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RESEARCH

Pembrolizumab plus Lenvatinib in patients with metastatic Renal Cell Carcinoma: real-world evidences from the international ARON- 1 study

Camillo Porta[1,2] · Francesco Massari[3,4] · Tarek Taha[5] · Enrique Grande[6] · Maria T. Bourlon[7] · Ravindran Kanesvaran[8] · Umberto Basso[9] · Javier Molina-Cerrillo[10] · Teresa Alonso-Gordoa[10] · Zin W. Myint[11] · Giuseppe Fornarini[12] · Thomas Buttner[13] · Se Hoon Park[14] · Yüksel Ürün[15] · Ugo De Giorgi[16] · Renate Pichler[17] · Pasquale Rescigno[18] · Tomas Buchler[19] · Hana Studentova[20] · Bohuslav Melichar[20] · Jawaher Ansari[21] · Veronica Mollica[3] · Jakub Kucharz[22] · Mimma Rizzo[2] · Alessandro Rizzo[23] · Ray Manneh Kopp[24] · Sebastiano Buti[25,26] · Fernando Sabino Marques Monteiro[27,28] · Andrey Soares[27,29] · Aristotelis Bamias[30] · Matteo Santoni[31]

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Abstract

Background Pembrolizumab plus lenvatinib is a treatment option for metastatic Renal Cell Carcinoma (mRCC). In the ARON-1 study we investigated we the real-world experiences gained from the use of this combination for mRCC.

Methods We retrospectively investigated real-world clinical outcomes of mRCC patients receiving pembrolizumab plus lenvatinib within the ARON-1 study. Overall survival (OS) was calculated from the start of pembrolizumab plus lenvatinib to death for any cause. Progression-Free Survival (PFS) was defined as the time from the start of pembrolizumab to progression or death from any cause. Duration of response (DoR) was defined as the time from the start of pembrolizumab to disease progression or death, whichever occurred first, in patients who achieved complete remission (CR) or partial response (PR). Overall Response Rate (ORR) was defined as the proportion of patients who achieve a CR or PR per RECIST criteria. Adverse events were retrospectively collected from electronic and paper charts and categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Results Overall, we included 202 mRCC patients treated with pembrolizumab plus lenvatinib. The median follow-up time was 15.1 months. The median OS was not reached (NR), with a median PFS of 25.6 months and an Overall Response Rate (ORR) of 59%. The median Duration of Response (DoR) was 26.2 months. G3-G4 adverse events (AEs) were observed in 92 patients (46%), with hypertension being the most common AE (13%).

Conclusions Pembrolizumab plus lenvatinib is an effective and tolerable treatment for mRCC also in the real-world setting.

Keywords ARON- 1 · Immune-combinations · Lenvatinib · Pembrolizumab · Real-world data · Renal cell carcinoma · Survival

Introduction

The present first-line standard of care for subjects affected by metastatic renal cell carcinoma (mRCC) is represented by an immune-based combination [1], either the immune doublet Ipilimumab plus Nivolumab [2, 3], or a combination of one immune checkpoint inhibitor and one vascular endothelial growth factor receptors tyrosine kinase inhibitor (VEGFR-TKI): Pembrolizumab plus Axitinib [4, 5], Nivolumab plus Cabozantinib [6, 7] and Pembrolizumab plus Lenvatinib [8, 9]. Two other such combinations, i.e. Avelumab plus Axitinib [10] and Toripalimab plus Axitinib [11] have been approved and are available in different parts of the world, but are endowed by a lower grade of recommendation according to major international guidelines due to the lack of overall survival benefit [12].

To date, in the absence of head-to-head comparisons, the choice between one of the above recommended combinations relies mainly on non-objective considerations, or on methodologically incorrect indirect comparison between

Aristotelis Bamias and Matteo Santoni: co-Senior authors

Camillo Porta and Francesco Massari have contributed equally to this work.

Extended author information available on the last page of the article

different randomized controlled trials (RCTs). Indeed, although modest, differences in terms of activity, efficacy and tolerability, exist between these combinations.

For example, in CheckMate 214 [2,3), the immune doublet Ipilimumab plus Nivolumab did not prove able to impact on progression-free survival (PFS), realistically due the time needed for the activation and the expansion of the effector cells of the immune system, making this combination possibly not the ideal one when a quick response is needed [13]. Conversely, the combination of Pembrolizumab plus Lenvatinib yielded the highest response rate and lowest progression rate ever observed in mRCC, as well as an extremely long overall survival (OS) [8,9) which, however, was observed also in the control arm of the CLEAR trial, realistically due to patients' selection.

Furthermore, is well known that randomized controlled trials are not representative of the mass of patients treated in a real-world setting. As brilliantly highlighted by Sir Michael Rawlins, then Chairman of the UK National Institute for Health and Care and Excellence, "*RCTs are generally undertaken in selected patient populations for a finite, usually relatively brief, period of time …*" while "*… In clinical practice the intervention is likely be used in a more heterogeneous population of patients—often with co-morbid illnesses, and frequently for much longer periods*" [14].

Therefore, real-world data may play a critical role in informing the decision-making process for cancer patients [15].

ARON-1 (NCT05287464) is a project that involves analysis of real-world data for patients with mRCC in multiple centers around the world. Here we report the results of a multicenter retrospective real-world analysis of treatments outcomes for patients with mRCC who received first-line treatment with pembrolizumab plus lenvatinib in 31 centers from 18 countries, participating into the ARON-1 project.

Patients and methods

Regulatory status

The ARON- 1 project was approved by the Ethics Committee of the Marche Region (2021 - 492) as well as by the Institutional Review Boards of each participating centers. The study was conducted according to Good Clinical Practice (GCP) and International Ethical Guidelines for Biomedical Research, and the protocol has been designed with the ethical principles laid down in the Declaration of Helsinki on human experimentation.

Study population

We retrospectively collected data from patients aged ≥ 18 years with a histologically confirmed diagnosis of RCC and histologically or radiologically confirmed metastatic disease. Data were collected relative to all mRCC patients treated, from September 1st 2021 to July 1st 2024, with first-line Pembrolizumab plus Lenvatinib in 31 centers from 18 different countries.

