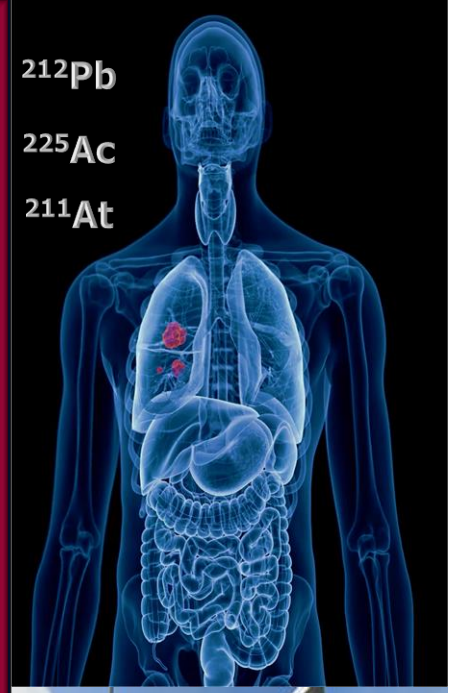

Clinical experience with targeted alpha-emitter therapy using peptide

Izabela Tworowska, PhD

RadioMedix
INNOVATING THERANOSTICS

Clinical studies of ^{212}Pb-DOTAMTATE and impact of dosimetry on the dose selection, design of the dose scalation studies

Systematic approach for estimation of the Pb212 organ absorbed doses

Pb212-DOTAMTATE pre-clinical studies (bioD) cumulative/max dose and design of the dose escalation studies	eIND clinical Pb203-DOTAMTATE • SPECT/CT imaging/PK	Phase I dose escalation of Pb212-DOTAMTATE in PRRT naïve patients • SPECT/CT imaging/PK

Goal: optimize dosing schedule to improve efficacy and minimize normal organ tox with min burden for patient

<table>
<tr><th colspan="2">Phase 1
Non-Randomized, Open-Label, Dose Escalation, of Pb^{212}-DOTAMTATE (AlphaMedix™) in Adult Subjects with Somatostatin Receptor Expressing Neuroendocrine Tumors (NET)</th><th colspan="2">Phase II
Open Label Study to Evaluate the Safety and Effectiveness of ^{212}Pb-DOTAMTATE in Subjects with Somatostatin Receptor Expressing Neuroendocrine Tumors</th></tr>
<tr><td>PRRT naïve patients
Dose escalation studies

22 patients

Cohort 1& 2 (SAD1 and 2)
7 patients/single therapy

DOSIMETRY
Cohort 3 (MAD 3)
4 patients/ 3cycles
Cohort 4 (MAD4)
12 patients/4 cycles</td><td>Patients progressed after PRRT

11 patients

Dosing as MAD4
4 cycles/8 weeks</td><td>PRRT naïve patients

Multi-center</td><td>Patients progressed after PRRT
Multi-center</td></tr>
<tr><td colspan="4">The primary objectives
To evaluate the efficacy of through overall response rate (ORR)
To assess the safety and tolerability
Secondary Objectives
To determine median Progression free survival (mPFS);
To determine the Overall Survival (OS);
To determine the Time to Tumor Progression (TTP); and
To evaluate the health-related quality of life (HRQL), relative to baseline.</td></tr>
</table>

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OBJECTIVES AND DEMOGRAPHIC INFORMATION

biopsy-proven unresectable or metastatic SSTR expressing NETs from different primary sites, and grades,

PK (22 pt)

Dosimetry
6 pt
(data
collected 12 pt)

Subject	Age	Sex	Type of NET	Stage	µCi/kg	Cumulative Dose (mCi)	Weight
SAD1-01	75	M	Midgut	IV	30.7	2.1	
SAD1-02	75	F	Pancreatic	IV		2.3	
SAD1-03	77	M	Pancreatic	IV		2.3	
SAD2-01	56	M	Rectal	IV	40.0	3.3	
SAD2-02	27	F	Midgut	IV		2.7	
SAD2-03	72	F	Midgut	IV		3.2	
MAD3 -01	61	F	Midgut	IV	52.0	15.0	
MAD3-02[a]	63	F	Pancreatic	IV		8.9	
MAD3-03	68	F	Midgut	IV		7.2	
MAD3-04	51	M	Pancreatic	IV		12.3	
MAD4-01	62	M	Midgut	IV	67.6	22.0	73
MAD4-02	45	M	Bronchial	IV		21.6	75
MAD4-03	71	F	Bronchial	IV		19.2	78
MAD4-04	39	F	Rectal	IV		21.8	74
MAD4-05	62	M	Pancreatic	IV		23.6	84
MAD4-06	49	F	Pancreatic	IV		18.4	67
MAD4-07	45	M	Rectal	IV		23.2	140
MAD4-08	60	M	Midgut	IV		18.7	65.7
MAD4-09	80	M	Bronchial	IV		22.6	78.7
MAD4-10	59	F	Bronchial	IV		22.9	83.9
MAD4-11	52	M	Pancreas	IV		22.13	79.4
MAD4-12	58	F	Pancreas	IV		14.1	51.9

[a] SAD3-02 dropped out of the study after the second cycle and was replaced by SAD3-04.

