Geographical differences in the management of metastatic *de novo* Renal Cell Carcinoma in the era of immune-combinations

Upfront or delayed partial or radical CN in three geographical areas

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Abstract

Background: The upfront treatment of metastatic renal cell carcinoma (mRCC) has been revolutionized by the introduction of immune-based combinations. The role of cytoreductive nephrectomy (CN) in these patients is still debated. The ARON-1 study (NCT05287464) was designed to globally analyze real-world data of mRCC patients receiving first-line immuno-oncology combinations. This sub-analysis is focused on the role of upfront or delayed partial or radical CN in three geographical areas (Western Europe, Eastern Europe, America/Asia).

Methods: We conducted a multicenter retrospective observational study in mRCC patients treated with first-line immune combinations from 55 centers in 19 countries. From 1152 patients in the ARON-1 dataset, we selected 651 patients with *de novo* mRCC. 255 patients (39%) had undergone CN, partial in 14% and radical in 86% of cases; 396 patients (61%) received first-line immune-combinations without previous nephrectomy.

Results: Median overall survival (OS) from the diagnosis of *de novo* mRCC was 41.6 months and not reached (NR) in the CN subgroup and 24.0 months in the no CN subgroup, respectively ($p<0.001$). Median OS from the start of first-line therapy was NR in patients who underwent CN and 22.4 months in the no CN subgroup ($p<0.001$). Patients who underwent CN reported longer OS compared to no CN in all the three geographical areas.

Conclusions: No significant differences in terms of patients' outcome seem to clearly emerge, even if the rate CN and the choice of the type of first-line immune-based combination varies across the different Cancer Centers participating in the ARON-1 project.

Keywords: ARON-1 study; Immunotherapy; Immune-oncology combinations; NCT05287464; Nephrectomy; Renal Cell Carcinoma; Survival; Tumor Response.

Introduction

Renal cell carcinoma (RCC) represents the eighth most common cancer in the Western countries, with a reported incidence of nearly 400,000 new cases diagnosed annually worldwide [1]. About 70% of RCC cases are identified in an early stage, thus requiring only surgical approach. On the other hand, approximately 25-30% of RCC patients presents with *de novo* metastatic disease, while relapses with distant metastases after surgical treatments occur in about 40% of patients per year. Until recently, for the systemic disease, the estimated 5-year survival rate is around 15% and distant metastases mostly occur in lungs, lymph nodes, liver, bone and brain [2], though unusual sites are also typical of this disease.

Partial or radical nephrectomy is the standard of care for localized RCC [3]. For almost two decades, upfront cytoreductive nephrectomy (CN) has been also the standard of care for patients presenting with metastatic disease at diagnosis [3]. The results of the Carmena trial [4−6]. investigating the role of upfront or delayed nephrectomy in RCC patients, together with the results obtained by immune-combinations in the first-line setting, have paved the way to a series of hypotheses to identify patients who are the ideal candidates to receive upfront CN followed by systemic therapy or systemic therapy alone.

Targeted anti-Vascular Endothelial Growth Factor/Receptor (VEGF/VEGFR) therapy represented the backbone of the therapeutic algorithm in metastatic clear-cell Renal Cell Carcinoma (ccRCC), until the recent advent of immune-combinations. This revolutionary approach has been established after the publication of the results of five phase III trials testing the combination of a VEGFR -Tyrosine Kinase Inhibitor (TKI) with an immune checkpoint inhibitor [7−10] or dual immunotherapy combination [11] versus sunitinib, the previous standard of care in the first-line setting. Immune combinations have improved OS and PFS of RCC patients, also increasing the rate of complete responses and patients'

Quality of Life (QoL) [12−14]. Nevertheless, real-world data, confirming the efficacy and tolerability of these novel agents in everyday practice are largely lacking.

The ARON-1 study (NCT05287464) was designed to globally analyze real-world data from metastatic RCC (mRCC) patients receiving first-line immuno-oncology combinations. in this sub-analysis, we investigated the role of upfront or delayed partial or radical CN in *de novo* mRCC patients treated by immune-combinations.

