2020 SNMMI Highlights Lecture: Oncology and Therapy, Part 2

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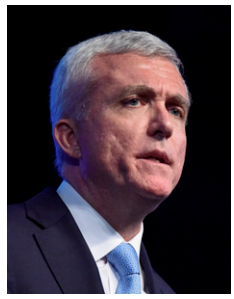
From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2020 Highlights Lectures were delivered on July 14 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the second part of the lecture by Andrew M. Scott, MD, Director, Department of Molecular Imaging and Therapy, and Head, Tumour Targeting Laboratory, Olivia Newton-John Cancer Research Institute, Austin Health (Melbourne, Australia), who spoke on oncology highlights from the meeting. Part 1 appeared in the December 2020 issue of Newsline. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2020;61[suppl 1]).*

Therapy was a very strong focus at the 2020 SNMMI meeting. We have seen remarkable progress in radionuclide therapy in the last 12 months, and I will highlight key abstracts presented on this topic at this meeting.

Novel Therapeutic Approaches

A number of single-site and multicenter ^{177}Lu–prostate-specific membrane antigen (^{177}Lu-PSMA) trials are ongoing, including the TheraP trial, the VISION study (for which we are looking forward to a readout toward the end of this year), as well as a number of other studies looking at combination treatments and earlier-stage treatments, such as the UpFront and ENZAp trials, which are being activated and are ongoing. We are seeing novel approaches with new targets, dosing, and scheduling, as well as rechallenge treatments. I will touch on a few of these important presentations, both for lutetium-based treatment as well as emerging clinical data on α-particle peptide-receptor radionuclide therapy (PRRT). I encourage everyone to continue to look at multicenter studies, so that the evidence we generate is meaningful and provides further supporting data about standardization, outcome improvement, and health economics for these new treatments.

At the 2020 American Society of Clinical Oncology (ASCO) meeting, Hofman and a consortium of researchers from 11 sites in the Australian and New Zealand Urogenital and Prostate Cancer Trials Group presented results from "TheraP: A randomized phase II trial of ^{177}Lu-PSMA-617 theranostic versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel." This is a potentially practice-changing study that should be kept in mind for context with other presentations I will be discussing. Two hundred patients went on trial in the study, of whom 99 were randomized to ^{177}Lu-PSMA and 101 to cabazitaxel. Eligibility required patients to have progressive disease with rising prostate-specific antigen (PSA) ≥ 20 ng/mL and to have high SUV_{max} (>20) on PSMA PET at any site, with at least an SUV_{max} of 10 at measurable sites and no ^{18}F-FDG–positive or PSMA-negative sites of disease before randomization to treatment with up to 6 cycles of ^{177}Lu-PSMA (q 6 weeks) or 10 cycles of cabazitaxel (q 3 weeks). The primary endpoint was PSMA response. Thirty-seven percent of patients responded to cabazitaxel with at least 50% PSA reduction compared to 66% for ^{177}Lu-PSMA. This was a relative difference of 78%; for a sensitivity analysis, the difference was 23% (P = .0016). The researchers found relatively few grade 3–4 adverse events with the PSMA treatment. The primary endpoint of this multicenter, prospective, randomized study was therefore positive. This is the type of information that will allow applications for regulatory approvals to be submitted for ^{177}Lu-PSMA. Together with the VISION trial, these are 2 of the most important radionuclide therapy trials in a multicenter setting that will be reported this year.



Andrew M. Scott, MD

One of the factors that can prevent patients from going onto ^{177}Lu-PSMA therapy is diffuse bone marrow involvement. In fact, this is an exclusion criterion for most large studies that have been conducted to date. At the 2020 SNMMI Meeting, Gafita et al. from the Technische Universität München (Germany), University Hospital Essen (Germany), Peter MacCallum Cancer Centre (Melbourne, Australia), Excel Diagnostics (Houston, TX), the University of California Los Angeles, and University Hospital Heidelberg (Germany) reported on the "Efficacy and safety of ^{177}Lu-PSMA radionuclide treatment in patients with diffuse bone marrow involvement: A multicenter retrospective study" [1284]. This analysis included 43 patients with extensive bone marrow disease and was designed to determine whether ^{177}Lu-PSMA in compassionate use could result in therapeutic efficacy. They found, despite a small incidence of grade 3–4 anemia,

