

Preclinical Assessment of ^{212}Pb - Radio-DARPin Therapeutic (RDT) Targeting DLL3 in SCLC



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Disclosures

- The presented research was funded by Molecular Partners and Orano Med
- All authors are employees of Molecular Partners or Orano Med
- Amelie Croset owns stocks in Molecular Partners

MP0712, the first ^{212}Pb -DLL3 targeted radiotherapy under investigation

Combining distinctive DARPin features with the power of ^{212}Pb for efficacious cancer therapy



HALF-LIFE
EXTENSION

**Tunable
albumin binding**

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**

SCLC as indication

- **Aggressive cancer** with high **unmet medical need**
 - 2L: mPFS ~3m; 5y OS ~3%^{1,2}
- **DLL3 is expressed in >85% of patients**³

DLL3 – a promising target

- **Homogeneous tumor expression**, but low expression level in patients
- No expression in healthy tissues
- **New treatments** with **room for improvement**: Tarlatamab (AMGEN) for 2L+; ORR ~40%

Molecular Partners

- **New class of therapeutics**: Designed Ankyrin Repeat Proteins (DARPins)
- **DARPins close gap** between small molecules and antibodies
- **7 clinical-stage compounds**, > 2500 patients treated

^{212}Pb for Targeted Alpha Therapy

- **Strong cytotoxicity** (dsDNA breaks)
- **Single alpha decay** (limited free daughters)
 - Limited irradiation of healthy tissues
- Relatively **short half-life** (10.6 h)
 - **Fast energy deposition** (efficacy)
 - **Easier waste management**

Collaboration with Orano Med

- The **leader** for ^{212}Pb & a committed partner
- **Reliable & scalable ^{212}Pb production**
- **Independent production capacities** (substantial inventory of purified ^{232}Th)

ASCO: Ph2 clinical data

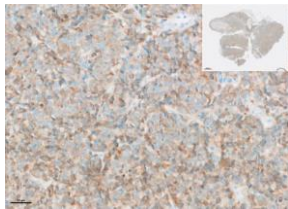
^{212}Pb -DOTAMTATE (AlphaMedix™)

*showed an **ORR of 55.6%**⁴*

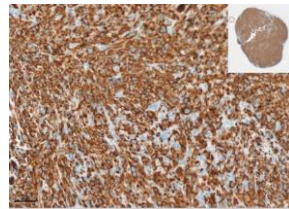
MP0712 showed favorable biodistribution and tumor specificity

