively extracted data for age, gender, tumor histology, nephrectomy status, sites of metastases, type of therapy, and response to therapy from paper and electronic charts. Patients with insufficient data for tumor assessment or response to therapy were excluded from the ARON-1 study.

First-line therapy was continued until evidence of clinical and/or radiological tumor progression, unacceptable toxicity, or death. Computed tomography or magnetic resonance imaging scans were performed in accordance with the local standard procedure every 8-12 wk. Physical and laboratory tests were carried out every 4-6 wk during follow-up.

The ARON-1 project was approved by the ethics committee of the Marche region (reference 2021-492) and was performed in accordance with the Declaration of Helsinki.

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

2.2. Study endpoints

The primary objective of our retrospective study was to assess outcomes for patients treated with first-line IO-based combinations or TKIs for advanced pRCC. Tumor radiological assessment was in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20] and data on tumor response (complete [CR], partial responses [PR], stable [SD] or progressive disease [PD]) were collected and analyzed. The overall response rate (ORR) was defined as the proportion of patients who achieved CR or PR according to RECIST. Overall survival (OS) was calculated from the start of treatment to death from any cause. Progression-free survival (PFS) was defined as the time from initiation of first-line therapy to progression or death from any cause. Time to second progression (PFS2) was defined as the time from initiation of first-line therapy to objective tumor progression on next-line treatment or death from any cause. Patients without tumor progression on the next line of treatment, death, or loss to follow-up at the time of analysis were censored at their last follow-up date.

2.3. Statistical analysis

OS, PFS, and PFS2 were estimated using the Kaplan-Meier method with Rothman's 95% confidence intervals (CIs). Survival distributions were compared using a log-rank test. Univariate and multivariable analyses were carried out using Cox proportional-hazard models, with hazard ratios and their 95% CIs calculated. Receiver operating characteristic analysis was used to identify potential survival cutoffs to better stratify patients within risk groups. The χ^2 test was applied to compare categorical variables between groups. The significance level was set at 0.05 and all p values were two-sided. Statistical analysis was performed using MedCalc v19.6.4 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Study population

The ARON-1 study included 3902 patients, of whom 200 (14%) had metastatic pRCC and were included in this analysis (Supplementary Fig. 1). Median follow-up was 22.9 mo (95% CI 18.7-58.4). The median patient age was 64 yr (range 21-87) and 147 patients (74%) were male. Sarcomatoid differentiation was observed in ten patients (5%). Most patients underwent nephrectomy (82%). The most frequent sites of metastases were the lungs (49%) and bones (21%).

First-line therapy was an IO-based combination for 73 patients (36%) and TKI treatment for 127 (64%); 96 patients (48%) had died at the time of analysis. Of the 136 patients with disease progression during first-line therapy, 109 received second-line therapies. Baseline clinical and pathological characteristics of the overall population are shown in Table 1. Data for first- and second-line treatment regimens are summarized in Table 2.

3.2. Survival analysis in the overall population

In the overall study population, median OS was 24.8 mo (95% CI 20.6-28.2) and median PFS was 8.7 mo (95% CI 6.9-45.8). Median OS was 22.5 mo (95% CI 16.5-27.1) in the TKI group and 28.8 mo (95% CI 20.7-36.5) in the IO group (p = 0.081; Fig. 1). The 1-yr OS rate (85% vs 73%; p = 0.038) and 2-yr OS rate (63% vs 47%; p = 0.023) were both higher in the IO group.

Median PFS was 6.4 mo (95% CI 5.0-45.7) in the TKI group and 17.4 mo (95% CI 11.3-45.8) in the IO group (p < 0.001; Fig. 1). The 1-yr PFS rate (62% vs 29%; p < 0.001) and 2-yr PFS rate (43% vs 11%; p < 0.001) were both higher in the IO group.

Thirty-five and 101 patients progressed during first-line immune-based combinations or TKIs, respectively. Of them, 27 patients (77%) and 82 patients (81%) received second-line therapies. Median PFS2 was 16.1 mo (95% CI 12.6-20.0) in the overall cohort, 20.5 mo (95% CI 16.1-27.5) in the IO group, and 13.3 mo (95% CI 10.4-19.3) in the TKI group (p = 0.047).

3.3. Survival analysis by IMDC risk group

Median OS was 25.2 mo (95% CI 17.3-56.7), 25.7 mo (95% CI 19.1-36.8), and 22.1 mo (95% CI 13.2-48.2; p = 0.654) for patients with good, intermediate, and poor risk features, respectively. In these three IMDC subgroups, median OS did not differ significantly between IO and TKI first-line treatment.

