SUPPLEMENTAL INFORMATION

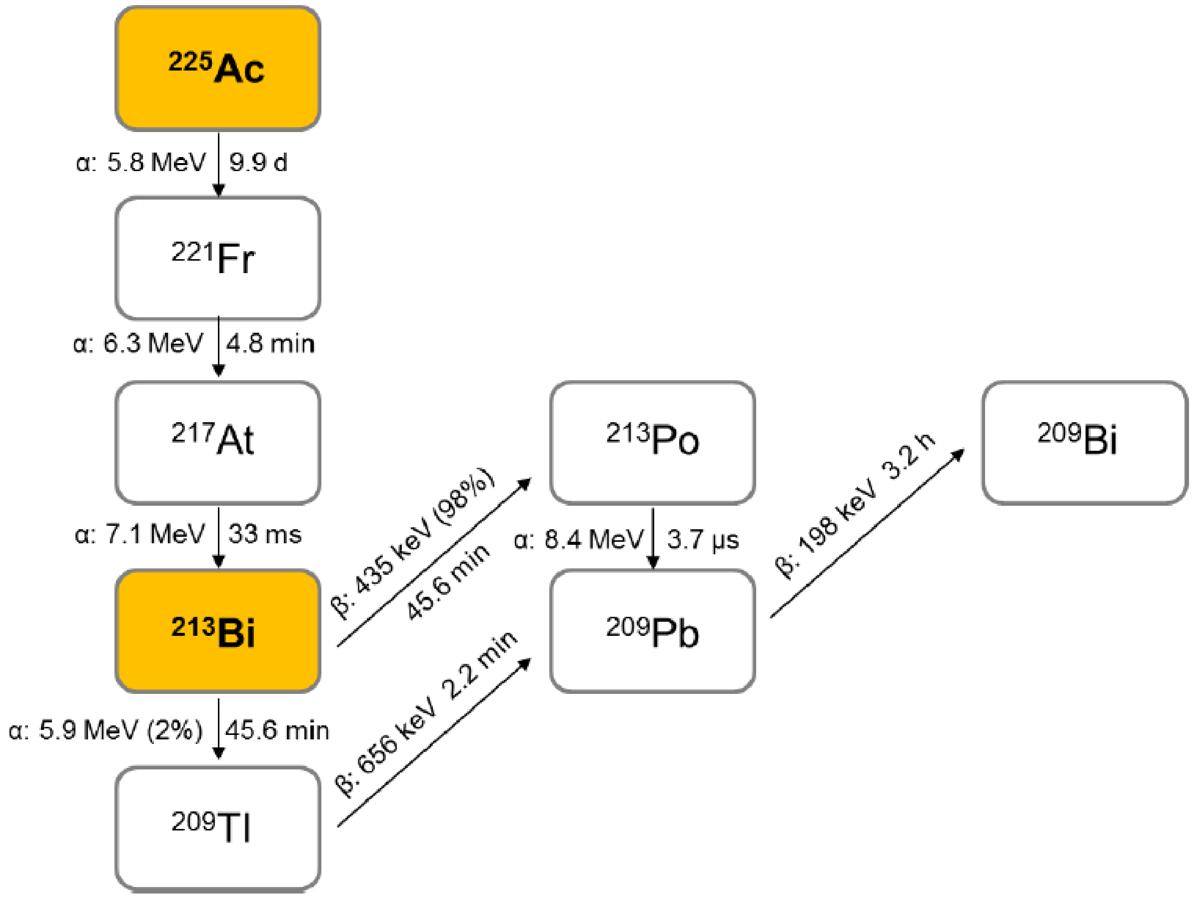
Here we provide background information about physical characteristics of ^{225}Ac, because this is not general knowledge but is helpful for understanding the main manuscript. However, it would exceed the scope of discussion inside of an original research paper. Therefore we provide this extract from the book:
"MIRD Monograph- Radiobiology and Dosimetry for Radiopharmaceutical Therapy with Alpha-Particle Emitters. Sgouros G, Ed. Society of Nuclear Medicine and Molecular Imaging Publishing, 2014".

