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Radionuclide Therapy of Metastatic Prostate Cancer

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The current mainstay of treatment in metastatic prostate cancer is based on hormonal manipulations. Standard androgen deprivation therapy and novel androgen axis drugs are commonly well tolerable and can stabilize metastatic hormone-sensitive prostate cancers for years. However, metastatic castration-resistant prostate cancer is still challenging to treat. Except taxanes, prostate cancer presents intrinsic resistance against conventional chemotherapies. The typically elderly patient population excludes more aggressive treatment regimens. First clinical trials evaluating immunotherapy or tyrosine-kinase-inhibitors against prostate cancer failed. In contrast, prostate cancer can be radiosensitive and external beam radiotherapy is effective in localized prostate cancer, thus providing a good rationale for the use of systemic radiopharmaceuticals in the metastatic setting. Beta-particle emitting "bone-seekers" have a long history and are effective as analgesics but do not improve survival because they are limited by red-marrow dose. Alpha emitting ^{223}Radium can be used in a dose that prolongs survival but is restricted to bone-confined patients. Currently radiolabeled high-affinity ligands to the prostate-specific membrane antigen are in clinical evaluation. While radioimmunotherapy approaches were limited by the long circulation time and slow tumor-accumulation of antibodies, low molecular weight PSMA-specific ligands offer an approx. ten-fold improved tumor to red-marrow ratio in comparison to the unspecific bone-seekers. Early clinical studies demonstrate that regarding surrogate markers, such as >50% PSA reduction (60%) and radiologic response (80%), PSMA-therapy exceeds the antitumor activity of all approved or other recently tested compounds; for example, PSA-response was only observed in approx. a total of 10% of patients treated with ipilimumab, sunitinib, cabozantinib, or xofigo, respectively and in approx. 30, 40, 50% of patients treated with abiraterone, cabazitaxel, or enzalutamide. Also progression free and overall survivals of these single-arm studies appear promising when compared to historical controls. Consecutively, the first PSMA-RLT recently advanced into phase-3 (^{177}Lu-PSMA-617; VISION-trial). Future developments aim to avoid off-target radiation by ligand-optimization and to outperform the antitumor activity of beta-emitter PSMA-RLT by labeling with highly focused, high energy transferring alpha-nuclides; however the latter potentially also increasing the risk of side-effects and additional early phase studies are needed to improve treatment protocols. Academically clinical research is developing prognostic tools to improve treatment benefit by selecting the most appropriate patients in advance.
Semin Nucl Med 49:313-325

Clinical Need and Rationale for Radionuclide Therapy of Prostate Cancer

The current mainstay of treatment in metastatic prostate cancer is based on hormonal manipulations. Standard androgen deprivation therapy (ADT) and novel androgen axis drugs (NAAD) are commonly well tolerable and can stabilize metastatic hormone-sensitive prostate cancers (mHSPC) for

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https://doi.org/10.1053/j.semnuclmed.2019.02.003
0001-2998/

years. Due to the intrinsic resistance of prostate tumors against chemotherapy and the typically elderly patient population which is excluding aggressive treatment regimens, taxane regimens are the only class of chemotherapy with proven clinical efficacy. However, the highest impact on survival was achieved when Docetaxel is applied to young patients with high tumor-burden as a combination therapy with ADT[1,2] while older ones or patients unfit for chemotherapy can benefit from early start of NAADs,[3] both in the mHSPC setting, respectively. Alternative treatment mechanisms, such as immunotherapy or tyrosine-kinase-inhibitors, appear promising but first clinical trials in this field failed.[4-7] Thus, therapy of metastatic castration-resistant prostate cancer (mCRPC) remains challenging and is of increasing epidemiological relevance in aging populations world-wide. Systemic radiopharmaceutical therapy appears promising, because external beam radiotherapy can be similar effective as prostatectomy in localized prostate cancer[8] and its radiosensitivity provides a good rationale for radionuclide based attempts in the metastatic stage.

Bone-Targeted Radionuclide Therapy

The first radionuclide evaluated in a phase-3 trial and consecutively approved for patients with mCRPC was ^{89}Sr which acts as a calcium analog.[9] The further use of radiotherapy against painful hot-spots was significantly reduced after ^{89}Sr treatment; however, survival was not different compared to placebo which was attributed to the remarkable high and often prolonged hematological toxicity with 32.8% of patients developing grade-3/4 thrombocytopenia.[9] Shorter durations of hematological toxicities were achieved by using beta-emitters with shorter half-life, which were targeting bone-metabolism by being tagged to phosphonates. Apart from that, in a study comparing ^{89}Sr, $^{186/188}$Re-HEDP, and ^{153}Sm-EDTMP in activities translating into similar red-marrow absorbed doses, all compounds were highly similar regarding the average deepness of thrombocytopenia as well as response-rate, magnitude, and duration of symptomatic improvement.[10] But none of these palliative useful radiopharmaceuticals could demonstrate an improvement of overall-survival, neither as a monotherapy versus placebo nor in combination with chemotherapy over chemotherapy alone, yet.[11,12]

Consecutively, ^{223}Ra, also a calcium-analog but in contrast to ^{89}Sr a short range alpha emitter, was clinically evaluated. Due to its short penetration range into the surrounding red-marrow (Fig. 1) the hematological toxicity was remarkable reduced, for example, not different to placebo in its phase-3 pivotal trial.[13] Simultaneously and probably due to the more focused dose delivery to osteoblastic lesions,[14] for the first-time also an improved survival was observed.[13] This was correlated with a significantly reduced number of skeletal events.

Recently, results of various other trials evaluating "bone-seeking" radionuclides have carefully been arranged for standardized presentation in a systematic review, but using different quality-of-life questionnaires it was not possible to compare the magnitude of symptomatic improvement directly.[15] However, the average pain response-rates to ^{89}Sr and ^{223}Ra were lower (50%-60%) in comparison to ^{153}Sm-EDTMP and ^{186}Re-/^{188}Re-HEDP (approx. 70%, respectively) and this is in line with the clinical findings reported in randomized clinical trials; ^{153}Sm-EDTMP patients can often decrease their analgesics,[16] in contrast ^{223}Ra most often only delays the time to increase them.[13] Consecutively, current trials are rather motivated to exploit the full potential of ^{223}Ra in prolonging survival but not in palliative care.

