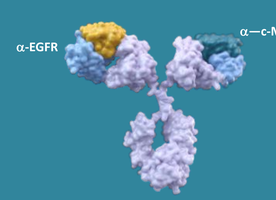
Merus

ABSTRACT 4999

Preclinical evaluation of MCLA-129, a bispecific antibody targeting EGFR and c-MET on solid tumor cells, in comparison with amivantamab



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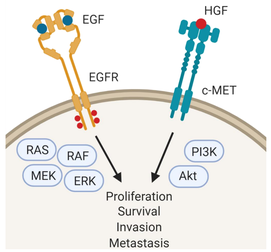
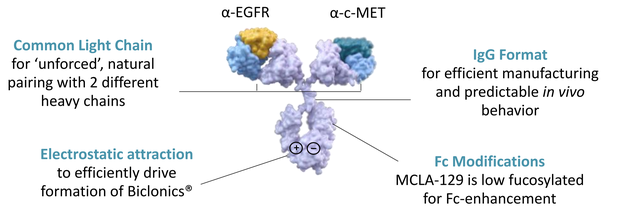
INTRODUCTION

- EGFR and c-MET activate similar intracellular signal transduction pathways to drive proliferation, survival and invasion
- MET/HGF pathway amplification plays a potential role in resistance to EGFR targeted treatment in solid tumors[1]
- In non-small cell lung cancer (NSCLC), resistance to tyrosine kinase inhibitor (TKI) inhibition of mutant EGFR is associated with increased c-MET signalling[2]
- *c-MET* exon-14 skipping mutations result in c-MET overexpression due to impaired c-MET degradation[3]



The MCLA-129 Biclonics®



AFFINITY OF MCLA-129 FOR EGFR AND c-MET

Table 1 | MCLA-129 affinity for EGFR and c-MET was evaluated using a cell-based assay. MCLA-129 and monovalent EGFR (EGFR×RSV) and c-MET (c-MET×RSV) binding antibodies derived from MCLA-129 were radiolabeled with ^{125}I. Cell-based affinities of the ^{125}I-labeled antibodies were measured in saturation binding experiments using HCC827, NCI-H1975 and NCI-H1993 cell lines.

Antibody	HCC827 (nM)	NCI-H1975 (nM)	NCI-H1993 (nM)
EGFR×RSV	2.553 ± 0.367	2.574 ± 0.286	2.066 ± 0.224
c-MET×RSV	2.033 ± 0.217	2.181 ± 0.162	1.802 ± 0.073
MCLA-129	1.778 ± 0.211	0.632 ± 0.085	0.706 ± 0.0714

- MCLA-129 binding to NSCLC cells expressing different levels of EGFR and c-MET was quantified using radiolabeled antibodies
- Scatchard plot analysis showed that the affinity of MCLA-129 for both EGFR and c-MET is in the low nanomolar range

MCLA-129 BINDING COMPETES WITH EGFR AND c-MET ANTIBODIES

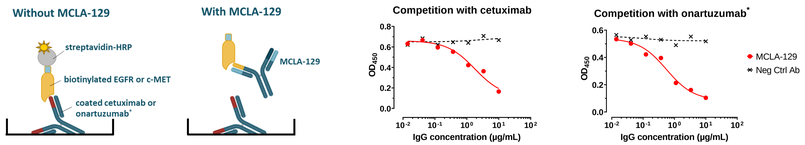


Figure 1 | ELISA to determine competition between antibodies to the EGFR and c-MET receptor. Left panel, schematic representation of the assay. Middle panel, binding of biotinylated EGFR to cetuximab in the presence of a dose range of MCLA-129. Right panel, binding of biotinylated c-MET to an analog of onartuzumab in the presence of a dose range of MCLA-129. * Analog antibody

- MCLA-129 competes with cetuximab for its binding site on EGFR, as has been reported for amivantamab[5]
- MCLA-129 competes with an analog of onartuzumab for its binding site on c-MET, which is distinct from amivantamab[5]

TUMOR CELL BINDING OF MCLA-129 AND AMIVANTAMAB

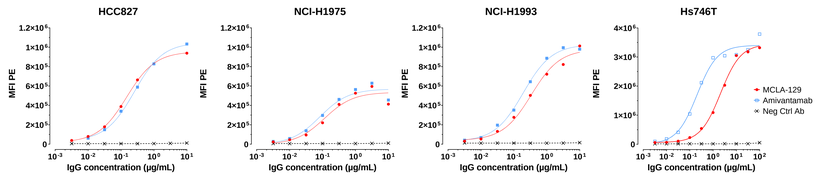


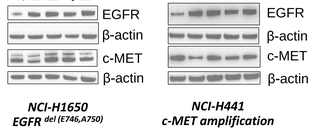
Figure 2 | Flow cytometry analysis of binding of MCLA-129 and amivantamab to tumor cell lines.

- MCLA-129 and amivantamab maximum binding to tumor cells harboring *EGFR* or *c-MET* exon14-skipping mutations expressing different levels of EGFR or c-MET

Table 2 | EGFR and c-MET mutations, amplifications and relative expression levels of the examined cell lines. NSCLC: non-small cell lung cancer; GC: gastric cancer; del: deletion; Amp: amplification.

