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Presentation Abstract

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Presentation Title:	Bispecific antibody targeting EGFR and cMet demonstrates superior activity compared to the combination of single pathway inhibitors
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Abstract Body:	Many tumors respond initially to targeted therapy, only to develop resistance over time thereby allowing the tumors to progress. In patients treated with EGFR small molecule inhibitors, the cMet pathway is often upregulated, either through MET gene amplification or an increase in the ligand HGF, to compensate and provide resistance to the EGFR monotherapy. Because both EGFR and cMet signal through some of the same survival and growth-promoting pathways, dual inhibition of these receptors may improve efficacy and prevent resistance through these mechanisms. We have designed a bispecific EGFR-cMet antibody (EM1-mAb) with multiple mechanisms of action resulting in superior activity compared to a combination of single EGFR and cMet inhibitors. Fab arm exchange was used to produce EM1-mAb, a technique that allows for efficient large-scale preparation of bispecific antibodies. EM1-mAb prevented binding of the ligands EGF and HGF to their respective receptors, EGFR (IC50 = 10 nM) and cMet (IC50 = 30 nM). Ligand-induced phosphorylation of each receptor was inhibited in cell-based assays. Blocking signaling from both EGFR and cMet with a combination of single monospecific antibodies resulted in an enhanced inhibition of pERK, a downstream effector of both receptors. The bispecific EM1-mAb further increased the potency of inhibition of pERK (55-65-fold) compared to the combination of single monospecific antibodies, suggesting an avidity effect on downstream signaling. EM1-mAb was evaluated in SCID-beige mice implanted with tumor cells engineered to express human HGF. Complete regression of 8/8

tumors was observed upon treatment with EM1-mAb dosed twice a week at 20 mg/kg. After the dosing period of four weeks, mice were monitored for an additional 10 weeks and no tumor regrowth was observed.
Our data demonstrate that the bispecific antibody EM1-mAb, generated using Fab arm exchange, inhibited EGFR and cMet pathways simultaneously, resulting in superior activity in cellular downstream signaling compared to the combination of single pathway inhibitors. These attributes allow for a more efficient path toward clinical development.

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