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# Harnessing imaging tools to guide immunotherapy trials: summary from the National Cancer Institute Cancer Imaging Steering Committee workshop

Lalitha K Shankar, Heiko Schöder, Elad Sharon, Jedd Wolchok, Michael V Knopp, Richard L Wahl, Benjamin M Ellingson, Nathan C Hall, Martin J Yaffe, Alexander J Towbin, Michael D Farwell, Daniel Pryma, Tina Young Poussaint, Chadwick L Wright, Lawrence Schwartz, Mukesh Harisinghani, Umar Mahmood, Anna M Wu, David Leung, Elisabeth G E de Vries, Ying Tang, Gillian Beach, Steven A Reeves

As the immuno-oncology field continues the rapid growth witnessed over the past decade, optimising patient outcomes requires an evolution in the current response-assessment guidelines for phase 2 and 3 immunotherapy clinical trials and clinical care. Additionally, investigational tools—including image analysis of standard-of-care scans (such as CT, magnetic resonance, and PET) with analytics, such as radiomics, functional magnetic resonance agents, and novel molecular-imaging PET agents—offer promising advancements for assessment of immunotherapy. To document current challenges and opportunities and identify next steps in immunotherapy diagnostic imaging, the National Cancer Institute Clinical Imaging Steering Committee convened a meeting with diverse representation among imaging experts and oncologists to generate a comprehensive review of the state of the field.

## Background

The past decade has witnessed the success of immunotherapies in treating a range of cancers, primarily driven by immune checkpoint inhibitors and genetically engineered T cells (eg, chimeric antigen receptor [CAR] T cells). Immunotherapies include several other classes of agents, such as vaccines, cytokines, and antibodies, and their derivatives (eg, radioimmunotherapy, antibody–drug conjugates, and bispecific antibodies).<sup>1</sup> Currently, immune checkpoint inhibitors are the most widely used drugs in this class. It has been recognised that certain aspects of the radiological response patterns of immunotherapies are not adequately accounted for by conventional response criteria, such as response evaluation criteria in solid tumours (RECIST) and response assessment in neuro-oncology (RANO). To better guide drug development and patient care, modified criteria have been proposed<sup>2–7</sup> and novel, complementary molecular imaging approaches are being developed to assess immunotherapy-induced changes in the tumour and its microenvironment that are more closely reflective of clinical outcomes.<sup>8,9</sup>

To provide a comprehensive review of the state of the field and offer guidance on next steps, the National Cancer Institute (NCI) Clinical Imaging Steering Committee convened a virtual meeting, entitled Harnessing Imaging Tools to Guide Immunotherapy Trials, on April 6, 2021. This meeting brought together imaging experts at the forefront of government and industry efforts to advance imaging in immunotherapy trials with the objectives of reviewing the utility of available diagnostic imaging tools (CT, magnetic resonance, F-fluorodeoxyglucose [FDG]-PET) and the current response-assessment guidelines for assessing immunotherapy, such as RECIST, immunotherapy RECIST (iRECIST), and immune RANO (iRANO) for predicting response in phase 2 and 3 immunotherapy clinical trials or clinical care; and assessing the role of

investigational tools, including image analysis of standard-of-care scans, such as CT, magnetic resonance, and PET, by use of more advanced analytics, such as texture, volume, and radiomics, functional magnetic resonance agents, and novel molecular imaging PET agents. Particular attention was paid to imaging agents that can be integrated into multicentre phase 2 and phase 3 trials in US NCI National Clinical Trials Network<sup>10</sup> and the NCI Community Oncology Research Program. This Policy Review highlights the landscape of different clinical imaging methods, including both standard-of-care and investigational approaches, and strategies and pathways for validating the novel imaging tools through either prospective trials or retrospective data analysis (table; figure; appendix pp 1–4).

## Current clinical landscape and standard of care

### The global landscape of immunotherapy oncology trials and NCI strategy

The immuno-oncology field has seen continued growth over the past several years with an increasing number of drugs in the development pipeline and in clinical trials, covering a wide range of target proteins (eg, LAG3, TIGIT, CTLA4, PD-L1, and PD-1).<sup>11</sup> There are currently two CTLA4 agents, seven PD-1 or PD-L1 agents, and one LAG3 agent that have received US Food and Drug Administration approval. There were almost 5000 immunotherapy drugs in development in 2020, and over 6000 active clinical trials investigating immunotherapy agents. This trend is also reflected in the NCI Cancer Therapy Evaluation Program. There are currently 128 active immunotherapy trials across NCI trial networks with an accrual of 8000 patients, with most investigating anti-PD-1 and PD-1 or PD-L1 as single agents or in novel combinations.

Immunotherapy has shown remarkable activity in a variety of cancers, but only a minority of patients receive durable benefit.<sup>12,13</sup> Strategies to optimise patient outcomes might rely on the use of biomarkers, including imaging

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	Current Status	Opportunities	Challenges
Clinical landscape and standard-of-care	The growth of the immuno-oncology field has necessitated modified response-assessment criteria and further development of advanced and molecular imaging approaches to better guide patient care and drug development	Continue assessment of the imaging tools under investigation to assess immuno-oncology-induced changes in the tumour and its microenvironment that could predict clinical outcomes	Need for the collection of additional data, the provision of greater access to these data, and additional clinical testing and validation; challenges in the establishment of clinical utility in predicting and monitoring clinical response to targeted immunotherapies, and the cost of and reimbursement for novel imaging agents; need for broader access to contrast agents and radiotracers
<b>Evolving size-based metrics</b>			
mRECIST	Consensus guidelines for use have been developed	Provide more accurate response assessments	Evaluation and validation is needed
Volume-based assessment	Ongoing evaluation in prospective studies as a secondary or exploratory endpoint	Utility of total tumour burden measurement and use in alternate endpoints in clinical trials	The identification of sites of disease for volumetric measurements and assessments of the accuracy of these measurements
mRANO	Evaluation in prospective studies as a secondary or exploratory endpoint	mRANO outperforms RANO and iRANO in showing a correlation between radiographic progression-free survival and overall survival	Ongoing evaluation and validation of mRANO as primary endpoint
<b>Advanced imaging techniques</b>			
PERCIST and evolving FDG-based, semi-quantitative metrics	Evaluation and application ongoing	Confirm accuracy in predicting response and identify true progression	Uneven success in assessment across disease sites
Radiomics	Advances made in computing and feature classification have enabled the quantification of image features and correlation with molecular parameters and clinical outcomes	Continue assessing improvement in evaluating response, identifying pseudoprogression, and prognosis	A complex array of factors influences the reproducibility of imaging radiomic feature extraction
Ferumoxetyl-enhanced MRI	Early application as a functional contrast agent for MRI to identify tumours that have a high density of tumour-associated macrophages, determine treatment, and assess response	Confirm whether ferumoxetyl is a biomarker for primary tumours given the colocalisation with tumour-associated macrophages in tumours	Testing is ongoing
<b>Molecular imaging agents</b>			
<sup>68</sup> Ga-NOTA-hGZP	Agent in multicentre phase 1 trial	Detect response to immune checkpoint inhibitors, tumour vaccines, and CAR T-cell-mediated cell therapy for solid tumours	Testing is ongoing
<sup>89</sup> Zr-Df-IAB2M2C	Agent in multicentre phase 2 trial	Image the distribution and abundance of CD8 <sup>+</sup> T cells in the tumour microenvironment	Confirmation of safety for repeat dosing and imaging, correlation of CD8 PET with CD8 immunohistochemistry, and correlation with RECIST and outcomes
<sup>18</sup> F-BMS-986192 (anti-PD-L1), <sup>68</sup> Ga-BMS-986192 (anti-PD-L1), <sup>89</sup> Zr-nivolumab (anti-PD-1)	Early clinical and pre-clinical testing	Evaluate as predictive biomarkers for treatment efficacy of PD-1 or PD-L1 blockade agents	Testing is ongoing
<sup>89</sup> Zr-atezolizumab (anti-PD-L1), <sup>89</sup> Zr-CX-072 (anti-PD-L1), <sup>89</sup> Zr-pembrolizumab (anti-PD-1), <sup>89</sup> ZED88082A (anti-CD8)	Studies ongoing: phase 2 study of <sup>89</sup> Zr-atezolizumab, first-in-human study of <sup>89</sup> Zr-CX-072, early clinical study of <sup>89</sup> Zr-pembrolizumab, phase 1/2 study of <sup>89</sup> ZED88082A	Investigate results that show an uptake in tumour lesions correlated with treatment response and patient survival	Testing is ongoing

