Pembrolizumab plus axitinib (P+A) versus other first-line (1L) systemic therapies for advanced/metastatic clear-cell renal cell carcinoma (ccmRCC) – a network meta-analysis (NMA)

Ian McGovern, MPH[1] • Andrew Simon, ScM[1] • Rohan Shirali, MS[1] • Yichen Zhong, MHS[2] • Rodolfo Perini, MD[2] • Maria Lorenzi, MSc[3] • Oluwakayode Adejoro, MD, MPH[2]

1. Precision Xtract, Boston, MA, USA;
2. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA;
3. Precision Xtract, Oakland, CA, USA.

Email: oluwakayode.adejoro@merck.com

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 overall response rate (ORR) in ccmRCC subjects treated with P+A versus (vs) sunitinib.
- 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. [6-8]
- 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 adults with mRCC; and perform NMA to obtain estimates of the comparative efficacy.

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 18 relevant 1L trials were identified (total ITT population: 10,547 participants). **(Figure 1)**
- 18 trials were included in the overall network **(Figure 2).** Connected networks were available for 10 RCTs for OS, 14 RCTs for PFS, and 14 RCTs for ORR **(Table 1).**
- ARCC, CABOSUN, and TemPa included only intermediate risk and poor risk patients, and were therefore excluded from base-case analyses and only considered for inclusion in risk-based subgroup analyses.
- VEG105192 included both first-line and 2L+ treatment among ccmRCC. 1L subgroup data was used in the analyses when available.

Figure 2: 1L Clear-cell network

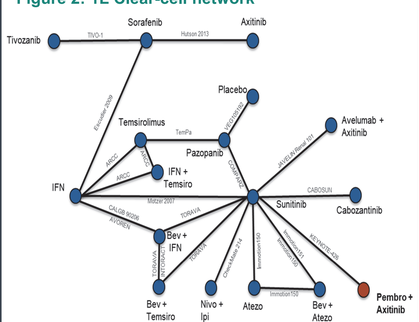
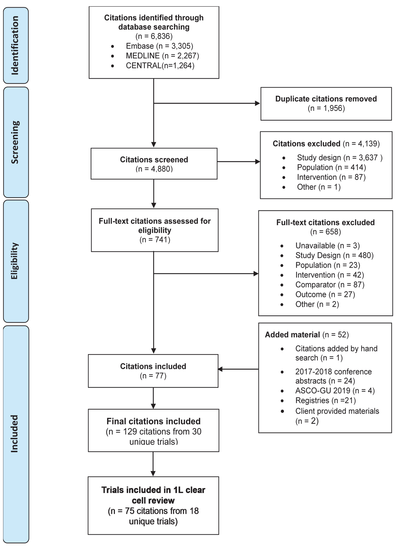


Table 1: 1L clear-cell outcome availability

Trial ID	Intervention	ORR	PFS		OS	
			HR	KM	HR	KM
ARCC[9]	Interferon alfa – Temsirolimus – Interferon alfa + Temsirolimus					
AVOREN[10]	Bevacizumab + Interferon alfa – Placebo + Interferon alfa	Y	Y	Y	Y	Y
CABOSUN[11]	Cabozantinib – Sunitinib					
CALGB 90206[12]	Bevacizumab + Interferon – Interferon	Y	Y	Y	Y	Y
CheckMate 214[13]	Nivolumab + Ipilimumab – Sunitinib	Y	Y	Y	Y	Y
COMPARZ[14]	Pazopanib – Sunitinib	Y	Y	Y	Y	Y
Escudier 2009[15]	Sorafenib – Interferon	Y	Y	Y		
Hutson 2013[16]	Axitinib – Sorafenib	Y	Y	Y		
IMmotion150[17]	Sunitinib – Atezolizumab + Bevacizumab – Atezolizumab	Y	Y	Y		
IMmotion151[18]	Sunitinib – Atezolizumab + Bevacizumab	Y	Y		Y	
INTORACT[19]	Temsirolimus + Bevacizumab – Interferon alpha + Bevacizumab	Y	Y	Y	Y	Y
JAVELIN Renal 101[20]	Avelumab + Axitinib – Sunitinib	Y	Y	Y	Y	Y
KEYNOTE-426[21]	Pembrolizumab + Axitinib – Sunitinib	Y	Y	Y	Y	Y
Motzer 2007[22]	Sunitinib – Interferon alpha	Y	Y	Y	Y	Y
TemPa[23]	Pazopanib – Temsirolimus					
TIVO-1[24]	Tivozanib – Sorafenib		Y	Y		
TORAVA[25]	Bevacizumab + Temsirolimus – Sunitinib – Interferon alfa + Bevacizumab	Y	Y	Y		
VEG105192[26]	Pazopanib – Placebo	Y	Y	Y	Y	

