



# Corporate Presentation

## Half-Year 2024 Earnings Call

August 27, 2024

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# Agenda & Speakers

## Welcome & Introduction



**Seth Lewis**  
SVP IR & Strategy

## Highlights & Outlook 2024



**Patrick Amstutz**  
CEO

## MP0533 & AML



**Philippe Legenne**  
CMO

## Radio-DARPin & MP0712



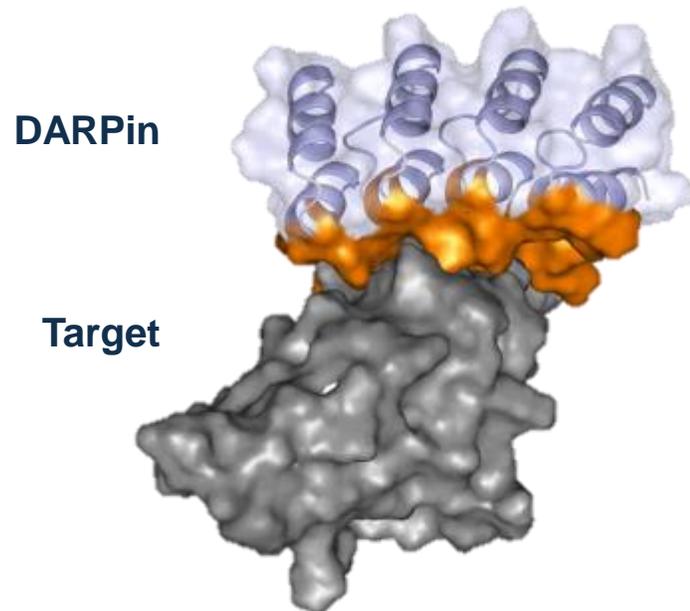
**Daniel Steiner**  
SVP Research & Technology

## Financial Overview



**Robert Hendriks**  
SVP Finance

# The DARPin Modality and Molecular Partners' Strategy



## What we invented

- New class of therapeutics: Designed Ankyrin Repeat Proteins (**DARPin**s)
- DARPin to **close the gap between small molecules and antibodies**
- 7 clinical-stage compounds, **>2500 patients treated**

## How we apply it

- **Unique DARPin solutions** for a defined medical problems not addressable by antibody designs
- Demonstrate **true patient value** with **early clinical readouts**
- Combine our **capabilities with world-class partners** to deliver innovative therapeutics

# Corporate Highlights – H1 2024

## MP0533

- Novel **tetra-specific T-cell engager** for AML patients with high unmet need
- **Encouraging initial clinical data** (safety & efficacy) despite suboptimal exposure
- Phase 1/2a study on track (**DR 8** open), dose-intensification planned to explore the full potential of MP0533

## Radio-DARPin Therapy (RDT) & MP0712

- Successful RDT platform optimization to **reduce kidney accumulation** and **increase tumor uptake**
- Announced **MP0712** as **lead DLL3-targeting <sup>212</sup>Pb-labelled RDT** to be co-developed with Orano Med
- Preclinical data on MP0712 presented at SNMMI 2024: attractive tumor to kidney ratio, efficacy & safety

## Switch-DARPin & MP0621

- Demonstrated logic-gated immune activation for **Switch-DARPin platform**
- Announced **MP0621**, a **cKit x CD16a x CD47 Switch-DARPin**, for next-generation HSCT conditioning
- Initial preclinical data presented at EHA 2024 indicate encouraging efficacy and safety profile

## MP0317

- Bi-specific CD40 agonist targeting FAP: **Favorable safety profile** and confirmed tumor-localized CD40 activation leading to **remodeling of tumor microenvironment** in patients presented at ASCO 2024

## Operations

- Strong financial position with CHF 159 M in cash as of June 30, 2024, with runway extended **into 2027**

# Philippe Legenne, CMO of Molecular Partners

- Excellent **operational execution** of clinical programs
- Special talent for **KOL** and **investigator engagement** for our trials
- Expert medic with **>20y experience & network in oncology** across a range indications and therapeutic modalities
- **Strong industry background** including leading positions at Novartis, GSK and Amgen
- **Team leader** and **people person**, able to lead and grow the clinical team at Molecular Partners





# R&D Update

Patrick Amstutz, CEO

# Pipeline

| MODALITY                      | CANDIDATE            | RESEARCH   | PRE-CLINICAL         | PHASE 1         | PHASE 2 | RIGHTS |                                |
|-------------------------------|----------------------|--|----------------------|-----------------|---------|--------|--------------------------------|
| Tetra-specific T-cell Engager | MP0533               | r/r AML and AML / MDS<br>CD33 x CD123 x CD70 x CD3 |                      |                 |         |        | MOLECULAR partners             |
| Radio-DARPin Therapy (RDT)    | MP0712               | SCLC & NETs<br>DLL3                                |                      | Co-development* |         |        | MOLECULAR partners<br>oranomed |
|                               | Undisclosed Programs | Solid Tumors                                       | In-house programs    |                 |         |        | MOLECULAR partners             |
|                               | Undisclosed Programs | Solid Tumors                                       | 2 partnered programs |                 |         |        | NOVARTIS                       |
| Switch-DARPin                 | MP0621               | AML / HSCT<br>cKit x CD16a x CD47                  |                      |                 |         |        | MOLECULAR partners             |
|                               | Undisclosed Program  | Immune cell engager                                |                      |                 |         |        |                                |
| Localized Agonist             | MP0317               | Advanced Solid Tumors<br>FAP x CD40                |                      |                 |         |        | MOLECULAR partners             |



# MP0533

Tetra-specific T-cell Engager for AML

# MP0533 Phase 1 Dose Escalation in R/R AML Patients

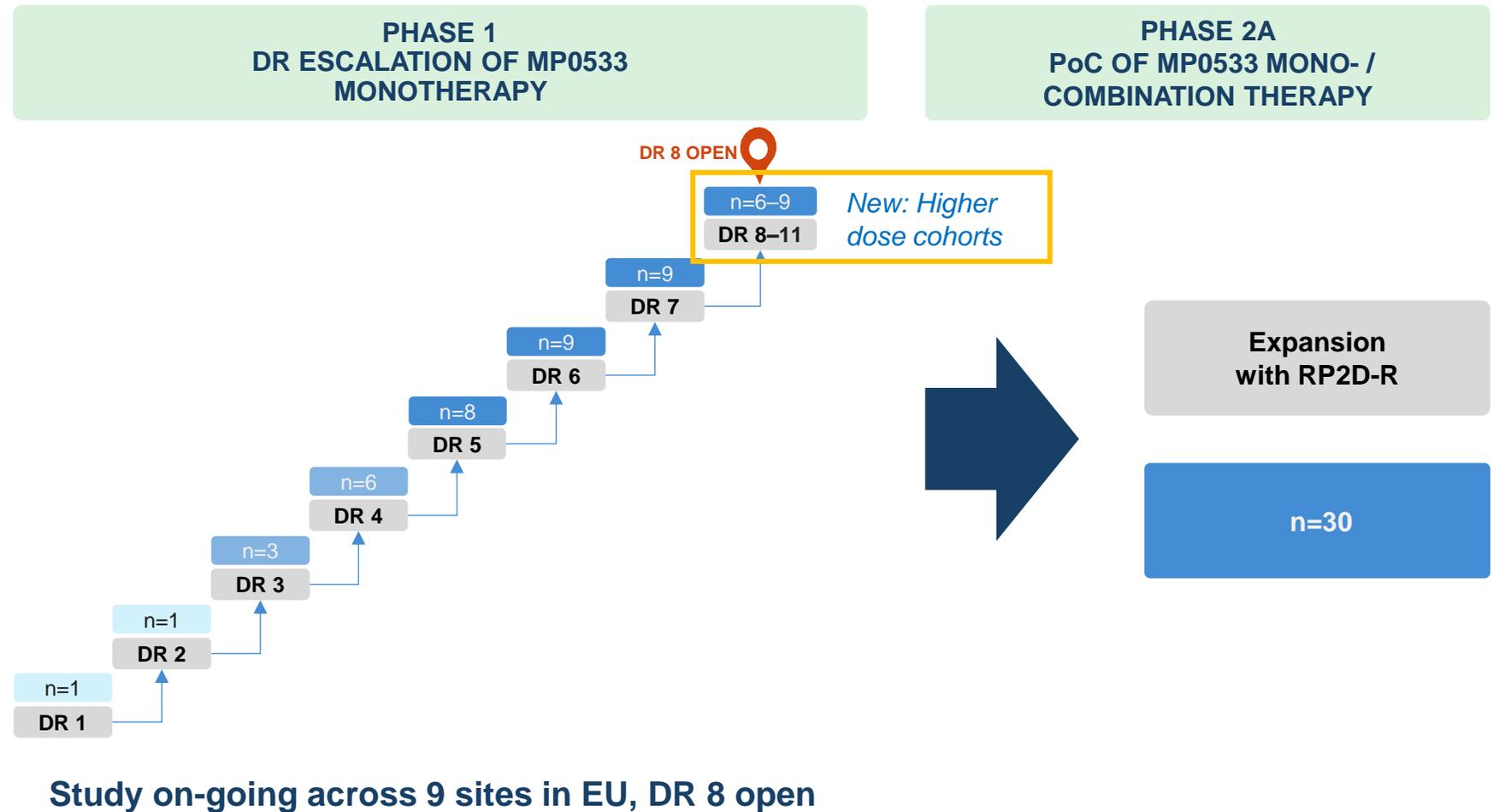
Rapid progress up to cohort 7 with need to explore higher doses

## STUDY DESIGN

- FIH, single-arm, open-label, Phase 1/2a study of MP0533 monotherapy (NCT05673057)

## STUDY OBJECTIVES

- Safety / tolerability
- PK / exposure
- Preliminary activity / PD
  - Clinical response as per ELN (incl. MRD status)
  - Blasts and LSCs counts
  - T-cell activity
  - MP0533 presence in BM
  - Target (co-)expression
  - Evolution of disease clonality



# MP0533 Phase 1 Patient Characteristics and Safety Profile

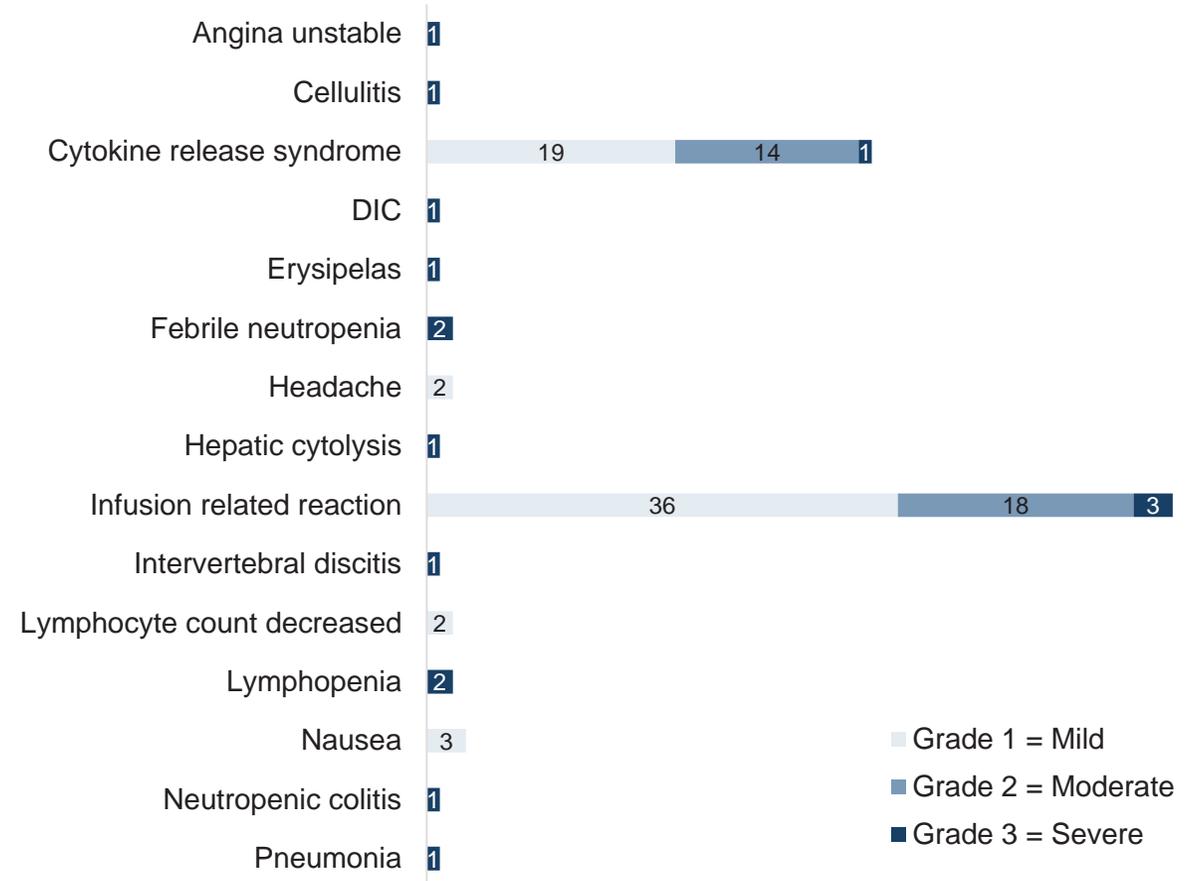
| BASILINE CHARACTERISTICS                            | DR COHORTS 1-6 (n=28)      |
|---|----------------------------|
| <b>Sex, n (%)</b>                                   |                            |
| Female / male                                       | 14 (50) / 14 (50)          |
| <b>Age</b>  |                            |
| Mean / Median (range)                               | 68 / 74 (22-82)            |
| <b>ECOG PS, n (%)</b>                               |                            |
| 0 / 1 / 2   | 11 (39) / 15 (54) / 2 (7)  |
| <b>Hematologic malignancy, n (%)</b>                |                            |
| AML / MDS/AML                                       | 19 (68) / 9 (32)           |
| <b>ELN risk category, n (%)</b>                     |                            |
| Intermediate / adverse                              | 4 (14) / 24 (86)*          |
| <b>No. of prior systemic treatment lines, n (%)</b> |                            |
| 1 / 2 / ≥3  | 12 (43) / 10 (36) / 6 (21) |

\*TP53 mutated: 7 (25%)

