



UNIVERSITY OF GOTHENBURG

^{211}At and Ovarian Cancer

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Background

- Research group led by Prof. Ragnar Hultborn and Prof. Lars Jacobsson (The TAT Group)
- Collaboration since 1994 in Gothenburg
- Radiation physics
- Oncology
- Nuclear chemistry

The Gothenburg efforts

- Labeling chemistry
- In vitro studies
- Animal studies
- Clinical studies (phase I study published)

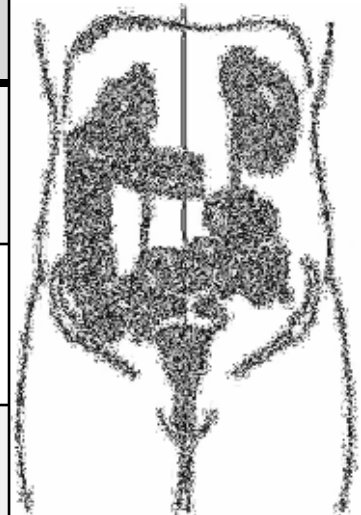
Overall aim:

To evaluate the efficacy and toxicity of ^{211}At , and other α -particle emitting nuclides.

Ovarian cancer

1–2% life time risk in European and American women.

Metastases	Frequency	Treatment	5-year survival
No	30%	Radical surgery	~85%
→ Abdominal	60%	Debulking surgery + chemotherapy	~35%
Distant	10%	Chemotherapy	~20%



A new additional therapy is needed.

Previous i.p. RIT of ovarian cancer

- Radionuclides used: ^{131}I , ^{90}Y (β -emitters).
- Promising results - but a phase III study was not successful.

Low absorbed doses to microscopic tumors owing to:

- **Too long half-life** (bone-marrow dose limiting due to high blood activity).
- **Too long particle range** for microscopic tumors.

Why ^{211}At ?

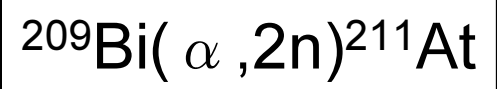
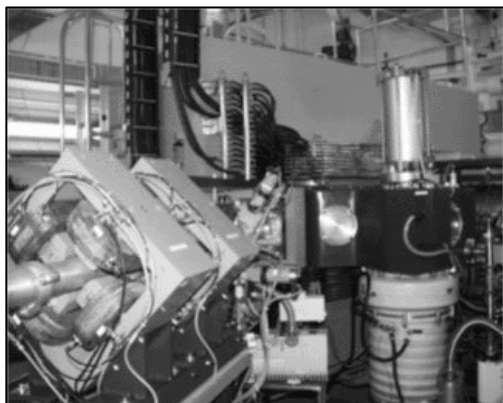
- The short range of the α -particles
 - High absorbed fraction in small tumors
- The high energy (high LET)
 - High abs. dose/decay, less dep. on cell cycle & oxygen
- The short half-life
 - Reduces normal tissue irradiation

Some concerns:

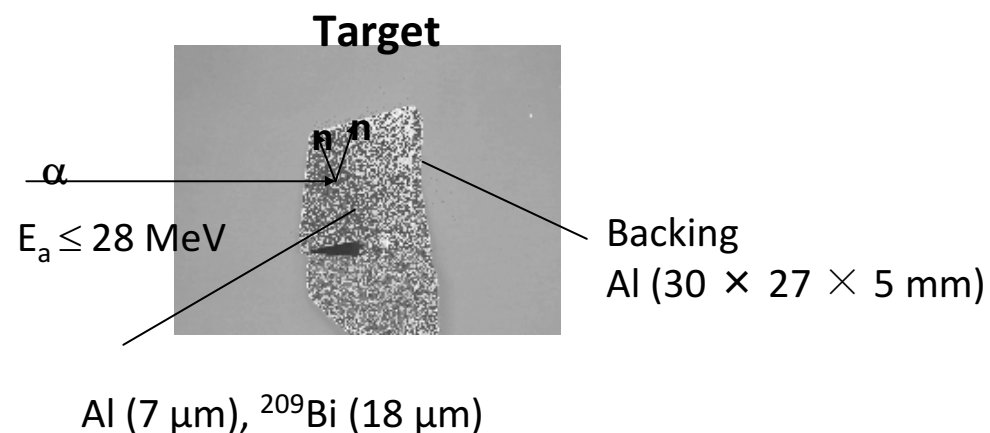
- Too short range
 - All tumor cells are not reached
- Normal tissue toxicity of the α -particles
 - Could decrease the therapeutic window
- Availability
 - Clinical applications may be difficult

