Real-world effectiveness in previously untreated advanced/metastatic renal cell carcinoma - a systematic literature review update

PCN37

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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]
- Before the recent introduction of immuno-oncology (IO) therapies, metastases occurred in approximately 30% of cases, which corresponds to a 5-year survival rate ranging from 0% to 20% for patients with 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 conducted to identify, and review published real-world evidence (RWE) studies to evaluate the treatment effectiveness of first-line (1L) treatments in aRCC patients.
- The results of this SLR can be used to, for example, benchmark survival data from RCTs or survival data extrapolation for economic modelling.

Methods

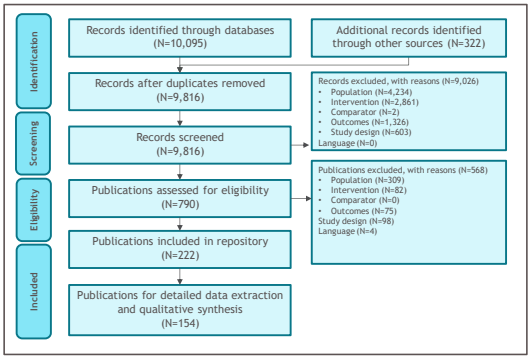
- This is an update to an existing SLR.[8] The publication count and results presented in this poster, reflect the original searches and update searches conducted in early 2020 (as presented in submitted abstract) and updated searches in August 2020.
- Searches in MEDLINE, MEDLINE-IN-PROCESS, Embase, and the ClinicalTrials.gov registry were carried out by two independent reviewers according to the Cochrane guidelines for systematic review of interventions.[9]
- Additionally, conference proceedings and websites of the American Society of Clinical Oncology (ASCO), ASCO-Genitourinary, National Comprehensive Cancer Network, European Society for Medical Oncology, European Conference for Clinical Oncology, and National Cancer Institute were hand searched.
- Search syntax were developed using a combination of MeSH/EMTREE terms and free-text terms related to aRCC, treatment response, survival outcomes, quality of life, and RWE clinical study design.
- For qualitative synthesis, additional selection criteria were applied, namely narrower population criteria (patients with clear-cell histology) and the primary objective of the study (to assess OS and/or progression-free survival (PFS)).

Results

Study selection

- In total, 222 publications were identified through the initial SLR[7] and the updated SLR (search up to August 7, 2020) (**Figure 1**).
- In total, 154 publications met the narrower inclusion criteria for qualitative synthesis (**Figure 1**). For these publications, the study design, patient characteristics, interventions, and ranges of median OS (mOS) and median PFS (mPFS) are described in this poster.

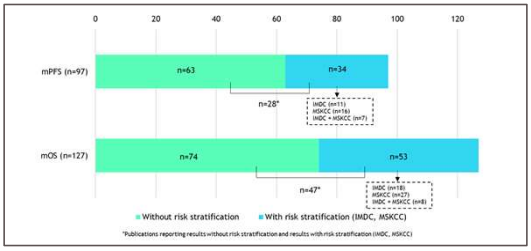
Figure 1. PRISMA diagram



Study design

- Studies were conducted in a prospective (n=26), prospective & retrospective (n=2), or retrospective (n=126) setting and were carried out in several countries, most frequently (with >10 publications) in the US (n=22), Japan (n=20), Italy (n=14), and Germany (n=11).
- In total, 143 publications reported mPFS (n=16), mOS (n=46), or both mPFS and mOS (n=81), with or without risk stratification (**Figure 2**). In total, 97 publications reported mPFS (only mPFS [n=16] or both mPFS and mOS [n = 81]), and 127 publications reported mOS (only mOS [n=46] or both mPFS and mOS [n=81]).

Figure 2. Number of publications reporting mPFS and/or mOS by risk stratification



Patient characteristics at baseline

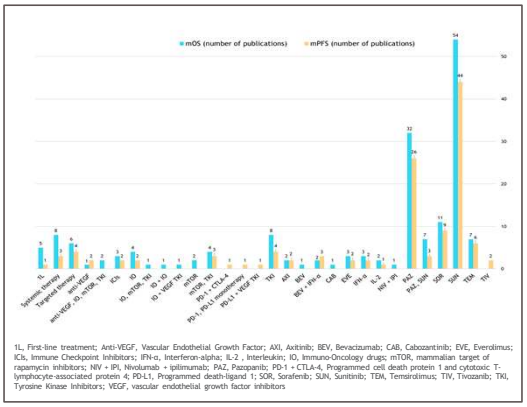
- Median age ranged from 50 to 78 years, whereas the proportion of males ranged from 37.5% to 90.7%, and one study[8] included only male patients. The studies used ECOG PS (n=58), MSKCC (n=54), or IMDC (n=51) prognostic scores, or a combination (n=18), to assess disease severity at baseline.

