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REVIEW ARTICLE

The Advantages and Challenges of Using FDG PET/CT for Response Assessment in Melanoma in the Era of Targeted Agents and Immunotherapy

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Abstract The treatment of melanoma has been revolutionised in recent years by advances in the understanding of the genomic landscape of this disease, which has led to the development of new targeted therapeutic agents, and the ability to therapeutically manipulate the immune system through inhibition of cancer cell-T-cell interactions that prevent an adaptive immune response. While these therapeutic interventions have dramatically improved the prospects of survival for patients with advanced melanoma, they bring significant complexity to the interpretation of therapeutic response because their mechanisms and temporal profile of response vary considerably. In this review, we discuss the mode of action of these emerging therapies and their toxicities to provide a framework for the use of FDG PET/CT in therapeutic response assessment. We propose that the greatest utility of PET in assessment of response to agents that abrogate signalling related to BRAF mutation is for early assessment of resistance, while in anti-CTLA4 therapy, immunological flare can compromise early assessment of response but can identify potentially life-threatening autoimmune reactions. For anti-PD1/PDL1 therapy, the role of FDG PET/CT is more akin to its use in other solid malignancies undergoing treatment with conventional chemotherapy. However, further research is required to optimise the timing of scans and response criteria in this disease.

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Introduction

Advanced melanoma was historically associated with a poor survival of six to nine months [1]. While some chemotherapy regimens, such as dacarbazine, resulted in tumour responses, these were uncommon and did not appear to prolong overall survival for the majority of patients [2]. After decades of lacking effective systemic therapies, melanoma has now become the exemplar of the two latest major breakthroughs in cancer treatments: molecular targeted therapy and immunotherapy. The first advance was development of small molecule inhibitors for BRAF-mutated melanomas, which specifically inhibit the most common oncogenic driver mutation responsible for melanoma cell proliferation and survival, and thereby extend patient survival [3]. The second major therapeutic advance was development of monoclonal antibodies targeting immune checkpoint receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death-1 (PD1) [4–6]. By blocking these inhibitory checkpoints on the immune system, cytotoxic T-cells are unleashed onto tumour cells, resulting in remarkable and durable responses in some patients with metastatic disease. These novel agents have distinct mechanisms of action compared to traditional cytotoxic chemotherapy. Consequently, imaging specialists need to understand the mechanisms by which these therapies influence tumour biology, as these can lead to differing patterns of imaging response, and toxicities that may also become manifest as imaging abnormalities.

BRAF-targeted treatment

Approximately 40–50% of metastatic melanomas are associated with a BRAF mutation, which results in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, which then drives cellular proliferation, melanoma growth and metastasis. Most of these mutations involve a substitution of valine with glutamic acid at the 600 codon (V600E) or valine with lysine (V600K), which can be targeted by oral BRAF inhibitors such as vemurafenib, dabrafenib or encorafenib. Other, less common mutations in this gene are variably sensitive to these agents or to MEK inhibitors (MEKi), such as cobimetinib, trametinib or binimetinib, but some are entirely resistant [7–9]. A phase III clinical trial, BRIM3, has demonstrated that vemurafenib significantly improved both progression-free survival (PFS) and overall survival (OS) when compared to chemotherapy using dacarbazine in BRAF-V600E mutant melanoma [10]. Dabrafenib, another BRAF inhibitor, also significantly increased PFS compared to dacarbazine [11]. Response rates are approximately 50–60% for BRAF inhibitors used as a single agent [10, 11].

While responses to BRAF inhibitors (BRAFi) can be extremely rapid and dramatic, acquired resistance eventually develops in most patients due to a range of secondary events including mutations that evolve in response to treatment [12–14]. Resistance to BRAFi can be prevented or delayed by the concurrent targeting of MEK, which is immediately downstream of BRAF in the MAPK pathway and which has been identified as the gene target of several resistance mechanisms. MEKi are now routinely started in combination with BRAFi based on results of several phase III trials. These include COMBI-D, which confirmed that the combination of dabrafenib (BRAFi) and trametinib (MEKi) prolonged OS significantly when compared to dabrafenib monotherapy [3]. Dabrafenib and trametinib was also compared to vemurafenib in a phase III study [15], which was ceased after pre-planned interim analysis confirmed prolongation of OS. A phase III study investigated vemurafenib in combination with cobimetinib or placebo and again confirmed an improvement in PFS with the combination [16]. The objective response rate was also increased at 70% versus 50%.

BRAF targeted therapy toxicities

BRAFi are generally well tolerated, but can be associated with fatigue, rash, arthralgia, photosensitivity or pyrexia. Inhibition of BRAF can cause paradoxical activation of the upstream raspberry gene leading to development of keratoacanthomas and squamous cell carcinomas. Interestingly, the combination of BRAFi and MEKi appears to reduce the incidence of these keratoacanthomas and squamous cell carcinomas [17, 18].

