Frontline immune checkpoint inhibitor-based combination therapy in metastatic renal cell carcinoma patients with poor performance status

Authors: Lucía Carril-Ajuria[1], Emeline Colomba[1], Carmen Romero-Ferreiro[2,3], Luigi Cerbone[1], Raffaele Ratta[4], Philippe Barthelemy[5], Clarisse Vindry[6], Aude Fléchon[6], François Cherifi[7], Elouen Boughalem[8], Claude Linassier[9], Giuseppe Fornarini[10], Sara Elena Rebuzzi[10], Marine Gross-Goupil[11], Carolina Saldana[12], Maricruz Martin-Soberón[13], Guillermo de Velasco[13], Ray Manneh[14], Cristina Pernaut[15], Ana Sanchez de Torre[16], Ronan Flippot[1], Bernard Escudier[1], Laurence Albiges[1].

Affiliations:

1. Medical Oncology Department, Institute Gustave Roussy, Villejuif, France
2. Instituto de Investigacion Sanitaria, Hospital 12 de Octubre (imas12), Madrid, Spain.
3. Faculty of Health Sciences, Universidad Francisco de Vitoria, 28223 Madrid, Spain.
4. Medical Oncology, Foch Hospital, Suresnes, 92151, France.
5. Medical Oncology, Hôpitaux Universitaires de Strasbourg / ICANS, Strasbourg, France.
6. Medical Oncology, Centre Léon Bérard, 69008 Lyon, France.
7. Medical Oncology, Centre François Baclesse, Caen, France.
8. Medical Oncology, Institut de Cancerologie de l'Ouest, 49055, Angers.
9. Medical Oncology, Centre Hospitalier Universitaire de Tours, Tours, France.
10. Medical Oncology, U.O. Oncologia Medica 1 RCCS Ospedale Policlinico San Martino, Genova, Italy.
11. Medical Oncology, Centre Hospitalier Universitaire Saint-André, Bordeaux, France.
12. Medical Oncology, Hôpital Henri Mondor, APHP, Univ Paris Est Creteil, Créteil, France.
13. Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain.
14. Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia.
15. Medical Oncology, University Hopital Severo Ochoa. Leganés, Madrid, Spain.
16. Medical Oncology, University Hospital Infanta Cristina. Parla, Madrid, Spain.

*Corresponding author:

Laurence ALBIGES, Gustave Roussy, Université Paris-Saclay, Département de médecine Oncologique, Villejuif, F-94805, France. Fax : 01 42 11 53 05. E-mail address: laurence.albiges@gustaveroussy.fr (L. Albiges).

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ABSTRACT

Background: Immune-checkpoint inhibitor-based combination therapy (ICI-based combination) is a new standard of care for metastatic clear cell renal cell carcinoma (mRCC) in the frontline setting. Patients with poor PS (≥2) were excluded from pivotal trials. Hence, the activity and safety of ICI-based combination therapy in this group of patients is still unknown.

Methods: We performed a multicentre retrospective study of PS≥2 mRCC patients who received frontline ICI-based combination, either nivolumab-ipilimumab (NI) or pembrolizumab-axitinib (AP). Patients characteristics, clinical outcomes and toxicity were collected. We analysed overall response rate (ORR), median progression-free survival (mPFS), median overall survival (mOS) and grade≥3 adverse events (G≥3AEs). The association between the predictive biomarker IPI (Immune Prognostic Index) and ORR/PFS/OS was also evaluated.

Results: We identified 70 mRCC patients with PS≥2 treated with ICI-based combination across 14 institutions between October 2017-December 2021, including 45 and 25 patients were treated with NI and AP respectively. Median age at diagnosis was 63 years, 51 (73%) were male, only 17 (24%) had prior nephrectomy, 50 (71%) had synchronous metastatic disease at diagnosis, and 16 (23%) had brain metastases. Respectively, 61 (87%) and 9 (13%) patients had ECOG (Eastern-Cooperative-Oncology-Group) PS 2 and 3, and 25 (36%) and 45 (64%) patients were intermediate and poor IMDC risk respectively. Among all, 91% were clear-cell RCC, 7 patients had sarcomatoid features. At the time of analysis (median follow-up 11.1 months) 41% patients were dead. Median PFS and mOS in the entire cohort were 5.4 months and 16.0 months respectively; ORR was 31%. No significant differences in ORR, PFS, OS or G≥3AEs were seen between NI and AP. The intermediate and poor IPI groups were significantly associated with reduced ORR and shorter PFS.

