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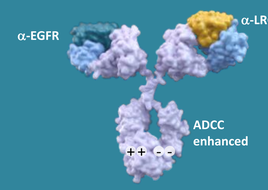
Phase I dose escalation study of MCLA-158, a first in class bispecific antibody targeting EGFR and LGR5, in metastatic colorectal cancer (CRC)



Abstract #62

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INTRODUCTION

- MCLA-158 is an ADCC enhanced human IgG1 Biclonics® bispecific antibody (bAb) targeting EGFR and LGR5.
- MCLA-158 was selected from functional screening of patient-derived organoids (PDO) generated from diagnostic/resection tissue of colorectal (CRC) patients.
- MCLA-158 exposure leads to EGFR signaling blockade and receptor degradation in LGR5+ cancer cells.
- MCLA-158 exhibits potent growth inhibition of *RASmut* and RAS*wt* CRC PDOs.
- Minimal growth inhibition is observed in non-tumoral PDOs treated with MCLA-158.
- In preclinical *in vivo* models MCLA-158 blocked metastasis initiation.

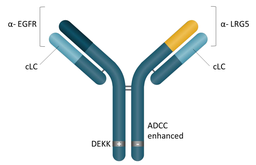


Figure 1 | MCLA-158 structure. A full-length, common light chain (cLC), CH3-engineered (DEKK), ADCC enhanced (GLYMAXX) bispecific antibody targeting EGFR and LGR5

PRECLINICAL BACKGROUND

- CRCs are formed by an organization of cells including cancer stem cells (CSCs) that exhibits long-term tumorigenic potential.
- Growth and survival of CRC cells depend on mitogenic signals triggered by receptor tyrosine kinases (RTKs) of the EGFR family.
- In colon cancer, CSCs are characterized by elevated levels of WNT pathway components including LGR5, and sustain self-renewal.
- MCLA-158 is a LGR5xEGFR bAb that binds with high affinity to EGFR (K_D: 0.22 nM) and LGR5 (K_D: 0.86 nM) in CHO antigen expressing cells, inducing EGFR signaling blockade and EGFR degradation resulting in potent and selective growth inhibitory activity against both wild type and oncogenic *KRAS* mutant cancers.
- MCLA-158 demonstrated potent anti-tumor activity in CRC, esophageal squamous, gastric adenocarcinoma and head & neck PDX models selected for high EGFR expression.

MCLA-158 induces EGFR degradation

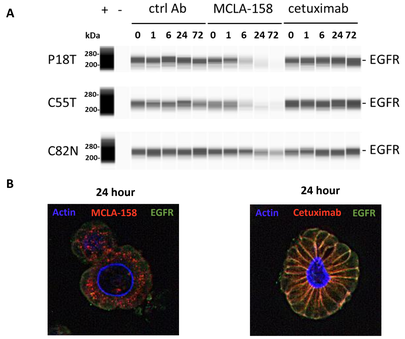


Figure 2 | MCLA-158 leads to EGFR degradation in EGFR+/LGR5+ colorectal cancer organoids. 2A, Virtual image of a capillary western blot, measuring EGFR levels in P18T (KRAS WT), C55T (KRAS G12V) and C82N (normal) organoid protein extracts. Antibodies were added at 1 µg/mL for the indicated timepoints, (+) = positive control, (-) = negative control. 2B, High magnification images of P18T organoids show that after 24h MCLA-158 localizes intracellularly in speckle-like patterns and overall EGFR expression is strongly reduced. For cetuximab-treated organoids EGFR expression is unaffected and mainly located at the cell membrane.

