Global Real-World Outcomes of Patients Receiving Immuno-Oncology Combinations for Advanced Renal Cell Carcinoma: The ARON-1 Study

Global real-world outcomes of patients receiving immuno-oncology combinations for advanced Renal Cell Carcinoma: the ARON-1 study

Running Title: Global real-world data on immuno-oncology combinations in mRCC

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Abstract

Background: Immuno-oncology combinations have achieved survival benefits in patients with metastatic Renal Cell Carcinoma (mRCC).

Objective: The ARON-1 study (NCT05287464) was designed to globally collect real-world data on the use of immuno-combinations as first-line therapy for mRCC patients.

Patients and Methods: Patients aged ≥18 years with a cytologically and/or histologically confirmed diagnosis of mRCC treated with first-line immuno-combination therapies were retrospectively collected from 47 International Institutions from 16 countries. Patients were assessed for overall survival (OS), Progression-Free Survival (PFS), and Overall Clinical Benefit (OCB).

Results: A total of 729 patients were included; tumour histology was clear cell RCC in 86% of cases; 313 patients received dual immuno-oncology (IO+IO) therapy while 416 were treated by IO-Tyrosine Kinase Inhibitors (IO+TKIs) combinations. In the overall study population, the median OS and PFS were 36.5 and 15.0 months, respectively. The median OS was longer with IO+TKIs compared to IO+IO therapy in the 616 patients with intermediate/poor IMDC risk criteria (55.7 vs 29.7 months, p=0.045). OCB was 84% for IO+TKIs and 72% for IO+IO combination (p<0.001).

Conclusions: Our study may suggest that immuno-oncology combinations are effective as first-line therapy in the mRCC real-world context, showing outcome differences between IO+IO and IO+TKIs combinations in mRCC subpopulations.

Clinical Trial Registration: NCT05287464

Key Points

- We showed real-world data on the use of immuno-combinations in patients with metastatic Renal Cell Carcinoma
- Our data seem to suggest a better outcome of patients treated by immunotherapy plus anti-angiogenic agents compared to dual immunotherapies

1. Introduction

Renal cell carcinoma (RCC) is one of the most frequent urinary tract tumors worldwide, and its incidence has been predicted to increase in the next years [1,2]. About 30% of patients present with local or distant recurrence after nephrectomy for localized disease [3]. Systemic treatment of metastatic RCC (mRCC) has been completely revolutionized by the development of immunotherapy (IO)-based combinations, which have improved the outcome and quality of life of mRCC patients [4−13].

Two distinct type of immuno-oncology combinations have been developed. The first one, defined as IO + IO, involves the use of two different immune checkpoint inhibitors, anti-Programmed Death (PD)-1 nivolumab and anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) ipilimumab. The second one, defined as IO + Tyrosine Kinase Inhibitor (TKI), involves the use of agents directed against-PD1 (nivolumab, pembrolizumab) or its ligand PD-L1 (avelumab, atezolizumab) combined with anti-Vascular Endothelial Growth Factor (VEGF)monoclonal antibody (bevacizumab) or VEGF receptors (VEGFR)-TKIs (axitinib, lenvatinib, cabozantinib)[4−13].

Although the rate of patients experiencing progression as best response (defined as primary refractory) to immune-based combinations is significantly lower than with anti-VEGFR TKIs [14−16], the necessity of identifying potential factors influencing their prognosis still represents a hot topic for uro-oncologists.

Currently, the choice of the best combination is mainly based on patients' clinical and histological characteristics and, even more, on clinicians' experience. On this scenario, real-world data may offer a crucial contribution to guide the decision-

making process in patients with mRCC [17−19]. The ARON project has been designed to create a global network to allow uro-oncologists to share and discuss their experiences on the use of immunotherapy and other emerging drugs for patients with genitourinary tumors. Specifically, the ARON-1 study (NCT05287464) was designed to globally collect real-world data on the use of immuno-oncologycombinations as first-line therapy for mRCC.