RECIST=response evaluation criteria in solid tumours. mRECIST=modified RECIST. RANO=response assessment for neuro-oncology. iRANO=immunotherapy RANO. mRANO=modified RANO. PERCIST=PET response criteria in solid tumours. FDG=F-fluorodeoxyglucose. CAR=chimeric antigen receptor.

Table: Summary of the state of the field and innovations under development

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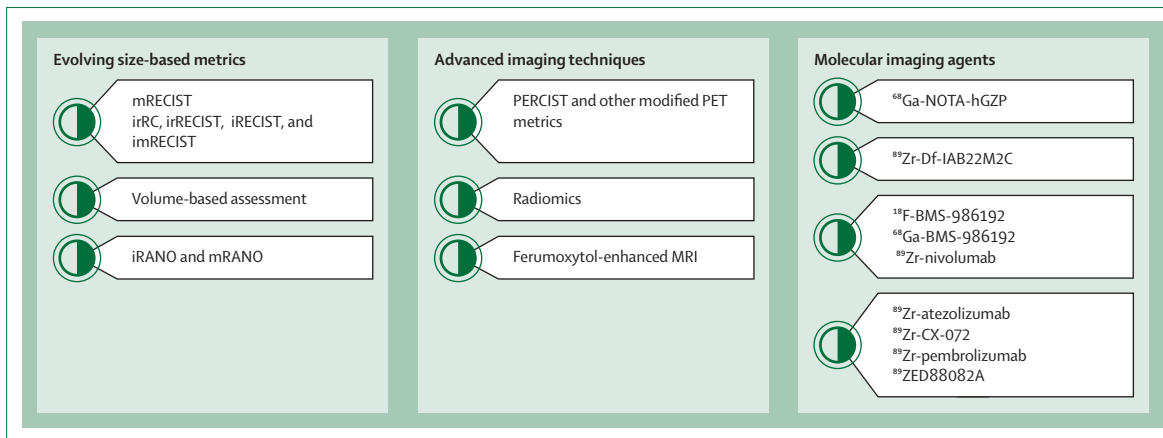
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See Online for appendix

biomarkers, to elucidate the interaction between the tumour and the immune system at the cellular and molecular levels, thereby providing insight into rational combination therapies to overcome intrinsic or acquired resistance. Imaging biomarkers might be useful in the development of immunotherapy in a range of applications, providing prognostic, predictive, or pharmacodynamic signals, or for assessment of the response to therapy. The mechanism of action for immunotherapy often involves the activation of tumour-infiltrating lymphocytes and the interplay of immune cells within the tumour microenvironment, which might manifest as enlargement of masses on CT and could be misinterpreted as tumour growth—also known as pseudoprogression (appendix p 5).

New criteria (eg, iRECIST<sup>4</sup> and immune-modified RECIST [imRECIST],<sup>5</sup> among others) that attempt to capture the differing patterns of immunotherapy treatment responses have been developed but have not yet been fully validated, primarily due to the need for ongoing collection of patient-level data to allow for proper validation of these new response criteria.

Despite tremendous progress in immunotherapy, more work remains. Collection of additional data and the provision of greater shared data access can allow for evaluations of competing criteria. Further evaluation of pseudoprogression might be improved with biopsy-driven, translational research efforts to help better characterise these phenomena.



**Figure: Imaging tools under development**

imRECIST=immune-modified response evaluation criteria in solid tumours. iRANO=immunotherapy response assessment for neuro-oncology. iRECIST=immunotherapy response evaluation criteria in solid tumours. irRC=immune-related response criteria. irRECIST=immune-related response evaluation criteria in solid tumours. mRANO=modified response assessment for neuro-oncology. mRECIST=modified response evaluation criteria in solid tumours. PERCIST=PET response criteria in solid tumours.

### Clinical characterisation and response assessment in immunotherapy

The importance of rethinking imaging in the assessment of response to immunotherapy was realised from the initial clinical trials of ipilimumab, a fully human monoclonal antibody that blocks the crucial immune checkpoint CTLA4.<sup>14</sup> In these studies, transient T-cell infiltration in the tumour microenvironment could not be distinguished conclusively from true progression with standard imaging criteria or standard imaging technologies. Also complicating the assessment is the mechanism-based time delay in response to immunotherapy compared with chemotherapy or targeted therapy, on which the traditional response criteria are based. There are general response patterns across immune checkpoint inhibitors, such as PD-1 and PD-L1 blockade agents. These patterns of response to immunotherapy might not be adequately reflected in the conventional RECIST criteria, prompting alternative response-assessment metrics based on retrospective analysis of phase 2 and phase 3 immunotherapy trial data. These metrics include immune-related response criteria (irRC),<sup>2</sup> immune-related RECIST (irRECIST),<sup>3</sup> iRECIST,<sup>4</sup> and imRECIST.<sup>5</sup> In addition to modified response criteria, innovative molecular imaging agents are being developed, which could shed light on the possibility of pseudoprogression being caused by immune infiltration. One approach that is currently in the most advanced stage of development is a zirconium-89-labelled CD8 minibody (<sup>89</sup>Zr-Df-IAB22M2C) PET-imaging agent, being studied in phase 2 clinical trials in patients being treated with immune checkpoint blockade agents (NCT03802123 and NCT05013099), which has been shown to accumulate in CD8<sup>+</sup> T cells in tumour lesions.<sup>15,16</sup>

### Evolving tumour metrics: from morphology to metabolism

Although consensus guidelines for multiple alternative response metrics (eg, irRC, irRECIST, iRECIST, and imRECIST) have been published, none have been adequately evaluated. Efforts are being made to assist with collecting additional data elements as proposed in iRECIST and ultimately to facilitate the evaluation of these modified response-assessment metrics. Other response-assessment criteria, such as PET response criteria in solid tumours (PERCIST) and RANO, are also undergoing similar evolution as immunotherapy becomes increasingly available for a broader range of cancer types.

