Synthesizing evidence on progression-free 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 (CM-9ER, NCT03141177), 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 only include sunitinib as a comparator. A network meta-analysis (NMA) allows 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 an NMA for progression-free survival (PFS) in the all-risk population receiving nivolumab + cabozantinib treatment for previously untreated aRCC patients.

Methods

- A systematic literature review (SLR) identified all published RCTs in **previously untreated** aRCC.[5] Available evidence was synthesized by evaluating whether the pre-defined relevant interventions formed a network of evidence for PFS 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 Score (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 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).[6]
- The network of evidence was clustered based on seven relevant comparator treatment arms:
  - Atezolizumab+bevacizumab (ATE+BEV)
  - Avelumab+axitinib (AVE+AXI)
  - Bevacizumab+interferon alfa (BEV+IFN)
  - Pazopanib (PAZ)
  - Pembrolizumab+axitinib (PEM+AXI)
  - Tivozanib (TIV)
  - Sunitinib (SUN)

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).[5]

Network Diagram

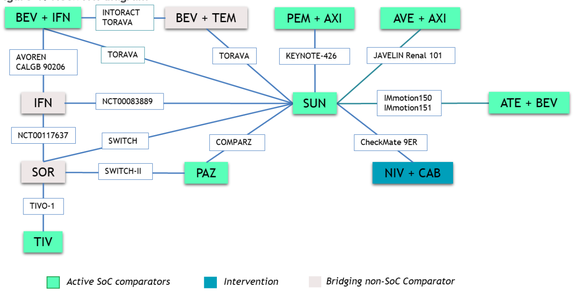
- The all-risk network included 15 studies (Table 1), which were relevant for forming a linked network (Figure 1).

Table 1. Overview of the study characteristics and treatments of the trials included in the all-risk PFS NMA

Trial Name	Treatment	n	Study Phase	Study Design*
CheckMate 9ER[4]	NIV+CAB	323	Phase 3	RCT
	SUN	328		
SWITCH[7]	SOR	182	Phase 3	Treatment sequencing
	SUN	183		
NCT00117637[8]	IFN	92	Phase 2	RCT
	SOR	97		
AVOREN[9]	BEV+IFN	327	Phase 3	RCT
	IFN	322		
IMmotion150[10]	ATE	103	Phase 2	RCT
	ATE+BEV	101		
	SUN	101		
NCT00083889[11,12]	SUN	375	Phase 3	RCT
	IFN	375		
COMPARZ[13,14]	PAZ	557	Phase 3	RCT
	SUN	553		
TIVO-1[15]	TIV	260	Phase 3	Cross-over design
	SOR	257		
JAVELIN Renal 101[16]	AVE+AXI	442	Phase 3	RCT
	SUN	444		
TORAVA[17]	BEV+TEM	88	Phase 2	RCT
	SUN	42		
	BEV+IFN	41		
SWITCH-II[18]	SOR	189	Phase 3	Treatment sequencing
	PAZ	188		
CALGB 90206[19,20]	BEV+IFN	369	Phase 3	RCT
	IFN	363		
INTORACT[21]	BEV+TEM	400	Phase 3	RCT
	BEV+IFN	391		
IMmotion151[22]	ATE+BEV	454	Phase 3	RCT
	SUN	461		
KEYNOTE-426[23]	PEM+AXI	432	Phase 3	RCT
	SUN	429		

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

Figure 1. Network diagram



Heterogeneity Assessment

- Trials that formed the evidence base differed on design and number of patients included; most trials were phase 3 RCTs that included >300 patients per treatment arm.
- Two studies were phase 2 trials and included ~100 or less patients per treatment arm and among the phase 3 studies, two had a treatment sequencing design and one was a cross-over study.
- Heterogeneity was present for several characteristics and was most evident in PD-L1 expression, number of metastatic sites, ECOG-PS, MSKCC/IMDC risk score, prior nephrectomy, and prior radiation therapy.

PD-L1 expression

- PD-L1 expression distribution, cut-off at 1%, was only reported in four trials (Table 2 in appendix). Heterogeneity was present in distribution across trials and the method of measurement differs between trials. IMmotion 150 and KEYNOTE-426 trials had a similar distribution of PD-L1 expression with cut-off 1% (range: 50-61%), which differs from the CheckMate 9ER and the JAVELIN Renal 101 trial (range: 24.7-29.9%). Moreover, the methods of testing and the scoring might have differed between trials.

