First-in-human study of AB001, a prostate-specific membrane antigen (PSMA) targeted ^{212}Pb alpha radioligand, in patients with metastatic castration resistant prostate cancer (mCRPC): Phase 0 experience

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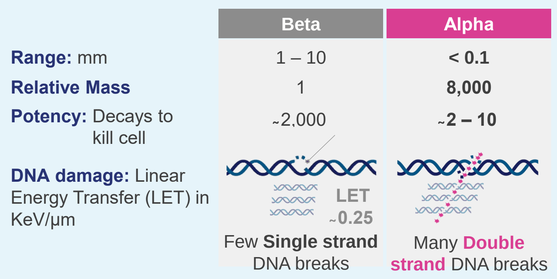
Introduction

AB001 is an Alpha Radioligand Therapy (ART) consisting of a PSMA-targeted small molecule radiolabeled with lead-212 (^{212}Pb)

- PSMA is commonly overexpressed in prostate cancer and has become an attractive target for imaging agents and therapies[1]
- PSMA-targeted therapies using the beta-emitter Lutetium-177 (^{177}Lu) are established treatment options for patients with mCRPC
- Early clinical data for alpha-emitter based therapies targeting PSMA have indicated promising anticancer activity in mCRPC, including cases unresponsive to treatment with ^{177}Lu-PSMA[2,3]

Non-clinical studies of AB001 demonstrated good tumor uptake, tumor growth inhibition, and promising biodistribution[4,5]

^{212}Pb is a promising *in vivo* alpha-particle generator, with physical decay properties that match the rapid tumor uptake and clearance achievable from small molecule or peptide targeting agents

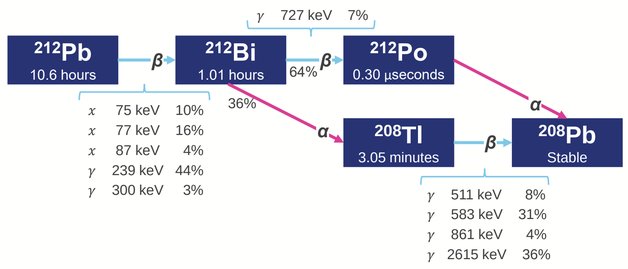


Aims

A Phase 0 first-in-human study of AB001 in patients with mCRPC to investigate:

- Feasibility of gamma camera imaging following a microdose of AB001
- Biodistribution of AB001
- AB001 uptake in metastatic lesions
- Evaluate pharmacokinetics and clearance
- Evaluate Safety, tolerability, and activity

^{212}Pb Decay Scheme[6]

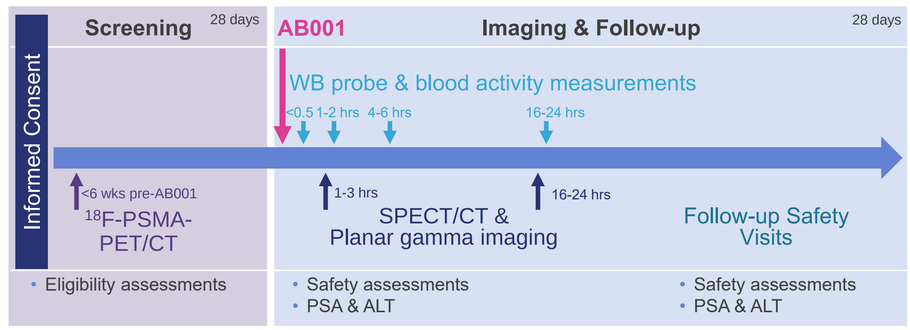


References: 1. Hawkey, N.M., et al., Clin Adv Hematol Oncol, 2022. **20**(4): p. 227-238. 2. Ballal, S., et al., Prostate, 2021. **81**(9): p. 580-591 3. Feuerecker, B., et al., Eur Urol, 2021. **79**(3): p. 343-350. 4. Stenberg, V.Y., et al., International Journal of Molecular Sciences, 2021. **22**(9): p. 4815. 5. Stenberg, V.Y., et al. Journal of Labelled Compounds and Radiopharmaceuticals, 2020. **63**(3): p. 129-143 6. Data: NuDat (NNDC, BNL, USA)

Study Design and Methods

This was single centre, open label, non-randomised, non-controlled study conducted at Oslo University Hospital. Key Inclusion and Exclusion criteria:

- Progressive mCRPC with PSMA-avid lesions by PSMA PET/CT
- ECOG performance status 0-2 and life expectancy >6 months
- Adequate hematopoietic, kidney, and liver function
- No prior PSMA-targeted radioligand therapy or concurrent cancers within 2 years



PSMA-PET/CT: GE Discovery PET/CT scanner; 200-252 MBq ^{18}F-PSMA-1007. PSMA-avid mCRPC lesion defined by 'SUV ≥ 3 times adjacent normal tissue'

Gamma Camera Imaging: Planar imaging & SPECT/CT; Siemens Symbia Intevo Bold SPECT/CT with high energy collimators[ref]. 40% energy window centred on 79 keV & 20% window centred on 239 keV were acquired simultaneously, dual scatter windows of 20% & 5%

Whole body (WB) probe measurements: ThermoFisher Scientific RadEye SX, with scintillation detector, FHZ514A; >1m distance and 60s measurement time

Blood sample activity: ^{212}Pb activity of full blood, plasma, and red blood cells measured separately. Hidex Automatic gamma counter; 55-300 keV efficiency factor 0.8236.

