# Combined MET and PD-L1 inhibition shows promise in MET-driven metastatic papillary renal cancer

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Advanced papillary renal cancer (PRC) has a poor prognosis with few treatment options available. Approximately 30% of patients with this

disease present alterations in the MET gene that encodes a hepatocyte growth factor receptor. Mutations in this gene are implicated in disease progression and can also contribute to cancer drug resistance. While the association of MET mutations with the development of this kidney cancer subtype has been well described, the effect of specifically targeting this gene is unclear.

Aimed at identifying new and more potent treatment avenues for these patients, the CALYPSO investigators spearheaded by Thomas Powles, Barts Cancer Institute, London (UK), have assessed the efficacy of different treatment combinations in patients with metastatic renal carcinoma, including the combination of savolitinib, a potent MET inhibitor, plus immunotherapy durvalumab which is already used to treat several tumor types, but not approved for renal cancer.

Results of the papillary renal cancer cohort, which was part of a wider study assessing the efficacy and toxicity of this combined approach in clear cell and papillary subsets that split into two separate expansion phases, have now published online ahead of print in the *Journal of Clinical Oncology*.

"Here we report he results of the metastatic papillary renal cancer cohort. Based on previous single arm studies showing that savolitinib monotherapy achieved response rates of 18% in patients with MET gene alterations, as well as promising preclinical data suggesting a positive interaction between MET and PD-L1 inhibition, this single arm study included 41 patients with advanced PRC, 17 of which had MET-driven tumors," says Cristina Suárez, a Clinical Investigator of the Vall d'Hebron Institute of Oncology's (VHIO) Genitourinary, Central Nervous System (CNS) Tumors, and Sarcoma Group, and first author of this study.

MET-driven status was defined as chromosome 7 gain, MET

amplification, MET kinase domain variations, or hepatocyte growth factor amplification, which expanded the clinical trial population given that all these alterations can be implicated in the progression of papillary renal cancer and influence cancer drug resistance. Treatment naïve or previously treated patients with metastatic PCR participated in this study and the primary endpoint was a confirmed response rate of higher than 50%.

The combination of savolitinib and durvalumab did not achieve the primary endpoint in the global treated population, but a positive response was observed in those patients with MET-driven tumors, with reported response rates of 29% and 53%, respectively. A median progression-free survival of 12 months was observed in the patients with MET-driven status versus 4.9 months in the global treated population. Adverse events were in line with expectations for these two agents with grade 3 or 4 adverse events in 17 (41%) patients.

"Our results show that this combination is tolerable and shows promising activity in patients with MET mutations. While the prognostic significance of MET alterations and PD-L1 expression is not well-defined, data from our exploratory biomarker analysis point to MET as a more promising new biomarker over PD-L1 for this treatment combination," adds Suárez.

She concludes, "While the numbers are small, the results of our subset study justify further evaluation of MET-driven tumors. Based on our data, the phase III SAMETA study is currently underway to investigatae savolitinib plus durvalumab versus sunitinib and durvalumab monotherapy in MET-driven, unresectable and locallly advanced or metastatic PRC."

**More information:** Cristina Suárez et al, Phase II Study Investigating the Safety and Efficacy of Savolitinib and Durvalumab in Metastatic

Papillary Renal Cancer (CALYPSO), *Journal of Clinical Oncology* (2023). DOI: 10.1200/JCO.22.01414