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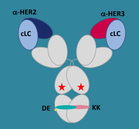


Phase 1/2 study of single agent MCLA-128, a full length IgG1 bispecific antibody targeting the HER3 pathway: overall safety at the recommended Phase 2 dose (R2PD) and preliminary activity in HER2+ metastatic gastric/gastroesophageal junction cancer (GC/GEJ)

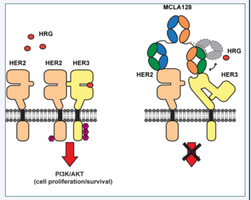
#664P

M Alsina[1], A Varga[2], A Amatu[3], JHM Schellens[4], P Witteveen[5], V Boni[6], V Moreno[7], P Nuciforo[1], A de Vries Schultink[4], K Bol[8], A Lourbakos[8], M Magin Ferrer[8], E Wasserman[8]

1. Vall d'Hebron University Hospital, Barcelona, Spain; 2. DITEP, Gustave Roussy, Villejuif, France; 3. Niguarda Hospital, Milan, Italy; 4. Netherlands Cancer Institute, Amsterdam, The Netherlands; 5. University Medical Center Utrecht, The Netherlands; 6. START CIOCC, Madrid, Spain; 7. START FJD, Madrid, Spain; 8. Merus N.V., Utrecht, The Netherlands.

BACKGROUND

- MCLA-128 is a bispecific humanized full-length IgG1 antibody that binds the transmembrane receptor tyrosine kinase human epidermal growth factor receptors 2 and 3 (HER2 and HER3). It was developed to inhibit HER2:HER3-driven cell growth and to overcome HER3-mediated resistance (primary or acquired) and/or relapse under HER2- or EGFR-targeted therapies, a phenomenon frequently observed in epithelial tumours.
- 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 (putative HRG domain), thus blocking oncogenic signalling via the HER2:HER3 heterodimer [Geuijen et al. 2018].



- Potent *in vitro* and *in vivo* anti-tumour activity is seen, including stronger inhibition of proliferation of HER2-amplified cells at high HRG concentrations compared to other anti-HER2 and anti-HER3 antibodies [Geuijen et al. 2018].
- Based on these data and translational PK-PD modeling [de Vries Schultink et al, 2018], a first-in-human study was initiated with an initial Phase 1 dose-finding part in advanced/metastatic epithelial solid tumours, followed by a Phase 2 expansion at the RP2D in selected patient cohorts.
- In the Phase 1 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 be 750 mg q3w [Calvo 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, including overall safety data at the RP2D and anti-tumour activity in gastric/gastroesophageal junction (GC/GEJ) patients.

STUDY DESIGN & OBJECTIVES

- In the Phase 2 part, patients with selected tumour indications are treated at the RP2D of 750 mg, 2 h IV, q3w, with premedication consisting of antipyretics, antihistamines and corticosteroids.
- Phase 2 study objectives:
  - ✓ **Primary objectives:** to characterize safety/tolerability at the RP2D, and anti-tumour activity according to RECIST v1.1, per local investigator's assessment.
  - ✓ **Secondary objectives:** to characterize the pharmacokinetics (PK) and immunogenicity profiles at the RP2D.
  - ✓ **Exploratory analyses:** identification of potential biomarkers and their relationship with anti-tumour activity.

PATIENT POPULATION

As of 15 February 2018, 100 patients had been enrolled in the Phase 2 part of the study, 97 of whom had been treated. Five expansion cohorts are being evaluated.

Demographics and disease characteristics

	Phase 2 part (N=100)	GC/GEJ (N=26*)
Age (years), median (range)	59 (30-81)	59 (30-81)
Gender (male), N (%)	26 (26%)	23 (89%)
ECOG PS (0/1), N (%)	36 (36%)/63 (63%)**	9 (35%) / 17 (65%)
N prior systemic lines, median (range)	4 (1-18)	2.5 (1-6)
N prior anti-HER2 lines, median (range)	-	1 (1-3)
N metastatic sites, median (range)	2.5 (1-6)	3 (1-6)
Tumour type		
Ovarian	37 (37%)	-
GC/GEJ	23 (23%)	14 (54%) / 12 (46%)
Endometrial	18 (18%)	-
Breast	14 (14%)	-
NSCLC	7 (7%)	-
CRC	1 (1%)	-

*GC/GEJ efficacy cohort includes 23 Phase 2 patients + 3 Phase 1 patients (1 at 750 mg q3w; 2 at 900 mg q3w)
** Missing data for 1 patient

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 1-27).

Related AEs in >2% of Phase 2 patients CTCAE v4.03 (N=97)

Preferred term (PT)	G1-4	G3-4
Diarrhoea	16 (16.5)	0
Asthenia	8 (8.2)	1 (1.0)
Fatigue	7 (7.2)	0
Infusion-related reaction	7 (7.2)	1 (1.0)
Nausea	6 (6.2)	0
Decreased appetite	5 (5.2)	0
Chills	3 (3.1)	0
Hypersensitivity	3 (3.1)	1 (1.0)*
Myalgia	3 (3.1)	1 (1.0)
Vomiting	3 (3.1)	0
Dyspnoea	2 (2.1)	1 (1.0)
Mucosal inflammation	2 (2.1)	0
Pyrexia	2 (2.1)	0
Stomatitis	2 (2.1)	0

*A 71-year-old GC patient had a grade 4 hypersensitivity reaction on D1C1 followed by cardiorespiratory arrest. The patient's baseline cardiac condition (severe aortic stenosis) contributed to the fatal outcome.

