[^{212}Pb]Pb-MP0712 in patients with small cell lung cancer (SCLC) and other Delta-like ligand 3 (DLL3) expressing solid tumors: a Phase 1/2a study to assess safety, tolerability, and efficacy

Poster #TPS3176
ASCO 2026

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Background

- SCLC is a highly aggressive NEC with poor prognosis and limited durable treatment options, representing a major unmet medical need
- DLL3 is a clinically validated target[1], highly expressed on the cell surface of SCLC and other high-grade NECs (Tab.1), while showing minimal expression in normal tissues making it an attractive target for radiopharmaceutical therapy
- DARPins are small engineered binding proteins (~18 kDa)
- [^{212}Pb]Pb-MP0712 is a clinical-stage DLL3-targeting alpha therapy combining a high-affinity DARPin with the therapeutic isotope ^{212}Pb (Fig. 1)
- [^{212}Pb]Pb-MP0712 showed a favorable safety profile, biodistribution and antitumor efficacy in mice (Fig. 3)
- Despite low surface density, repeated internalization and replenishment cycles of DLL3 could allow efficient tumor loading of [^{212}Pb]Pb-MP0712 without saturating binding sites[3]
- First patient imaging and dosimetry data with [^{203}Pb]Pb-MP0712 from compassionate care showed robust tumor uptake that increased throughout the imaging period (Fig. 2A), while the washout from healthy organs, including kidney, was visible from 24 h onwards (Fig. 2B)[4,5]

Molecular structure of MP0712

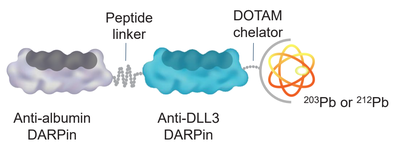


Figure 1: Design of [^{203}Pb]Pb-MP0712/[^{212}Pb]Pb-MP0712 with one HSA-binding (for half-life extension) and one DLL3-binding DARPin domain

DLL3 expression in NEC

Indication	SCLC	LC NEC of the lung	Cervical NEC	GEP NEC	Bladder NEC
DLL3 expression	+++	+++	++	++	++

Table 1. Relative DLL3 expression levels across NEC subtypes based on transcriptomic profiling reported by Lozada et al.[6] High DLL3 expression is observed in SCLC, and LCNEC, whereas intermediate expression is seen in cervical NECs, GEP NECs, and bladder NEC reflecting site-dependent heterogeneity in DLL3 expression

SPECT/CT imaging showed specific tumor uptake of [^{203}Pb]Pb-MP0712

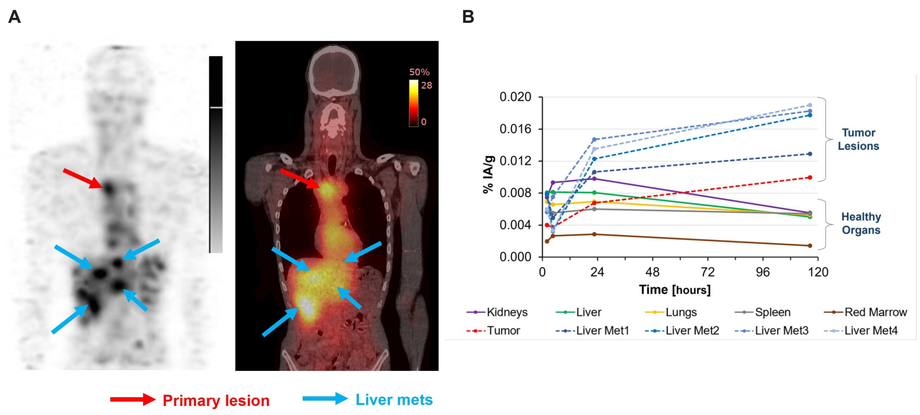


Figure 2: First-in-human data of of [^{203}Pb]Pb-MP0712 from a named patient access program under South Africa's Section 21 compassionate care program in patients with SCLC and other DLL3^{+} neuroendocrine cancers[3,4] **A)** SPECT/CT imaging 116 h post injection and **B)** biodistribution profile of ^{203}Pb-MP0712 in a patient with metastatic SCLC

[^{212}Pb]Pb-MP0712 induced complete tumor regression in xenograft models

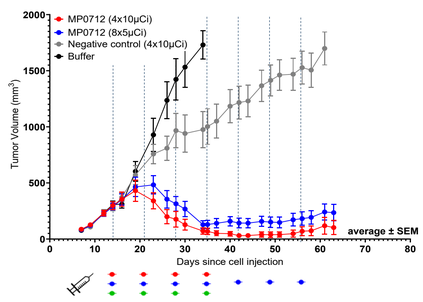


Figure 3: In vivo efficacy study of [^{212}Pb]Pb-MP0712 in NCI-H82 tumor bearing mice. MP0712 was injected 4 x 10 µCi every week or every 2 weeks (40 µCi cumulative) and 8 x 5 µCi every week or every 2 weeks (40 µCi cumulative) into the tail vein of R2G2 mice xenografted subcutaneously with NCI-H82 cells[2]