Investigated treatments

- 1L treatment with sunitinib or pazopanib were the most investigated (>25 publications), whereas immuno-oncology (IO) therapies and immune-checkpoint inhibitors (ICIs) have become available more recently and as such are investigated less frequent (**Figure 3**).
- Additionally, many publications reported mOS and mPFS by type of therapy (e.g. targeted therapy, systemic therapy), drug class (e.g. IO, mTOR, TKI), or by study population treated with various drug classes (e.g. anti-VEGF, IO, mTOR, or TKI), rather than by a specific drug (e.g. sunitinib).

Results (Continued)

Figure 3. Frequency of investigated Tx among publications reporting mOS and mPFS



1L, First-line treatment; Anti-VEGF, Vascular Endothelial Growth Factor; AXI, Axitinib; BEV, Bevacizumab; CAB, Cabozantinib; EVE, Everolimus; ICIs, Immune Checkpoint Inhibitors; IFN-α, Interferon-alpha; IL-2 , Interleukin; IO, Immuno-Oncology drugs; mTOR, mammalian target of rapamycin inhibitors; NIV + IPI, Nivolumab + ipilimumab; PAZ, Pazopanib; PD-1 + CTLA-4, Programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4; PD-L1, Programmed death-ligand 1; SOR, Sorafenib; SUN, Sunitinib; TEM, Temsirolimus; TIV, Tivozanib; TKI, Tyrosine Kinase Inhibitors; VEGF, vascular endothelial growth factor inhibitors

mOS and mPFS outcomes

- Lowest mOS (1.1 months) was observed in patients with very rare sarcomatoid RCC and treated with sunitinib or pazopanib,[11] whereas lowest mPFS for patients that were not stratified according to risk status was 3.4 months (temsirolimus treatment).[12] Highest mOS and mPFS were 79.1 and 39.7 months, respectively. However, these results were from a retrospective, registry-based study included aRCC patients that were continuously treated for at least 24 months with anti-VEGF therapy.[13]
- A clear trend was observed between mOS and mPFS versus risk status of aRCC patients; maximum OS and PFS decreased while patients' risk status increased (Figure 4).
- In some studies, for example a study that investigated patients treated with nivolumab in combination with ipilimumab, mOS was not yet reached.[14]

Survival in patients with favorable-risk status

- The highest mOS (133 months) was reported for aRCC patients with a favorable risk treated with IFN-α, this group of patients had a very low sample size (n=15).[15] The second longest mOS in patients with a favourable risk was substantially shorter with 97.1 months (sunitinib, n=73).[16] The lowest mOS (12 months) was reported in patients that received therapy with interleukin-2 or interferon-α, without targeted therapy.[17] mPFS ranged from 2.9 months to 39.6 months in patients treated with IFN-α and targeted therapy (sunitinib, sorafenib or pazopanib), respectively.[18,19]

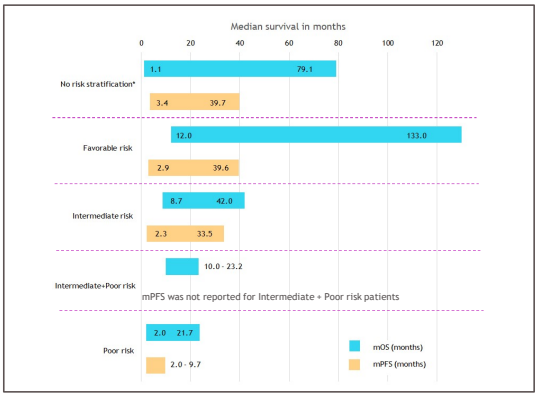
Survival in patients with intermediate-risk status

- In intermediate risk status patients, mOS ranged from 8.7 to 42 months in patients treated with IFN or TKI (one of the following; sunitinib, pazopanib or sorafenib).[20,21] For mPFS, observed ranges were 2.3 to 33.5 months when treated with everolimus or sunitinib, respectively.[12,16]

Survival in patients with poor-risk status

- In patients with poor risk status, mOS ranged from 2 months in patients treated with sorafenib with 95% of patients having ≥3 metastases to 21.7 months when treated with systemic therapy consisting of one of the following; sunitinib, sorafenib, axitinib, and pazopanib, everolimus, temsirolimus or cytokines.[22,23] mPFS ranged from 2.0 to 9.7 months in patients treated with sorafenib or sunitinib.[22,21]

Figure 4. Observed ranges in mOS and mPFS



- Reported ranges in mOS and mPFS must be read with caution, due to heterogeneity among studies with regard to patient characteristics, study design, study quality, and studied treatments but consistently show that patients with more risk factors have a poorer prognosis.

Conclusions

- There is still a considerable unmet need for improved survival in patients with aRCC in the real-world setting, especially in patients with poor prognosis, according to this SLR update assessing recent real-world effectiveness data.
- Currently, there are only a few RWE studies available that evaluate newer treatments and combinations thereof. In these studies there is little follow-up, hence, it would be worthwhile to re-evaluate once more mature data becomes available for these treatments.

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