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Presentation Abstract

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Presentation Title:	**Circulating biomarkers of MetMAb activity in a phase Ia dose escalating clinical trial**.
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Author Block:	Congfen Li, Ihsan Nijem, John zheng, Marina Lipkind, Premal Patel, Amy Peterson, Ellen Filvaroff, Mark merchant, Priti S. Hegde. Genentech, South San Francisco, CA
Abstract Body:	The HGF/Met pathway has attracted interest as a promising target for cancer therapy both due to direct pathway activation in solid tumors as well as to activation as a mechanism of resistance to EGFR pathway inhibition. MetMAb is a recombinant, humanized, monovalent monoclonal antibody that antagonizes HGF driven Met signaling and is currently being evaluated in a clinical trial for NSCLC in combination with Erlotinib, and in phase 1 (in all solid tumors) in combination with Avastin. In this study we explored the utility of candidate pharmacodynamic biomarkers (PDB) in monitoring responses to MetMAb in the Phase Ia clinical trial, including a downstream marker of Met signaling, IL-8, and two proximal markers, serum HGF and shed Met (sMet) extracellular domain (ECD). A panel of four distinct secreted proteins including VEGF, PAI1, IL-8, uPAR were evaluated as potential biomarkers of Met pathway inhibition in preclinical models of efficacy. Of these, IL-8 demonstrated a desirable dynamic range that prompted its evaluation as a potential biomarker of drug activity in a Phase Ia dose ranging study with MetMAb using an MSD based ELISA assay. Circulating IL-8 levels, decreased as early as 24 hours after drug administration in patients that had higher than normal physiologic levels at baseline, irrespective of the MetMAb dose administered. In addition, a dose dependent increase in sMet was observed in all patients. These results are consistent with those obtained in preclinical studies that show that MetMAb can prevent normal clearance of hu-Met-ECD in mice. A trend towards increased circulating HGF levels post MetMAb administration was observed in most patients. However, an exception was noted in one gastric cancer patient that showed an objective complete response to MetMAb treatment. This patient demonstrated significantly higher levels of serum HGF and upon treatment showed an immediate and sustained decrease in circulating serum HGF. These data along with the observation that this patient's tumor co-expressed Met and HGF suggests that MetMAb decreased serum HGF by disrupting an autocrine loop that was driving high serum HGF levels and sustaining tumor growth. The data show that IL-8, HGF and sMet levels can be modulated by treatment with MetMAb. As modulation of IL-8 was observed in most dose groups the utility of this marker to guide dose response is minimal. MetMAb can bind to and prevent the clearance of the Met ECD and the results presented here confirm this phenomenon in patients. Correspondingly, there appears to be no utility of sMet as a biomarker for response to MetMAb. The reduction in serum HGF observed in one patient with an objective CR suggests utility HGF as a MetMAb biomarker may depend on tumor biology. Together, these data have allowed the translation of preclinical biology in humans and demonstrate Met pathway inhibition using MetMAb.