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First-in-Human Radiopharmaceutical Therapy (RPT) of [$^{203/212}$Pb]VMT01 for Patients with Pretreated Unresectable or Metastatic Melanoma (NCT05655312)

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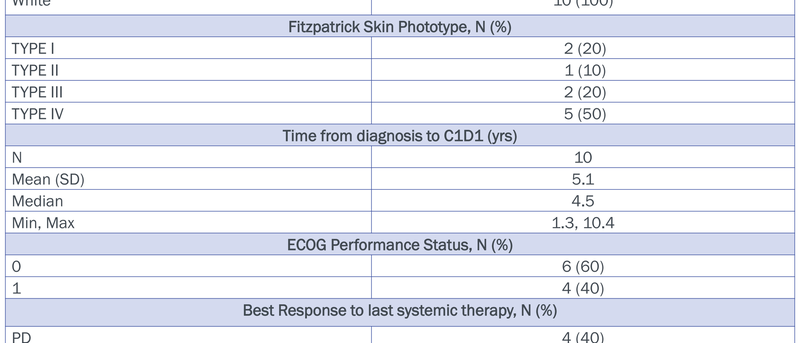
Background

- Immune checkpoint inhibitors (ICI) are effective in melanoma, but many patients still progress after PD-1 therapy; PFS for current 2L+ therapies, including lifileucel, remains limited between 2.1 – 4.1 months[4,5,6,9]
- Melanocortin-1 receptor (MC1R) is a novel target for radiopharmaceutical therapy (RPT) and is found highly expressed on melanoma tissue [2]
- ^{203}Pb and ^{212}Pb is a promising theranostic isotope pair for RPT of cancer
- VMT01 is a MC1R-targeted RPT that can be radiolabeled with either ^{203}Pb (patient selection and dosimetry assessments) or ^{212}Pb (alpha particle therapy)
- In preclinical experiments [^{212}Pb]VMT01 demonstrated direct monotherapy activity with direct cell killing (cytoreduction); in addition, through induction of immunologic cell death (ICD) which is immunostimulatory, cooperation of [^{212}Pb]VMT01 and ICIs could be demonstrated[3]
- Here we present the initial safety, dosimetry and efficacy findings from the first two cohorts

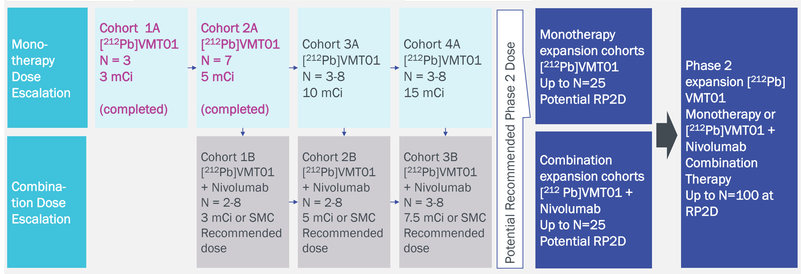
Proposed Mechanism of Action for [^{212}Pb]VMT01 [7]



Study Design

- Patients were being selected for MC1R expression by [^{203}Pb]VMT01 SPECT/CT
- The first two cohorts incorporated voluntary, multiple-time points dosimetry using [^{203}Pb]VMT01 SPECT/CT scans
- Up to 3 treatment cycles of [^{212}Pb]VMT01, 8 weeks apart

Primary Objectives	To determine the MTD, MFD, and RP2D as mono- and in combination with PD-1 inhibitor (nivolumab)	MC1R Dosimetry	[^{203}Pb]VMT01 SPECT/CT
MC1R Imaging Patient Selection	[^{203}Pb]VMT01 SPECT/CT [^{68}Ga]VMT02 PET/CT	Design Methodology	mTPI-2



Nivolumab will be administered 480 mg Q4W up to 24 months

Patient Characteristics (N=10)

Age		
N	10	
Mean (SD)	67.2	
Median	67	
Range	49, 81	
Sex, N (%)		
Female	4 (40)	
Male	6 (60)	
Race, N (%)		
White	10 (100)	
Fitzpatrick Skin Phototype, N (%)		
TYPE I	2 (20)	
TYPE II	1 (10)	
TYPE III	2 (20)	
TYPE IV	5 (50)	
Time from diagnosis to C1D1 (yrs)		
N	10	
Mean (SD)	5.1	
Median	4.5	
Min, Max	1.3, 10.4	
ECOG Performance Status, N (%)		
0	6 (60)	
1	4 (40)	
Best Response to last systemic therapy, N (%)		
PD	4 (40)	
SD	6 (60)	
	Prior Lines Systemic Therapy (median)	Prior Lines IO Therapy (median)
Cohort 1 (3mCi) (N = 3)	5	3
Cohort 2 (5 mCi) (N = 7)	5	3

