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

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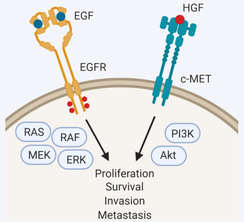
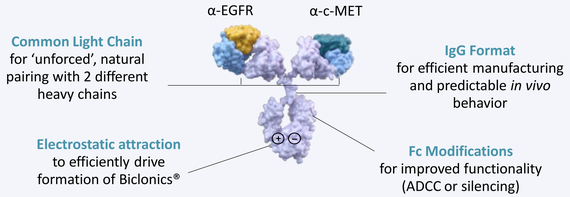
BACKGROUND & RATIONALE

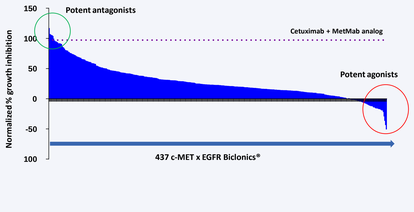
- EGFR and c-MET activate the same signalling pathways to drive proliferation, survival and invasion.
- MET/HGF amplification has a potential role in resistance to EGFR targeted treatment (e.g. NSCLC, GBM)[1].
- In NSCLC, resistance to TKI inhibition of mutant EGFR is associated with c-MET signalling[2].
- In patients treated with EGFR-TKIs, high circulating HGF predicted poor prognosis.

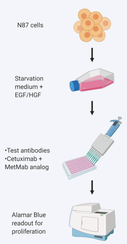


THE BICLONICS® PLATFORM

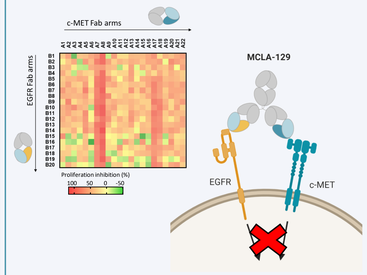


UNBIASED SCREENING



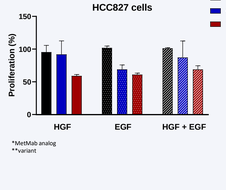


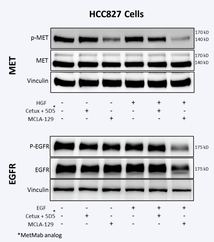
MCLA-129 SELECTION & CHARACTERISTICS



- 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 8 Biclonics® based on potency of c-MET inhibition.
- MCLA-129 competes with the ligand binding domains of EGFR and c-MET.

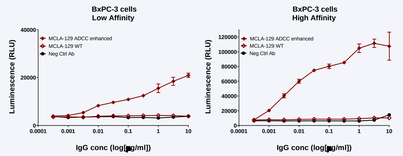
c-METxEGFR BICLONICS® REVERSE HGF RESISTANCE





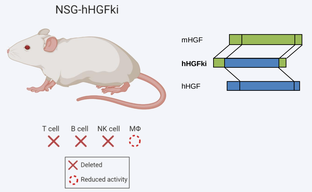
- Combination of EGF and HGF reverses TKI inhibition in both NSCLC cell lines.
- MCLA-129 restores sensitivity of NSCLC cell lines to Erlotinib.
- MCLA-129 inhibits HGF and EGF induced phosphorylation of receptors.
- MCLA-129 is more potent in HCC827 cells than Cetuximab + MetMab analog (5D5).

INFLUENCE OF RECEPTOR DENSITY ON ADCC

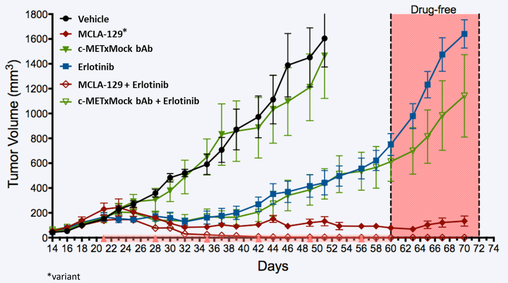


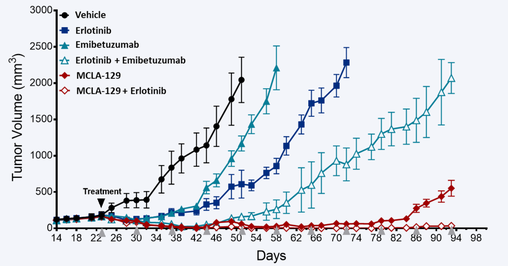
- Afucosylation of MCLA-129 is required for ADCC activity.
- Cells expressing both EGFR and c-MET, i.e. BxPC-3, are preferentially targeted by ADCC.

MCLA-129 INHIBITS TKI RESISTANT NSCLC



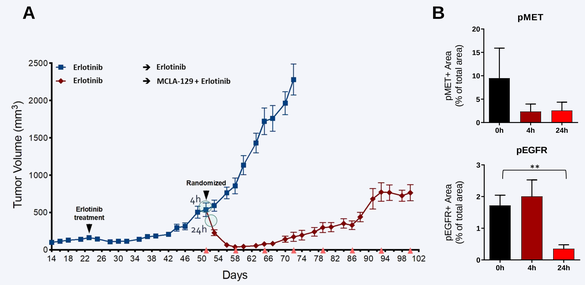
- HCC827 tumor cells were engrafted into immunodeficient NOD SCID gamma (NSG) human hepatocyte growth factor knock-in (hHGFki) mice, that express human HGF in place of endogenous mouse HGF (NSG-hHGFki mice, stk#014553)[3].
- The mice were treated with: Erlotinib (6 mg/kg) once daily (QD) and antibodies/ antibodies combinations (25mg/kg) weekly.

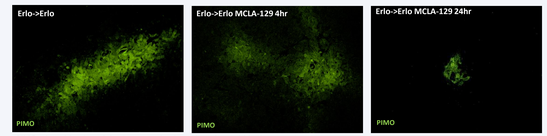




- Treatment with MCLA-129 led to sustained HCC827 growth inhibition both alone or when combined with Erlotinib and this activity was maintained after treatment was stopped.
- Inhibition of tumor growth induced by MCLA-129 was greater than that induced by the anti-c-MET benchmark antibody Emibetuzumab.
- 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.

MCLA-129 REVERSES ACQUIRED TKI RESISTANCE





PIMO: pimonidazole staining (representing hypoxic regions within the tumor)

*(A) Tumor volume (circles), (B) % of phosphorylated receptors in tumor sections, and (C) hypoxic tumor area in mice sacrificed: 2hr post Erlotinib 6mg/kg QD treatment (0h) or 4h and 24h after MCLA-129 administration and 2hr after Erlotinib 6mg/kg QD treatment. *p<0.05.*

- hHGFKi mice engrafted with HCC827 tumors and treated daily with Erlotinib exhibited rapid tumor growth after a period of control; at day 51 (tumors >500 mm³) mice were randomized to continue Erlotinib treatment alone or in combination with MCLA-129.
- In mice receiving the combination of Erlotinib 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).

KEY FINDINGS AND CONCLUSIONS

- MCLA-129 is a high-affinity, ADCC-enhanced cLC 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 NSG-hHGFki 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

1. Tsuji et al. *Oncotarget*. 2017;8(42):71805-71816
2. Engelman et al. *Science.* 2007;316(5827):1039-1043.
3. Goyama et al. *Blood.* 2015;125(17):2630-2640.

Disclosures

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