Review Article

Meeting Report from the Prostate Cancer Foundation PSMA-Directed Radionuclide Scientific Working Group¹

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Abstract

Introduction. The Prostate Cancer Foundation (PCF) convened a PSMA-Directed Radionuclide Scientific Working Group on November 14, 2017, at Weill Cornell Medicine, New York, NY.

Methods. The meeting was attended by 35 global investigators with expertise in prostate cancer biology, radionuclide therapy, molecular imaging, prostate-specific membrane antigen (PSMA)-targeted agents, drug development, and prostate cancer clinical trials. The goal of this meeting was to discuss the potential for using PSMA-targeted radionuclide agents for the treatment of advanced prostate cancer and to define the studies and clinical trials necessary for validating and optimizing the use of these agents.

Results. Several major topic areas were discussed including the overview of PSMA biology, lessons and applications of PSMA-targeted PET imaging, the nuances of designing PSMA-radionuclide agents, clinical experiences with PSMA-targeted radionuclides, PCF-funded projects to accelerate PSMA-radionuclide therapy, and barriers to the use of radionuclide treatments in widespread clinical practice.

Discussion. This article reviews the major topics discussed at the meeting with the goal of promoting research that will validate and optimize the use of PSMA-radionuclide agents for the treatment of advanced prostate cancer.

Key Words

Radiopharmaceuticals, radiation therapy, radionuclides, prostate-specific membrane antigen (PSMA), clinical trials, nuclear medicine, radiology, urology, medical oncology

Introduction

Prostate-specific membrane antigen (PSMA)-targeted radionuclide therapies (PSMA-TRT) are an emerging class of agents being developed and tested for the treatment of prostate cancer. These agents consist of PSMA-targeted small molecules or antibodies conjugated to alpha or beta particle-emitting isotopes. While PSMA-targeted radioligands have been studied as imaging and/or therapeutic agents for almost twenty years [1, 2], recent reports including a 2016 report from Germany demonstrating

remarkable radiographic and prostate-specific antigen (PSA) responses in highly pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) with ^{225}Ac -PSMA-617 [3], and extensive clinical experience with ^{177}Lu -PSMA-TRT in Germany since 2013 as well as in Australia, have stimulated renewed interest in this field. Additional motivation for TRT development is derived from the 2013 United States Food and Drug Administration (U.S. FDA) approval of ^{223}Ra which moved radioisotopes into the clinic for prostate cancer, and the 2017 European Medicines Agency (EMA) and 2018 U.S. FDA approvals of the first peptide receptor targeted radionuclide therapy for cancer, somatostatin-targeted ^{177}Lu (lutetium Lu 177 dotatate).

The previous reports on the clinical activity of PSMA-TRTs suggest that these agents may confer clinical benefits in men with advanced prostate cancer. Several clinical trials are now planned or underway to test various PSMA-targeted agents conjugated to various radioisotopes as mono- or combination therapies. However, numerous clinical questions exist including how to optimally use these agents to maximize potency while minimizing toxicity, how to effectively combine PSMA-TRTs with other treatments, sequencing, dose, schedule, and patient selection.

In recognition of the promise of this treatment class coupled with the critical need for new life-prolonging treatments for patients with advanced prostate cancer, the Prostate Cancer Foundation (PCF) convened the PCF PSMA-Directed Radionuclide Scientific Working Group meeting to address many unanswered biological and clinical questions surrounding the use of this therapy.

The meeting was held at Weill Cornell Medicine, New York, New York on November 14, 2017. The meeting was attended by 35 basic, translational, and clinical scientists from several academic institutions in the U.S., Australia, and Europe, and from the NIH/NCI and Bayer Pharmaceuticals. There were 13 speakers and six scientific areas covered: 1) the basic science of PSMA; 2) lessons and applications of PSMA-targeted PET imaging; 3) development and optimization of PSMA-TRTs; 4) clinical experiences with PSMA-TRTs; 5) PCF-funded projects to accelerate the validation of PSMA-TRT; and 6) barriers to the use of TRTs in widespread clinical practice.

This article is an in-depth review of the presentations from the meeting. It is hoped that assembling and reporting this knowledge will accelerate the development of research programs and clinical trials to validate the efficacy and optimize the use of PSMA-TRTs for the treatment of advanced prostate cancer.

Overview of PSMA Biology

PSMA, is a type II transmembrane protein expressed on prostate cancer cells as well as a limited number of normal tissues. PSMA, also known as glutamate carboxypeptidase II (GCPII) or folate hydrolase 1 (FOLH1), is a metallo-enzyme that hydrolyzes poly-glutamated folate molecules and other proteins/peptides with carboxyterminated glutamates.

Neil Bander (Weill Cornell Medicine and NewYork-Presbyterian Hospital) presented a body of data credentialing PSMA as a target for prostate cancer. PSMA is the single most prostate-specific cell membrane antigen known, is present in ~90-95% of prostate cancer cases, and generally increases in expression during prostate cancer progression and following treatment with androgen deprivation therapy (ADT), including modern potent androgen receptor (AR)-targeting drugs abiraterone and enzalutamide. PSMA is rapidly internalized when engaged with an antibody or a ligand. These features have led to numerous investigations into the use of PSMA-targeted agents for the treatment and imaging of prostate cancer.

While normal prostate cells and prostate cancer cells express the highest levels of PSMA in the body, other cells express PSMA at lower levels, including the proximal tubules of the kidney, salivary glands (parotid and sub-mandibular), small bowel, and a subset of astrocytes. Additionally, PSMA is expressed in the neovasculature of a number of other solid malignancies including renal cell carcinoma.

PSMA is expressed in a highly polarized fashion on the luminal surface of prostate glands. Basement membrane, tight junctions, basal cell layers, and the blood brain barrier are thought to form barriers to the ability of systemic agents to target PSMA on luminal surfaces or in the brain, particularly with larger molecules such as antibodies. However, as invasive and metastatic prostate cancer have breached these

barriers, tissue penetration with PSMA-targeted agents is far more efficient in prostate cancer as opposed to normal tissues.

PSMA levels on prostate cancer cells are prognostic. Several studies, collectively representing several thousand cases, have reported that PSMA expression correlates with Gleason grade, disease recurrence, progression, and survival [4-9]. Prostate cancer aggressiveness is also associated with a negative correlation between PSMA expression and AR activity [10].

PSMA expression is negatively regulated by AR, but at the same time is tightly linked to AR expression. AR-positive prostate cancer cell lines (typically adenocarcinomas) universally express PSMA, whereas AR-negative lines, including AR-negative small cell or neuroendocrine prostate cancer (NEPC) are PSMA-negative. However, PSMA expression increases dramatically in the absence of androgens in AR-positive cell lines including AR-positive CRPC. In vitro and in animal models, the increase in PSMA levels seen under androgen-deprivation conditions do not peak until after two weeks. As such, PSMA-targeted antibody drug conjugates (ADC) have been found to synergize with ADT and enzalutamide in murine CRPC models [Bander et al., unpublished, [11]].

Another important property of PSMA that makes it amenable to therapeutic targeting, is constant cycling of the protein between the cell membrane and cytoplasm, which results in continuous internalization of cognate PSMA binders. This has been demonstrated with fluorescently-labeled PSMA-targeted J591 antibodies as well as small ligands, which can be observed entering the cytoplasm and localizing within lysosomes and sites adjacent to the nucleus [12, 13]. PSMA-targeting agents with a longer in vivo half-life are typically internalized to a greater degree.

The role for PSMA in prostate cancer is yet unclear. PSMA expression is tightly linked to prostate cancer in humans, suggesting that there may be a driving role. PSMA may provide a way to deliver increased folate to tumors, which may support faster cell growth [14]. However, circulating folate is not polyglutaminated, and should be able to enter the tumor independent of PSMA. Overall, convincing evidence that PSMA plays a functional role in prostate cancer development or progression is thus far lacking.

