**INTRODUCTION**

- MCLA-158 is an ADC composed of a humanized IgG1 anti-EGFR monoclonal antibody (mAb) targeting EGFR and LGR5.
- MCLA-158 was selected from Functional screening of patient-derived organoids (PDO) generated from diagnostic/excision 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 4T1 and CRC PDO.
- Minimal growth inhibition is observed in non-tumoral PDOs treated with MCLA-158.
- In preclinical in vivo models MCLA-158 blocked metastasis initiation.

**PRECLINICAL BACKGROUND**

- CRCs are formed by an organization of cells including cancer stem cells (CSCs) that exhibits long-term humoral characteristics. Long-term survival of CRCs depends on mitigating signals triggered by mesenchymal tyrosine kinases (MTKs) of the EGFR family.
- A CSC-rich tumor shows CD133+ cell areas located in the tumor core preferentially expressing CD133, common to tumor-initiating cells (TICs) and associated with the expression of stemness genes.
- Most CRCs, CSCs, and organoids are characterized by elevated levels of CSC pathway components including LGR5, and maintain self-renewal.
- MCLA-158 is a LGR5-directed ADC that binds with high efficacy to EGFR (Kd = 0.33 nM) and LGR5 (Kd = 0.16 nM) in CHO antigen expressing cells, including EGFR signaling blockade and receptor degradation resulting in patient and selective intracellular signaling suppression associated with CSC depletion.

**OBJECTIVES AND METHODS**

**DOSE ESCALATION**

- Metastatic Colorectal Cancer (mCRC) patients were enrolled in a Safety and Pharmacokinetics study across 2 dose levels: MCLA-158 10 mg/kg (N=27) and MCLA-158 30 mg/kg (N=27).

**PK, receptor occupation, and cytokines**

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

- A total of 33 patients with metastatic CRC were treated with MCLA-158 single agent arm. 11 dose levels (5 to 1500 mg) were administered.
- All patients were pretreated with oxaliplatin/irinotecan-based combination chemotherapy, all K-RAS patients were excluded.
- Tumoral EGFR expression (IC) at baseline was ≥ 12%
- Median LGR5+ cell expression (ISI) at baseline was ≤ 5%.

**RESULTS**

- No dose limiting toxicities (DLTs) were observed.
- No deaths were attributed to the study drug.
- No grade 4 skin toxicities were seen.
- No rash and dermatitis were seen from dose ≥ 150 mg.
- No adverse events were noted in patients with EGFR mutations.
- No progression of disease was observed.
- Median number of cycles was 6 (range 2-9).
- In patients with ≥ 1 prior chemotherapy, median days to progression was 16 (range 2-70).

**CONCLUSIONS**

- MCLA-158 was well tolerated, throughout the dose escalation. No maximum tolerated dose was established. No DLTs were observed. The RPD was established at 1500 mg based on RO and predicted exposure.
- In a heavily pretreated population of mCRC patients, the CR at 12 weeks was 23% and associated with relatively higher expression of EGFR in tumors.
- No objective responses were observed. The cStDx analysis showed that most mCRC patients with progression after 2 cycles harbored a KRAS mutation or other genetic alterations in the EGFR pathway signatures.
- MCLA-158 exposure led to EGFR signaling blockade and receptor degradation in LGR5+ cancer cells. Potent antitumor efficacy was observed in PDO models selected for high EGFR expression.

**MCLA-158 efficacy in patient derived organoids**

**Contact Information**


*Vall d’Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain, †Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, ‡University Hospital 12 de Octubre, Madrid, Spain, §Sarah Cannon Research Institute/Tennessee Oncology, Nashville, USA, ¨Oncology Therapeutic Development, Chicky, France, ¶Merrin NV, Utrecht, The Netherlands, #Institut Gustave Roussy, Villejuif, France