

Molecular characteristics of MP0712, a clinical stage ^{212}Pb -based Radio-DARPin candidate for targeted anti-DLL3 radiotherapy of small cell lung cancer (SCLC)

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Disclosures

- This research was funded by Molecular Partners and Orano Med
- All authors & the presenter are employees of Molecular Partners or Orano Med
- Val Nassiri is employee and stock owner of Molecular Partners

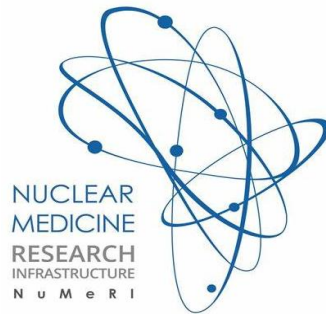
Acknowledgments



We thank the entire teams at Molecular Partners and Orano Med

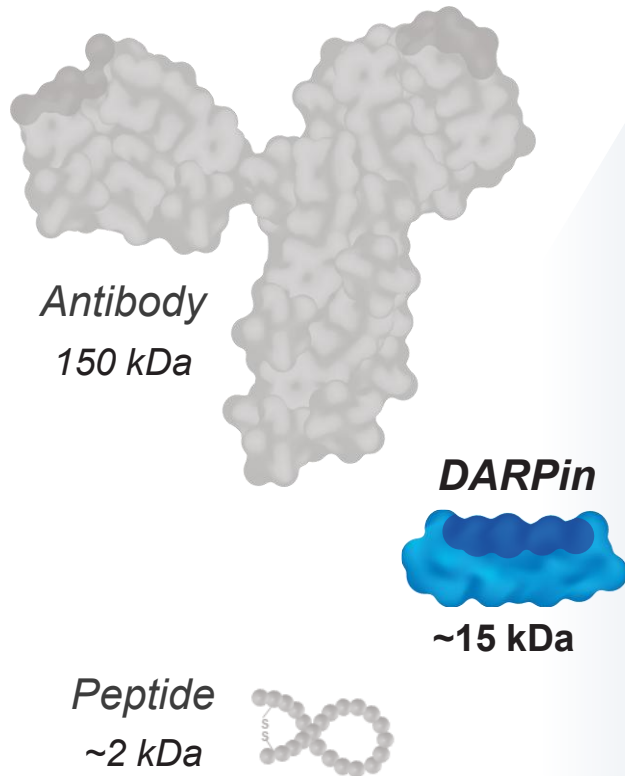
NuMeRI Team

Mike Sathekge
Joseph Kabunda
Honest Ndlovu
Kamo Ramonaheng
Sandile Sibiyi
Cindy Davis



Patients and their Families

DARPin Features for Tumor Targeting of Radionuclides



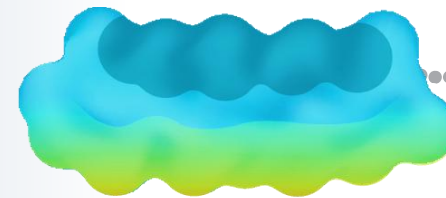
DARPins are small binding proteins derived from natural ankyrin repeat proteins

DARPin key features

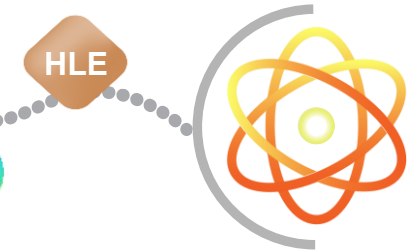
- ✓ **Small size** (~15 kDa)
→ *Deep tumor penetration*
- ✓ **Broad target range** (100's)
→ *Opening indications*
- ✓ **High affinity** (low pM range)
→ *Long tumor retention*
- ✓ **High selectivity**
→ *Low normal tissue*
- ✓ **High stability**
→ *Surface engineering for low kidney*
- ✓ **Clinical Validation**
→ *8 clinical compounds, > 2500 patients treated*

HALF-LIFE EXTENDER

- Tailored exposure
- Promote tumor uptake



LINKER & CHELATOR



SURFACE ENGINEERING

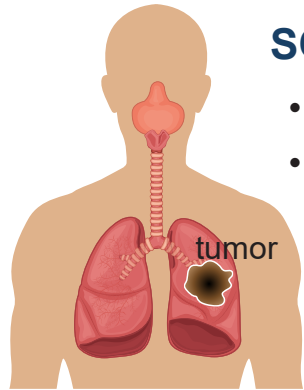
- Enabled by high stability
- Reduce kidney accumulation

α-EMITTING ISOTOPE

- Proven clinical efficacy
- High energy deposition

Radio-DARPin

MP0712: Why DLL3-Targeting Radiotherapy for SCLC?



SCLC: critical unmet need (2L)

- mPFS: ~3 months^{1,2}
- 5-year OS: ~3%^{1,2}



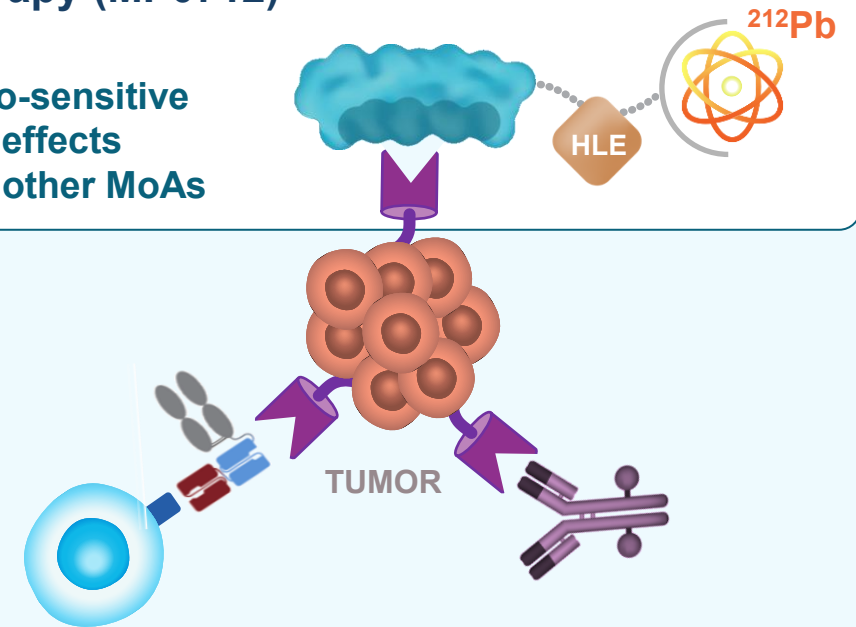
DLL3

DLL3: validated target

- Expressed in >85% of patients with SCLC³
- Expression in multiple neuroendocrine cancers (e.g., LC, Bladder, GEP)
- No expression in healthy tissues
- Tumor-targeting shown with DLL3 radio-diagnostic mAb (⁸⁹Zr-Sc16.56)^{4,5}
- Clinical validation by T cell engagers (e.g., tarlatamab)⁶ and ADCs (e.g., ZL-1310)⁷

