Peer Review File

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Reviewer #1

This is a meta-analysis of the available randomized trials for adjuvant TKI in renal cell carcinoma. Five RCTs were included, with two trials (SORCE and ASSURE) stratified by unique treatment arms, for a total of seven cohorts analyzed separately in the analysis. The result was that neither OS or DFS were statistically improved with adjuvant TKI, though the DFS 95%CI was nearly significant (HR 0.93, 95CI 0.87-1.02).

Overall Impressions and Major Concerns:

Comment 1:

- This is a methodologically valid meta-analysis on an important topic.
- The outcome highlights that though there may be a small signal in DFS improvement, it does not appear that there will ever be an OS improvement for this treatment strategy, calling into question the use of DFS as a surrogate endpoint in this setting.
- There is a glut of meta-analyses on this exact topic to be found in the literature, though this appears to be the only one including the SORCE trial data.
- It is unclear how much the addition of the SORCE data adds to the most up-to-date meta-analysis (cited below), as sorafenib has largely been abandoned as first-line therapy for any setting in RCC.

Reply:

Thank you for pointing this out and thank you for your positive feedback regarding the methodology of our work.

The choice of including the SORCE trial has been oriented by the identification and inclusion of all clinical trials evaluating tyrosine kinase inhibitors in the adjuvant setting of renal cell carcinoma. Although we are aware that sorafenib is less and less used in the metastatic setting of renal cell carcinoma – especially if we look at recently published and presented data of the CheckMate 9ER, the CheckMate 214, the KEYNOTE-426, and other trials evaluating immune-based combinations, there is no doubt that sorafenib played a – historical - part in medical treatment of renal cell carcinoma (Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356(2): 125–134) (Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, Heng DY, Larkin J, Ficarra V. Renal cell carcinoma. Nat Rev Dis Primers. 2017 Mar 9;3:17009.)

Minor Concerns:

Comment 2: Title, and various points throughout the manuscript: it would be more accurate to call these drugs tyrosine kinase inhibitors, and not VEGF or angiogenesis inhibitors.

Reply:

Thank you for this comment. We acknowledge that the term “tyrosine kinase inhibitors” might be more accurate. However, we would kindly ask to maintain the original title since agents such as sorafenib, sunitinib, etc inhibit angiogenesis (for example, 1) sorafenib is a protein kinase inhibitor with activity against VEGFR, PDGFR, RAF kinases, etc; 2) sunitinib inhibits cellular signaling by

targeting PDGF-R, VEGFRs, c-KIT, RET, etc; 3) pazopanib targets angiogenesis via inhibition of VEGFR, PDGFR, c-KIT and FGFR; etc).

However, as regards the body of the manuscript, we modified according to your suggestions, as you could find in the Revised Manuscript (green)

Comment 3: Please elaborate more in the background section. A reader who is unfamiliar with this topic will not be informed by this version.
Reply:
Thank you for this comment. We expanded this section, in order to include more details regarding the setting of our study. In particular, we added the following part (red):

Renal cell carcinoma (RCC) represents the most commonly diagnosed kidney cancer worldwide, comprising the 4% of all solid tumours (1, 2). Radical surgical resection is the standard of care for patients with localized disease, and although the 70% of all RCC cases are diagnosed with early-stage or locally advanced disease, approximately the 20-40% of patients progress toward metastatic disease following radical surgery (3, 4). Recent years have witnessed remarkable changes in the therapeutic landscape of RCC, with the advent of several targeted agents and immune checkpoint inhibitors (ICIs), as single-agents or as part of immune-based combinations in the metastatic setting (5-8). Conversely, adjuvant treatment in renal cell carcinoma is still a problematic issue despite several adjuvant therapies have been tested in an attempt to improve clinical outcomes for RCC patients (9). Indeed, none of the compounds evaluated in this field have shown a convincing clinical benefit justifying an inclusion in clinical practice (10).

In addition, we added the following ten references, related to recent studies, only for a matter of consistency. We believe this could be helpful to introduce the topic.
In particular, we added the following (orange):

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69:7–34.
2. Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017; 3:17709
3. Capitanio U, Montorsi F. Renal cancer. Lancet. 2016; 387(10021):894-906.
4. Williamson SR, Taneja K, Cheng L. Renal cell carcinoma staging: pitfalls, challenges, and updates. Histopathology. 2019; 74(1):18–30.
5. Santoni M, Massari F, Di Nunno V, et al. Immunotherapy in renal cell carcinoma: latest evidence and clinical implications. Drugs Context. 2018 Jun 5;7:212528.
6. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal- cell carcinoma. N Engl J Med. 2017; 376:354–366.
7. Calvo E, Porta C, Grunwald V, Escudier B. The current and evolving landscape of first-line treatments for advanced renal cell carcinoma. Oncologist. 2019; 24(3):338–348.
8. Massari F, Mollica V, Rizzo A, Cosmai L, Rizzo M, Porta C. Safety evaluation of immune-based combinations in patients with advanced renal cell carcinoma: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020 Aug 16.