Median PFS in patients with good, intermediate or poor risk features was 9.9 mo (95% CI 5.8-39.7), 9.3 mo (95% CI 6.9-45.8), and 6.2 mo (95% CI 3.6-10.4, p = 0.250), respectively. Median PFS was significantly longer for IO versus TKI treatment in the good-risk (39.7 mo, 95% CI 16.5-39.7 vs 5.8 mo, 95%CI 4.2-8.7; p < 0.001) and intermediate-risk (12.2 mo, 95% CI 7.1-45.8 vs 7.3 mo, 95% CI 4.8-45.7; p = 0.047) subgroups (Fig. 2), but the difference did not reach significance in the poor-risk subgroup (12.2 mo, 95% CI 2.3-12.2 vs 6.2 mo, 95% CI 3.2-15.8; p = 0.093).

3.4. Survival analysis by site of metastasis

Stratification by site of metastasis revealed that IO versus TKI therapy was associated with longer median OS among patients with liver metastases (not reached [NR], 95% CI NR-NR vs 10.3 mo, 95% CI 5.1-20.6; p = 0.041, Fig. 3). There were no significant OS differences for IO versus TKI treatment among patients with lung metastases (20.7 mo, 95% CI 17.4-26.7, vs 22.5 mo, 95% CI 13.2-56.7; p = 0.306) or bone metastases (12.2 mo, 95% CI 3.5-28.8, vs 17.1 mo, 95% CI 10.3-24.0; p = 0.587).

Median PFS was significantly longer with IO versus TKI therapy for patients with lung metastases (16.5 mo, 95%CI 8.8-45.8 vs 6.5 mo, 95% CI 4.6-34.5; p = 0.008; Fig. 3). There were no significant PFS differences for IO versus TKI treatment among patients with bone metastases (6.6 mo, 95% CI 4.0-7.1 vs 5.3 mo, 95%CI 3.6-26.1; p = 0.179) or liver metastases (8.8 mo, 95% CI 3.7-19.7 vs 4.0 mo, 95% CI 3.1-34.5; p = 0.059).

3.5. Survival analysis by treatment regimen

We also stratified patients according to the first-line IO or TKI regimen. Median follow-up was 18.7 mo (95% CI 15.2-44.8) for IO + TKI therapy and 26.1 mo (95% CI 16.7-55.0)

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

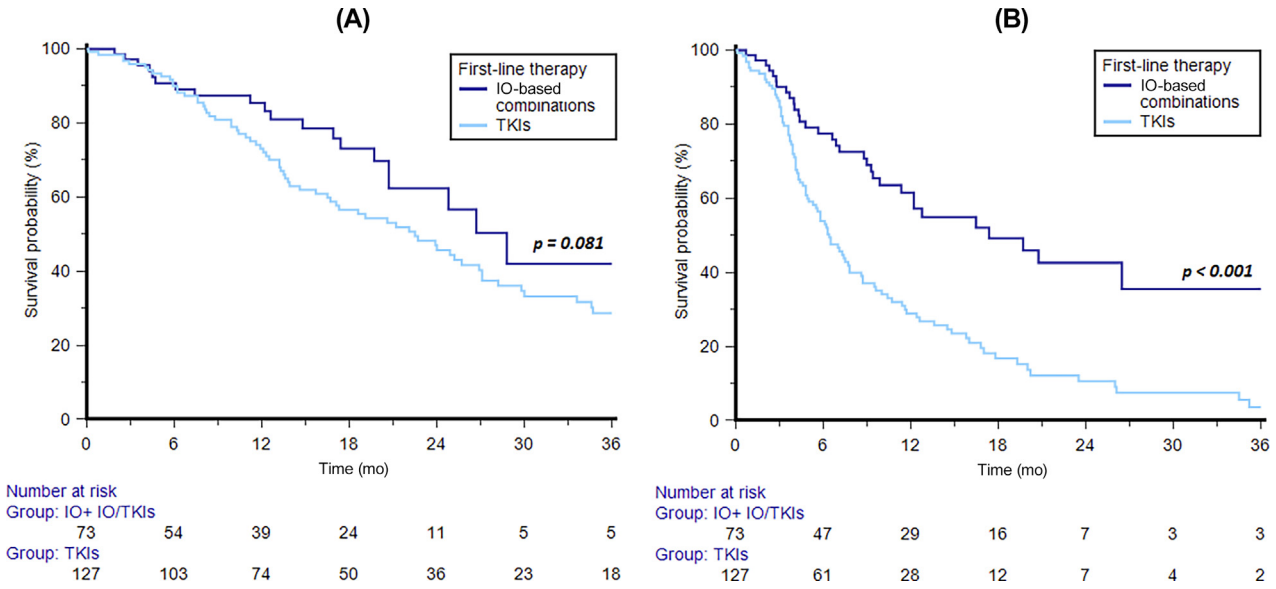


Fig. 1 – Kaplan-Meier curves for (A) overall survival and (B) progression-free survival for patients with papillary renal cell carcinoma receiving first-line immuno-oncology (IO)-based combinations or tyrosine kinase inhibitors (TKIs).