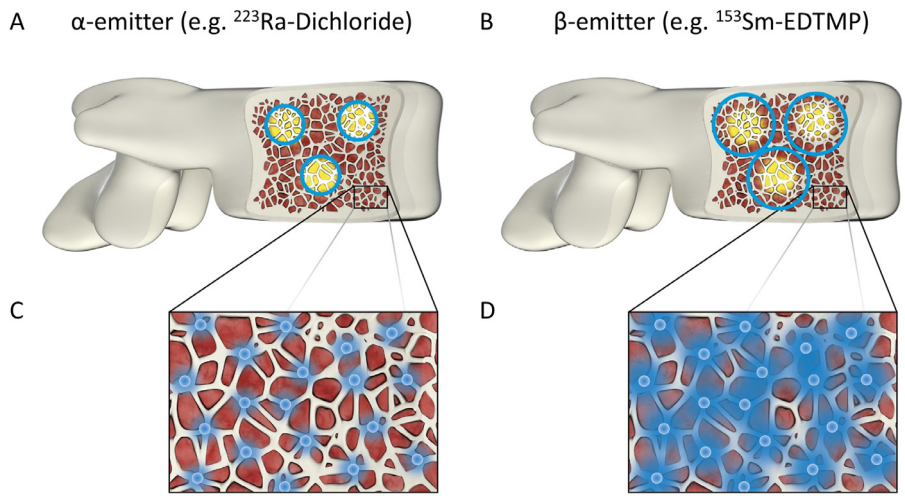

Figure 1 Absorbed dose distribution with alpha- (A) and beta- (B) emitting radiopharmaceuticals. Alpha-emitters transfer their energy highly focused to targeted metastasis (yellow) with very few spill-out radiation to surrounding tissue (blue circle; 0.1 mm). In contrast, beta emitting radiopharmaceuticals deliver off-target radiation in the range of their max. beta penetration range (blue circle; 0.5-5 mm). In case of bone-targeting radionuclide therapy the unspecific uptake in healthy trabecular bone (black square—zoom-area) arises few issues if alpha-emitting ^{223}Ra is used (C), but beta-emitting "bone-seekers" can deliver relevant off-target dose to unaffected red-marrow (D).

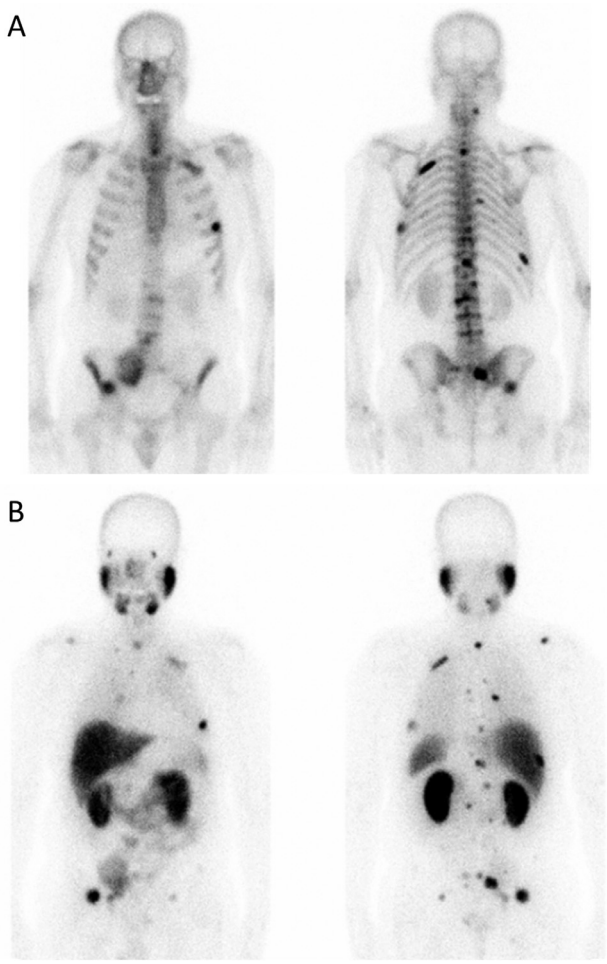

Figure 2 Uptake in osteoblastic bone metastases by unspecifically targeting the surrounding bone matrix reaction (A). PSMA-specific but tissue-independent uptake in metastatic lesions (B) increases tumor to red-marrow ratio but introduces new dose-limiting organs (salivary glands, kidneys). Content of this figure was originally published by the authors in a modificated form in J Nucl Med. 2018;59:1373-79.

Unfortunately, an interim analysis of the phase-3 ERA-223 trial (yet unpublished), evaluating the combination of ^{223}Ra and abiraterone/prednisolone, found an increased risk of fractures (26% vs 8% placebo) and consecutive deaths (34.7% vs 28.2%) for the combination therapy. As most skeletal events were not pathologic fractures but related to osteoporosis this observation does not contradict the earlier observation that ^{223}Ra can decrease skeletal events at tumor sites.[17] Nevertheless, it currently prohibits early-stage use of ^{223}Ra because abiraterone is already commonly accepted as a first line in mCRPC and even for mHSPC and was considered responsible for the good outcomes in both the ^{223}Ra/abiraterone and the placebo/abiraterone arm of this trial. In addition, due to the prolonged overall-survival under NAADs, visceral metastasis—once a rarity—becomes an increasing issue in mCRPC, now affecting up to 50% of patients.[18] Thus, the relevance of ^{223}Ra even in the advanced-stage setting is decreasing.

Due to the decreasing clinical impact of bone-seeking radiopharmaceuticals targeting the unspecific environmental reaction of osteoblastic bone-metastases only, this article places its main focus on PSMA-targeted radionuclide therapy, directly addressing cancer cells independently from their location (Fig. 2).