Conclusion: We report the first cohort of PS≥2 mRCC patients treated with frontline ICI-based combination therapy. The survival outcomes in our cohort were inferior to that reported in pivotal trials. No significant differences in ORR, PFS, OS or toxicity were seen between NI and AP. Prospective real-world studies are needed to confirm these results.

Keywords: renal cell carcinoma, poor performance status, combination therapy, immune checkpoint inhibitors, immunotherapy, kidney cancer

Introduction

Immune checkpoint inhibitor (ICI) combinations, with another ICI or with a vascular endothelial growth factor receptor-tyrosine kinase inhibitor (TKI) have become the standard of care in fist line setting for metastatic renal cell carcinoma (mRCC) (1–5). Currently four ICI combinations are available after demonstrating significant improvement in survival compared to sunitinib monotherapy: nivolumab+ipilimumab (NI, intermediate-poor IMDC risk patients), and three ICI-TKIs: pembrolizumab+axitinib (AP), nivolumab+cabozantinib (nivo-cabo) and pembrolizumab+lenvatinib (pembro-lenva) (across all IMDC risk groups) (2–5). These combinations have not only demonstrated survival benefit but have also shown an unprecedented benefit in the rate of complete responses (9-15%) with a mPFS ranging between 12 and 24 months (2–5).

In the absence of head-to-head trials and ~~of~~ validated predictive markers, treatment choice for mRCC is guided in the clinical practice by the interpretation of existing data as clinical features of the patient/disease including tumor burden, performance status, IMDC risk group, outcomes and patient's preferences (1–5).

The ECOG and Karnofsky scales of performance status (ECOG PS and KPS) describe the level of function and capability of selfcare and play a key role in treatment decision (6,7). Patients with poor performance status may represent a heterogeneous population, as it can can be either disease burden-induced or comorbidity-dependent. Performance status is an established prognostic factor across solid-tumors, including mRCC (8–10). Poor performance status (KPS <70/ECOG PS≥2) is included in both the International Metastatic RCC Database Consortium (IMDC) risk model and the Memorial Sloan-Kettering Cancer Center Score, as an independent poor prognostic factor (11,12). Importantly, of the five prognostic factors that make up the IMDC score, poor performance status is the one with the highest prognostic weight (13).

The four ICI-based combinations (NI, AP, nivo-cabo and pembro-lenva) were approved by the Food and Drug Administration (FDA) regardless performance status (2–5). However, patients with poor performance status were underrepresented in pivotal trials. A Karfnosky performance status score (KPS)<70% was an inclusion criteria for these trials, and only 15-20% of patients included these trials had a KPS of 70-80% (ECOG PS 2 =

KPS of 60-70%). Thus, the efficacy of ICI-based combinations in this population is still unclear. Data from prospective and retrospective studies evaluating the role of ICI in other tumor models and focusing on poor PS were reported for non-small cell lung cancer (NSCLC) and advanced urothelial carcinoma (aUC) suggested antitumor activity with good tolerability, but as expected, a consistently worse overall survival (14–25). Similarly, retrospective studies conducted in melanoma showed that patients with poor PS associated worse objective response rates (ORR), progression-free survival (PFS) and overall survival (OS) than those with good PS under ICI (26,27). These could be supported by the findings of Wang et al. in patients with gastric cancer suggesting that poor PS is associated to an imbalance of circulating T cells (28). In this study, Wang and colleagues determined the association between circulating T cell subpopulations in peripheral blood and PS in patients with gastric cancer and observed that advanced gastric cancer patients with poor PS presented a decreased $CD4^+/CD8^+$ ratio compared to those with good PS (28).

We hypothesized that mRCC with poor PS (ECOG PS≥2) would present worse clinical outcomes than pivotal studies including PS 0-1 patients. Furthermore, on the rational that ICI may be less active in poor PS patients, we hypothesized that an ICI-TKI combination would be more effective than double ICI in this subgroup of patients. Thus, the aims of our study were to investigate the clinical outcomes of poor PS mRCC patients under ICI-based combination therapy and, to compare the efficacy and safety of AP and NI in mRCC patients in this underrepresented population.

