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Pembrolizumab in advanced renal cell carcinoma: a meta-analysis providing level 1a evidence

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ABSTRACT

The recent introduction of immunotherapy in the first line setting of advanced renal cell carcinoma (aRCC) has dramatically improved patients' prognosis. The aim of the current meta-analysis was to provide level 1a evidence supporting the use of pembrolizumab plus tyrosine kinase inhibitors (TKI) as first-line treatment for advanced RCC. All published randomized prospective trials including patients with advanced RCC treated with pembrolizumab in combination with TKIs vs Sunitinib were included in this meta-analysis. An algorithm was used to reconstruct survival data from the published Kaplan-Meier curves of overall survival

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(OS), progression free survival (PFS) and duration of response (DoR) from the included trials. Restricted mean survival time (RMST) with 95% confidence interval (CI) for comparison among the different regimens was calculated. Main outcomes were differences in RMST for OS, PFS and DoR for pembrolizumab plus TKIs vs sunitinib arm. Reconstructed survival data from 1,573 patients were retrieved from 2 trials (KEYNOTE-581 and KEYNOTE-426) comparing pembrolizumab plus TKI (lenvatinib or axitinib, respectively) to sunitinib. Patients who received pembrolizumab-lenvatinib or pembrolizumab-axinitinib had better OS (24-month **Δ**RMST of 1.79 months [95% CI: 0.12-2.50; $P < 0.001$]), PFS (24-month **Δ**RMST of 3.83 months [95% CI: 2.93-4.74; $P < 0.001$]) and DoR (24-month **Δ**RMST of 2.32 months [95% CI: 0.97-3.67; $P < 0.001$]) relative to sunitinib. Pembrolizumab-lenvatinib combination gave a marginal benefit in terms of OS, PFS and DoR relative to pembrolizumab-axitinib group. By relying on individual survival data, we provided a level-1a evidence supporting the use of pembrolizumab plus TKI for first-line aRCC treatment.

ARTICLE INFO

Keywords: mRCC; Advanced RCC, Pembrolizumab, Immunotherapy, Overall survival, Progression free survival

Introduction

Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor (TKI), has represented the standard of care in advanced renal cell carcinoma (aRCC) for several years.[1] Recently, multiple treatment alternatives have become available, with pure immune-oncology (IO) combinations and IO-TKI combination therapies being major actors in this dynamic and rapidly evolving scenario. Nivolumab plus ipilimumab,[2,3] pembrolizumab plus axitinib,[4,5] avelumab plus axitinib[6,7] and nivolumab plus cabozantinib[8] received approval by the US Food and Drug Administration (FDA) for treatment-naïve aRCC. The use of lenvatinib plus pembrolizumab has been recently approved in the same context. Although it showed promising results in the KEYNOTE-581/CLEAR randomized clinical trial (RCT),[9] it is of fundamental impotance the confirm its positive impact in metastatic RCC. Pembrolizumab is at this time the only drug used in an IO-TKI combination with at least 2 RCTs comparing its efficacy relative to sunitinib.

Pembrolizumab is a monoclonal antibody that selectively blocks the programmed death-1 (PD-1) transmembrane protein on T-cells, B-cells and NK-cells. As a result, the immune system is activated and tumoral cell apoptosis promoted **(Supplementary Fig 1)**.[10,11] TKIs are small molecules that, by targeting the tyrosine kinase of VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR-α, PDGFR-ß as well as several other receptor tyrosine kinases, mainly inhibit cancer-driven neoangiogenesis.[12,13] The combined targeted actions of these 2 agents might have a beneficial impact on cancer growth arrest. Their combined activity is also being tested in adjuvant and neoadjuvant setting.[14]

In order to provide level 1a evidence for the use of pembrolizumab-TKI combination for first line treatment of aRCC, by relying on reconstructed survival data form the two published RCTs, we performed a meta-analysis assessing overall survival (OS), progression-free survival (PFS) and duration of response (DoR) in this setting.

Materials & Methods

Methodology and Search Strategy

We performed a meta-analysis of phase III RCTs comparing a combination therapy of pembrolizumab plus TKI to sunitinib in the setting of treatment-naïve aRCC. The review was conducted on the base of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The protocol of the review and meta-analysis was registered on PROS-

PERO (CRD42021245595). A completed PRISMA 2009 checklist was used to describe the methodology of our study (**Supplementary Table 1**). ESMO-Magnitude of Clinical Benefit Scale (V1.1) was used to score the benefit of each included trial.

