

# MP0712, the first anti-DLL3 <sup>212</sup>Pb Radio-DARPin (RDT) candidate for targeted radiotherapy of Small Cell Lung Cancer (SCLC)

Poster/abstract  
#346

2025 AACR  
Annual Meeting

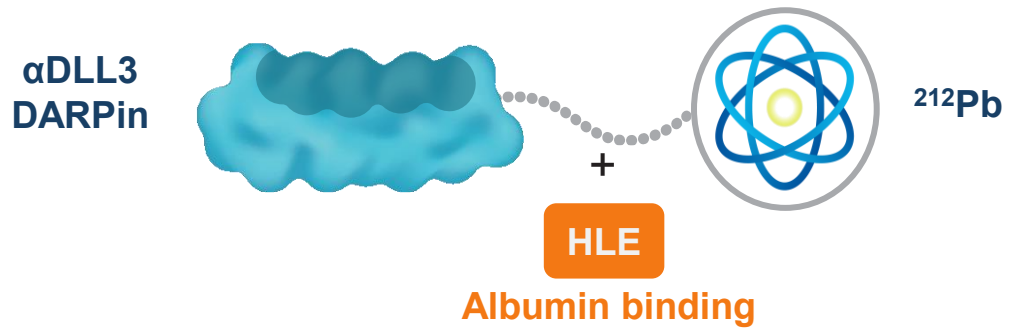
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## Introduction

- DLL3 is a promising target for radioligand therapy as it is highly upregulated in SCLC and other high-grade neuroendocrine tumors, while not expressed in healthy tissue.
- Designed Ankyrin Repeat Proteins (DARPin)s are binding proteins with high specificity and affinity that can be generated against a broad range of tumor targets and thus serve as ideal vectors.
- By leveraging the intrinsic properties of DARPins and the learnings from our platform optimization we achieved efficient tumor uptake and penetration, while limiting exposure of healthy tissues.
- <sup>212</sup>Pb is a radioisotope with a short decay half-life and a favorable decay chain, allowing high energy deposition on tumor in a short time frame.
- Here we present preclinical results of MP0712, our DLL3-targeting <sup>212</sup>Pb-based Radio-DARPin Therapeutic (RDT) combining the advantages of a small protein-based delivery vector and the short-lived alpha particle-emitting radioisotope <sup>212</sup>Pb.

## MP0712 characteristics and target indication



Small protein-based delivery vector based on Radio-DARPin platform (HLE, half-life extension)

### MP0712 properties

- Specific binding with high affinity
- Affinity to hDLL3: 0.2 nM by SPR
- Human cell binding: ~2 nM on NCI-H82 ± HSA
- Good developability

### <sup>212</sup>Pb advantages

- Safety: alpha precursor with clean decay chain
- Efficacy: high energy deposition on tumor in short time (half-life of 10.6 h)

### SCLC as indication

- Aggressive cancer with high unmet medical need
  - 2L: mPFS ~3 mos; 5-year OS ~3%<sup>1,2</sup>
- DLL3 is expressed in >85% of patients<sup>3</sup>

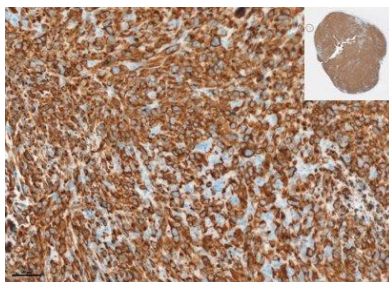
### DLL3 a promising target

- Homogeneous & low tumor expression
- No expression in healthy tissues
- New treatments with room for improvement: Tarlatamab for 2L+; ORR ~40% / DoR 9.7 mos<sup>4</sup>

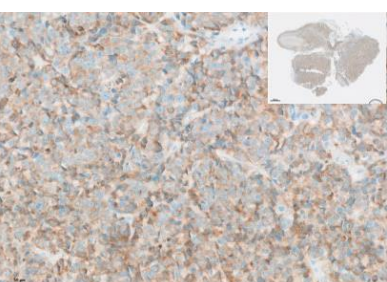
## MP0712 showed favorable biodistribution and tumor specificity

