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ABSTRACT
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MCLA-129, a human anti-EGFR and anti-c-MET bispecific antibody, in patients with advanced NSCLC and other solid tumors: an ongoing phase 1/2 study

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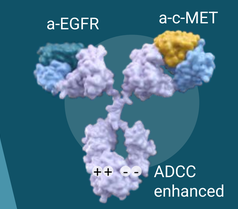


INTRODUCTION & BACKGROUND

- EGFR and c-MET activate similar intracellular signal transduction pathways to drive cancer cell proliferation, survival and invasion. In EGFR mutant non-small cell lung cancer (NSCLC), resistance to tyrosine kinase inhibitors (TKIs) is associated with increased c-MET signalling.[1]
- MCLA-129, an antibody-dependent cellular cytotoxicity (ADCC) enhanced full-length human IgG1 Biclonics® antibody targeting EGFR and c-MET, was developed in an empiric biological screen based on inhibition of proliferation, migration and overcoming TKI resistance **(Figure 1)**.[2]
- MCLA-129 inhibits ligand-dependent phosphorylation of EGFR and c-MET and displays ADCC and antibody-dependent cellular phagocytosis (ADCP) towards multiple NSCLC cell lines across a range of EGFR and c-MET expression levels and EGFR mutation genotypes.[2]
- MCLA-129 led to dose-dependent tumor inhibition in vivo, in multiple different NSCLC models including an EGFR exon20ins patient-derived NSCLC xenograft model.[3]
- MCLA-129-CL01 is an open-label phase 1/2 first in human trial (NCT04868877). Here, we report safety, pharmacokinetics (PK), pharmacodynamics (PD), antitumor activity and initial Recommended Phase 2 Dose (RP2D) of MCLA-129.

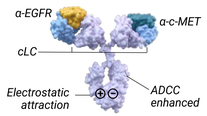
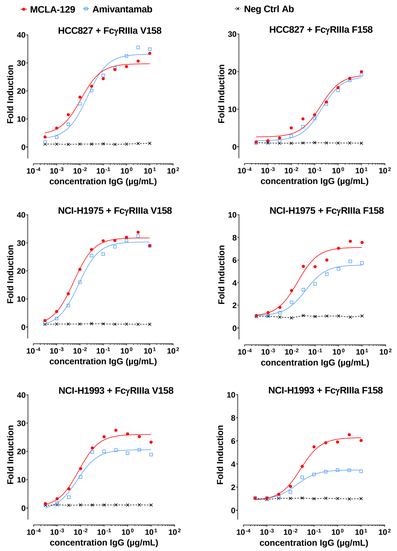


Figure 1 | MCLA-129 structure. A full-length, common light chain (cLC), electrostatic CH3-engineered (DEKK), ADCC enhanced (GlymaxX®) bispecific antibody targeting EGFR and c-MET



Cell line	EGFR mutation	Amplification
NCI-HCC827	del (E746,A750)	EGFR
NCI-H1975	L858R, T790M	NA
NCI-H1993	NA	c-MET

Figure 2 | ADCC activity of MCLA-129 in comparison to amivantamab. ADCC was tested against NSCLC cell lines expressing variant levels of EGFR and c-MET using both high (FcγRIIIa 158V) and low (FcγRIIIa 158F) affinity–variant effector cells

METHODS

- Patients enrolled in the dose escalation phase:
  - *Non-Small Cell Lung Cancer (NSCLC) harboring any activating EGFR mutation and/or c-MET mutation or amplification*
  - *Gastric cancer/Gastro Esophageal Junction adenocarcinoma harboring an EGFR amplification and/or c-MET amplification*
  - *Head and neck squamous cell cancer (HNSCC) or esophageal squamous cell cancer (ESCC) without biomarker selection*
- Dose escalation (100 mg – 1500 mg) was guided by an adaptive Bayesian Logistic Regression Model following the Escalation With Overdose Control principle
- Patients received intravenous MCLA-129 (flat dose) every 2 weeks (q2w), over a minimum of 2 hours
- Primary objective of escalation phase is to determine the maximum tolerated dose (MTD) and/or the initial RP2D
- Main secondary objectives are to evaluate antitumor activity, to characterize the PK of MCLA-129 including a population PK model and to assess changes in cytokines following administration of MCLA-129
- Exploratory objectives are to evaluate potential pharmacodynamic biomarkers of response to therapy, explore biomarkers in tumor and blood samples predictive of response or resistance to therapy and to evaluate additional biomarkers to investigate the drug and pathomechanism of disease