thrombocytopenia, or neutropenia, a substantial therapeutic response in the majority of patients treated, with 58% of patients experiencing a ≥50% decline in PSA at 12 weeks, with a median overall survival of 11.6 months and median time-to-pain progression of 8.3 months. An objective radiologic response (RECIST 1.1) was seen in 39% of patients. The authors concluded that "even in heavily pretreated patients with mCRPC presenting with diffuse bone marrow involvement, Lu-PSMA has important clinical antitumor activity and acceptable toxicity." They added that "acceptable safety outcomes do not support exclusion of these patients from future Lu-PSMA trials" or from the availability of ^{177}Lu-PSMA in the real-world setting.

^{225}Ac-PSMA treatment was reported last year at the SNMMI meeting, and encouraging data were presented again at this year's meeting. Yadav et al. from the All India Institute of Medical Sciences (New Delhi) reported on "Clinical experience on ^{225}Ac-PSMA-617 targeted α therapy in mCRPC patients: Safety and efficacy results" [589]. The study included a total of 28 patients, of whom 15 were refractory to ^{177}Lu-PSMA treatment. The remaining 13 had not received previous ^{177}Lu-PSMA treatment. The researchers found an overall 63.6% disease control rate after 4 cycles of ^{225}Ac-PSMA-617, which was more commonly seen in patients who had not received previous ^{177}Lu-PSMA-617 treatment. However, more than half of patients who had been refractory to ^{177}Lu-PSMA showed complete/partial responses or stable disease on imaging after ^{225}Ac-PSMA-617 therapy. Figure 1 is an example of a patient who had a very good response after 4 treatments. We look forward to data from multicenter prospective studies with α-particle–labeled PSMA in the future.

The use of α-particle therapy in somatostatin-receptor (SSTR)–positive patients is also showing promise. Delpassand et al. from Excel Diagnostics and Nuclear Oncology Center (Houston, TX), RadioMedix Inc. (Houston, TX), and Orano Med LLC (Plano, TX) reported on "First-in-human dose escalation of AlphaMedix for targeted α-emitter therapy of neuroendocrine tumors (NETs)" [415]. The study included 16 adult patients (7 men, 9 women; median age, 68 years [range, 27–75 years]) with biopsy-proven unresectable or metastatic NETs from different primary sites. In a dose-escalation protocol with the ^{212}Pb-DOTAMTATE agent given in 4 cycles at 8-week intervals, the researchers were able to extend treatment in 1 cohort up to a total effective dose of 22 mCi, with no clinically significant hematologic, renal, or hepatic toxicities to date. Dramatic decreases in tumor burden and a positive impact on quality of life were seen in all participants who received 3 cycles of therapy at the highest dose tested. In the 3 patients in the highest cohort (4 cycles), the overall response rate was 100% by RECIST criteria, showing almost complete responses on ^{68}Ga-DOTATATE PET/CT (Fig. 2), with no progression on monitoring at 15 months after treatment initiation. This is a very interesting study and illustrates the safety and potential efficacy of this approach. I congratulate the authors on presenting these data at this meeting.

