Overview of Emerging Th-227 Radiotherapy

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Organization of Agreement States Annual Meeting

August 20, 2019

Disclosures

Consultant for:

- Bayer HealthCare Pharmaceuticals
- Sirtex Medical

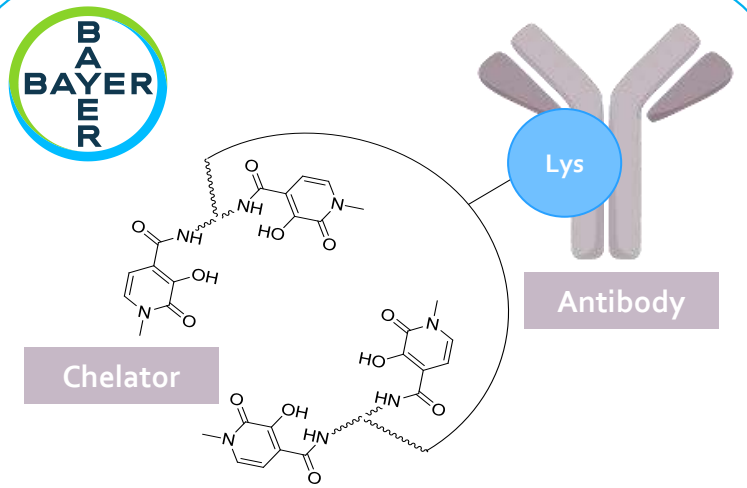
Overview

- What are targeted thorium conjugates
- Is there a clinical need
- Why alpha emitters

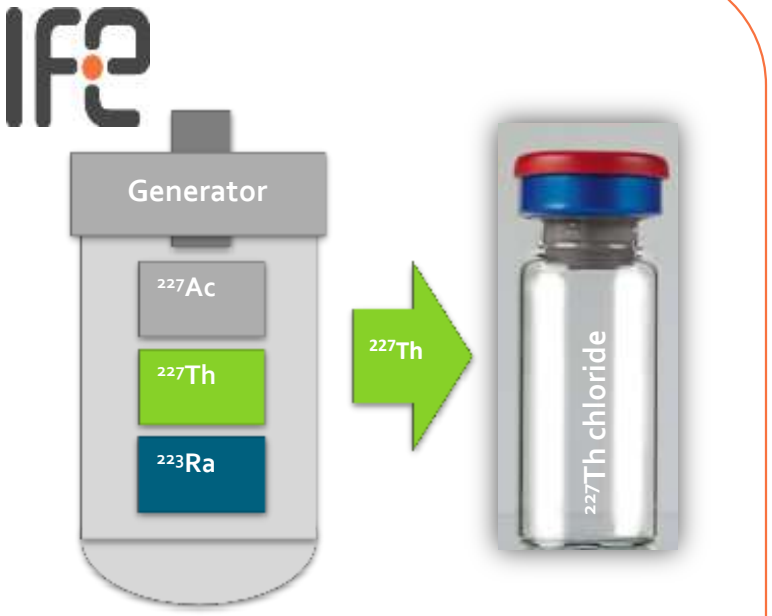
Regulatory Review

- How to detect contamination
- How to measure activity
- How to administer
- When to release patients
- How to dispose of waste