Summary and Outlook

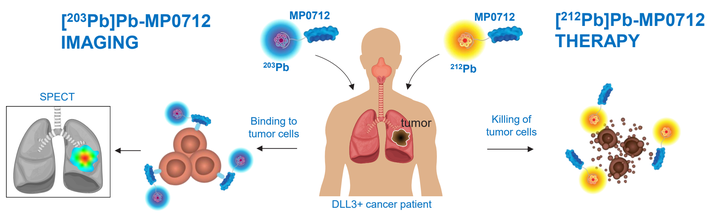
- This FIH study is evaluating the safety, tolerability, dosimetry, and preliminary activity of [^{212}Pb]Pb-MP0712 in patients with DLL3-expressing SCLC, LC NEC of the lung and epNECs
- MP0712's design with high affinity to DLL3 and half-life extended properties is hypothesized to support efficient internalization, enabling strong tumor uptake despite low DLL3 cell-surface expression[3]
- [^{212}Pb]Pb-MP0712 demonstrated promising preclinical efficacy and biodistribution, with favorable safety profile[2]
- FIH imaging from compassionate use of [^{203}Pb]Pb-MP0712 show specific uptake in DLL3-positive lesions in patients with SCLC and other NECs, with favorable clearance profile [4,5]
- Beyond monotherapy, future studies will explore optimized combination regimens including immune-modulating agents

Enrolment status

- This FIH study is open for recruitment at 5 centers in the US, with 4 additional centers planned to open in Q2 2026
- It is registered on ClinicalTrials.gov under NCT07278479

Study design

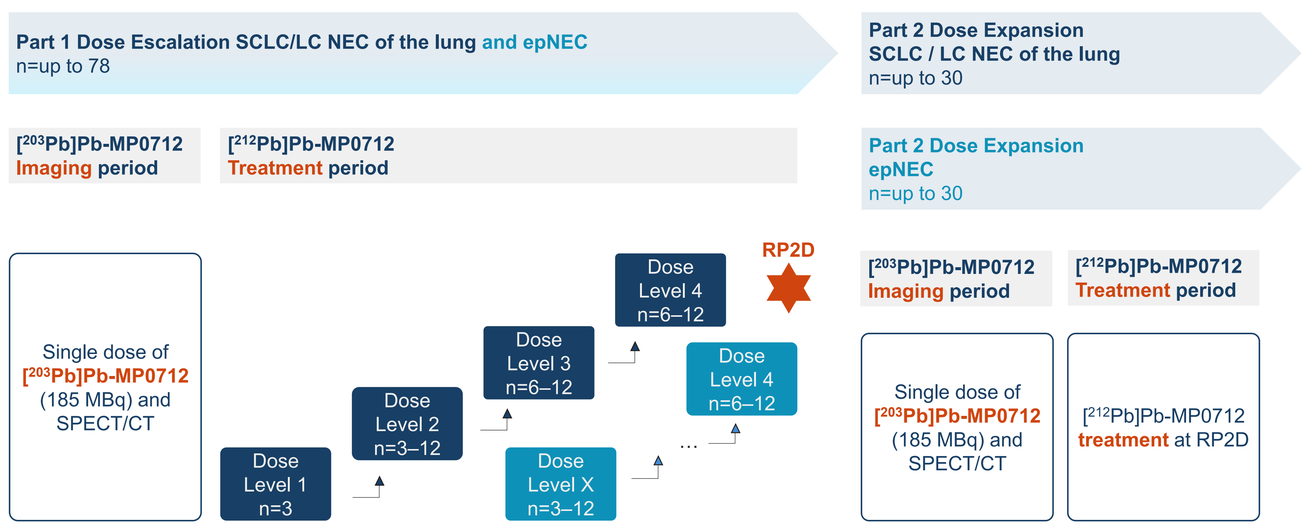
- This FIH Phase 1/2a study evaluates the safety, biodistribution, dosimetry, and preliminary antitumor efficacy of [^{212}Pb]Pb-MP0712
- The study has two parts
- Part 1: dose escalation
  - Cohorts receive escalating doses of [^{212}Pb]Pb-MP0712 to estimate the MTD and determine the RP2D, with DLTs assessed during the first 28 days of treatment
  - Dose escalation is guided by BLRM-EWOC
  - SRC review of available cumulative safety, dosimetry, and PK data after each cohort
  - Dose escalation starts in the group with SCLC/LC NEC of the lung
  - Dose confirmation for epNEC starts at a pharmacologically-active dose level identified in patients with SCLC/LC NEC of the lung
- Part 2: dose expansion
  - Two groups with 30 patients each to assess preliminary antitumor efficacy of [^{212}Pb]Pb-MP0712 at RP2D in SCLC/LC NEC of the lung or epNEC
  - Primary endpoint is ORR, defined as the percentage of patients who achieve a partial response or complete response as measured by RECIST v1.1
- Both study parts include an imaging period with [^{203}Pb]Pb-MP0712, used as an imaging and dosimetry surrogate for [^{212}Pb]Pb-MP0712 enabling DLL3 imaging and dosimetry.