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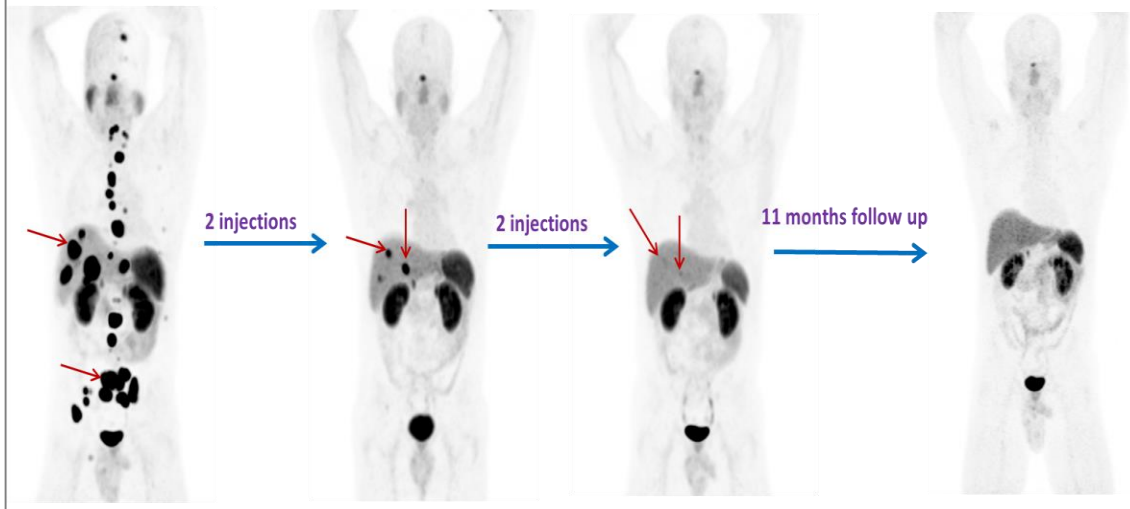
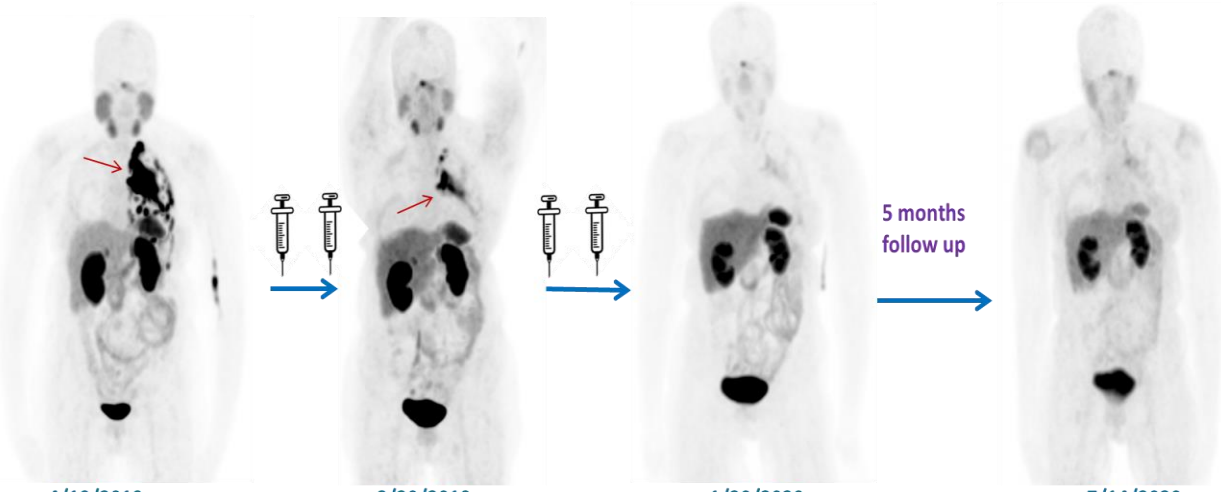
^{68}Ga-DOTATATE PET/CT scans

MAD4-02: 47 year old man with metastatic bronchial carcinoid



^{68}Ga-DOTATATE PET/CT scans

MAD4-03: 72 year old woman with bronchial carcinoid



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PRRT NAIVE PATIENTS - SUMMARY OF RADIOLOGICAL RESPONSE

9 OUT OF 12 PATIENTS (75%)

PRRT naïve patients	Last treatment	Response by RECIST v.1.1
MAD4-01	7-Nov-19	**PR**
MAD4-02	19-Nov-19	**CR**
MAD4-03	3-Dec-19	**CR**
MAD4-04	19-May-20	SD
MAD4-05	21-May-20	**PR**
MAD4-06	28-May-20	**CR***
MAD4-07	19-Nov-20	**PR**
MAD4-08	1-Dec-20	SD
MAD4-09	9-Feb-21	SD
MAD4-10	18-Mar-21	**PR**
MAD4-11	20-Jul-21	**PR**
MAD4-12	29-Jul-21	**PR**

Proteomics and genomics
WREN, Novigenix tests

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PHASE I STUDY IND # 135150 FOR PRRT PROGRESSED SUBJECTS

- Enrolled 11 subjects with biopsy-proven unresectable or metastatic SSTR expressing NETs from different primary sites, and grades, and prior PRRT, with at least one measurable lesion who progressed after receiving prior PRRT

- 4 cycles of ^{212}Pb-DOTAMTATE at 67.6 µCi/kg/cycle.

