^{225}Ac-DOTATATE (RYZ101) dosimetry results from Part 1 of the ACTION-1 Trial

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Background

- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, alpha-emitting radiopharmaceutical therapy being developed for somatostatin receptor 2-expressing (SSTR2+) solid tumors

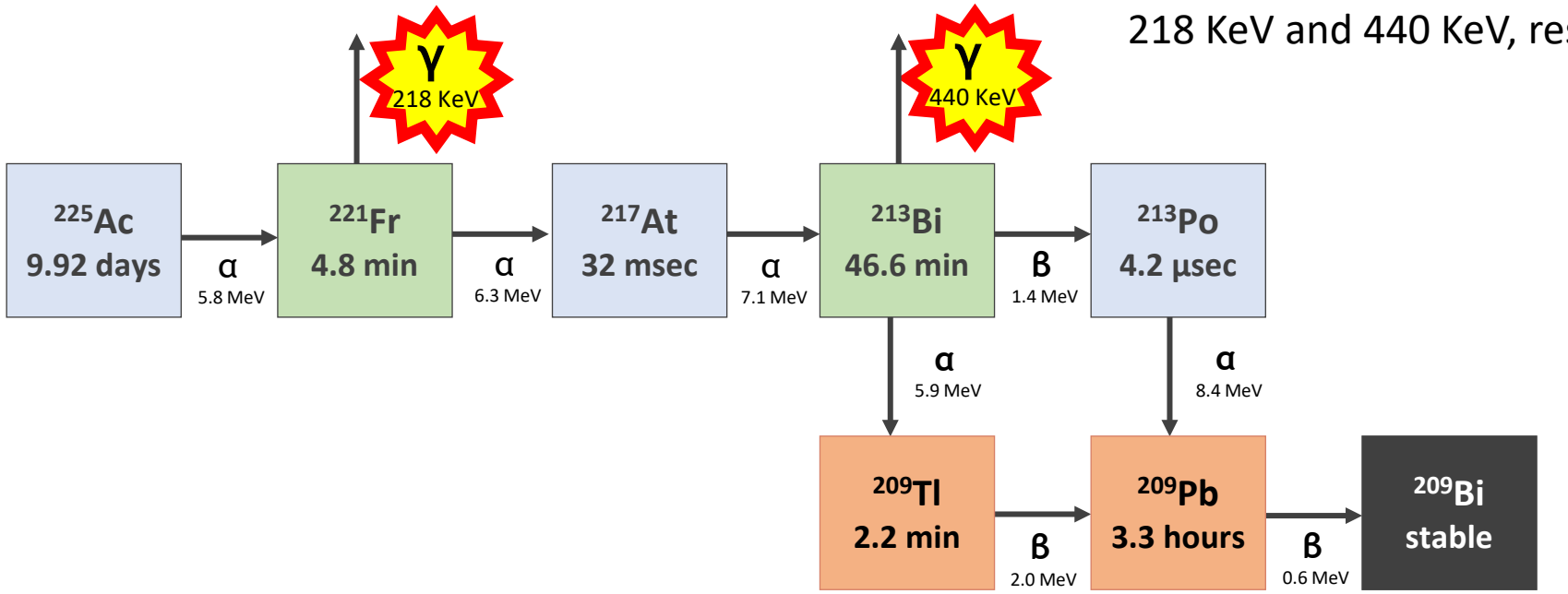
- ACTION-1 (NCT05477576) is a Phase 1b/3 trial comparing RYZ101 to standard-of-care therapy in patients with gastro-enteropancreatic neuroendocrine tumors (GEP-NETs) that have progressed following ^{177}Lu-labelled somatostatin analogue (SSA) therapy:[1]

- A first-of-its-kind dosimetry sub-study was conducted in Phase 1b to determine the feasibility of ^{225}Ac dosimetry with ^{225}Ac-DOTATATE by imaging ^{225}Ac daughters

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT05477576. Accessed August 9, 2023

Key Question: As 225Ac-Dotatate has 4 alpha emissions, are we sure the daughter product emissions are localized in the tumor lesions?