Table 1 – Baseline patient characteristics overall and by first-line treatment group

Parameter	Patients, *n* (%)			*p* value
	Overall cohort (n = 200)	IO-IO or IO-TKI (*n* = 73)	TKI (*n* = 127)	
Sex				0.873
Male	147 (74)	53 (73)	94 (74)	
Female	53 (26)	20 (27)	33 (26)	
Mean age, yr (range)	64 (21–87)	65 (34–84)	64 (21–87)	–
Metastasis at diagnosis	84 (42)	34 (47)	50 (40)	0.319
Previous nephrectomy	164 (82)	52 (71)	112 (88)	**0.003**
Sarcomatoid differentiation	10 (5)	6 (8)	4 (3)	0.122
IMDC risk group				0.177
Favorable risk	57 (29)	17 (23)	40 (31)	
Intermediate risk	112 (56)	47(64)	65 (51)	
Poor risk	31 (15)	9 (13)	22 (18)	
Common sites of metastasis				
Lung	98 (49)	39 (53)	59 (46)	0.323
Bone	41 (21)	13 (18)	28 (22)	0.481
Liver	35 (18)	14 (19)	21 (17)	0.714
Brain	10 (5)	4 (5)	6 (5)	1.000
First-line IO regimen	–		–	–
IO-IO		18 (25)		
IO-TKI		55 (75)		

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immuno-oncology agent; TKI = tyrosine kinase inhibitor.

for IO + IO therapy. Median OS was 24.8 mo (95% CI 17.4-24.8) for pembrolizumab + axitinib, 28.8 mo (95% CI 14.8-28.8) for nivolumab + ipilimumab, 11.2 mo (95% CI 3.5-11.2) for nivolumab + cabozantinib, and 36.5 mo (95% CI 36.5-36.5) for pembrolizumab + lenvatinib. The 1-yr OS rate was 88.7% for pembrolizumab + axitinib, 83.3% for nivolumab + ipilimumab, 43.3% for nivolumab + cabozantinib, and 100% for pembrolizumab + lenvatinib. There was no significant difference in median OS between the IO + TKI (24.8 mo, 95% CI 20.7-36.5) and IO + IO (28.8 mo, 95% IC 14.8-28.8) subgroups (p = 0.655; Supplementary Fig. 2).

Median PFS was 17.4 mo (95% CI 11.3-39.7) for pembrolizumab + axitinib, 19.7 mo (95% CI 8.8-45.8) for nivolumab + ipilimumab, 6.9 mo (95% CI 2.3-7.1) for nivolumab + cabozantinib, and NR (95% CI NR-NR) for pembrolizumab + lenvatinib. Median PFS did not significantly differ between the IO + TKI (16.5 mo, 95% CI 11.4-39.7) and IO + IO (19.7 mo, 95% CI 8.8-45.8) subgroups (p = 0.663; Supplementary Fig. 2).

3.6. *Response rate*

The response distribution was CR 2%, PR 30%, SD 45%, and PD 23% in the overall study population, 2% CR, 39% PR, 43% SD, and 16% PD in the IO group, and CR 2%, PR 25%, SD 45%, and PD 28% in the TKI group. There were significant differences between the IO and TKI groups in ORR (41% vs 27%; p = 0.037) and the proportion of cases with a primary tumor refractory to first-line therapy (16% vs 28%; p = 0.041).

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

Table 2 – Distribution of treatment regimens

Treatment	Patients, *n* (%)
First-line IO-based combination therapy	73
Nivolumab + ipilimumab	18 (25)
Pembrolizumab + axitinib	39 (53)
Nivolumab + cabozantinib	12 (16)
Pembrolizumab + lenvatinib	4 (6)
Progression during first-line IO therapy	35 (48)
Second-line treatment for patients with progression on first-line IO therapy	27 (40)
Cabozantinib	24 (33)
Everolimus	2 (3)
Pembrolizumab + lenvatinib	1 (1)
First-line TKI treatment	127
Sunitinib	99 (78)
Cabozantinib	17 (13)
Pazopanib	11 (9)
Progression during first-line TKI treatment	101 (80)
Second-line treatment for patients with progression on first-line TKI therapy	82 (65)
Nivolumab	35 (28)
Cabozantinib	26 (20)
Everolimus	10 (8)
Axitinib	6 (5)
Sorafenib	3 (2)
Sunitinib	2 (2)

IO = immuno-oncology agent; TKI = tyrosine kinase inhibitor.

Among the IO-based combinations, pembrolizumab + lenvatinib was associated with the highest ORR (Fig. 4).

3.7. *Univariate and multivariable analyses*

In the overall study population, multivariable analyses revealed that the presence of bone or liver metastases was associated with both OS and PFS on (Table 3). Interestingly, first-line IO-based therapy was significantly associated with longer PFS in comparison to TKI therapy (Table 3).

