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Network meta-analysis for an efficacy assessment of avelumab + axitinib in the first-line treatment of International mRCC Database Consortium favorable-risk patients with advanced renal cell carcinoma

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CONCLUSIONS

- This study assessed the relative efficacy of avelumab + axitinib, based on the final analysis of the JAVELIN Renal 101 phase 3 trial,[1] compared with alternative first-line (1L) treatment options for patients with International mRCC Database Consortium (IMDC) favorable-risk advanced renal cell carcinoma (aRCC)
  - Comparisons were performed using a standard network meta-analysis (NMA), which was conducted in June 2025 based on a systematic literature review (May 2024)[2] and supplementary literature searches (June 2025)
- Results for overall survival (OS) showed that avelumab + axitinib performed numerically better (point estimate of hazard ratio [HR] < 1) than three comparators—sunitinib, nivolumab + cabozantinib, and pembrolizumab + lenvatinib—and similarly to nivolumab + ipilimumab
  - For progression-free survival (PFS), avelumab + axitinib performed significantly better than nivolumab + ipilimumab, numerically better than sunitinib, and similarly to nivolumab + cabozantinib
  - Although the NMA results did not show any statistically significant differences in most comparisons (95% credible intervals [CrIs] contained 1), avelumab + axitinib generally showed numerical improvements or at least comparable OS and PFS
- These findings support the use of avelumab + axitinib as 1L treatment for patients with IMDC favorable-risk aRCC

PLAIN LANGUAGE SUMMARY

- This study looked at how well the combination of avelumab and axitinib works compared with other treatments for people with advanced kidney cancer whose disease has been classed as favorable risk, and who are receiving their first treatment
  - Favorable risk means that people are predicted to live longer, on average, than people whose disease is classed as poor risk
- The other treatments investigated were sunitinib, nivolumab plus ipilimumab, pembrolizumab plus lenvatinib, and nivolumab plus cabozantinib
  - No clinical trials have been done with different groups of people receiving all of these different treatments, so researchers used a type of analysis that combines results from different clinical trials
- Researchers found that people treated with avelumab plus axitinib seemed to live longer than people who received three of the other four treatments
  - They also found that people treated with avelumab plus axitinib seemed to live longer without their disease getting worse than people who received two of the other treatments
- Overall, these results support the use of avelumab plus axitinib as a first treatment for people with advanced kidney cancer classed as favorable risk

BACKGROUND

- Choice of treatment for aRCC (stage IV) may be influenced by the patient's risk status, as determined by the presence of IMDC criteria that can be used to categorize patients as favorable, intermediate, or poor risk[3]
- Combination treatment with avelumab (an anti-PD-L1 immune checkpoint inhibitor) and axitinib (an anti-vascular endothelial growth factor receptors tyrosine kinase inhibitor) is indicated as a 1L treatment for adult patients with aRCC[4,5]
  - In the JAVELIN Renal 101 phase 3 trial, 1L treatment with avelumab + axitinib resulted in significantly longer PFS and a higher ORR vs sunitinib in patients with aRCC, irrespective of IMDC risk group[1]
    - Final analyses of OS favored avelumab + axitinib vs sunitinib, but differences did not reach statistical significance
- Extended follow-up has been reported from phase 3 trials of different 1L treatment options for aRCC, including subgroup data in patients with IMDC favorable risk
- In the absence of head-to-head trials comparing different 1L treatments, this study aimed to assess the relative effects of 1L avelumab + axitinib vs other treatments in patients with IMDC favorable-risk aRCC using indirect treatment comparison methods
  - Relevant treatment comparators for which favorable-risk subgroup data have been reported (identified via a systematic literature review and feasibility assessment) include sunitinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib, and nivolumab + cabozantinib

METHODS

- Subgroup data from 4 randomized trials were suitable for indirect treatment comparison: JAVELIN Renal 101 (avelumab + axitinib, n=188), CheckMate 214 (nivolumab + ipilimumab, n=249), CheckMate 9ER (nivolumab + cabozantinib, n=146), and CLEAR (pembrolizumab + lenvatinib, n=234)
  - In all included trials, patients in the control arm received sunitinib treatment[1,6-8]
- Study heterogeneity was assessed based on trial designs and patient characteristics, which were generally comparable across studies (**Table 1**)
- IMDC favorable-risk subgroup data for OS and PFS in all 4 included trials were analyzed in standard Bayesian NMAs[9] using sunitinib as the common comparator (**Figure 1**)
  - Both fixed- and random-effects models were fitted to the data, and model comparison methods were used to compare the goodness of fit
  - Preferred models were identified based on clinical plausibility of the estimated relative treatment effects and goodness-of-fit statistics, such as deviance information criterion (to compare between alternative models) and/or the total residual deviance, which is compared with the number of unique data points[10]
- Standard NMA methods using HRs were assessed to be suitable, as the proportionality of hazard was deemed reasonable in the JAVELIN Renal 101 trial and comparator trials[9]