Role of FDG PET/CT for BRAF treatment response assessment

Traditionally, conventional imaging such as CT or MRI has been used for therapeutic response assessment, with reduction in tumour size being a surrogate for treatment benefit and patient survival. Anatomical assessments of response, such as the World Health Organisation (WHO) criteria and the Response Criteria In Solid Tumours (RECIST), were developed to standardise therapeutic response assessment for clinical trials. Although often relatively slow in confirming response, RECIST performs reasonably well in predicting survival for cytotoxic therapies including most conventional chemotherapy and radiotherapy regimens that lead to death of cells to effect lesion regression, but is less helpful in situations where inhibition of cell proliferation is the most common mechanism of response [19].

Importantly, small molecule inhibitors of oncogenic pathways can be associated with an improvement in patient survival despite a lack of reduction in tumour dimensions on conventional imaging. This was exemplified by early experience with imatinib treatment of gastrointestinal stromal tumour (GIST) but has also been observed with epidermal growth factor receptor (EGFR) inhibitors for non-small cell lung cancer [19–21]. Further, RECIST only assesses tumour response in five target lesions, and does not consider the overall disease burden, or heterogeneity in responses between the different target lesions. Functional imaging can address these two main limitations, given its ability to provide an early biological readout of response in lesions that have not changed in size as well as its ability to quantify changes in total tumour burden.

Accurate therapeutic response assessment is, of course, contingent on accurate staging to correctly identify sites for monitoring. For staging melanoma, PET/CT has been shown to be significantly superior to CT with a sensitivity and specificity of 92% and 94% compared to 58 and 45%, respectively [22]. This superior accuracy has been shown to confer a high management impact [23–27]. Most often, discordant results lead to alteration of the management plan from surgery to systemic therapy after identification of more extensive disease than seen on conventional workup. Melanoma spreads to a wide variety of organs. This dissemination particularly includes extra-nodal sites that are often difficult to identify or measure on anatomic imaging alone. Inability to precisely define the margin of a lesion does not preclude its monitoring by PET. More sensitive detection of lesions also enables earlier detections of new deposits as a means of confirming disease progression on treatment. This is important for recognising development of therapeutic resistance.

FDG PET provides assessment of the cellular metabolism, and exploits cancer cells' preference for glycolysis regardless of oxygen conditions, known as the Warburg effect [28]. The

complex adaptive benefits of this metabolic reprogramming to cancer cells and the genetic alterations driving this have recently been nicely summarised [29]. Beyond its role in diagnosing and staging cancer [30], FDG PET after therapy is correlated with clinical benefit in various cancers treated with cytotoxic therapies. These are reviewed in more detail elsewhere in this edition. Whether using qualitative assessment [31], or the semi-quantitative techniques used for the European Organisation of Research and Treatment of Cancer (EORTC) or PET Response Criteria In Solid Tumours (PERCIST) criteria [32, 33], a reduction in FDG uptake is generally associated with a better prognosis than if this isn't observed. A comparison between the EORTC and PERCIST approaches in colorectal cancer found similar associations with OS [34].

While reduction in viable cells with resultant shrinkage of lesions is usually eventually seen in melanoma that is responding to BRAF inhibition, reduction in FDG uptake occurs much more rapidly [35] (Fig. 1). This is because effective down-regulation of extra-cellular signal regulated kinase (ERK), the terminal gene of the MAPK pathway, suppresses glycolysis via a network of transcriptional regulators of glycolysis [36]. Thus, lack of early reduction in FDG uptake can indicate primary refractory disease sites as demonstrated by the lack of PET response in rare variant BRAF mutations that aren't responsive to MAPK pathway inhibition (Fig. 2). This inhibition doesn't necessarily lead to cell death as reflected by the observation that despite rather homogeneous responses with respect to reduction in standardized uptake values (SUVs) in patients receiving therapeutic doses of BRAFi, the degree of eventual RECIST response can be highly variable [35]. Cell survival mechanisms including high expression of anti-apoptotic proteins, use of alternative substrates and autophagy may allow cells to survive until glycolytic metabolism can be restored. Persistence or reactivation of FDG uptake is a feature of resistance. However, it is important to recognise that development of new cutaneous lesions with high FDG uptake can reflect accelerated growth of squamous cell carcinomas and keratoacanthomas and should therefore initiate clinical examination before assuming disease progression.