Oral lenvatinib at 20 mg was given once daily along with intravenous pembrolizumab at 200 mg once every 3 weeks. Lenvatinib dose could be reduced sequentially to 14 mg, 10 mg, 8 mg, or 4 mg once-daily doses based on drug-related toxicities. First-line therapy was continued until the evidence of clinical and/or radiological tumor progression, unacceptable toxicities, or death. Contrast-enhanced Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) scans were carried out following standard local procedures every 8 or 12 weeks, while physical examination and laboratory tests were performed every 4 or 6 weeks during treatment.

For each patient, data about age, gender, histology, International mRCC Database Consortium (IMDC) risk group, nephrectomy status, sites of metastases, treatment-related adverse events (TRAEs), activity/efficacy, as well as post-first line treatments received were retrospectively extracted from patients' charts (in electronic or paper form). Patients with inadequate data relative to tumor assessment or lost at follow-up were excluded from the analysis.

Study endpoints

The primary objective of this sub-analysis of ARON-1 was to assess the real-world activity, efficacy, and safety of first-line Pembrolizumab plus Lenvatinib in mRCC. Tumor radiological assessment was conducted according to the RECIST 1.1 criteria [16] and designated as complete [CR] or partial responses [PR], stable [SD] or progressive disease [PD]. Overall Response Rate (ORR) was defined as the proportion of patients who achieve a CR or PR per RECIST criteria. OS was calculated from the start of first-line treatment to death for any cause, while PFS was defined as the time from the start of treatment to progression or death from any cause. Duration of response (DoR) was defined as the time from the start of pembrolizumab to disease progression or death, whichever occurred first, in patients who achieved CR or PR.

TRAEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 [17].

Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date.

Body Mass Index (BMI) was defined as a person's weight in kilograms divided by the square of height in meters. Patients were stratified according to BMI into two groups: overweight/obesity (≥ 25 kg/m^2) and underweight/normal weight (< 25 kg/m^2).

Statistical analysis

The statistical analysis was performed by MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

The Kaplan–Meier method with Rothman's 95% confidence intervals (95% CI) was utilized for OS, PFS and DoR, and comparisons between survival distributions were analyzed with the log-rank test. Landmark analysis was performed designating 12 and 24 months as the time point during follow-up period in order to reduce potential biases related to the follow-up time. Univariate and multivariate analyses were performed by using Cox proportional hazard models, Hazard Ratio (HR) and their 95% CI. The chi-square test and Fisher test were used to compare groups for categorical variables. Significance levels were set at a value of 0.05, and all *p* values were two-sided.

Table 1 Patient characteristics

Characteristics	Overall no. (%)
Total patients	202 (100)
Gender	
Male	141 (70)
Female	61 (30)
Age (years)	
Median (range)	62 (24–86)
BMI ≥ 25 kg/m^2	127 (63)
Clear cell histology	171 (85)
Non-clear cell histology	
Papillary	31 (15)
Other	16 (8)
	15 (7)
Sarcomatoid de-differentiation	25 (12)
Metastatic at diagnosis	103 (51)
Previous nephrectomy	124 (61)
Site of metastasis, individual	
Lung	136 (67)
Distant lymph nodes	79 (39)
Bone	70 (35)
Liver	49 (24)
Brain	13 (6)
IMDC prognostic risk group	
Favorable	51 (25)
Intermediate	98 (49)
Poor	53 (26)

BMI, Body Mass Index

Results

Patient population

Of the 4868 patients included in the ARON-1 dataset, 202 received first-line pembrolizumab plus lenvatinib and were thus included in this analysis.

Median age was 62 years; 141 (70%) were males and 61 (30%) females.

Clear cell histology was predominant (85%), with 25 patients (12%) presenting sarcomatoid de-differentiation; 124 patients (61%) underwent nephrectomy, whose only 4 (2%) as deferred surgery. Four patients (2%) underwent metastasectomy during treatment with pembrolizumab plus lenvatinib (2 for lung metastases and 2 for liver metastases). Lung (67%), distant lymph nodes (39%) and bone (35%) were the most common metastatic sites. Good, intermediate and poor IMDC features were present in 25%, 49% and 26% of all cases, respectively.

Patients' characteristics are reported in Table 1.

Survival analysis

The median follow-up time was 15.1 months (95% CI 10.1–32.5). The median OS in the overall study population was not reached (NR, 95% CI 26.9–NR, Fig. 1), with a 2 year-OS rate of 67%. Fifty patients (25%) had died at the time of data analysis.

In the 12- and 24-month OS landmark analyses, the median OS was 34.1 months (95% CI 27.3–36.5) and NR (95% CI 31.9–NR), respectively (Fig. 2). For the 12- and 24-month PFS landmark analyses, the median PFS was 33.6 months (95% CI 25.6–56.5) and 51.6 months (95% CI 26.2–56.5), respectively (Fig. 2).

The median OS was NR (95% CI 26.9–NR) in patients aged < 70y and 27.3 months (95% CI 12.1–31.6) in patients aged ≥ 70y ($p = 0.364$), with a 2y-OS rate of 71% vs 56% ($p = 0.039$). The median OS was NR in both males (95% CI 25.1–NR) and females (95% CI 19.2–NR, p = 0.710). No differences were found between patients with a BMI ≥ 25 kg/m^2 and those with BMI < 25 kg/m^2 (NR, 95% CI 27.3–NR, vs 26.9 months, 95% CI 19.2–36.0, $p = 0.252$).

