Efficacy and safety in previously untreated, advanced/metastatic renal cell carcinoma - A systematic literature review update

PCN14

Kraan CW[1], Nientker KE[1], May JR[2], Malcolm B[2], Ejzykowicz F[3], Kurt M[3], Chun DS[3,4], Branchoux S[5], Ho S[2], Spoorendonk JA[1]

[1]Pharmerit – an OPEN Health Company, Rotterdam, The Netherlands; [2]Bristol Myers Squibb, Uxbridge, UK; [3]Bristol Myers Squibb, Princeton, NJ, USA; [4]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [5]Bristol Myers Squibb, Rueil-Malmaison, France.

Background & Objective

- 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]
- Metastases occur in approximately 30% of cases, which corresponds to a low 5-year survival rate ranging from 0% to 20% in metastatic disease.[2-4]
- Based on the risk factors at prognosis, patients are often categorized as having either favorable risk, intermediate risk, or poor risk in terms of survival, which reflects approximately 20%, 50%, and 30% of the patients, respectively.[5] The Memorial Sloan-Kettering Cancer Center (MSKCC) or International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores are commonly used for risk assessment: they categorize patients into favorable risk (0 risk factors), intermediate risk (1-2 risk factors), or poor risk (3-6 risk factors).[6,7]
- This systematic literature review (SLR) was performed to identify all available efficacy and safety data for patients with previously untreated aRCC.

Methods

- This poster presents an update to an existing SLR.[8] The publication count and results reflect the original and updated searches conducted up and until early 2020 (as presented in abstract) and the updated searches in July 2020.
- Literature was identified via electronic searches in Medline, EMBASE databases and the Cochrane Library.
- In addition, a grey-literature search was carried out to identify unpublished studies through the search of trial registries and conference proceedings as recommended in the National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal.
- Screening was conducted within the population, intervention, comparator, outcomes, and study (PICOS) framework with a set of pre-specified inclusion/exclusion criteria. Studies were assessed for inclusion by two independent reviewers.

Results

Study selection

- A total of 14,027 citations were captured during the original and updated searches.
- A total of 121 relevant publications referring to 57 trials could be included for data extraction according to the PICOS criteria (see Figure 1).

Study design

- Twenty-six trials were phase 3, 25 were phase 2, and two were an early phase 1. All were randomized controlled trials, mostly conducted internationally.
- Blinding varied across trials (12 double-blinded, 1 quadruple-blinded, 1 blinded, 29 open-label, and 14 did not report blinding). Sample sizes of the trials were mostly under 1000 patients.
- A wide range of 1L treatments were identified, including receptor kinase inhibitors, kinase inhibitors, cytokines, and recombinant humanized monoclonal antibodies.
- Five trials reported to have used a cross-over design. Only efficacy endpoints based on 1L treatment from these studies were used in this review.

Patient characteristics at baseline

- Fifty-one trials reported the proportion of males per treatment arm (range, 50% to 90%).
- Fifty trials reported mean (N=3) or median (N=47) age of the study populations, and the median age of the trial populations varied between 49 and 68 years.
- Eighteen trials reported ethnicity. Caucasian patients were the most represented in these studies (range, 69% to 100%). The second-most prominent ethnic group in the included trials were Asian patients (range, 1% to 25%).
- Most publications reported Eastern Cooperative Oncology Group (ECOG) (N=32), or MSKCC (N=34), or IMDC (N=6) prognostic scores at baseline for severity assessment. Patients with favorable, intermediate, and poor MSKCC prognosis at baseline were consistently reported across most of the included publications. Only six trials reported IMDC scores at baseline.

Authorized or recommended treatments

- To narrow down the results (57 trials), the remainder of the results section focuses on treatments that have received marketing authorization by FDA and EMA, as well as treatments that will be available in the upcoming years (9 trials).[8-17]
- Table 1 shows the treatments that are approved or recommended for the treatment of 1L RCC based on National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines published in 2019 and 2020, respectively.[1,18,19]
- Figure 2 shows the frequency of approved or recommend treatments for 1L RCC that are identified in this SLR.

