

SNMMI Diversity, Equity, and Inclusion Task Force Statement

Hyewon Hyun, MD, Chair, SNMMI Diversity, Equity, and Inclusion Task Force, and Alan Packard, PhD, SNMMI President

The SNMMI Diversity, Equity, and Inclusion (DE&I) Task Force was created this year under the leadership of Alan Packard, PhD, SNMMI President, and is chaired by Hyewon Hyun, MD. With this new task force, SNMMI is working to embrace and integrate diversity, inclusion, and equity into its organizational values to intentionally enact change. This will require understanding of existing disparities and their root causes. Through the efforts of the task force over the last 2 months, proposed amendments to the SNMMI Bylaws have been initiated and a Diversity, Equity, and Inclusion statement has been adopted by the Board of Directors.

The proposed amendments account for major changes in the organizational framework of the bylaws to achieve DE&I among SNMMI leadership (i.e., officers, Board, House of Delegates, council/chapter leadership, membership, etc.). The DE&I Task Force petitioned that the current process, whereby only individuals who are current members of the House of Delegates (chapter, council, or center delegates) are eligible to serve as candidates for the Board of Directors, was too limiting and recommended that the SNMMI Bylaws be amended to allow for at least 2 of the 4 nontechnologist Director-at-Large positions to be selected from among qualified candidates in the general membership. The DE&I Task

Force further recommended that these individuals be elected by the general membership rather than the SNMMI House of Delegates. Finally, the DE&I Task Force also recommended that every effort be made to choose at least 1 candidate from a group that is underrepresented in the medical profession relative to their numbers in the general population (as defined by the Association of American Medical Colleges). These proposed amendments will be voted on during the SNMMI House of Delegates meeting in January.

The task force also developed a DE&I Statement to communicate SNMMI's vision and commitment to eliminate all forms of discrimination and to promote diversity, equity, and inclusion throughout the organization and for all its stakeholders. The complete statement is below.

We urge all nuclear medicine and molecular imaging professionals to commit to this statement and to support and actively participate in these efforts.

The efforts of the task force are just beginning. The launch event held in December was a success and served as an avenue to start this important conversation within the nuclear medicine and molecular imaging community. We are excited about the programming and educational events that are planned for this month and hope that you will join us!

Statement on Diversity, Equity, and Inclusion: SNMMI DE&I Task Force

At SNMMI, we are proud to celebrate diversity and to champion an inclusive, safe, and welcoming environment that respects each member of our professional and patient community, regardless of such considerations as race or ethnicity, national or geographic background, sexual orientation or gender identity, religious or political beliefs, age, socioeconomic circumstances, and ability or disability.

We recognize that discrimination, violence, and aggression affect the lives of millions of people in the United States and around the world every day. As nuclear medicine and molecular imaging professionals, we are committed to promoting a diverse community that is dedicated to equity and excellence in research, education, patient care, and service. SNMMI is dedicated to eliminating disparities, based on race or any other form of discrimination, within the membership and leadership of the Society, by raising awareness, promoting advocacy, improving representation, and creating intentional educational programs.

2020 SNMMI Highlights Lecture: Oncology and Therapy, Part 2

Andrew M. Scott, MD, Director, Department of Molecular Imaging and Therapy, Austin Health; Head, Tumour Targeting Laboratory, Olivia Newton-John Cancer Research Institute; Professor, School of Cancer Medicine, La Trobe University; Professor, University of Melbourne; Melbourne, Australia

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.

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,



Andrew M. Scott, MD

thrombocytopenia, or neutropenia, a substantial therapeutic response in the majority of patients treated, with 58% of patients experiencing a $\geq 50\%$ 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.

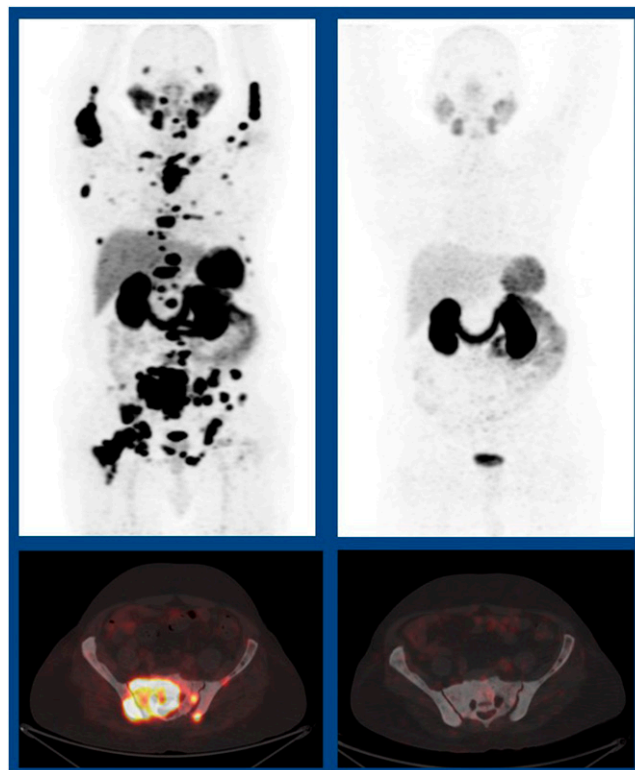


FIGURE 1. ^{225}Ac -PSMA-617 targeted α -therapy in metastatic castration-resistant prostate cancer. Example ^{68}Ga -PSMA-11 PET/CT images from patient at baseline (left; prostate-specific antigen [PSA] = 48.5 ng/mL) and after 4 cycles of ^{225}Ac -PSMA-617 (right; PSA undetectable).

