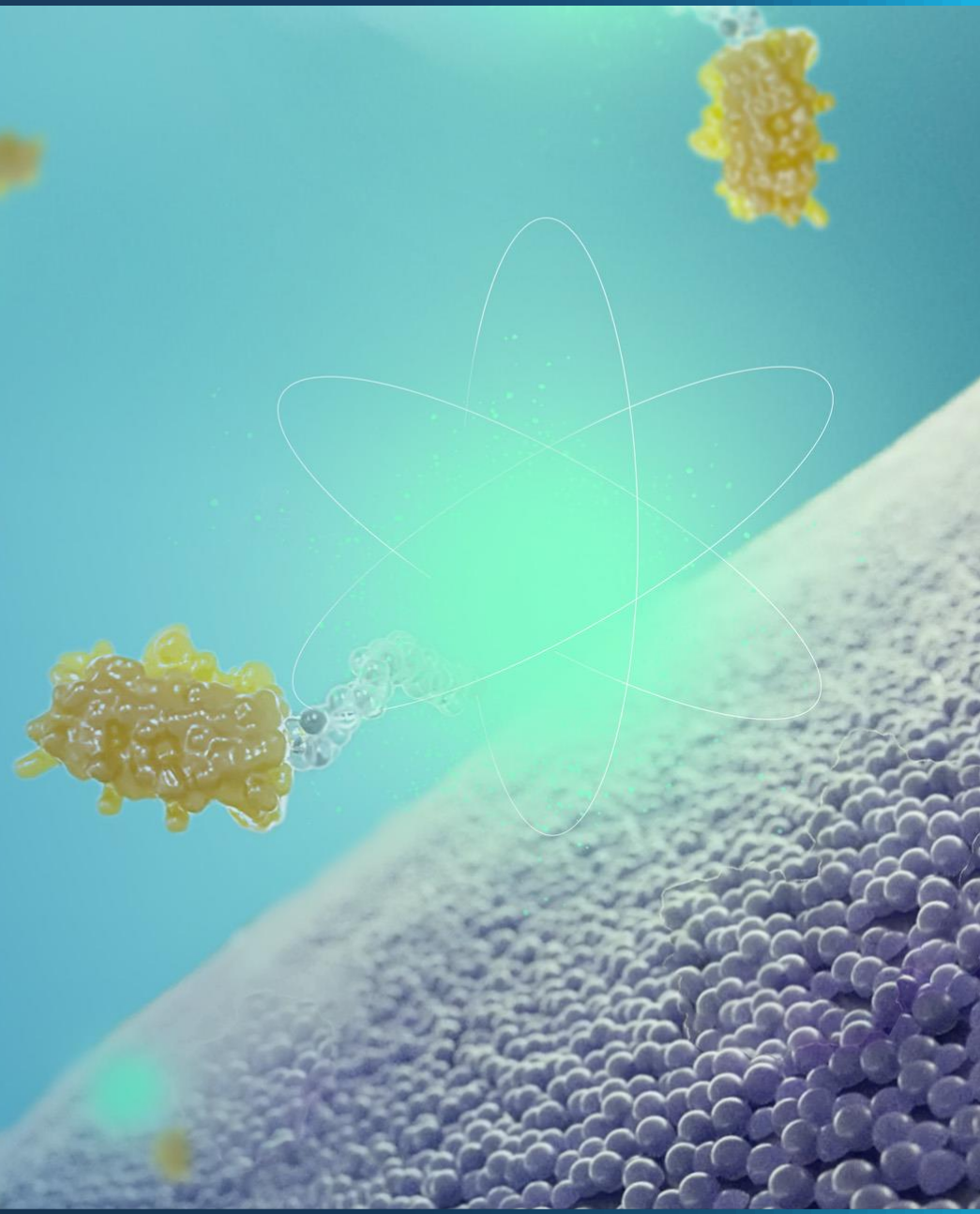
MOLECULAR partners

Extending the Boundaries of Targeted Cancer Therapies with Radio-DARPins and Next-Gen Immune Cell Engagers



Patrick Amstutz, CEO

JPMorgan HealthCare Conference

January 15, 2025

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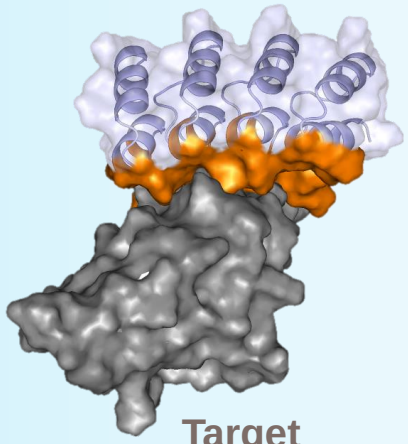
Molecular Partners at a Glance

Extending the Boundaries of Targeted Cancer Therapies

DARPin
Designed Ankyrin Repeat Protein



Our Pipeline: Patient Value

- Differentiated **Assets** with focus in Oncology, including
- **MP0533, MP0712 & more** for patients across indications with high unmet medical need

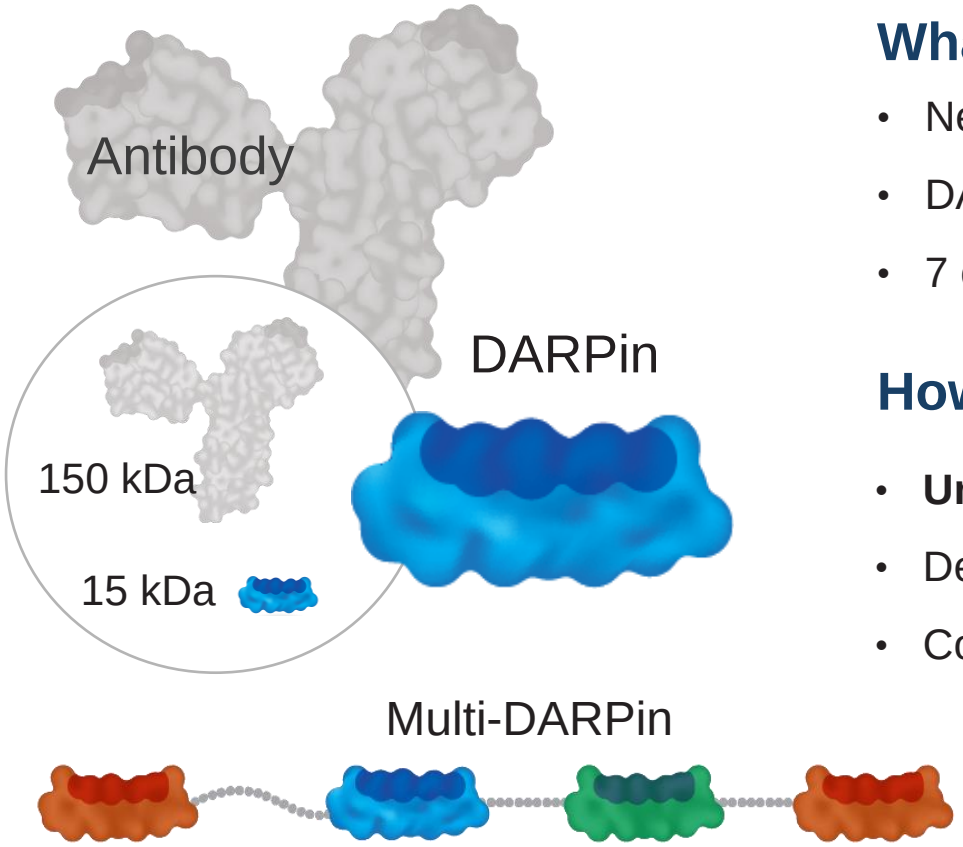
Our Capabilities: Technology, Team, Collaborations

- Proprietary DARPin Platforms, including **Radio-DARPins** and **Switch / T cell engagers**
- Strong international team to execute up to clinical POC and
- Global partnerships to access technology & capabilities (Orano Med)

Our Company: MOLN

- **Well financed** into 2027 through key value inflection points (CHF ~149 M)
- Operations & listing in Switzerland (SIX, 2014) and US (Nasdaq, 2021)

The DARPin Modality and Molecular Partners' Strategy



What we invented

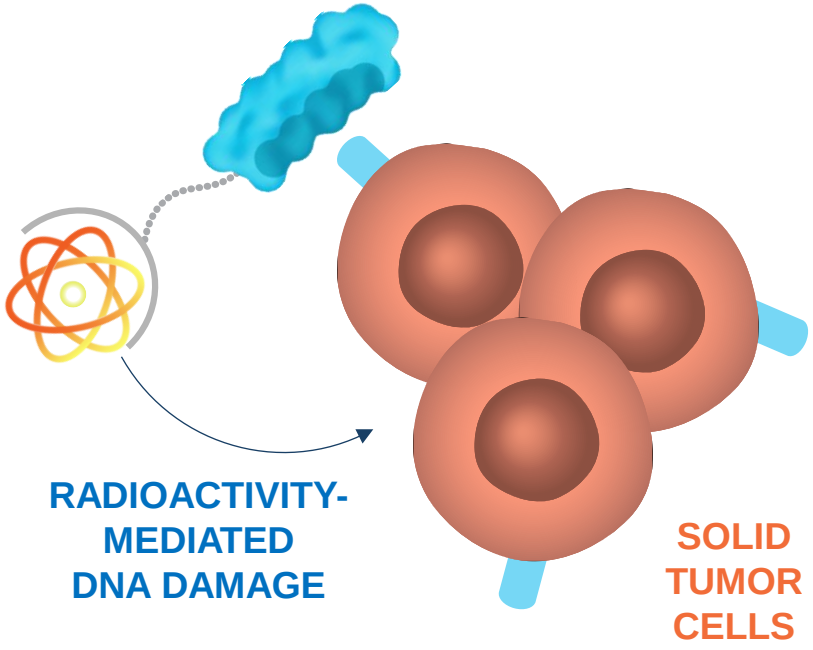
- New class of therapeutics: Designed Ankyrin Repeat Proteins **(DARPins)**
- DARPins **close the gap between small molecules and antibodies**
- 7 clinical-stage compounds, **>2500 patients treated**

How we apply it

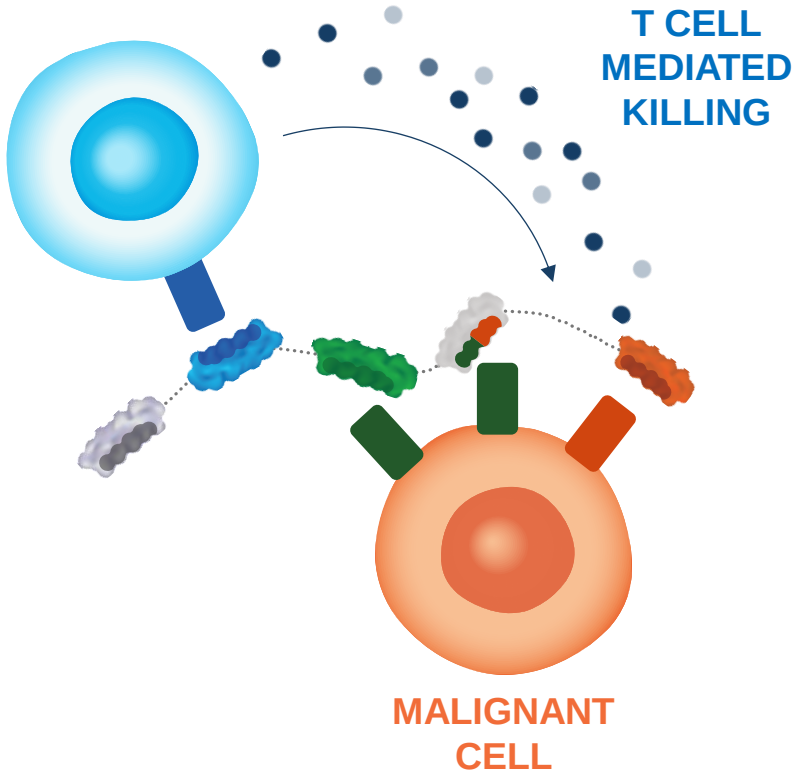
- **Unique DARPin solutions**, not addressable by antibody designs
- Demonstrate **true patient value** with **early clinical readouts**
- Combine our **capabilities with world-class partners**

