[^{225}Ac]Ac-SSO110 and [^{177}Lu]Lu-SSO110 demonstrate significantly better efficacy than [^{225}Ac]Ac-DOTA-TATE in the treatment of SSTR2-positive tumor xenografts

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Background/Aim

SSO110 (DOTA-JR11) is a somatostatin receptor 2 (SSTR2) antagonist currently under clinical development as [^{177}Lu]Lu-SSO110 in small cell lung cancer (SCLC). Compared to SSTR2 agonist, SSO110 targets a significantly higher number of binding sites and has longer residence time on SSTR2-positive tumor cells. DOTA-TATE and DOTAM-TATE coupled to the α-emitters ^{225}Ac and ^{212}Pb, respectively, are currently being tested in clinical studies. Since [^{177}Lu]Lu-SSO110 demonstrated significantly better efficacy than [^{177}Lu]Lu-DOTA-TATE in different xenograft models[1,2] the aim of this study was to identify the optimal isotope(s) (^{225}Ac, ^{212}Pb, ^{161}Tb, ^{177}Lu) for SSO110 (Fig. 1). Further, the anti-tumor efficacy of [^{177}Lu]Lu-SSO110 and [^{225}Ac]Ac-SSO110 was compared to [^{225}Ac]Ac-DOTA-TATE.

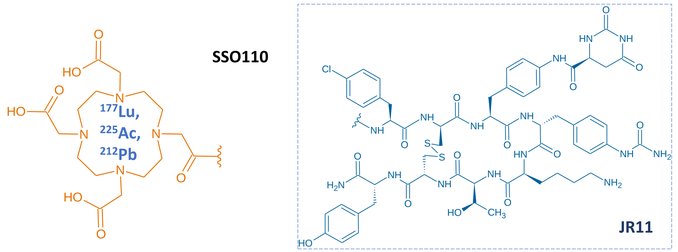


Figure 1: Structure of the antagonist SSO110 (DOTA-JR11) and SSO110 (JR11)

Materials and Methods

Quality control of radiolabeled compounds

- Radiolabeling purity of all compounds used in the studies was ≥ 95%, assessed by High-Performance Liquid Chromatography (HPLC) and/or instant Thin Layer Chromatography (iTLC).

In-vivo biodistribution studies

- Balb/c nude mice were engrafted with SSTR2+ NCI-H69 tumor cells (xenograft model for SCLC).
- For assessment of [^{225}Ac]Ac-SSO110 distribution, tumor-bearing mice (n=4) were injected with 90 kBq/1 µg [^{225}Ac]Ac-SSO110 and biodistribution (%ID/g) was assessed in harvested organs/tissues at 4h, 24h, 96h using liquid scintillation counting.
- For assessment of [^{212}Pb]Pb-SSO110 distribution, tumor-bearing mice (n=5) were injected with 450 kBq/1 µg [^{212}Pb]Pb-SSO110 and %ID/g was assessed at 1h, 4h, 24h using a gamma counter.

In-vivo efficacy studies

- Efficacy studies were performed in the SSTR2+ NCI-H69 xenograft model mice.
- Mice were randomized based on tumor volume before start of treatments.
- In single- (n=5/6) and multi-dose (n=5 for 750 kBq [^{212}Pb]Pb-SSO110, n=10 for all other groups) studies, treatment with [^{177}Lu]Lu-SSO110 was compared to [^{212}Pb]Pb-SSO110 and SSO110, with an average tumor volume at treatment start of 240 mm^3 and 260 mm^3, respectively.
- Escalating single-doses (n=8/9) of [^{225}Ac]Ac-SSO110 were compared to [^{177}Lu]Lu-SSO110, [^{225}Ac]Ac-DOTA-TATE and vehicle, with an average tumor volume at treatment start of 160 mm^3.
- All mice were monitored for clinical signs and body weight changes throughout the studies. Other safety-relevant endopints (organ weights, blood chemistry) were included at end of study.

