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REVIEW

NAVIGATING THE PROSTATE CANCER FRONTIERS

Targeted alpha therapy in prostate cancer: review of available agents in clinical practice

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ABSTRACT

Targeted alpha therapy (TAT) has shown promise in prostate cancer patients, both hormone-sensitive and castration-resistant, with or without prior treatment. TAT's radiobiological properties explain why it is more potent than other forms of ionizing radiation, such as the clinically approved [^{177}Lu]Lu-PSMA-617. Although most TAT agents used in compassionate care or clinical trials target the prostate-specific membrane antigen (PSMA), some alternatives are yet to be used clinically, some of which aim to address PSMA-negative prostate cancer. These include [^{223}Ra]RaCl2, which is approved for palliative bone pain, and a variety of other non-PSMA antigen or receptor-targeting medicines. Whereas this study focuses on TAT medicines that are currently available for clinical use, it also explores these preclinical agents.

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Recent years have seen a paradigm shift in prostate cancer, with the incorporation of targeted therapy with predominantly β-emitting therapeutic agent [^{177}Lu] Lu-PSMA-617(Pluvicto-Novartis Holding AG. Postfach Basel, Switzerland being included as part of the standard-of-care.[1] [^{177}Lu]Lu-PSMA-617 was approved by the Food and Drug Administration(FDA) due to the good results of the Phase III VISION trial which reported superior survival benefits in patients treated with [^{177}Lu]Lu-PSMA-617 and standard-of-care therapy compared to the control group who received only standard-of-care therapy.[1] [^{177}Lu]Lu-PSMA-617 was initially approved for the treatment of patients with PSMA-positive metastatic castrate-resistant prostate cancer (mCRPC) who had been treated with chemotherapy. Recently, it has been approved for use in mCRPC patients who had never received chemotherapy. The PSMAFore phase III Trial's findings, which showed significantly greater survival advantages for patients in this group, made the approval possible.[2] Whereas the PSA responses ≥50% were 46% and 51% in the VISION and PSMAFore trials respectively, Sathekge *et al.* in their multi-center WARMTH Act study, the PSA responses ≥50% were 57% in patients who had received either or a combination of the clinically approved therapies. Amongst these were patients who had been treated with [^{177}Lu]Lu-PSMA.[3] This is consistent with the known high potency of

targeted alpha treatment (TAT) attributable to its radiobiological characteristics.

Although vectors targeting the transmembrane receptor prostate-specific membrane antigen (PSMA) have been the mainstay in prostate cancer TAT and are used in clinical practice, numerous other new agents have been studied preclinically.[4, 5] This narrative review will discuss TAT in prostate cancer, delving deep into the currently clinically available agents, PSMA and non-PSMA based. We will also briefly review TAT's radiobiological properties, as well as the properties of the most routinely employed radioisotopes.

TAT physics and radiobiology

α-emitting radionuclides/TAT are known to cause more severe damage than other types of ionizing radiation. The greater potency of TAT is attributed to the physics and radiobiology of α-emitting radionuclides. α-particles, heavy $^{4}He2+$ nuclei, with short path lengths of up to 100μm in water and 40μm in bone. This is far lower than other types of ionizing radiation but translates to a substantially higher linear energy transfer (LET) of 50-230 keV/μm at the apex of the Bragg curve where a particle/ionizing radiation comes to rest.[6]

TAT's radiobiological effects are astounding. There are direct and indirect effects. The word "direct effects" denotes that ionizing radiation impacts the energy directly to cells, while the latter implies that intermediates are responsible for the cell cytotoxicity. It is also crucial to recognize that indirect effects may occur on the cell harboring the radiation or cells immediately adjacent to and those at sites remote from the radiation. The existence of such amplifies the cytotoxicity of TAT.[7] More irreparable double-strand deoxyribonucleic acid (DNA) breaks are seen with TAT compared to other forms of ionizing radiation as part of direct radiation effects. With no intermediates direct effects, radiation damage from TAT is possible even in relatively hypoxic tissues. This direct impact is further amplified by some reactive species mainly reactive oxygen species (ROS), arising from the ionization of water. Furthermore, other organelles and the cellular membrane are also radiated as the radiation and the ROS encounter these. Cumulatively, this makes cell survival almost impossible. The short path length of TAT confers significant clinical benefits. The resultant concentrated energy transfer implies that treatment of micrometastases with minimal off-target toxicity is feasible. An example is in bone/marrow metastases myelotoxicity is minimal due to the less radiation to adjacent progenitor cells.[8]