## Acceptable safety profile for MP0533 reported for DR 1-6‡:

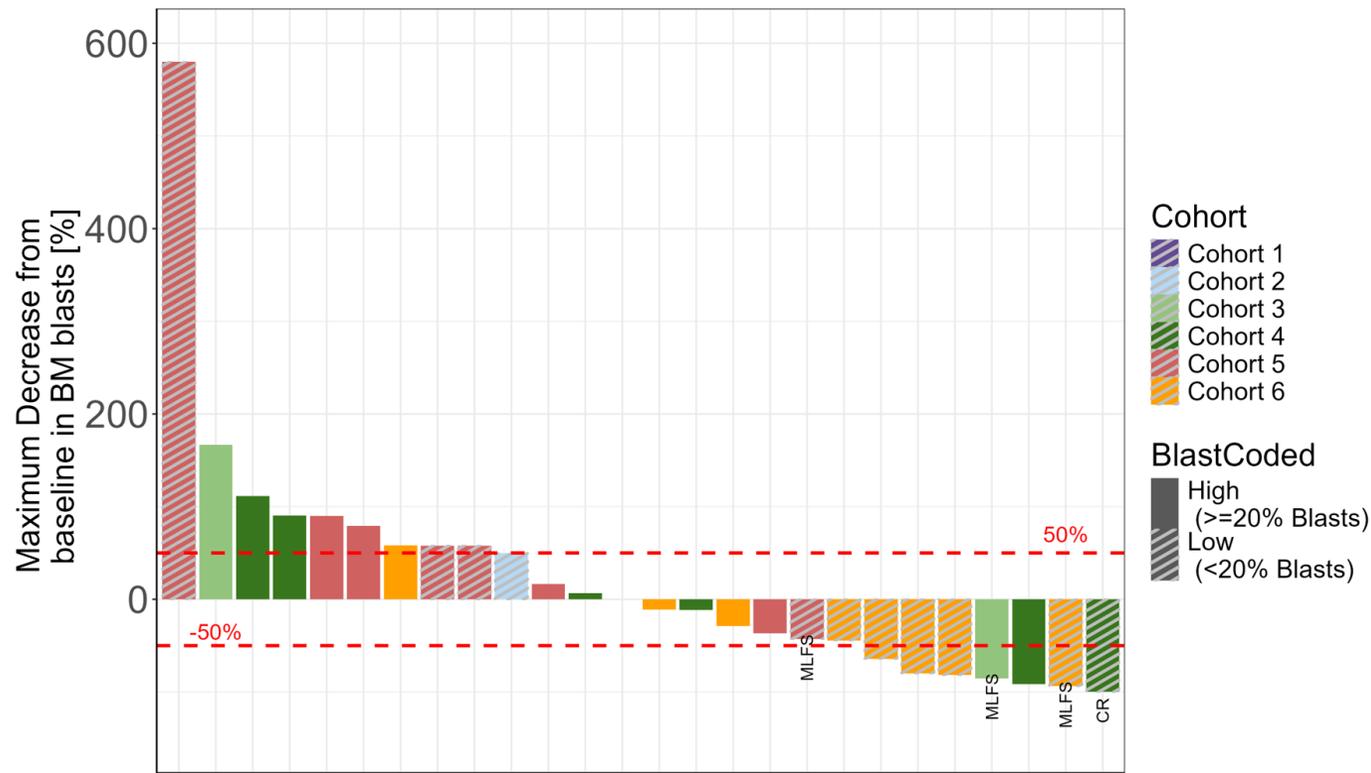
- IRR and CRS are the most frequent MP0533-related TEAEs (mostly Grade 1-2, occasional Grade 3)
- No DLTs up to DR 6

## MP0533-RELATED TEAEs‡

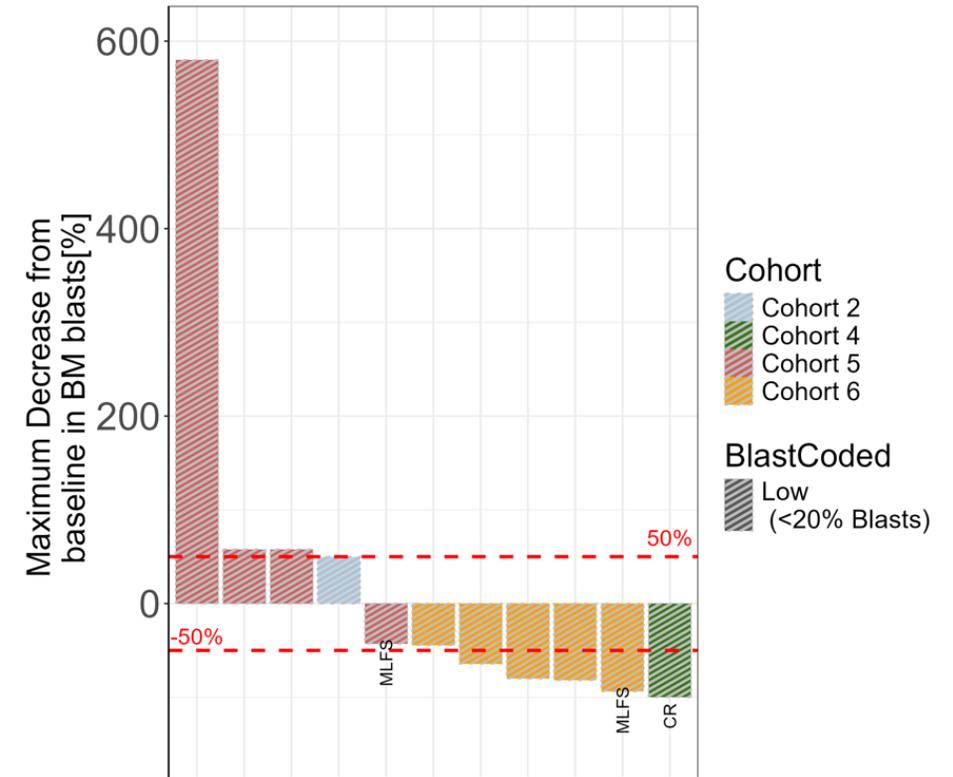


# Encouraging Blast Reduction Observed, Particularly in Patients with Lower Disease Burden\*

7 of 26 evaluable patients displayed >50% blast reduction in the bone marrow



5 of 11 patients with **lower disease burden\*** displayed blast reduction >50 %

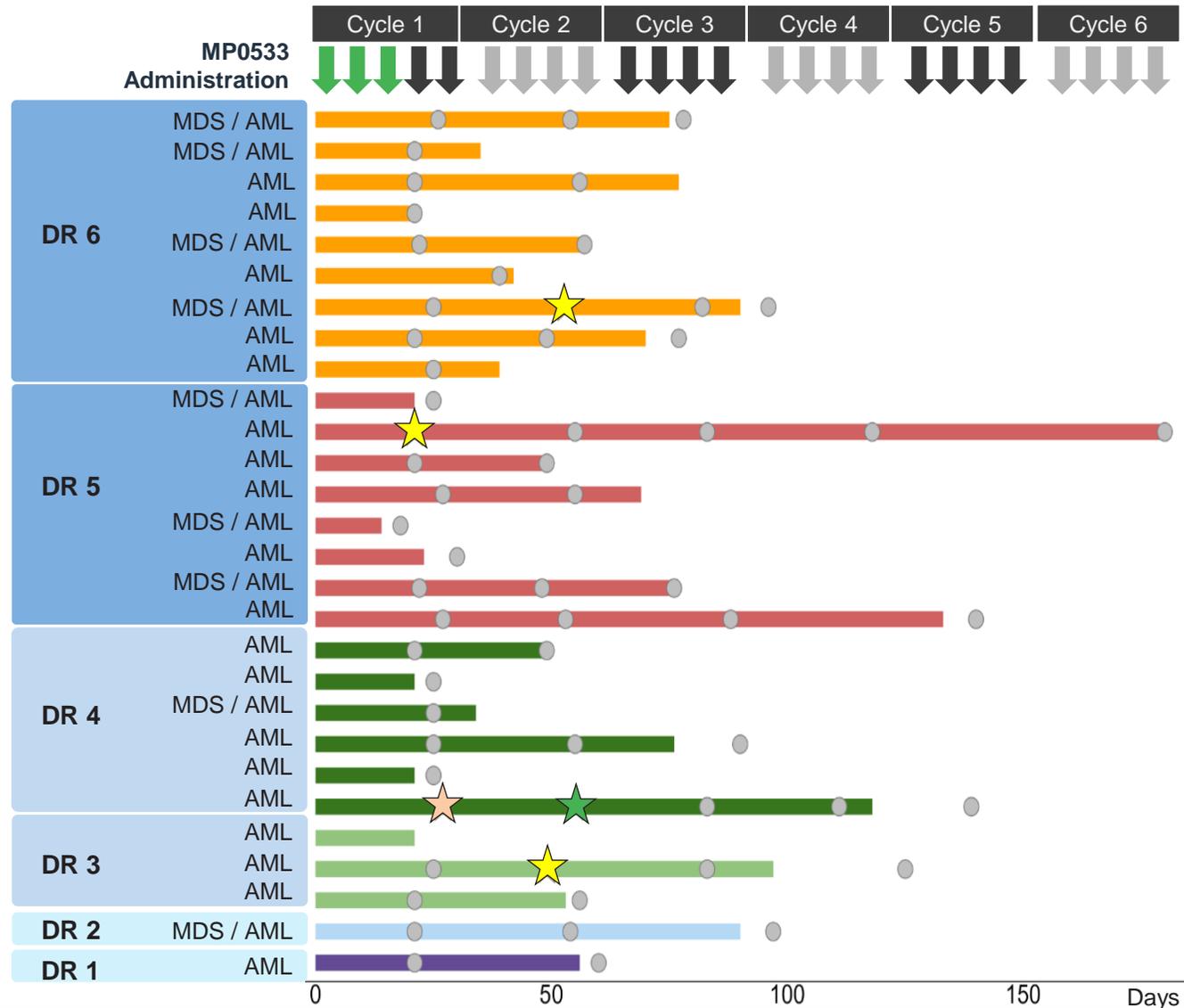


# MP0533 Treatment & Clinical Response

## Four responders reported in DR 3-6:

- CR in 1 patient at DR 4
- MLFS in 3 patients, 1 each at DR 3, DR 5 and DR 6

DR 8 open; data collection & analysis on-going for DR 7



## LEGEND

- ★ CR
- ★ CRi
- ★ MLFS
- No ELN response

Response (2022 ELN<sup>1</sup>) was assessed every 4 weeks until disease progression and results are presented as indicated

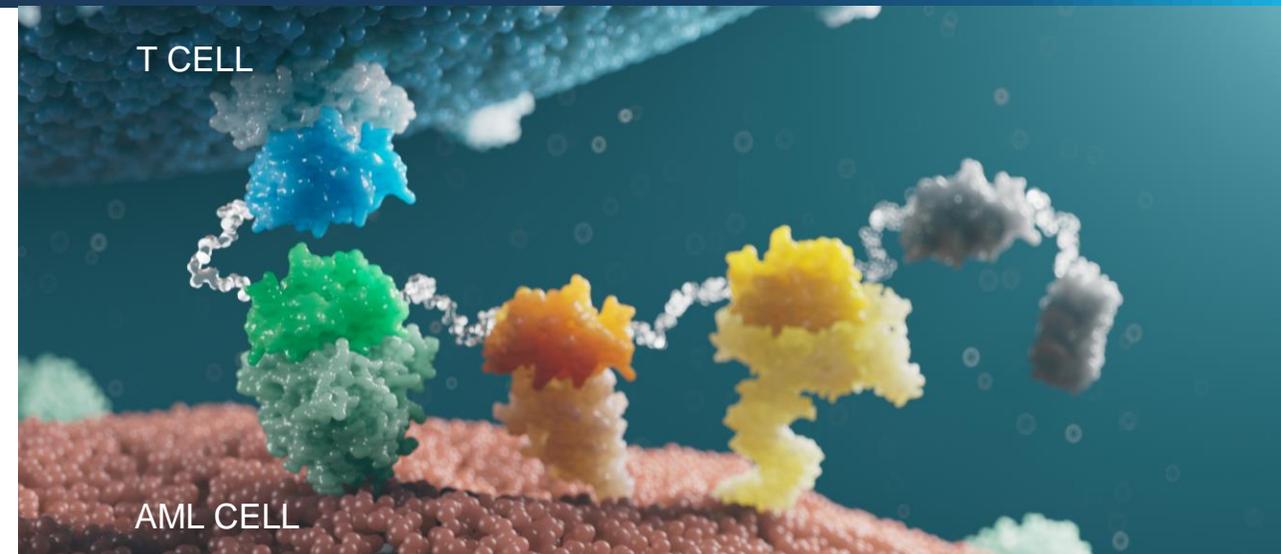
Arrows at the top indicate MP0533 administration at D1, D5, D8, D15 and weekly thereafter

Step-up dosing is presented in green arrows

Color changes in blue arrows indicate start of a new 28-day cycle

# MP0533 Summary

- **Rapid progress of MP0533 phase 1** with engaged clinical experts & sites
  - DR 8 open, 28 patients treated in DR 1–6
- **Acceptable safety profile** supports higher dosing
  - IRRs & CRS as most frequent MP0533-related TEAEs
- **Encouraging initial antitumor activity** in highly heterogeneous r/r AML population
  - 4 responders reported (1 responder per cohort, DR 3–6)
  - Encouraging reduction in BM blasts observed
- Need to **improve suboptimal exposure** to **unleash the full potential of MP0533**
  - Increase response rate, depth and durability



## **MP0533 Outlook**

- Protocol being amended for **both higher & more frequent dosing** (in first weeks)
- Clinical update on the program in H2 2024 and on the **amended dosing scheme in 2025**
- **Results** from these activities will **gate future development**



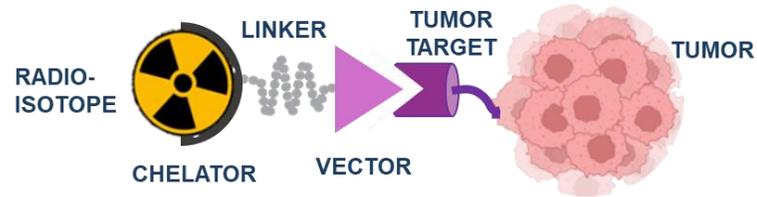
# Radio-DARPin Therapy & MP0712 as first program

Platform & Pipeline



# Targeted Radiotherapy: “Old” Modality Turned Hot Through Precision

## A TARGETED RADIOTHERAPEUTIC:



- Potential to “**see what you treat**” and “**treat what you see**” in a powerful and targeted manner
- Proven clinical **benefit for oncology patients**;
  - Therapies with beta emitters established, data with alpha emitters on the rise
- **Supply chain** challenges remain
- **Opportunity**: Broaden the target & indication space with **vectors** amenable to selective tumor uptake

Example of a prostate cancer patient with extensive bone metastasis treated with  $^{225}\text{Ac}$ -PSMA-617:

IMAGE → THERAPY → IMAGE



$^{225}\text{Ac}$ -PSMA-617

8 MBq →

7 MBq →

8 MBq →



# DARPinS Have the Potential to Broaden the Target Space

## LMW Molecules

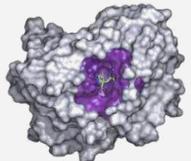


Generally good affinity and tumor uptake, low accumulation in kidneys

Limited number of targets with cavity where a LMW targeting moiety can be identified

