2019 SNMMI Highlights Lecture: Oncology and Therapy

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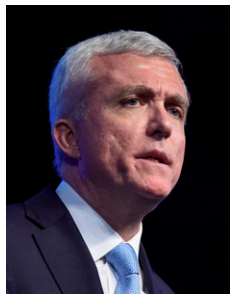
From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2019 Highlights Lectures were delivered on June 25 at the SNMMI Annual Meeting in Philadelphia, PA. In this issue we feature the first part of the lecture by Andrew 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 2 will appear in the February 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 *(2019;60 [suppl 1]).*

It is an honor to be here to give the Oncology and Therapy Highlights of the 2019 SNMMI Meeting. At the 2019 meeting of the American Society of Clinical Oncology (ASCO), which was held 3 weeks ago in Chicago (IL), a number of presentations focused on what were considered to be the major advances in oncology in the last 12 months. Progress in rare cancers was named the ASCO Clinical Advance for 2019 (https://www.asco.org/research-progress/reports-studies/clinical-cancer-advances-2019/clinical-cancer-advances-2019-glance). Of the 5 cited principal areas of major progress in rare cancers for the last year, one was a nuclear medicine therapy, the first in more than 30 years: ^{177}Lu-DOTATATE in somatostatin receptor–positive midgut neuroendocrine tumors. This is a reflection of the profile that nuclear medicine is achieving in the oncology community. As a consequence, these are exciting times as we move forward with new diagnostics and therapeutics. As part of their review, ASCO also announced what they considered to be the great challenges in oncology across the world and identified new research priorities to meet these challenges, including:

- Identifying strategies that better predict response to immunotherapies;
- Better defining patient populations that benefit from postoperative (adjuvant) therapy;
- Translating innovations in cellular therapies to solid tumors;
- Increasing precision medicine research and treatment approaches in pediatric cancers; and
- Increasing equitable access to cancer clinical trials.



Andrew Scott, MD

Most of these priorities are, in fact, related to work that is currently being done in nuclear medicine, particularly in research on strategies that better predict response to immunotherapies and predictive factors for response to adjuvant therapy. In addition, we have the capability to assist with development of cellular therapies. We are supported in this effort by our expertise and experience in clinical precision medicine and access to cancer clinical trials. Over the last few years in nuclear medicine globally we have seen a marked increase in adoption and progress of clinical trials, particularly in oncology. We are therefore quite well positioned, strategically, to move the field forward.

One of the challenges when reviewing Oncology and Therapy abstracts at the SNMMI meeting is that they constitute a very large proportion of all abstracts presented. Oncology was the focus of 696 presentations, or 53% of all scientific abstracts. Fewer than 3% could be covered in this presentation, and I apologize that I was not able to present on every abstract. Presenters this year came from 34 countries. Of those focusing on clinical therapy and diagnosis, 80% came from outside the United States. Of those focusing on basic and translational oncology topics, 64% came from outside the United States. These statistics highlight the global influence of the SNMMI meeting.

In this lecture, I will be touching on 5 main themes that I think encompass the principal areas of focus at this meeting from a diagnostic and therapeutic oncology perspective. These are: novel molecular imaging probes; immunooncology, which is such an important advance in the treatment of many types of cancers; molecular imaging in treatment response assessment; prostate cancer, which has such a very strong focus within nuclear medicine at the moment in imaging and theranostics; and novel therapeutics and trials.

Novel Molecular Imaging Probes

When thinking about novel imaging probes, it is important to think holistically as to what is the nature of a cancer and what it is about a cancer that actually causes it to grow in an unrestricted way and allows it to metastasize. This provides context to the targets and the metabolic processes for which we can evaluate. It is in that context that I encourage you to always think of a cancer not merely as a group of cells but also to also consider the tumor

microenvironment. Novel targets for imaging probes may involve tumor cells (e.g., cell surface receptors, signaling pathways, and metabolic processes), the tumor supporting structures (e.g., vasculature, lymphatics, extracellular matrix, and fibroblasts), and cellular infiltrates (which can be inflammatory, immune activating, immune suppressive, or bone marrow derived). Changes in the microenvironment can impact responses to standard chemotherapies, biologic therapies, and immunotherapy. Two of the key components of the tumor microenvironment are fibroblasts and extracellular matrix, which form the basic structure from which small tumors grow, and which is essential for metastatic lesions to grow beyond small cell clusters.

