Comparison of the anti-tumoral activity of two somatostatin receptor ligands radiolabeled with Lutetium-177 (satoreotide tetraxetan [SSO110] and DOTA-TATE) as monotherapy or combined with chemotherapy in mice bearing AR42J SSTR2-positive tumors

Olivier Raguin[(1)], Marcel Krueger[(2)], Peggy Provent[(1)], Funda Cay[(2)], Elodie Marie Dit Chatel [(1)], Marie Lux[(1)], Ben Pais[(3)], Cyril Berthet[(1)]

[(1)] Oncodesign-services, 21000 Dijon, France, [(2)] Werner Siemens Imaging Center, Germany, [(3)] SRT-Biomedical, Netherlands, consultant to Ariceum Therapeutics, Berlin, Germany

#5044

Scan the QR-code to receive an electronic copy

Introduction

Background:

SSTR2: Somatostatin receptor type 2

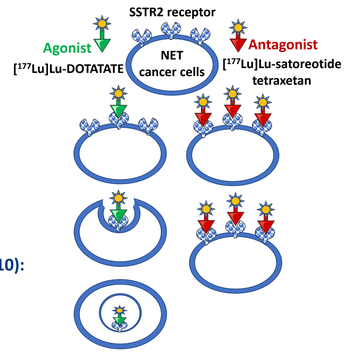
- High expression in low-grade Gastro-Entero-Pancreatic Neuroendocrine Tumors (GEP-NETs)
- A valuable therapeutic target

[^{177}Lu]Lu-DOTA-TATE: SSTR2 agonist

- Established clinical treatment for GEP-NETs

[^{177}Lu]Lu-satoreotide tetraxetan (= [^{177}Lu]Lu-SSO110): SSTR2 antagonist

- Higher affinity to SSTR2 positive tumor cells[(1)]
- Higher level of DNA double strand breaks [(1)]



OBJECTIVES:

1. Compare the *in vivo* anti-tumoral activity and the potential toxicity of [^{177}Lu]Lu-satoreotide tetraxetan to that of [^{177}Lu]Lu-DOTA-TATE

2. Study the anti-tumoral activity and the potential toxicity of [^{177}Lu]Lu-satoreotide tetraxetan combined with CAPTEM chemotherapy (Capecitabine + Temozolomide)

Methods & Experiments

Animals:

- Female Swiss *Nude* mice obtained from Charles River
- Tumor induced by subcutaneous injection of rate AR42J tumor cells into the right flank of animals
- Monitoring:
  - Animal physical well-being was monitored daily
  - Body weight and tumor volume were monitored at least twice weekly
- All procedures with animals were approved by the responsible local authorities (Regierungspraesidium Tuebingen, Tuebingen, Germany, licence R12/19G + R01/20G).

Treatments:

1. Comparison of anti-tumoral activity:

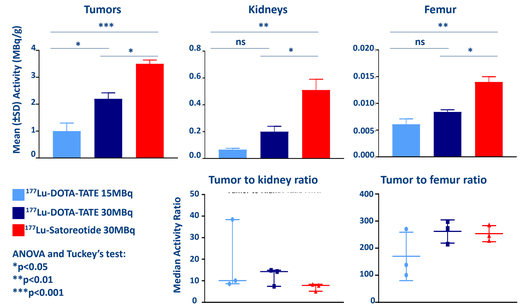
	Treatment	n	Route	Schedule
1	Vehicle	10	Intravenous	once weekly, 4 weeks
2	^{177}Lu-satoreotide tetraxetan 15 MBq	15	Intravenous	once weekly, 4 weeks
3	^{177}Lu-DOTA-TATE 15 MBq	15	Intravenous	once weekly, 4 weeks
4	^{177}Lu-DOTA-TATE 30 MBq	10	Intravenous	once weekly, 4 weeks

2. Combined therapies:

	Treatment	n	Route	Schedule
1	Vehicle	8	Intravenous	once weekly, 4 weeks
2	+ 200 mg/kg Capecitabin and 20 mg/kg Temozolomide (CAPTEM)	8	Oral	
3	^{177}Lu-satoreotide tetraxetan 15 MBq	8	Intravenous	once weekly, 4 weeks
4	^{177}Lu-satoreotide tetraxetan 15 MBq + 200 mg/kg Capecitabin and 20 mg/kg Temozolomide (CAPTEM)	8	Intravenous Oral	once weekly, 4 weeks
5	^{177}Lu-satoreotide tetraxetan 20 MBq	11	Intravenous	once weekly, 3 weeks
6	^{177}Lu-satoreotide tetraxetan 20 MBq + 200 mg/kg Capecitabin and 20 mg/kg Temozolomide (CAPTEM)	11	Intravenous Oral	once weekly, 3 weeks

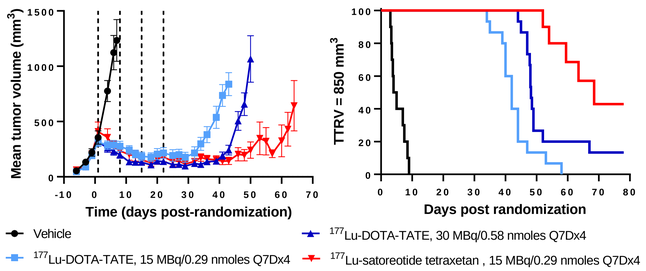
Results

- **Biodistribution of [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-satoreotide tetraxetan at 96 h after the fourth injection of the radiopharmaceuticals:**



