[\textsuperscript{225}Ac]Ac-DOTA- girentuximab for targeted alpha therapy of CAIX-expressing renal cell cancer xenografts

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Need for treatment in advanced renal cell carcinoma

- 30% advanced stage at diagnosis
- Poor prognosis: OS 5y = 15-30%
- Unmet need for responsive treatments
Tumor-specific CA IX expression

- CA IX overexpressed in >95% of clear cell RCC
- Targeted by girentuximab
- Imaging with $[^{89}\text{Zr}]\text{Zr-DFO-girentuximab}$
- 2016: Clinical study with $^{177}\text{Lu}$
- Now: Preclinical study with $^{225}\text{Ac}$
Aim of study

• Proof of concept: $^{225}$AcAc-DOTA-girentuximab

• BALB/c mice and SK-RC-52 tumor cells

• Assessment of \textit{in vivo} targeting properties in CA IX xenograft mice

• Assessment of therapeutic efficacy in CA IX xenograft mice

• Assessment of toxicity in mice
Timeline preclinical studies

\[^{225}\text{Ac}]\text{Ac-DOTA-girentuximab Tracer injection}\]

Tumor inoculation
- Day -x
- SK-RC-52

Biodistribution
- Day 1,3,7 (n=15)

Therapeutic efficacy
- Day 0-30 (n=20)
- Overall wellfare
- Tumor growth

Therapeutic efficacy
- Day 0-100 (n=12)
- Overall wellfare
- Renal imaging
- Serum sampling
- Histology

[225Ac]Ac-DOTA-girentuximab Tracer injection
- 3.7 kBq
- 9.3 kBq
- 18.5 kBq

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In vivo biodistribution
Assessment therapeutic efficacy

[\textsuperscript{225}Ac]Ac-DOTA-girentuximab Tracer injection

- Day 0
- Tumor inoculation
- Day-x
- SK-RC-52

Day 1,3,7 (n=15)
- Biodistribution

Day 0-30 (n=20)
- Therapeutic efficacy
  - Overall wellfare
  - Tumor growth

Day 0-100 (n=12)
- Toxicity
  - Overall wellfare
  - Renal imaging
  - Serum sampling
  - Histology
Assessment therapeutic efficacy

- 4 groups (n=20 total):
  - 3.7, 9.3, 18.5 kBq and control

- Tumor measurement 2 x per week

- Plotting mean doubling time of tumor
Mean doubling time increases with higher dosing

(Mean ± SD)

- Control: 17.3 ± 4.8 days
- 3.7 kBq: 22.4 ± 11.1 days
- 9.3 kBq: 33.9 ± 23.9 days
- 18.5 kBq: 31.1 ± 19.8 days
Challenging decay chain

- $^{225}\text{Ac}$ (10d)
- $^{221}\text{Fr}$ (4.9m)
- $^{217}\text{At}$ (32ms)
- $^{213}\text{Bi}$ (45.6m)
- $^{209}\text{TI}$ (2.2m)
Bismuth-213 presence in kidney
Assessment of toxicity

[\[^{225}\text{Ac}]\text{Ac-DOTA-girentuximab}\]

- **Tracer injection**
  - **Day 0**
  - **Day 0-30 (n=20)**

- **Tumor inoculation**
  - **Day-x**
  - **Day 1,3,7 (n=15)**

- **Biodistribution**
  - **SK-RC-52**

- **Therapeutic efficacy**
  - **Overall welfare**
  - **Tumor growth**

- **Toxicity**
  - **Day 0-100 (n=12)**
  - **Overall welfare**
  - **Renal imaging**
  - **Serum sampling**
  - **Histology**
Assessment toxicity

- 4 groups (n=12 total):
  - 3.7, 9.3, 18.5 kBq and control
- Overall wellfare
- Hematotoxicity (blood sampling BL, 3, 6, 9, 12 weeks)
- Renal toxicity (Imaging 4+8 weeks and pathology 12 weeks)
Normal weight and no hematotoxicity
Quantification of renal imaging
Pathology kidneys

Control

3.7 kBq

9.3 kBq

18.5 kBq
Conclusions

• $^{225}$Ac-Ac-DOTA- girentuximab:
  • Shows high tumor:blood ratio at 72 and 168 hrs
  • Decrease of tumor doubling time in 9.3 and 18.5 kBq
  • Potential nephrotoxicity in 18.5 kBq

• Need to find balance between therapeutic efficacy and toxicity

• Comparison studies with $^{177}$Lu
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Thank you for your attention!