The bispecific antibody MCLA-129 impairs NSCLC tumor growth by targeting EGFR and c-MET, inhibiting ligand-induced signaling and promoting ADCC and ADCP

INTRODUCTION

- EGFR and c-MET activate the same intracellular signal transduction pathways to drive proliferation, survival and invasion.
- MET/HGF amplification plays a potential role in resistance to EGFR-targeted treatments in NSCLC.
- In vitro and in vivo, HGF promotes tumor growth and the presence of HGF or a competing anti-HGF antibody decreases tumor growth.

AVIDITY AND AFFINITY TO NSCLC CELL LINES

- MCLA-129 displays increased avidity and selectivity for NSCLC tumor cells due to the avidity effect caused by simultaneously binding to both EGFR and c-MET.

UNBIASED FUNCTIONAL SCREENING

- Specific combinations of c-MET and EGFR Fab arms in the Biclonics® format result in either potent antagonistic or agonistic activity.
- MCLA-129 was selected from a panel of Biclonics® based on potency of c-MET inhibition.

MCLA-129 BLOCKS EGFR AND c-MET LIGAND BINDING

- MCLA-129 competes with both the EGFR and the HGF ligands to bind the EGFR and c-MET receptors.
- Reference antibodies were anti-EGFR antibody cetuximab, the anti-c-MET MetFab brivalent antibody and the anti-HGF negative control.

MCLA-129 FACILITATES ADCC AND ADCP

- Both the EGFR and the c-MET Fab arms contribute to Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) activity due to avidity binding.
- MCLA-129 displays ADCC activity over a broad range of EGFR expression levels.

MCLA-129 INHIBITS TKI RESISTANT NSCLC TUMOR GROWTH IN VIVO

- MCLA-129 Fc-domain mediates inhibition of tumor growth in vivo.
- Treatment with MCLA-129 led to HCC827 tumor growth inhibition in immunocompromised NOD SCID gamma mice that express human HGF instead of endogenous mouse HGF (NSG-HGF/Ki mice).

CONCLUSIONS

- MCLA-129 is an ADC-enhanced common light chain bispecific human IgG1 Biclonics® antibody specifically targeting the receptor tyrosine kinases EGFR and c-MET.
- MCLA-129 blocks EGFR and HGF binding to their respective receptors EGFR and c-MET.
- MCLA-129 promotes Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and Antibody-Dependent Cell-Mediated Phagocytosis (ADCP).
- MCLA-129 significantly inhibits NSCLC cell line derived tumor growth in immunocompetent mice.
- MCLA-129-mediated tumor reduction was enhanced when combined with Erlotinib.
- MCLA-129 can overcome HGF-mediated TKI resistance.

These data provide support for the Phase 1/2 study of MCLA-129 in NSCLC and other solid tumors.