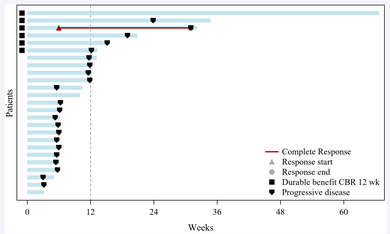
AEs OF SPECIAL INTEREST

- **Infusion related reactions (IRRs):** Eighteen (19%) patients had PTs reported by investigators as manifestations of IRRs (including IRR, vomiting, hypersensitivity, pyrexia, nausea, etc.). Most patients (16/18) experienced G1-2 events in cycle 1.
- **Decreased cardiac ejection fraction:** No clinically significant suspected cardiac AEs occurred. Two of 36 patients with ≥1 post-baseline evaluation had grade 2 LVEF decreases; neither were symptomatic or with LVEF < 50%.
- **Diarrhoea**: No grade 3-4 diarrhoea or diarrhoea requiring treatment discontinuation was observed.

GC/GEJ ANTI-TUMOUR ACTIVITY

- Anti-tumour activity (RECIST v1.1) is reported in 26 GC/GEJ patients, all with locally confirmed HER2 amplification (2+ IHC confirmed by FISH, or 3+ IHC).
- At the efficacy cut-off of 12 August 2018, of 25 evaluable GC/GEJ patients, 1 had a CR lasting 5.8 months and 10 had SD (range 2.3 to 15.4 months; Fig. 1, 2).
- The clinical benefit rate (CBR; CR + PR + SD ≥ 12 weeks) was 24% (6/25 patients; Table & Fig. 1). Central analysis confirmed all 6 CBR patients as HER2 positive (Table).
- Retrospective central review of available fresh tumour samples taken at study entry showed 3/15 (20%) patients with a best response of PD had loss of HER2 expression.

Fig. 1: Swimmer plot of treatment duration (weeks), response and CBR (N=25)



Characteristics of GC/GEJ patients with CBR

Pt ID / tumor type	Metastatic sites	N prior lines	N HER2 lines	HER2 status IHC/FISH*	MCLA dose (mg)	N inf.	Best response (RECIST)	Duration CR/PR/SD (weeks)
#1 GEJ	lung, lymph node, pleura	2	2	3+/Amp (A)	900	17	SD	66.7
#2 GEJ	abdomen/viscera, peritoneum, omentum	3	3	2+/Amp (F)	750	12	SD	23.9
#3 GC	lymph node	1	1	3+/Amp (F)	750	10	CR	25.1
#4 GEJ	mediastinum	2	1	3+/Amp (A)	750	6	SD	19.0
#5 GEJ	bone, liver, lung, pleura	3	1	2+/Amp (A)	750	5	SD	14.9
#6 GC	bone, liver, lymph node	1	1	3+/Amp (F)	750	4	SD	12.1

*Centrally confirmed; Amp, amplified; A, archived biopsy; F, fresh biopsy; inf, infusion.

Fig. 2: Best % change from baseline in target lesions in patients with measurable disease (N=23)

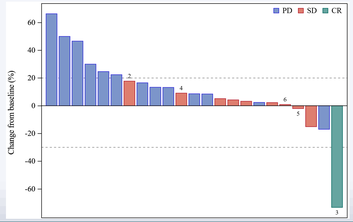
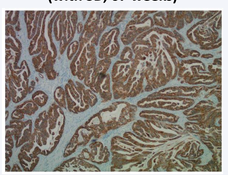
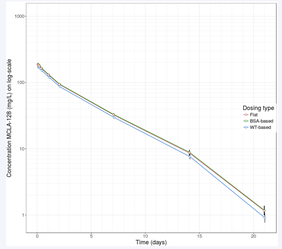


Fig. 3: Example IHC of HER2 ICH3+ tumour tissue from patient #1 (with SD, 67 weeks)



PK & IMMUNOGENICITY

- PK data from 96 evaluable Phase 2 patients were assessed by non-compartmental analysis. Mean C_{max} was 250 µg/mL; AUC_{∞} was 26400 µg·h/mL; V_{ss} was 3.9 L; CL was 33 mL/h ; T½ was 101 h. Mean trough levels were 6.9 µg/mL, well above the *in vitro* concentrations that result in 50% HER2/3 receptor occupancy.
- 6 out 129 patients had a positive anti-drug-antibody (ADA) titre. Only one patient (previously reported [Alsina et al 2017]), presented elevated titres (this patient, treated at 160 mg, showed elevated titres at day 36 with no apparent effect on PK).



Mean (±SD) of 1000 simulated MCLA-128 concentration-time profiles (Cycle 1) following flat, body surface area (BSA) and weight (WT)-based dosing.

Simulations using a population PK model based on the combined data from Phase 1 and 2 patients (N=128) demonstrated that a fixed dose of MCLA-128 in patients with various solid tumors is appropriate.

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 q3w.
- MCLA-128 shows a low risk for immunogenicity.
- Promising evidence of activity of single agent MCLA-128 including a durable complete response has been shown in HER2-positive metastatic GC/GEJ pretreated patients progressing on 1 to 3 prior HER2 therapies.
- Loss of HER2 protein in fresh tumour samples highlights a need to integrate tumour evaluation at study entry into patient selection in future studies with MCLA-128.
- MCLA-128 warrants further evaluation in combination in GC/GEJ patients.

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- Calvo et al. *Cancer Res.* AACR 2016;76 (14 Suppl) CT050
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CONTACT

Enquiries@Merus.nl. Study funded by Merus N.V.
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