PSMA may simply be an epiphenomenon due to its relationship to AR expression and act as a barometer of AR activity. More studies are needed into the role of PSMA in prostate cancer.

Prostate Cancer as a Radiation-Sensitive Disease

The biology of prostate cancer metastases make them highly amenable to targeting with systemic radionuclide therapy. Prostate cancer metastases occur most commonly in the bone marrow and lymph nodes, where they grow as small-volume tumors that are readily accessible to both small and large molecule targeting agents. Prostate cancer can have a prolonged natural history, and micro-metastatic or recurrent disease can be detected by PSA increases months or years before the appearance of overt metastases on imaging. This lead time offers the potential to treat recurrent prostate cancer when tumors are microscopic in size and tumor burden is very limited. Prostate cancer is also radiation-sensitive and responds to treatment with external beam radiotherapy, brachytherapy, and radionuclides. The alpha particle-emitting calcium-mimetic ^{223}Ra has an overall survival benefit for the treatment of bone metastatic prostate cancer and was approved by the U.S. FDA in 2013 [15]. These studies, along with the initial clinical experiences with several hundreds of patients treated with various PSMA-targeted TRTs, support rationale for development of additional tumor-directed systemic TRTs for the treatment of metastatic prostate cancer.

PSMA-Targeted Radionuclides as PET Imaging Agents

The ability to detect prostate cancer earlier and with more accuracy has the potential to significantly improve patient management, treatment and outcomes. Martin Pomper (Johns Hopkins University) discussed positron emission tomography (PET) imaging using PSMA-targeted agents, which appear to have superior sensitivity and specificity for detecting prostate cancer compared with current standard imaging ($^{99\text{m}}\text{Tc}$ -methylene diphosphonate bone scintigraphy (bone scan) and computed tomography (CT)), and have emerged as a highly promising new prostate cancer molecular imaging technology [16].

PSMA-targeted PET imaging has also improved our understanding of PSMA expression and targeting in the body, and will likely be a critical imaging biomarker for PSMA-TRT.

PSMA-targeted PET agents have been developed using urea-based small molecule inhibitors of PSMA including N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-(18F-fluorobenzyl)-L-cysteine (¹⁸F-DCFBC) and the improved derivative ¹⁸F-DCFPyL [17-23], ⁶⁸Ga-PSMA-11 (aka HBED-CC) and ⁶⁸Ga/¹⁷⁷Lu-PSMA-617 [24, 25], as well as anti-PSMA antibodies such as ⁸⁹Zr-J591 [26]. ¹⁸F-DCFPyL is currently the PET imaging agent of choice among investigators at Johns Hopkins and this radiotracer has been comprehensively studied [21, 23]. The high standardized uptake values (SUV) of ¹⁸F-DCFPyL enable detection of metastatic prostate tumors with as few as 14 million cells, and up to four-fold more lesions than conventional imaging with CT plus bone scan [16, 27]. ⁶⁸Ga-PSMA PET/CT (PSMA-11, PSMA I&T, and others) has been extensively used for prostate cancer imaging, with an estimated 10,000 patients imaged worldwide. ⁶⁸Ga-PSMA-11 PET images are similar to those produced using ¹⁸F-DCFPyL, but by virtue of the ¹⁸F radioisotope, which has a shorter positron path range than ⁶⁸Ga, and the ability to administer higher amounts of radiopharmaceutical, ¹⁸F-DCFPyL can produce images with less background [28]. ⁸⁹Zr-J591 PET imaging has also been shown to detect tumors in early metastatic CRPC patients better than bone scan, CT, and ¹⁸F-fluorodeoxyglucose (FDG) PET combined [26]. Regardless of agent used (⁶⁸Ga-PSMA-11, ¹⁸F-DCFPyL or ⁸⁹Zr-J591, etc.), the results consistently show that PSMA PET out-performs any other prostate cancer imaging modality currently available. Two classification schemes for prostate cancer using PSMA-targeted PET imaging known as “PSMA-RADS version 1.0” and “PROMISE” have recently been published [29-31].

Studies are currently underway that aim to support approval by the U.S. FDA for a PSMA-targeted PET radioligand. The registrational phase II/III OSPREY trial (ClinicalTrials.gov Identifier NCT02981368) is evaluating the diagnostic performance of ¹⁸F-DCFPyL PET/CT relative to histopathology, for detecting prostate cancer in pelvic lymph nodes in patients with high risk localized prostate cancer undergoing radical prostatectomy with lymphadenectomy (cohort A), and in patients with evidence of local recurrence or metastatic disease willing to undergo biopsy (cohort B). Two additional phase II/III trials led by the SNMMI (Society of Nuclear Medicine and Molecular Imaging) Clinical Trials Network (CTN) are testing

⁶⁸Ga-PSMA-11 in intermediate to high-risk pre-prostatectomy patients and in patients with biochemical recurrence (ClinicalTrials.gov Identifiers NCT02919111, NCT02918357).

Further optimization of PSMA-targeted PET imaging requires understanding the degree and heterogeneity of radiotracer uptake in different lesions (discussed in more detail below). In addition, radiotracer localization to different tissues has different kinetics, which may necessitate further optimization of imaging timepoints. A study found that ¹⁸F-DCFPyL SUV levels in bone continued to markedly increase over time after the typical imaging time point of 60 minutes, suggesting that imaging at later times may result in additional positive findings [23].

PSMA-targeted agents continue to be studied pre-clinically for indications beyond PET imaging. Dual-modality PSMA-targeted ligands are being developed that support subsequent modification with a second imaging or therapeutic isotope [32]. PSMA-targeted contrast agents for magnetic resonance (MR)-based imaging and PSMA-targeted dextran agents for chemical exchange saturation transfer (CEST) imaging are also being studied [33, 34].

The Impact of PSMA-targeted PET Imaging on Management and Treatment of Prostate Cancer

PSMA-targeted PET detection of metastatic prostate tumors even at very low PSA levels will inevitably result in a migration of patients with rising PSA but “M0” (undetectable metastases by bone scan/CT) to M1 status. Under current NCCN guidelines, M0 patients with PSA values ≥ 0.2 ng/ml post-radical prostatectomy are stratified to receive either continued active surveillance, salvage external beam radiation, or ADT. However, earlier detection of metastases by PSMA-targeted PET could move treatment earlier as well as to add salvage pelvic lymph node dissection, stereotactic ablative radiation therapy (SABR), or even PSMA-TRT to these options. In the ongoing PCF-funded ORIOLE trial (ClinicalTrials.gov Identifier NCT02680587), ¹⁸F-DCFPyL PET/CT imaging is being used to identify patients with hormone-sensitive oligometastatic prostate cancer, who are randomized to receive SABR to all metastatic sites versus observation [35].

The use of PSMA-targeted PET imaging for clinical trials of new prostate cancer therapies will likely change the definition of objective responses. A number of studies are now evaluating the impact of PSMA-targeted PET imaging for evaluating treatment responses in various settings.

Whether PSMA-targeted PET will direct appropriate changes in patient management is a critical question. In a study of 70 patients experiencing biochemical recurrence post-prostatectomy, ^{68}Ga -PSMA-11 PET/CT imaging was found to change patient management in 29% of cases [36]. In another study, ^{68}Ga -PSMA PET/CT changed radiotherapy planning in patients in both the primary staging and biochemical recurrence settings, particularly in favor of stereotactic body radiation therapy (SBRT) over radiation to the prostate bed [37]. ^{68}Ga -PSMA-11 PET/CT was also found to result in actually implemented management changes in more than 50% of prostate cancer patients with biochemical recurrence [38]. ^{68}Ga -PSMA-11 PET/CT also implies a major impact on salvage radiotherapy planning in 19% of prostate cancer patients with early biochemical recurrence (PSA < 1.0 ng/mL) [39]. A randomized clinical trial comparing the accuracy of ^{68}Ga -PSMA PET/CT imaging versus CT plus bone scan for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy is being conducted in Australia (ACTRN12617000005358).