Study schematic

Key eligibility criteria

- Aged ≥18 years
- SCLC after ≥2 prior systemic therapies or not eligible for standard second-line therapy, or
- LC NEC of the lung after ≥1 prior systemic therapy, or
- epNECs including GEP, cervical, bladder, or other DLL3-expressing epNECs (excluding Merkel cell carcinoma and neuroendocrine prostate cancer) after ≥1 prior systemic therapy
- DLL3-positive disease by [^{203}Pb]Pb-MP0712 SPECT/CT (epNECs in Parts 1 and 2; SCLC or LC-NEC of the lung in Part 2)
- Prior DLL3-targeted therapy allowed
- ≥1 measurable lesion per RECIST v1.1
- ECOG performance status 0–2
- Clinically stable, asymptomatic CNS and/or meningeal disease permitted



Assessments	
Safety	Clinical and laboratory assessments with continuous AE monitoring (CTCAE v5.0) and long-term safety up to 5 years
Efficacy	Tumor response assessed by RECIST v1.1
PK / Radiation PK	Blood, serum, and urine sampling (extended sampling in subgroup)
Imaging	SPECT/CT for DLL3-expressing tumor lesions Biodistribution and dosimetry for [^{203}Pb]Pb-MP0712 and [^{212}Pb]Pb-MP0712 in subgroups
Biomarkers	Immunogenicity and exploratory biomarker analyses

Study objectives

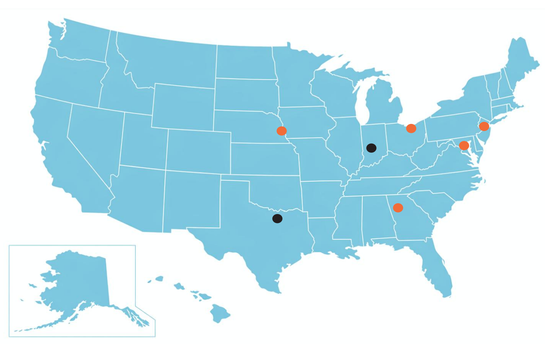
Primary

Part 1	• Safety and tolerability of [^{212}Pb]Pb-MP0712 • MTD and/or RP2D
Part 2	• Preliminary antitumor activity of [^{212}Pb]Pb-MP0712 (ORR)

Main Secondary

Part 1	• PK, biodistribution, and dosimetry of [^{203}Pb]Pb-MP0712 and [^{212}Pb]Pb-MP0712 • PK of MP0712 • Safety and tolerability of [^{203}Pb]Pb-MP0712
Part 2	• Safety and tolerability of [^{212}Pb]Pb-MP0712 and [^{203}Pb]Pb-MP0712 • Preliminary anti-tumor activity of [^{212}Pb]Pb-MP0712 (DOR, PFS, OS) • PK, biodistribution, and dosimetry of [^{203}Pb]Pb-MP0712 and [^{212}Pb]Pb-MP0712 and PK of MP0712

Study locations



Study centers
- United Theranostics Princeton, NJ
- Nebraska Cancer Specialists, NE
- United Theranostics Maryland, MD
- Emory University School of Medicine, GA
- University Hospital Cleveland, OH
- and additional US sites upcoming

Orano Med manufacturing sites
- Plano, TX
- Indianapolis, IN

References & Abbreviations

References: [1]IMDELLTRA® (tarlatamab-dlle) [package insert] U.S. Food and Drug Administration 2024; Phase 2 DeLLphi-301 study (NCT05060016); [2]Croset et al., AACR 2025; [3]Riesenberg et al., AACR 2026; [4]Kabunda (NuMeRi) et al., TWC 2026; [5]Lizak et al., TWC 2026; [6]Lozanda et al., Cancer Res Commun; 5(2) Feb 2025.

Abbreviations: BLRM-EWOC, Bayesian Logistic Regression Model according to the escalation with overdose control; CNS, central nervous system; CT, computed tomography; DARPin, designed ankyrin repeat protein; DCR, disease control rate; DLL3, delta-like ligand 3; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; epNEC, extrapulmonary neuroendocrine carcinoma; FIH, first-in-human; GEP NEC, gastroenteropancreatic neuroendocrine carcinoma; HSA, human serum albumin; LC NEC, large cell neuroendocrine carcinoma; MTD, Maximum tolerated dose; NEC, neuroendocrine carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic(s); RP2D, recommended Phase 2 dose; SCLC, small cell lung cancer; SPECT, single photon emission computed tomography; SRC, safety review committee.

Acknowledgments: We thank the study patients and their families, as well as the study investigators, nurses and clinical personnel

This poster is also presented at the 2026 SNMMI Annual Meeting

For any questions, please contact: info@molecularpartners.com / attn. of Kathrin Gollmer