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 Universitätsklinikum 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,

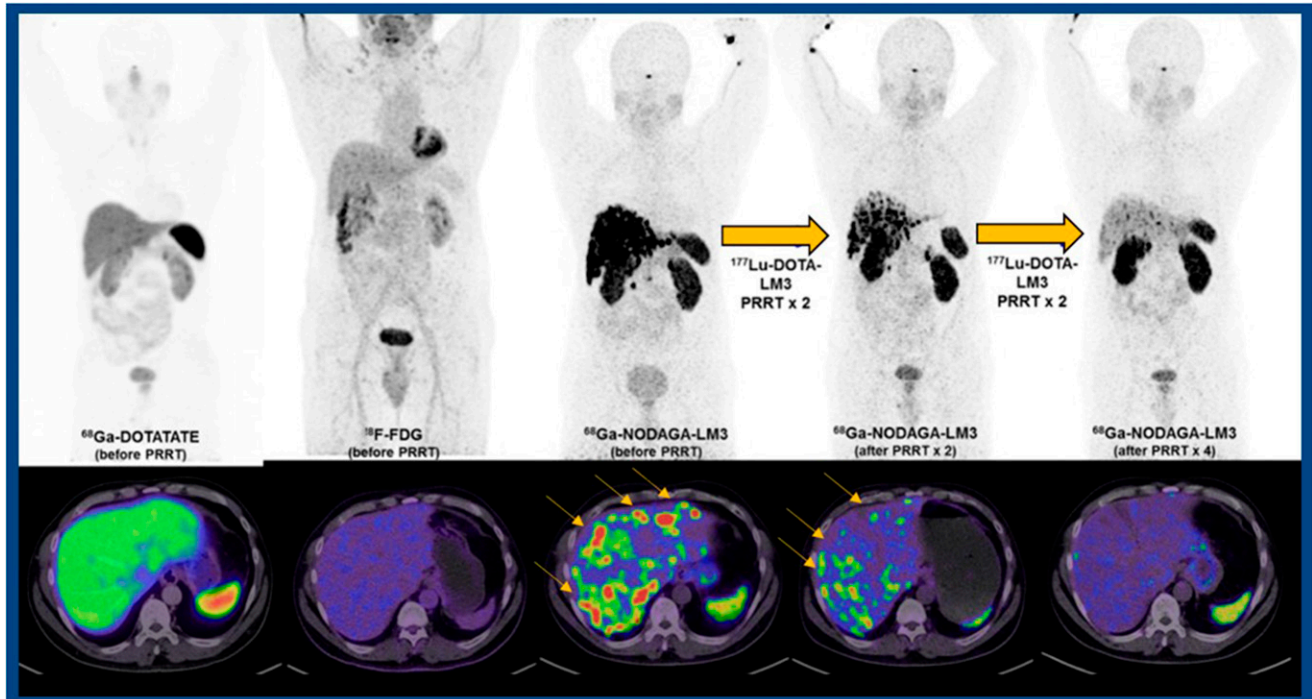


FIGURE 3. First-in-human study of novel somatostatin-receptor (SSTR) antagonist ^{177}Lu -DOTA-LM3 for peptide-receptor radionuclide therapy (PRRT) in patients with advanced metastatic neuroendocrine neoplasms and low SSTR agonist binding. Example images in a patient imaged (left to right): with ^{68}Ga -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.