Giesel et al. from University Hospital Heidelberg and the Nationale Centrum für Tumorerkrankungen Heidelberg (Germany) reported on "Intensity of tracer uptake in FAPI-PET/CT in different kinds of cancer" [289]. These researchers have introduced a revolutionary approach to the targeting of cancers through identifying a small molecule that can bind to fibroblast activation protein (FAP), which is expressed on activated fibroblasts within the marker environment of cancers. FAP was first reported more than 25 years ago as part of a program to identify new targets in the microenvironment of cancers. Although prior clinical studies have evaluated antibodies against FAP, the small molecule that this group has generated and labeled with ^{68}Ga has shown remarkable imaging results across a broad range of cancer types. The main tumor type that typically expresses FAP is soft tissue sarcomas (and only a portion of those), so it is clear that this tracer is targeting fibroblasts in the tumor microenvironment. The spectrum of tumor types showing uptake of the FAP tracer can be seen in Figure 1, highlighting the potential for FAP targeting and imaging, which may also lead in the future to opportunities for new therapies. This image was named the 2019 SNMMI Image of the Year, not only for the results in a wide range of cancers but for the potential of FAP-targeted diagnostics to serve as a predictive biomarker, enhancing identification of appropriate patients for specific treatments.

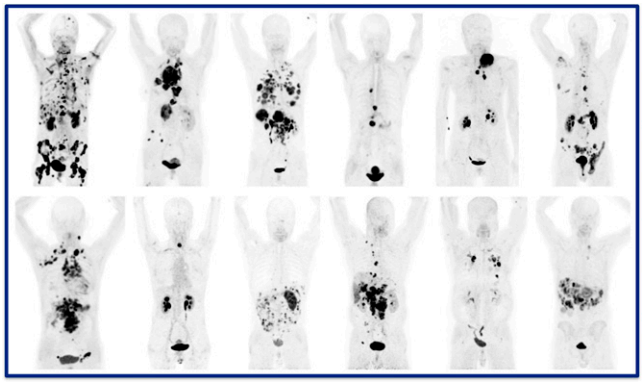


FIGURE 1. ^{68}Ga-FAPI PET/CT in patients reflecting 12 different tumor entities. Top row, left to right: breast cancer, non–small cell lung cancer, colorectal cancer, pancreatic cancer, carcinoma of unknown primary, and prostate cancer. Bottom row, left to right: ovarian cancer, esophageal cancer, small intestine cancer, cholangiocarcinoma, sarcoma, and gastroenteropancreatic neuroendocrine tumor. This image was named the 2019 SNMMI Image of the Year, not only for the results in a wide range of cancers but for the potential of FAP-targeted diagnostics to enhance identification of appropriate patients for specific treatments.

FAP expression is also present in wound healing and in fibrotic conditions. Röhrich et al. from the Charité Universitätsmedizin Berlin (Heidelberg, Germany) and the Universitätsklinik Heidelberg (Germany) reported on "Fibroblast activation protein–specific PET/CT imaging in idiopathic pulmonary fibrosis with lung cancer" [298]. These researchers explored imaging results in pulmonary fibrosis in 9 patients with interstitial lung disease (ILD) and lung cancer and also evaluated a mouse model of ILD (Fig. 2). Dynamic uptake curves were evaluated in blood pool and areas of fibrosis and tumor. Fibrosis showed rapid plateauing of uptake, which slowly declined with time; however, tumor uptake showed a gradual progressive increase in uptake and then gradual decline, clearly indicating a potential kinetic difference between benign fibrotic conditions and cancer. As these conditions can overlap in patients, this information is very important in assisting with appropriate diagnosis.

Ulaner et al. from Memorial Sloan Kettering Cancer Center (New York, NY) reported on "^{89}Zr-trastuzumab PET/CT for prediction of response to HER2-targeted therapy in patients with HER2 mutant lung cancer: An exploratory phase 2 trial" [144]. They looked at ^{89}Zr-trastuzumab targeting as an immunoPET tracer and biomarker to predict response to trastuzumab emtamzine (T-DM1) therapy. T-DM1 treatment is U.S. Food and Drug Administration (FDA) approved in HER2-positive breast cancer. In this study they focused on HER2-positive lung cancer patients to see whether imaging could predict potential response to T-DM1 treatment. In the patient shown in Figure 3, uptake of the antibody is seen within the area of the tumor in the right lung, in comparison to the metabolic uptake of ^{18}F-FDG before and after T-DM1 therapy. The uptake of the ^{89}Zr-trastuzumab tracer itself was very predictive of response to

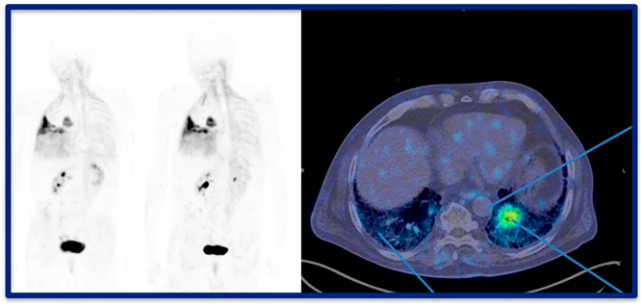


FIGURE 2. FAP-specific PET/CT in pulmonary fibrosis with lung cancer. Left: Tracer uptake in a patient with idiopathic lung fibrosis at 10 and 60 min after injection. Right: PET/CT of pulmonary fibrosis, used to generate dynamic curves for perfusion, fibrosis, and tumor. The perfusion curve (not pictured) showed the classic washout of a small molecule. Fibrosis rapidly plateaued and then slowly declined. Tumor uptake, however, showed a gradual progressive increase and then gradual decline, clearly indicating a potential kinetic difference between benign fibrotic conditions and cancer.