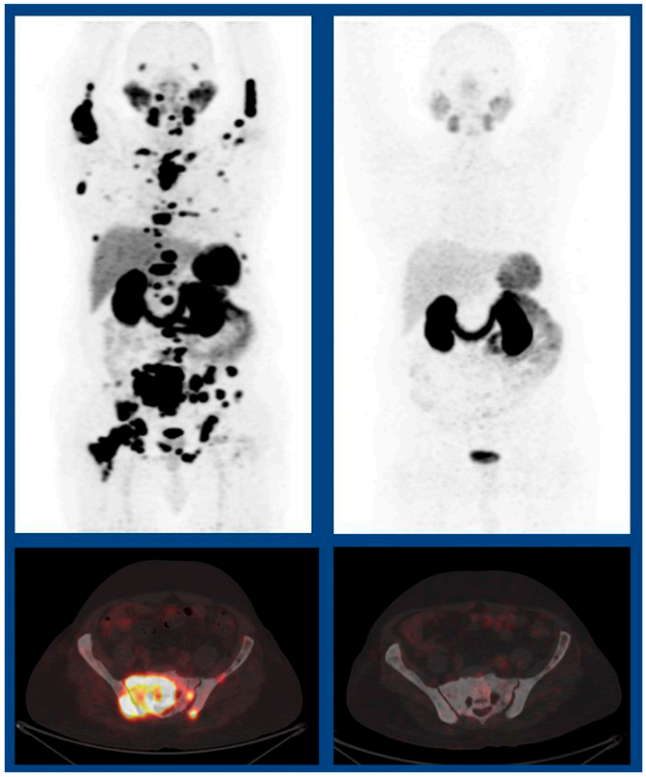


FIGURE 1. ^{225}Ac-PSMA-617 targeted α-therapy in metastatic castration-resistant prostate cancer. Example ^{68}Ga-PSMA-11 PET/CT images from patient at baseline (left; prostate-specific antigen [PSA] = 48.5 ng/mL) and after 4 cycles of ^{225}Ac-PSMA-617 (right; PSA undetectable).

Another intriguing approach is to look at the use of antagonists to SSTRs in patients with negative SSTR expression but advanced metastatic NETs. Zhang et al. from the Zentralklinik Bad Berka (Germany) and the Universitätklinikum Freiberg (Lorrach, Germany) reported on "First-in-human study of a novel SSTR antagonist ^{177}Lu-DOTA-LM3 for peptide-receptor radionuclide therapy in patients with advanced metastatic neuroendocrine neoplasms and low SSTR agonist binding" [414]. This study included both diagnostic and therapeutic approaches, and the researchers shared data gathered over the last 2 years. Fifty-one patients (mean age, 51.6 ± 13.9 years [range, 27–76 years]) with advanced metastatic neuroendocrine neoplasms underwent PRRT with ^{177}Lu-DOTA-LM3, and ^{68}Ga-NODAGA-LM3 PET/CT was used for patient selection and follow-up. ^{177}Lu-DOTA-LM3 was found to be safe, with very few serious adverse events (aside from thrombocytopenia) and high absorbed tumor doses compared to dose levels in normal organs like kidneys and liver. Partial remission was seen in 17 patients (36.2%), stable disease in 23 (48.9%), and progressive disease in 7 (14.9%). Figure 3 shows early marked distribution of the tracer within metastatic disease within the liver before ^{177}Lu-DOTA-LM3 treatment and substantial response after 4 treatments. This presentation showed innovation in looking at different ways to approach a target receptor that is being utilized for standard therapy and focusing on

