^{225}Ac-SSO110 as next-generation SSTR2 targeting radiopharmaceutical for small cell lung cancer and other aggressive neuroendocrine neoplasms

Anika Jaekel, Prachi Desai, Manuel Sturzbecher-Hoehne, Dennis Mewis, Germo Gericke, Manfred Ruediger
Ariceum Therapeutics GmbH, Berlin, Germany

Abstract number: 575

Background/Aim

SSO110 (DOTA-JR11) is a somatostatin receptor 2 (SSTR2) antagonist currently under clinical development in small cell lung cancer (SCLC). Binding of SSO110 targets a higher number of SSTR2 binding sites (Fig. 1) and shows longer tumor retention than the SSTR2 agonist DOTATATE translating into higher anti-tumor efficacy of ^{177}Lu-SSO110 compared to ^{177}Lu-DOTATATE.[1,2] The aim of this study was to identify the most potent radionuclide (^{225}Ac, ^{212}Pb, ^{161}Tb, ^{177}Lu) for SSO110 in comparison to DOTATATE to guide further clinical development.

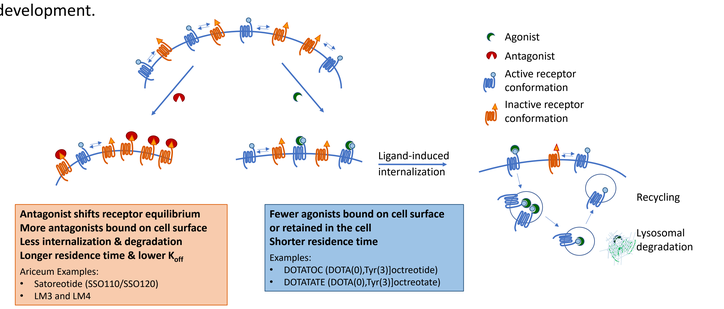

Figure 1: SSO110 differs from SSTR2 agonists by having a lower K_{off} rate and binding to the inactive receptor conformation.

Materials and Methods

Quality control of radiolabeled compounds

- Radiochemical 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 models

- Balb/c or Swiss nude mice were engrafted with SSTR2-positive NCI-H69 (SCLC model) or AR42J (pancreatic cancer model).
- Mice were randomized based on tumor volumes before start of treatments.

In vivo efficacy studies

- In the NCI-H69 model, single- (n=5/6) and three bi-weekly doses (n=10; Q2W x 3) of ^{212}Pb-SSO110 and ^{177}Lu-SSO110 were compared. Unlabelled SSO110 was included as control.
- In NCI-H69 and AR42J models, single-doses (n=7/8) of ^{225}Ac-SSO110, ^{161}Tb-SSO110, ^{177}Lu-SSO110 and ^{225}Ac-DOTATATE were compared. ^{161}Tb-DOTATATE was only evaluated in the SCLC model. Vehicle was injected as control.
- AR42J tumors were collected at the end of the study and evaluated histopathologically to assess mitotic index, %necrosis, and cellular phenotype after treatment with ^{225}Ac-SSO110 and ^{225}Ac-DOTATATE in comparison to vehicle.

Safety-related assessments

- All mice were monitored for clinical signs and body weight changes throughout the studies.
- Other safety-relevant endpoints (organ weights, blood chemistry) were analyzed at study end.
- In selected studies, histopathological assessment of intestines, kidneys, and liver was conducted at study end.

^{177}Lu-SSO110 shows superior anti-tumor efficacy over ^{212}Pb-SSO110 in a multi-dose study in the NCI-H69 SCLC xenograft model

- A single dose treatment with ^{212}Pb-SSO110 induced a dose-dependent delay in tumor growth.
- Interestingly, the effects of 21.5 MBq ^{177}Lu-SSO110 and 500 kBq ^{212}Pb-SSO110 on tumor volume reduction and growth delay were comparable (Fig. 2A).
- Multi-dose treatment with 20 MBq ^{177}Lu-SSO110 induced complete tumor remissions in 100 % of mice, leading to 100% survival, whereas 50% of mice treated with the highest dose of ^{212}Pb-SSO110 showed tumor re-growth (Fig. 2B).