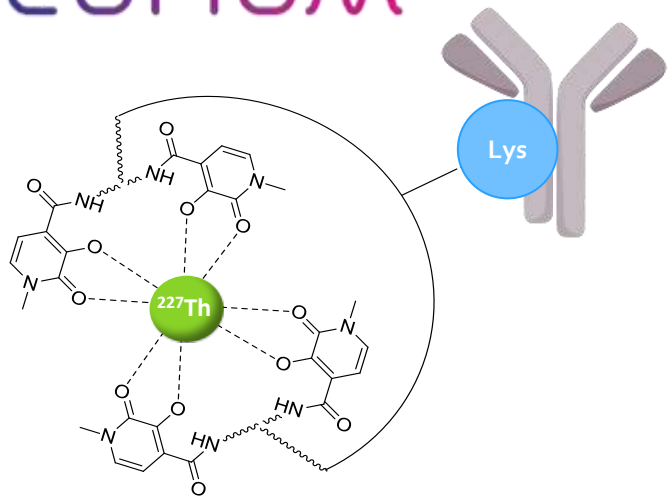
Targeted Thorium Conjugates Process



Conjugate manufacturing



Radionuclide purification in Norway

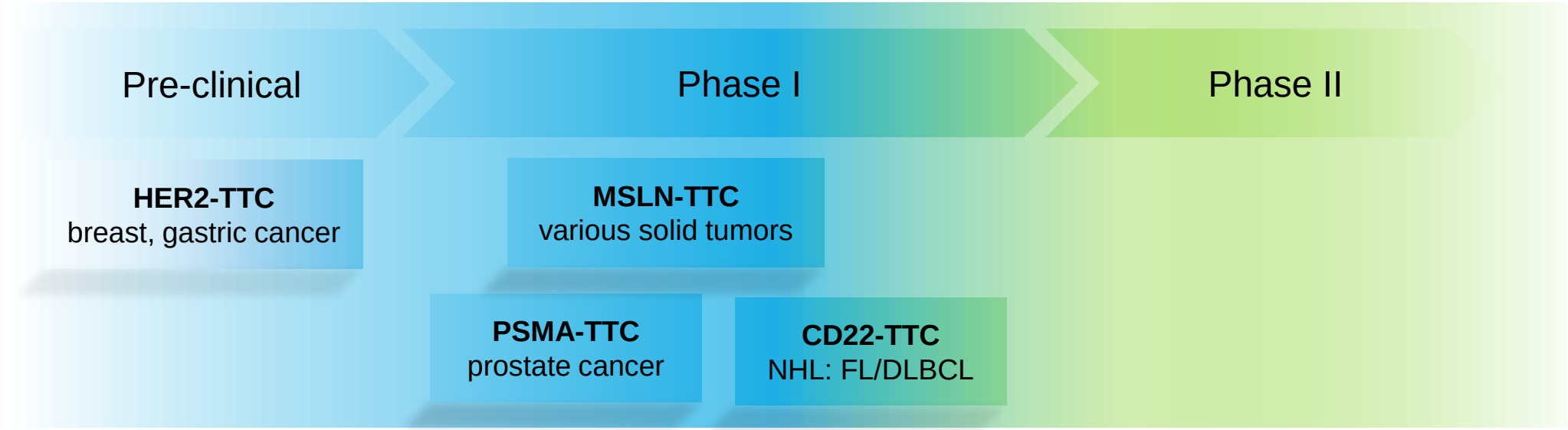


Manufacturing in St. Louis

Patient dose

End user

Pipeline of Products



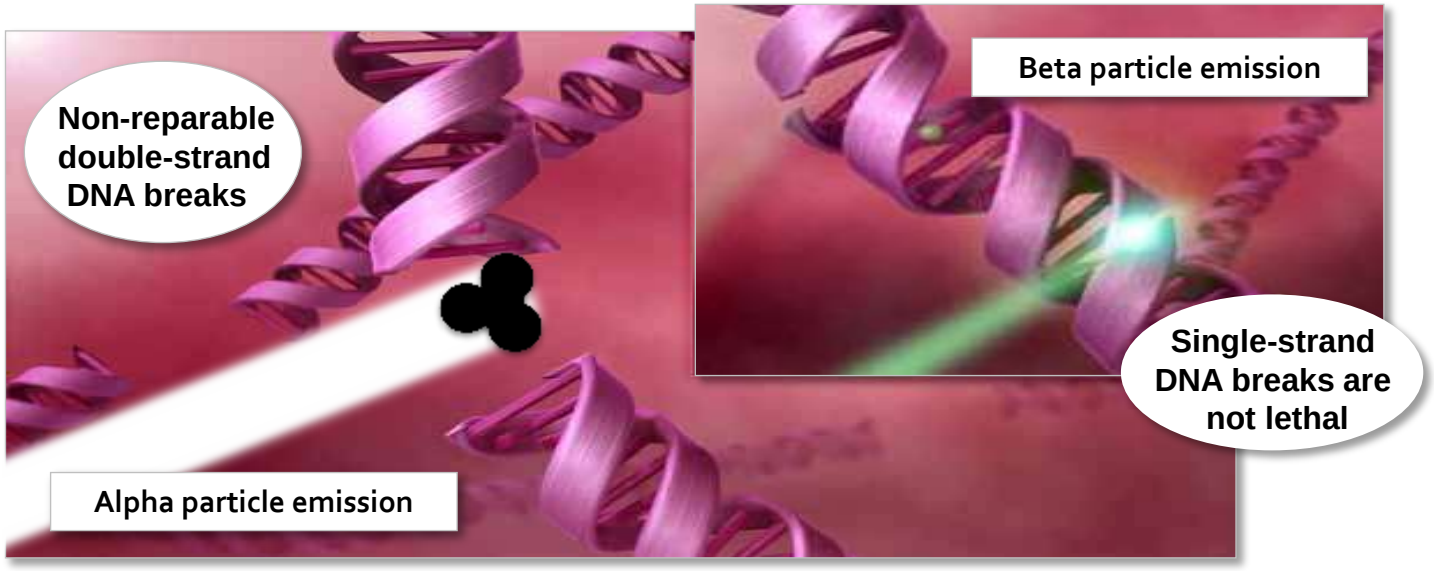
PSMA-TTC - prostate cancer

MSLN-TTC - mesothelioma, ovarian cancer, pancreatic cancer

CD22-TTC - non-Hodgkin lymphoma with focus on follicular lymphoma and diffuse large B cell lymphoma