Indirect cytotoxicity is also seen in tumor cells devoid of radiation, which can either be in the vicinity or distant from the irradiated cell termed bystander and abscopal effects respectively. These two phenomena are manifestations of immune system activation mediated by damage-associated molecular patterns (DAMPs). These may be nucleic acids, proteins, ions, glycans and some metabolic products which under steady states do not trigger an immune response but with slight changes in physical properties they become DAMPs and are sensed by the innate immune receptors triggering an immune response.[9] The release of the DAMPs by the irradiated cells results in the activation of a local inflammatory and systemic inflammatory response in the case of the bystander effect and the abscopal effects respectively.[10-12]

The scope of radionuclides that have been explored for TAT in prostate cancer is constantly evolving. However the promising radionuclides for TAT in prostate cancer include: [^{225}Ac]Ac, [^{211}At]At, [^{213}Bi]Bi, [^{212}Pb]Pb, [^{149}Tb]Tb, [^{227}Th]Th, [^{223}Ra]Ra, [^{211}At]At. Their respective physical properties are depicted in Table I.

In addition to the chemistry of the radionuclide-ligand pair, the radionuclide's physical qualities and biological aspects, particularly the ligand's pharmacokinetics, are important. It should be noted that the effective half-life or residence time of a radionuclide-ligand combination is mostly governed by the shorter biological or physical half-life of the two. The biological half-life of the ligand should

TABLE I.—*Radionuclide respective physical properties.*

Radionuclide	Half-life	Emitted ionizing radiation	Total α-energy emitted/decay	Range in tissue (μm)	LET (KeV/μm)
[^{225}Ac]Ac	9.9 days	4α, 2β	27.9	47-85	61-230
[^{211}At]At	7.2days	1α, 1ε	6.9	55-80	71-230
[^{213}Bi]Bi	45.6min	2α, 2β	8.5	40-100	65-230
[^{212}Pb]Pb	10.6hours	1α, 2β	7.9	40-100	61-230
[^{149}Tb]Tb	4.1hours	1α, 1ε/2ε 1β^{+}/2β^{+}	0.7	25	140
[^{227}Th]Th	18.7days	4α, 2β	32.8	50-70	71-230
[^{223}Ra]Ra	11.4days	4α, 2β	26.8	46-70	71-230

be compatible with that of the isotopes. As a result, ligands with rapid internalization and a short biological half-life (quick washout) should be combined with radionuclides with shorter half-lives. To also optimize the cytotoxicity of a particular theranostic agent, ligands with longer biological half-lives should be combined with long-lived radionuclides.[13]

Therapeutic targets explored with TAT

PSMA

TAT's most common target in prostate cancer has been the type II transmembrane glycoprotein receptor prostate-specific membrane agent (PSMA). PSMA is encoded by the folate hydrolase 1 gene located in the short arm of chromosome 11 and possesses enzymatic activities such as glutamate carboxypeptidase II and folate hydrolase activity. It consists of 750 amino acids, 19 of which are in the intracellular domain, 24 in the transmembrane domain and the rest in the extra-cellular domain.[14] In prostate cancer, PSMA facilitates metabolism, proliferation and metastases through various mechanisms. PSMA ligand binding induces clathrin-dependent endocytosis, which is critical for delivering the high LET associated with TAT.[15, 16] Although extensively expressed by prostate cancer, particularly castration-resistant prostate cancer (CRPC), PSMA expression has been reported in numerous other malignancies and normal organs, accounting for off-target toxicities such as xerostomia in the latter.[17, 18]

Other

Other targets in prostate cancer therapy, other than PSMA, have been investigated primarily in the preclinical domain, apart from bone-targeted therapy with [^{223}Ra]RaCl2. These include and are not limited to immunotherapy conjugates that target C26, hK2, and Cadherin.