Targeted radiotherapy (MP0712)

- Phase 0/1
- **SCLC highly radio-sensitive**
- **Manageable side effects**
- **Combinable with other MoAs**



T cell engagers

- Tarlatamab approved
- **40% RR**
- 9.7 months DoR
- **Substantial side effects**

Antibody-drug conjugates

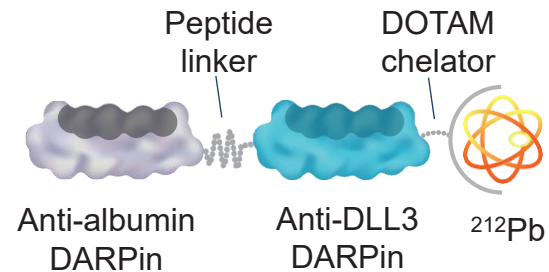
- Phase 1/2
- 70% RR
- **DoR: 5–6 months**
- Manageable side effects

1. Treatment of R/R SCLC, UpToDate; 2. SEER; 3. Rojo et al., Lung Cancer 2020; 4. Tendler et al., Lancet Oncol 2024; 5. Thummalapalli et al., JCO Precis Oncol 2025; 6. Phase 2 DeLLphi-301 study (NCT05060016); 7. Dy et al., AACR-NCI-EORTC 2025.

2L, 2nd line; ADC, antibody-drug conjugate; DoR, duration of response; GEP, gastroenteropancreatic; HLE, half-life extension; LC, large cell; MoA, mechanism of action; mPFS, median progression-free survival; OS, overall survival; RR, response rate; SCLC, small cell lung cancer.

MP0712: Clinical-stage Radio-DARPin–based Targeted Alpha Therapy

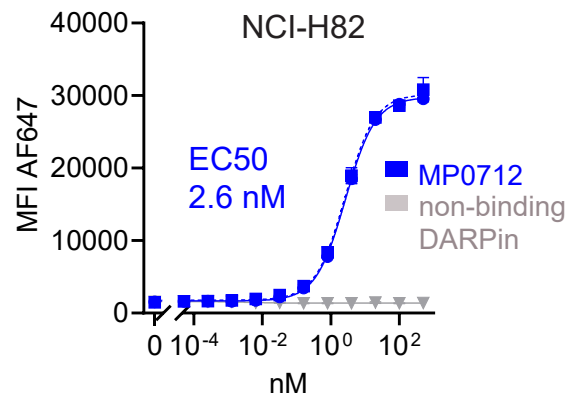
Molecular structure



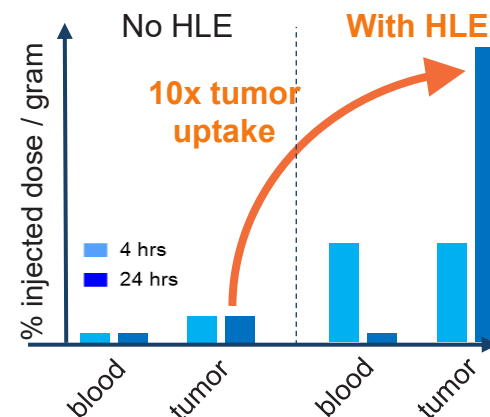
Affinity (SPR)*

Affinity to hDLL3		Affinity to HSA
- HSA	+ HSA	
K_D [nM]	K_D [nM]	K_D [nM]
0.243	0.350	98

Cell binding**



Optimal half-life for tumor uptake of MP0712



- Co-developed by Molecular Partners and Orano Med
- Combines a high-affinity anti-DLL3 DARPin with the potent therapeutic isotope ^{212}Pb
- Half-life extended (albumin binding) to boost tumor uptake over time despite low DLL3 cell-surface copy number

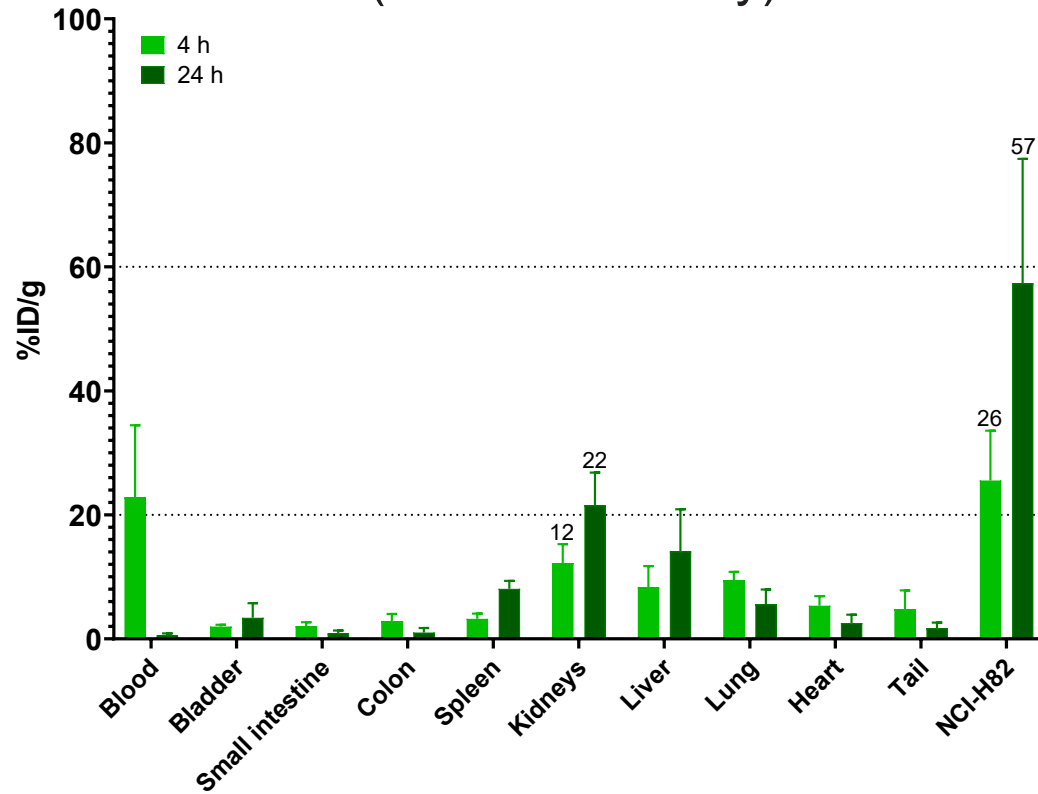
* K_D values of MP0712 binding to hDLL3 in absence and presence of HSA, and binding to HSA.