DARPin Platforms to Build Therapeutics

Radio-DARPin Therapy



Next-Gen Immune Cell Engagers



Pipeline

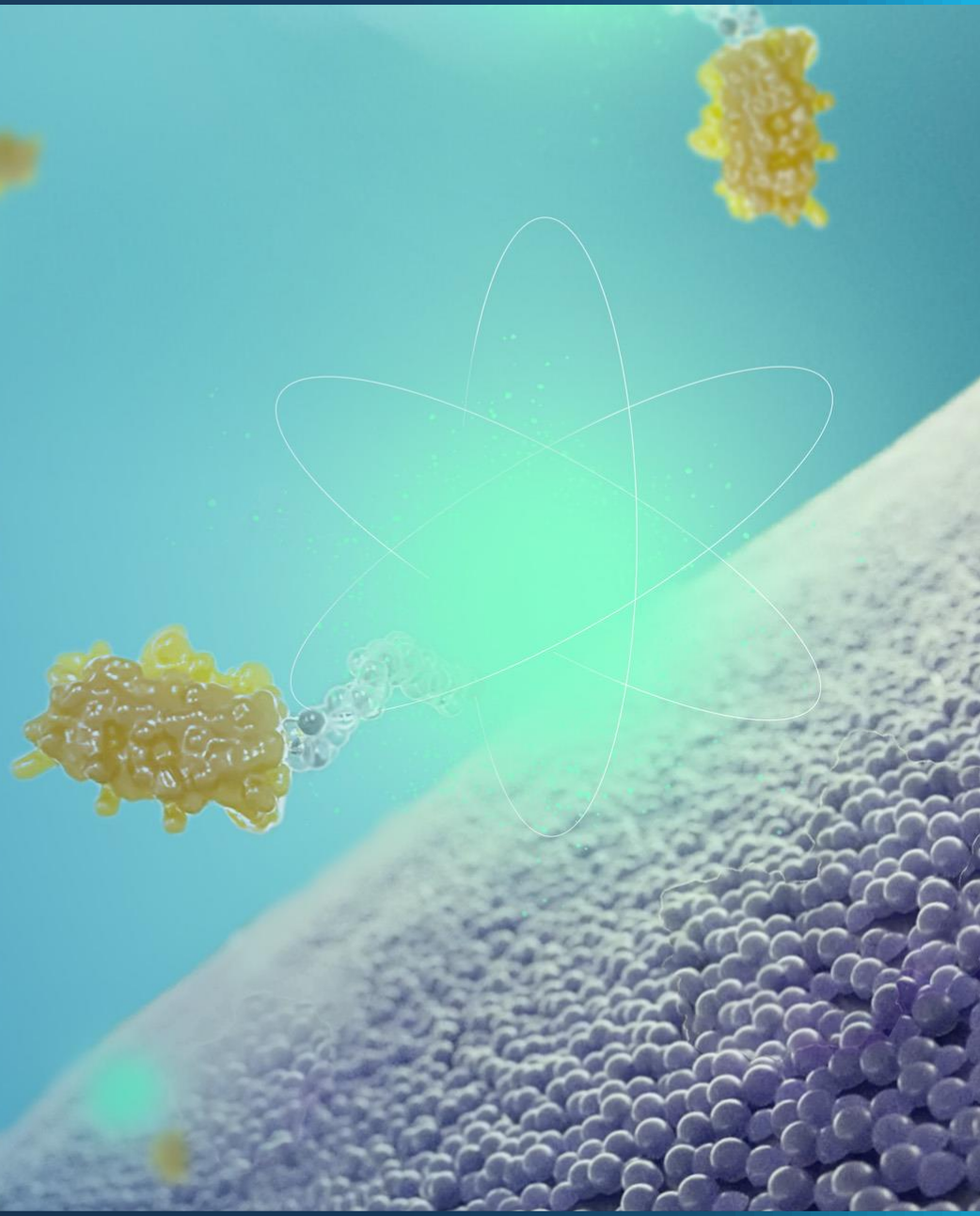
MODALITY	CANDIDATE	RESEARCH	PRE-CLINICAL	PHASE 1	PHASE 2	PARTNER
Radio–DARPin Therapy (RDT)	**MP0712 (DLL3)**	**SCLC & NETs** *^{212}Pb - DLL3*	*Co-development**			oranomed
	RDT x MSLN	**Ovarian** *^{212}Pb - MSLN*	*Co-development**			
	Undisclosed Programs	**Solid Tumors**	*Up to 8 programs**			
	Undisclosed Programs	**Solid Tumors**	*2 partnered programs*			NOVARTIS
Next-Gen Immune Cell Engagers	**MP0533**	**r/r AML and AML/MDS** *CD33 x CD123 x CD70 x CD3*				
	Switch-DARPin T-cell Engager	*CD3 x costim x TAAs*				
	MP0621	**HSCT** *cKit x CD16a x CD47*				
	MP0317	**Advanced Solid Tumors** *FAP x CD40*				*To partner with leading academic institution for IIT*

*The co-development agreement with Orano Med includes up to 10 RDT programs, including MP0712.
AML, acute myeloid leukemia; DLL3, Delta-like ligand 3; HSCT, hematopoietic stem cell transplant; IIT, investigator-initiated trial; MDS, myelodysplastic syndrome; MSLN, mesothelin; NET, neuroendocrine tumor; r/r, relapsed/refractory; SCLC, small cell lung cancer.

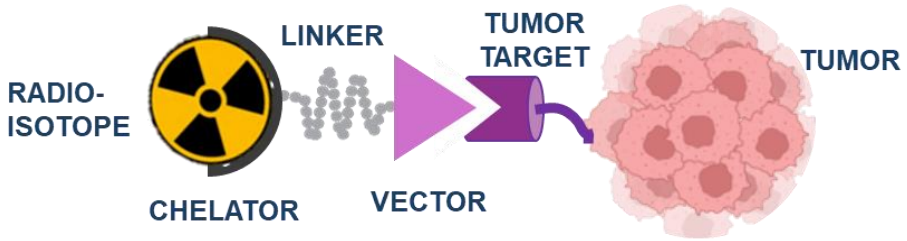
MOLECULAR partners

Radio-DARPin Therapy & MP0712

Custom-engineered to create vectors ideal for radiopharmaceuticals



Targeted Radiotherapy: “Old” Modality Turned Hot Through Precision

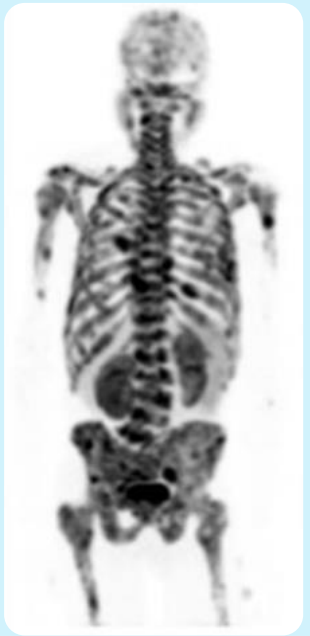


- “See what you treat” & “treat what you see”
- Enables early validation or kill point
- Proven clinical benefit for oncology patients
- **Limitation:** current vectors not applicable to all targets
- **Opportunity:** Broaden the target space with next generation vectors

➔ **DARPins have ideal properties as vectors for radioisotope delivery**

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

IMAGE → THERAPY → IMAGE



^{225}Ac-PSMA-617

8 MBq →

7 MBq →

8 MBq →

July 2017, PSA = 782 ng/ml
PET/CT, 68Ga-PSMA-11

May 2018, PSA = 0.04 ng/ml
PET/CT, 68Ga-PSMA-11

PET/CT scan pictures adapted from Sathekge M, et al. 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study. Eur J Nucl Med Mol Imaging 46, 129–138 (2019). https://doi.org/10.1007/s00259-018-4167-0.

Radio-DARPins as Versatile Therapeutic Candidates

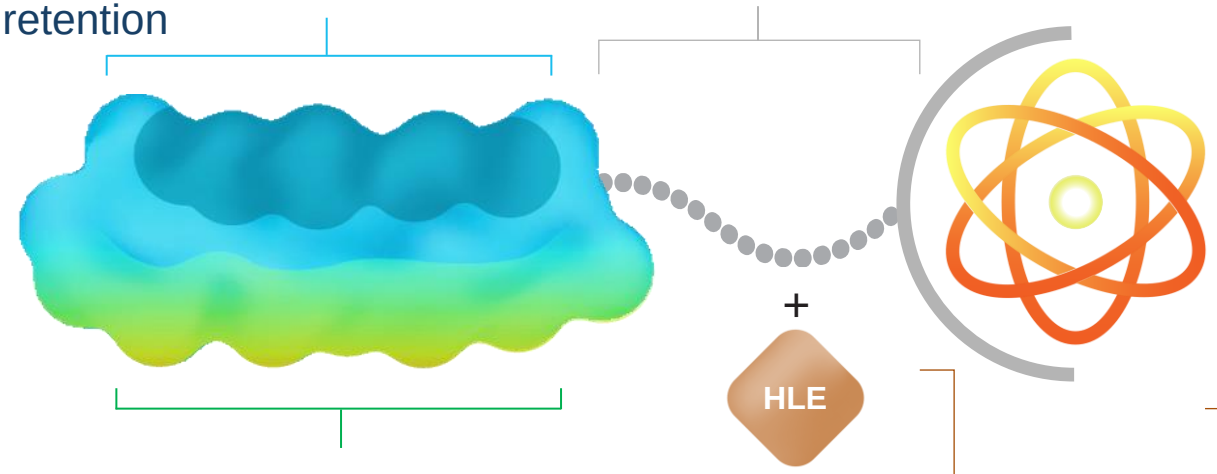
Combining versatile DARPin features with the power of ^{212}Pb for next-gen Targeted Alpha Therapy

DARPin: IDEAL VECTOR FOR RADIOPHARMACEUTICALS

- Proven selective targeting
- High affinity, tumor retention
- Broad target space
- Small size

LINKER & CHELATOR

- Established DOTAM



^{212}Pb: ALPHA-EMITTING THERAPEUTIC ISOTOPE

- Proven clinical efficacy
- Fast & high energy deposition
- Safe profile
- Ideal waste management

SURFACE ENGINEERING

- High stability
- Reduced kidney accumulation

HALF-LIFE EXTENDER

- Half-life tuning
- Promote tumor uptake

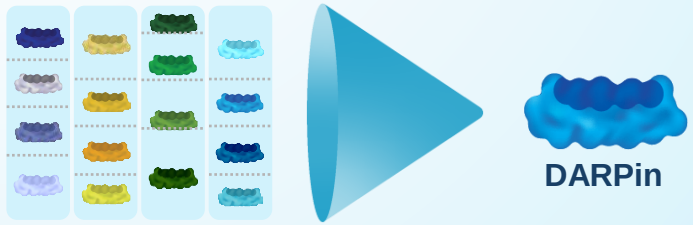
Global Partnership to Develop ^{212}Pb Radio-DARPin Therapeutics

Combining DARPin versatility with the power of ^{212}Pb for next-gen Targeted Alpha Therapy

MOLECULAR PARTNERS

PIONEERS of DARPIN THERAPEUTICS

- Proprietary DARPins as ideal vectors for radiotherapeutics
- Manufacturing capabilities of DARPins
- Operational excellence in clinic

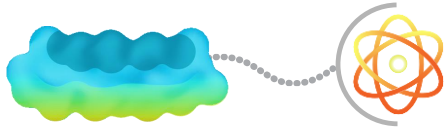


DARPin Engine:
Rapid selection, development & manufacturing of candidates

FULL VALUE CHAIN PARTNERSHIP

- **World class technologies combined**
- **Ability for rapid candidate testing/cycling**
- **Strategic impact: up to 10 radiotherapy products**

