



Verona, December 6th 2013

To the Editor-in-Chief of
World Journal of Clinical Urology

Dear Editor,

Enclosed please find a thoroughly revised version of the manuscript entitled "**Targeting**" renal cell carcinoma patients with "targeted" agents: are we there yet?" that we wish to resubmit for publication in *World Journal of Clinical Urology* (file name:WJCU-6693-review.doc).

Authors: Francesca Maines, Sara Pilotto, Michele Milella, Francesco Massari, Vanja Vaccaro, Alessandra Felici, Giampaolo Tortora, Emilio Bria.

ESPS Manuscript NO: **6693**

We would like to thank the reviewers for their thoughtful and stimulating comments that have prompted us to revise the manuscript accordingly.

We thus hope that the quality of the manuscript has now substantially improved according to the suggestions of reviewers.

A point-by-point rebuttal description of the performed revisions follows herein:

Reviewer 00531495:

- As correctly suggested by the reviewer, we added a table [Table 1] to summarize the results about evaluation of biomarkers for targeted therapies in mRCC. To improve clarity and clinical relevance of reported data, we focused mainly on molecular or biological factors evaluated in phase III and/or pivotal trials of targeted agents. We reported clinical outcomes (PFS and/or OS, if available) according both to single biomarker both to every target therapy.

Reviewer 00469307:

- Accordingly to reviewer's comment, we updated "Materials and Methods" section reporting search strategy and date of search. Moreover, we added to the manuscript a PRISMA diagram to show selection process of the included studies [Figure 1].
- At the end of the results section we reported the sentence "...Although biomarkers evaluation has been performed in patients enrolled in phase II, phase III or even pivotal clinical trials of targeted therapies in mRCC, the obtained data are mostly the result of secondary endpoints or retrospective evaluations. Moreover, the studies were not usually neither designed nor powered to show significant difference in molecular or biological factors and the tissue sample collection was in most cases desirable but not mandatory. Moreover, external validation of biomarkers results usually lacked, affecting accordingly accuracy and reproducibility of the data. Considering all these limits and consequently, the high attrition bias, the strength of the results and consequently the levels of evidence are doubtless low, suggesting that to date, biomarkers evaluation cannot be applied in clinical decision making" to explain why levels of evidence of a biomarkers-based approach are today low, affecting therefore both clinical relevance both applicability of biomarkers in daily therapeutic choices. To date, there are not recommendations uniformly supported by guidelines to use biomarkers in RCC treatment.



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Reviewer 00503202:

- No revisions were required.

Moreover, format has been updated and references and typesetting were corrected.

We hope that the changes made to the original manuscript address the main points raised by referees and that the revised manuscript will now be acceptable for publication.

Sincerely yours,

Francesca Maines on behalf of all authors