High tumor uptake of ^{225}Ac- and ^{212}Pb-labeled SSO110 in NCI-H69 xenograft model

- ^{225}Ac- and ^{212}Pb-labeled SSO110 demonstrated high tumor uptake of 10.3 %ID/g and 4.7 %ID/g, respectively, at 4 h post injection (p.i.) (Fig. 2).
- The highest normal tissue uptakes for ^{225}Ac- or ^{212}Pb-labeled SSO110 were observed in kidneys (13.9% ID/g or 10.5% ID/g, respectively), followed by pancreas (1.2% ID/g or 0.9% ID/g, respectively) and stomach (1.3% ID/g or 0.6% ID/g, respectively).
- [^{225}Ac]Ac-SSO110 showed tumor-to-kidney ratios that increased from 0.75 (4h) to 1.4 (96h) over time indicating clearance from kidney while being retained in the tumor.
- For [^{212}Pb]Pb-SSO110, tumor to kidney ratios stayed lower and constant at 0.4 over time (1h, 4h, 24h).

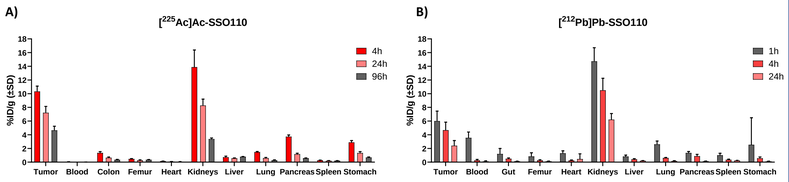


Figure 2: Ex-vivo biodistribution of **A)** [^{225}Ac]Ac-SSO110 and **B)** [^{212}Pb]Pb-SSO110 in NCI-H69 tumor-bearing mice.

[^{212}Pb]Pb-SSO110 does not prolong median survival compared to [^{177}Lu]Lu-SSO110 in NCI-H69 xenograft model

- In the single-dose study, 21.5 MBq [^{177}Lu]Lu-SSO110 and different doses of [^{212}Pb]Pb-SSO110 showed significant and comparable tumor growth delay and prolongation of survival (Fig. 3A).
- In the multi-dose study, administration of 20 MBq [^{177}Lu]Lu-SSO110 Q2W x 3 was more effective (100% complete tumor remissions) than different regimens and doses of [^{212}Pb]Pb-SSO110 (max. 50% complete tumor remissions) until the end of the study.

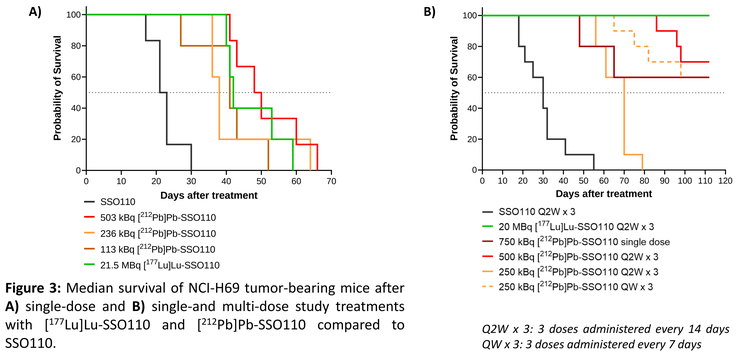
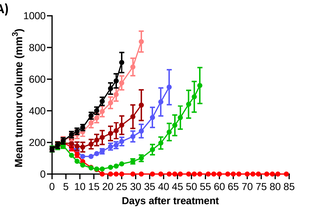


Figure 3: Median survival of NCI-H69 tumor-bearing mice after **A)** single-dose and **B)** single-and multi-dose study treatments with [^{177}Lu]Lu-SSO110 and [^{212}Pb]Pb-SSO110 compared to SSO110.

