Mechanism of action of MCLA-129, a bispecific antibody that targets EGFR and c-MET and impairs growth of EGFR exon 20 insertion mutant non-small cell lung cancer

Abstract 336

INTRODUCTION

- EGFR and c-MET activate the same intracellular signal transduction pathways to drive proliferation, survival and invasion
- MET/EGF amplification plays a potential role in resistance to EGFR targeted treatment in solid tumors
- In non-small cell lung cancer (NSCLC), resistance to TKI inhibition of mutant EGFR is associated with increased c-MET signalling

THE MCLA-129 BICLONICS®

- The MCLA-129 epitope is located on Domain II of c-MET
- The EGFR residues critical for MCLA-129 binding overlap with the EGF-binding site

THE MCLA-129 BICLONICS®

- MCLA-129 inhibits EGFR and c-MET dimerization
- Reference antibody was the anti-RSV IgG negative control

MCLA-129 PROMOTES ADCC AND ADCP OF NSCLC CELLS

- MCLA-129 promotes ADCC and ADCP of NSCLC cells

MCLA-129 INHIBITS EGFR AND c-MET PHOSPHORYLATION

- Ligand-dependent phosphorylation of EGFR and c-MET was assessed in vitro in NCI-H1650 (EGFR - STAT, AKT, EGFR expression) and NCI-H322M (NSCLC) cells
- MCLA-129 inhibits phosphorylation of EGFR and c-MET

The epitope of MCLA-129 overlaps with EGF binding site

- MCLA-129 inhibits ligand-induced EGFR and c-MET receptor dimerization and phosphorylation
- MCLA-129 promotes Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and Antibody-Dependent Cell-Mediated Phagocytosis (ADCP) of NSCLC cells
- MCLA-129 significantly inhibits growth of a patient-derived EGFR exon20ins tumor in a preclinical xenograft model

CONCLUSIONS

- MCLA-129 is a Fc-enhanced common light chain bispecific human IgG1 Biclonic® antibody specifically targeting the receptor tyrosine kinases EGFR and c-MET
- The epitope for MCLA-129 overlaps with EGF binding site
- MCLA-129 inhibits ligand-induced EGFR and c-MET receptor dimerization and phosphorylation
- MCLA-129 promotes Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and Antibody-Dependent Cell-Mediated Phagocytosis (ADCP) of NSCLC cells
- MCLA-129 significantly inhibits growth of a patient-derived EGFR exon20ins tumor in a preclinical xenograft model

These data provide support for the ongoing phase 1/2 study of MCLA-129 in patients with solid tumors, including NSCLC with EGFR exon20ins (Study MCLA-129-C271, NCT04868877)

References

2. Engelman et al. Science. 2007;316(5827): 1039-1044

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MCLA-129 INHIBITS EGFR EXON20INS PDX TUMOR GROWTH

- Patient-derived NSCLC-LXFE2478 xenograft with EGFR exon 20 insertion
- Insertion of 9 nucleotides affecting the EGFR tyrosine kinase domain (M766, A767insASV)
- Implanted in nude mice having normal activity of the Fc receptor-expressing NK and myeloid cells
- MCLA-129 treatment leads to dose-dependent tumour shrinkage

Figure 1 | Ligand-dependent phosphorylation of EGFR and c-MET assessed by immunoblotting. Serum-starved NCI-H1650 were incubated with EGF (100 ng/ml) and HGF (100 ng/ml) in the presence of MCLA-129, negative control antibody and reference antibodies anti-EGFR cetuximab and anti-c-MET Embeutuzumab analog (each 10 μg/ml).

Figure 2 | β-galactosidase enzyme complementation assay to determine the inhibitory effect of MCLA-129 on ligand-induced EGFR and c-MET receptor dimerization. Left, a reporter cell line ligand binding induces dimerization of chimeric receptors and the formation of a fully reconstituted active β-galactosidase enzyme. Enzyme activity is detected by chloroform/methanol. Middle and right panels, inhibitory effect of MCLA-129 on EGF (10 ng/ml) induced EGFR and HGF (150 ng/ml) induced c-MET dimerization in the presence of NCLA-129 or negative control antibody.

Figure 3 | Fold Induction of EGFR and c-MET phosphorylation with MCLA-129 treatment over vehicle control. Vehicle, MCLA-129, 2.5 mg/kg, QW, MCLA-129, 8 mg/kg, QW, MCLA-129, 25 mg/kg, QW.

Figure 4 | ADCC induced by MCLA-129 and monoclonal c-MET and EGFR binding antibodies having the same Fab domains as MCLA-129 against NSCLC cell lines using high affinity FcRγRIIa 15RV-variant effector cells.

Figure 5 | ADCC induced by MCLA-129 and monoclonal c-MET and EGFR binding antibodies having the same Fab domains as MCLA-129 against NSCLC cell lines using low affinity FcRγRIIa 15RV-variant effector cells.

Figure 6 | ADCC induced by MCLA-129 against NSCLC cell line HCC827. pH-sensitive pilrodo dye labelled HCC827 target cells were incubated with MCLA-129 and monoclonal anti-EpCAM microphage effector cells. ADCC was assessed on the IntraCyte™ system (pHrodo-Red fluorescence > 25 RCU).

Figure 7 | Activity of MCLA-129 on EGFR exon20ins PDX tumor growth in ADCC-competent mice. EGFR exon20ins PDX engrafted into nude mice. MCLA-129 was administered at 2, 8 or 20 mg/kg q.p. weekly to mice with established tumors. Upper panel, mean tumor volume ± SEM is shown. Lower panels, individual tumor volume is shown.