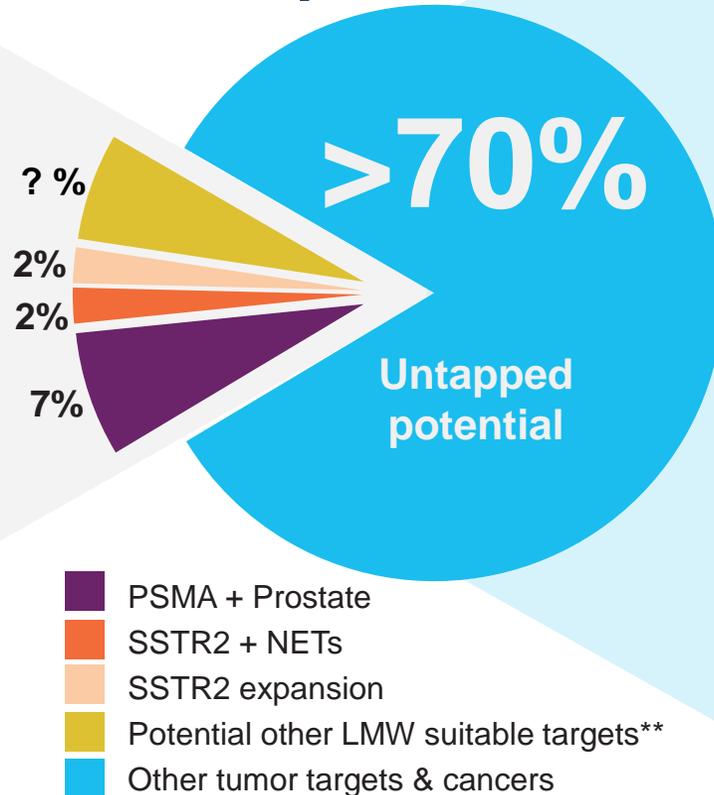
### Target Examples:

PSMA  
SSTR2



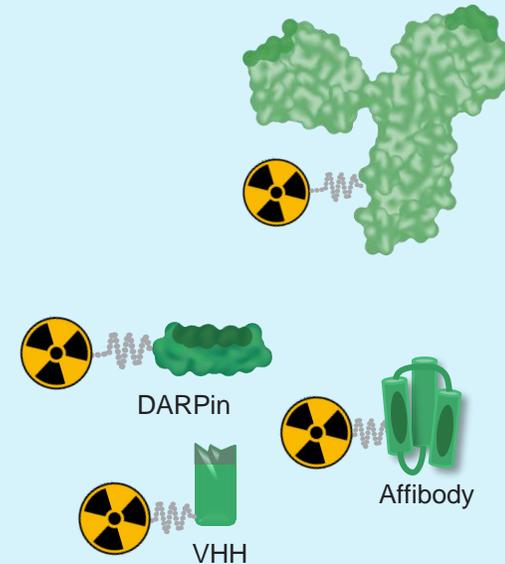
PSMA (1Z8L)

## Target Space\*



## Expanding with other targeting moieties

High affinity & specificity binding of protein surfaces of broad range of tumor targets



### Antibodies

- Long circulation → risk of bone marrow toxicity
- Low tumor penetration

### Small proteins

- High kidney accumulation → risk of renal toxicity
- Suboptimal tumor uptake

### Cyclic-peptides

- High kidney accumulation → risk of renal toxicity
- High affinity & selectivity can be challenging → target space?

# Opportunity to Evolve DARPins to Radio-DARPins

Enabled by the robust architecture of the DARPin scaffold

Proteins < 60 kDa are reabsorbed by kidneys

Breast cancer patient imaged after treatment with a Her2 DARPin:

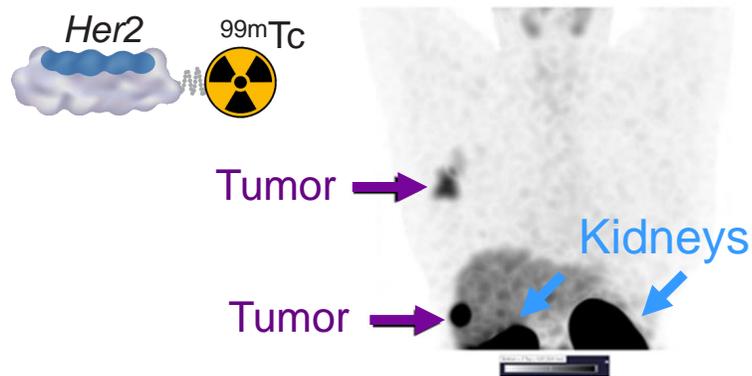
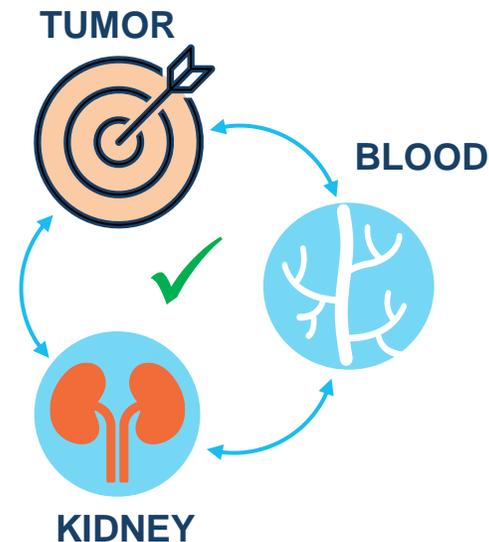


Image kindly provided by Dr. Bragina  
Research Centrum for Oncotheranostics, Tomsk



## Intrinsic DARPin properties



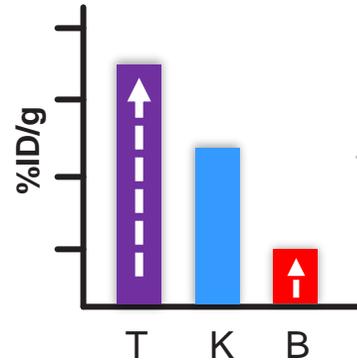
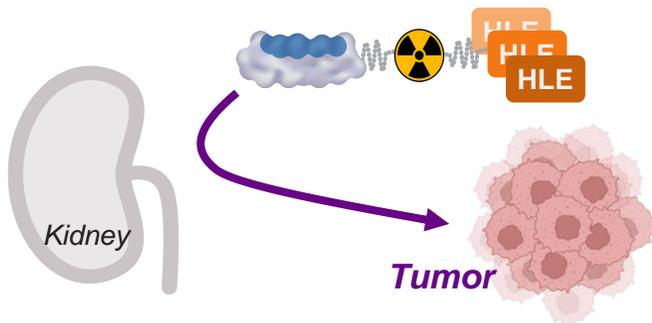
- ✓ **Small size** (~15 kDa)  
→ Deep tumor penetration  
→ Short systemic half-life
- ✓ **High affinity** (pM range)  
→ Long tumor retention
- ✓ **High selectivity**  
→ Low accumulation in other tissues
- ✓ **High stability**  
→ Surface engineering

## Unlocking DARPins for radiotherapeutic applications

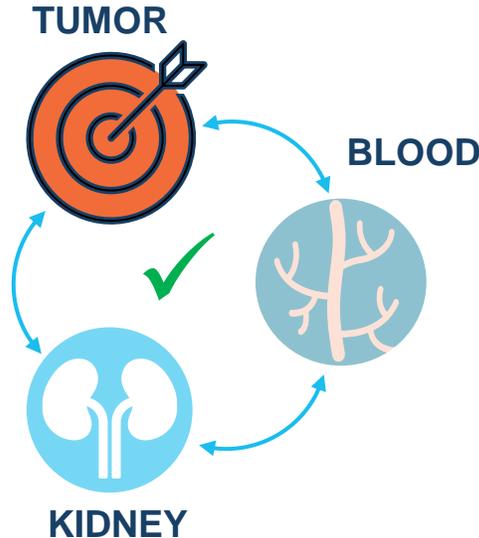
- Increase selective but moderate tumor uptake
- Reduce strong kidney accumulation

# Radio-DARPin Platform Ready to Deliver Product Candidates

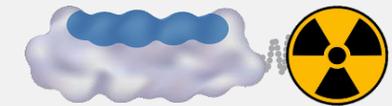
**Increased tumor uptake**  
by half-life extension (HLE)\*



**Optimized  
biodistribution  
properties**

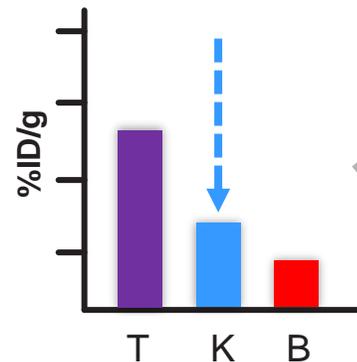
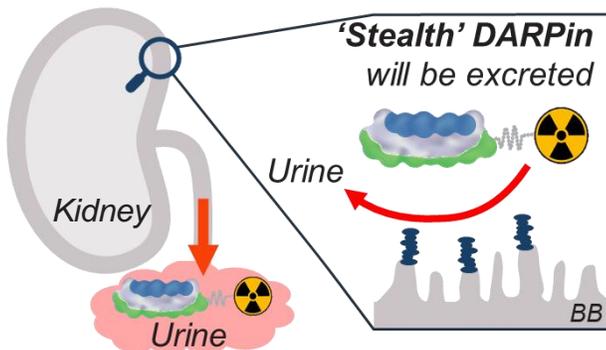


**Intrinsic DARPin  
properties**



- ✓ **Small size** (~15 kDa)  
→ Deep tumor penetration  
→ Short systemic half-life
- ✓ **High affinity** (pM range)  
→ Long tumor retention
- ✓ **High selectivity**  
→ Low accumulation in other tissues
- ✓ **High stability**  
→ Surface Engineering

**Reduced kidney accumulation**  
by surface engineering (*Stealth-DARPin*)\*



# MP0712: the First $^{212}\text{Pb}$ -DLL3 Targeted Radiotherapy

Combining distinctive DARPin features with the power of  $^{212}\text{Pb}$  for efficacious cancer therapy

## SCLC as indication

- Aggressive cancer with high unmet medical need
  - 2L: mPFS ~3m; 5y OS ~3%<sup>1,2</sup>
- DLL3 is expressed in >85% of patients<sup>3</sup>

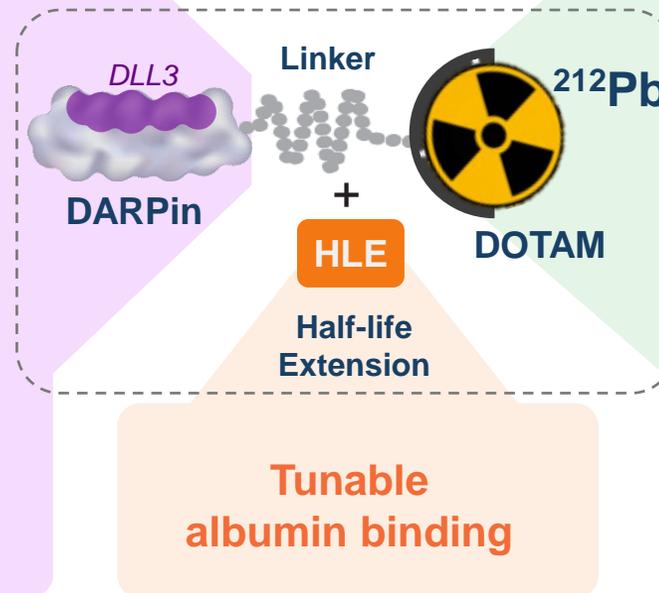
## DLL3: a promising target

- Homogeneous tumor expression, but low expression level in patients
- No expression in healthy tissues
- New treatments with room for improvement: Tarlatamab (AMGEN) for 2L+; ORR ~40%

## Diverse set of DARPins against DLL3

- Good developability
- Specific binding with high affinity

## Product composition



## $^{212}\text{Pb}$ for targeted alpha therapy

- Strong cytotoxicity (dsDNA breaks)
- Single alpha decay (limited free daughters)
  - Limited irradiation of healthy tissues
- Relatively short half-life (10.6 h)
  - Fast energy deposition (efficacy)
  - Easier waste management

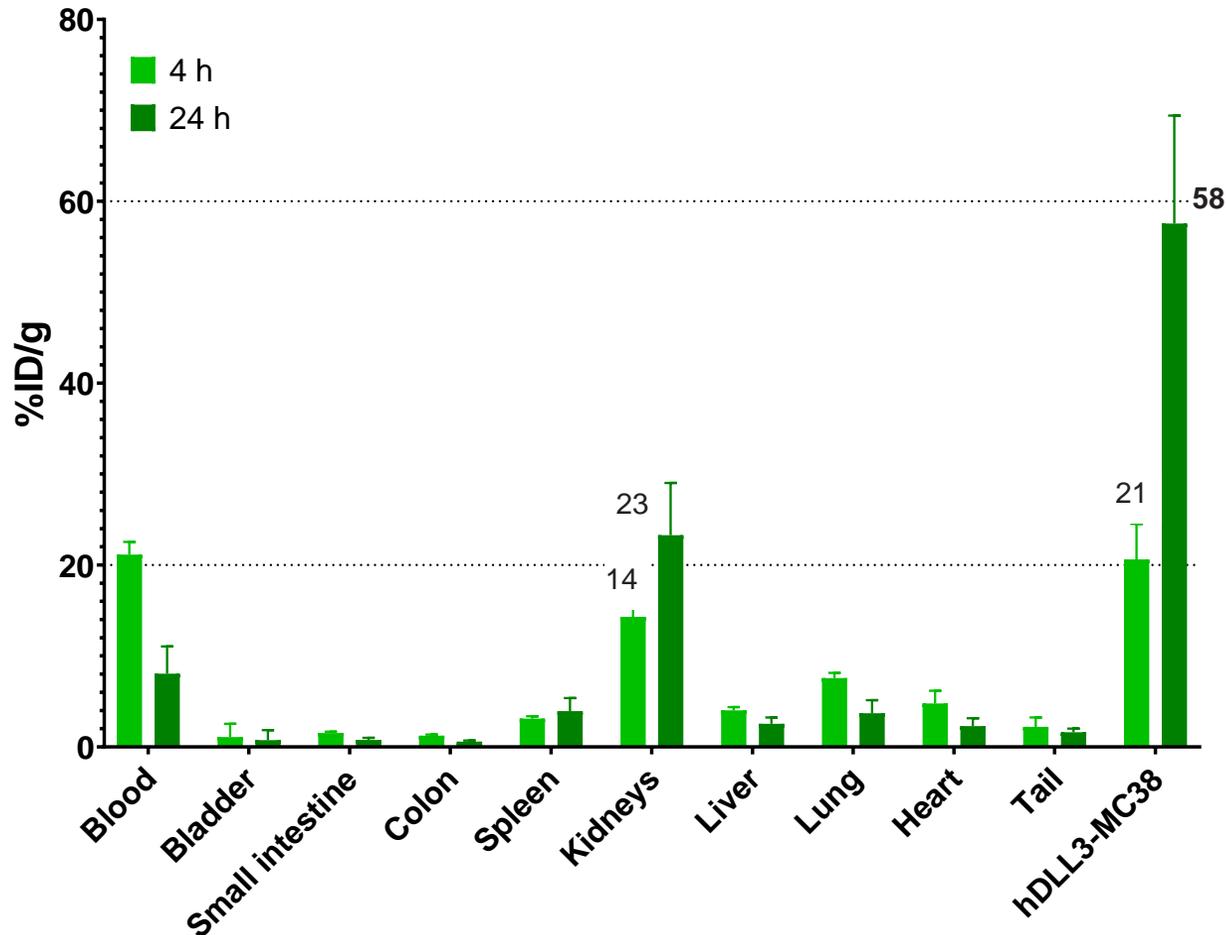
## Co-Development with Orano Med

- The leader for  $^{212}\text{Pb}$  & a committed partner
- Reliable & scalable  $^{212}\text{Pb}$  production
- Independent production capacities (substantial inventory of purified  $^{232}\text{Th}$ )