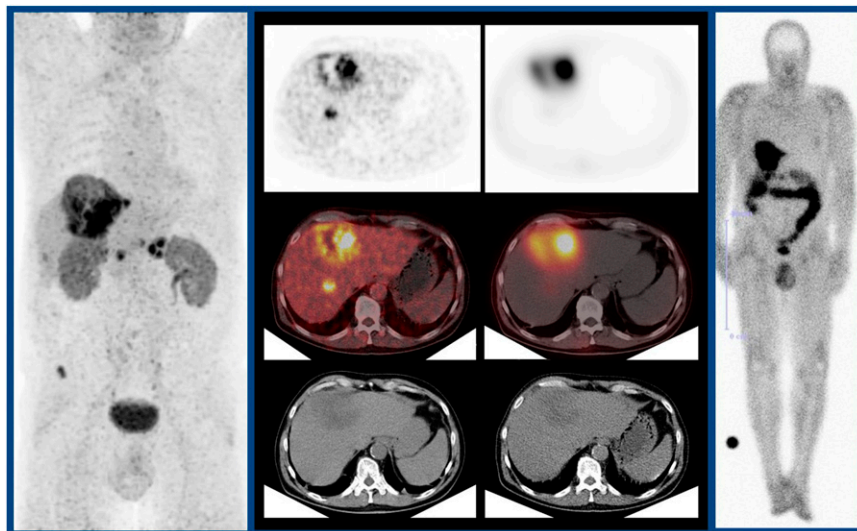


FIGURE 4. Peptide-targeted radionuclide therapy with ^{177}Lu -FAP-2286 in adenocarcinomas. Example imaging in a patient with pancreatic adenocarcinoma with hepatic, lymph node, and bone metastases. Left full-body and column of 3: ^{68}Ga -FAP-2286 PET/CT. Right column: ^{177}Lu -FAP-2286 SPECT/CT. Right 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 $^{64}\text{Cu}/^{67}\text{Cu}$ 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

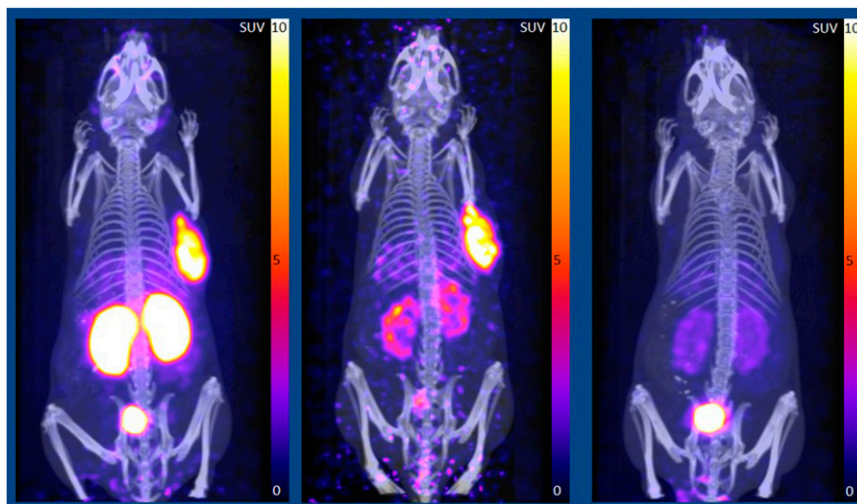


FIGURE 5. $^{64}\text{Cu}/^{67}\text{Cu}$ bifunctional prostate-specific membrane antigen (PSMA) ligand as a theranostic for prostate cancer. PET/CT images (maximum intensity projections) of ^{64}Cu -CuSAR-bisPSMA (2–3 MBq) in LNCaP tumor-bearing mouse at 1 hour (left) and 24 hours (middle) after injection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

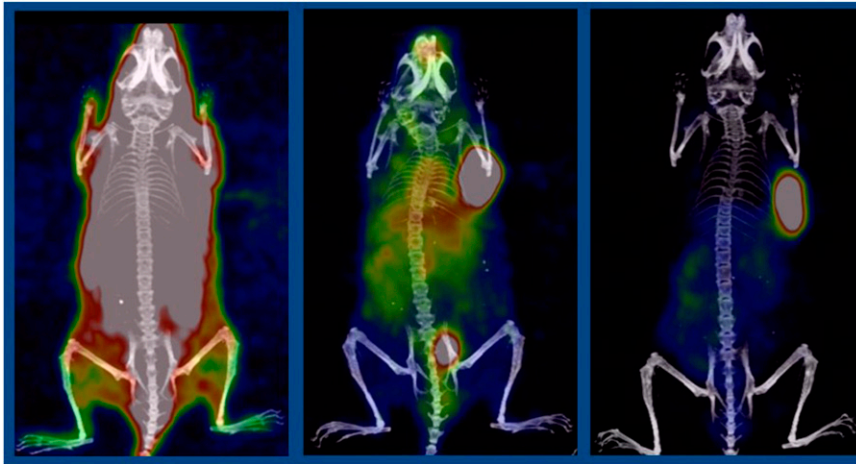


FIGURE 6. Self-assembling and disassembling (SADA) bispecific antibodies (BsAbs) for curative 2-step pretargeted radioimmunotherapy. PET/CT imaging in a mouse model with ^{86}Y -DOTA bispecific antibody: IgG-scFv-BsAb (left; 2-step, with no clearing agent); IgG-scFv-BsAb (middle; 3-step, with clearing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