PSMA-Ligands—Recent Developments

In a previous article published in this journal, we already described the structure and clinical impact of PSMA as a target structure.[19] In brief, the majority (approx. 85%) of prostate cancer demonstrates an overexpression of PSMA. A large extracellular domain is easily accessible for binding of ligands. In addition to antibodies such as J591,[20] PSMA can also be targeted with small inhibitors of its glutamate-carboxypeptidase activity, that is, ureas[21] or esters of glutamic acid[22] that fit into the pocket of its catalytic domain. A recent review[23] summarized the benefit of additional cotargeting of the lipophilic accessory pocket[24] and arene-binding site[25] of the PSMA protein crystal. The ligands PSMA-617 and PSMA-I&T have already been translated clinically. In this review we only focus on recent developments since 2016, promising to affect clinical application soon. One approach is to replace the Glu-ureido group with other motifs that cannot be cleaved by peptidases, for example, irreversible binding to PSMA with phosphoramidates.[26] However, affinity to PSMA alone is no good predictor for the clinical performance of one particular high-affinity ligand. For example PSMA-11 (affinity IC50 12.1 nM)[27] clinically presented a faster tumor-uptake than PSMA-617 (affinity IC50 2.3 nM)[28] in PSMA-PET/CT.[29] The antibody J591 was even measured with <2 nM affinity to PSMA[20] in competitive binding assays, but suffers from slow accumulation kinetics in vivo. Thus, it seems questionable if focusing on affinity may be of major impact for development of future ligands.

However, in contrast to the low-molecular-weight PSMA-ligands, the J591 antibody presents a beneficial lower salivary gland uptake; therefore it was warranted to improve its targeting-velocity by downsizing. Some interesting single-chains variable domain, Fab fragments and diabody approaches derived from PSMA-antibodies have preclinical been described recently.[30-32] One of the most promising, the minibody IAB2M, weights around one half of J591 (80 kDa vs 150 kDa) and presents accelerated plasma clearance (Fig. 3) promising to reduce red-marrow dose and consecutively ameliorate the severe hematological toxicities that have been observed with ^{177}Lu-J591[33] while simultaneously maintaining low off-target radiation to salivary glands.[34,35] Thus, the IAB2M approach might also be a solution to cope with the salivary gland toxicity reported for PSMA-targeting alpha-therapy with ^{225}Ac; however, the longer circulation time even of the minibody is bearing the risk to cause issues regarding the translocation of ^{225}Ac daughter nuclides which are dropped from the chelator due to the recoil of the first alpha-decay and—as long as the shuttle molecule has not been internalized—can redistribute unspecific in the body and harm other organs. For example it

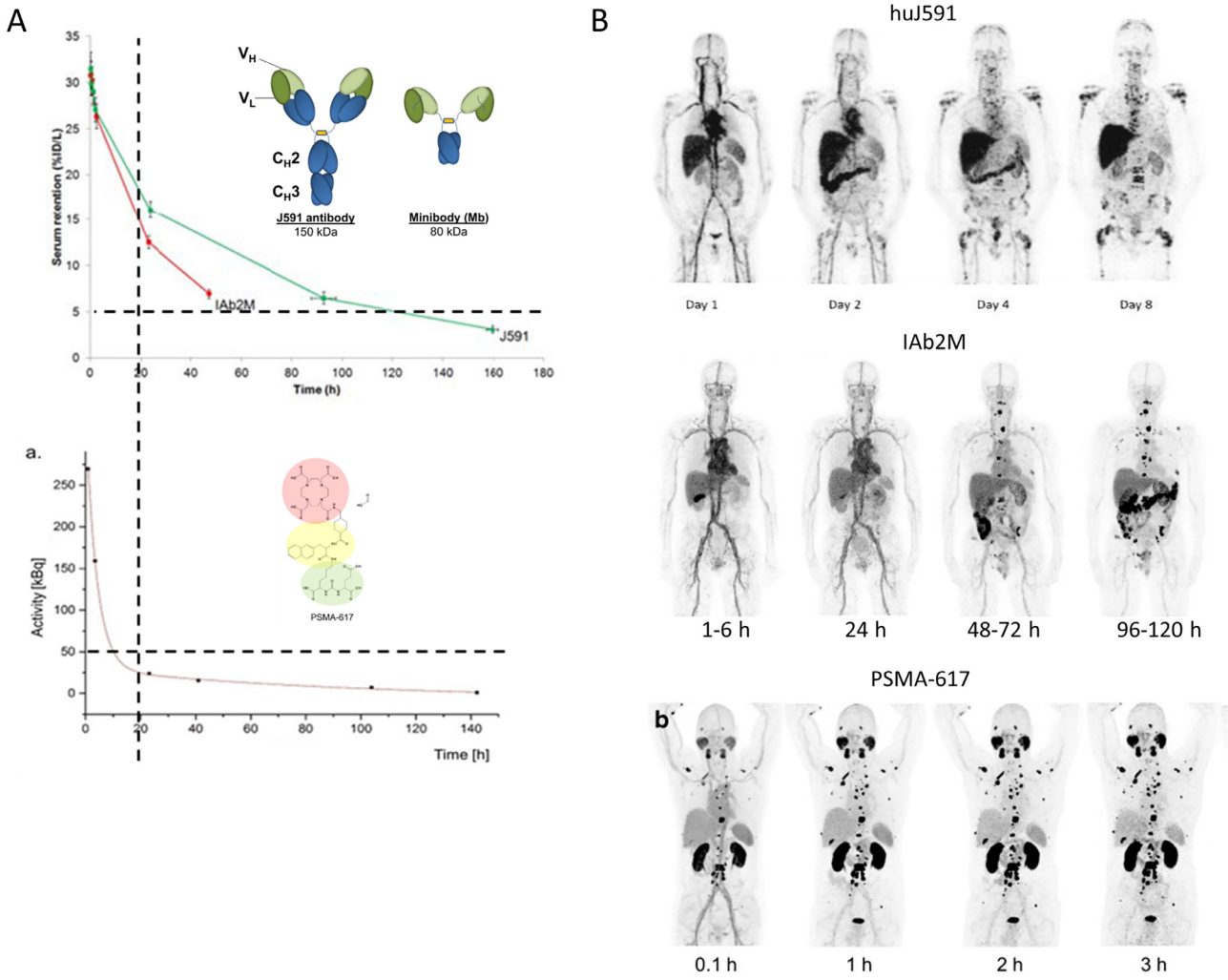

Figure 3 Relationship between molecular size of shuttle molecule and pharmacokinetics. The 150 kDa full-length mAB J591 presents a serum half-life of approx. 2 days, the 80 kDa minibody IAb2M of apprx. 1 day, the 1 kDa PSMA-617 of <1 hour (A). Vice versa, quantitatively relevant tumor accumulation is observed approx. 4 days, 2 days, 1 hour (B). The small molecule but not the antibody derived ligands present specific but not PSMA-related off-target accumulation in the salivary glands. Part of this figure were originally published in Pandit-Taskar et al J Nucl Med December 1, 2016 vol. 57 no. 12 1858-1864 SNMMI and in Pandit-Taskar et al Eur J Nucl Med Mol Imaging (2014) 41: 2093. License number 4518361434439.

