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LETTERS TO THE EDITOR

Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer

***Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*[1]**

This eUpdate outlines updated treatment recommendations for first-line advanced clear cell renal cancer (Figure 1).[1] The changes are based on recent data for the combination of cabozantinib and nivolumab, which is now recommended as front-line therapy for advanced disease [I, A].[2] This is based on data from the CheckMate 9ER study, which is one of a number of practice-changing studies comparing programmed cell death protein 1 (PD-1) inhibitors plus vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) versus sunitinib in the front-line setting.[3,4] Results showed that the study met the primary endpoint of progression-free survival, with a median of 16.6 months for the combination versus 8.3 months for sunitinib ($P < 0.0001$). There was also a significant overall survival advantage for cabozantinib and nivolumab at interim analysis (18.1 months median follow-up) [hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.40-0.89; $P < 0.001$]. Reponses rates also significantly favoured the combination (56% versus 27% and HR 0.51, 95% CI 0.41-0.64, respectively). These benefits appeared to be irrespective of International Metastatic Database Consortium (IMDC) prognostic subgroups and programmed death-ligand 1 (PD-L1) biomarker status. No new adverse event (AE) signals were identified and AE profiles were in line with expectation. A large proportion of patients (56%) had dose reductions of cabozantinib from 40 mg to 20 mg. Quality-of-life data favoured the cabozantinib and nivolumab combination.

Cross-trial comparisons between these front-line combination trials, such as axitinib/pembrolizumab or ipilimumab/nivolumab, are not advised.[2-4] The recommendations for these other combinations have not changed from the previous eUpdate.

Recommendation

- The combination of cabozantinib and nivolumab is now recommended as front-line therapy for advanced disease [I, A].

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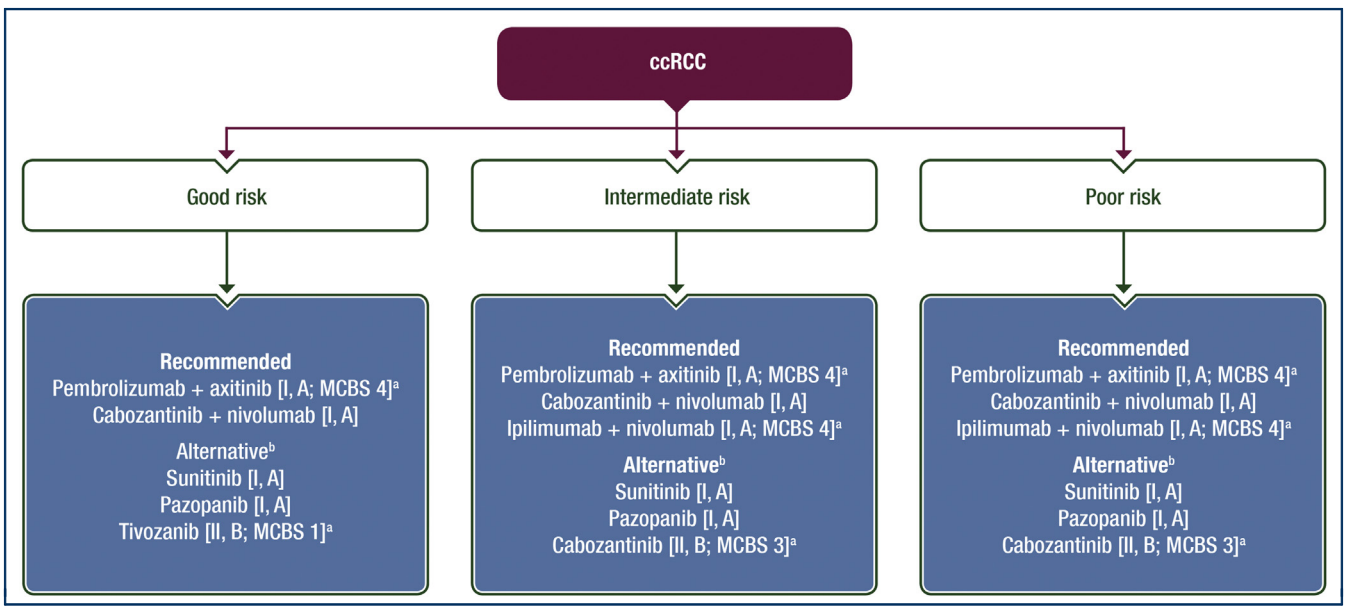

Figure 1. Systemic first-line treatment of ccRCC.
ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; MCBS, Magnitude of Clinical Benefit Scale.
[a] ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[b] Where recommended treatment not available or contraindicated.

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Key role for liquid biopsy in the elimination of breast cancer surgery following neoadjuvant therapy

We read with great interest the review in *Annals of Oncology* by Heil et al. on the potential elimination of breast cancer surgery after neoadjuvant therapy.[1] However, the discussion on this debatable topic is not complete without mentioning the recent achievements of liquid biopsy technology using analysis of circulating cell-free DNA (cfDNA). In the paper, the authors address the clinical challenge using four key questions: (i) what are the best diagnostic outcome measures? (ii) which tools can be used to confirm residual disease? (iii) what is the cost of missed residual tumor? and (iv) how to design future clinical trials? We claim that cfDNA is the potential answer to these four questions.

Recent publications in the field of cfDNA detection in the context of residual disease post-neoadjuvant therapy exhibit results that are numerically better than invasive biopsies with sensitivities of 87%-100% and specificities of 97%-100%.[2,3] Furthermore, liquid biopsy has unique additional advantages, such as its ease of use and its ability to create a potential window of opportunity (almost 1 year[3]) between molecular and clinical relapse.

In our view, the cost of missing residual cancer and the design of future trials coalesce. Carefully planned studies that address the omission of breast surgery should enroll well-informed patients with the highest chance of achieving pathologic complete response (e.g. post-menopausal hormone receptor negative, HER2-positive, node-negative patients) and compare all state-of-the-art technologies together: magnetic resonance imaging, positron emission tomography, cfDNA, and repeated invasive biopsies.

Taken together, we believe that liquid biopsy has a potential to dramatically de-escalate therapy for breast cancer patients and prospective clinical trials are more than warranted.

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DISCLOSURE

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