Astatine production

PET and Cyclotron Unit, Rigshospitalet, Copenhagen



Energy: 28 MeV He⁺⁺
Irr. time: Up to 8 h
Yield: Max 2 GBq
Frequency: 2–3 times/month



Nude mice studies

Toxicity

Bone marrow:

White blood cell counts - RBE

J Nucl Med, 2005,46:464–71

Kidneys:

Glomerular filtration rate

Cancer Biother Radiopharm, In press

Peritoneum:

Trans membrane transport

Manuscript

Therapeutic efficacy

Local therapy: Intraperitoneal microscopic tumors

J Nucl Med 2005;46:1907–15

J Nucl Med 2006;47:1342–50

Int J Radiat Oncol Biol Phys 2006;66:1228–37

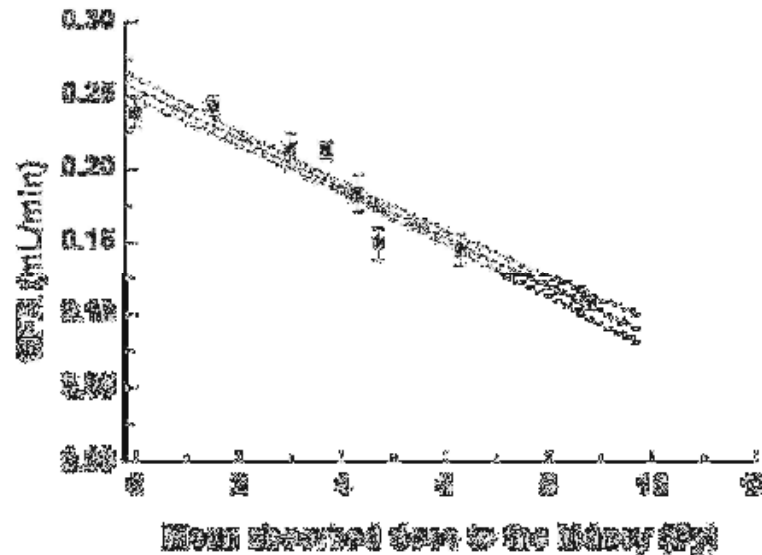
Nucl Med Biol 2006;33:1065–72

Macroscopic tumors

J Nucl Med 2005;46:2061–7

