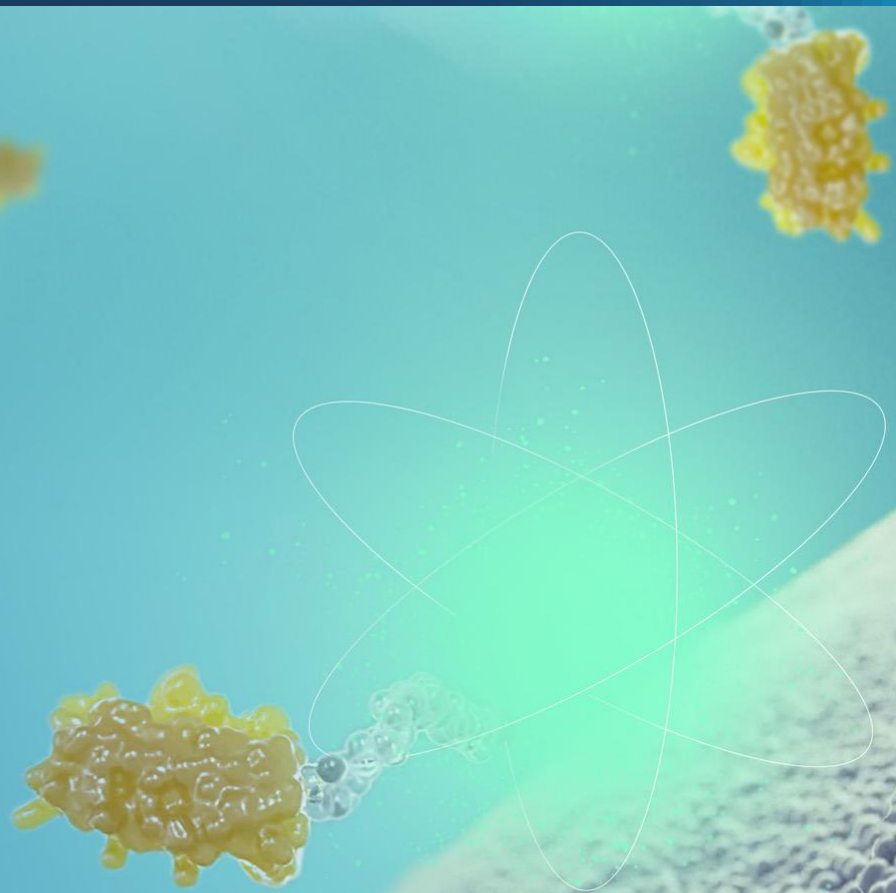
MOLECULAR partners

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



Patrick Amstutz, CEO

January 13, 2025

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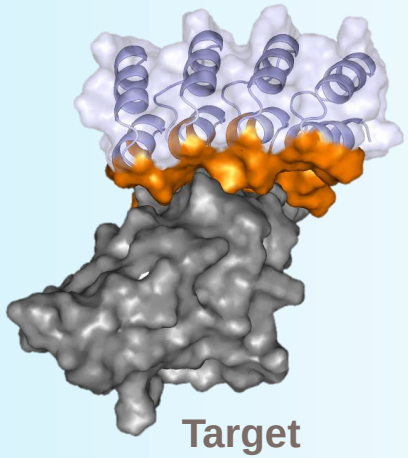
Extending the Boundaries of Targeted Cancer Therapies

Radio-DARPins and Next-Gen Immune Cell Engagers

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

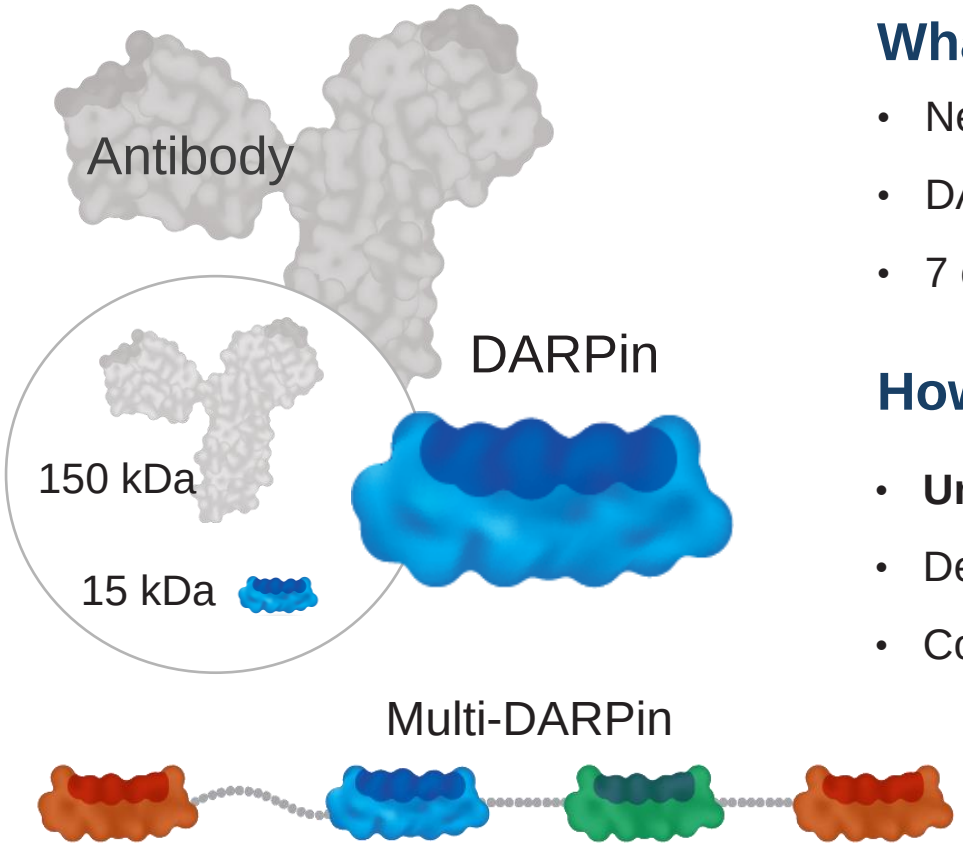
Our Capabilities: Technology, Team, Collaborations

- 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

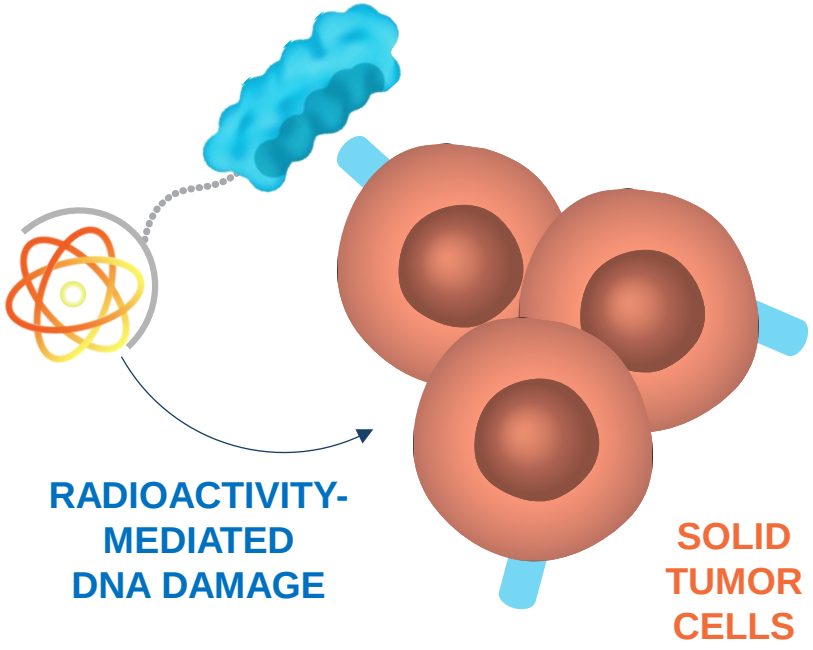
- New class of therapeutics: Designed Ankyrin Repeat Proteins **(DARPins)**
- DARPins **close the gap between small molecules and antibodies**
- 7 clinical-stage compounds, **>2500 patients treated**

How we apply it

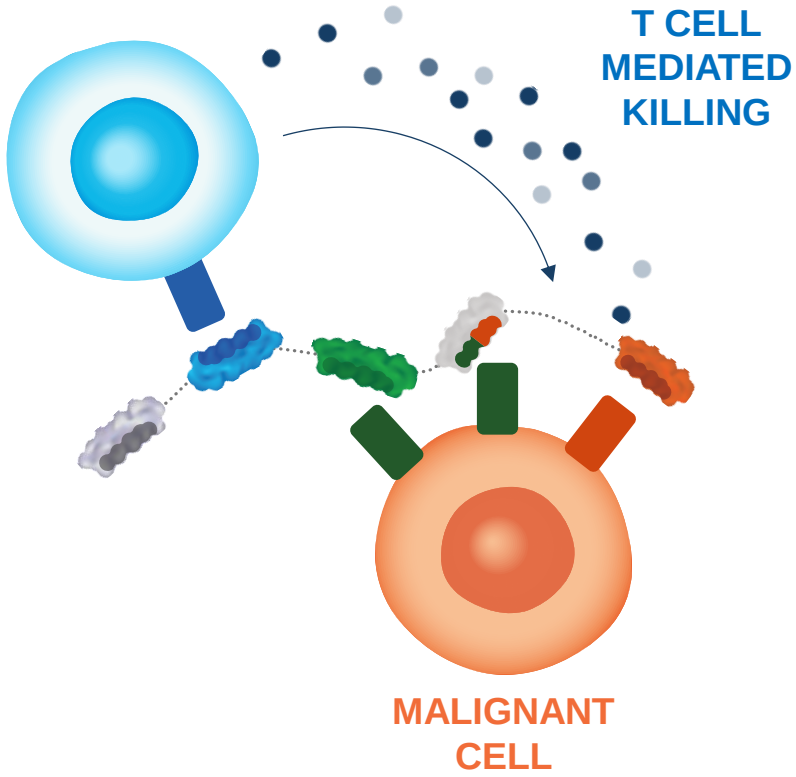
- **Unique DARPin solutions**, not addressable by antibody designs
- Demonstrate **true patient value** with **early clinical readouts**
- Combine our **capabilities with world-class partners**

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.

Pipeline & 2025 News Flow

MODALITY	CANDIDATE	NEXT MILESTONES
Radio–DARPin Therapy (RDT)	**MP0712 (DLL3)**	**IND submission; Start of FIH study & first images (H2‘25)**
	RDT x MSLN	**Candidate nomination; Pre-clinical update (AACR 2025)**
	Undisclosed Programs	**Additional targets selected; Pre-clinical updates**
	Undisclosed Programs	
Next-Gen Immune Cell Engagers	**MP0533**	**Amended dosing scheme; Cohorts 8 (H1) and 9 (H2’25) data**
	Switch-DARPin T-cell Engager	**Pre-clinical update (AACR 2025)**
	MP0621	
	MP0317	**Investigator-initiated trial start (H1’25)**

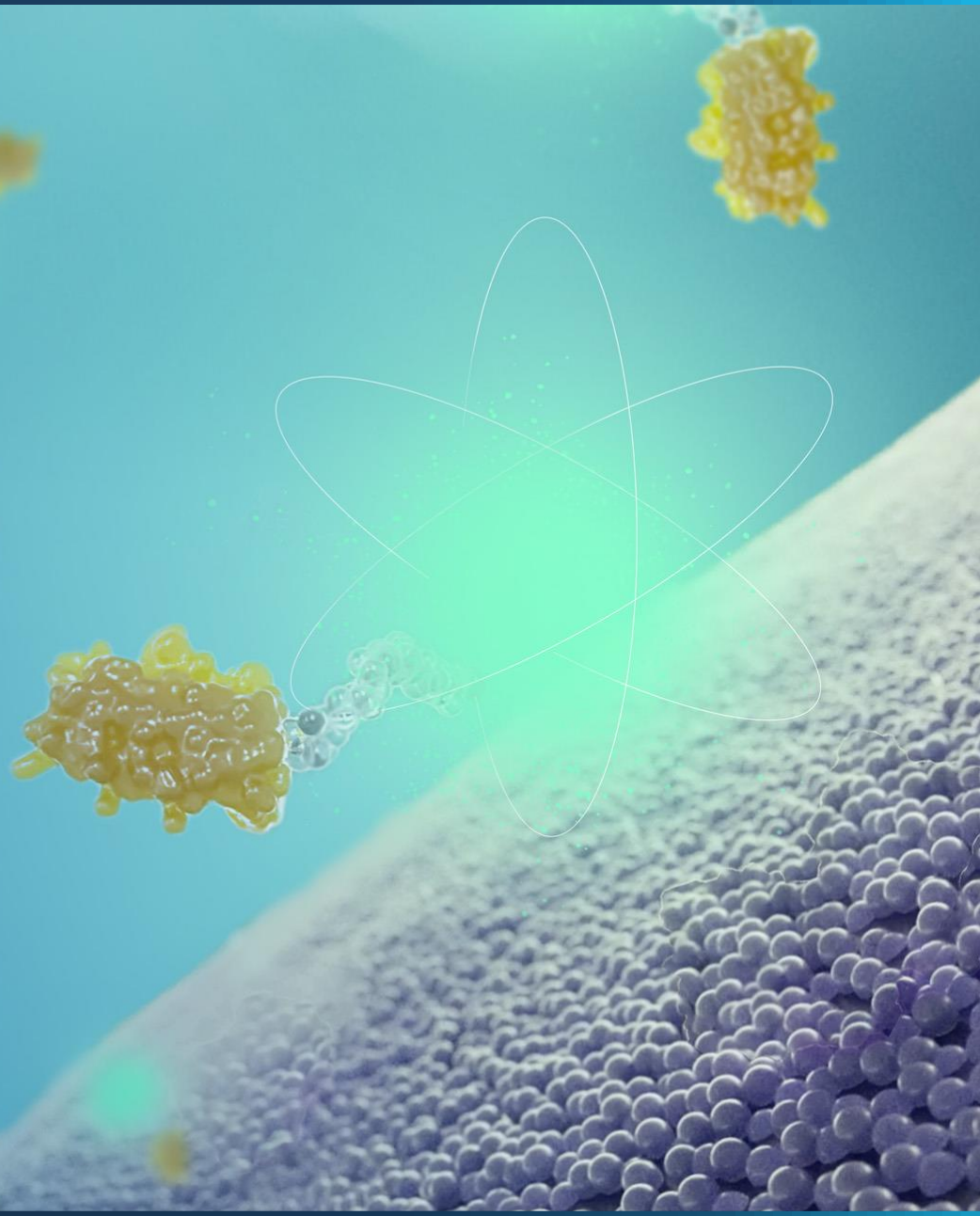
MOLECULAR partners

*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.