2. Patients and Methods

2.1 Study population

The ARON-1 study (NCT05287464) retrospectively collected data from patients aged ≥18 years with a cytologically and/or histologically confirmed diagnosis of mRCC treated with first-line immuno-combination therapies.

The ARON-1 study collected data of patients treated from January 1st 2016 to July1st 2022 in 47 International Institutions from 16 countries. Clinical data and laboratory parameters from patients' paper and electronic charts were collected. The study population included adults with clear-cell RCC (ccRCC) or non-clear-cell RCC(nccRCC). Data on histology, nephrectomy status, International mRCC Database Consortium (IMDC) criteria, sites of metastases, type of immuno-combination and response to therapy were retrospectively collected. Patients without enough data on tumor assessment, or response to therapy were excluded from our study.

Follow-up was usually carried out by means of physical examination and laboratory tests every 4–6 weeks, while imaging was performed following standard local procedures every 8–12 weeks.

2.2 Study endpoints

Disease status was evaluated using standard RECIST 1.1 criteria [20]. Overall Survival (OS) was calculated from the start of first-line immuno-oncology combination until death. Progression-Free Survival (PFS) was defined as the time from the start of treatment to progression or death from any cause, whichever occurred first. Patients without tumor progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit. Data on tumor response (complete [CR] or partial responses [PR], stable [SD] or progressive disease [PD]) were collected and analyzed.

2.3 Statistical Analysis

The Kaplan-Meier method with Rothman's 95% confidence intervals (CI) was used to estimate the survival curves of both OS and PFS. Comparisons were performedby using the log-rank test. Univariate and multivariate analyses were carried out by Cox proportional hazards models. A survival receiver operating characteristic (ROC) analysis was adopted to identify potential cut-offs that better stratify patients into risk groups. The chi-square test was used to compare categorical end-points. Differences were considered statistically significant when the *p*-value was <0.05, and all *p* values were two-sided. The statistical analysis was performed by MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

The research was carried out in accordance with the approval by the ethics committee of the Marche Region (2021-492) and was performed in accordance with the Declaration of Helsinki.

3. Results

3.1 Study Population

Seven hundred and twenty-nine patients were included in our analysis. The median follow-up time was 18.1 months (95%CI 14.4−67.8);540 patients (74%) were males. The median age was 63 years (range 25−88). Tumour histology was predominantly ccRCC (625, 86%); among the 104 nccRCC patients, histology showed a papillary type I or II RCC in 28 cases and chromophobe RCC in 11 cases (Table 1); sarcomatoid differentiation was observed in 117 patients (16%).

Lung (70%), lymph nodes (51%), and bone (34%) were the most common sites of metastasis. Basing on IMDC criteria, 113 patients (16%) were at favourable-risk, 425 (58%) at intermediate-risk, and 191 (26%) at poor-risk. Patients' characteristics are summarized in Table 1. No significant differences were found in terms of baseline clinico-pathological features between patients receiving IO + IO and those treated by IO + TKI, except for a higher proportion of patients with lung metastases treated by nivolumab and ipilimumab and for a different IMDC group stratification, related to the fact that IO + IO combination was approved only for intermediate and poor risk RCC patients (Table 1).

Nivolumab and ipilimumab was the first-line therapy in 313 patients (43%), while 416 patients (57%) received IO + TKI combinations; by the time of analysis, 101 (32%) and 60 patients (14%), respectively, treated by IO + IO or IO + TKI had demised at

the time of analysis.

3.2 Survival analysis

In the overall study population, the median OS was 36.5 months (95%CI 24.8−60.8). One hundred and sixty-one patients (22%) were dead at the time of analysis. Male patients showed longer median OS than females, although the difference was not statistically significant (55.8 vs 28.4, *p*=0.104, Figure 1). Furthermore, no statistically significant differences were observed between patients aged ≥70y and <70y (28.1 months, 95%CI 25.9−60.8, vs 41.0 months, 95%CI 32.7−55.7, *p*=0.117, Figure 1).