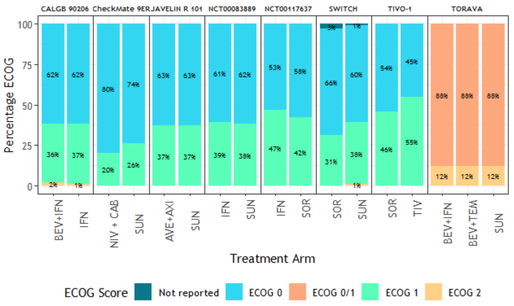
Metastatic sites

- Metastatic site numbers and location data were only reported in five trials (Table 3 and 4 in appendix, respectively). Therefore, it was difficult to determine the heterogeneity of this patient characteristic within the trials included in the all-risk PFS NMA.

ECOG-PS

- ECOG-PS data were reported in eight of the 15 studies. TORAVA trial was the only one not reporting shares of ECOG-PS 0 and 1 together but not separately. It was also the only trial which reported the proportion of patients with ECOG score 2. Over one-third of patients in JAVELIN Renal 101 had an unreported ECOG-PS, which makes it difficult to compare this study with the other trials. The distribution of ECOG-PS in the other trials were comparable (Figure 2).

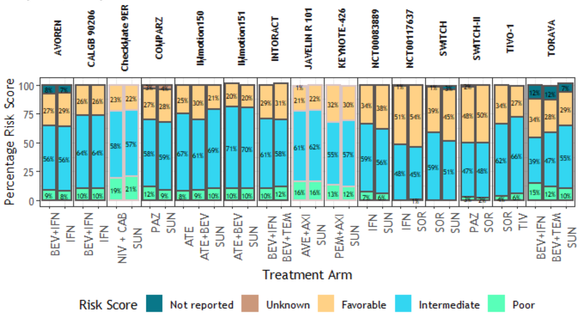
Figure 2. Histogram for the distribution of ECOG in studies included in the network.



MSKCC/IMDC risk score

- MSKCC/IMDC risk score data were reported in all 15 trials (Figure 3). The proportion of favorable, intermediate, and poor risk scores of patients varies 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.

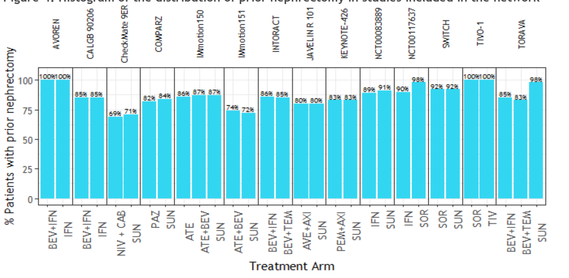
Figure 3. Histogram of the distribution of risk scores in studies included in the network



Prior nephrectomy

- Prior nephrectomy data were reported in 14 out of 15 trials (Figure 4). The figure shows the substantial heterogeneity across trials. The AVOREN and TIVO-1 trials only included patients with a prior nephrectomy (100%). CheckMate 9ER and IMmotion 151 trials had a relatively lower proportion of patients with prior nephrectomy (~70%) compared with other studies.

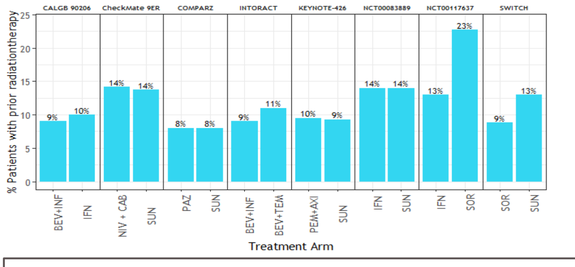
Figure 4. Histogram of the distribution of prior nephrectomy in studies included in the network



Prior use of radiation therapy

- Prior use of radiation therapy data were reported in eight trials (Figure 5). The figure shows that most trials included between 8% to 14% of patients who had used radiation therapy, except for the sorafenib treatment arm in the trial NCT0017637, which had a proportion of 23% of the patients. This percentage also differs from the interferon treatment arm within the same trial.

Figure 5. Histogram of the distribution of prior radiation in studies included in the network



Conclusions

- The current study showed that it is feasible to perform an NMA to compare PFS in previously untreated aRCC. However, 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, prior radiation therapy, PD-L1 expression, and the number of metastatic sites. These imbalances in prognostic risk score across trials may bias NMA results.
- Based on this result, we suggest performing scenario analyses to assess impact on results. For example, omitting the outlier trials with different study designs (SWITCH and TIVO-1 trials due to cross-over design) and/or baseline characteristics (such as NCT00117637 trial). In addition, we suggest to perform a meta-regression to adjust for differences in patients risk score across trials.