HER2-TTC; HER2-positive breast cancer, gastric cancer

Mechanism of Action

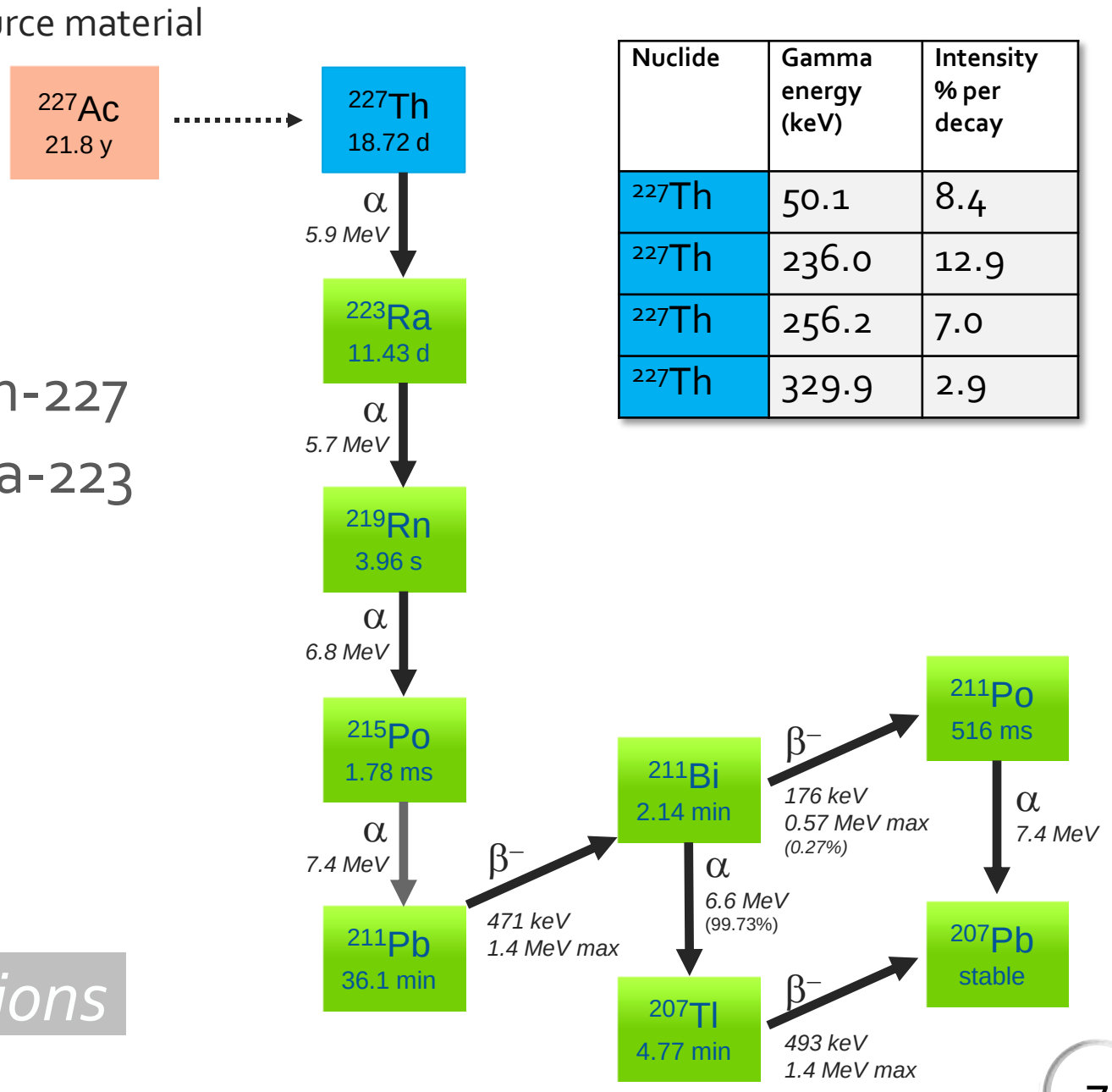


	α-particle	β-particle
Linear energy transfer	High 50–230 keV/µm	Low 0.2 keV/µm
Cellular DNA damage	Frequent double-stranded breaks	Base damage or single-stranded breaks
Difficulty repairing DNA damage	High	Low
Hits required to kill cell	Very few (1–20 hits)	Many (~2000 hits)