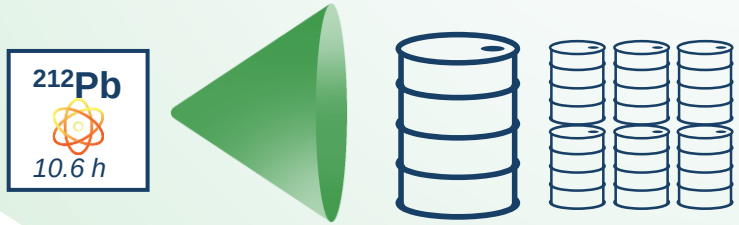
^{212}Pb RADIO-DARPin CANDIDATES



ORANO MED

PIONEERS of TARGETED ALPHA THERAPY

- Unique independent supply of ^{212}Pb as alpha emitting therapeutic isotope
- Large scale GMP manufacturing capabilities
- Strong pre-clinical and clinical expertise in radiotherapeutics



22,000 drums of ^{232}Th, providing virtually unlimited raw starting material for ^{212}Pb production

INDIANA, US:
Industrial scale manufacturing
Global shipping hub
ATLab US

TEXAS, US:
Preclinical development
GMP supply for early clinical phases

SWITZERLAND:
Preclinical assessment
DARPin engine, fast & high throughput

FRANCE:
^{212}Pb starting material
ATLab Europe

MP0712, the first ^{212}Pb-DLL3 Targeted Radiotherapeutic for SCLC

SCLC: critical unmet need, limited treatment options

- Median progression free survival (mPFS) ~3 months[1,2]
- 5y overall survival (OS) ~3%[1,2]

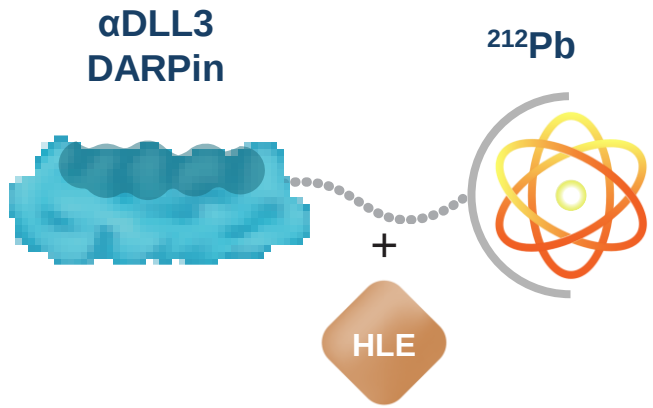
DLL3: a validated target for SCLC

- Expressed in >85% of SCLC patients[3] and in neuroendocrine cancers
- No expression in healthy tissues
- Tarlatamab[4], approved DLL3 targeting drug (T cell engager)
  - ORR ~40%, DOR 9.7 months, PFS 4.3 months

MP0712: targeted delivery of alpha radiation with ^{212}Pb

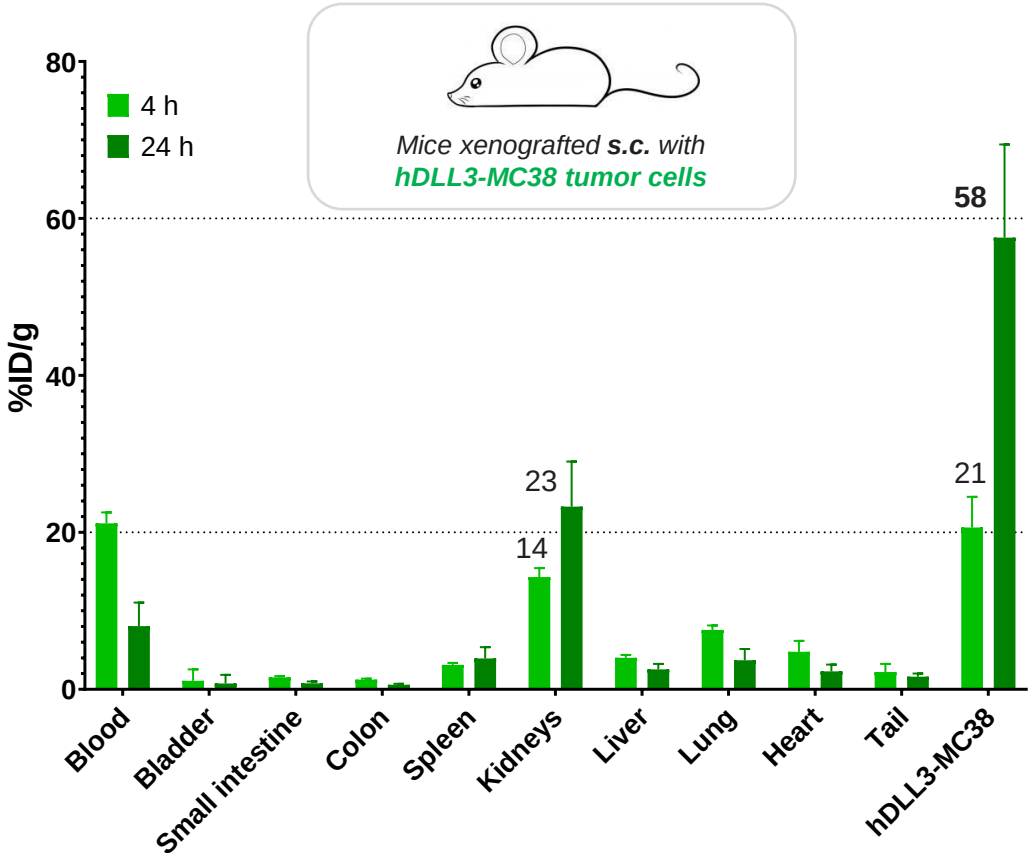
- DLL3 DARPin optimized for selective delivery of payload to tumor
- ^{212}Pb payload: high energy alpha emissions in short time frame, works with low target copy number (no need for internalization)
- Potential for combinations with immunotherapy

MP0712 product composition



1.Treatment of refractory and relapsed small cell lung cancer, UpToDate; 2. SEER; 3. Rojo et al., Lung Cancer 2020; 4. Phase 2 DeLLphi-301 study (NCT05060016).
DOR, duration of response; HLE, half-life extension; ORR, overall response rate; SCLC, small cell lung cancer.

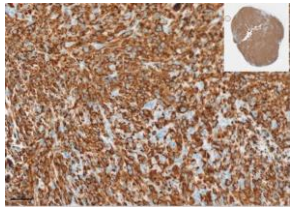
MP0712: Attractive Biodistribution Profile in Clinically-Relevant Model



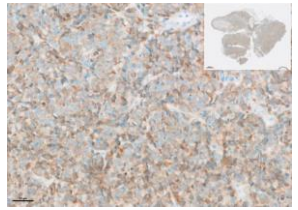
*Mice xenografted **s.c.** with*
hDLL3-MC38 tumor cells

DLL3 expression & distribution by IHC

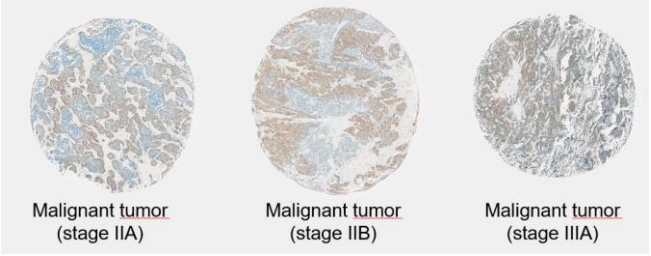
hDLL3-MC38 tumors



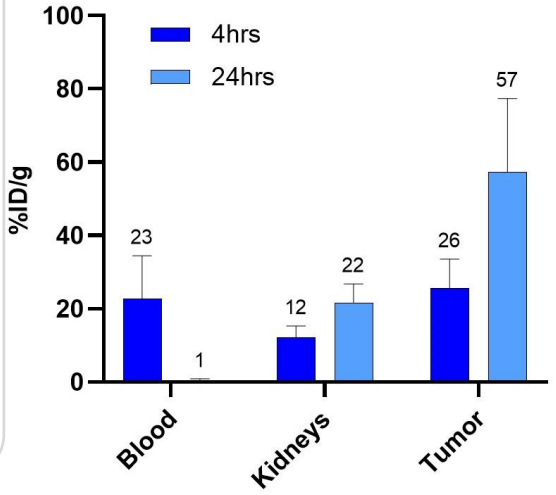
NCI-H82 tumors



Human SCLC tumors



*Mice xenografted **i.v.** with*
NCI-H82 tumor cells

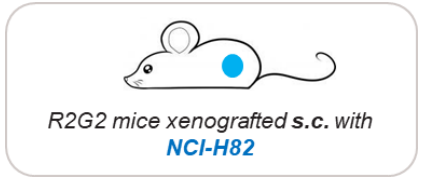


- **MP0712 reached T:K ratios > 2 in mouse model matching clinically relevant DLL3 expression levels**
- **Selective uptake in DLL3-expressing tumors confirmed high target specificity of MP0712** *(data not shown)*

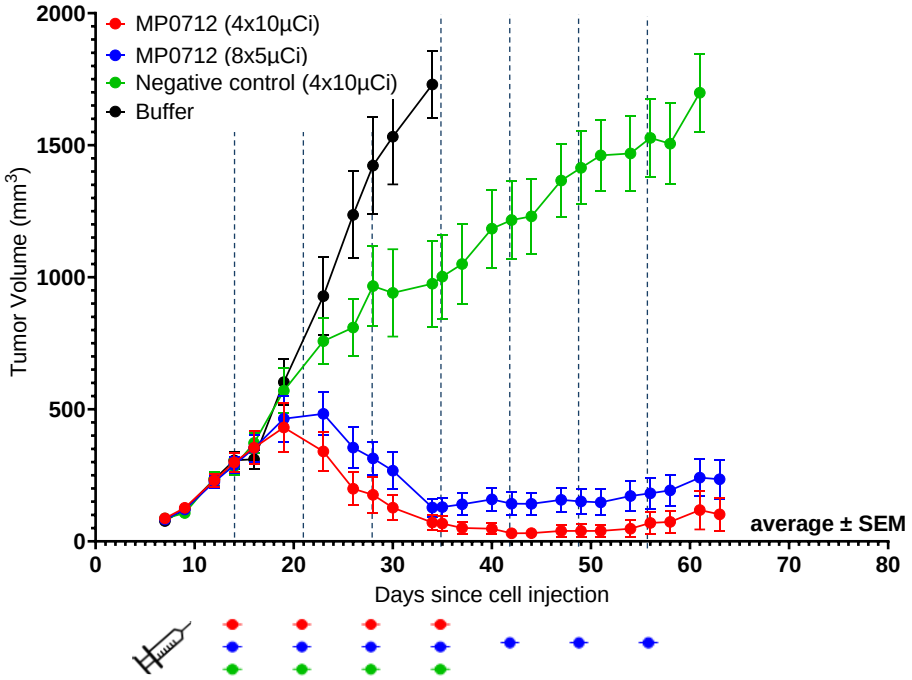
Croset et al, EANM 2024 (oral presentation)
Lizak et al, SNMMI 2024 (oral presentation)

hDLL3-MC38 and NCI-H82 mouse models:
^{212}Pb-DOTAM-DARPin - single injection - dose : 10 µCi (0.01 mg/kg)

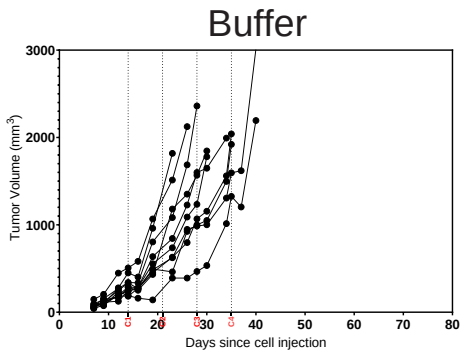
MP0712: Potent Efficacy at Clinically-Relevant Dose

