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VIOLET: First-in-Human Results of Terbium-161 [^{161}Tb]Tb-PSMA-I&T Dual Beta–Auger Radioligand Therapy in Patients with mCRPC: A Single-Center, Single-Arm, Phase 1/2 Study

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First-in-human results of terbium-161 [^{161}Tb]Tb-PSMA-I&T dual beta–Auger radioligand therapy in patients with metastatic castration-resistant prostate cancer (VIOLET): a single-centre, single-arm, phase 1/2 study

James P Buteau, Louise Kostos, Price A Jackson, Jing Xie, Mohammad B Haskali, Ramin Alipour, Lachlan E McIntosh, Brittany Emmerson, Lisa MacFarlane, Claire A Martin, Joanna Chan, Sarah E Williams, Kerry E Jewell, Michal Eifer, Anthony J Hamilton, William Q Harris, Tim Akhurst, Lewis Au, Anthony J Cardin, Luc Furic, Raghava K Kashyap, Grace Kong, Aravind S Ravi Kumar, Declan G Murphy, Rajeev Ravi, Javad Saghebi, Shahneen Sandhu, Ben Tran, Arun A Azad, Michael S Hofman**

2022: FDA Approval of Pluvicto (^{177}Lu vipivotide tetraxetan)

- For PSMA+ mCRPC pts previously treated with an ARPI + taxane chemotherapy
  - VISION: ^{177}Lu-PSMA-617 + SOC vs SOC
    - OS benefits: 15.3 vs 11.3 mo
  - TheraP: ^{177}Lu-PSMA-617 vs cabazitaxel
    - Superior PSA-PFS (HR: 0.63), PSA50 response (66% vs 37%)
    - No difference in OS (19.1 vs 19.6 mo)
- **March 2025:** FDA approval for PSMA+ mCRPC pts previously treated with APRI & who are considered appropriate for <u>delaying taxane-based chemotherapy</u>
  - PSMAfore: ^{177}Lu-PSMA-617 vs ARPI switch
    - rPFS: 9.3 vs 5.6 mo (HR: 0.41, $p<0.001$)

Morris et al. Lancet, 2024
Sartor et al. NEJM, 2021
Hofman et al. Lancet, 2021

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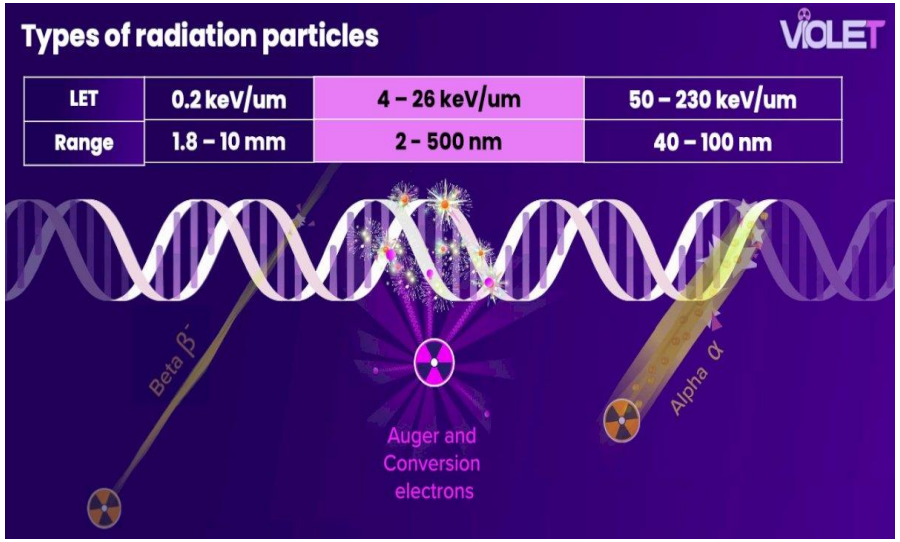
Why do we need another radionuclide and what limitations does it overcome?