Materials and Methods

Study population

We conducted a multicentre retrospective observational study of patients aged ≥18 with metastatic disease at diagnosis of RCC, treated with first-line immune combinations between January 1st 2016 to October 1st 2022 from 55 centers in 19 countries.

We collected information about age, gender, tumor histology, nephrectomy, International mRCC Database Consortium (IMDC) criteria, sites of metastases, type of immuno-combination and response to therapy from patients' paper and electronic charts. Patients with insufficient data on tumor assessment or response to therapy were excluded from the ARON-1 study.

Duration of therapy and tumor assessment protocols were decided by the treating physicians. Commonly, first-line therapy was continued till the evidence of clinical and/or radiological tumor progression, unacceptable toxicities, or death. Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed following standard local procedures, usually every 8–12 weeks. Physical and laboratory tests were normally carried out every 4–6 weeks during patients' follow-up.

Study endpoints

Primary end point of this analysis was overall survival (OS), whichwas calculated from the start of treatment until death for any cause. Progression-free survival (PFS) and tumor response rate were secondary end points. PFS was defined as the time from the start of immune-combination to progression or death from any cause, whichever occurred first. Patients without disease progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit. Tumor response to therapy was assessed according to RECIST 1.1 criteria [15] and defined as complete (CR), partial (PR), stable disease (SD) or progressive disease (PD). Overall Response Rate (ORR) was calculated by the sum of CR and PR rates.

Statistical Analysis

OS and PFS were estimated using the Kaplan-Meier method with Rothman's 95% confidence intervals (CI). Comparisons between survival distributions were performed by the log-rank test. Univariate and multivariate analyses were performed by using Cox proportional hazard models, Hazard Ratio (HR) and their 95 % confidence intervals (95%CI) were reported. A survival receiver operating characteristic (ROC) analysis was adopted to identify potential cut-offs that better stratify patients in risk groups. The chi-square test was used to compare each group for categorical variables. Significance levels were set at a value of 0.05, and all *p* values were two-sided. Body Mass Index (BMI) was defined as a person's weight in kilograms divided by the square of height in meters. Based on the World Health Organization (WHO) classification, patients were included in the overweight/obesity group when BMI was>25 kg/m^2.

MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was employed for data analysis.

Results

Study Population

From 1152 patients treated with immune-combinations as first-line therapy in the ARON-1 dataset, we selected 651 patients with *de novo* metastatic RCC (Figure S1). The median follow-up time from the diagnosis of *de novo* mRCC was 31.5 months (95%CI 24.4−38.5), while it was 26.7 months (95%CI 21.0−33.8) from the start of first-line therapy; 193 patients (30%) were dead at time of analysis.

Among the 651 selected patients, 255 patients (39%) had undergone CN, which was partial or radical in 36 (14%) and 219 (86%), respectively; 396 patients (61%) with *de novo* mRCC received first-line immune combinations without previous nephrectomy.

Sixteen patients (7%) underwent delayed CN after the beginning of first-line therapy; in these patients, median time from the start of first-line therapy was 10.3 months (95%CI 4.6−17.6). Patients who underwent delayed CN yielded, according to RECIST 1.1, 2 CR, 7 PR and 7 SD as best response to first-line immune combinations.

Among the 651 selected patients, 469 (72%) were males. Median age was 64 years (range 25−82). Tumour histology was clear cell RCC in 583 patients (90%); in the 68 non-clear cell RCC patients, papillary histology was observed in 46 cases and chromophobe RCC in 7; sarcomatoid differentiation was reported in 102 patients (16%). Distant metastases to the lung or bone were identified in 478 (73%) and 268 (41%) patients. Stratified by IMDC criteria, 429 (66%) and 222 (34%) had intermediate-risk or poor-risk IMDC criteria, respectively.

IO + IO combination was the first-line therapy in 295 patients (46%), while 356 patients (54%) received IO + TKI combinations. Baseline clinical and pathological characteristics of the overall population are shown in Table 1.

Survival analysis from the diagnosis of de novo mRCC

The overall population median OS from the diagnosis of *de novo* mRCC was 41.6 months (95%CI 30.8−57.3). Median OS was not reached - NR (95%CI NR−NR) in the CN subgroup and 24.0 months (95%CI 19.7−30.8) in the no CN subgroup, respectively (p<0.001, Figure 1).