Methods

Study design and population

This observational multicenter study included all consecutive poor PS mRCC patients treated with frontline ICI-based combination therapy between October 2017 and December 2021, from 14 institutions across four countries (France, Spain, Italy and Colombia). Eligibility criteria included poor PS (ECOG PS≥2) mRCC patients with measurable disease by the Response Evaluation Criteria of Solid Tumors (RECIST) receiving NI or AP combination as standard of care (at least one cycle). Standardized chart review collected date of diagnosis, age at diagnosis, gender, date of nephrectomy, date of first metastasis, type of metastatic site at initiation of systemic treatment, and prognostic factors according to the International

Metastatic RCC Database Consortium (IMDC) risk model. All patients had regular computed tomography scanner evaluation based on local practice. The response by RECIST was determined locally.

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, the guidelines of the International Conference on Harmonization of Pharmaceuticals for Human Use, and the Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review board at each participating center.

Statistical analyses

The patient's characteristics (sex, age at diagnosis, ECOG Performance Scale, site of metastases, International Metastatic RCC Database Consortium (IMDC) risk group, derived neutrophil-to-lymphocyte ratio (dNLR= absolute neutrophil count/[white blood cell concentration-absolute neutrophil count), Immune Prognostic Index (IPI) group (based on dNLR≥3 and LDH greater tan upper limit of normal (UPN)), prior nephrectomy, grade, number of lines, and type of systemic therapy) were described (median and interquartile range [IQR] for continuous variables and absolute and relative frequencies for categorical variables) for the global population and for the different treatment groups.

The endpoints were ORR, median PFS and OS. Best response was determined by local assessment every 8-12 weeks according to RECIST 1.1 criteria as partial response (PR), complete response (CR), stable disease (SD), and progressive disease (PD). The ORR was defined as CR + PR and disease control rate (DCR) as CR + PR + SD. DCR and ORR were compared between the different treatment groups using Fisher's exact test. PFS was defined as the time between start of therapy and disease progression or death of any cause, whichever occurred first. OS was defined as the time between start of therapy and death of any cause. Patients who were still alive and undergoing treatment at final analysis were censored at the date of last follow-up (FU). These two time-to-events were estimated by using the Kaplan Meier (KM) method, and the median with its 95% confidence interval (CI) was reported. The median follow-up from the date of the first-line therapy was estimated using the reverse KM method. We compared median PFS and OS at the first line according to the IMDC, dNLR (high ≥3 or low <3) and IPI groups (good, 0 factors; intermediate, 1 factor; and poor, 2 factors) (log-

rank test); and according to the type of systemic treatment (stratified log-rank test). For the latter, no interpretation can be performed based on the KM estimation considering the observational design. Covariates with p<0.2 in the UVA were entered into the MVA model. The cut-off date for the analysis was 30TH December 2021. The statistical analyses were performed with SAS software 9.4 (SAS Institute). All p values <0.05 were considered statistically significant.

Results

Patient characteristics

We identified 70 mRCC patients with poor PS treated with frontline ICI-based combination therapy, NI or AP, across 14 institutions from four countries (France, Spain, Italy, and Colombia). Patient's characteristics are described in Table 1. Forty-five (64%) and 25 (36%) patients were treated with NI and AP, respectively, all as standard of care. Median age at diagnosis was 63 years (range: 30-83) and 51 (73%) patients were male. Only seventeen (24%) patients underwent prior nephrectomy and 50 (71%) patients had synchronous metastatic disease at diagnosis.

Respectively, in the whole cohort, 61 (87%) and 9 (13%) patients had ECOG (Eastern Cooperative Oncology Group) PS 2 and 3, and 25 (36%) and 46 (64%) patients were intermediate and poor IMDC risk. Of the 25 patients with intermediate IMDC risk, 19 (76%) patients had two risk factors.

Most patients had clear-cell RCC (90%), and seven patients had sarcomatoid features. At the start of first line therapy, 52 (74%), 36 (51%), 17 (24%), 16 (23%) and 16 (23%) had lung, bone, liver, brain, and adrenal metastasis respectively.

Overall response rate

The ORR and DCR for the whole population were 33% and 52% respectively. No statistically significant differences in ORR and DCR were seen between NI and AP (ORR: 23% NI and 42% AP, p=0.379; DCR: 43% NI and 63% AP, p= 0.316) (Table 2). The two patients achieving CR were in the NI group.