Morris et al. Lancet, 2024
Sartor et al. NEJM, 2021
Hofman et al. Lancet, 2021

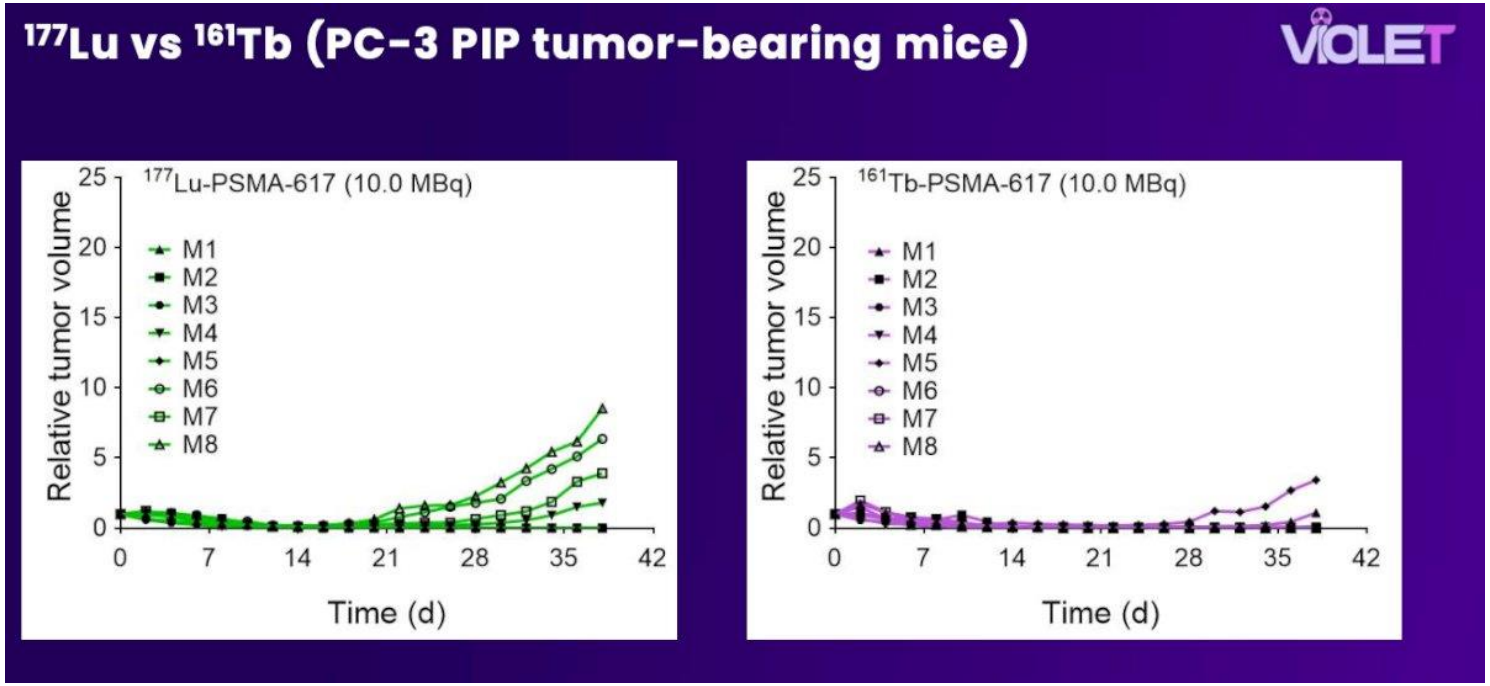
What is ^{161}Tb?

- Beta emitting radionuclide with similar energy & $T_{1/2}$ to ^{177}Lu (target larger tumor volume), but **<u>additionally</u>** emits conversion and Auger electrons
  - Deposit energy over a much shorter distance (nm to µm)
  - Better targeting of micrometastatic deposits → Increased double-strand DNA damage that may overcome mechanisms of resistance to ^{177}Lu



Early Evidence for ^{161}Tb

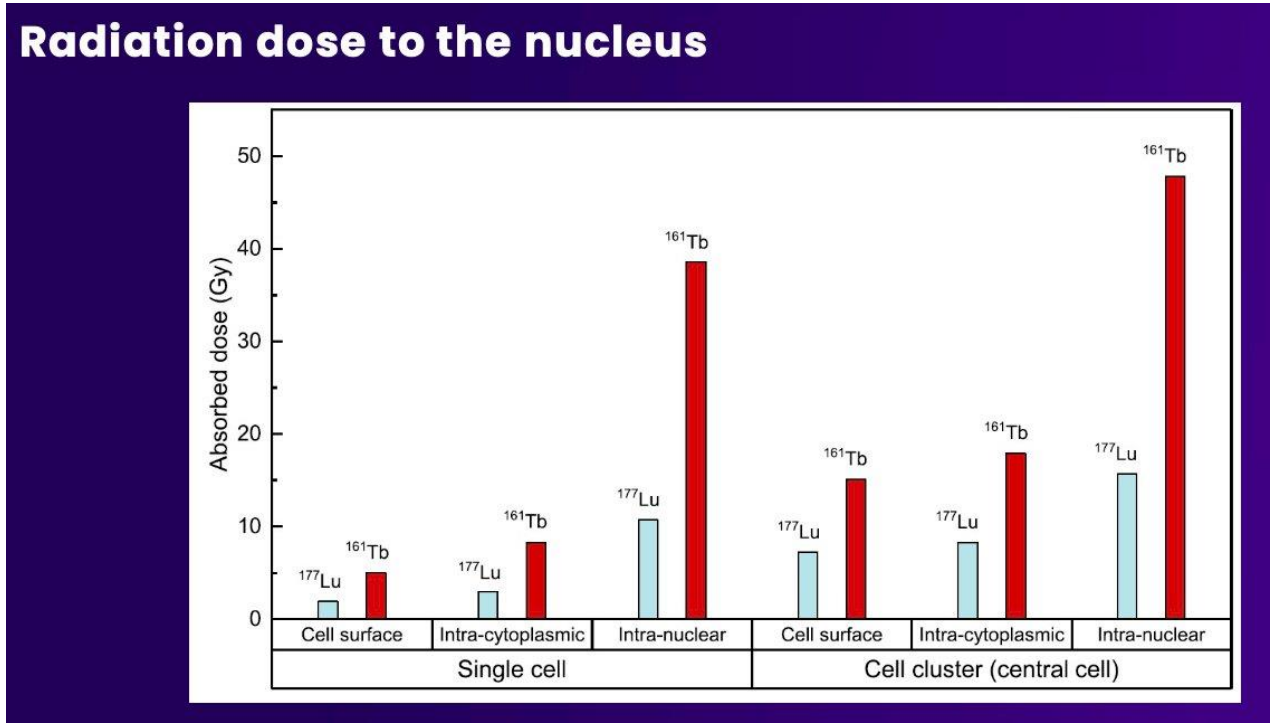
- ^{161}Tb-PSMA-617 demonstrated superior in vitro and in vivo efficacy in tumor-bearing mice compared to ^{177}Lu-PSMA-617
  - Supports theory that additional emission of conversion and Auger electrons from ^{161}Tb contributes to an enhanced therapeutic effect.