- Response to treatment measured per RECIST 1.1 and ^{68}Ga/^{64}Cu-DOTATATE PET/CT.

Subject ID	Age	Primary Tumor location	Grade	Cumulative dose	Weight
MAD4-R01	81	Sm. Bowel	G1	19.7	71
MAD4-R02	65	Thymus	n/a	23.0	88.9
MAD4-R03	70	Pulmonary	G3	22.3	89.9
MAD4-R04	64	Pancreatic	G2	22.6	92.53
MAD4-R05	56	Sm. Bowel	G2	22.3	74.47
MAD4-R06	70	Pancreatic	G3	23.1	56.9
MAD4-R07	69	Sm. Bowel	n/a	23.1	105.2
MAD4-R08	61	Midgut	n/a	5.7*	84.8
MAD4-R09	53	Sm. Bowel	G2	17.2	84.8
MAD4-R10	65	Pancreatic	G2	15.8	67.14
MAD4-R11	35	Pancreatic	G2	23.2	73.02

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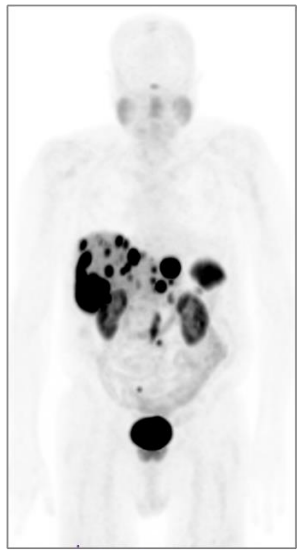
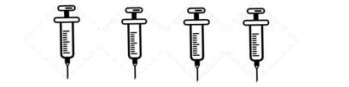
MAD4-R01- 81 year old man with refractory G1, neuroendocrine tumor of the small bowel.
Treated previously (2017) with ^{177}Lu-DOTATATE PRRT

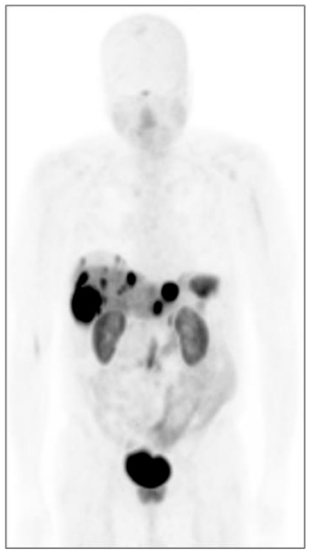


4/28/2021

^{68}Ga-DOTATATE PET/CT scans

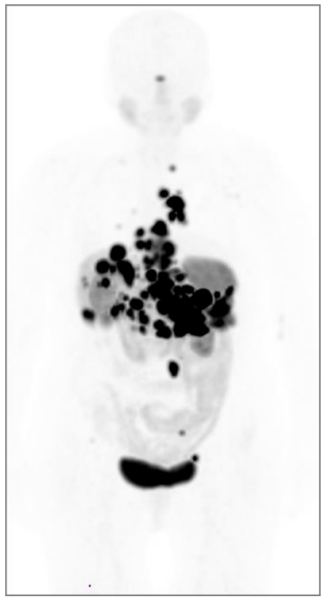


Response by RECIST: SD



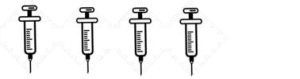
12/14/2021

MAD4-R06 71 year old man with refractory G3 pulmonary carcinoid. Treated previously (2017) with ^{177}Lu-DOTATATE