ASCO: Ph2 clinical data  $^{212}\text{Pb}$ -DOTAMTATE (AlphaMedix<sup>TM</sup>) showed an ORR of 55.6%<sup>4</sup>

# MP0712: $^{212}\text{Pb}$ -DLL3 Lead Candidate with Attractive BioD Profile

## Biodistribution profile of $^{212}\text{Pb}$ -DLL3 x RDT lead candidate

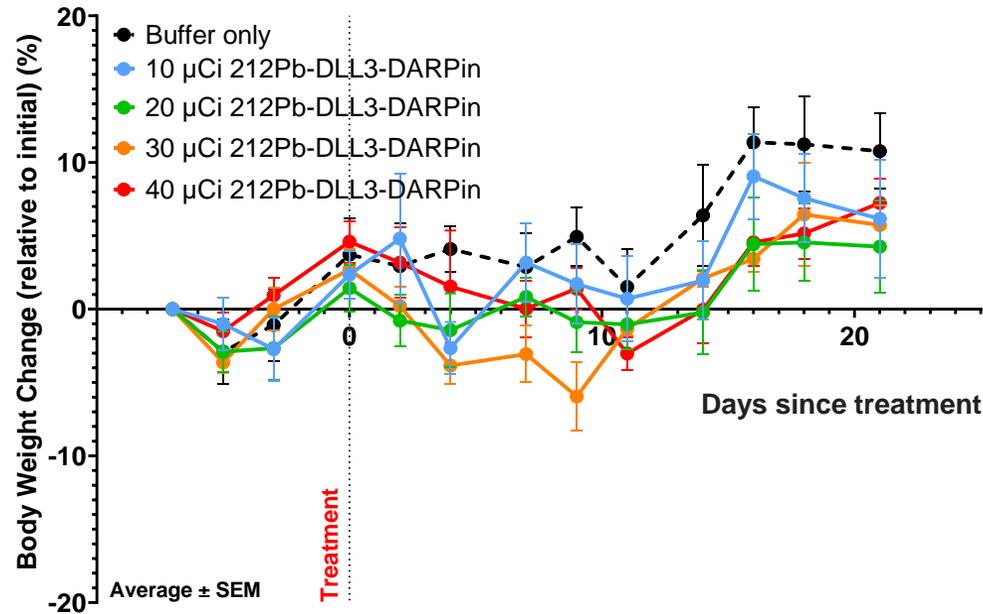


| Time Point | Tumor : Kidney |
|------------|----------------|
| 4 h        | 1.4 : 1        |
| 24 h       | 2.5 : 1        |

- **MP0712 selected as Lead Candidate for  $^{212}\text{Pb}$ -DLL3 Radio-DARPin Therapy**
- Encouraging biodistribution profile with **T:K Ratio >2** in MC38 model
- Similar profile in NCI-H82 model (patient relevant DLL3 expression) with T:K ratio >1 (*data not shown*)

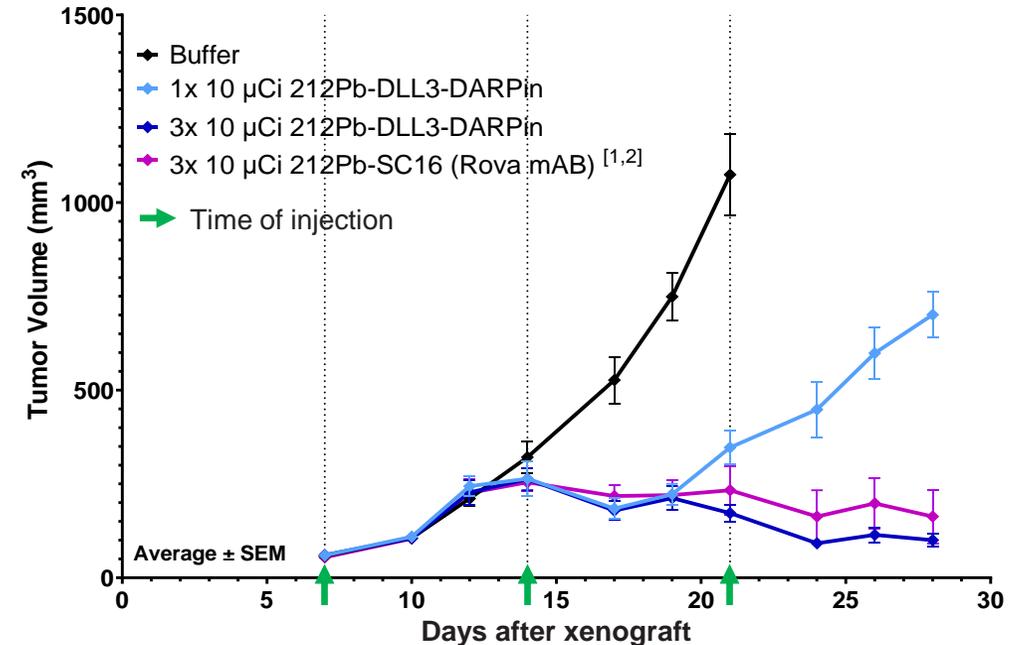
# Favorable Safety & Potent Efficacy of $^{212}\text{Pb}$ -DLL3 RDT Candidate

## Dose range finding in wt mice



- All treatments up to 40  $\mu\text{Ci}$  were well tolerated
- Treatment shows a favorable safety profile suggesting its potential for clinical use

## Efficacy in MC38-hDLL3 model



- Significant and durable inhibition of tumor growth (comparable to benchmark mAb)
- Treatment shows profound antitumor activity at clinically relevant dose

Lizak et al, SNMMI 2024 (oral presentation)

# $^{212}\text{Pb}$ has Key Advantages as Radioisotope Amenable to Radiotherapy

## Selectivity

Localized and limited exposure of healthy cells with alpha particles

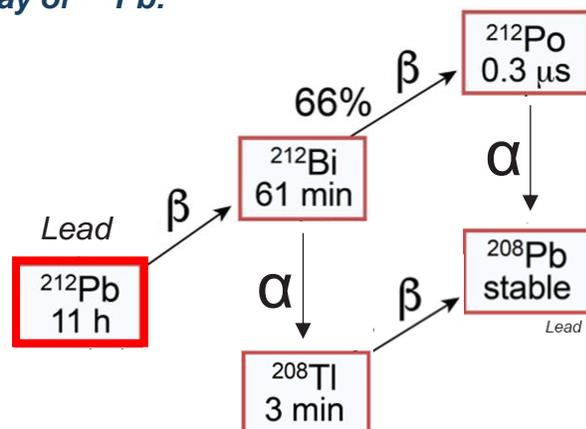
## Safety

Clean decay profile:  $^{212}\text{Pb}$  is an alpha precursor with low risk for long-lived free daughter radionuclides

## Waste management

Less problematic thanks to short half-life

### Decay of $^{212}\text{Pb}$ :



Adapted from Li et al., *Current Medicinal Chemistry*, 2020

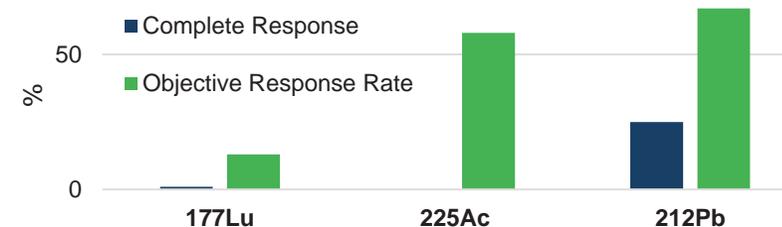
## Efficacy

Short decay half-life leads to high energy deposition on tumor in short time frame

$^{212}\text{Pb}$  demonstrated efficacy and good tolerability in GEP-NET patients treated with AlphaMedix™: 57% ORR in ph 1+2 combined (Strosberg et al, ASCO 2024)

$^{212}\text{Pb}$  bears best-in-class potential for certain indications

|              | Beta                         | Alpha            |                  |
|--------------|------------------------------|------------------|------------------|
|              | <b>177Lu</b> (1)             | <b>225Ac</b> (2) | <b>212Pb</b> (3) |
| Therapy      | 177Lu-DOTATATE (=Luthatera®) | 225Ac-DOTATATE   | 212Pb-DOTAMTATE  |
| Phase        | Phase 3 NETTER-1             | Comp. use        | Phase 1          |
| Patients (n) | 111                          | 26               | 12               |



Clinical data comparing  $^{212}\text{Pb}$  with other radioisotopes in treatment-naïve NET patients treated with SSTR-targeting RLTs

# Orano Med – Partner to Co-develop Radio-DARPin Therapies



“Endless” starting material as basis for  $^{212}\text{Pb}$  supply

## Leader in targeted alpha therapies

Large-scale, reliable, independent production and supply capabilities of  $^{212}\text{Pb}$

- Proprietary stockpile
- Achieve high purity of  $^{212}\text{Pb}$
- 4 GMP sites available or in construction across US and EU (incl. 2 AT Labs)
- Excellent logistics

**Clinical capabilities** demonstrated with  $^{212}\text{Pb}$  and AlphaMedix™ in Phase 2 study in collaboration with RadioMedix

## Strong partner for RDTs

Proven collaboration track record over past 2 years

- Trust, complementary and deep expertise

**Co-development agreement** signed on Jan 5, 2024:

- 50:50 cost and profit share
- Up to three tumor antigens including DLL3
- Molecular Partners commercialization rights for DLL3



22,000 drums of  $^{232}\text{Th}$



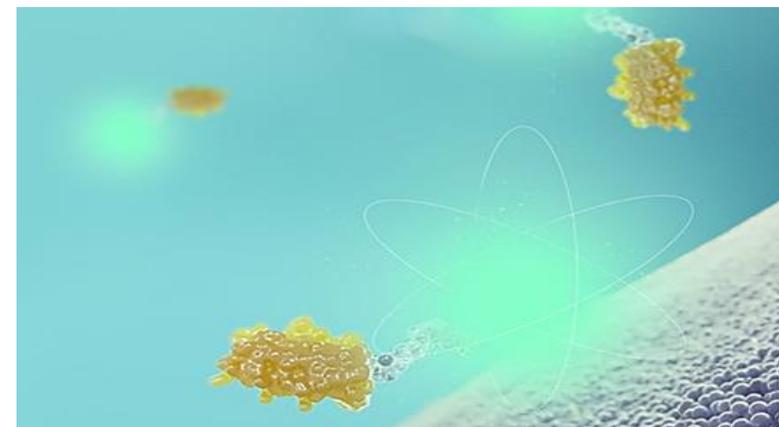
Lead-212 is obtained **chemically** by **successive extractions and purifications** of the descendants of thorium-232



Orano Med owns more than 20,000 drums of highly purified thorium-232 offering virtually unlimited supply

# Summary – Radio-DARPin Therapy (RDT) & MP0712

- Successful RDT platform optimization **with attractive biodistribution profile** (tumor, kidney, blood)
- **MP0712 selected as Lead Candidate for targeted  $^{212}\text{Pb}$ -DLL3 Radio-DARPin Therapy**
- IND-enabling activities initiated with Orano Med; **initial clinical data expected in 2025**

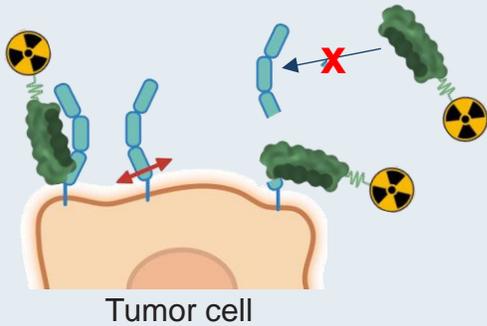


| TARGET                        | RESEARCH | DEV. | RIGHTS             |
|-------------------------------|----------|------|--------------------|
| DLL3                          | MP0712   |      | MOLECULAR partners |
| Target 2*                     |          |      | oranomed           |
| Target A                      |          |      | MOLECULAR partners |
| Target B                      |          |      |                    |
| Target X                      |          |      | NOVARTIS           |
| Target Y                      |          |      |                    |
| Several targets in evaluation |          |      |                    |

## RDT Outlook:

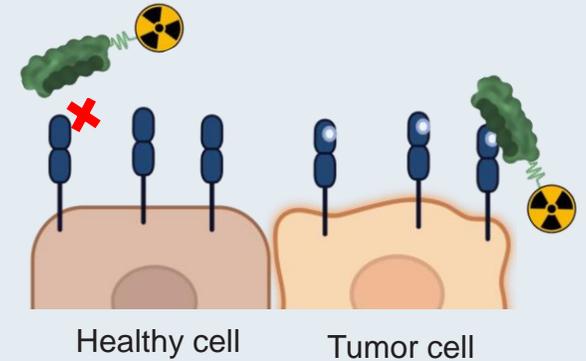
- **Advance MP0712 and additional pipeline candidates**
- **Evolve RDT platform for next differentiated RDT programs**
- **Progress collaboration projects with Orano Med and Novartis**

# Outlook: Leverage DARPin Differentiation to build RDT portfolio

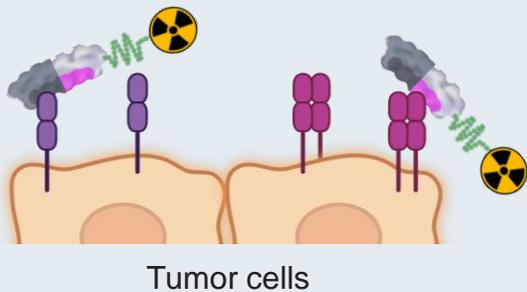


Selectivity for **membrane-bound antigen vs shed antigen** for high tumor uptake

Selectivity to antigens with **high surface homology** to other targets



## *2in1 DARPin*



**Bi-specific** DARPins to achieve **broader distribution in tumors & overcome heterogeneity**, especially for targeted alpha therapy