PubMed, EMBASE, Web of Science, Scopus databases were searched for studies indexed until March 20, 2021. Search was performed on April 2, 2021. The following keywords were used to identify potential reports: (renal cell carcinoma OR kidney cancer OR renal cancer) AND (metastatic or advanced) AND ((systemic OR first-line) AND (therapy OR treatment)) AND (RCT OR randomized clinical trial AND pembrolizumab). References from commentaries, editorials, conference publications, review articles, and from included studies were hand-searched and cross-referenced for completeness. We considered only English language RCTs, while non-English studies, observational studies, review articles, commentaries, editorials and articles without peer-review were excluded. Conference abstracts reporting unpublished data were included. Titles and abstracts of manuscripts were used to screen for initial study inclusion. Full text review was performed when the abstract was not sufficient to determine study inclusion.

Study Review Methodology and Risk of Bias Assessment

To optimize methodological quality, two authors completed the study selection independently (G.F. and U.C.). Disagreements were resolved by consensus with all co-authors. Risk of bias was determined using The Cochrane Collaboration's tool.[16]

Outcome Measures

The primary outcome of the study was to compare OS, PFS and DoR among patients who received pembrolizumab plus TKI combination therapies relative to sunitinib. All examined outcomes were assessed using restricted mean survival times (RMST) up to 12, 24 and 36 months of follow-up. RMST is a measure of average survival time up to a time point and can be measured as the area under the survival curve from time zero up to a time point[17] and is an alternative approach to "classical" survival analysis based on median survival or hazard rates estimation, that may overcome some of its limitation.[18]

Data Extraction

For each trial, we extracted the following data: trial name, author, sample size, intervention, baseline patient and tumor characteristics, overall survival, progression-free survival, and duration of response. Two authors (G.F. and A.M.) extracted data independently, and any disagreement was resolved by consensus among all authors. Survival data were reconstructed using published Kaplan Meier (KM) curves on OS, PFS and DoR to indirectly extract individual data points on survival probability and time to event through a digital reconstruction of figures.[19-21]

Statistical analysis

RMST up to 18, 24 and 36 months for OS and PFS and up to 18 and 24 months for DoR was estimated employing a reconstructed survival data approach to obtain pooled survival probability curves. This approach requires the assumption that the number of deaths in each unit of follow-up time has a negative binomial distribution to be satisfied. Also, a gamma frailty process was used to shape the correlation between the number of outcome occurrence across time units within each RCT and the heterogeneity among RCTs. RMSTs and associated 95% confidence intervals (CI) up to 18, 24 and 36 months were derived from the area under the survival probability curve. To support the use of RMST instead of traditional hazard ratios, we tested the assumption of proportionality of hazards on the reconstructed datasets, using the Grambsch and Therneau test.[22]

Table 1
Baseline characteristics of patients in the experimental arms of included trials.

Characteristics	KEYNOTE-426	KEYNOTE-581 (CLEAR)
Median age, yr	62	64
Male sex, %	71.0	71.8
Nephrectomy, %	82.6	73.8
IMDC risk group, %		
Favorable	31.9	31.0
Intermediate	55.1	59.2
Poor	13.0	9.3
Not reported	–	0.6
Site of metastasis, %		
Lung	72.2	70.1
Lymph nodes	46.1	47.9
Bone	23.8	23.9
Liver	15.3	16.9
Adrenal gland	15.5	–
No. of organs with metastases, %		
1	26.4	27.3
≥2	72.9	71.5
PD-L1 combined positive score, %		
≥1	59.3	30.1
<1	40.7	31.5
Not available	–	38.3

OS, PFS and DoR were compared between pembrolizumab-TKI combination therapies and sunitinib. Therefore, reconstructed data were grouped based on the category of treatment received: sunitinib, pembrolizumab-lenvatinib or pembrolizumab-axinitinib. Given that 24 months were the common maximum follow-up time across all treatment groups, we estimated 24-month RMST to perform comparisons of the outcomes over the maximum common study period.[23] Moreover, 18- and 36-month RMSTs were also assessed, considering that a considerable proportion of patients in each treatment group reached long follow-up times.

All analyses were performed using the R statistical package v3.6.1 (R Project for Statistical Computing) and STATA 14 (StataCorp LP, College Station, TX). All tests were 2-sided, with a significance level set at $P < 0.05$.

Results

Study Selection

Through electronic search and after title, abstract and full-text review, two first-line RCTs examining pembrolizumab-TKIs combination therapy relative to sunitinib in the setting of treatment-naïve advanced RCC were identified (**Supplementary Fig 2**).

