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Updated Results from the Ongoing Phase 1/2a Study of MP0533, a Tetra-Specific Designed Ankyrin Repeat Protein (DARPin; CD33 x CD123 x CD70 x CD3), in Patients with Relapsed/Refractory AML or MDS/AML

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INTRODUCTION

- The tetra-specific CD3-engager DARPin MP0533 is designed for avidity-driven T-cell-mediated killing of AML cells expressing at least 2 of the 3 leukemia-associated antigens CD33, CD123, and CD70, while sparing healthy cells.[1]

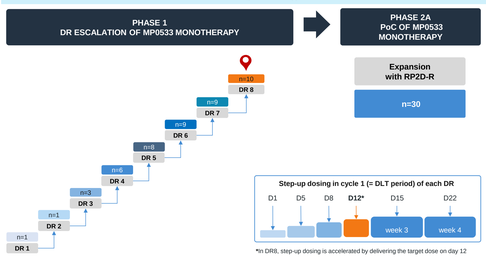
AIM

- To report the data of DRs 1–8 from the ongoing first-in-human, multicenter, single-arm, open-label, dose-escalation study of MP0533 in adults with r/r AML or MDS/AML (NCT05673057).

METHODS

- The trial assesses safety/tolerability, PK/PD, immunogenicity, and preliminary antileukemic activity of MP0533 monotherapy.
- DR1–7 included step-up dosing on days 1, 5, 8, and target dose on day 15.
- In DR8, step-up dosing is accelerated by delivering the target dose on day 12.
- In all cohorts, weekly dosing begins after the target dose application, starting on day 15, and continues in 28-day cycles.
- The dose escalation follows a Bayesian logistic regression model, considering both CRS and non-CRS DLTs.
- TEAEs are assessed according to NCI CTCAE v5.0.
- Response is assessed at weeks 4, 8, and 12, then every 12 weeks, using the 2022 ELN criteria.[2]
- Soluble biomarkers (e.g., cytokines) in blood are measured to evaluate target engagement and T-cell activation.
- Centralized molecular MRD testing uses a genomics-based NGS myeloid panel assay covering 65 genes and quantitative or droplet digital PCR for selected mutations.
- MP0533 concentrations in serum were measured using a free ECLIA assay with a LLOQ of 1 ng/mL. ADAs were measured using an ECLIA acid dissociation assay with a sensitivity of 69 ng/mL.
- Informed consent is obtained from all patients.

Phase 1/2a study design DR 1–8



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1. Bianchi M et al., Cancer Immunol Res 2024;12(7):921–943.
2. Döhner H et al., Blood 2022;140(12):1345–77.

CONTACT INFORMATION

For any questions, please contact: info@molecularpartners.com, attention of Mariola Dymkowska.

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Abbreviations: ABS, absolute; ADA, anti-drug antibody; AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BLQ, below limit of quantification; CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery, CRS, cytokine release syndrome; DERC, Dose Escalation Review Committee; DIC, disseminated intravascular coagulation; DLT, dose-limiting toxicity; DR, dose regimen; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; ELN, European Leukemia Net; IRR, infusion-related reaction; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; MRD, minimal residual release; NCI CTCAE, national cancer institute common terminology criteria for adverse events; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD, pharmacodynamics; PK, pharmacokinetics; PoC, proof of concept; RP2D-R, recommended phase 2 dose regimen; r/r, relapsed/refractory; TEAE, treatment-emergent adverse event; WBC, white blood count.

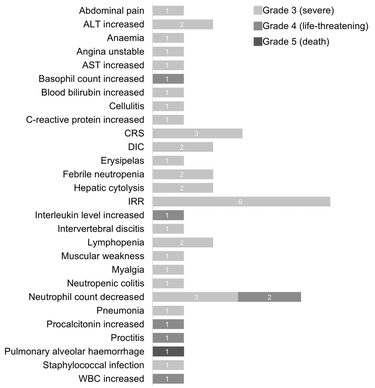
PATIENT BASELINE CHARACTERISTICS

Characteristic	DR 1–8 (n=47)
Sex, n (%)	
Female / male	19 (40) / 28 (60)
Age, years	
Mean / median (range)	68 / 73 (22–82)
ECOG performance status, n (%)	
0 / 1 / 2	14 (30) / 30 (64) / 3 (6)
Initial diagnosis, n (%)	
AML / MDS/AML	34 (72) / 13 (28)
Risk category, n (%)	
Unknown / favorable / intermed. / adverse	1 (2) / 2 (4) / 12 (26) / 32 (68)
No of prior systemic treatment lines, n (%)	
1 / 2 / ≥3	21 (44) / 13 (28) / 13 (28)