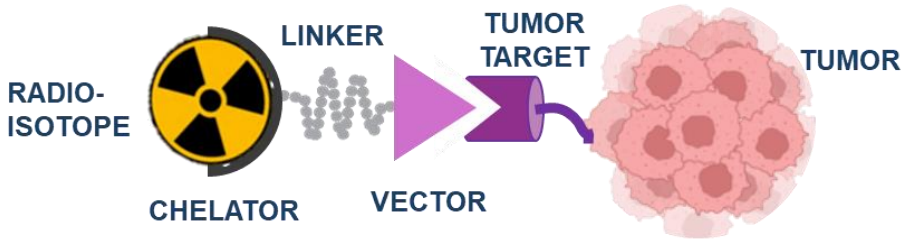
MOLECULAR partners

Radio-DARPin Therapy & MP0712

Custom-engineered to create vectors ideal for radiopharmaceuticals



Targeted Radiotherapy: “Old” Modality Turned Hot Through Precision

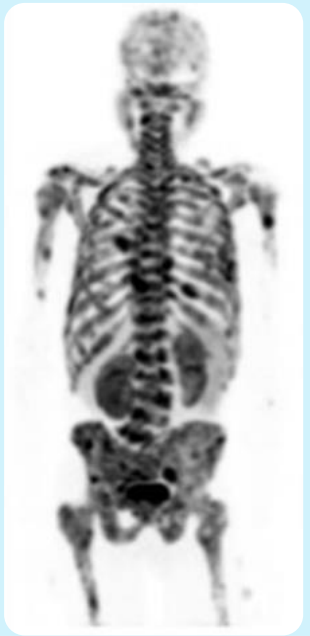


- “See what you treat” & “treat what you see”
- Enables early validation or kill point
- Proven clinical benefit for oncology patients
- **Limitation:** current vectors not applicable to all targets
- **Opportunity:** Broaden the target space with next generation vectors

➔ **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

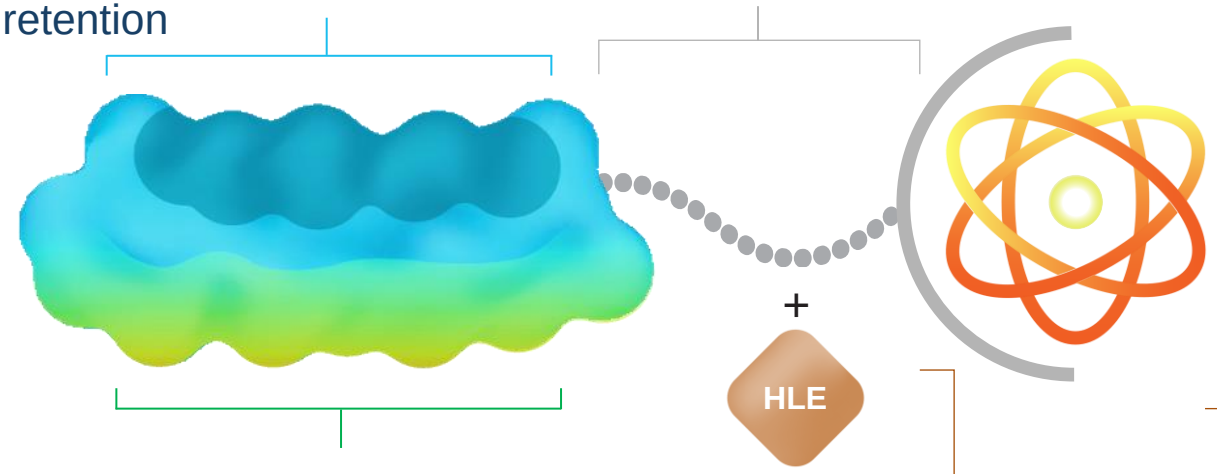
Combining versatile DARPin features with the power of ^{212}Pb for next-gen Targeted Alpha Therapy

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
- Reduce kidney accumulation

HALF-LIFE EXTENDER

- Half-life tuning
- Promote tumor uptake

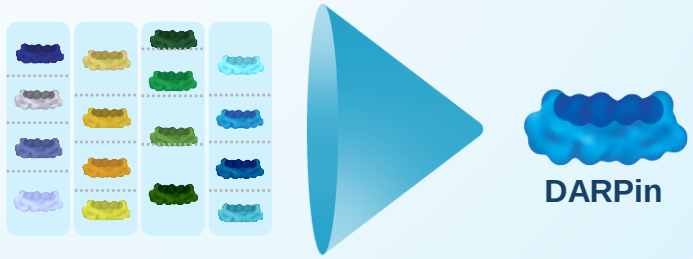
Global Partnership to Develop ^{212}Pb Radio-DARPin Therapeutics

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

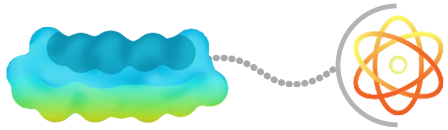


DARPin Engine:
Rapid selection, development & manufacturing of candidates

FULL VALUE CHAIN PARTNERSHIP

- **World class technologies combined**
- **Ability for rapid candidate testing/cycling**
- **Strategic impact: up to ten (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 in North America

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) ~3m[1,2]
- 5y overall survival (OS) ~3%[1,2]

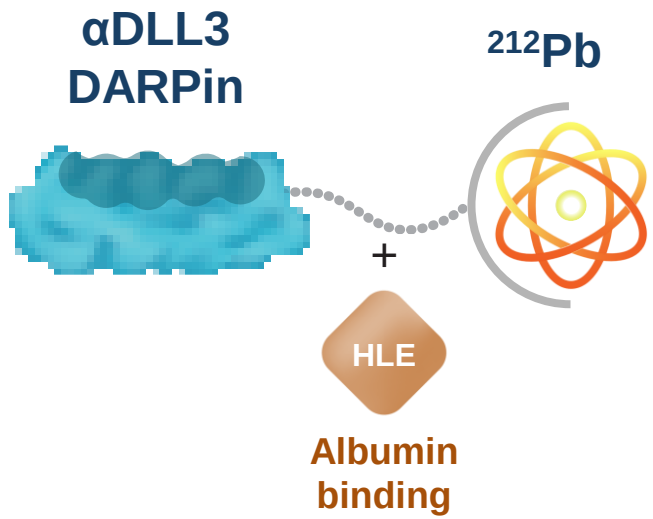
DLL3: a validated target for SCLC

- 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)
  - Overall response rate (ORR) ~40%; duration of response (DOR) 9.7 months; progression-free survival (PFS) 4.3 months

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

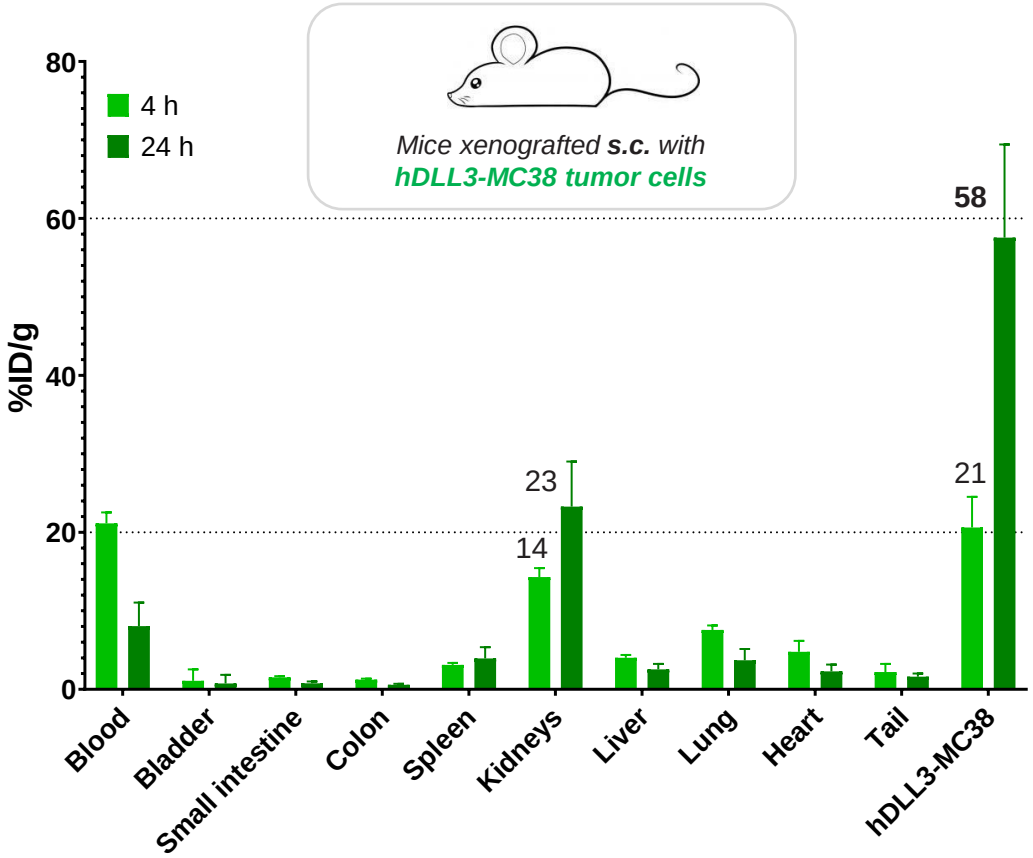
- DLL3 DARPin optimized for selective delivery of payload to tumor
- ^{212}Pb payload: high energy alpha emissions in short time frame
- Potential for combinations with immunotherapy

MP0712 - Product composition



1. Treatment of refractory and relapsed small cell lung cancer, UpToDate; 2. SEER; 3. Rojo et al., Lung Cancer 2020. HLT, half-life tuning; SCLC, small cell lung cancer. 4. Phase 2 DeLLphi-301 study (NCT05060016)

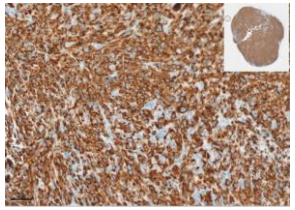
MP0712: Attractive Biodistribution Profile in Clinically-Relevant Model



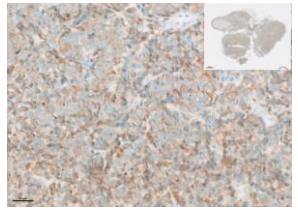
*Mice xenografted **s.c.** with*
hDLL3-MC38 tumor cells

DLL3 expression & distribution by IHC

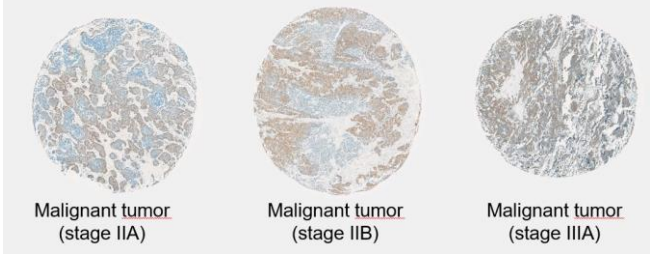
hDLL3-MC38 tumors



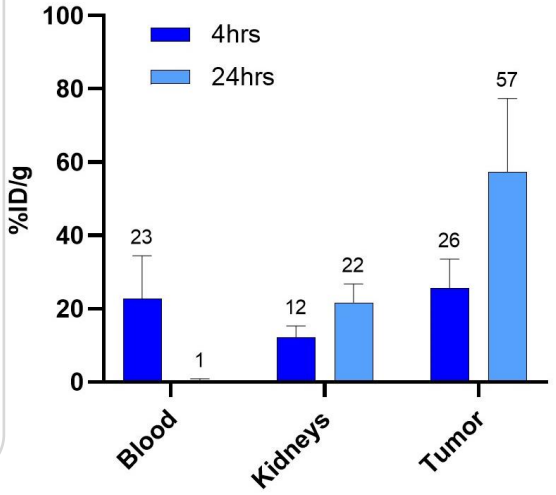
NCI-H82 tumors



Human SCLC tumors



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

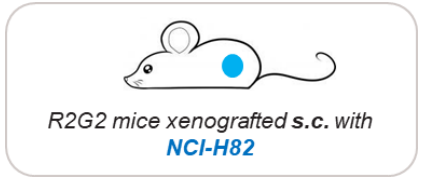


- **MP0712 reached T:K ratios > 2 in mouse model matching clinically relevant DLL3 expression levels**
- **Selective uptake in DLL3-expressing tumors confirmed high target specificity of MP0712** *(data not shown)*