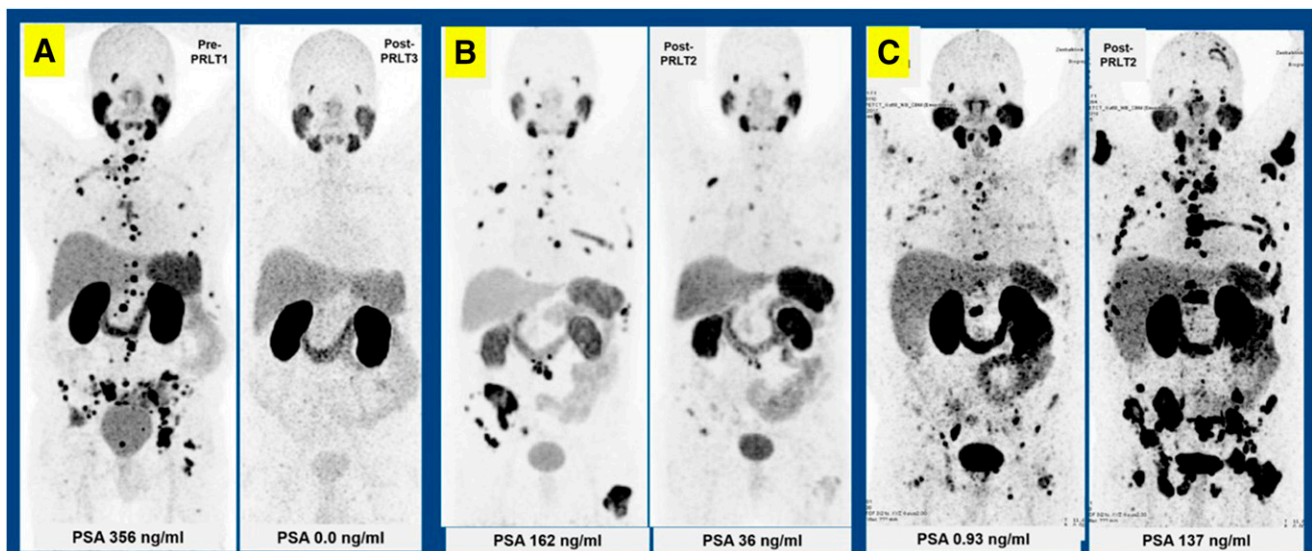


FIGURE 7. Germline gene variants and therapy response in patients referred for radioligand therapy with ^{177}Lu -PSMA. Examples in patients with: (A) CHEK2 mutation showing complete response; (B) BRCA2 mutation with partial response; (C) and BRCA1 mutation with progressive disease following ^{177}Lu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

Humana Decision to Deny PET/CT Coverage

On November 6, SNMMI received information on the recent decision by Humana Inc. (Louisville, KY) (Policy Number: HCS-0506-010) to deny coverage for PET/CT (CPT codes 78429–78433) on the basis that it is “experimental/investigational” and “not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature.” The revised policy, to take effect February 4, 2021, indicated that Humana members may NOT be eligible under the Plan for PET with concurrently acquired CT for (but not limited to):

- Cardiac indications; OR
- Gastric or esophageal oncologic indications; OR
- Neurologic indications; OR
- Total body PET/CT (uEXPLORER) for screening (e.g., cancer).

SNMMI joined several other medical societies, including the American Society of Nuclear Cardiology (ASNC), in questioning and opposing this decision. In 2016, ASNC imaging guidelines/SNMMI procedure standards (1) detailed the quality components required to perform PET nuclear cardiology procedures. In 2020, a multidisciplinary appropriate use criteria document (2) published by SNMMI stated: “The high spatial and contrast resolution in concert with photon attenuation-free images of PET have led to high image quality associated with the highest sensitivity and specificity of PET/CT perfusion imaging in the detection and characterization of coronary artery disease (CAD)” (3–6). Publication of these peer-reviewed documents validated the role of cardiac PET/CT and led to reimbursement by the Centers for Medicare and Medicaid Services (CMS), as well as other payers, for these procedures with Category I codes.

In a response protesting the Humana decision, SNMMI noted also that PET/CT with ¹⁸F-FDG has an established role in evaluating esophageal cancers and cancers of the gastro-esophageal junction, as affirmed by national CMS coverage policies. In addition, several neurologic indications benefit from and are appropriate for PET/CT. Although screening low-risk patients for cancer with PET is not routine, the appropriateness of evaluating high-risk patients for cancer is defined by the clinical context and question.

Almost all commercially available PET scanners are now hybrid PET/CT systems, and these newer systems have numerous other improvements over older models. With this policy, Humana would require its members to provide PET services using less advanced instrumentation than is currently available. Hybrid PET/CT systems also reduce scan time and patient motion, leading to higher quality images. CT attenuation correction can also be customized for body habitus, further improving image quality. For cardiac PET, extensive published literature documents the additional diagnostic value contributed by review of the CT

attenuation map image. SNMMI concluded its protest by noting that “Implementing this revised policy will deny patients access to state-of-the-art imaging procedures that are the standard of care for making potentially life-saving clinical decisions.”