Q2W x 3: 3 doses administered every 14 days
QW x 3: 3 doses administered every 7 days

Complete tumor regression observed with single dose [^{225}Ac]Ac-SSO110 but not with [^{225}Ac]Ac-DOTA-TATE in NCI-H69 xenograft model

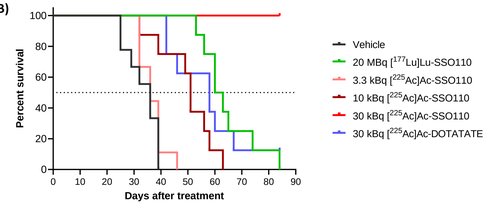
- Significant tumor growth inhibition was observed in all treatment groups (except 3.3 kBq [^{225}Ac]Ac-SSO110) (Fig. 4A).
- Single dose of 30 kBq [^{225}Ac]Ac-SSO110 and 20 MBq [^{177}Lu]Lu-SSO110 showed superior tumor volume reduction compared to 30 kBq [^{225}Ac]Ac-DOTA-TATE (Fig. 4A).
- Injection of only 30 kBq [^{225}Ac]Ac-SSO110 induced durable complete responses in the NCI-H69 model, resulting in 100% survival of treated mice (Fig. 4B).



Day 25: Vehicle vs.	Significance
20 MBq [^{177}Lu]Lu-SSO110	p<0.0001
3.3 kBq [^{225}Ac]Ac-SSO110	p=0.3601
10 kBq [^{225}Ac]Ac-SSO110	p=0.0015
30 kBq [^{225}Ac]Ac-SSO110	p<0.0001
30 kBq [^{225}Ac]Ac-DOTA-TATE	p<0.0001

Day 25: 30 kBq [^{225}Ac]Ac-DOTA-TATE vs.	Significance
Vehicle	p<0.0001
20 MBq [^{177}Lu]Lu-SSO110	p=0.0029
3.3 kBq [^{225}Ac]Ac-SSO110	p<0.0001
10 kBq [^{225}Ac]Ac-SSO110	p=0.4007
30 kBq [^{225}Ac]Ac-SSO110	p=0.0004

Two-Way ANOVA (Geisser-Greenhouse Correction, Dunnett's multiple comparison test



Treatment	Median survival
Vehicle (control)	36 days
20 MBq [^{177}Lu]Lu-SSO110	61.5 days
3.3 kBq [^{225}Ac]Ac-SSO110	36 days
10 kBq [^{225}Ac]Ac-SSO110	51 days
30 kBq [^{225}Ac]Ac-SSO110	Not defined
30 kBq [^{225}Ac]Ac-DOTA-TATE	58 days

Figure 4: A) Mean tumor volumes and **B)** Survival of mice treated with [^{177}Lu]Lu-SSO110 , [^{225}Ac]Ac-SSO110, and [^{225}Ac]Ac-DOTA-TATE in the NCI-H69 xenograft model.

Conclusions & Outlook

- ✓ **Complete durable responses were observed after treatment with [^{225}Ac]Ac-SSO110 but not with [^{225}Ac]Ac-DOTA-TATE in the NCI-H69 xenograft model.**
- ✓ Single dose of [^{177}Lu]Lu-SSO110 showed superior anti-tumor efficacy to [^{225}Ac]Ac-DOTA-TATE regarding tumor volume reduction and prolongation of median survival.
- ✓ [^{225}Ac]Ac-SSO110 showed high tumor uptake and its biodistribution profile is highly similar to [^{177}Lu]Lu-SSO110[2] as expected. [^{225}Ac]Ac-SSO110 was well tolerated.
- ✓ [^{177}Lu]Lu-SSO110 showed better efficacy than different regimens and doses of [^{212}Pb]Pb-SSO110 in in the NCI-H69 xenograft model, thus not warranting further investigations into [^{212}Pb]Pb-SSO110.
- ✓ Our data highlight the potential of [^{225}Ac]Ac-SSO110 and [^{177}Lu]Lu-SSO110 to outperform SSTR2-targeting agonists that are approved or in clinical development. The superior pharmacokinetic profile of SSO110 translates into higher pre-clinical efficacy with several isotopes.
- ✓ **These data warrant clinical investigation of [^{225}Ac]Ac-SSO110 and a Phase 1 clinical trial in SSTR2+ patients is planned to start in Q1/2025.**

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