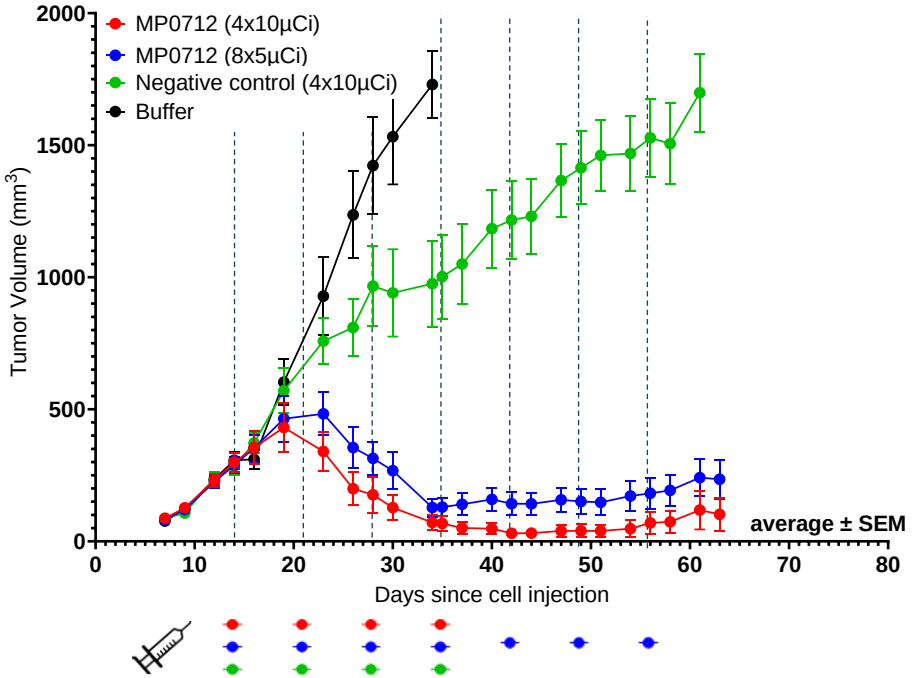
hDLL3-MC38 and NCI-H82 mouse models: ^{212}Pb-DOTAM-DARPin - single injection - dose : 10 µCi (0.01 mg/kg)

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

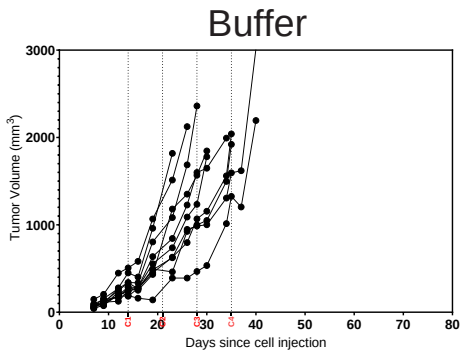
MP0712: Potent Efficacy at Clinically-Relevant Dose

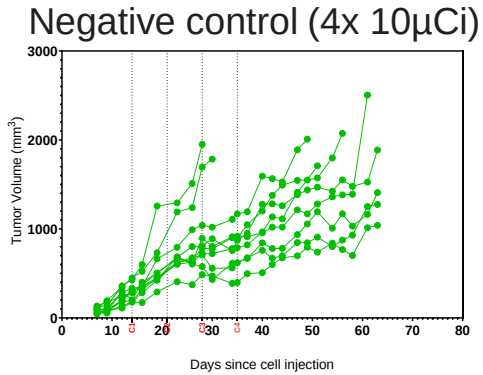


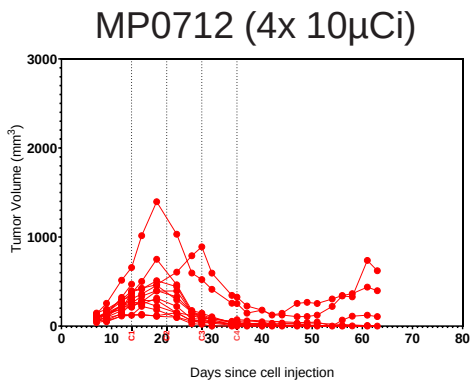
*R2G2 mice xenografted **s.c.** with*
NCI-H82

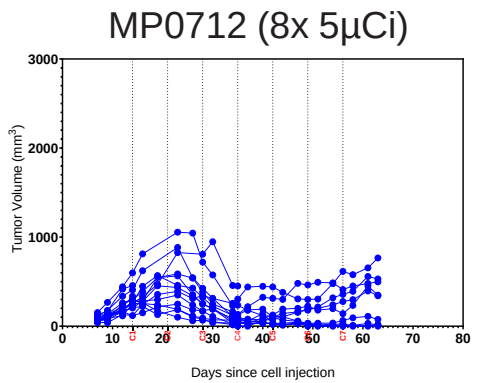


Tumor growth curve for each animal







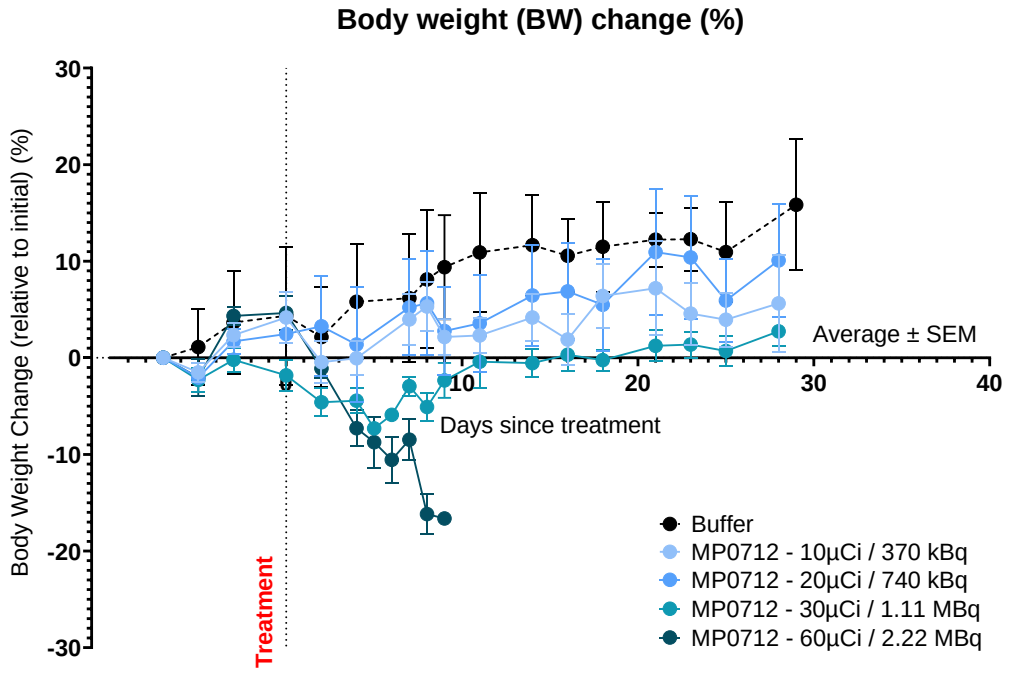


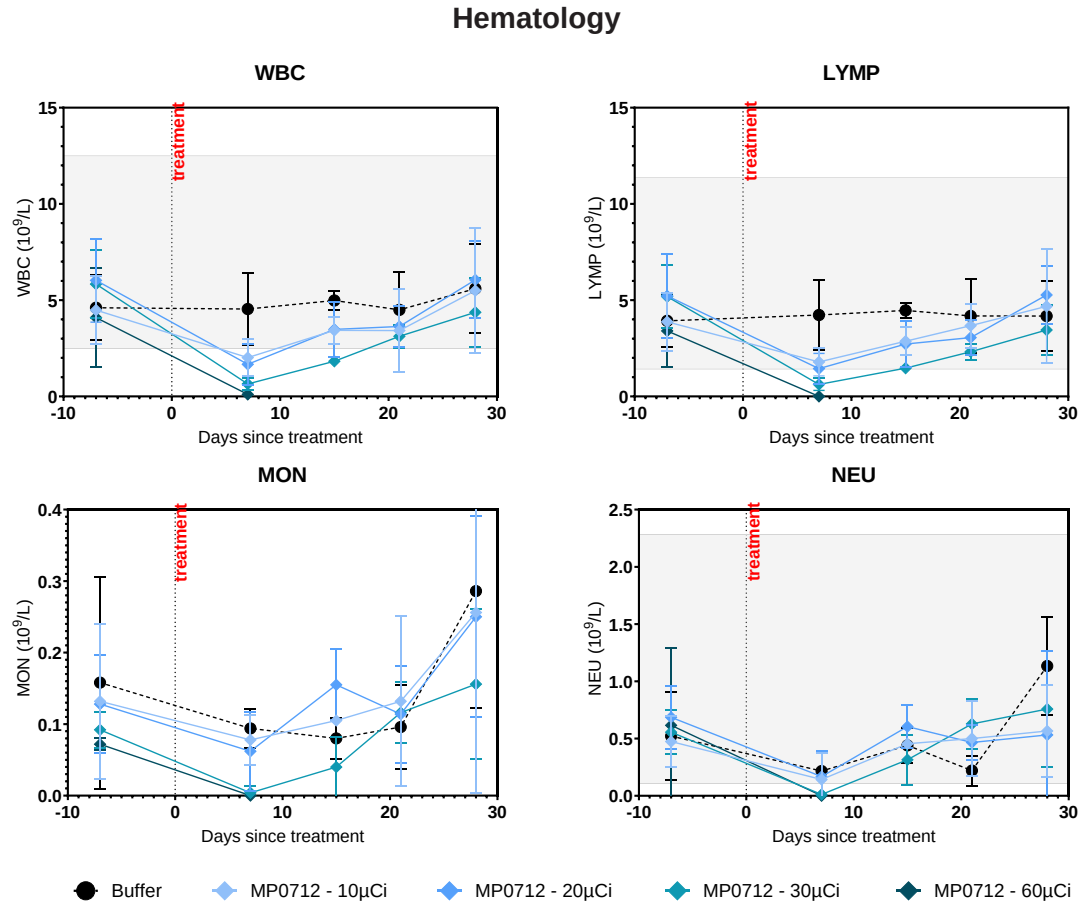
- **MP0712 induces complete and durable tumor regression in NCI-H82 tumor model at 10µCi injected every week**
- **At day 63, complete tumor regression is seen for ~70% of mice at <u>4x 10µCi</u> and ~20% of mice at <u>8x 5µCi</u>**

Steiner et al, TRP 2024 (oral presentation)

Efficacy study in NCI-H82 tumor model / MP0712 and negative control injected
4 x 10µCi at 0.01mg/kg or 8 x 5µCi at 0.01mg/kg every 1; 10µCi = 370kBq

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 30µCi / 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), secondarily 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

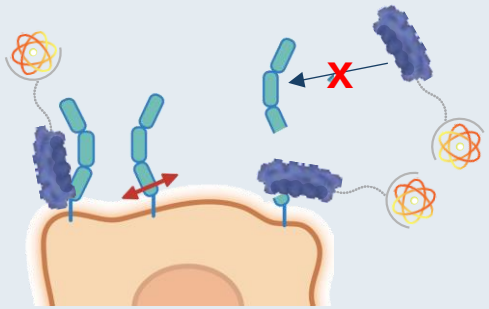
→ **Phase 2a - Dose Expansion and PoC**
Main objective: Efficacy signals, confirm safety and RP2D

→ **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.