At the same time that SNMMI responded to the Humana decision, ASNC sent the company a letter concurring with the objections raised and expressing similar concerns about Humana’s noncoverage decision for SPECT/CT (CPT codes 78830 and 78832). The revised policy states that “Humana members may NOT be eligible under the Plan for the following for any indications:

- CAD used in conjunction with MRI for prostate biopsy (e.g., DynaCAD); OR
- CAD used in conjunction with ultrasound for prostate biopsy (e.g., Fusion Bx 2.0); OR
- Diagnostic CT scan used in conjunction with PET/CT; OR
- MRI/CT; OR
- PET/MRI; OR
- SeeFactorCT3; OR
- SPECT/CT; OR
- SPECT/MRI.”

On November 13, Johannes Czernin, MD, from the University of California at Los Angeles, and Andrei Iagaru, MD, from Stanford University (CA) published a strongly worded editorial ahead of print in *The Journal of Nuclear Medicine* referring to the decision as an “injustice” (7). SNMMI’s letter to Humana is available at http://s3.amazonaws.com/rdcms-snmml/files/production/public/Humana_PET-CT_Letter_final%2011-13-20.pdf. The ASNC letter is available at https://www.asnc.org/files/ASNC_Letter_to_Humana_10_29_20.pdf.

REFERENCES

1. Dilsizian V, Bacharach SL, Beanlands SR, et al. ASNC Imaging Guidelines/SNMMI Procedure Standard for Positron Emission Tomography (PET) Nuclear Cardiology Procedures. *J Nucl Cardiol*. 2016;23:1187–1226.
2. Schindler TH, Bateman TM, Berman DS, et al. Appropriate use criteria for PET myocardial perfusion imaging. *J Nucl Med*. 2020;61(8):1221–1265.
3. Bateman TM, Dilsizian V, Beanlands RS, DePuey EG, Heller GV, Wolinsky DA. American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging joint position statement on the clinical indications for myocardial perfusion PET. *J Nucl Cardiol*. 2016;23:1227–1231.
4. Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *JACC Cardiovasc Imaging*. 2010;3:623–640.
5. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease: Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653.
6. Gould KL, Johnson NP, Roby AE, et al. Regional, artery-specific thresholds of quantitative myocardial perfusion by PET associated with reduced myocardial infarction and death after revascularization in stable coronary artery disease. *J Nucl Med*. 2019;60:410–417.
7. Czernin J, Iagaru A. Humana and ¹⁸F-FDG PET/CT: Another sequel to the injustice of being judged by the errors of others. *J Nucl Med*. 2020;61:e-published on November 13 ahead of print.

DOE Isotope Program Releases Annual Update on Medical Isotopes

On October 14 the U.S. Department of Energy Isotope Program (DOE IP) released the *2020 Annual Update on Medical Isotopes*. The document details ongoing research, development, and production of medically relevant isotopes within the DOE IP and includes updates to program initiatives such as stable isotope production, isotope harvesting, nuclear data, and the University Isotope Network. The DOE Isotope Program supports production and associated techniques of radioactive and stable isotopes that are in short supply for research and other applications. A goal of the program is to make critical isotopes more readily available to meet domestic U.S. needs. The program coordinates and supports isotope production at universities, national laboratories, and commercial accelerator and reactor facilities throughout the United States to produce a reliable supply of domestic isotopes. Included are the medically relevant isotopes $^{225}\text{Ac}/^{213}\text{Bi}$, ^{227}Ac , ^{72}As , ^{211}At , ^{60}Co , ^{67}Cu , ^{177}Lu , $^{212}\text{Pb}/^{212}\text{Bi}$, ^{223}Ra , ^{227}Th , $^{228}\text{Th}/^{224}\text{Ra}$, ^{89}Sr , ^{90}Sr , $^{188}\text{W}/^{188}\text{Re}$, ^{86}Y , and ^{65}Zn . ^{99}Mo is not within the program's purview and is overseen by the National Nuclear Security Administration, a semi-autonomous agency within the DOE. The DOE IP also makes investments to develop new production and processing capabilities for critical isotopes.

The DOE IP is the only mission-essential program within the DOE Office of Science. Throughout the COVID-19 pandemic, the program's operations have been staffed and operational. Irradiations, processing, and purification operations continue, with shipments made to both domestic and international users.

Updates to DOE IP Initiatives

Enriched Stable Isotope Production. The DOE discontinued producing enriched stable isotopes in the Y-12 Plant calutrons (Oak Ridge, TN) in 1998. To reestablish this domestic capability, the DOE IP commissioned a prototype stable isotope enrichment plant at Oak Ridge National Laboratory (ORNL). Using an electromagnetic isotope separator (EMIS), it produced the world's only supply of ^{96}Ru . ORNL is now using the machine to develop methods for producing highly enriched ^{176}Yb for use in the production of no-carrier-added ^{177}Lu . Meanwhile, a small cascade of gas centrifuges was effective at enriching small quantities of ^{98}Mo and ^{100}Mo . The DOE IP is supporting a substantial scale-up of the prototype plant and has provided funds to

install several additional EMIS machines to expand production in the next few years. Starting in 2025, the Stable Isotope Production Facility will host an expanded centrifuge capability dedicated to producing enriched ^{129}Xe for hyperpolarized lung imaging. Further expansions are planned in the \$230-million Stable Isotope Production and Research Center at ORNL. With commissioning of the center planned around 2028, DOE will be capable of using multiple technologies and making multiple products simultaneously under 1 roof.