In a meta-analysis of four independent studies, ^{68}Ga -PSMA-11 PET/CT was found to have a specificity of 98% for pre-operative staging of prostate cancer, and a sensitivity of only 61%. The same analysis also found that ^{18}F -DCFPyL PET/CT had a specificity of 89% and sensitivity of 71% for preoperatively detecting pelvic lymph node metastases [40]. These data suggest that there are many sites of disease being missed with PSMA-targeted PET imaging. Larger and more definitive studies on the sensitivity and specificity of PSMA-targeted PET imaging are needed. Also, understanding how to leverage positive and negative findings on PSMA-targeted PET could be highly informative in patient management.

Michael Gorin (Johns Hopkins University) discussed applications of PSMA-targeted imaging for patients with localized prostate cancer. Such applications include improving prostate cancer screening and staging, aiding in selection of patients for active surveillance, surgical guidance, and focal therapy planning. An ongoing phase II trial at Johns Hopkins aims to evaluate the performance of ^{18}F -DCFPyL PET/CT for the detection of clinically significant prostate cancer in men undergoing a prostate biopsy

following PSA screening (ClinicalTrials.gov Identifier NCT03471650). Patients on this trial will undergo a standard 12-core biopsy plus additional biopsies of ^{18}F -DCFPyL-avid sites. Another trial aims to examine the ability of the PSMA-targeted SPECT agent $^{99\text{m}}\text{Tc}$ -MIP-1404 to identify active surveillance candidates amongst men with low-risk prostate cancer electing prostatectomy (Clinical Trials.gov Identifier NCT02615067). It will be critical to determine whether PSMA-targeted PET imaging can be used to stratify patients who should and should not receive local therapy.

Whether PSMA-targeted imaging can be used to guide surgery is also being explored. Studies have evaluated the use of near-infrared or fluorescently-tagged PSMA-targeted agents for surgical guidance in animal models [41, 42]. Additionally, Maurer and coworkers have demonstrated the feasibility of using a handheld gamma probe to intraoperatively detect disease-involved lymph nodes that have taken up an ^{111}In -labeled PSMA-targeted radioligand [43]. Efforts are also underway to overlay ^{18}F -DCFPyL PET data on the intraoperative view during robotic radical prostatectomy [Gorin and Stoianovici, unpublished].

Tumor Heterogeneity of PSMA Expression: What does it mean for PSMA-Targeted Therapy and Imaging?

Despite reports that PSMA is expressed on 90-95% of prostate cancer cases, PSMA can be heterogeneously expressed as a function of AR signaling and other mechanisms within a single individual. PSMA expression is suppressed by AR signaling and increases following treatment with AR-targeted therapy in both castration-sensitive and castration-resistant disease [Bander et al., unpublished, [44]]. The therapeutic and imaging-based implications of intra-patient and inter-patient heterogeneity of PSMA expression remain poorly understood. A discussion was led by Michael Morris (Memorial Sloan Kettering Cancer Center (MSK)) on this topic.

PSMA heterogeneity has been described at both the lesion and circulating tumor cell (CTC) level. For example, detection of putative prostate metastases with PSMA-targeted PET imaging versus ^{18}F -FDG PET imaging was found to be discordant, with some lesions detected by one method but not the other [Hofman et al., ESMO 2017]. PSMA heterogeneity observed upon PET imaging may also be a product of

differential tracer uptake into different tissue sites. For instance, ^{89}Zr -J591 PET imaging was found to be far more sensitive and accurate for imaging bone lesions (mean SUV 8.9) compared with soft tissue lesions (mean SUV 4.8) [26]. In a study that examined PSMA expression in prostate cancer CTCs, 43% of CRPC patients with enumerable CTCs (all but one of whom had tumor on PSMA-targeted PET imaging) were found to have both PSMA-positive and PSMA-negative CTCs [Morris et al., ESMO 2017]. These studies suggest that multi-modality methods may be necessary to assess complete tumor burden and determine the presence of residual disease.

PSMA heterogeneity also has implications for treatment responses and patient outcomes. A study comparing ^{18}F -FDG PET versus ^{18}F -dihydrotestosterone (^{18}F -DHT) PET (which detects AR expression) for the detection of lesions in mCRPC patients who had not yet been treated with enzalutamide or abiraterone, found that patients with predominantly discordant lesions had worse overall survival than patients with predominantly concordant lesions [45]. Patients with at least one ^{18}F -FDG-positive / ^{18}F -DHT-negative lesion had the worst outcomes, suggesting this phenotype represents metabolically active lesions resistant to AR-targeted treatment [45]. PCF recently funded Morris and team to examine tumor heterogeneity and the clinical utility of ^{18}F -PSMA and ^{18}F -DHT PET imaging in prostate cancer.

Overall, PSMA heterogeneity can be described by lesion, disease site (CTCs vs. soft tissue vs. bone), intensity, disease activity, and AR signaling. PSMA-targeted PET imaging will likely serve as a predictive biomarker for response to PSMA-targeted treatments. However, the role of PSMA heterogeneity as a predictive or prognostic biomarker, the extent of PSMA imaging necessary to benefit clinically from PSMA-targeted treatment, and whether or not PSMA-targeted (or other) treatment should be discontinued if PSMA becomes undetectable by imaging are unknown. Also, because PSMA is more uniformly expressed in pre-abiraterone/enzalutamide-treated disease and may be lost in AR-negative CRPC, whether PSMA-targeted therapy should be sequenced prior to these treatments deserves consideration. While heterogeneity in PSMA expression is anticipated in post-abiraterone or enzalutamide treated tumors, studies are needed to assess PSMA heterogeneity in tumors prior to these treatments. How to best detect PSMA heterogeneity is also of question (inclusion of other imaging modalities vs. serum assays). Defining which tools are needed to screen patients for eligibility for PSMA-TRT is critical.

Optimization of PSMA-Targeted Radionuclide Agents

Selection of PSMA-Delivery Molecule: Protein, Peptide, Chemical, Other?

Neil Bander discussed rationale for selecting optimal PSMA-delivery molecules for radionuclide therapy. There are at least two general types of PSMA-targeting agents in development: antibodies and small molecules. Several critical differences exist between these agents, including binding sites on PSMA, pharmacokinetics (PK), and bio-distribution. How these differences impact efficacy and toxicity was discussed.

PSMA-targeted antibodies and small molecules bind to different regions of PSMA. PSMA-targeted small molecules developed thus far are all based on the same basic glutamate-urea-lysine moiety that binds the enzymatic pocket of PSMA, but differ in the linkers and chelators used (Figure 1) [46]. The J591 antibody binds a site that has been mapped to the apical region of the extracellular domain of PSMA which is distant from the enzymatic pocket [2, 47, 48]. Simultaneous administration of anti-PSMA small molecules and antibodies are non-competitive and dual administration leads to additive targeting [Bander et al., unpublished].

Antibody mass is in the range of 150kD compared with ~1.4kD for PSMA-targeted peptides/small molecules. Antibodies have a significantly longer in vivo half-life of 3-7 days (or more) compared with ~3 hours for the peptides. This difference in PK is partially a function of size, as small molecules are quickly excreted through the kidney and bladder, while antibodies are too large for glomerular filtration and are able to recirculate for a much longer time. While small molecules have the advantage of rapid biodistribution in the body, including tumor, this is offset by their rapid excretion. Conversely, antibodies penetrate tissues much more slowly than small molecules but this slower penetration is compensated for by the significantly longer residence time of antibodies in the body. Several analyses have demonstrated that antibodies have superior and more uniform tumor uptake compared to small molecules, due to an improved balance between in vivo half-life and vascular and tissue penetration kinetics [49-51]. Whether radiolabeled PSMA-targeted antibodies or small molecules will ultimately have better anti-tumor efficacy remains to be determined.

