MP0533 (CD33 X CD123 X CD70 X CD3), A TETRA-SPECIFIC CD3-ENGAGING DARPin FOR THE TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY AML OR MDS/AML: RESULTS OF AN ONGOING PHASE 1/2A STUDY

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INTRODUCTION

- The development of targeted immunotherapy for AML faces significant challenges due to clonal heterogeneity and the absence of a single, specific target antigen on AML cells.
- MP0533 is a tetra-specific CD3-engaging DARPin that simultaneously targets CD33, CD123, and CD70, leading to avidity-driven T cell-mediated killing of AML blasts and leukemic stem cells.[1]
- MP0533's affinity to each target is calibrated to preferentially kill malignant cells co-expressing at least two of the three antigens.[1]

AIM

- To report data of the first 7 dose regimens (DRs) from the first-in-human, multicenter, single-arm, open-label, phase 1/2a study of MP0533 in adults with relapsed/refractory AML or MDS/AML (NCT05673057).

METHODS

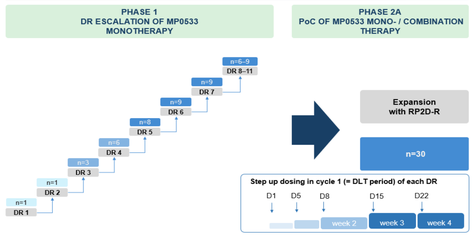
STUDY OBJECTIVES

- The study assesses the safety/tolerability, PK, and preliminary antileukemic activity of MP0533 monotherapy.
- In addition, exploratory outcome measures include pharmacodynamics and immunogenicity.

STUDY TREATMENT & ASSESSMENTS

- After initial step-up dosing on days 1, 5, and 8, patients receive their MP0533 target dose weekly from day 15 in 28-day cycles until disease progression or unacceptable toxicity.
- 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 using the 2022 ELN criteria.[2]
- T-cell activation is measured by cytokine secretion and flow cytometry in peripheral blood samples, evaluating intracellular and surface activation markers on CD8+ subsets of T cells.
- MP0533 target engagement is monitored by assessing changes in sCD33 and IL-3 and by flow cytometry in BMA.
- ADAs directed against MP0533 are detected in human serum using an ECL-based direct assay using acid dissociation treatment. The assay was developed, qualified and validated at Molecular Partners. The assay comprised three tiers for screening, confirmation and titration of ADAs.

PHASE 1/2A STUDY DESIGN



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AUTHOR CONTACT INFORMATION

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PATIENT CHARACTERISTICS

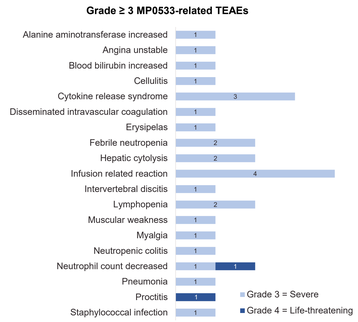
BASELINE CHARACTERISTIC	DR 1–7 (n=37)
Sex, n (%) Female / male	16 (43) / 21 (57)
Age Mean / Median (range)	68 / 74 (22–82)
ECOG PS, n (%) 0 / 1 / 2	13 (35) / 21 (57) / 3 (8)
Hematologic malignancy, n (%) AML / MDS/AML	27 (73) / 10 (27)
ELN risk category, n (%) Unknown / favorable / intermediate / adverse	1 (3) / 1(3) / 8 (21) / 27 (73)*
No. of prior systemic treatment lines, n (%) 1 / 2 / ≥3	17 (46) / 11 (30) / 9 (24)

*TP53 mutated: 10 (27%)

CONCLUSIONS

- **MP0533 dosed weekly showed an acceptable safety profile in the first 7 DRs of this ongoing phase 1/2a study.**
- **Current MP0533 DR scheme results in limited response rates, with evidence of pharmacodynamic activity.**
- **Further development of MP0533 will aim to optimize exposure to increase the rate, depth and duration of response (protocol amendment is in development).**