Created in part with BioRender.com



# Financial Overview

Robert Hendriks, SVP Finance

# H1 2024 Financial Highlights

- Strong financial position with CHF 159.1 million in cash (including short term deposits) as of June 30, 2024
- Revenue of CHF 4.3 million from the Novartis radioligand collaboration
- Net cash used in operating activities of CHF 32.8 million in H1 2024
- Operating loss of CHF 31.8 million and net loss of CHF 26.4 million in H1 2024
- Updated FY 2024 expense guidance of CHF 65–75 million (previous guidance CHF 70–80 million)
- Company expected to be funded into 2027, excluding any potential payments from R&D partnerships

# Key Figures H1 2024

| CHF MILLION, EXCEPT PER SHARE AND FTE DATA                      | H1 2024 | H1 2023 | CHANGE |
|---|---------|---------|--------|
| Revenues  | 4.3     | 3.5     | 0.8    |
| Total operating expenses  | (36.1)  | (34.5)  | (1.6)  |
| Operating result  | (31.8)  | (31.0)  | (0.8)  |
| Net financial result  | 5.4     | 0.2     | 5.2    |
| Net result  | (26.4)  | (30.8)  | 4.4    |
| Basic net result per share (in CHF)                             | (0.80)  | (0.94)  | 0.14   |
| Net cash used in / generated from operations                    | (32.8)  | (29.8)  | (2.9)  |
| Cash balance (including short-term time deposits) as of June 30 | 159.1   | 218.2   | (59.1) |
| Number of FTEs as of June 30                                    | 161.9   | 168.5   | (6.6)  |



# Outlook

Patrick Amstutz, CEO

# 2024 Outlook and Upcoming Milestones

## MP0533

- Protocol being amended for **both higher & more frequent dosing** (in first weeks)
- Clinical update with data of **amended dosing scheme expected in 2025**

## Radio-DARPin Therapy (RDT) & MP0712

- Advance MP0712 into IND-enabling studies with **initial clinical data expected in 2025**
- Expand portfolio with **differentiated RDT programs**, update in H2 2024
- Continue to progress RDT collaborations with Orano Med and Novartis

## Switch-DARPin & MP0621

- Update on MP0621 preclinical studies in H2 2024
- Switch-DARPin for next-generation immune cell engagers, update at SITC 2024

## MP0317

- Final data from the FIH dose-escalation Phase 1 study to be presented at SITC 2024
- Clinical exploration of combinations possibly via investigator-initiated trials

**CHF ~159 million cash\*** (incl. short-term time deposits) ensures **funding into 2027**



**Thank You**

# Appendix

# Financial Guidance for Full-Year 2024

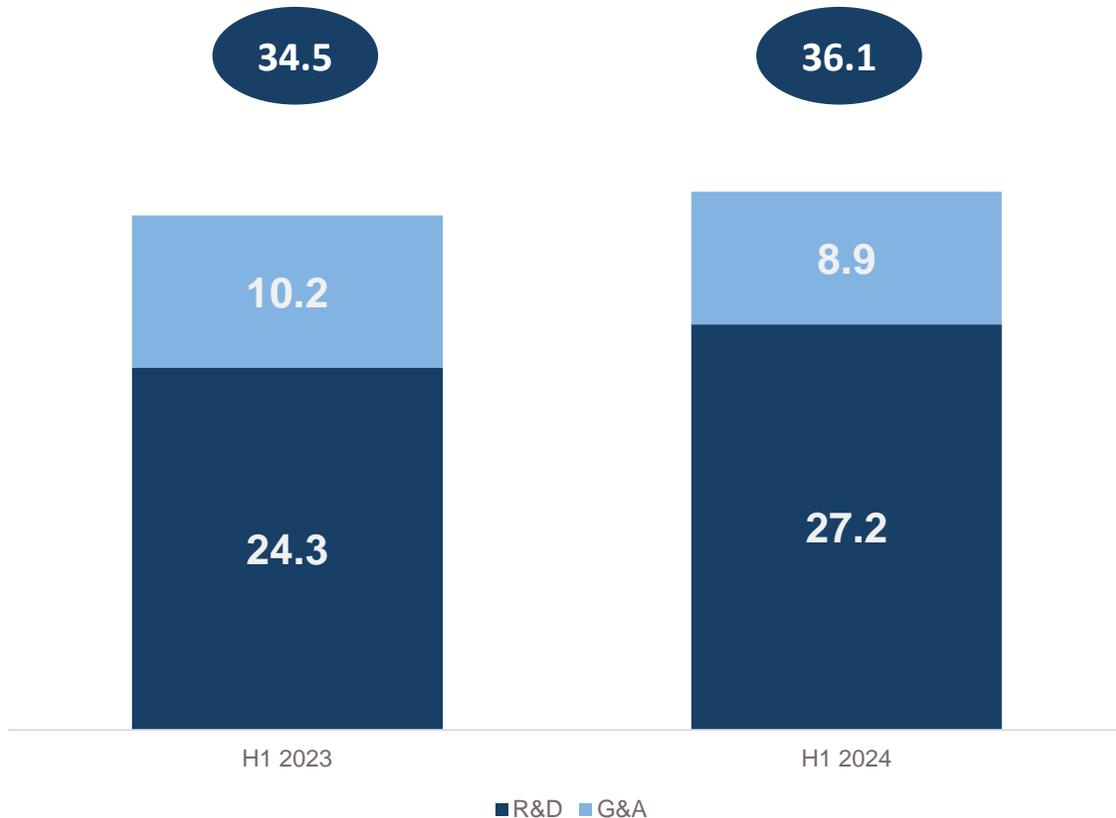
Total expenses of CHF 65–75 million [previous forecast CHF 70–80 million] for FY2024, of which around CHF 8 million is non-cash effective costs

With CHF 159.1 million cash at hand (incl. short-term time deposits) and no debt, the Company is funded into 2027, excluding any potential receipts from R&D partners

Guidance subject to progress and changes of pipeline as well as financial markets

# Operating Expenses

in CHF million (incl. depreciation & amortization)

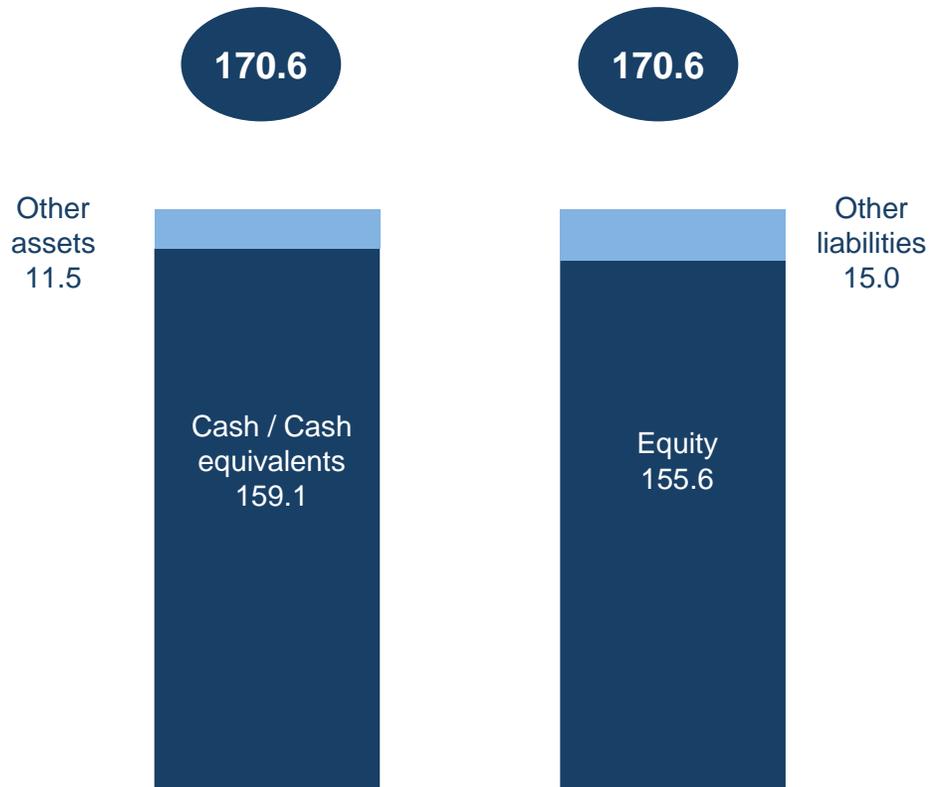


## Comments

- In H1 2024 main expense positions and drivers were:
  - CHF 20.1 million people-related expenses
  - CHF 10.9 million external R&D costs
  - CHF 5.1 million other (consulting and professional fees, facility, D&O insurance and general office expenses plus depreciation)
- Included are CHF 3.5 million non-cash effective costs

# Balance Sheet

as of June 30, 2024 (CHF million)



## Comments

Strong and debt free balance sheet

CHF 159.1 million cash balance (incl. time deposits) – 93% of total assets

Equity base of CHF 155.6 million

CHF 11.5 million of other assets include PPE of CHF 5.0 million, prepayments as well as other receivables for total of CHF 6.5 million.

CHF 15.0 million of other liabilities include CHF 0.6 million in relation to Novartis (revenue to be recognized), CHF 3.0 million lease liability, CHF 1.8 million for accrued employee benefits plus CHF 9.6 million for other current liabilities



# Switch-DARPin Platform & MP0621 as first program for HSCT in AML

Targeted and conditional activation of immune cells

# Next-Generation Conditioning for HSCT in AML and Beyond

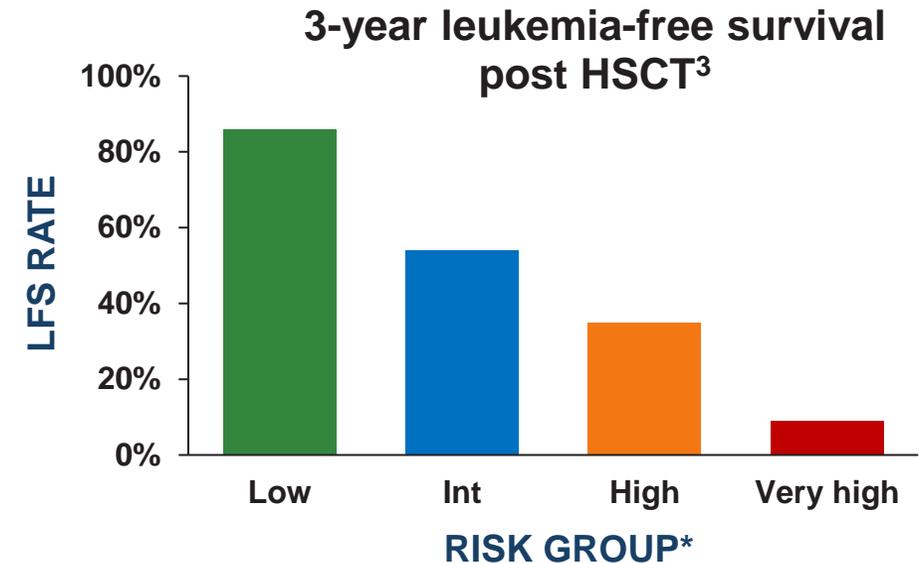
**HSCT is potentially curative for AML, however:**

**Conditioning regimens followed by HSCT do not always kill all AML cells<sup>1,2</sup>**

→ Many patients **relapse post HSCT**, especially AML patients with poor cytogenetic risk profile

**High-intensity conditioning regimen bears high toxicity<sup>1,2</sup>**

→ Many patients receive **reduced intensity conditioning with higher risk of relapse** or do not qualify for HSCT



## Opportunity for next-generation conditioning regimen

- Induce deep molecular remission to kill all AML clones, including in patients with poor cytogenetic risk profile
- Limit toxicity to allow access to HSCT for more AML patients, including elderly or frail patients
- Beyond AML: broaden applicability of HSCT for other diseases (e.g., genetic diseases) by improving safety of conditioning regimen

# MP0621: cKit x CD16a x CD47 Switch-DARPin

Our solution for a safe conditioning regimen and long-term disease control

## cKit (CD117)

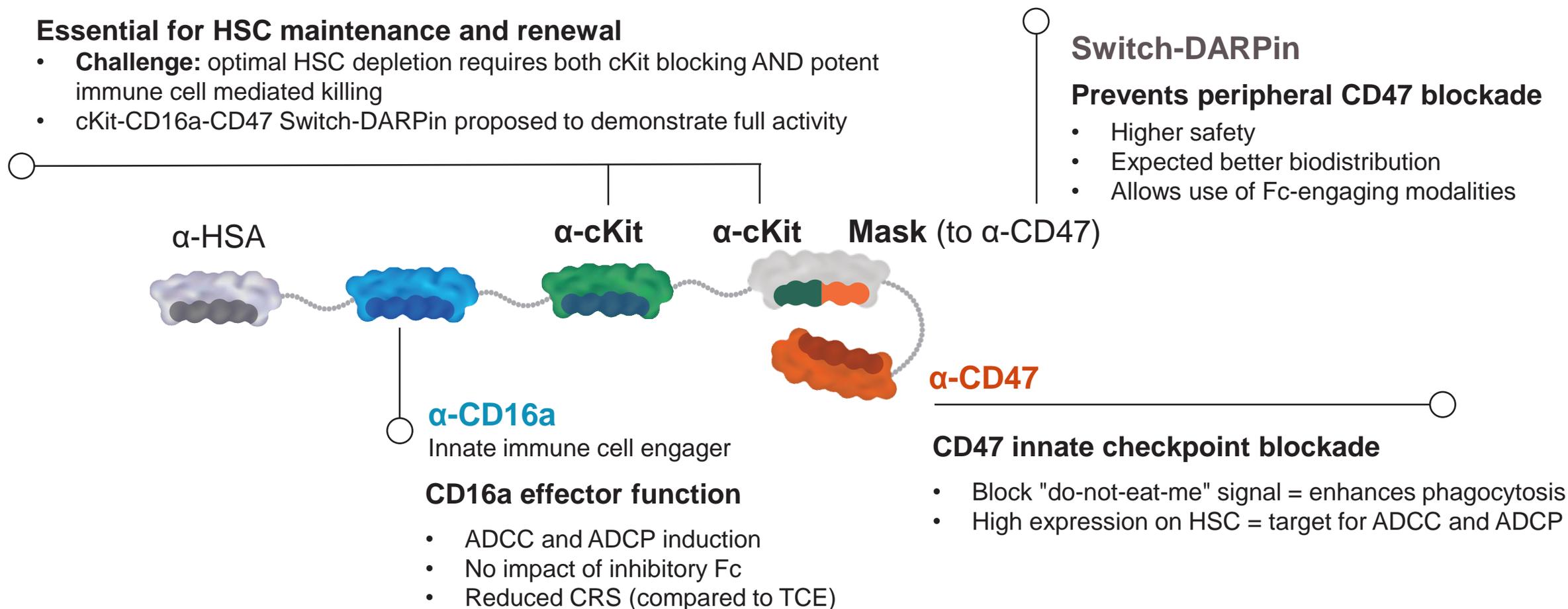
### Essential for HSC maintenance and renewal

- **Challenge:** optimal HSC depletion requires both cKit blocking AND potent immune cell mediated killing
- cKit-CD16a-CD47 Switch-DARPin proposed to demonstrate full activity