DLL3 expression & distribution by IHC

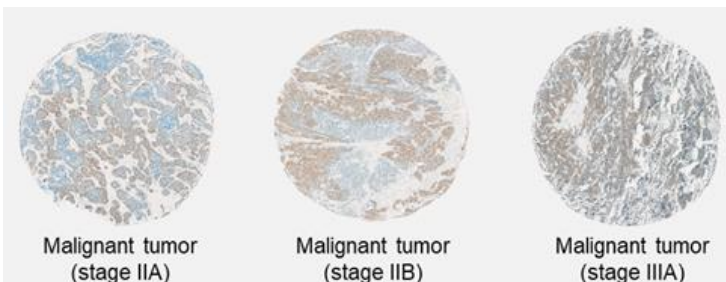
hDLL3-MC38 tumors



NCI-H82 tumors



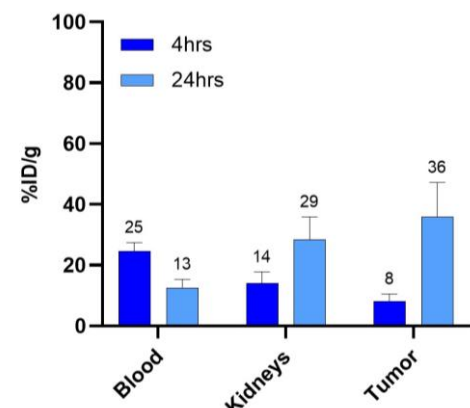
Human SCLC tumors



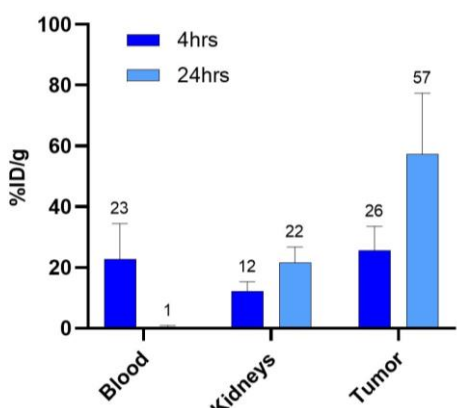
R2G2 mice xenografted s.c. with NCI-H82

R2G2 mice xenografted i.v. with NCI-H82

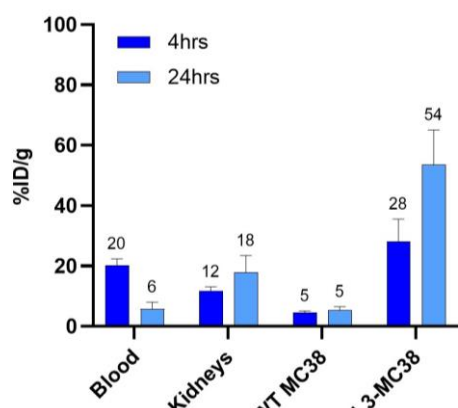
ATH nude mice double xenografted s.c. with hDLL3-MC38 + WT-MC38



T:K at 4 h = 0.6 / at 24 h = 1.2



T:K at 4 h = 2.1 / at 24 h = 2.6



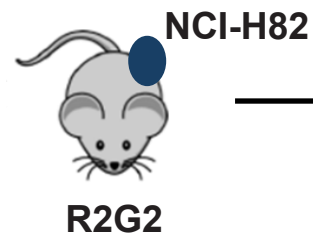
T:K at 4 h = 2.3 / at 24 h = 3.0

- MP0712 biodistribution studies done in different mouse models expressing DLL3
- <sup>212</sup>Pb-DOTAM-DARPin injected 1x10μCi at 0.01mg/kg

- MP0712 reached T:K ratios >2 in mouse models matching clinically relevant DLL3 expression levels

- Selective uptake in DLL3-expressing tumors confirmed high target specificity of MP0712