No differences in ORR between NI and AP were seen neither according to site the presence of liver, brain, or bone metastasis at diagnosis (all p>0.1). However, the presence of brain metastasis at start of frontline ICI-based combination therapy was a negative predictor of response (p=0.047). In patients with brain metastases, AP was associated with a high ORR than NI, although it did not reach statistical significance (33% AP vs 0% NI, p=0.051, n=16). Intracranial response was not assessed.

No association was noted between IMDC risk groups (intermediate and poor) and response to ICI-based combination therapy. Inflammatory markers such as lactate dehydrogenase (p=0.019), the dNLR (high ≥3 vs low <3, p=0.013) and the Immune Prognostic Index (IPI) were significantly associated with the absence of response to ICI-based combination therapy (IPI good: ORR 22.5%, IPI intermediate: ORR 7.5% and IPI poor: ORR 0.0%, p=0.044). In patients with at least 1 IPI factor (intermediate and poor IPI groups), responses were significantly superior with AP than NI (50% AP vs 0% NI, p=0.02). Further, when analysing separately the response in the NI and the AP group according to these inflammatory markers, LDH, dNLR and IPI did not impact the response to AP but were however strongly associated with lack of response to NI (LDH log rank p = 0.008 and dNLR log rank p=0.043; ORR according to IPI groups: good ORR 20.8%, intermediate and poor ORR 0%, p = 0.005).

Median Overall survival and Progression-free survival

Median duration of follow-up was 11.1 months (95% IC: 7.9-12.7). At the time of analysis, 41% of patients were dead. Median PFS and mOS in the entire cohort were 5.4 months and 16.0 months respectively. No significant differences in PFS (NI: 3.8 months, 95% CI: 2.6-7.6; and AP: 6.0 months, 95% CI: 2.8-11.6, p= 0.842) or OS (NI: 9.8 months, 95% CI: 5.5-16.0, and AP: not-reached (NR), p= 0.286) were seen between the NI and AP groups (Figure 1A-B, Table 2).

No significant differences were seen in mPFS or OS according to IMDC risk groups. Of note, there was no favourable risk group as all patients had at list one IMDC risk factor. In contrast, the IPI was significantly associated with worse mPFS (p<0.0001) and worse mOS (p=0.0011) (Figure 2A-B). The association between IPI and worse mPFS (Poor vs good IPI PFS HR=3.9, 95%CI: 1.4-10.6, p=0.006 and Intermediate vs good IPI PFS HR=9.0, 95%CI: 2.7-29.2, p<0.001) remained significant after MVA adjustment (covariates with p-value <0.2: grade 3-4, LDH UNL,

dNLR and histological subtype), however the association with worse mOS only remained significant for the IPI intermediate group.

The dNLR was able to stratify according to mPFS (p=0.004) and OS (p=0.003). No significant differences in PFS or OS were seen between NI or AP according the dNLR, sites of metastasis, nutritional status or other relevant clinical parameters.

Toxicity

Sixteen (23%) patients in the whole cohort presented grade 3-4 adverse events (gr3-4 AEs). No significant differences in the rate of g3-4 AEs were seen between NI (25%) and AP (20%) (p=0.636). One treatment-related death was reported in the NI group due to myocarditis. No treatment-related deaths were reported in patients treated with PA, although a case of treatment-related acute coronary syndrome was reported with PA. High grade endocrine toxicities, including one case of hypophysitis and two cases of hypothyroidism, and high grade skin (one patient), renal (two patients) and hematological (one patient) immune-related toxicities were only reported for patients treated with NI. High grade colitis and hepatitis were reported in both treatment arms (NI: two cases of colitis and one of hepatitis; PA: one case of colitis and another of hepatitis). The only case of high grade fatigue was reported in the PA group.

Discussion

We reported for the first time a real-life cohort of poor PS mRCC patients treated with ICI-based combination therapy in frontline setting. Immune-checkpoint combination therapy, either ICI-ICI or ICI-TKI, has become the first-line standard treatment in mRCC (1). However, as in other solid tumours, patients with poor performance status were excluded from most pivotal trials (4–7). Real-world retrospective studies conducted in other tumor types have consistently shown that poor PS is a predictor of worse response and survival outcomes with ICI (16,21,27,30,31). Currently, no real-world evidence supports the use of ICI-based combination therapy in mRCC patients with poor PS.