In patients with good, intermediate and poor risk criteria, the median OS was not reached (NR, 95%CI NR−NR), 55.7 months (95%CI 28.4−60.8) and 19.2 months (95%CI 12.5−32.7), respectively (*p*<0.001, Figure 1). Previous nephrectomy was associated with median longer OS (55.7 months, 95%CI 41.0−60.8, vs 18.4 months, 95%CI 16.2−28.1, *p*<0.001, Figure 1).

Patients with ccRCC showed longer median OS compared to those with nccRCC histology (41.0 months, 95%CI 29.7−60.8, vs 18.0 months, 95%CI 12.6−36.5, *p*=0.005, Figure 1). Of note, the presence of sarcomatoid differentiation was correlated with shorter median OS (26.4 months, 95%CI 20.0−41.0, vs 36.5 months, 95%CI 28.4−60.8, *p*=0.014, Figure 1).

The best cut-off for the number of metastatic sites was calculated by ROC curve and resulted >3. In our study population, 141 patients (19%) presented >3 metastatic sites and had a significantly shorter median OS (22.1 months, 95%CI 16.8−41.0) compared to patients with ≤3 metastatic sites (55.7 months, 95%CI 30.7−60.8, *p*<0.001, Figure 2). Brain metastases were associated with the worst

median OS (18.4 months, 95%CI 13.2−41.0 vs 36.5 months, 95%CI 29.7−60.8, *p*=0.024, Figure 2), followed by bone (26.0 months, 95%CI 20.0−29.7 vs 60.8 months, 95%CI 36.5−NR, *p*<0001, Figure 2) and liver metastases (28.4 months, 95%CI 19.1−60.8 vs 41.0 months, 95%CI 29.7−60.8, *p*=0.024, Figure 2).

In the overall study population, median PFS was 15.0 months (95%CI 12.2−17.1).No statistically significant differences in terms of PFS were found between men and women (14.6 months, 95%CI 12.0−17.0 vs 15.9 months, 95%CI 9.9−44.5, *p*=0.979) and between patients aged ≥70y and <70y (15.5 months, 95%CI 10.4−21.5, vs 15.0 months, 95%CI 12.2−18.8, *p*=0.742).

Patients with good, intermediate and poor risk criteria showed a median PFS of 28.4, 15.0 and 11.0 months, respectively (*p*<0.001, Figure S1). Longer median PFS was observed in patients who underwent previous nephrectomy (20.1 months, 95%CI 15.9−25.1, vs 9.0 months, 95%CI 6.8−11.3, p<0.001, Figure S1), while no significant difference was found between ccRCC and nccRCC patients (15.2 months, 95%CI 12.2−18.7, vs 13.0 months, 95%CI 6.9−25.1, *p*=0.168). Sarcomatoid differentiation was correlated with shorter PFS (6.7 months, 95%CI 5.5−15.8, vs 15.5 months, 95%CI 12.9−21.6, *p*<0.001, FigureS1), as well as the presence of >3 metastatic sites (6.9 months, 95%CI 4.8−11.3, vs 16.4 months, 95%CI 14.1−21.5, *p*<0.001, Figure S1). Bone metastases were associated with worst PFS (10.4 months, 95%CI 8.0−12.9, vs 20.1 months, 95%CI 15.2−28.4, *p*<0.001, Figure S1), while no statistically significant differences were found with the presence of liver (11.3 months, 95%CI 7.5−21.7, vs 15.8 months, 95%CI 12.9−18.8, *p*=0.129) or brain metastases (10.4 months, 95%CI 5.5−13.0, vs 15.8 months, 95%CI 12.9−18.8, *p*=0.088).

3.3 Role of prognostic factors

At univariate analysis, IMDC criteria, previous nephrectomy, tumor histology, sarcomatoid differentiation, number of metastatic sites >3, bone, liver and brain metastases were significant predictors of OS (Table 2). At multivariate analysis, IMDC criteria, previous nephrectomy, tumor histology, sarcomatoid differentiation, and bone metastases proved to be significantly associated with OS (Table 2).