### Modified RECIST metrics: facilitating validation of consensus guidelines for response assessment of immunotherapy

Evaluation and eventual validation of these proposed consensus guidelines for the response assessment of immunotherapy require the imaging community to continue to work closely with the clinical oncology community in implementing these modified RECIST metrics in clinical trials. The primary issue for these modified criteria is to address the concept of new lesions, which could be part of the immune response not necessarily related to progressive disease. With the collection of data, how often this phenomenon occurs in conjunction with specific therapies and in specific solid tumours can be assessed. Likewise, iRECIST might be better able to differentiate stable and progressive disease categorically in a clinical trial and in an individual patient. In some cases, stable disease alone provides clinical benefit, so it is crucial to ensure that this information is optimally collected. It is imperative that essential data elements recommended

in these guidelines are collected in a structured way not only to enable these modified RECIST metrics to be evaluated, but also to provide the ground truth for the development of new imaging tools and biomarkers for immunotherapy. To facilitate consistent data collection to maximise data usability in validating iRECIST, the NCI Imaging and Radiation Oncology Core has developed electronic forms that can be integrated into the workflow of CT and MRI in clinical care and clinical trials, making it easier for radiologists to document and collect data elements per iRECIST. These data-recording tools are being made available to the imaging community. Other network groups also have similar initiatives to facilitate consistent data collection (appendix pp 1–4). These studies are assessing the performance of both RECIST and iRECIST in predicting clinical outcomes, such as progression-free survival.

#### Modified RANO (mRANO)

The first radiographic response assessment specific to brain tumours was introduced in 1990 by Macdonald and colleagues<sup>17</sup> by substantially improving upon the Levin criteria<sup>18</sup> and the WHO oncology response criteria.<sup>19</sup> The Macdonald criteria were retained as the standard response-assessment criteria for over 20 years. The RANO criteria were developed in 2010<sup>20</sup> and are considered to be an extension of the Macdonald criteria. Notably, they include qualitative assessments of T2 and T2 fluid-attenuated inversion recovery hyperintensity, although this hyperintensity is difficult to assess quantitatively. They also include other important improvements (eg, defining measurable vs non-measurable disease, specific inclusion or exclusion criteria, requirement for confirmatory scans, recommendations for the care of patients with equivocal imaging changes, and criteria for non-enhancing tumour progression). Similar to RECIST, the RANO response assessment is divided into four categories: complete response, partial response, stable disease, and progressive disease. iRANO criteria were proposed in 2015<sup>6</sup> to allow patients to better tolerate transient changes that might occur during initial treatment due to inflammation or pseudoprogression. A drawback of iRANO is that it includes an arbitrary 3-month window to confirm progressive disease, which causes excessive censoring in glioblastoma trials. An updated set of criteria based on new data, version 2.0, is in development. In 2017, an mRANO was developed<sup>7</sup> to improve upon RANO and iRANO in assessing immunotherapy. In a prospective, phase 2 trial of convection-enhanced delivery of an IL4R-targeted immunotoxin (MDNA55-05) in recurrent glioblastoma,<sup>21</sup> mRANO outperformed both RANO and iRANO in showing a correlation between radiographic progression-free survival and overall survival. Currently, mRANO is being used in many trials as secondary and exploratory endpoints for immunotherapy and other therapeutics in glioblastoma (eg, NCT01564914, NCT01866449, NCT02441322, NCT02326441, NCT03296696, and

NCT02871843). The conventional RANO is still considered the gold standard for response assessment in glioblastoma as the primary endpoint for regulatory purposes.

#### Advanced imaging techniques

Besides linear tumour size and metabolism-based metrics (eg, the immune variants of RECIST, PERCIST, and RANO), image analysis of standard-of-care scans, such as CT, MRI, and PET, with more advanced analytics, such as volume and radiomics, functional MRI agents, and metabolic changes, has also shown promise in improving the tumour response assessment for immunotherapy.

#### PERCIST and FDG-PET or CT in guiding immunotherapy trials

FDG uptake is indicative of glucose utilisation and although elevated glucose utilisation is commonly seen in cancers,<sup>22</sup> it is not specific to cancer.<sup>23,24</sup> FDG-PET has been mostly used for imaging cancers (appendix p 6), but it has also been used to image inflammatory and infectious processes.<sup>23,24</sup>

Challenges exist for FDG-PET and CT in assessing the response to immune checkpoint inhibitors, especially early after treatment is initiated. Soon after treatment, an immune response in tumours can appear on FDG-PET scans as an increased uptake versus baseline signal due to the imaging of the immune and inflammatory infiltrate by lymphocytes and macrophages in the tumour microenvironment and, therefore, could be misinterpreted as tumour progression (ie, pseudoprogression).<sup>4</sup> Delayed response to immune modulators also leaves a window of time for tumours to continue to grow before therapeutic effects dominate. FDG-PET has been useful in identifying various immunotherapy-related adverse events in organs such as the gastrointestinal and endocrine systems.<sup>25</sup> Early identification and management can decrease the severity of such adverse events.

In addition, immune response in normal tissues can appear to suggest new tumour or tumour progression, which sometimes can be dramatic (eg, sarcoid-like reactions).<sup>26,27</sup> Caution should be exercised when interpreting FDG-PET images, particularly in the period relatively soon after the initiation of immunotherapy (eg, days to months).

PERCIST was developed to provide a framework for assessing metabolic tumour response with FDG-PET.<sup>28</sup> It has been evaluated in patients treated with immune checkpoint inhibitors, with more success in patients with melanoma than in patients with lung cancer in predicting patient outcomes (appendix p 7).<sup>29–33</sup> It has also been applied with success in patients treated with other immunomodulators. For example, a PERCIST FDG-PET assessment at day 9 of anti-IGF1R antibody treatment predicted survival in sarcoma;<sup>34</sup> similarly FDG PERCIST-like criteria predicted response to <sup>131</sup>I-anti-B1 (CD20) radioimmunotherapy treatment

of non-Hodgkin lymphoma,<sup>35</sup> and response to CAR T-cell therapy.<sup>36</sup>

Given the possibility of new lesions developing or existing lesions showing increased FDG uptake during therapy, PERCIST can be misleading in the early stages (ie, weeks) of assessing immunotherapy response. Several modifications of PERCIST for patients undergoing immunotherapies have been proposed (eg, PET response criteria for immunotherapy, immune PERCIST, and immune-modified PERCIST 5),<sup>37</sup> mainly addressing how the appearance of new lesions on PET should be classified. There are currently insufficient data to define one set of criteria as preferable to another. Regardless, despite the challenges, FDG-PET is a valuable tool in clinical studies of immune checkpoint inhibitors. It appears that pseudoprogression is common with CTLA4 blockade therapies and at early timepoint assessments after the initiation of treatment.<sup>2,38</sup> Assessment of progression with FDG-PET at 3 months after therapy might reflect true progression more reliably than RECIST and FDG-PET imaging at earlier time points. Currently, it is uncertain how to best assess response or progression with FDG-PET at early timepoints after therapy and prospective studies could be informative. Some of the considerations regarding the interpretation of FDG-PET following immunotherapy have been reviewed and show the potential pitfalls in reading PET scans in patients treated with immunotherapy.<sup>37,39</sup>