Adverse Events Summary

- No dose-limiting toxicities (DLTs) were observed among any patients
- Treatment-related AEs were low frequency (in 30% of patients), and all were of low grade (all Gr 1 except for a single case of Gr 2 anemia)
- One SAE was reported, hemoptysis. This was attributed to the patient's underlying condition (metastatic melanoma) and not related to [^{212}Pb]VMT01
- **No AEs led to treatment discontinuation**

Treatment-emergent Adverse Events (TEAEs)

TEAE by Preferred Term and Grade (Frequency >1 and / or Grade >1

	[^{212}Pb]VMT01 3 mCi (N=3)			[^{212}Pb]VMT01 5 mCi (N=7)			Total (N=10)		
Grade	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Total Number of TEAEs Reported for All patients	31	6	-	12	12	4	43	18	4
AEs by Preferred Term and Grade Reported per Patient [no of pts with AE (% of pts treated per cohort)]									
Grade 1 and Frequency > 1	-	-	-	-	-	-	-	-	-
Anaemia	3 (100)	-	-	-	1 (14)	-	3 (30)	1 (10)	-
Lymphocyte count decreased	2 (67)	1 (33)	-	1 (14)	1 (14)	1 (14)	3 (30)	2 (20)	1 (10)
Nausea	2 (67)	-	-	1 (14)	1 (14)	-	3 (30)	1 (10)	-
Hyponatraemia	2 (67)	-	-	-	-	-	2 (20)	-	-
Platelet count decreased	2 (67)	-	-	-	-	-	2 (20)	-	-
Abdominal pain	-	-	-	-	1 (14)	-	-	1 (10)	-
Back pain	-	-	-	-	1 (14)	-	-	1 (10)	-
Grade ≥2	-	-	-	-	-	-	-	-	-
Cough worsening, not coded	-	-	-	-	1 (14)	-	-	1 (10)	-
COVID-19	-	2 (67)	-	-	-	-	-	2 (20)	-
Dysphagia	-	-	-	-	1 (14)	-	-	1 (10)	-
Dyspnoea (incl 'Dyspnea worsening, not coded')	-	1 (33)	-	-	1 (14)	-	-	2 (20)	-
Fatigue (incl 'Fatigue worsening, not coded')	-	-	-	-	2 (28.6)	1 (14)	-	2 (20)	1 (10)
Haemoptysis	-	-	-	-	-	1 (14)	-	-	1 (10)
Hepatic vein thrombosis	-	-	-	-	1 (14)	-	-	1 (10)	-
Pneumonitis, not coded	-	-	-	-	1 (14)	1 (14)	-	1 (10)	1 (10)
Sinusitis	-	1 (33)	-	-	-	-	-	1 (10)	-
Urinary tract infection	-	1 (33)	-	-	-	-	-	1 (10)	-

[^{203}Pb]VMT01 Theranostic Dosimetry for [^{212}Pb]VMT01 (3 Subjects)

Dosimetry Summary

- Dosimetry with [^{203}Pb]VMT01 shows high kidney estimates for [^{212}Pb]VMT01
- Mean estimated cumulative dose to kidneys for Cohort 1 subjects (3 cycles at 3 mCi) was 25.8 Gy
- Cumulative dose estimates to kidneys for Cohort 2 subjects (2 cycles at 5 mCi) was between 25.6 Gy and 29.6 Gy
- **Despite high dosimetry estimates to the kidneys, no renal toxicities have been reported to date**

ROI	Dose Coefficients (Gy/mCi) and Cumulative Dose to Date (Gy)						Mean Coefficient, & Est'd Cumulative Dose	
	01-116		02-117		03-114			
	Coefficient (Gy/mCi)	Cumulative 2 x 5 mCi (Gy)	Coefficient (Gy/mCi)	Cumulative 1 x 5 mCi (GY)	Coefficient (Gy/mCi)	Cumulative 2 x 5 mCi (Gy)	Coefficient Mean ± SD (Gy/mCi)	Cumulative 3 x 3 mCi (Gy)
Liver	0.22	2.21	0.12	0.62	0.15	1.52	0.17 ± 0.05	1.49
Kidneys	2.96	29.6	3.07	15.4	2.56	25.6	2.87 ± 0.27	25.8
Spleen	0.23	2.27	0.34	1.72	0.29	2.85	0.29 ± 0.06	2.57
Marrow	0.11	1.08	0.08	0.41	0.08	0.82	0.09 ± 0.02	0.81
Tumors	0.25	2.53	0.14, 0.15	0.70 - 0.77	0.17, 0.26, 0.28	1.72 - 2.83	0.21 ± 0.06	1.26 - 2.55

Note: MC1R is expressed in normal renal parenchyma.[9] Tumor dosimetry does not account for partial volume effects