Renal toxicity in nude mice

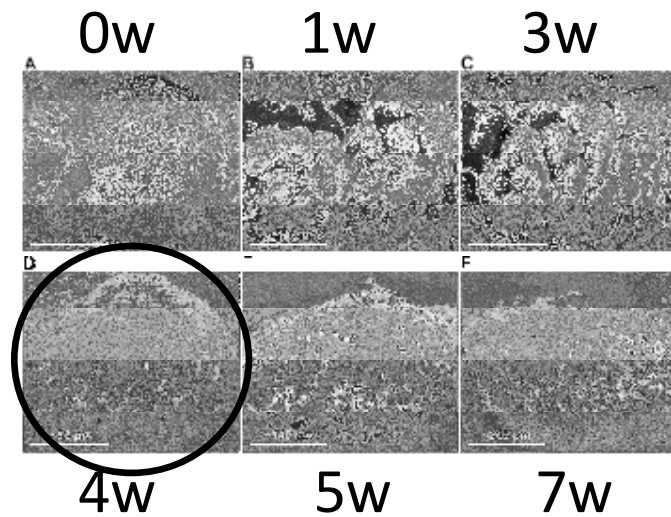
^{211}At -MX35 F(ab')₂



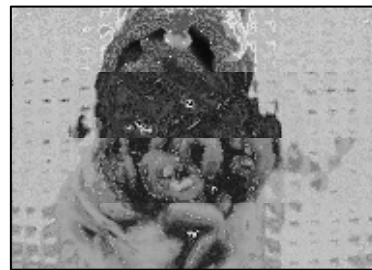
- Moderate kidney uptake.
- Tolerable mean absorbed dose to kidneys (~10 Gy).
- Renal toxicity is not critical in therapy using ^{211}At -MX35 F(ab')₂.

Nude mice tumor model

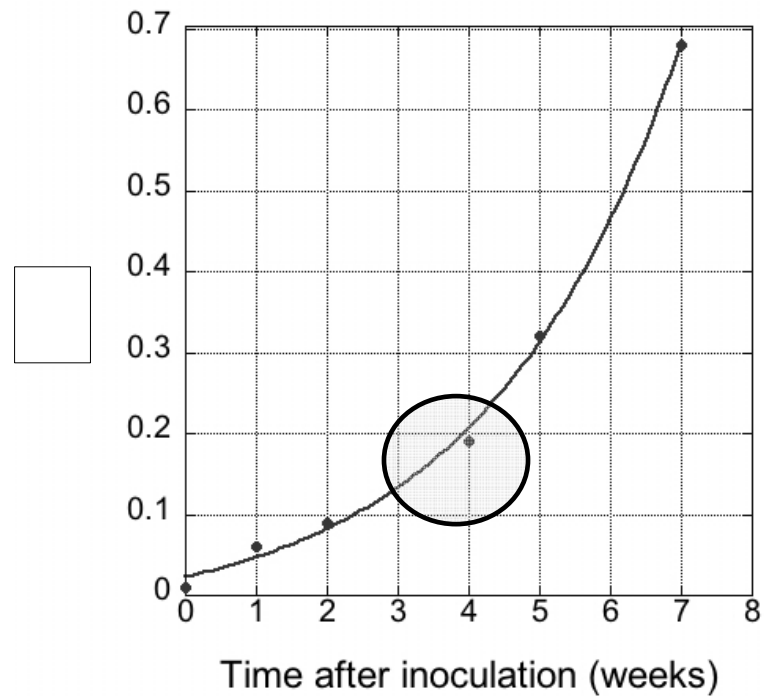
10^7 OVCAR-3 cells i.p.



Macroscopic tumors 8 weeks post treatment.



Maximal tumor diameter (mm)



Therapeutic efficacy on i.p. tumors

- Short term

Dissection 2 months after therapy:

- No macroscopic tumors
- No microscopic tumors
- No ascites

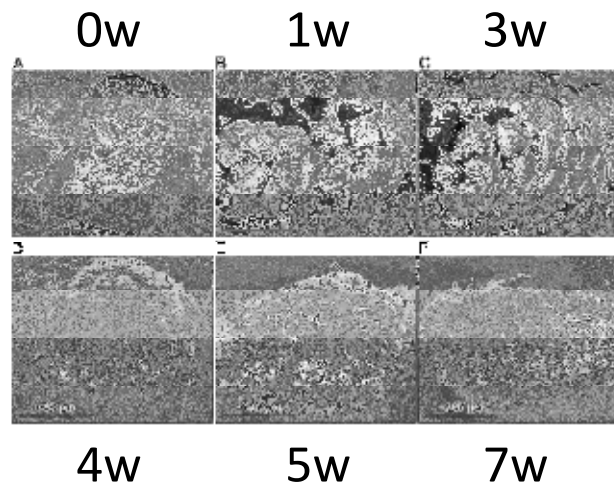
Tumor free fraction (TFF)