[^{225}Ac]Ac

The unique physical and chemical properties of [^{225}Ac]Ac have made it a highly sought-after radionuclide in labelling various prostate cancer-targeting ligands. Commonly obtained from [^{229}Th]Th by chemical separation processes other methods high-quality such as cyclotron production of [^{225}Ac]Ac using electroplated [^{226}Ra]Ra targets have demonstrated significant potential which will address the unmet clinical trial needs.[19, 20] [^{225}Ac]Ac has a long half-life of 9.9 days and its decay pathway is unique in that 4α and 2β^- particles are produced through various daughter intermediates as it decays to [^{209}Bi]Bi. Although challenging, biodistribution imaging and dosimetry are possible by imaging the energies 218keV and 440keV gamma emissions with yields of 11.6% and 26.1% for [^{221}Fr]Fr and [^{213}Bi]Bi respectively.[21]

PSMA-targeting [^{225}Ac]Ac agents

As mentioned earlier, ligand binding to the PSMA receptor results in clathrin-dependent endocytosis. This can be achieved by using ligands targeting either the intracellular or extracellular domains. Intracellular binding agents showed dismal outcomes, and the move has been to use agents that bind to the extracellular domain. PSMA targeting agents that have been used are mainly monoclonal antibodies(mAb) or small Glu-urea-based molecules. Amongst the extracellular binding mAb, J591 has been the most successful. However, considering the pitfalls known with mAb such as longer circulation times and slower lesional uptake, lower tumor-penetrability and slow clearance from the non-target tissues, small molecules have gained significant popularity.[22]

Small molecules

[^{225}Ac]Ac-PSMA-617

Amongst the PSMA TAT [^{225}Ac]Ac-PSMA-617 has been the most explored. In their first-in-human compassionate work in patients who had exhausted multiple lines of conventional therapy, Kratochwil and colleagues reported complete PSA and imaging responses in two of the patients treated with [^{225}Ac]Ac-PSMA-617 at activities administered every two months. The only clinically significant side effect was xerostomia.[23] In their follow-up study aimed at developing a treatment protocol for [^{225}Ac]Ac-PSMA-617, they extrapolated its dosimetry from time-activity curves derived from [^{177}Lu]Lu-PSMA-617 scans extrapolated to the physical half-life of [^{225}ac]Ac, They established that in clinical practice severe xerostomia was dose-limiting if the activity exceeded 100kBq/kg per cycle, at 50kBq/kg no toxicity was observed but the anti-tumor effect was not reasonable. They established that activities of 100kBq/kg per cycle repeated 8-weekly had a favorable biochemical response and reasonable toxicity.[24] Further to this various groups have evaluated its safety and efficacy in patients who had received either first line second, third and fourth-line regimens. Notable studies include that of the same group which showed at

least 50% PSA decline in 63% of patients and enduring responses in 5-patients beyond 2-years.[25] Various groups have replicated these results with PSA response of at least 57% including patients heavily pretreated with *e.g.* [^{177}Lu]Lu-PSMA. Excellent results have been seen in patient pre-chemotherapy and/or post-androgen deprivation and the *de novo* metastatic hormone-sensitive prostate cancer.[26, 27] In a much larger study of 73 patients, Sathekge *et al.* PSA decline of more than 50% was seen in 70% of patients and complete resolution in 29% of patients, median progression fee survival and overall survivals were 15.2months and 18-months respectively.[28] Although the cohorts were much smaller Yadav *et al.* brought up an important aspect of [^{225}Ac]Ac-PSMA-617 therapy, the quality of life. They reported improvements in the quality of life objectively using validated tools such as the visual analog score, analgesic score, Eastern Cooperative Oncology Group performance status, Karnofsky performance status, NCCN-FACT FPSI-17 EORTC-QLQ-30 and BM-22 questionnaires.[29, 30] [^{225}Ac]ACPSMA undergoing a phase 1 AcTion trial [clinicaltrials.gov. NCT04597411].

[^{225}Ac]Ac-PSMA I&T

Currently undergoing a phase 1 clinical trial after showing promise in first-in-human studies is [^{225}Ac]Ac-PSMA-I&T(ClinicalTrials.gov, (NCT05902247). In their report, Zacherl *et al.* retrospectively evaluated 14 patients treated with [^{225}Ac]Ac-PSMA I&T. A total of 34 cycles were given (median dose, 7.8 MBq; range, 6.0–8.5), with 1 cycle in 3 patients, 2 cycles in 7 patients, 4 cycles in 3 patients, and 5 cycles in 1 patient. They observed PSA response ≥ 50% in 50% of patients overall, whereas 5/11 patients who had prior [^{177}Lu]Lu-PSMA showed a decline in PSA ≥ 50%. The side effect profile was also acceptable. Surprisingly one patient did not report any xerostomia, whereas 2/3 patients with Grade 3 anemia had existing Grade 2 anemia at baseline.[31] An interesting part is the SPECT/CT imaging of this molecule by the group in Munich, which showed minimal variances in SPECT/CT imaging and urine-based dosimetry.[21]