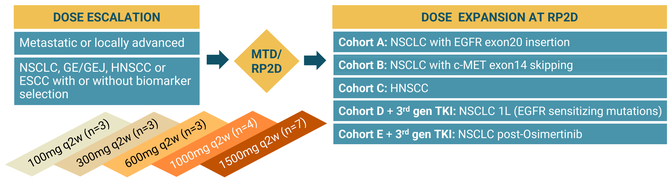


Figure 3 | MCLA-129-CL01 clinical trial (NCT04868877) design; n = number patients included per cohort

RESULTS

PATIENTS

- As of the cut off date of 08 May 2022, a total of 20 patients were enrolled and treated at 8 sites (US and EU)
- Patients were diagnosed with NSCLC (N=16), HNSCC (N=2) , GEJ (N=1) and ESCC (N=1)
- All patients with NSCLC had an alteration of EGFR or c-MET receptor; one patient with GEJ had a c-MET amplification; all other patients (N=3; 2 HNSCC and 1 ESCC) were included without biomarker selection
- At follow up (15 Aug 2022), the median duration of exposure was 12.6 weeks (range: 3–43 weeks)
- Six of the 20 patients continue to receive treatment at the cut off date

Table 1: Patient Characteristics	N=20
Age (years), median (range)	**65.5 (43–79)**
Female / Male	**60% / 40%**
ECOG 0 / 1 (%)	**65% / 35%**
Tumor type	
NSCLC	*16*
HNSCC	*2*
GEJ	*1*
ESCC	*1*
Mutation status NSCLC, n= 16	
EGFR del19	*8*
EGFR L858R	*4*
c-MET exon 14	*2*
EGFR exon 20	*1*
EGFR other: G719A, R776C	*1*
N of Metastatic Sites, median (range)	**2 (1-6)**
Brain involvement	*20%*
N of Lines of Prior Therapies, median (range)	**3 (1*-7)**
Prior Osimertinib	*12 **
Prior anti-PD-(L)1 inhibitors	*10*
Prior c-MET inhibitors	*3 ***
Race (%)	
Caucasian	*75%*
Asian	*25%*

** data updated post data cut off date*
*** including anti-EGFR/anti-c-MET bispecific antibodies*

SAFETY

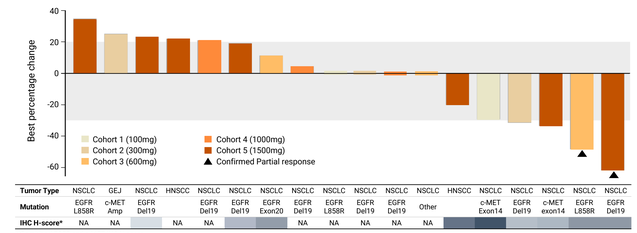
- Safety results are based on 20 patients who received one or more doses of MCLA-129 across all dose levels tested (analysis follow up 15 Aug 2022)
- No dose limiting toxicities (DLTs) were reported
- Most frequent AEs were infusion-related reactions (IRR)
  - *90% any grade, one patient (5%) grade 3, no grade 4-5*
  - *The majority of events occurred during the first infusion*
- Dermatitis acneiform was observed in 15% of patients, all grade 1-2
- Pruritis was observed in 15% of patients, all grade 1-2, except for one patient
- No treatment-related grade 4 or 5 AEs reported
- No patients discontinued MCLA-129 treatment due to toxicity
- No Interstitial Lung Disease reported

Table 2: Most frequent adverse events (>10%)	*Irrespective of causality*		*Suspected related*	
Preferred term	All grades n(%)	Grade 3-4 n(%)	All grades n(%)	Grade 3-4 n(%)
Any event	**19 (95%)**	**9 (45%)**	**19 (95%)**	**4 (20%)**
Infusion related reaction*	18 (90%)	1 (5%)	18 (90%)	1 (5%)
Dyspnea	11 (55%)	1 (5%)	9 (45%)	1 (5%)
Flushing	9 (45%)		9 (45%)	
Nausea	9 (45%)		8 (40%)	
Fatigue	6 (30%)	1 (5%)	3 (15%)	
Back pain	5 (25%)		2 (10%)	
Chills	5 (25%)		5 (25%)	
Myalgia	5 (25%)		4 (20%)	
Vomiting	5 (25%)		5 (25%)	
Cough	4 (20%)		3 (15%)	
Abdominal pain	3 (15%)		1 (5%)	
Arthralgia	3 (15%)		2 (10%)	
Dermatitis acneiform	3 (15%)		3 (15%)	
Lipase increased	3 (15%)		2 (10%)	
Oedema peripheral	3 (15%)		-	-
Pruritus	3 (15%)	1 (5%)	3 (15%)	1 (5%)

