UPDATE FROM THE ONGOING PHASE I MULTINATIONAL STUDY OF MCLA-117, A BISPECIFIC CLEC12A X CD3 T-CELL ENGAGER, IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA

EUROPEAN HEMATOLOGY ASSOCIATION

EP538

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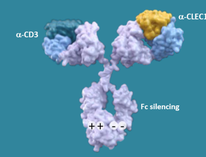

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INTRODUCTION

- MCLA-117 Biclonics® binds with high affinity to CLEC12A, expressed on AML blasts and leukemic stem cells, and with relative lower affinity to CD3 expressed on T cells.
- Targeting CLEC12A-expressing cells by MCLA-117 is designed to preferentially eradicate AML blasts and leukemic stem cells, while sparing normal hematopoietic stem cells.
- In preclinical studies, MCLA-117 activated resting T cells resulting in killing of CLEC12A$^+$ AML blasts and T cell cytokine release[1].
- The PK profile associated with the full-length IgG format permits short (2-hr) intravenous administration and the silenced Fc region effector function permits specificity for CLEC12A, to avoid side effects caused by non-specific Fcγ receptor-mediated T cell activation.

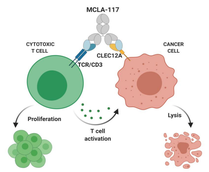


Fig 1 |MCLA-117 mode of action

OBJECTIVES & METHODS

- The study aims were to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, preliminary efficacy of MCLA-117, and to determine the MTD/RP2D.
- MCLA-117 is given as a single agent including a ramp-up phase, currently at 5/15/25 mg flat dose on Days 1, 4, and 8, followed by weekly infusion at the target dose starting on Day 15. Mandatory premedication included H1/H2 blockers, no steroids.

Cohort	D1	D3	D5	D8	D11	D15	D22
1	25 µg	50 µg	100 µg	200 µg	300 µg	450 µg	675 µg
2	100 µg	200 µg	400 µg	750 µg	1000 µg	1250 µg	1500 µg
Cohort	D1		D4		D8, D15, D22		
3	300 µg		1 mg		2 mg		
4	600 µg		2 mg		6 mg		
5	600 µg		2 mg		9 mg		
6	1 mg		3 mg		15 mg		
Cohort	D1		D4		D8	D15	D22
7	1 mg		3 mg		15 mg	25 mg	25 mg
8a	1 mg		3 mg		25 mg	40 mg	40 mg
8b	3 mg		10 mg		25 mg	40 mg	40 mg
9	5 mg		15 mg		25 mg	60 mg	60 mg
10	5 mg		15 mg		25 mg	120 mg	120 mg
11	5 mg		15 mg		25 mg	240 mg	240 mg
12	5 mg		15 mg		25 mg	400 mg	400 mg

Table 1 | Dose escalation scheme at Cycle 1 of treatment

BASELINE CHARACTERISTICS

As of 31 March 2020, 58 patients have been treated across 11 dose levels and received a median of 5 infusions (target dose range 0.675-240 mg).

Characteristics	% (N=58)
Median age, year (range)	72.5 (19-86)
Female / Male	36.2 / 63.8
Primary AML	51.7
Secondary AML	44.8
High risk MDS (IPSS-R score >6)	3.4
ECOG 0 / 1 / 2	31.0 / 48.3 / 20.7
AML WHO classification:	
- AML NOS	57.1
- AML with myelodysplasia related changes	25.0
- AML with recurrent genetic abnormalities	12.5
- Therapy related myeloid neoplasms	5.4
Prior HSCT	8.6
Disease status at study entry	
primary refractory / relapsed / untreated	60.3 / 29.3 / 10.3

Characteristics	% (N=58)
AML cytogenetic risk	
- low	10.3
- intermediate	50.0
- high	34.5
- not applicable	3.4
- missing	1.7
Number of prior lines of anti-AML treatment	
- 0	8.6
- 1	31.0
- 2	8.6
- 3	17.2
- ≥ 4	34.5
CLEC12A expression median (range, Q1-Q3)	61.5 (2-100, 28-78)

RESULTS

Ramp-up scheme for gradual increase of MCLA-117 serum concentrations and IL-6 response

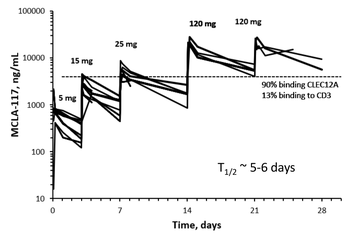


Fig 2 | Serum concentrations of MCLA-117 (n=9) following ramp-up and target dose (120 mg). Horizontal line indicates level of predicted monovalent binding to CLEC12A and CD3.