Results

Three patients with progressive mCRPC on standard of care therapies were included: 73-89 years old, ECOG 1, PSA levels 0.44 -15 µg/L

On baseline PSMA-PET all patients had at least three PSMA-avid metastatic lesions; range SUVmax 10.1 - 77.4

Each patient received a microdose of 9.4 ± 0.3 MBq AB001 (i.v.)

- There were no adverse reactions related to AB001
- No signal of efficacy by PSA or ALP (expected for a microdose)

Metastatic Lesion Visualisation

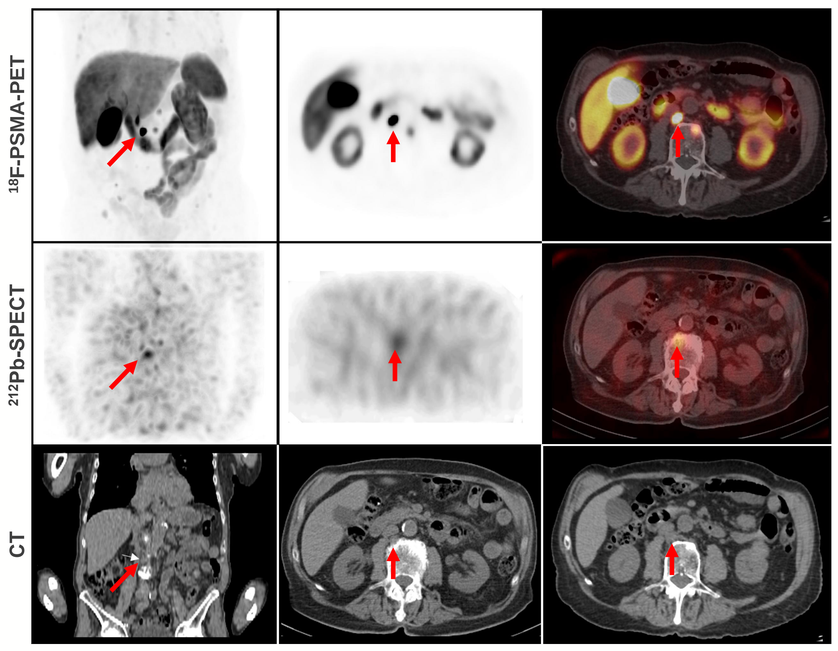


Figure 1: Retrocaval lymph node tumor metastasis (red arrows) demonstrated in patient ID03 with SUVmax 77 from 18F-PSMA-PET (a,b,c) and measuring 11x14x16mm on CT (g,h,i). AB001 uptake demonstrated on ^{212}Pb SPECT imaging at 4 hours post-administration (d,e,f).

The most PSMA-avid lesion, a retrocaval lymph node metastasis with short-axis diameter 11 mm, was visualized with AB001 uptake on post-therapy SPECT/CT.

Uptake of AB001 was not clearly demonstrated in other lesions. This may be attributed to the lower PSMA-expression of these metastases (due to tumor biology and limited tumor progression) demonstrated by PSMA PET, combined with injected AB001 microdose and imaging system limitations.

Table 1: mCRPC lesion assessment by PSMA-PET planar gamma camera/SPECT

Patient	Lesion location	Lesion size (cm)	PSMA-PET SUVmax	PSMA-PET SUVmean	Gamma Imaging AB001 uptake
ID01	Pubic bone	N.A.	10.1	5.7	N
	Bladder wall	2.8 x 1.3 x 1.7	15.9	9.0	N
	Seminal vesicle	1.2 x 0.8 x 1.0	10.6	6.2	N
ID02	Sternum	N.A.	28.6	14.7	N
	Rib	N.A.	30.9	20.6	N
	Vertebra	N.A.	18.9	11.3	N
ID03	Retrocaval LN	1.1 x 1.4 x 1.6	77.4	45.0	Y*
	Rib	N.A.	17.4	11.1	N
	Vertebra	N.A.	13.6	8.0	N