Table 1. Baseline characteristics of the favorable-risk population in phase 3 trials (where reported)

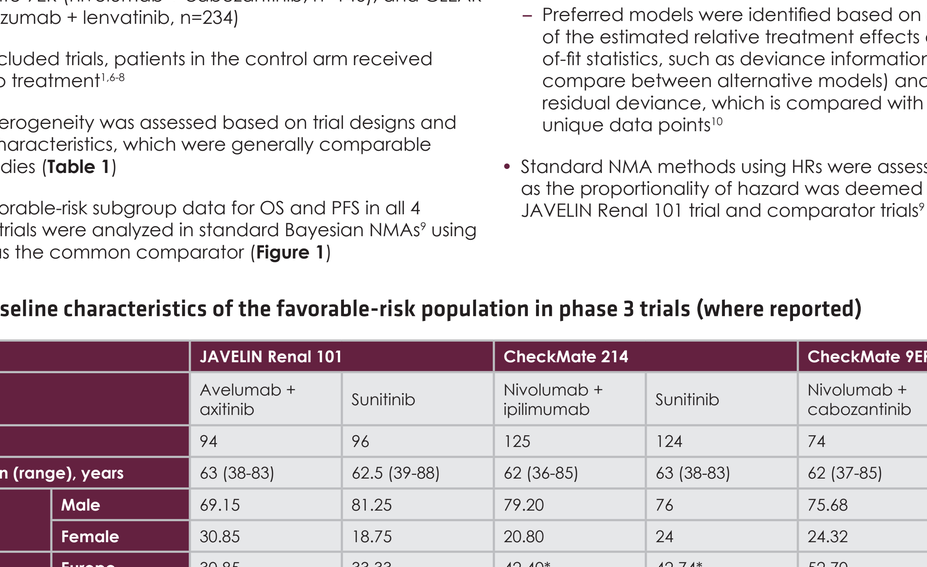
Trial		JAVELIN Renal 101		CheckMate 214		CheckMate 9ER	
Treatment		Avelumab + axitinib	Sunitinib	Nivolumab + ipilimumab	Sunitinib	Nivolumab + cabozantinib	Sunitinib
Patients, n		94	96	125	124	74	72
Age, median (range), years		63 (38-83)	62.5 (39-88)	62 (36-85)	63 (38-83)	62 (37-85)	61 (41-80)
Sex, %	Male	69.15	81.25	79.20	76	75.68	68.06
	Female	30.85	18.75	20.80	24	24.32	31.94
Pooled region, %	Europe	30.85	33.33	42.40*	42.74*	52.70	51.39
	N America	53.19	46.88	33.60†	33.87†		
	Asia	4.26	8.33	24.00	23.39	47.30	48.61
	Rest of world	11.7	11.46				
Prior nephrectomy, %		93.62	95.83	89.60	95.16	91.89	86.11
IMDC favorable prognostic score, %		100	100	100	100	97.30	97.22
PD-L1 status, %	Positive	55.32	61.46	10.40	10.48	14.86	13.89
	Negative	34.04	31.25	81.60	79.03	83.78	84.72
	Unknown	10.64	7.29	8.00	10.49	1.36	1.39

In the CLEAR trial, baseline characteristics in the favorable-risk population have not been reported.

IMDC, International Metastatic RCC Database Consortium.

*In the CheckMate 214 trial, Canada and Europe was reported as a combined pooled region; these data are reported here. †In the CheckMate 214 trial, USA was reported as a separate region; these data are reported here.