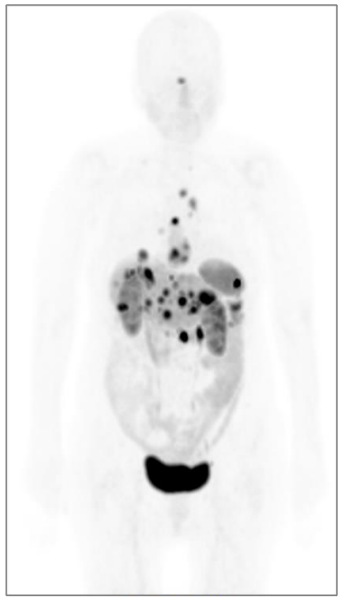


4/6/2021

^{64}Cu-DOTATATE PET/CT scans



Response by RECIST: PR



11/10/2021

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PRRT PROGRESSED PATIENTS- SUMMARY OF RADIOLOGICAL RESPONSE

4 OUT OF 11 PATIENTS (36.4%)

PRRT PROGRESSED PATIENTS	LAST TREATMENT	STATUS	LAST VISIT	RESPONSE BY RECIST V.1.1
MAD4-R01	3-Dec-20	Alive	10 month follow up	SD
MAD4-R02	17-Dec-20	Alive	15 months follow up	**PR**
MAD4-R03	15-Sep-21	Alive	6 months follow up	SD
MAD4-R04	9-Sep-21	Alive	6 month follow up	**CR**
MAD4-R05	23-Sep-21	Alive	3 months follow up	**PR**
MAD4-R06	16-Sep-21	Deceased*	2 months post INV4	**PR**
MAD4-R07	16-Nov-21	Deceased*	2 months post INV4	**PR**
MAD4-R08	1st and last dose: 5/6/2021	Deceased*	0.5 months post INV1	N/A
MAD4-R09	16-Dec-21	Alive	3 months follow up	SD
MAD4-R10	30-Sep-21	Alive	Due to elevated Cr: not completed the last dose.	SD
MAD4-R11	1-Feb-22	Alive	3 months follow up	**PR**

*not drug releated

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COMMON ADVERSE EVENTS

Summary of AEs in > than 5 PRRT naïve subjects

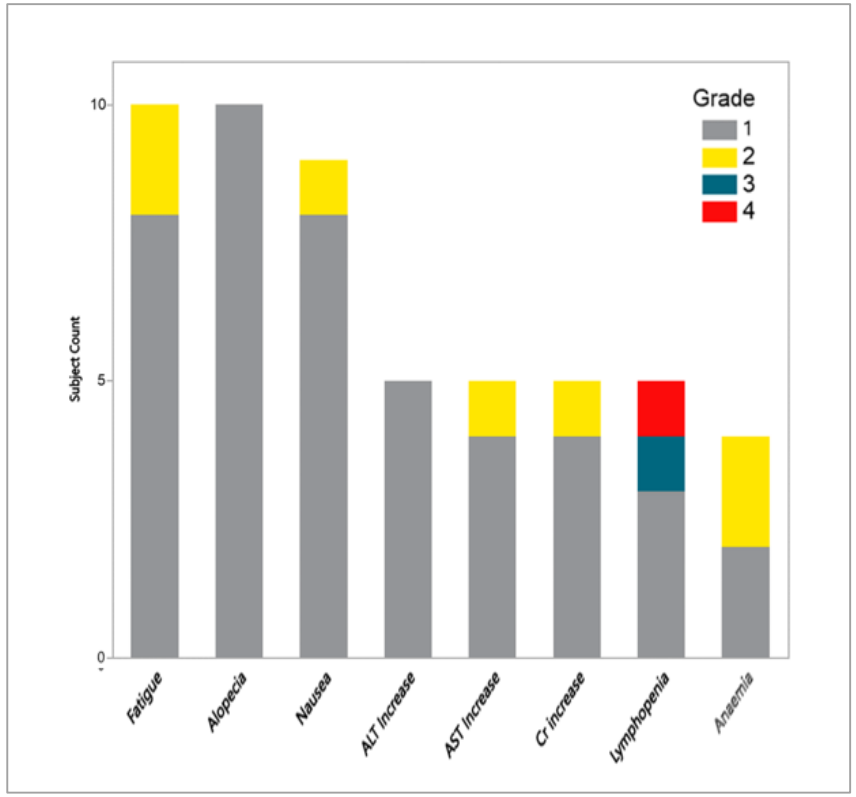
AE (PRRT naive)	n (%) [b]
Alanine aminotransferase increased	6 (27)
Alopecia	13 (59)
Bone pain	5 (23)
Fatigue	11 (50)
Hyperglycaemia	8 (36)
Nausea	12 (55)
Diarrhoea	5 (23)
Lymphopenia [b]	10 (46)

Total number of subjects = 22.
[b] Includes the preferred terms lymphopenia and white blood cell count decreased.