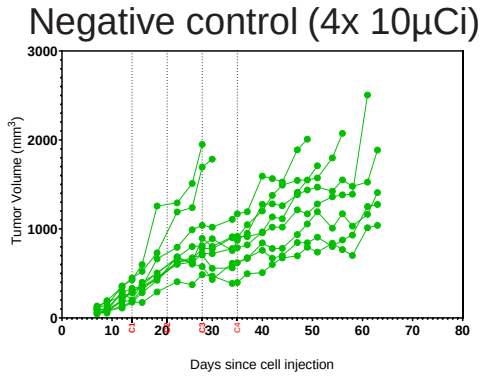


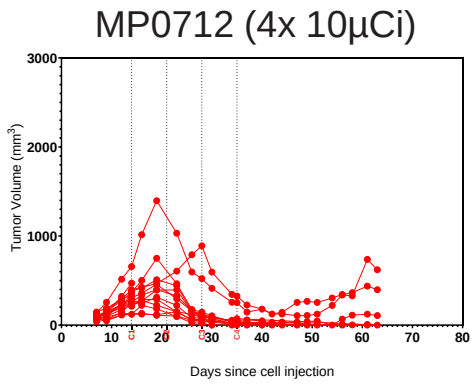
*R2G2 mice xenografted **s.c.** with*
NCI-H82

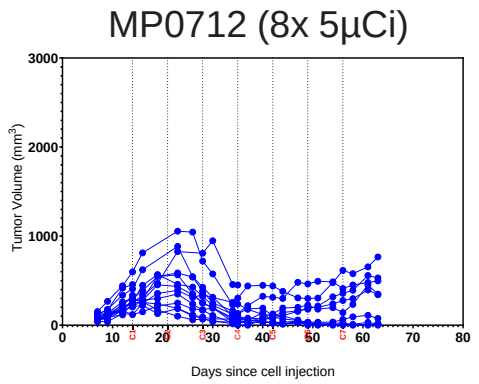


Tumor growth curve for each animal



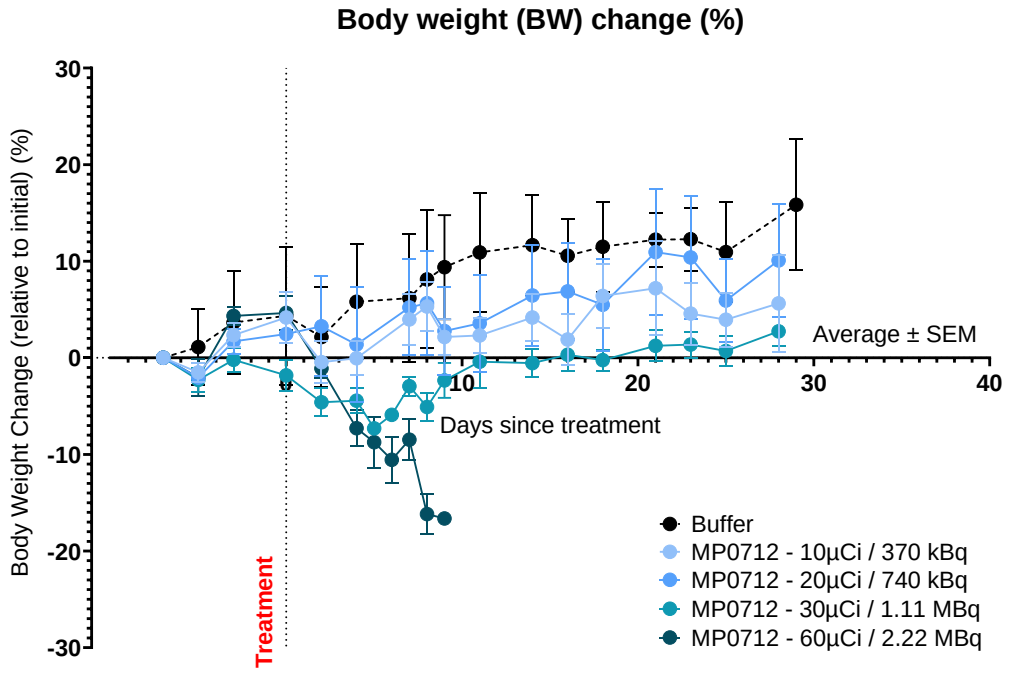


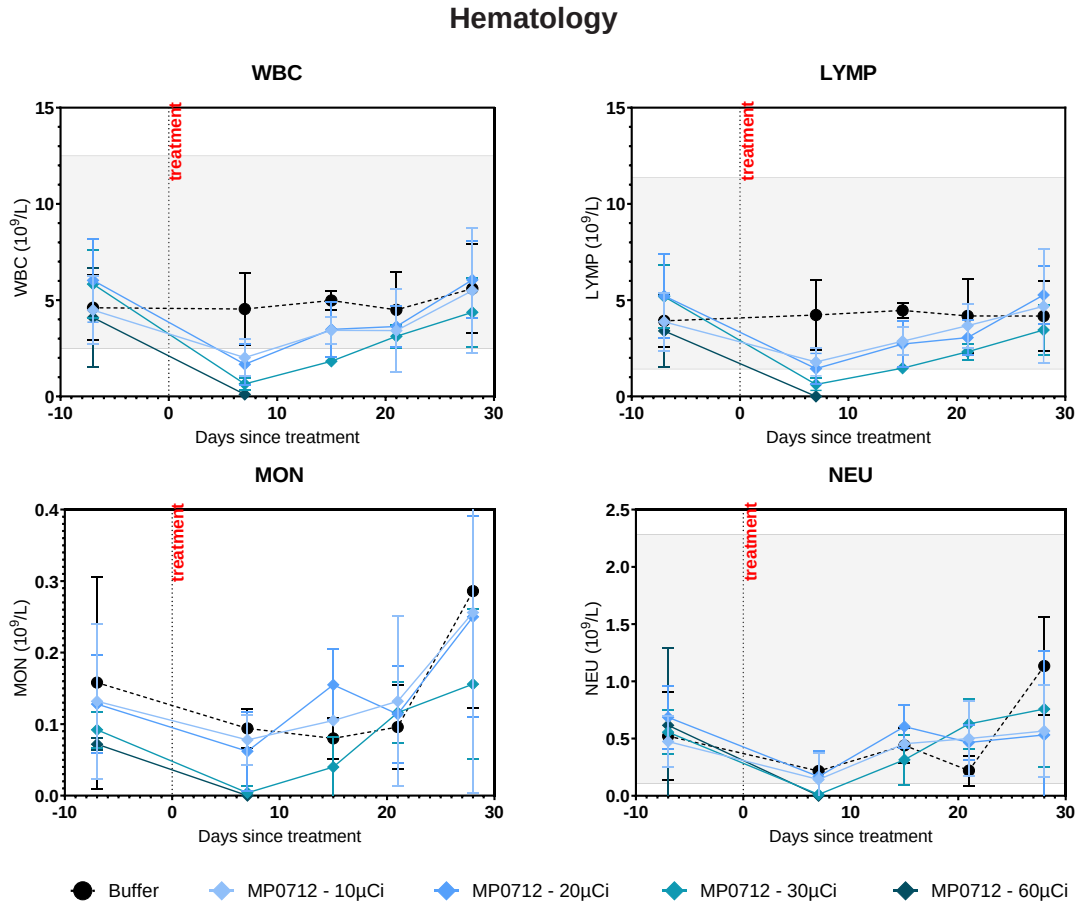




- **MP0712 induces complete and durable tumor regression in NCI-H82 tumor model at 10µCi injected every week**
- **At day 63, complete tumor regression is seen for ~70% of mice at 4x 10µCi and ~20% of mice at 8x 5µCi**

MP0712: Favorable Safety Profile at Clinically-Relevant Dose





- **Complete recovery of body weight loss after 10 days**
- **Complete recovery of hematologic profile after 28 days**
- **MP0712 treatment up to 30 µCi / 1.11 MBq well tolerated**

Croset et al, EANM 2024 (oral presentation)

MP0712 DRF study done in WT mice / ^{212}Pb-DOTAM-DARPin injected once from 10 to 60µCi. WBC, white blood cells; LYMP, lymphocytes, MON, monocytes; NEU, neutrophils.

Outline of MP0712 Clinical Development Strategy

- Patients: Focus on Small Cell Lung Cancer (SCLC), secondly on Neuro Endocrine Prostrate (NEPC)
- Biodistribution and dosimetry Phase 0 and Phase 1 studies to start in H2 2025, initial clinical data by YE

IMAGING & DOSIMETRY

Phase 0 – Imaging of **MP0712 with ^{203}Pb** (biodistribution/dosimetry)
Main objective: Imaging and Full Dosimetry to support dose strategy for ^{212}Pb
N = 5–10 patients

Purpose:
➔ Build confidence to reach relevant therapeutic level in tumor lesions

THERAPY

Phase 1 - ^{212}Pb Dose Escalation
Main objective: Safety, RP2D
N = 15–20 patients

→ **Phase 2a – Dose Expansion and PoC**
Main objective: Efficacy signals, confirm safety and RP2D

→ **Registration study**
2L+ SCLC patients

→ Phase 2s
- 1–2L combination with IO SCLC
- PoC in NEPC patients

RP2D, recommended phase 2 dose; YE, year-end.

^{212}Pb x MSLN Targeted Radio-DARPin for Ovarian Cancer

Combining distinctive DARPin features with the power of ^{212}Pb for next-gen targeted alpha therapy

Ovarian Cancer (OC): high medical need and marginal progress

- > 50% patients die within 5y post-diagnosis (diagnosis often in late stage)
- Poor treatment options: ~80% recurrence rate post 1L chemo, limited 2L options (FR-alpha targeted Tx relevant for only 40% patients)

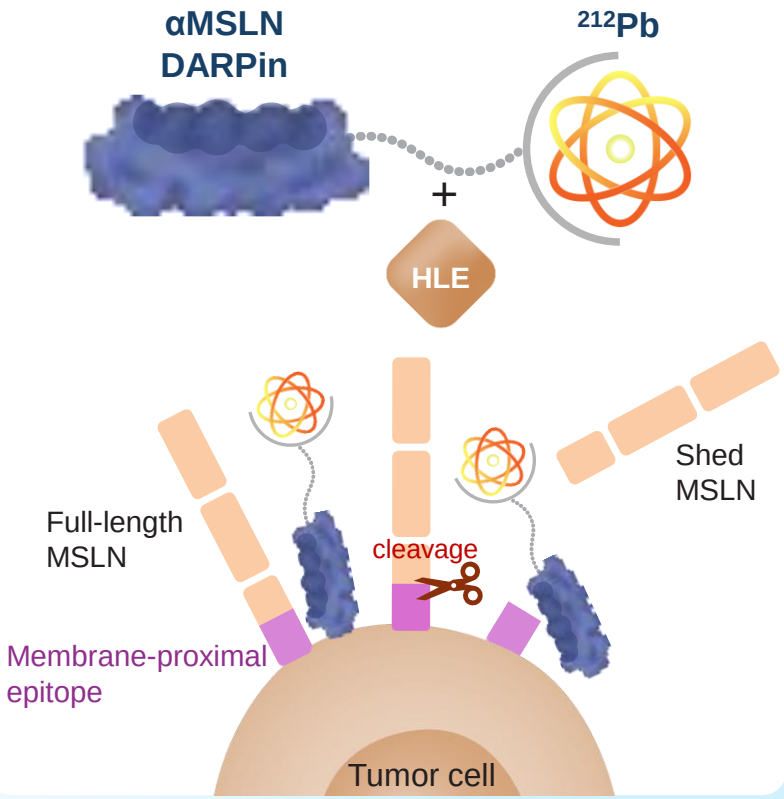
Mesothelin (MSLN): a promising target for OC as 1st indication

- Highly expressed in OC (>80% prevalence), expression maintained in metastases
- Shed MSLN detected in serum of OC patients, might limit efficacy of MSLN-targeted therapies[1,2,3,4] (e.g., CAR T/NK, ADC, TCE in development)