### Switch-DARPin

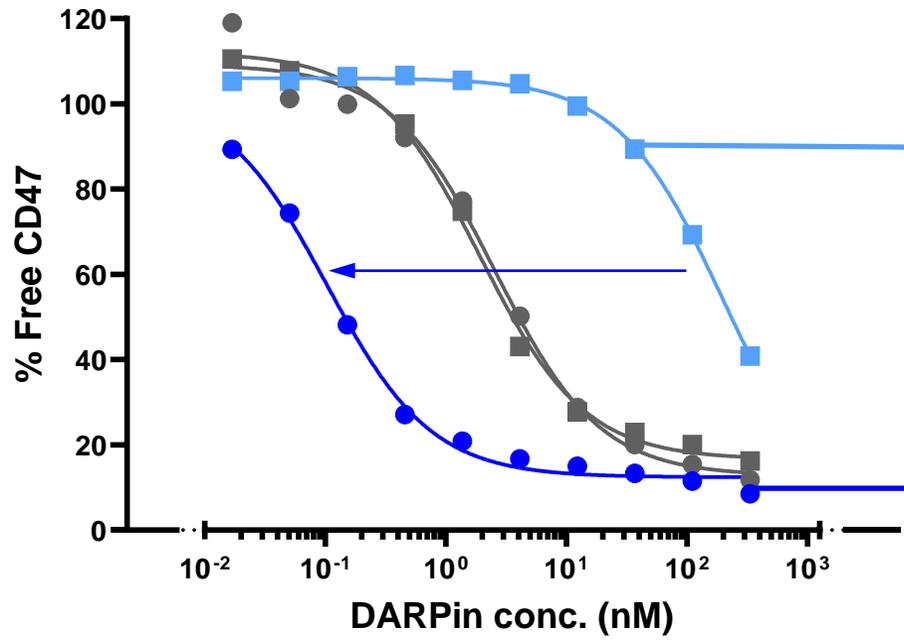
#### Prevents peripheral CD47 blockade

- Higher safety
- Expected better biodistribution
- Allows use of Fc-engaging modalities

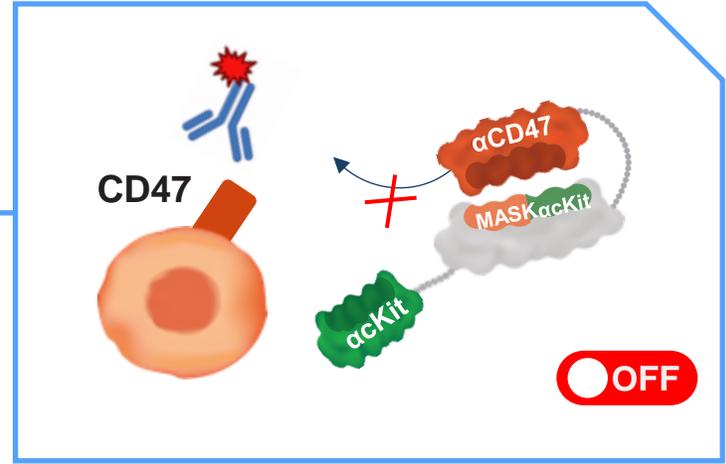


# Switch-DARPin POC - CD47 is Blocked Only on cKit Positive Cells

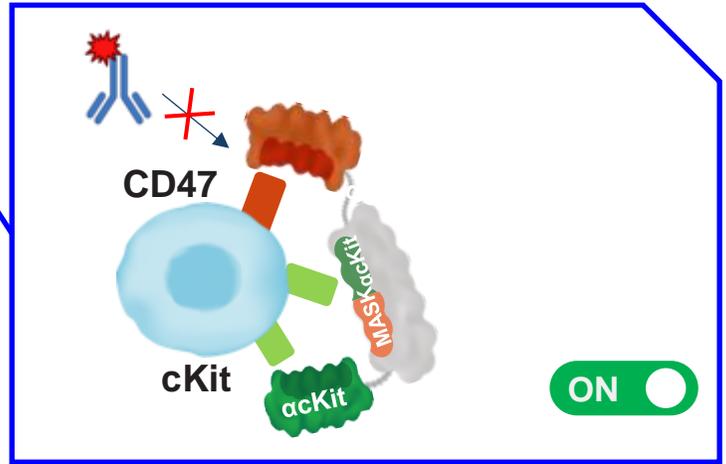
c-Kit-dependent CD47 blockade



- MP0621 on cKit<sup>+</sup> cells
- MP0621 on cKit<sup>-</sup> cells
- α-CD47 on cKit<sup>+</sup> cells
- α-CD47 on cKit<sup>-</sup> cells



**cKit Negative cells**  
Switch is OFF  
CD47 is NOT blocked



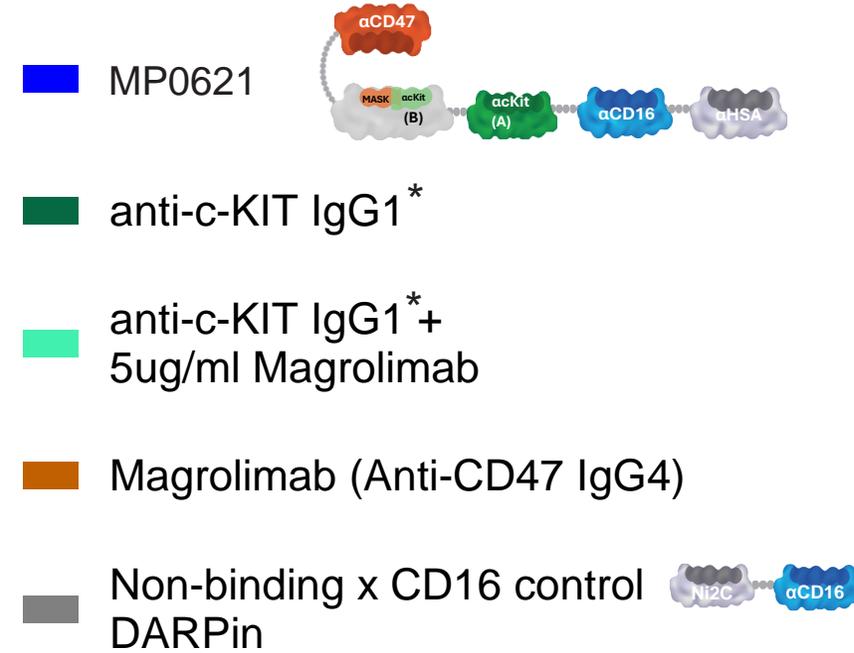
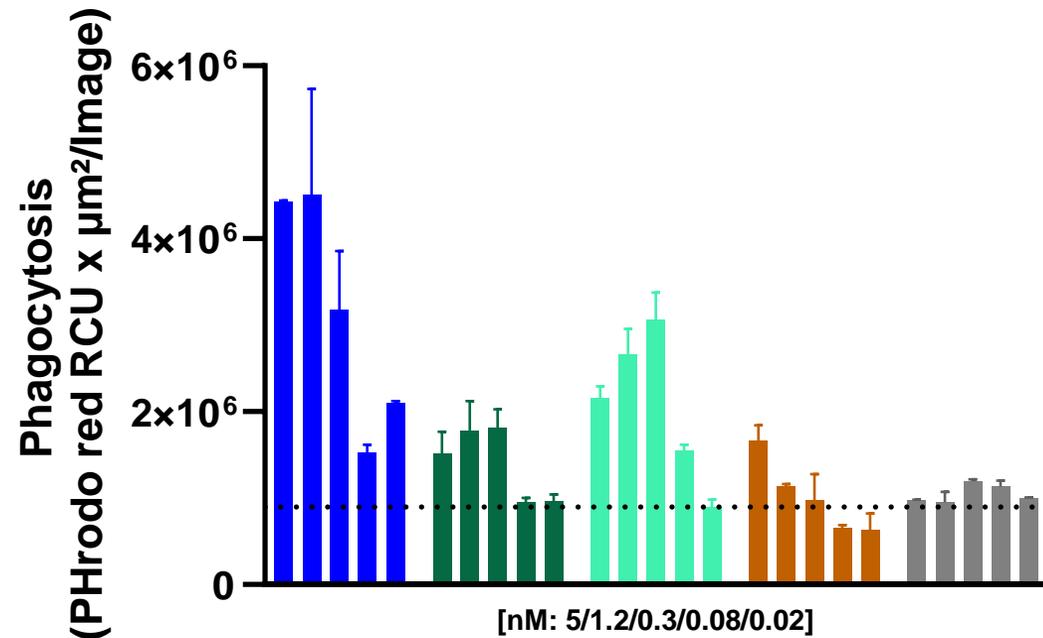
**cKit Positive cells**  
Switch is ON  
CD47 is Blocked

 anti-CD47 detection agent

# MP0621 shows superior ADCP activity compared to a combo of anti-cKit Ab\* + Magrolimab

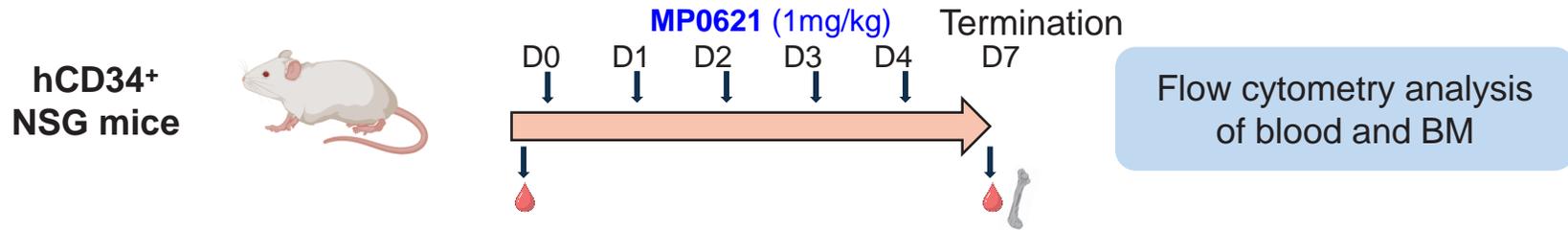
## ADCP assay

M0-like Macrophages + Kasumi-1 AML cell line



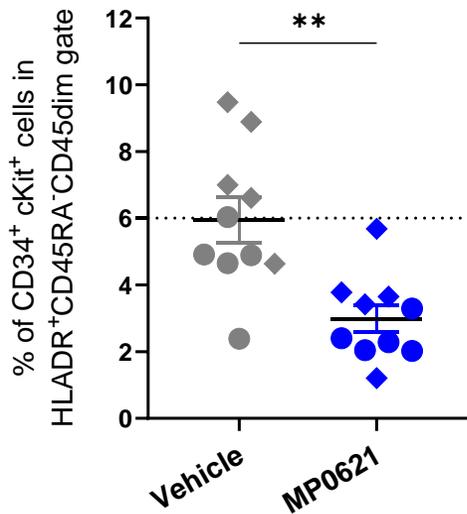
\*Fc-active version of JSP-191, reproduced by MP

# MP0621 depletes cKit<sup>+</sup> cells in the bone marrow without affecting circulating immune cells in humanized mice

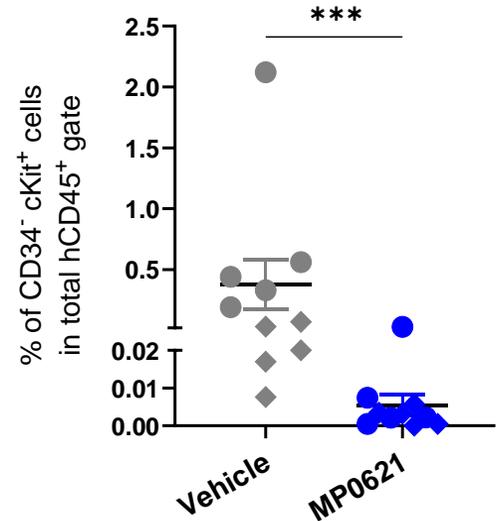


## Targeted cKit<sup>+</sup> cells depleted in bone marrow

hcKit<sup>+</sup> hCD34<sup>+</sup> cells, incl. HSCs

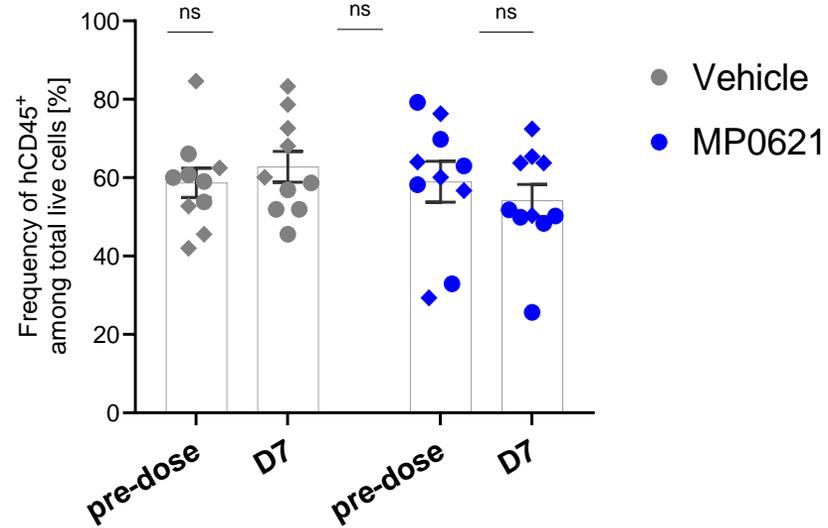


hcKit<sup>+</sup> hCD34<sup>-</sup> cells



## Immune cells in blood

hCD45<sup>+</sup> immune cells



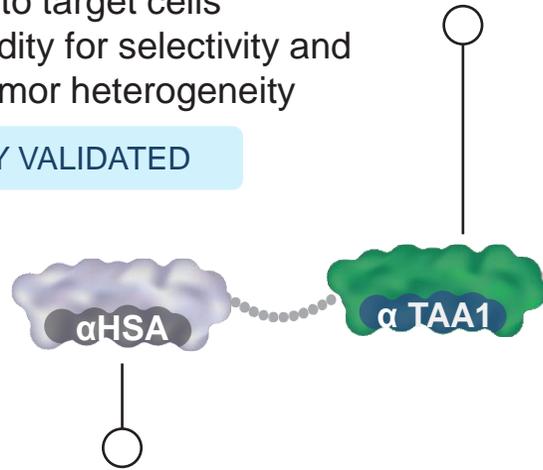
# Potential logic-gated Switch-DARPin Concepts

## Swiss knives for enhanced immune engagers

### 1<sup>st</sup> Antigen Binder

- Anchoring to target cells
- Adding avidity for selectivity and address tumor heterogeneity