Cell line	Tumor type	EGFR alterations	Relative EGFR expression	c-MET alterations	Relative c-MET expression
HCC827	NSCLC	del (E746, A750)	8.9	-	1.0
NCI-H1975	NSCLC	L858R, T790M	1.0	-	1.0
NCI-H1993	NSCLC	-	2.0	Amp	2.4
Hs746T	GC	-	0.5	exon14, Amp	3.3

LACK OF DOWNMODULATION OF EGFR AND c-MET



- MCLA-129 and amivantamab treatment have no effect on EGFR or c-MET total protein levels
- Positive controls Sym004* and emibetuzumab* induce EGFR or c-MET reduction

Figure 3 | EGFR and c-MET downmodulation in NSCLC cell lines assessed by immunoblotting. NCI-H1650 and NCI-H441 cells were incubated for 48 hours with MCLA-129, amivantamab, or negative control antibody, or with reference analog antibodies anti-EGFR Sym004 and anti-c-MET emibetuzumab (each 10 µg/mL). * Analog antibodies

ADCP OF MCLA-129 AND AMIVANTAMAB

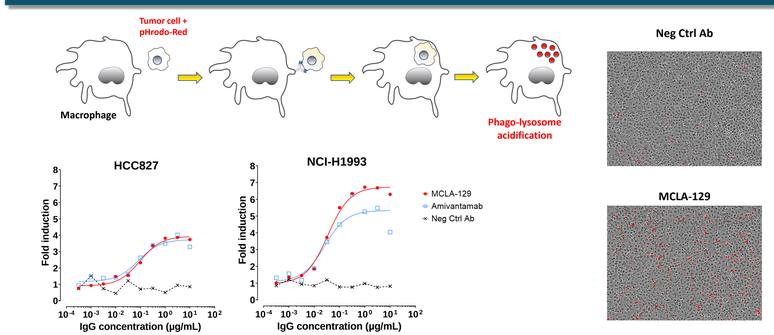


Figure 4 | ADCP induced against NSCLC cell lines HCC827 and NCI-H1993. pH-sensitive pHrodo dye-labeled HCC827 and NCI-H1993 target cells were incubated with MCLA-129, amivantamab, or negative control antibody and primary macrophage effector cells. ADCP was assessed on the Incucyte® system (pHrodo-Red fluorescence > 25 RCU).

- MCLA-129 and amivantamab induce antibody-dependent cell-mediated phagocytosis (ADCP) of tumor cells

ADCC OF MCLA-129 AND AMIVANTAMAB

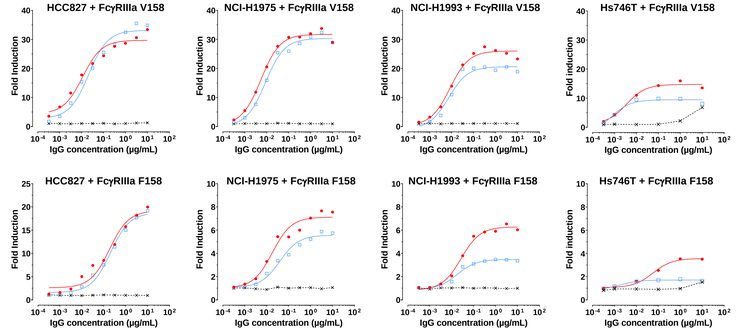


Figure 5 | ADCC induced by MCLA-129 and amivantamab towards tumor cell lines. High-affinity FcγRIIIa V158-variant (upper panel) or low-affinity FcγRIIIa F158-variant effector cells (lower panel) were used in ADCC reporter assays.

- Antibody-dependent cell-mediated cytotoxicity (ADCC) activity induced by MCLA-129 is more potent than that induced by amivantamab with either high-affinity (FcγRIII 158V) or low-affinity (FcγRIII 158F) variant Fcγ receptor effector cells

INHIBITION OF ADCC BY SOLUBLE EGFR AND c-MET

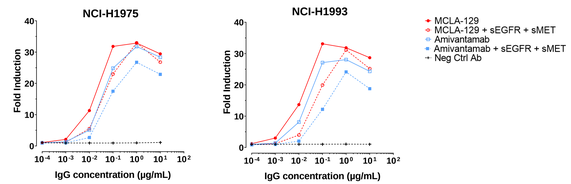


Figure 6 | Effect of soluble EGFR and c-MET on ADCC activity induced by MCLA-129 and amivantamab against NSCLC cell lines. sEGFR: soluble EGFR (100 ng/mL); sMET: soluble c-MET (2000 ng/mL).

- In the presence of soluble receptors, ADCC activity of MCLA-129 observed to be preserved to a greater extent than that of amivantimab

SUMMARY

- MCLA-129 is an Fc-enhanced common light chain bispecific human IgG1 Biclonics® antibody that specifically targets the receptor tyrosine kinases EGFR and c-MET
- MCLA-129 binds EGFR and c-MET with low nanomolar affinity
- MCLA-129 competes with an analog of the c-MET binding antibody onartuzumab for the same HGF-binding region of c-MET, which is distinct from the binding site of amivantamab
- No downmodulation of EGFR or c-MET was observed upon MCLA-129 or amivantamab treatment
- MCLA-129 and amivantamab induce ADCP of tumor cells
- ADCC activity of MCLA-129 is similar to or more potent than amivantamab, and observed to be preserved to a greater extent than amivantimab in the presence of soluble EGFR and c-MET
- These data provide support for the ongoing phase 1/2 study of MCLA-129 in patients with solid tumors (Study MCLA-129-CL01, NCT04868877)

References [1] Tsuji et al. Oncotarget. 2017; 8(42): 71805-71816; [2] Engelman et al. Science. 2007; 316(5827): 1039-1043; [3] Kong-Beltran et al. Cancer Res . 2006; 66(1): 283-289; [4] Zheng et al. MAbs. 2016; 8(3): 551-561; [5] Neijssen et al. J Biol Chem. 2021; 296:100641.

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