In this extremely unfavourable cohort (poor PS patients, 64% poor IMDC, 23% with brain metastasis, previous nephrectomy only in 24%), objective response rate (31%), mPFS (5.4 months) and mOS (16.0 months) were as expected inferior to the results reported with

first-line ICI combination therapy in pivotal trials (4–7). These results where worse than those observed with NI in the Checkmate 214 in intermediate/poor IMDC risk mRCC patients (ORR: 42.4%, mPFS: 11.6 months, and mOS: 47 months) (4). However, this could be explained by a higher percentage of poor risk patients in our cohort (64 % vs 21% in the Checkmate 214) as well as the rest of previously mentioned unfavourable features of our population. These results are consistent with previous prospective and retrospective studies evaluating the efficacy of ICI in cancer patients with poor PS (16,21,23,27,30,32–34).
Regarding the ICI-based combination therapy used, we reported no statistically significant difference between NI and PA in terms of ORR, PFS or OS, although ORR, mPFS and mOS were numerically higher with PA (ORR: 42%, mPFS: 6.0 months and mOS: NR) than with NI (ORR: 23%, mPFS: 3.8 months and mOS: 9.8 months).

Although poor PS does not necessarily equal the poor risk category according to standard classifications (the IMDC or the MSKCC), the IMDC risk score failed to stratify patients into two different prognostic groups. This could be due to the small sample size , or to the prognostic burden of PS2 (13). However, the IPI was able to stratify patients according to PFS and OS. The IPI, initially developed in NSCLC (LIPI: lung immune prognostic index) by Mezquita et al., is a simple clinical score based on baseline LDH and dNLR which has been shown to associated with treatment outcomes in NSCLC, melanoma and RCC (35–37). To date, there are only two studies which have evaluated the role of IPI in mRCC. In the study conducted by Meyers et al., including NSCLC (302), melanoma (131) and mRCC (145) patients under ICI regardless of treatment line, IPI was associated with OS and PFS in mRCC patients treated with ICI, however only the association with OS remained significant in the MVA (36). The second study evaluating the role of IPI in mRCC is the post-hoc analysis of the NIVOREN trial which confirmed an association between IPI and OS/PFS in previously treated mRCC treated with nivolumab (37). Our results reported for the first time the association between IPI and survival outcomes in mRCC treated with combination therapy in mRCC. Of note, although IPI correctly stratified patients according to PFS, the discriminatory value of IPI for OS was limited to the poor group. This could be explained by the small sample size. In the absence of reliable biomarkers in mRCC, the validation of the potential prognostic, and/or predictive, value of IPI in prospective randomized studies is needed.

A major concern when treating cancer patients with poor PS is the potential higher risk of toxicities under systemic therapy. In this regard, prospective studies such as the phase 2 PePS2 study assessing pembrolizumab in ECOG PS2 NSCLC patients or the single arm phase 3b SAUL

trial assessing atezolizumab in advanced urothelial carcinoma patients with poor PS suggest that ICI can be administered safely in patients with poor PS (32,33). Moreover, retrospective studies comparing the efficacy and safety of ICI in poor versus good PS NSCLC patients have shown similar rates of immune-related grade 3-4 adverse events regardless performance status (14,23–25).

Interestingly, in our study the rate of grade 3-4 adverse events with ICI-based combination therapy was lower than those previously reported in pivotal trials (4–7). Moreover, we noticed no significant differences in the rate of grade 3-4 AEs between AP (20%) and NI (25%) in this frail real-life population.

The strengths of our study are that first, we provided for the first-time real world-evidence on the efficacy and safety of ICI-based combination therapy in mRCC patients with poor PS. Second, this is the first study to compare the efficacy and safety of dual ICI and ICI-TKI in mRCC patients with poor PS. Our study has however several limitations including the retrospective design, small sample size, short follow up, heterogeneity in clinical practice and data collection, geographic heterogeneity, and the absence of centralized response assessment. Also, whether the poor PS was driven by the tumour or by other comorbidities was not collected and thus its impact on clinical outcomes was not evaluated.

Conclusion

In conclusion, we report the first cohort of mRCC patients with poor PS treated with frontline ICI-based combination therapy. The survival outcomes in our cohort were, as expected, inferior to that reported in pivotal trials. Efficacy outcomes (ORR, mPFS and OS) were numerically higher with AP than NI, although they did not reach statistical significance. Interestingly, both treatment strategies were well tolerated with a lower rate of g3-4 AEs than that reported in pivotal trials and without significant differences between them, which supports the safety of ICI-based combination therapy in this population. Prospective real-world studies including a larger number of patient and with a longer FUP are needed to confirm these results.