Median OS in the overall study population stratified by ECOG PS was 33.0 months (95% CI 26.9–36.5) in patients with ECOG PS = 0–1 and NR in patients with ECOG PS ≥ 2 (p = 0.006, Fig. 3), with a 2 year-OS rate of 70% vs 55% ($p = 0.041$). Similarly, median PFS was shorter in patients with ECOG PS ≥ 2 compared to 0–1 (13.6 months, 95% CI 1.2–13.6 vs 25.6 months, 17.3–51.6, p = 0.001, Fig. 3). By

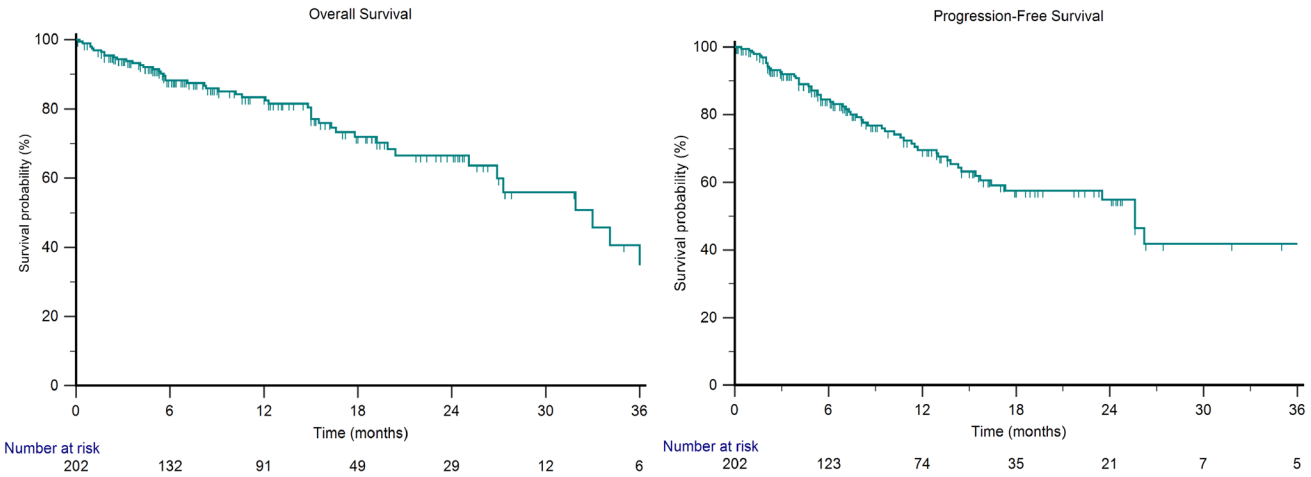

Fig. 1 Overall Survival and Progression-Free Survival in mRCC patients treated with first-line pembrolizumab plus Lenvatinib

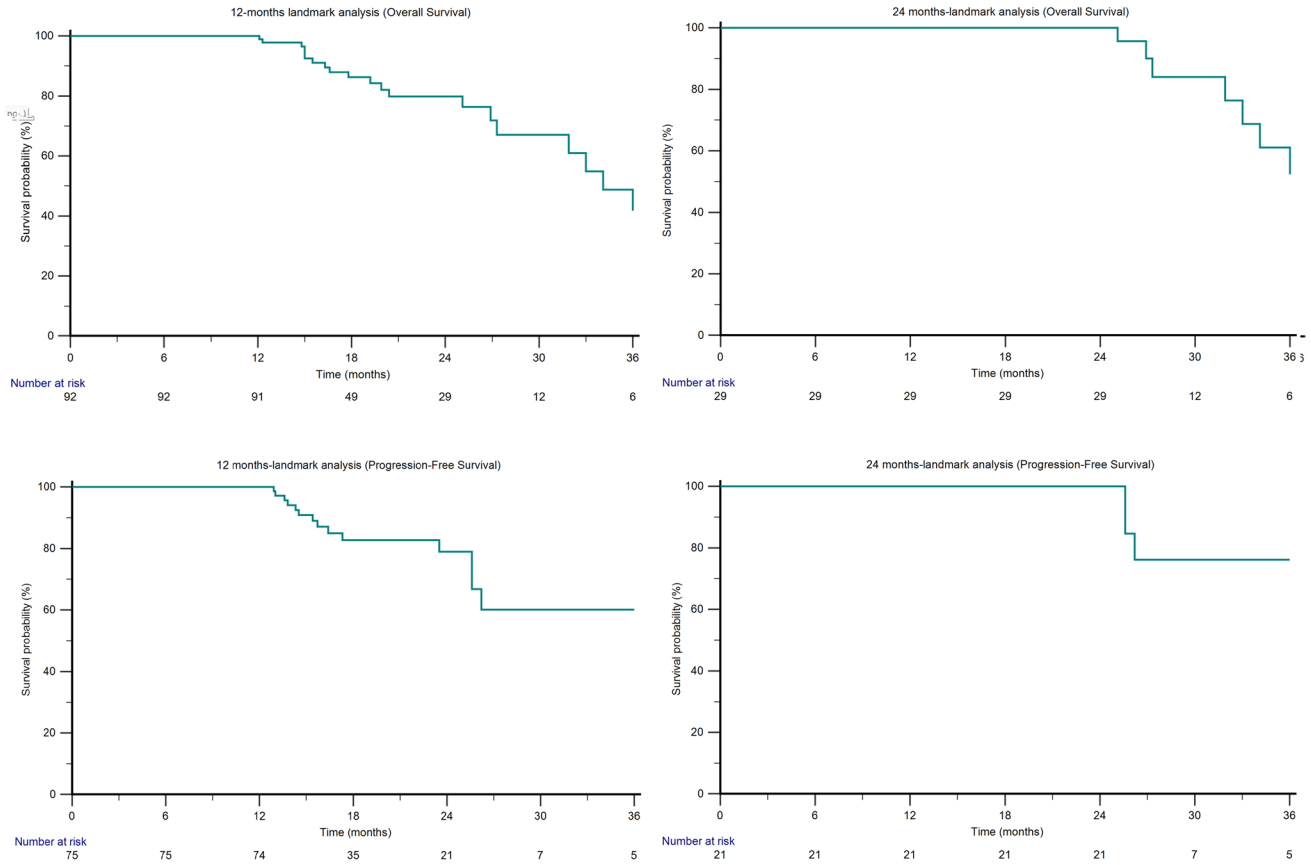

Fig. 2. 12-months and 24-month landmark analyses for Overall Survival and Progression-Free Survival in mRCC patients treated with first-line pembrolizumab plus Lenvatinib

stratifying patients basing on IMDC group, the median OS was NR in the good-risk subgroup, 30.4 months (95% CI 25.1–63.6) in intermediate-risk patients and 26.9 months (95% CI 14.8–31.9) in patients with poor risk features ($p = 0.156$).