**Binding of MP0712 to NCI-H82 cells assessed by Flow Cytometry.

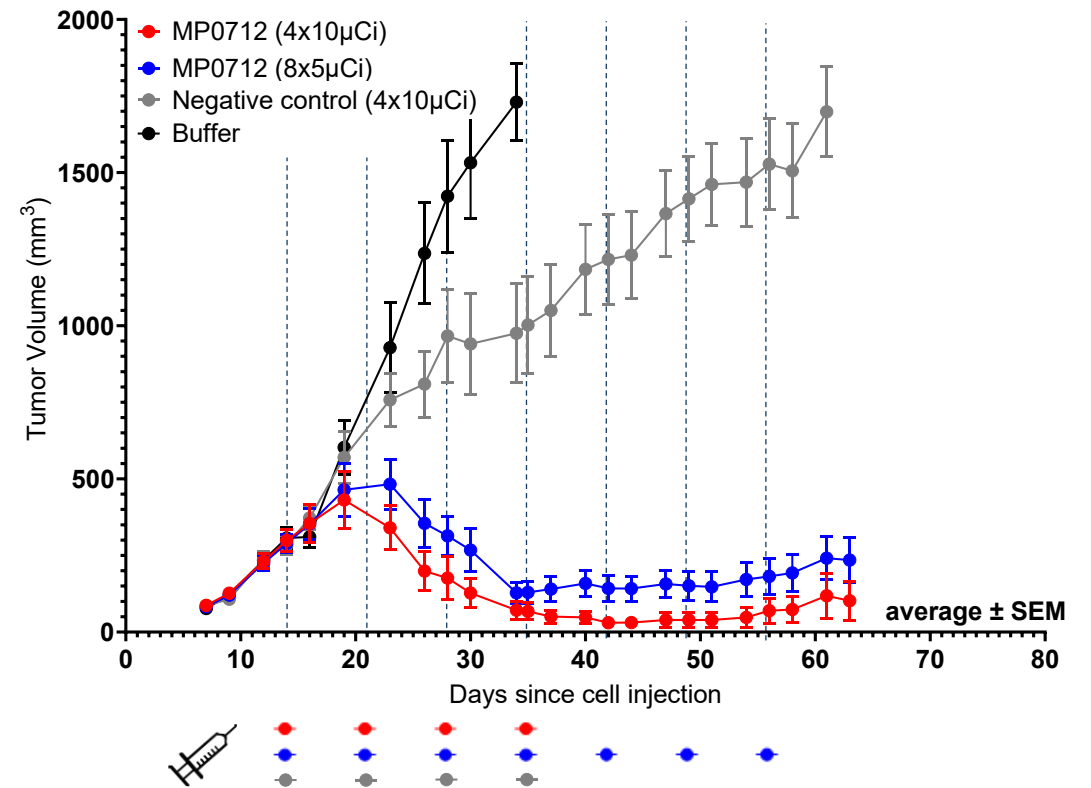
MP0712: Favorable Biodistribution and Potent Efficacy

In mouse models matching the low DLL3 expression levels of patients

High Tumor Accumulation (Tumor > Kidney)

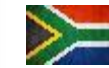
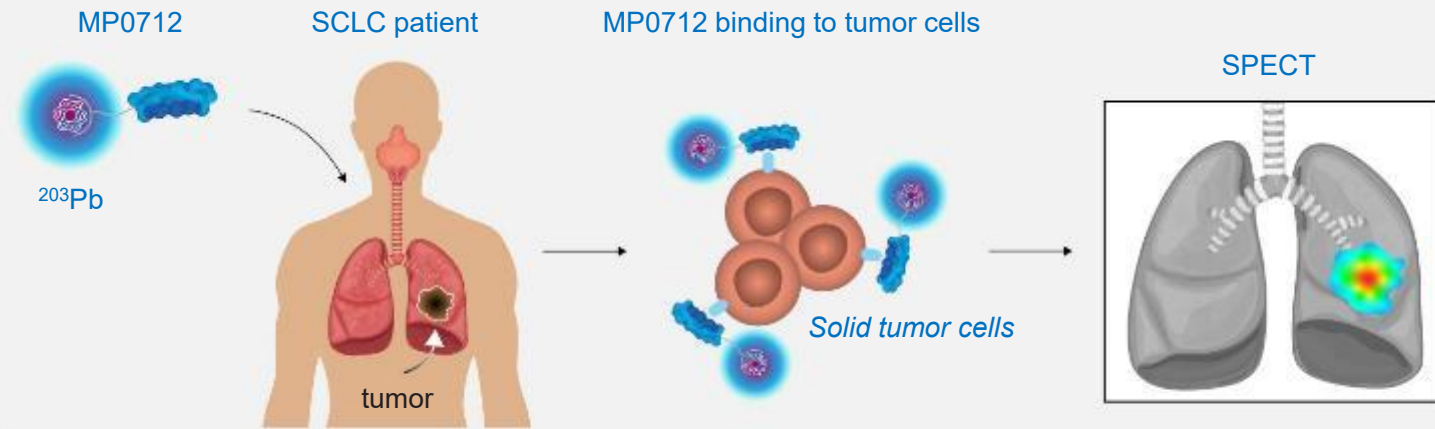