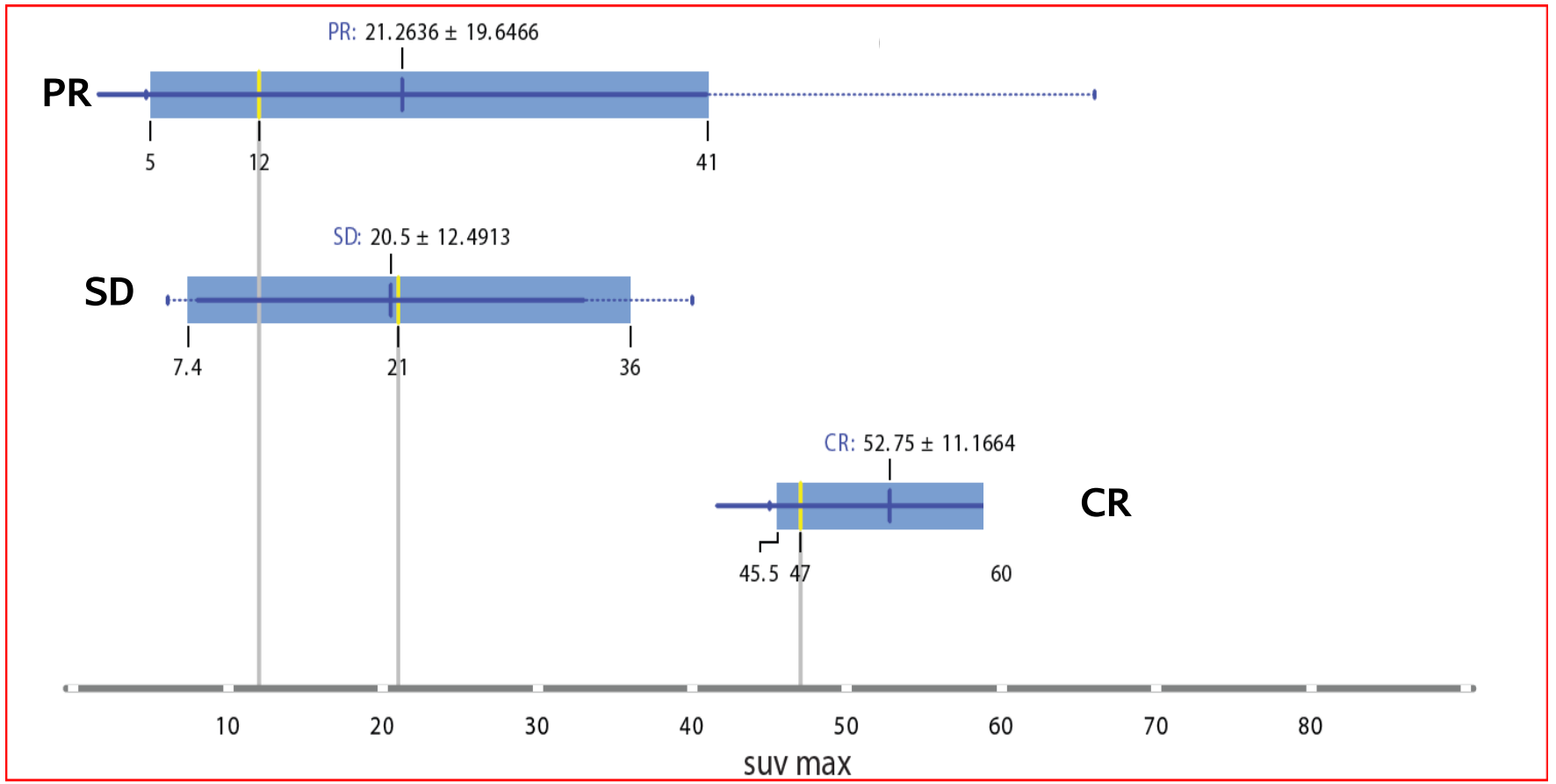
Summary of AEs in > than 4 PRRT progressed subjects

AE PRRT refractory	n (%) [a]
Alanine aminotransferase increased	4 (36)
Aspartate aminotransferase increased	4 (36)
Anaemia	4 (36)
Alopecia	11 (100)
Fatigue	11 (100)
Nausea	10 (91)
Lymphopenia [b]	5 (46)

Total number of subjects =11.



CORRELATION OF RESPONSE SUV_{MAX}, CUMULATIVE DOSE AND MAX DOSE/80KG (WHISKER PLOTS)

