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Response to Crizotinib in a Patient with MET-mutant Papillary Renal Cell Cancer After Progression on Tivantinib

Mark N. Stein^{a,*}, Kim M. Hirshfield^a, Hua Zhong^b, Eric A. Singer^c, Siraj M. Ali^d, and Shridar Ganesan^a

^aRutgers Cancer Institute of New Jersey; Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

^bRutgers Cancer Institute of New Jersey; Department of Pathology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

^cRutgers Cancer Institute of New Jersey; Section of Urologic Oncology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

^dFoundation Medicine, Cambridge, Massachusetts, USA

A 62-yr-old man presented with hematuria and intractable hiccups. Imaging studies showed 7-cm complex bilateral renal masses and bulky aortocaval lymphadenopathy. Right renal mass fine needle aspiration demonstrated renal cell carcinoma, likely non-clear cell histology.

The patient was enrolled in a phase 1 clinical trial of sunitinib plus hydroxychloroquine, with stable disease for 7 mo followed by disease progression with development of palpable left supraclavicular adenopathy. Supraclavicular node biopsy demonstrated metastatic papillary renal carcinoma, type 1 (Fig. 1). Based on this diagnosis, the patient was enrolled in phase 2 trial of the MET proto-oncogene, receptor tyrosine kinase (MET) inhibitor tivantinib (ARQ197) with or without erlotinib (ClinicalTrials.gov identifier NCT01688973). After 2 mo of tivantinib monotherapy, he developed new pulmonary and hepatic lesions. Disease growth continued during 2 mo of temsirolimus treatment. He continued to experience intractable hiccups, with impaired quality of life.

Formalin-fixed, paraffin-embedded tissue from the supraclavicular lymph node specimen containing metastatic tumor was submitted to a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited laboratory (Foundation Medicine, Inc., Cambridge, MA, USA) for targeted genomic profiling of a set of cancer-associated genes including *MET*. The tumor harbored missense base substitution *METH1094L* (Fig. 1). This *MET* alteration (also known as H1112L) is in the conserved kinase domain and has been characterized in vitro as leading to constitutive activation [1,2].

*Corresponding author. Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903, USA. mark.stein@rutgers.edu (M.N. Stein).

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Based on the presence of the activating MET mutation, crizotinib—a potent competitive MET inhibitor—was initiated. One month of treatment led to symptomatic improvement, hiccup resolution, and improved respiratory symptoms. Restaging after 2 mo of treatment showed improvement in pulmonary and hepatic metastases and decreased adenopathy, with a partial response by Response Evaluation Criteria In Solid Tumors 1.1, based on a 34% decrease in tumor measurements compared with baseline (Fig. 1). The patient remained on crizotinib therapy for 5 mo until he experienced disease progression and died in hospice shortly thereafter.

Tivantinib is a novel non-adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET currently being developed for treatment of MET-mutant cancers, including papillary renal cell cancer [3–5]. Treatment with single-agent tivantinib resulted in rapid disease progression, suggesting that tivantinib may not be a clinically effective MET inhibitor in the setting of an activating MET mutation. This is consistent with recent reports showing that tivantinib does not appear to function as a selective MET inhibitor in *in vitro* cell-based assays [6–9]. Patients with known MET alterations, including those who do not respond to tivantinib, should be considered for clinical trials using treatment with crizotinib or other ATP-competitive MET inhibitors.

This report also demonstrates the potential benefits and challenges of realizing the goal of personalized cancer medicine. Without knowledge of a tumor's genomic profile, it is unlikely that the patient would have been rechallenged with a second agent targeting the tumor alteration in an off-label setting. Although our patient was able to receive crizotinib through a commercial insurance carrier, many others in similar circumstances may not have access to rationally selected medications in an off-label context. Future pharmaceutical, insurance provider, academic, and government initiatives are urgently required to match patients with tumors harboring well-characterized, therapeutically targetable genetic alterations with the appropriate drugs.

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Fig. 1. Supraclavicular node biopsy demonstrated metastatic papillary renal carcinoma, type 1. (A) Hematoxylin and eosin staining of lymph node biopsy showing papillary renal cell carcinoma. Immunohistochemistry 100× for (B) CK-7 and (C) carbonic anhydrase. (D) Next-generation sequencing results of tumor specimen showing MET mutation. (E) Representative computed tomography (CT) images prior to crizotinib. (F) Representative CT images after 2 mo of crizotinib.