Custom Built Biology for Patients

September 2022

Molecular Partners AG, Switzerland
(SIX: MOLN, NASDAQ: MOLN)

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Molecular Partners H1 Highlights

Science Highlights:

MP0533: Tri-specific T-cell engager for AML

- On track to reach clinical initiation by end 2022
- Presentation at EHA 2022 Congress

MP0317: Bi-specific CD40 local agonist

- In Phase 1 – enrollment ongoing at 1 mg/kg dose level
- Publication in *Cancer Immunology Research*
- Data in H2/2022

Ensovibep: Tri-specific anti-viral in COVID-19

- Positive Phase 2 data from EMPATHY trial
- Licensed to Novartis, CHF 210 million received, to date
- EUA submitted and pending, Novartis engaging with the FDA to develop a Ph III protocol

DARPin-radioligand therapies:

- Deal with Novartis on 2 targets: CHF 18.6 million received, to date
- Internal research – ongoing

Abicipar:

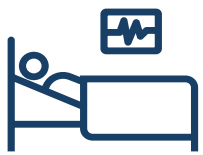
- FDA supports single safety trial for approval
- Reviewing path forward outside MP

Operational Highlights:

- Reported cash and equivalents as of June 30, 2022: CHF ~285 million
- Consistent, disciplined spend rate
  - Runway into 2026

Strategy: Highly Differentiated Programs, True Patient Value

PATIENT VALUE

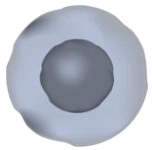


We aim to drive **true patient value** with an **early clinical read-out** by directly changing the course of disease

DARPin ADVANTAGE

We leverage the advantages of **DARPins** to provide **unique solutions** to patients with high medical need, no satisfactory solutions and well-defined disease biology

BIOLOGY



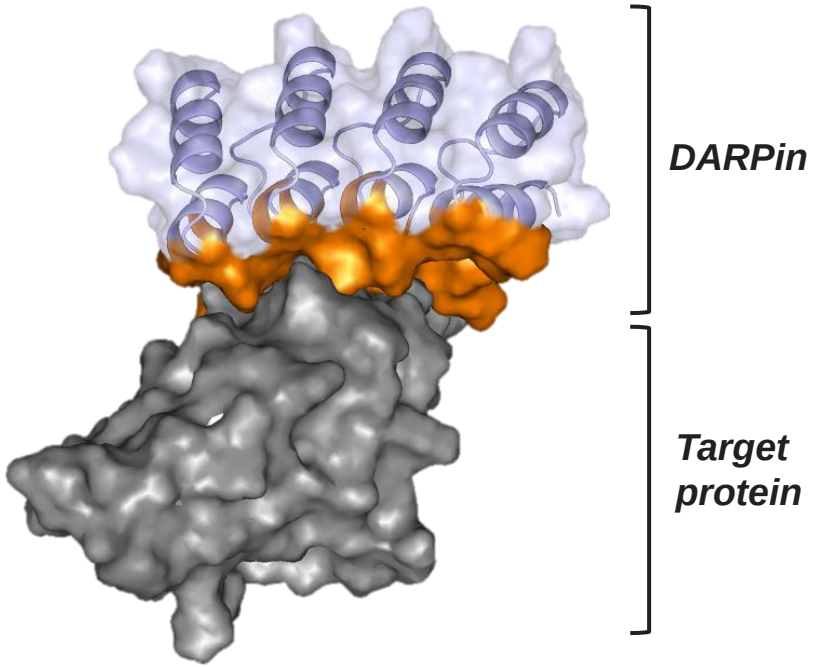
We target **biological hypothesis** that can be tested in relevant preclinical models with translatable value – focus on oncology and virology

PARTNERING

We share an open mindset and **collaborate** with world leading companies, scientists and clinicians from ideation to approval

DARPins: The Core of our Drug Engine

DARPins are binding proteins derived from natural ankyrin repeat proteins



DARPin **KEY PROPERTIES**	DARPin **ADVANTAGE**
Small size (15 kDa)	➢ Deep tissue penetration ➢ High molar concentration
Rigid protein scaffold	➢ Ultra-high binding affinity and selectivity
Simple & robust architecture	➢ Turn-key multispecifics ➢ Easy coupling of payloads

Translating DARPin Properties into Differentiated Therapeutics

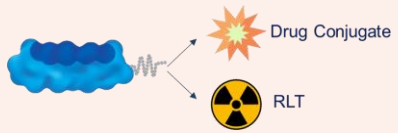
Delivery vectors "radical simplicity"

Multi-specificity-enabled possibilities

Conditional activation "radical complexity"

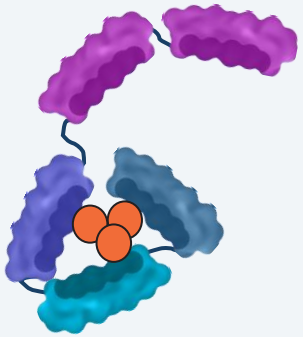
RLT & DDC

Small size: high affinity delivery, limited systemic exposure



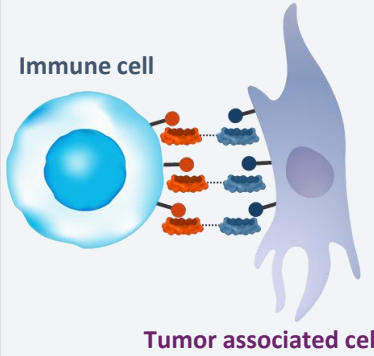
Ensovibep

Cooperative binding to inhibit SARS-Cov-2 and prevent escape



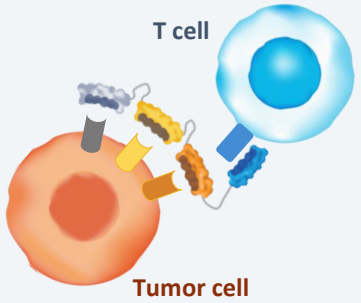
MP0310 & MP0317

Tumor localized clustering activates effector cells in tumor



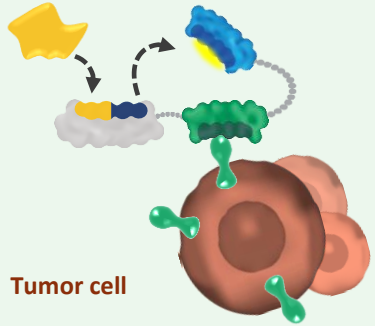
MP0533

Avidity driven TCE for tumor specificity and heterogeneity



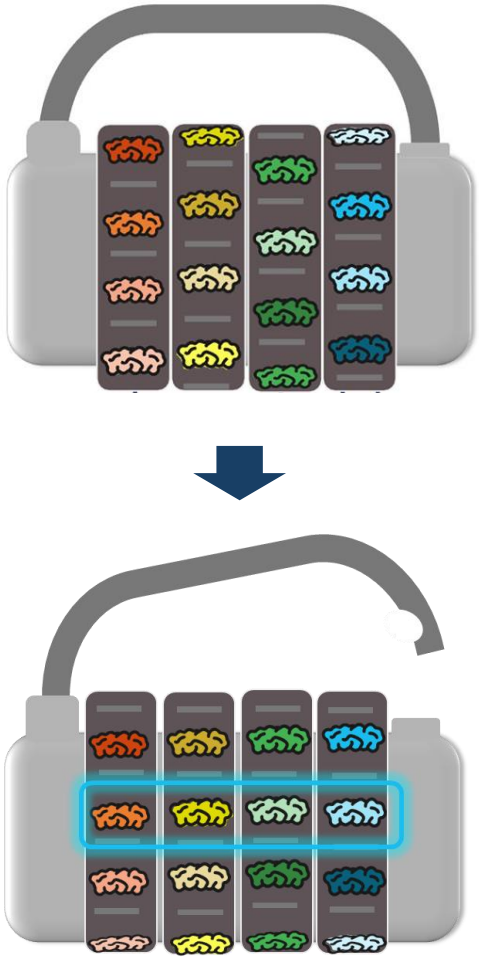
SWITCH

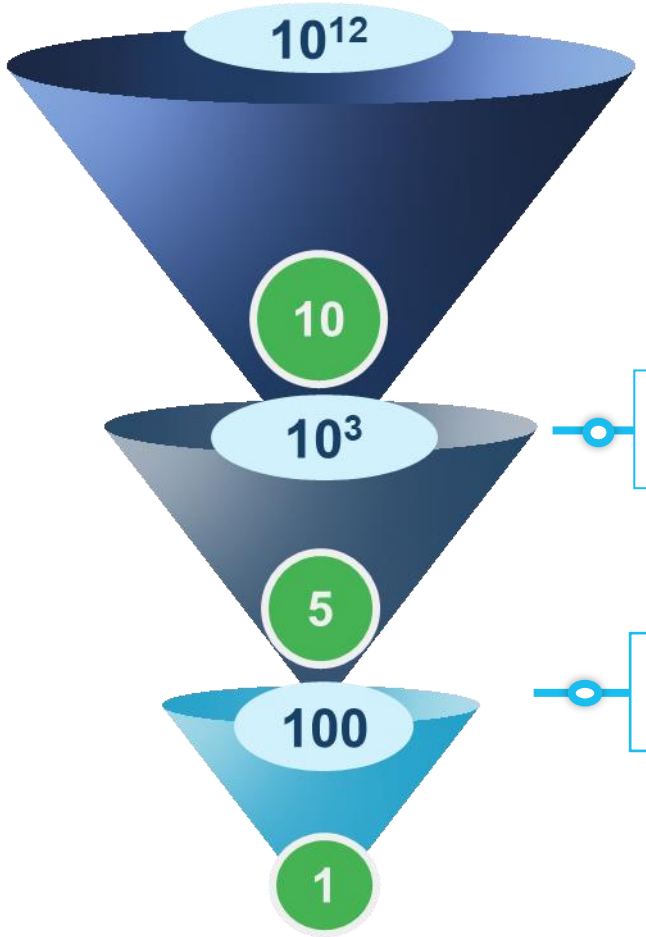
Programming highly potent effectors to omit off-tumor activity



Exploiting the Multi-DARPin Platform

Allows screening for function sweet spot





Library used to generate binders against TAAs
Identified functional DARPin modules to each TAA