Subgroup analyses showed that this advantage was observed also in patients aged >70y (NR, 95%CI NR−NR, vs 29.2 months, 95%CI 15.6−41.6, p=0.003) and in both patients with clear cell (NR, 95%CI NRNR, vs 26.5 months, 95%CI 19.7−30.8, p<0.001) and non-clear cell RCC (NR, 95%CI NR−NR, vs 22.0 months, 95%CI 13.5−25.5, p=0.032), in patients with sarcomatoid differentiation (NR, 95%CI NR−NR, vs 22.0, 95%CI 7.7−22.0 p=0.036), as well as in patients with a BMI ≥25 kg/m^2 (NR, 95%CI NR-NR, vs 26.5 months, 95%CI 19.7−44.0, p<0.001) and <25 kg/m^2 (44.2 months, 95%CI 40.8−51.7, vs 17.8 months, 95%CI 12.6−41.6, p<0.001).

We further stratified patients by metastatic sites, showing that CN was associated with longer OS in patients with metastases to the lungs (57.3 months, 95%CI 57.3−57.3 vs 22.0 months, 95%CI 17.4−30.4, p<0.001), bone (NR, 95%CI NR−NR, vs 19.7 months, 95%CI 13.5−31.7, p=0.002), lymph nodes (NR, 95%CI NR−NR, vs 22.6 months, 95%CI 15.9−36.3, p<0.001), and liver (NR, 95%CI NR−NR, vs 17.8 months, 95%CI 12.8−30.8, p=0.019), while the median OS was numerically longer but without a statistically significant difference in patients with brain metastases (34.2 months, 95%CI 6.5−34.2, vs 19.2 months, 95%CI 11.9−29.8, p=0.417), probably due to the small number of patients included in this subgroup.

The best cut-off for the number of metastatic sites was calculated by ROC curve and resulted >2. The OS benefit of CN was observed in both patients with 1-2 metastatic sites (NR, 95%CI NR−NR, vs 30.4 months, 95%CI 22.0−44.0, p<0.001) and in the subgroup

with >2 metastatic sites (34.2 months, 95%CI 21.7−34.2, vs 19.7 months, 95%CI 14.6−29.8, p=0.022).

Of note, the median OS in patients who underwent delayed CN was NR (95%CI NR−NR), with 15 of the 16 patients with ongoing first-line immune combinations.

The median OS from the start of first-line immune combinations was 35.3 months (95%CI 28.2−51.6) and was 51.6 months (95%CI 35.3−51.6) in intermediate-risk patients and 15.4 months (95%CI 11.1−22.1) in patients with poor-risk features (p<0.001).

Survival analysis from the start of first-line therapy

The median OS from the start of first-line therapy was not reached (95%CI NR−NR) in patients who underwent CN and 22.4 months (95%CI 18.0−29.6) in the no CN subgroup (p<0.001, Figure 1). In the intermediate-risk subgroup, 194 patients underwent CN and showed a longer median OS from the start of first-line therapy (NR, 95%CI NR−NR) compared to the 235 in the no CN subgroup (29.6 months, 95%CI 22.4−35.3, p<0.001). This benefit was observed also in the poor-risk subgroup (34.2 months, 95%CI 11.7−34.2 vs 14.6 months, 95%CI 11.9−17.8, p=0.038).

We further stratified patients by type of first-line immune combination. In the intermediate risk subgroup, the median OS from the start of first-line therapy was NR (95%CI NR−NR) in patients receiving IO+TKIs and 40.2 months (95%CI 28.4−51.6) in patients treated by IO+IO dual immunotherapy (p=0.032). Otherwise, no difference between IO+TKIs and IO+IO combinations were found in the poor-risk subgroup (22.1 months, 95%CI 10.4−22.1 vs 12.5 months, 9.5−20.9, p=0.280).

In the CN subgroup, the median OS was NR (95%CI NR−NR) in patients treated with IO+TKIs and 51.6 months (95%CI 29.7−51.6) with IO+IO combination (p=0.181). In the no CN subgroup, the median OS was 22.1 months (95%CI 18.0−30.4) with IO+TKIs and

19.7 months (95%CI 12.5−28.4) with IO+IO combination (p=0.033).