RDT x MSLN: targeted delivery of alpha radiation with ^{212}Pb

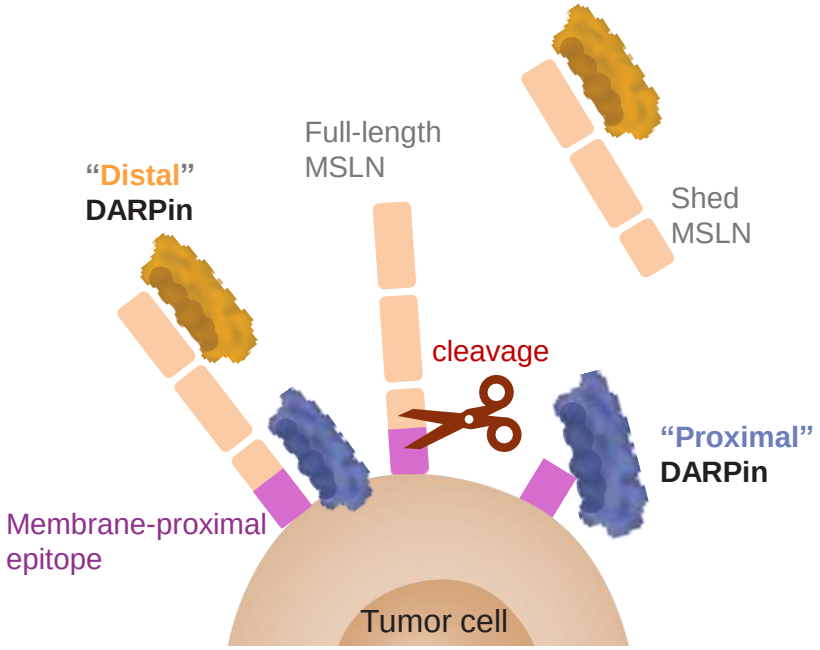
- MSLN DARPin targets membrane-proximal epitope (and not shed MSLN)
- ^{212}Pb payload: high energy alpha emissions in short time frame
- Potential for combinations with immunotherapy (incl. next-gen TCEs)

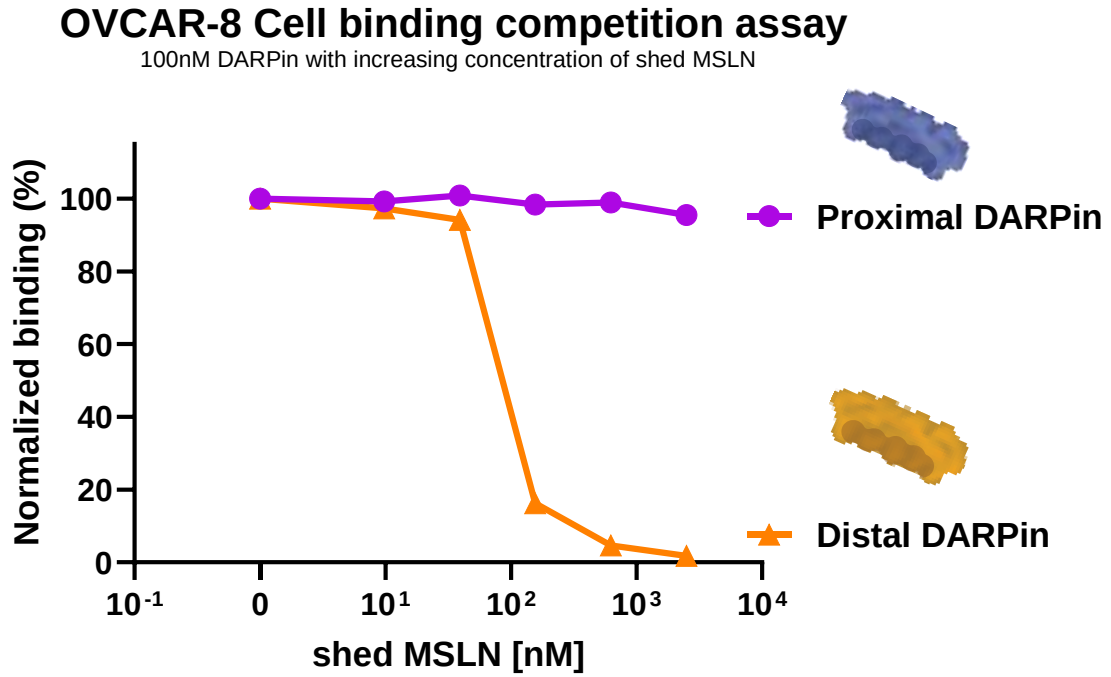
Product composition



1. Awuah et al. 2016; 2..Zhang et al. 2011; 3.Smith et al. 2024 (ASCO poster); 4.Pastan et al, 2024.

DARPin activity is maintained despite shed MSLN

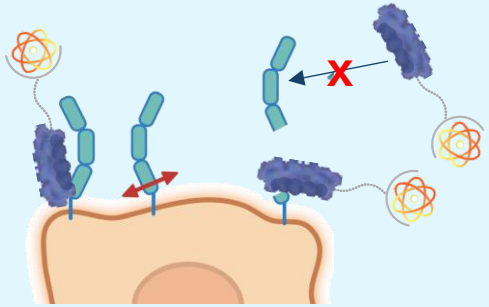




Binding maintained in presence of shed MSLN

Binding inhibited in presence of shed MSLN

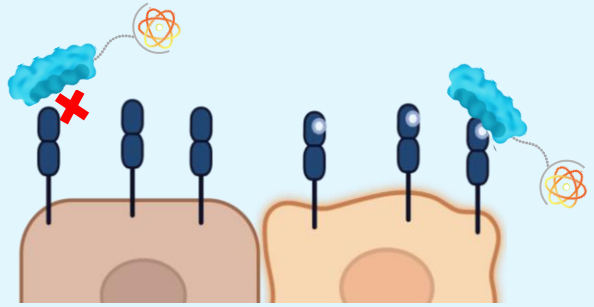
Continue to Leverage DARPin Differentiation to Build Portfolio of Radio-DARPin candidates



Tumor cell

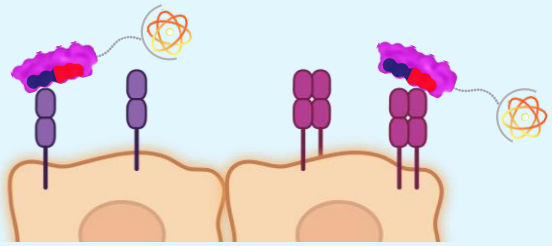
Selectivity for **membrane-bound antigen** vs **shed antigen** for high tumor uptake

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



Healthy cell Tumor cell

2in1 DARPin



Tumor cells

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

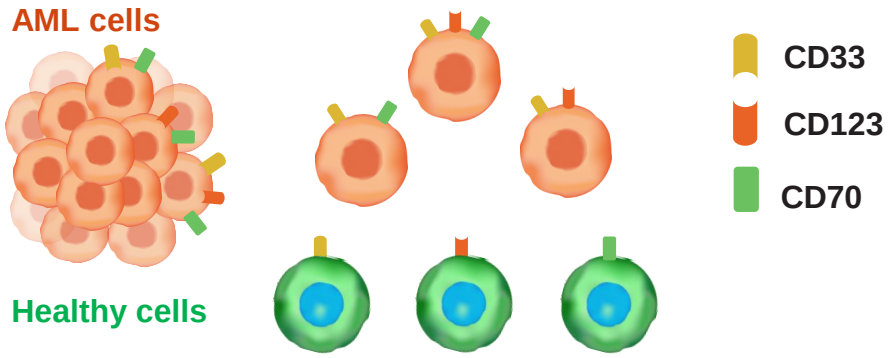
MOLECULAR partners

MP0533

Tetra-specific T-cell Engager for AML

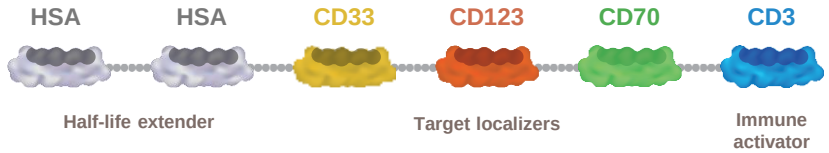
MP0533 Enables Avidity-Driven Selective Killing of AML Cells

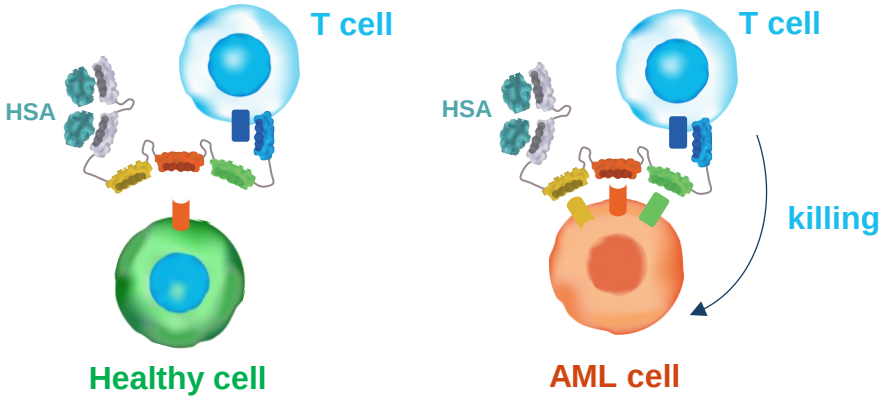
AML-associated antigens are also expressed on healthy cells



- **AML** bears a **high risk of relapse** due to **persistent LSCs**
- **AML cell population is heterogeneous** → differentiation from healthy cells (e.g., HSCs) feasible through their **co-expression of CD33, CD123, CD70**

MP0533: avidity-driven selectivity and T cell-mediated killing



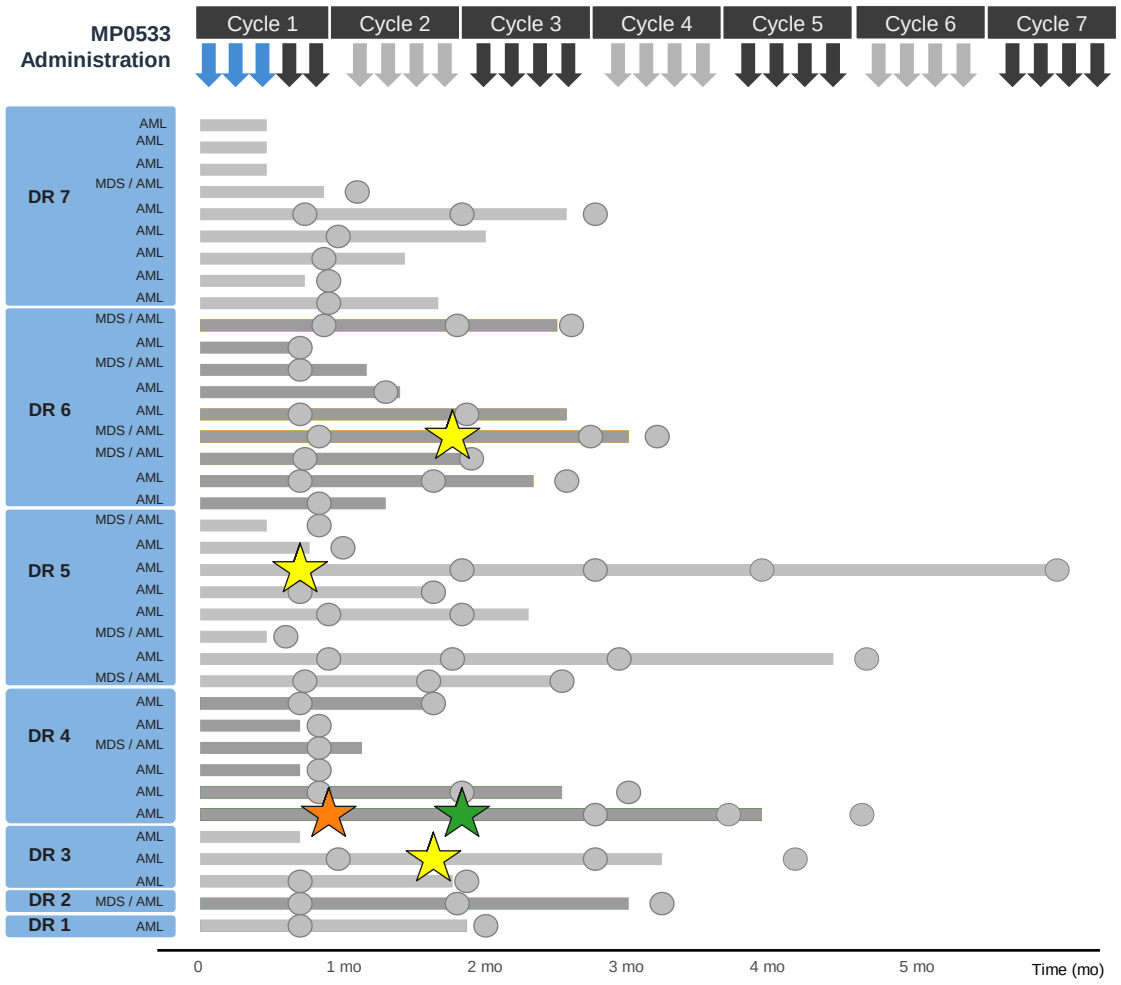


- MP0533 designed to induce **T cell-mediated killing** preferentially when **2 or 3 AML-associated antigens** are co-expressed
- Potential **to kill all AML cells (blasts and LSCs)** despite heterogeneity, **ensuring long-term disease control**