Regarding tumor histology, the median OS was NR (95% CI 25.1–NR) in patients with clear cell RCC, while it was 31.9 months (95% CI 19.9–36.5) in patients with papillary RCC and NR in patients with other non-clear cell histologies, with a 2y-OS rate of 66%, 76% and 56%, respectively.

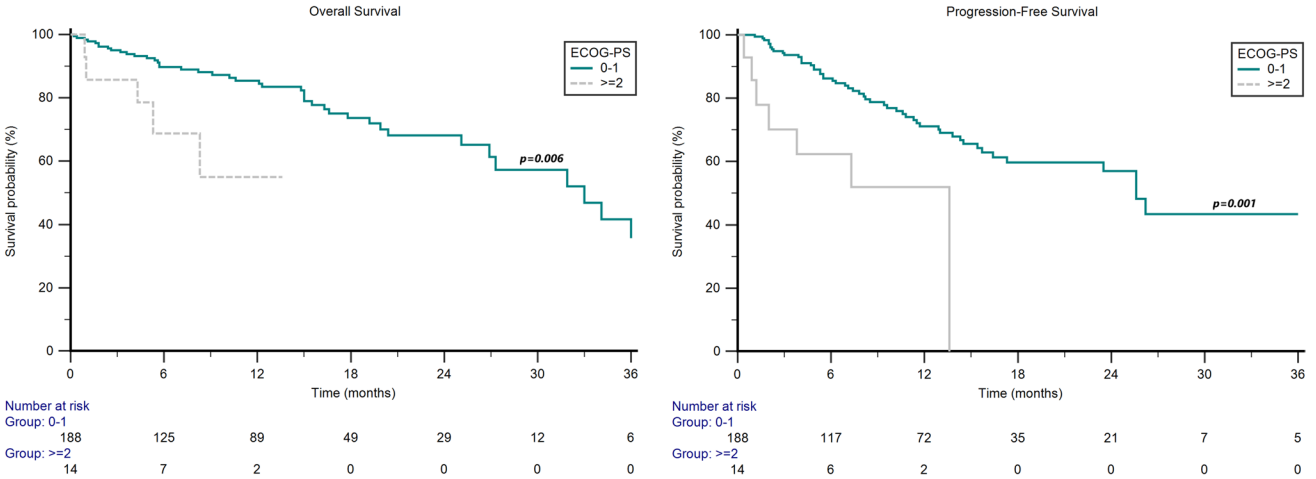

Fig. 3 Overall Survival and Progression-Free Survival in mRCC patients treated with first-line pembrolizumab plus lenvatinib stratified by ECOG Performance Status

Furthermore, the median OS was longer in patients without sarcomatoid differentiation (NR, 95% CI 28.4–NR, vs 26.9 months, 95% CI 17.8–26.9), although the difference was not statistically significant ($p = 0.171$).

The median OS was NR (95% CI 34.1–NR) in patients who underwent nephrectomy and 19.9 months (95% CI 15.0–31.9) in subjects who did not receive nephrectomy ($p < 0.001$, Fig. 4), with a 2 year-OS rate of 74% vs 48% ($p < 0.001$).

Patients with metastatic disease at RCC diagnosis showed shorter median OS (26.9 months, 95% CI 16.6–33.0) compared with patients with metachronous mRCC (NR, 95% CI 27.3–NR, $p = 0.003$, Fig. 4).

We also stratified patients by metastatic sites. A statistically significant difference was found between patients with or without lung metastases (31.9 months, 95% CI 25.1–34.1, vs NR, 95% CI 20.4–NR, $p = 0.018$, Fig. 4), while no differences were found in patients with or without metastases to distant lymph nodes ($p = 0.776$), bone ($p = 0.971$), liver ($p = 0.528$) or brain ($p = 0.624$).

We further analyzed the 136 patients with lung metastases, whose 89 patients (65%) presented concomitant metastatic sites. The median OS was longer in patients with lung metastases as only metastatic site compared to subjects with other concomitant metastatic sites (36.0 months, 95% CI 17.8–36.5 vs 27.3 months, 95% CI 19.9–33.0), although the difference was not statistically significant ($p = 0.521$).

Prognostic factors in patients receiving pembrolizumab plus lenvatinib therapy

In the overall study population, nephrectomy, lung metastases and G3-G4 hypertension were significantly associated with OS at both univariate and multivariate analysis (Table 2).

Response to pembrolizumab plus lenvatinib first-line therapy

In the overall study population, we reported 17 CR (8%), 104 PR (51%), 56 SD (28%) and 25 PD (13%), with an ORR of 59%. The median DoR was 26.2 months (95% CI 25.6–NR) in the CR + PR subgroup, being NR (95% CI NR–NR) in patients who achieved CR and 25.6 months (95% CI 23.5–NR) in patients with PR.

In good-risk patients, we reported 7 CR (14%), 23 PR (45%), 17 SD (33%) and 4 PD (7%), with an ORR of 59%. In the 98 patients with intermediate IMDC risk, we observed 7 CR (7%), 56 PR (57%), 23 SD (23%) and 12 PD (13%), with an ORR of 64%. As for the poor-risk subgroup, we showed 3 CR (6%), 25 PR (47%), 16 SD (30%) and 9 PD (17%), with an ORR of 53% and a +10% of patients primary refractory to pembrolizumab plus lenvatinib compared to the good-risk subgroup.

In the 171 patients with clear cell RCC, we found 15 CR (9%), 86 PR (50%), 50 SD (29%) and 20 PD (12%), with an ORR of 59%. In patients with papillary RCC, we reported 1 CR (6), 10 PR (63), 3 SD (19) and 2 PD (12), with an ORR of 69%, while in patients with non-papillary non clear cell histology we reported 1 CR (7%), 8 PR (53%), 3 SD (20%) and 3 PD (20%), with an ORR of 60%.