Recombination of DARPin modules:
TAA1 x TAA2 x TAA3 x …

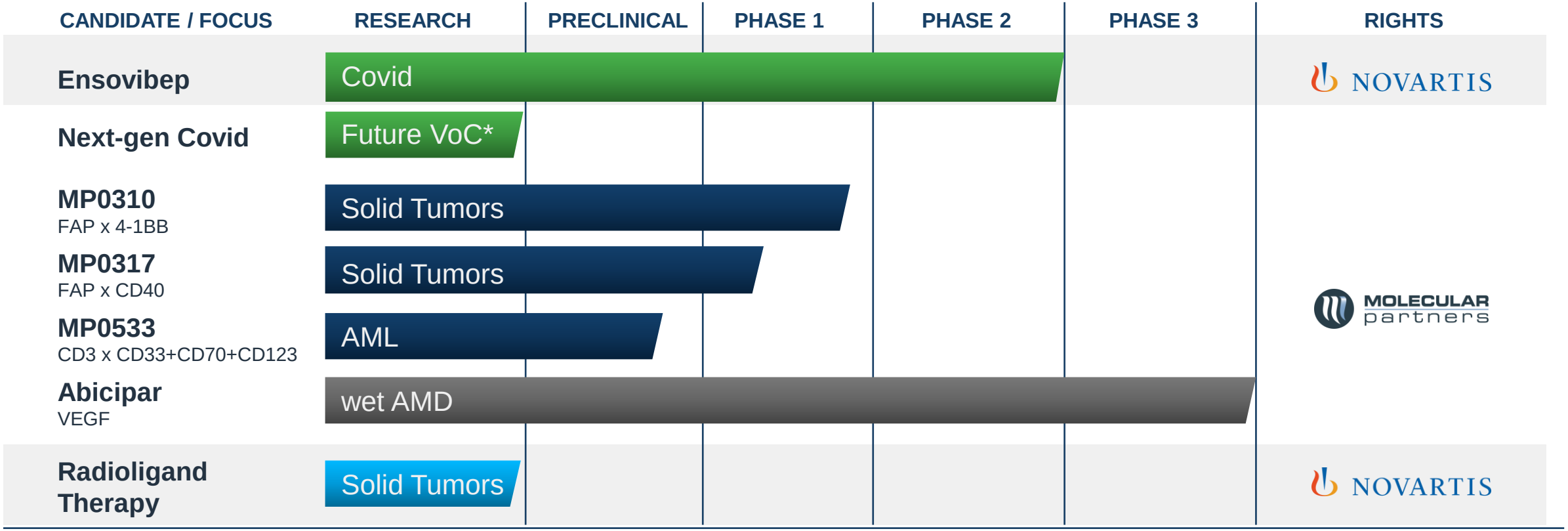
Screening of multi-domain DARPins
Functional Multi-DARPin candidates

Affinity & **format** & **half-life optimization**
Recombination of DARPin modules

Screening of multi-domain DARPins
Multi-DARPin lead molecule

Multiple iterations

Pipeline



PLATFORM DISCOVERY AREAS

Radical simplicity & conditional activation

Additional infectious diseases

Infectious disease
Ophthalmology
Oncology
Discovery oncology

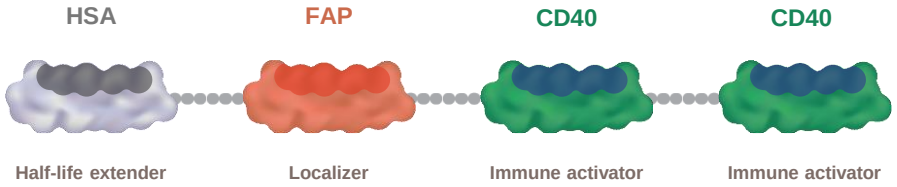
* VoC = Variant of Concern, including the F486V mutation

MOLECULAR
partners

MP0317

Multispecific Immune Activators

MP0317: Localized CD40 Engager



Clinical Problem

- Immune Checkpoint Inhibitors have transformed cancer treatment, yet most patients still fail to respond
  - One cause of resistance or lack of activity is the absence of intra-tumoral immune cell activation
- Current CD40 agonists activate intra-tumoral but also peripheral immune cells, leading to dose-limiting toxicity

DARPin Solution

- **MP0317: Long-acting DARPin co-targeting both FAP and CD40**
  - FAP is a stromal target stably expressed at high density in various tumors and absent systemically
  - CD40 requires multimerization for its activation
- **MP0317 aims for FAP-dependent CD40 multimerization for intra-tumoral immune activation w/o systemic tox**

Reason to believe

- ✓ Pre-clinical data demonstrates tumor localized immune activation without systemic toxicity
- ✓ Clinical data with MP0310 (FAPx4-1BB) demonstrating tumor localization of FAP-targeting DARPin
- ✓ Phase 1 dose-escalation trial ongoing with MP0317 – **1 mg/kg dose reached without systemic toxicity**

Next value

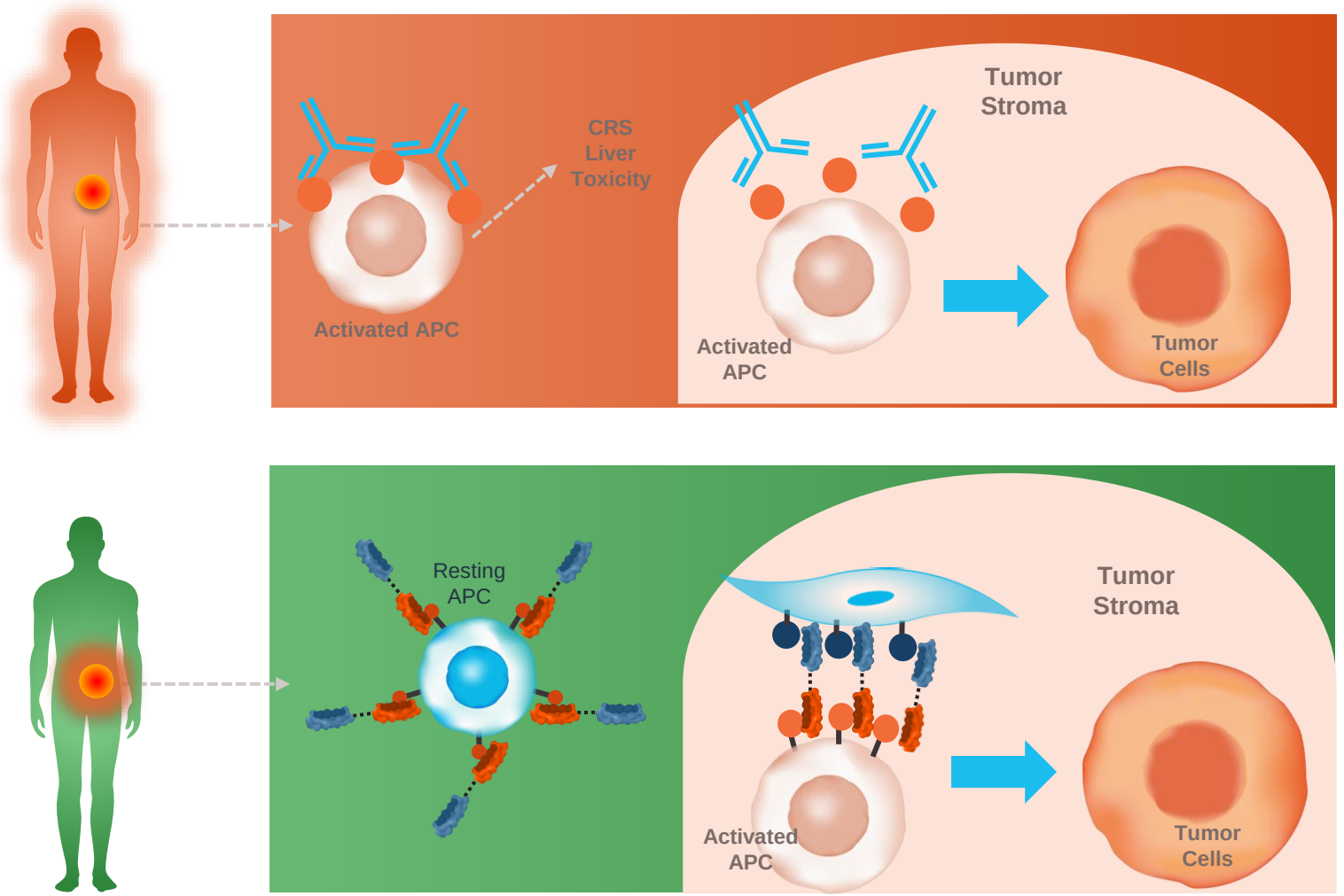
- PD markers from paired biopsies to demonstrate tumor local immune cell activation (Q1/23)
- Partnering for combination trials (H1/23)