#### Advanced analytics for CT images: radiomics

There is great potential for developing radiomic biomarkers for immunotherapy trials by taking advantage of all the existing imaging data and clinical outcome data from completed clinical studies. Radiomics, which extracts quantitative features from medical images by use of data characterisation algorithms, has the potential to uncover disease characteristics that are difficult to identify by visual assessment. Although the concept of radiomics is not new, advances in computing and feature classification now enable quantification of image features and uncover the relationship of these features or their change over time with other molecular parameters or clinical outcomes. Because of the higher dimensions of data used to derive certain radiomic features, compared with what is typically used for conventional imaging assessment, radiomic feature analysis shows promise to improve the understanding of the disease and its progression with or without treatment. Of particular interest is its potential to address the challenges in evaluating response to immunotherapy. In a 2018 study, the CT radiomic signature of CD8<sup>+</sup> cells predicted the immune phenotype of tumours and inferred clinical outcomes for patients with cancer who had been treated with anti-PD-1 or anti-PD-L1 immunotherapy.<sup>40</sup> In patients with lung cancer, radiomic phenotypes derived from CT images were associated with underlying

molecular pathways.<sup>41</sup> Ongoing efforts to evaluate cohorts of patients from the Lung Cancer Master Protocol are underway.<sup>42</sup> In a cohort of patients with melanoma treated with pembrolizumab from two phase 3 trials, a composite radiomic feature outperformed RECIST in predicting overall survival;<sup>43</sup> radiomic signatures also helped identify pseudoprogression in immunotherapy trials earlier than iRECIST. Before radiomic signatures can be used for clinical care or regulatory decision making for drug development, understanding factors that influence the reproducibility of imaging radiomic feature extraction is important. Several parameters were studied,<sup>44–46</sup> and additional efforts might be needed to define and standardise imaging acquisition and reconstruction parameters to reduce variability of radiomic feature extraction. This standardisation could prove to be a challenge in clinical practice. The role and benefit of radiomics in this context, although promising, remains to be assessed and validated in large multicentre trials.

#### Novel MRI contrast agent: ferumoxytol-enhanced MRI

In addition to PET tracers, MRI could provide complementary information to improve response assessment of immunotherapy, and clinical trials are ongoing.<sup>47</sup>

Cancer and inflammation often coexist and share the same tissue-infiltrating cells (lymphocytes, macrophages, and mast cells),<sup>48</sup> underscoring the role of inflammation in the tumour microenvironment. This relationship provides opportunities to image the inflammatory components of the cancer microenvironment. A high number of tumour-associated macrophages (TAMs) is associated with tumour progression and overall poor prognosis in cancers of the breast, prostate, lung, and pancreas.<sup>49,50</sup> M2 macrophages are particularly important because they can promote progression and migration of tumour cells by secreting proangiogenic factors.<sup>51</sup> M2 TAMs can be detected by immunohistochemical staining of upregulated CD163. The proportion and amount of TAMs M1 and M2 can vary across patients and across tumours and might correlate with resistance to immune checkpoint blockade agents. New therapies that target these macrophages are entering into clinical practice. Whether combining these agents with immunotherapy agents can lead to more predictable and durable responses remains to be seen. To answer this question, developing the means to image intratumoural inflammation non-invasively to assess the contribution of TAM-targeted therapies to the overall response is important. One approach is to use ferumoxytol, an agent approved by the US Food and Drug Administration for treatment of iron deficiency anaemia, as a contrast agent for MRI to identify tumours that have a high density of TAMs to select patients for treatment with TAM-modulating therapies and for monitoring response.<sup>52,53</sup> Images obtained early (ie, 0–15 h) after the intravenous administration of ferumoxytol largely reflect the vascular

distribution of this agent, whereas images obtained at later timepoints (ie, 1–10 days) largely report on its uptake by macrophages. Ferumoxytol-enhanced MRI improved the detection of metastatic lymph nodes<sup>54</sup> and quantified inflammation at the target organ in type 1A diabetics with active insulinitis.<sup>55</sup> Ferumoxytol was found to colocalise with TAMs in tumours, suggesting it could potentially serve as a biomarker for primary tumours, such as in pancreatic cancer,<sup>56,57</sup> as TAMs are one of the most abundant immune cell populations in the pancreatic tumour stroma.<sup>58</sup> Ferumoxytol enhancement on MRI was also found to be correlated with TAM density in the tumours in paediatric and young adult patients with lymphoma and bone sarcoma.<sup>47</sup>

### Molecular imaging agents in clinical development

One of the main challenges complicating response assessment of immunotherapy is pseudoprogression, which can be observed during immunotherapy on traditional imaging, such as CT and FDG-PET-CT. Novel imaging agents aiming to differentiate true tumour growth from changes in the tumour microenvironment might aid in assessing immunotherapy. Imaging can take a broad range of approaches in this regard, by interrogating immune cells directly (eg, CD3, CD8, and reporter genes for CAR T cells), immune modulators (eg, CTLA4, PD-1, and PD-L1), and immune cell activity (eg, granzyme B and nucleoside analogues). Some novel PET imaging agents that are currently in clinical development attempt to probe tumour microenvironment changes associated with immunotherapy, some of which we discuss in the following sections.

#### PET agent targeting granzyme B

Granzyme B is a serine protease that presents in the granules of T cells, including natural killer cells and cytotoxic T cells. When the T cells interact with tumour cells, granzyme B is released along with pore-forming protein perforin, allowing active granzyme B to enter tumour cells and mediate apoptosis. <sup>68</sup>Ga-NOTA-hGZP, a gallium-68-labelled peptide targeting extracellular granzyme B in the tumour microenvironment, is proposed to be able to detect response to immune checkpoint inhibitors, tumour vaccines, and CAR T-cell-mediated cell therapy for solid tumours.

Data from mouse models showed that <sup>68</sup>Ga-NOTA-hGZP PET imaging correlates with histological granzyme B assessment in tumours; combination therapy of anti-PD-1 plus anti-CTLA4 antibodies produced a higher PET signal intensity than anti-PD-1 monotherapy alone or vehicle alone. This graded response potentially allows rank ordering of efficacy early in a trial. It predicted responders and non-responders to checkpoint inhibitors before changes in CT tumour volume were present, allowing an early response assessment non-invasively.<sup>8</sup>

The agent is currently being investigated in a multicentre phase 1 trial of 20 patients with solid

tumours or lymphoma treated with pembrolizumab (NCT04169321). In this trial, a single <sup>68</sup>Ga-NOTA-hGZP PET is performed between day 14 and day 42 (ie, before cycle two and through cycle three) and CT scan is performed at 6 months. Excisional biopsy and contrast-enhanced CT scan at the time of imaging is optional. Three sites are recruiting and scanning patients. Preliminary analysis of images showed a favourable biodistribution profile and tracer accumulation at tumour sites.<sup>59</sup>

#### PET agent targeting CD8<sup>+</sup> T cells

The PET agent <sup>89</sup>Zr-Df-IAB22M2C (crefmirlimab) is designed to image the distribution and abundance of CD8<sup>+</sup> T cells in the tumour microenvironment. It is composed of an engineered, fully humanised anti-CD8 minibody IAB22M2C with a high binding affinity to CD8<sup>+</sup> cells, conjugated with desferoxamine and labelled with <sup>89</sup>Zr. In-vitro assessment of <sup>89</sup>Zr-Df-IAB22M2C showed no effect on proliferation, depletion, or cytokine release in normal human T cells. In humanised mouse models, there was no effect on T-cell populations or cytokine release. The anti-CD8-minibody <sup>89</sup>Zr-Df-IAB22M2C revealed a high sensitivity for detecting intratumoural CD8<sup>+</sup> T-cell infiltrates in a mouse model.<sup>60</sup>

The first-in-human phase 1 study of <sup>89</sup>Zr-Df-IAB22M2C in patients with cancer (NCT03107663) has been completed in patients with solid tumours eligible for, or already on, checkpoint inhibitor therapy.<sup>15,16</sup> The agent was found to be safe and showed rapid clearance. Uptake was seen in T-cell-rich tissues, including spleen, bone marrow, and lymph nodes; no to low uptake was seen in normal organs, such as muscle, heart, brain, and lungs. Tumour uptake was variable (maximum standard unit value ranging from 0 to 20) and seen in ten (67%) of 15 patients. The minibody protein dose range with the most favourable distribution was 0.5–1.5 mg, and the most favourable imaging time appeared to be 24 h, although tumours were seen as early as 1–2 h post injection.