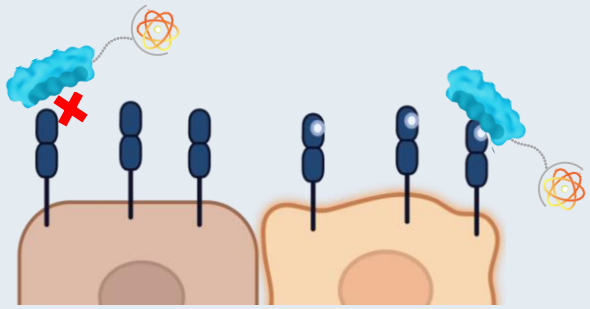
Continue to Leverage DARPin Differentiation to build Portfolio of Radio-DARPin candidates



Tumor cell

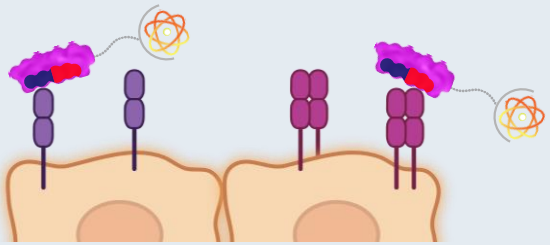
Selectivity for **membrane-bound antigen** vs **shed antigen** for high tumor uptake

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

Created in part with BioRender.com

^{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: 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)

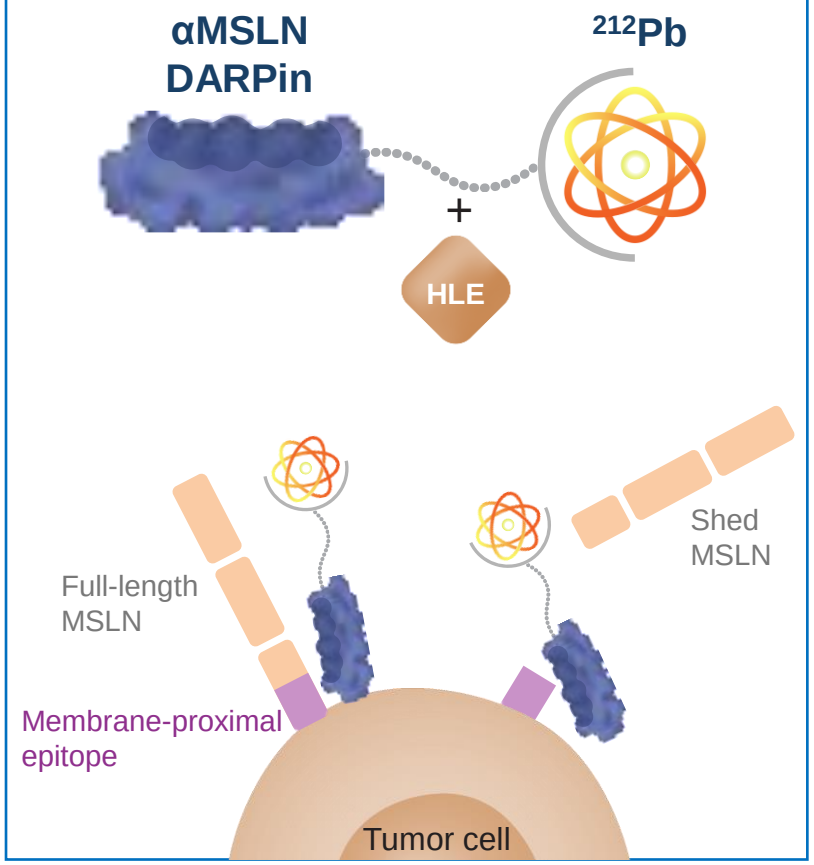
Mesothelin (MSLN): a promising target for ovarian cancer as 1st indication

- 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

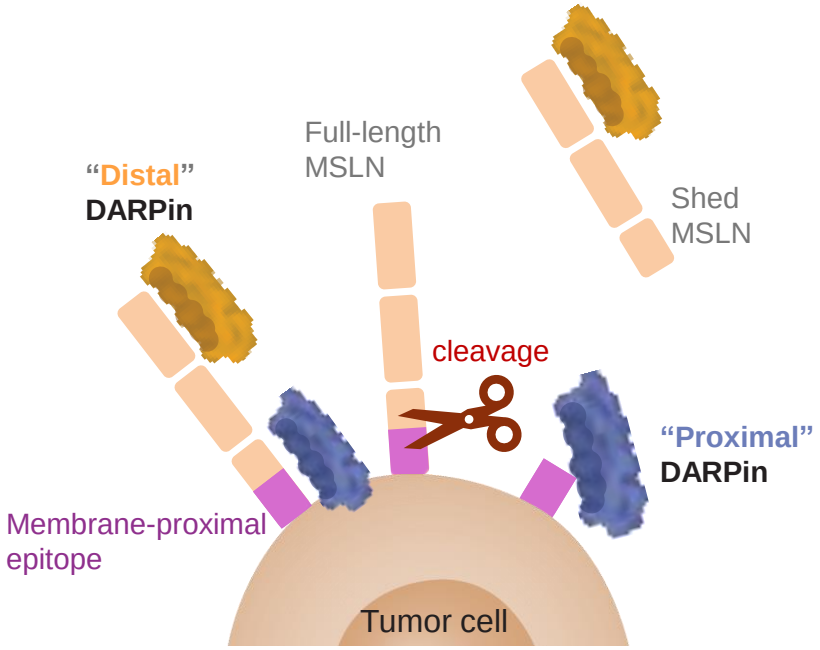
- MSLN DARPin targets membrane-proximal epitope (and not shed MSLN)
- ^{212}Pb payload: high energy alpha emissions in short time frame
- Potential for combinations with immunotherapy (incl. next-gen T cell engagers)

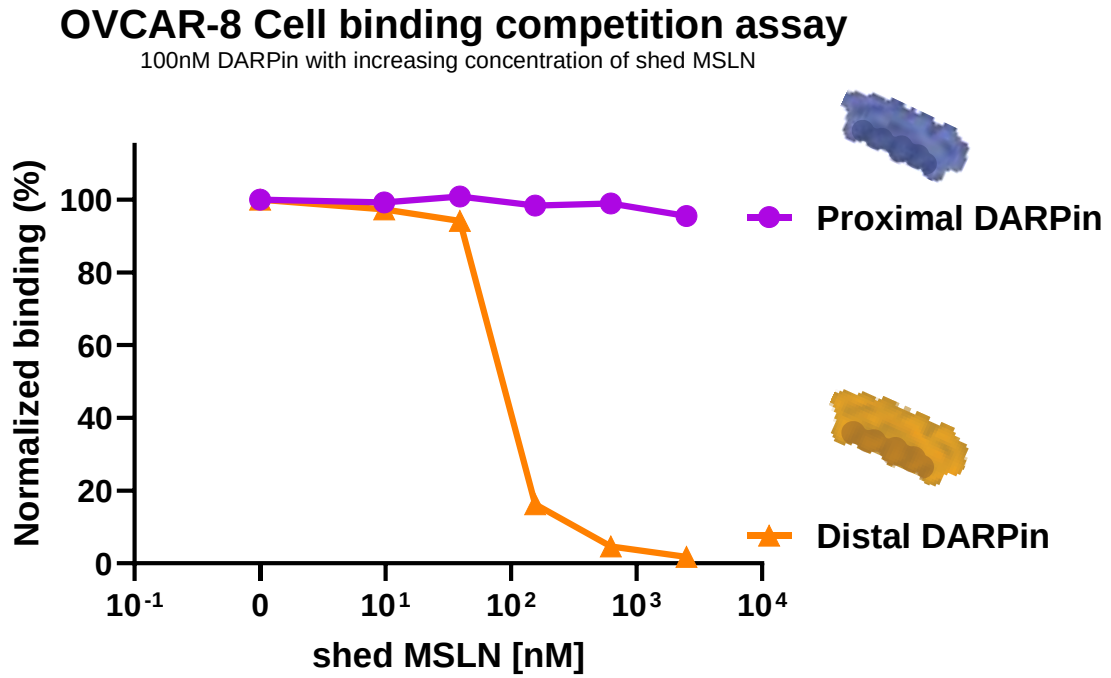
Product composition



[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

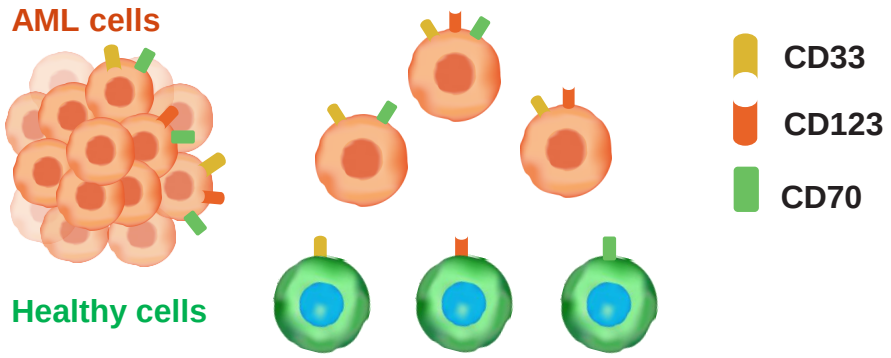
MOLECULAR partners

MP0533

Tetra-specific T-cell Engager for AML

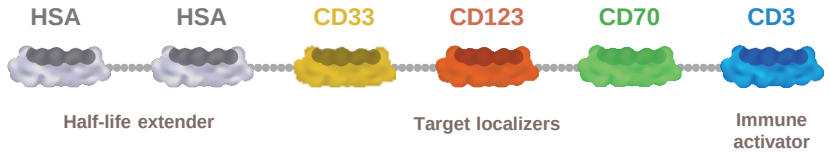
MP0533 Enables Avidity-Driven Selective Killing of AML Cells

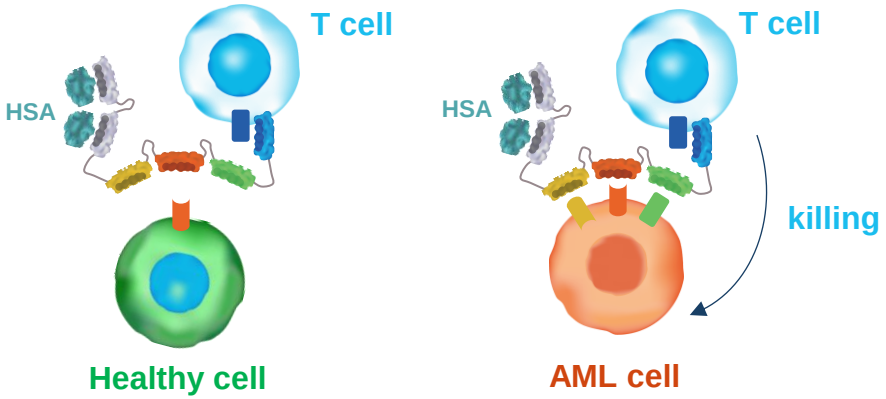
AML-associated antigens are also expressed on healthy cells



- **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.

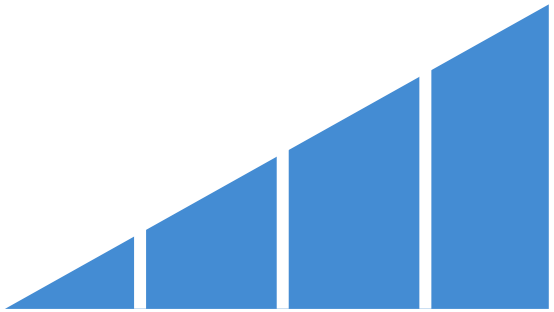
MP0533 Phase 1/2a Study in Patients with R/R AML/MDS

Protocol amendment to optimize MP0533 exposure

Initial Protocol

Dose Escalation (DR 1–7)

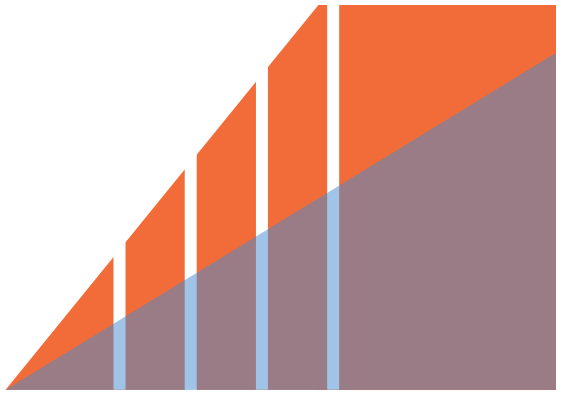
- Limited clinical activity
- Target-mediated drug disposition (TMDD) = **low exposure**
- Loss of exposure (LoE) in some patients (ADA)



Amended Dosing Scheme

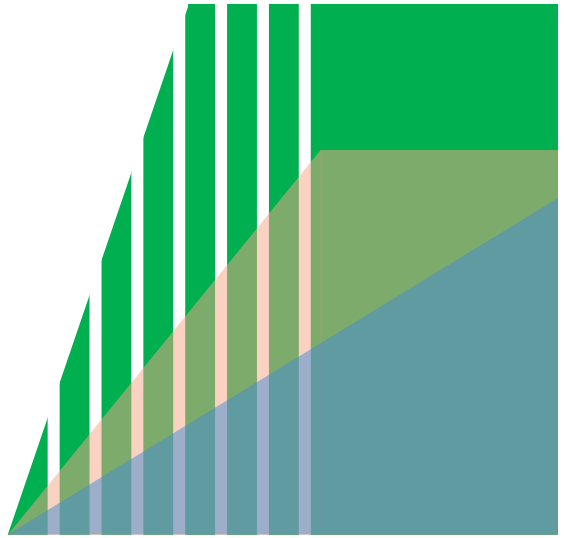
Intermediate densification (DR 8)

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



Further dose densification (DR 9–10)