- Long term

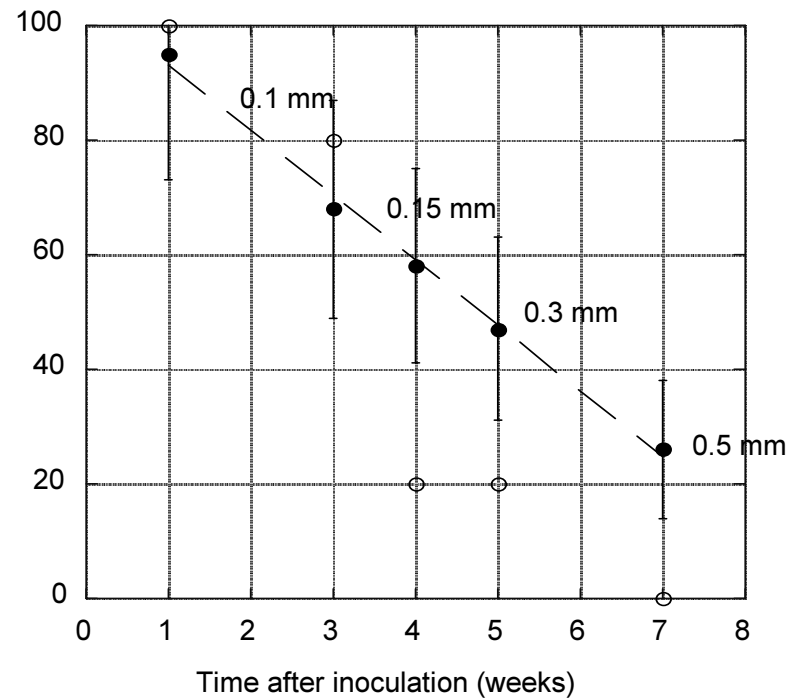
Dissection 7 months after therapy

Microscopic tumors - Efficacy related to tumor size

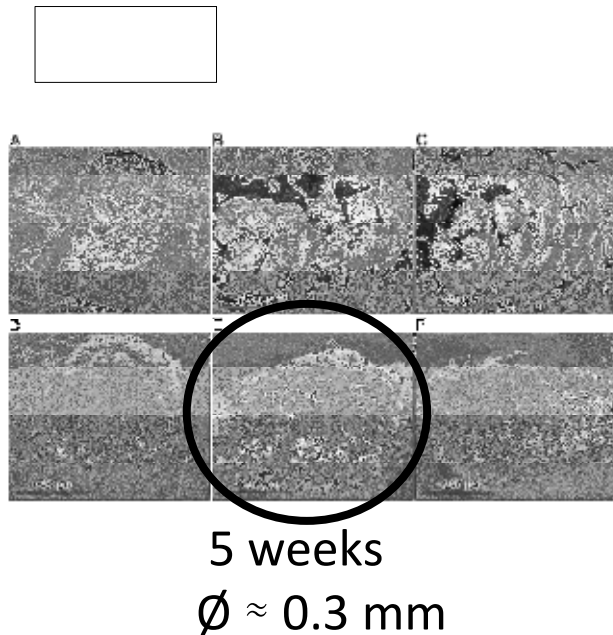


J Nucl Med 2006;47:1342–1350

Tumor free fraction (%) (400 kBq i.p.)

