Correlation of germline MET mutation with response to the dual Met/VEGFR-2 inhibitor foretinib in patients with sporadic and hereditary papillary renal cell carcinoma: Results from a multicenter phase II study (MET111644).

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**Background:** Activating mutations and/or amplifications in MET have been described in patients (pts) with papillary renal cell carcinoma (PRC). Foretinib, an oral multi-kinase inhibitor targeting...
MET, VEGF, RON, AXL, and TIE-2 receptors, was evaluated in a phase 2 study in pts with PRC. An important objective of this study was to evaluate whether activation of the MET receptor pathway by mutation, amplification, or gain of chromosome 7 was predictive for or correlated with clinical outcomes. **Methods:** Pts were stratified based on status of MET pathway activation. Blood samples were collected at screening for determination of germline MET mutational status. Archival tumor tissue samples were obtained for the analysis of somatic MET mutation, amplification of the MET locus (7q31), and gain of chromosome 7 using standardized assays. **Results:** A total of 74 pts were enrolled on the trial (37 each in intermittent and daily dosing arms); overall efficacy and safety data are reported separately at this meeting. Sixty-seven pts were evaluable for both mutation status and response. 5/10 pts (50%) with a germline MET mutation experienced a PR, while 5 pts (50%) had SD as their best response, including 4 pts who demonstrated tumor SLD reductions of > 10%, but did not achieve PR by RECIST 1.0. Responses were also seen in pts without germline MET mutation. However, the presence of a germline MET mutation was highly predictive of a response as only 5/57 pts (9%) without a mutation experienced a PR. Other measures of MET pathway activation did not appear to correlate with activity with only 1/5 pts (20%) with somatic MET mutation having a PR; furthermore, in the absence of a concomitant MET mutation, no responses were seen in patients with MET amplification (n=2) and only 1/18 (5%) pts with a gain of chromosome 7 experienced a PR. **Conclusions:** The presence of germline MET mutations correlated strongly with activity of the MET inhibitor foretinib in pts with PRC. These data provide early proof of principle that MET may be a valid therapeutic target in a subset of patients with PRC.

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