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

Samuel Mehr[1], Michael Stumpp[2], Philippe Legenne[2], Kathrin Gollmer[2], Paul Baverel[2], Antje Wegener[3], Volker Wagner[3], Libuse Tauchmanova[2], Ticiana Leal[4]

[1]Department of Nuclear Oncology, Nebraska Cancer Specialists, Omaha, NE, USA, [2]Molecular Partners AG, Zurich-Schlieren, Switzerland; [3]Orano Med LLC, Plano, USA; [4]Winship Cancer Institute of Emory University, Atlanta, GA, USA

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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, 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[2]
- 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

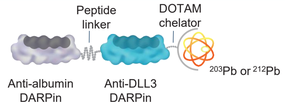


Figure 1: Design of [^{203}Pb]Pb-MP0712/[^{212}Pb]Pb-MP0712 with one HSA-binding (for half-life extension) and one DLL3-binding DARPin domain

Specific tumor uptake of [^{203}Pb]Pb-MP0712

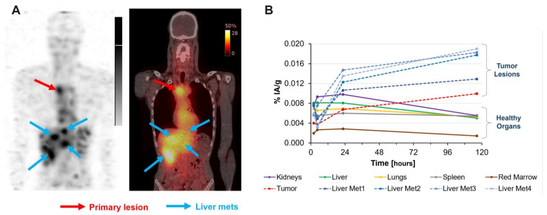


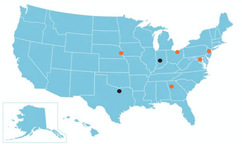
Figure 2: FIH data of of [^{203}Pb]Pb-MP0712 from a named patient access program under South Africa's Section 21 compassionate care program in patients with SCLC and other DLL3^{+} neuroendocrine cancers[3,4] **A)** SPECT/CT imaging 116 h post injection and **B)** biodistribution profile of ^{203}Pb-MP0712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

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]
- 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

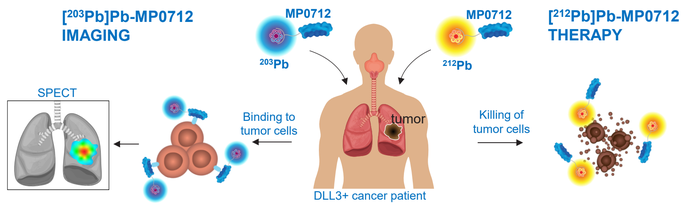


Study centers
- United Theranostics Princeton, NJ
- Nebraska Cancer Specialists, NE
- United Theranostics Maryland, MD
- Emory University School of Medicine, GA
- University Hospital Cleveland, OH
- and additional US sites upcoming

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

Study design

- This FIH Phase 1/2a study evaluates the safety, biodistribution, dosimetry, and preliminary antitumor efficacy of [^{212}Pb]Pb-MP0712
- 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

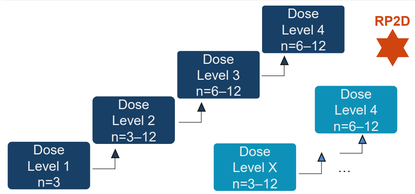
- Aged ≥18 years
- SCLC after ≥2 prior systemic therapies or not eligible for standard second-line therapy, or
- LC NEC of the lung after ≥1 prior systemic therapy, or
- epNECs including GEP, cervical, bladder, or other DLL3-expressing epNECs (excluding Merkel cell carcinoma and neuroendocrine prostate 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

Part 1 Dose Escalation SCLC/LC NEC of the lung and epNEC
n=up to 78

[^{203}Pb]Pb-MP0712 Imaging period

Single dose of **[^{203}Pb]Pb-MP0712** (185 MBq) and SPECT/CT

[^{212}Pb]Pb-MP0712 Treatment period



Part 2 Dose Expansion SCLC / LC NEC of the lung
n=up to 30

Part 2 Dose Expansion epNEC
n=up to 30

[^{203}Pb]Pb-MP0712 Imaging period

Single dose of **[^{203}Pb]Pb-MP0712** (185 MBq) and SPECT/CT

[^{212}Pb]Pb-MP0712 Treatment period

[^{212}Pb]Pb-MP0712 **treatment** at RP2D

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

clinicaltrials.gov

Study objectives

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

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; NEC, neuroendocrine carcinoma; LC NEC, large cell neuroendocrine carcinoma; MTD, Maximum tolerated dose; 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.

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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.

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