Synthesizing evidence on overall survival and assessing the feasibility of network meta-analyses in previously untreated advanced/metastatic renal cell carcinoma patients

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Background

- Kidney cancer, of which renal cell carcinoma (RCC) accounts for approximately 85%, is the 7th most common cancer worldwide in men, and the 10th most common cancer worldwide in women.[1]
- Nivolumab (Opdivo®) is an immunoglobulin G4 human monoclonal antibody (IgG4 HuMAb) that binds to the programmed cell death-1 (PD-1) receptor, blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2.[2,3]
- Within the phase 3 randomized controlled trial (RCT) CheckMate 9ER, nivolumab + cabozantinib is being compared to sunitinib in previously untreated advanced or metastatic renal cell carcinoma (aRCC) patients with a clear-cell component.[4]
- Knowledge concerning the comparability of clinical efficacy across interventions is essential beyond the available head-to-head comparisons, which would mostly include only sunitinib as a comparator. A network meta-analysis (NMA) allow synthesis of evidence for differences in relative treatments; however, the validity of performing a NMA needs to be assessed by analysing the networks of evidence and the heterogeneity across relevant trials.

Objective

- The current study investigates the feasibility of conducting a NMA for overall survival (OS) in the all-risk population receiving nivolumab + cabozantinib treatment for previously untreated aRCC patients versus relevant interventions.

Methods

- A systematic literature review (SLR) identified all published RCTs in 1L aRCC.[5] Available evidence was synthesized by evaluating whether the pre-defined relevant interventions formed a network of evidence for OS outcomes in the all-risk population.
- Clinical heterogeneity was assessed for each population, intervention, comparison, outcome, and study type (PICOS):
  - **Population**: age, sex, Eastern Co-operative Oncology Group Performance Status (ECOG)-PS, Memorial Sloan Kettering Cancer Center score (MSKCC)/ International Metastatic RCC Database Consortium score (IMDC), prior nephrectomy, prior use of radiation therapy, PD-L1 status, metastatic sites, race, region
  - **Intervention**: treatment type, dose, and regimen
  - **Outcomes**: definition of OS, stratified versus unstratified results
  - **Study characteristics**: study phase, number of patients, study aim, study design (for example, cross-over design), follow-up duration
- Feasibility assessment was based on the framework by Cope et al. (2014).[6]
- The network of evidence was clustered based on six relevant comparator treatment arms:
  - Atezolizumab+bevacizumab (ATE+BEV)
  - Avelumab+axitinib (AVE+AXI)
  - Bevacizumab+interferon alfa (BEV+IFN)
  - Pazopanib (PAZ)
  - Pembrolizumab+axitinib (PEM+AXI)
  - Sunitinib (SUN)

Results

Systematic Literature Review

- The SLR was performed and identified all available RCTs in previously untreated aRCC patients using MEDLINE, MEDLINE-IN-PROCESS, EMBASE and the Cochrane library, the last search update was on June 4th, 2020. A total of 14,027 records were identified, of which 121 satisfied the PICOS criteria. For the NMA, only RCTs were considered (N=57).[5]

Network Diagram

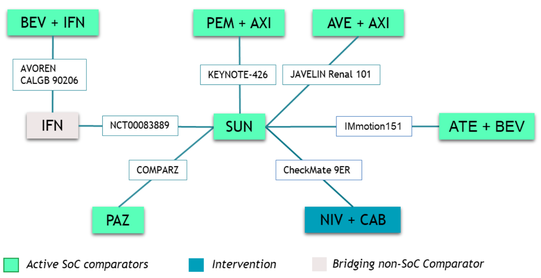
- The all-risk network included eight studies (Table 1), which were relevant for forming a linked network, Figure 1.

Table 1. Overview of the study characteristics treatments investigated of the trials included in the NMA

Trial Name	Treatment	n	Study Phase	Study Design*
CheckMate 9ER[4]	NIV+CAB	323	Phase 3	RCT
	SUN	328		
AVOREN[7]	BEV+IFN	327	Phase 3	RCT
	IFN	322		
NCT00083889[8,9]	SUN	375	Phase 3	RCT
	IFN	375		
COMPARZ[10,11]	PAZ	557	Phase 3	RCT
	SUN	553		
JAVELIN Renal 101[12]	AVE+AXI	442	Phase 3	RCT
	SUN	444		
CALGB 90206[13,14]	BEV+IFN	369	Phase 3	RCT
	IFN	363		
IMmotion151[15]	ATE+BEV	454	Phase 3	RCT
	SUN	461		
KEYNOTE-426[16]	PEM+AXI	432	Phase 3	RCT
	SUN	429		

*Possible study design types: RCT, cross-over design and treatment sequencing

Figure 1. Network diagram for the all-risk population



Heterogeneity Assessment

- Trials characteristics were assessed to be very similar: all studies are phase 3 trials. None of the trials had a treatment sequencing or cross-over study design and all trials had a large amount of patients included (>300 patients per treatment arm; Table 1).
- Heterogeneity was present and was most evident in MSKCC/IMDC risk score, ECOG-PS score, prior radiation therapy, and prior nephrectomy.

ECOG-PS

- The ECOG-PS was only reported by four studies including the CheckMate 9ER (Table 2). The trials that reported on the ECOG-PS scores had a similar distribution of the scores in their patients. However, since the other trials did not report on ECOG-PS scores, it was unclear whether patients had similar ECOG-PS scores in studies included in the OS NMA for the all-risk population.