has been reported that renal uptake of free ^{213}bismuth can contribute 60% of the kidney dose in addition to the specific uptake of ^{225}Ac-labeled antibodies.[36] In comparison to the 150 kDa full-length antibody the 80 kDa minibody again benefits from its shorter circulation time, however it is still far away from the low-molecular-weight Glu-ureas such as the 1 kDa PSMA-617.[28] Thus, it still remains an open question for future studies how the respective pros and cons might balance in the clinical setting.

Another recent strategy to optimize PSMA-ligands was the introduction of albumin binding motifs to the linker region.[37-44] The rationale was that proteins below 60 kDa are filtrated in the glomeruli of the kidneys followed by tubular reabsorption. Modest binding to albumin (approx. 67 kDa) was emphasized as an option to reduce kidney dose, while the higher affinity to PSMA might still be sufficient to pull the ligand out of its albumin binding. In sum: all authors were somehow successful with regard to enhance the tumor-to-kidney ratio. Due to the longer circulation time, that is, an increased arterial input function, also the tumor-uptake (as %ID) increased. Unfortunately, due to the prolonged circulation time the ratio tumor-to-blood decreased inverse to albumin-affinity. With red-marrow toxicity being the acute dose limiting factor, the therapeutic range, that is, the ratio tumor to dose-limiting-organ, could decrease. Yet, there are no data from human beings available so far to estimate how the 1-2 kDa ligands reversible bound to 60-70 kDa albumin perform in comparison to an inherent 80 kDa minibody. It seems that the affinity to albumin was chosen too strong in the first attempts.[37-40,44] But more systematical evaluations[41-43] demonstrate that especially very moderate albumin binders appear to have some potential to gradually improve the therapeutic window in PSMA-RLT (Fig. 4).

One variable that has not yet been evaluated for PSMA-RLT is the ideal amount of peptide providing the optimum

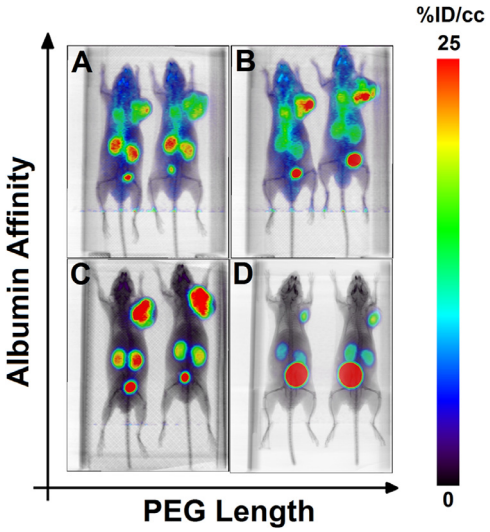

Figure 4 Bispecific ligands to PSMA and albumin aim to increase tumor-uptake. Best results are obtained with relatively moderate albumin-binding (C), elsewise increase in perfusion dependent background activity may reduce tumor-to-blood ratios (A,B). By courtesy of John Babich, Weill Cornell Medical College NY. Revision mandatory.

tumor to normal organ ratio. When introducing new radiopharmaceuticals most researchers aim for highest possible specific activity, that is, to label the desired treatment activity to as little amount of precursor as possible, because low density of target receptors might limit tumor uptake by target saturation. Nevertheless, if there are very few tracer-molecules in comparison to targets in both tumor and dose-limiting organs, then rather perfusion than the quantitative receptor expression defines the uptake ratios. Theoretical, the therapeutic window could even improve beyond onset of tumor-occupancy, as long as the saturation effect in dose limiting organs prevails; preloading with "cold" CD20 antibodies up-front to radioimmunotherapy is following this concept.[45] However, the number of PSMA copies per tumor cell, perfusion of individual tumor lesions and overall tumor-burden are patient individual variables; thus optimization work would either be very sophisticated and time-consuming on an individual patient basis or average values are used. Mathematical modeling revealed that the currently given amounts of PSMA-ligand (100-150 μg PSMA-617 or 200-250 μg PSMA-I&T per cycle) are in the appropriate order of magnitude for most patients.[46]

Radionuclides for PSMA-RLT

The most appropriate radionuclide for one specific scope of application depends on the pharmacokinetics of its intended shuttle molecule. Mathematical, after four effective half-lifes only 1/16 = 6,25% of the baseline activity is left. As >90% of absorbed dose is transferred from the nuclide to the respective target tissue only these 4 half-lifes are of interest regarding toxicities and therapeutic effects. Generally, the biological half-life in tumor (approx. 60-160 hours for PSMA-617) should be similar (between 1/4 and 4-fold) to the physical half-life. Longer biological tumor-retention of the shuttle-molecule does no more translate into higher tumor absorbed doses because at this time >93% of activity had already decayed physically. If the radiopharmaceutical leaves the body much faster, a lot of decays do no more contribute to tumor dose but present an issue for environmental protection after excretion. Another rule of thumb requests that both tumor targeting and blood-clearance (or clearance from other dose-limiting organs) of a pharmaceutical should also be 4-fold faster than the physical half-life of its radiolabel. Moderate gamma abundancy is welcome to obtain distribution imaging and detect contaminations; higher gamma emission probabilities are rather considered challenges for radiation protection. Several nuclides have been considered appropriate matches to be combined with PSMA-targeting small molecules or minibodies; Table 1 presents the relevant physical characteristics of the most promising beta-emitters. Other nuclides that would fulfill rule of thumb requirements, for example, ^{169}Er ($t_{1/2}$ 9.4d; Emax 340 keV), ^{153}Sm ($t_{1/2}$ 46.7 h; Emax 825 keV), or ^{186}Re ($t_{1/2}$ 89 h; Emax 1 MeV) are currently not available with sufficient specific activities appropriate for labeling of PSMA-ligands.