In vivo activity of MCLA-158 in gastric, esophageal and head & neck cancers

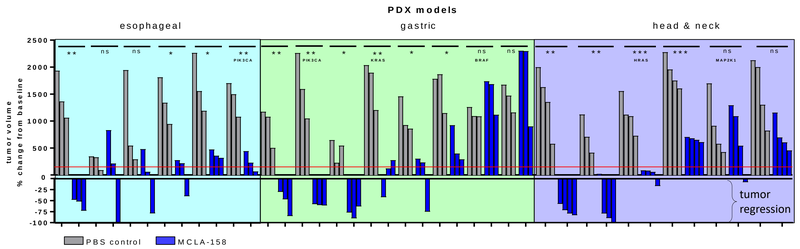
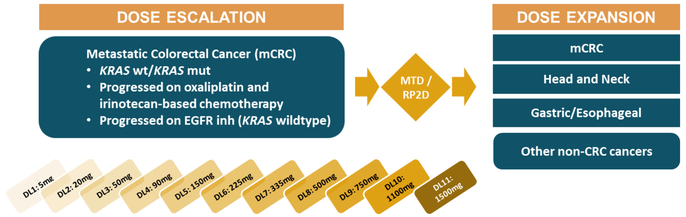


Figure 3 |MCLA-158 demonstrated tumor regression or growth inhibition in esophageal squamous, gastric adenocarcinoma and head & neck PDX models. Efficacy of MCLA-158 was tested in 6 esophageal, 8 gastric and 6 head & neck PDX models. All transplanted tumors expressed high levels of EGFR. Mice (n=3 or 4/group) were treated with 25 mg/kg/week MCLA-158 for 6 weeks. Fold change in tumor volume was calculated at the timepoint when all the animals were in the experiment. Unpaired t-test (*= p>0.05; **= p>0.01; ***= P>0.001; ns = not significant). Red line indicates stable disease threshold. Known pathogenic mutations for each model genes are indicated in the graph.

MCLA-158 demonstrated tumor significant growth inhibition in esophageal squamous (4/6), and gastric adenocarcinoma (6/8) and head & neck (4/6) PDX models selected for high EGFR expression.

OBJECTIVES AND METHODS

Phase I study, first in human, single agent , multicenter, at 5 sites in USA, Spain, France and Belgium



Objectives of Dose Escalation

Primary: to determine the recommended phase 2 dose (RP2D)

Secondary: Determine preliminary antitumor activity, pharmacokinetics (PK), immunogenicity and correlate biomarkers

Exploratory biomarkers were evaluated in in tumor tissue (FFPE and organoids), and blood (proteomics, CTCs, ctDNA)

Treatment: intravenous MCLA-158 (flat dose) every 2 weeks (q2w) over 4 hours during cycle 1 –Subsequent infusion can be reduced to 2 hours

Premedication: antihistamines, paracetamol and steroids

RESULTS

Patient characteristics

- A total of 33 patients with metastatic CRC were treated with MCLA-158 single agent across 11 dose levels (5 to 1500 mg). As of 7 September 2020, a median number of 2 (range 1-6) cycles were administered.
- All patients were previously treated with oxaliplatin/irinotecan-based combination therapies, all KRASwt patients were exposed to EGFR inhibitors.
- Tumoral EGFR expression (IHC) at baseline was low in the majority of patients: 61% of patients had IHC score 0 or 1+, for 75% of patients the H-score was below 60 (median H-score 15.5, Q1-Q3: 0 – 57.8)
- Median LGR5 mRNA expression (ISH) at baseline was H-score 158. **

Patient Characteristics	N=33
Age (years), median (range)	58 (35 – 76)
Female / Male	48% / 52%
ECOG 0 / 1	67% / 33%
***RAS* Status**	
Wild Type	18 (55%)
Mutant (KRAS)	14 (42%)
Mutant (NRAS)	1 (3%)
EGFR H-score*, n=28	
Median (range)	15.5 (0 – 200)
Q1-Q3	0 – 57.8
EGFR IHC score, %, n=28	
0 / 1+ / 2+ / 3+	29 / 32 / 32 / 7
Soluble EGFR (ng/mL), n= 22	
Median (range)	2.6 (0.9-7.4)
LGR5 ISH H-score, n=28**	
Median (range)	158 (0 – 323)
Q1-Q3	99 – 214
N of Metastatic Sites, median (range)	3 (1 – 12)
Liver involvement	28 (85%)
N of Lines of Prior Therapies, median (range)	4.0 (1 – 10)
Prior chemotherapy	33 (100%)
Prior oxaliplatin-based or inotecan-based chemotherapy	33 (100%)
Prior EGFR inhibitors (if *KRAS* wildtype)	18 (55%)
Prior anti-angiogenic therapies	25 (76%)