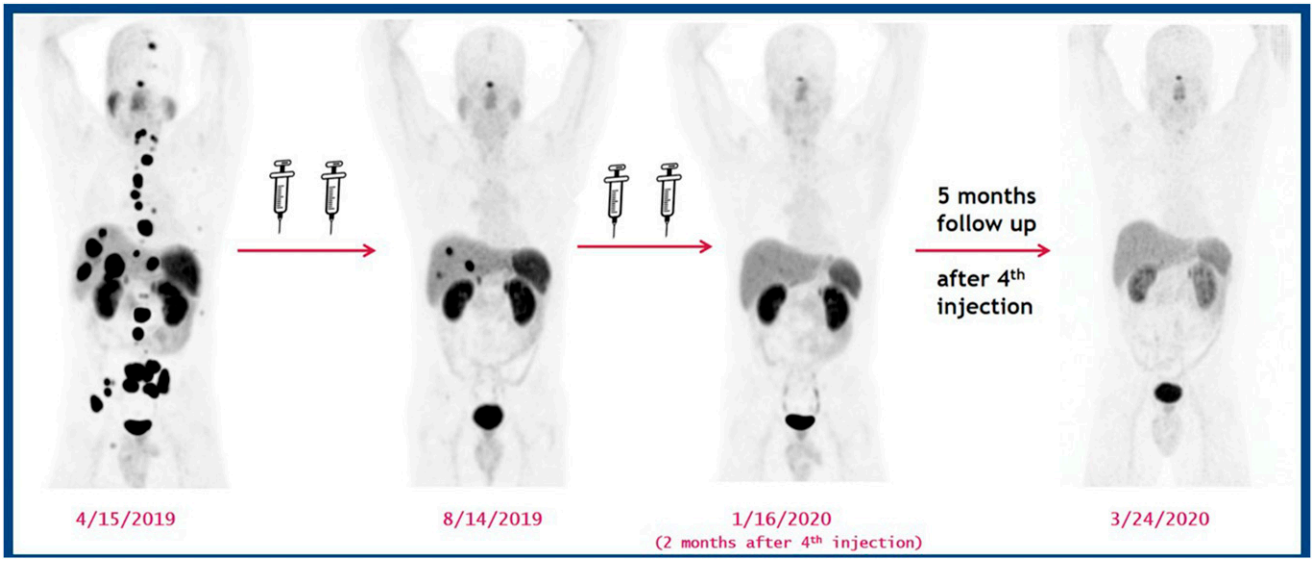


FIGURE 2. ^{212}Pb-DOTAMTATE for targeted α-therapy in neuroendocrine tumors. ^{68}Ga-DOTATATE PET/CT images in 46-year-old man with metastatic bronchial carcinoid at (left to right) baseline, after 2 rounds of treatment, 2 months after the 4th injection, and at 5-month follow-up after the 4th injection.

patients in whom gallium-DOTATATE uptake is not very high. This is an important area for potential study, and I look forward to multicenter trials with this approach in the future.

Last year the imaging of fibroblast-activation protein (FAP) in patients with cancer was the SNMMI meeting Image of the Year. This year, Baum et al. from the Zentralklinik Bad Berka (Germany), King Chulalongkorn Memorial Hospital/Thai Red Cross Society (Bangkok Thailand), 3B Pharmaceuticals GmbH (Berlin, Germany), and Loma Linda University (San Diego, CA) reported on "Peptide-targeted radionuclide therapy using Lu-177 FAP-2286 in diverse adenocarcinomas: Feasibility, biodistribution,