Toxicity of CD40 antibodies has so far limited their activity

Systemic Immune activation of APC
leads to **toxicity**

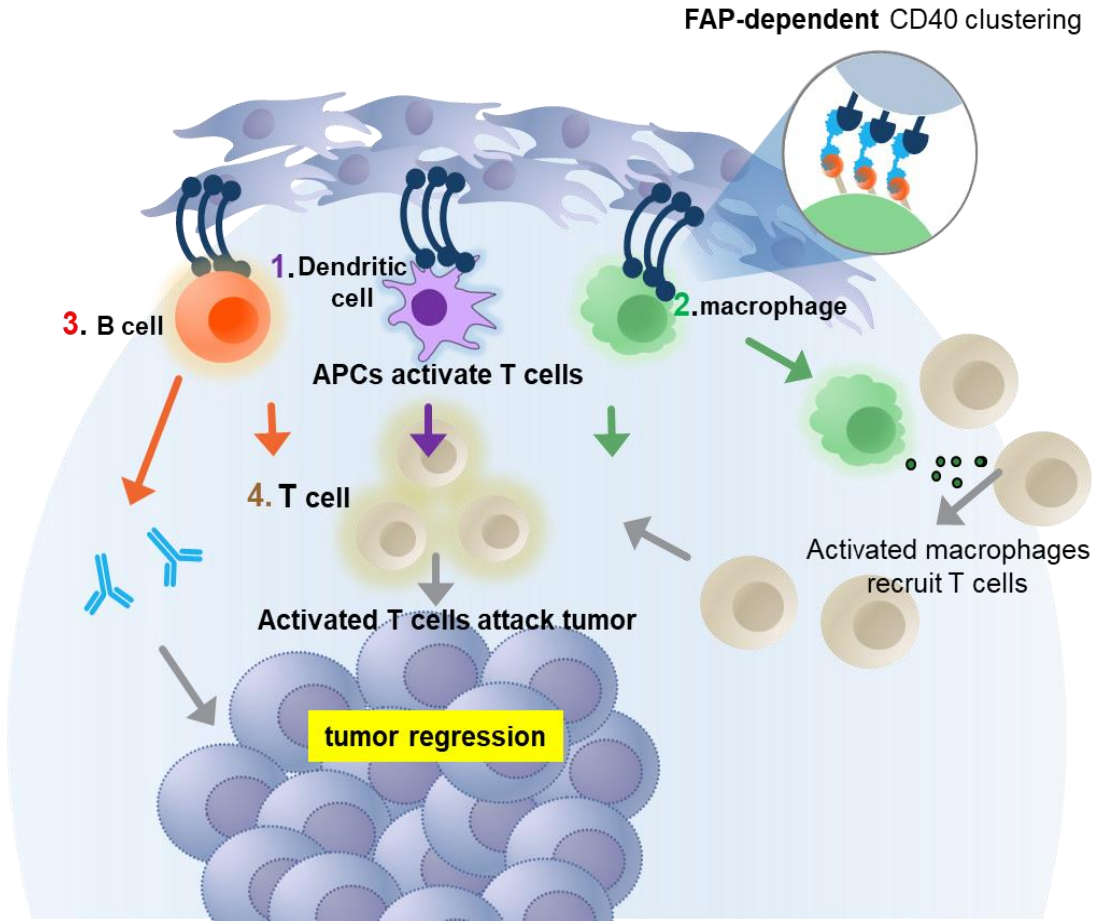
Low MTD

Our solution:
Increasing therapeutic window via a tumor-localized approach



MP0317's Potential Promise

- **CD40 is a clinically validated target** involved in activation of antigen presenting cells (APCs)
- **MP0317 holds the promise to overcome limitations of systemic CD40 agonists** and expand therapeutic window
- **Limited direct competition** (most assets still systemic)
- **Supportive preclinical package** with single agent efficacy in a mouse FAP^{high} tumor model
- **Encouraging early safety data supportive of partnering for combination therapies**



CD40 Open for Multiple Combination (IO or Other)

+ Chemo / Radio Therapy

- Direct **tumor killing**
- Release of tumor **antigens**
- Debulking aids **immune cell access**

+ Anti-cancer vaccines (intratumoral)

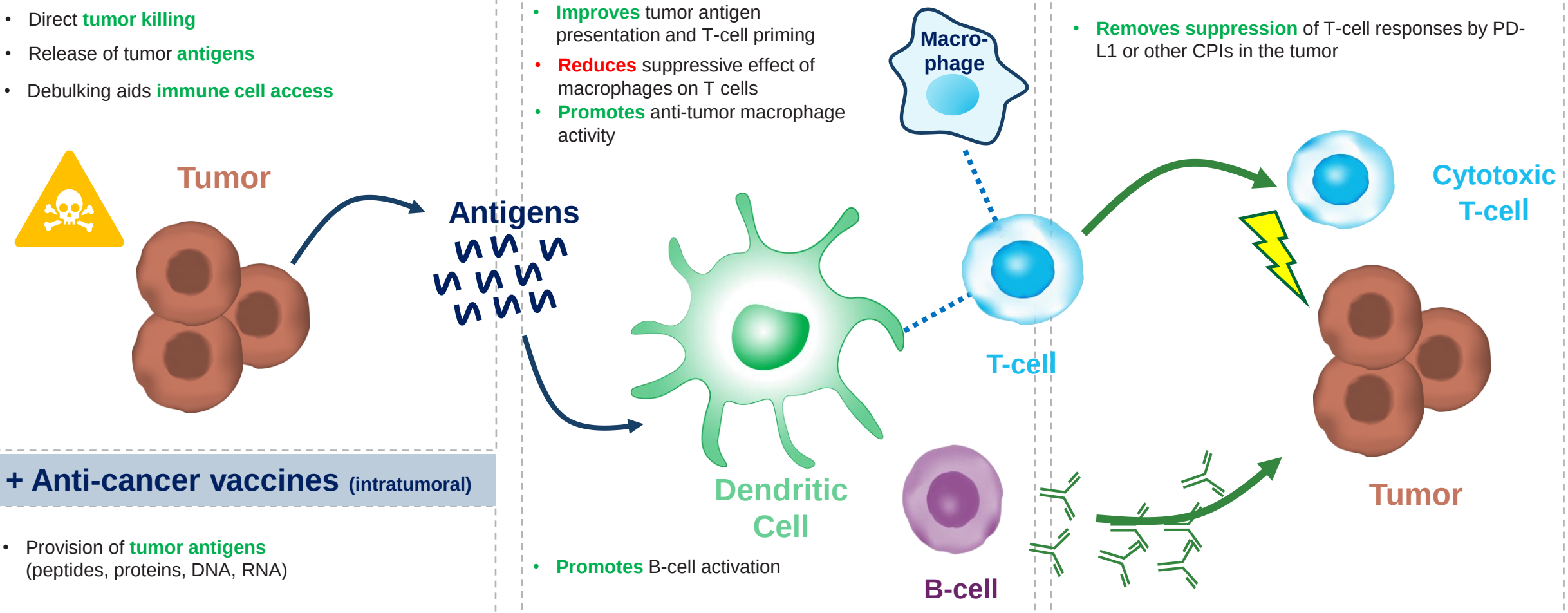
- Provision of **tumor antigens** (peptides, proteins, DNA, RNA)

CD40 agonism

- **Improves** tumor antigen presentation and T-cell priming
- **Reduces** suppressive effect of macrophages on T cells
- **Promotes** anti-tumor macrophage activity
- **Promotes** B-cell activation

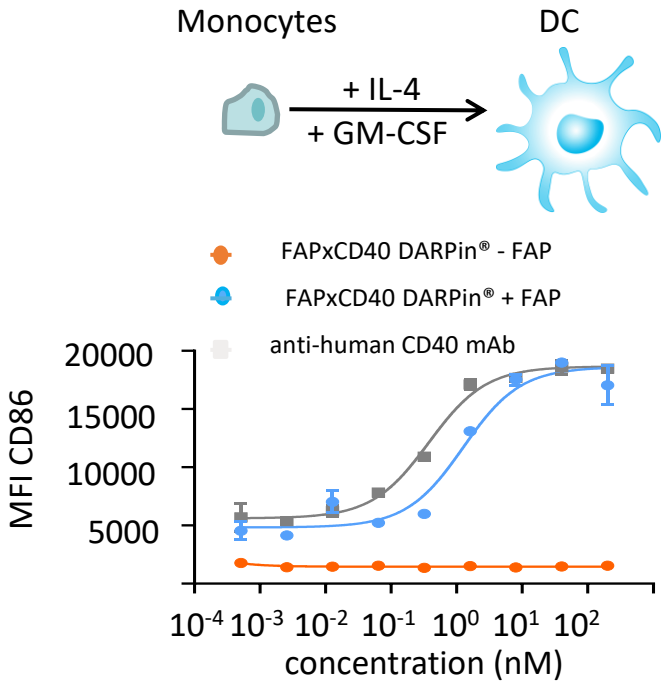
+ PD(L)-1 blockade or other CPIs

- **Removes suppression** of T-cell responses by PD-L1 or other CPIs in the tumor

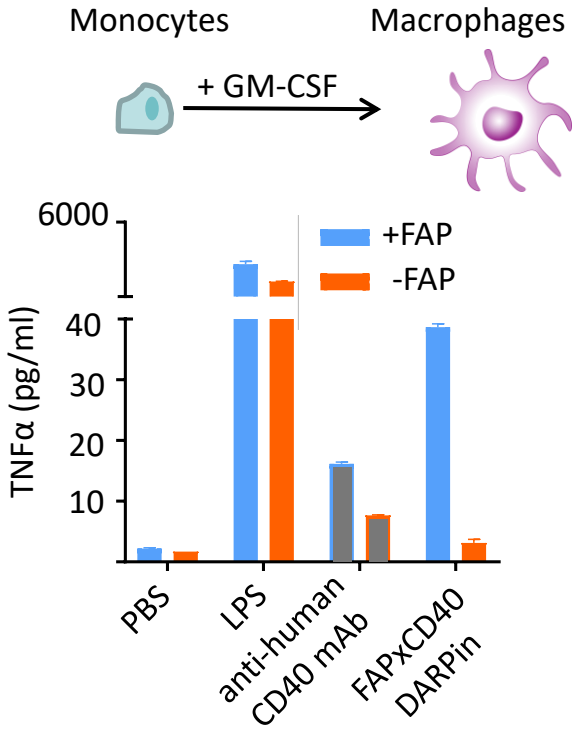


MP0317 Activates all APCs in a FAP-Dependent Manner *in vitro*

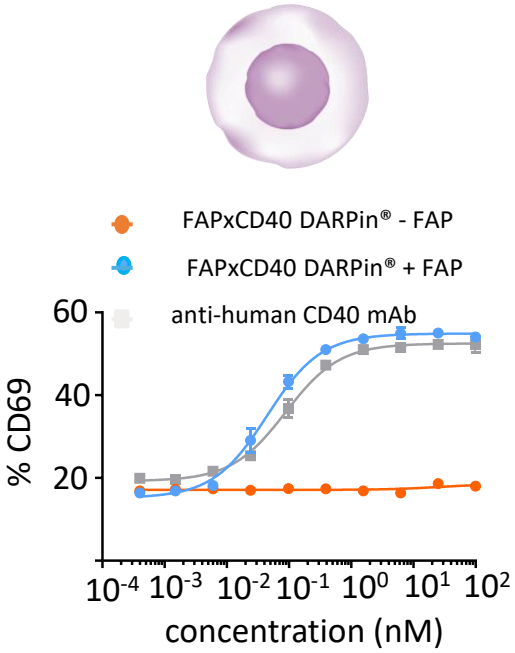
1 **Dendritic cells**:



2 **Macrophages**:

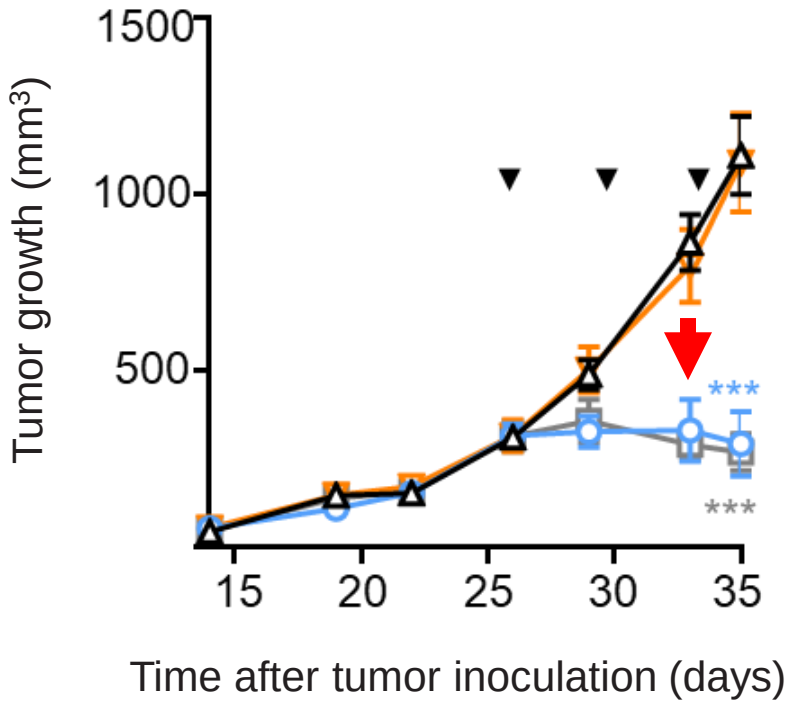


3 **B cells**:

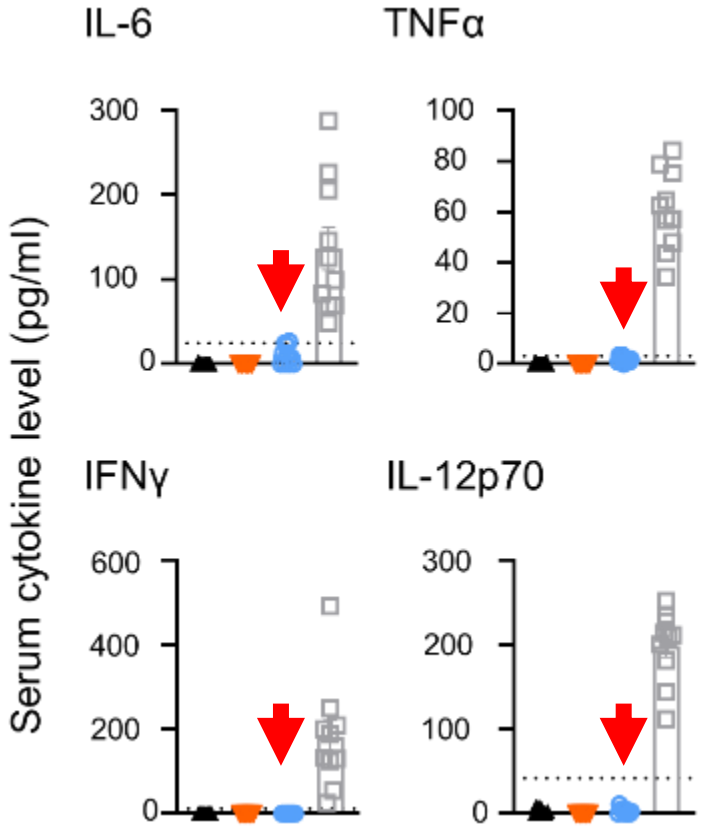


MP0317 Shows Therapeutic Activity without Cytokine Release

Efficacy



Peripheral cytokine release



Vehicle

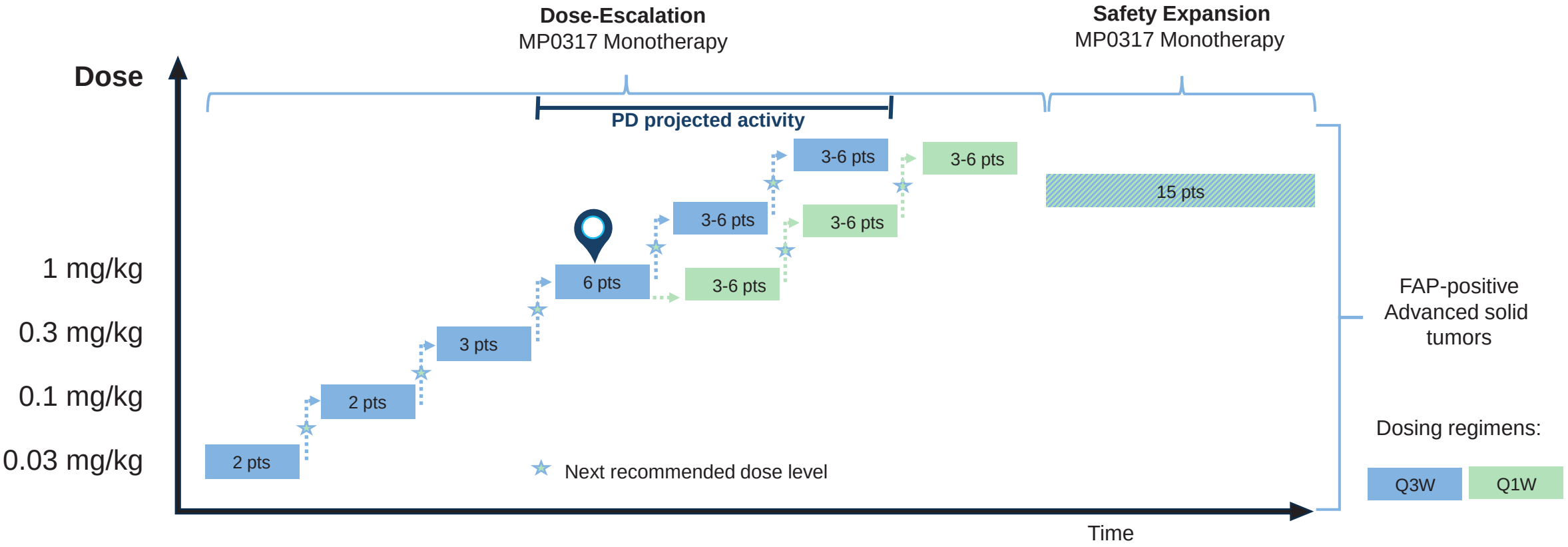
Neg. CTRL*

mFAP x mCD40

mCD40 Ab

MC38-FAP
Colorectal cancer

MP0317-CP101 Clinical Trial Update



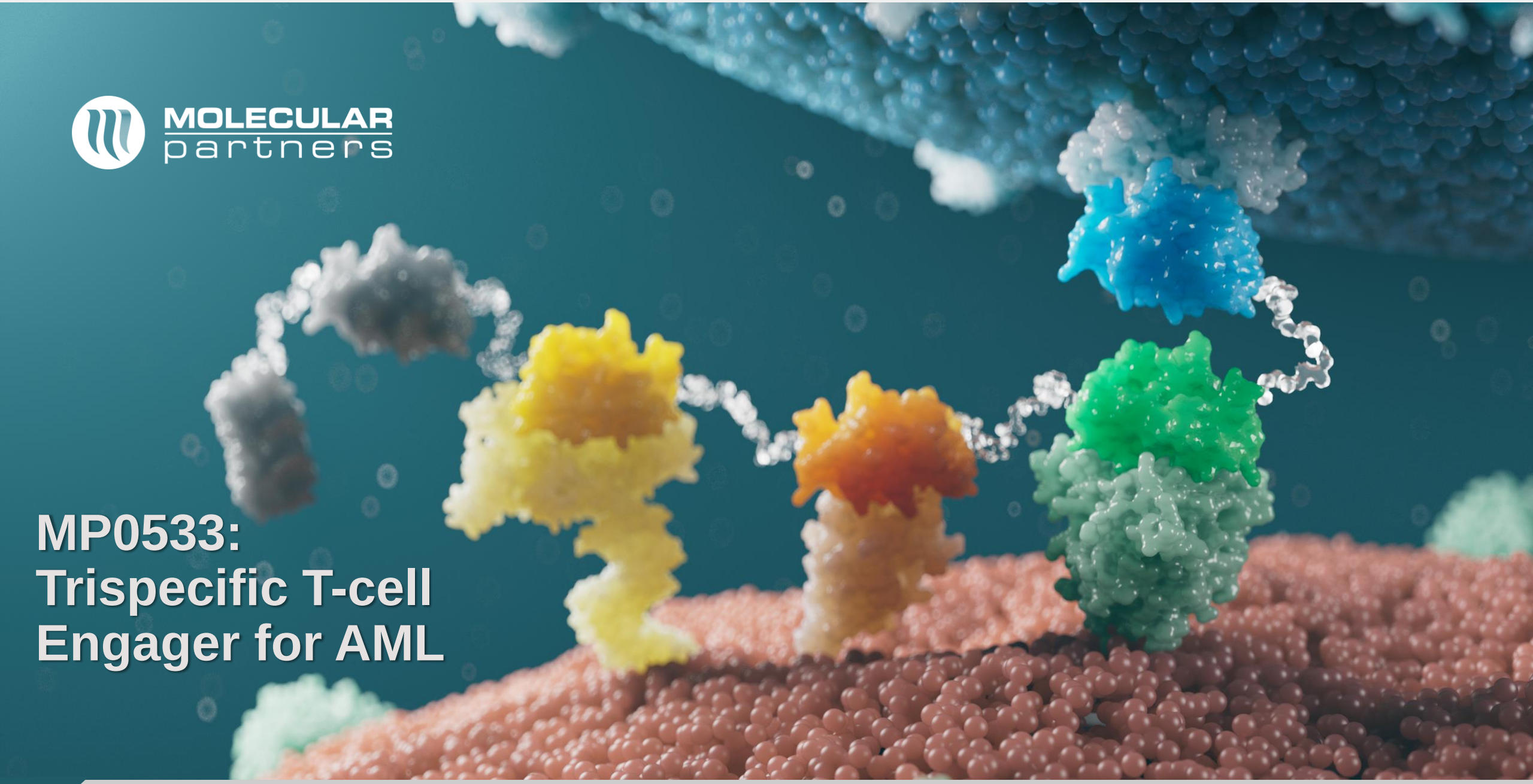
Next:

- Communication of emerging clinical data in H2/22
- PD data on tumor-immune activation expected Q1-23
- Select partners for combination trials

Recruiting at 1 mg/kg dose

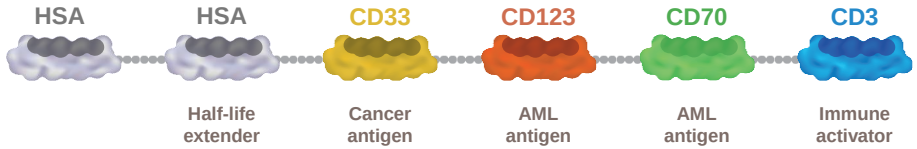
MP0317 Status Update and Next Steps

- Ongoing Phase I dosing escalation, expected to be completed in Q4 2022
  - No DLTs / drug-related SAEs up to Cohort 4 (1 mg/Kg)
  - Initiating weekly dosing in parallel to every-3-weeks
- Submitted for scientific presentation in H2
- Establish ideal combination partners for phase II