RBE – Relative Biological Efficacy

Alpha radiation offers the promise of a highly localized radiation zone due to short path length of the emitted particle with high linear energy transfer during this range. Bystander effects can be observed even at moderate doses and the efficacy of TAT is less dependent from fractionation, dose rate and tumor hypoxia than beta-radiation (*1,2*). However, in regard to the prospective interpretation of dosimetry studies some confusion was induced by the IRCP which introduced a weighting factor of 20 for alpha vs. beta radiation. However, this factor only considers stochastically effects and was intended only to be used for radiation protection issues. In contrast, the RBE describes a weighting factor including deterministic effects important for biological endpoints such as toxicity or tumor control. After a review of literature the US Department of Energy suggested an RBE of 3-5 for alpha emitters in general (*3*) and taking into account the average LET of the alpha particles emitted in the ^{225}Ac decay chain RBE=5 should be the most appropriate assumption (*1,2,4*). In a review about human beings with accidental exposure to radionuclides the RBE of alpha over beta radiation for induction of secondary leukemia and bone cancer was also estimated in the range of 2-5 (*5*). Thus, the Sv_{RBE5} was considered predictive for the deterministic effects of ^{225}Ac-PSMA-617 in comparison to the effects observed after beta-radiation based PSMA-RLT.

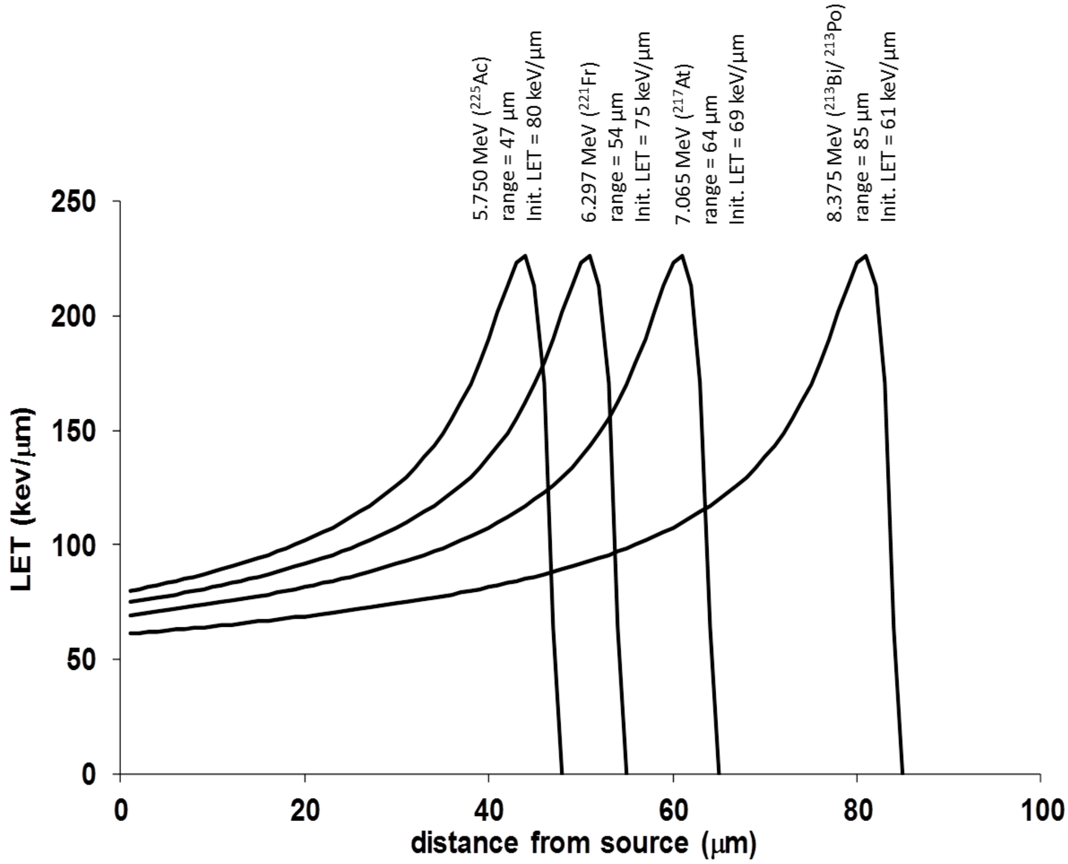
1. MIRD Monograph- Radiobiology and Dosimetry for Radiopharmaceutical Therapy with Alpha-Particle Emitters. Sgouros G, Ed. Society of Nuclear Medicine and Molecular Imaging Publishing, 2014. [book]
2. Sgouros G, Roeske JC, McDevitt MR, Palm S, et al. MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy.
3. Feinendegen LE, McClure JJ. Meeting report - Alpha-emitters for medical therapy - Workshop of the United States Department of Energy - Denver, Colorado, May 30-31, 1996. *Radiat Res.* 1997;148:195-201.
4. Howell RW, Goddu SM, Narra VR, Fisher DR, Schenter RE, Rao DV. Radiotoxicity of gadolinium-148 and radium-223 in mouse testes: relative biological effectiveness of alpha-particle emitters in vivo. *Radiat Res.* 1997;147:342-348.
5. Harrison JD, Muirhead CR. Quantitative comparisons of cancer induction in humans by internally deposited radionuclides and external radiation. *Int J Radiat Biol.* 2003;79:1-13.