- As of 14 Apr 2025, 47 patients were treated (19 women, 28 men).
- Median age at enrolment was 73 years (range 22–82).
- ELN genetic risk was classified as adverse in 32 patients (68%) and intermediate in 12 (26%).
- Twenty-six patients (56%) received ≥2 prior treatment lines.

MP0533 SAFETY PROFILE

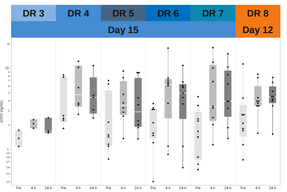
MP0533-related TEAEs of Grade ≥3 (DR 1–8)



- Overall, 236 MP0533-related TEAEs were recorded, of which 44 were of Grade 3 or above.
- The most frequent MP0533-related TEAEs were CRS in 31 patients (66%) and IRRs in 24 patients (51%); 3 CRS and 6 IRRs transiently reached Grade 3 (incl. 1 IRR in DR 8); all others remained Grade ≤2.
- Three investigator-assessed DLTs were recorded; 1 was confirmed as a DLT by the DERC (fatal pulmonary hemorrhage in context of DIC in DR 8) and resulted in a target dose decrease for subsequent patients in DR 8.

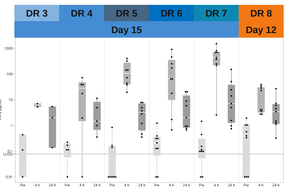
MP0533 TARGET ENGAGEMENT AND T-CELL ACTIVATION

sCD33



LLoQ of the assay is 0.28 pg/mL

IFNγ

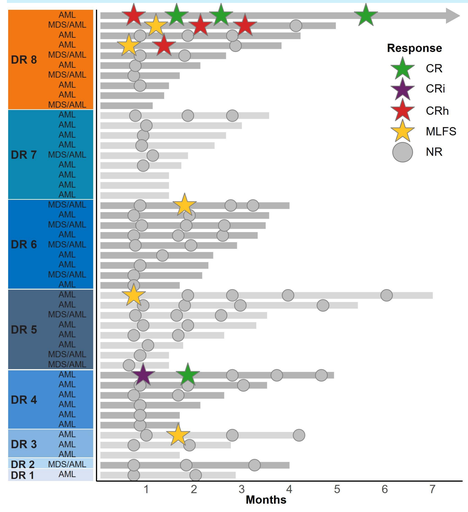


LLoQ of the assay is 0.08 pg/mL

- ELISA/ECLIA assays were used to assess serum levels of sCD33 and IFNγ at pre-dose, and at 4 h and 24 h post-infusion of the respective MP0533 target dose on cycle 1 day 15 for DR 3–7, and on cycle 1 day 12 for DR 8.
- Similar results were seen for sCD27 (CD70 ligand) and CXCL10 (IFNγ downstream marker).
- Box plots show data distribution and central lines denote the median.

