MP0533, A CD3-ENGAGING DARPin TARGETING CD33, CD123, AND CD70 IN PATIENTS WITH RELAPSED/REFRACTORY AML OR MDS/AML: PRELIMINARY RESULTS OF A PHASE 1/2A STUDY

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INTRODUCTION

- Developing targeted immunotherapy for AML is challenging due to clonal disease heterogeneity and the lack of single AML-specific tumor antigens
- MP0533 is a tetra-specific, half-life extended CD3-engaging DARPin, designed to simultaneously target the TAAs CD33, CD123, and CD70[1]
- MP0533's affinity to each TAA is tuned to preferentially kill malignant cells which co-express ≥2 of the 3 antigens, while preserving a therapeutic window towards healthy cells[1]
- Preclinically, MP0533 induced tumor-specific endogenous T-cell response in *ex vivo* AML patient samples and led to T-cell–mediated tumor eradication in AML xenograft mouse models, with limited cytokine release or other serious ARs[1]

AIM

- To present initial data of the first 4 DRs of the ongoing first-in-human, multicenter, single-arm, open-label, phase 1/2a study of MP0533 monotherapy in patients with R/R AML or MDS/AML (NCT05673057)

METHODS

STUDY OBJECTIVES

- To evaluate MP0533 monotherapy safety/tolerability, pharmacokinetics, and pharmacodynamics, as well as preliminary antileukemic activity

KEY PATIENT ELIGIBILITY CRITERIA

- Adult patients with R/R AML or MDS/AML
- ECOG PS of 0 to 2
- Life expectancy of ≥12 weeks

STUDY TREATMENT & ASSESSMENTS

- Patients receive MP0533 weekly starting at day 15 of a 28-day cycle after a stepwise dose increase on days 1, 5, and 8, until disease progression or unacceptable toxicity
- MP0533 DR escalation is guided by two Bayesian logistic regression models, estimating the joint probability of CRS and non-CRS DLTs
- Bone marrow examinations are performed at weeks 4, 8, and 12 and every 12 weeks thereafter
- Responses are determined using 2022 ELN criteria[2] with an assessment of hematologic improvement
- TEAEs are assessed according to NCI CTCAE v5.0

REFERENCES

1. Bianchi M et al., Blood 2022;140(Suppl 1):2251–2
2. Döhner H et al., Blood 2022; 140(12):1345–77

AUTHOR CONTACT INFORMATION

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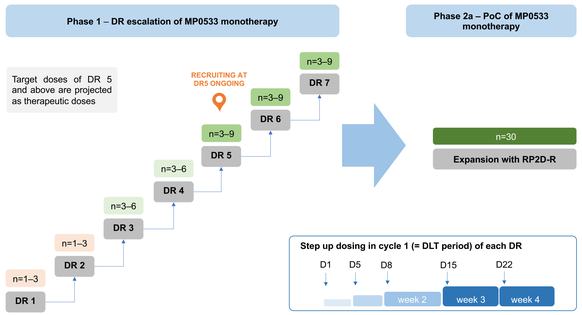
PHASE 1/2A STUDY DESIGN



PATIENT BASELINE CHARACTERISTICS

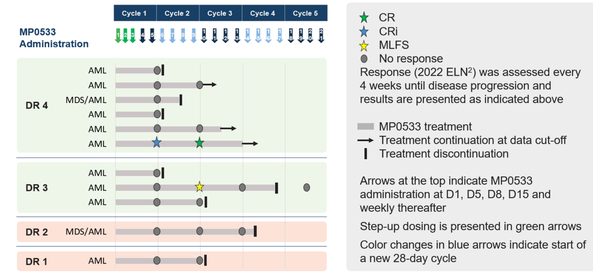
Baseline Characteristics	DR cohorts 1–4 (N=11)
Sex, n (%)	
Female / male	5 (45) / 6 (56)
Age	
Mean / Median (range)	66 / 75 (26–81)
ECOG PS, n (%)	
0	4 (36)
1	5 (45)
2	2 (18)
Hematologic malignancy, n (%)	
AML / MDS/AML	9 (82) / 2 (18)
ELN risk category, n (%)	
Intermediate / adverse	1 (9) / 10 (91)*
No. of prior systemic treatment lines, n (%)	
1	4 (36)
2	5 (45)
3	2 (18)

* TP53 mutated: 3 (27%)