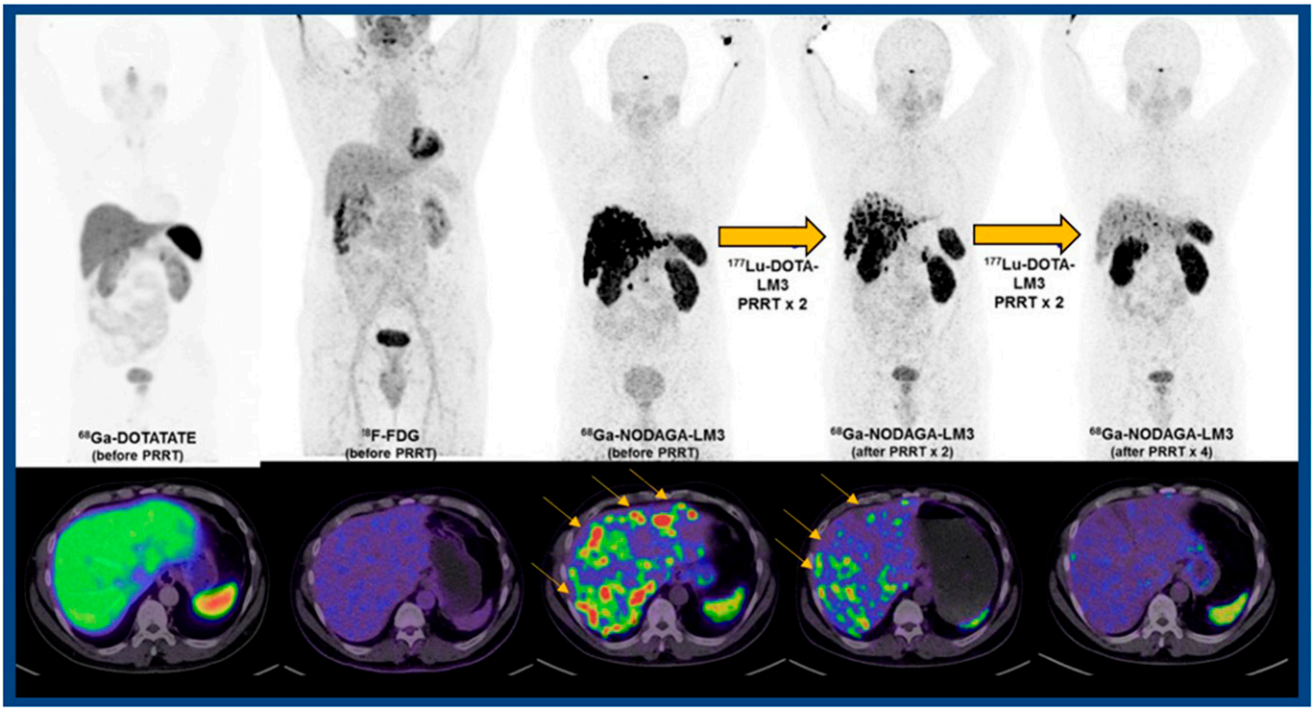


FIGURE 3. First-in-human study of novel somatostatin-receptor (SSTR) antagonist ^{177}Lu-DOTA-LM3 for peptide-receptor radionuclide therapy (PRRT) in patients with advanced metastatic neuroendocrine neoplasms and low SSTR agonist binding. Example images in a patient imaged (left to right): with ^{68}Ga-DOTATATE and ^{18}F-FDG before PRRT and with ^{68}GA-NODAGA-LM3 before, after 2 cycles, and after 4 cycles of ^{177}Lu-DOTA-LM3 treatment.

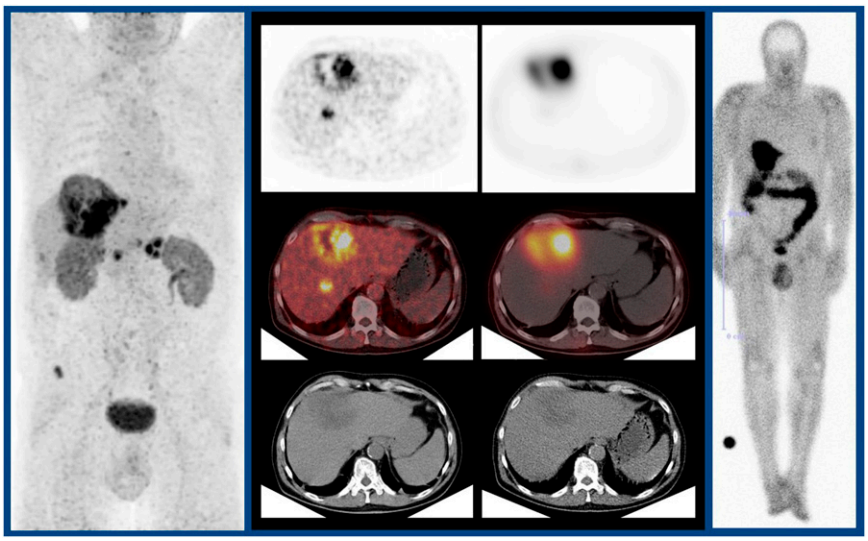


FIGURE 4. Peptide-targeted radionuclide therapy with ^{177}Lu-FAP-2286 in adenocarcinomas. Example imaging in a patient with pancreatic adenocarcinoma with hepatic, lymph node, and bone metastases. Left full-body and column of 3: ^{68}Ga-FAP-2286 PET/CT. Right column: ^{177}Lu-FAP-2286 SPECT/CT. Right full body: ^{177}Lu-FAP-2286 scintigraphy.

and preliminary dosimetry in a first-in-human study" [633]. This was a small study of 11 patients with advanced adenocarcinomas (5 pancreatic, 4 breast, and 1 each ovarian and colorectal) and explored the safety and tolerability of this approach. ^{177}Lu-FAP-2286 therapy was administered after prior confirmation of significant tumor uptake on ^{68}Ga-FAP-2286 FAP PET/CT (Fig. 4). The authors observed long tumor retention of the therapeutic agent, calling it "a highly promising treatment option in a broad spectrum of cancers." This is the first demonstration of FAP-targeted theranostics using this particular probe and highlights the potential of targeting FAP for treatment of a range of advanced cancers.