Characteristics of Included Trials

The KEYNOTE-426 and the KEYNOTE-581/CLEAR were included in the meta-analysis. The KEYNOTE-426 included 432 patients treated with pembrolizumab-axinitinib and 429 patients treated with sunitinib. Median follow-up was 31 months. The KEYNOTE-581/CLEAR included 355 patients treated with pembrolizumab-lenvatinib and 357 patients treated with sunitinib. Median follow-up was 27 months.

All RCTs enrolled treatment-naïve patients with a clear-cell component, starting from 2016. Across all experimental arms of the RCTs, median age ranged from 62 to 64 years (Table 1). Rates of previous nephrectomy ranged from 73.8% in KEYNOTE-581/CLEAR to 82.6% in KEYNOTE-426. Finally, the distribution of IMDC risk group was comparable among RCTs, where intermediate

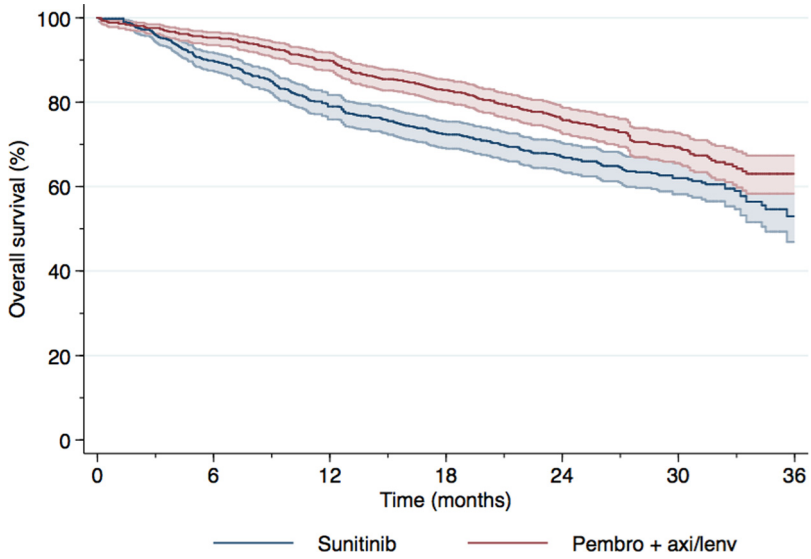

Fig. 1. Overall survival of patients with aRCC using reconstructed survival data derived from the KEYNOTE-426 and the KEYNOTE-582.

risk patients was the most common. The 2 RCTs had also similar metastatic burden at start of follow up. Finally, PDL-1 expression was also similar.

The reconstructed Kaplan-Meier curves for each outcome of interest, stratified by trial, are displayed in **Supplemental Figures 4, 5** and **6.** The numbers at risk in the curves demonstrate accurate data reconstruction compared to the original studies allowing for subsequent meta-analysis.

Study Quality and Risk of Bias Assessment

According to the Cochrane Risk of Bias tool, all studies were at low risk of selection (random sequence generation), attrition and reporting bias. Similarly, allocation concealment was not determinable in all RCTs and all were at risk of performance bias. With regard to detection bias, all studies were at low risk of detection bias (**Supplementary Fig 3**). All studies scored A grade according to ESMO-Magnitude of Clinical Benefit Scale (V1.1) (**Supplementary Material 1**).

Overall Survival

Pooled KM curves depicting OS of patients enrolled in the included RCTs, divided into sunitinib vs pembrolizumab-TKI combination therapy, using reconstructed data, are reported in Figure 1. OS probabilities of patients treated with pembrolizumab-TKI combination at 18, 24 and 36 months were 83%, 76% and 63%, respectively. Similarly, at 18, 24 and 36 months, OS probabilities of patients treated with sunitinib were 72%, 65% and 54% respectively. Median OS was not reached neither for patients treated with sunitinib nor for those treated with pembrolizumab-TKI combination.

When the Grambsch and Therneau test was employed on the reconstructed datasets for the comparison of survival data between pembrolizumab-TKI and sunitinib, a *P*-value of 0.038 was obtained proving evidence of violation of the proportional hazard assumption.

Table 2 displays the results of the differences in RMST up to 18-, 24- and 36-month. With regard to 24-month RMST, there was a significant difference for patients treated with

Table 2
Differences in restricted mean survival time (delta RMST) up to the time point of interest according to treatment arm. RMST for duration of response was calculated only up to 24 months.