Muller et al. EJNMMI, 2019

Early Evidence for ^{161}Tb

- Dosimetric model study: ^{161}Tb consistently demonstrated substantially higher absorbed doses compared to ^{177}Lu across all intracellular localizations (intranuclear: 38.6 Gy vs 10.7 Gy)



Alcocer-Avila et al. EJNMMI Phys, 2020

Study Objective

Investigate the safety and activity of [^{161}Tb]Tb-PSMA-I&T in mCRPC patients

Study Design and Participants

- Single center, investigator-initiated, phase I/II trial at the Peter MacCallum Cancer Center (supported by the Prostate Cancer Foundation)
- Eligibility criteria:
  - Progressive mCRPC previously received ≥1 ARPI & taxane (or unfit)
  - PSMA+ disease on PSMA-PET/CT (^{68}Ga or ^{18}F)
    - SUV_{max} ≥20 in 1 lesion & SUV_{max} ≥10 in measurable soft tissue metastases
    - No discordance findings on FDG PET
  - ECOG 0–2
  - Adequate bone marrow, hepatic, renal function

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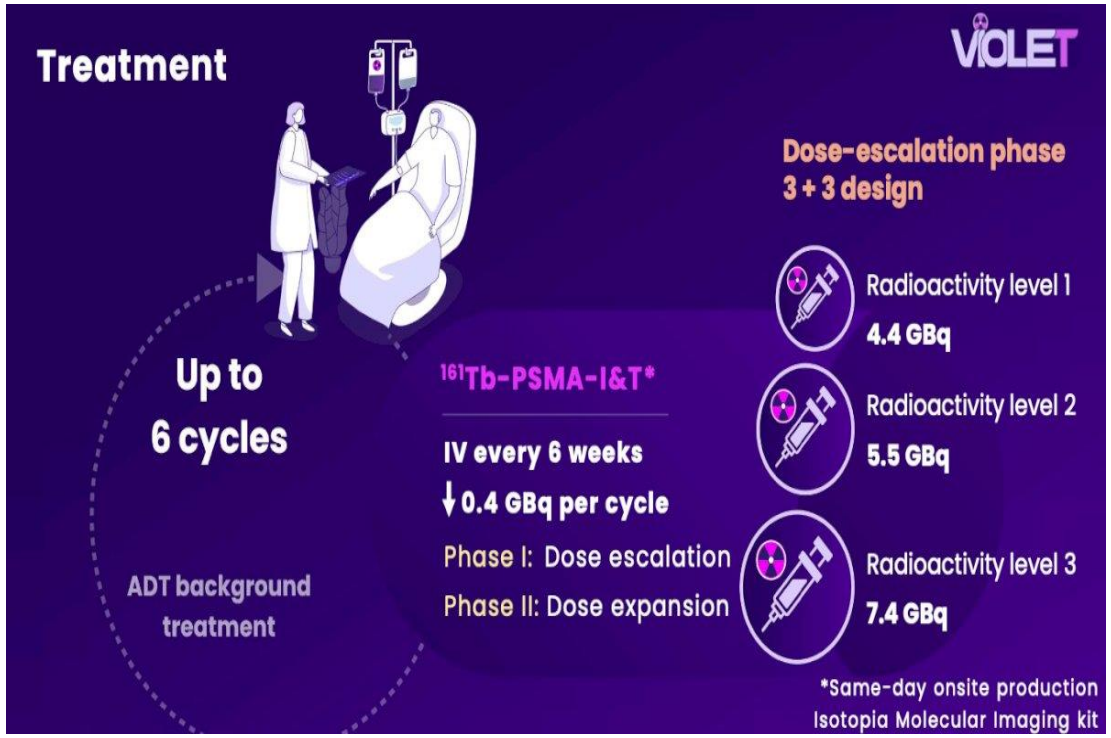
Study Design and Procedures

- Dose-escalation (phase I) and dose-expansion (phase II) design
- Standard 3+3 dose escalation approach with 3 radioactivity levels of [^{161}Tb]Tb-PSMA-I&T: 4.4, 5.5, 7.5 GBq
- Up to 6 cycles administered IV every 6 weeks, reduced by 0.4 GBq for each cycle
  - Due to expected decreasing tumor burden w/ each cycle
- [^{161}Tb]Tb-PSMA-I&T produced on-site
- All pts continued ADT during study



Study Endpoints

Phase I:

- Dose-limiting toxicities
- Maximum tolerated dose
  - Highest dose at which <1/3 or <2/6 pts experienced a dose-limiting toxicity
- Recommended phase 2 dose

Phase II:

- Adverse events
- Radiation absorbed dose
- PSA response rates
- rPFS
- PSA-PFS
- PFS
- OS
- ORR
- PROs