^{177}Lu and α-particle therapies are not the only promising new approaches in radionuclide cancer treatment. McInnes et al. from the University of Melbourne, Cyclotek Australia Pty Ltd (Bundoora), Peter MacCallum Cancer Centre (Melbourne), Clarity Pharmaceuticals (Sydney; all in Australia), and the Idaho Accelerator Center (Pocatello) reported on "A ^{64}Cu/^{67}Cu bifunctional PSMA ligand as a theranostic for prostate cancer" [1215]. This sarcophagine ligand containing 2 glutamine-urea-lysine functional groups labeled with ^{64}Cu demonstrated selective tumor accumulation and excellent tumor retention over 24 hours in a PSMA-expressing LNCaP mouse model of prostate cancer (Fig. 5). Tumor uptake was selectively blocked with PSMA inhibitor 2-(phosphonomethyl)pentanedioic acid. They found that the therapeutic response following ^{67}Cu-PSMA treatment was comparable to that with ^{177}Lu-PSMA (I&T) at low- and high-dose levels. We look forward to the results of future studies exploring this unusual theranostic pairing of ^{64}Cu and ^{67}Cu.

It is clear that we can achieve remarkable specificity with peptides, urease-based molecules, and antibodies for targeting cancer, but a complicating factor with these radiolabeled molecules can be nonspecific toxicity related to red marrow exposure. Santich et al. from Memorial Sloan Kettering Cancer Center and the Weill Cornell Medical College (both in New York, NY) reported on "Self-assembling and disassembling (SADA) bispecific antibodies for curative 2-step pretargeted radioimmunotherapy" [34]. This group has

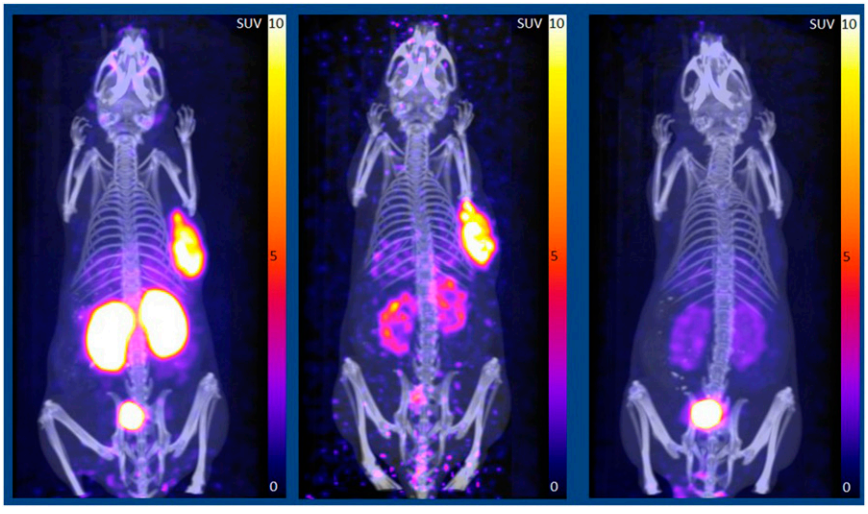


FIGURE 5. ^{64}Cu/^{67}Cu bifunctional prostate-specific membrane antigen (PSMA) ligand as a theranostic for prostate cancer. PET/CT images (maximum intensity projections) of ^{64}Cu-CuSAR-bisPSMA (2–3 MBq) in LNCaP tumor-bearing mouse at 1 hour (left) and 24 hours (middle) after injection and at 1 h after tracer injection in the presence of the known PSMA inhibitor PMPA (right).