Arms	ΔRMST up to 18 mo of follow-up (95% CI)	ΔRMST up to 24 mo of follow-up (95% CI)	ΔRMST up to 36 mo of follow-up (95% CI)
Overall survival			
Pembrolizumab+Levantinib vs sunitinib	1.32 (0.79-1.82)	2.04 (1.24-2.83)	3.09 (1.67-4.52)
Pembrolizumab+Axinitinib vs sunitinib	1.11 (0.60-1.61)	1.59 (0.82-2.35)	2.30 (0.96-3.64)
Pembrolizumab+TKI vs sunitinib	1.20 (0.76-1.64)	1.79 (1.12-2.50)	2.68 (1.52-3.84)
Progression-free survival			
Pembrolizumab+Levantinib vs sunitinib	3.57 (2.80-4.35)	5.11 (4.00-6.21)	7.01 (5.14-8.61)
Pembrolizumab+Axinitinib vs sunitinib	1.97 (1.19-2.75)	2.82 (1.75-3.90)	4.06 (2.57-5.56)
Pembrolizumab+TKI vs sunitinib	2.68 (2.03-3.34)	3.83 (2.93-4.74)	5.38 (4.12-6.65)
Duration of response			
Pembrolizumab+Levantinib vs sunitinib	1.85 (0.97-2.72)	3.27 (1.87-4.67)	NA
Pembrolizumab+Axinitinib vs sunitinib	NA	NA	NA
Pembrolizumab+TKI vs sunitinib	1.17 (0.32-2.02)	2.32 (0.97-3.67)	NA

For the KEYNOTE-426 duration of response at 18 and 24 months was not available since the curve stops at 15 months. Up to this time limit, there was no difference between pembrolizumab/axitinib and sunitinib arm.

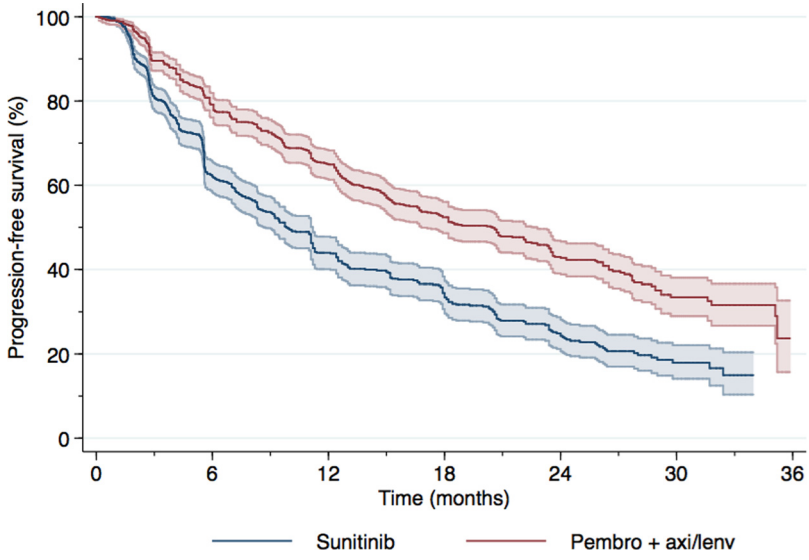

Fig. 2. Progression-free survival of patients with aRCC using reconstructed survival data derived from the KEYNOTE-426 and the KEYNOTE-582.

pembrolizumab-TKI vs sunitinib (**Δ**RMST 1.79 months [95% CI: 1.12-2.50; $P < 0.001$]). Analogous results were recorded for 18-month (**Δ**RMST 1.20 months [95% CI: 0.76-1.64; $P < 0.001$]) and 36-month (**Δ**RMST 2.68 months [95% CI: 1.52-3.84; $P < 0.001$]) RMST.

Progression-Free Survival

Pooled KM curves depicting PFS of patients enrolled in the included RCTs, divided into sunitinib or pembrolizumab-TKI combination therapy, using reconstructed data, are reported in Figure 2. PFS probabilities of patients treated with pembrolizumab-TKI combination at 18, 24

