MP0712, the first anti-DLL3 ^{212}Pb Radio-DARPin (RDT) candidate for targeted radiotherapy of Small Cell Lung Cancer (SCLC)

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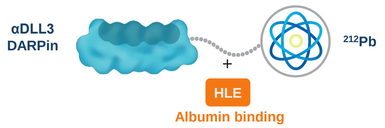
Introduction

- 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 (DARPins) 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.
- ^{212}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 ^{212}Pb-based Radio-DARPin Therapeutic (RDT) combining the advantages of a small protein-based delivery vector and the short-lived alpha particle-emitting radioisotope ^{212}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

^{212}Pb advantages

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

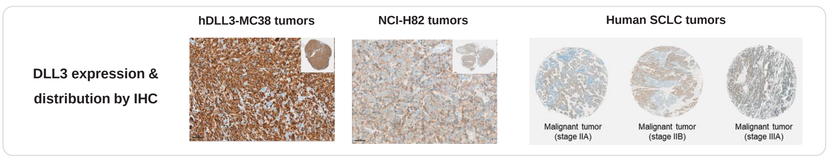
SCLC as indication

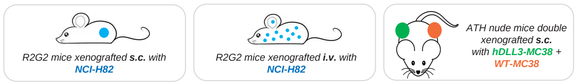
- Aggressive cancer with high unmet medical need
  - 2L: mPFS ~3 mos; 5-year OS ~3%[1,2]
- DLL3 is expressed in >85% of patients[3]

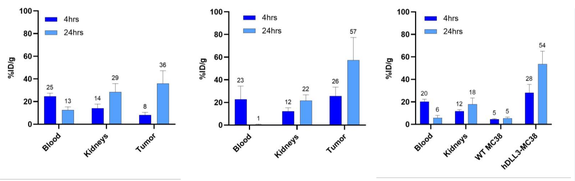
DLL3 a promising target

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

MP0712 displayed favorable biodistribution and tumor specificity



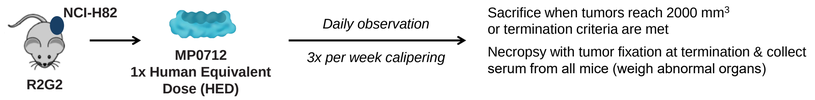




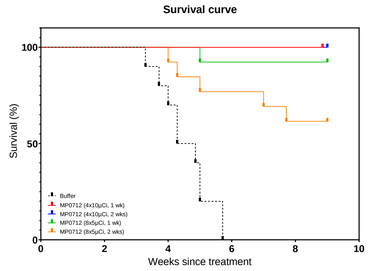
- MP0712 biodistribution studies done in different mouse models expressing DLL3
- ^{212}Pb-DOTAM-DARPin injected 1x10µCi at 0.01mg/kg

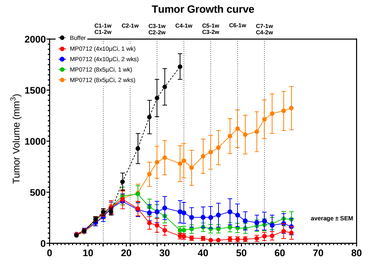
- MP0712 reached T:K ratios >2 in mouse models matching clinically relevant DLL3 expression levels
- Selective uptake in DLL3-expressing tumors confirmed high target specificity of MP0712

MP0712 demonstrated good efficacy & complete tumor reduction



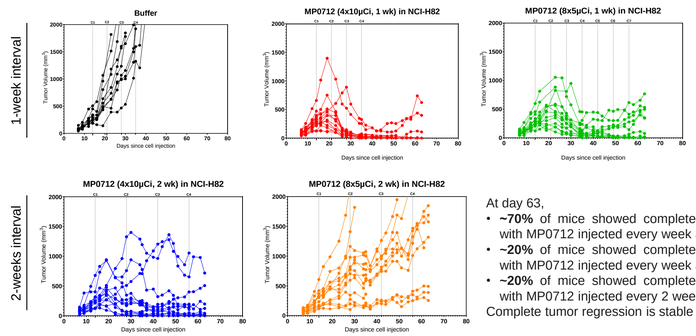
	A	B	C	D	E
Molecules	Buffer only	MP0712			
Dose	4 x buffer	4 x 10 µCi (40 µCi cumulative)		8 x 5 µCi (40 µCi cumulative)	
Interval	1 week	1 week	2 weeks	1 week	2 weeks





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

MP0712 was injected 4 x 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. Animals were under observation daily and 3x per week tumors were measured by caliper. Animals were sacrificed when tumors reached 1500 to 2000mm^3 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

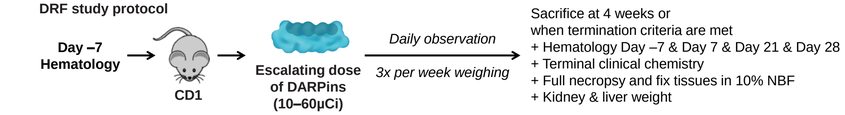
Complete tumor regression is stable after treatment

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

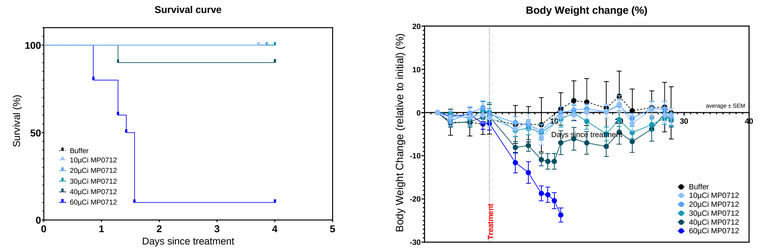
- MP0712 treatment resulted in complete tumor regression
- Significant effect for the doses of 4 x 10 µCi injected every week and every 2 weeks
- Significant effect for the doses of 8 x 5 µCi injected every week but not significant when injected every 2 weeks

MP0712 showed a favorable safety profile

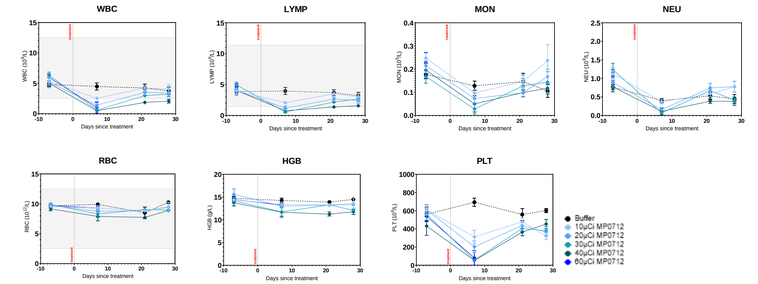
DRF study protocol



Survival curves and BW change (%)



Hematology profile



- 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 ^{212}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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Conflict of interest disclosures: All authors with affiliation 1) are employees and stock owners of Molecular Partners; and all authors with affiliation 2) are employees of Orano Med.

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

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