The impact of clinical heterogeneity on conducting network meta-analyses for progression-free survival of previously untreated intermediate- or poor-risk advanced/metastatic renal cell carcinoma therapies

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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]
- Knowledge concerning the comparability of clinical efficacy across interventions is essential beyond the available head-to-head comparisons, which would mostly only include sunitinib as a comparator. A network meta-analysis (NMA) can be used the synthesis of evidence for differences in relative treatments; however, the validity of performing a NMA needs to be assessed by analyzing the networks of evidence and the heterogeneity across relevant trials.

Objective

- The current study investigates the feasibility of conducting a NMA for progression-free survival (PFS) in the previously untreated intermediate-/poor-risk aRCC population.

Methods

- A systematic literature review (SLR) identified all published RCTs in previously untreated aRCC.[4] Available evidence was synthesized by evaluating whether the pre-defined relevant interventions formed a network of evidence for PFS outcomes in the intermediate-/poor-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) and/or 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 PFS, 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).[5]
- The network of evidence was clustered based on eight relevant comparator treatment arms:
  - Avelumab + axitinib (AVE+AXI)
  - Cabozantinib (CAB)
  - Bevacizumab + interferon alfa (BEV+IFN)
  - Nivolumab + Ipilimumab (NIV+IPI)
  - Pazopanib (PAZ)
  - Pembrolizumab + axitinib (PEM+AXI)
  - Sunitinib (SUN)
  - Temsirolimus (TEM)

Results

Systematic Literature Review

- The SLR was performed and identified all available RCTs in previously untreated aRCC using MEDLINE, MEDLINE-IN-PROCESS, EMBASE and the Cochrane library, the last 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).[4]

Network Diagram

- In the intermediate-/poor-risk population base case, the network included nine studies (see Table 1), which were relevant for forming a linked network. Table 2 reports the efficacy outcomes reported in the nine trials included. Finally, Figure 1 shows the network of evidence for PFS in the intermediate-/poor-risk population.

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

Trial Name	Treatment	n	Study Phase	Study Design*
AVOREN[6]	BEV+IFN	327	Phase 3	RCT
	IFN	322		
CABOSUN[7,8]	CAB	79	Phase 2	RCT
	SUN	78		
CALGB 90206[9,10]	BEV+IFN	369	Phase 3	RCT
	IFN	363		
CheckMate-214[11]	NIV+IPI	425	Phase 3	RCT
	SUN	422		
GLOBAL ARCC[12]	TEM	209	Phase 3	RCT
	IFN	207		
JAVELIN Renal 101[13]	AVE+AXI	442	Phase 3	RCT
	SUN	444		
KEYNOTE-426[14]	PEM+AXI	432	Phase 3	RCT
	SUN	429		
NCT00083889[15]	SUN	375	Phase 3	RCT
	IFN	375		
TemPa[1]	TEM	35	Phase 2	RCT
	PAZ	34		

*Possible study design: cross-over design, RCT or treatment sequencings

Figure 1. Network diagram

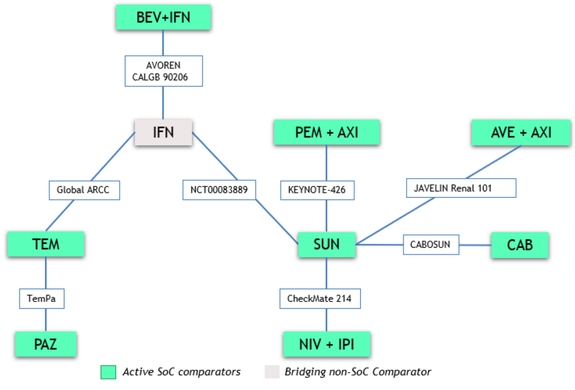


Table 2. Overview of the efficacy data of trials included in the NMA

Trial name	Treatment / Comparator	Risk population	PFS HR (95% CI)
AVOREN[16]	BEV+IFN / IFN	Intermediate	0.55 (0.44-0.70)
		Poor	0.81 (0.46-1.42)
CABOSUN[7,8]	CAB / SUN	Intermediate/poor	0.48 (0.31-0.74)
		Intermediate	0.52 (0.32-0.82)
		Poor	0.31 (0.11-0.92)
CALGB 90206[9,10]	BEV+IFN / INF	Intermediate	NR, KM available
		Poor	NR, KM available
CheckMate-214[17]	NIV+IPI / SUN	Intermediate/poor	0.76 (0.63-0.91)
		Intermediate	0.80* (0.60-0.99)*
		Poor	0.63* (0.26-1.00)*
GLOBAL ARCC[12]	TEM / IFN	Intermediate/poor	0.70 (0.58-0.86)
JAVELIN Renal 101[13]	AVE+AXI / SUN	Intermediate	0.76 (0.60-0.95)
		Poor	0.51 (0.34-0.77)
KEYNOTE-426[14,18]	PEM+AXI / SUN	Intermediate/poor	0.69 (0.56-0.84)
		Intermediate	0.70 (0.54-0.91)
		Poor	0.58 (0.35-0.94)
NCT00083889[19]	SUN / IFN	Intermediate	0.39 (0.28-0.54)
		Poor	0.53 (0.23-1.23)
TemPa[1]	TEM / PAZ	Intermediate/poor	1.36 (0.84-2.22)