** Grouped term covering all AEs occurring within 24 hours of the infusion considered by the investigator as an IRR*

ANTI-TUMOR ACTIVITY

- Eighteen patients were evaluable for response in the dose escalation phase
- Antitumor activity, including 2 confirmed PR and 4 additional patients with > 20% reduction in target lesion size, was observed among heavily pretreated patients, across multiple tumor types and dose levels



**Combined EGFR and c-MET IHC H-score*

Figure 6 | Antitumor activity. Best percent change in sum of target lesions in patients evaluable for response. Immunohistochemistry (IHC) was performed on baseline tissue biopsy; color intensity reflects combined (EGFR + c-MET) IHC H-Score; NA = not available

Table 3 – Patients with evidence of antitumor activity (RECIST v1.1)					
Dose level (mg)	Tumor type	Mutation	Best response (% target lesions)	Cycle received	Prior treatments
1500	HNSCC		SD (-20%)	2	PB Cet N
100	NSCLC	c-MET exon 14	SD (-29.2%)	5	PB Cr Cap P
300	NSCLC	EGFR 19del	PD (-31.4%)	11 (+)	PB O P
1500	NSCLC	c-MET exon14	uPR (-33.3%)	3	PB Tep P
600	NSCLC	EGFR L858R	PR (-48.2%)	8 (+)	PB O P
1500	NSCLC	EGFR 19del	PR (-59.6%)	5 (+)	PB O N

PB: platinum based chemotherapy; O: osimertinib; N: nivolumab; P: pembrolizumab; Cr: crizotinib; Cap: capmatinib; Cet: cetuximab; Tep: tepotinib; (+) patient ongoing; PR partial response; uPR unconfirmed partial response; SD stable disease; PD progression disease

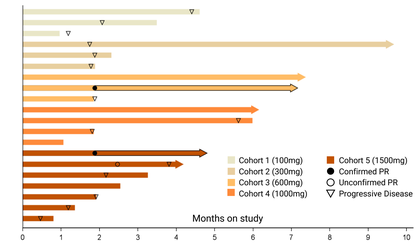


Figure 7 | Duration of exposure and time on therapy. Arrows indicate treatment is ongoing at the cutoff date

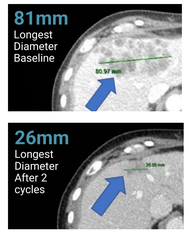


Figure 8| Patient with L858R EGFRm NSCLC: regression of liver metastasis at first tumor assessment

PHARMACOKINETICS & PHARMACODYNAMICS

- Saturation of non-linear target mediated clearance was observed after second dose at doses of ≥600 mg q2w **(Figure 4)**
- The estimated mean half-life at steady-state is ~200 hours based on population PK analysis
- Maximal inhibition of soluble EGFR and soluble c-MET occurs at doses of 1000 mg q2w and higher **(Figure 5)**
- The dose of 1500 mg q2w was predicted to achieve >95% tumor target engagement of EGFR and c-MET throughout the dosing cycle (data not shown)

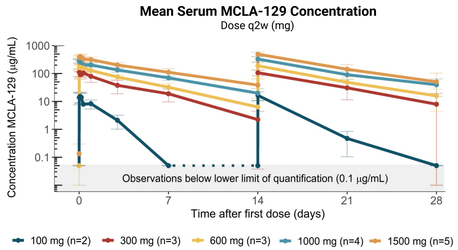


Figure 4| MCLA-129 Pharmacokinetics. Mean concentration-time profiles of MCLA-129 (± standard deviation) during the first treatment cycle

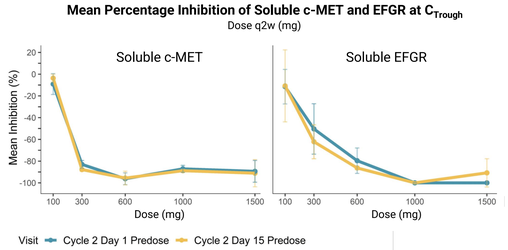


Figure 5| Soluble EGFR and c-MET inhibition. Mean observed inhibition of soluble EGFR and soluble c-MET (± standard deviation)

CONCLUSIONS

- MCLA-129 was observed to be well tolerated with a manageable safety profile
- Maximal inhibition of soluble EGFR and soluble c-MET was achieved at 1000 & 1500 mg q2w
- Tumor target engagement is predicted to be >95% throughout the dosing cycle at 1500 mg q2w
- Antitumor activity was observed among heavily pretreated patients, across multiple tumor types and dose levels
- Initial RP2D is 1500 mg IV q2w; expansion cohorts are enrolling

CONTACT

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