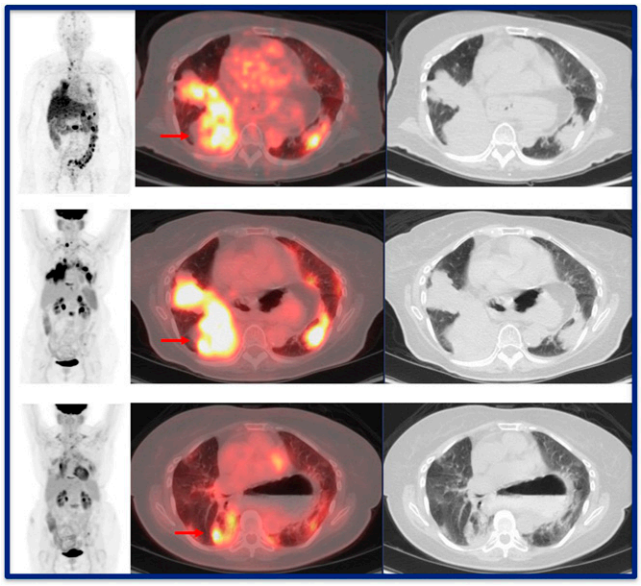


FIGURE 3. ^{89}Zr-trastuzumab PET/CT for prediction of response to trastuzumab emtamzine (T-DM1) therapy in patients with HER2 positive lung cancer. PET images acquired with: (top row) pretreatment ^{89}Zr-trastuzumab, demonstrating tracer-avid lung malignancy (arrow); (middle row) pretreatment ^{18}F-FDG PET demonstrating an ^{18}F-FDG–avid right lung malignancy (arrow); and (bottom row) ^{18}F-FDG PET acquired 8 weeks after initiation of HER2-targeted therapy demonstrating a partial metabolic response (arrow). Uptake of ^{89}Zr-trastuzumab was highly predictive of response to T-DM1 therapy.

T-DM1 therapy. These types of biomarker studies are essential if we are going to understand the best way to select patients for this type of treatment. This is an innovative study, and I commend this group for using a theranostic approach to understand the way that antibody drug conjugate therapies may work in patients.

Kang et al. from Peking University First Hospital (Beijing, China), the University of Wisconsin–Madison, and the Shanghai Jiao Tong University Affiliated Sixth People's Hospital (China) reported on "^{64}Cu-labeled F(ab')$_2$ fragments of daratumumab for early visualization of CD38-positive lymphoma" [350]. These researchers generated F(ab')$_2$ fragments of an antibody that binds to CD38, which is expressed in a large proportion of lymphomas. They labeled these antibody fragments with ^{64}Cu and, in mouse models of lymphoma, were able to show very high uptake extending for up to 48 hours (Fig. 4), compared to uptake in controls and also to the intact antibody. We know that F(ab')$_2$ fragments have faster blood clearance, and, therefore, tumor-to-blood ratios can be improved. This is an elegant way to demonstrate a probe that could potentially be used to predict responsiveness to this CD38 treatment approach.

Urothelial bladder cancer (UBC) can present diagnostic challenges. We know that ^{18}F-FDG studies are problematic in UBC because of normal renal tracer excretion. Thakur et al. from Thomas Jefferson University/Hospital (Philadelphia, PA), Johns Hopkins Medicine (Baltimore, MD), and Kahramanmaras Sutcu Imam University (Turkey) reported on "PET imaging of urothelial bladder cancer: Addressing an unmet need" [502]. This group hypothesized that vasoactive intestinal peptide and pituitary adenylate cyclase–activating peptide receptors expressed in high density on UBC cells can be targeted by PET to identify locoregional disease and metastatic lesions. They used the TP3805 molecule labeled with ^{64}Cu in 15 patients diagnosed with invasive UBC scheduled for radical cystectomy. Presurgical images were compared with surgical pathology. As seen in the patient study in Figure 5, they were able to demonstrate remarkable images of tracer uptake in the bladder tumor. In this study the tracer showed 91% sensitivity, 100% specificity, 100% positive predictive value, and 80% negative predictive value. I like this study, because it shows an innovative approach to a common clinical question that is quite difficult to address. This first-in-human study of UBC imaging provides data that point to possible future applications in therapy.