MP0533: Trispecific T-cell Engager for AML

MP0533 – Avidity-driven Selective Killing of Blasts & LSC in AML



Clinical Problem

- AML remains a deadly disease for most patients, especially non-transplant eligible ones
- Leukemic stem cells (LSCs) play a key role in initiating and sustaining AML, while blasts drive disease intensity
- LSCs are less sensitive to chemo and their selective targeting is a challenge, lack of selective markers

DARPin Solution

- **MP0533: DARPin binding to CD33xCD70xCD123 (optimized affinity) and CD3 (T-cell activation)**
  - Blasts and LSC co-express CD33, CD70 and CD123, while healthy cells (HSC) show mostly mono-expression
  - Killing of cells that co-express 2 or more targets, while mono expressing cells are spared
- **MP0533 is designed to preferentially kill Blasts and LSCs, opening a therapeutic window**

Reason to believe

✓ Preclinical results from cell-based and animal models demonstrate MoA described above

✓ *Ex-vivo* patient samples: preferential killing of LSCs & Blasts (potentially to open therapeutic window)

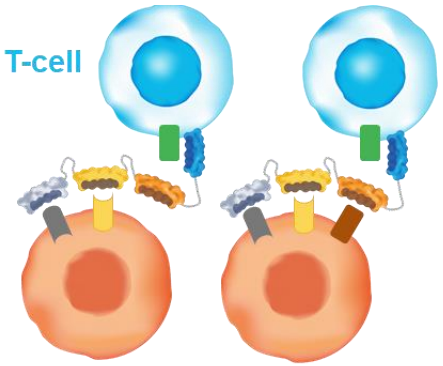
Next value

- FIH clinical studies initiating in H2/2022, mono-activity expected

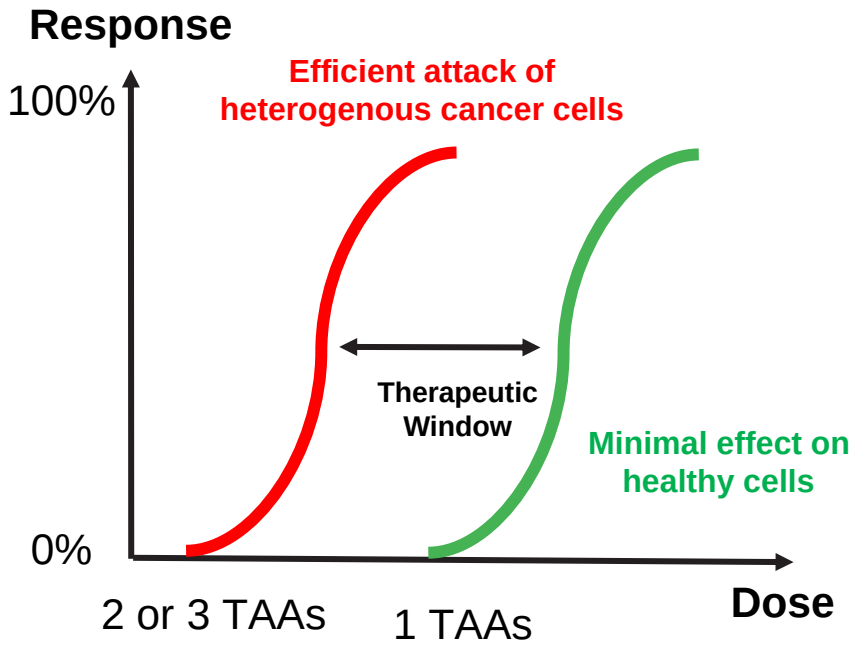
Avidity-Driven Specificity Against Leukemic Stem Cells and Blasts in AML

- Persistence of LSCs is the driver of relapse in AML
- Targets in AML are also on healthy cells, leading to on-target toxicity (unclean targets)
- Goal: avidity-driven killing of LSCs and blasts, with reduced killing of HSCs and other healthy cells

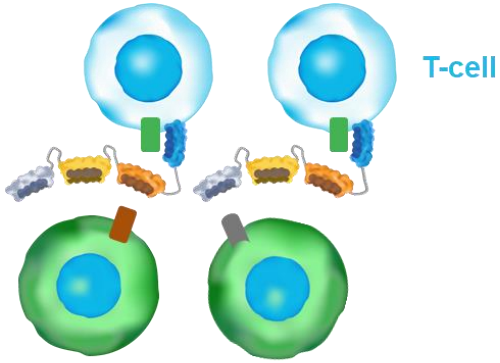
Multiple targets
High avidity engagement



Malignant cell
LCSs or blasts



Single targets
Low affinity engagement



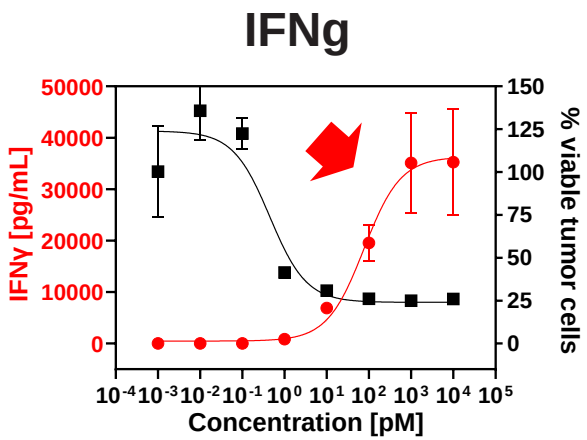
Healthy normal cell
HSC or myeloid cells

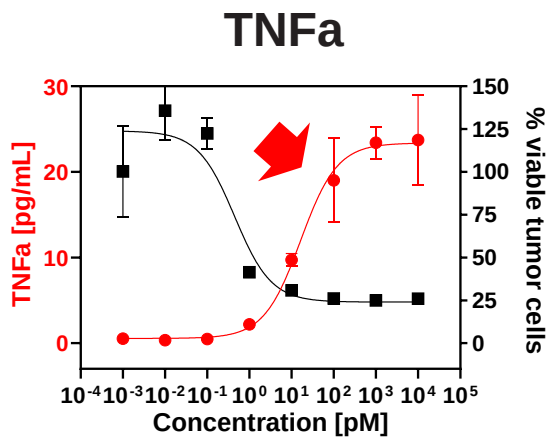
Low Cytokine Release Under ‘Close-to-patient’ Conditions

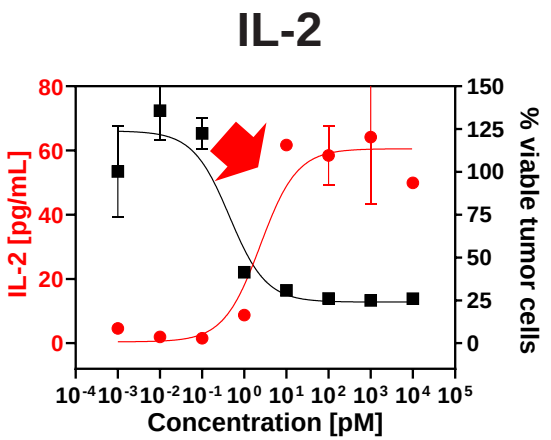
Primary autologous setting

- Primary AML BMMCs (bone marrow mononuclear cells) with 80% blast content in bone marrow (E:T of ≈1:20); 5-day assay