These results were used to guide the design of the phase 2 study (NCT03802123) in patients with metastatic solid tumours who are initiating checkpoint inhibitor therapy (ipilimumab, nivolumab, or pembrolizumab as standard-of-care). <sup>89</sup>Zr-Df-IAB22M2C PET-CT imaging (1 milliCurie; 1.5 mg cold minibody; 24 h after injection), with biopsies conducted before treatment (eg, baseline) and 4–5 weeks after therapy initiation. The objectives are to investigate the safety of repeat dosing and imaging, the correlation of CD8 PET with CD8 immunohistochemistry, and the correlation with RECIST and outcome (appendix p 7). This is a multicentre, ongoing trial with ten sites currently active. Several pharmaceutical companies using CD8 immuno-PET in conjunction with ongoing therapy studies are starting trials soon. Infrastructure to support conducting phase 2 trials has

been established, including PET scanner validation and radiopharmaceutical manufacturing and supply.

Activated T cells can also be imaged with the PET radiotracer  $^{18}\text{F}$ -arabinofuranosyl guanine ( $^{18}\text{F}$ -AraG).<sup>61,62</sup> Following cellular uptake and phosphorylation by mitochondrial deoxyguanosine kinase and, to a lesser degree, cytoplasmatic deoxycytidine kinase enzymes,  $^{18}\text{F}$ -AraG becomes trapped inside the cell. Although its uptake is not cell-specific, activated CD8<sup>+</sup> cells show the greatest increase in uptake compared with baseline measurements.<sup>62</sup> Initial, small, phase 2 trials are ongoing in patients with lymphomas (NCT05096234) and solid tumours (NCT04260256), correlating the imaging signal with T-cell infiltrates in tumour biopsies and RECIST responses to treatment with CAR T cells and immune checkpoint inhibitors.

#### PET agents targeting PD-1 and PD-L1

PET imaging agents targeting PD-1 or PD-L1 can non-invasively quantify their protein concentrations; therefore, they might serve as predictive biomarkers for treatment efficacy of PD-1 or PD-L1 blockade agents. An anti-PD-L1 adnectin, BMS-986192, labelled with  $^{18}\text{F}$ , was studied along with  $^{89}\text{Zr}$ -nivolumab for PET imaging in a first-in-human phase 1 study in patients with melanoma or non-small-cell lung cancer treated with nivolumab (NCT03520634). Uptake of both agents in tumours quantified by PET correlated with PD-L1 and PD-1 expression in tumour biopsies assessed by immunohistochemistry. Tumour uptake of both tracers correlates with response to nivolumab treatment.<sup>63</sup>

An ongoing phase 1 study in patients with oral cavity squamous cell carcinoma (NCT03843515) is evaluating serial PET imaging with  $^{18}\text{F}$ -BMS-986192 (anti-PD-L1) and  $^{18}\text{F}$ -FDG at baseline and after a single dose of nivolumab in the neoadjuvant setting. The primary endpoints are serious adverse events, tumour maximum standard unit value for FDG-PET, and tumour maximum standard unit value for anti-PD-L1 PET; the secondary endpoint is to study the correlation between PET data and blood and tissue markers.

Advances in radiochemistry also facilitate the development of novel PET agents. The two-step radiolabelling of short-lived  $^{18}\text{F}$  for BMS-986192 presents challenges for clinical application. To optimise the PET tracer for anti-PD-L1 adnectin BMS-986192, a simpler, one-step labelling chemistry was developed for conjugation with  $^{68}\text{Ga}$ .<sup>64</sup> The imaging agent  $^{68}\text{Ga}$ -BMS-986192 has shown favourable imaging properties in PD-L1-positive xenograft tumours in animal models and is to be tested in the clinic.<sup>64</sup>

#### Additional PET agents targeting PD-1, PD-L1, and CD8

Several other PET imaging agents targeting PD-1, PD-L1, or CD8 are showing promise in clinical development. The PET imaging agent  $^{89}\text{Zr}$ -atezolizumab (anti-PD-L1) was administered before treatment in

patients with solid tumours; the patients were then treated with atezolizumab until disease progression. Part A of the study (NCT02453984) assessed tracer protein dose for imaging and schedule; part B (NCT02478099) implemented imaging with the optimal dose and imaging timepoint (ie, day 7 after injection).<sup>65</sup> In total, 22 patients were evaluable. Uptake of  $^{89}\text{Zr}$ -atezolizumab was high in lymphoid tissues and at sites of inflammation; uptake was high in tumours but heterogeneous, varying within and among lesions, patients, and tumour types.  $^{89}\text{Zr}$ -atezolizumab tumour uptake correlated with RECIST response, progression-free survival, and overall survival. Progression-free survival and overall survival correlated not with PD-L1 staining of tumour biopsies.

The second agent, CX-072, is a protease-activatable anti-PD-L1 antibody (probody). CX-072 can be activated in vivo by proteases present in the tumour microenvironment, thereby potentially reducing anti-PD-L1-mediated toxicities. In a mouse model,  $^{89}\text{Zr}$ -CX-072 accumulates specifically in PD-L1-expressing tumours with limited uptake in peripheral lymphoid tissues.<sup>66</sup> The imaging agent might support the development of CX-072 as an immunotherapy (NCT03013491).<sup>67</sup> The first-in-human biodistribution and pharmacokinetic study showed  $^{89}\text{Zr}$ -CX-072 uptake in tumours and modest uptake in normal lymphoid organs, with no unexpected uptake in other healthy tissues.<sup>68</sup>

A study with  $^{89}\text{Zr}$ -pembrolizumab in 18 patients with melanoma and non-small-cell lung cancer, before receiving treatment with anti-PD-1 antibody, showed that  $^{89}\text{Zr}$ -pembrolizumab uptake in tumour lesions correlated with treatment response and patient survival (appendix p 8).  $^{89}\text{Zr}$ -pembrolizumab also showed uptake in lymphoid tissues and at sites of inflammation.<sup>9</sup>

In the PET imaging study with a  $^{89}\text{Zr}$ -labelled, one-armed, CD8-specific antibody ( $^{89}\text{ZED88082A}$ ; NCT04029181), uptake of this radiopharmaceutical can be seen in lymphoid tissues and tumour lesions 2 days after tracer injection.<sup>69</sup> Uptake in tumour lesions was heterogeneous within and between patients. To conclude, these studies provide insight into essential characteristics for immunotherapy and into the heterogeneity of their presence between lesions in a patient and between patients, which is information not obtained with a biopsy from a single tumour site.