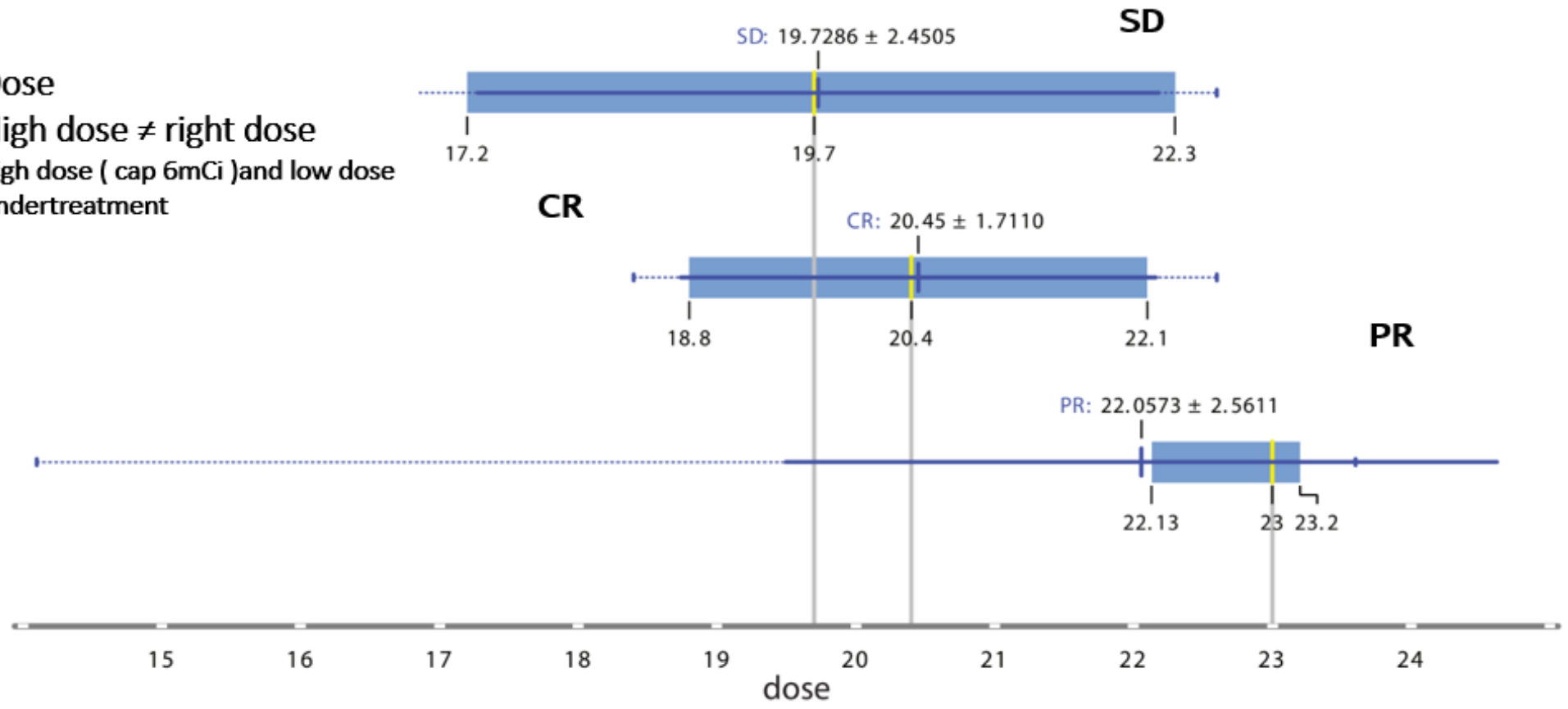


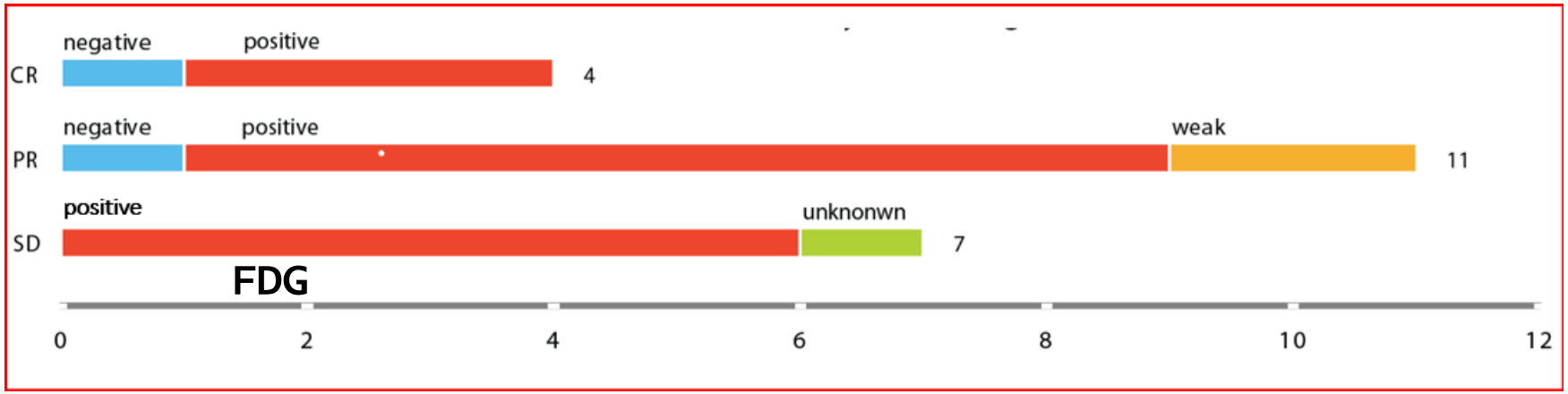
SUVmax

Dose

High dose ≠ right dose

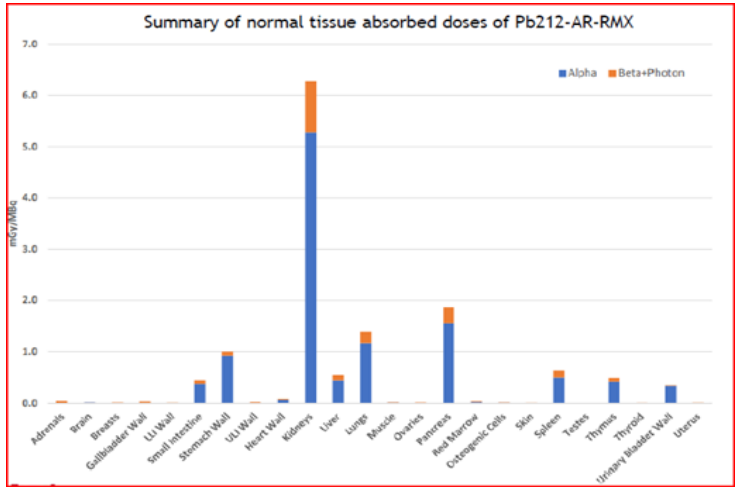
high dose (cap 6mCi)and low dose undertreatment





Estimation of the Pb212 organ absorbed doses

Pb212-DOTAMTATE pre-clinical studies
cumulative/max dose and design of the dose escalation studies