4. Discussion

In this retrospective multicenter study, we analyzed real-world outcomes of first-line IO-based combinations or TKIs in metastatic pRCC. We found no significant difference in median OS between IO-based combinations and TKI therapy (p = 0.081), but IO-based combinations were associated with significantly better 1-yr (p = 0.038) and 2-yr (p = 0.023) OS rates, median PFS (p < 0.001), 1-yr and 2-yr PFS rates (both p < 0.001), and the ORR (p = 0.037). Interestingly, there was no significant difference in median OS between the IO and TKI groups after stratification by IMDC risk group, while median PFS was better with IO-based treatment for patients in the IMDC good risk (p < 0.001) or intermediate risk (p = 0.047) group. The combination with the best ORR (75%) was pembrolizumab + lenvatinib, in accordance with results achieved in ccRCC [9]. However, our data should be evaluated with caution as patients receiving first-line pembrolizumab + lenvatinib represented the smallest group (6% of patients).

Our results are consistent with findings from previous prospective [10–13] and retrospective [21–23] studies. A retrospective study by Graham et al [21] included 1145 patients with metastatic nccRCC, of whom 54.9% had pRCC. Therapy regimens included TKIs (74.3% of cases), mTOR inhibitors (15%) and ICI-based therapy (10.7%). Median OS was 28.6 mo in the ICI group, 16.4 mo in the TKI group, and 12.2 mo in the mTOR group, confirming better survival with ICI-based therapies. These data are concordant with our study, although our cohort had more patients treated with IO combinations. Of note, the study by Graham et al [21] also included patients treated with ICI monotherapy, while we included only IO-based combinations.

The retrospective NEMESIA study by Stellato et al [22] involve an Italian series of 32 patients with nccRCC (60%

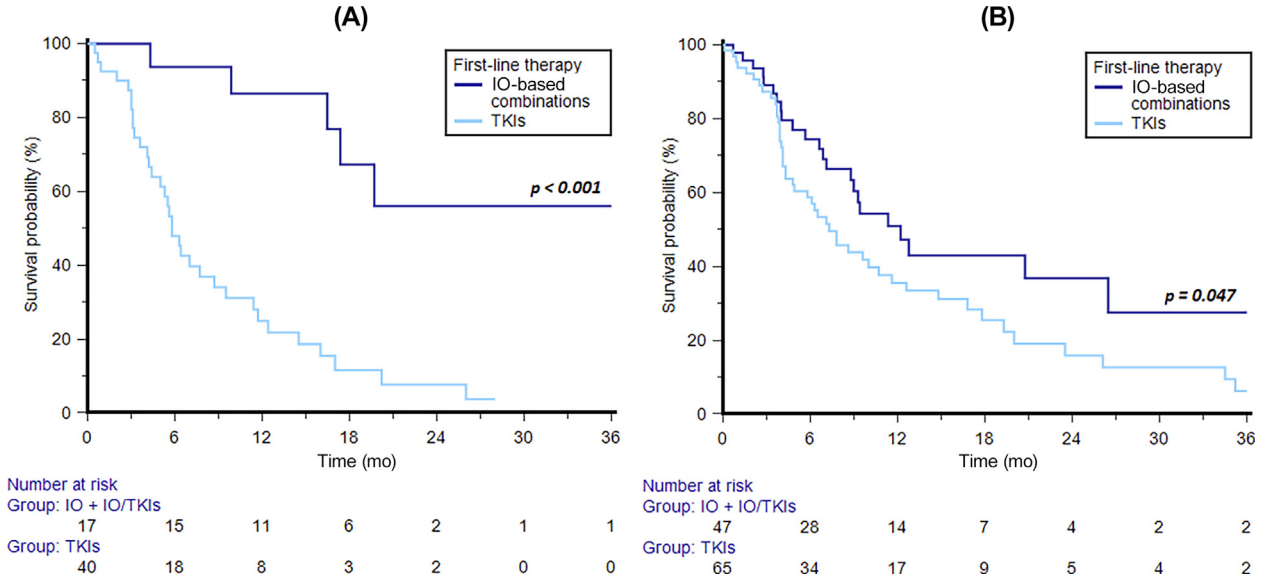


Fig. 2 – Progression-free survival for patients with papillary renal cell carcinoma receiving first-line immuno-oncology (IO)-based combinations or tyrosine kinase inhibitors (TKIs): (A) good risk group and (B) intermediate risk group.