#### Discussion

Imaging remains the primary tool for assessing treatment effect in solid tumours and lymphomas (panel). Conventional response-assessment criteria, such as RECIST, RANO, and response assessment in paediatric neuro-oncology, are the current standard for regulatory decisions despite shortcomings in differentiating true tumour growth from immune cell infiltration in the tumour microenvironment (ie, pseudoprogression) subsequent to immune therapies, especially immune



### Panel: Recommendations on imaging tools to guide immunotherapy trials from the National Cancer Institute Cancer Imaging Steering Committee

- Use promising imaging modalities prospectively in immunotherapy treatment trials to assess how they could inform patient selection or patient care
- Accelerate data analysis on completed studies and use completed trial datasets to assess performance of modified assessment criteria (eg, immunotherapy response evaluation criteria in solid tumours and immunotherapy response assessment for neuro-oncology) and radiomics
- Continue to expand efforts to harmonise data collection and facilitate uniform image assessment across sites and trials to assess performance of modified metrics

### Search strategy and selection criteria

This Policy Review was developed from a workshop conducted by the Clinical Imaging Steering Committee of the National Cancer Institute. Additional articles were found through searches of the authors' own files, and searches from March 3, 2021, to Dec 1, 2022 on PubMed and ClinicalTrials.gov for articles published in English up until Dec 1, 2022. We searched using search terms "PET-CT", "MR", "RANO", "PERCIST", "RECIST", "18F-AraG", "Radiomics", "Response assessment", "Predictive marker", "Immunotherapy", "Immuno-oncology", "Cancer", "Molecular imaging", "Functional imaging", and "Clinical trials". We focused our search on human studies.

checkpoint inhibitors. Modified consensus guidelines for response assessment of immune therapies attempt to ascertain the effects of immune response from true tumour growth, primarily by delaying the time of tumour imaging assessment after immunotherapies until the immune response has subsided. These modified guidelines have shown a better correlation with clinical outcomes in retrospective analyses in some studies; however, validation is required by use of a larger number of cases of retrospective data and prospective data. Emerging techniques, including radiomics derived from CT or MRI, novel MRI contrast agents enhancing detection of immune cell infiltration, and novel PET tracers specifically probing immune molecular pathways (eg, PD-1, PD-L1, CD8<sup>+</sup> T cells, and granzyme B), are promising in filling gaps in knowledge and will need evaluation in multicentre clinical trials. Combining novel imaging tools to probe different aspects of immune response, or combining imaging with tissue-based or blood-based biomarkers to assess multi-dimensions of the disease, could further improve the assessment of immunotherapy.

### Conclusion

The NCI National Clinical Trials Network continues to encourage and support the assessment of imaging

tools and imaging biomarkers, and many of the network's completed, ongoing, and upcoming clinical trials might provide the imaging data to address the challenges in the response assessment of immunotherapies and validate the novel imaging tools and biomarkers. Going forward, it will be important to determine their clinical utility, alone or in combination, to predict and monitor treatment response and to study the effect that such imaging tools and biomarkers might have; for instance, on the selection of differential therapies or early termination of immune checkpoint blockade. The designs of clinical trials for the assessment of these roles are distinct and NCI clinical trial consortia, among others, offer a conduit for these important investigations.<sup>70,71</sup> Funding opportunities are available through various mechanisms in the National Institutes of Health (NIH) to support such discoveries and development.<sup>72-74</sup> Overall, there is considerable interest in and support for activities in current and planned immunotherapy trials that use diagnostic imaging for both predictive capabilities and response assessment.

### Contributors

LKS, HS, ES, JW, MVK, RLW, BME, NCH, MJY, AJT, MDF, DP, TYP, CLW, LS, MH, UM, AMW, DL, EGE<sup>d</sup>V, and SAR conceptualised this Policy Review and developed the methods. All authors curated, analysed, and interpreted the data. LKS, JW, MVK, RLW, AMW, EGE<sup>d</sup>V, and GB contributed the figure. YT wrote the first draft of the manuscript. All authors revised, reviewed, and approved the final version.

### Declaration of interests

EGE<sup>d</sup>V reports institutional financial support for clinical trials or contracted research from Amgen, Genentech, Roche, CytomX, G1 Therapeutics, Bayer, Synthon, Servier, Regeneron, Crescendo Biologics, GE Healthcare, and AstraZeneca; institutional financial support for advisory boards and consultancy from National Surgical Adjuvant Breast and Bowel Project, Daiichi Sankyo, and Crescendo Biologics; and non-financial interests, including non-remunerated activities and public positions as a member of the European Society for Medical Oncology (ESMO)–Magnitude of Clinical Benefit Scale working party, chair of the ESMO Cancer Medicines Working Group, co-chair of the RECIST committee, and a member of the expert panel for the selection of WHO Essential Medicine List. MDF reports institutional grant or contract payments from Merck, Bristol Myers Squibb, ImaginAb, and Carisma Therapeutics, and consulting fees and meeting and travel support from ImaginAb. DL reports stock ownership in Bristol Myers Squibb. UM reports grants, royalties and license, consulting fees, meeting and travel support, licensed patents, leadership interest, stock, receipt of materials, and other financial or non-financial interests in CytoSite Biopharma. TYP reports grants or contracts from the Pediatric Brain Tumor Consortium Neuroimaging Center; royalties from Springer; and honoraria for grand rounds, visiting professorships, and invited lectures from Cornell University, University of California San Francisco, and University of Rochester. DP reports grants to or contracts with his institution from Siemens, 511 Pharma, Nordic nanovector, Lantheus, and Fusion Pharmaceuticals; royalties or licenses to him and his institution from Trevarx; consulting fees from Siemens, Fusion Pharmaceuticals, 511 Pharma, Ipsen, Bayer, Molecular Targeting Technologies, and Curium; patents from At-211 parthanatrace; participation on an Isotope Technologies Munich (ITM) data and safety monitoring committee; and stock with Molecular Targeting Technologies and Trevarx. LS reports institutional grants or contracts from Johnson & Johnson, patents from Varian Medial Systems, and data and safety monitoring board or advisory board participation with Merck, BMS, and Regeneron. YT provided medical