Reduction of Established Tumors



MP0712 Development Pathway

1. Imaging

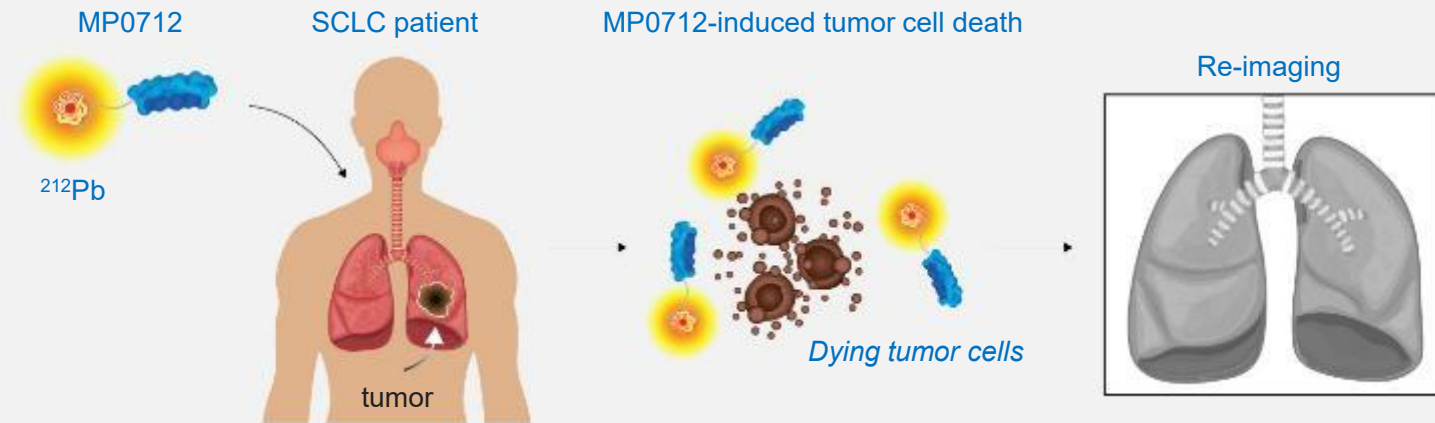


Named Patient Access Program:

- Imaging and dosimetry with ^{203}Pb
- Option for treatment with ^{212}Pb

*Request from NuMeRI, Pretoria, South Africa**

2. Treatment



Phase 1/2a Study:

- Safety of ^{212}Pb
- Efficacy signals
- Includes an imaging and dosimetry step with ^{203}Pb

*MP has accepted a request from Nuclear Medicine Research Infrastructure (NuMeRI) to provide MP0712 under the legal framework in South Africa for compassionate care (also referred to as Section 21 of the Medicines and Related Substances Act).

SPECT/CT Imaging with ^{203}Pb -MP0712 in a Patient with Metastatic SCLC

Patient characteristics

- 69-year-old male (smoker)
- Small cell neuroendocrine carcinoma of the lung
- Stage III at referral (mediastinal lesion)