AML, acute myeloid leukemia; HSC, hematopoietic stem cell; HSA, human serum albumin; LSC, leukemic stem cells.

MP0533 Treatment and Clinical Response

Dose Escalation (DR 1–7)



DR 1–7: 4 responders reported, manageable safety

Legend

Response (2022 ELN[1]) was assessed every 4 weeks until disease progression and results are presented as:

CR · CRi · MLFS · No ELN response

Patients with ongoing treatment at data cut-off · Patients who discontinued treatment

Arrows at the top indicate MP0533 administration at D1, D5, D8, D12 (DR 8 only), D15 and weekly thereafter

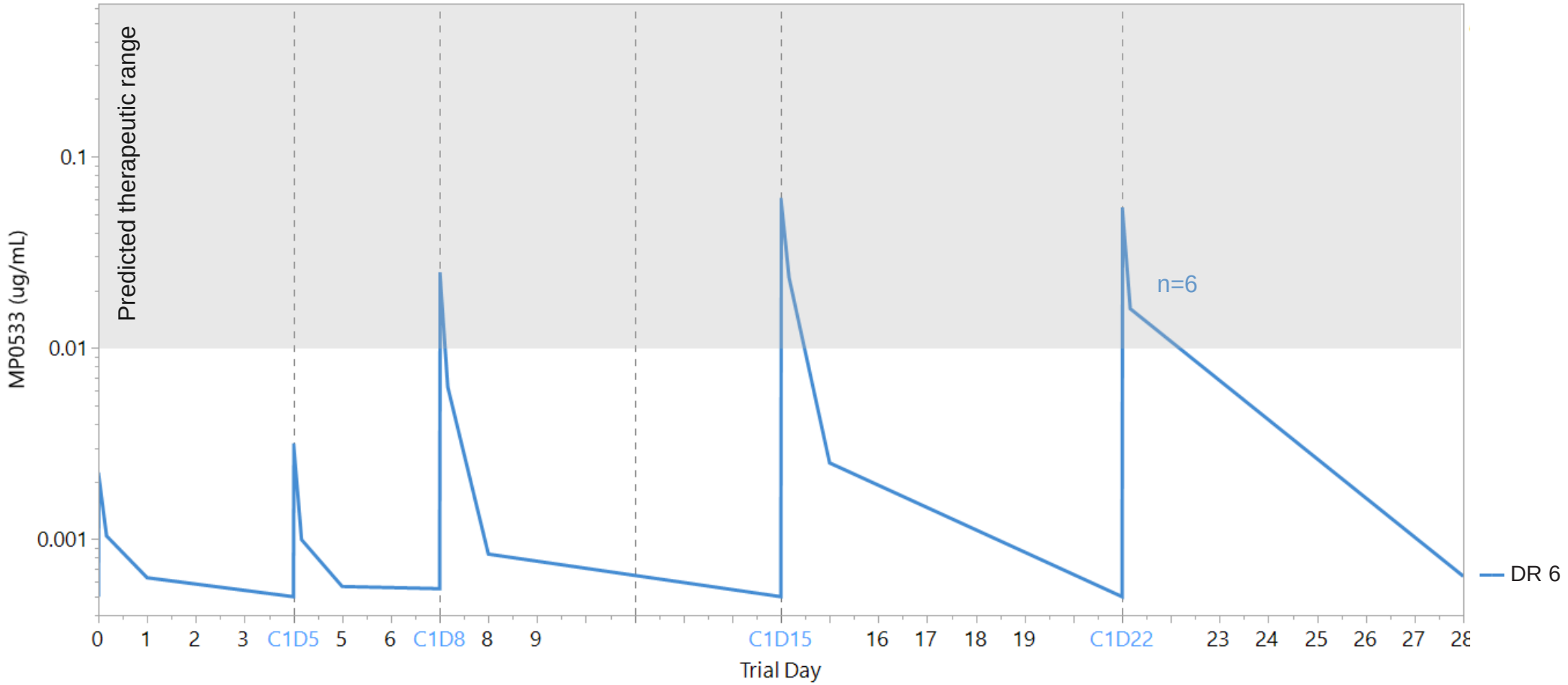
Step-up dosing at DR 1–7 · D12 dose at DR 8

Color changes in grey: start of a new 28-day cycle

1. Döhner et al. Blood 2022;140(12)1345-77.

CR, complete response; CRi, CR with incomplete hematologic recovery; ELN, European LeukemiaNet; MLFS, morphologic leukemia-free state.

Improved MP0533 exposure at DR 8 with steeper and denser step-up dosing regimen



Data cut-off: 3 December 2024

Preliminary data as study is ongoing, subject to final data validation.

n = number of evaluable patients at data cut-off.

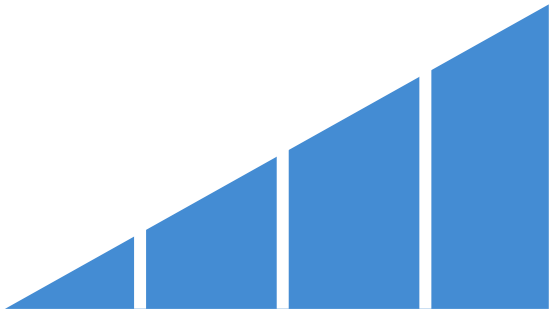
MP0533 Phase 1/2a Study in Patients with R/R AML/MDS

Protocol amendment to optimize MP0533 exposure

Initial Protocol

Dose Escalation (DR 1–7)

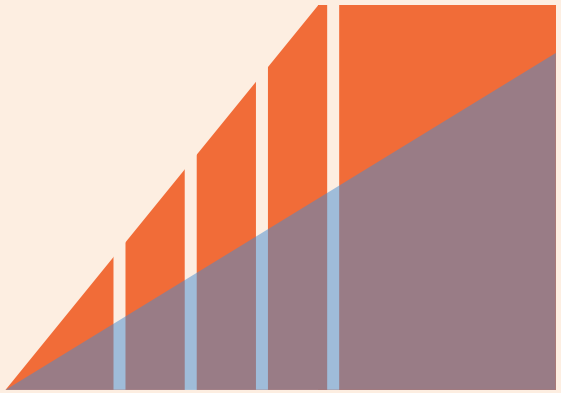
- Limited clinical activity
- Target-mediated drug disposition (TMDD) = **low exposure**
- Loss of exposure (LoE) in some patients (ADA)



Amended Dosing Scheme

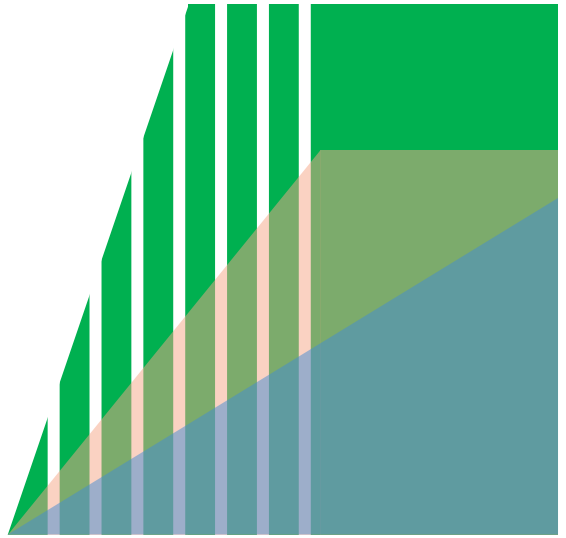
Intermediate densification (DR 8)

- **Additional day12 dose** allows **steeper & faster dose escalation (step-up-dosing),** addressing TMDD



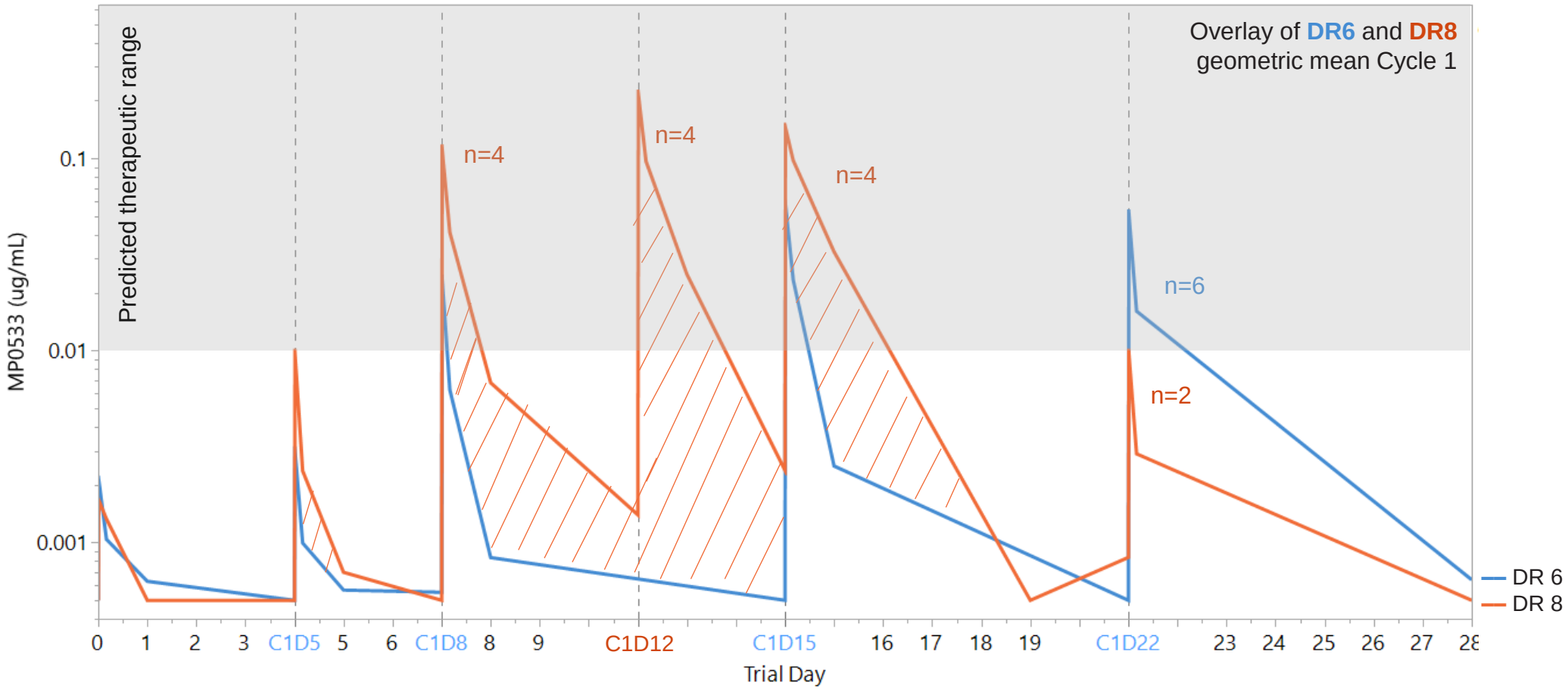
Further dose densification (DR 9–10)

- **High dose frequency for 1st cycle**
- Premedication for **LoE mitigation**



ADA, anti-drug antibody; DR, dose regimen.