Differences in size impact the bio-distribution of PSMA-targeted agents. PET imaging has demonstrated that uptake of PSMA-targeted small molecules occurs not only in tumor, but in the kidney, bladder, spleen, GI tract and salivary and lacrimal glands. In contrast, PET imaging with ^{89}Zr -J591 antibody has demonstrated uptake of the antibody in tumor with excretion primarily by the liver, minimal uptake in the urinary tract and no uptake in the salivary or lacrimal glands.

Differences in bio-distribution have translated into differences in adverse events observed with PSMA-TRTs. The primary dose-limiting adverse event following treatment with ^{177}Lu -J591 (as well as other radiolabeled antibodies) is myelosuppression [52-54] as a result of the long circulation time during which the marrow receives 'bystander' radiation. The most common related adverse event following treatment with small molecule-targeted PSMA-TRTs is xerostomia (dry mouth) due to salivary gland targeting, although the severity of xerostomia is far greater with ^{225}Ac -PSMA-617 than ^{177}Lu -PSMA-617, demonstrating the far greater potency of alpha-particle versus beta-particle labeled agents [[3, 55], [Hofman, ESMO 2017]]. Alpha-particle-labeled PSMA-targeted antibodies are not anticipated to result in xerostomia, based on lack of salivary gland uptake with ^{89}Zr -J591 PET imaging. Toxicity-reduction strategies need to be further studied and optimized (both dose and timing) for both antibody and small molecule-based PSMA-TRTs. The absolute safety of the small molecule-targeting PSMA-TRTs will require the results of careful, randomized clinical trials that are ongoing.

Overall, both antibody and small molecule-based PSMA-TRTs have demonstrated significant anti-tumor efficacy [52-73], though it remains to be determined which agent offers the best balance between efficacy and toxicity. A favorable balance between toxicity and efficacy might be achieved by using beta particle-labeled small molecules or alpha particle-labeled antibodies. Phase I and II ^{177}Lu -PSMA-617 (ClinicalTrials.gov Identifiers NCT03042468, NCT03042312) and phase I ^{225}Ac -J591 (ClinicalTrials.gov Identifier NCT03276572) trials are underway. The Australian phase II ^{177}Lu -PSMA-617 trial (ACTRN12615000912583) has recently been completed [Hofman et al., Lancet Oncology, in press] and is discussed in more detail below.

The differences in bio-distribution and toxicity of antibodies versus small molecules combined with their ability to target different regions of PSMA leave open room for combination treatment strategies. As relatively small increases in dose have been shown to translate into a significant therapeutic benefit, it may be efficacious to combine these targeting modalities to increase targeting of PSMA, without increased toxicity. As discussed in more detail below, a phase I trial is being initiated at Weill Cornell Medicine/ NewYork-Presbyterian Hospital to test the combination of ^{177}Lu -J591 plus ^{177}Lu -PSMA-617.

Isotope Selection

Identification of the optimal PSMA-targeted radionuclide for treatment of prostate cancer requires consideration of safety, efficacy and feasibility characteristics of different isotopes, as discussed by William Goeckeler (Bayer Pharmaceuticals). Radioactive isotopes can be generally divided into those that primarily emit alpha particles and those that primarily emit beta particles. Both types of isotopes are capable of delivering a high localized dose of radiation to tumors.

Alpha decay is the emission of a helium nucleus (two neutrons and two protons) from the nucleus of the isotope. Alpha decay is associated with atomic nuclei that are too large and thus is restricted to a relatively small number of heavy elements with high mass numbers. Beta decay occurs in neutron-rich isotopes from the decay of a neutron into a proton plus a high energy electron which is emitted as a beta particle. Alpha particles are ~8,000 times larger than beta particles and carry significantly more energy (5-8 MeV vs. 0.1-1 MeV). Alpha particles have much shorter ranges (50-80 μm) than beta particles (2-4 mm), and release a significantly higher amount of energy over a far shorter track. Thus, alpha emitters are more cytotoxic than beta emitters per unit dose of radiation, and therapeutic doses of radiation can be achieved with lower levels of uptake. However, the longer range of beta particles may help to overcome poor or heterogeneous uptake of targeting molecules within tumors.

Alpha emitters with therapeutic value include ^{225}Ac and ^{227}Th . They decay through a series of four and five alpha emissions, respectively, plus two beta emissions, and transmit about 97% of their energy through alpha particle emissions. There are a larger number of beta emitters suitable for radiotherapy,

with a wider variety of decay properties. Though earlier studies focused on ^{131}I and ^{90}Y , ^{177}Lu is the current beta-emitting isotope of choice for PSMA-targeted and other cancer therapeutic applications as it has more favorable emission properties, production feasibility, and radiation safety issues than ^{131}I and ^{90}Y .

It is critical to understand the decay chain of the isotope, as toxicity and clinical utility depend on the half-life and emission type of the “daughters,” the timing of the decay of each daughter relative to its bio-distribution, and radio-sensitivity of the organs and tissues involved [74]. Alpha decay results in a recoil of ~70 keV on the isotope nucleus, which can break chemical bonds (typically 5-10 eV) and detach the isotope nucleus from the targeting molecule. Thus, the pharmacokinetics of various isotopes need to be considered to maximize the number of on-target decays and minimize the number of decays that occur in normal tissue. ^{225}Ac and ^{227}Th both have a series of alpha-emitting daughters which can result in exposure of tissues to radioactivity if the isotope becomes detached from the targeting molecule and redistributed. The first daughter produced by decay of ^{227}Th is ^{223}Ra , which has a half-life of 11.4 days and could lead to additional organ exposure if redistributed (the other decays occur relatively quickly). However, the extent to which ^{223}Ra produced by ^{227}Th decay and redistributing to bone would result in toxicity to bone marrow or contribute a therapeutic effect on prostate cancer bone metastases remains to be determined. The first two decays of ^{225}Ac occur relatively quickly, while the third decay has a half-life of ~45 minutes and if dissociated from the targeting molecule at this step, could expose other tissues if the subsequent daughter radionuclides are redistributed [75].

Feasibility of production is also an important consideration for selecting a therapeutic isotope that can be effectively scaled and distributed to medical centers. ^{227}Th is produced commercially through neutron radiation of ^{226}Ra . ^{225}Ac can potentially be obtained commercially through a number of routes including through irradiation of ^{226}Ra or from the alpha decay of ^{229}Th , which can be obtained in research quantities from decay of ^{233}U . ^{177}Lu is routinely produced in high yield by direct neutron radiation of ^{176}Lu . This method also results in the co-production of low levels of the long-lived (160 day) beta- and gamma-emitting $^{177\text{m}}\text{Lu}$. It is also possible to produce ^{177}Lu through neutron irradiation of ^{176}Yb to form ^{177}Yb followed by beta decay (1.9 hour half-life) to ^{177}Lu . This method requires the subsequent chemical

separation of the ^{177}Lu from the target ^{176}Yb , but the resulting ^{177}Lu has very high specific activity and is free from the long-lived $^{177\text{m}}\text{Lu}$ impurity [76]. Labeling chemistry has been developed to efficiently and stably conjugate ^{177}Lu to targeting molecules. Labeling of targeting molecules with ^{225}Ac and ^{227}Th is more challenging but has been successfully established using DOTA and HOPO chelators, respectively.