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

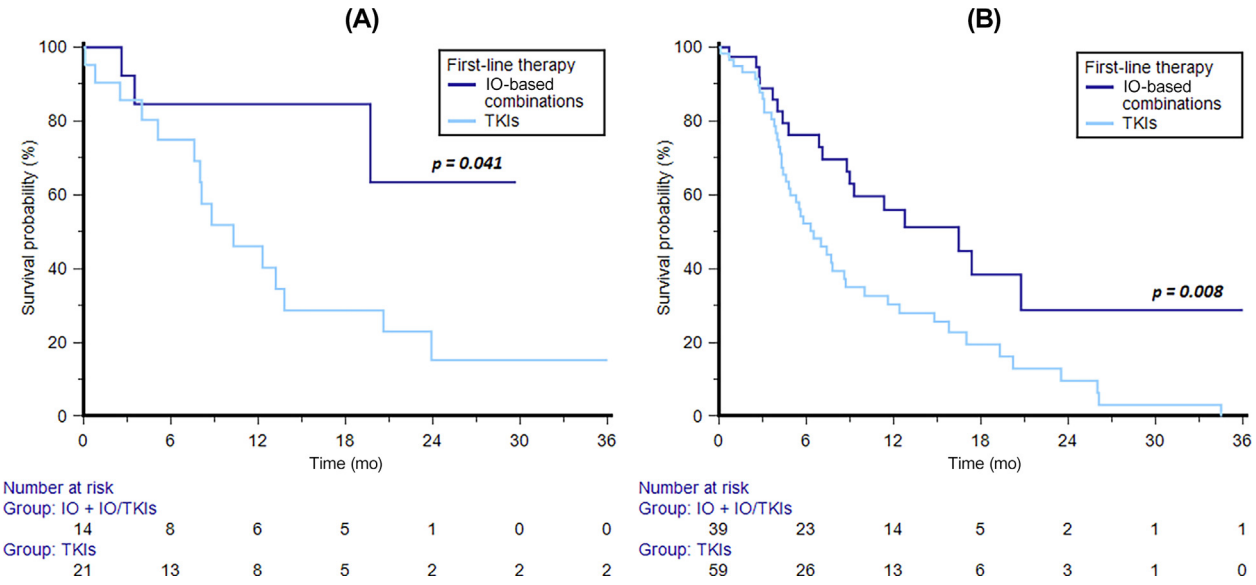
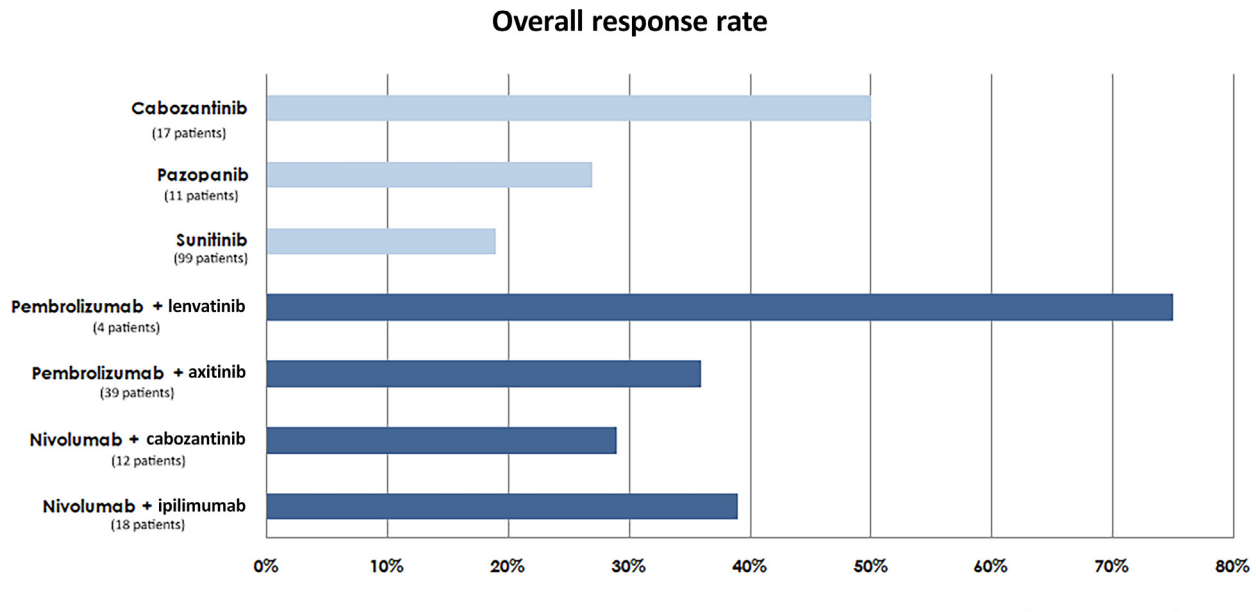


Fig. 3 – (A) Overall survival for patients with liver metastases and (B) progression-free survival for patients with lung metastases of papillary renal cell carcinoma receiving first-line immuno-oncology (IO)-based combinations or tyrosine kinase inhibitors (TKIs).