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#### References

- Sanmamed MF, Chen L. A paradigm shift in cancer immunotherapy: from enhancement to normalization. *Cell* 2018; **175**: 313–26.
- Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15**: 7412–20.
- Bohnsack O, Hoos A, Ludajic K. Adaptation and modification of the immune related response criteria (IRRC): IrRECIST. *Proc Am Soc Clin Oncol* 2014; **32** (suppl 15): e22121 (abstr).
- Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017; **18**: e143–52.
- Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. *J Clin Oncol* 2018; **36**: 850–58.
- Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol* 2015; **16**: e534–42.
- Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics* 2017; **14**: 307–20.
- Goggi JL, Hartimath SV, Hwang Y, et al. Examining immunotherapy response using multiple radiotracers. *Mol Imaging Biol* 2020; **22**: 993–1002.
- Kok IC, Hooiveld JS, van de Donk PP, et al. <sup>89</sup>Zr-pembrolizumab imaging as a non-invasive approach to assess clinical response to PD-1 blockade in cancer. *Ann Oncol* 2022; **33**: 80–88.
- National Cancer Institute. NCTN: NCI's National Clinical Trials Network. May 29, 2019. <https://www.cancer.gov/research/infrastructure/clinical-trials/nctn> (accessed Dec 22, 2022).
- Upadhya S, Hubbard-Lucey VM, Yu JX. Immuno-oncology drug development forges on despite COVID-19. *Nat Rev Drug Discov* 2020; **19**: 751–52.
- Ott PA, Hodi FS, Kaufman HL, Wigginton JM, Wolchok JD. Combination immunotherapy: a road map. *J Immunother Cancer* 2017; **5**: 16.
- Sharma P, Allison JP. The future of immune checkpoint therapy. *Science* 2015; **348**: 56–61.
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711–23.
- Pandit-Taskar N, Postow MA, Hellmann MD, et al. First-in-humans imaging with <sup>89</sup>Zr-Df-1AB22M2C anti-CD8 minibody in patients with solid malignancies: preliminary pharmacokinetics, biodistribution, and lesion targeting. *J Nucl Med* 2020; **61**: 512–19.
- Farwell MD, Gamache RF, Babazada H, et al. CD8-targeted PET imaging of tumor infiltrating T cells in patients with cancer: a phase I first-in-human study of <sup>89</sup>Zr-Df-1AB22M2C, a radiolabeled anti-CD8 minibody. *J Nucl Med* 2022; **63**: 720–26.
- Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; **8**: 1277–80.
- Levin VA, Crafts DC, Norman DM, Hoffer PB, Spire JP, Wilson CB. Criteria for evaluating patients undergoing chemotherapy for malignant brain tumors. *J Neurosurg* 1977; **47**: 329–35.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
- Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28**: 1963–72.
- Ellingson BM, Sampson J, Achrol AS, et al. Modified RANO, immunotherapy RANO, and standard RANO response to convection-enhanced delivery of IL4R-targeted immunotoxin MDNA55 in recurrent glioblastoma. *Clin Cancer Res* 2021; **27**: 3916–25.
- Kelloff GJ, Hoffman JM, Johnson B, et al. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. *Clin Cancer Res* 2005; **11**: 2785–808.
- Vaidyanathan S, Patel CN, Scarsbrook AF, Chowdhury FU. FDG PET/CT in infection and inflammation—current and emerging clinical applications. *Clin Radiol* 2015; **70**: 787–800.
- Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. *Radiographics* 1999; **19**: 61–77.
- Gandy N, Arshad MA, Wallitt KL, Dubash S, Khan S, Barwick TD. Immunotherapy-related adverse effects on <sup>18</sup>F-FDG PET/CT imaging. *Br J Radiol* 2020; **93**: 20190832.
- Kikano EG, Avril S, Marshall H, Jones RS, Montero AJ, Avril N. PET/CT variants and pitfalls in breast cancers. *Semin Nucl Med* 2021; **51**: 474–84.
- Parihar AS, Haq A, Wahl RL, Haghghat Jahromi A. Progression or response: new liver lesions in a patient with responding Hodgkin lymphoma. *J Nucl Med Off Publ Soc Nucl Med* 2022; published online Oct 13. <https://doi.org/10.2967/jnumed.122.264995>.
- Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; **50** (suppl 1): 122S–50S.
- Cho SY, Lipson EJ, Im HJ, et al. Prediction of response to immune checkpoint inhibitor therapy using early-time-point <sup>18</sup>F-FDG PET/CT imaging in patients with advanced melanoma. *J Nucl Med* 2017; **58**: 1421–28.