Clinical Experiences with PSMA-Targeted Radionuclides

Radiolabeled PSMA-Targeted J591 Antibody for the Treatment of Prostate Cancer

Neil Bander (Weill Cornell Medicine and NewYork-Presbyterian Hospital) discussed the experience at Weill Cornell Medicine with clinical trials testing PSMA-targeted J591 antibody-based radionuclides for prostate cancer treatment.

J591 is a humanized anti-PSMA antibody developed by Bander and colleagues [1, 2, 12, 77, 78]. At Weill Cornell Medicine and/or MSK, 16 clinical trials (four of which are still active) have been conducted to test J591, J591-TRTs and J591-ADCs as single agent or combination therapies in prostate and other cancers. J591 has some antibody dependent cell-mediated toxicity (ADCC) activity, and some responses were seen in a trial testing unconjugated J591 in combination with IL-2 [68].

Early J591-ADC trials (2002-2005) were plagued by poor drug-linker technology in which the cytotoxic drug was found to detach from the antibody rapidly in patients [79]. A current version with new pharmacology, a new cytotoxic drug, and a new linker is now in a multi-national phase I trial (ClinicalTrials.gov Identifier NCT02991911).

Thirteen radionuclide trials testing J591 conjugated to various radioisotopes including ^{90}Y , ^{111}In , ^{177}Lu , and ^{225}Ac have been conducted or are ongoing. As PSMA is also highly expressed on tumor neovasculature of many cancer types, two non-prostate trials tested ^{111}In -J591 and confirmed tumor localization [80, 81]. An ongoing multicenter randomized trial is testing ketoconazole plus ^{177}Lu -J591 in M0 CRPC (ClinicalTrials.gov Identifier NCT00859781) to see if it can delay the onset of radiographic metastatic disease. A phase I trial testing ^{225}Ac -J591 is underway (ClinicalTrials.gov Identifier NCT03276572).

Approximately 400 patients with progressing mCRPC have been treated with J591-TRT in these trials, none of whom were selected based on PSMA expression. PSMA imaging and bone scans were conducted in ~200 of these patients, 90% of whom showed J591 successfully targeted all tumor sites detected in bone scans. The primary toxicity observed following J591-TRT is transient platelet and white blood cell declines as a result of bystander marrow radiation as the radiolabeled antibody circulates. No symptomatic or serious non-hematologic toxicities have been observed.

In a phase II trial testing single dose ^{177}Lu -J591 in progressing mCRPC, because of paucity of data with these agents, the U.S. FDA requested starting the dose at a slightly lower level (65 mCi/m^2) than the maximum tolerated dose (MTD) determined in the phase I trial (70 mCi/m^2). This resulted in a two-stage trial, first testing 65 mCi/m^2 in 15 patients, followed by the 70 mCi/m^2 dose in 32 patients [54]. Importantly, this trial found a significant increase in response with just a small increase in dose; median overall survival (mOS) was 11.9 months with 65 mCi/m^2 versus 21.8 months with 70 mCi/m^2 [54]. PSA declines were also more common with the higher versus lower dose (46.9% vs. 13.3% for $\geq 30\%$ PSA decline; 65.5% vs. 46.7% for any PSA decline) [54]. In patients with measurable disease, radiographic responses were also more frequent and pronounced in the higher dose cohort. This suggests that the doses tested in this trial lie along a steep region in the dose-response curve, and that even higher doses would have a greater therapeutic effect, could they be made tolerable. Imaging of ^{177}Lu -J591 targeting in these patients found that 44 of 47 patients (94%) had accurate targeting of known sites of disease. However, the intensity of uptake varied between patients and appeared to correlate with response. Patients with the lowest quartile of PSMA uptake on ^{177}Lu -J591 or ^{111}In -J591 imaging had a lower likelihood of PSA decline. Overall, this trial demonstrated that single dose ^{177}Lu -J591 is well-tolerated, with predictable, reversible myelosuppression, and accurately targets known sites of metastatic disease. An apparent dose-response relationship exists, with increased PSA responses and survival seen at the phase I MTD compared with the slightly lower dose. Those with poor ^{177}Lu -J591 or ^{111}In -J591 planar/SPECT imaging by semi-quantitative assessment had less likelihood of response.

In the initial phase I ^{177}Lu -J591 study, several patients who responded to treatment but later progressed were given additional doses of ^{177}Lu -J591. In these patients, a lower response was seen to the later

dosing compared with the initial dose. This suggests that tumors that remain following PSMA-TRT were more treatment resistant, potentially due to selection of cells with lower PSMA expression and/or greater radio-resistance, and that in general, sub-maximal doses given with long intervals between doses are more likely to clone resistant cells and be less effective.

To increase the effective dose given within a short time frame without increasing toxicity, a phase I dose escalation trial tested fractionated doses of ^{177}Lu -J591 (ClinicalTrials.gov Identifier NCT00538668) in 49 patients. A dose-response was observed with more PSA declines and longer survival (87.5% PSA decline, 58.8% >30% decline, 29.4% >50% decline). Fourteen of 17 patients (82%) with detectable CTC counts experienced CTC declines. As in the single-dose phase II study, less intense PSMA imaging was associated with poorer responses. Median OS was 43.9 months in patients who received the recommended phase II dose, versus 15.3 months in patients who received lower doses [72].

This fractionated dose schedule was further built upon by combining with docetaxel (ClinicalTrials.gov Identifier NCT00916123), the only standard of care for mCRPC at the time. Patients were treated with standard dose docetaxel (75mg/m²) plus two fractionated doses of ^{177}Lu -J591 given two weeks apart to cohorts of 3-6 patients, starting at 20 mCi/m², and escalating in 5 mCi/m² increments to a maximum of 45 mCi/m². The primary endpoints in this trial were toxicity, and determinations of the MTD and the recommended phase II dose. Of the 15 patients entered, 11 (73%) had $\geq 50\%$ PSA decline, and 12/15 (80%) had $\geq 30\%$ PSA decline. Of five patients with measurable disease, there were three partial responses (PR), one with stable disease (SD), and one with progressive disease (PD) by RECIST criteria. This study showed that combining fractionated-dose ^{177}Lu -J591 + docetaxel is tolerable, feasible, and that both agents can be given in combination at their full dose. In addition, the combination appears to have significant anti-tumor activity [Tagawa et al., manuscript in preparation, [73]].

Collectively, these trials demonstrated that J591-TRT can successfully target metastatic CRPC in ~90% of unselected mCRPC patients. Higher doses are associated with improved efficacy but also dose-limiting toxicities, particularly reversible myelosuppression. Fractionated dosing allows a higher cumulative dose and better responses while avoiding dose-limiting marrow toxicity. Several current and planned trials at Weill Cornell Medicine were discussed in more detail by Scott Tagawa (below).

The German Experience from the THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging at Zentralklinik Bad Berka

Richard Baum (THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging) discussed the experience at the ENETS Center of Excellence at Zentralklinik Bad Berka, Germany, with TRT for prostate cancer. Over the past 20 years, almost 1,500 patients with primarily somatostatin receptor-positive neuroendocrine tumors have been treated with over 5,300 therapy cycles of various ^{177}Lu -, ^{90}Y -, and ^{213}Bi -labeled radiopharmaceuticals (mostly with somatostatin-targeting DOTATATE or DOTATOC peptides).

