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Research Category:	Translational/'Bench to Bedside' Research
Title of Abstract:	MET-mediated acquired resistance to entrectinib in ROS1-driven NSCLC
Please copy and paste your abstract here: (no more than 300 words):	ROS1 gene fusion-positive (ROS1+) tumors comprise 1-2% of all diagnosed lung adenocarcinomas. Currently, there are two ROS1 tyrosine kinase inhibitors (TKIs) which are US FDA approved, crizotinib and entrectinib, both of which generate tumor response rates in excess of 70% and demonstrate prolonged disease control. However, acquired resistance to TKIs is inevitable, and has been reported in ROS1+ NSCLC tumors or cancer cell models, and include ROS1 kinase domain mutations, activation of bypass signaling pathways, or phenotypic transformation. To better understand mechanisms of acquired TKI resistance in ROS1+ NSCLC, our lab utilized primary, patient-derived cancer cell models harboring ROS1 rearrangements. Herein, using a patient-derived NSCLC cancer cell line (CUTO28) harboring a TPM3-ROS1 fusion, we derived an entrectinib-resistant cell line (CUTO28-ER) through in vitro culture under drug selection. In CUTO28-ER cells, we identified: (1) MET-mediated bypass signaling as an acquired resistance mechanism to entrectinib, (2) upregulation of MET signaling is accomplished via MET gene amplification, and (3) resistance could be overcome by the dual ROS1/MET inhibitor crizotinib. This is the first reported case of MET-mediated acquired

resistance in a ROS1+ cancer. This finding was supported by another primary, patient-derived cell line (CUTO38) harboring a CD74-ROS1 fusion; CUTO38s were derived from a NSCLC patient following disease progression on entrectenib in the clinic. CUTO38 is resistant to entrectinib in vitro and displays elevated MET expression, increased MET phosphorylation, and dependence on MET for cell proliferation and survival. Notably, MET activation in CUTO38 was not generated by gene amplification, MET exon 14 splicing, MET gene fusion, or autocrine HGF expression, suggesting alternate means of MET activation. These findings suggest interrogation of MET biomarkers should be performed in ROS1+ NSCLC patients who experience progression on ROS1 TKIs, since there are clinically available MET and dual ROS1/MET inhibitors that may overcome drug resistance in these patients.