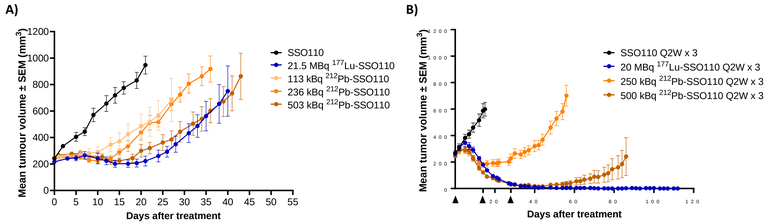

Figure 2: Mean tumor volumes after **A)** single-dose and **B)** multi-dose treatments of NCI-H69 SCLC tumor-bearing mice with ^{212}Pb-SSO110 and ^{177}Lu-SSO110. *Q2Wx3: 3 doses administered every 14 days*

Superior anti-tumor activity of SSO110 over DOTATATE across different isotopes (Lu-177, Ac-225, Tb-161)

- In a first study, a single dose of 30 kBq ^{225}Ac-SSO110 (human equivalent dose: 7.3 MBq) induced complete tumor remissions and long-term survival, in contrast to ^{225}Ac-DOTATATE, which at the same dose was less efficacious than a standard dose of 20 MBq ^{177}Lu-SSO110 (Fig. 3A).
- In a second study, 21 kBq and 42 kBq ^{225}Ac-SSO110 demonstrated significantly better anti-tumor activity than 42 kBq ^{225}Ac-DOTATATE, 20 MBq ^{161}Tb-DOTATATE and 20 MBq ^{161}Tb-SSO110 (Fig. 3B).
- 20 MBq ^{177}Lu-SSO110 was slightly more potent then 42 kBq ^{225}Ac-DOTATATE and 20 MBq ^{161}Tb-SSO110 (Fig. 3B).
- No adverse clinical side effects were observed up to the highest dose ^{225}Ac-SSO110 tested (90 kBq).

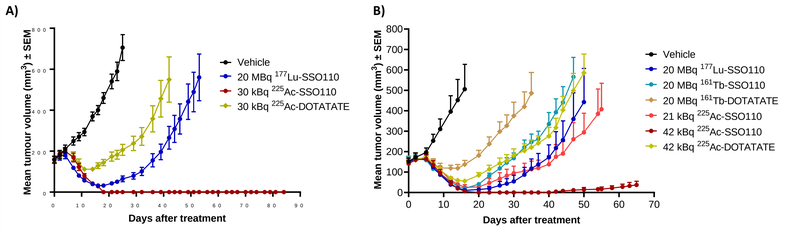

Figure 3: Mean tumor volumes of NCI-H69 tumor-bearing mice after single-dose treatments with **A)** ^{177}Lu-SSO110, ^{225}Ac-SSO110 and ^{225}Ac-DOTATATE and **B)** ^{177}Lu-, ^{161}Tb-, and ^{225}Ac-SSO110 and ^{161}Tb- and ^{225}Ac-DOTATATE.

Single doses of ^{225}Ac-SSO110 effectively control AR42J tumor growth, resulting in 100% survival

- 37 kBq ^{225}Ac-SSO110 induced tumor growth inhibition immediately after treatment, resulting in 100% survival (Fig. 4A, B).
- 37 kBq ^{225}Ac-DOTATATE could not control tumor growth and median survival was reached after 33 days.
- 20 MBq ^{161}Tb-SSO110 demonstrated moderately better efficacy than 20 MBq ^{177}Lu-SSO110.
- Histopathological assessment of tumors treated with 37 kBq ^{225}Ac-SSO110 showed a lower mitotic index, higher necrosis, and a regressing phenotype (Fig. 4C) of neoplastic cells compared to tumors treated with vehicle or 37 kBq ^{225}Ac-DOTATATE (Table 1).
- All treatments were well-tolerated.