Facility for Rare Isotope Beams (FRIB) Isotope Harvesting. The DOE Office of Nuclear Physics is constructing the FRIB at Michigan State University (East Lansing). The DOE IP will establish isotope harvesting there to provide large quantities of rare isotopes starting around 2024.

Nuclear Data. The accelerators at Brookhaven National Laboratory (BNL; Upton, NY) and Los Alamos National Laboratory (LANL; NM) both recently underwent upgrades to increase production and analytical capabilities. A collaborative effort of BNL, LANL, and Lawrence Berkeley National Laboratory (CA) is underway to provide nuclear data of importance to the isotope community and allow the DOE IP to take full advantage of improvements to increase production yields at these facilities.

University Isotope Network (UIN). Two universities were selected for research funding in FY 2019 and an additional 4 for FY 2020 to encourage development of routine isotope production capabilities or production-related technologies. These awards aim to bolster DOE IP efforts to establish a regional production network for short-lived medically relevant isotopes or boutique isotopes for which there are no commercial suppliers.

Also detailed in the annual DOE IP report were updates on individual α -emitters, emerging isotopes, newly available isotopes, isotopes under development, and other routinely available medically relevant isotopes (including diagnostic, therapeutic, and theranostic combinations).

For more information on the availability of current or new isotopes contact the National Isotope Development Center at contact@isotopes.gov. For a full list of isotopes produced by the DOE IP and to request a quote, see www.isotopes.gov. Signing up at www.isotopes.gov/subscribe allows users to receive announcements and newsletters from the DOE IP, focusing on information about isotope availability, DOE IP funding opportunity announcements, and breaking news.

Improving Radionuclide Availability

Alan B. Packard, PhD, 2020–2021 SNMMI President

In 2009, the unexpected shutdown of the National Research Universal (NRU) reactor at Chalk River in Canada led to a worldwide shortage of ^{99}Mo from which nuclear medicine has yet to completely recover. Recently, however, there has been significant progress in the production of both ^{99}Mo and other radionuclides that are essential to the practice of nuclear medicine. SNMMI is committed to supporting improvements in the radionuclide supply chain so that nuclear medicine practitioners and patients are not faced with similar shortages in the future.

Although the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator was developed in the late 1950s, it was not until 1970, when the “instant kit” was developed, that there was a rapid expansion in the development of new $^{99\text{m}}\text{Tc}$ radiopharmaceuticals. The development of new $^{99\text{m}}\text{Tc}$ radiopharmaceuticals was so successful that more than 80% of all nuclear medicine procedures are now performed with $^{99\text{m}}\text{Tc}$ —more than 15 million studies per year in the United States. The continued use of these radiopharmaceuticals depends on reliable sources of ^{99}Mo for production of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators that supply the $^{99\text{m}}\text{Tc}$. However, while the United States consumes approximately 50% of all ^{99}Mo produced worldwide, the ^{99}Mo used here is produced primarily at facilities located outside the country.

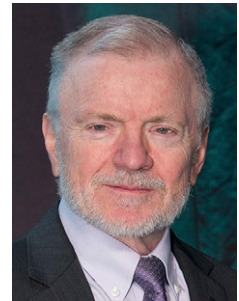
The absence of domestic ^{99}Mo production became a significant problem during the 2000s, with several unwelcome developments. The most dramatic was the 9/11 terrorist attacks, which raised significant concern about terrorists gaining access to the highly enriched uranium (HEU) used to produce ^{99}Mo . The second was the 2009 NRU reactor shutdown, which lasted more than a year and caused a worldwide shortage of ^{99}Mo .

These issues led the U.S. Congress to pass the American Medical Isotope Production Act (AMIPA) in 2013. This legislation mandated that the U.S. eliminate the exportation of HEU for medical isotope production by 2020 and provided \$100 million to support the development of domestic production of ^{99}Mo . It also required that this effort be “technology neutral”; in other words, it was up to applicants to develop innovative ways to make ^{99}Mo without using HEU.