In consideration of the respective plasma half-lifes of J591 and IAB2M of 1 day versus 2 day and about 2 versus 4 days to reach about 90% of their tumor-plateau, according to this rule of thumb the 6.7 days half-life of ^{177}Lu ranges at the lower limit, the half-lifes of ^{225}Ac (9.9 days) or ^{227}Th (18.7 days) more appropriate for the full-length antibody. The small molecules PSMA-617 and PSMA-I&T have been described to reach their maximum tumor-uptake between 4 and 24 hours p.i. followed by a biological half-life of approx. 4-5 days; accordingly a wide range of radionuclides between 1 and 20 days could be considered appropriate.

Another characteristic to be taken into account is the linear energy transfer (LET) and tissue range of a nuclide. A long path-length has been considered beneficial to cope with a heterogeneous expression of the target receptor within one particular tumor lesion, which might be relevant for prostate-cancer which is known for their strong genetical and phenotyp heterogeneity.[47,48] A shorter penetration range safes dose from surrounding tissue and might be beneficial in case of disseminated red-marrow infiltration. It is mathematically possible to project a radionuclide's tumor-cell kill rate as a function of the underlying tumor lesion size.[49] According to this modelling, ^{177}Lu performs best for tumor diameters in a range of 1.2-3.0 mm, the optimal lesion size to be treated with ^{90}Y is 28-42 mm.[49] Nuclides that have already been approved in the clinical setting are ^{90}Y (Zevalin) and ^{177}Lu (LuTATHERA). Despite remarkable different beta-energies marking both limits of the spectrum, that is, the of mean/max tissue penetration is about 3/11 mm for ^{90}Y and 0.3/1.0 mm for ^{177}Lu, the clinical findings were not much different.[50] Thus, the potential to further improve PSMA-RLT by using a different beta-emitter seems limited. Half-life and radiation safety issues related with the coemission of gammas (dose rate constants also in Table 1) might have some practical consequences, i.g. whether a compound could be given in the out-patient setting. Theoretically ^{67}Cu

Table 1 Physical characteristics of beta-emitters appropriate to be used in PSMA-RLT

	Tb-161	I-131	Lu-177	Y-90	Cu-67
Physical half-life	6.9 d	8.05 d	6.7 d	2.7 d	2.6 d
Beta energies (emission probability)	590 keV	606 keV (89% abundance)	490 keV	2280 keV	580 keV
Alpha/beta range in water (max)	0.09 mm	2.3 mm	1.8 mm	11.3 mm	2.1 mm
Gamma energies	75 keV (10%)	364 keV (82% abundance)	113 keV (3% abundance)	Bremsstrahlung	185 keV (49%)
	45-49 keV (35%)	637 keV (7% abundance)	210 keV (11% abundance)	511 keV co-incidence (0.003%)	91-93 keV (23%)
		284 keV (6% abundance)			
		723 keV (2% abundance)			
		80 keV (3% abundance)			
		29-34 keV (4.5% / x-rays)			
Dose rate constants [μSv.m^2 / GBq.h]	na	65.70	5.94	1.00	19.80

offers an ideal physical half-life close to the biological half-life in tumor while simultaneously providing the favorable beta-energy of ^{177}Lu. Thus, several PSMA-ligands appropriate for copper-labeling have been developed and PET-labeled with ^{64}Cu[51,52]; nevertheless, the poor availability of it therapeutic analog ^{67}Cu presents a major limitation. Due to the low-LET of beta-particles, the tumor-dose in beta-RLT depends on the cross-fire effect and theoretical it is rarely possible to achieve sterilizing tumor doses in micro metastasis. Accordingly, a complete PSA response was observed in <1% of patients treated with ^{177}Lu/^{90}Y-PSMA. The high-LET of alpha-particle emitters and Auger electrons are promising avenues to improve the efficacy of PSMA-RLT with regard to micro-metastasis. For the Auger emitters ^{161}Tb and ^{111}In only pre-clinical models are available[53,54] and due to tissue ranges of <10 μm tumor-heterogeneity and internalization present new challenges. Also the high whole-body und consecutively red-marrow dose arising from the gamma coemissions of ^{111}In and the limited availability of ^{161}Tb are relevant limitations. In contrast, first clinical results already available for alpha-emitting ^{225}Ac-PSMA-617 indicate that PSMA-TAT has realistic potential to provide an additional benefit in comparison to beta-PSMA-RLT within reasonable time.[55,56] A 10% PSA complete remission rate (Fig. 5) and duration of tumor control exceeding second generation hormone-therapies (Fig. 6) are remarkable results for advanced stage patients already suffering from disseminated bone(marrow)-infiltration[57] and even 40% complete PSA remissions were observed in early stage patients.[58] Promising dosimetry approximations reported for a ^{212}Pb-labeld PSMA-ligand warrants further investigation.[59] Its introduction could help to overcome supply limitations of clinical useful alpha-emitters and in comparison to ^{225}Ac ($t_{1/2}$ 9.9 days) the short half-life of ^{212}Pb ($t_{1/2}$ 10.6 hours) could reduce environment protection issues in the out-patient setting. However, a dosimetry study revealed that a further decrease in half-life of the radiolabel (^{213}Bi; $t_{1/2}$ 0.8 hours) would negatively affect the ratio between tumor and dose-limiting organs.[60]

PSMA-RLT: From Prove of Mechanism to Phase-3

Blueprint for all new radioactive drugs are always radioiodine conjugates because labeling with halogens can simply be done to the backbone of each shuttle-molecule—in this case the already available unlabeled GCP-inhibitors developed by Alan Kozikowski years ago[61]—without need for an additional chelator-moiety. Thus, first clinical steps were conducted in 2011-2013 with ^{131}I-MIP1095[62] applied as a single-shot therapy close to the maximum tolerable dose estimated by ^{124}I-MIP1095 PET/CT. Long in-patient isolation (approx. 1 week) was needed due to radiation protection issues related to the coemission of high energy gammas from this nuclide. Therefore, repeated treatment was postponed until progression of disease reoccurred. It was observed that the duration of response significantly decreased with each