Figure 1. IMDC favorable-risk network diagram



RESULTS

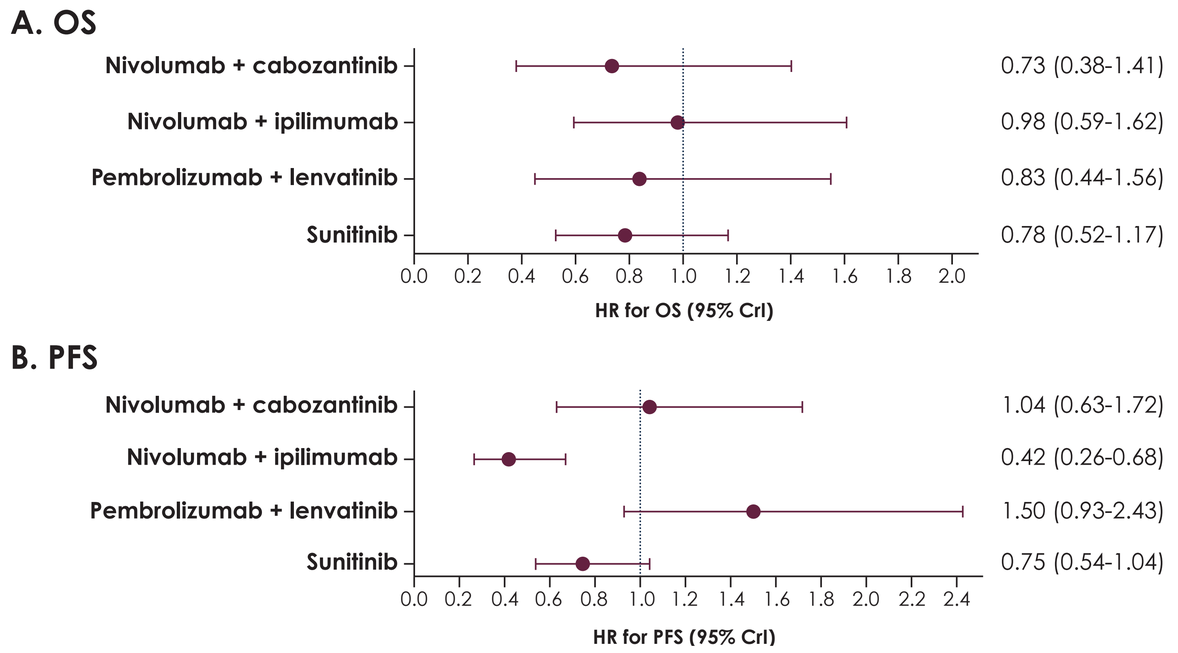
- Both the fixed-effects and random-effects analyses (based on a noninformative uniform prior for the between-study heterogeneity) were performed
  - The fixed-effects models were preferred because (1) they had lower deviance information criterion statistics (**Table 2**); (2) random-effects models had wide CrIs due to the sparse network; and (3) each network link was sourced from one trial only (therefore pairwise assessment of heterogeneity was not possible)
- OS NMA results (**Figure 2A**) showed that avelumab + axitinib performed
  - Numerically better than sunitinib (HR, 0.78 [95% CrI, 0.52-1.17]), nivolumab + cabozantinib (HR, 0.73 [95% CrI, 0.38-1.41]), and pembrolizumab + lenvatinib (HR, 0.83 [95% CrI, 0.44-1.56])
  - Similarly to nivolumab + ipilimumab (HR, 0.98 [95% CrI, 0.59-1.62])
- For PFS (**Figure 2B**), avelumab + axitinib performed
  - Significantly better than nivolumab + ipilimumab (HR, 0.42 [95% CrI, 0.26-0.68])
  - Numerically better than sunitinib (HR, 0.75 [95% CrI, 0.54-1.04])
  - Similarly to nivolumab + cabozantinib (HR, 1.04 [95% CrI, 0.63-1.72])
  - Numerically worse than pembrolizumab + lenvatinib (HR, 1.50 [95% CrI, 0.93-2.43])

Table 2. Model fit statistics for the favorable-risk population: fixed and random effects

	OS		PFS	
Model fit statistic	Fixed-effects model	Random-effects model	Fixed-effects model	Random-effects model
Mean residual deviance, $\bar{D}_{res}$	3.97	4.01	3.99	4.00
Leverage, p_D	3.97	4.01	3.99	4.00
Deviance information criterion	7.94	8.03	7.98	8.00
Between-trials heterogeneity, mean (SD)	NA	2.49 (1.45)	NA	2.49 (1.44)

NA, not applicable; **OS**, overall survival; **PFS**, progression-free survival.

Figure 2. Characteristics of included studies (N=117)



HR, hazard ratio; **PFS**, progression-free survival; **OS**, overall survival.

LIMITATIONS

- The evidence base was limited, with all treatments of interest supported by only 1 trial each; these analyses therefore rely on the robustness of each trial when forming relative treatment effect estimates
- Typically, random-effects models would be preferred with the consideration of capturing heterogeneity, but as reported earlier, these models led to uninterpretable results and are not presented
- None of the trials included were specifically designed to assess outcomes in the IMDC favorable-risk population and results were derived from subgroup analyses; randomization in each trial was not stratified by IMDC risk
- To increase transparency and to understand comparability across studies, baseline characteristics were examined; it was found that key characteristics were comparable except for PD-L1 status (higher proportion of PD-L1+ in the JAVELIN Renal 101 trial)
- Baseline characteristics in the IMDC favorable risk subgroup were not available in the CLEAR trial[8]; therefore, it is uncertain whether characteristics in this subgroup were similar to other trials
- These analyses were focused on relevant treatment comparators in the avelumab + axitinib resubmission to NICE; therefore, favorable-risk subgroup data for pembrolizumab + axitinib from the KEYNOTE-426 study were not included, as this treatment combination is not recommended by NICE[11-13]

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