DLL3 expression & distribution by IHC

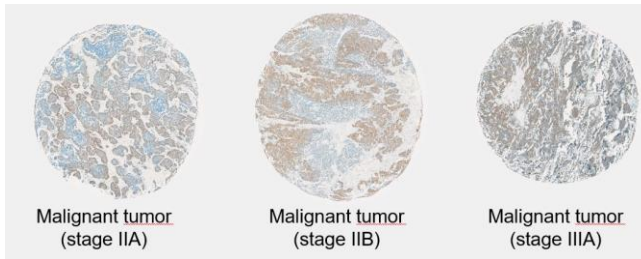
NCI-H82 tumors



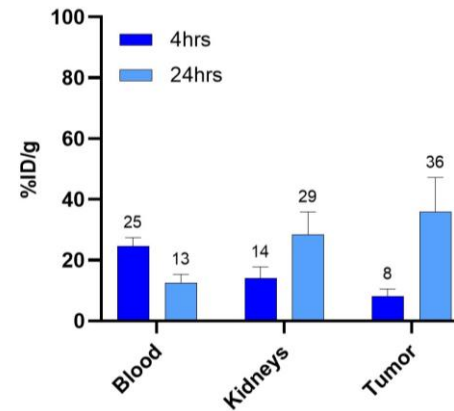
hDLL3-MC38 tumors



Human SCLC tumors



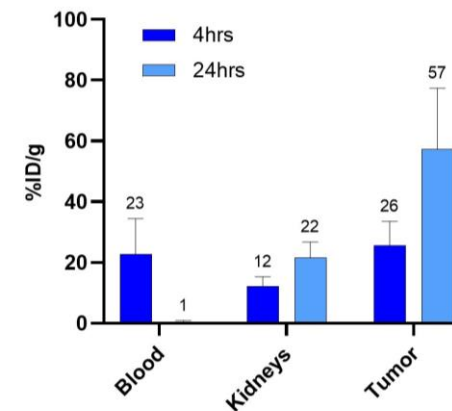
R2G2 mice xenografted s.c. with NCI-H82



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



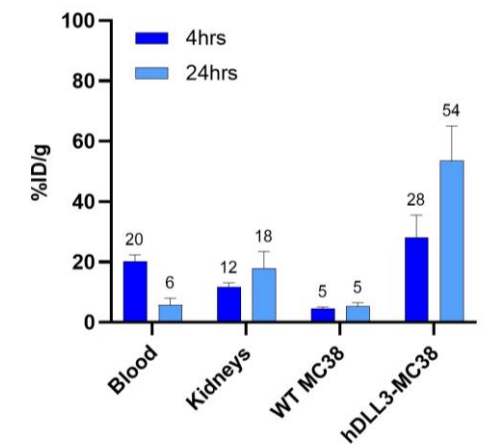
R2G2 mice xenografted i.v. with NCI-H82



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



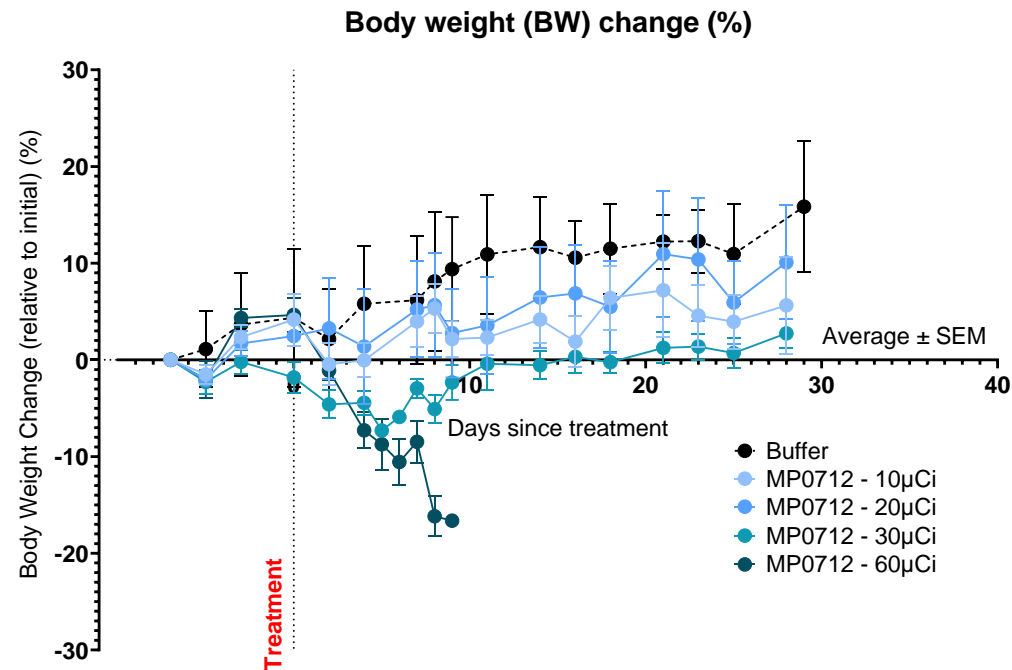
ATH nude mice double xenografted s.c. with hDLL3-MC38 + WT-MC38