CD123-CD3 DART



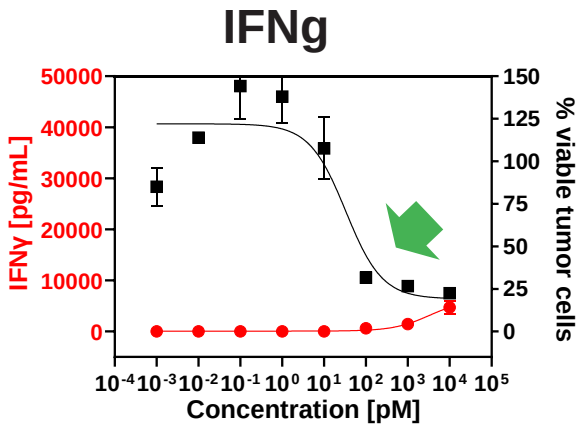


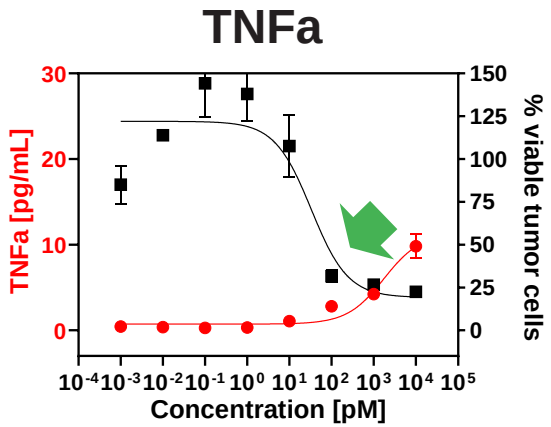


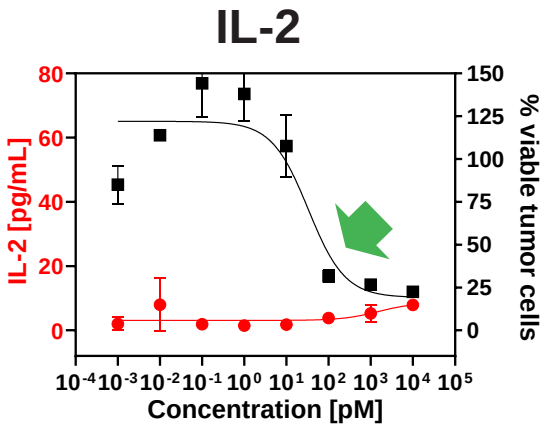
Cytokine release

Tumor cell killing

MP0533



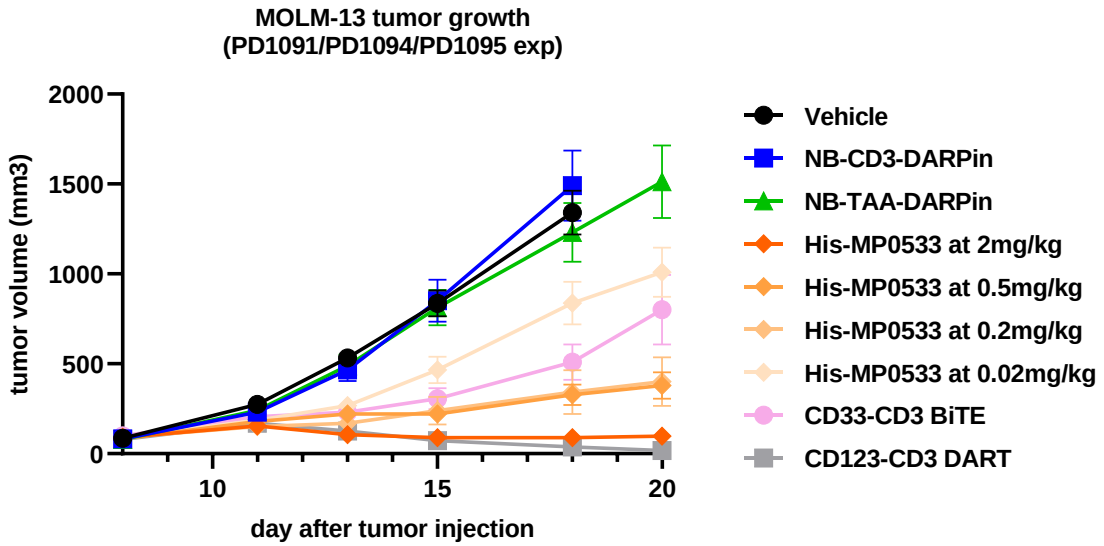


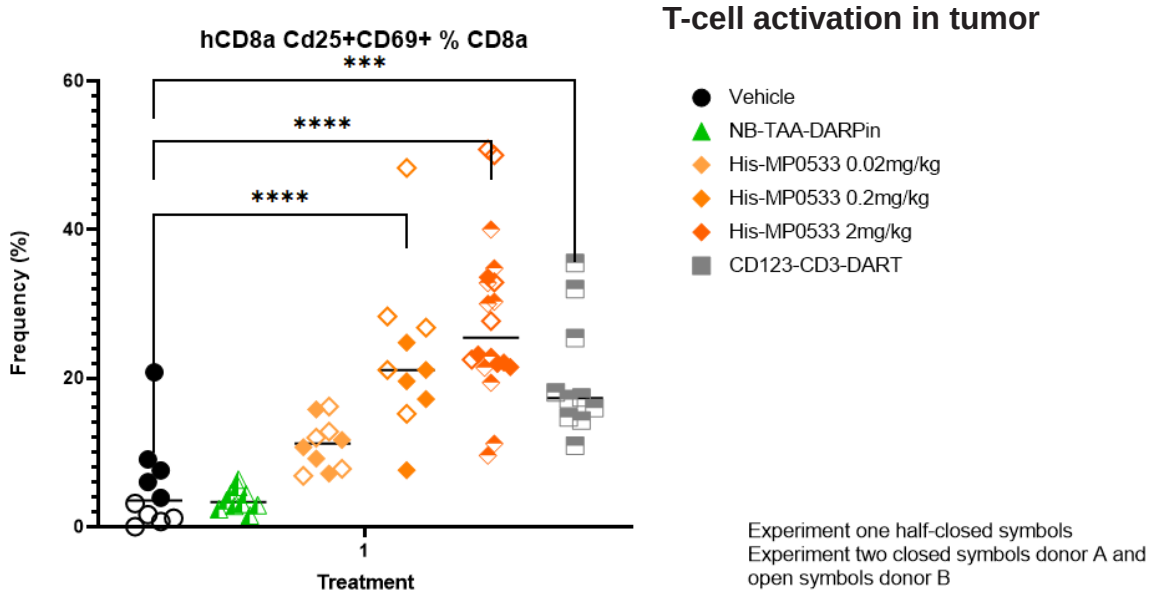


Note: very low cytokine levels for MP0533 in this assay are likely also dependent on low T-cell count *in autologous AML samples (higher cytokine levels were measured in assays with cell lines and higher E:T)*

Good *in-vivo* efficacy of His-MP0533* in AML tumors

In vivo efficacy in line with competitors



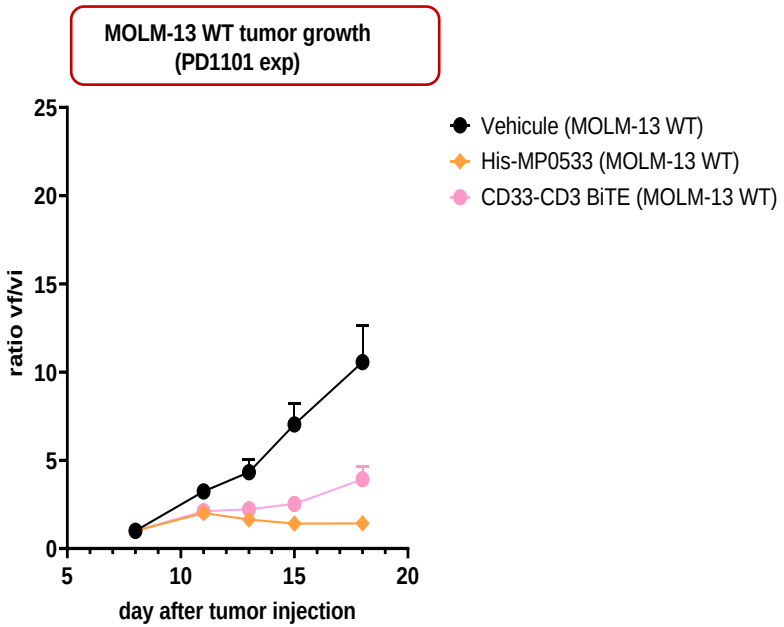


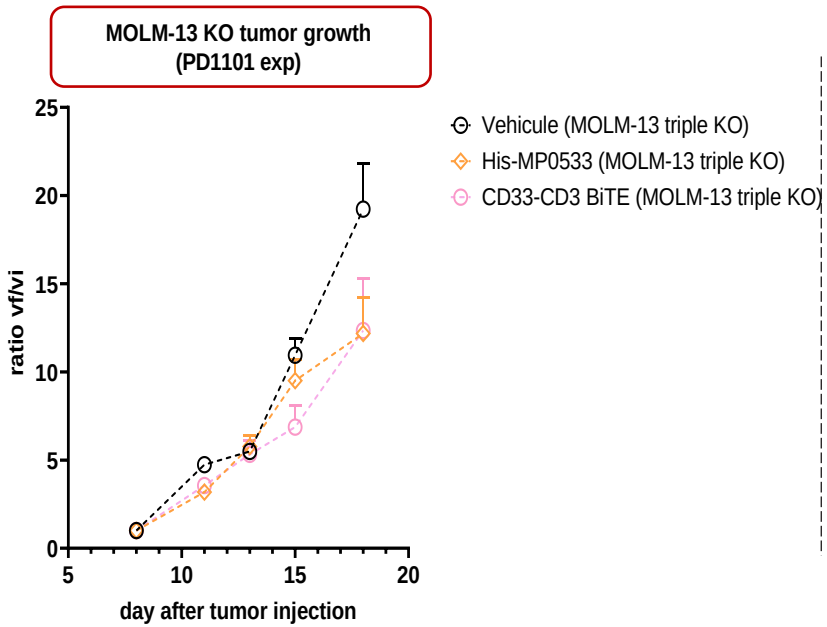
- ✓ His-MP0533 showed a significant efficacy in MOLM-13 WT tumors
- ✓ His-MP0533 induced T-cell activation in MOLM-13 tumors. Level of T-cells activation correlated with His-MP0533 efficacy *in vivo*.
- ✓ No increase of cytokines/chemokines released in mouse serum - only in tumors.
- ✓ Level of cytokines/chemokines release correlate with His-MP0533 efficacy and T-cell activation in tumors only.

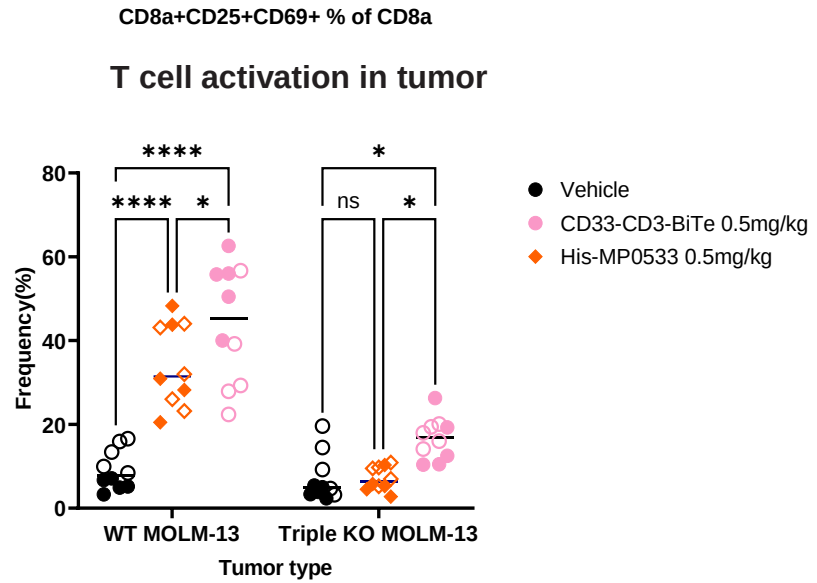
**His-MP0533 has a 6x His-tag attached during the research stage*