Authors' contributions

LCA: conceptualization and design, methodology, data acquisition, manuscript drafting, critical revision, and project administration. EC: conceptualization and design, data acquisition, critical review, and supervision. CRF: methodology, formal statistical analysis, and critical review. LC, RR, PB, CV, AF, FC, EB, CL, GF, SER, MGG, CS, MMS, GdV, RM, CP, AST and RF: data acquisition and critical review. BE and LA: conceptualization and design, data acquisition, critical review, and supervision.

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Tables

Table 1. Baseline patient's and tumour's characteristics.

Characteristics	All patients (n=70)	NI (n=45)	AP (n=25)
Age at diagnosis (years), median (range)	63 (30-83)	68 (31-83)	61 (30-83)
Male, n (%)	51 (73)	36 (80)	15 (60)
Metastatic at diagnosis, n (%)	50 (71)	35 (78)	17 (68)
Prior nephrectomy, n (%)	17 (24)	12 (27)	7 (28)
Clear cell, n (%)	63 (91)	41 (91)	23 (92)
Sarcomatoid features, n (%)	7 (1)	5 (11)	2 (8)
Führman/ISUP Grade 3-4, n (%)	34 (62)	20 (61)	14 (64)
NA	15	12	3
Site of metastases, n (%)			
Lung	52 (74)	32 (71)	20 (80)
Adrenal	20 (29)	12 (27)	8 (32)
Bone	36 (51)	26 (58)	10 (40)
Liver	17 (24)	9 (20)	8 (32)
Brain	16 (23)	10 (22)	6 (24)
ECOG PS			
2	61 (87)	42 (93)	19 (76)
3	9 (13)	3 (7)	6 (24)
IMDC risk group, n (%)			
Intermediate	25 (36)	17 (38)	8 (32)
Poor	45 (64)	28 (62)	17 (68)
LIPI group, n (%)			
Good	20 (48)	10 (40)	10 (59)
Intermediate	15 (36)	10 (40)	5 (29)
Poor	7 (17)	5 (20)	2 (12)
NA	28	20	8

dNLR group, n (%)			
Low	42 (72)	24 (65)	18 (86)
High	16 (28)	13 (35)	3 (14)
NA	12	8	4

ISUP: International Society of Urological Pathology ; IMDC :International Metastatic RCC Database Consortium; IPI: international prognostic index ;dNLR : Derived neutrophil-to-lymphocytes ratio ; NA : not available; NI: nivolumab-ipilimumab; and AP: axitinib-pembrolizumab.

Table 2. Efficacy and toxicity outcomes according to the type of ICI-based combination

Systemic treatment	N	**ORR (%)**	P-value	**DCR (%)**	P-value	**mPFS (mo)**	P- value	**mOS (mo)**	P- value	**G≥3 AEs (%)**	P-value
NI	45	23	**0.379**	43	**0.319**	3.8	**0.842**	9.8	**0.286**	25	**1.0**
AP	25	42		63		6.0		NR		20	

ORR: objective response rate; DCR: disease control rate; mPFS: median progression-free survival; mOS: median overall survival; G≥3 AEs: grade≥3 adverse events; NI: nivolumab-ipilimumab; and AP: pembrolizumab-axitinib.

Figures

Figure 1. Kaplan-Meier survival curves according to type of ICI-based combination therapy: A) overall survival and B) progression-free survival.