- 30 Amrane K, Le Goupil D, Quere G, et al. Prediction of response to immune checkpoint inhibitor therapy using <sup>18</sup>F-FDG PET/CT in patients with melanoma. *Medicine* 2019; **98**: e16417.
- 31 Kitajima K, Watabe T, Nakajo M, et al. Tumor response evaluation in patients with malignant melanoma undergoing immune checkpoint inhibitor therapy and prognosis prediction using <sup>18</sup>F-FDG PET/CT: multicenter study for comparison of EORTC, PERCIST, and imPERCIST. *Jpn J Radiol* 2021; **40**: 75–85.
- 32 Rossi G, Bauckneht M, Genova C, et al. Comparison between <sup>18</sup>F-FDG PET-based and CT-based criteria in non-small cell lung cancer patients treated with nivolumab. *J Nucl Med* 2020; **61**: 990–98.
- 33 Donegani MI, Ferrarazzo G, Marra S, et al. Positron emission tomography-based response to target and immunotherapies in oncology. *Medicina* 2020; **56**: 373.
- 34 Hyun O J, Lubner BS, Leal JP, et al. Response to early treatment evaluated with <sup>18</sup>F-FDG PET and PERCIST 1.0 predicts survival in patients with ewing sarcoma family of tumors treated with a monoclonal antibody to the insulinlike growth factor 1 receptor. *J Nucl Med* 2016; **57**: 735–40.
- 35 Torizuka T, Zasadny KR, Kison PV, Rommelfanger SG, Kaminski MS, Wahl RL. Metabolic response of non-Hodgkin's lymphoma to 131I-anti-B1 radioimmunotherapy: evaluation with FDG PET. *J Nucl Med* 2000; **41**: 999–1005.
- 36 Shah NN, Nagle SJ, Torigian DA, et al. Early positron emission tomography/computed tomography as a predictor of response after CTL019 chimeric antigen receptor—T-cell therapy in B-cell non-Hodgkin lymphomas. *Cytotherapy* 2018; **20**: 1415–18.
- 37 Lopci E, Hicks RJ, Dimitrakopoulou-Strauss A, et al. Joint EANM/SNMMI/ANZSNM practice guidelines/procedure standards on recommended use of [<sup>18</sup>F]FDG PET/CT imaging during immunomodulatory treatments in patients with solid tumors version 1.0. *Eur J Nucl Med Mol Imaging* 2022; **49**: 2323–41.
- 38 Aide N, Hicks RJ, Le Tourneau C, Lheureux S, Fanti S, Lopci E. FDG PET/CT for assessing tumour response to immunotherapy: report on the EANM symposium on immune modulation and recent review of the literature. *Eur J Nucl Med Mol Imaging* 2019; **46**: 238–50.
- 39 Parihar AS, Dehdashti F, Wahl RL. <sup>18</sup>F-FDG positron emission tomography (PET) based response assessment in malignancies. *Radiographics* 2023; **43**: e220122 (in press).
- 40 Sun R, Limkin EJ, Vakalopoulou M, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol* 2018; **19**: 1180–91.
- 41 Grossmann P, Stringfield O, El-Hachem N, et al. Defining the biological basis of radiomic phenotypes in lung cancer. *eLife* 2017; **6**: e23421.
- 42 Lam VK, Papadimitrakopoulou V. Master protocols in lung cancer: experience from lung master protocol. *Curr Opin Oncol* 2018; **30**: 92–97.
- 43 Dercle L, Zhao B, Gönen M, et al. Early readout on overall survival of patients with melanoma treated with immunotherapy using a novel imaging analysis. *JAMA Oncol* 2022; **8**: 385–92.
- 44 Lu L, Sun SH, Afran A, et al. Identifying robust radiomics features for lung cancer by using in-vivo and phantom lung lesions. *Tomography* 2021; **7**: 55–64.
- 45 Haarbuerger C, Müller-Franzes G, Weninger L, Kuhl C, Truhn D, Merhof D. Radiomics feature reproducibility under inter-rater variability in segmentations of CT images. *Sci Rep* 2020; **10**: 12688.
- 46 Traverso A, Wee L, Dekker A, Gillies R. Repeatability and reproducibility of radiomic features: a systematic review. *Int J Radiat Oncol Biol Phys* 2018; **102**: 1143–58.
- 47 Aghighi M, Theruvath AJ, Pareek A, et al. Magnetic resonance imaging of tumor-associated macrophages: clinical translation. *Clin Cancer Res* 2018; **24**: 4110–18.
- 48 Trinchieri G. Innate inflammation and cancer: is it time for cancer prevention? *F1000 Med Rep* 2011; **3**: 11.
- 49 Larionova I, Tuguzbaeva G, Ponomaryova A, et al. Tumor-associated macrophages in human breast, colorectal, lung, ovarian and prostate cancers. *Front Oncol* 2020; **10**: 566511.
- 50 Yu M, Guan R, Hong W, et al. Prognostic value of tumor-associated macrophages in pancreatic cancer: a meta-analysis. *Cancer Manag Res* 2019; **11**: 4041–58.
- 51 Yoshikawa K, Mitsunaga S, Kinoshita T, et al. Impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreas head. *Cancer Sci* 2012; **103**: 2012–20.
- 52 Mohanty S, Yerneni K, Theruvath JL, et al. Nanoparticle enhanced MRI can monitor macrophage response to CD47 mAb immunotherapy in osteosarcoma. *Cell Death Dis* 2019; **10**: 36.
- 53 Huang Y, Hsu JC, Koo H, Cormode DP. Repurposing ferumoxytol: diagnostic and therapeutic applications of an FDA-approved nanoparticle. *Theranostics* 2022; **12**: 796–816.
- 54 Harisinghani M, Ross RW, Guimaraes AR, Weissleder R. Utility of a new bolus-injectable nanoparticle for clinical cancer staging. *Neoplasia* 2007; **9**: 1160–65.
- 55 Gaglia JL, Guimaraes AR, Harisinghani M, et al. Noninvasive imaging of pancreatic islet inflammation in type 1A diabetes patients. *J Clin Invest* 2011; **121**: 442–45.
- 56 Hayano K, Miura F, Wada K, et al. Diffusion-weighted MR imaging of pancreatic cancer and inflammation: prognostic significance of pancreatic inflammation in pancreatic cancer patients. *Pancreatol* 2016; **16**: 121–26.
- 57 Hedgire SS, Mino-Kenudson M, Elmi A, Thayer S, Fernandez-del Castillo C, Harisinghani MG. Enhanced primary tumor delineation in pancreatic adenocarcinoma using ultrasmall super paramagnetic iron oxide nanoparticle-ferumoxytol: an initial experience with histopathologic correlation. *Int J Nanomedicine* 2014; **9**: 1891–96.
- 58 Yang S, Liu Q, Liao Q. Tumor-associated macrophages in pancreatic ductal adenocarcinoma: origin, polarization, function, and reprogramming. *Front Cell Dev Biol* 2021; **8**: 607209.
- 59 Heidari P, McConathy JE, Larimer B, Wehrenberg-Klee E, Sullivan RJ, Mahmood U. Interim analysis of a first-in-human first-in-class phase I study of granzyme B PET imaging for assessing single agent immune checkpoint inhibition response in melanoma and non-small cell lung cancer. RSNA Annual Meeting; November, 2022 (abstr).
- 60 Olafsen T, Jiang ZK, Romero J, et al. Abstract LB-188: sensitivity of <sup>89</sup>Zr-labeled anti-CD8 minibody for PET imaging of infiltrating CD8<sup>+</sup> T cells. *Cancer Res* 2016; **76**: LB-188 (abstr).
- 61 Namavari M, Chang Y-F, Kusler B, Yaghoubi S, Mitchell BS, Gambhir SS. Synthesis of 2'-deoxy-2'-[<sup>18</sup>F]fluoro-9-β-D-arabinofuranosylguanine: a novel agent for imaging T-cell activation with PET. *Mol Imaging Biol* 2011; **13**: 812–18.
- 62 Levi J, Lam T, Goth SR, et al. Imaging of activated T cells as an early predictor of immune response to anti-PD-1 therapy. *Cancer Res* 2019; **79**: 3455–65.
- 63 Niemeijer AN, Leung D, Huisman MC, et al. Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer. *Nat Commun* 2018; **9**: 4664.
- 64 Robu S, Richter A, Gosmann D, et al. Synthesis and preclinical evaluation of a <sup>68</sup>Ga-labeled adnectin, <sup>68</sup>Ga-BMS-986192, as a PET agent for imaging PD-L1 expression. *J Nucl Med* 2021; **62**: 1228–34.
- 65 Bensch F, van der Veen EL, Lub-de Hooge MN, et al. <sup>89</sup>Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer. *Nat Med* 2018; **24**: 1852–58.
- 66 Giesen D, Broer LN, Lub-de Hooge MN, et al. Probody therapeutic design of <sup>89</sup>Zr-CX-072 promotes accumulation in PD-L1-expressing tumors compared to normal murine lymphoid tissue. *Clin Cancer Res* 2020; **26**: 3999–4009.
- 67 Naing A, Thistlethwaite F, De Vries EGE, et al. CX-072 (pacmilimab), a Probody PD-L1 inhibitor, in advanced or recurrent solid tumors (PROCLAIM-CX-072): an open-label dose-finding and first-in-human study. *J Immunother Cancer* 2021; **9**: e002447.
- 68 Kist de Ruijter L, Hooiveld-Noeken JS, Giesen D, et al. First-in-human study of the biodistribution and pharmacokinetics of <sup>89</sup>Zr-CX-072, a novel immunopet tracer based on an anti-PD-L1 probody. *Clin Cancer Res* 2021; **27**: 5325–33.
- 69 Kist de Ruijter L, Van de Donk PP, Hooiveld-Noeken JS, et al. Whole-body CD8<sup>+</sup> T cell visualization before and during cancer immunotherapy: a phase 1/2 trial. *Nat Med* 2022; published online Dec 5. <https://doi.org/10.1038/s41591-022-02084-8>.

- 70 Lin FI, Huang EP, Shankar LK. Beyond correlations, sensitivities, and specificities: case examples of the evaluation of advanced imaging in oncology clinical trials and cancer treatment. *Acad Radiol* 2017; **24**: 1027–35.
- 71 Huang EP, Lin FI, Shankar LK. Beyond correlations, sensitivities, and specificities: a roadmap for demonstrating utility of advanced imaging in oncology treatment and clinical trial design. *Acad Radiol* 2017; **24**: 1036–49.
- 72 National Institutes of Health. National Cancer Institute's investigator-initiated early phase clinical trials for cancer treatment and diagnosis (R01 clinical trial required). <https://grants.nih.gov/grants/guide/pa-files/PAR-18-560.html> (accessed Dec 22, 2022).
- 73 National Institutes of Health National Cancer Institute. Funding opportunities. <https://itcr.cancer.gov/funding-opportunities> (accessed Dec 22, 2022).
- 74 National Institutes of Health National Cancer Institute. Biomarker, imaging and quality of life studies funding program (BIQSFP). Aug 5, 2022. <https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp> (accessed Dec 22, 2022).

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