In a cohort of patients with a very complex clinical condition, multiple endocrine neoplasia type 1 (MEN-1), Antwi and colleagues from the Hôpital Bicêtre University (Paris, France), Lille University Hospital (France), the University of Bern (Switzerland), University Hospital Basel (Switzerland), and the Royal Free Hospital (London, UK) reported that "^{68}Ga-exendin-4 PET/CT detects insulinomas in patients with hypoglycemia in multiple endocrine neoplasia type 1" [477]. They developed a ^{68}Ga-labeled probe against the glucagon-like peptide-1 receptor (GLP-1R) and were able to show quite exquisite uptake within very small lesions (Fig. 6). Using both PET and MR together, they were able to identify very small insulinomas in patients with endogenous hyperinsulinemic hypoglycemia in whom standard anatomic imaging had great difficulty in identifying the state of disease. In this context and in this particular cancer type, this provides an opportunity to markedly improve our accuracy in staging this disease. The authors concluded that GLP-1R PET/CT can not only selectively identify insulinomas among multiple pancreatic neuroendocrine tumors in patients with MEN-1, but that, in combination with MR, it has the potential to guide surgical procedures and avoid unnecessary pancreatic resections, a result that could render "blind" pancreatic resections obsolete. This was a very interesting study that I hope will be extended into larger, multicenter studies in the future.

Immunooncology

Immunooncology remains one of the most important new treatments in cancer care. Those of us who are imaging oncology patients on a routine basis will be seeing more and more patients who are being treated with immune checkpoint therapy. A broad range of targets and therapeutic antibodies are now approved (Table 1), aiming to release the normal immune system response to cancer by targeting immune checkpoints that exist within tumors. In the programmed cell death–1 protein/programmed death ligand–1

