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

Poster 952

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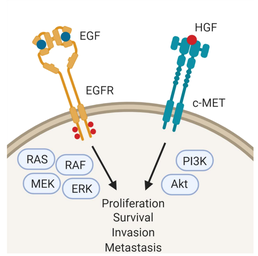
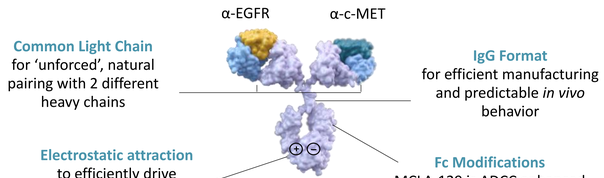
INTRODUCTION

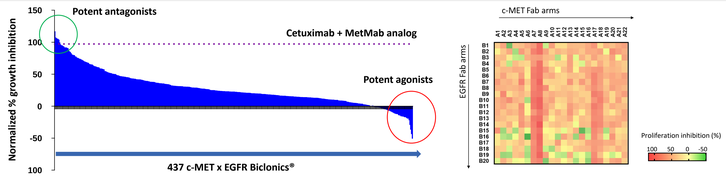
- EGFR and c-MET activate the same intracellular signal transduction pathways to drive proliferation, survival and invasion.
- MET/HGF amplification plays a potential role in resistance to EGFR targeted treatment in solid tumors.[1]
- In non-small cell lung cancer (NSCLC), resistance to TKI inhibition of mutant EGFR is associated with increased c-MET signalling.[2]
- In patients treated with EGFR-TKIs, high circulating HGF predicts poor prognosis.



THE BICLONICS® PLATFORM

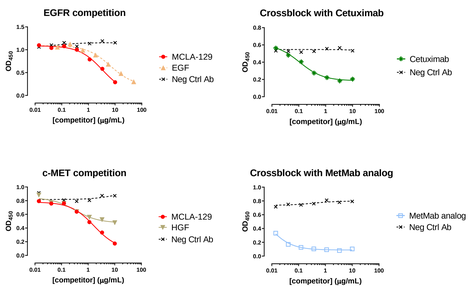


UNBIASED FUNCTIONAL SCREENING



- 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

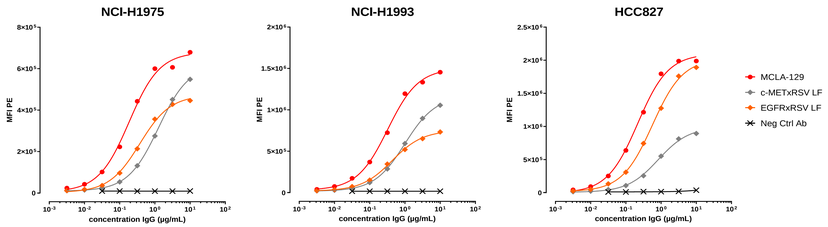


- MCLA-129 competes with both the EGF and the HGF ligands to bind the EGFR and c-MET receptors.
- Reference antibodies were anti-EGFR antibody cetuximab, the anti-c-MET MetMab bivalent analog and the anti-RSV IgG negative control.

Figure 1 | Blocking ELISA to determine ligand blocking capacity of MCLA-129. Upper panel, binding of EGFR in the presence of EGF or a competing anti-EGFR antibody to MCLA-129 or EGF. Lower panel, binding of c-MET in the presence of HGF or a competing anti-c-MET antibody to MCLA-129 or HGF.

AVIDITY AND AFFINITY TO NSCLC CELL LINES

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



Cell line	EGFR mutations	EGFR amplification	Relative EGFR expression	c-MET mutations	c-MET amplification	Relative c-MET expression
NCI-H1975	L858R, T790M	N	1.0	WT	N	1.0
NCI-H1993	WT	-	2.0	WT	Y	2.4
HCC827	del (E746, A750)	Y	8.9	WT	N	1.0

Figure 2 | Flow cytometry analysis of binding of MCLA-129, monovalent c-MET and EGFR binding antibodies having the same binding domains as MCLA-129 to NSCLC cell lines.

MCLA-129 FACILITATES ADCC AND ADCP

MCLA-129 potentiates ADCC against NSCLC cells

- 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.