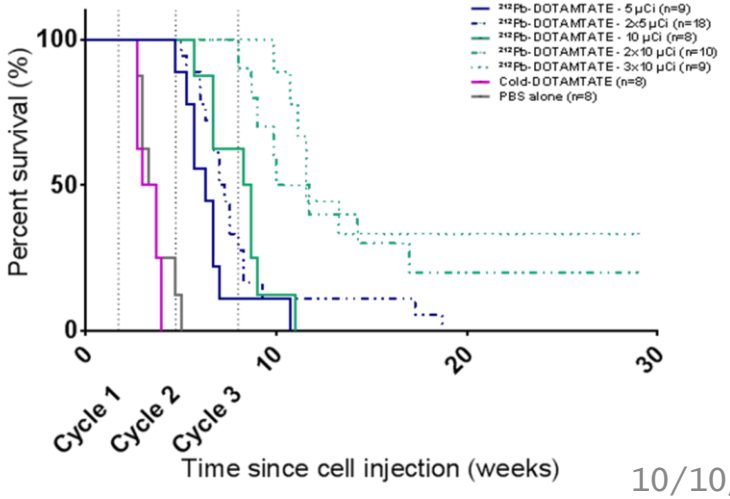


ß-PRRT

- Red marrow- DLO for the max tolerated single dose
- Kidneys– DLO for the cumulative dose

^{212}Pb-DOTAMTATE

- Kidneys - dose limiting organs
- Cumulative dose of 23.8mCi ~absorbed dose 23Gy for kidneys
- 24mCi cap cumulative dose; 6mCi/cycle/80kg or higher
- 10uCi NOAEL
- HED 2.8mCi/70kg patient (starting dose in dose escalation)



DOSE	MST[week]
5uCi	6.3
2X5uCi	7.1
10uCi	8.5
2x10uCi	10.9 (20%)
3x10uCi	11.6 (33%)
Cold AR-RMX	3.4
PBS	3.5

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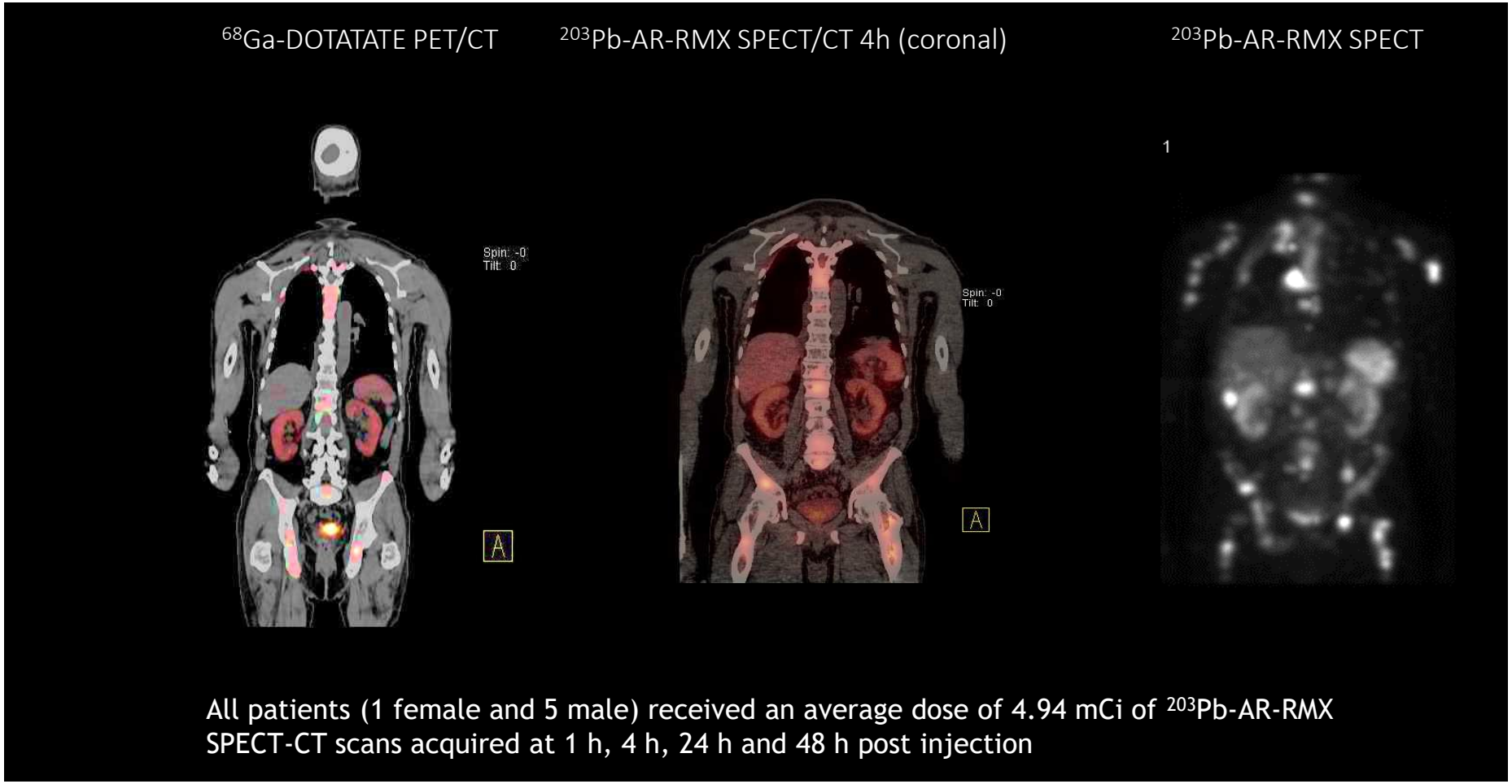
Dosimetry of ^{203}Pb-DOTAMTATE mimic ^{203}Pb-octreotate analog (IND # 130960)

