Preclinical evaluation of MCLA-129: a bispecific antibody targeting c-MET and EGFR

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BACKGROUND & RATIONALE

- c-MET and EGFR activate the same signalling pathways to drive proliferation, survival and invasion.
- MET/HGF amplification has a potential role in resistance to EGFR targeted treatment (e.g. NSCLC, GBM).
- In NSCLC, resistance to TKi inhibition of mutant EGFR is associated with c-MET amplification.
- In patients treated with EGFR-Tihs, high circulating c-MET predicted poor outcome.

THE BICLONICS® PLATFORM

- Common Light Chain for ‘unforced’, natural pairing with 2 different heavy chains.
- Electrostatic attraction to efficiently drive formation of Biclonics®.
- NGS Specific combinations of c-MET and EGFR Fab arms in the Biclonics® format result in either potent antagonistic or agonistic activity.
- MCLA-129 selected from a panel of Biclonics® based on potency of c-MET inhibition.
- MCLA-129 carries with the ligand binding domains of EGFR and c-MET.

MCLA-129 SELECTION & CHARACTERISTICS

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MCLA-129 INHIBITS TKI RESISTANT NSCLC

- HCC827 tumor cells were engrafted into immunodeficient NOD SCID gamma (NSG) mice and a decrease in the hypoxic tumor area (C) and a decrease in the hypoxic tumor area (C).
- In mice receiving the combination of Emibetuzumab and MCLA-129 tumor volume decreased dramatically (A) and was associated with inhibition of EGFR and c-MET phosphorylation (B) and a decrease in the hypoxic tumor area (C).

MCLA-129 REVERSES ACQUIRED TKI RESISTANCE

- MCLA-129 is a high-affinity, ADCC-enhanced CLs Biclonics® targeting human EGFR and c-MET.
- MCLA-129 was selected from a large panel of bispecific antibodies using an unbiased screen of ligand-dependent proliferation and migration assays.
- MCLA-129 can overcome HGF mediated Erlotinib resistance in NSCLC cell lines in vitro.
- MCLA-129 shows tumor shrinkage in the Erlotinib resistant HCC827 in immunocompromised NOD SCID gamma mice by inhibiting phosphorylation of EGFR and c-MET.
- These preclinical data suggest MCLA-129 could benefit NSCLC patients that become resistant to EGFR targeted therapies and warrants clinical evaluation.

References

2. Engenhart et al. J Immunother Cancer; 2019;9(9):e001253

Disclosures


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KEY FINDINGS AND CONCLUSIONS

- MCLA-129 is in clinical development.
- MCLA-129 is a novel bispecific antibody with the potential to overcome acquired resistance to EGFR and c-MET inhibitors.
- MCLA-129 has shown promising preclinical activity in multiple tumor models.
- MCLA-129 is being evaluated in a phase 1 clinical trial for the treatment of NSCLC patients with acquired resistance to EGFR and c-MET inhibitors.

Unbiased screening

- Combination of EGFR and HGF reversal TKI inhibition in both NSCLC cell lines.
- Combination of HGF and c-MET reversal TKI inhibition in both NSCLC cell lines).
- MCLA-129 inhibits HGF and EGFR induced phosphorylation of receptors.
- MCLA-129 is more potent in HCC827 cells than Cetuximab+ Kevzala analog (SDS).

Influence of receptor density on ADCC

- Association of MCLA-129 is required for ADCC activity.
- Cells expressing both EGFR and c-MET, i.e. BxPC-3, are preferentially targeted by ADCC.
- Treatment with MCLA-129 led to sustained HCC827 growth inhibition both alone or when combined with Erlotinib and this activity was maintained after treatment was stopped.
- Inhibition of tumor growth induced by MCLA-129 was greater than that induced by the anti- c-MET antibody Emibetuzumab.
- The combination treatment of MCLA-129 with Erlotinib fully inhibited HCC827 tumor growth up to 94 days of treatment in contrast to all other treatments.

Key findings

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