Comparative efficacy of pembrolizumab plus axitinib (P+A) versus first-line systemic therapies for elderly patients with advanced/metastatic RCC (mRCC): a systematic literature review and network meta-analysis

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BACKGROUND AND OBJECTIVE

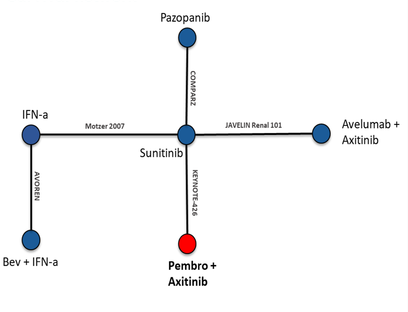
- Renal cell carcinoma (RCC) is the most common type of kidney cancer;[1] accounting for approximately 90% of primary renal neoplasms and 3-4% of all adult malignancies.[2] At the time of RCC diagnosis, 16% of patients present with metastatic disease.[3] Historically, metastatic RCC (mRCC) has been one of the most treatment-resistant malignancies and clinical outcomes were generally poor.[4]
- Within the past couple years the arrival of immune checkpoint inhibitors have transformed the survival in mRCC patients.[5]
- KEYNOTE-426, a phase III RCT, demonstrated statistically and clinically meaningful improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) in clear-cell (cc) mRCC subjects treated with P+A versus (vs) sunitinib.
- Approximately half of new diagnoses of mRCC occur in elderly patients (≥65 years old).[3] A previous network meta-analysis of ccmRCC treatment found that elderly participants had worse treatment outcomes compared to participants under 65.[6]
- In the absence of head-to-head clinical trial evidence of pembrolizumab plus axitinib versus all competing interventions of interest, an indirect treatment comparison by means of a network meta-analysis (NMA) of randomized controlled trials (RCTs) provides a valid alternative. [7-9]
- The aim of the study was to conduct a systematic review of the efficacy and safety of pembrolizumab + axitinib and competing interventions for the treatment of mRCC; and perform NMA to obtain estimates of the comparative efficacy in elderly participants.

METHODS

Evidence Base

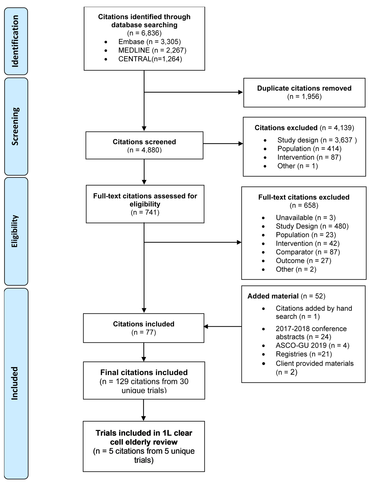
- An SLR of RCTs was performed including searches of EMBASE, MEDLINE, and CCTR, and relevant conferences. The original search was conducted in November 2018 and an update search was conducted in February 2019.
- Citations identified by the searches were screened in duplicate using a pre-determined set of inclusion and exclusion criteria.
- A total of 5 relevant trials with elderly subgroup data were identified (**Figure 1**).
- A connected network of subgroup data for elderly participants was available for PFS, but not OS or ORR. The network of PFS among elderly participants consisted of 5 trials[10-14] (**Figure 2**).
- ARCC[15] included only intermediate and poor risk participants. Although elderly PFS subgroup data were reported, the trial was not included in the elderly subgroup analysis due to the risk restrictions.
- VEG105192[16] included both first-line and 2L+ treatment among ccmRCC. The trial reported PFS subgroup data for participants over 65, but not participants over 65 receiving first-line treatment.

Figure 2: 1L Clear-cell 65+ progression-free survival network



Abbreviations: *ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; KM, Kaplan-Meier curve;*

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram



Baseline participant characteristics

- None of the five trials included in the PFS analysis reported baseline participant characteristics for the elderly subgroup. The five trials contained between 36.6% and 39.1% participants over the age of 65.

In the overall 1L clear-cell mRCC population for the five trials:

- Age was similar across trials; the median age ranged from 59-62 years. The proportion of female participants ranged from 22.5% to 32%.
- Memorial Sloan-Kettering Cancer Center (MSKCC) risk was reported among four of the five trials. The majority of participants were intermediate risk (range: 56-69%) followed by favorable risk (range: 19-38%) and then poor risk (range: 6-12%).