## MP0712 showed good efficacy & tumor reduction



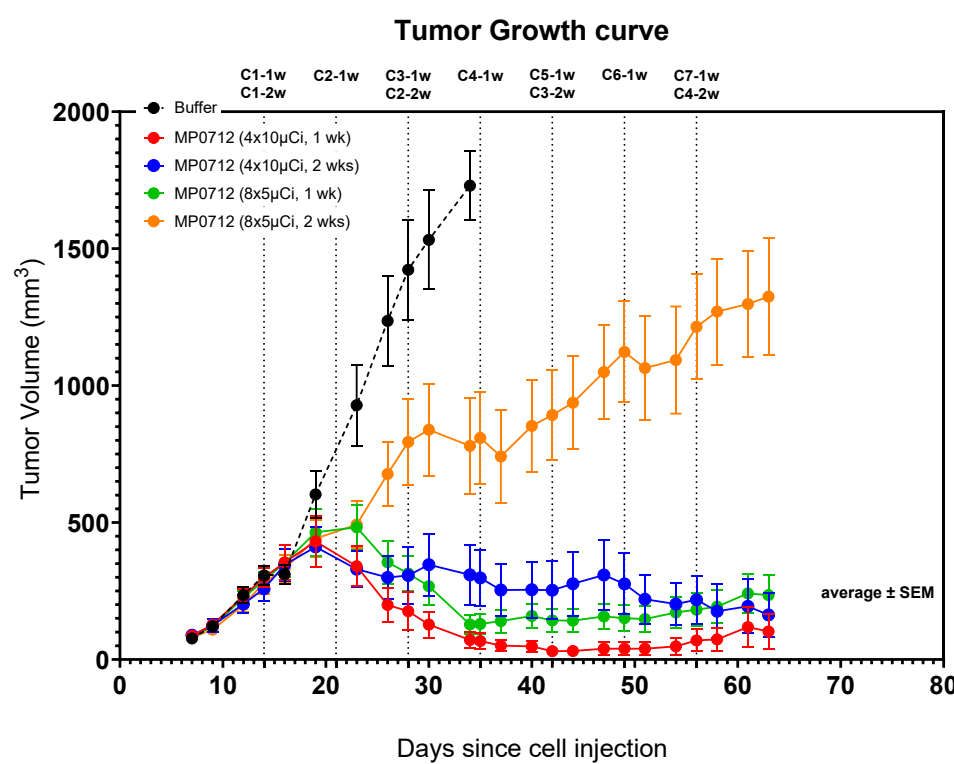
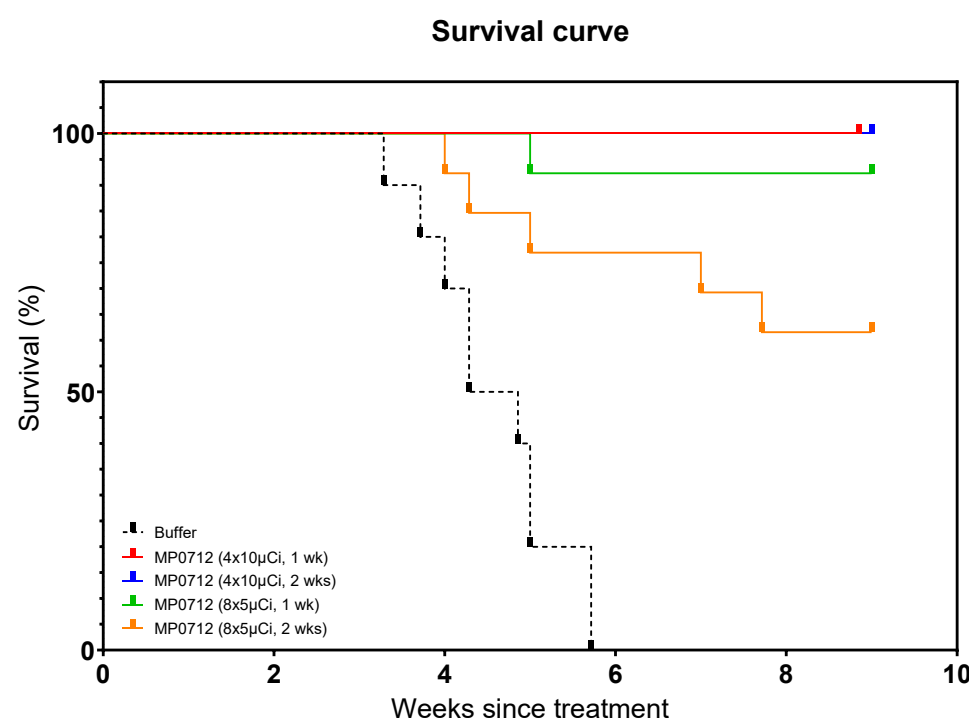
MP0712  
1x Human Equivalent Dose (HED)