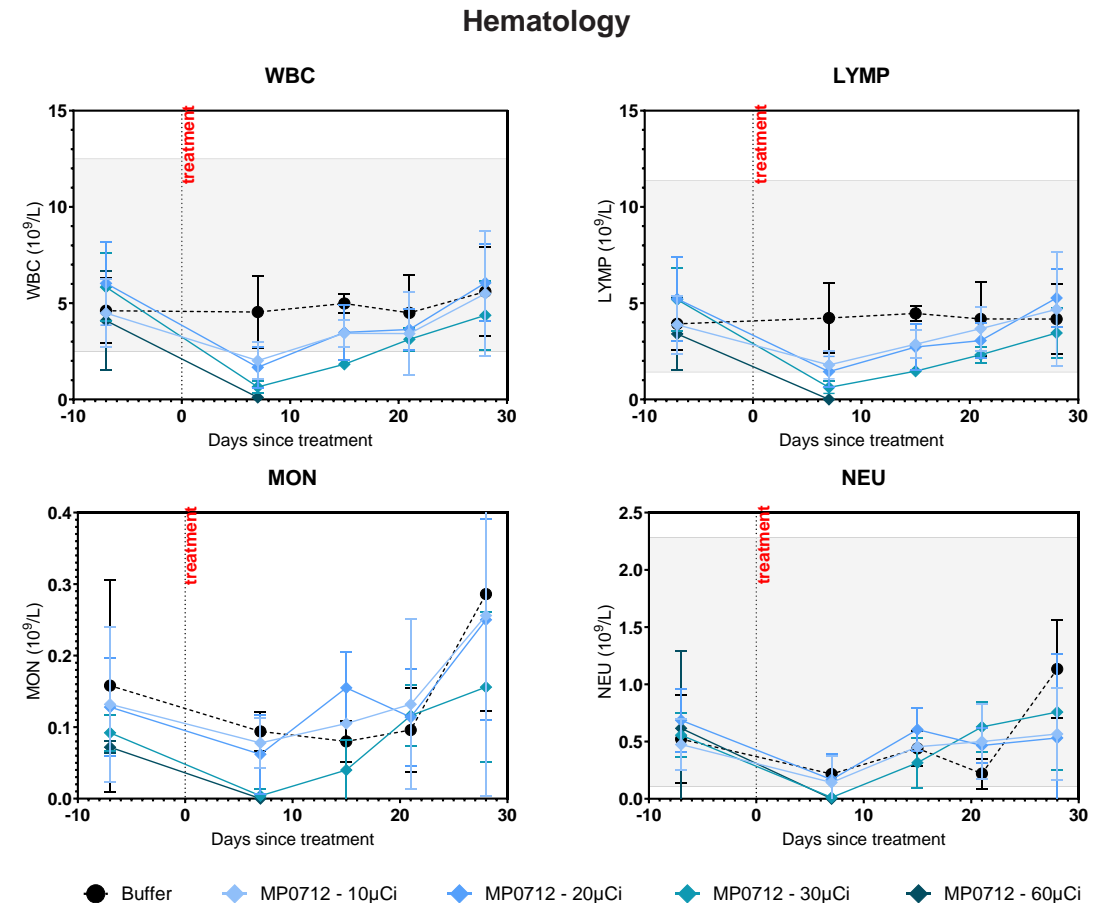
T:K at 4h = 2.4 / at 24h = 3

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

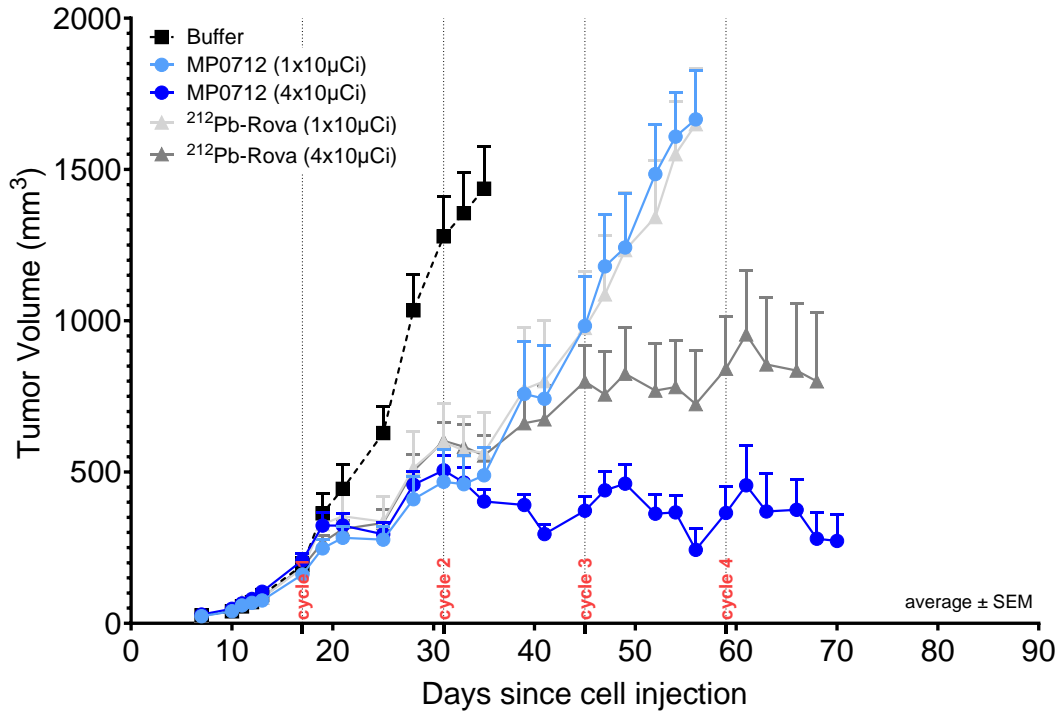
MP0712 showed a favorable safety profile