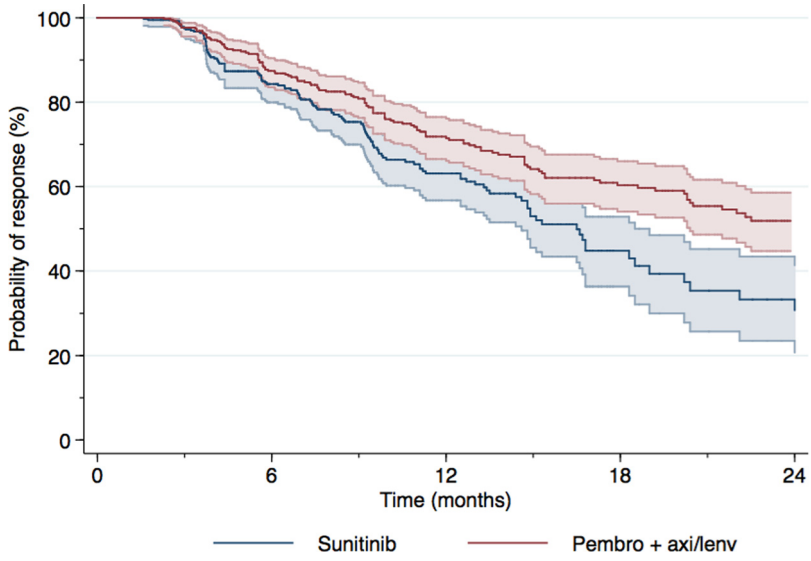

Fig. 3. Duration of response of patients with aRCC using reconstructed survival data derived from the KEYNOTE-426 and the KEYNOTE-582.

and 36 months were 52%, 43% and 24%, respectively. Similarly, at 18, 24 and 36 months, PFS probabilities of patients receiving sunitinib were 33%, 24% and 15% respectively. The estimated median PFS (95% CI) was 9.8 (9.0; 11.2) for patients treated with sunitinib and 20.1 (17.1; 22.8) for those treated with pembrolizumab-TKI combination.

When the Grambsch and Therneau test was employed on the reconstructed datasets from the included RCTs for the comparisons of survival data between pembrolizumab-TKI and sunitinib, a *P*-value of 0.049 was obtained, proving evidence of violation of the proportional hazard assumption.

With regard to 24-month RMST, there was a significant difference for patients treated with pembrolizumab-TKI vs sunitinib (**Δ**RMST 3.83 months [95% CI: 2.93-4.74; $P < 0.001$]). Analogous results were recorded for 18-month (**Δ**RMST 2.68 months [95% CI: 2.03-3.34; $P < 0.001$]) and 36-month (**Δ**RMST 5.38 months [95% CI: 4.12-6.65; $P < 0.001$]) RMST.

Duration of Response

Pooled KM curves depicting DoR of patients enrolled in the included RCTs, divided into treatment groups (sunitinib vs Pembrolizumab-TKI combination therapy), using reconstructed data, are reported in Figure 3. DoR probabilities of patients treated with pembrolizumab-TKI combination at 18, 24 and 36 months were 60%, 52% and 26%, respectively. Similarly, at 18, 24 and 36 months, DoR probabilities of patients receiving sunitinib were were 45%, 31% and 34% respectively. The estimated median DoR (95% CI) was 16.5 (14.8; 19.0) for patients treated with sunitinib and 5.8 (20.5; 27.2) for those treated with pembrolizumab-TKI combination.

When the Grambsch and Therneau test was employed on the reconstructed datasets from the included RCTs for the comparisons of survival data between pembrolizumab-TKI and sunitinib, a *P*-value of 0.55 was obtained, not proving evidence of violation of the proportional hazard assumption.

With regard to 24-month RMST, there was a significant difference for patients treated with pembrolizumab-TKI vs sunitinib (**Δ**RMST 2.32 months [95% CI: 0.97-3.67; $P = 0.001$]). Similar results were recorded for 18-month RMST (**Δ**RMST 1.17 months [95% CI: 0.32-2.02; $P = 0.007$]).

Discussion

In the context of treatment-naïve aRCC, several combination therapies recently joined the available treatment armamentarium, mostly combining checkpoints inhibitors with small molecules. A few randomized clinical trials were recently published, two including pembrolizumab in combination with axinitinib (KEYNOTE-426) or lenvatinib (KEYNOTE-581/CLEAR). At this time pembrolizumab is the only drug used in a immunotherapy-TKI combination with at least 2 RCTs comparing its efficacy relative to sunitinib. By relying on published KMs, we reconstructed survival data and provided for the first time level-1a of evidence for the use of pembrolizumab plus TKI in the setting of aRCC.