*Numbers are pooled from Escudier et al.(2019)[21] NR: not reported, KM: Kaplan Meier curve

Results (Continued)

Heterogeneity Assessment

- The heterogeneity assessment for the intermediate-/poor-risk population for PFS included nine trials.
- Reporting was scarce for the baseline characteristics in the intermediate-/poor-risk population, and many of the trials could not be included due to a shortage of information.
- For the characteristics that were reported across a sufficient number of trials, such as age and sex, the populations did appear to be homogenous. Other relevant characteristics were assessed and are presented below

ECOG-PS

- ECOG-PS was only reported for two of the trials. The results are shown in Table 3 and demonstrate that the ECOG-PS scores of patients differ substantially between trials. For example, the proportion of patients with an ECOG-PS of zero ranges from 2.9% to 46%.

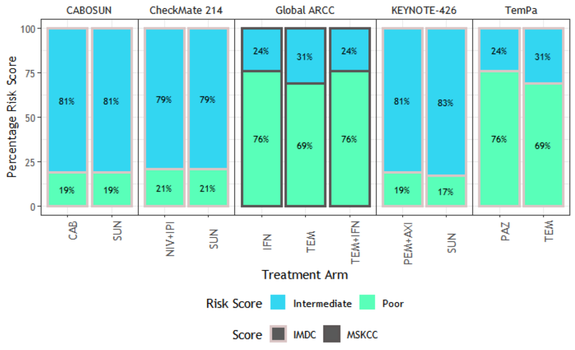
Table 3. Distribution of ECOG-PS in studies included in the NMA

Trial Name	Treatment	n	ECOG 0	ECOG 1	ECOG 2
CABOSUN[10,11]	CAB	79	46.0%	42.0%	13.0%
	SUN	78	46.0%	41.0%	13.0%
TemPa[1]	TEM	35	2.9%	40.0%	57.1%
	PAZ	34	2.9%	35.3%	61.8%

MSKCC/IMDC risk score

- MSKCC/IMDC risk score were reported in five trials (Figure 2). Both the risk score definition as well as the distribution differed across trials. Figure 2 shows that even between studies that use the same definition, the risk score distribution varies (e.g. TemPa trial compared to the other trials).

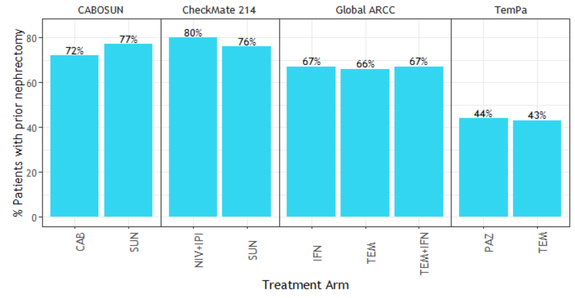
Figure 2. Histogram of the distribution of risk scores in studies included in the NMA



Prior nephrectomy

- Prior nephrectomy was reported in four trials. In three of four trials, the percentage of patients who had a prior nephrectomy is similar (between 66% and 80%). Only in the TemPa trial, the number of patients undergone a prior nephrectomy appears to be much lower in each treatment arm compared to the other studies (<45%; Figure 3).

Figure 3. Histogram of the distribution of prior nephrectomy in studies included in the NMA



Prior use of radiation therapy, PD-L1 expression, and metastatic sites

- Prior use of radiation therapy and PD-L1 expression was exclusively reported in the Checkmate 214 trial. Metastatic sites information, in particular bone metastasis, were reported across two trials only, namely Checkmate 214 and CABOSUN trials. However, the percentages of patients with bone metastasis differed between the two trials, ranging from 22% to 23% in the Checkmate 214 trial and 36% to 37% in the CABOSUN trial.

Race of patients

- Race of patients was only reported in two trials (Table 4). Across these, there is homogeneity with regards to race, in both trials most of the patients were predominantly white (>75%).

Table 4. Distribution of race of patients in studies included in the NMA

Trial name	Treatment	n	White	Black	Asian	Other	Not reported
CABOSUN[11]	CAB	79	89.0%	4.0%	-	9.0%	-
	SUN	78	96.0%	3.0%	-	1.0%	-
TemPa[1]	TEM	35	77.1%	-	-	22.9%	-
	PAZ	34	76.5%	-	-	23.5%	-

Conclusions

- Due to the scarcity of reporting of relevant baseline characteristics for the intermediate-/poor-risk population, we can conclude that for several characteristics, such as prior use of radiation, PD-L1 expression, and metastatic sites homogeneity between trials cannot be confirmed.
- For some of the characteristics that were reported across trials, like age and sex, there seems to be homogeneity. However, differences between trials were seen regarding the proportion of patients with higher ECOG-PS. Moreover, due to the unavailability of evidence we are unable to draw any conclusions for other characteristics such as prior radiation, PD-L1 expression, metastatic sites, and race.
- In order to perform a NMA, we advise to eliminate heterogeneity in the evidence caused by prognostic risk score. We recommend excluding studies reporting outcomes only for the intermediate-risk population.

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Acknowledgments

- This study was supported by Bristol Myers Squibb.

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