- -, compared with; +, in combination with

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



Baseline participant characteristics

- Age was similar across trials; the median age ranged from 58-64 years. The proportion of female participants ranged from 16.5% to 43.5%.
- ECOG performance status was reported among eight trials, four of which included ECOG 2 participants. Of trials reporting ECOG status, most trials were predominantly comprised of patients with ECOG 0 (range: 41-62%) or 1 (range: 24-59%).
- Among the 11 trials that reported MSKCC risk, the majority of participants were intermediate risk (range: 24-69%).

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 HRs in terms of OS and 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. For the proportion of patients experiencing response, a binomial likelihood and logit link were used and relative effects were expressed as odds ratios (OR).[6]
- Although violations to the proportional hazards' assumption are acknowledged for some interventions; short follow-up and the small sample sizes of the at-risk population near the end of follow-up contributed to large uncertainty and wider CrIs in the time-varying HR analyses results. Thus, constant HR NMA results were considered stable and appropriate.

RESULTS

- For OS, pembrolizumab + axitinib (P+A) had a statistically meaningful benefit over 7 out of 9 interventions evaluated. The estimated HRs for P+A versus avelumab + axitinib (A+A) and nivolumab + ipilimumab (N+I) favored P+A, but were not statistically significant.
- For PFS, P+A had a statistically meaningful benefit over 11 out of 13 comparator interventions evaluated. The results favored P+A over N+I but were not statistically significant, and P+A showed no difference compared to A+A.
- For ORR, P+A had a statistically meaningful benefit over 11 out of 12 comparator interventions evaluated. The results favored A+A over P+A, but were not statistically significant.

Figure 3: HRs estimated from fixed-effects NMA of OS: P+A vs. comparator intervention

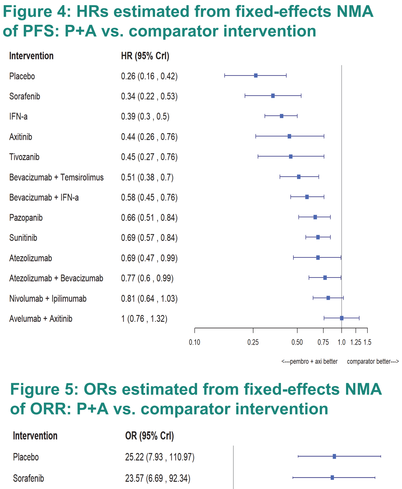


Figure 4: HRs estimated from fixed-effects NMA of PFS: P+A vs. comparator intervention