Progression-Free Survival and subsequent therapies

The median PFS was 25.6 months (95% CI 16.4–36.0, Fig. 1). Sixty-two patients (31%) progressed during pembrolizumab plus lenvatinib therapy; of them, 47 (75,8%)

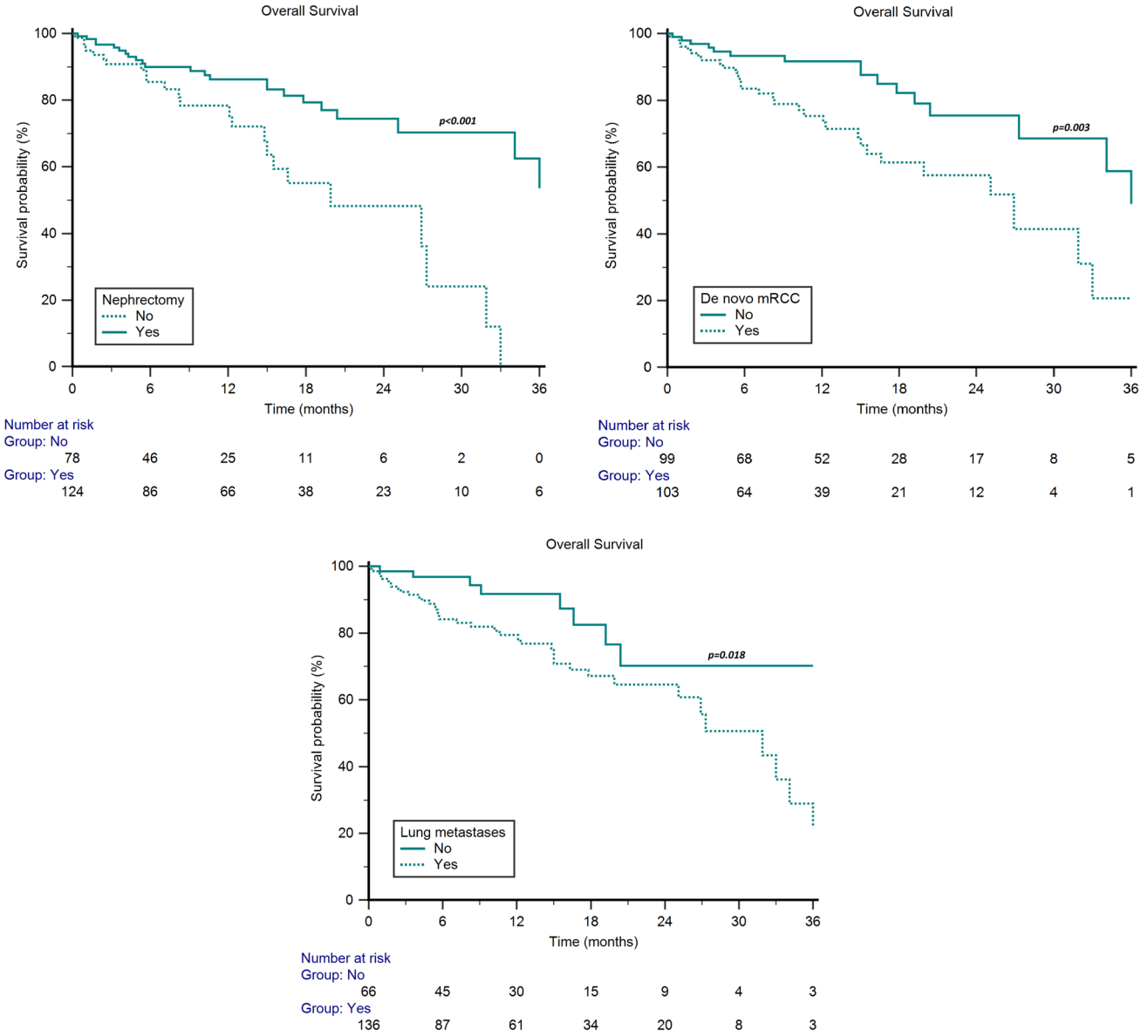

Fig. 4 Overall Survival in mRCC patients treated with first-line pembrolizumab plus lenvatinib stratified by previous nephrectomy, time to metastatic disease and lung metastases

received successive treatments (33 patients received cabozantinib, 6 other IO + TKI or IO + IO combinations, 3 sunitinib, 3 were enrolled in clinical trials, 1 lenvatinib plus everolimus and 1 pazopanib). The median PFS of second-line therapy was 12.7 months (95% CI 6.6–21.6).

Safety, dose reductions and treatment interruptions

G3-G4 adverse events (AEs) were observed in 92 patients (46%) and in the 41% of patients aged ≥ 70y. Hypertension (13%), fatigue (11%) and diarrhea (9%) were the two most frequent SAEs (Table 3).

The median OS was significantly longer in patients presenting G3-G4 AEs (NR, 95% CI 31.9–NR vs 27.3 months, 95% CI 19.3–34.3, $p = 0.031$, Fig. 5). By stratifying patients basing on the type of G3-G4 AEs, a longer median OS was observed in those developing G3-G4 hypertension (NR, 95% CI NR–NR vs 31.9 months, 95% CI 20.4–36.0, $p = 0.011$, Fig. 5).

Lenvatinib dose reductions were registered in 77 patients (38%, 3% started lenvatinib at 10 or 14 mg/d, 35% reduced the dose during treatment, Table 3). Sixty-seven (33%) and 34 patients interrupted lenvatinib or pembrolizumab due to G3-G4 AEs, respectively (Table 3).