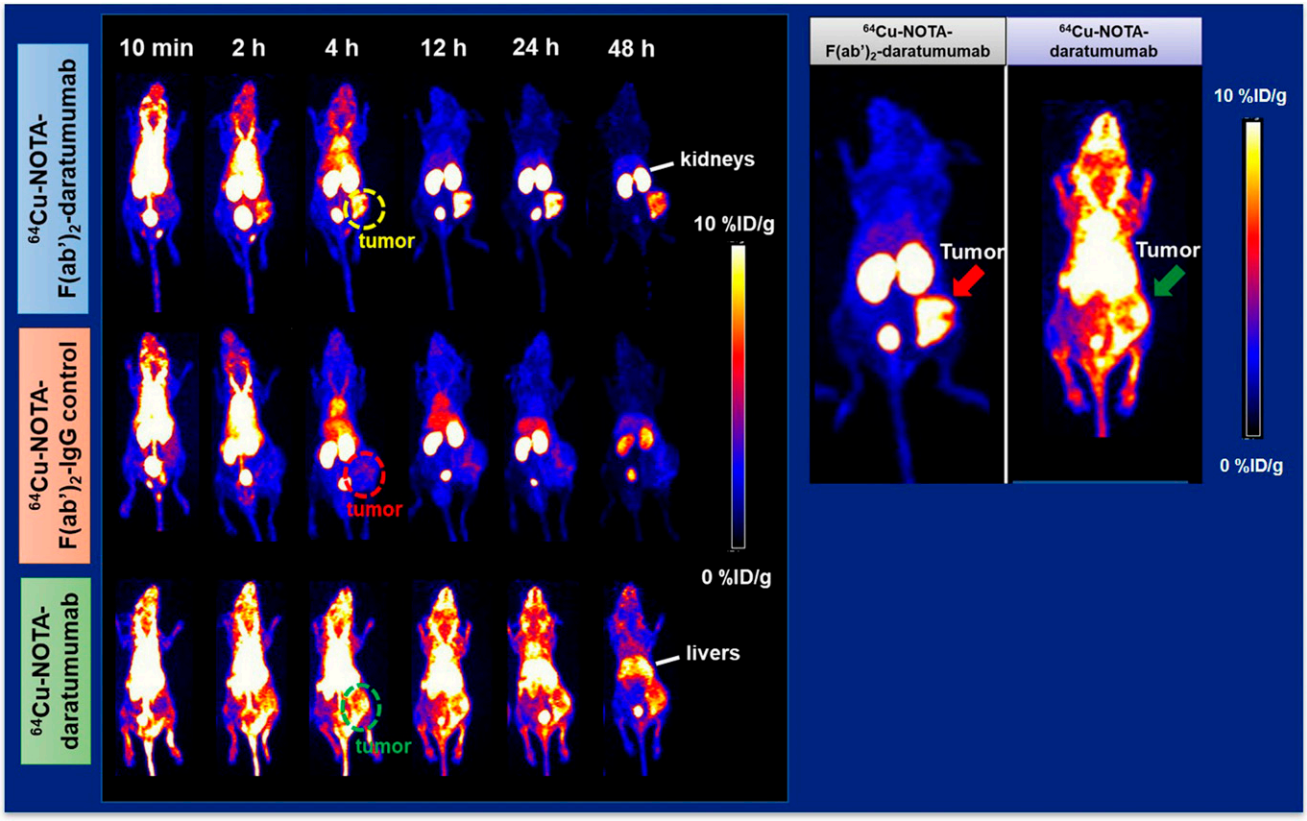


FIGURE 4. ^{64}Cu-labeled F(ab')$_2$ fragments of daratumumab for early visualization of CD38-positive lymphoma. Left block: Imaging at 10 minutes and 2, 4, 12, 24, and 48 hours with ^{64}Cu-NOTA-F(ab')$_2$ daratumumab (top row); ^{64}Cu-NOTA-F(ab')$_2$-IgG (control) (middle row); and ^{64}Cu-NOTA-daratumumab (bottom row). Right block: Enlarged focus on difference in imaging results at 12 hours with ^{64}Cu-NOTA- F(ab')$_2$ daratumumab (left) and ^{64}Cu-NOTA-daratumumab (right). This probe has potential usefulness in predicting responsiveness to CD38 treatment approaches.

(PD-1/PD-L1) space alone, an enormous amount of clinical activity is already underway. In a recent review article, Tang et al. (*Nature*. 2018;17:854–855) reported that more than 2,250 active trials are currently exploring therapy with PD-1/PD-L1 inhibitors. These trials do not just focus on PD1/PD-L1 antibodies alone, and many trials are evaluating their effects in combination with different antibodies, chemotherapy, and other therapeutics.

The complexity of the immune response to these agents, often amplified in combination treatment studies, creates significant challenges in interpreting both therapeutic responses and toxicities. This is also the case because, despite the fact that remarkable responses are being achieved in many individuals, not all patients respond to treatment, and responses also vary depending on the type of cancer. Moreover, combined immune checkpoint therapy, for example PD-1 and CTLA-4 inhibitors together, can be delivered to increase response but with markedly increased toxicity. Assessment of response is also challenging because true assessment may take time, and patients can appear to get worse before they actually respond. Toxicity profiles can be complex, and patients may present with changes on imaging studies before these are evident clinically, which means that we must focus more closely on the ways in which we analyze and assess these patients. Most of these patients will be coming to nuclear medicine for ^{18}F-FDG PET scans as part of their staging, and they will have many scans during their treatment course.

Molecular Imaging of Response to Immunotherapy

Iravani et al. from the Peter MacCallum Cancer Center (Melbourne, Australia) and St. Louis University (MO) reported on "Response assessment and immune-related adverse events as detected by FDG PET/CT in patients treated with combined CTLA-4 and PD-1 checkpoint inhibitors as first-line therapy in advanced melanoma" [647]. This group has made a number of important observations. Most adverse events tended to occur fairly early in treatment but could also occur quite late. Of note, up to 40% of immune-related adverse events were detected by ^{18}F-FDG PET/CT before these presented clinically. We are all familiar with the types of immune-response adverse events that can occur, and it is very important that we are familiar with the patterns of imaging abnormalities in order to provide accurate information to our oncology colleagues who are treating these patients.

A range of criteria have been reported to interpret ^{18}F-FDG PET in immune checkpoint therapy. In a recent article

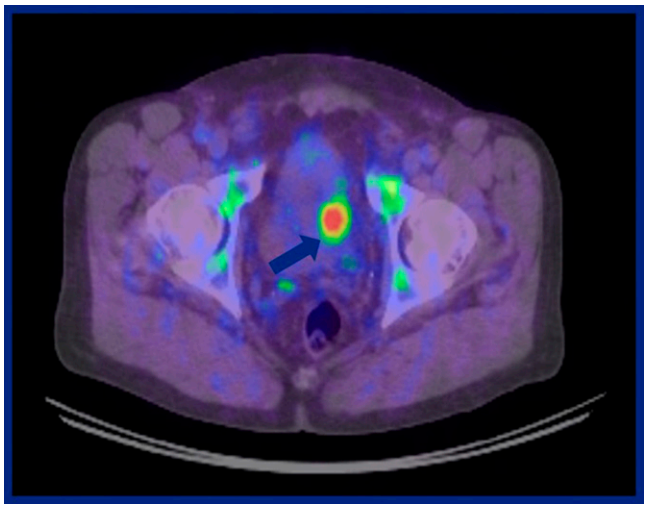


FIGURE 5. PET imaging of urothelial bladder cancer (UBC). ^{64}Cu-TP3805 was used to target vasoactive intestinal peptide and pituitary adenylate cyclase–activating peptide (VPAC) receptors expressed in high density on UBC cells, for identification of locoregional disease and metastatic lesions. Tracer uptake in UBC (arrow) was clearly evident. This was a first-in-human study of UBC imaging targeting VPAC receptors and provided data that point to possible future applications in therapy.

