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Soluble MAdCAM-1 predicts outcomes in patients with metastatic renal cell carcinoma: Results from three independent clinical trials

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Background

Patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICI) or VEGFR tyrosine kinase inhibitors (TKI) may develop resistance driven by gut dysbiosis affecting the MAdCAM-1/α4β7 axis (Fidelle et al., *Science* 2023). We evaluated plasma soluble MAdCAM-1 (sMAdCAM-1), a surrogate of dysbiosis, as a prognostic biomarker in mRCC in three independent clinical trials.

Methods

sMAdCAM-1 was measured using the Human Luminex Discovery Assay in plasma from 1,051 patients across the phase 3 JAVELIN Renal 101 trial (1st line avelumab + axitinib vs. sunitinib) as training cohort and the phase 2 SURF (1st line sunitinib) and NIVOREN (nivolumab post-TKI) trials as validation cohorts. Optimal cutoff was determined using the maximum log-rank statistic. Cox regression models analyzed associations with progression-free survival (PFS) and overall survival (OS).

Results

An optimal cutoff at the 25th percentile was found based on OS in the training cohort. Higher sMAdCAM-1 at baseline was associated with improved PFS (HR 0.75 [0.59–0.96], P=0.021) and OS (HR 0.59 [0.41–0.85], P=0.004), even after adjustment for IMDC risk groups. Patients with an increase in sMAdCAM-1 from baseline to the C3 visit were more likely to have a response to therapy (OR 1.88 [1.34–2.65], P<0.001). The prognostic value of sMAdCAM-1 was confirmed in the 2 validation cohorts. In addition, immunotherapy-based regimens were associated with an increase in sMAdCAM-1 (P<0.001 in all cohorts), while TKI alone reduced sMAdCAM-1 (P<0.01). Combining sMAdCAM-1 with IMDC enhanced the 18-month OS prediction vs. IMDC alone (AUC: 0.72 vs. 0.68; P=0.01). Finally, stool metagenomics revealed that low sMAdCAM-1 levels associated with an immunosuppressive gut microbiota, which was promoted by TKIs and reduced by ICIs.

Conclusions

Higher sMAdCAM-1 levels at baseline or their increase during the first cycles of therapy were associated with improved outcomes in patients with mRCC. Our study supports a paradigm shift in the management of mRCC, paving the way to biomarker-guided clinical trials investigating microbiota-targeted interventions aimed at enhancing the efficacy of standard ICI-based therapies.

Clinical trial identification

JAVELIN Renal 101 trial: NCT02684006.

SURF trial: NCT02689167.

GETUG-AFU26-NIVOREN trial: NCT03013335.

Legal entity responsible for the study

The authors.

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Disclosure

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Other, Professor at HMS, Please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, Other, The institution filed patents related to biomarkers of immune checkpoint blockers, and circulating tumor DNA. No money made and some patents were abandoned.: Filed patents. All other authors have declared no conflicts of interest.