No Off-target Killing *in vivo*

In vivo selectivity to TAA-expressing MOLM-13 tumors







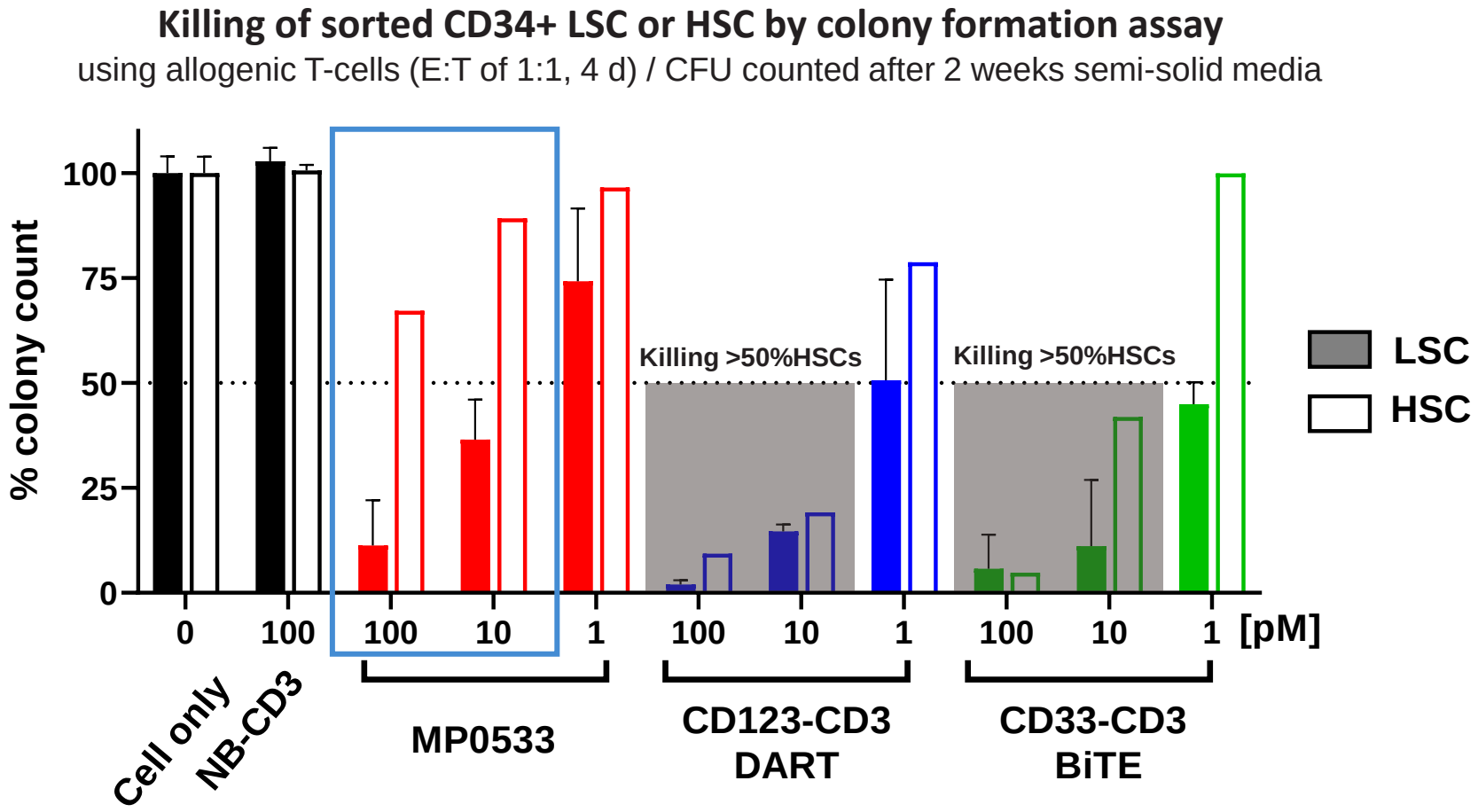
✓**His-MP0533 showed a significant efficacy in MOLM-13 WT (wild-type) tumors**

✓**But no efficacy in MOLM-13 triple KO (knock-out) tumors (growing on the same mice)**

✓**His-MP0533 induced T-cell activation only in MOLM-13 WT tumors (expressing 3x TAAs)**

MP0533 Shows Larger Therapeutic Window
Compared to CD123-DART and CD33-BiTE

Successfully killing leukemic stem cells (LSC, full bars) while sparing hematopoietic stem cells (HSC, empty bars) *in vitro*



MP0533 Phase 1: Open Label, Multicenter Dose Escalation Study in AML or HR-MDS Patients

Main inclusion criteria:

- Diagnosis of AML or MDS/AML according to the ELN recommendation 2022 refractory or relapsed to pretreatment with HMA (with or without venetoclax), induction chemotherapy or allogeneic HSCT
  - No active active GvHD requiring immune-suppressive therapy
  - No signs of CNS AML
  - No leucostasis
  - No use of immunosuppressive drug
- Number of patients: 20-45

Primary endpoint:

- Safety and Tolerability

Main secondary/ exploratory endpoints:

- Efficacy
- Pharmacokinetics
- T-cell Activation
- Cytokine Release
- Effect on LSCs

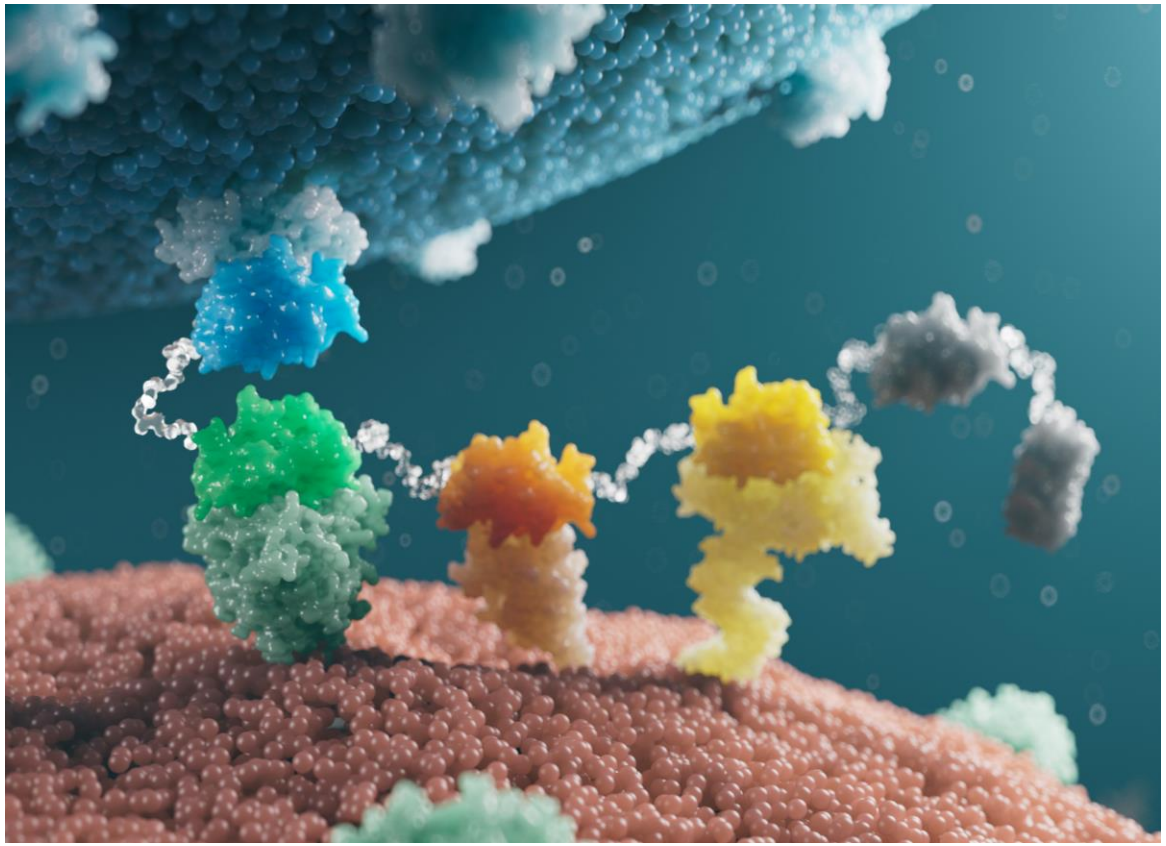
Trial initiation planned for late 2022

Abbreviations: AML = Acute myeloid leukemia; HR-MDS = high-risk myelodysplastic syndrome; ELN = European LeukemiaNet; HMA = hypomethylating agents; HSCT = Hematopoietic Stem Cell Transplantation ; GvHD = graft vs host disease; LSC = leukemic stem cells;

MP0533: a Unique DARPin Solution for AML Patients

- ✓ **Very good progress on translational data generation path**
- ✓ **Advanced clinical interactions with KOLs and CROs will enable timely protocol completion and submission**
- ✓ **Progress requirements met:**
  - Critical data on MoA, safety & efficacy
  - TPP refinement
  - Biomarker plan
  - Competition analysis
  - CMC feasibility

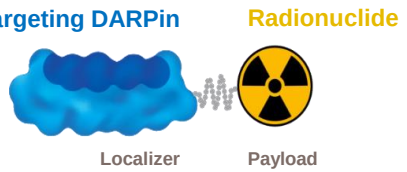
➢ **Phase 1 clinical trial initiation H2 2022**



MOLECULAR partners

DARPin Radio-Ligand-Therapy (RLT) and DARPin Drug-Conjugates

DARPin-based Radioligand Therapy (RLT)



Clinical Problem

- Radiation provides a highly effective way to kill tumor cells
  - External beam radiation is successful, however limited to well-localized tumor lesions
  - The delivery of therapeutic radionuclides by tumor-targeting vectors is a powerful methodology for the treatment of disseminated cancers, but is restricted by either low tumor accumulation and/or dose-limiting toxicities

DARPin Solution

- **Small, mono-DARPin with ultra-high affinity to a tumor-associated antigen, coupled to a radionuclide**
  - **High tumor accumulation, limited systemic exposure, deep tumor penetration and long tumor retention**
  - Generation of optimized DARPin platform with **limited kidney toxicity**

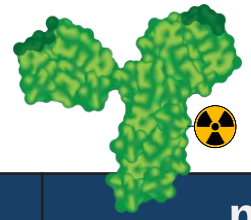
Reason to believe

- ✓ Affinity driven tumor accumulation of small-sized / ultra-high affinity mono-DARPins in mouse tumor models
- ✓ Ongoing collaboration with Novartis, a leader in RLTs: US$20 million up-front

Next value

- Optimize RLT-DARPin platform for limited kidney exposure
- Validate DARPin RLT potential and select first drug candidate(s)
- Novartis: US$560 million milestones, up to double digit royalties if drugs receive market authorization

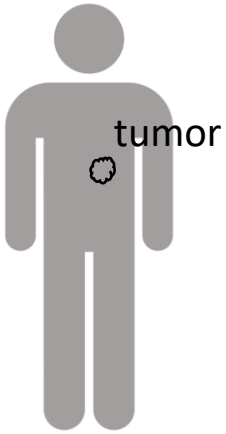
Challenges of Delivery Vectors for Radionuclides