* possible range 0-300, ** possible range 0-400

Table 1 | Patient characteristics and prior treatment of colorectal cancer patients (N=33)

MCLA-158 safety profile

- No dose limiting toxicities (DTLs) were observed.
- No deaths were attributed to the study drug.
- No grade 3-4 skin toxicities were seen.
  - Rash and dermatitis were seen from dose ≥ 335 mg.
  - All events were mild or moderate.
  - Acneiform dermatitis or rash were reported for 36% of patients
- Low incidence of diarrhea, a single grade 3 event.
- 22 patients (66.7%) experienced infusion-related reactions, most of which were Grade 1-2 and managed with medication including paracetamol, H1 antagonists, and steroids.
  - 4 patients had grade 3 IRR.
  - All except 1 IRR event occurred in the first cycle of treatment.

	Irrespective of causality		Suspected related	
	All grades	Grade 3-4	All grades	Grade 3-4
Preferred term	n(%)	n(%)	n(%)	n(%)
-- Any event	32 (97.0%)	12 (36.4%)	29 (87.9%)	5 (15.2%)
Nausea	9 (27.3%)	1 (3.0%)	8 (24.2%)	1 (3.0%)
Chills	8 (24.2%)	1 (3.0%)	8 (24.2%)	1 (3.0%)
Dermatitis acneiform	8 (24.2%)	0	8 (24.2%)	0
Vomiting	8 (24.2%)	0	6 (18.2%)	0
Pyrexia	7 (21.2%)	0	3 (9.1%)	0
Diarrhoea	6 (18.2%)	1 (3.0%)	5 (15.2%)	1 (3.0%)
Rash	6 (18.2%)	0	6 (18.2%)	0
Asthenia	5 (15.2%)	0	0	0
Dyspnoea	5 (15.2%)	2 (6.1%)	4 (12.1%)	1 (3.0%)
Anaemia	4 (12.1%)	1 (3.0%)	0	0
Back pain	4 (12.1%)	0	0	0
Bronchospasm	4 (12.1%)	1 (3.0%)	3 (9.1%)	1 (3.0%)
Conjunctivitis	3 (9.1%)	0	0	0
Constipation	3 (9.1%)	0	0	0
Cough	3 (9.1%)	0	0	0
Dysphonia	3 (9.1%)	0	0	0
Erythema	3 (9.1%)	0	3 (9.1%)	0
Fatigue	3 (9.1%)	0	0	0
Flushing	3 (9.1%)	0	3 (9.1%)	0
Gastrooesophageal reflux disease	3 (9.1%)	0	0	0
Oedema peripheral	3 (9.1%)	0	0	0

Related G3 AEs of hypotension, hypoxia, hypertension and hypophosphatemia were reported in 1 patient each.

Table 2 | Most frequent treatment-emergent adverse events in ≥ 7.5% patients (N=33)

RESULTS

MCLA-158 antitumor activity and target expression in mCRC patients

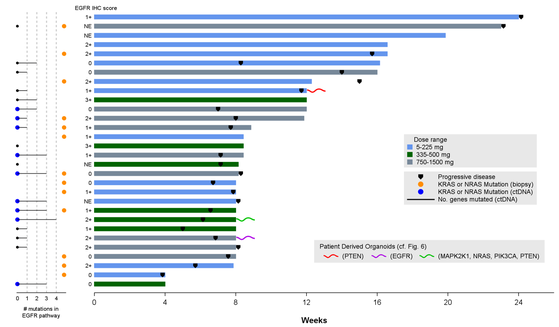


Figure 4 | Duration of exposure, indicators next to the Y-axis list EGFR IHC score, KRAS/NRAS mutation and number of mutations in EGFR pathway genes

Duration of exposure is defined as the time between first dose and the planned end date of the last cycle in which the last dose of MCLA-158 was administered. For 28-day cycle with 2 infusions, the last date of exposure is the date of the first infusion in the last cycle + 27 days.