	Nivolumab + Ipilimumab	Nivolumab + Cabozantinib	Pembrolizumab + Axitinib	Pembrolizumab + Lenvatinib	Sunitinib	Pazopanib	Cabozantinib
ORR	39%	29%	36%	75%	19%	27%	50%

Fig. 4 – Overall response rate (ORR) by type of first-line therapy.

with papillary histology) treated with pembrolizumab + axitinib. Median PFS was 10.8 mo, slightly shorter than the 17.4 mo in our study for IO combinations, and the ORR was 43.7%, versus 36% for our patients treated with pembrolizumab + axitinib.

Regarding the different IO-based combinations used, the availability of these agents reflects their approval by the relevant regulatory body in countries around the world. In particular, the most common regimens in our IO cohort were pembrolizumab + axitinib (53%) and nivolumab + ipilimumab (25%), which were the first two combinations approved, while only a minority of patients were treated with nivolumab + cabozantinib (16%) or pembrolizumab + lenvatinib (6%). Of note, the best median OS, median PFS, and ORR results were observed for patients treated with pembrolizumab + lenvatinib, similar to findings for ccRCC. Several trials have investigated IO-based combinations in nccRCC, with mostly concordant results. In the phase 1b

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

Table 3 – Univariate and multivariable analyses for overall and progression-free survival

Parameter	Univariate Cox regression		Multivariable Cox regression	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Overall survival				
Sex (female vs male)	0.82 (0.51–1.30)	0.393		
Age (≥65 vs <65 yr)	1.44 (0.95–2.17)	0.083		
IMDC prognostic group	1.08 (0.79–1.46)	0.637		
Nephrectomy (yes vs no)	0.99 (0.56–1.76)	0.999		
Sarcomatoid features (yes vs no)	1.14 (0.44–2.91)	0.788		
Lung metastases (yes vs no)	1.10 (0.72–1.67)	0.669		
Bone metastases (yes vs no)	2.17 (1.37–3.42)	**<0.001**	2.22 (1.40–3.51)	**<0.001**
Liver metastases (yes vs no)	2.02 (1.20–3.37)	**0.008**	2.09 (1.25–3.49)	**0.005**
First-line therapy (TKI vs IO-based)	1.54 (0.94–2.51)	0.084		
Progression-free survival				
Sex (female vs male)	0.88 (0.60–1.30)	0.528		
Age (≥65 vs <65 yr)	0.95 (0.67–1.33)	0.749		
IMDC prognostic group	1.14 (0.87–1.50)	0.324		
Nephrectomy (yes vs no)	1.08 (0.69–1.70)	0.725		
Sarcomatoid features (yes vs no)	0.67 (0.24–1.83)	0.431		
Lung metastases (yes vs no)	1.10 (0.78–1.57)	0.572		
Bone metastases (yes vs no)	1.69 (1.13–2.53)	**0.011**	1.53 (1.02–2.30)	**0.040**
Liver metastases (yes vs no)	1.89 (1.24–2.90)	**0.003**	2.02 (1.31–3.10)	**0.001**
First-line therapy (TKI vs IO)	2.40 (1.62–3.55)	**<0.001**	2.31 (1.55–3.44)	**<0.001**

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immuno-oncology agent; TKI = tyrosine kinase inhibitor.

COSMIC-021 trial, the ORR was 31% with cabozantinib + atezolizumab in the nccRCC subgroup [10]. Recent results for the phase 2, single-arm KEYNOTE-B61 trial [11] of pembrolizumab + lenvatinib in advanced nccRCC, including 93 patients with pRCC, revealed durable antitumor activity, median PFS of 18 mo, an estimated 12-mo OS rate of 82%, and a better ORR in comparison to TKI or ICI monotherapy. Of note, the ORR was 49% for the overall population and 54% for patients with pRCC, with eight patients experiencing a CR. Nivolumab + cabozantinib was assessed in a phase 2 trial [12] that revealed median PFS of 12.5 mo, median OS of 28 mo, and an ORR of 47.5%. Cohort 1 in this study consisted of 32 patients with pRCC, six with unclassified RCC, and two with translocation-associated RCC who had received one prior systemic therapy or none. Lastly, the phase 3b/4 CheckMate 920 trial [13] evaluated the combination of nivolumab + ipilimumab and included a cohort of 18 patients with untreated pRCC. In the overall nccRCC population, 12-mo PFS was 22.7%, 12-mo OS was 72.6%, and ORR was 19.6%.

To date, all studies on nccRCC have involved small populations and mixed histologies. Two randomized trials in pRCC are currently ongoing. The phase 3 SAMETA trial (NCT05043090) is randomizing patients with MET-driven pRCC to savolitinib + durvalumab or durvalumab monotherapy versus sunitinib. PAXIPEM (NCT05096390) is a phase 2 non-biomarker-driven trial of axitinib with or without pembrolizumab in the first-line setting.