* Only visualised on SPECT/CT

Biodistribution to Normal Tissue

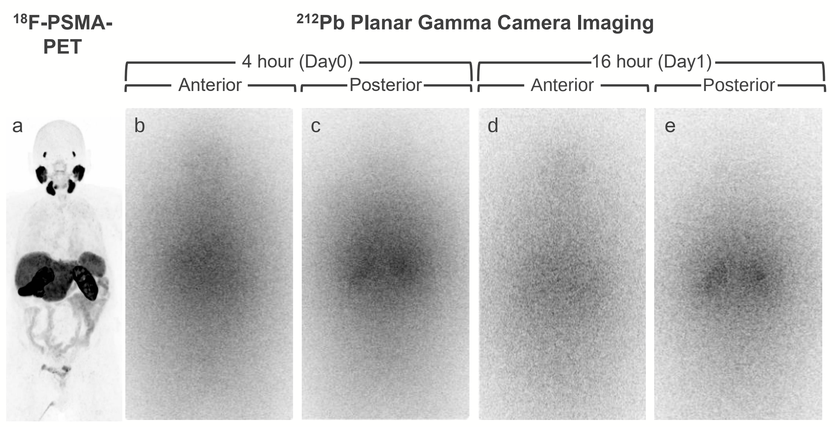


Figure 2: Baseline ^{18}F-PSMA-PET (a) as refence for planar gamma camera imaging post-administration of AB001 for Patient ID01 (b-e). MIP (scaling 0-20) and WB summed (scaling 0-max).

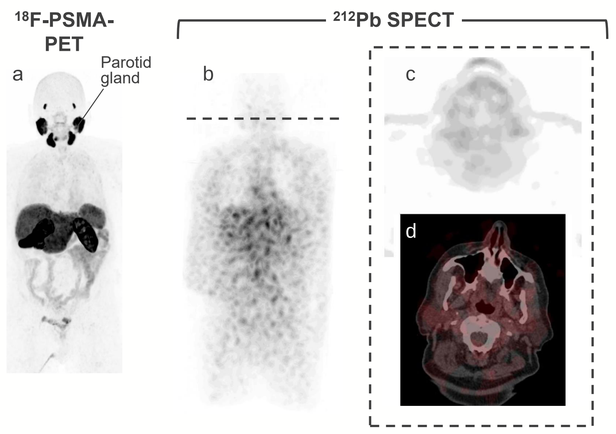


Figure 3: ^{18}F-PSMA-PET at baseline (a) compared to SPECT imaging for patient ID01 following administration of AB001: whole body MIP (anterior view) (b); and axial sections through the cranium at the level of the parotid salivary glands; SPECT (c) and fused SPECT/CT (d).

Normal tissue visibility of AB001, defined as uptake clearly distinguishable from adjacent tissue, was demonstrated for kidneys, urinary bladder with contents, and the liver. Blood pool uptake (defined as heart and/or large vessels) was seen. There was no visualization of the salivary glands.

Table 2: Normal tissue assessments of planar gamma camera and/or SPECT images performed post-administration of AB001

Tissue	Patient	ID01	ID02	ID03
Salivary glands		N	N	N
Kidneys		Y	Y	Y
Liver		N	N	Y
Spleen		N	N	N
Blood pool		Y	N	Y
Bone marrow		N	N	N
Small bowel inc contents		N	N	N
Urinary bladder inc contents		N*	Y	Y

*Limited bladder filling due to incontinence

Pharmacokinetics

- Blood analyses indicated stability of the AB001 ligand after administration
- Whole-body probe measurements demonstrated an effective half-life of 8 hours

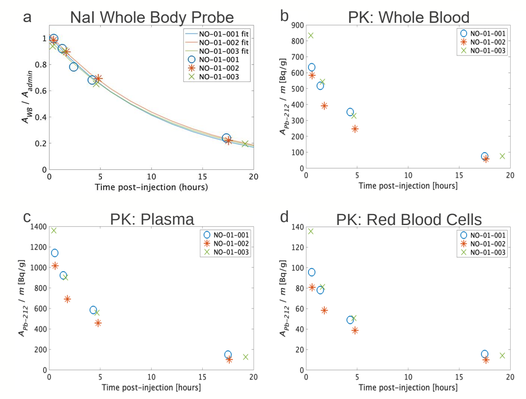


Figure 4: Whole Body activity as measured by a NaI whole body probe (a) after normalization against administered activity, for all three patients. A mono-exponential curve fit for each patient is included (solid lines). ^{212}Pb activity PK measurements from whole blood (a), plasma (b), and red blood cells (c).

Conclusions

- AB001 was safely administered to mCRPC patients in a phase 0 clinical study
- Gamma camera imaging was feasible but challenging at a 10 MBq microdose
- AB001 demonstrated metastatic targeting of mCRPC and a promising biodistribution, including potentially low salivary gland uptake
- AB001 constitutes a promising ^{212}Pb ART that should be investigated in a Phase 1 study

Contacts

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