Decay scheme of ^{225}Ac and daughter nuclides



Supplemental Fig. 1: Decay scheme of ^{225}Ac and daughter nuclides. Co-emission of gamma photons: ^{221}Fr: 12% (218keV), ^{213}Bi: 26% (440keV).

Tissue range of ^{225}Ac and daughter nuclides

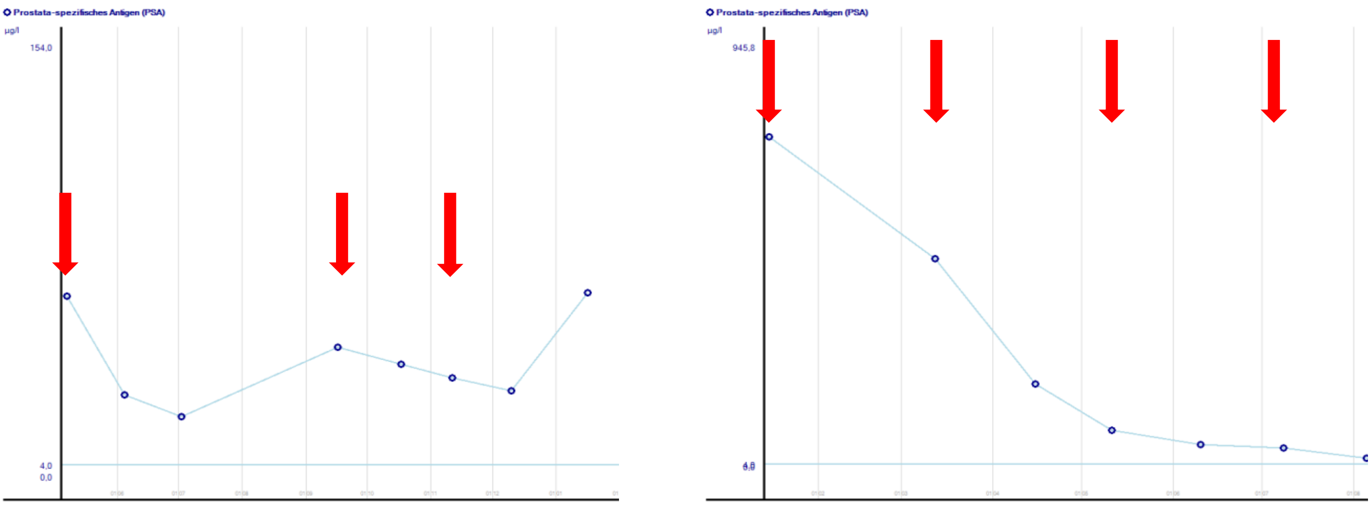


Supplemental Fig. 2: Linear Energy Transfer and respective tissue range of the 4 alpha particles emitted from ^{225}Ac and its daughter nuclides (*courtesy of George Sgouros, Director of Radiopharmaceutical Dosimetry at Johns Hopkins School of Medicine*).

Experience with treatment interval

A

B



Supplemental Fig. 3:

A patient with favorable biochemical response to the 1st cycle paused 4 months until 2nd cycle; PSA relapsed in between and succeeding cycles were less effective than the initial response (A). Applications every 2 months in 200 kBq/kg (1st cycle) and 100kBq/kg (2nd, 3rd, 4th cycle) dose resulted in a continuous decline of PSA.