Th-227 Decay Chain

- $T_{1/2}$ = 18.7 days
- Ac-227 parent radionuclide of Th-227
- Th-227 parent radionuclide of Ra-223
- Total decay energy
  - 95.7% emitted as α particles
  - 3.1% emitted as ß particles
  - 1.2% emitted as γ or x-rays

Predominantly alpha emissions



Nuclide	Gamma energy (keV)	Intensity % per decay
^{227}Th	50.1	8.4
^{227}Th	236.0	12.9
^{227}Th	256.2	7.0
^{227}Th	329.9	2.9

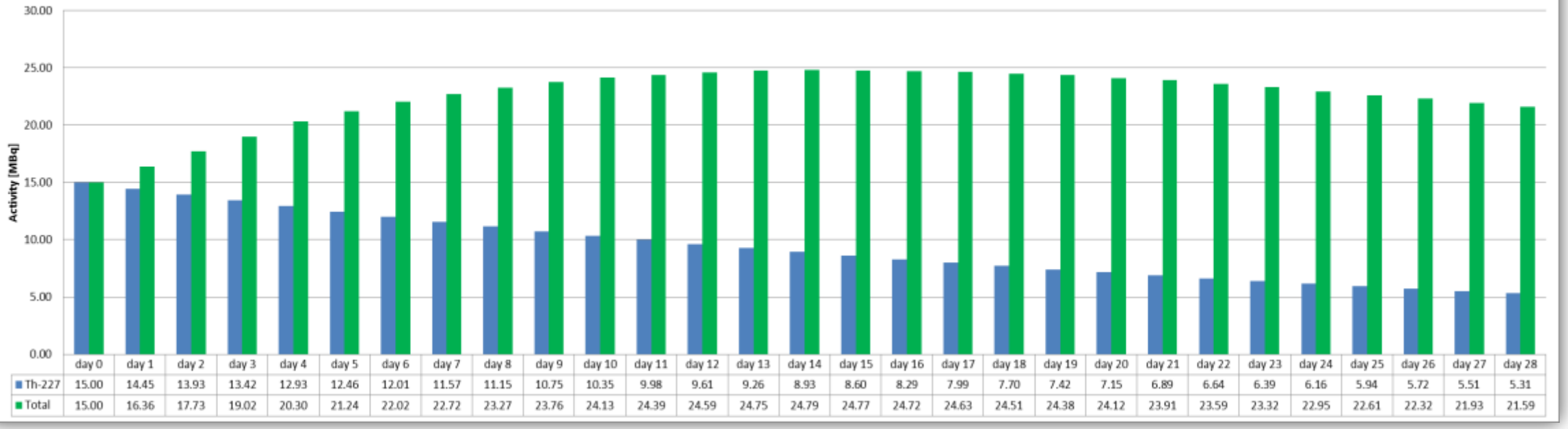
Regulatory Considerations

- Activity Measurement
- Exposure Risks
  - Internal & External
- Contamination Detection
- Disposal of Waste