Since 2013, American companies have made considerable progress in developing a reliable domestic supply of ^{99}Mo that does not rely on HEU, in some cases with the support of AMIPA and in some cases without. Companies supported by AMIPA include:

- NorthStar Medical Radioisotopes (Beloit, WI), which introduced its RadioGenix generator in 2018 and continues to improve their ^{99}Mo production process;

- SHINE Medical Technologies (Janesville, WI), which is using a deuterium–tritium (DT) generator as a neutron source with a low-enriched uranium (LEU) solution target. The company has demonstrated that their ^{99}Mo is compatible with existing generator designs and expects to bring its ^{99}Mo to the market in late 2021;



Alan B. Packard, PhD

- Niowave (Lansing, MI), which is using an electron linac as a neutron source, also with an LEU solution target, and expects to be in production in 2024 or 2025; and
- Northwest Medical Isotopes (Corvallis, OR), which is using LEU targets in existing reactors, such as the University of Missouri MU Research Reactor (Columbia) and plans to enter the market in 2023.

One company not supported by AMIPA that has made considerable progress is BWX Technologies (Lynchburg, VA), which is using the Ontario Power Generation reactors to irradiate novel ^{98}Mo targets and produce high specific activity ^{99}Mo . BWX Technologies has developed a new generator that is approximately the same size as existing generators and can produce $^{99\text{m}}\text{Tc}$ that is compatible with existing kits.

SNMMI has been working closely with U.S. government agencies, particularly the Department of Energy, as well as industry and other stakeholders in the United States and internationally, and will continue to do so until there is a reliable domestic supply of ^{99}Mo . During the COVID-19 pandemic, SNMMI worked with government and industry to alleviate transportation problems caused by the sharp decrease in international flights. Moving forward, SNMMI will continue to keep its members informed on new developments in the status of ^{99}Mo production and availability.

Beyond the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator, innovation in radionuclide production extends in many other directions. One example is the development of a cyclotron method for production of ^{68}Ga that circumvents the shortage of ^{68}Ge used in the $^{68}\text{Ge}/^{68}\text{Ga}$ generator while possibly also reducing costs. A second example is development of alternative production methods for ^{225}Ac to supplement the limited supply of ^{225}Ac available from the Oak Ridge National Laboratory (TN) ^{229}Th generator. These innovations are enhancing the supply of radionuclides essential to nuclear medicine, providing the foundation the profession needs to grow and advance.

FDA Guidance on Clinical Trial Diversity

The U.S. Food and Drug Administration (FDA) on November 9 issued final guidance to ensure that individuals in clinical trials represent the populations most likely to use the potential medical product under investigation. In an accompanying statement, Stephen M. Hahn, MD, FDA Commissioner, noted that one important step that researchers and medical product sponsors can take to confront health care disparities is to make sure that clinical trials for medical products are more inclusive of multiple populations.

The statement read, in part: “We have seen these health care disparities, for example, during our fight against COVID-19, as certain segments of the population (e.g., older adults, pregnant women, children, and racial and ethnic minorities) are affected in different ways. This difference in impact illustrates why we must encourage developers of any medical product such as treatments or vaccines for COVID-19—as well as medical products more broadly—to endeavor to include diverse populations to understand their risks or benefits across all groups. To further promote and protect public health, it is important that people who are in clinical trials represent the populations most likely to use the potential medical product.” The guidance includes recommendations on designing and executing clinical trials of drugs and biologics that include people with different demographic characteristics (e.g., sex, race, ethnicity, age, location of residency) and nondemographic characteristics (e.g., patients with organ dysfunction, comorbid conditions, and disabilities; those at weight range extremes; and populations with diseases or conditions with low prevalence).

The guidance, first issued as a draft in 2019, provides the agency’s current thinking on steps to broaden eligibility criteria in clinical trials through inclusive trial practices, trial designs, and methodologic approaches. The guidance

aims to provide recommendations on how sponsors can increase enrollment of underrepresented populations in their clinical trials as well as on how product sponsors can improve clinical trial diversity by accounting for logistic and other participant-related factors that could limit participation. For example, clinical trials requiring frequent visits to specific sites may place an added burden on participants. Sponsors are encouraged to think about reducing visit frequency, when appropriate, in addition to considering whether flexibility in visit windows is possible and whether electronic communications (such as phone, email, social media platforms, or other digital health technology tools) can replace site visits and provide investigators with real-time data.

The guidance provides recommendations on broadening clinical trial eligibility criteria for investigational drugs intended to treat rare diseases and on improving enrollment and retention of participants with rare diseases. The guidance notes that sponsors should consider early engagement with patient advocacy groups and patients to elicit suggestions for designing trials in which participants would be willing to enroll. The guidance also includes other high-level considerations about inclusion of other important groups, including but not limited to: women (including pregnant women), racial and ethnic minorities, children, and older adults, and provides references to more specific guidances. The complete guidance document is available at: <https://www.fda.gov/media/127712/download>.