✓ CLINICALLY VALIDATED



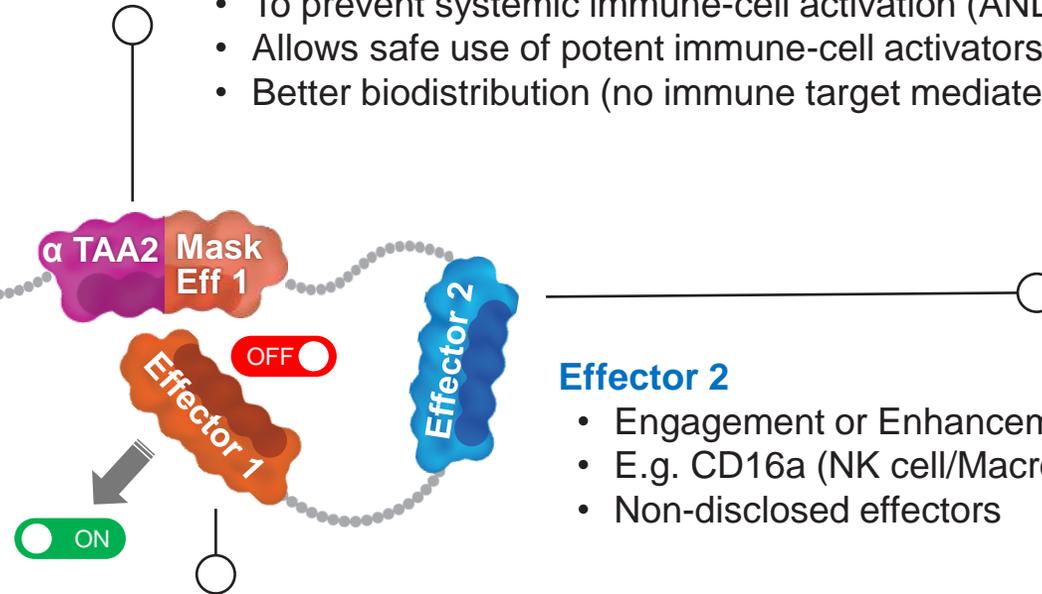
### HSA Binding DARPin(s)

- For half-life extension

✓ CLINICALLY VALIDATED

### 2-in-1 DARPin: Exclusive Binding to 2<sup>nd</sup> Antigen or Masking Effector 1

- To prevent systemic immune-cell activation (AND gate)
- Allows safe use of potent immune-cell activators
- Better biodistribution (no immune target mediated sink)



### Effector 2

- Engagement or Enhancement of immune response
- E.g. CD16a (NK cell/Macrophage engagement)
- Non-disclosed effectors

### Effector 1 (Switched on/off by Masking DARPin)

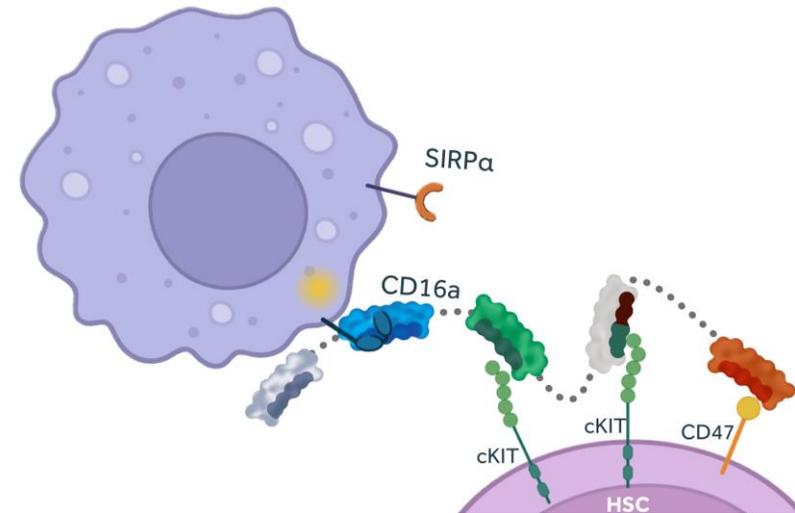
- Engagement or enhancement of immune responses
- E.g. CD47 (block don't-eat-me signal)
- E.g. CD3 ("Signal 1" T-cell engagement)

✓ CD3 TCE CLINICALLY VALIDATED

# Switch-DARPin & MP0621 – Summary

## Summary

- ✓ Dual-binding DARPin (the “Switch”) provides a **logic-gated “on/off” function** to a multi-specific DARPin
- ✓ Conditional, target-specific immune activation demonstrated for **Switch-DARPin platform** *in vitro*
- ✓ MP0621 as first program: a **cKit x CD16a x CD47 Switch-DARPin** as next-gen therapeutic supporting HSCT for AML patients & beyond
- ✓ **Positive preclinical data** presented at EHA 2024: MP0621 effectively depletes targeted cells *in vivo* with a safe profile



## Outlook

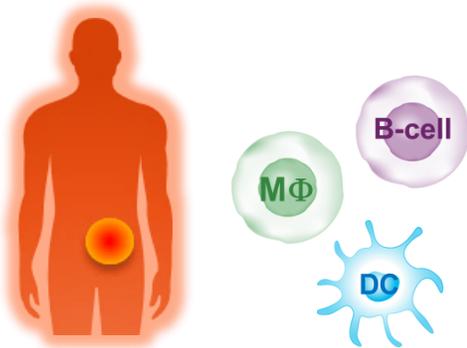
- Update on MP0621 preclinical studies in H2 2024
- Switch-DARPins for next-generation immune cell engagers, update at SITC 2024

# MP0317

Tumor-localized Immunotherapy

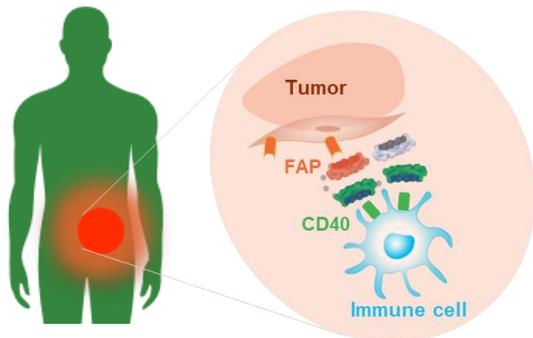
# MP0317: Unlocking CD40 Activity Through Local Activation

## Problem: Toxicity of CD40 Antibodies Has So Far Limited Their Activity

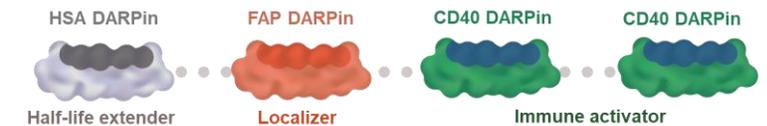


- **CD40 agonists** can activate **B cells, DCs and MΦ** to enhance the efficacy of IO drugs, especially in “cold tumors”
- **Systemic activation of CD40 via mAbs** has been hampered by **significant toxicities**, therefore **limiting their potential of reaching a therapeutically active dose**

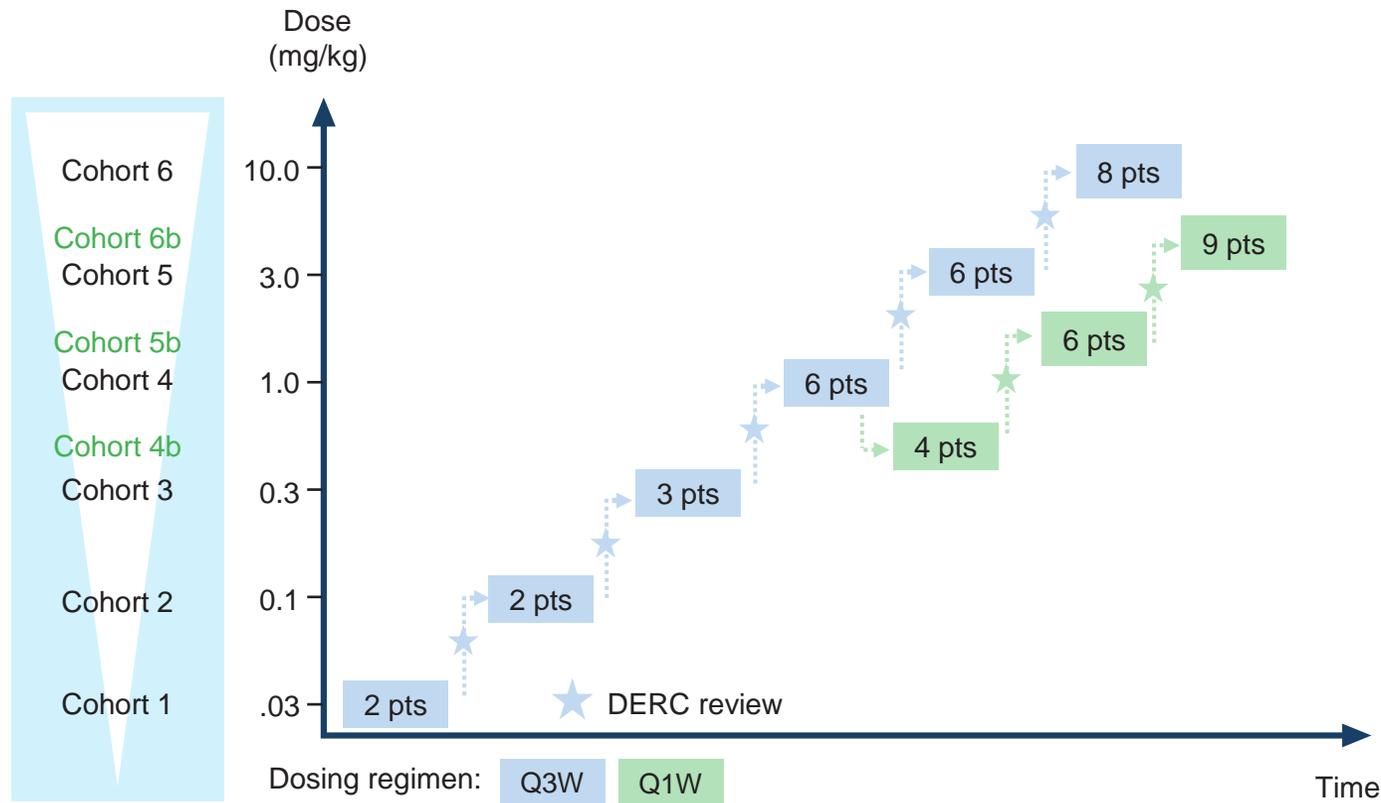
## Solution: MP0317 – FAP-dependent tumor-localized CD40 activation



- **FAP is a validated tumor target** overexpressed in at least 28 different cancer types and its expression is not downregulated during disease progression
- **MP0317** is designed to bind tumor-localized FAP and induce CD40-mediated **activation of immune cells in the tumor**, thereby overcoming systemic toxicity and allowing a **wider therapeutic dosing range**