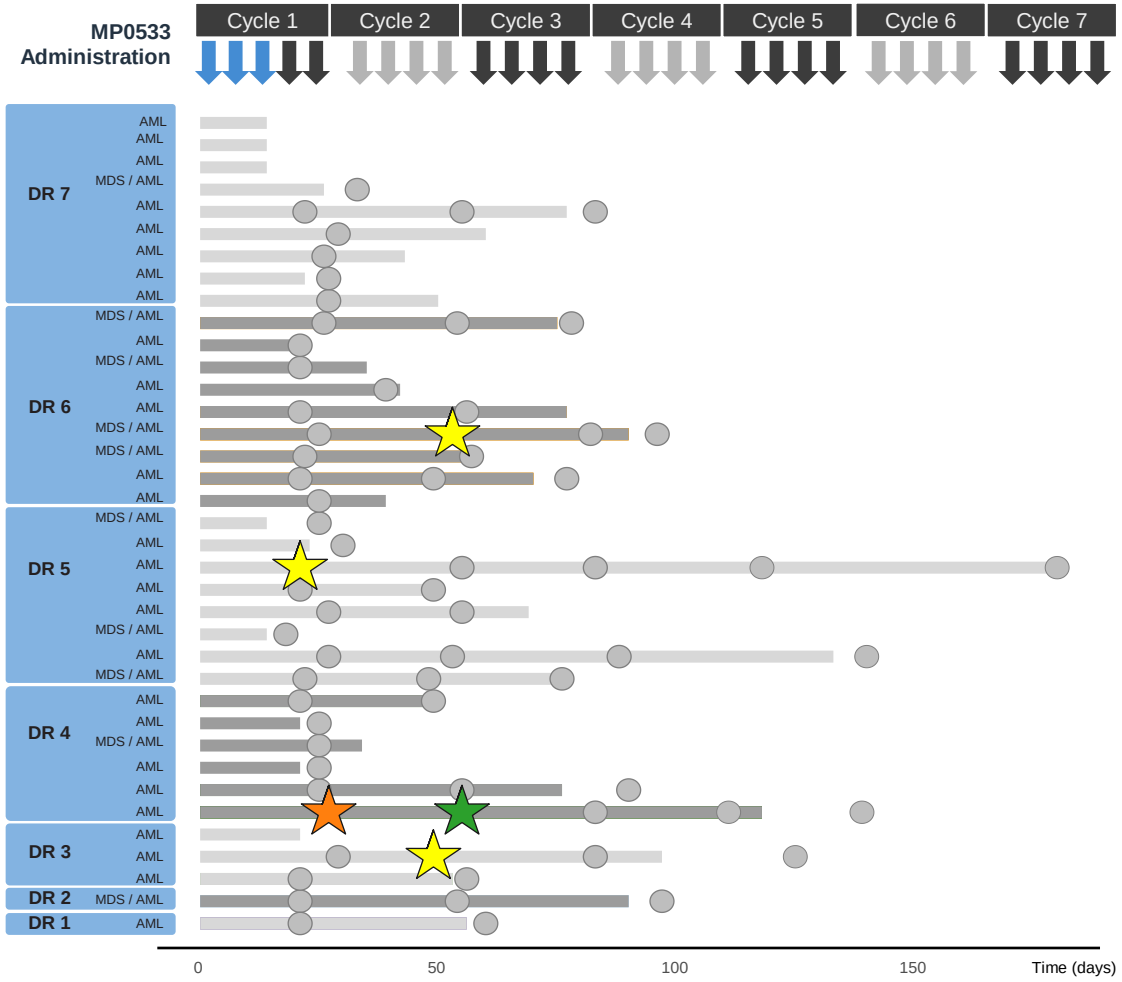
- **High dose frequency for 1st cycle**
- Premedication for **LoE mitigation**



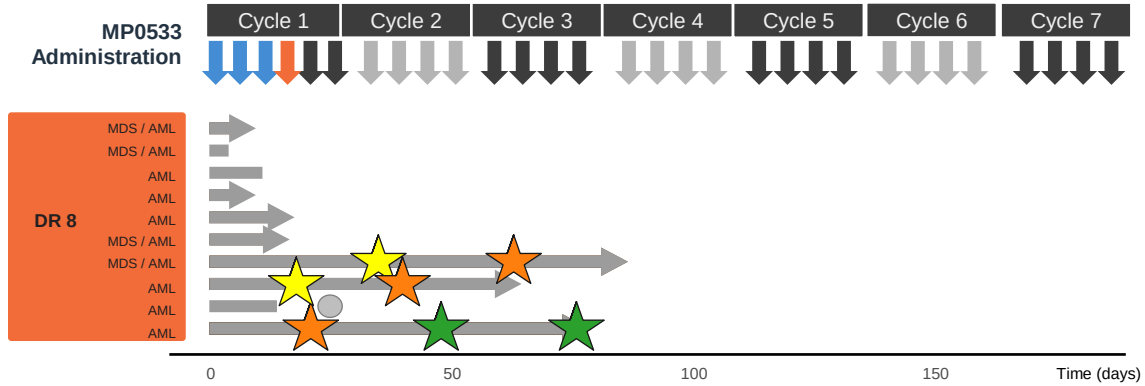
ADA, anti-drug antibody; DR, dose regimen.

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

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

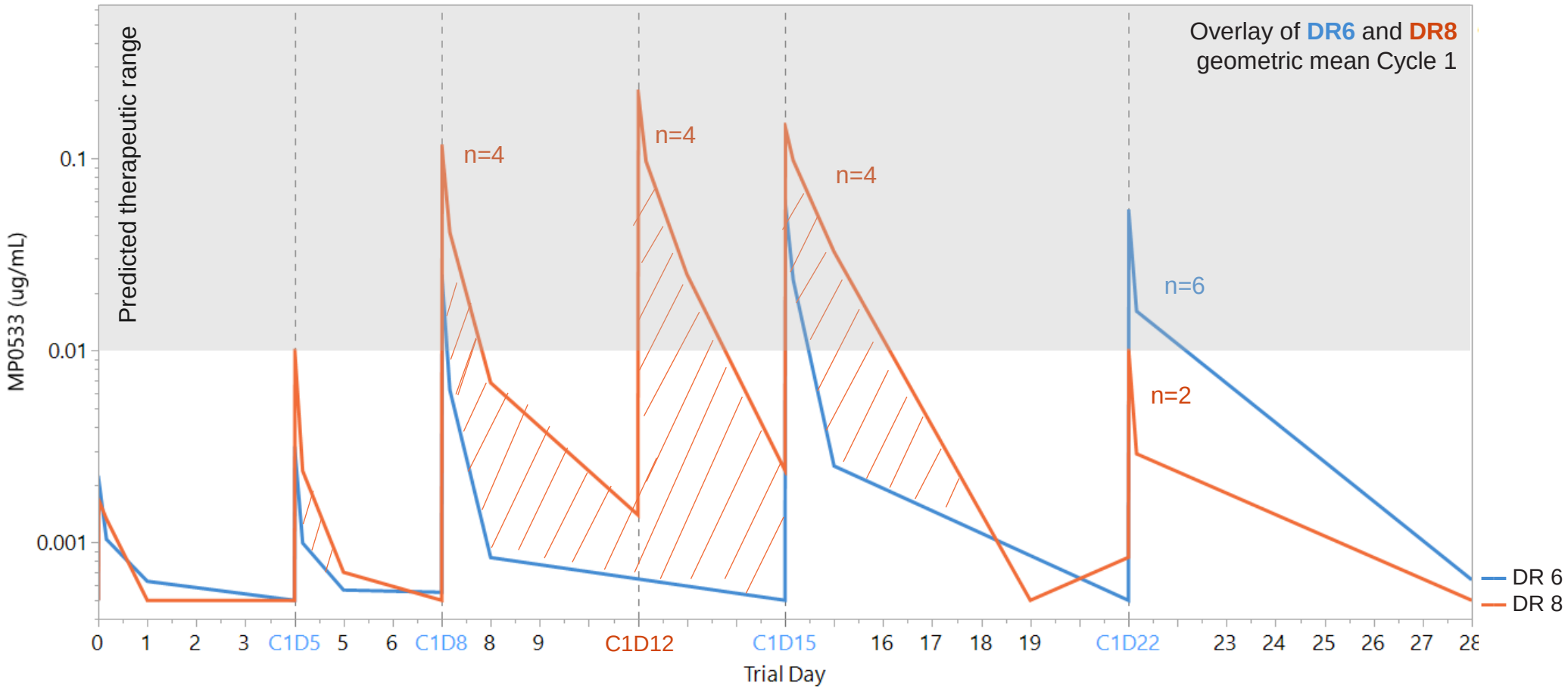
Data cut-off: 16 December 2024

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

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 (16 Dec 2024)

MOLECULAR partners

Switch-DARPin Platform

Targeted and conditional
activation of immune cells

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

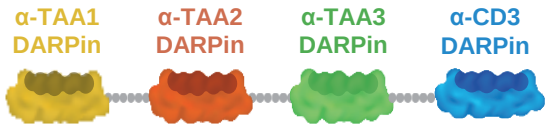
Challenges with current TCEs

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

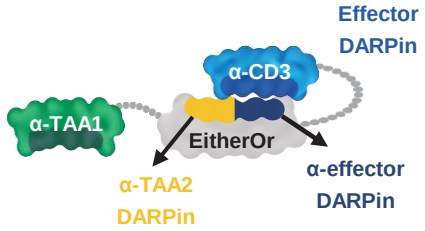
Narrow therapeutic window
- CRS and on-target toxicity limit dosing
- Mitigation strategies (e.g. lower CD3 affinity) lead to lower activity
- Conditional activation depends on the environment (e.g proteases)

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

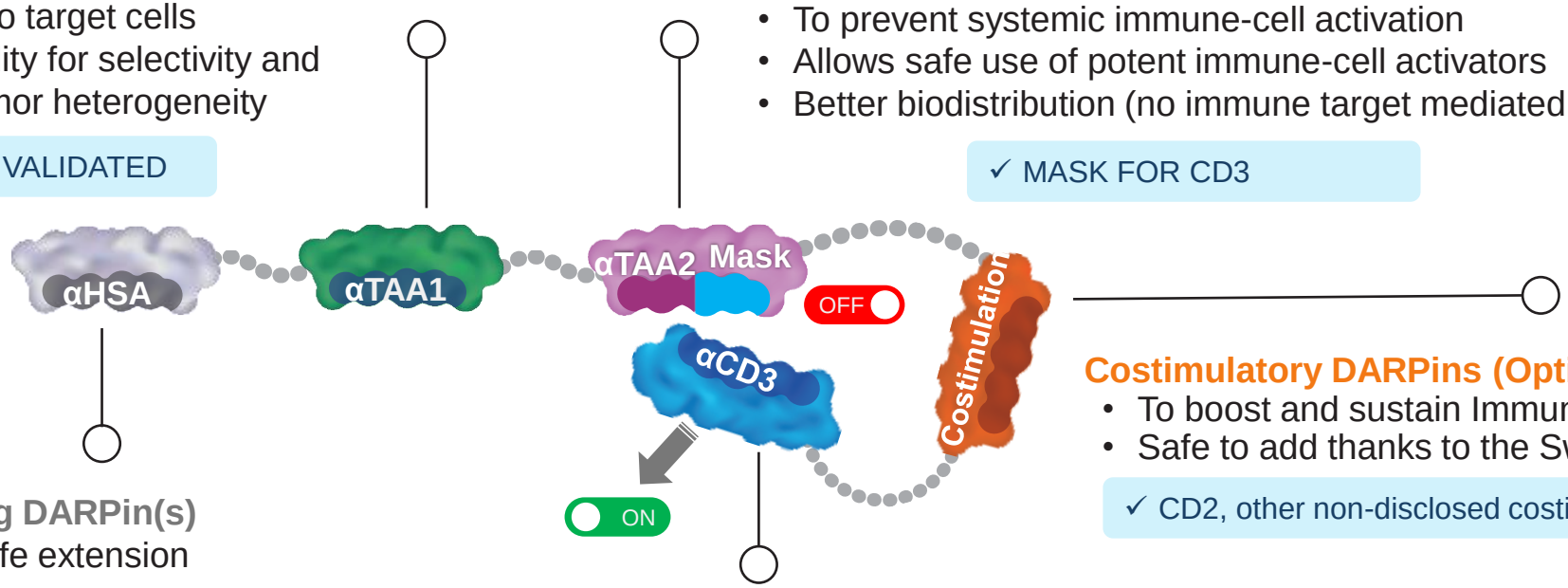
Swiss knives for targeted and conditional immune activation