Target Organ	Alpha	%Total	Beta	%Total	Photon	%Total	Total	EDE Cont.	ED Cont.
Adrenals	2,16E+01	99,32	1,16E-01	0,53	3,39E-02	0,16	2,18E+01	1,01E+00	6,66E-02
Brain	2,16E+01	99,42	1,16E-01	0,53	1,21E-02	0,06	2,17E+01	4,19E-01	6,65E-02
Breasts	2,16E+01	99,43	1,16E-01	0,53	1,16E-02	0,05	2,17E+01	3,26E+00	1,09E+00
Gallbladder Wall	2,16E+01	99,33	1,16E-01	0,53	3,33E-02	0,15	2,18E+01	7,19E-01	0,00E+00
LLI Wall	2,16E+01	99,40	1,16E-01	0,53	1,96E-02	0,09	2,17E+01	0,00E+00	2,61E+00
Small Intestine	2,16E+01	99,36	1,16E-01	0,53	2,35E-02	0,11	2,17E+01	0,00E+00	6,65E-02
Stomach Wall	2,16E+01	99,36	1,16E-01	0,53	2,41E-02	0,11	2,17E+01	0,00E+00	2,61E+00
ULI Wall	2,16E+01	99,36	1,16E-01	0,53	2,35E-02	0,11	2,17E+01	0,00E+00	6,65E-02
Heart Wall	2,16E+01	99,39	1,16E-01	0,53	2,09E-02	0,10	2,17E+01	0,00E+00	0,00E+00
Kidneys	7,39E+02	99,52	3,64E+00	0,49	1,19E-01	0,02	7,43E+02	4,46E+01	1,62E+01
Liver	9,50E+01	99,45	4,87E-01	0,51	4,17E-02	0,04	9,56E+01	5,73E+00	4,77E+00
Lungs	2,16E+01	99,41	1,16E-01	0,53	1,78E-02	0,08	2,17E+01	2,61E+00	2,61E+00
Muscle	2,16E+01	99,41	1,16E-01	0,53	1,63E-02	0,08	2,17E+01	0,00E+00	6,65E-02
Ovaries	2,16E+01	99,39	1,16E-01	0,53	2,09E-02	0,10	2,17E+01	5,44E+00	4,35E+00
Pancreas	2,16E+01	99,33	1,16E-01	0,53	3,32E-02	0,15	2,18E+01	4,65E-01	6,66E-02
Red Marrow	4,63E+01	99,72	1,17E-01	0,25	1,84E-02	0,04	4,65E+01	5,57E+00	5,57E+00
Osteogenic Cells	3,50E+02	99,92	2,80E-01	0,08	2,24E-02	0,01	3,50E+02	1,05E+01	3,50E+00
Skin	2,16E+01	99,43	1,16E-01	0,53	1,03E-02	0,05	2,17E+01	0,00E+00	2,17E-01
Spleen	2,14E+02	99,47	1,10E+00	0,51	5,67E-02	0,03	2,15E+02	1,29E+01	9,80E-01
Testes	2,16E+01	99,42	1,16E-01	0,53	1,39E-02	0,06	2,17E+01	0,00E+00	0,00E+00
Thymus	2,16E+01	99,41	1,16E-01	0,53	1,62E-02	0,07	2,17E+01	0,00E+00	6,65E-02
Thyroid	2,16E+01	99,41	1,16E-01	0,53	1,54E-02	0,07	2,17E+01	6,52E-01	1,09E+00
Urinary Bladder Wall	2,16E+01	99,40	1,16E-01	0,53	1,87E-02	0,09	2,17E+01	0,00E+00	1,09E+00
Uterus	2,16E+01	99,39	1,16E-01	0,53	2,11E-02	0,10	2,17E+01	0,00E+00	6,65E-02
Total Body	2,78E+01	99,43	1,47E-01	0,52	1,76E-02	0,06	2,80E+01	0,00E+00	0,00E+00
Effective Dose Equivalent (mSv/MBq)								9,38E+01	
Effective Dose (mSv/MBq)									4,72E+01

Supplemental Table 1:
Normal organ absorbed doses and relative contribution of alpha vs. beta and photon radiation for 4 patients (mean values) calculated with OLINDA male adult phantom.