[^{225}Ac]Ac-SibuDAB, ^{225}Ac-PSMA-TO-1, [^{225}Ac]Ac-RPS-074 and [^{225}Ac]Ac macropa-derived radioconjugates

A disadvantage of small molecular weight molecules is the rapid renal clearance, which is excellent in imaging but may lead to a lower radiation dose at the target. Therefore, this has facilitated modifications in the PSMA to prolong their circulation and tumor retention times. Enhancing albumin binding through the incorporation of extender linkers is a typical example. In that case, [^{225}Ac]Ac-SiBuDAB which contains ibuprofen has been developed. Although, [^{225}Ac]Ac-SiBuDAB has shown comparable radiolabeling and hematological effects as [^{225}Ac]Ac-PSMA-617, favorable tumoral uptake has been observed, notably, the doubling of tumoral uptake at 48hrs compared to [^{225}Ac]Ac-PSMA-617. In their animal models, Busslinger *et al.*, this translated to improved therapeutic response and overall survival.[32] Similar findings were seen with, [^{225}Ac]Ac-RPS-074, [^{225}Ac]Ac-labeled macropa-derived radioconjugates which also target PSMA and albumin.[33-35] The possible disadvantage is that extended circulation of [^{225}Ac]Ac may result in increasing undesired exposure of off-target tissues due to the recoil of the respective daughter radionuclides.

Monoclonal antibodies ([225Ac]Ac-J591 and [^{225}Ac]Ac-Macropa Pelgifatamab targeting PSMA

[^{225}Ac]Ac-J591/ [^{225}Ac]Ac-DOTA-J591 is the commonest [^{225}Ac]Ac labelled mAb targeting the PSMA receptor.[36] The first-in-human Phase 1 dose escalation trial of a single dose of [^{225}Ac]Ac-J591 in patients with pretreated progressive mCRPC is also showing promising results. In one retrospective study, the group reported PERCIST-objective response rate for osseous, nodal, visceral, and prostatic lesions of 53%, 28%, 56%, and 38%, respectively after treatment with ([^{225}Ac]Ac-J591.[37, 38] Another [^{225}Ac]Ac radiolabeled mAb that currently undergoing Phase 1 clinical trial is [^{225}Ac]Ac-Macropa Pelgifatamab, which was evaluated in-vitro with potent cytotoxicity seen in PSMA expressing and not PSMA negative cell lines ClinicalTrials.gov ID NCT06052306).[39]

[^{225}Ac]Ac-iPSMA-RGD

The tumor microenvironment expresses both PSMA and RGD, which serve as the basis for this molecule. Furthermore, tumor cells express PSMA, while the RGD detects integrins. These features theoretically translate to high potent/cytotoxicity due to the synergistic recognition of PSMA and integrins. This has yet to be assessed in prostate and other malignancies.[40]

Non-PSMA targeting [^{225}Ac]Ac agents

Despite the promising results with [^{225}Ac]Ac PSMA, some patients may not demonstrate significant benefit, mainly due to loss of PSMA expression. This justifies the need to target other prostate cancer molecular and metabolic targets.

CD46

Bidkar *et al.* detected both PSMA-devoid and PSMA-positive prostate cancer with the CD46-targeted tracer [^{89}Zr] Zr-DFO-YS5, setting the groundwork for the pursuit of CD46-targeted TAT. The same group additionally delivered high tumoral doses to prostate cancer cell-derived and patient-derived xenografts in both PSMA expression and negative tumors using the immunotherapy compound [^{225}Ac]Ac-DOTA-YS5.[41] They also reported that high radiation doses were delivered to tumoral lesions relative to normal organs at risk in their biodistribution studies, dosimetry assessment and therapeutic evaluations of the CD-26 targeting radioimmunotherapy agent [^{225}Ac]Ac-Macropa-PEG4-YS5, suggesting that [^{225}Ac]Ac-Macropa-PEG4-YS5 could be translated clinically.[42]

Human kallikrein 2(K2) and PSA

A serine protein, hK2 is expressed in prostate tissue, resembles PSA and is targeted by the antibody hu11B6. It is upregulated by DNA damage as part of the DNA damage response. [^{225}Ac]Ac-hu11B6 has been successfully labeled.[43] Its mechanism of action is unique in the sense that as [^{225}Ac]Ac-hu11B6 causes DNA damage with a consequent DNA-damage response(DDR), hK2 is further activated resulting in further uptake of [^{225}Ac]Ac-hu11B6 a vicious cycle.[43] A PSA targeting [^{225}Ac][Ac labelled agent, [^{225}Ac]Ac-hu5A10 has also been evaluated preclinically and has showed a significantly higher median survival compared to its [^{90}Y]Y labeled counterpart. These however remain to be translated clinically.[44]