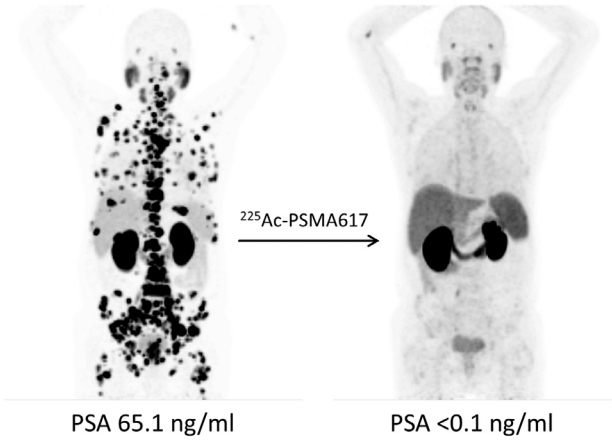

Figure 5 Therapy with ^{225}Ac-PSMA-617 currently presents the option with the highest developed antitumor activity regarding biochemical and imaging based complete remissions. Patient with multifocal bone metastasis (average tumor-uptake > salivary glands) before (A) and after (B) PSMA-targeting alpha-therapy.

succeeding cycle.[63] Thus, later treatment protocols with ^{177}Lu-PSMA, aiming to increase the periods of progression free survival, were based on fractionated administration timed at the projected PSA-nadir. Introduction of ^{177}Lu presented an improvement regarding radiation protection issues and increased in vivo stability. First proof-of-mechanism for the second generation ligand PSMA-617 was demonstrated in 2014.[64]

The clinical value of dosimetry modeling of therapeutic radiopharmaceuticals is that it provides an approximation of their maximum tolerable doses which allows that empirical dose-escalation trials can be shortened and partially omitted. Several groups calculated dosimetry estimates for PSMA-617[65-73] and PSMA-I&T.[74-76] Results were highly consistent even between different methods and found average doses to kidneys (0.5-0.9 Gy/GBq), red-marrow (0.01-0.05 Gy/GBq) and tumor (range 0-22, mean 6 Gy/GBq) for both ligands. Thus, the tumor to red-marrow ratio is >10-fold higher in comparison to ^{153}Sm-EDTMP (tumor 22 Gy/GBq vs red-marrow 1.5 Gy/GBq) and ^{223}Ra (tumor 2 Gy/MBq vs red-marrow 0.14 Gy/MBq).[77-80] However, their appropriateness to project clinical maximum tolerable doses was only validated by a single traditional dose escalation attempt.[81] No reliable tumor dosimetry data are available for ^{131}I-MIP1095 and ^{177}Lu-J591 and therefore their therapeutic range cannot be compared directly. Nevertheless, red-marrow dose is also about 10-fold higher (0.3 Gq/GBq) for both compounds, respectively[62,82]; either due to the long circulation time of the antibody or a 50% gamma contribution predominantly arising from extraosseous source organs—and it is unlikely that such a drawback could ever be compensated by tumor-uptake.

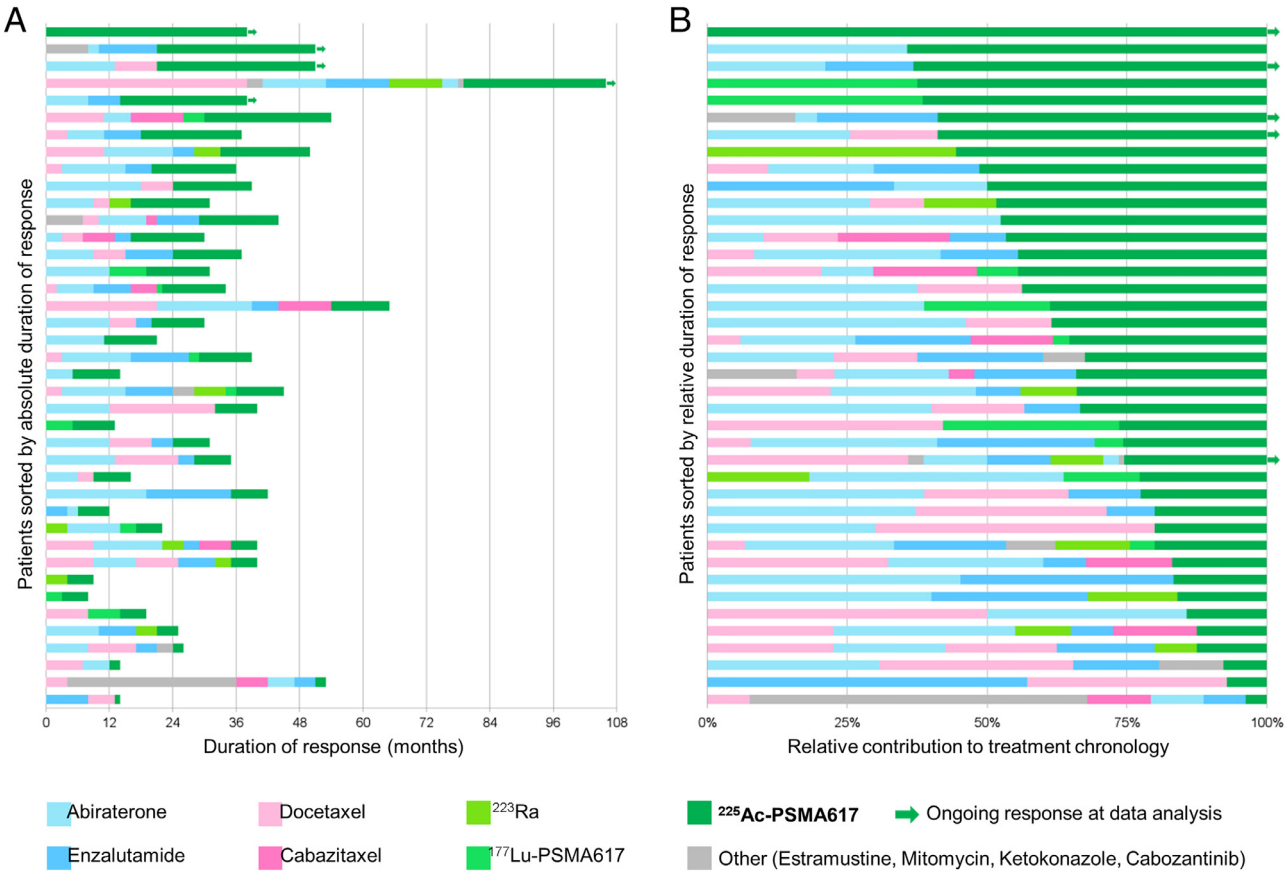

Figure 6 Duration of tumor control in month (left) and relative to the duration of previous hormonal and chemotherapeutical treatment lines (right). Originally published by the authors in J Nucl Med. 2018;59:795-802.