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

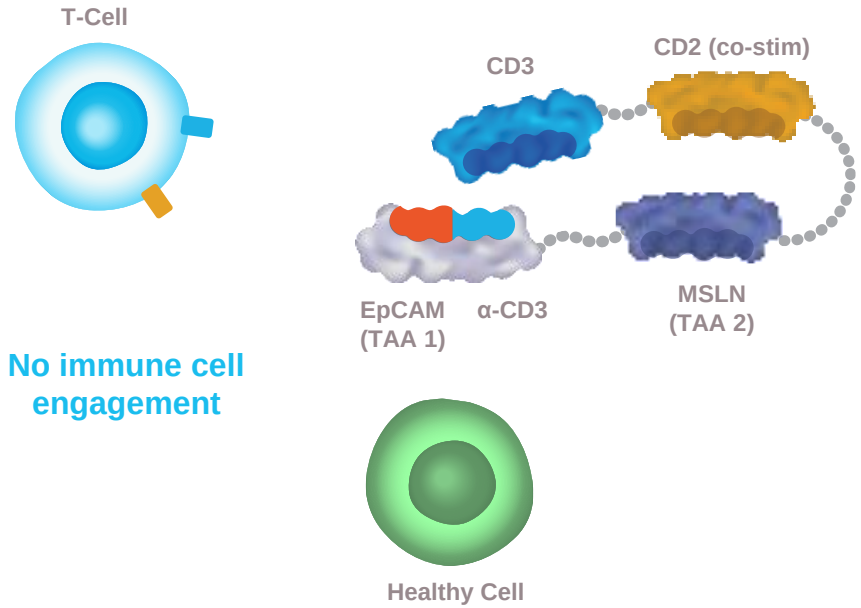
✓ CD3 TCE CLINICALLY VALIDATED

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

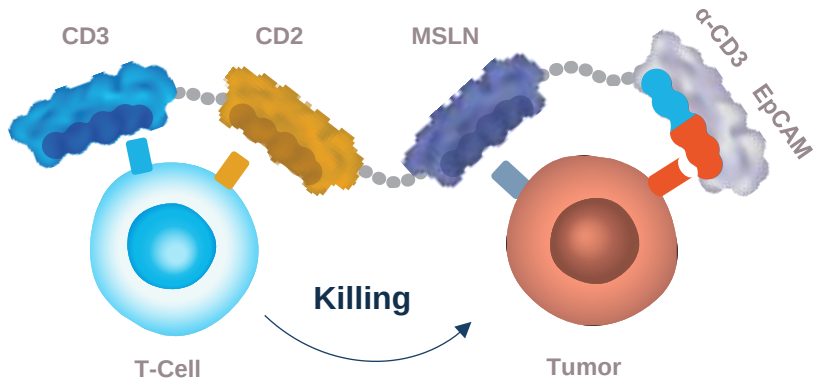
OFF **CD3 DARPin masked by 2-in-1 Switch in absence of TAAs**



No immune cell engagement

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

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

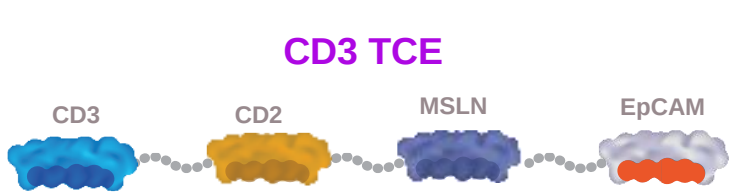


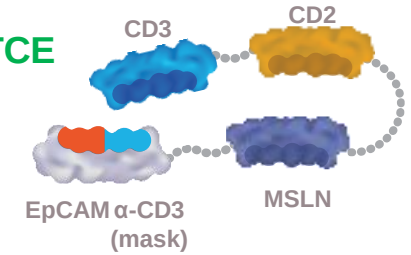
Immune cell-mediated killing

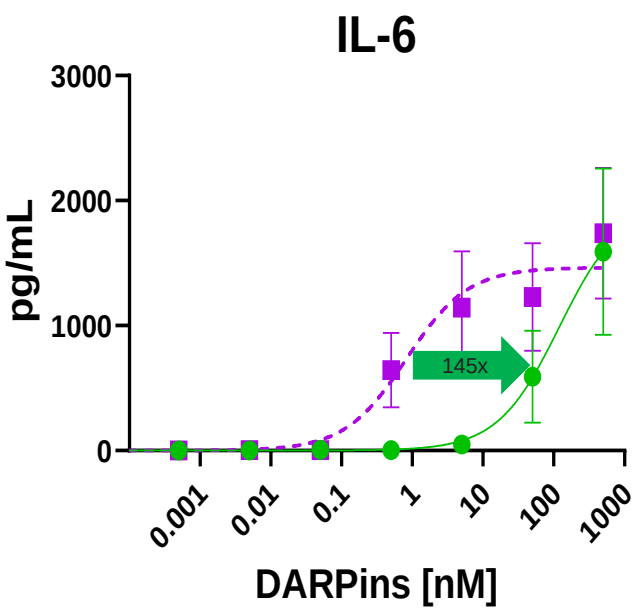
- **TCE is activated to kill the tumor cell**
- **TCE is stimulated (no exhaustion)**

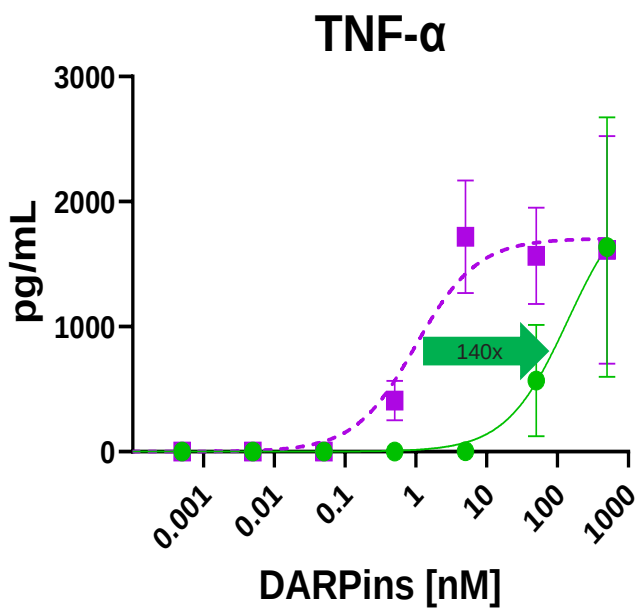
TAA, tumor associated antigen; TCE, T cell engager.

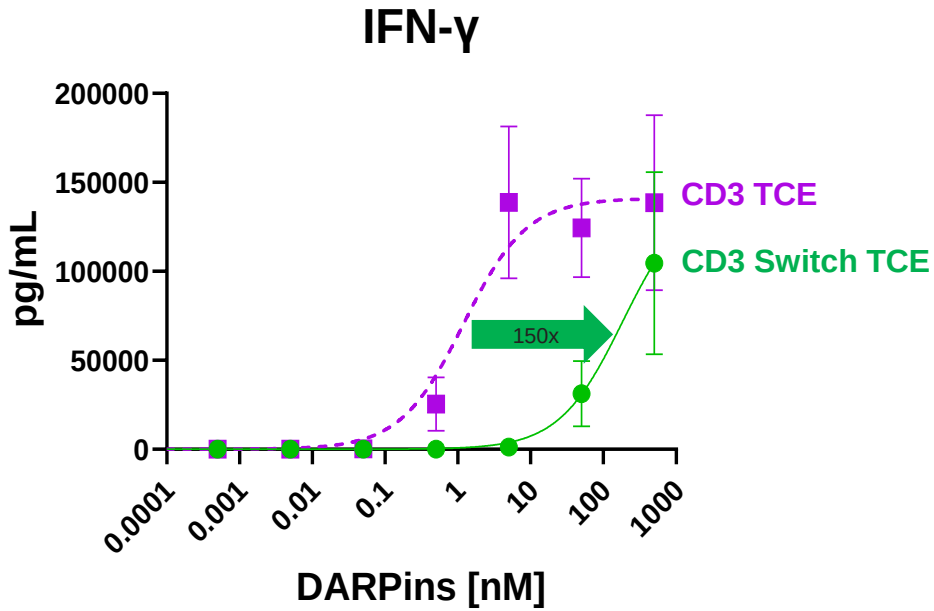
Switch-DARPin reduces cytokine release in whole blood assay





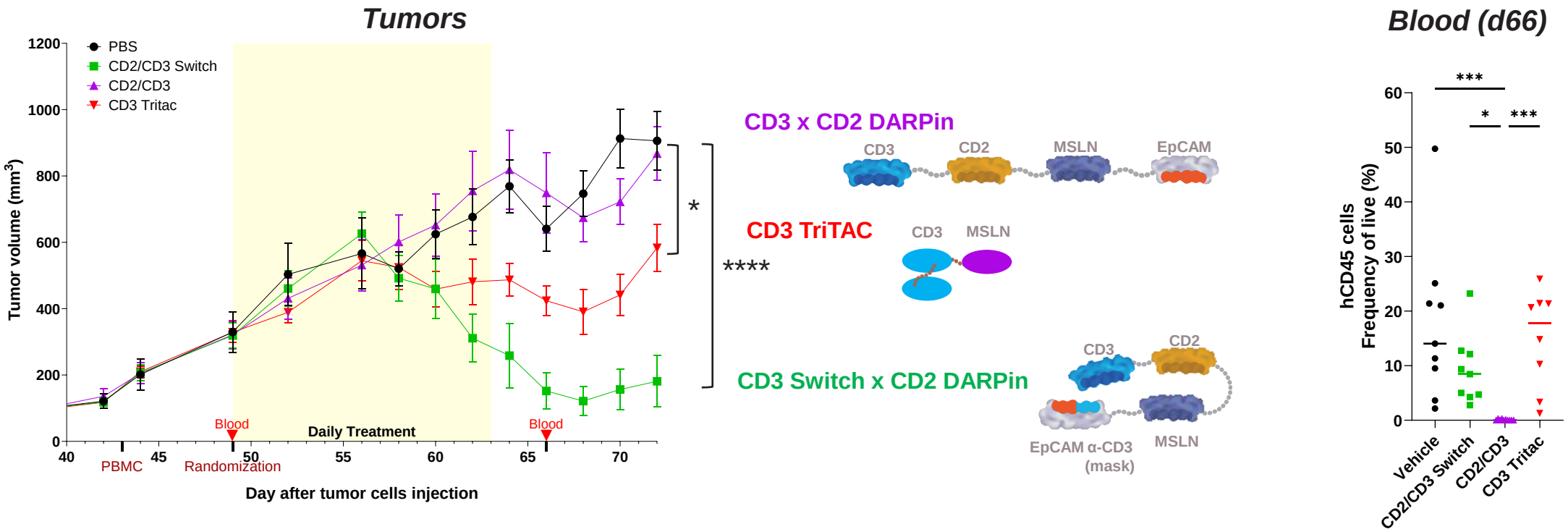






n=3. Average +/- SEM

Switch-DARPin leads to tumor regression pre-clinically

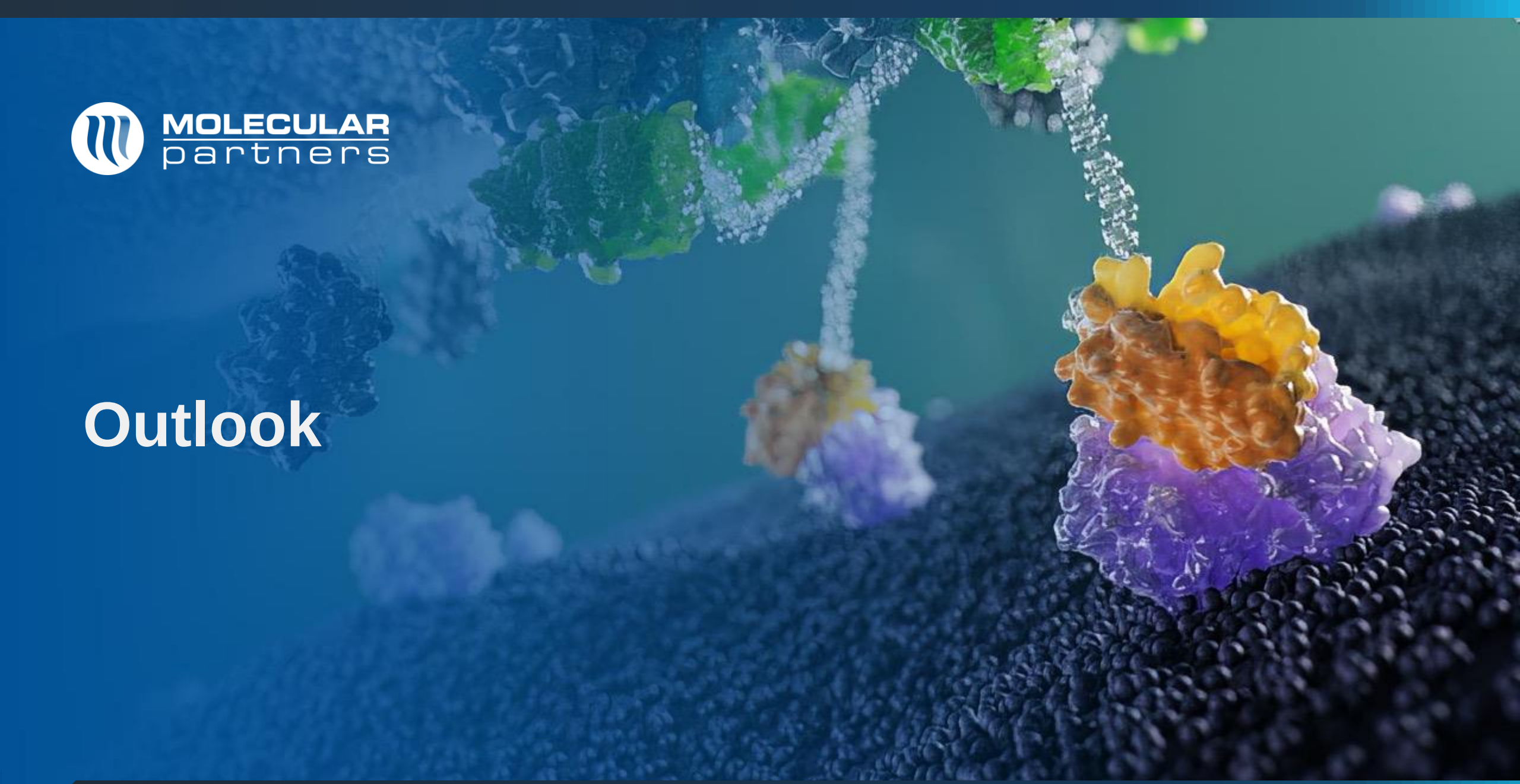


- EpCAM-MSLN-CD2/CD3 Switch induces tumor regression more efficiently than a MSLN-CD3 engager (Tritac).
- Non switched CD2/CD3 DARPin is not efficacious, likely due to loss of CD45+ T cells as a result of T cell fratricide