Treatment history

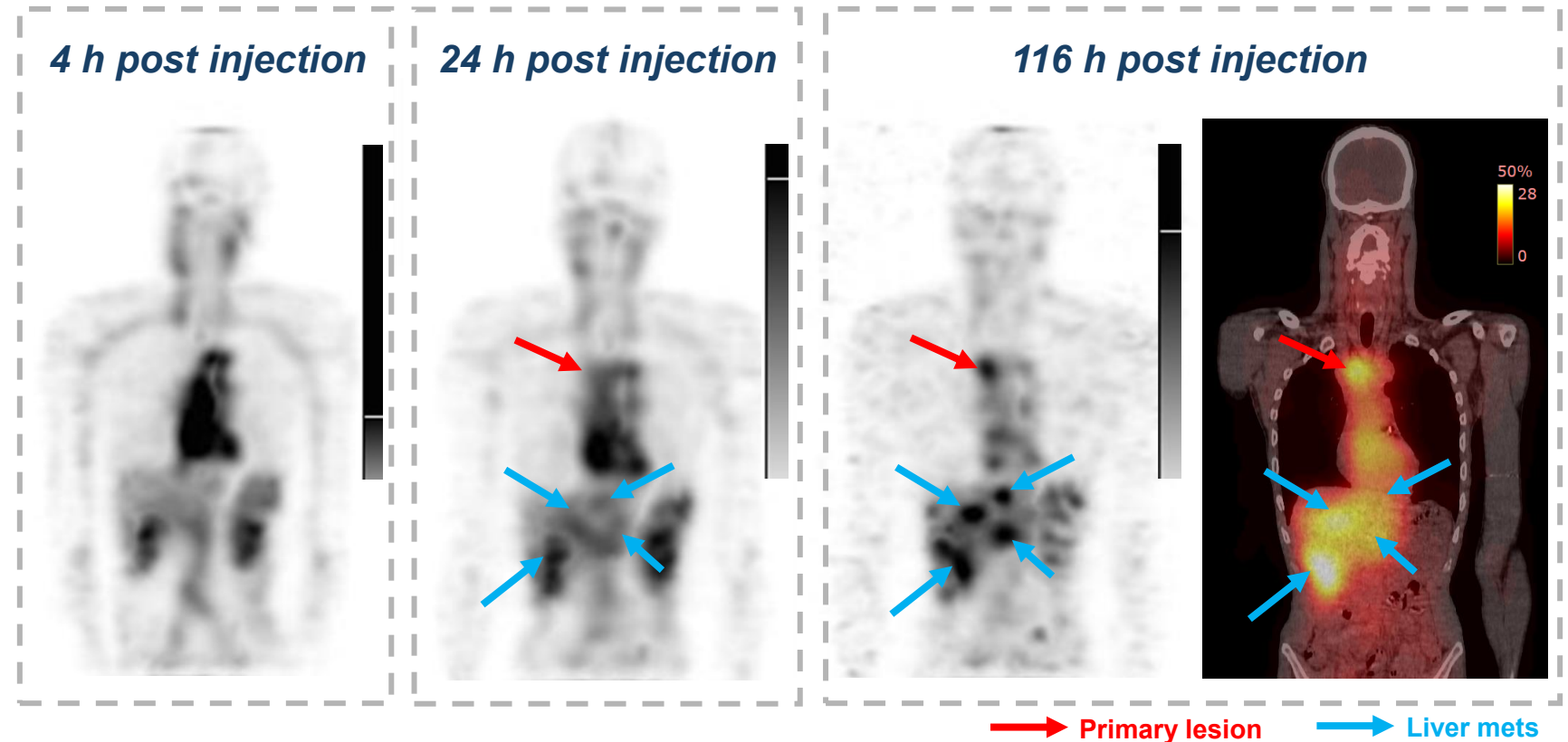
- Radio- & chemotherapy

Dosing

- 185 MBq of ^{203}Pb -MP0712

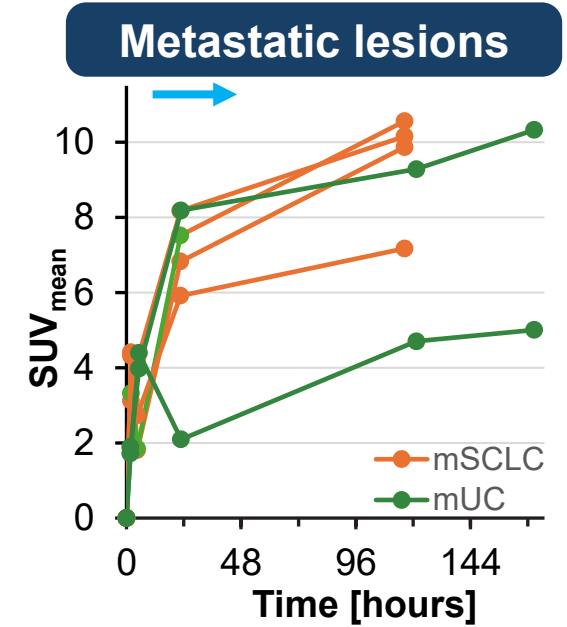
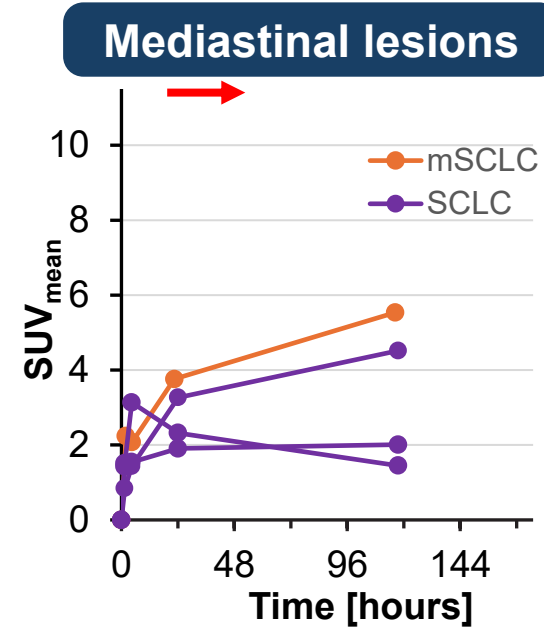
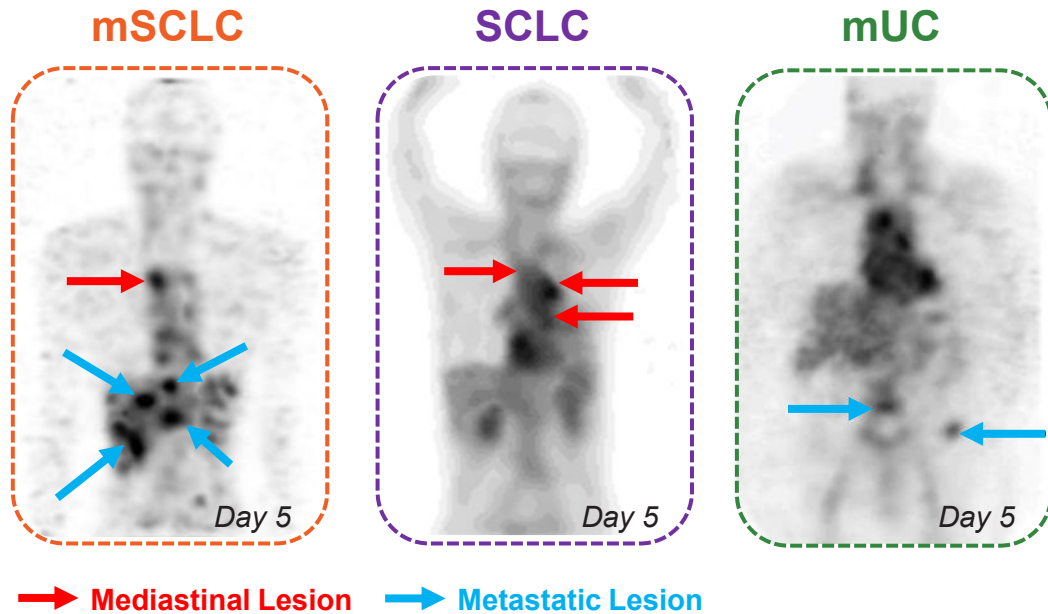
Result