- As of the cut off date, all patients had discontinued treatment.
- Efficacy population included 30 CRC patients who either had at least 1 postbaseline tumor assessment or discontinued due to progressive disease.
- No objective responses were reported.
- The clinical benefit rate (CBR), defined as the number of patients without disease progression for > 12 weeks, was 23%. These patients were characterized by
  - Higher tumoral expression of EGFR
  - Absence of *KRAS* mutations as detected in ctDNA.
- The odds of clinical benefit in patients with EGFR IHC score 2+ or above was 3 times higher than in patients with IHC score 0 or 1+ although this did not reach statistical significance.
- No correlation of clinical benefit with baseline LRG5 expression was observed.
- All patients with *KRAS* mutations as detected in ctDNA had progressed at the first tumor assessment (outright progressors).

PK, receptor occupancy, and cytokines

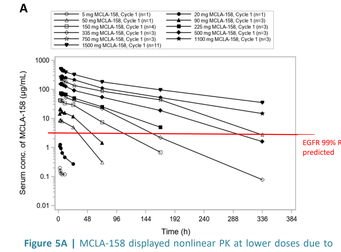


Figure 5A | MCLA-158 displayed nonlinear PK at lower doses due to target-mediated clearance. Terminal half-life was 4 days at the RP2D of 1500 mg q2w.

- Linear PK observed at doses above 750 mg suggested full target saturation.
- More than 99% receptor occupancy (RO) was predicted for the entire 2 weeks dosing interval at 750 mg and above.
- At 1500 mg q2w (RP2D) mean steady state trough levels exceed those of cetuximab (250 mg/m2) and panitumumab (6 mg/kg)

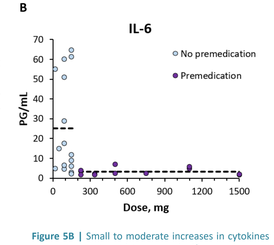


Figure 5B | Small to moderate increases in cytokines were observed, which were significantly reduced after premedication (only shown for IL-6).

MCLA-158 efficacy in patient derived organoids

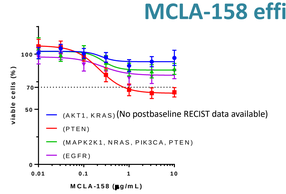


Figure 6 | MCLA-158 efficacy in organoids derived from patients with liver metastases. Organoids were generated from tumor biopsy samples collected at baseline and prior to treatment, and were tested for MCLA-158 efficacy. Organoids were split the day before treatment and cultured in the presence of 5 ng/mL EGF. After 5 days of MCLA-158 treatment, cell viability was assessed using Cell-Titer Glo. The dotted line indicates 30% inhibition. Only the PDO from the patient indicated with the red line showed > 30% growth inhibition with MCLA-158 *ex vivo*. Mutations in EGFR signaling pathway genes, as measured in ctDNA from the corresponding patients, are shown between brackets. Corresponding patients from whom postbaseline RECIST data was available are indicated in Figure 4.

CONCLUSIONS

- MCLA-158 was well tolerated, throughout the dose escalation. No maximum tolerated dose was established. No DLTs were observed. The RP2D was established at 1500 mg based on RO and predicted exposure.
- In a heavily pretreated population of mCRC patients, the CBR at 12 weeks was 23% and associated with relatively higher expression of EGFR in tumor.
- No objective responses were observed. The ctDNA analysis showed that most mCRC patients with progression after 2 cycles harbored a *KRAS* mutation or other genetic alterations in the EGFR signaling pathway.
- MCLA-158 exposure led to EGFR signaling blockade and receptor degradation in LGR5+ cancer cells. Potent antitumor efficacy was observed in PDX models selected for high EGFR expression.
- Enrollment is ongoing exploring gastro-esophageal and head & neck tumors. Preliminary evidence of antitumor activity has been observed.

Contact Information

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