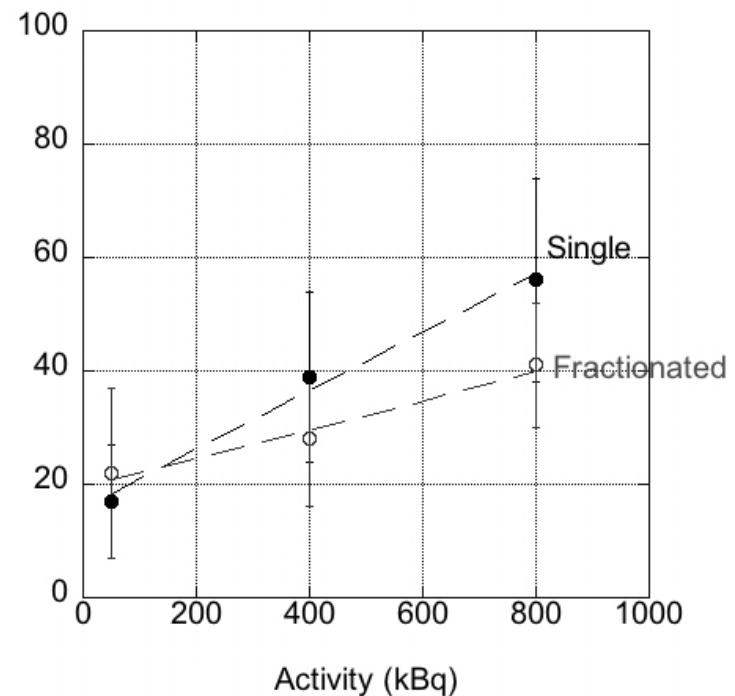


Microscopic tumors - Fractionated therapy, 3 in 8 days



**No gain in efficacy, but
lower myelotoxicity!**

Tumor free fraction (%)



Nucl Med Biol 2006;33:1065–1072

Clinical phase I study

- Women with recurrent ovarian cancer in remission after second line chemotherapy.
- No major adhesions in the peritoneal cavity.
- Informed consent.
- Nine patients included.

J Nucl Med 2009;50:1153–1160

Logistics of the phase I study

Preparations

- Laparoscopy
- Peritoneal catheter insertion
- Peritoneal scintigraphy with ^{99m}Tc
- Pretreatment with KClO_4 or KI (P. 6–9)

Sampling

- Blood (1–48h)
- I.p. fluid (1–24h)
- Urine (1–48h)
- Gamma camera (1–48 h)

Infusion/therapy

- 1–2 L Extraneal solution
- 33–120 MBq ^{211}At -MX35 F(ab')₂
- 0.2 MBq ^{125}I -HSA