- Stage IV by MP0712 - SPECT with 4 liver mets



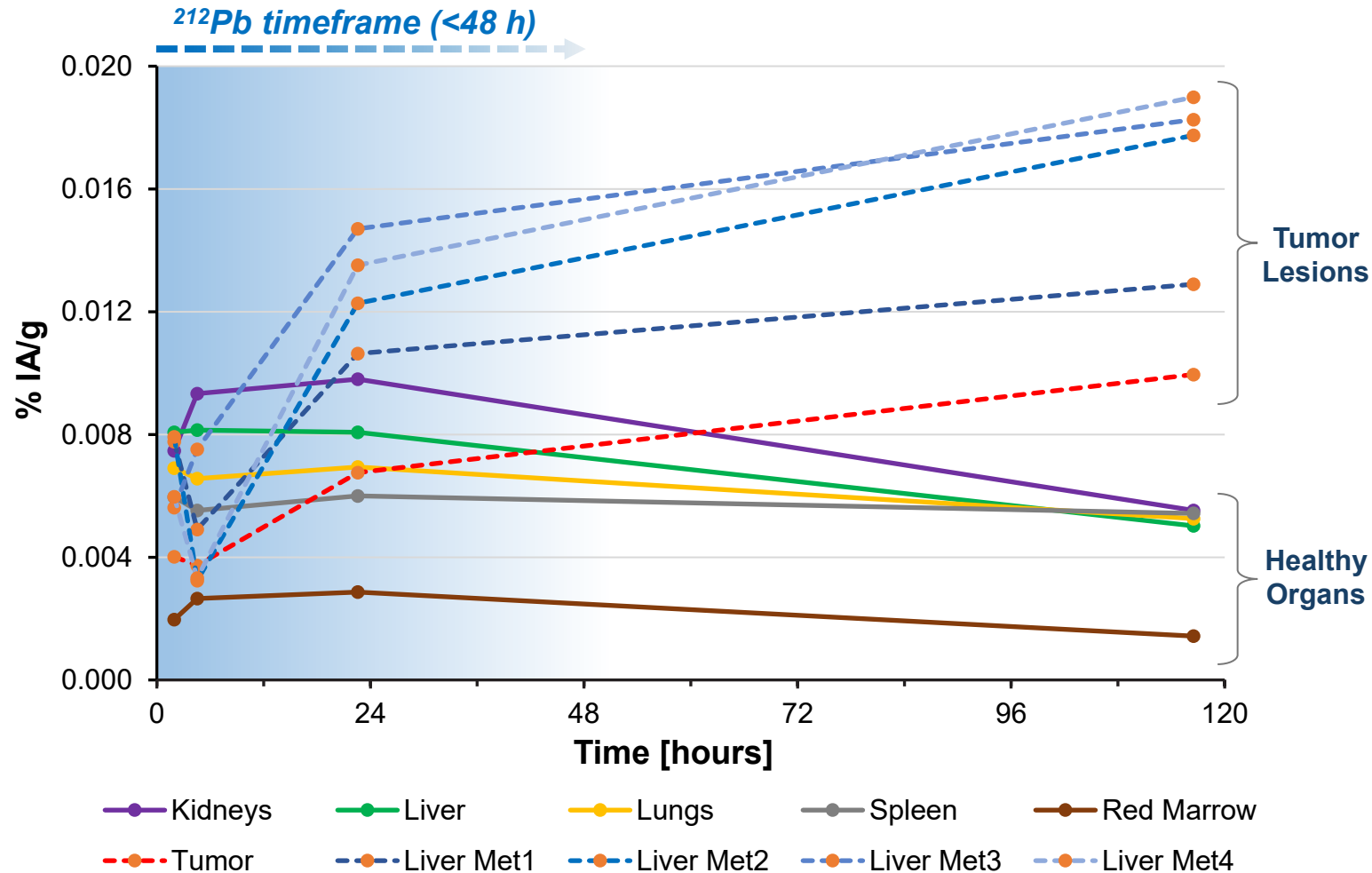
Initial high blood pool, followed by specific uptake in primary & metastatic lesions over time in line with MP0712 MoA

^{203}Pb -MP0712 Uptake in Tumor Lesions



- **Progressive uptake** of MP0712 across different tumor types
 - ~80% of uptake reached at 24 h
 - **Strong tumor retention** with continued uptake during imaging period (up to 7 days)
- **Preferential uptake in metastatic lesions**
 - **Phase 1 study** in US expected to enroll **metastatic SCLC patients**

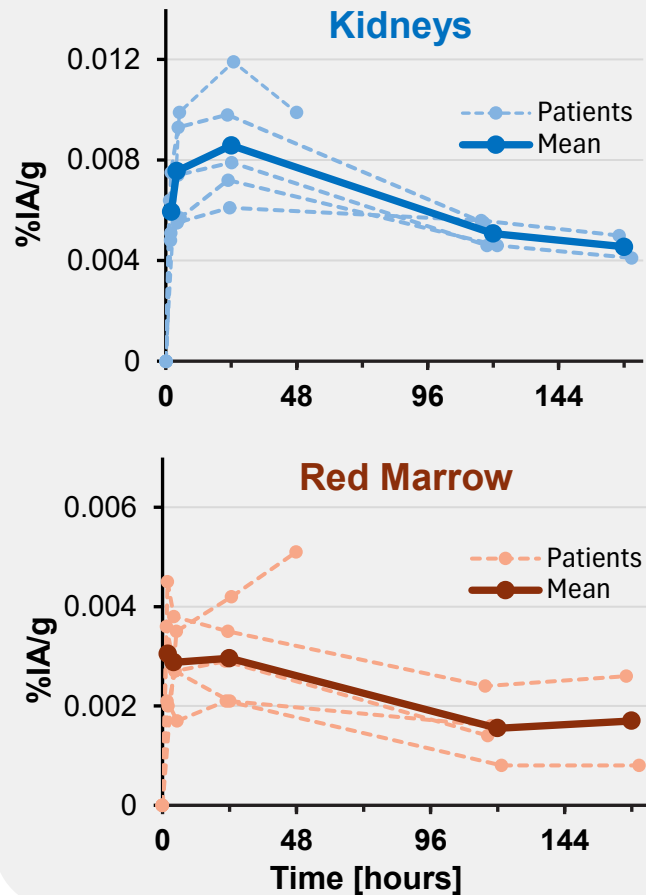
Biodistribution Profile of ^{203}Pb -MP0712 in Patient with mSCLC



- **Continued tumor uptake** during imaging period (up to 116 h)
- **Higher uptake in liver metastases** as compared to primary lesion
- **Washout from healthy organs** visible from 24 h onwards
- Healthy organ profile consistent with profile observed in other patients

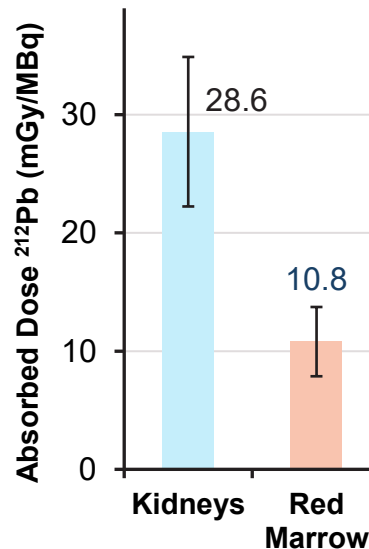
MP0712 Organ Dosimetry & Projection to Phase 1