➢ **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

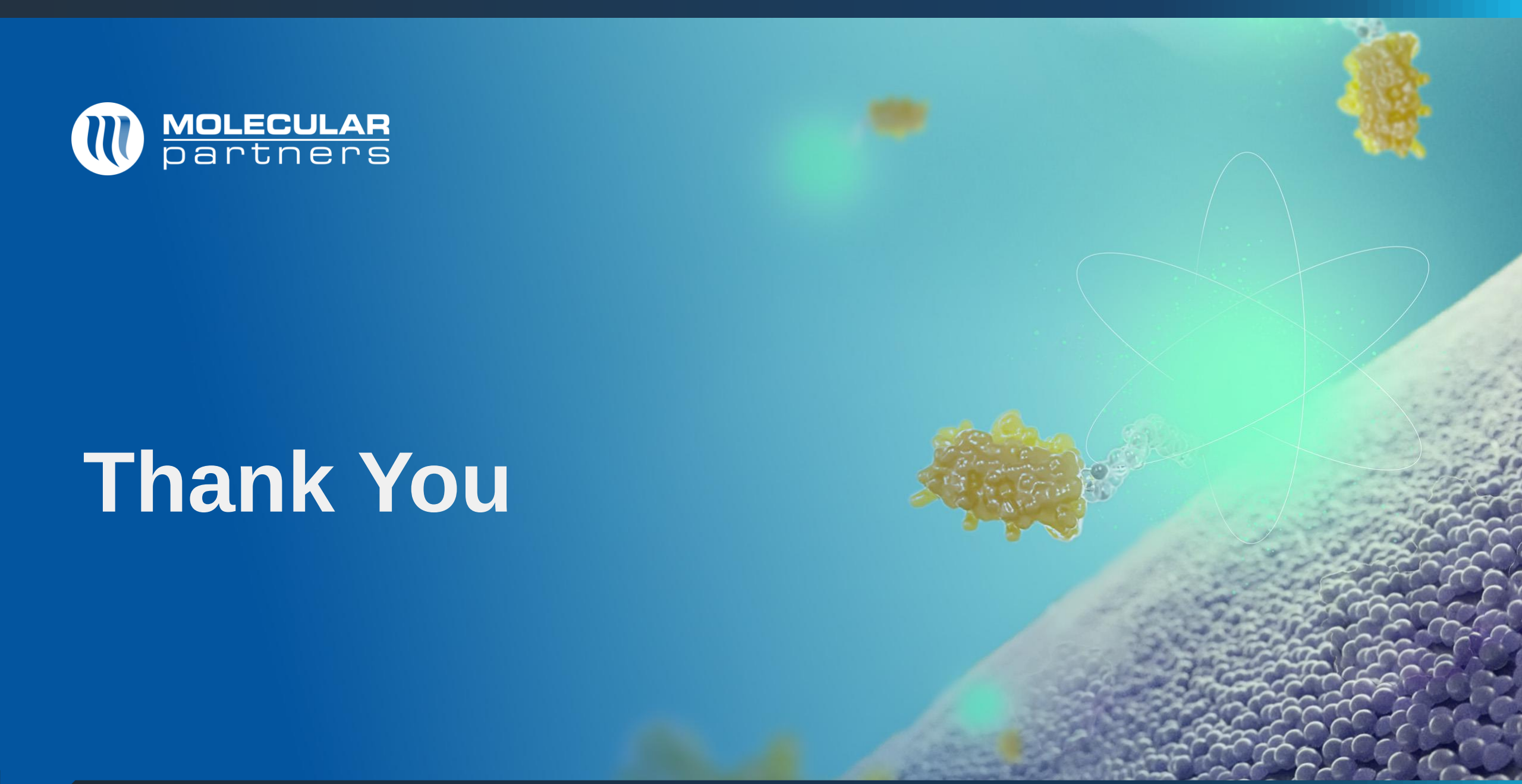
MP0712	• Submit IND applications of MP0712, ^{212}Pb x DLL3 RDT, for phase 0 and 1 studies, H1 2025 • First-in-Human studies to start in H2 2025 • Initial clinical data by end 2025
Radio-DARPin Therapy (RDT)	• MSLN preclinical update at AACR 2025, therapeutic candidate selection • Additional ^{212}Pb 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 additional cohorts on 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.

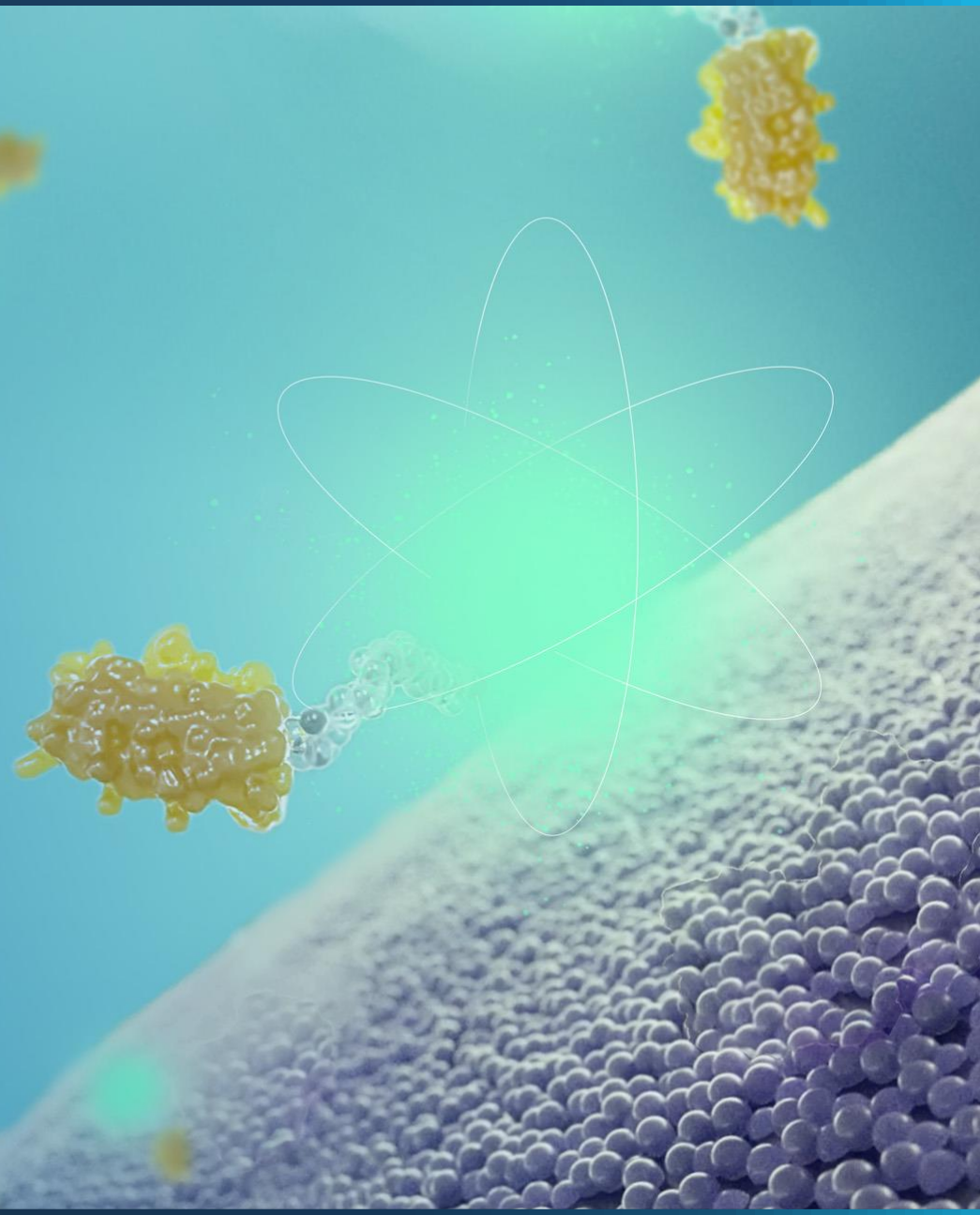
MOLECULAR partners

Thank You



MOLECULAR partners

Back-up

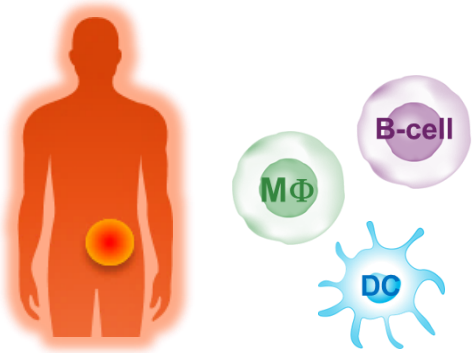


MP0317

Tumor-localized Immunotherapy

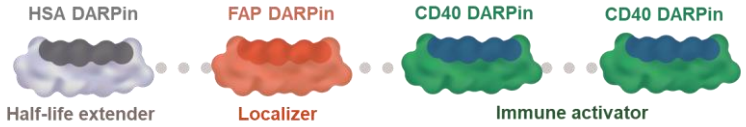
MP0317: Unlocking CD40 Activity Through Local Activation

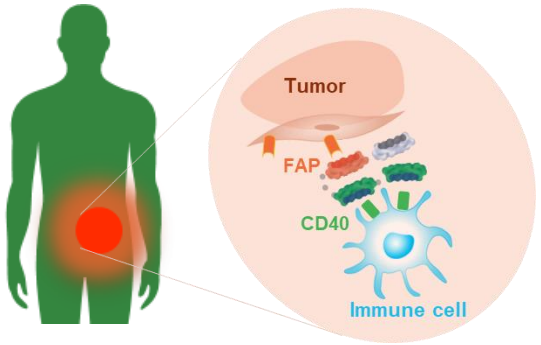
Problem: Toxicity of CD40 Antibodies Has So Far Limited Their Activity



- **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



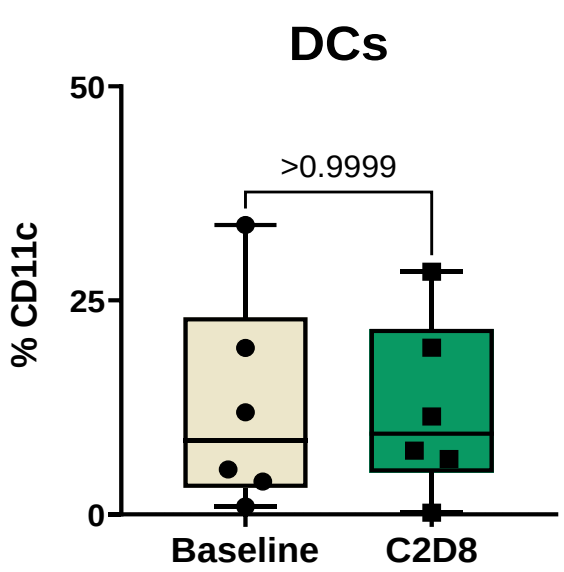


- **FAP is a validated tumor target** overexpressed in at least 28 different cancer types and its expression is not downregulated during disease progression
- **MP0317** is designed to bind tumor-localized FAP and induce CD40-mediated **activation of immune cells in the tumor**, thereby overcoming systemic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

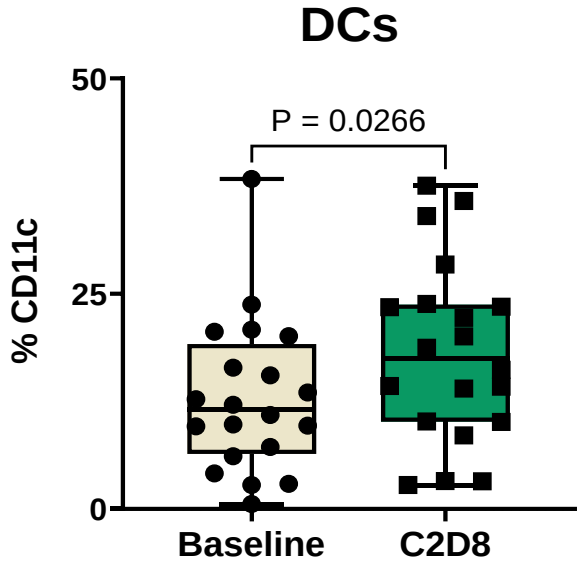
DC, dendritic cell; FAP, fibroblast activation protein; HSA, human serum albumin; MΦ, macrophage; mAb, monoclonal antibody; IO: immuno-oncology.

