MCLA-128 is a bispecific humanciligen full-length IgG1 antibody that binds to the transmembrane receptor tyrosine kinase human epidermal growth factor receptors type 2 (HER2) and 3 (HER3) and was developed to inhibit HER2-HER3 driven cell growth and to overcome HER2-mediated resistance (primary or acquired) and/or reliance under HER2 or EGFR-targeted therapies, a phenomenon frequently observed in epithelial tumours and carcinomas.

MCLA-128 acts via two independent mechanisms of action: 1) inhibition of HER2-HER3 signalling and 2) elimination of tumour cells via enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).

Using a DOCK & BLOCK® mechanism identified by X-ray crystal structure, MCLA-128 docks to the HER2 domain I, which orients the HER3 binding arm to block the HER3 domain III (pseudokinase domain), thus blunting oncogenic signalling via the HER2-HER3 heterodimer (Gauvin et al. 2018).

Potential in vitro and in vivo anti-tumour activity is seen, including stronger inhibition of HER2-amplified cells at high HRG concentrations compared to other anti-HER2 and anti-HER3 antibodies (Gauvin et al. 2018).

Based on these data and translational PK-PD modeling (de Vries et al. 2018), a first-in-human study was initiated with an initial dose phase 1 finding in advanced/metastatic epithelial solid tumours, followed by a Phase 2 expansion in the RP2D in selected patient cohorts.

In the Phase 2 part, no DLTs were observed from 40 to 900 mg MCLA-128 (Flat dose) every 3 weeks (q3w). The RP2D of single agent MCLA-128 was determined to 750 mg q3w (Cali et al. 2016).

Early evidence of anti-tumour activity has been observed in metastatic breast cancer (Alsina et al. 2017) supporting further development of MCLA-128 in combination.

We report data from the ongoing Phase 2 part on overall safety data at the RP2D and anti-tumour activity in gastrin/gastroesophageal junction (GC/GEJ) patients.

**SAFETY - RP2D**

At the safety cut-off date (15 February 2018), the 97 patients treated in the Phase 2 part at 750 mg q3w had received a median of 2 cycles (range 1-7).

**CONCLUSIONS**

Single agent MCLA-128 administered at the RP2D is well tolerated, with a low incidence of grade 3-4 related toxicity.

PK data support flat dosing of MCLA-128 at 750 mg every 3 weeks.

MCLA-128 shows a low risk for immunogenicity.

Promising evidence of activity of single agent MCLA-128 including a durable complete response in a HER2+ double primary tumour patient in combination with other agents.

MCLA-128 shows a low risk for immunogenicity.

MCLA-128 warrants further evaluation in combination in GC/GEJ patients.

**REFERENCES**


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