As for PFS, previous nephrectomy, sarcomatoid differentiation, number of metastatic sites >3, and bone metastases were significantly associated with OS at both univariate and multivariate analyses, while IMDC criteria did not prove to be significantly correlated with PFS at multivariate analysis (Table 2).

3.4 Comparison of Overall Survival: IO + IO vs IO + TKI

At the time of data cut-off, nivolumab plus ipilimumab was ongoing in 158 of the 313 patients. The median follow-up time for this combination was 18.8 months (95%CI 15.5−88.8). At the time of data cut-off, treatment with IO + TKI was ongoing in 307 of the 416 patients, with a median follow-up time of 17.6 months (95%CI 16.9−64.3). Second and third-line treatments stratified by first-line immuno-combination are reported in Table S1.

In the 616 patients with intermediate/poor IMDC risk criteria, the use of an IO + TKI combination yielded a longer median OS, as compared to the IO + IO doublet (55.7 months, 95%CI 27.3−60.8, vs 29.7 months, 95%CI 25.9−41.0, p=0.045, Figure 3).

We further stratified IMDC intermediate/poor risk patients by clinico-pathological features. Stratified by sex, no significant differences were observed in male

patients treated by IO + TKI vs IO + IO (male: 55.7 months, 95%CI 22.1−60.8, vs NR, 95%CI NR−NR, *p*=0.364; females: NR, 95%CI NR−NR, vs 25.0 months, 95%CI 16.0−41.0, *p*=0.089). The two combinations showed similar median OS in intermediate/poor risk patients aged >70y (IO+ TKI: 28.1 months, 95%CI 18.4−60.8, vs IO + IO: 26.4 months, 95%CI 22.2−28.4, *p*=0.859).

A trend toward a longer median OS was observed in intermediate/poor risk patients who underwent nephrectomy treated by IO + TKI, although the difference was not statistically significant (55.7 months, 95%CI 32.7−60.8, vs 41.0 months, 95%CI 29.7−41.0, *p*=0.682).

Stratified by tumor histology, IO + TKI combination registered a not statistically significant longer median OS in both ccRCC (55.7 months, 95%CI 27.3−60.8, vs 30.2 months, 95%CI 26.0−41.0, *p*=0.162) and nccRCC intermediate/poor risk patients (18.0 months, 95%CI 12.6−18.0, vs 15.2 months, 95%CI 7.6−16.5, *p*=0.107).

Among the 114 mRCC cases with sarcomatoid differentiation, 54 received IO + TKI combination, reporting a statistically non significant prolongation of the median OS compared to the 60 patients treated by IO + IO therapy (NR, 95%CI NR−NR, vs 25.0 months, 95%CI 8.9−41.0, *p*=0.190).

Finally, based on site of metastases, the difference in favor of IO + TKI combinations was statistically significant in intermediate/poor risk patients with lung (60.8 months, 95%CI 27.3−60.8, vs 28.3 months, 95%CI 20.0−41.0, *p*=0.028, Figure 3) and liver metastases (55.7 months, 95%CI 22.1−60.8, vs 25.9 months, 95%CI 10.0−30.2, *p*=0.033, Figure 3), while it was not significant in patients with bone (27.3 months, 95%CI 19.1−55.7, vs 22.2 months, 95%CI 15.4−28.3, *p*=0.159) or brain metastases (22.1 months, 95%CI 18.0−22.1, vs 13.2 months, 95%CI 6.0−41.0, *p*=0.221).

3.5 Comparison of Progression-Free Survival: IO + IO vs IO + TKI in intermediate/poor risk patients

The median PFS was longer in patients with Intermediate/poor risk IMDC criteria treated by IO + TKI compared to IO + IO combination (15.9 months, 95%CI 11.0−20.6 vs 11.1 months, 95%CI 7.2−14.6, *p*=0.011, Figure S2).