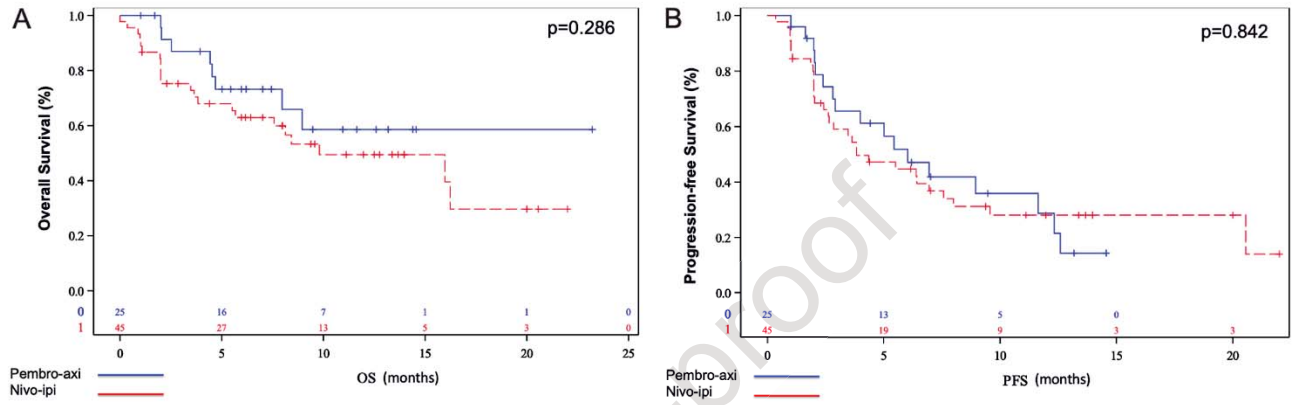
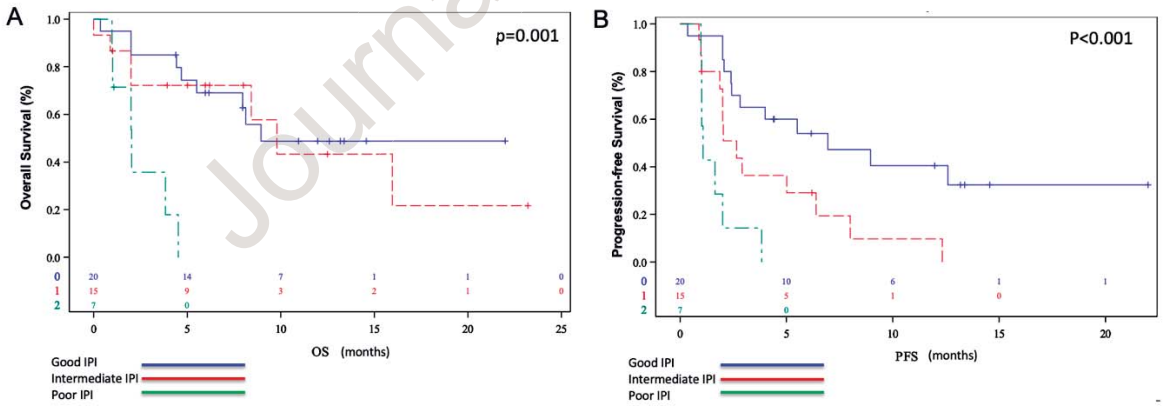


Figure 2. Kaplan-Meier survival curves according to IPI group: A) overall survival and B) progression-free survival.



- First cohort of poor PS mRCC treated with front line ICI-based combination therapy.
- The survival outcomes were inferior to that reported in pivotal trials.
- No significant differences in ORR, PFS or OS were seen between NI and AP.
- Both NI and AP were well tolerated without significant differences between them.

Declaration of Interest Statement

LCA: BMS Belgium Travel, Accommodation and Expenses.

EC: Consulting or Advisory Role - BMS; Ipsen ; Sanofi;GSK; Eisai; Merck; Janssen; Pfizer; Travel, Accommodations, Expenses - BMS Brazil; Pfizer; IPSEN.

BE: Honoraria - Bristol-Myers Squibb; EUSA Pharma; Ipsen; Novartis; Oncorena; Pfizer; Roche/Genentech Consulting or Advisory Role - AVEO; Bristol-Myers Squibb; EUSA Pharma; Ipsen; Novartis; Pfizer; Roche/Genentech Research Funding - BMS France (Inst) Travel, Accommodations, Expenses - Bristol-Myers Squibb; Ipsen; MSD; Pfizer; Roche/Genentech.

LA: Consulting fees compensated to the institution for Pfizer, Novartis, Bristol Myer Squibb, Ipsen, Roche, MSD, Astra Zeneca, Merck, Amgen, Astellas, Exelixis, Corvus Pharmaceuticals, Peloton Therapeutics, outside the submitted work.

RM: Honoraria for advisory role and speaker: BMS, MSD, Pfizer, Ipsen, AstraZeneca, Roche, Janssen, Astellas, Tecnofarma.

AF : Honoraria : BMS, Ipsen,, MSD, Pfizer. Travel, Accommodations, Expenses - BMS; Ipsen; MSD; Pfizer

Rest of authors declare no conflicts of interest.