Statistical Analyses & Sample Size

- Pre-specified sample size: 30–36 patients
  - Allow for 24 patients treated at the MTD (assuming probability of ≥1 DLT of 64%)
- Safety population: All pts who received ≥1 cycle in the dose escalation or expansion phases
- Activity analysis was conducted for all patients who received at ≥1 cycle of [^{161}Tb]Tb-PSMA-I&T
- Time-to-event outcomes were reported using Kaplan Meier curves

Baseline Characteristics

	All patients (n=30)
Age, years	69·0 (66·0–74·8)
Sex	
Male	30 (100%)
Female	0
Time since diagnosis of prostate cancer, years	6·5 (4·0–11·8)
Gleason score at diagnosis	
≤7	9 (30%)
≥8	17 (57%)
Unknown	4 (13%)
De novo metastatic at diagnosis	15 (50%)
PSA at screening, ng/mL	26·9 (10·1–70·0)
ECOG performance status	
0	12 (40%)
1	18 (60%)
Previous radiotherapy	23 (77%)
Prostate with or without regional lymph nodes	14 (47%)
Palliative	19 (63%)
Prostatectomy	14 (47%)
Taxane chemotherapy	20 (67%)
Docetaxel	20 (67%)
Cabazitaxel	4 (13%)
ARPI	30 (100%)
Abiraterone	14 (47%)
Darolutamide	2 (7%)
Enzalutamide	17 (57%)
PARP inhibitor	2 (7%)
PSMA SUV_{mean}	8·2 (7·4–10·8)
≥10	8 (27%)
PSMA tumour volume, mL	212·4 (79·4–526·8)
FDG tumour volume*, mL	17·9 (6·4–168·3)
≥200	7 (23%)
Metastases on PSMA PET-CT	
Nodal	19 (63%)
Bone	22 (73%)
Visceral	2 (7%)

Treatment Summary

	Treatment		
	Below MAD* (n = 6)	MAD* (n = 24)	Total (n = 30)
[^{161}Tb]Tb-PSMA-I&T Cycles received, n (%)			
1	0	1 (4%)	1 (3%)
2	0	1 (4%)	1 (3%)
3	0	3 (12%)	3 (10%)
4	1 (17%)	1 (4%)	2 (7%)
5	1 (17%)	1 (4%)	2 (7%)
6	4 (67%)	17 (71%)	21 (70%)
Total number of [^{161}Tb]Tb-PSMA-I&T Cycles received			
Mean (SD)	5.5 (0.8)	5.1 (1.5)	5.2 (1.4)
Median [range]	6.0 [4.0 - 6.0]	6.0 [1.0 - 6.0]	6.0 [1.0 - 6.0]
IQR	5.2 - 6.0	4.8 - 6.0	5.0 - 6.0
[^{161}Tb]Tb-PSMA-I&T total radioactivity (GBq)			
Mean (SD)	22.1 (3.7)	33.3 (9.3)	31.1 (9.6)
Median [range]	20.8 [18.1 - 26.7]	38.3 [7.2 - 39.7]	38.0 [7.2 - 39.7]
IQR	19.9 - 25.2	31.2 - 38.6	21.1 - 38.5
[^{161}Tb]Tb-PSMA-I&T dose delay due to adverse events, n (%)			
No	6 (100%)	21 (88%)	27 (90%)
Yes	0	3 (12%)	3 (10%)
Reason for [^{161}Tb]Tb-PSMA-I&T dose delay due to adverse events, n (%)			
Covid-19 infection (unrelated to [^{161}Tb]Tb-PSMA-I&T)	0	1 (33%)	1 (33%)
Pain SAE with long hospitalization (unrelated to [^{161}Tb]Tb-PSMA-I&T)	0	1 (33%)	1 (33%)
SAE resulting in leg amputation (unrelated to [^{161}Tb]Tb-PSMA-I&T)	0	1 (33%)	1 (33%)
[^{161}Tb]Tb-PSMA-I&T permanently discontinued, n (%)			
No	4 (67%)	17 (71%)	21 (70%)
Yes	2 (33%)	7 (29%)	9 (30%)
Reason for permanent [^{161}Tb]Tb-PSMA-I&T discontinuation, n (%)			
Death	1 (50%)	0	1 (11%)
Unequivocal disease progression	1 (50%)	7 (100%)	8 (89%)
Study status, n (%)			
Death	2 (33%)	5 (21%)	7 (23%)
Follow up	4 (67%)	16 (67%)	20 (67%)
Treatment**	0	3 (12%)	3 (10%)