Table 2: ECOG performance status for trials in the all-risk OS network

Study	Trial name	Treatment	n	ECOG 0	ECOG 1	ECOG 2
Choueiri, 2020[4]	CheckMate 9ER	NIV+CAB	323	79.6%	20.4%	-
		SUN	328	73.5%	25.9%	-
Motzer 2007[8], 2009[9]	NCT00083889	SUN	375	62%	38%	-
		IFN	375	61%	39%	-
Choueiri 2020[12]	JAVELIN Renal 101[12]	AVE+AXI	442	63%	37%	-
		SUN	444	63%	37%	-
Rini 2008[13], 2010[14]	CALGB 90206	BEV+IFN	369	62%	36%	2%
		IFN	363	62%	37%	1%

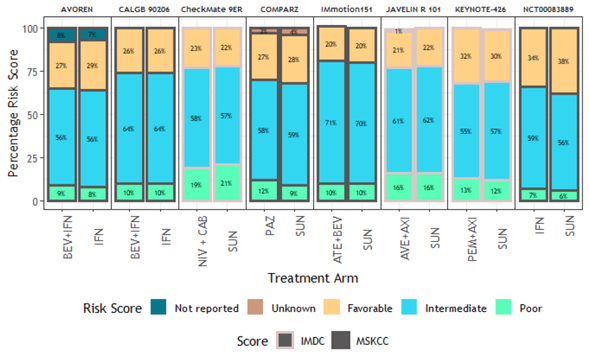
[1]ECOG score unreported in 38% of AVE+AXI arm and 35% of SUN arm in JAVELIN Renal 101

Results (Continued)

MSKCC/IMDC risk score

- MSKCC/IMDC risk score data were reported in all eight trials (Figure 2). The distribution of favorable, intermediate, and poor risk scores of patients varied substantially across trials, even when using the same risk score. A few trials had a relatively large proportion of patients with unknown/not reported MSKCC risk scores, which makes comparison across trials even more complicated.

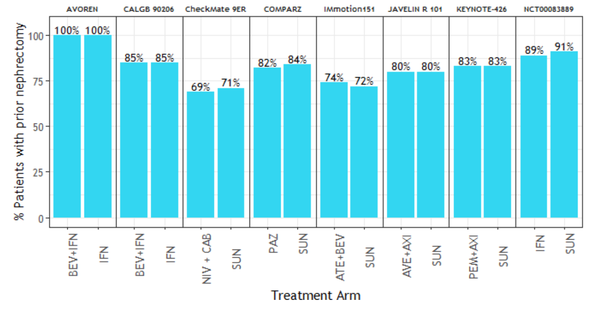
Figure 2. Histogram for the distribution risk of scores in the studies included in the network



Prior nephrectomy

- Prior nephrectomy proportions of patients in each study per treatment arm are presented in Figure 3. AVOREN only included patients with a prior nephrectomy. Moreover, trials CheckMate 9ER and IMmotion 151 had a smaller proportion of patients with prior nephrectomy (~70%) in comparison to the other trials, which had a proportion of around 85% of patients with prior nephrectomy included in the trial.

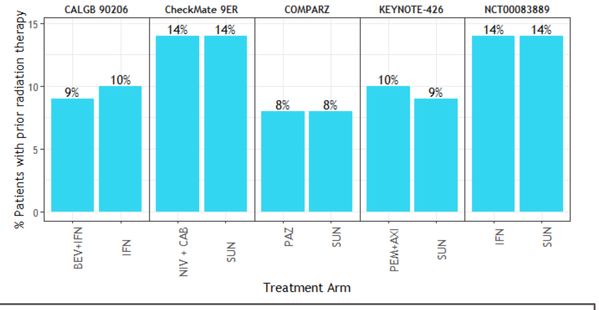
Figure 3. Histogram of the distribution of prior nephrectomy in studies included in the all-risk scores



Radiation therapy

- Prior use of radiation therapy proportion of patients was reported for five trials (Figure 4). The histogram shows that trial CheckMate 9ER and NCT00083889 had around 14% of patients who had previously used radiation therapy, counter to the ~9% of the other trials. This difference is relatively large (1.5 times as big), however, only five trials reported on the prior use of radiation therapy and, therefore, it was difficult to draw conclusions about the heterogeneity within the network.

Figure 4. Histogram of the distribution of prior use of radiation therapy in studies included in the network



Conclusions

- While it is feasible to perform a NMA to determine the comparative efficacy of relevant interventions on OS in previously untreated aRCC patients, results must be interpreted with caution because unobservable heterogeneity may compromise the validity of the results.
- Moreover, there was evident heterogeneity across the trials for ECOG-PS, MSKCC/IMDC risk score, prior nephrectomy, and prior radiation therapy. These differences between trials may have an influence over the size of the treatment effect, thus causing bias in the estimates and hence generating a biased NMA.
- Based on this result, we suggest performing covariate adjustment for an all-risk HR-based NMA, to account for heterogeneity between studies regarding characteristics that are potential treatment effect modifiers, i.e. meta-regression.
- In addition, we suggest performing scenario analyses to assess impact on results. For example, omit trials that have a larger proportion of patients with a favorable risk score.

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