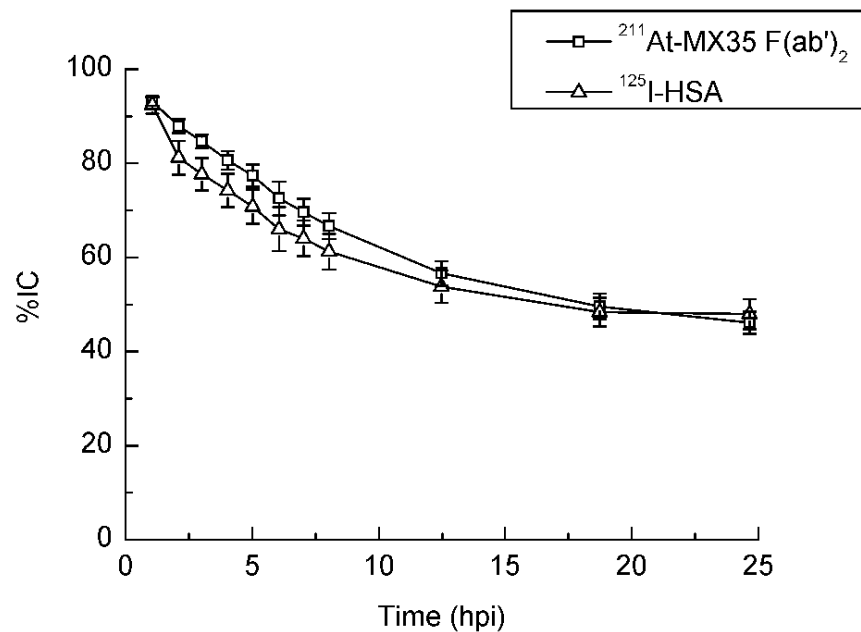
Follow up

- Hematology
- TSH
- Creatinine
- HAMA

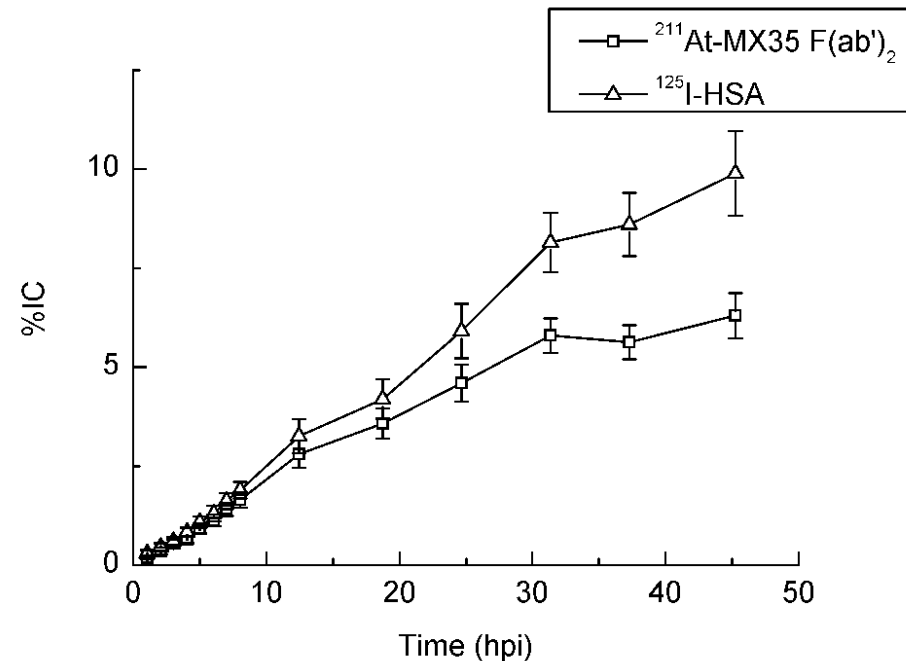
Pharmacokinetics in patients

Pharmacokinetics was related to the initial activity concentration (IC) of the infused $^{211}\text{At-MX35 F(ab')}_2$ solution.