Adverse Events

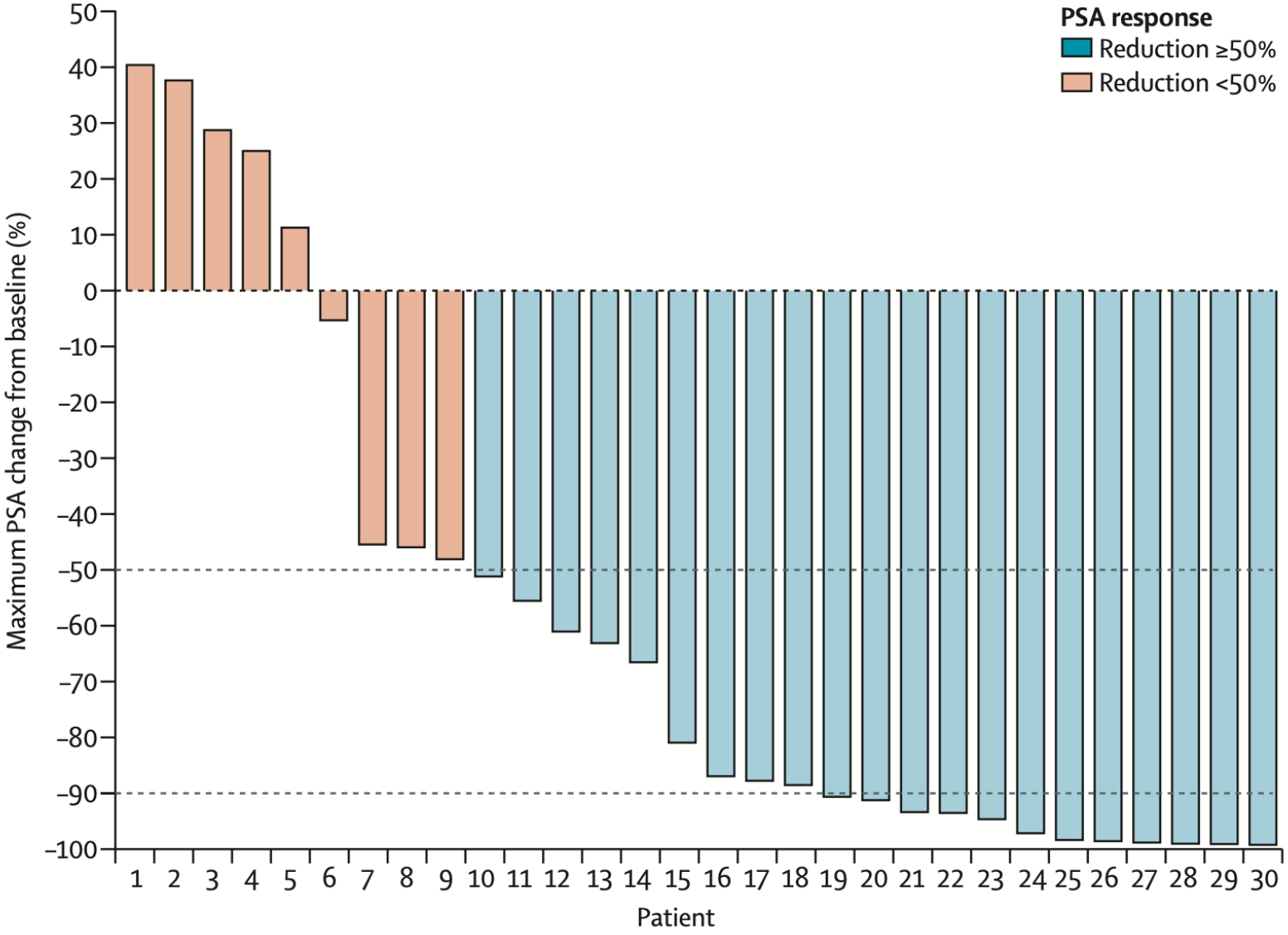
Treatment-Related AEs

	Grade 1	Grade 2	Grade 3
Lymphocyte count decreased	8 (27%)	10 (33%)	1 (3%)
Pain	3 (10%)	0	1 (3%)
Anaemia	16 (53%)	4 (13%)	0
White blood cell count decreased	7 (23%)	4 (13%)	0
Neutrophil count decreased	3 (10%)	3 (10%)	0
Fatigue	12 (40%)	1 (3%)	0
Presyncope	0	1 (3%)	0
Dry mouth	21 (70%)	0	0
Nausea	7 (23%)	0	0
Thrombocytopenia	6 (20%)	0	0
Constipation	4 (13%)	0	0
Dry eye	3 (10%)	0	0
Anorexia	1 (3%)	0	0
Diarrhoea	1 (3%)	0	0
Renal injury	1 (3%)	0	0
Vomiting	1 (3%)	0	0
Any adverse event*	13 (43%)	14 (47%)	2 (7%)

Serious AEs

Serious adverse event	Days from C1D1	Duration (days)	Grade	Related	Action
Myocardial infarction	192	1	5	No	N/A
Skin infection	87	15	3	No	None
Fever	191	10	3	No	None
Pain	2	0	3	Definitely	None
Pain	126	33	3	No	Drug delay
Wound complication	108	24	3	No	Drug delay
Wound complication	167	59	3	No	Drug delay
Kidney infection	186	8	3	No	None
Kidney infection	33	2	3	No	None