Geographical differences

The geographical distribution of the rate of CN among metastatic *de novo* patients included by each Country in the ARON-1 study is illustrated in Figure 2.

The median OS from the diagnosis of metastatic *de novo* disease was 44.0 months (95%CI 29.2−44.2) in Western Europe, NR (95%CI NR−NR) in Eastern Europe and 41.6 months (95%CI 25.5−57.3) in patients from America/Asia (Figure 3).

Patients who underwent CN reported longer OS compared to no CN in all the three geographical area (Western Europe: NR, 95%CI NR−NR, vs 23.7 months, 95%CI 19.2−36.3, p<0.001; Eastern Europe: NR, 95%CI NR−NR, vs 29.8 months, 95%CI 16.4−29.8, p=0.005; America/Asia: 57.3 months, 95%CI 40.8−57.3, vs 25.5 months, 95%CI 17.4−31.7, p<0.001, Figure 3).

Of note, just 3 patients (2%) among those treated in Eastern Europe, America and Asia underwent delayed CN after the start of first-line immune combination. Furthermore, the rate of partial nephrectomy was 17% in Western Europe, 3% in Eastern Europe and 8% in America/Asia (p=0.002).

The geographical distribution of the use of IO+IO and IO+TKI combinations in metastatic *de novo* patients included in the ARON-1 study is illustrated in Figure 4.

The median OS from the start of first-line immune-combinations was 32.7 months (95%CI 25.0−40.6) in Western Europe, NR (95%CI NR−NR) in Eastern Europe and 40.8 months (95%CI 24.3−51.6) in America/Asia (Figure 5).

In Western Europe, patients treated by first-line IO+TKIs showed longer OS compared to those receiving IO+IO combination (NR, 95%CI NR−NR, vs 26.0 months, 95%CI 19.0−40.2, p=0.043, Figure 5). In Eastern Europe, the difference between IO+TKIs and

IO+IO was slightly significant (NR, 95%CI NR−NR, vs NR, 95%CI NR−NR, *p*=0.085, Figure 5), while no differences were found in America/Asia (NR, 95%CI NR−NR, vs 30.2 months, 95%CI 17.9−51.6, *p*=0.259, Figure 5).

Discussion

In this study, we analyzed the role of CN in patients with de novo mRCC treated with immune-combinations, focusing on potential geographical differences. In terms of overall benefit from CN, our results are in line with those recently published by Bakouny *et al.* [16], who reported longer OS in patients who underwent CN in both the subgroups receiving first-line TKIs or immune combinations, thus supporting previous data from both prospective studies (however performed in the era of cytokines-based immunotherapy), as well as from large real-world series (however retrospective and performed mainly in the targeted therapy era).

Although the presence of a larger number of patients in the Western Europe subgroup does not allow a definite and statistically correct comparison between the different geographical area involved in this study, no significant differences in terms of patients' outcome seem to clearly emerge in our analysis, even if the rate of patients who underwent CN and the choice of the type of first-immune combination varies across the different Cancer Centers globally involved in the ARON-1 project and reflects both the clinicians' confidence with the different immune combinations and the availability of these drugs in each Country.

It is evident that the choice to refer a patient to CN reported in Figure 2 just reflects the indication given by uro-oncologists from internationally recognized Cancer Centers involved in the management of RCC and participating to the ARON-1 study and cannot be generalized as a national tendency in each country. Nevertheless, some data clearly emerge from our analysis. First, the reduced rate of CN in all involved Cancer Centers

compared to the TKI era may reflect the growing confidence of clinicians in the use of immune combinations due the advantages demonstrated against sunitinib in the first-line setting. In contrast, the very low rate of patients who underwent delayed CN (6%), according to the CARMENA schedule [4], may indicate that physicians participating in this study do not consider data obtained with TKIs directly applicable to patients managed in the immune-combination era. Similar data from a small French retrospective study have been published by Pignot *et al*. [17]. They analysed data from 30 patients, showing 19 cases (63%) in which surgeons faced difficulties due to adhesions or inflammatory changes and pathological responses in 17% of patients. All together, these data support the need for prospective studies aimed to identify the best candidate to receive delayed CN in the immune combination era.