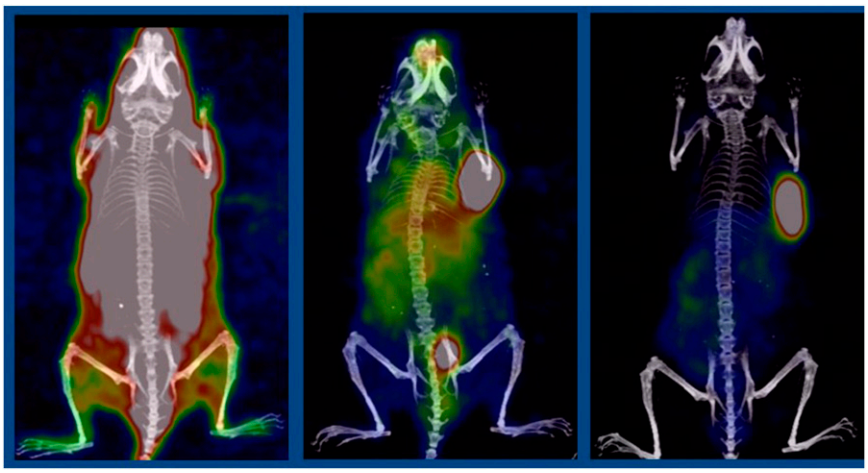


FIGURE 6. Self-assembling and disassembling (SADA) bispecific antibodies (BsAbs) for curative 2-step pretargeted radioimmunotherapy. PET/CT imaging in a mouse model with ^{86}Y-DOTA bispecific antibody: IgG-scFv-BsAb (left; 2-step, with no clearing agent); IgG-scFv-BsAb (middle; 3-step, with clearing agent); and SADA BsAb (right; 2-step, with no clearing agent).

been pioneering the concept of multistep targeting. In this study they assembled monomers against both PSMA and DOTA through a SADA complex that allowed tetramers to be formed which can then form dynamic interplay with monomers. Using this approach, they looked at both imaging and subsequent therapy in a mouse model. When standard immunoglobulin-G–based bispecific antibodies were used without a clearing agent, prolonged blood pool retention was seen at 48 hours, and clearing agents were helpful in visualizing tumor uptake. By using this SADA approach, at 48 hours the authors were able to achieve remarkable uptake in tumor compared to background and also showed substantial therapeutic efficacy with both ^{225}Ac and ^{177}Lu in neuroblastoma and small-cell lung cancer models (Fig. 6). This novel 2-step SADA platform, then, induces rapid elimination of unbound antibody without a clearing agent, allowing for tumor-specific delivery of ^{177}Lu and ^{225}Ac (and potentially other) isotopes. This is an interesting approach of looking at protein engineering to create a molecule that can become both large and small to assist with dynamic and increased uptake in tumor compared to that which can be achieved with conventional targeting proteins.

Pharmacogenomics, the science of exploring germline and somatic mutations as predictors of therapy response in cancer, is an increasingly important focus in patient selection. Certain germline mutations can enhance the susceptibility of patients to response, depending on the mutations and types of therapies that are given. Baum et al. from the Zentralklinik Bad Berka (Germany), Universitäts Klinikum Ulm (Germany), and the Tulane University Medical School (New Orleans, LA) reported on "Germline gene variants and therapy response in patients referred for radioligand therapy with ^{177}Lu-PSMA: A huge step towards pharmacogenomics in theranostics of prostate cancer" [1272]. They found that checkpoint kinase 2 (CHEK2), a tumor suppressor gene that encodes the protein