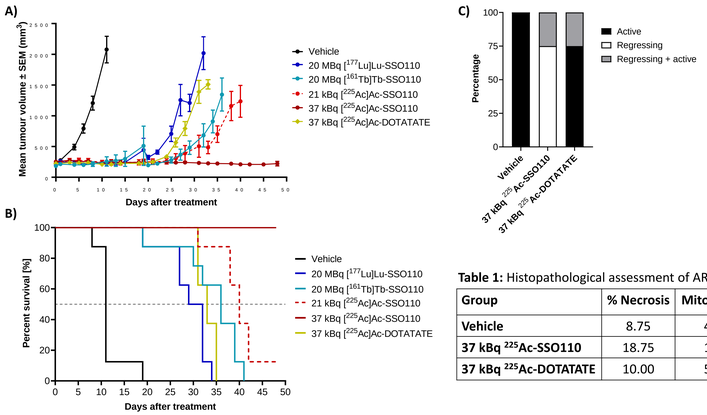

Table 1: Histopathological assessment of AR42J tumors

Group	% Necrosis	Mitotic index
Vehicle	8.75	40.75
37 kBq ^{225}Ac-SSO110	18.75	14.13
37 kBq ^{225}Ac-DOTATATE	10.00	52.25

Figure 4: A) Mean tumor volumes and **B)** percent survival of mice treated with ^{177}Lu-, ^{161}Tb-, ^{225}Ac-SSO110, and ^{225}Ac-DOTATATE in AR42J xenograft model. **C)** Histopathological assessment of tumor phenotypes after different treatments.

Conclusions & Outlook

- **The combination of Actinium-225 and SSO110 outperforms all other compounds** evaluated.
- **SSO110 shows superior efficacy over DOTATATE across all isotopes tested (Lu-177, Ac-225, Tb-161).**
- **^{212}Pb-SSO110 was not superior to ^{177}Lu-SSO110 and ^{225}Ac-SSO110**, likely due to the long tumor half-life of SSO110 (> 7 days), which aligns better with long-lived isotopes.
- ^{161}Tb-SSO110 demonstrated modestly better efficacy than ^{177}Lu-SSO110, but only in the AR42J model with high and homogenous target expression.
- Our data highlight the **potential of ^{225}Ac-SSO110 to outperform SSTR2-targeting agonists** that are either approved or in clinical development.
- Based on promising clinical data from LuSato1 (^{177}Lu-SSO110) and the exceptional preclinical activity of ^{225}Ac-SSO110, a global Phase I/II clinical study (SANTANA-225) is being initiated to evaluate ^{225}Ac-SSO110 in patients with ES-SCLC or Merkel Cell Carcinoma receiving immune checkpoint inhibitor monotherapy.

Contact

Anika Jaekel, PhD
Head of Translational Biology & Non-Clinical Pharmacology
Ariceum Therapeutics GmbH
Robert-Roessle-Str. 10, D-13125, Berlin, Germany
a.jaekel@ariceum-therapeutics.com
+0049 30 9489 3360

References

1. Plas, Pascale, et al. Comparison of the Anti-Tumour Activity of the Somatostatin Receptor (SST) Antagonist [^{177}Lu]Lu-Satoreotide Tetraxetan and the Agonist [^{177}Lu]Lu-DOTA-TATE in Mice Bearing AR42J SST2-Positive Tumours. Pharmaceuticals 15.9 (2022): 1085.
2. Dalm, Simone U. Comparison of the therapeutic response to treatment with a ^{177}Lu-labeled somatostatin receptor agonist and antagonist in preclinical models. Journal of Nuclear Medicine February 2016, 57 (2) 260-265