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Appendix

Table 2: Distribution of PD-L1 expression for trials in the all-risk PFS network

Trial name	Treatment	n	< 1% cut-off n (%)	≥ 1% cut-off n (%)	Cut-off Not Applicable
CheckMate 9ER[4]	Nivolumab + cabozantinib	323	232 (71.8%)	81 (25.1%)	10(3.1%)
	Sunitinib	328	240 (73.2%)	81 (24.7%)	7(2.1%)
JAVELIN Renal 101[16]	Avelumab + axitinib	442	132 (29.9%)	270 (61.1%)	40(9.0%)
	Sunitinib	444	120 (27.0%)	290 (65.3%)	34(7.0%)
IMmotion150[22*]	Atezolizumab	103	-	54 (52%)	-
	Atezolizumab + bevacizumab	101	-	50 (50%)	-
	Sunitinib	101	-	60 (59%)	-
KEYNOTE-426[23]	Pembrolizumab + axitinib	432	167 (38.7%)	243 (56.3%)	22(5.0%)
	Sunitinib	429	158 (36.8%)	254 (59.2%)	17(4.0%)

*Only ≥ 1% cut-off n (%) data reported

Table 3: Distribution of number of metastatic sites for trials in the all-risk PFS network

Trial name	Treatment	n	1 metastatic site	≥2 metastatic sites	NA %
CheckMate 9ER[4]	Nivolumab + cabozantinib	323	63 (19.5%)	259 (80.5%)	0.3
	Sunitinib	328	69 (21%)	256 (78%)	-
SWITCH[7]	Sorafenib	182	38 (21%)	138 (78%)	-
	Sunitinib	183	51 (29%)	123 (70%)	-
COMPARZ[13,14]	Pazopanib	557	117 (21%)	439 (79%)	1
	Sunitinib	553	108 (20%)	445 (81%)	-
TIVO-1[15]	Tivozanib	260	76 (29%)	184 (71%)	-
	Sorafenib	257	88 (34%)	169 (66%)	-
TORAVA*[17]	Bevacizumab + temsirolimus	88	-	48 (55%)	-
	Sunitinib	42	-	22 (52%)	-
	Bevacizumab + interferon	41	-	20 (49%)	-
KEYNOTE-426[23]	Pembrolizumab + axitinib	432	114 (26.4%)	315 (72.9%)	3
	Sunitinib	429	96 (22.4%)	331 (77.2%)	2

*Only ≥2 metastatic sites data reported

Table 4: Distribution of location of metastatic sites reported for trials in the all-risk PFS network

Trial name	Treatment	n	Lung	Lymph Node	Bone	Liver	Adrenal Gland	Brain
CheckMate 9ER[4]	Nivolumab + cabozantinib	323	n=238 73.7%	n=130 40.2%	n=54 16.7%	n=73 22.6%	n=36 11.1%	-
	Sunitinib	328	n=249 75.9%	n=131 39.9%	n=50 15.2%	n=53 16.2%	n=36 11.0%	-
SWITCH[7]	Sorafenib	182	79%*	48%*	12%*	20%*	-	3.4%*
	Sunitinib	183	72%*	40%*	17%*	24%*	-	2.3%*
COMPARZ[13,14]	Pazopanib	557	n=424 76%	n=223 40%	n=110 20%	n=86 15%	-	-
	Sunitinib	553	n=425 77%	n=247 45%	n=85 15%	n=110 20%	-	-
TIVO-1[15]	Tivozanib	260	82%*	70%*	23%*	26%*	30%*	-
	Sorafenib	257	79%*	65%*	20%*	19%*	22%*	-
IMmotion151[22]	Atezolizumab + bevacizumab	454	75%*	47%*	20%*	17%*	-	-
	Sunitinib	461	71%*	47%*	20%*	18%*	-	-
KEYNOTE-426[23]	Pembrolizumab + axitinib	432	n=312 72.2%	n=199 46.1%	n=103 3.8%	n=66 5.3%	n=67 15.5%	-
	Sunitinib	429	n=309 72.0%	n=197 45.9%	n=103 24.0%	n=71 16.6%	n=76 17.7%	-

*Patients number not reported