PHASE 1/2A STUDY OF MP0533, A TETRA-SPECIFIC T CELL ENGAGER (CD33 X CD123 X CD70 X CD3), IN PATIENTS WITH RELAPSED/REFRACTORY AML OR MDS/AML: INITIAL RESULTS FROM OPTIMIZED TREATMENT REGIMEN INCLUDING DENSIFIED MP0533 DOSING AND ADAPTED PREMEDICATION

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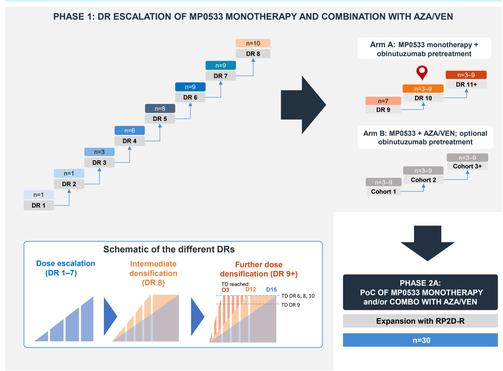
INTRODUCTION

- MP0533 is a tetra-specific CD3-engaging DARPin molecule designed for avidity-driven T cell-mediated killing of AML cells expressing ≥2 of the 3 leukemia-associated antigens CD33, CD123, and CD70, while sparing healthy cells.[1]
- MP0533 is evaluated for the treatment of adults with AML or MDS/AML.
- We report the latest result update of the ongoing first-in-human, multicenter, open-label, Phase 1/2a study (NCT05673057) comprising the data of DR 1–9.

METHODS

- Primary and secondary study objectives are to determine the safety/tolerability, RP2D-R, PK, and preliminary antileukemic activity of MP0533.
- In addition, exploratory outcome measures include pharmacodynamics, immunogenicity, and MRD.
- DR 1–7 included MP0533 step-up dosing on day 1, 5, 8, followed by TD on day 15.
- DR 8 implemented a higher starting dose and steeper step-up dosing to reach the TD on day 12 (incl. 83% of the TD administered already on day 8).
- Across DR 1–8, TD on day 15 was followed by weekly dosing (28-day cycles).
- For DR 9+, MP0533 is administered with higher frequency vs. DR 8 in cycle 1 and beyond, reaching the TD on day 3. Obinutuzumab is given on 2 consecutive days >3 days prior to the first MP0533 dose to mitigate ADAs.
- TEAEs are assessed according to NCI CTCAE v5.0.
- Response is assessed at weeks 4, 8, and 12 using the 2022 ELN criteria,[2] with additional BM assessment at week 2 in DR 9.
- Centralized molecular MRD testing uses a genomics-based NGS myeloid panel assay covering 65 genes and quantitative or droplet digital PCR for selected hotspot mutations.

Study design Phase 1/2a



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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.

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CONTACT INFORMATION

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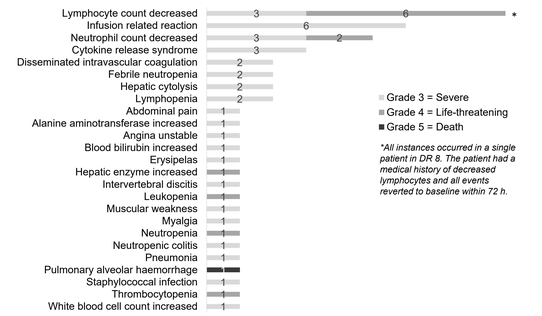
PATIENT BASELINE CHARACTERISTICS

Characteristic	DR 1–9 (n=54)
Sex, n (%)	
Female / male	22 (41) / 32 (59)
Age	
Mean / Median (range)	68 / 73 (22–82)
ECOG PS, n (%)	
0 / 1 / 2	16 (30) / 35 (65) / 3 (5)
Hematologic malignancy, n (%)	
R/R AML / MDS/AML	40 (74) / 14 (26)
ELN 2022 risk category, n (%)	
Unknown / favorable / intermediate / adverse	1 (2) / 3 (5) / 14 (26) / 36 (67)
No. of prior treatment regimens, n (%)	
1 / 2 / ≥3	23 (43) / 14 (26) / 17 (31)

Data cut-off: 01 Sept. 2025

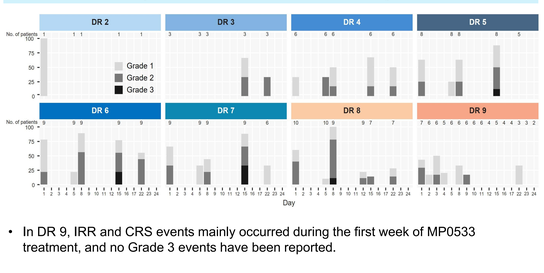
MP0533 SAFETY PROFILE

MP0533-related TEAEs of Grade ≥3 (DR 1–9)