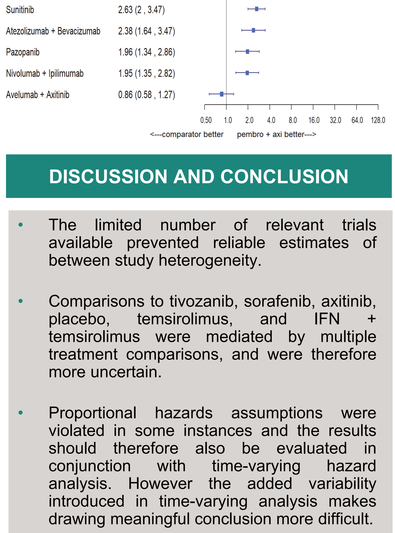
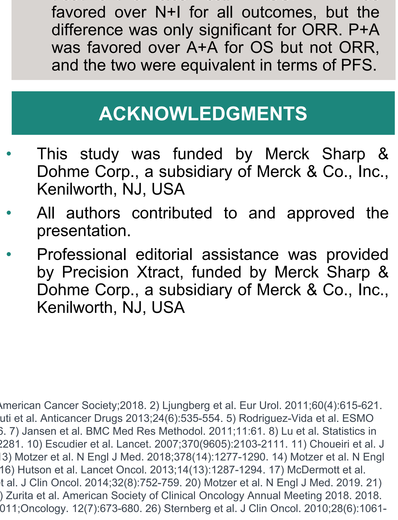


Figure 5: ORs estimated from fixed-effects NMA of ORR: P+A vs. comparator intervention



DISCUSSION AND CONCLUSION

- The limited number of relevant trials available prevented reliable estimates of between study heterogeneity.
- Comparisons to tivozanib, sorafenib, axitinib, placebo, temsirolimus, and IFN + temsirolimus were mediated by multiple treatment comparisons, and were therefore more uncertain.
- Proportional hazards assumptions were violated in some instances and the results should therefore also be evaluated in conjunction with time-varying hazard analysis. However the added variability introduced in time-varying analysis makes drawing meaningful conclusion more difficult.
- In conclusion, this study suggests that treatment with P+A results in significantly improved OS, PFS, and ORR relative to competing systemic therapies for 1L treatment of clear cell mRCC. P+A was favored over N+I for all outcomes, but the difference was only significant for ORR. P+A was favored over A+A for OS but not ORR, and the two were equivalent in terms of PFS.

ACKNOWLEDGMENTS

- This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
- All authors contributed to and approved the presentation.
- Professional editorial assistance was provided by Precision Xtract, funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

REFERENCES: 1) American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society;2018. 2) Ljungberg et al. Eur Urol. 2011;60(4):615-621. 3) Institute NC. SEER Cancer Stat Facts: Kidney and Renal Pelvis Cancer. 2018; 4) Buti et al. Anticancer Drugs 2013;24(6):535-554. 5) Rodriguez-Vida et al. ESMO Open. 2017;2(2):e000185. 6) Dias et al. Medical Decision Making. 2013;33(5):641-656. 7) Jansen et al. BMC Med Res Methodol. 2011;11:61. 8) Lu et al. Statistics in Medicine. 2004;23(20):3105-3124. 9) Hudes et al. N Engl J Med. 2007;356(22):2271-2281. 10) Escudier et al. Lancet. 2007;370(9605):2103-2111. 11) Choueiri et al. J Clin Oncol. 2017;35(6):591-597. 12) Rini et al. J Clin Oncol. 2008;26(33):5422-5428. 13) Motzer et al. N Engl J Med. 2018;378(14):1277-1290. 14) Motzer et al. N Engl J Med. 2013;369(8):722-731. 15) Escudier et al. J Clin Oncol. 2009;27(8):1280-1289. 16) Hutson et al. Lancet Oncol. 2013;14(13):1287-1294. 17) McDermott et al. Nature medicine. 2018;24(6):749-757. 18) NCT02420821. Clinicaltrials.gov. 19) Rini et al. J Clin Oncol. 2014;32(8):752-759. 20) Motzer et al. N Engl J Med. 2019. 21) MSD. Client Provided. 2018. 22) Motzer et al. N Engl J Med. 2007;356(2):115-124. 23) Zurita et al. American Society of Clinical Oncology Annual Meeting 2018. 2018. 24) Motzer et al. J Clin Oncol. 2013;31(30):3791-3799. 25) Negrier et al. The lancet. 2011;Oncology. 12(7):673-680. 26) Sternberg et al. J Clin Oncol. 2010;28(6):1061-1068.

Presented at ISPOR EU 2019; Copenhagen, Denmark; November 2-6, 2019.