The median PFS was longer in females treated by IO + TKI vs IO + IO combination (44.5 months, 95%CI 9.6−44.5, vs 5.9 months, 95%CI 4.4−15.8, *p*=0.004, Figure S2). No significant differences were observed in males (13.0 months, 95%CI 10.4−20.1, vs 12.2 months, 95%CI 8.3−15.2, *p*=0.208), patients aged >70y (23.2 months, 95%CI 8.5−27.6, vs 11.3 months, 95%CI 6.3−16.4, *p*=0.097) and those with previous nephrectomy (16.6 months, 95%CI 11.4−27.6 vs 15.8 months, 95%CI 10.4−23.9, *p*=0.612), clear cell histology (14.7 months, 95%CI 10.4−20.1 vs 12.0 months, 95%CI 7.8−15.2, *p*=0.078) or sarcomatoid differentiation (6.6 months, 95%CI 4.0−18.8 vs 6.7 months, 95%CI 4.2−17.1, *p*=0.723). On the other hand, nccRCC patients showed longer median PFS with IO + TKI combination (NR, 95%CI NR−NR vs 6.9 months, 95%CI 4.0−15.2, *p*=0.018, Figure S2).

By stratifying patients according to metastatic sites, the use of IO + TKI combination registered a statistically significant longer median PFS compared to IO + IO only in intermediate/poor risk patients with liver metastases (16.6 months, 95%CI 10.8−27.6 vs 5.8 months, 95%CI 3.6−11.5, *p*=0.004, Figure S2), while no significant differences were found in patients with lung (11.4 months, 95%CI 9.6−18.8 vs 10.4 months, 95%CI 6.5−15.0, *p*=0.120), bone (11.0 months, 95%CI 8.0−16.6 vs 6.8 months, 95%CI 4.8−11.3, *p*=0.077) or brain metastases (10.4 months, 95%CI 3.6−13.0 vs 5.5 months,

95%CI 2.1−10.4, *p*=0.306).

3.6 Comparison of Response to first-line therapy: IO + IO vs IO + TKI

In the overall study population, the percentages of patients experiencing a CR, PR, SD and PD were 6%, 43%, 30%, and 21%, respectively. In patients treated by IO + IO combination, the response rate were CR=11%, PR=32%, SD=29% and PD=28% (Table S1). Otherwise, IO + TKI combinations yielded CR=3%, PR=51%, SD=30% and PD=16% (Table S1). The difference between the type of responses obtained by these two combinations were statistically significant (*p*<0.001, Table S1).

4. Discussion

The selection of the ideal candidate to receive IO + IO or IO + TKI combinations is challenging due to the lack of direct comparisons between these different approaches. In this situation, the use of real world data is integral to understanding the utilization patterns and outcomes of new treatments among cancer patients treated in the academic and the community settings and provides fundamental data on the outcome of patients ineligible to clinical trials [21,22], who constitute a not negligible proportion in daily clinical practice; and indeed, the use of rigorous real world evidence has been advocated across different malignancies [23].

The ARON-1 study has been designed to investigate for the presence of factors influencing the prognosis of mRCC treated by immuno-oncology combinations and to retrospectively compare the efficacy of the different combinations available across the globe. Our data showed that the main prognostic factors validated for mRCC patients treated with targeted monotherapy can also be

applied to patients treated with immuno-combinations (i.e. IMDC, liver-bone-brain met, nephrectomy, sarcomatoid differentiation, number of metastatic sites, clear cell vs non-clear cell histology).

If some of these factors are well known, some more insight deserves the putative favorable prognostic role of a previous cytoreductive nephrectomy. For years, this role has been a cornerstone in the overall management of mRCC, being supported not only by old randomized data coming from the age of cytokines-based immunotherapy, but also by huge retrospective series [24,25] and by at least one meta-analysis [26]. Our results further increase the amount of data still suggesting a positive role for cytoreductive nephrectomy, leading to a key question: in terms of evidence-making, is it more important a single randomized controlled phase III clinical trial (what's more, not free from criticisms) or a bulk of retrospective evidence from real world practice? In the absence of a clear cut answer, the clinical judgment on each given patient should replace any dogmatic attitude, as already claimed by Motzer and Russo in the editorial comment to the CARMENA publication [27].