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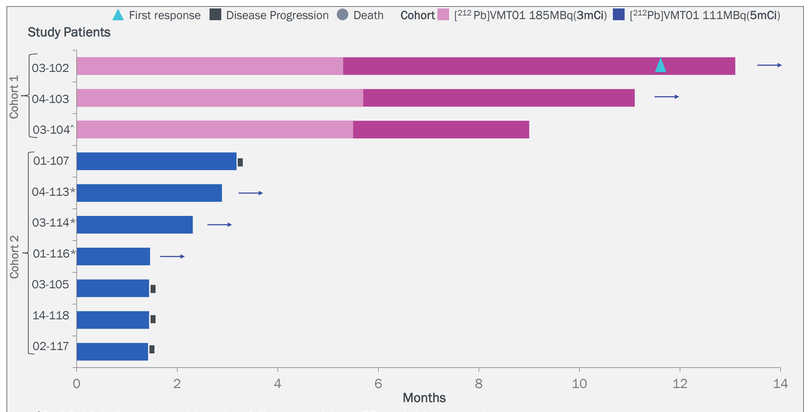
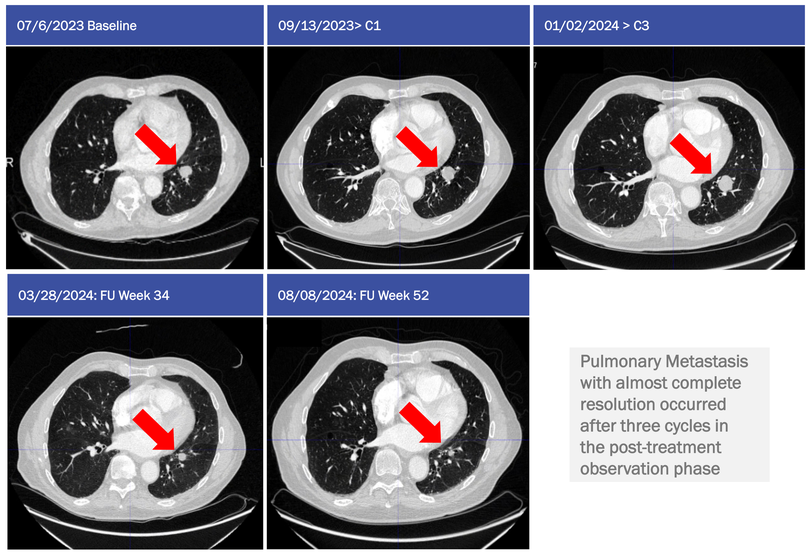
Preliminary Efficacy



^Pt 03-104 discontinued imaging follow-up (without PD) to initiate a maintenance therapy
*Notes: Data cutoff (DCO) 04-SEP-2024. Patients 113, 114 and 116 had PD after DCO.

Patient with uPR after [^{212}Pb]VMT01



Pulmonary Metastasis with almost complete resolution occurred after three cycles in the post-treatment observation phase

Efficacy Summary

- In Cohort 1, all subjects completed the planned treatment cycles; two subjects showed prolonged SD of 9 months and 11 months, respectively, from start of treatment
- One subject in Cohort 1 developed an objective response (PR – unconfirmed to date) after completion of all three VMT01 administrations and is still on trial after 13 months from start of treatment
- In Cohort 2, all subjects progressed after either the first cycle (3 subjects) or the second cycle (4 subjects)
- Preclinical experiments demonstrated higher immunostimulatory efficacy in combination with immune checkpoint inhibitors at lower doses whereas direct cytotoxic tumor effects were observed at higher activity doses[3]; here we see a delayed anti-tumor response at a lower dose with monotherapy
- We hypothesize that low-dose monotherapy in Cohort 1 leads to immunostimulatory activation within the tumor microenvironment (TME) resulting in prolonged disease control. This suggests the potential for the cooperation of [^{212}Pb]VMT01 with ICI in patients
- **Unexpectedly, we may have defined between Cohort 1 and Cohort 2 dose levels with VMT01 which may delineate the immunostimulatory and immunosuppressive effects on the TME in melanoma**

Conclusion

- At 3 mCi and 5 mCi activity levels, [^{212}Pb]VMT01 was safe and no DLTs were observed
- Dosimetry demonstrates high kidney estimates limiting monotherapy escalation
- SMC recommendation included dose reduction to 1.5 mCi for both monotherapy and the upcoming combination cohort with nivolumab
- **An objective response and prolonged PFS was observed at the 3 mCi activity level**
- The observed efficacy in Cohort 1 may be a result of the immunostimulatory effect of low dose ^{212}Pb-targeted alpha particle radiation on the TME, as observed in preclinical studies
- An amendment to test lower dose levels for monotherapy is planned
- **The combination cohort with nivolumab is active and now open for enrollment**

Acknowledgement

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