Daily observation

3x per week caliper

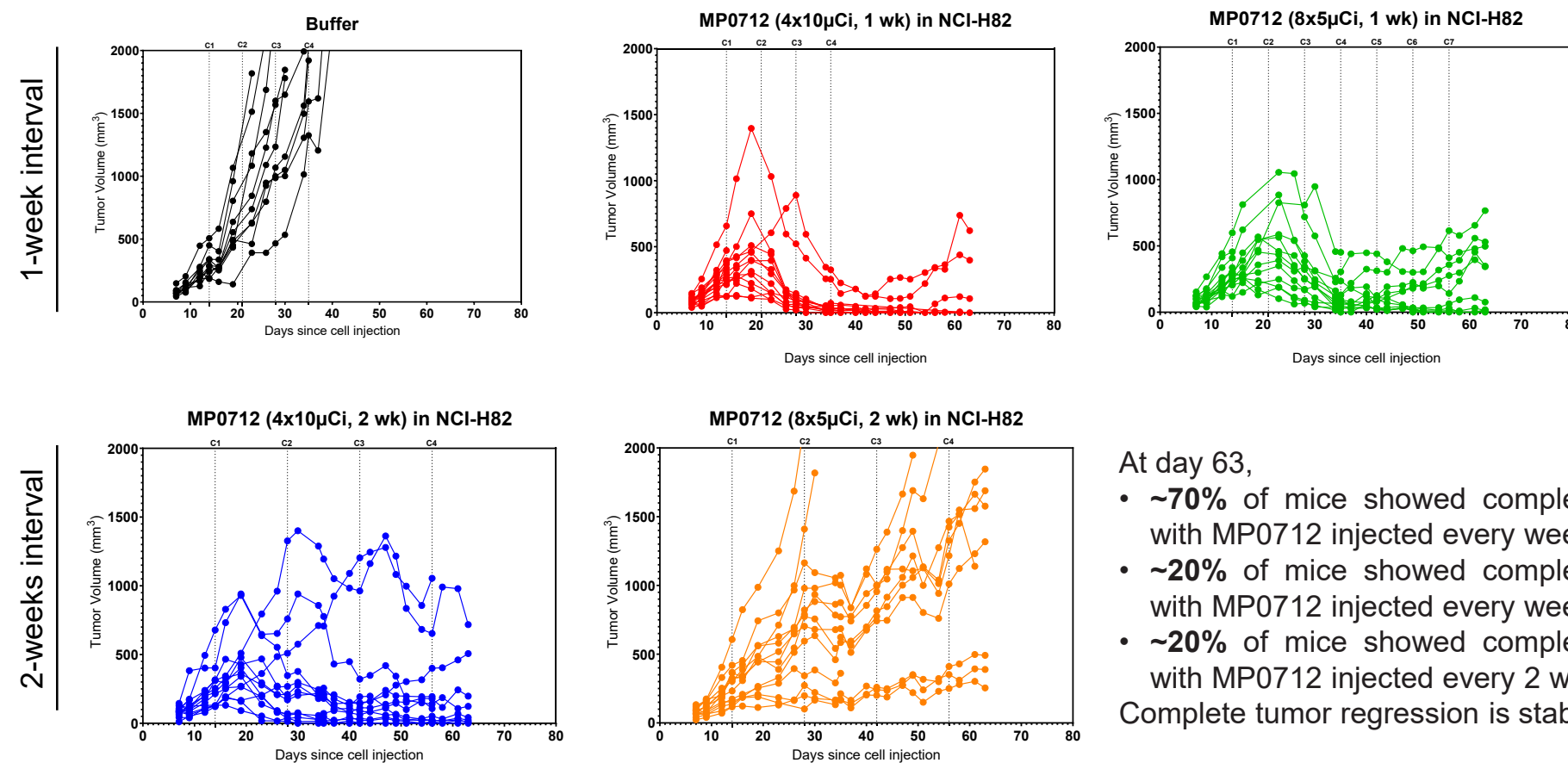
Sacrifice when tumors reach 2000 mm<sup>3</sup> or termination criteria are met  
Necropsy with tumor fixation at termination & collect serum from all mice (weigh abnormal organs)

	A	B	C	D	E
Molecules	Buffer only	MP0712			
Dose	4 x buffer	4 x 10 μCi (40 μCi cumulative)		8 x 5 μCi (40 μCi cumulative)	
Interval	1 week	1 week	2 weeks	1 week	2 weeks



### In vivo efficacy study of MP0712 in NCI-H82 tumor bearing mice

MP0712 was injected 4 x 10μCi 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. Animals were under observation daily and 3x per week tumors were measured by caliper. Animals were sacrificed when tumors reached 1500 to 2000mm<sup>3</sup> or if termination criteria were met. The data are expressed as average +/- SEM on the graph above and as single curve on the graphs below. Dotted lines represent the different cycle of injections (Cx-wx).