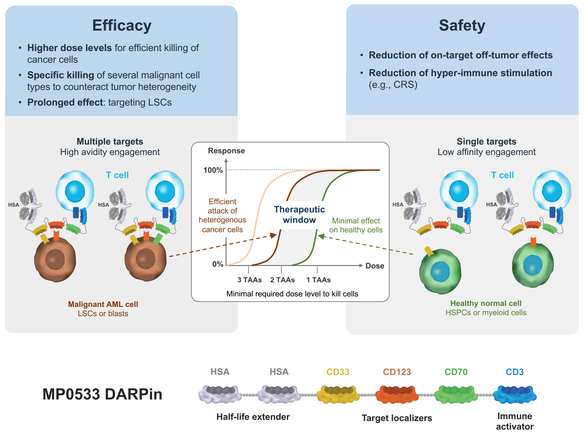
Data cut-off: 24 Oct 2023

MP0533 TREATMENT & CLINICAL RESPONSE

- As of 24 Oct 2023, enrollment in the first 4 cohorts was complete; a total of 11 patients were treated
- One of 6 patients achieved CR in DR 4 and one patient out of 3 achieved MLFS in DR 3
- Three patients in DR 4 are still on MP0533 treatment and enrollment in DR 5 is ongoing



MP0533 PROPOSED MODE OF ACTION

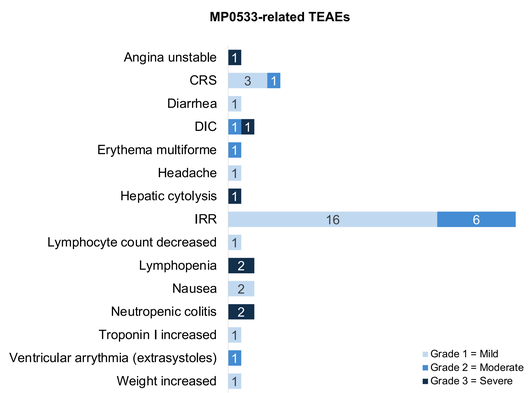


Tetra-specific, half-life extended CD3-engaging DARPin, simultaneously targeting the TAAs CD33, CD123 and CD70

Design enables avidity-driven T cell-mediated killing of LSCs and malignant blasts known to co-express ≥2 of these 3 TAAs, while sparing health cells

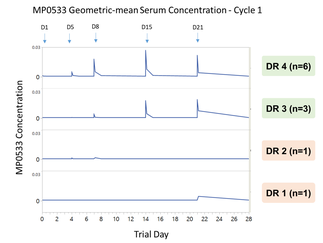
Abbreviations: AML, acute myeloid leukemia; AE, adverse event; AR, adverse reaction; BLQ, below limit of quantification; CRS, cytokine release syndrome; DARPin, Designed Ankyrin Repeat Protein; DIC, disseminated intravascular coagulation; DLT, dose-limiting toxicity; DR, dose-escalation regimen; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, European LeukemiaNet; E:T, effector to target ratio; HSPC, hematologic stem and progenitor cell; IRR, infusion-related reaction; MDS, myelodysplastic syndrome; LSC, leukemia stem cell; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PoC, proof of concept; R/R, relapsed/refractory; RP2D-R, recommended phase 2 dose regimen; TAA, tumor-associated antigen; TEAE, treatment-emergent adverse event.

MP0533 HAS A FAVORABLE SAFETY PROFILE



- As of 24 Oct 2023, all 11 patients received ≥1 MP0533 dose (103 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 43 MP0533-related TEAEs have been reported, with IRR and CRS being the most frequent
- No DLTs have been observed in any of the MP0533 DRs so far
- No Grade ≥4 drug-related TEAEs were reported
- 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 specific MP0533 dosage, including step-up dosing

FREE MP0533 EXPOSURE LEVELS IN SERUM



- Although MP0533 concentrations were detectable in DR 1 and DR 2, most values were BLQ
- For DR 3 and DR 4, MP0533 concentrations were in line with the model predictions and reaching levels close to the predicted pharmacological activity expected with DRs 5–7

CONCLUSIONS

- Initial results of this ongoing phase 1/2a study indicate an acceptable safety profile for weekly MP0533 monotherapy up to DR 4 in 11 patients with R/R AML or MDS/AML:
  - No DLTs observed, and CRS and IRRs reported were of Grade 1/2
- Preliminary response data are encouraging for this first tetra-specific T-cell engager, with 2 responders in DRs 3–4 reported to date:
  - Best overall response achieved was CR in one patient who received MP0533 at DR 4, and MLFS in one patient treated with MP0533 at DR 3
- Preliminary PK data in line with PKPD modeling and early signs of efficacy from DRs 3–4 suggest that MP0533 monotherapy should deliver robust benefit to the patients at the projected therapeutic dose range (from DR 5 onwards)
- The study continues enrolling patients into DR 5

ACKNOWLEDGMENTS

We thank the study patients and their families, and the study investigators, nurses and clinical personnel.