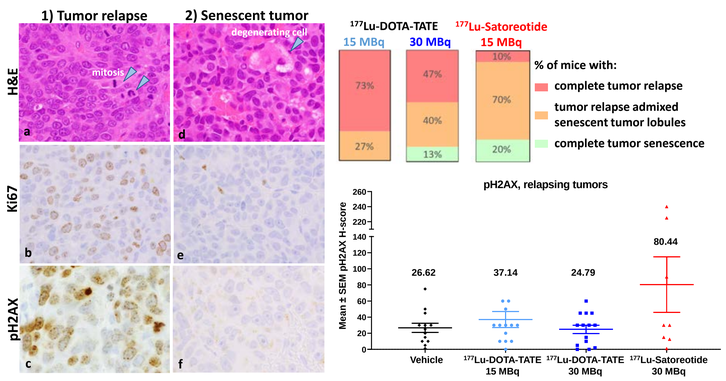
→ **[^{177}Lu]Lu-satoreotide tetraxetan exhibited higher tumor uptake and similar tumor-to-kidney and tumor-to-femur ratios compared with [^{177}Lu]Lu-DOTA-TATE.**

- **Anti-tumoral effects of [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-satoreotide tetraxetan:**
  Treatments started on D0 and ended on D21.



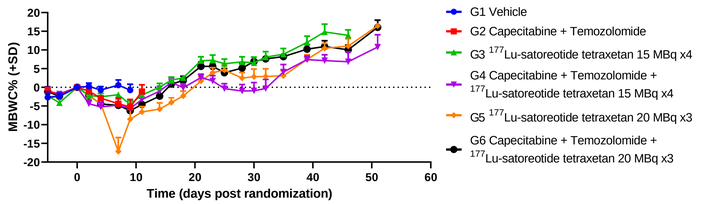
→ **[^{177}Lu]Lu-satoreotide tetraxetan induced stronger delay of tumor relapse and longer median survival after monotherapy compared to [^{177}Lu]Lu-DOTA-TATE.**

- **Histopathological and immunohistochemical analyses at the end of the study: Two distinct tumor phenotypes were noted: 1) re-growing/relapsing and 2) senescent phenotypes:**



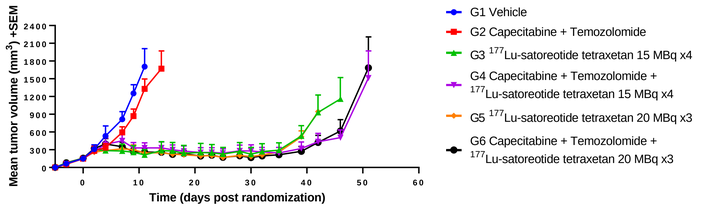
→ **At 15 MBq dose, tumor senescence was observed only for [^{177}Lu]Lu-satoreotide tetraxetan.**

- **Anti-tumoral activity study of [^{177}Lu]Lu-satoreotide tetraxetan combined with CAPTEM chemotherapy regimen in AR42J rat pancreatic tumor model**
  - **Mean body weight change:**



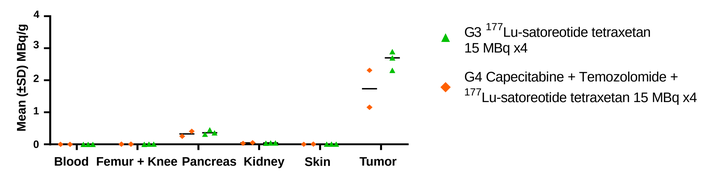
→ **Treatments were well tolerated, only a mild and transient BW loss was observed in all groups.**

  - **Anti-tumoral effect:**



→ **A complete response was observed after treatment with [^{177}Lu]Lu-satoreotide tetraxetan. No improvement with the chemotherapy regimen was recorded at this [^{177}Lu]Lu-satoreotide tetraxetan dose and in this tumor model.**

- **Biodistribution of [^{177}Lu]Lu-satoreotide tetraxetan at 15MBq alone or in combination with CAPTEM chemotherapy (24 hours post second [^{177}Lu]Lu-satoreotide tetraxetan treatment):**



→ **The biodistribution of [^{177}Lu]Lu-satoreotide tetraxetan was not modified by the CAPTEM regimen.**

Conclusion

Comparison of anti-tumoral activity:

- Repeated administrations of [^{177}Lu]Lu-satoreotide tetraxetan were able to potentiate peptide receptor radionuclide therapy with a **higher tumor uptake, a longer median survival** and a **favorable efficacy/safety profile** compared to [^{177}Lu]Lu-DOTA-TATE.

Combined therapy:

- CAPTEM chemotherapy regimen did not display any anti-tumoral activity in AR42J tumor-bearing mice model. The combination with ^{177}Lu-satoreotide tetraxetan did not improve the anti-tumoral activity of [^{177}Lu]Lu-satoreotide tetraxetan.
- The biodistribution of [^{177}Lu]Lu-satoreotide tetraxetan in AR42J tumors was not modified by the chemotherapy regimen.

[(1)] Plas P, Limana L, et al. Pharmaceuticals. 2022 Aug 30;15(9):1085. doi: 10.3390/ph15091085.

oncodesign-services.com

Follow us on LinkedIn!