Invented within the academically setting and without commercial support, clinical translation was first done as an "unproven intervention in clinical practice" (Helsinki declaration Art. 37), which—due to regulatory issues—can only be evaluated retrospectively. However, >50%-PSA-response rates of 40%-50% and only 10% grade-3/4 hematological adverse events (similar to the placebo arm of comparable patient cohorts[13]) were consistently reported from several hospitals world-wide, offering this promising new option in the last-line setting.[83-89] An initiative of the German society of nuclear medicine organized a multicenter evaluation of these data with statistical numbers analog to a typical phase-2 study[90] and demonstrated a very promising 45% biochemical response rate and very well tolerability. The strength of this trial was number of $n = 145$ patients (from 12 contributing centers), sufficient for statistical interpretation; but retrospective design was considered a major limitation. However, a second phase-2 with $n = 30$ patients but treated within a stringent prospective protocol confirmed the favorable results with an even higher biochemical (57%) and imaging response rate (82% in patients with measurable disease) and also few (13%) thrombocytopenia as the only Grade-3/4 toxicities.[91] Consecutively, ^{177}Lu-PSMA-617 is currently evaluated in a randomized, controlled, prospective phase-3 (Trial registry number: NCT03511664).

Prognostic Factors and Patient Selection

It is the natural character of any molecular targeted therapy, that it can only be effective if the target structure is sufficiently expressed from the majority of tumor lesions, respectively. Unfortunately, prostate cancer is characterized by high genetic and phenotyp heterogeneity, especially in the late-stage setting. For example transdifferentiation to neuroendocrine prostate cancer can lead to a reduced expression of PSMA.[92] One major difference between the German multicenter study (response rate 45%), and the prospective phase-2 (response rate 57%) was different patient selection. In Germany PSMA-PET was only compared to its related CT-scan,[90] in Australia a comparison of PSMA-PET and FDG-PET was done (Fig. 7); resulting in 30% (13/43) excluded patients.[91] Another group compared PSMA-PET with ^{18}F-NaF-bone-PET and found that only 351/468 (75%) osteoblastic lesions were also PSMA-positive.[93] An intraindividual comparison of planar PSMA scintigraphy with conventional bone scan revealed that 10% of the patients had PSMA-negative tumor phenotype.[94]

In addition PSMA-expression is not a black versus white decision but the tumor absorbed dose presents a continuous scale between negative to very high. Voxel based dosimetry analysis revealed that a mean whole-body tumor absorbed dose of <10 Gy rarely translated into a biochemical response and vice versa.[95] Unfortunately such sophisticated and time-consuming approaches are hardly to apply in clinical practice. Fortunately, the SUVs of the related pretherapeutic PSMA-PET/CT somehow correlates ($r = 0.62$) with tumor absorbed dose and is simple to evaluate.[95] According to current clinical experience (rule of thumb) but not based on systematical data, tumor-uptake >1.5-2 fold liver background seems to be a valuable threshold for ^{68}Ga-PSMA-11 (Fig. 7), tumor-uptake > salivary gland uptake a comparable analog for ^{18}F-PSMA-1007,[96] that presents higher and more heterogeneous liver-uptake due to its hepatobiliary clearance but is closer related to the chemical structure of its PSMA-617 therapy analog (Fig. 8).[97]

Other predictive factors for negative treatment outcome of PSMA-RLT are low baseline hemoglobin, presence of visceral metastasis, rising lactate dehydrogenase and PSA non-response.[98,99] However, all of these are known unspecific markers for aggressive or very advanced tumors and prognosis might be even worse under placebo. Therefore randomized controls would be needed to draw a final conclusion if these factors should be considered for patient stratification approaches.

Future Perspectives

Anticipating success of the phase-3 pivotal trial of ^{177}Lu-PSMA617 it is predictable, that PSMA-RLT will be evaluated in earlier treatment lines. In current indication, that is, mCRPC after secondary hormonal manipulation, it is assumed that PSMA-expression is constitutively overexpressed because PSMA genes are suppressed by androgen and this effect should attenuate with increasing hormonal independency of tumors. However, in mHSPC PSMA-expression can be influenced by hormonal effects. In preclinical studies a temporarily PSMA overexpression was observed at the beginning of ADT.[100-104] However, such an effect was only found for therapy with abiraterone and enzalutamide but not for Luteinising hormone-releasing hormone and bicaluatmide in men evaluated with PSMA-PET/CT.[105] Thus, further research is needed to improve PSMA-protocols regarding simultaneously hormonal manipulations when aiming for earlier line therapy.