- At day 63,
- ~70% of mice showed complete tumor regression with MP0712 injected every week at 4 x 10 μCi,
  - ~20% of mice showed complete tumor regression with MP0712 injected every week at 8 x 5 μCi,
  - ~20% of mice showed complete tumor regression with MP0712 injected every 2 weeks at 4 x 10 μCi
- Complete tumor regression is stable after treatment

Dunnett's multiple comparisons test	Summary	Adjusted P-value
Buffer only vs. MP0712 (4 x 10 μCi, 1 wk)	****	<0.0001
Buffer only vs. MP0712 (4 x 10 μCi, 2 wks)	***	0.0006
Buffer only vs. MP0712 (8 x 5 μCi, 1 wk)	***	0.0002
Buffer only vs. MP0712 (8 x 5 μCi, 2 wks)	ns	>0.9999

- MP0712 treatment resulted in complete tumor regression
- Significant effect for the doses of 4 x 10 μCi injected every week and every 2 weeks
- Significant effect for the doses of 8 x 5 μCi injected every week but not significant when injected every 2 weeks

## MP0712 showed a favorable safety profile

### DRF study protocol

Day -7  
Hematology



Escalating dose of DARPins (10-60μCi)

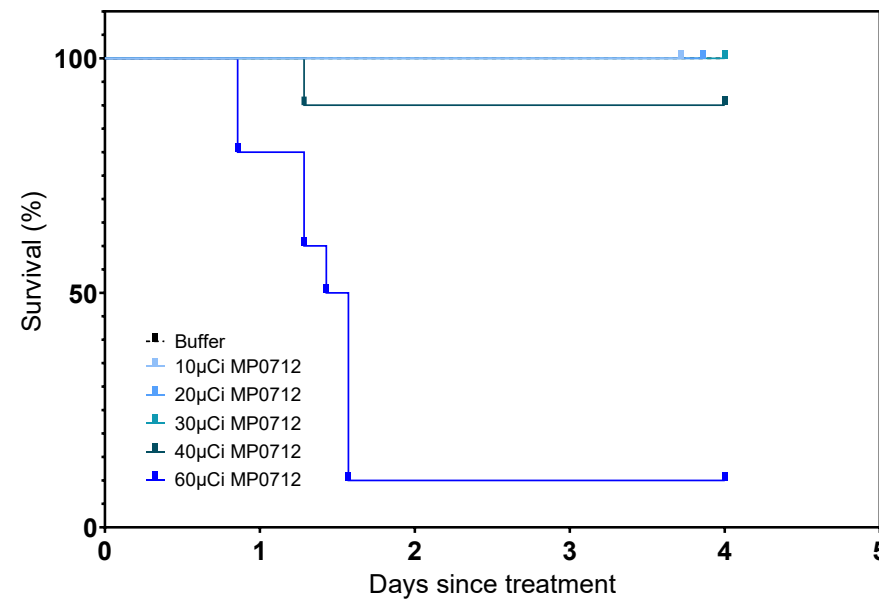
Daily observation

3x per week weighing

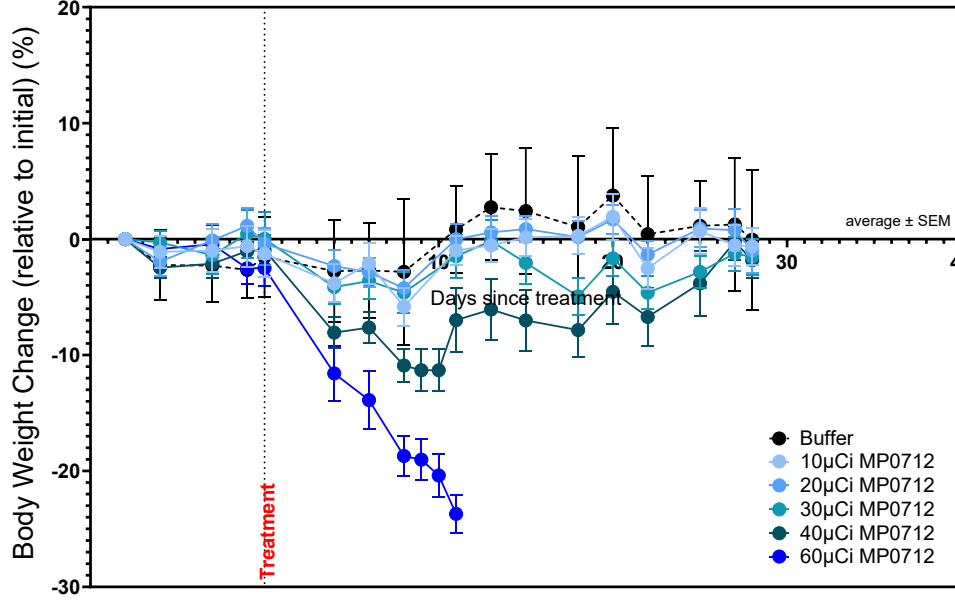
Sacrifice at 4 weeks or when termination criteria are met  
+ Hematology Day -7 & Day 7 & Day 21 & Day 28  
+ Terminal clinical chemistry  
+ Full necropsy and fix tissues in 10% NBF  
+ Kidney & liver weight