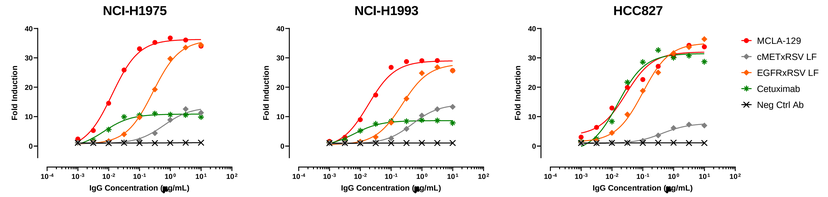


Figure 3 | ADCC activity induced by MCLA-129 and monovalent c-MET and EGFR binding antibodies having the same binding domains as MCLA-129 against NSCLC cell lines.

MCLA-129 promotes ADCP against NSCLC cells

- Both the EGFR and the c-MET Fab arms contribute to Antibody-Dependent Cell-Mediated Phagocytosis (ADCP) activity.
- MCLA-129-promoted ADCP activity was superior over the ADCP activity mediated by the anti-EGFR benchmark antibody cetuximab.

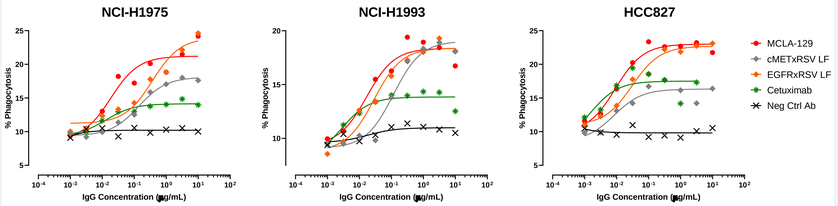


Figure 4 | ADCP activity induced by MCLA-129 & control IgGs against NSCLC cell lines. NSCLC target cells were labelled with the pH-sensitive pHrodo dye and incubated with the indicated IgGs in presence of primary macrophage effector cells, ADCP was assessed by flow cytometry.

MCLA-129 INHIBITS TKI RESISTANT NSCLC TUMOR GROWTH IN VIVO

MCLA-129 Fc-domain mediates inhibition of tumor growth in vivo

- Nude mice show normal activity of the Fc receptor expressing NK and myeloid cells.
- Murine HGF does not activate human c-MET.
- MCLA-129 reduces tumor growth in immunocompetent nude mice in a Fc-mediated manner and independent of c-MET signaling inhibition.

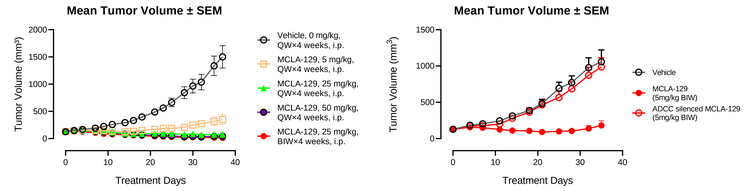


Figure 5 | Activity of MCLA-129 on tumor growth in immune competent mice. HCC827/ER1 EGFR del (E746, A750), c-MET ampl tumor cells engrafted into nude mice. MCLA-129 treatment as indicated.

MCLA-129 inhibits c-MET/EGFR-mediated 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-hHGFki mice, stk#014553)[3] which was enhanced when combined with Erlotinib.
- MCLA-129 induced shrinkage of HCC827 tumors in NSG-hHGFki mice that became Erlotinib resistant (Figure 6, right panel).

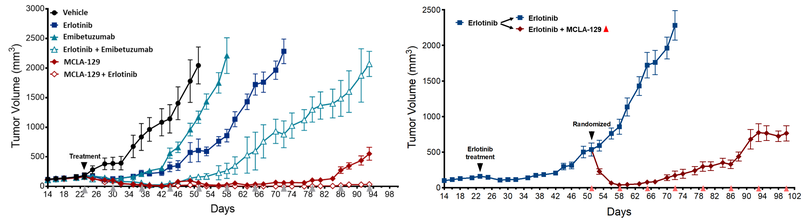


Figure 6 | Activity of MCLA-129 on tumor growth in immune compromised mice. HCC827 EGFR del (E746, A750) tumor cells engrafted into NSG-hHGFki mice. Erlotinib (6 mg/kg) once daily and combinations with antibodies (25 mg/kg) weekly.

CONCLUSIONS

- MCLA-129 is an ADCC-enhanced common light chain bispecific human IgG1 Biclonics® antibody specifically targeting the receptor tyrosine kinases EGFR and c-MET.
- MCLA-129 blocks EGF 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 EGFR-TKI resistance.
- These data provide support for the Phase 1/2 study of MCLA-129 in patients with NSCLC and other solid tumors (Study MCLA-129-CL01), which is expected to open in 2021.

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References

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