published in the *European Journal of Nuclear Medicine and Molecular Imaging* (2019;46:238–250), Aide et al. reviewed the literature and detailed a number of immune-related reporting schemes that can be used to interpret ^{18}F-FDG PET in patients undergoing immune checkpoint therapy. Additional refinement of such criteria was reported at this meeting by Ito et al. from the Memorial Sloan Kettering Cancer Center (New York, NY), the National Cancer Center Hospital (Tokyo, Japan), and the Technical University of Munich (Germany), who looked at "^{18}F-FDG PET/CT for monitoring immunotherapy with PD-1 blockade in patients with advanced melanoma" [645]. The study included 83 patients who were treated with PD-1 blockade (nivolumab plus ipilimumab [n = 28] and pembrolizumab [n = 55]) and who underwent PET/CT imaging before and after treatment. Imaging results were assessed using both PET Response Criteria in Solid Tumors (PERCIST) and immune PERCIST (imPERCIST), summing lean body mass–corrected SUV (SUL_{peak}) in up to 5 lesions with the highest ^{18}F-FDG uptake. Of note is that for imPERCIST the appearance of new tracer-avid lesions alone was not considered to be progressive metabolic disease (PMD). By PERCIST, 13 patients showed complete metabolic response, 25 showed partial metabolic response (PMR), 6 showed stable metabolic disease (SMD), and 39 showed PMD. When new lesions were not considered to represent PMD, the number of patients with PMD by imPERCIST decreased by 18 (shifted to 12 PMR and 6 SMD). Both assessment techniques were significantly associated with overall survival, and 2-year survival rates were quite similar between the groups as assessed by PERCIST and imPERCIST. This means we must be very careful when looking at new lesions to interpret them within the context of whether they are the result of immune-related adverse events or are truly representative of progressive disease. The clinical status of these patients often becomes a critical part of that interpretation.

As the current generation of CTLA-4, PD-1, and PD-L1 inhibitors are now being extensively used, a large group of second- and third-generation immunooncology drugs are being introduced in trials that are aiming not merely to target immune checkpoints but also to dampen the immune-suppressive environment within a cancer. This is being done by exploring the range of cellular infiltrates within specific cancers that can repress immune response, as well as other microenvironment factors. The tumor microenvironment is linked to the host immune response and to response to immunooncology drugs. Modulation of the microenvironment and immune-suppressive cells can enhance immune checkpoint therapy. Imaging of the immune environment provides important information on prognosis, prediction of response, and resistance to therapy.

Nigam et al. from the University of Pittsburgh (PA) provided a very interesting study on "Development of myeloid-derived suppressor cell (MDSC)–CD11b tracer for

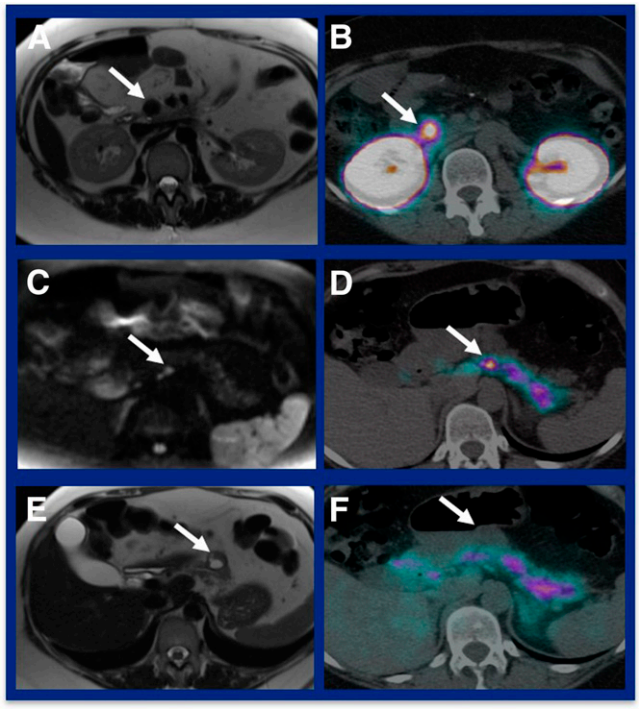


FIGURE 6. Glucagon-like peptide-1 receptor (GLP-1R) imaging in 3 patients with multiple endocrine neoplasia type 1 (MEN-1). MR (A) and MR plus ^{68}Ga-exendin-4 PET (B) showed an insulinoma ≥2 cm. (D) MR plus ^{68}Ga-exendin-4 PET showed an insulinoma <2 cm that was missed on MR alone (C). (F) MR plus ^{68}Ga-exendin-4 PET showed a nonfunctional neuroendocrine tumor that was indeterminate on MR (E). GLP-1R PET/CT may not only selectively identify insulinomas among multiple pancreatic neuroendocrine tumors in patients with MEN-1 but, in combination with MR, has the potential to guide surgical procedures and avoid unnecessary pancreatic resections.