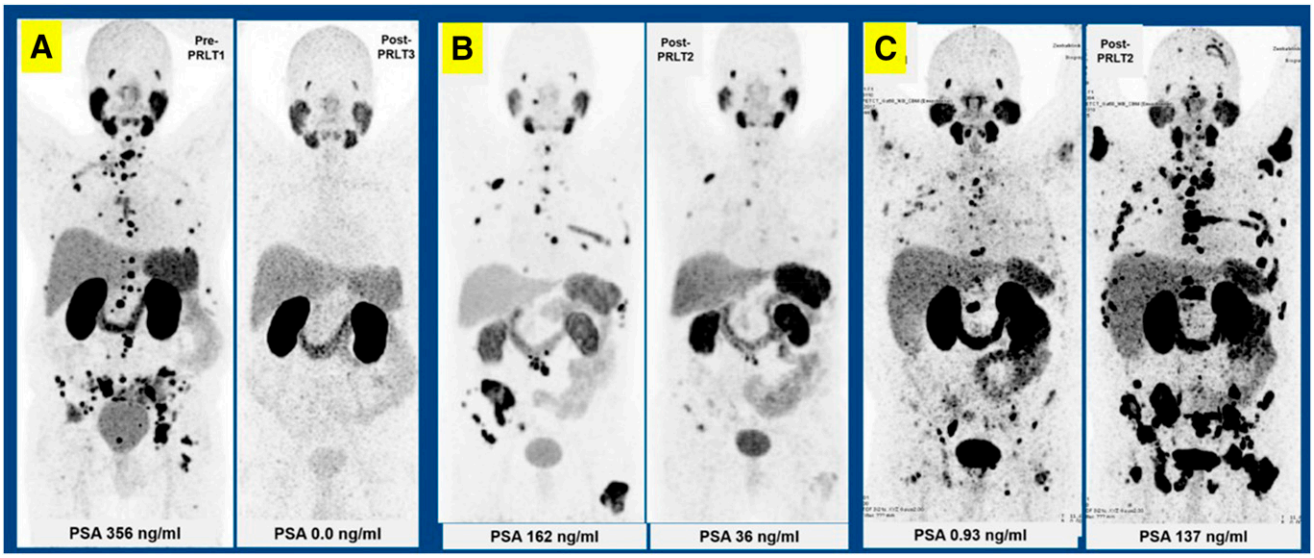


FIGURE 7. Germline gene variants and therapy response in patients referred for radioligand therapy with ^{177}Lu-PSMA. Examples in patients with: (A) CHEK2 mutation showing complete response; (B) BRCA2 mutation with partial response; (C) and BRCA1 mutation with progressive disease following ^{177}Lu-PSMA therapy.

CHK2, was highly predictive of response to ^{177}Lu-PSMA treatment, whereas a number of the other radiosensitizing or prognosis-determining germline mutations (such as BRCA1 or BRCA2) were not so predictive. Figure 7 shows examples, first in a patient with CHEK2 mutations showing complete remission in response to PRLT (left; 100% had PSA responses) and responses in patients with the BRCA2 (middle; 66.7% responded) and BRCA1 (right; 50% responded) mutations. The authors are also investigating the influence of germline mutations on overall survival. This is only the beginning of the process of exploring genomic information to assist in deciding whether patients are more likely to respond to therapy. I hope that these types of genomic as well as blood-based biomarkers will become a routine part of radionuclide clinical trials in the future.

Impact of COVID-19 on Cancer Patients

I will touch very briefly on the impact of COVID-19, particularly in the near-term future, on nuclear medicine practice and on patients with cancer. We saw multiple presentations at this conference on the impact of COVID-19—we have all been affected. Numerous articles have been published on how the practice of nuclear medicine has been changed during the pandemic. A very important thing to bear in mind is that reported incidences of cancer over the last 3 to 4 months prior to this meeting dropped anywhere from 40% to 75%. This is related to a number of factors, primarily the fact that patients are not being screened or are choosing not to follow up on symptoms. This has been highlighted in a range of early papers, notably by Kuderer et al. in the *Lancet* (2020;395[10241]:1907–1918), Richards et al. in *Nature Cancer* (2020 May 20; online ahead of print), and Wise in the *British Medical Journal* (2020 Apr 29;369:m1735), reporting that not only are there delays in diagnosis and treatment but that mortality could substantially increase in patients with cancer still to be diagnosed, simply because diagnosis will occur at later disease stages. In the June 19 issue of *Science* (2020;358[6497]:129), Sharpless looked at cumulative excess deaths that may occur in the United States alone from breast and colon cancer because of delays in diagnosis related to the pandemic. In a study from the German Society of Nuclear Medicine in conjunction with the International Atomic Energy Agency, the impact of COVID-19 on nuclear medicine therapy was assessed from 434 sites in 73 countries around the world. Not only was there an ~60% overall reduction in diagnostic tests being performed in nuclear medicine but an additional 45% reduction in therapeutic studies was seen over the previous 3 months, with a more than 60% reduction in routine thyroid overactivity treatment. This impact has been felt in all countries, with a profound reduction across the range of different therapeutic modalities—an effect that is likely to continue if the virus experiences future surges. This will affect the number of patients we will see, as well as the extent of disease. We must be prepared to respond quickly when cancer diagnoses ramp up again.

Summary

It has been an honor to present the highlights of oncology imaging and therapy as reported at the SNMMI 2020 Annual Meeting. Molecular imaging and therapy in oncology continue to make substantial progress, with increased recognition in the oncology field for the role of nuclear medicine in patient care. The increasing number of multicenter trials in both diagnosis and therapy are encouraging and likely to move new applications and agents forward. At the same time, recovery from the COVID-19 pandemic will require careful planning and thoughtful resource allocation. Even in these difficult times, nuclear medicine plays a pivotal role in understanding both cancer biology and advancing the care of cancer patients.