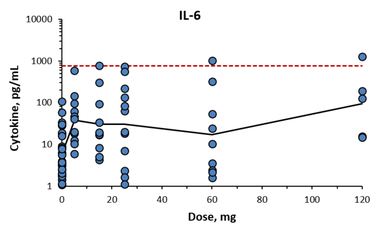


Fig 3 | Serum IL-6 levels, predose and 4h post infusion during ramp-up and target dose (60/120 mg). Black line connects geomeans of each dose. Red line indicates mean IL-6 level reported for Blincyto[3].

RESULTS

MCLA-117 safety profile

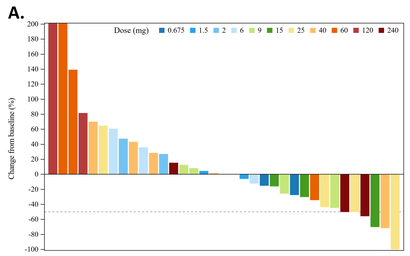
Overall (N=58)		
Preferred Term	**All grade (%)**	**Grade 3 – 4** (%)**
At least one related TEAE	79	22.4
Cytokine release syndrome*	36.2	8.6
Pyrexia	32.8	0
Chills	22.4	0
Infusion site phlebitis	12.1	0
Nausea	12.1	0
Vomiting	12.1	0
Hypotension	6.9	0
Tachycardia	6.9	0
Confusional state	5.2	0
Febrile neutropenia	5.2	5.2
Headache	5.2	0
Hypertension	5.2	3.4
Hypoxia	5.2	3.4
Infusion related reaction	5.2	0

*CRS events graded according to ASTCT consensus[2].
** Only one grade 4 suspected related event reported (transient asymptomatic ALT elevation in the setting of CRS).

Table 2 | Summary of related TEAEs in ≥5% of treated patient

- No dose limiting toxicities observed.
- No deaths attributed to study drug.
- 2 related SAEs seen in 2 pts, transient G3-4 liver enzyme elevations and G1-3 skin toxicity (G3 resolved).
- 1 related G4 ALT elevation occurred after CRS G2 event, treated with tocilizumab. Re-challenge didn't cause a new episode of transaminitis or CRS.
- 21 patients experienced CRS (36.2%), most of which Grade 1-2. 16 were treated with tocilizumab which readily reverted CRS. Most events recovered within 24 hrs.
- All suspected related neurological events were G1-2.
- 1 related AE (G3 fatigue) led to treatment discontinuation.

BM blast reduction across several dose levels



% change from baseline in BM blast count by CLEC12A expression

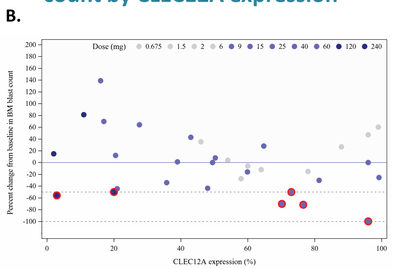


Fig 4 | Best % change from baseline in bone marrow (BM) blast count, of patients with postbaseline assessment, by (A) dose level and (B) CLEC12A expression at baseline. BM blast reduction of ≥50% observed in 6 patients (marked with red circles), 4 had CLEC12A >70% and 2 patients with low CLEC12A (3% and 20%) received the highest dose of 240 mg.

T cell activation demonstrated by post-dose CD69 upregulation in PB T cells and T cell margination

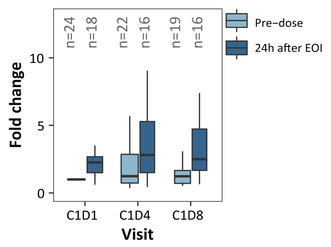


Fig 5 | Percentage of CD69+ T cells increased post dosing. Only patient cohorts 7-10 included. Number of patients indicated above each box.