^{203}Pb Time-activity curves

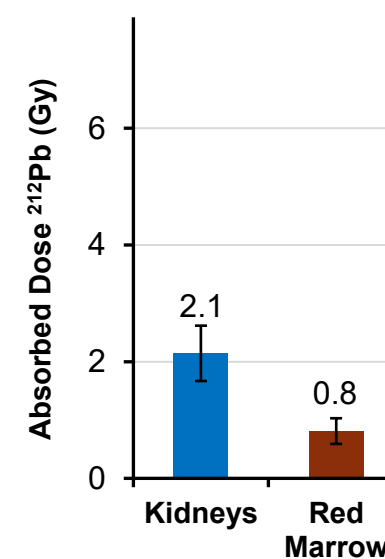


Dosimetry extrapolations suggest kidneys & red marrow as potential dose-limiting organs for ^{212}Pb -MP0712

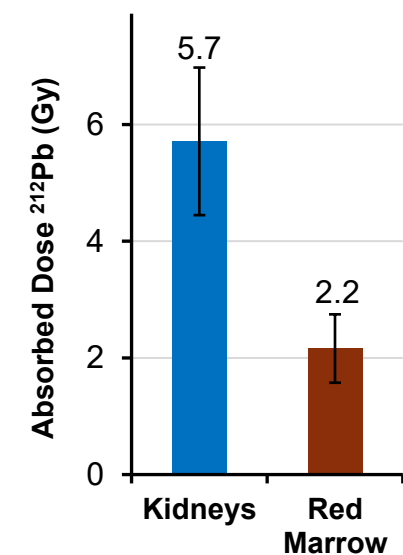
^{212}Pb Dose Coefficient



1x 75 MBq ^{212}Pb

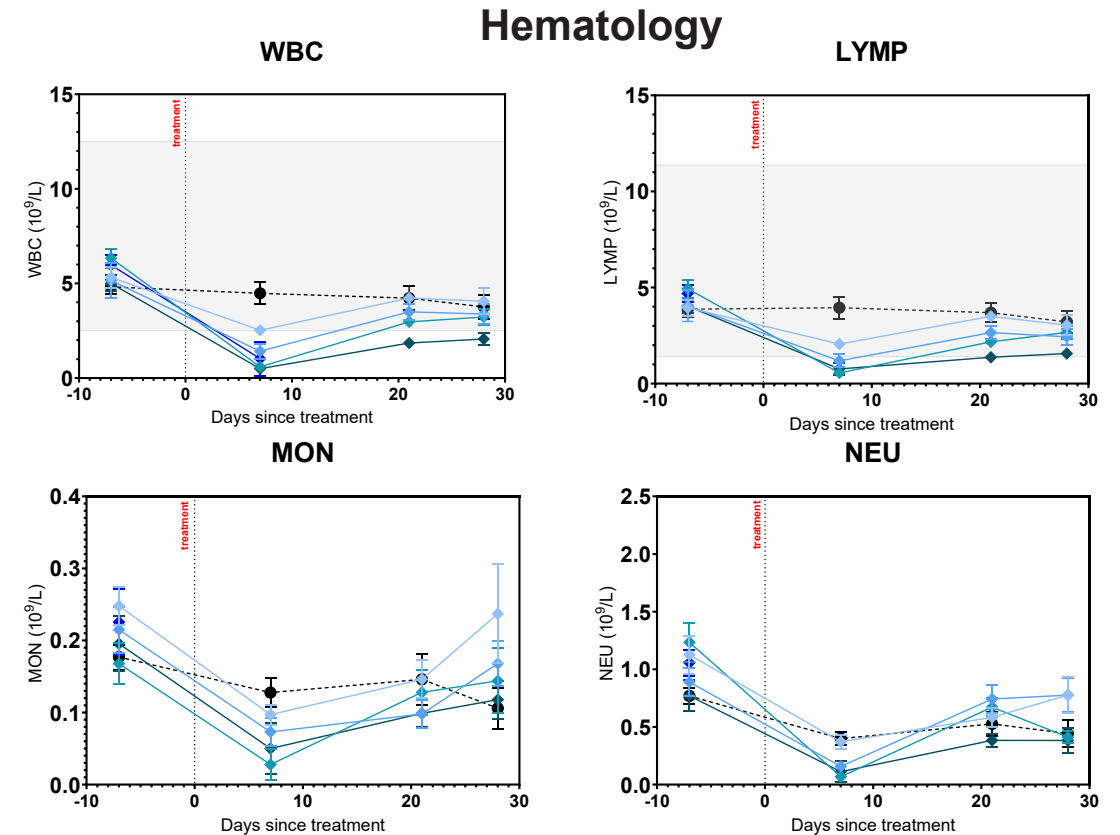
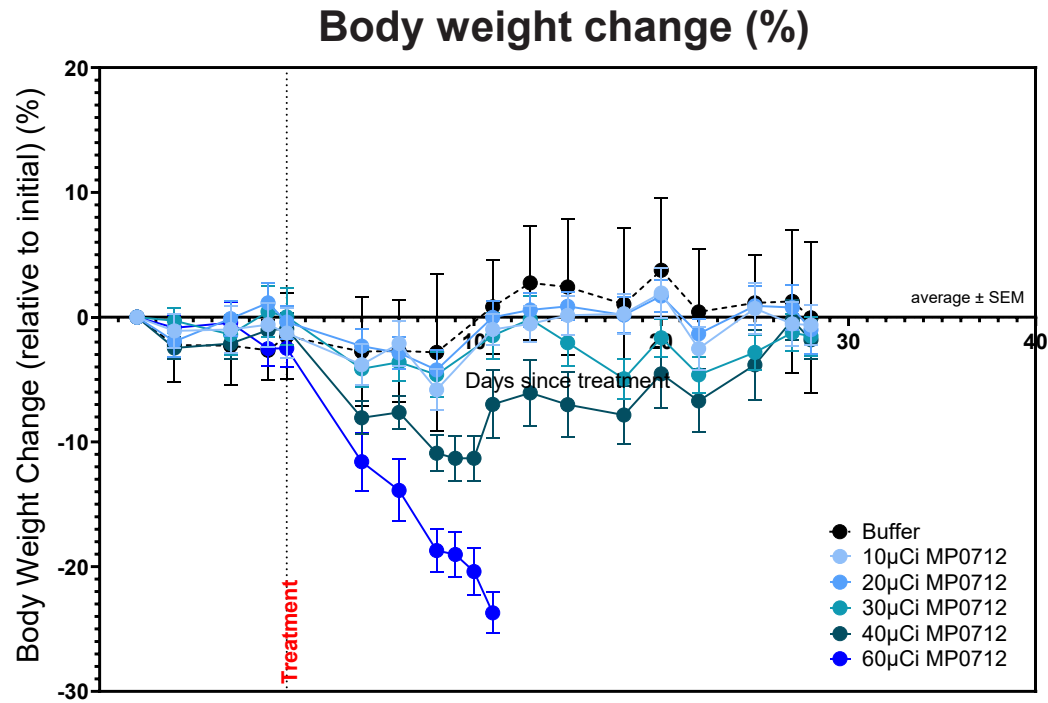