For our TKI cohort, median OS was 22.5 mo and median PFS was 6.5 mo, in line with previous studies of sunitinib and cabozantinib. The SUPAP trial [24] of sunitinib reported median OS of 17.8 mo for type I and 12.4 mo for type II pRCC, and corresponding median PFS times of 6.6 mo and 5.5 mo. Cabozantinib, investigated in the SWOG 1500 study, resulted in median OS of 20 mo and median PFS of 9 mo. Furthermore, our ORR with single-agent TKI was 27%, which is higher than in the ESPN and SUPAP trials [24,25], probably because our more selected population of patients only had papillary histology.

Our study has several limitations, first and foremost of which is the retrospective nature. Furthermore, there was no central radiological or, more importantly, histological review . Tumor evaluations were performed in the study centers every 8-12 wk, and this time variability may have influenced the PFS results.

We had no information on concomitant medications or relevant comorbidities because of a lack of data. Consequently, our findings should be interpreted with caution. Prospective studies investigating IO combinations in pRCC are warranted, especially in light of recent information for this histological subtype [2] that led to a change from the historical division into types I and II.

Another limitation is that multiple comparisons were performed for very small subgroups (metastatic sites, IMDC groups, and treatment regimens) in an already limited cohort.

A strength of our study is the large pRCC cohort from multiple referral centers worldwide, which provides good representation of treatment availability and clinical management practices in different countries.

5. Conclusions

Our study shows that IO-based combinations are the preferable option for first-line treatment of metastatic pRCC, with better 1-yr and 2-yr OS rates, median PFS, and ORRs in comparison to TKIs.

Author contributions: **Veronica Mollica** had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Massari, Santoni, Mollica, Grande.
Acquisition of data: Massari, Santoni.
Analysis and interpretation of data: Massari, Santoni.
Drafting of the manuscript: Massari, Santoni, Mollica.

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011

Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Massari, Santoni.
Obtaining funding: None.
Administrative, technical, or material support: All authors.
Supervision: All authors.
Other: None.

Financial disclosures: **Veronica Mollica** certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: **Francesco** Massari has received research support and/or honoraria from Advanced Accelerator Applications, Astellas, BMS, Janssen, Ipsen, MSD, and Pfizer outside the submitted work. **Ondrej** Fiala has received honoraria from Roche, Janssen, GSK, and Pfizer for consultations and lectures unrelated to this project. Javier Molina-Cerrillo has consultant, advisor, or speaker roles for Ipsen, Roche, Pfizer, Sanofi, Janssen, and BMS, and has received research grants from Pfizer, Ipsen, and Roche, all unrelated to this project. **Zin W**. Myint has received research support from Merck unrelated to this project. Ravindran Kanesvaran has received speaker bureau and advisory board fees from Pfizer, MSD, BMS, Eisai, Ipsen, Johnson & Johnson, Merck, Amgen, Astellas, and Bayer, all unrelated to this project. **Sebastiano** Buti has received speaker and advisor honoraria from BMS, Pfizer, MSD, Ipsen, AstraZeneca, and Merck, all unrelated to this project. Camillo Porta has received honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, Ipsen, and MSD, and has acted as a protocol steering committee member for BMS, Eisai, and MSD, all unrelated to this project. Enrique Grande has received honoraria for speaker engagements, advisory roles, or continuous medical education from Adacap, Amgen, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol-Myers Squibb, Caris Life Sciences, Celgene, Clovis Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA Pharma, Ipsen, ITM Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific, and has received research grants from Pfizer, AstraZeneca, Astellas, and Lexicon Pharmaceuticals, all unrelated to this project. Matteo Santoni has received research support and honoraria from Janssen, Bristol-Myers Squibb, Ipsen, MSD, Astellas, and Bayer, all unrelated to this project. The remaining authors have nothing to disclose.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.03.011.