Objective: safety, distribution, dosimetry Pb212 organ absorbed doses based on SPECT/CT



All patients (1 female and 5 male) received an average dose of 4.94 mCi of ^{203}Pb-AR-RMX SPECT-CT scans acquired at 1 h, 4 h, 24 h and 48 h post injection

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DOSIMETRY RESULTS (clinical – PRRT NAIVE PATIENTS)

Estimated ^{212}Pb-DOTAMTATE absorbed dose from ^{203}Pb (eIND) and ^{212}Pb imaging (Phase I)

Dose (mGy/MBq)	RBE=3		RBE=5	
	Pb-203 Extrapolation to Pb-212	Pb-212 Imaging	Pb-203 Extrapolation to Pb-212	Pb-212 Imaging
Spleen	35.7 ± 23.6	12.0 ± 5.5	58.5 ± 38.7	19.7 ± 9.0
Kidneys	14.5 ± 3.3	14.0 ± 6.2	23.7 ± 5.4	22.6 ± 10.6
Liver	12.9 ± 6.6	13.0 ± 6.1	21.2 ± 10.9	21.1 ± 10.2
Lungs	5.9 ± 3.8	3.1 ± 1.5	9.7 ± 6.2	5.0 ± 2.4
Red Marrow	1.9 ± 1.3	2.6 ± 1.1	3.1 ± 2.1	4.2 ± 1.7
Heart Wall	3.5 ± 0.6	2.1 ± 1.7	5.8 ± 1.1	4.2 ± 2.5

- 203Pb vs 212Pb imaging: higher except for the red marrow.
- Higher variation of ^{203}Pb data
- Red marrow - dose-limiting organ
- Cumulative dose (20.6 mCi) ~2 Gy for red marrow
- Majority of patients: dose ≥ 20mCi cumulative (no hematological tox)

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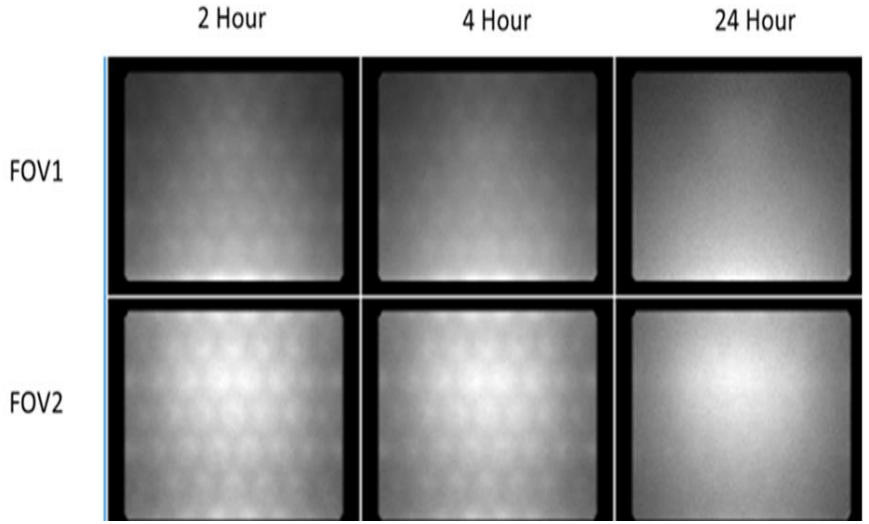
Lesson learned:

- Quantitative Pb-^{212}SPECT imaging is challenging
- Artefacts due to the high energy 2.6 MeV photons (Tl-208)



SUMMARY

- Estimation of Pb212 absorbed doses based on TAT imaging (Pb212) - CHALLENGING BUT REWARDING
- Dosing approach: cap max 6mCi for 80 kg (convenient from commercial point of view, potential undertreatment of patients)
- High/bullet dose (1-2 cycle, doses adjustment in the following cycles)
- No shortcuts: critical value of dosimetry data from pre-clinical/clinical studies (Pb203/Pb212)- reduction of risk
- NIST standards for accurate dose estimation; standardization of imaging/dosimetry protocols
- Determination of tumor absorbed doses not only organ absorbed doses (if feasible)
- Standardized reporting and sharing dosimetry data (database; deficiency of clinical trial.gov)

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Small Business Technology Transfer (STTR)

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Patent: PCT/US2018/013640 WO2018132751A1