The center was also the first worldwide to treat prostate cancer patients with any ^{177}Lu -labeled PSMA-targeted small molecule (PSMA-I&T provided by Prof. H.J. Wester, TU Munich) in 2013, and has treated 224 patients with over 649 cycles using both ^{177}Lu -PSMA-I&T as well as ^{177}Lu -PSMA-617 (both referred to here as ^{177}Lu -PSMA) as of September 2017. On average, 6.51 GBq were delivered per cycle (range 1-12 GBq), typically starting with a high dose in the first cycle (~9 GBq), followed by reduced doses. Most patients received 3-4 cycles, with an interval of 6-8 weeks between cycles, with some patients receiving up to 11 cycles. Patients tended to be heavily pre-treated, and all had progressive disease at the time of treatment initiation. Patients treated had been referred to the center for PSMA-TRT, and were deemed eligible for treatment following confirmation of target expression with ^{68}Ga -PSMA PET/CT imaging. Pre-treatment ^{68}Ga -PSMA PET/CT imaging revealed most patients had bone and/or lymph node metastases. Post-treatment, ^{177}Lu -PSMA SPECT/CT was performed to examine PSMA-TRT uptake at disease sites. Patients were then monitored with PSA and clinical indicators for progression, and were re-staged with PSMA PET/CT before administration of additional cycles. The treatment was discontinued if PSMA expression disappeared after successful treatment (therapy response as defined by molecular imaging).

Overall, any PSA decline was observed in 157 of 224 patients (70%) treated with ^{177}Lu -PSMA and $\geq 50\%$ PSA reductions were observed in 121 of 224 patients (54%). Median radiographic progression (using CT) was 18 months and mOS was 27 months. ^{68}Ga -PSMA PET/CT was used to monitor ^{177}Lu -PSMA-treated patients ($n = 200$) for best molecular therapy response based on the European Organization for Research and Treatment of Cancer (EORTC) criteria [82]. With a mean follow up of 16 months (range: 3-55

months), 33% of patients had a partial response, 28% had stable disease, and 34% had progressive disease. Nine of the 200 patients (4.5%) exhibited a complete molecular remission. Cases of exceptional responses to ^{177}Lu -PSMA-617 were presented. For example, one patient with PSA of 45 ng/ml and widespread metastatic disease went into complete PSA and radiographic remission after treatment with two cycles of ^{177}Lu -PSMA-617.

No nephrotoxicity or hepatotoxicity has been observed with ^{177}Lu -PSMA treatment in this series of patients and only very few cases ($n = 5$; 2.2 %) of grade 3-4 hematological toxicity (especially associated with extensive bone marrow involvement or after extensive chemotherapy), with follow-up of up to four years in some patients. No evidence of significant or severe xerostomia was observed.

Chemotherapy-naïve patients had better mOS with ^{177}Lu -PSMA compared to patients who had previously received chemotherapy (38 months vs. 19 months) [Kulkarni et al., submitted]. Previous or concomitant treatment with abiraterone or enzalutamide was associated with improved mOS (40 months vs. 19 months), suggesting these treatments may synergize with ^{177}Lu -PSMA. mOS has not yet been reached at 55 months in 18 patients who were initially diagnosed with metastatic prostate cancer and received ^{177}Lu -PSMA as first line treatment before commencement of any hormone therapy or chemotherapy. These results have implications for optimizing, sequencing and designing combinations treatments using ^{177}Lu -PSMA, however these hypotheses need to be tested in randomized clinical trials. Whether the immune system plays a role in driving response to ^{177}Lu -PSMA treatment is also an important question. Future studies should address the role of the immune system in responses to ^{177}Lu -PSMA treatment and the potential for combination treatment with immunotherapies.

The German center has also tested the use of alpha particle-emitting ^{213}Bi -PSMA-617 in 10 patients, and only minor responses or no responses were seen (most likely due to underdosing of ^{213}Bi), although complete remissions with this treatment have been reported in some cases in Pretoria, South Africa [83]. ^{225}Ac is more likely to be the alpha-emitting isotope of choice for PSMA-targeted radioligand therapy, based on successes in Heidelberg, Germany, where over 100 patients have been treated thus far.

Studies are underway to evaluate strategies to avoid xerostomia associated with PSMA-TRT, particularly with ^{225}Ac -PSMA-617. Baum and colleagues found that injection of salivary glands with botulinum toxin resulted in a 60% decrease in uptake on ^{68}Ga -PSMA-11 PET/CT imaging [84]. More studies into the mechanisms and efficacy of botulinum toxin and other strategies to reduce xerostomia are needed.

Results from the Australian Phase II Theranostic ^{177}Lu -PSMA-617 Trial

Scott Williams (Peter MacCallum Cancer Centre, Australia) discussed results from a phase II clinical trial conducted at the Peter MacCallum Cancer Centre, Australia, testing efficacy, safety, and quality of life of patients with mCRPC treated with ^{177}Lu -PSMA-617 (ACTRN12615000912583). Results from this trial were first presented publicly at the 2017 ESMO Meeting [Hofman et al., *Lancet Oncology*, in press]. Patients in this trial were pre-screened with both ^{68}Ga -PSMA-11 and ^{18}F -FDG PET. To be eligible, patients were required to have both high PSMA expression ($\text{SUV}_{\text{tumor}} > 1.5 \times \text{SUV}_{\text{liver}}$) and an absence of metastatic lesions that were ^{18}F -FDG-avid with corresponding low ^{68}Ga -PSMA-11 expression.

Of 43 patients assessed, 13 were not eligible (7 were rejected due to discordance between PSMA and FDG PET imaging findings), while 30 were treated with up to 4 cycles of ^{177}Lu -PSMA-617 (mean dose 7.5 GBq). At 12 weeks following the first dose, 50% experienced a PSA decline of $\geq 50\%$ and 27% experienced a PSA decline $> 80\%$. Of best PSA responses, 57% experienced a PSA decline of $\geq 50\%$ and 43% experienced a PSA decline $> 80\%$. Median progression-free survival (PFS) was 6.3 months and mOS was 12.7 months in these patients. A case of an exceptional response was presented, in which a patient with widespread mCRPC on ^{68}Ga -PSMA-11 PET/CT and PSA of 967 ng/ml had a complete radiographic response and PSA drop of 99% to 7 ng/ml at 3 months post-treatment with ^{177}Lu -PSMA-617.

Patients were assessed for adverse events that occurred within 12 weeks after the last injection of ^{177}Lu -PSMA-617, or more than 12 weeks if determined to be related to ^{177}Lu -PSMA-617. Pre-treatment hematotoxicity was observed in most patients. Grade 3/4 hematological events associated with ^{177}Lu -PSMA-617 included transient and self-limiting declines in hemoglobin (7%), neutrophils (7%), and platelets (13%). No grade 3/4 non-hematological toxicities were observed. Grade 1/2 non-hematological

events experienced included xerostomia (63%), nausea (50%), vomiting (20%), fatigue (17%), dry eyes (7%), anorexia (7%), and bone pain (7%). No infusion-related reactions or renal toxicity were observed.

Patients were imaged with SPECT/CT after the first cycle of ^{177}Lu -PSMA-617 to evaluate tissue targeting dosimetry. This revealed that uptake of ^{177}Lu -PSMA-617 was significantly higher at tumor sites (mean 47.98 Gy) compared with other normal tissues including parotid (mean 3.95 Gy), kidneys (mean 3.12 Gy), bone marrow (mean 0.80 Gy) and spleen (mean 0.52 Gy).

Overall, these results demonstrate that ^{177}Lu -PSMA-617 can have significant activity in mCPRC with manageable toxicity, and represents a promising new therapeutic option for mCRPC. Results from longer follow-up on this trial are highly anticipated. Williams, Hofman and colleagues have subsequently initiated a national randomized phase II trial to compare the efficacy of ^{177}Lu -PSMA-617 versus cabazitaxel as second-line therapy in 200 mCRPC patients eligible for cabazitaxel (ANZUP protocol 1603; ClinicalTrials.gov Identifier NCT03392428).

Because radiation therapy is known to induce anti-tumor immune responses, Williams and colleagues are also initiating a phase Ib clinical trial testing the safety of ^{177}Lu -PSMA-617 in combination with the checkpoint inhibitor pembrolizumab. Correlative studies are also being performed in conjunction with this trial to identify mechanism of action and develop predictive biomarkers of response and resistance.