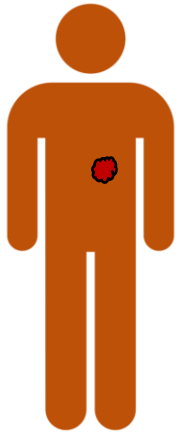
	mAB	LMW compounds
Size	150 kDa	1-2 kDa
Affinity	high (bivalent)	low
Specificity	high	limited
High tumor load ➢ concentration at site of action	+	+
Deep tumor penetration ➢ access site of action	-	+
Long tumor retention ➢ maintenance at site of action	+	-
Limited normal tissue exposure ➢ improved safety profile	-	(+)

Mono-DARPins as Ideal Delivery Vectors for Radionuclides

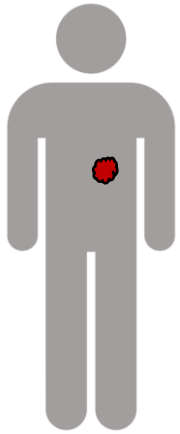
Designed for efficient tumor targeting with limited systemic exposure

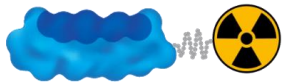


Drug infusion



Infusion stopped





Small size (15 kDa)
fast extravasation &
deep tumor penetration

Homogeneous **access to tumor cells** for killing

Small size (15 kDa)
rapid systemic
clearance

Limited normal tissue exposure for **improved safety**

High affinity (< 50 pM)
long tumor retention

Maintenance on tumor for **complete local killing**

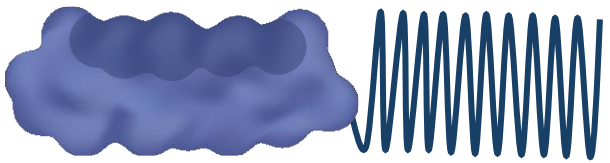
Abicipar

Abicipar – Long-acting Anti-VEGF in Wet AMD

- **wAMD market & remaining medical need**
  - US 10 bn$ /year
  - Competitors: Eylea & **Faricimab** – fix 8 weeks, treat and extend (T&E) to 16 week
  - T&E is sub-optimal in the real-world setting: patients lose vision

- **Abicipar history, value and path forward**
  - Abicipar has two successful Ph3 trials (Cedar, Sequoia; 2019); non-inferiority with 12-week dosing
  - Abicipar was returned to MP last year (2021), following an FDA CRL in 2020 (15% inflammation)
  - Potential inflammation causing agent identified in preclinical studies and to be removed for future clinical studies (2021/22)

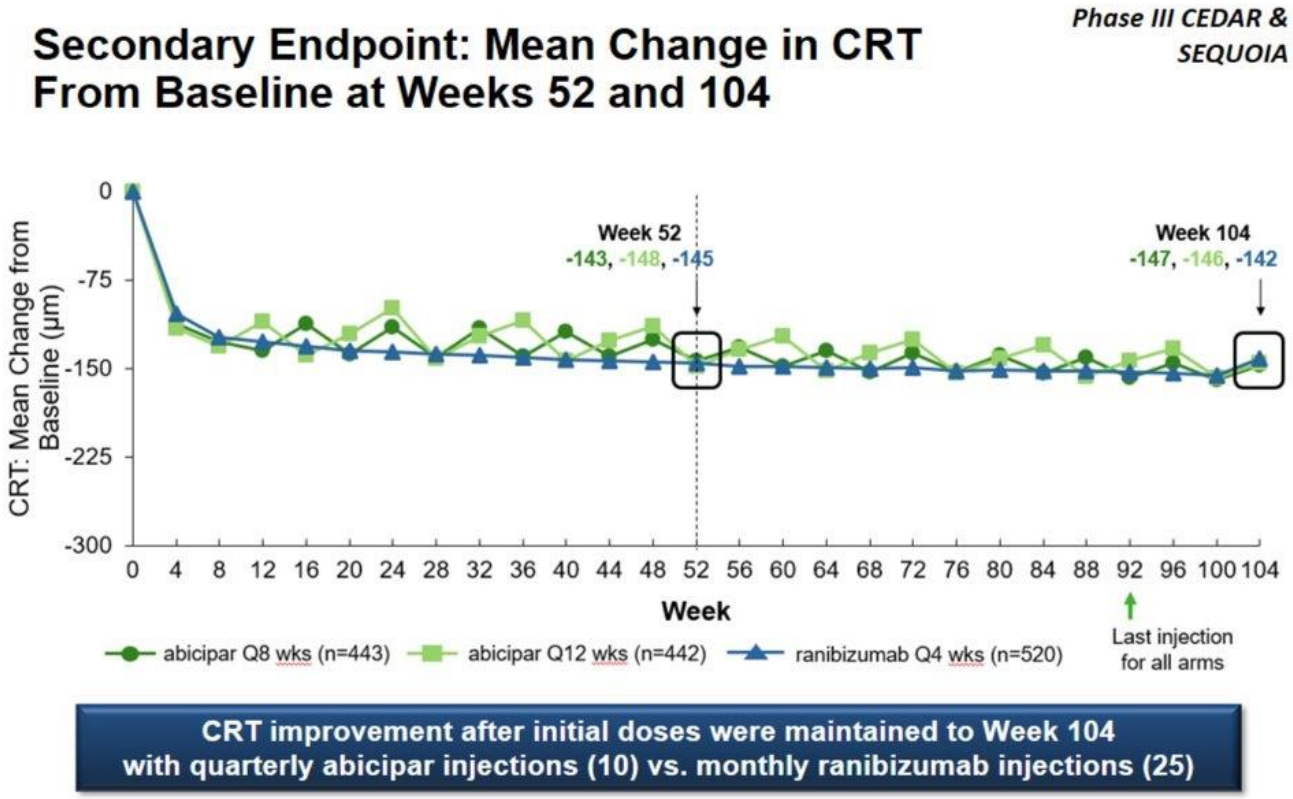
- **Path forward: FDA supports single safety trial as path to approval**
  - Single safety trial vs Eylea
  - 550 pts total
  - 40 week read out



Anti-VEGF DARPin

PEG

Abicipar Non-inferiority Shown in CEDAR & SEQUOIA (Phase 3)



CRT = central retinal thickness

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

- Abicipar as effective as Lucentis
  - 10 injections instead of 25 (2 y)
  - CRT “biomarker” for activity
- Fixed Q12w regimen proven
  - Potential to simplify visits
- Side effect profile (15% inflammation) lead to CRL
- **Potential inflammation causing agent identified and to be removed**

exploring opportunities to develop Abicipar outside MP

Summary and financial guidance

H1 2022 Financial Highlights

- Strong financial position with CHF 285.1 million in cash (including short term deposits) as of June 30, 2022
- Revenue of CHF 184.5 million primarily due to payment received from Novartis upon exercise of option to in-license global rights to ensovibep
- Net cash from operating activities of CHF 151.0 million in H1 2022
- Operating profit of CHF 146.3 million and net profit of CHF 148.6 million in H1 2022
- Company expected to be funded into 2026, excluding any potential payments from R&D partnerships
- Updated FY 2022 expense guidance of CHF 70-80 million
- 3.5 million treasury shares created on Aug 25, 2022

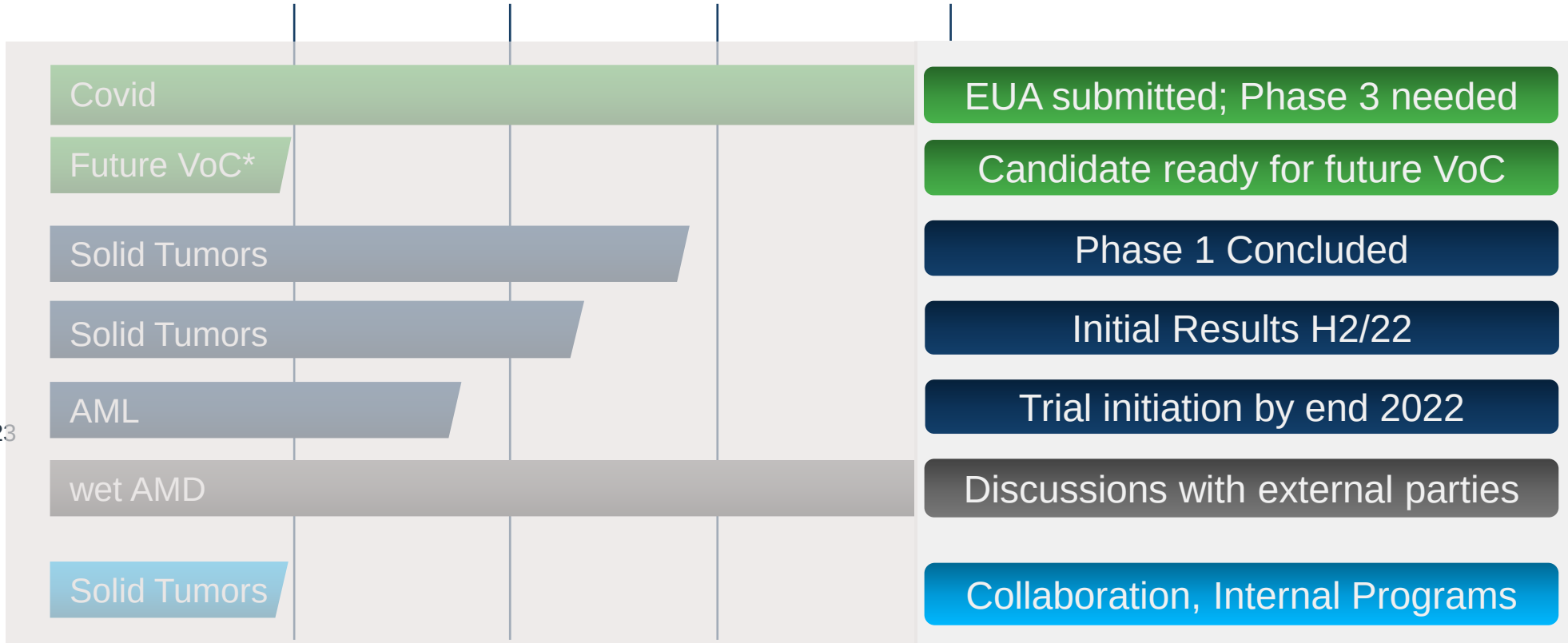
Financial Guidance for Full-Year 2022

- Total expenses of CHF 70-80 million for FY2022,
  of which around CHF 9 million non-cash effective costs

- With CHF 285.1 million cash at hand (incl. short-term time deposits) and no debt, the Company is funded into 2026, excluding any potential receipts from R&D partners

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

Summary and H2 Newsflow



Infectious disease
Ophthalmology
Oncology
Discovery oncology

Cash into 2026

* VoC = Variant of Concern, including the F486V mutation

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