Cadherin targeting

[^{225}Ac]Ac-E4G10 is an alpha-emitting antibody capable of reacting with vascular endothelial cadherin. This has been investigated in a prostate cancer mouse model and has shown tumor growth inhibition, biochemical response and prolonged survival. The importance of these findings is that they were substantiated by immunohistochemistry which revealed lower vessel density and enhanced apoptosis in [^{225}Ac]Ac-E4G10 treated tumors.[45]

[^{211}At]At

[^{211}At]At the rarest element on earth can be obtained via cyclotron bombardment of [^{209}Bi]Bi accelerated at approximately 28MeV, which puts it at an advantage in terms of sustainability. Although it resembles a halogen such as iodine it also bears metalloid behavioral tendencies.[46] Its half-life is 7.2 hours with a radioactive following a branched decay scheme by alpha emission to [^{207}Bi]Bi or by electron capture to [^{211}Po]Po at 41,8% and 58.2% respectively. After electron capture, [^{2111}Po]Po decays immediately by alpha emission to stable [^{207}Pb]Pb, in addition to characteristic polonium X-rays produced via electron capture decay of [^{211}Po]Po. These characteristic X-rays allow in-vivo biodistribution and dosimetry imaging of [^{211}At] At-based agents.[47]

PSMA-targeting agents

Kiess and colleagues were amongst the first to synthesize and evaluate an [^{211}At]At-labelled small molecule targeting PSMA in vitro. The compound (2S)-2-(3-(1-carboxy-5-(4-[^{211}At]At-astatobenzamido)pentyl)ureido)-pentanedioic acid ([^{211}At]At-6) was tested on PSMA positive and negative prostate cancer cells at a dose of 740kBq.[48] They reported significant PSMA-specific cellular uptake on imaging and microscale dosimetry, decreased clonogenic survival in PSMA-positive cells and delayed tumor growth in the respective tumours.[48] Various other groups followed with preclinical evaluation of other compounds. One notable group reported findings on four different PSMA targeting agents namely [^{211}At]YC-550; [^{211}At] HS-549; [^{211}At]GV-620, [^{211}At]GV-904.[49] In their work, they compared these four compounds to[^{211}At] DCABzL which had demonstrated promise in vitro and in xenograft models derived from a similar cell line that the authors intended to use. The downside to [^{211}At] DCABzL, also a PSMA targeting agent developed by the same group, which precluded clinical translation was the insufficient in vivo stability and high and prolonged retention of [^{211}At] At in the kidney. The radiochemical yield amongst these compounds([^{211}At]YC-550; [^{211}At]HS-549; [^{211}At]GV-620, [^{211}At]GV-904) was at least 50%. The free [^{211}At]At resulted in accumulation within the thyroid gland, which was seen mainly with compounds other than [^{211}At]GV-620 which was by far the most stable compound in-vivo. This translated to less thyroid gland/off-target uptake which therefore meant [^{211}At]GV-620 emerged as the agent of choice for clinical translation.[49] Despite this, in vivo dehalogenation or off-target organ uptake remained an issue, which prompted the same group to synthesize [^{211}At]At-3-Lu.[50] In addition to cell uptake, internalization and biodistribution studies, they performed long-term toxicity studies like the studies done with [^{211}At] DCABzL including tissue chemistries and histopathology preclinically. They noted little off-target toxicity, in-vivo stability and favorable histopathological findings and dose dependent

survival in both flank and metastatic models with [^{211}At]At-3-Lu.[50] However, this has recently been outperformed by the third generation [^{211}At]At-YF2, which has specifically shown higher cellular uptake, internalization, longer tumoral retention and cytotoxicity. The dosimetry results are soon to be expected.[51]