Session on Three PCF-Funded Challenge Awards

Based on promising anecdotal reports of the efficacy and potential for deep and long-term remissions observed in mCRPC patients treated with PSMA-TRT, in 2017 the PCF prioritized funding high impact investigations into these treatments. Following rigorous peer-review of applications, three research teams were ultimately selected to receive \$1 million PCF Challenge Awards to perform definitive studies into the biology, optimal use, efficacy, and potential treatment combinations for PSMA-TRT [85]. Representatives from each of these teams presented on their prior experiences with PSMA-TRT and the proposed studies that received support from PCF.

Optimization of PSMA-Targeted Radiation at Weill Cornell Medicine

Scott Tagawa (Weill Cornell Medicine) discussed clinical trials and correlative studies that have been initiated at Weill Cornell Medicine/NewYork-Presbyterian Hospital, in part through support by PCF, with the goal of optimizing the dose and schedule of PSMA-TRT. Three clinical trials are being conducted based on rationale that higher therapeutic efficacy can be achieved with lower toxicity by dose fractionation and/or by combining radiolabeled PSMA-targeted antibody and small molecule-based TRT.

Building upon the results of dose-fractionated ^{177}Lu -J591 and to decrease the likelihood of resistance due to repopulation, a phase I trial has been initiated to test a single cycle of fractionated dose ^{177}Lu -PSMA-617 in men with progressive mCRPC who have previously received second generation AR-targeted therapy (ClinicalTrials.gov Identifier NCT03042468). Standard bone scan and CT along with ^{68}Ga -PSMA-11 PET imaging is performed at baseline and used to monitor tumor burden in patients after treatment. The starting dose of ^{177}Lu -PSMA-617 was 200 mCi (7.4 GBq) divided over two doses, two weeks apart, escalating up to 600 mCi (22.2 GBq). The primary endpoint is to define dose limiting toxicity and MTD. Multiple secondary and exploratory endpoints are included, including biochemical and radiographic PFS, and OS. Correlative studies include identification of tumor mutations and immune parameters that correlate with response and outcomes. This study opened in January 2017, and as of November 2017 was dosing the fourth cohort (500 mCi) with no dose-limiting toxicity yet observed. Once the MTD is established, the trial will transition to phase II and open at multiple centers, and additional funding will be sought.

An anecdotal case from the first cohort of this trial was presented, in which a 73 year old patient with mCRPC who had previously progressed after prostatectomy, salvage radiation, ADT, Sipuleucel-T, abiraterone, enzalutamide, ^{223}Ra , and docetaxel, received 2 doses of ^{177}Lu -PSMA-617 (100 mCi each). The patient experienced a >50% PSA decline which was maintained for over 20 weeks with only low-grade adverse events. However, biochemical progression occurred at 6 months, followed by radiographic progression. Further results from this trial are awaited.

As discussed in detail by Bander (above), PSMA-targeted antibodies and small molecules target different sites of PSMA and have different normal organ exposure. Bander showed, in a pre-clinical study, that combined targeting of radiolabeled J591 and PSMA-617 was non-competitive and resulted in an additive dose to the tumor [Bander et al., unpublished]. These properties suggest that combining these treatments may enable higher therapeutic dose to tumors without increased toxicity. To test this hypothesis, a phase I dose escalation trial is being initiated to test fractionated dose ^{177}Lu -PSMA-617 plus ^{177}Lu -J591 in mCRPC. Patients on this trial will receive a fixed fractionated dose of ^{177}Lu -J591 (two doses, two weeks apart) with escalating concurrent doses of ^{177}Lu -PSMA-617. This trial is anticipated to open in mid-2018.

^{225}Ac -PSMA-617 has been shown in case reports to have significant potential for clinical activity, but also can result in severe xerostomia [3, 86]. Tagawa and team hypothesize that because antibodies typically have lower penetration of off-target tissues compared with small molecules and no detectable targeting of salivary glands, either pairing beta-emitters to PSMA-targeting small molecules or pairing alpha-emitters to PSMA-targeting antibodies may achieve high efficacy with reduced toxicity. Thus, in addition to trials testing ^{177}Lu -PSMA-617, a phase I dose escalation trial testing ^{225}Ac -J591 was initiated in men with progressive mCRPC (ClinicalTrials.gov Identifier NCT03276572). Doses started at 0.36 μCi (13.3 KBq)/Kg, and will escalate up to a maximum of 2.52 μCi (93.3 KBq)/Kg or until the MTD is determined. The trial will include genomic, clinical, imaging, and immune response endpoints and correlative studies. The first patient on this trial was treated in October 2017.

Overall, in addition to determining optimal dosing, schedules, and combinations of PSMA-TRT, these studies aim to prospectively and retrospectively assess the optimal patient population and identify candidate biomarkers to select patients to receive these treatments. These studies will lend significant insight into optimal isotope-targeting agent combinations that can achieve high efficacy without significant toxicity.

University of California, Los Angeles (UCLA) Study to Elucidate Mechanisms of Effectiveness and Resistance to ^{177}Lu -PSMA-617

There is a critical need to better identify which patients will and will not respond to PSMA-TRT and elucidate the underlying biology. Wolfgang Fendler (UCLA) discussed PCF-supported studies being conducted at UCLA under the leadership of Johannes Czernin, to test the efficacy of ^{177}Lu -PSMA-617, understand the biology of treatment responses and resistance, and develop biomarkers to stratify patients that will vs. won't respond to this treatment.

PSMA expression levels are hypothesized to effect the efficacy of PSMA-TRT and may act as a biomarker to identify patients likely to benefit from this treatment. With support from PCF, Czernin and colleagues are developing mouse models to study the efficacy of PSMA-TRT in prostate cancers with different levels of PSMA expression. The level of PSMA protein expression will be determined using quantitative flow cytometry and correlated with therapeutic responses to PSMA-TRT and intensity of PSMA-targeted PET imaging scans. Tumor tissue will be obtained from mice treated with PSMA-TRT to identify possible mechanisms of resistance.

A phase II clinical trial (RESIST-PC) is being conducted to compare the efficacy and safety of two different dose regimens (24 vs. 30 GBq) of ^{177}Lu -PSMA-617 (ClinicalTrials.gov Identifier NCT03042312). The trial opened in October 2017, and twelve patients had been treated by the time of this meeting. In PCF-supported correlative studies, pre- and post-treatment tumor biopsies from responding and non-responding patients will be profiled for changes in the tumor proteome and phospho-proteome using mass spectrometry, with the aim of identifying predictive biomarkers able to stratify patients into responders versus non-responders. Based on findings from clinical trial correlatives and the animal studies, cell stress response pathways that are induced by PSMA-TRT and associate with resistance to treatment will be characterized and tested as potential treatment targets to improve efficacy when combined with PSMA-TRT. This study will also enable probing of questions including whether certain mutations, such as in DNA damage repair genes or p53, are associated with responses to PSMA-TRT.

These studies will help to elucidate the mechanisms of response and resistance to PSMA-TRT and aid in the development of new rationally designed combination therapies and predictive biomarkers for PSMA-TRT.

Peter MacCallum Cancer Centre Study to Harness Synergies Between ^{177}Lu -PSMA-617 and Olaparib to Improve Clinical Outcome of Men with mCRPC

Scott Williams (Peter MacCallum Cancer Centre, Australia) discussed a PCF-supported study being conducted at the Peter MacCallum Cancer Centre under the leadership of Shahneen Sandhu, to examine the efficacy of combining ^{177}Lu -PSMA-617 with PARP-inhibitors.