Figure 1. PRISMA diagram

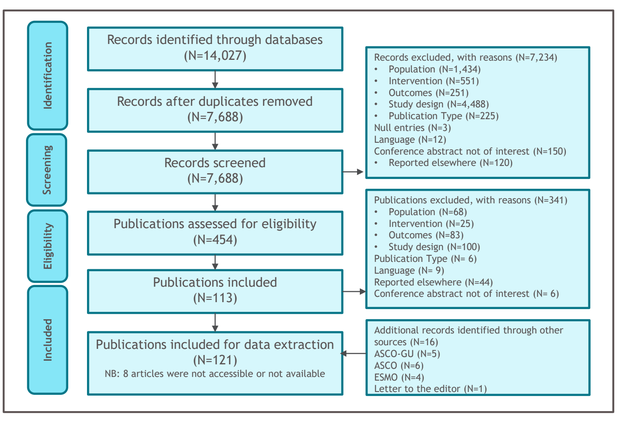
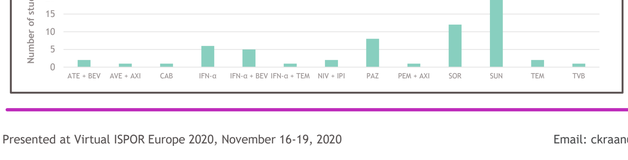


Table 1. Overview of authorized or recommended treatments

Authorized or recommended treatments	
— Cabozantinib (CAB)	— Avelumab + axitinib (AVE + AXI)
— Sunitinib (SUN)	— Pembrolizumab + axitinib (PEM + AXI)
— Bevacizumab + interferon-α (BEV + IFN-α)	— Sorafenib (SOR)
— Nivolumab + ipilimumab (NIV + IPI)	— Tivozanib (TVB)
— Pazopanib (PAZ)	— Temsirolimus (TEM)
— Atezolizumab + bevacizumab (ATE + BEV)	

Figure 2. Frequency of trials investigating authorized or recommended treatments



Results (Continued)

Efficacy outcomes

- Most frequently reported efficacy outcomes for patients not stratified according to MSKCC/IMDC risk status were median OS (mOS), median PFS (mPFS), and objective response rate (ORR). Table 2 shows the efficacy outcomes for all 57 trials, and for treatments that have received marketing authorization as well as treatments that will be available in the market in the upcoming years.
- The mOS, mPFS, and ORR for the recently authorized and/or recommended treatments in 1L aRCC are reported in Figure 3.
- The mOS and mPFS outcomes stratified by MSKCC/IMDC risk status, where reported, are presented in Figure 4 and Figure 5.
- Novel immuno-oncology (IO) therapies under investigation, such as nivolumab + ipilimumab and others (e.g. pembrolizumab + axitinib, or avelumab + axitinib), have shown promising results in all risk status aRCC patients with long follow-up and mOS yet to be reached.

Table 2. Efficacy outcomes

	All trials (N=57)	Trials investigating authorized or recommended treatments (N=9)
mPFS	1.9 – 17.3 months	4.7 – 17.1 months
mOS	7.1 – 42.7 months	18.3 – 37.9 months
ORR	0 – 60.2 %	8.1 – 60.2 %

Figure 3. mPFS, mOS, and ORR for authorized or recommended treatments for 1L RCC

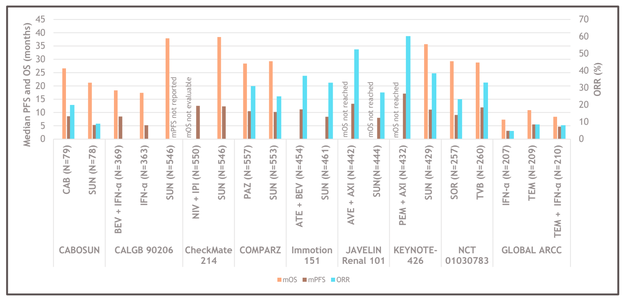


Figure 4. mOS for authorized or recommended treatments for 1L RCC, stratified by MSKCC or IMDC risk status