Watabe *et al.* in their tumor xenograft models after subcutaneous implantation of human prostate cancer cells used [^{211}At]PSMA1, [^{211}At]PSMA5, or [^{211}At]PSMA6 to evaluate biodistribution and histopathological evaluation of organs at risk at 3- and 6 weeks past administration.[52] In this work, [^{211}At]PSMA5, showed higher tumor retention and an excellent treatment effect but minimal side effects were noted in normal organs.[52] In their follow-up study on mice and non-human primates they administered MBq/kg, 12 MBq/kg, 35 MBq/kg, and vehicle control, with follow-ups at 1 day (N.=10 per group) and 14 days (N.=5 per group in four groups in their toxicity study.[53] No significant myelosuppression or renal dysfunction was seen in mice, monkeys had mild leukopenia 24-h post administration. Although high uptake was noted in both the kidneys and thyroid gland no histopathological abnormalities were seen, Overall, no irreversible toxicities were seen.[53] Manuals have therefore been developed to aid in the proper use of [^{211}At]PSMA5 in clinical trials of TAT.[54] The same group has also translated this clinically. In their first in human study in a male with mCRPC refractory to androgen receptor signaling inhibitors, docetaxel, and cabazitaxel they did SPECT/CT imaging targeting the 79 keV X-rays of [^{211}Po]Po. They demonstrated similar uptake pattern as [^{18}F]F-PSMA-1007 in both normal and malignant tissues.[55] In all their work, it is evident that amongst the three, [^{211}At]PSMA5 is better suited for prospective in-human trials.

Other [^{211}At]At based vectors for PSMA TAT that have shown promise include [^{211}At]PSAt-3-Ga and [^{211}At]At-NpG-PSMA. They have shown significant in-vivo stability and anti-tumor effects with minimal side effects.[56, 57]

Non-PSMA targeting agents

PSCA targeting

[^{211}At]At-labeled to the anti-PSCA A11 minibody is one compound that has shown promise. It is specific for the prostate stem cell antigen (PCSA). PCSA is a cell surface glycoprotein overexpressed in over 90% of both localized prostate cancer and bone metastases. Dose-dependent cytotoxicity was observed in PC3-PSCA cells implanted subcutaneously and intra-tibial in nude mice. This still awaits clinical translation.[58]

[^{213}Bi]Bi

A product of [^{225}Ac]Ac. [^{213}Bi]Bi is an alpha/beta emitter with a half-life of 46 minutes. 97.8% is beta decay to [^{213}Po]Po which emits an alpha, at a half-life of 4.2μ seconds. The other 2.2% of [^{213}Bi]Bi decays by alpha emission to [^{209}Tl]Tl. The concurrent production of 440 KeV gamma rays allows for in vivo imaging of [^{213}Bi]Bi biodistribution, pharmacokinetic and dosimetry studies.[59] Two compounds have mainly been evaluated in this domain the mAb [^{213}Bi]J591 and the miniprotein [^{213}Bi]Bi-PSMA-617, with the latter theoretically having a better side effect profile relative to the former. The short half-life of [^{213}Bi]Bi is not compatible with the longer biological half-life of J591 which has longer blood pool residence times, decreased vascular permeability and slower tumoral uptake allowing the extra-cellular disintegration of [^{213}Bi]Bi effectively radiating off-target organs.[60-62] This has precluded the further clinical evaluation of [^{213}Bi]Bi-J591, as compared to [^{225}Ac]Ac-J591. Two groups have reported the feasibility and dosimetry of [^{213}Bi]Bi-PSMA-617. The Pretoria group showed a good PSA response(more than 80% decline) and an excellent molecular imaging response on pre and, post therapy [^{68}Ga]Ga-PSMA-11 PET/CT imaging after two cycles of therapy in a patient who had progressed on conventional therapy.[63] The pursuit for clinical use of [^{213}Bi]Bi-PSMA-617 was halted by reports showing suboptimal responses compared to [^{225}Ac]Ac-PSMA-617.[64]

[^{149}Tb]Tb

[^{149}Tb]Tb, a radiolanthanide has a physical half-life of 4.1hirs. It emits multiple different particulate and non-particulate radiation: a-particles (3.97 MeV, 16.7%), electron capture (76.2%), positron emission (7.1%), gamma rays (165 keV, 26.4%), and X-rays.[65] This possibility of both single-photon emission computed tomography and PET imaging in addition to TAT allows for accurate retrospective dose estimations to plan future applications and minimize off-target toxicity.[66] The radiolabeled agents that have been investigated are mainly PSMA-617-based. In a mouse model, [^{149} Tb]Tb-PSMA-617 administration was associated with delayed tumor growth in the group. Unfortunately, the radiation dose to the kidneys was more than 10-times that of [^{177}Lu]Lu-PSMA-617 which together with the limited supply, production challenges, and high recoil with radiolysis of the radiotracer by [^{149}Tb]Tb has

hampered the pursuit for [149Tb]Tb-PSMA-617. The latter of which increased bone marrow toxicity.[66-68]