MP0533 SAFETY PROFILE

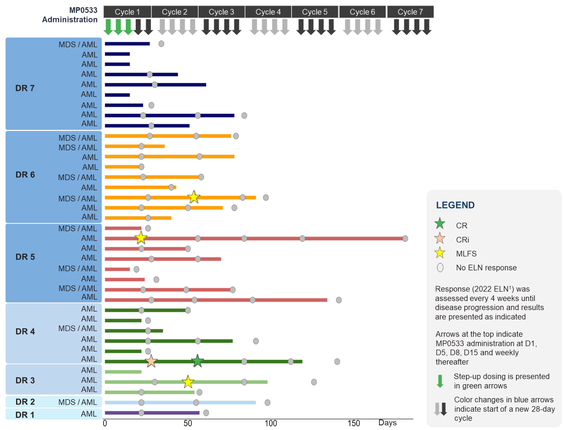


- As of 14 Oct 2024, all 37 patients received ≥1 MP0533 dose (345 infusions administered in total).
- The observed overall study AE profile was consistent with the underlying disease in this elderly and heavily pretreated population with many comorbidities.
- A total of 173 MP0533-related TEAEs have been reported, with IRR (n=68) and CRS (n=47) being the most frequent.
- IRR and CRS events predominantly occurred during treatment cycle 1, typically within 24 h following MP0533 administration; notably, these events were observed regardless of the MP0533 dosage, including step-up dosing.
- Two DLTs have been reported in cohort 7.
- Two Grade 4 drug-related TEAEs were reported.

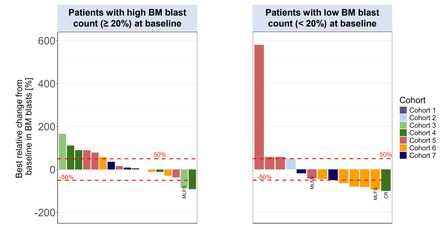
REFERENCES

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

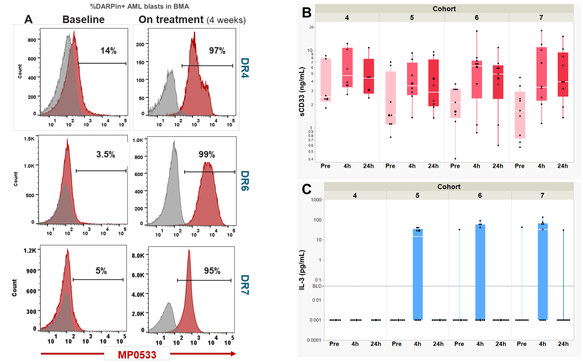
MP0533 TREATMENT & CLINICAL RESPONSE



- As of 14 Oct 2024, enrollment in 7 cohorts was complete and 37 patients were treated.
- 1 patient achieved CR in DR 4 and MLFS was observed in 1 patient each at DR 3, 5 and 6.
- 8 of 30 evaluable patients displayed ≥50% blast reduction in the bone marrow.
- 6 of 13 patients with baseline disease burden <20% blasts in the bone marrow displayed blast reduction ≥50%.
- None of the patients in DR 7 still receive MP0533 treatment, and enrollment for DR 8 is ongoing.



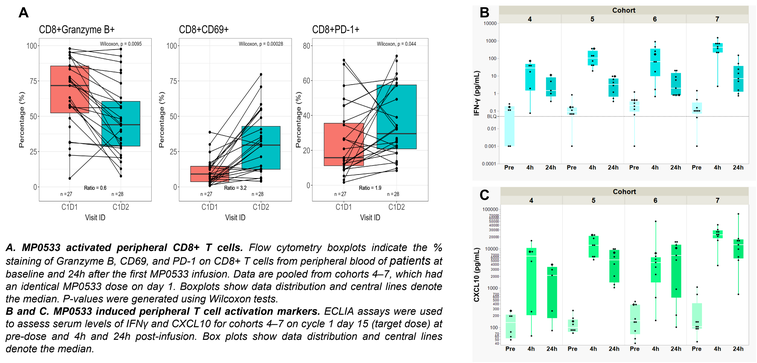
TARGET ENGAGEMENT BY MP0533



A. MP0533 engaged AML blasts from BMA. *Flow cytometry histograms indicate % DARPin staining of BMA AML blasts sampled at baseline and week 4 of MP0533 treatment. Data are from individual patients on the indicated cohorts that had confirmed peripheral MP0533 exposure.*