9. Meissner MA, McCormick BZ, Karam JA, Wood CG. Adjuvant therapy for advanced renal cell carcinoma. Expert Rev Anticancer Ther. 2018 Jul;18(7):663-671.
10. Wood E, Donin N, Shuch B. Adjuvant Therapy for Localized High-Risk Renal Cell Carcinoma. Urol Clin North Am. 2020 Aug;47(3):345-358.

Comment 4: In the methods section, please include a justification for stratifying the SORCE and ASSURE treatment arms to be analyzed separately in the meta-analysis.
Reply:
Thank you for this comment.

We added the following part, in order to better describe this methodology (purple):
Of the eligible studies, two trials contained three arms (two experimental arms and one control arm); for clearer presentation and for data analysis, we split the SORCE and the ASSURE trials as follows: ASSURE sorafenib; ASSURE sunitinib; SORCE 1 year; SORCE 3 years).

Comment 5: There are significant differences in the risk-status of included patients between studies, which should be remarked on in the discussion. Notably, patients in the STRAC trial were the highest risk, and demonstrated the highest DFS benefit. This may be a coincidence, but on the surface it implies that the other trials may not have had high enough risk cohorts to have a positive result for this endpoint.
Reply:
Thank you for pointing this out. And we are aware this is an important issue in interpreting the results of trials regarding the adjuvant setting.

In fact, S-TRAC suggested significant difference in DFS in favor of sunitinib. However, important differences in enrolled subjects exist among distinct trials.

In particular, we added the following parts (blue):

In fact, a mandatory aspect of adjuvant therapy is certainly to select patients who are at increased risk of disease recurrence and to spare low-risk RCC patients from toxicity of adjuvant therapies. (…)

Moreover, the included studies presented important differences in terms of patient populations (4); in fact, the S-TRAC trial enrolled a higher-risk population and the study protocol had important restriction on histologic subtypes compared with ASSURE, something that could have played an important role in the highest DFS benefit observed in S-TRAC (9, 10). More specifically, one-third of patients of the ASSURE trial had low-risk tumors – pT1 and pT2 – and the ATLAS and the PROTECT studies included an important proportion of these patients (11% and 14%, respectively). Conversely, the S-TRAC only enrolled patients affected by high risk tumors (≥pT3). This issue raises an extremely important question in this setting: the DFS improvement in this trial – as previously stated – could be related to the enrollment of patients that were at higher risk of recurrence.

Comment 6: Recommend including AE data in the summary table, as these drugs have high toxicity and this is a significant concern for clinicians in their decision to pursue adjuvant targeted therapy.

Riaz IB, Faridi W, Husnain M, et al. Adjuvant Therapy in High-Risk Renal Cell Cancer: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2019;94(8):1524-1534.

Reply:
Thank you for this suggestion. We added a column in Supplementary Table 1, including the most frequently observed adverse events grade 3 or more (in red).

With regard to the ATLAS trial, since the Supplementary Appendix did not include the proportion of the single adverse event grade 3 or more, we included the overall percentage.

Reviewer #2
Comment 1: There is no additional information regarding the published manuscript from 2019, see reference 1.
Reply:
Thank you for pointing this out.
We expanded this section, as required also by Reviewer 1, in order to include more details regarding the setting of our study.

In particular, we added the following part (red):

Renal cell carcinoma (RCC) represents the most commonly diagnosed kidney cancer worldwide, comprising the 4% of all solid tumours (1, 2). Radical surgical resection is the standard of care for patients with localized disease, and although the 70% of all RCC cases are diagnosed with early-stage or locally advanced disease, approximately the 20-40% of patients progress toward metastatic disease following radical surgery (3, 4). Recent years have witnessed remarkable changes in the therapeutic landscape of RCC, with the advent of several targeted agents and immune checkpoint inhibitors (ICIs), as single-agents or as part of immune-based combinations in the metastatic setting (5-8). Conversely, adjuvant treatment in renal cell carcinoma is still a problematic issue despite several adjuvant therapies have been tested in an attempt to improve clinical outcomes for RCC patients (9). Indeed, none of the compounds evaluated in this field have shown a convincing clinical benefit justifying an inclusion in clinical practice (10).