TABLE 1
Approved Immunooncology Drugs

Therapy type	Therapy name	Company	Target
Immune checkpoint	Ipilimumab	Bristol-Myers Squibb	CTLA-4
	Nivolumab	Myers Squibb	PD-1
	Pembrolizumab	Merck	PD-1
	Atezolizumab	Roche/Genentech	PD-L1
	Avelumab	Merck KGaA	PD-L1
	Durvalumab	AstraZeneca/Medimmune	PD-L1
T-cell therapy	Tisagenlecleucel	Novartis AG	CD19
	Axicabtagene ciloleucel	Gilead	CD19
CD3-bispecific	Blinatumomab	Amgen	CD19, CD3

Adapted from Tang J, Shalabi A, Hubbard-Lucey VM, "Comprehensive analysis of the clinical immune-oncology landscape" (*Ann Oncol.* 2018;29[1]:84–91), and used here with permission from Oxford University Press.

immune PET imaging in a glioblastoma model" [1035]. They generated an antibody that bound to mouse human CD11b, which is expressed on MDSCs. These are bone marrow–derived cells that migrate into tumors and populate the microenvironment and may be responsible for suppressing an immune response, and therefore impact on the effectiveness of immunooncology drugs. In this study an orthotopic model of glioma was evaluated (Fig. 7). High uptake of a zirconium-labeled antibody against MDSCs was shown, which is an elegant demonstration of the ability to identify microenvironment suppressive cells. The authors concluded that this immunoPET approach has the ability to quantify MDSCs and tumor-associated macrophages at the tumor site and allows for better patient stratification for immunotherapy and monitoring of targeted treatment response. I hope this group will be able to extend these studies into humans in the near future.

A very nice study was reported by Kumar et al. from Johns Hopkins Medicine (Baltimore, MD), who described "A PET imaging strategy to quantify the residence time and kinetics of antibody therapeutics at the tumor" [211]. These researchers developed a high-affinity 14-amino acid human-specific PD-L1–binding cyclic peptide labeled with ^{18}F (^{18}F-DK222). They evaluated uptake of this tracer in mice with syngeneic tumors treated with different types of PD-L1 inhibitors. After tracer injection, they saw exquisite uptake in tumors, which was reduced in mice treated with PD-L1 inhibitors. Durvalumab, which has a higher affinity to PD-L1, was shown to have a longer duration of activity compared with some of the other PD-L1 inhibitors (Fig. 8). These data led to the authors' conclusion that "Target engagement

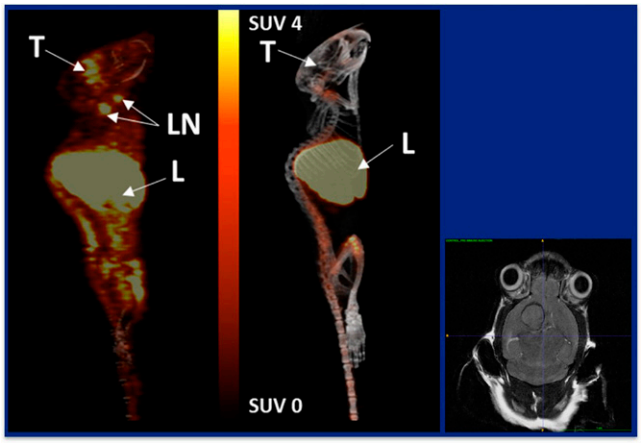


FIGURE 7. Imaging myeloid-derived suppressor cell (MDSC)–CD11b receptors in gliomas. Left block: ^{89}Zr-CD11b mAb PET/CT imaging of (left) an orthotopic mouse model of glioma 72 hours after injection and (right) imaging with a blocking dose (yielding 10-fold lower specific activity). Right image: MR imaging of a GL261 glioma in the right brain. This tracer has the potential to quantify MDSCs and tumor-associated macrophages at the tumor site and allow for better patient stratification for immunotherapy and monitoring of targeted treatment response.

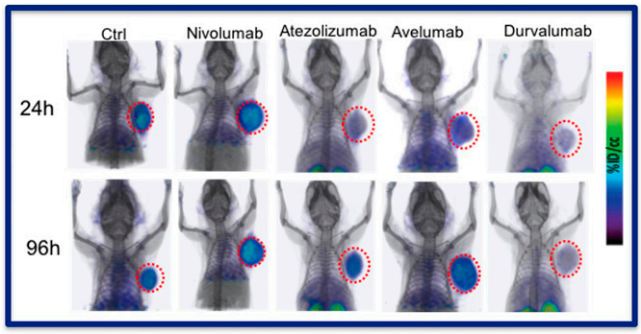


FIGURE 8. High-affinity 14-amino acid human-specific PD-L1–binding cyclic peptide (^{18}F-DK222) imaging of tumors in mice with syngeneic tumors at (top row) 24 and (bottom row) 96 hours after treatment initiation. Left to right: controls, nivolumab-treated, atezolizumab-treated, avelumab-treated, and durvalumab-treated mice. Durvalumab had a longer duration of activity compared with other PD-L1 inhibitors. This suggests a future ability to image PD-L1 in a way that predicts response to these immunooncology drugs.