B and C. MP0533 induced peripheral target engagement biomarkers. *ELISA/ECLIA assays were used to assess serum levels of sCD33 and IL-3 (CD123 ligand) for cohorts 4–7 on cycle 1 day 15 (target dose) at pre-dose and 4h and 24h post-infusion. Box plots show data distribution and central lines denote the median.*

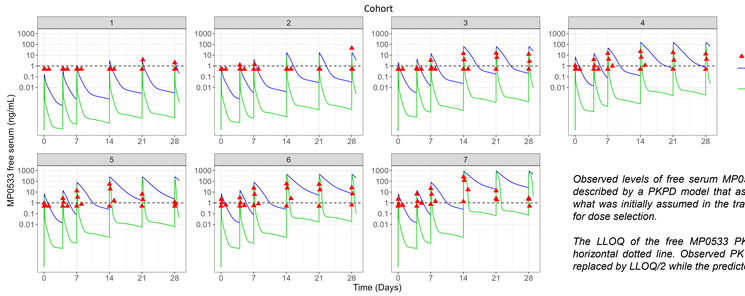
ACTIVATION OF PERIPHERAL T CELLS BY MP0533



A. MP0533 activated peripheral CD8+ T cells. *Flow cytometry boxplots indicate the % staining of Granzyme B, CD69, and PD-1 on CD8+ T cells from peripheral blood of patients at baseline and 24h after the first MP0533 infusion. Data are pooled from cohorts 4–7, which had an identical MP0533 dose on day 1. Boxplots show data distribution and central lines denote the median. P-values were generated using Wilcoxon tests.*
B and C. MP0533 induced peripheral T cell activation markers. *ECLIA assays were used to assess serum levels of IFNγ and CXCL10 for cohorts 4–7 on cycle 1 day 15 (target dose) at pre-dose and 4h and 24h post-infusion. Box plots show data distribution and central lines denote the median.*

MP0533 EXPOSURE CHARACTERISTICS TREATMENT CYCLE 1 AND BEYOND

Free MP0533 exposure impacted by TMDD during cycle 1



Observed levels of free serum MP0533 during cycle 1 are best-described by a PKPD model that assumes a higher TMDD than what was initially assumed in the translational PKPD model used for dose selection.

The LLOQ of the free MP0533 PK assay is indicated by the horizontal dotted line. Observed PK data below the LLOQ were replaced by LLOQ/2 while the predicted PK were not truncated.

Free MP0533 exposure impacted by ADAs beyond cycle 1 day 21

	PATIENTS DISPLAYING REDUCED EXPOSURE (C_{MAX})	MEDIAN TIME OF REDUCED EXPOSURE	MEDIAN TIME OF ADA ONSET
DR 1	0 / 1 (0%)	N/A	Day 56
DR 2	1 / 1 (100%)	Day 84	Day 84
DR 3	2 / 3 (67%)	Day 28	Day 28
DR 4	2 / 6 (33%)	Day 21	Day 21
DR 5	5 / 8 (63%)	Day 21	Day 21
DR 6	6 / 9 (67%)	Day 21	Day 14
DR 7	4 / 9 (44%)	Day 21	Day 21
Total	**20 / 37 (54%)**	**Day 21**	**Day 21**

ADAs were measured using an acid dissociation assay (with a high sensitivity of 69 ng/mL) and detected in 24 of 37 patients (65%), with a median time of ADA onset of 21 days. In 20 patients (54%), ADA presence contributed to clearing MP0533 from the circulation earlier than anticipated.

Abbreviations: ADA, anti-drug antibody; AML, acute myeloid leukemia; AE, adverse event; BMA, bone marrow aspirate; CRS, cytokine release syndrome; DARPin, Designed Ankyrin Repeat Protein; DLT, dose-limiting toxicity; DR, dose-escalation regimen; ECL, electrochemiluminescent; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; ELN, European LeukemiaNet; IRR, infusion-related reaction; LLOQ, lower limit of quantification; MDS, myelodysplastic syndrome; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PKPD, pharmacokinetics/pharmacodynamics; R/R, relapsed/refractory; RP2D-R, recommended phase 2 dose regimen; TEAE, treatment-emergent adverse event; TMDD, target-mediated drug disposition.