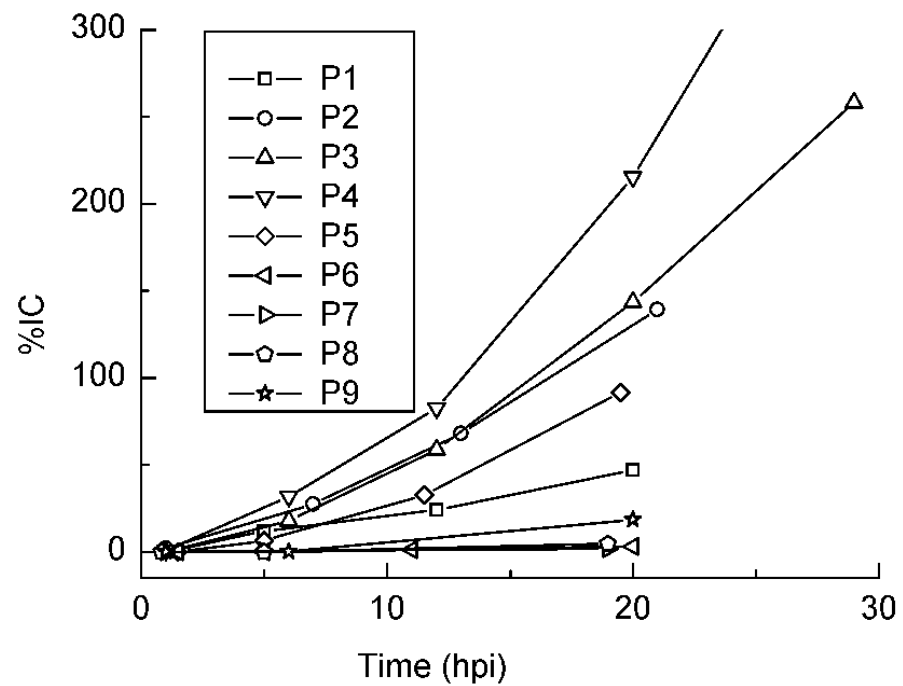
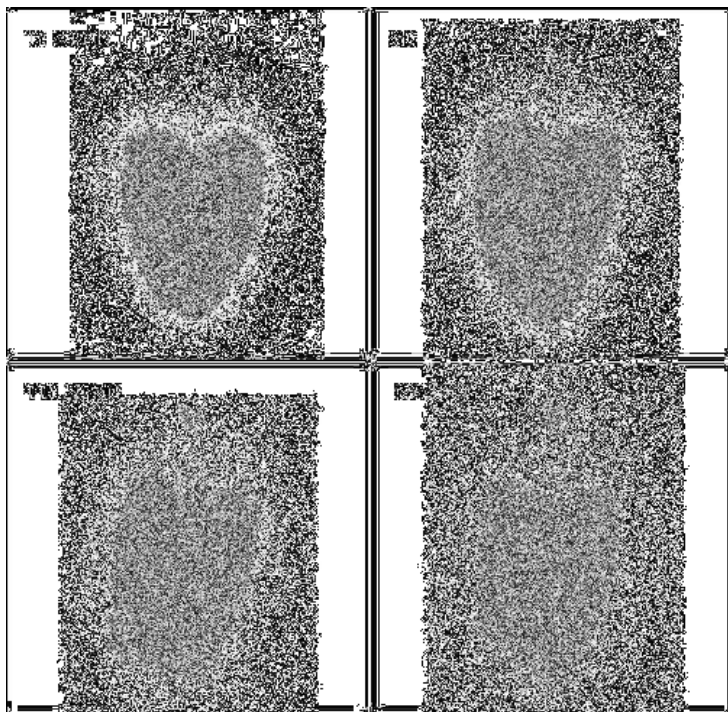
Peritoneal fluid



Plasma



Pharmacokinetics in patients - thyroid uptake



Conclusions phase I study

1. Intraperitoneal administration of ^{211}At -MX35 F(ab')₂ can most probably achieve therapeutic absorbed doses in microscopic intraperitoneal tumors, without observed or estimated toxicity.
2. Maximum tolerable absorbed dose to peritoneum in humans is not known.

The 9 patients:

- Two still without any sign of disease.
- Two with relapse, although not peritoneal.
- Five have died in their disease. Two without peritoneal relapse.
- Total: Only 3/9 have had peritoneal relapse ~4 y after therapy.

Note: The 9 patients included were all in a much more advanced stage than the intended patient population for a phase II-III study, which will be given the treatment directly after primary chemotherapy.

Motif for a phase II study

- Microscopic peritoneal tumors might be the cause of relapse
- Low radiation risk
- Feasible therapy

85 patients needed for detection of $\geq 30\%$ decrease in recurrence within 2.5 years.

Collaboration between different centers?

Future/ongoing work

- **Clinical phase II study**
- **Possible improvements**
 - Add i.v. injection
 - Smaller antibody fragments
 - Pretargeting
 - ^{213}Bi (in collaboration with ITU, Karlsruhe)
- **Other types of cancer**
 - Prostate cancer, breast cancer.

Authors

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Alpha emitting radionuclides

Astatine-211

- + Good physical properties ($T_{1/2}$, daughters).
- + Chemistry under development.
- + Specific activity (antigenic sites).
- + "Unlimited source" due to $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$.
Cost: Approx. 2000 Euro per patient.
- Few production facilities, limited capacity.

Alpha emitting radionuclides cont.

Bismuth-213

- + Good physical properties ($T_{1/2}$, daughters).
- + Chemistry well established.
- + Generator produced.
- Limited source of Ac-225?

The TAT Group

www.TargetedAlphaTherapy.com



Thank you for your attention!