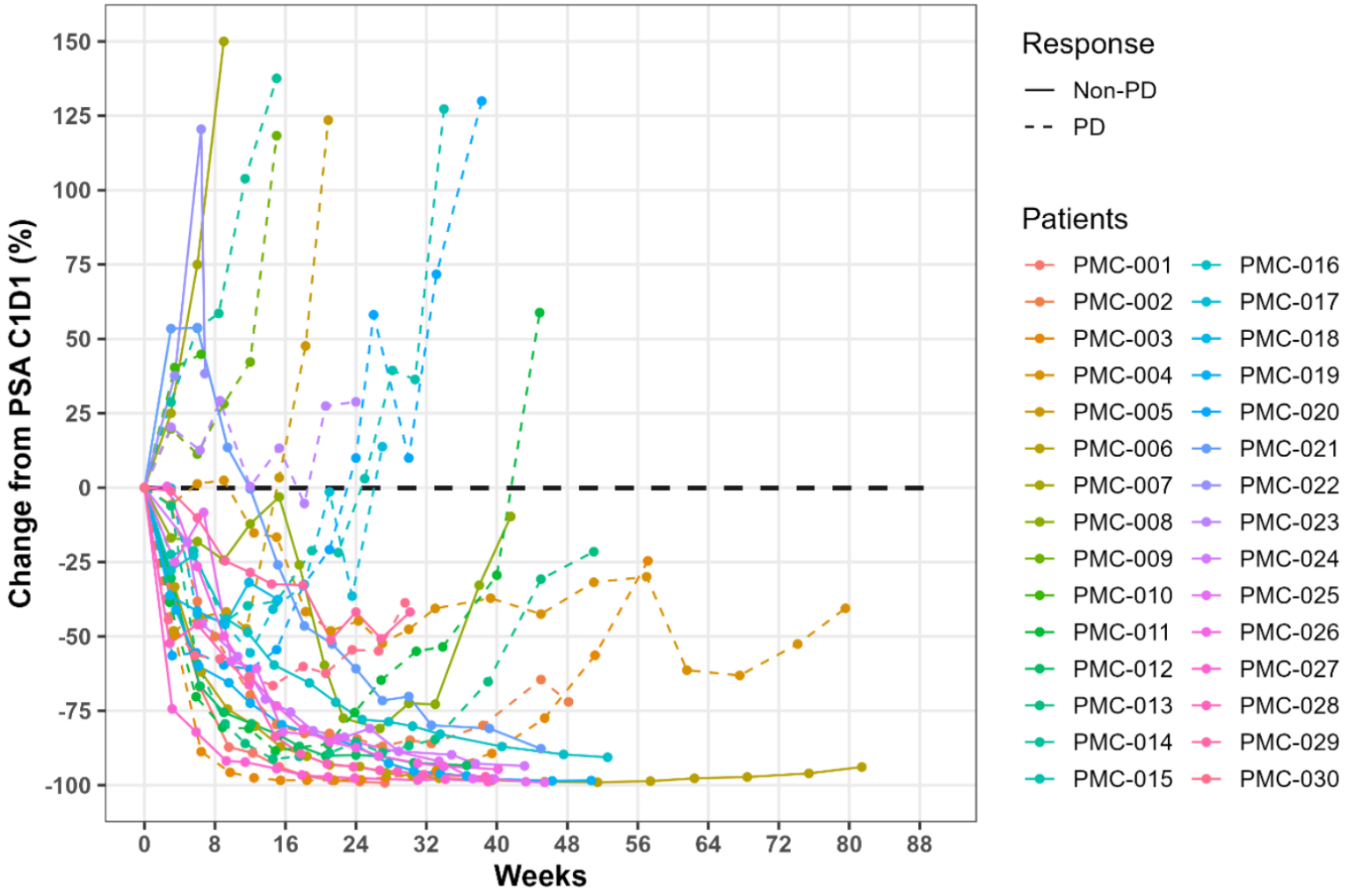
Waterfall Plot of Best PSA Response



PSA50 Response Rate: 70% (95% CI 51-85)

PSA90 Response Rate: 40% (95% CI 23-59)

Spider Plot of PSA Percentage Changes from Baseline



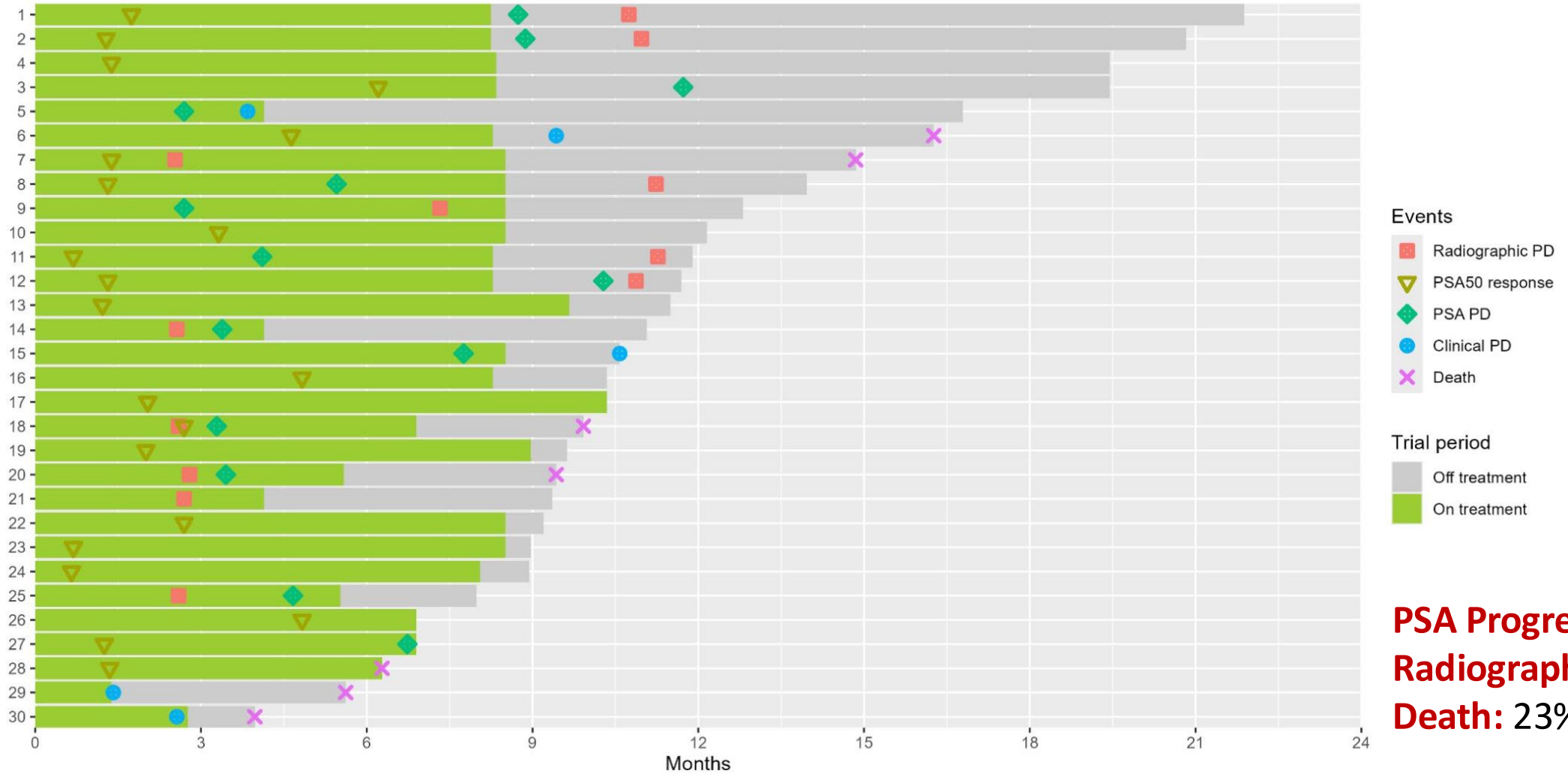
Objective Responses (RECIST 1.1; n=12)