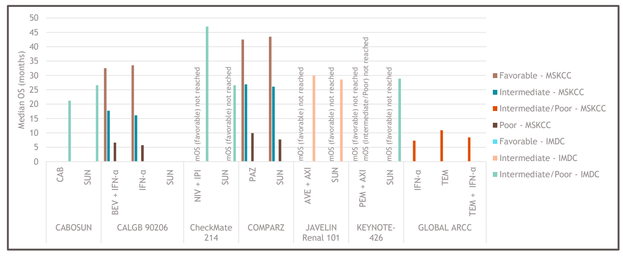
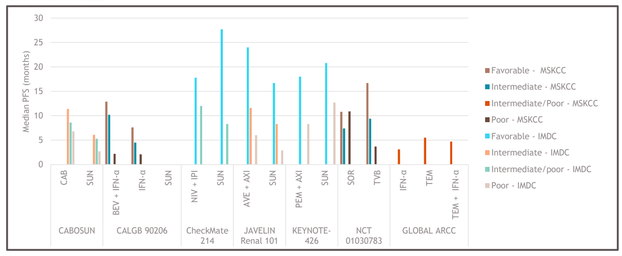


Figure 5. mPFS for authorized or recommended treatments for 1L RCC, stratified by MSKCC or IMDC risk status



Safety outcomes

- Both all cause AEs and treatment-related AEs were considered for evaluating the safety for the treatments of interest.
- Twenty-seven trials reported the proportion of patients experiencing at least one AE during the course of the trial, ranging between 48% and 100%.
- Patients experiencing grade ≥3 AEs were reported in 39 trials, ranging between 4% and 88%.
- The most commonly reported AEs across the included trials were diarrhea (3%-88%), fatigue (8%-93%), and hypertension (0%-81%).

Conclusions

- This SLR provides a comprehensive and thorough review of clinical trials evaluating the efficacy and safety of 1L treatments for aRCC.
- The SLR reported a wide variety of treatments evaluated for efficacy and safety in 1L aRCC. Overall, a wide range of values for efficacy outcomes were seen across trials and treatments assessed. Efficacy outcomes are related to the severity of the disease of the patients that are included in the trial. Therefore, the heterogeneity between trials (e.g. patient and study characteristics) makes it difficult to naïvely compare these studies.
- Efficacy results of newly introduced treatments seem to be more consistent when assessed by prognostic risk groups.
- This updated SLR highlights that there is still a considerable unmet need for improved survival in aRCC patients, with novel IO therapies showing assuring results. The results are consistent with the earlier review presented in 2018.

References

1. Escudier, B. et al. *Ann Oncol* 2019;30
2. Kalra, S. et al. *BJU International* 2016;117
3. Mekhail, T.M. et al. *J Clin Oncol* 2005;23
4. Ballarin, R. et al. *World journal of gastroenterology* 2011;17
5. Heng, D. Y. et al. *The* Lancet 2013;14
6. Motzer, R. J. et al. *J Clin Oncol* 1999;17
7. Ko, J. J. et al. *The Lancet. Oncology* 2015;16
8. Motzer, R. J. et al. *N Engl J Med* 2013;369
9. Tannir, N. M. et al. *J Clin Oncol* 2020;38
10. Choueiri, T. K. et al. *Eur J Cancer* 2018;94
11. Rini, B. I. et al. *J Clin Oncol* 2008;26
12. Rini, B. I. et al. *J Clin Oncol* 2010;28
13. Rini, B. I. et al. *Lancet* 2019;393
14. Choueiri, T. K. et al. *Ann Oncol* 2020;31
15. Plimack, E. R. et al. *J Clin Oncol* 2020;38
16. Motzer, R. J. et al. *J Clin Oncol* 2013;31
17. Hudes, G. et al. *N Engl J Med* 2007;356
18. Jonasch E. *J Natl Compr Canc Netw* 2019;17
19. ESMO Guidelines Committee *eUpdate ESMO* 2020

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Email: ckraan@pharmerit.com