- Overall, 258 MP0533-related TEAEs were recorded, of which 48 were of Grade ≥3.
- The most frequent MP0533-related TEAEs were CRS in 37 patients (65%) and IRRs in 25 patients (46%); 3 CRS and 6 IRRs transiently reached Grade 3 (incl. 1 IRR in DR 8, none in DR 9); all others remained Grade ≤2.
- The increased dosing frequency in DR 8 and 9 was not associated with an increased incidence or severity of IRR or CRS.
- Asymptomatic liver enzyme elevations, including Grade 3 events, were observed across all cohorts; in patients remaining on study treatment, these improved or stabilized without clinical intervention.
- Three investigator-assessed DLTs were recorded: muscular weakness and myalgia in DR 7, fatal pulmonary hemorrhage in context of DIC in DR 8 and an asymptomatic Grade 4 liver test elevation in DR 9; the latter 2 were confirmed as DLT by the DERC.
- Mild to moderate transient IRRs, liver enzyme elevations, and WBC increase were observed following obinutuzumab infusions in a single patient each but did not interfere with the patients' ability to continue with scheduled study treatment.

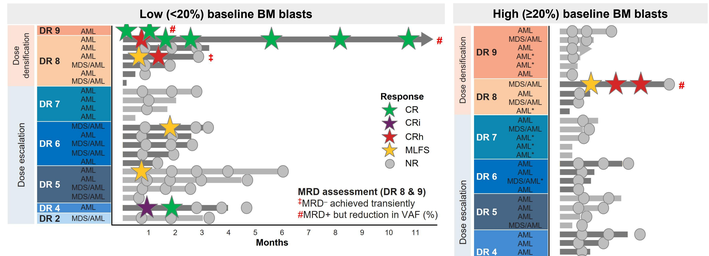
Proportion of IRR & CRS events in cycle 1



- In DR 9, IRR and CRS events mainly occurred during the first week of MP0533 treatment, and no Grade 3 events have been reported.

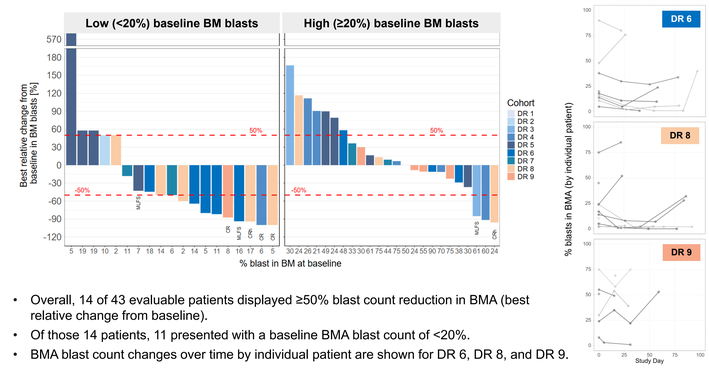
MP0533 TREATMENT & CLINICAL RESPONSE

Treatment duration and individual patient responses



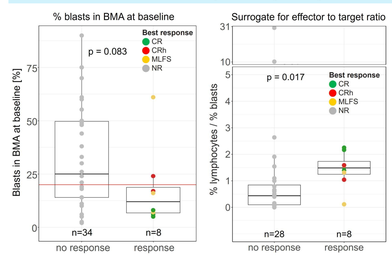
- As of 01 Sept. 2025, 54 patients were treated with MP0533.
- On average, patients received 8 TDs (range 0–44); 9 patients continued beyond cycle 3.
- Eight of 48 evaluable patients achieved a response:
  - 5 patients achieved a CR/CRh (1 each in DR 4 and 9, and 3 in DR 8),
  - 3 patients reached a MLFS (1 each in DR 3, 5, 6).
- Six of the responders had a low disease burden (<20% BM blasts) at baseline.
- The longest duration of response is close to 1 year at the time of data cut-off (1 patient in DR 8).
- 4 responders were evaluated for molecular MRD (i.e., patients in DR 8 and 9 with ≥2 consecutive clinical response assessments based on BMA):
  - 1 achieved transient MRD negativity,
  - 3 showed reduced VAF (%) of detected mutations, albeit not below the MRD negativity threshold.