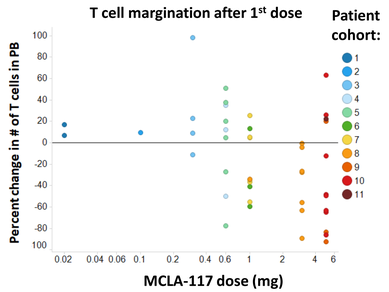


Fig 6 | Reduction in peripheral blood T cells 24 hours post 1st dose. Odds ratio of T cell margination upon first infusion is 1.5 per 1 mg increase (95% CI: 1.1-2.2).

Blast count reduction associated with cytokine elevations, T-cell margination and recovery in one patient in cohort 8

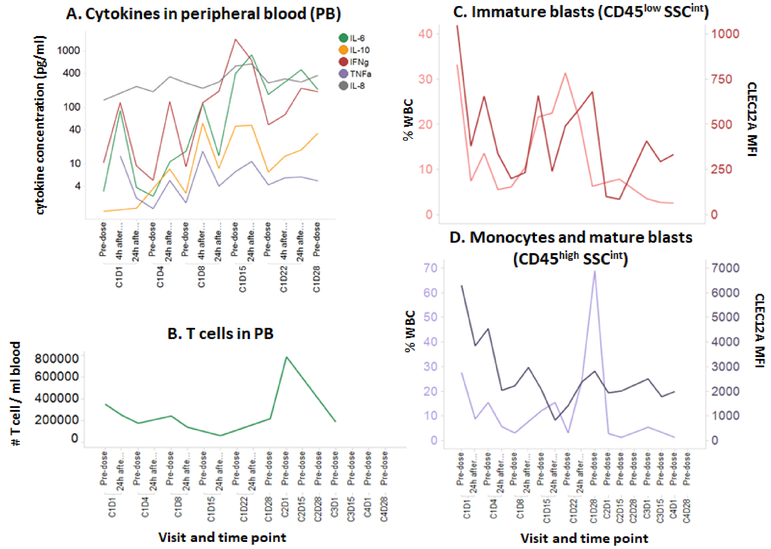


Fig. 7 | T cell activation observed by (A) cytokine secretion including IFN-γ and (B) peripheral T cell numbers at 1st dose followed by recovery at end of cycle 1. (C-D) Not only AML blasts, but also monocytes (which are difficult to distinguish from mature blasts) express CLEC12A. Percentage CLEC12A$^+$ cells was reduced at 1st dose and remained low from Cycle 2 onwards. CLEC12A MFI decreased on all CLEC12A$^+$ cells, but no outgrowth of CLEC12A^{low} cells in cycles 2-4.

CONCLUSIONS

- MCLA-117 is safe and well tolerated with manageable CRS events, following a ramp-up dosing scheme. No MTD reached up to dose of 240 mg.
- Clinical activity is observed with ≥ 50% blast reduction in BM, including 1 patient achieving morphological leukemia free state.
- Pharmacokinetics is dose proportional with a half-life of about 5-6 days across all dose levels.
- Pharmacodynamic activity is evident by activation and margination of peripheral T cells.
- Given the observed clinical activity, enrollment into the planned dose expansion cohorts will not be initiated. Further evaluation of the clinical trial data and characteristics of responses is ongoing.
- Potential ways to further improve clinical activity:
  - Pharmacometric modelling to understand optimal dose window
  - Optimize T cell activation (e.g. dosing regimen, drug combinations)
  - Patient selection based on CLEC12A expression levels

Contact Information

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Disclaimers:
1) Clinical trial funded by Merus N.V.: Enquiries@merus.nl
2) Due to the COVID-19 pandemic, not all data could be source verified.

References

1. **van Loo et al**. (2019), *Expert Opin Biol Ther, 19:7, 721-733, DOI: 10.1080/14712598.2019.1623200*

2. **Lee et al.** (2019), *Biol Blood Marrow Transplant. 25(4):625-638, DOI: 10.1016/j.bbmt.2018.12.758*

3. **Zhu et al.** *(2016), Clin Pharmacokinet, DOI 10.1007/s40262-016-0405-4*