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



MP0712 showed good efficacy & tumor stabilization



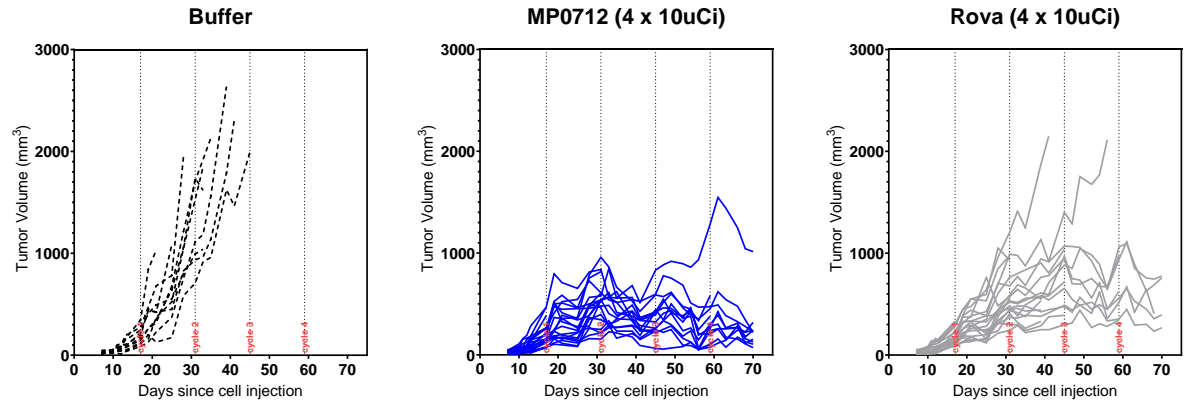
Median survival

Buffer	MP0712 1x10 μ Ci	MP0712 4x10 μ Ci	Rova 1x10 μ Ci	Rova 4x10 μ Ci
4.7 wks	7.9 wks	15.7 wks	7.9 wks	8.9 wks