In addition, we added the following ten references, related to recent studies, only for a matter of consistency. We believe this could be helpful to introduce the topic.
In particular, we added the following (orange):

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69:7–34.
2. Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017; 3:17709

3. Capitanio U, Montorsi F. Renal cancer. Lancet. 2016; 387(10021):894-906.
4. Williamson SR, Taneja K, Cheng L. Renal cell carcinoma staging: pitfalls, challenges, and updates. Histopathology. 2019; 74(1):18–30.
5. Santoni M, Massari F, Di Nunno V, et al. Immunotherapy in renal cell carcinoma: latest evidence and clinical implications. Drugs Context. 2018 Jun 5;7:212528.
6. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal- cell carcinoma. N Engl J Med. 2017; 376:354–366.
7. Calvo E, Porta C, Grunwald V, Escudier B. The current and evolving landscape of first-line treatments for advanced renal cell carcinoma. Oncologist. 2019; 24(3):338–348.
8. Massari F, Mollica V, Rizzo A, Cosmai L, Rizzo M, Porta C. Safety evaluation of immune-based combinations in patients with advanced renal cell carcinoma: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020 Aug 16.
9. Meissner MA, McCormick BZ, Karam JA, Wood CG. Adjuvant therapy for advanced renal cell carcinoma. Expert Rev Anticancer Ther. 2018 Jul;18(7):663-671.
10. Wood E, Donin N, Shuch B. Adjuvant Therapy for Localized High-Risk Renal Cell Carcinoma. Urol Clin North Am. 2020 Aug;47(3):345-358.

Comment 2: Methods: You identified 6 + 1 studies for evaluation but included are only 5 trials. why do you excluded 2 without comment to these?
Reply:
Thank you for this comment.

In effect, our analysis was focused on 5 trials: ASSURE, S-TRAC, PROTECT, ATLAS, SORCE. Of note, since SORCE and ASSURE had three arms (two experimental arms and one control arm), we decided to split these two trials as follows: ASSURE sorafenib, ASSURE sunitinib, SORCE 1 year and SORCE 3 years.

We included the following part (purple), in order to better explain the rationale of our choice:

Of the eligible studies, two trials contained three arms (two experimental arms and one control arm); for clearer presentation and for data analysis, we split the SORCE and the ASSURE trials as follows: ASSURE sorafenib; ASSURE sunitinib; SORCE 1 year; SORCE 3 years).

Comment 3: Results: very short, no explaining
Reply:
Thank you for this comment.

We expanded this section, adding some methodological details (level of heterogeneity and the type of model – fixed or random) and the number of studies reporting results about the two outcomes of interest: disease-free survival and overall survival.

In particular, we modified as follows (brown):

Six trials provided OS data on patients receiving tyrosine kinase inhibitors as adjuvant treatment versus placebo. According to the results of our analysis, a pooled OS-Hazard Ratio (HR) of 0.98 was observed (95% CI 0.88-1.09, I^2=0%, p=0.54) (Figure 2). The results showed low heterogeneity; therefore, a fixed effects model was used.
Seven trials provided DSF results regarding RCC patients treated with experimental treatment versus placebo; a pooled DFS-HR of 0.93 was obtained (95% CI 0.84-1.02, I^2= 35%, p=0.16) (Figure 3). Low heterogeneity was observed in this analysis, and thus, a fixed effects model as used.

Comment 4: Discussion: the comparison of other agents or other malignancies is missing. the thesis of the manuscript is not be answered in this discussion or conclusion. I think it is too early to ask about right strategy if it there is no comparing trial/ agent available at the moment.
Reply:
Dear Reviewer,

Thank you for these comments. We extensively modified the paper according to your suggestions, discussing the results of this meta-analysis , modifying large sections of the Discussion, and adding specific details regarding the patient populations included (blue), as follows:

As known, several studies assessing the combination between PD-1/PD-L1 inhibitor and a target agent have been published (7, 8). In metastatic setting, the CheckMate214, the KEYNOTE-426 and the JAVELIN Renal 101 have shown important clinical benefits compared to sunitinib alone, shaping the – novel - outlook of first-line setting. In addition, new data presented at ESMO 2020 have recently suggested that another immune-based combination, nivolumab plus cabozantinib, could represent a new front-line treatment option for patients with metastatic RCC. In fact, the Checkmate 9ER has provided interesting results regarding this combination, which has been shown to be superior to sunitinib in terms of PFS, OS and response rate. These findings add to mounting evidence reporting the advantages of combination therapies over monotherapy as first-line treatment in metastatic RCC.

Interestingly, despite an effective role of antiangiogenic drugs in metastatic disease (as monotherapy or in combination with other anticancer agents) (…)

In fact, a mandatory aspect of adjuvant therapy is certainly to select patients who are at increased risk of disease recurrence and to spare low-risk RCC patients from toxicity of adjuvant therapies. (…)

Moreover, the included studies presented important differences in terms of patient populations (4); in fact, the S-TRAC trial enrolled a higher-risk population and the study protocol had important restriction on histologic subtypes compared with ASSURE, something that could have played an important role in the highest DFS benefit observed in S-TRAC (9, 10). More specifically, one-third of patients of the ASSURE trial had low-risk tumors – pT1 and pT2 – and the ATLAS and the PROTECT studies included an important proportion of these patients (11% and 14%, respectively). Conversely, the S-TRAC only enrolled patients affected by high risk tumors (≥pT3). This issue raises an extremely important question in this setting: the DFS improvement in this trial – as

previously stated – could be related to the enrollment of patients that were at higher risk of recurrence.