[212Pb]Pb/[212Bi]Bi

[212Pb]Pb is an interesting radionuclide which is an in vivo radionuclide generator. It emits beta radiation, however, its daughter [212Bi]Bi emits alpha radiation. Its relatively longer half-life of 10.64hrs justifies its use relative to [212Bi]Bi half-life 61-minutes.[69] Promising preclinical results with [212Pb]Pb-L2 and [212Pb]Pb-NG001 and [212Pb]Pb-PSMA-617 have been reported.[70-73] Griffiths *et al.* recently reported a first-in-human SPECT/CT imaging in a patient with mCRPC post administration of 60Mbq of [212Pb]Pb-ADVC001as part of the TheraPb clinical trial (NCT05720130). This was achieved by imaging 238.6 keV and 75 to 91 keV g-emissions produced after the β-decay of [212Pb]Pb to its a-emitting progeny [212Bi]Bi. The SPECT/CT images showed prompt tumoral uptake, persistent tumor retention at 20hrs and concordance with the pretherapy [18F]F-DCFPyl PET/CT images.[74]

[227Th]Th

[227Th]Th is obtained from the decay of [227Ac]Ac. Having a half-life of 18.7 days, it decays by alpha emission to [223Ra]Ra. Interestingly the [223Ra]Ra further decays to [207Pb]Pb through multiple daughter radionuclides. Though an additional 5α and 2 β particles are produced this is not without untoward effects. These daughters recoil and may cause off-target toxicity.[75, 76] Despite this efficacy has been reported in the PSMA targeting [227Th]Th-PSMA-TTC with/without darolutamide within preclinical prostate cancer models.[77, 78] A phase 1 clinical trial with the primary objective to define the safety and tolerability profile and Maximal Tolerated Dose (MTD) of AY2315497/[227Th]Th-PSMA-TTC alone, or in combination with darolutamide just having finished active recruitment. ClinicalTrials.gov Identifier: NCT0372747

[223Ra]Ra

As discussed in the section on [227Th]Th, [223Ra]Ra decays to [207Pb]Pb through multiple daughter radionuclides. It is a calcimimetic and has been approved as Xofigo® for the treatment of castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease. This was based on the ALSYMPCA trial(ClinicalTrials.gov number, NCT00699751) which showed significant survival benefits.[79, 80] In the same vein, some follow-up clinical trials such as the MEDAL trial which is A phase II randomized trial of metastasis-directed therapy with alpha emitter radium-223 in men with oligometastatic castration-resistant prostate cancer are currently ongoing.[81]

TABLE II.—*Ongoing clinical trials on TAT in prostate cancer, their respective settings and outcome.*

Target	Radionuclide	Radiopharmaceutical	Phase	Setting	Outcome	Trial number
PSMA	[225Ac]Ac	[225Ac]Ac -J591	I	mCRPC treated with prior ARPI	DLT, MTD	NCT03276572
		[225Ac]Ac -J591	I/II	mCRPC treated with prior ARPI	DLT, MTD, RP2D	NCT04506567
		[225Ac]Ac -J591	I	mCRPC treated with prior ARPI	DLT	NCT04576871
		[225Ac]Ac -J591	I	mHSPC	DLT, MTD	NCT05567770
		[225Ac]Ac J591 with 177Lu-PSMA-I&T	I/II	mCRPC treated with prior ARPI	DLT, MTD, RP2D, PSA decline	NCT04886986
		[225Ac]Ac -J591 with pembrolizumab and ARPI	I/II	mCRPC treated with prior ARPI	DLT, RP2D, response rate	NCT04946370
		[225Ac]Ac -J591 pembrolizumab and ARPI	I/II	mCRPC	Optimal dose	NCT04946370
		[225Ac]Ac -FPI-2265 (PSMA-I&T)	II	mCRPC with prior ARPI	PSA50, safety	NCT05219500
		[225Ac]Ac -PSMA-617	I	mCRPC	RP2D	NCT04597411
		[225Ac]Ac -PSMA-R2	I/II	mCRPC treated with prior ARPI in post-177Lu and pre-177Lu settings	MTD, RDE	NCT05983198
		[225Ac]Ac -Macropa Pelgifatamab/ BAY3546828	I	mCRPC	TEAEs, DLTs, ORR, PSA response	NCT06052306
	[212Pb]Pb	[212Pb]Pb -ADVC001	I/IIa	mCRPC with prior ARPI and no prior exposure to 177Lu	RP2D	NCT05720130
	[227Th]Th	BAY 2315497	I	mCRPC	safety, tolerability, MTD	NCT03724747
hK2	[225Ac]Ac	[225Ac]Ac -DOTA-h11B6 (JNJ-69086420)	I	mCRPC with prior ARPI	AE, DLT	NCT04644770

