available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Maxine Sun, Lorenzo Marconi, Tim Eisen, et al. Adjuvant Vascular Endothelial Growth Factor–targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis. Eur Urol 2018;74:611–20

Systematic Review Findings on the Role of Adjuvant Vascular Endothelial Growth Factor–targeted Therapy in Renal Cell Carcinoma

We applaud Sun and colleagues [1] for the publication of the first systematic review and meta-analysis on the adjuvant role of VEGF-targeted therapy in renal cell carcinoma. Although only three randomized controlled trials on this topic exist, this pooled analysis is helpful in understanding both their differences and overall implications.

The main conclusion of the review is that these agents probably do not improve overall or disease-free survival, but come at the expense of very substantially increased grade 3 and 4 adverse events, a finding with which we agree. Meanwhile, we would like to argue that the value of this review would have been further enhanced by inclusion of a summary of the findings in a table that includes a GRADE certainty-of-evidence rating as well as absolute effect size estimates (Table 1). Whereas we have high confidence that overall survival is not improved, we would argue that we can only be moderately certain that disease-free survival is not improved, given that the pooled absolute effect size at 3-yr follow-up of 23 fewer events per 1000 patients has a confidence interval (CI) that ranges from nine more to 54 fewer, thereby reflecting important imprecision. For the outcome of grade 3 and 4 adverse events, this presentation helps to illustrate the dramatic magnitude of the undesirable effects of 425 more per 1000 (95% CI 342–518 more).

We would like to encourage these and other systematic review authors to routinely apply not only the high methodological standards reflected in the recently updated AMSTAR instrument, which includes an a priori written protocol (which this review does not reference), but also GRADE [2]. Use of a common transparent methodological framework for rating the certainty of the estimates of effect in high-quality systematic reviews as pioneered by Cochrane and the European Association of Urology would go a long way towards conserving valuable health care resources and enhancing collaboration among societies [3,4].

Table 1 – Summary of findings for adjuvant VEGFR-TT compared to placebo for localized RCC

Outcome	Participants (studies)	Certainty of the evidence (GRADE)[a]	Relative effect (95% CI)	Anticipated absolute effect[b]	
				Risk with placebo	Risk difference with adjuvant VEGFR-TT
Time to death from any cause (OS) Median follow-up 3 yr	3693 (3 RCTs)	⊕⊕⊕⊕ HIGH	HR 0.98 (0.83–1.14)	110 per 1000	2 fewer per 1000 (18 fewer to 14 more)
Time to RCC recurrence (DFS) Median follow-up 3 yr	3693 (3 RCTs)	⊕⊕⊕ MODERATE[c]	HR 0.92 (0.82–1.03)	364 per 1000	23 fewer per 1000 (54 fewer to 9 more)
Grade 3–4 adverse events	3615 (3 RCTs)	⊕⊕⊕⊕ HIGH	RR 2.84 (2.48–3.24)	231 per 1000	425 more per 1000 (342 more to 518 more)

CI = confidence interval; HR = hazard ratio; RR = risk ratio; RCT = randomized controlled trial; OS = overall survival; RCC = renal cell carcinoma; DFS = disease-free survival; TT = targeted therapy.

[a] GRADE grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

[b] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c] Downgraded by one level for imprecision: wide CI that crosses the threshold of a clinically relevant effect.

DOI of original article: https://doi.org/10.1016/j.eururo.2018.05.002.

https://doi.org/10.1016/j.eururo.2018.11.006
0302-2838/Published by Elsevier B.V. on behalf of European Association of Urology.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Sun M, Marconi L, Eisen T, et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. Eur Urol 2018;74:611–20.
[2] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[3] Dahm P, Chapple CR, Konety BR, et al. The future of clinical practice guidelines in urology. Eur Urol 2011;60:72–4.
[4] Knoll T, Omar MI, Maclennan S, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the European Association of Urology. Eur Urol 2018;73:290–300.

Eu Chang Hwang[a,b]
Michael C. Risk[b]
Philipp Dahm[b,*]

[a]*Department of Urology, Chonnam National University Medical School, Gwangju, Republic of Korea*
[b]*Urology Section, Minneapolis Veterans Healthcare System and Department of Urology, University of Minnesota, Minneapolis, MN, USA*

*Corresponding author. Urology Section, Minneapolis Veterans Healthcare System and Department of Urology, University of Minnesota, Minneapolis, MN 55417, USA. Tel. +1 612 4673532; Fax. +1 612 4672232.
E-mail address: pdahm@umn.edu (P. Dahm).

November 1, 2018