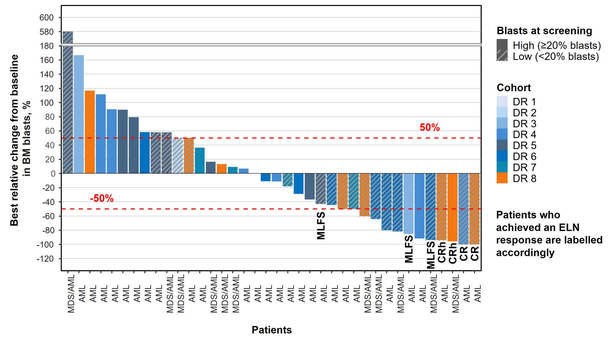
MP0533 TREATMENT & CLINICAL RESPONSE

Treatment duration and individual patient responses



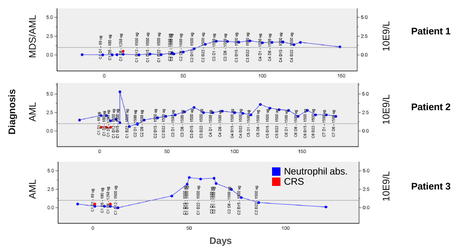
- In cohort 1–7, 4 of 33 evaluable patients achieved a response:
  - 3 patients (1 each in cohort 3, 5, 6) reached a MLFS
  - 1 patient in cohort 4 achieved a CR
- In cohort 8 with the accelerated step-up dosing, 3 of 8 evaluable patients responded after cycle 1:
  - 1 patient achieving CR
  - 2 patients achieving a CRh as best overall response
- One patient in DR 8 is still on treatment and shows a response duration of at least 6 months.
- On average, patients received 7 target doses (range 0–28); 9 patients continued beyond cycle 3.

Best relative change of blast count from baseline (bone marrow aspirate)



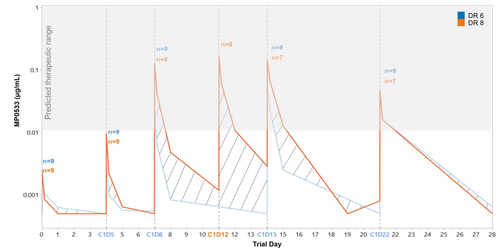
- Overall, 13 of 38 evaluable patients displayed ≥50% blast count reduction in bone marrow, including 10 patients with a low bone marrow blast count at baseline (<20%).
- Assessment of MRD status is ongoing.

Absolute neutrophil count improvement in DR 8 responders



- All 3 responders in DR 8 demonstrated improved neutrophil count compared to baseline, and 2 maintained it for ≥12 weeks.
- No use of G-CSF was required among these responders.

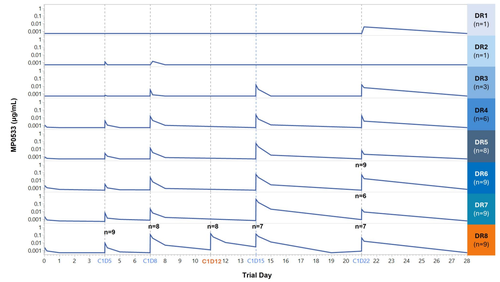
FREE SERUM MP0533 EXPOSURE INCREASE DR 8 VS DR 6



- The additional step-up dose and anticipation of target dose on day 12 in DR 8 resulted in an improved exposure profile compared to DR 6 with same target dose on day 15.

MP0533 EXPOSURE TREATMENT CYCLE 1 AND BEYOND (DR 1–8)

Geometric mean of free serum MP0533 exposure over the first cycle of treatment



Free serum MP0533 exposure impacted by ADAs

DR	Ratio of patients with reduced exposure (C_{max})	Time to reduced exposure (median)	Time to ADA onset (median)
1	0 of 1 (0%)	N/A	Day 56
2	1 of 1 (100%)	Day 84	Day 84
3	2 of 3 (67%)	Day 28	Day 28
4	2 of 6 (33%)	Day 21	Day 21
5	5 of 8 (63%)	Day 21	Day 21
6	6 of 9 (67%)	Day 21	Day 14
7	4 of 9 (44%)	Day 21	Day 21
8	5 of 9 (56%)	Day 28	Day 28
Total	25 of 46 (54%)	Day 21	Day 21

- ADAs were detected in 31 patients (66%) with a median onset time of 21 days.
- In 25 patients (54%), ADA presence coincided with reduced serum MP0533 exposure levels, comprising also 6 patients who achieved a response, including the patient in DR 8 with durable response.

CONCLUSIONS & OUTLOOK

- MP0533 shows an acceptable safety profile across all cohorts after adjustment of the target dose in DR 8.
- Serum PK data confirmed higher drug exposure in cycle 1 for DR 8 with the accelerated step-up dosing compared to the previous dosing schemes.
- The observed response rate of 3 of 8 patients in DR 8 is encouraging.
- Overall, the preliminary antileukemic activity, safety, and PK/PD data from DR 8 support the currently ongoing further dose optimization to enhance MP0533 exposure and maximize its therapeutic benefit by:
  - Increased dosing frequency for faster escalation to therapeutically relevant doses
  - Introduction of anti-CD20 pretreatment to mitigate ADAs
- Additionally, future study cohorts will evaluate the combination of azacitidine/venetoclax with MP0533.