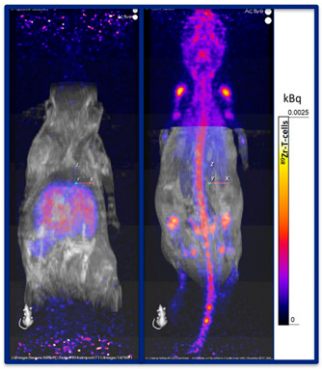


FIGURE 9. PET/MR imaging of T cell biodistribution in treatment-naïve mice after adoptive cell transfer. Biodistribution and organ uptake studies showed that both primary human and mouse T cells have similar spatial and temporal biodistribution for up to 1 week after ^{89}Zr-labeled tracer injection. This provides a technique for quantifying adoptively transferred T cells in vivo. Left: MR maximum intensity projection image after injection of ^{89}Zr-labeled T cells. Right: After injection of ^{89}Zr-[oxinate]$_4$ only.

and tumor residence kinetics of different monoclonal antibodies targeting PD-L1 can be quantified noninvasively at the tumor and independently of the biophysical properties and pharmacokinetics of the monoclonal antibodies." This opens the possibility that we may be able to image PD-L1 in a way that predicts the ability of these immunooncology drugs to cause responses in patients. As I mentioned earlier, this is one of the grand challenges that has been identified for the oncology field in the next few years.

Maria et al. from the University of Southern California Keck School of Medicine (Los Angeles) reported on "Simultaneous PET/MRI measurement of primary T cell biodistribution in naïve mice following adoptive cell transfer" [277]. These researchers asked whether there is a difference in biodistribution between trafficking of primary human T-cells in naïve NOD scid IL-2R-gamma (NSG) mice and primary mouse T cells in naïve Balb/c mice. Animals underwent simultaneous PET/MR imaging up to 5 days after injection of ^{89}Zr-labeled T cells (Fig. 9), tissues and organs of interest were dissected, and their activity was measured using a gamma counter to validate PET quantification. The conclusion was that, based on biodistribution imaging as well as measured organ uptake, both primary human and mouse T cells have similar spatial and temporal biodistribution for up to 1 week after intravenous injection. This provides a technique for quantifying adoptively transferred T cells in vivo using ^{89}Zr PET, which could potentially be extended into human studies.

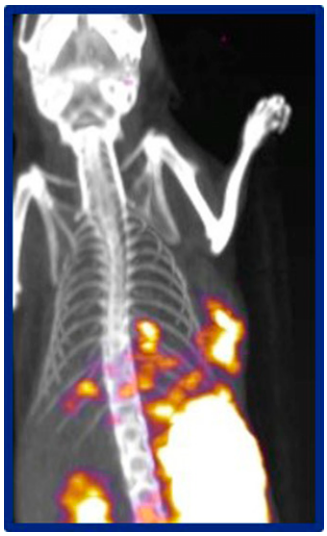


FIGURE 10. Granzyme B PET imaging to track T cells in response to immunotherapy. PET/CT imaging with a probe against granzyme B was acquired in mice bearing CT26 or MC38 syngeneic tumors at 6 or 12 days after initiation of a combined immune checkpoint anti-PD-1 plus anti-CTLA-4 therapy. Granzyme B PET identified immune phenotypes associated with response to immunotherapy.

Larimer et al. from the Massachusetts General Hospital (Charlestown) reported that "Granzyme B PET imaging permits stratified ex vivo analysis to better understand response to immunotherapy" [275] and provided important insights into the way in which the activation of T cells can be tracked by PET. They used PET/CT imaging (Fig. 10) with a probe against granzyme B in mice bearing CT26 or MC38 syngeneic tumors at 6 or 12 days after initiation of combined immune checkpoint anti-PD-1 plus anti-CTLA-4 therapy. Three-dimensional regions of interest were drawn to calculate tumor-to-blood ratios. Imaging and additional ex vivo single-cell aggregation studies and cytokine-based analyses showed a direct relationship between CD8 T cells within tumors and within draining lymph nodes as a correlate to granzyme-B uptake and the activation of T cells within these tissues. These data provide an important scientific foundation for the use of this probe as a way of looking at activated T cells in human trials and potentially predicting response to immunooncology drugs.

[*This highlight lecture will continue in the February 2020 issue of Newsline*.]