U.S. Food and Drug Administration

⁶⁴Cu-SARTATE Receives Rare Pediatric Disease Designation

Clarity Pharmaceuticals (Sydney, Australia) announced on September 9 that the U.S. Food and Drug Administration (FDA) had granted Rare Pediatric Disease Designation (RPDD) to ⁶⁴Cu-SARTATE, a diagnostic for clinical management of neuroblastoma. Alan

Taylor, PhD, Clarity’s Executive Chair, said, “We are very excited to have received the RPDD status for the diagnostic application of SARTATE in children with neuroblastoma. This comes shortly after Clarity has been granted RPDD for the treatment of neuroblastoma with ⁶⁷Cu-SARTATE for the therapeutic application, announced on the 3rd of June 2020.”

The FDA defines an RPD as a serious or life-threatening disease primarily affecting individuals aged 18 years or younger that impacts fewer than 200,000 people in the United States. The program is intended to facilitate development of new drugs and biologics for prevention and treatment of RPDs. Neuroblastoma accounts for ~15% of pediatric cancer mortality, and high-risk neuroblastoma accounts for ~45% of all neuroblastoma cases, with 5-year survival rates of only 40%–50%.

“We have seen incredibly strong support from our collaborators and advisors in the development of SARTATE for neuroblastoma and are looking forward to the results from our U.S.-based trial at the Memorial Sloan Kettering Cancer Center [MSKCC; New York, NY],” said Taylor. “It is evident that there is a large unmet need in the management and treatment of this devastating disease, and we are aiming to improve outcomes for this important patient population with both the diagnostic and therapeutic applications of SARTATE.” The trial, “⁶⁷Cu-SARTATE peptide receptor radionuclide therapy administered to pediatric patients with high-risk neuroblastoma: A multi-center, dose-escalation, open-label, non-randomized, phase 1-2a theranostic clinical trial” (NCT04023331), plans to enroll 34 participants in the investigation of the paired radiopharmaceuticals. MSKCC is currently recruiting, and sites in Ohio, South Carolina, Texas, and Wisconsin will begin enrollment soon. Clarity announced on November 3 that ⁶⁷Cu-SARTATE treatment had been initiated

in the first patient at MSK, following a positive diagnostic scan with ^{64}Cu -SARTATE.

One incentive the FDA provides to companies for the investment required in developing agents for diagnosis and treatment of RPDs is eligibility for a tradable Priority Review Voucher (PRV). The PRV shortens the FDA review period for a New Drug Application (NDA) for another product to an expedited period of 6 months, which is a significant benefit for drug developers. PRVs may be sold or transferred to another company. To date, PRVs have been sold for between \$67.5 million and \$350 million, with the most recent PRV being purchased by Merck from Lumos Pharma for a value of \$100 million in July 2020.

Clarity Pharmaceuticals

IAEA and GACCF to Advance Oncology Training

The International Atomic Energy Agency (IAEA) and the Global Access to Cancer Care Foundation (GACCF) announced on November 3 the signing of a collaboration to help authorities in low- and middle-income countries train nuclear medicine and radiation treatment professionals in cancer care, with a special focus on training to provide quality cancer care for women and children. The program will work through virtual training courses and on-location teaching to practitioners in health facilities, will mobilize resources to support

countries in the establishment of nuclear and radiation medicine services, and will raise awareness of unequal access to cancer services. Both organizations already provide training to the staff of treatment centers across the developing world and indicated that by harmonizing their efforts, these activities can more easily be scaled up.

“This new partnership will not only support the work the IAEA is already doing in terms of enhancing training for cancer care professionals worldwide, but it also represents a new way of engaging with global partners like foundations and the private sector to accelerate the adoption of latest know-how on how to use nuclear technologies to effectively and sustainably offer cancer treatment to much larger numbers of patients in developing countries,” said IAEA Deputy Director General Dazhu Yang.

“GACCF is on the front lines providing life-saving cancer treatment education for medical specialists and creating access to radiotherapy treatments throughout the developing world. Together with the IAEA we will be able to provide cancer care professionals with the education and tools they need to save lives,” said Tonya Steiner, Executive Director and CEO of GACCF.

International Atomic Energy Agency

Pheo Para Alliance CoE Clinical Care Program

Pheo Para Alliance (Bethesda, MD), a patient advocacy group, announced on November 17 the launch of its Center of Excellence Program intended to “provide an environment where patients receive the best possible pheochromocytoma and paraganglioma care through a geographically diverse network of clinical centers.” An open call for applications from interested health care institutions was set to open on January 1, with a deadline of March 15. The group’s medical advisory board, including physicians and researchers in pheochromocytoma and paraganglioma, created the program’s criteria with the goals of: increasing access to multidisciplinary, coordinated clinical care for diagnosis and treatment of these diseases; educating professionals and newly diagnosed patients and their families; and facilitating related research. The program offers 2 designations. The Clinical Center designation recognizes emerging centers providing quality, multidisciplinary patient care and facilitate pheochromocytoma and paraganglioma research. The Center of Excellence designation recognizes centers that provide cutting-edge, quality, multidisciplinary care and actively participate in pheochromocytoma and paraganglioma research. The Alliance plans to announce its first designated centers in early 2021. More information is available at <http://www.pheopara.org/coe>.