Table 2 Univariate and multivariate analysis in mRCC patients receiving first-line pembrolizumab plus lenvatinib

Overall survival (overall population)	Univariate cox regression		Multivariate Cox Regression	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Sex (females vs males)	1.12 (0.62–2.02)	0.711		
Age (> = 70y vs < 70y)	1.32 (0.72–2.41)	0.368		
BMI (> 25 vs ≤ 25)	0.72 (0.41–1.27)	0.256		
Nephrectomy (yes vs no)	0.36 (0.20–0.66)	**< 0.001**	0.42 (0.23–0.76)	**0.004**
Histology (nccRCC vs ccRCC)	1.01 (0.79–1.29)	0.924		
Sarcomatoid differentiation (yes vs no)	1.75 (0.78–3.96)	0.178		
IMDC group (poor vs good/intermediate)	1.76 (0.94–3.30)	0.078		
Lung metastases (yes vs no)	2.33 (1.13–4.82)	**0.022**	2.12 (1.02–4.43)	**0.044**
Distant lymph node metastases (yes vs no)	0.96 (0.66–1.39)	0.822		
Bone metastases (yes vs no)	1.01 (0.55–1.84)	0.973		
Liver metastases (yes vs no)	1.23 (0.65–2.32)	0.531		
Brain metastases (yes vs no)	0.85 (0.23–2.41)	0.626		
Hypertension (G3–G4)	0.24 (0.07–0.79)	**0.019**	0.26 (0.08–0.87)	**0.028**
Fatigue (G3–G4)	1.07 (0.45–2.52)	0.876		
Diarrhea (G3–G4)	0.67 (0.27–1.71)	0.406		
Hand foot syndrome (G3–G4)	0.23 (0.03–1.70)	0.151		
Hypothyroidism (G3–G4)	0.29 (0.04–2.13)	0.224		

BMI = Body Mass Index; ccRCC = clear cell Renal Cell Carcinoma; IMDC = International Metastatic RCC Database Consortium; nccRCC = non-clear cell Renal Cell Carcinoma

Table 3 G3–G4 adverse events, drug interruptions and dose reductions

Characteristics	Overall 202 (%)
G3–G4 adverse events	92 (46)
G3–G4 Hypertension	27 (13)
G3–G4 Fatigue	23 (11)
G3–G4 Diarrhea	18 (9)
G3–G4 Hand-Foot Syndrome	12 (6)
G3–G4 Hypothyroidism	8 (4)
Initial lenvatinib dose reduction	7 (3)
Successive lenvatinib dose reductions	70 (35)
Lenvatinib interruptions due to G3–G4 adverse events	67 (33)
ICI interruptions due to G3–G4 adverse events	34 (17)

The median OS was longer in patients who reduced lenvatinib dose compared to those receiving standard dose (NR, 95% CI 26.9–NR vs 25.1 months, 95% CI 17.8–34.1, $p < 0.001$, Fig. 5). On the other hand, no significant differences were found between patients who interrupted or not lenvatinib due to G3-G4 AEs (27.3 months, 95% CI 25.1–36.5 vs NR, 95% CI 31.9–NR, $p = 0.456$), as well as between patients who interrupted or not pembrolizumab due to G3-G4 AEs (NR, 95% CI 19.9–NR vs NR, 95% CI 25.1–NR, $p = 0.724$).

Discussion

From a temporal standpoint, the combination of Pembrolizumab and Lenvatinib was the latest of all 1st line combinations to reach the clinic and, with all the caveats relative to the indirect comparison of studies which are different one from the other (often very different), the one that yielded the higher antitumor activity [18] and longer PFS [8, 9].

In a real-world setting like the one emerging from the ARON-1 database, we were able to confirm at least the former, while the relatively short follow-up prevents a meaningful survival comparison with the CLEAR study.

If the remarkably long OS reported in CLEAR appears to be, at least partly, flawed by the fact that the trial's control arm (Sunitinib) outperformed all expectations in terms of OS (median OS at a 4-year follow-up: 53,7 months in the experimental arm vs 54,3 months in the control arm) [9], realistically due to a more favourable patients' mix in terms of distribution among the three IMDC risk groups (IMDC risk-favourable: 31%, -intermediate: 59.2%, -poor: 9.3%), the patients in our case series are better distributed among the three prognostic groups, reflecting everyday clinical practice more than the CLEAR study population. Indeed, in the ARON-1 population receiving pembrolizumab plus lenvatinib, 25% had favourable, 49% intermediate and 26% poor IMDC risk.

Therefore, given the 2y-OS rate reported in CLEAR (79.2% of the patients in the lenvatinib-plus-pembrolizumab group were alive at 24 months) [8], the 2y-OS rate of 67%