PARP-inhibitors target the PARP1 pathway, a DNA repair pathway that cancer cells with DNA damage repair (DDR) pathway alterations including BRCA1/2 and ATM mutations become reliant on, in a synthetic-lethal manner. The PCF International Dream Team found that DDR gene mutations are present in ~25-30% of mCRPC [87]. Subsequently, the phase II TO-PARP clinical trial demonstrated that CRPC harboring DDR mutations are sensitive to treatment with the PARP-inhibitor olaparib [88]. Phase II and III clinical trials testing PARP-inhibitors in mCRPC with DDR gene alterations are underway.

PARP-inhibitors may also be synergistic with DNA-damaging agents, including radiation and radionuclide therapy. A clinical trial has been initiated at the NCI to test the combination of ^{223}Ra with olaparib in mCRPC (ClinicalTrials.gov Identifier NCT03317392). ^{177}Lu is primarily a beta-emitter, and emits low-dose sparsely ionizing (low-LET) radiation, which produces 20-50 times more ssDNA breaks than dsDNA breaks. ssDNA breaks are usually non-lethal to cells and can be repaired by base excision repair, in which PARP plays a critical role. Therefore, Sandhu and team hypothesized that synergy may be achieved by combining ^{177}Lu -PSMA-617 with PARP-inhibitors. Additionally, up to a third of mCRPC will have DDR mutations and be sensitive to PARP-inhibition.

Based on this rationale, a phase I dose escalation study is being initiated to test the combination of ^{177}Lu -PSMA-617 with olaparib. Olaparib doses will start at 50 mg b.d. and escalate to a maximum of 250 mg b.d. for 21 days per cycle. Concurrently, patients will receive up to 3 cycles of ^{177}Lu -PSMA-617 every 6 weeks. The primary objective is to determine the MTD, dose-limiting toxicities, and the recommended phase II dose for the combination. The trial will include a number of secondary objectives including PFS and OS. Serial liquid and tumor biopsies will be taken for correlative studies aimed to identify mechanism of action and develop predictive biomarkers of response and resistance. The relationship between DDR

alterations and response will be specifically assessed. In addition, the immune microenvironment of tumors will be analyzed.

The team has also proposed to perform preclinical studies on human prostate cancer cell lines and mouse models treated with ^{177}Lu -PSMA-617 plus olaparib in order to better understand mechanisms of action, response and resistance.

The Bayer PSMA-Targeted Thorium Conjugate Program

Hartwig Hennekes (Bayer Pharmaceuticals) discussed a program at Bayer to develop a thorium-conjugated PSMA-TRT. This program was initiated based on Bayer's success in establishing a global footprint for the alpha-particle emitting radiotherapy ^{223}Ra , which is now approved for the treatment of mCRPC in 52 countries. To leverage the global ^{223}Ra manufacturing and supply chain that has been developed, other alpha-emitting TRTs are being explored. ^{227}Th (an alpha-emitter) is a precursor of ^{223}Ra and uses the same manufacturing sources. ^{227}Th has a half-life of 18.7 days, which simplifies manufacturing logistics, and moreover is similar to the half-life of therapeutic antibodies in plasma. Targeted thorium conjugates (TTC) have been developed that are highly stable and can be conjugated to a range of targeting molecules using a 3,2-hydroxypyridinone (3,2-HOPO) based chelator. ^{227}Th -labeled antibodies targeting PSMA, CD22, MSLN, and HER2 are being developed and tested for the treatment of various types of cancer. ^{227}Th -anti-CD22 (epratuzumab-TTC) is currently in phase I trials for non-Hodgkin lymphoma.

A ^{227}Th -labeled PSMA-targeted antibody (PSMA-TTC) is in preclinical development for mCRPC. PSMA-TTCs have shown strong selective cytotoxicity for PSMA-positive versus PSMA-negative cells lines. In vitro studies have found that PSMA-TTCs induce G2 arrest, dsDNA breaks, and immunogenic cell death including upregulation of calreticulin, a critical component of MHC class I antigen processing and presentation. In prostate cancer xenograft mouse models, PSMA-TTCs exhibited preferential uptake into tumors compared with other tissues, and dose-dependent suppression of tumor growth, including in a bone-metastatic model. Further preclinical development is underway.

Challenges of Integrating Radiopharmaceutical Therapy into Practice Patterns in University and Private Clinics

Oliver Sartor (Tulane University) led a discussion on the challenges faced in integrating radiopharmaceutical therapy into practice in academic and community practices.

A foremost challenge involves issues with licensure and administration. As radiopharmaceuticals are classified as controlled substances, they are typically administered by radiation oncologists or nuclear medicine physicians instead of the medical oncologist or urologist overseeing care of the patient. This necessitates a multidisciplinary team approach for the use of radionuclides, which may also require inclusion of radiation safety officers and radiation committees. Such approaches are more easily enacted in multidisciplinary centers, while smaller centers and community practices would need to overcome barriers including the development of partnerships with nuclear medicine or radiation oncology practices to administer radionuclide treatment. Experiences with ^{223}Ra are a primary source of lessons learned for these treatments. The Large Urology Group Practice Association (LUGPA), the largest urology practice association in the U.S., is working to get these groups and their associated physicians licensed to administer ^{223}Ra . Alongside these barriers are the misaligned focuses of oncologists and nuclear medicine physicians on patient versus imaging outcomes. More homogeneous nuclear medicine physician training programs that include patient management are needed. Appropriate management of TRT-associated toxicities such as myelosuppression and xerostomia are also challenging and may be best addressed with a multi-disciplinary approach.

Another challenge to administering radiopharmaceuticals are financial disincentives relative to other, more profitable therapies. For many physicians and all hospitals, profitability is a primary concern. A model in which everyone in the supply chain makes a profit would improve incentive to administer radiopharmaceuticals. In addition, models need to be established to ensure reimbursement and access. Such issues and relevant endpoints, including validation that the cost of treatment is acceptable relative to patient benefit, need to be addressed and integrated into clinical trials. Investing and integrating more intelligent patient selection into clinical trials is also necessary. In the CAR-T cell field, due to the extremely high cost, there is an emerging model in which payment for treatment is only required if

responses are demonstrated. How to anticipate which data will be needed to allow for reimbursement will enable access in the end.

Due to the half-life and radioactive nature of radiopharmaceuticals, creation of a manufacturing and supply chain that can rapidly and efficiently deliver radiopharmaceutical therapy to centers globally is necessary. Supply chain management and delivery of radiation across international borders is challenging. Dealing with patient no-shows to scheduled treatments is also more challenging with radiopharmaceuticals than with treatments with longer shelf-life. A history of commercial failure despite scientific success (Bexxar and Zevalin being examples) is also a stymie to pharmaceutical companies considering this space.

Nevertheless, demonstration that PSMA-TRT can significantly impact patient outcomes will likely provide incentive for all stakeholders to tackle and overcome these and other barriers.

Conclusion

Overall, the PCF PSMA-Directed Radionuclide Scientific Working Group meeting addressed the current state of knowledge surrounding PSMA-targeted imaging and PSMA-TRTs, discussed ongoing and planned clinical trials necessary to optimize the use of and validate the efficacy of these treatments, and highlighted barriers to successful use of these agents in different practice models. Of utmost importance is the execution of appropriately designed clinical trials to find the optimal dose, exposure, and isotope/agent, determine how to properly manage and minimize toxicities, and identify the optimal patient population, treatment combinations, and sequencing that will maximize benefit. PSMA-TRTs have demonstrated a potential to significantly impact survival and even result in complete responses in some patients. Hence, it is hoped that the knowledge shared at this working group meeting will accelerate the studies necessary for the validation and use of these agents, and ultimately improve the outcomes of men with prostate cancer.

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Figure 1. Chemical structure of PSMA-targeted small molecules developed thus far. All are based on the same basic glutamate-urea-lysine moiety that binds the enzymatic pocket of PSMA, but differ in the linkers and chelators used. Figure reproduced from Chatalic KLS, et al. [46].

Figure1 .

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