PR: 50% (95% CI 21-79)

SD: 17% (95% CI 23-59)

PD: 33% (95% CI 10-65)

Swimmer's Plot



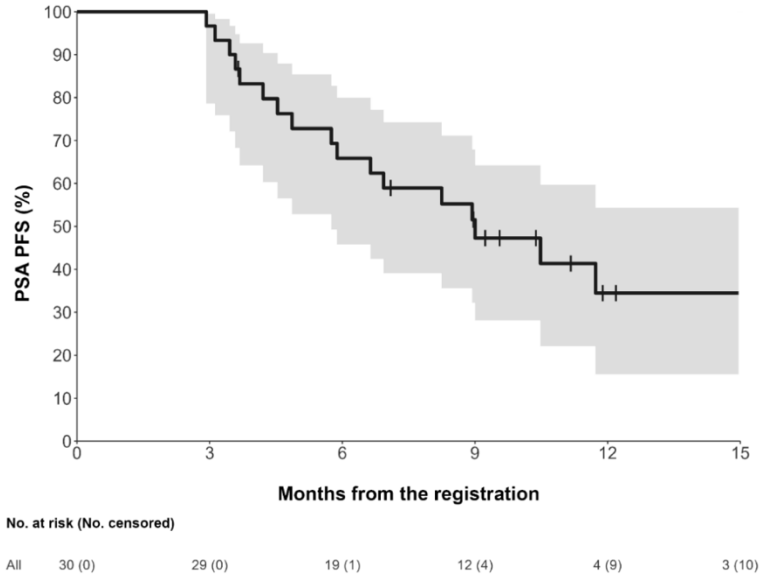
Events
- Radiographic PD
- PSA50 response
- PSA PD
- Clinical PD
- Death

Trial period
- Off treatment
- On treatment

PSA Progression: 47%
Radiographic Progression: 40%
Death: 23%

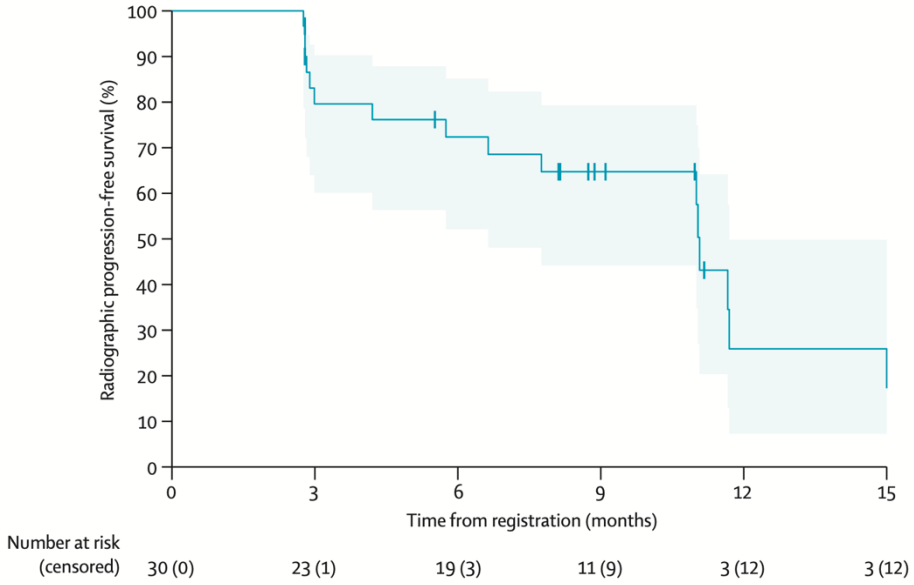
Survival Outcomes (Median F/U: 11.9 months)