Activity Measurement

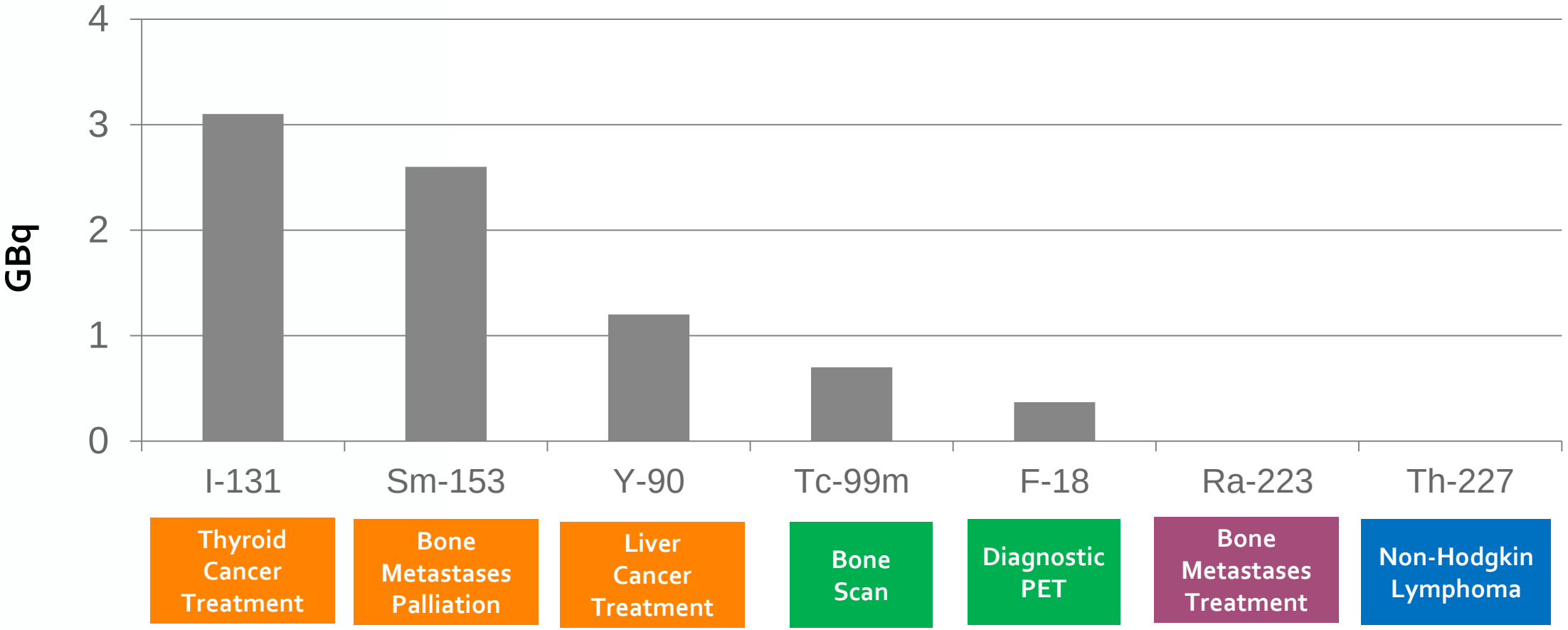
- Use standard dose calibrator
- Apply correction factor for Ra-223 in-growth

Read-out **Activity over shelf-life of technical sample (thorium-227 chloride)**



	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14	day 15	day 16	day 17	day 18	day 19	day 20	day 21	day 22	day 23	day 24	day 25	day 26	day 27	day 28
Th-227	15.00	14.45	13.93	13.42	12.93	12.46	12.01	11.57	11.15	10.75	10.35	9.98	9.61	9.26	8.93	8.60	8.29	7.99	7.70	7.42	7.15	6.89	6.64	6.39	6.16	5.94	5.72	5.51	5.31
Total	15.00	16.36	17.73	19.02	20.30	21.24	22.02	22.72	23.27	23.76	24.13	24.39	24.59	24.75	24.79	24.77	24.72	24.63	24.51	24.38	24.12	23.91	23.59	23.32	22.95	22.61	22.32	21.93	21.59

Activity Comparisons



*Alpha pharmaceuticals are prescribed on a one-digit **MBq** scale*

Exposure Risks

During Preparation & Administration

Shielded vial & prep area

Plastic-backed absorbent paper

Appropriate PPE

Saline flushes through IV

Good hygiene practices

Internal and external exposure risks are low

Patient Release

Tc-99m	Ra-223	Ra-223	Th-227	Th-227
1110 MBq	4 MBq	4 MBq	4 MBq	4 MBq
Dose rate (µSv/h)	22.2	0.2*	0.2	< 0.2*	*TBD*

*derived from exposure rate constants

Exposure to others negligible; TTC patients immediately releasable

Waste Considerations

Patients at Home

- Urine and feces may be radioactive for up to 10 days post-administration
  - Use good hygiene practices (e.g. thoroughly wash hands)
  - Flush disposable items used for clean-up
  - Launder items contaminated with bodily fluids

Items at Facility

- Radioactive waste should be sealed in plastic bags and stored in a secure area
  - Equipment used for administration (e.g. syringes, infusion lines, ports)
  - Remaining drug solution, technical samples used for calibration dial setting
  - Contaminated PPE
- No measurable long-lived impurities
- Up to 12 months decay-in-storage recommended (e.g. 7 MBq → 10 Bq)

Summary

- TTCs may provide new, effective cancer treatment options using alpha emitters
- Gamma emissions allow for routine detection and measurement
- Radium-223 in-growth addressed through limited shelf life and a correction factor
- External radiation exposure is very low; easy to shield
- Outpatient treatment; patient is immediately releasable
- Unintended internal exposure unlikely and avoidable following general hygiene rules
- Excretion to be addressed by providing patients with simple precautions
- Decay waste in storage