1x 200 MBq ^{212}Pb



- At Phase 1 starting dose (75 MBq) and at highest anticipated single dose (200 MBq) all healthy organs are within EBRT limits
- Monitor hematologic recovery to guide repeated dosing strategies

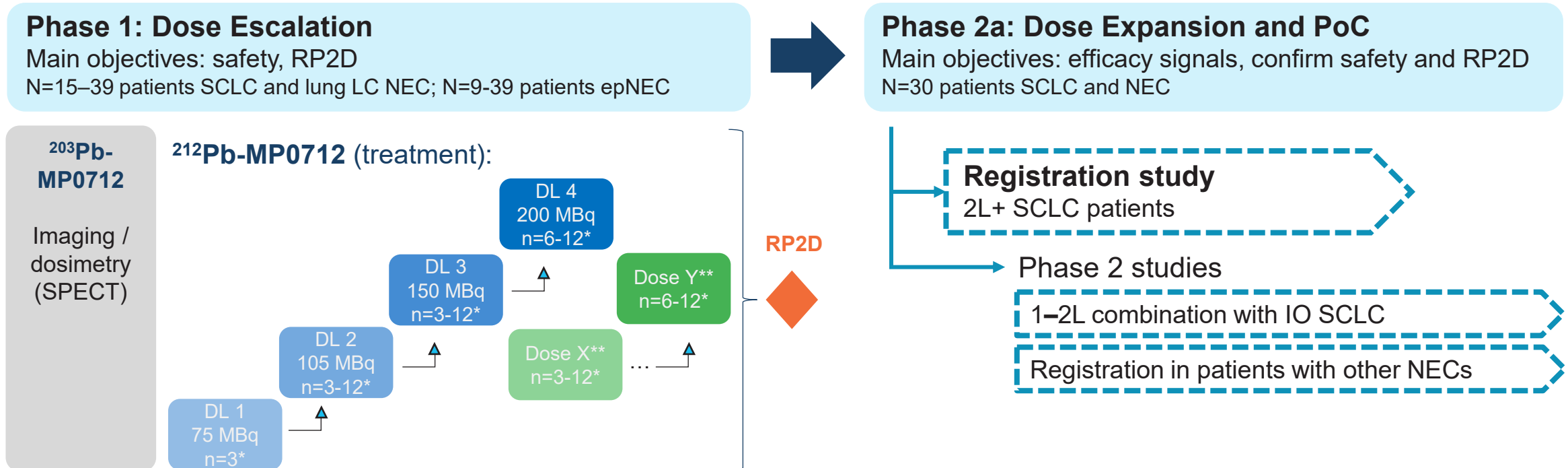
MP0712 Preclinical Safety Data Support Heme Recovery Hypothesis



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

MP0712 Phase 1/2a Study for SCLC and other NECs

- First-in-Human, US multicenter, Phase 1/2a study of MP0712 monotherapy (NCT07278479)
- Patients with SCLC and other NECs
 - Every patient will be imaged (^{203}Pb) before treatment (^{212}Pb)
 - Patient pre-selection on DLL3 expression: not planned for SCLC and LC NEC of lung, foreseen for epNEC



* Evaluable patients (Bayesian Logistic Regression Model guided dose escalation)

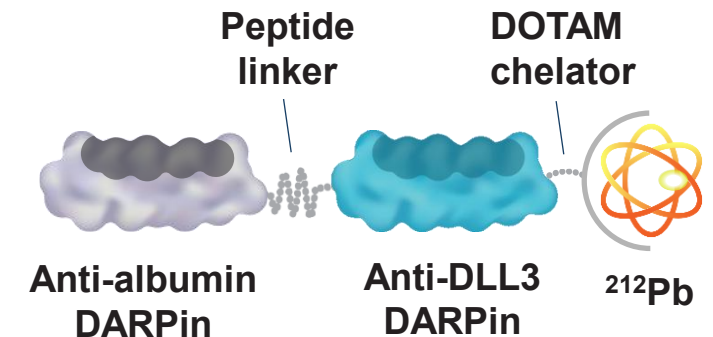
**epNEC to start at a dose level previously tested in SCLC or LC NEC of lung at which a first signal of pharmacological activity is detected. RP2D for epNEC is anticipated to be same as RP2D for SCLC/LC NEC of lung.

1/2 L, 1st/2nd line; DL, dose level; IO, immuno-oncology; (LC) NEC, (large cell) neuroendocrine cancer; PoC, proof-of-concept; RP2D, recommended phase 2 dose.

MP0712 – Summary & Outlook

- Clinical-stage DLL3-targeting alpha radioligand therapy for SCLC
- Combines a high-affinity DARPin as vector with the potent therapeutic isotope ^{212}Pb
- Favorable safety profile, biodistribution and antitumor efficacy in mice
- Initial patient imaging from compassionate use shows robust accumulation in tumors inline with preclinical data
- Half-life extension may offer a target-specific advantage, despite low DLL3 surface density to achieve efficient tumor loading of MP0712

MP0712 is currently evaluated in a first-in-human phase I study in SCLC and other DLL3+ tumors (NCT07278479)



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