Improved MP0533 exposure at DR 8 with steeper and denser step-up dosing regimen



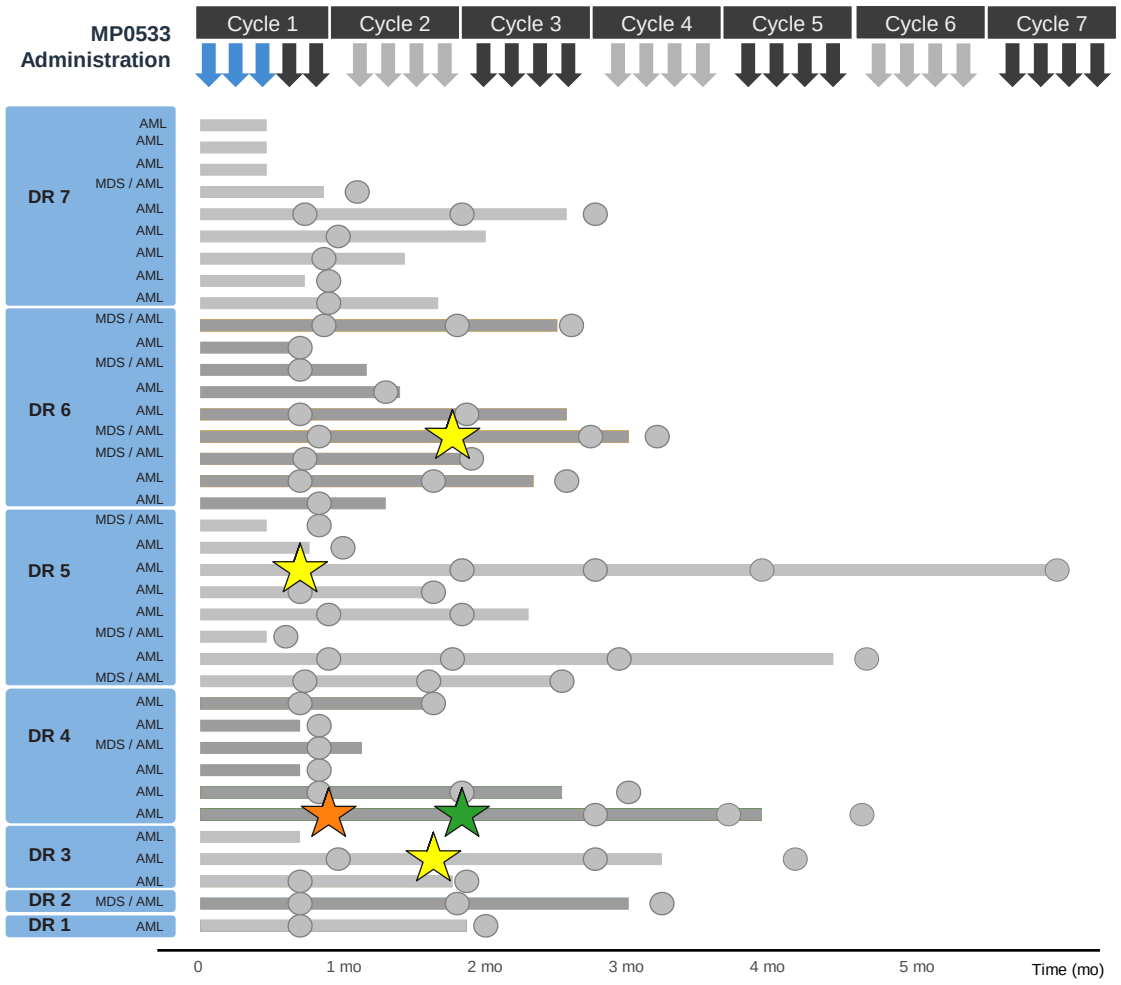
Data cut-off: 3 December 2024

Preliminary data as study is ongoing, subject to final data validation.

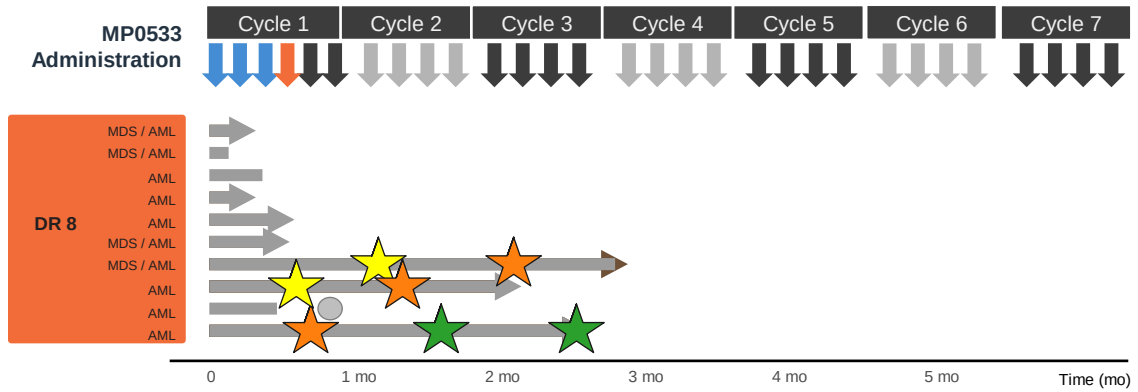
n = number of evaluable patients at data cut-off (16 Dec 2024)

MP0533 Treatment and Clinical Response

Dose Escalation (DR 1–7)



Intermediate densification (DR 8)



DR 1–7: 4 responders reported, manageable safety

DR 8: At least 3 responders and manageable safety reported to-date, evaluation and dosing on-going

DR 9+ (further dose densification): update in 2025

Legend

Response (2022 ELN[1]) was assessed every 4 weeks until disease progression and results are presented as:

CR · CRi · MLFS · No ELN response

Patients with ongoing treatment at data cut-off · Patients who discontinued treatment

Arrows at the top indicate MP0533 administration at D1, D5, D8, D12 (DR 8 only), D15 and weekly thereafter

Step-up dosing at DR 1–7 · D12 dose at DR 8

Color changes in grey: start of a new 28-day cycle

MOLECULAR partners

Switch-DARPin Platform

Targeted and conditional
activation of immune cells

Overcoming Limitations of Current T Cell Engager platforms with Combinable DARPin Solutions

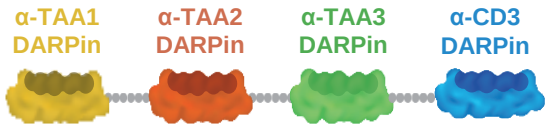
Challenges with current TCEs

Lack of tumor-specific targets
- Multi-specific antibody generation is technically challenging

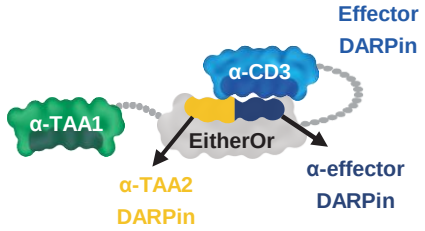
Narrow therapeutic window
- CRS and on-target toxicity limit dosing
- Mitigation strategies (e.g. lower CD3 affinity) lead to lower activity
- Conditional activation depends on the environment (e.g proteases)

Impaired T cell function
- T cell exhaustion & immune suppression limit activity
- Co-stimulation comes with safety challenges

DARPin TCE Solutions



Multi-TAA-specific TCE
✓ Clinical validation



Switch-DARPin
(conditional activation)
✓ Preclinical validation

T cell co-stimulation
(e.g. CD2, others)
✓ Preclinical validation

Solutions can be combined

CRS, cytokine release syndrome; TAA, tumor-associated antigen; TCE, T cell engager.

Logic-gated Switch-DARPins for Next-Gen T Cell Engagers

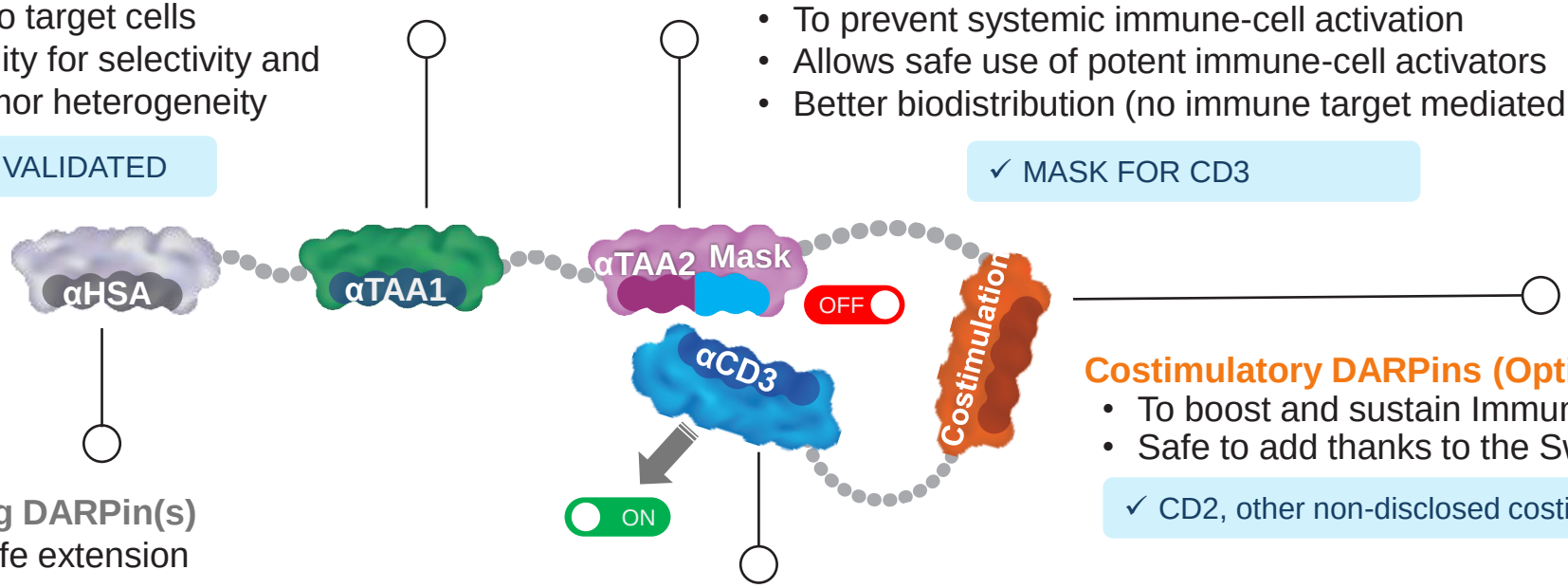
Swiss knives for targeted and conditional immune activation

1st Antigen Binder
- Anchoring to target cells
- Adding avidity for selectivity and address tumor heterogeneity

✓ CLINICALLY VALIDATED

Switch DARPin: TAA-dependent Masking of TCE DARPin
- To prevent systemic immune-cell activation
- Allows safe use of potent immune-cell activators
- Better biodistribution (no immune target mediated sink)

✓ MASK FOR CD3



HSA Binding DARPin(s)
- For half-life extension

✓ CLINICALLY VALIDATED

Costimulatory DARPins (Optional)
- To boost and sustain Immune response
- Safe to add thanks to the Switch

✓ CD2, other non-disclosed costim.