# MP0317 Phase 1 Study Design and Status

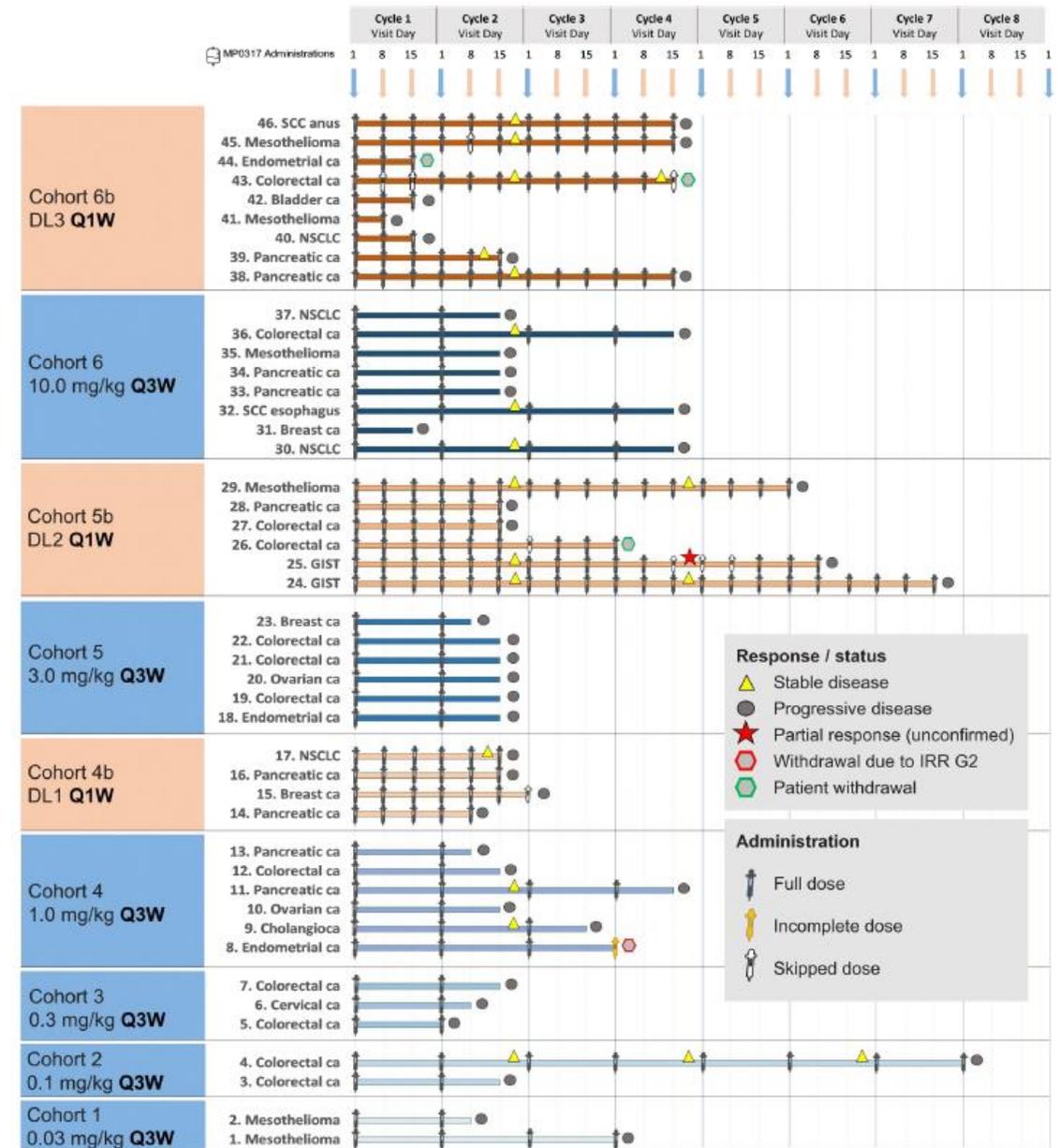


## STUDY DESIGN

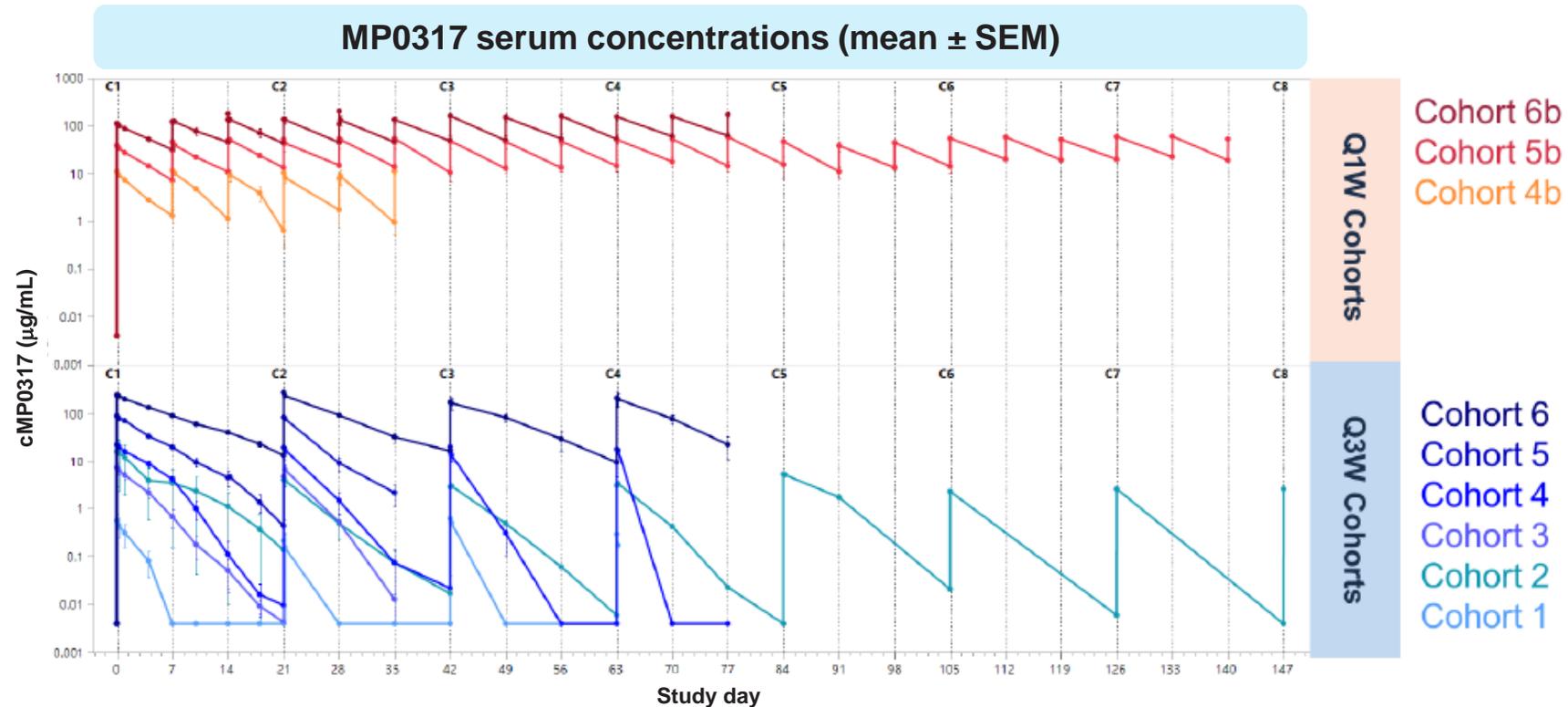
- **FIH, multi-center, dose-escalation study of MP0317 monotherapy** (9 dose cohorts; Q1W and Q3W dosing; NCT05098405)
- **Eligible patients:** adults with advanced solid tumors
- **Primary objectives:** safety/tolerability, recommended dose for expansion & combination
- **Secondary objectives:** PK, PD, and preliminary antitumor activity
- **Centers:** 4 sites in France and The Netherlands

# MP0317 Phase 1 Study Final Data at ASCO 2024

- A total of **46 patients treated** in 9 cohorts
  - Median age (range): 63 years (35–79)
  - ECOG PS 0 / 1, n (%): 22 (48) / 24 (52)
  - Medial prior regimen (range): 4 (1–13)
- **Favorable safety profile** across all tested dose cohorts up to highest planned dose (10 mg/kg)
  - Only 1 patient with a DLT (cohort 6; Grade 3 AST and ALT increase)
  - Most frequent Ars: fatigue and Grade 1–2 IRRs
- **Clinical evidence** of tumor-localized CD40 pathway and immune cell activation, leading to **TME remodeling**



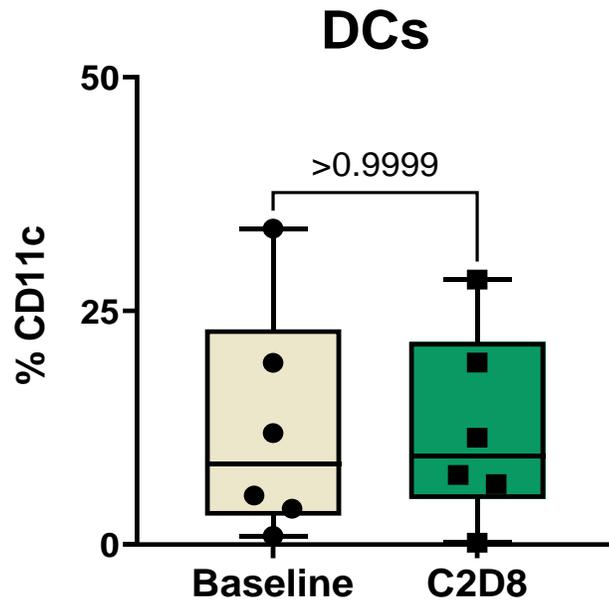
# MP0317 Serum PK is Suitable for Q3 and Q1 dosing



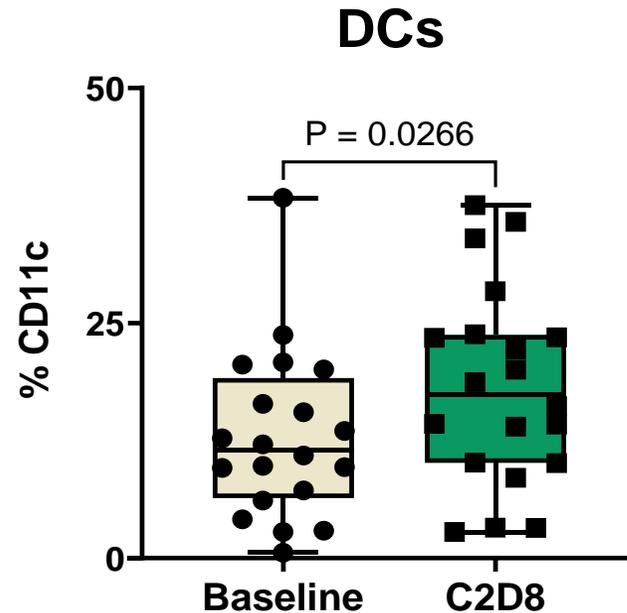
- PK profile is consistent with **half-life extended properties of DARPins**
- **MP0317 exposure shows dose-proportionality** throughout the treatment period analyzed
- **Sustained exposure** is observed at higher doses with both regimens overcoming TMDD and the impact of ADAs

# MP0317 Tumor-localized CD40 Activation and TME Modulation

MP0317 low doses or not detected in tumor (n=6)



MP0317 higher doses and detected in tumor (n=20)



- Bulk RNA sequencing in paired tumor biopsies (n=19) shows that MP0317 presence tends to be associated with:
  - Increase in abundance of plasma and T follicular helper cells
  - DC maturation gene signature
  - IFN $\gamma$  downstream activation gene signature scores
- Increases observed in CXCL10 serum levels corroborate these findings

Evaluable paired tumor biopsies from treated patients were analyzed with mIF. Low doses:  $\leq 0.1$ mg/kg; higher doses:  $\geq 0.3$ mg/kg. Upper (75%), median, and lower (25%) percentiles are indicated. P-values are derived from paired ranked sum Wilcoxon test.



# MP0533

Tetra-specific T-cell Engager for AML

# Patients with AML Have a High Unmet Medical Need

**69** YEARS  
OLD

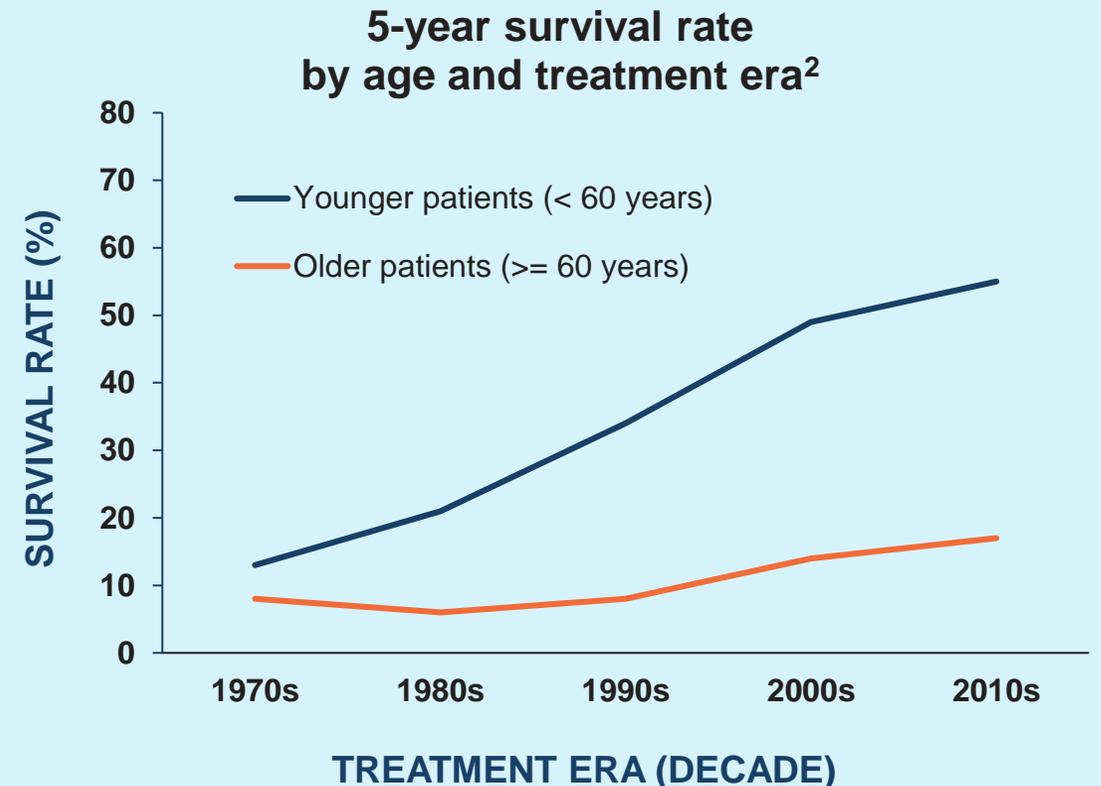
Median age of AML  
patients at diagnosis<sup>1</sup>

**31.7%**

Overall 5-year  
survival rate<sup>1</sup>

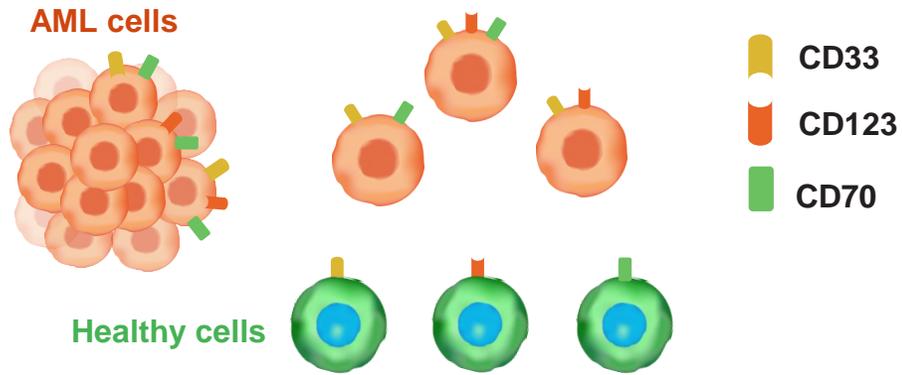
Despite 50 years of progress, elderly and frail patients are often not eligible for high-intensity conditioning and HSCT, and thus have limited treatment options and poor survival outcomes<sup>2</sup>

- Lack of broad and clean AML surface targets
- Risk of clonal escape even after high-intensity conditioning/HSCT



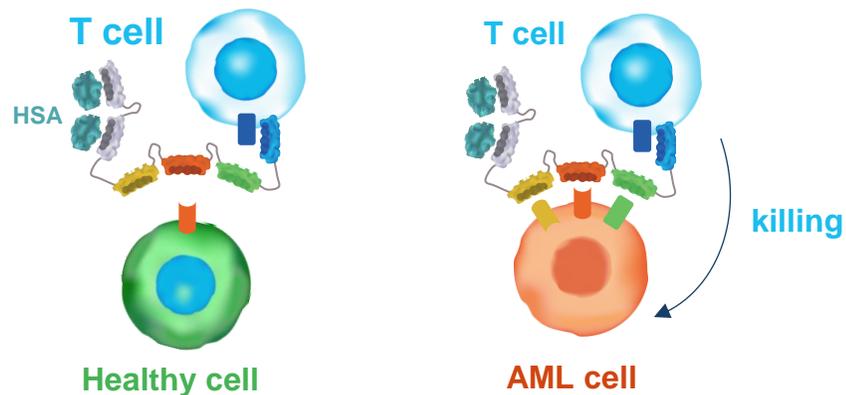
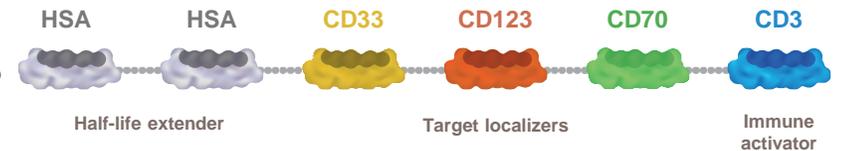
# MP0533: Avidity-Driven Selectivity for Cancer Cells in AML

**Problem: AML tumor-associated antigens are expressed on healthy cells**



- **AML remains a deadly disease** and persistence of **leukemic stem cells (LSCs)** drives relapse
- **AML cell population is heterogeneous**: individual AML blasts and LSCs lack a clean target. AML cells can be differentiated from healthy cells (e.g. HSCs) by their **co-expression of specific targets** (e.g. CD33, CD123, CD70)

**Solution: MP0533 – Avidity-driven selectivity and killing by T cells**



- MP0533 is designed to induce **T cell-mediated killing preferentially when two or three target antigens (CD33, CD123, CD70) are co-expressed**
- MP0533 is hypothesized to preserve healthy cells hence **opening a therapeutic window**
- MP0533 has the potential to kill all AML cells (blasts and LSCs) despite heterogeneity, ensuring **long term disease control**

# An optimized dosing schedule of MP0533 is pursued to overcome CD123 and CD33-driven antigen sink

→ Achieve early and maintain consistently therapeutic drug levels in AML/MDS patients