^{221}Fr and ^{213}Bi emit imageable gamma rays at 218 KeV and 440 KeV, respectively



- Upon α decay, an enormous recoil energy leads to dislocation of the radionuclide from the chelator
- The first two daughters, ^{221}Fr and ^{217}At, are assumed to decay where ^{225}Ac decays, due to short T1/2 (4.8 min and 32 ms)
- The third daughter, ^{213}Bi, has a half-life of 46.6 min, which may be sufficient for redistribution and off-target decay

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ACTION-1 Dosimetry sub-study methods

Population

Key eligibility criteria

- G1–2 GEP-NETs progressed after ^{177}Lu-SSA
- ECOG status 0–2 and adequate hematologic and renal function.

Treatment

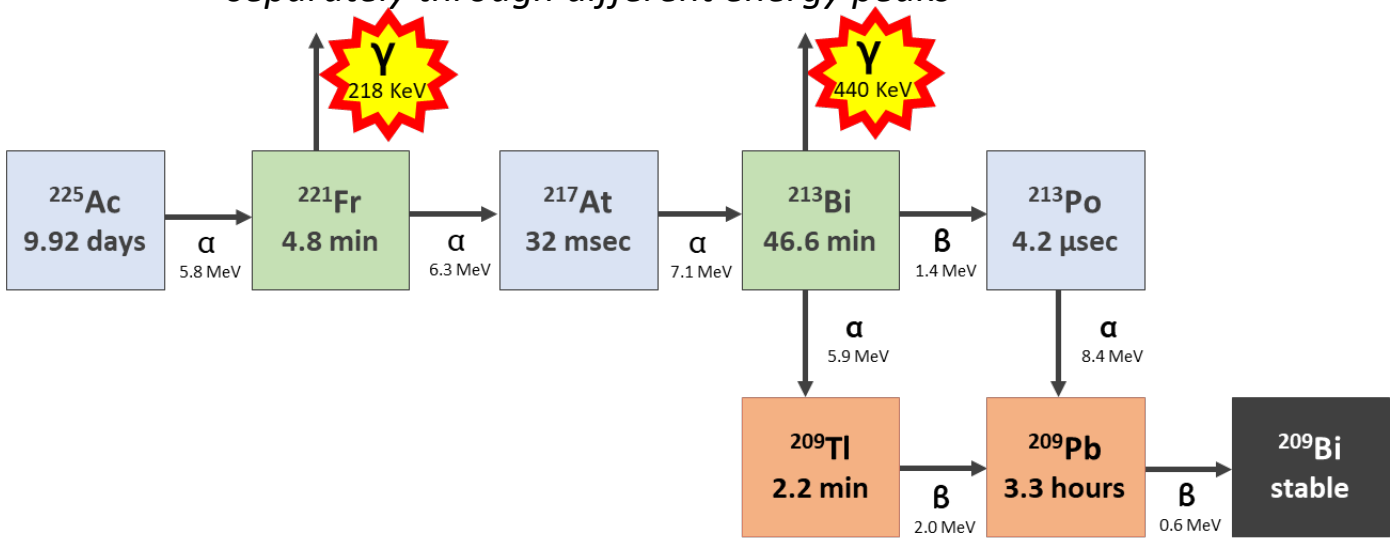
225Ac-DOTATATE 120 kBq/kg (3.2 µCi/kg) administered IV Q8W X 4 cycles

SPECT/CT imaging

Cycle 1
4 ± 1 hour; 24 ± 2 hours; 168 ± 24 hours post-infusion

Cycle 4
4 ± 1 hour; 24 ± 2 hours; 168 ± 24 hours post-infusion

Gamma emissions from ^{221}Fr and ^{213}Bi were imaged separately through different energy peaks