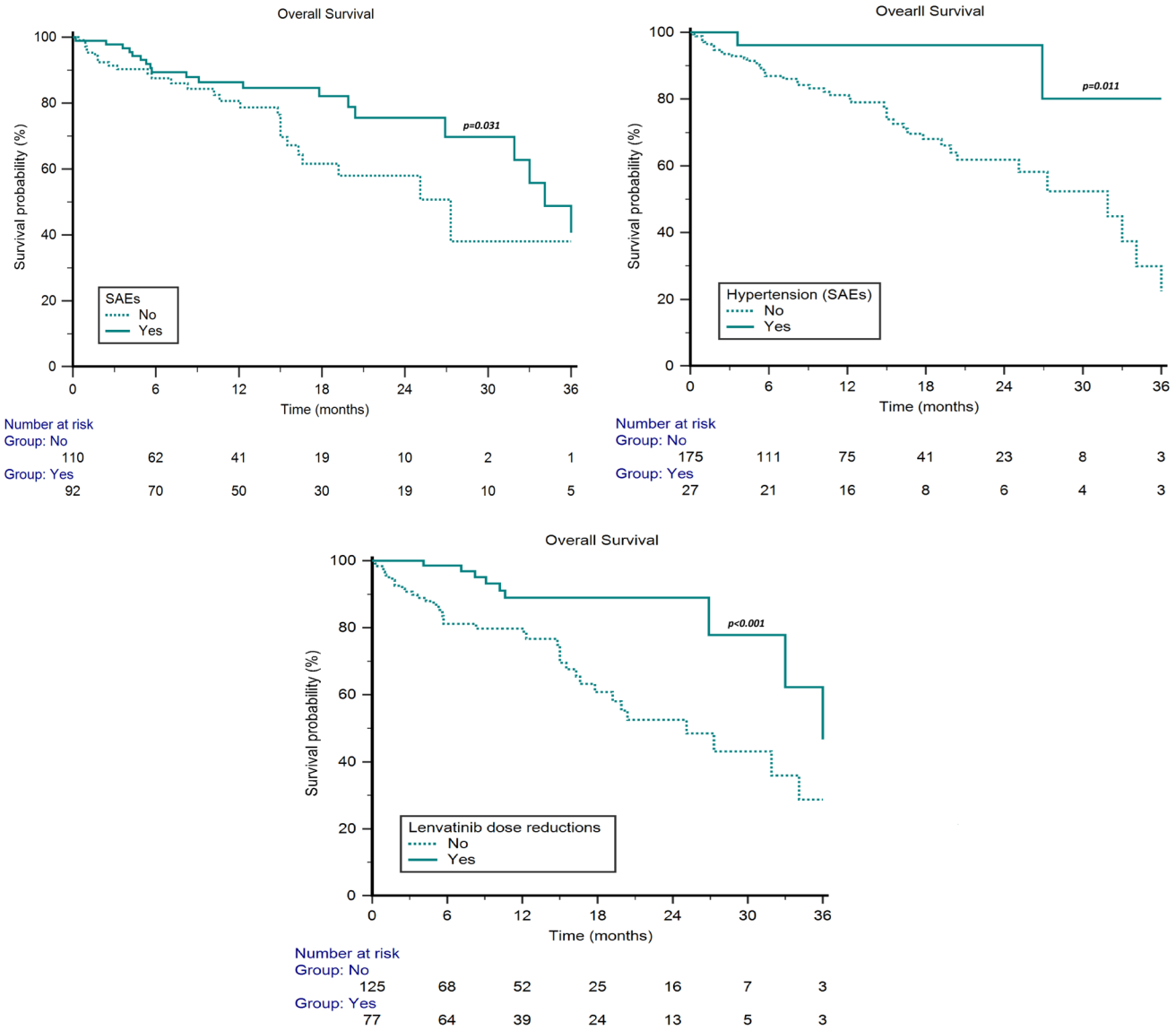

Fig. 5 Overall Survival in mRCC patients treated with first-line pembrolizumab plus lenvatinib stratified by Severe Adverse Events (SAEs), G3-G4 hypertension and lenvatinib dose reductions

we observed in our patient population, although slightly lower as compared to that of the CLEAR study, looks as a real-world confirmation of the efficacy of the Pembrolizumab-Lenvatinib combination as a 1st line treatment of mRCC.

One of the major criticisms of the results of CLEAR relates to the progressive reduction in the difference in OS between the two treatment arms, starting from the 24 th month of treatment when, per protocol, immunotherapy was stopped; this observation lead to the hypothesis that stopping immunotherapy could be detrimental to the long term efficacy of the combination. Beyond the fact that we do have neither a control arm, nor adequate information relative to the timing of immunotherapy discontinuation, the short follow-up of our case series does not allow us to confirm or dismiss the above observation.

Not surprisingly, efficacy and antitumor activity were less marked in elderly patients, in patients with IMDC poor risk features, with sarcomatoid component, with non-clear cell histologies, and with synchronous metastases, all conditions which are known to be characterized by a poorer prognosis. Despite all the above, the combination of Pembrolizumab plus Lenvatinib proved to be active also in these prognostically ominous subgroups. In particular, the activity observed in patients with non-clear cell histologies corroborates the recently published results of the Keynote-B61 trial [19]. In that single arm phase II trial, at a median follow-up of 14.9 months (quite similar to our),

the confirmed objective response rate was 49%, including a 6% complete response rate and a 44% partial response rate. In our case series, the ORR was 69% in patients with papillary RCC (CR: 6%, PR: 63%) and 60% in those with other non-clear cell histologies (CR: 7%, PR: 53%).

Another recent retrospective study suggested that a limited number of patients progressing on the Pembrolizumab plus Lenvatinib combination did receive further lines of active antitumor treatment [20]; on a larger case series, we did not confirm this finding. Indeed, 75,8% of our patients progressing on the combination did receive further lines of treatment, suggesting that the use of such an active combination does not impair the possibility of receiving further treatments post-progression.

In terms of tolerability, no new safety signals emerged from our real-world experience; notably enough, median OS was significantly longer in patients presenting G3-G4 AEs, and especially hypertension, a typical on-target effect of antiangiogenic agents; this clearly suggests that, at least in a frontline treatment setting, the multikinase inhibitor Lenvatinib acts mainly as an antiangiogenic agents, although its activity on targets other than VEGFRs may nevertheless contribute to its potent antitumor activity. Another important finding is that dose reductions or temporary treatment stops due to G3-G4 AEs did not impair this combination's antitumor activity and efficacy, a finding that has been already observed with another potent multikinase inhibitor such as Cabozantinib.

Although we cannot support this suggestion from the experience here reported, it's our opinion that Lenvatinib treatment should be started at full dose and eventually dose reduced or temporarily interrupted only in case of severe toxicities not manageable with adequate supportive measures.

Of course, the retrospective nature of this analysis inevitably entails some, often relevant, limitations; the lack of standardization in the timing of response evaluation makes PFS estimates less precise as compared to those deriving from RCTs. Furthermore, toxicities reporting is for sure less precise as compared to clinical trials.

Finally, as already stressed, the median follow-up of our case series is still short, given the recent availability of the Pembrolizumab plus Lenvatinib combination on a global level, preventing us to evaluate long-term efficacy and safety.

As a whole, however, we were able to confirm the activity, efficacy and safety of the Pembrolizumab plus Lenvatinib combination in a real-world setting, thus confirming it as one of the present standards of 1st line therapy for mRCC, particularly recommended in our opinion whenever a profound response, as a putative surrogate marker of a really prolonged survival, is our main therapeutic goal.