DLT: dose-limiting toxicity; MTD: maximum tolerable dose; RP2D: recommended phase 2 dose; PSA: prostate-specific antigen; TEAEs: treatment-emergent adverse events; ORR: objective response rates: ARPI: androgen-receptor pathway inhibitors; mCRPC: metastatic castration-resistant prostate cancer, hK2: human kallikrein 2.

TABLE III.—*TAT agents that have not gone into clinical trials.*

Radionuclide	Target	Preclinical/clinical	Compound	Comments/Clinicaltrial.org
	PSMA	Preclinical	[^{225}Ac]Ac-SiBuDAB	Increased albumin binding
			[^{225}Ac]Ac-RPS-074	
			[^{225}Ac]Ac-labeled macropa-derived radio-conjugates	
	PSA	Preclinical	[^{225}Ac]Ac-hu5A10	N/A
	Cadherin	Preclinical	[^{225}Ac]Ac-E4G10	N/A
[^{211}At]At	*PSMA*	Clinical	[^{211}At]PSMA5	SPECT/CT images in an FIH report were congruent with [^{18}F]F-PSMA-1007
		Preclinical	[^{211}At] DCABzL	[^{211}At]GV-620, performed better. Good in-vivo stability and less off-target toxicity(mainly thyroid gland)
			[^{211}At]At-6	
			[^{211}At]YC-550	
			[^{211}At]HS-549	
			[^{211}At]GV-620	
			[^{211}At]GV-904	
			[^{211}At]At-3-Lu	[^{211}At]At-3-Lu was synthesized for better in-vivo stability but outperformed by [^{211}At] At-YF2
			[^{211}At]At-YF2	
			[^{211}At]PSMA1	Outperformed by [^{211}At]PSMA5
			[^{211}At]PSMA6	
			[^{211}At]PSAt-3-Ga	N/A
			[^{211}At]At-NpG-PSMA	N/A
	PSCA		[^{211}At]At- anti-PSCA A11	N/A
[^{213}Bi]Bi	PSMA	Clinical	[^{213}Bi]Bi-PSMA-617	Less efficacious compared to [^{225}Ac]Ac-PSMA-617
		Preclinical	[^{213}Bi]Bi-J591	No clinical translation due to the mAb properties *vs.* the short-lived [^{213}Bi]Bi $T_{1/2}$: 46-mins
[^{149}Tb]Tb	PSMA	Preclinical	[^{149} Tb]Tb-PSMA-617	Risk of radiolysis very high
[^{212}Pb]Pb/[^{212}Bi]Bi	PSMA	Preclinical	[^{212}Pb]Pb-L2	N/A
			[^{212}Pb]Pb-NG001	N/A
			[^{212}Pb]Pb-PSMA-617	N/A
[^{223}Ra]Ra	Bone	Clinical	[^{223}Ra]$RaCl_2$	Phase 3 trial completed

Conclusion and future perspectives:

TAT has demonstrated superiority relative to other forms of ionizing radiation in the treatment of prostate cancer. This is attributable to its astounding radiobiological properties. In the clinic, the [^{177}Lu]Lu-PSMA-617 the current clinically approved agent is far outweighed by TAT, especially the PSMA-targeted radioligand therapies. Although PSMA-targeted therapies have found a niche in PSMA-positive prostate cancer, they falter when it comes to PSMA-negative or de-differentiated prostate cancer. This can be addressed by employing various other TAT agents targeting a vast majority of molecular targets in prostate cancer. Some of these are already undergoing clinical trials whereas some have shown promise in preclinical work. Table II shows the radiopharmaceuticals undergoing clinical trials whereas Table III shows those that have been evaluated preclinically and/or clinically but are yet to undergo clinical trials. The future of TAT in the prostate is expected to rise in the future with multiple emerging molecular targeted therapies other than PSMA.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
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