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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.