Also combination therapies could become an interesting field of future research. Radiation mediated immunological mechanisms can lead to tumor response even in nonradiated lesions. This led to the theory that, in the presence of endogenous cancer-specific antigens exposed by cancer necrosis, an innate immune response can adapt to respond toward those antigens via a cross-talk mechanism, resulting into the so called abscopal effect.[106] Thus, there would be a good rational for combination of PSMA-RLT with either immune-checkpoint or DNA-repair inhibitors such as pembrolizumab or olaparib. Nevertheless, reports on the role of mutations in DNA-repair associated genes are controversial. Patients harboring such mutations presented favorable response to ^{223}Ra therapy,[107] but in a case report about a patient with germline BRCA2-muation response to PSMA-RLT was exceptional poor.[108] Statistically more reliable numbers are needed. Testing in the neoadjuvant setting, that is, before prostatectomy, offers a potential strategy to evaluate prognostic markers

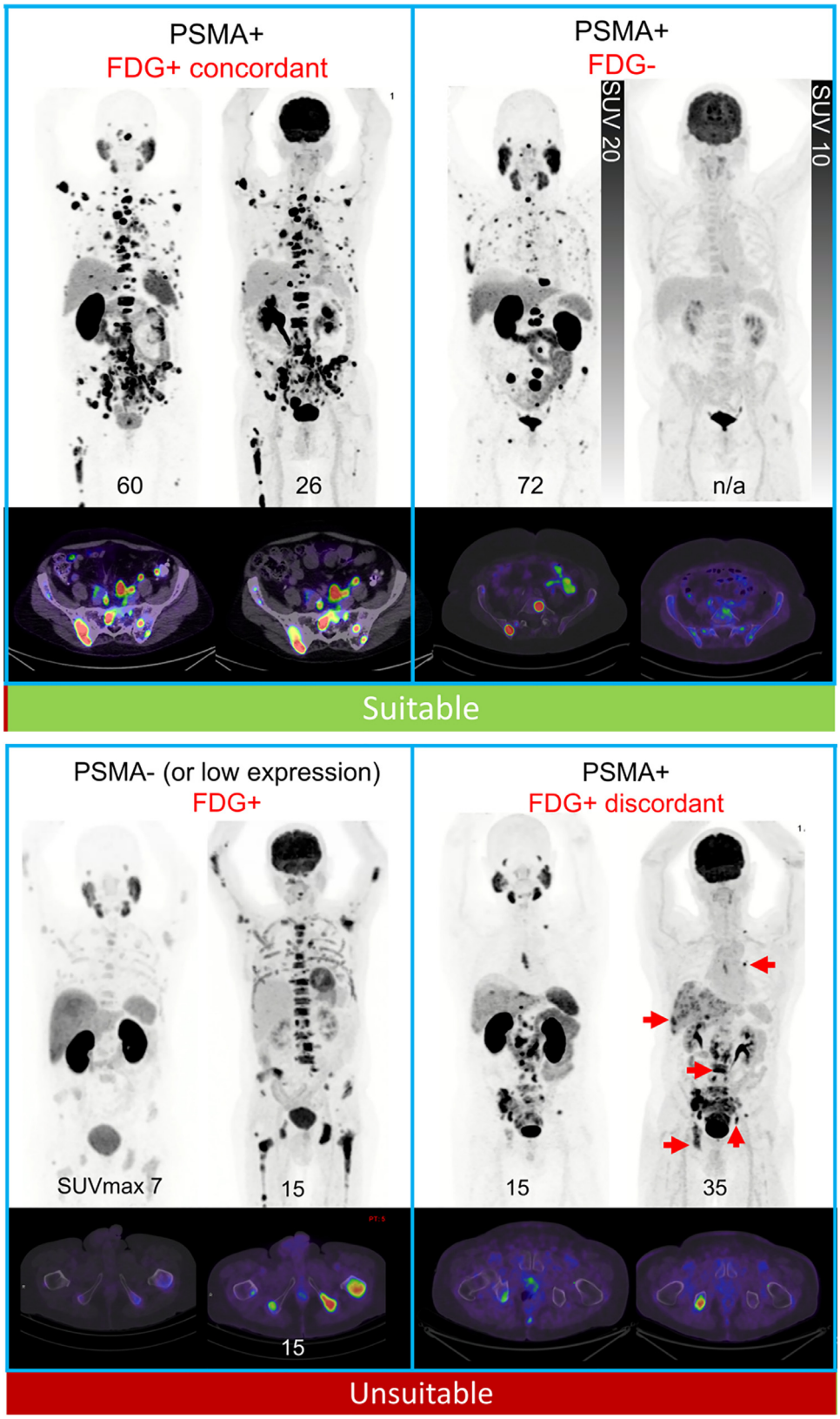

Figure 7 Patient stratification based on functional imaging: Using a second imaging modality (eg, FDG-PET/CT), patients with sufficient uptake of the radiopharmaceutical in all viable tumor lesions can be identified in advance. Molecular-targeting therapies cannot be effective in target negative lesions; response probability can be increased by eliminating patients with relevant target-negative disease. By courtesy of Michael Hofman, Peter MacCallum Cancer Centre Melbourne.

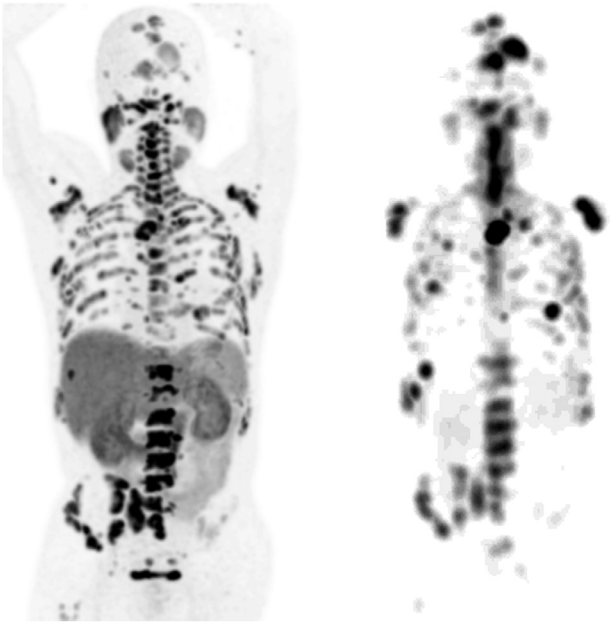

Figure 8 Theragnostic tandems: target positive tumor phenotypes are routinely demonstrated with ligands optimized for diagnostic purpose—i.g. ^{18}F-PSMA-1007 (A)—and due to identical target receptor and similar chemical structure correlate to the biodistribution of their therapeutic analog (^{177}Lu-PSMA-617 SPECT; B).

without the challenges of interlesion heterogeneity complicating evaluations in the multifocal mCRPC stage and should become ethically reasonable once the antitumor activity of ^{177}Lu-PSMA617 has been proven in its phase-3.

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