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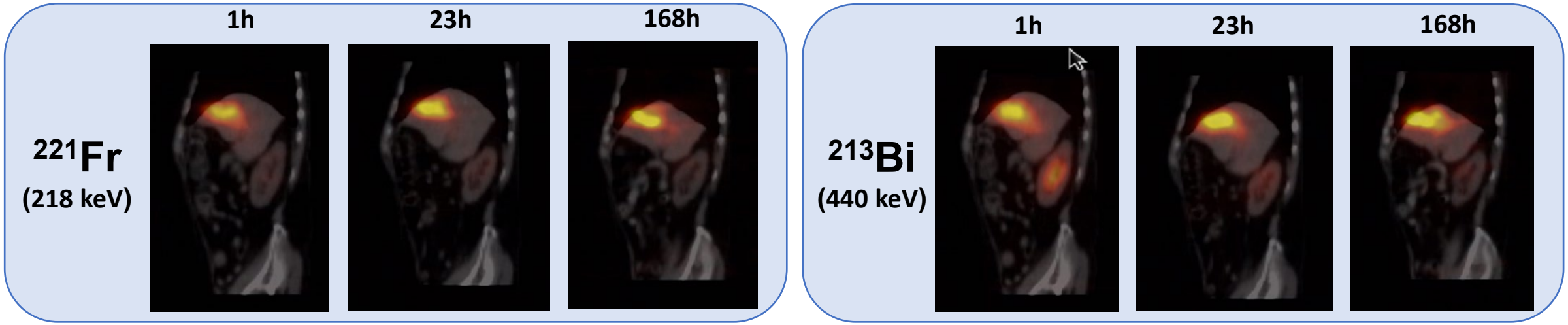
Results

Cycle 1: SPECT images were acquired in 2 different energy windows
218.2 keV (±20%) to localize ^{221}Fr & 440 keV (±20%), and to localize ^{213}Bi



Results: ^{221}Fr & ^{213}Bi stay within tumor. Minor fraction of free ^{213}Bi goes to kidneys.

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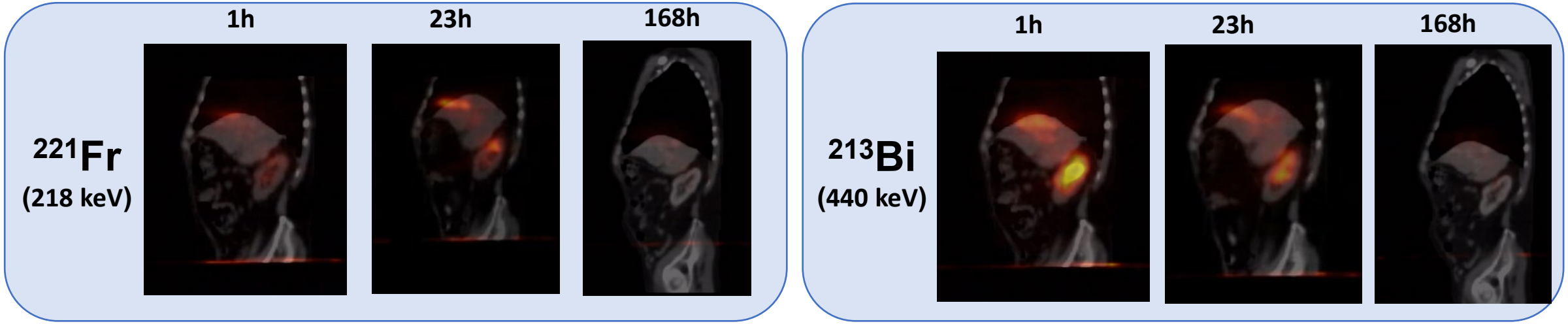
Results

Cycle 4: SPECT images were acquired in 2 different energy windows 218.2 keV (±20%) to localize ^{221}Fr & 440 keV (±20%), and to localize ^{213}Bi



Compared to cycle 1, there is a decrease in tumor uptake and increase in kidney uptake.