PSA-PFS



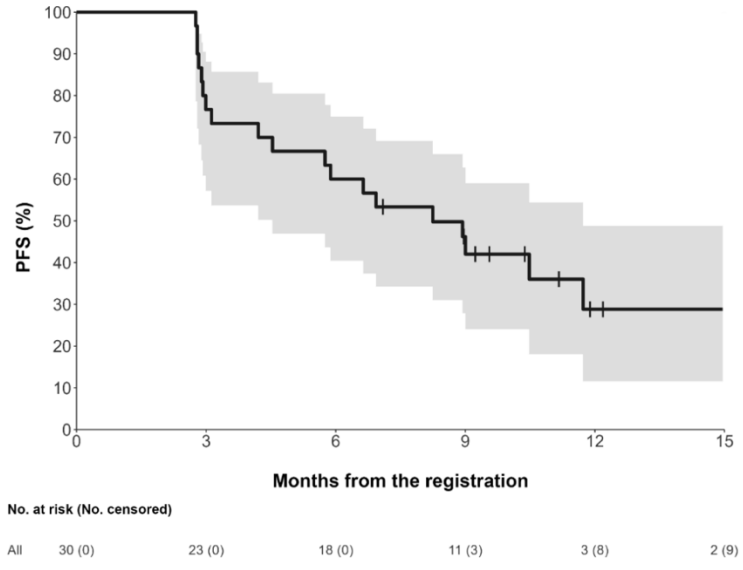
Median: 9.0 mo (95% CI 5.7-15.1)

rPFS



Median: 11.1 mo (95% CI 6.6-11.7)

PFS



Median: 8.2 mo (95% CI 4.5-11.7)

Three-Timepoint Quantitative SPECT @ Cycle 1

BL [^{68}Ga]Ga-PSMA-11 PET-CT | SPECT-CT @ 4 h | SPECT-CT @ 24 h | SPECT-CT @ 96 h | Radiation absorbed in mets/normal organs

[^{161}Tb]Tb-PSMA-I&T retention in metastases, washout of normal organs over time

Radiation Absorbed Dose to Normal Organs @ C1

	Dose per GBq (Gy/GBq))	Total absorbed dose (Gy)
Parotid		
Mean (SD)	0·15 (0·07)	1·02 (0·53)
Median [range]	0·14 [0·01 - 0·30]	0·90 [0·05 - 2·28]
IQR	0·10 - 0·16	0·76 - 1·13
Submandibular		
Mean (SD)	0·16 (0·08)	1·12 (0·58)
Median [range]	0·14 [0·05 - 0·32]	0·94 [0·38 - 2·41]
IQR	0·10 - 0·24	0·75 - 1·64
Kidney		
Mean (SD)	0·36 (0·11)	2·46 (0·85)
Median [range]	0·34 [0·11 - 0·56]	2·28 [0·77 - 4·19]
IQR	0·28 - 0·42	1·85 - 2·86
Liver		
Mean (SD)	0·08 (0·04)	0·57 (0·31)
Median [range]	0·08 [0·03 - 0·21]	0·54 [0·22 - 1·55]
IQR	0·05 - 0·09	0·35 - 0·65
Spleen		
Mean (SD)	0·06 (0·03)	0·43 (0·19)
Median [range]	0·06 [0·03 - 0·13]	0·38 [0·20 - 1·03]
IQR	0·04 - 0·08	0·28 - 0·50

Within the range of published studies for [^{177}Lu[Lu]-PSMA-I&T and [^{177}Lu]Lu-PSMA-617

Discussion

- VIOLET is the first reported trial using ^{161}Tb in ***ANY*** cancer type
  - Favorable safety profile: few (7%) grade 3-4 TRAEs, no dose reductions, and no treatment discontinuations for toxicity
  - This is despite additional radiation from Auger and conversion electrons
    - **The highest radioactivity level of 7.4 GBq of ^{161}Tb is equivalent to ~10 GBq of ^{177}Lu

- **Important considerations**:
  1. Current infrastructure, logistics, and procedures used for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T RLT can be transferred to use of [^{161}Tb]Tb-PSMA-I&T → supports generalizability
  2. Identical radioprotective measures currently used for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T can be followed
  3. ^{161}Tb with high radionuclide purity can be produced in nuclear reactors with similar methods to ^{177}Lu production

- Registered clinical trials using ^{161}Tb in mCRPC:
  - PROGNOSTICS: Swiss single-center, phase 1a/b study investigating [^{161}Tb]Tb-SibuDAB
  - REALITY: German registry assessing various radionuclide therapies

Take Home Messages

- [^{161}Tb]Tb-PSMA-I&T had an encouraging safety profile at the maximum administered dose of 7.4 GBq in pts with progressive mCRPC

- An additional cohort to assess a higher 9.5 GBq dose is currently recruiting

- ***This data from VIOLET provides a platform for further clinical evaluation of [^{161}Tb]Tb-PSMA-I&T in pts with mCRPC and in earlier disease indications, leveraging superior treatment of micrometastatic disease***