References

[1] Barthélémy P, Rioux-Leclercq N, Thibault C, et al. Non-clear cell renal carcinomas: review of new molecular insights and recent clinical data. Cancer Treat Rev 2021;97:102191. https://doi.org/10.1016/j.ctrv.2021.102191.
[2] WHO Classification of Tumours Editorial Board. Classification of tumours of the urinary and male genital systems. ed. 5. Lyon, France: IARC Press; 2022.
[3] The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med 2016;374:135–45. https://doi.org/10.1056/NEJMoa1505917.
[4] Lobo J, Ohashi R, Amin MB, et al. WHO 2022 landscape of papillary and chromophobe renal cell carcinoma. Histopathology 2022;81:426–38. https://doi.org/10.1111/his.14700.
[5] Tateo V, Mollica V, Rizzo A, Santoni M, Massari F. Re: WHO classification of tumours, 5th edition, volume 8: urinary and male genital tumours. Eur Urol 2023;84:348-9. https://doi.org/10.1016/j.eururo.2023.04.030.
[6] Marchetti A, Rosellini M, Mollica V, et al. The molecular characteristics of non-clear cell renal cell carcinoma: what's the story morning glory? Int J Mol Sci 2021;22:6237. https://doi.org/10.3390/ijms22126237.
[7] Pal SK, Tangen C, Thompson Jr IM, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. Lancet 2021;397:695–703. https://doi.org/10.1016/S0140-6736(21)00152-5.
[8] McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. J Clin Oncol 2021;39:1029–39. https://doi.org/10.1200/JCO.20.02365.
[9] Vogelzang NJ, Olsen MR, McFarlane JJ, et al. Safety and efficacy of nivolumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase IIIb/IV CheckMate 374 study. Clin Genitourin Cancer 2020;18:461–468.e3. https://doi.org/10.1016/j.clgc.2020.05.006.
[10] Pal SK, McGregor B, Suárez C, et al. Cabozantinib in combination with atezolizumab for advanced renal cell carcinoma: results from the COSMIC-021 study. J Clin Oncol 2021;39:3725–36. https://doi.org/10.1200/JCO.21.00939.
[11] Albiges L, Gurney H, Atduev V, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2023;24:881–91. https://doi.org/10.1016/S1470-2045(23)00276-0.
[12] Lee CH, Voss MH, Carlo MI, et al. Phase II trial of cabozantinib plus nivolumab in patients with non-clear-cell renal cell carcinoma and genomic correlates. J Clin Oncol 2022;40:2333–41. https://doi.org/10.1200/JCO.21.01944.
[13] Tykodi SS, Gordan LN, Alter RS, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. J Immunother Cancer 2022;10:e003844.
[14] de Vries-Brilland M, McDermott DF, Suárez C, et al. Checkpoint inhibitors in metastatic papillary renal cell carcinoma. Cancer Treat Rev 2021;99:102228. https://doi.org/10.1016/j.ctrv.2021.102228.
[15] Rosellini M, Marchetti A, Tassinari E, et al. Guiding treatment selection with immunotherapy compared to targeted therapy agents in patients with metastatic kidney cancer. Exp Rev Precis Med Drug Dev 2022;7:131–49. https://doi.org/10.1080/23808993.2022.2156786.
[16] Porta C, Bamias A, Zakopoulou R, et al. Geographical differences in the management of metastatic de novo renal cell carcinoma in the era of immune-combinations. Minerva Urol Nephrol 2023;75:460–70. 10.23736/S2724-6051.23.05369-7.
[17] Santoni M, Massari F, Myint ZW, et al. Clinico-pathological features influencing the prognostic role of body mass index in patients with advanced renal cell carcinoma treated by immuno-oncology combinations (ARON-1). Clin Genitourin Cancer 2023;21:e309–19. https://doi.org/10.1016/j.clgc.2023.03.006.
[18] Santoni M, Buti S, Myint ZW, et al. Real-world outcome of patients with advanced renal cell carcinoma and intermediate- or poor-risk International Metastatic Renal Cell Carcinoma Database Consortium criteria treated by immune-oncology combinations: differential effectiveness by risk group? Eur Urol Oncol 2024;7:102–11. https://doi.org/10.1016/j.euo.2023.07.003.
[19] Santoni M, Massari F, Myint ZW, et al. Global real-world outcomes of patients receiving immuno-oncology combinations for advanced renal cell carcinoma: the ARON-1 study. Target Oncol 2023;18:559–70. https://doi.org/10.1007/s11523-023-00978-2.
[20] Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1—update and clarification: from the RECIST Committee. Eur J Cancer 2016;62:132–7. https://doi.org/10.1016/j.ejca.2016.03.081.
[21] Graham J, Wells JC, Dudani S, et al. Outcomes of patients with advanced non-clear cell renal cell carcinoma treated with first-line

immune checkpoint inhibitor therapy. Eur J Cancer 2022;171:124–32. https://doi.org/10.1016/j.ejca.2022.05.002.

[22] Stellato M, Buti S, Maruzzo M, et al. Pembrolizumab plus axitinib for metastatic papillary and chromophobe renal cell carcinoma: NEMESIA (non clear metastatic renal cell carcinoma pembrolizumab axitinib) study, a subgroup analysis of I-RARE observational study (Meet-URO 23a). Int J Mol Sci 2023;24:1096. https://doi.org/10.3390/ijms24021096.

[23] Bimbatti D, Pierantoni F, Lai E, et al. Advanced non-clear cell renal cell carcinoma treatments and survival: a real-world single-centre experience. Cancers 2023;15:4353. https://doi.org/10.3390/cancers15174353.

[24] Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). Ann Oncol 2015;26:1123–8. https://doi.org/10.1093/annonc/mdv149.

[25] Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016;69:866–74. https://doi.org/10.1016/j.eururo.2015.10.049.

Please cite this article as: F. Massari, V. Mollica, O. Fiala et al., Papillary Renal Cell Carcinoma: Outcomes for Patients Receiving First-line Immune-based Combinations or Tyrosine Kinase Inhibitors from the ARON-1 Study, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.03.011