T cell engager DARPin (Switched on/off by Masking DARPin)
- Possible to use potent CD3-engager thanks to Switch

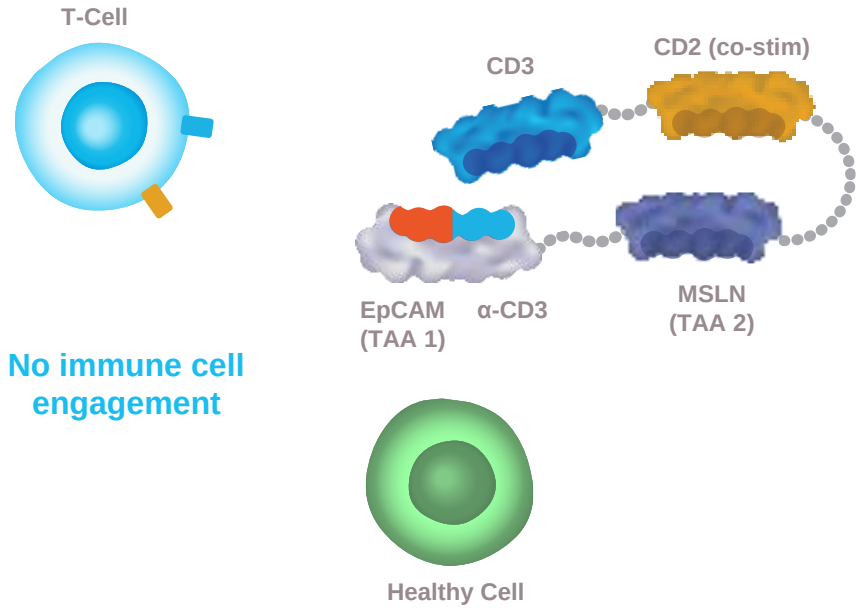
✓ CD3 TCE CLINICALLY VALIDATED

HSA, human serum albumin; TAA, tumor-associated antigen.

CD3 Switch-DARPin for Next-gen TCEs with Enhanced Function

Tackling current limitations of TCEs in solid tumors

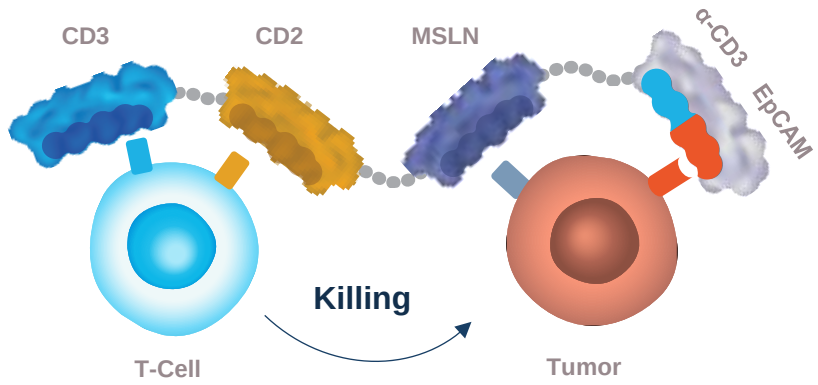
OFF **CD3 DARPin masked by 2-in-1 Switch in absence of TAAs**



No immune cell engagement

- **TCE is silent and inactive in circulation**

ON **Binding to TAAs releases CD3 Switch-DARPin**

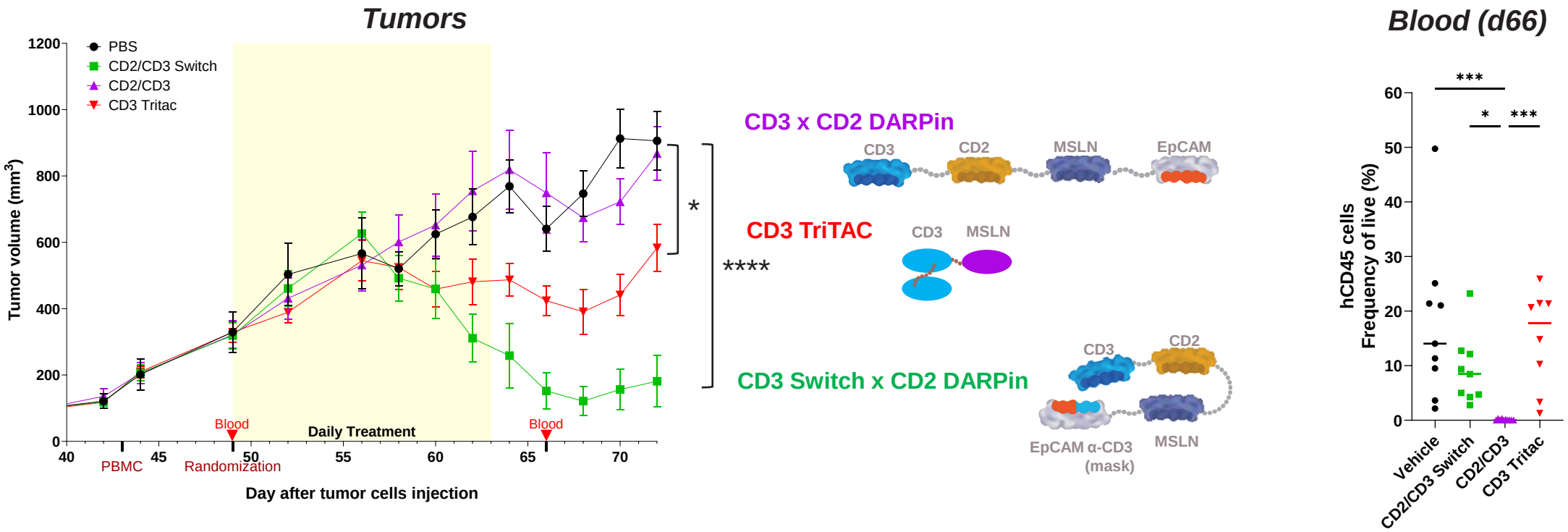


Immune cell-mediated killing

- **TCE is activated to kill the tumor cell**
- **TCE is stimulated (no exhaustion)**

TAA, tumor associated antigen; TCE, T cell engager.

Switch-DARPin leads to tumor regression pre-clinically

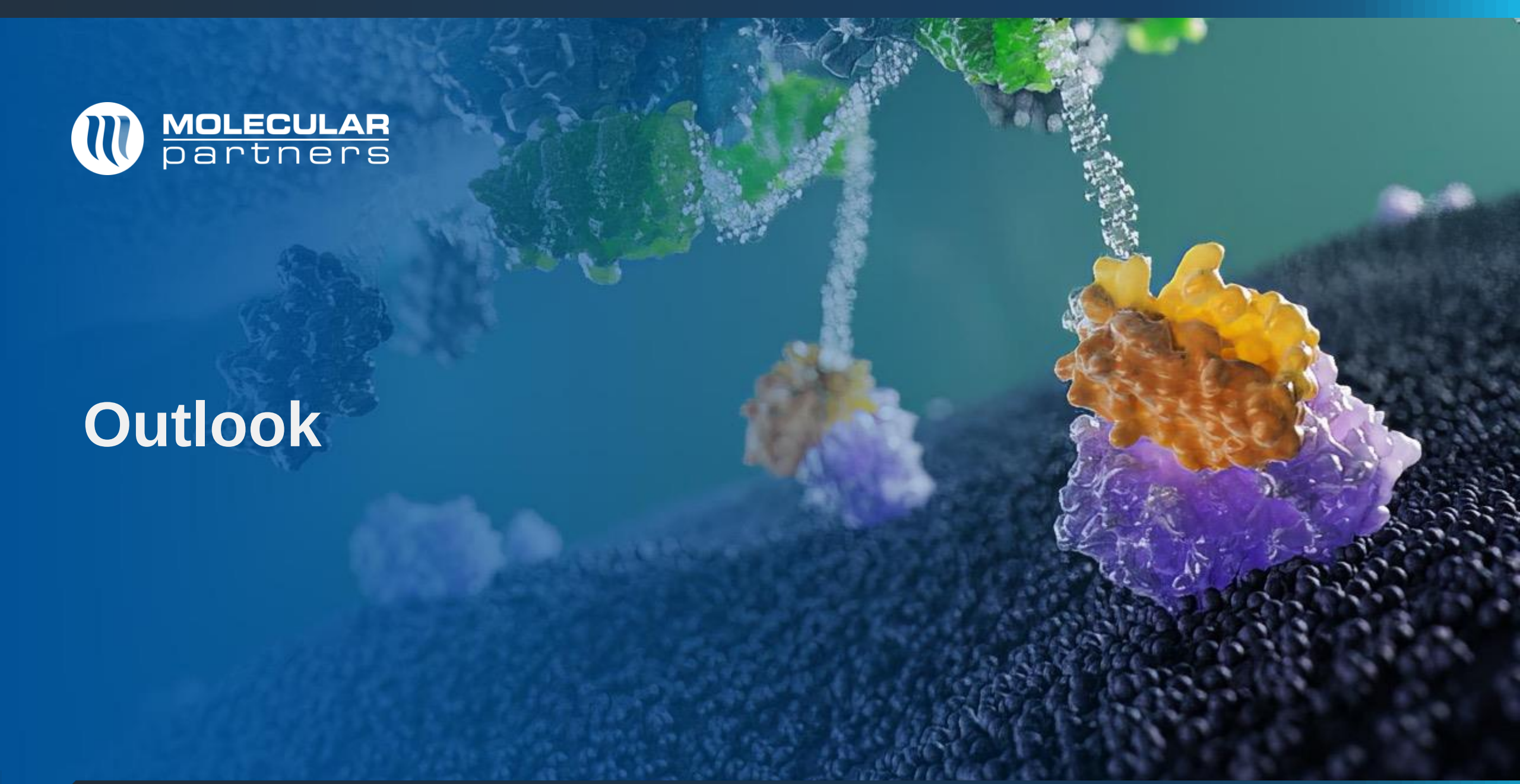


- EpCAM-MSLN-CD2/CD3 Switch induces tumor regression more efficiently than a MSLN-CD3 engager (Tritac).
- Non switched CD2/CD3 DARPin is not efficacious, likely due to loss of CD45+ T cells as a result of T cell fratricide

➢ **Masking CD3 DARPin allows for "silent" T cell engager (TCE) in the periphery** while demonstrating potent efficacy on tumors, potentially allowing for better safety profile of TCEs

OVCAR-3 s.c. model: 10 mice/group, 2 PBMC donors engrafted at 100mm³, average +/- SEM, two-way ANOVA. Daily i.v. treatment from d49: DARPin @ 3.8mg/kg, Tritac @ 0.25 mg/kg

Robinson et al, SITC 2024 (poster presentation)



Outlook

2025 Outlook and Upcoming Milestones

MP0712	• IND applications of MP0712, ^{212}Pb x DLL3 RDT, for phase 0 and 1 studies, H1 2025 • First-in-Human studies start in H2 2025 • Initial clinical data H2 2025
Radio-DARPin Therapy (RDT)	• MSLN update at AACR 2025, therapeutic candidate selection • Additional ^{212}Pb x RDT programs nominated, in collaboration with Orano Med
MP0533	• Comprehensive clinical data from Phase 1 cohort 8 in H1 2025 • Protocol amendment acceptance and implementation of improved dosing regime, H1 2025 • Data from cohorts with amended dosing scheme in H2 2025
Switch-DARPin	• Preclinical update on CD3 Switch T cell engager at AACR 2025 • Evaluation of partnering opportunities with Switch platform, including MP0621 (cKit)

CHF ~149 million cash* (incl. short-term time deposits) ensures **funding into 2027**

*Unaudited financials as per December 31, 2024.
IND, investigational new drug.

MOLECULAR partners

Twenty Years of Pioneering
DARPin Therapeutics for Patients

Thank You