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Author contributions Credit Author Statement Conceptualization: Camillo Porta, Matteo Santoni, Francesco Massari Data curation: Matteo Santoni, Francesco Massari Formal analysis: Fernando Sabino Marques Monteiro, Alessandro Rizzo Investigation: Tarek Taha, Sebastiano Buti, Maria T. Bourlon, Ravindran Kanesvaran, Umberto Basso, Javier Molina-Cerrillo, Teresa Alonso-Gordoa, Zin W. Myint, Giuseppe Fornarini, Thomas Buttner, Se Hoon Park, Yüksel Ürün, Ugo De Giorgi, Renate Pichler, Pasquale Rescigno, Tomas Buchler, Hana Studentova, Jawaher Ansari, Jakub Kucharz22, Mimma Rizzo, Alessandro Rizzo, Ray Manneh Kopp Methodology: Matteo Santoni, Fernando Sabino Marques Monteiro Project administration: Matteo Santoni Supervision: Aristotelis Bamias, Andrey Soares, Enrique Grande, Bohuslav Melichar Writing—original draft: Camillo Porta, Matteo Santoni, Francesco Massari, Veronica Mollica Writing—review & editing: Aristotelis Bamias, Andrey Soares.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Massari F, Rizzo A, Mollica V et al (2021) Immune-based combinations for the treatment of metastatic renal cell carcinoma: a meta-analysis of randomised clinical trials. Eur J Cancer 154:120–127
2. Motzer RJ, Tannir NM, McDermott DF et al (2018) Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 378:1277–1290
3. Tannir NM, Albigès L, McDermott DF et al (2024) Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 8-year follow-up results of efficacy and safety from the phase III CheckMate 214 trial. Ann Oncol. https://doi.org/10.1016/j.annonc.2024.07.727
4. Rini BI, Plimack ER, Stus V et al (2019) Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1116–1127
5. Powles T, Plimack ER, Soulières D et al (2020) Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended

follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol 21:1563–1573
6. Choueiri TK, Powles T, Burotto M et al (2021) Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 384:829–841
7. Powles T, Burotto M, Escudier B et al (2024) Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended follow-up from the phase III randomised CheckMate 9ER trial. ESMO Open 9:102994
8. Motzer R, Alekseev B, Rha SY et al (2021) Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 384:1289–1300
9. Motzer RJ, Porta C, Eto M et al (2024) Lenvatinib plus pembrolizumab versus sunitinib in first-line treatment of advanced renal cell carcinoma: final prespecified overall survival analysis of CLEAR, a phase III study. J Clin Oncol 42:1222–1228
10. Motzer RJ, Penkov K, Haanen J et al (2019) Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1103–1115
11. Yan XQ, Ye MJ, Zou Q et al (2024) Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study. Ann Oncol 35:190–199
12. Powles T, Albiges L, Bex A et al (2024) Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 35:692–706
13. Porta C, Rizzo M (2019) Immune-based combination therapy for metastatic kidney cancer. Nat Rev Nephrol 15:324–325
14. De RM (2008) Testimonio: on the evidence for decisions about the use of therapeutic interventions. Clin Med (Lond) 8:579–588
15. Tang M, Pearson SA, Simes RJ, Chua BH (2023) Harnessing real-world evidence to advance cancer research. Curr Oncol 30:1844–1859
16. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
17. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
18. Motzer RJ, Choueiri TK, Hutson T, et al. (2024) Characterization of responses to lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma at the final prespecified survival analysis of the phase 3 CLEAR study. Eur Urol 86(1):4–9.
19. Albiges L, Gurney H, Atduev V et al (2023) 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 24:881–891
20. Voss MH, Powles T, McGregor B et al (2022) Impact of subsequent therapies in patients with advanced renal cell carcinoma (aRCC) receiving Lenvatinib plus Pembrolizumab (LEN + PEMBRO) or Sunitinib (SUN) in the CLEAR study. J Clin Oncol 40(Suppl.6):Abs.4514

Authors and Affiliations

Camillo Porta[1,2] · Francesco Massari[3,4] · Tarek Taha[5] · Enrique Grande[6] · Maria T. Bourlon[7] · Ravindran Kanesvaran[8] · Umberto Basso[9] · Javier Molina-Cerrillo[10] · Teresa Alonso-Gordoa[10] · Zin W. Myint[11] · Giuseppe Fornarini[12] · Thomas Buttner[13] · Se Hoon Park[14] · Yüksel Ürün[15] · Ugo De Giorgi[16] · Renate Pichler[17] · Pasquale Rescigno[18] · Tomas Buchler[19] · Hana Studentova[20] · Bohuslav Melichar[20] · Jawaher Ansari[21] · Veronica Mollica[3] · Jakub Kucharz[22] · Mimma Rizzo[2] · Alessandro Rizzo[23] · Ray Manneh Kopp[24] · Sebastiano Buti[25,26] · Fernando Sabino Marques Monteiro[27,28] · Andrey Soares[27,29] · Aristotelis Bamias[30] · Matteo Santoni[31]

✉ Camillo Porta
camillo.porta@gmail.com

[1] Interdisciplinary Department of Medicine, University of Bari "A. Moro", Bari, Italy

[2] Division of Medical Oncology, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Piazzale G. Cesare 11, 70124 Bari, Italy

[3] Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[4] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

[5] Royal Marsden NHS Foundation Trust, London, UK

[6] Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain

[7] Department of Hemato-Oncology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico - Universidad Panamericana, Escuela de Medicina, Mexico City, Mexico

[8] Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

[9] Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto IOV IRCCS, Padua, Italy

[10] Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain

[11] Division of Medical Oncology, Markey Cancer Center, University of Kentucky, Lexington, KY, USA

[12] IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[13] Department of Urology, University Hospital Bonn (UKB), Bonn, Germany

[14] Department of Hematology and Oncology, Sungkyunkwan University Samsung Medical Center, Seoul, South Korea

[15] Department of Medical Oncology, Faculty of Medicine, Ankara University, Ankara, Turkey

[16] Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

[17] Department of Urology, Medical University of Innsbruck, Innsbruck, Austria

[18] Centre for Cancer, Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, UK

[19] Department of Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

[20] Department of Oncology, Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic

[21] Medical Oncology, Tawam Hospital, Al Ain, UAE

[22] Department of Uro-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology Warsaw, Warsaw, Poland

[23] IRCCS Istituto Tumori "Giovanni Paolo II", 70124 Bari, Italy

[24] Clinical Oncology, Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia

[25] Medical Oncology Unit, University Hospital of Parma, Parma, Italy

[26] Department of Medicine and Surgery, University of Parma, Parma, Italy

[27] Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Brazil

[28] Oncology and Hematology Department, Hospital Sírio Libanês, Brasília, Brazil

[29] Oncology Unit, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil

[30] 2nd Propaedeutic Department of Internal Medicine, ATTIKON University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[31] Medical Oncology Unit, Macerata Hospital, Macerata, Italy