Our study revealed that pembrolizumab-TKIs combinations showed more favorable survival outcomes relative to sunitinib, in terms of OS, PFS and DoR. Indeed, a difference of 1.2, 1.8 and 2.7 months in the OS between pembrolizumab-TKI combination therapy and sunitib groups has been found at 18, 24 and 36 months. A difference of 2.7, 3.8 and 5.4 months in the PFS between pembrolizumab-TKI combination therapy and sunitinib groups has been found at 18, 24 and 36 months. Finally, a difference of 1.2 and 2.3 months in the DoR between pembrolizumab-TKI combination therapy and sunitinib groups has been found at 18 and 24 months. In addition, this benefit was not lowered by the fact that pembrolizumab-TKI combination arms had mostly the same rate of serious adverse events (Grade 3 or higher as for the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.) compared to sunitinib in both RCTs: 82.4% of the patients who received pembrolizumab-lenvatinib vs 71.8% of those who received sunitinib in the KEYNOTE-582 and 75.8% of patients who received pembrolizumab-axitinib vs 70.6% of those who received sunitinib in the KEYNOTE-426.[6,9] The most common high grade adverse event was hypertension in both RCTs.

From our sensitivity analysis, pembrolizumab-lenvatinib combination gave a marginal benefit in terms of OS, PFS and DOR relative to pembrolizumab-axitinib group. The choice between the two combination therapies must be driven by oncologist expertise, patient's preference, drug availability and cost-benefit analysis. The rates of adverse events leading to discontinuation of the drug was 25.6% for lenvatinib and 30.5% for axitinib.[6,9]

In addition to provide clear evidence of benefit of the use of pembrolizumab-TKI combination in first line treatment of aRCC, our study has several potential methodological strengths. Indeed, treatment response kinetics may not be constant due to a non-linear pattern of distribution of events over time, thus implying the risk of violation of the proportionality of hazards assumption. This intrinsic limitation of hazard ratios, which were at the base of most of the published meta-analyses in this context, renders these previous meta-analyses less accurate than ours.

Despite its strengths, this study is not devoid of limitations. First, the examined populations, that, although similar in terms of demographics, local tumor management and IMDC risk groups, were not identical. Indeed, differences in patients' geographic origin, metastatic burden or performance status prior to therapy may exist among RCT cohorts. However, these data were not implemented in the survival meta-analysis. Second, the diversity of single agents within the therapeutic class of TKIs (ie, lenvatinib and axitinib) may lead to divergent treatment responses, which may remain undisclosed when all pembrolizumab-TKI regimens are examined together. In our supplementary analysis, a marginal benefit of lenvatinib over axitinib combination with pembrolizumab seemed to emerge in OS, PFS and DoR. Third, we are still unable to differentiate clinical indications toward the use of pembrolizumab-based combinations and the combination of nivolumab and cabozantinib, which currently represents another Level 1a of evidence standard-of-care based on the results of the CheckMate-9ER study.[8] In this study at a median follow-up of 18.1 months, the median PFS was 16.6 months (95% CI: 12.5-24.9) with nivolumab plus cabozantinib and 8.3 months (95% CI: 7.0-9.7) with sunitinib (HR 0.51; 95% CI: 0.41-0.64; P-value < 0.001). The probability of overall survival at 12 months was 85.7% (95% CI: 81.3-89.1) with nivolumab plus cabozantinib and 75.6% (95% CI: 70.5-80.0) with sunitinib (HR 0.60; 95% CI: 0.40-0.89; P-value $= 0.001$). Rates of adverse events was 75.3% in the combination arm, which were very similar to those seen for the combination of pembrolizumab and axitinib or lenvatinib.

Taken together, through the use of reconstructed individual data to estimate the survival impact of different therapies, we overcome biases associated with traditional meta-analysis methodologies and demonstrated that pembrolizumab-TKI combinations are superior to sunitinib in terms of OS, PFS and DoR, using 18-, 24- and 36-month RMST.

Conclusion

By relying on individual survival data, we provided for the first-time level 1a of evidence supporting the use of pembrolizumab plus TKI in the setting of aRCC. Moreover, we demonstrated the magnitude of the benefit at different time intervals after treatment's initiation.

Contributors

Conceptualization: AM, UC, GF, AN; Data curation: GF, AM, LN, DR; Formal analysis: GF, AM, LN; Data interpretation: all authors; Funding acquisition: none; Methodology: GF, AM, LN; Project administration: none; Writing – original draft: UC, GF; Writing– review & editing: all authors; Supervision: AN, PK, AB, AS, FM.

GF, AM, LN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Luca Vitale created the figures and graphics.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2022.100875.

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