### Survival curves and BW change (%)

Survival curve

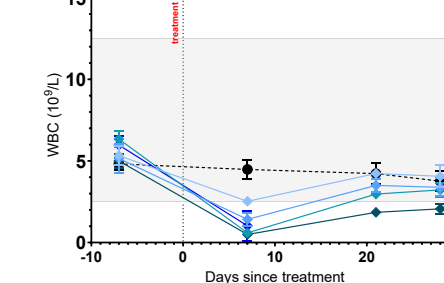


Body Weight change (%)

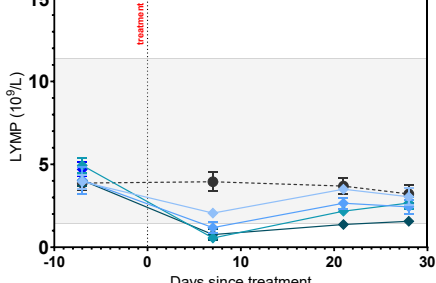


### Hematology profile

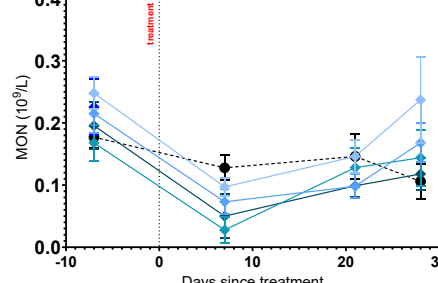
WBC



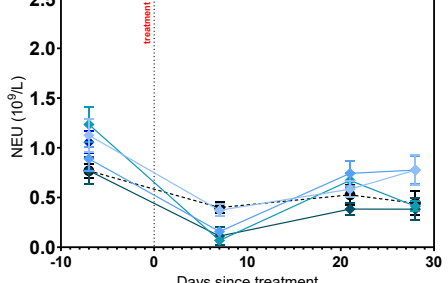
LYMP



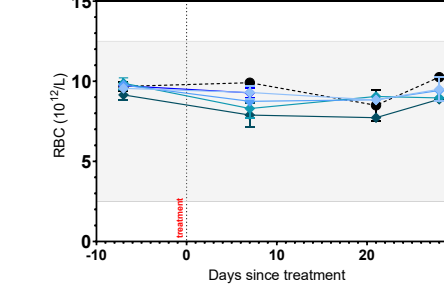
MON



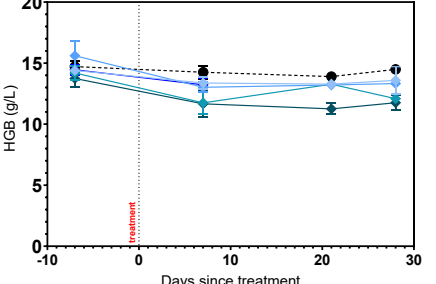
NEU



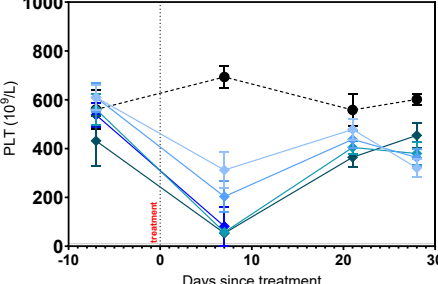
RBC



HGB



PLT



- Complete recovery of body weight loss after 10 days
- Complete recovery of hematologic profile after 28 days
- MP0712 treatment up to 30 μCi well tolerated

## Conclusion

- MP0712, the first <sup>212</sup>Pb-DLL3 Targeted Radio-DARPin Therapy
  - High tumor uptake
  - Reached T:K > 2 in mouse models expressing DLL3
  - Induced good efficacy & tumor reduction
  - Showed a favorable safety profile *in vivo* up to 40 μCi
- IND-enabling package completed
- Initial first-in-human clinical data expected in 2025

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For any questions, please contact: info@molecularpartners.com / attention of A. Croset.

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