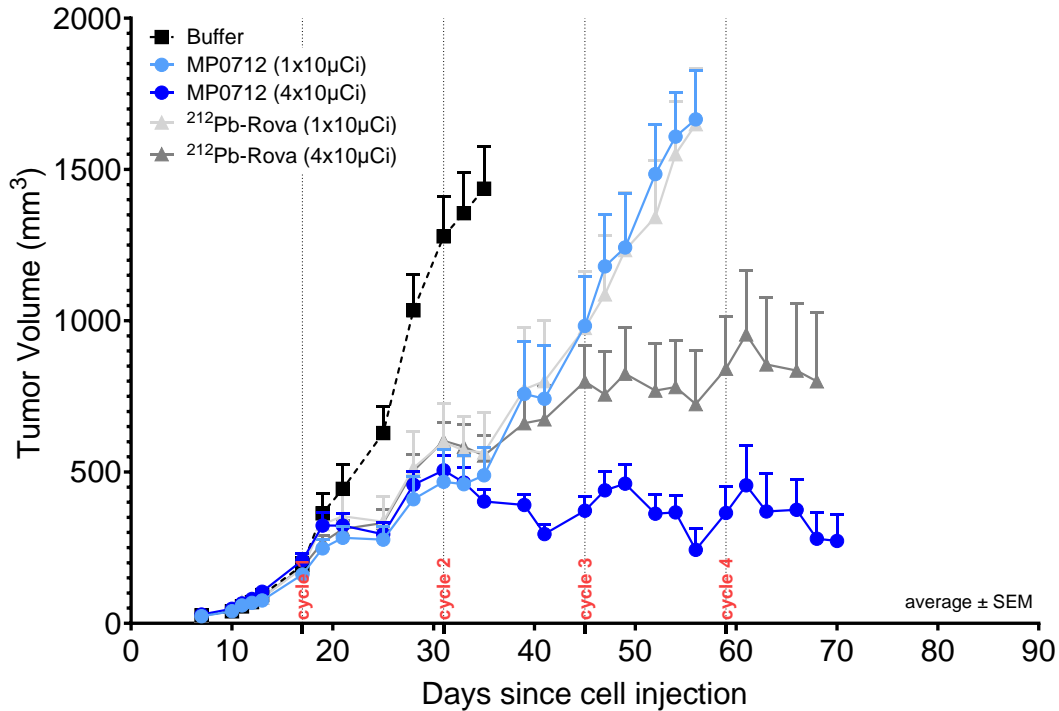
R2G2 mice xenografted s.c. with
NCI-H82

Tumor growth curve for each animal



- **MP0712 induced tumor stabilization in NCI-H82 tumor model**

MP0712 showed good efficacy & tumor stabilization



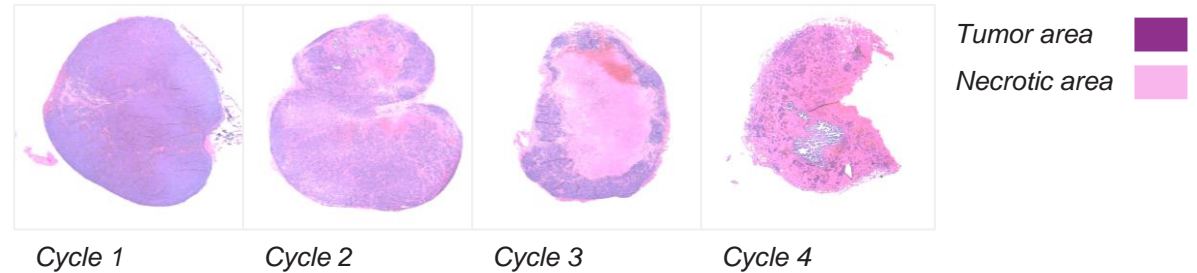
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R2G2 mice xenografted s.c. with
NCI-H82

Effect of MP0712 cycles in tumor vs necrotic area

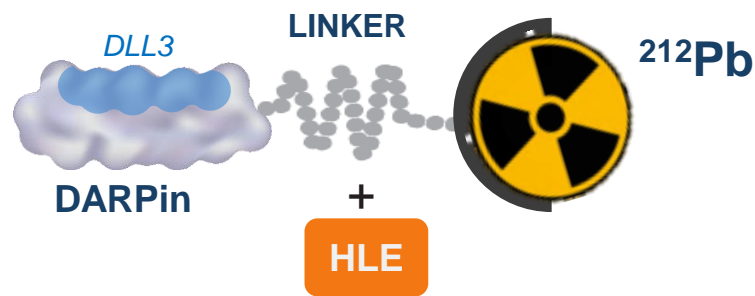


- Significant effect of MP0712 treatment on tumor vs necrotic tissue after cycles 3 and 4.

- **MP0712 induced tumor stabilization in NCI-H82 tumor model**
- **A significant induction of necrotic vs tumor tissue was observed post MP0712 treatment**

Summary

- ✓ **MP0712, the first ^{212}Pb -DLL3 Targeted Radio-DARPin Therapy**
 - High tumor uptake observed
 - Reached T:K > 2 in mouse models expressing DLL3
 - Showed a favorable safety profile *in vivo* up to 30 μCi
 - Induced good efficacy & tumor stabilization
- ✓ **IND-enabling package** working towards completion
- ✓ **Initial FIH clinical data expected in 2025!***



TARGET	RESEARCH	PRECLINICAL	RIGHTS
DLL3	MP0712		MOLECULAR partners
Target 2			oranomed
Target A			MOLECULAR partners
Target B			
Target X			NOVARTIS
Target Y			
Several targets in evaluation			

Outlook

- **Advance MP0712 and additional pipeline candidates**
- **Continue to evolve our RDT platform**
- **Progress collaboration projects with Orano Med**

Acknowledgments

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Contributing authors of this presentation

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Thank you for your interest!