Our study presents several limitations, mainly due to its retrospective nature. A centralized review of radiological imaging was not performed and patient not assessable for response were excluded. Furthermore, we had no available data on concomitant medications or other comorbidities that could affect the efficacy of first-line therapy. In addition, it is important to notice that patients undergoing radical surgery are frequently in better clinical conditions, and this element could have introduced selection bias in our analysis. Therefore, our results should be interpreted with caution and need a larger prospective validation or further, real-world analyses, with the attempt of reducing some bias.

Conflicts of Interest

Matteo Santoni has received research support and honoraria from Janssen, Bristol Myers Squibb, Ipsen, MSD, Astellas and Bayer, all unrelated to the present paper.

Francesco Massari has received research support and/or honoraria from Astellas,

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Roberto Iacovelli is an advisory board member for Astellas, BMS, Eisai, Ipsen, Janssen, MSD, Novartis, Pfizer, and Sanofi, and a consultant for Astellas, Eisai, MSD, and Pfizer, he received institutional study founds for research activity from Pfizer ad BMS.

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Table Legends

Table 1. Baseline patients' characteristics.

Patients	*Overall 651 (%)*	*Geographical Distribution*			
		Western Europe (468 pts)	*Eastern Europe (84 pts)*	*America & Asia (99 pts)*	*p*
Gender					
Male	469 (72)	333 (71)	62 (74)	74 (75)	0.801
Female	182 (28)	135 (29)	22 (26)	25 (25)	
Median age, years (y)	64	64	63	65	-
Range	25 – 92	25 – 91	31 – 88	28 – 92	
BMI ≥ 25 kg/m²	319 (49)	212 (45)	49 (58)	58 (59)	0.086
Metastatic at diagnosis	651(100)	468 (100)	84 (100)	99 (100)	-
Past nephrectomy	255 (39)	177 (38)	39 (46)	39 (39)	0.456
Clear cell histology	583 (90)	410 (88)	78 (93)	95 (96)	0.100
Sarcomatoid differentiation	102 (16)	69 (15)	15 (18)	18 (18)	0.809
IMDC prognostic group					
Intermediate	429 (66)	317 (68)	52 (62)	60 (61)	0.538
Poor	222 (34)	151 (32)	32 (38)	39 (39)	
Common sites of metastasis					
Lung	478 (73)	333 (71)	63 (75)	82 (83)	0.127
Lymph nodes (non-regional)	281 (43)	214 (46)	32 (38)	35 (35)	0.259
Bone	268 (41)	202 (43)	32 (39)	34 (34)	0.424
Liver	134 (21)	91 (19)	20 (24)	23 (23)	0.665
Brain	58 (9)	43 (9)	6 (7)	9 (9)	0.840
Type of immuno-combination					
Nivolumab plus ipilimumab	295 (46)	174 (37)	70 (84)	51 (52)	-
Pembrolizumab + axitinib	307 (47)	276 (59)	11 (13)	20 (20)	
Nivolumab + cabozantinib	28 (4)	13 (3)	1 (1)	14 (14)	
Pembrolizumab + lenvatinib	21 (3)	5 (1)	2 (2)	14 (14)	

Figure Legends

Figure 1. Overall Survival from the diagnosis of de novo mRCC and from the start of first-line immune combinations stratified by cytoreductive nephrectomy.

Figure 2. Geographical distribution of the rate of cytoreductive nephrectomy among metastatic *de novo* RCC patients.

Figure 3. Overall Survival from the diagnosis of de novo mRCC by geographical areas and stratified by cytoreductive nephrectomy in Western Europe, Eastern Europe and America/Asia.

Figure 4. Geographical distribution of the use of immune combinations among metastatic *de novo* RCC patients.

Figure 5. Overall Survival from the start of first-line therapy by geographical areas and stratified by type of immune combination in Western Europe, Eastern Europe and America/Asia.

Supplementary materials

Figure S1. Patients' selection process from the ARON-1 study.