Change of blast count from baseline (BMA)



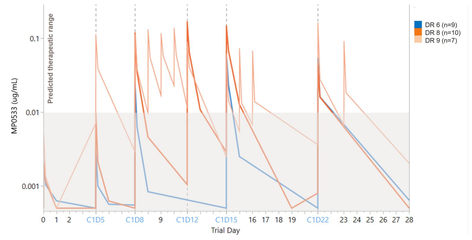
- Overall, 14 of 43 evaluable patients displayed ≥50% blast count reduction in BMA (best relative change from baseline).
- Of those 14 patients, 11 presented with a baseline BMA blast count of <20%.
- BMA blast count changes over time by individual patient are shown for DR 6, DR 8, and DR 9.

Exploratory analysis of response correlation



- Two parameters which correlated best to response were % blasts in BMA at baseline (a measure of tumor burden) and the ratio of % of lymphocytes to blast, which serves as a surrogate effector to target ratio.
- Based on currently available data, an exploratory genetic analysis showed no trend between genetic alterations (mutations, translocations) and response across all patients.
- Limitations of this exploratory analysis: multiple MP0533 dose levels and few patients.

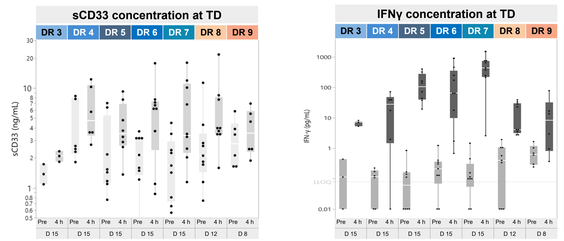
MP0533 TREATMENT EXPOSURE



Overlay of DR 6, DR 8, and DR 9 geometric mean over treatment cycle 1. Notes: In DR 9 TD is administered at day 3 but samples only collected from day 5 onwards.

- DR 8 and 9 showed improved free serum exposure levels in treatment cycle 1 compared to DR 6, with broader coverage of the projected dose range above 10 ng/mL.
- ADAs were detected in 34 patients (across all DRs) with a median onset time of 21 days. In 27 patients (53%), ADA presence coincided with reduced serum MP0533 exposure levels and the loss of T cell activation (using surrogate biomarkers).
- Of the 8 patients who achieved a response, 6 were ADA-positive and 2 ADA-negative (both underwent prior HSCT). Response occurred before loss of exposure.
- Obinutuzumab pre-treatment was feasible in DR 9 and did not increase the safety risks. Its impact on ADA formation was moderate to none so far but is currently still under investigation in DR 10.

MP0533 TARGET ENGAGEMENT AND T CELL ACTIVATION



- Peripheral sCD33 was induced in all DRs 4 h after drug administration, indicating MP0533 target engagement.
- The comparable induction of IFNγ across DR 3–9, following TD administration, suggested that faster MP0533 step-up dosing and dose densification in DR 9 did not exhaust T cells.

CONCLUSIONS & OUTLOOK

- In this ongoing first-in-human study, MP0533 monotherapy shows an acceptable safety profile across DR 1–9, and densified MP0533 dosing, including up to daily administration, appears tolerable.
- Serum PK analyses confirm that the therapeutic window is reached with densified DRs; accelerated step-up dosing and higher dosing frequency in DR 8 and 9 resulted in increased exposure in treatment cycle 1 compared to DR 1–7.
- Six of the 8 responders according to ELN criteria and 11 of 14 patients who achieved a reduction in BM blasts of ≥50% presented with <20% BM blast at baseline.
- One patient in DR 8 is in ongoing long-term CR for close to 1 year at data cut-off.
- Development of ADAs coincided often with reduced serum levels of MP0533, though most responses were achieved early after initiation of treatment.
- The study is ongoing in DR 10.
- Overall, the pooled data from DR 1–9 indicate that patients with low disease burden at baseline may benefit most from MP0533 and independent of their genetic risk profile; the results support further investigation in this population.

Abbreviations: ADA, anti-drug antibody; AML, acute myeloid leukemia; AE, adverse event; BM(A), bone marrow (aspirate); AZA, azacitidine; CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery, CRS, cytokine release syndrome; DARPin, Designed Ankyrin Repeat Protein; DERC, Dose Escalation Review Committee; DIC, disseminated intravascular coagulation; DLT, dose-limiting toxicity; DR, dose-escalation regimen; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, European LeukemiaNet; IFNγ, interferon-gamma; IRR, infusion-related reaction; h, hours; HSCT, hematopoietic stem cell transplant; LLOQ, lower limit of quantification; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; MRD, measurable residual release; n, number; NR, no response; NGS, next-generation sequencing; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; no., number; PCR, polymerase chain reaction; PK pharmacokinetics; PoC, proof of concept; R/R, relapsed/refractory; RP2D-R, recommended phase 2 dose regimen; sCD33, soluble CD33; TD, target dose; TEAE, treatment-emergent adverse event; VAF, variant allele frequency; VEN, venetoclax; WBC, white blood count.