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)



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

Summary of MP0317 Phase 1 Study:

- A total of **46 patients treated** in 9 cohorts
  - Median age (range): 63 years (35–79)
  - 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**

Outlook:

- Clinical combinations via **investigator-initiated trials**

Steeghs et al. ASCO 2024 poster presentation.

DC, dendritic cell; mIF. multiplex immuno-fluorescence; TME, tumor microenvironment.

MOLECULAR partners

MP0621 Switch-DARPin

Targeted and conditional
activation of immune cells

MP0621: cKit x CD16a x CD47 Switch-DARPin

Next-Generation Conditioning Regimen for HSCT

Target cKIT to eliminate HSCs/LSCs

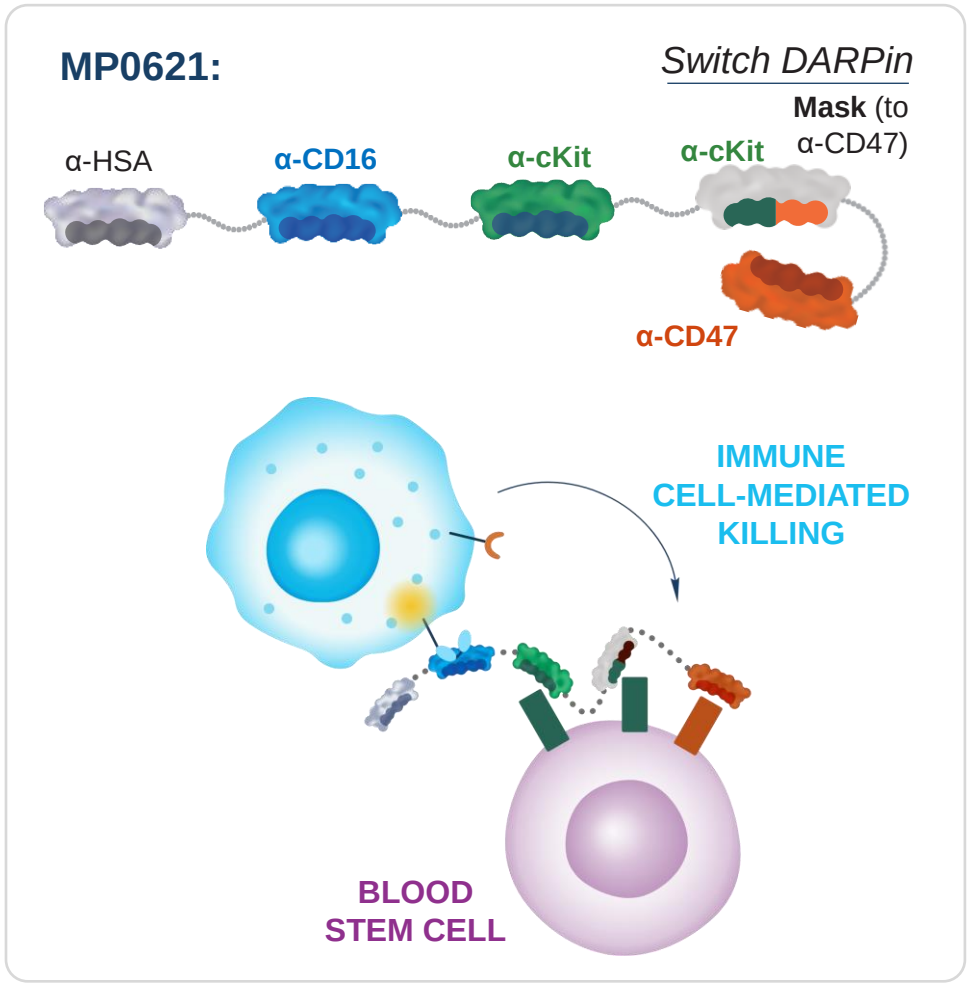
- cKIT is critical for stem cell maintenance and renewal[1, 2]
- Simple antagonists (mAbs) to cKIT are not potent enough

Engage NK cells and macrophages (MΦ) via CD16a to kill HSCs/LSCs

- Effective and safe approach
- NK and MΦ activity is limited by CD47 expression on HSC/LSCs[3]

Conditionally block CD47 on LSCs/HSCs to boost NK cell and MΦ killing activity

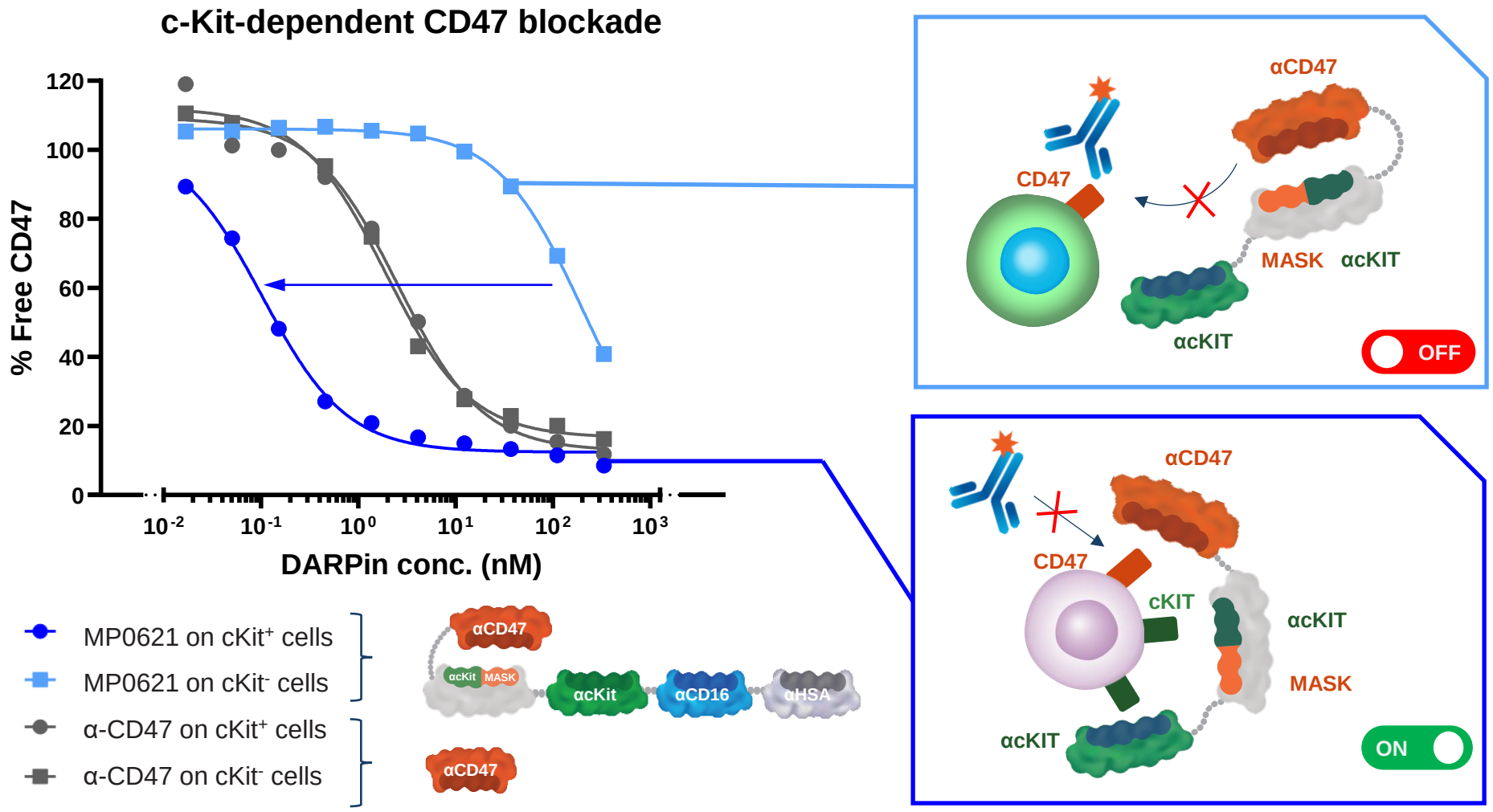
- CD47 is expressed as "do-not-eat-me signal" and prevents killing of HSCs/LSCs[1,3]
- Switch DARPin allows conditional local blocking of CD47 on HSCs/LSCs, prevents peripheral CD47 blockade



MOLECULAR partners

1- Valent et al., Int J Mol Sci 2019, 2- Rev in Kent et al., molecular pathways 2008, 3 - Chhabra, Weissman and Shizuru, STM 2016.
HSC, hematopoietic stem cell; LSC, leukemic stem cell; mAb, monoclonal antibody; MoA, mode of action; MΦ, macrophage.

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



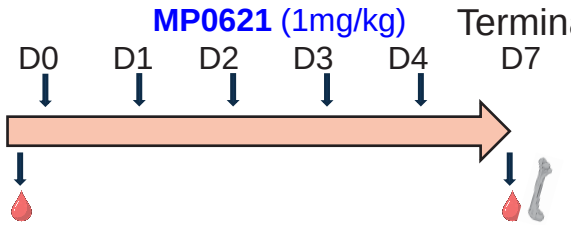
cKit Negative cells
Switch is OFF
CD47 is NOT blocked

cKit Positive cells
Switch is ON
CD47 is Blocked

anti-CD47 detection agent

MP0621 Depletes cKit+ Cells in Bone Marrow Without Affecting Circulating Immune Cells in Humanized Mice

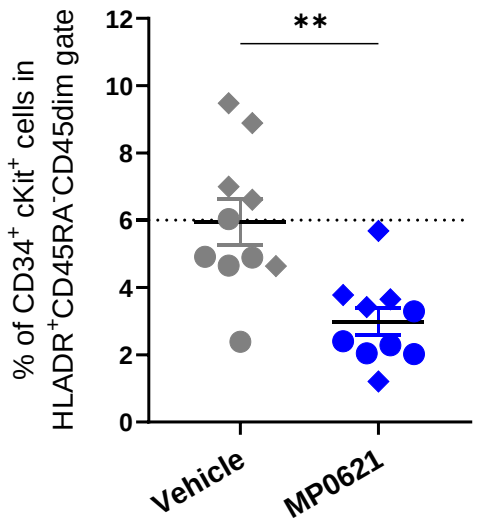
hCD34⁺ NSG mice



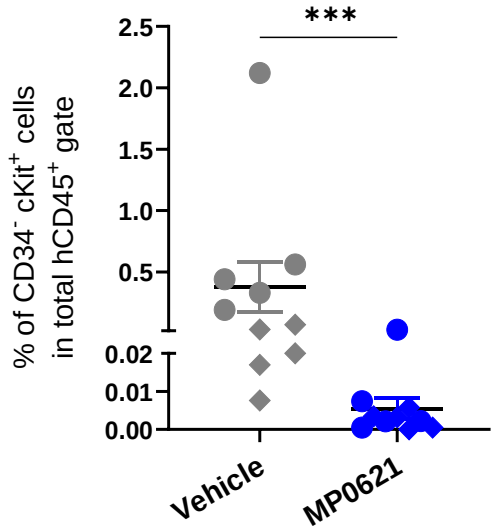
Flow cytometry analysis of blood and BM

Targeted cKit+ cells depleted in bone marrow

hcKit+ hCD34+ cells, incl. HSCs

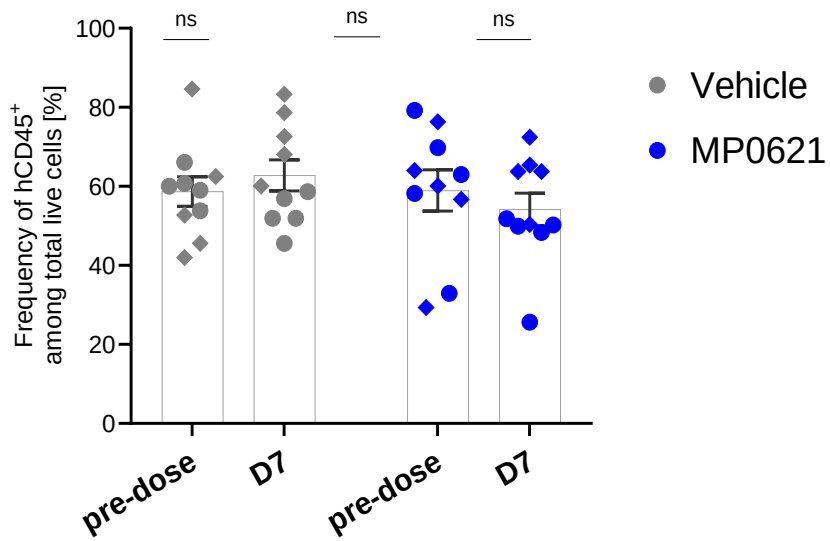


hcKit+ hCD34- cells



Immune cells in blood

hCD45+ immune cells



Link et al, EHA 2024 (poster presentation)