Network meta-analysis

- JAGS through R-3.4.0 was used to perform the analyses in a Bayesian framework with non-informative prior distributions. The 95% credible intervals (CrI) were presented. All results were based on fixed effect models as there was insufficient data to estimate between-study heterogeneity under a random-effects model.
- The NMA of reported hazard ratios (HRs) in terms of PFS, assuming proportional hazards between treatments, was performed using a regression model with a contrast-based normal likelihood for the log HR of each trial in the network.[7]
- None of the trials that reported elderly subgroup data for PFS included a Kaplan-Meier curve (KM curve), so time-varying HR analysis was not feasible.
- The PFS HRs and 95%CI for COMPARZ[11] and Motzer 2007[14] were imputed from forest plots included in the publications that were digitized. The PFS HRs from the other three publications were extracted from reported values.

RESULTS

- Among elderly participants, pembrolizumab + axitinib demonstrated superior PFS compared to four out of the five comparator interventions.
- P+A showed a statistically significant improvement in PFS compared to interferon-alpha (IFN-α), bevacizumab in combination with IFN-α, pazopanib and sunitinib.
- PFS benefit favored P+A over avelumab in combination with axitinib (A+A) but was not statistically significant.

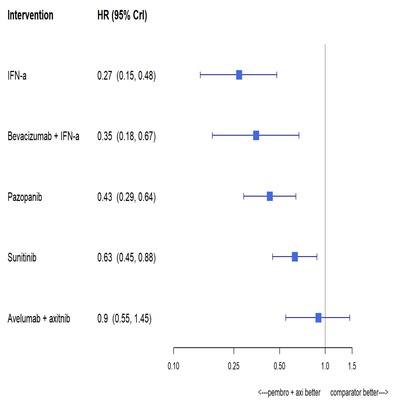
Table 1: Hazard ratios estimated from fixed-effects network meta-analysis of progression-free survival among elderly participants

Sunitinib	**0.43 (0.27, 0.67)**	**0.55 (0.32, 0.96)**	**0.68 (0.55, 0.84)**	**1.43 (1.01, 2.03)**	**1.59 (1.14, 2.22)**
2.34 (1.49, 3.74)	**IFN-a**	1.30 (0.98, 1.73)	1.59 (0.96, 2.67)	**3.34 (1.88, 5.93)**	**3.73 (2.09, 6.58)**
1.80 (1.05, 3.11)	0.77 (0.58, 1.02)	**Bevacizumab + IFN-a**	1.23 (0.68, 2.20)	**2.58 (1.36, 4.92)**	**2.87 (1.50, 5.41)**
1.47 (1.19, 1.81)	0.63 (0.37, 1.04)	0.81 (0.45, 1.47)	**Pazopanib**	**2.09 (1.40, 3.15)**	**2.33 (1.57, 3.46)**
0.70 (0.49, 0.99)	**0.30 (0.17, 0.53)**	**0.39 (0.20, 0.74)**	**0.48 (0.32, 0.71)**	**Avelumab + Axitinib**	1.11 (0.69, 1.80)
0.63 (0.45, 0.88)	**0.27 (0.15, 0.48)**	**0.35 (0.18, 0.67)**	**0.43 (0.29, 0.64)**	0.90 (0.55, 1.45)	**Pembrolizumab+ Axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 9.35; Deviance: 4.33

Note: *HR below 1 indicates that the row treatment has lower risk of progression or death compared to the column treatment*

Figure 3: Forest plot of hazard ratios estimated from fixed-effects NMA of progression-free survival among elderly participants: P+A vs. comparator intervention



DISCUSSION AND CONCLUSION

- It should be noted that results and their corresponding conclusions must be made with caution as there was some variation in potential effects modifiers between trials and treatment arms, including performance score and PD-L1 expression. However, subgroup analysis of these potential effect modifiers did not identify trends in relative treatment effects that differed substantially from base-case analysis.
- The limited number of relevant trials available prevented reliable estimates of between study heterogeneity.
- The lack of reported KM curves prevented analysis of time-varying hazard ratios
- Comparisons to bevacizumab + IFN-a were mediated by multiple treatment comparisons, and were therefore more uncertain.
- The results observed in this elderly subgroup analysis were consistent with the results from the overall population, which suggests that age may not be a strong effect modifier in this population.
- In conclusion, this study suggests that treatment with P+A results in significantly improved PFS relative to competing systemic therapies for 1L treatment of ccmRCC among elderly participants. The PFS results favored P+A over A+A, but were not statistically significant.

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