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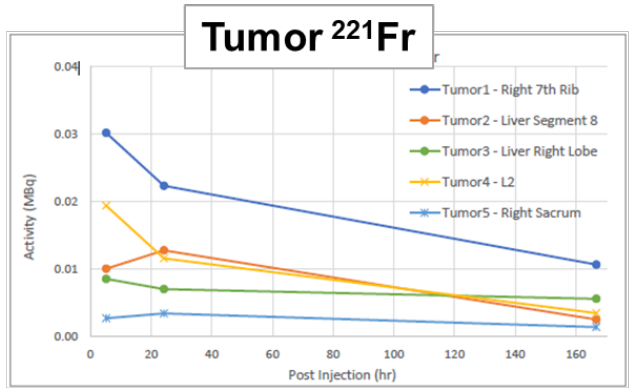
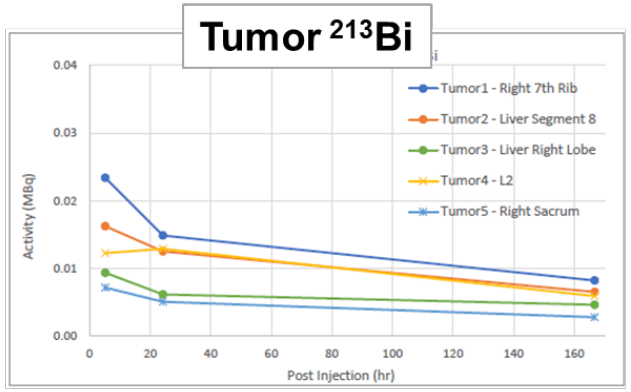
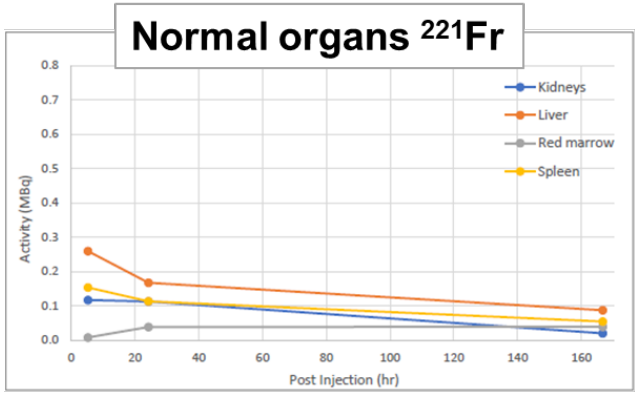
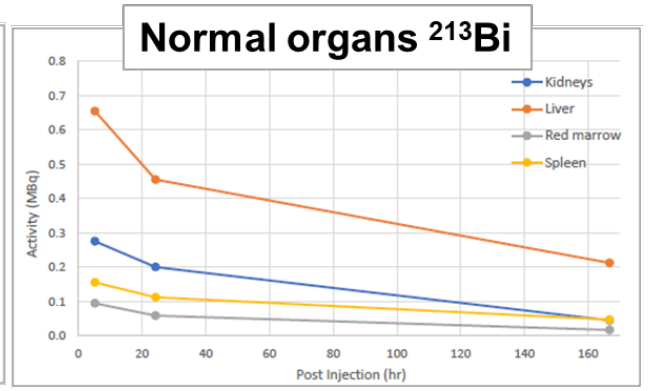
Cycle 1 time-integrated activity coefficients (TIAC)









Source organs and lesions	Mean (SD) TIAC, MBq-hr/MBq (hr)	
	^{221}Fr	^{213}Bi
Kidneys	2.10 (1.05)	3.76 (1.00)
Liver	11.70 (6.65)	13.50 (5.82)
Red bone marrow	0.67 (0.55)	1.11 (0.59)
Spleen	2.55 (1.33)	2.14 (1.12)
Lesions 1–5	2.64 (3.98)	2.02 (3.47)

TIAC for ^{221}Fr and ^{213}Bi confirm ^{213}Bi stays with the delivery agent, with a minor fraction of free ^{213}Bi going to kidneys

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Total estimated absorbed dose of RYZ101 for full treatment course

- The recommended ^{225}Ac-DOTATATE dose for phase 3 of ACTION-1 is 10.2 MBq (275 µCi) x 4 cycles
- Assuming a similar dose distribution for each cycle, the total estimated absorbed dose for 4 cycles (40.8 MBq [1100 µCi]) is:

Organ	Total estimated absorbed dose across 4 cycles Mean, Gy
Tumors	**117**
Kidneys	22.3
Liver	17.7
Red bone marrow	1.1
Spleen	35.6

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Conclusions

- This is the first data on ^{225}Ac dosimetry in humans based on direct imaging of ^{225}Ac daughters. ^{221}Fr and ^{213}Bi can be imaged separately and simultaneously by SPECT/CT.

- ***This is the first demonstration that the daughter products of ^{225}Ac stay with the delivery agent, proving multiple α emissions occur within the tumor for therapy.***

- ACTION-1 dosimetry data suggest a favorable tumor-to-background profile, supportive of RYZ101 for treatment of SSTR+ GEP-NETs

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Thank you!

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