As far as the indirect comparison between the two strategies, the median OS was longer with IO + TKI compared to IO+IO therapy, in patients with intermediate/poor risk features. Furthermore, OCB was +11% higher with the IO+TKIs combination. These data were consistent with those recently published in a meta-analysis on first-line immuno-combinations [28].

Another interesting (and at a certain extent worrisome) finding emerging from our study is the extremely low percentage of patients who did receive a second- or a third-line treatment. Although the relatively short follow-up may account, at least in

part, for this finding, it is clear that the use of combinations ultimately limits our choice for further treatment lines.

Of course our study presents several limitations, including its retrospective nature. At first, our follow-up of 18 months and the 22% of deaths may represent a bias for OS assessment. Secondly, we did not perform a centralized review of radiological imaging, neither we had no available data on the concomitant use of medications that could influence the efficacy of first-line therapy. As a consequence of all the above, our findings should be interpreted with caution and are in need possibly of a larger prospective validation.

Nevertheless, our data clearly suggest for patients for whom dimensional reduction of disease burden is needed (e.g. spinal cord compression, pain), one of the available IO-TKI combinations might be the best choice, considering the lower percentage of primary refractory patients compared to IO-IO combination in the present study; moreover, these data are consistent with the data of randomized trials [6-11].

In 2019, Dudani *et al*. [29] published a first retrospective comparison between 75 patients treated by IO+IO and 113 by IO+TKIs from the IMDC dataset, with a median follow-up of 11.7 months. In our study, reporting a longer follow-up and a larger study population, the efficacy of IO + IO and IO + TKI combinations varies across different clinico-pathological subgroups. Prospective clinical trials directly comparing distinct IO + IO and IO + TKIs combinations are thus sorely needed.

5. Declarations

No external funding was used in the preparation of this manuscript.

6. Authors' contributions

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7. 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.

R. Kanesvaran has received fees for speaker bureau and advisory board activities from the following companies; Pfizer, MSD, BMS, Eisai, Ipsen, Johnson and Johnson, Merck, Amgen, Astellas and Bayer.

Enrique Grande has received honoraria for speaker engagements, advisory roles or funding of 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. EG has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals

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Camillo Porta has received honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, General Electric, Ipsen and MSD and acted as a Protocol Steering Committee Member for BMS, Eisai and MSD.

The other authors declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

8. Ethics approval

The research was carried out in accordance with the approval by the ethics committee of the Marche Region (2021-492) and was performed in accordance with the Declaration of Helsinki.

9. Availability of data

All data generated or analyzed during this study are included in this published article (and its supplementary information files). The datasets generated during and/or analyzed during the current study are not publicly available in accordance with all the Centers participating to the ARON project but are available from the corresponding author on reasonable request.

10. Acknowledgements

None to declare.

11. References

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Table Legends

Table 1. Patients' characteristics. Statistically significant values were reported in bold. IMDC = International mRCC Database Consortium; IO = Immunotherapy; RCC = Renal Cell Carcinoma; TKI = Tyrosine Kinase Inhibitor. Statistically significant values were reported in bold.

Table 2. Univariate and Multivariate analyses of predictors of Progression-Free Survival and Overall Survival in mRCC patients treated with first-line immuno-combinations. Statistically significant values were reported in bold.

Figure Legends

Figure 1. Median Overall Survival in mRCC patients treated with first-line immuno-combinations stratified by clinico-pathological features.

Figure 2. Median Overall Survival in mRCC patients treated with first-line immuno-combinations stratified by number and type of metastatic site.

Figure 3. Comparison between the median Overall Survival obtained by IO + IO vs IO + TKI combination in intermediate/poor risk mRCC patients stratified by clinico-pathological features.

Supplementary Materials

Table S1. Response to first-line therapy and drug distribution in the second- and third-line settings. Statistically significant values were reported in bold.

Figure S1. Median Progression-Free Survival in mRCC patients treated with first-line immuno-combinations stratified by clinico-pathological features.

Figure S2. Comparison between the median Progression-Free Survival obtained by IO + IO vs IO + TKI combination in intermediate/poor risk mRCC patients stratified by clinico-pathological features.