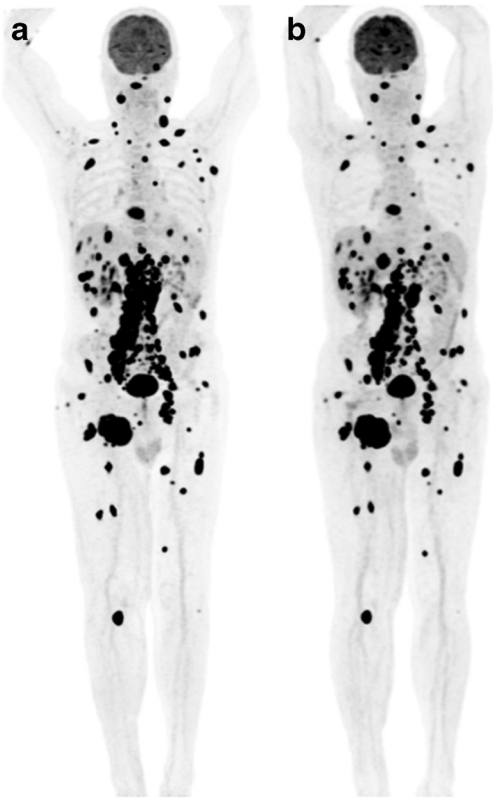

Fig. 2. **a**. Although a BRAF mutation was confirmed in this patient with widespread metastatic disease at baseline, it involved the I598 rather than the V600 locus. In silico modelling was unable to predict its sensitivity to vemurafenib. **b**. Early FDG PET suggested likely primary resistance with lack of reduction FDG uptake at site of disease on the baseline scan. Primary resistance was confirmed by subsequent progression on treatment

While both the EORTC and PERCIST criteria were developed to standardise therapeutic response assessment using FDG PET, they primarily consider the intensity of uptake as

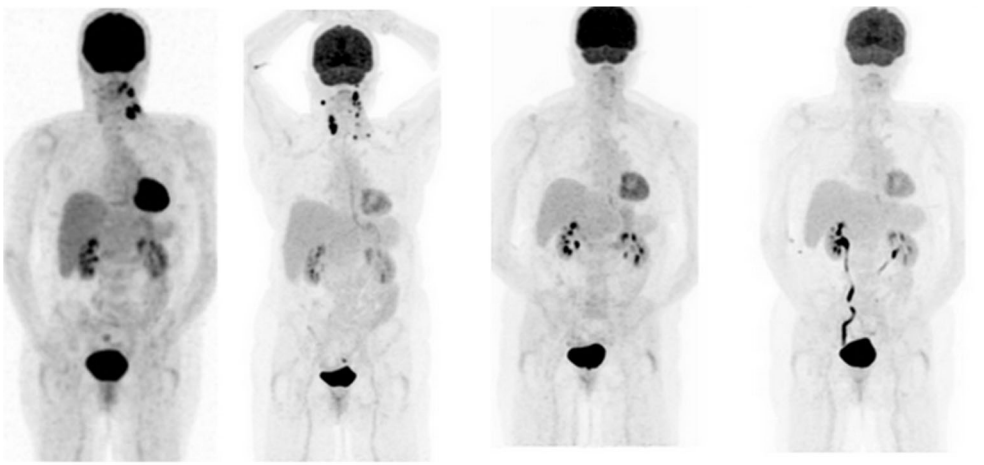

Fig. 1 Following resection of a scalp melanoma, this patient developed left cervical nodal metastases. Early post-surgery surveillance FDG PET/CT revealed progression of disease both within and beyond the nodal dissection site. Based on the presence of a V600E BRAF mutation, the patient was commenced on combined inhibition of BRAF and MEK inhibitor. Within 2 weeks of commencing treatment, there was a complete metabolic response that was sustained beyond 12 months

reflected by the SUV (SUVmax and SUVpeak, respectively). In addition to changes in SUV metrics, quantitation of the total tumour disease burden can be performed using %injected dose (%ID) or metabolic tumour volume (MTV). Our group has previously investigated changes in these two parameters in patients enrolled in the phase 1 study of vemurafenib. Reductions in %ID and MTV over the first 15 days of treatment were significantly associated with OS [35]. It should be noted that %ID represents a composite of both the intensity and volume of disease and, unlike SUV, can be recorded as zero when no residual abnormality is apparent, thereby providing a value of 100% reduction for a qualitative complete metabolic response (CMR). Furthermore, early reductions of MTV was also shown to be highly prognostic of OS after combination of vemurafenib and cobimetinib in a phase 1B study [37].

Although the responses to BRAFi tend to be marked and homogenous, a minority of patients do have heterogeneity in lesional response. Carlino et al. observed that 26% of the 23 patients in the phase 1b study of dabrafenib had a heterogeneous responses [38]. Heterogeneous responses were defined as 'when lesions responded (CMR/PMR) alongside progressing or new lesion(s), or responding lesions with >10% of lesions having 'stable metabolic disease'. Heterogeneous responses were associated with a shorter time to progression but was not associated with OS. Study of heterogeneous or progressive lesions may deepen the understanding of resistance mechanisms or the alternative metabolic pathways that enable resistant melanoma clones to bypass BRAF inhibition. This, in turn, may present future therapeutic targets for cancer metabolism.

There is emerging evidence suggesting that therapy directed at the MAPK pathway may exert its effect by modulating immune responses [39–41]. Furthermore, MEK inhibition potentiates anti-tumour T-cells and increases anti-PD1 regression in an in vivo model [42–44]. We have observed presumed immune responses on FDG PET with BRAF and MEK inhibition. These changes include activation of lymph nodes in the lymphatic drainage basin of metastatic sites and increased splenic uptake. These changes generally occur several weeks after commencing treatment with BRAF and MEK inhibition. An immune flare response and should be considered if there is increased or ongoing FDG uptake in the context of progressive tumour shrinkage or when accompanied by increased activity in the spleen (Figs. 3 and 4).

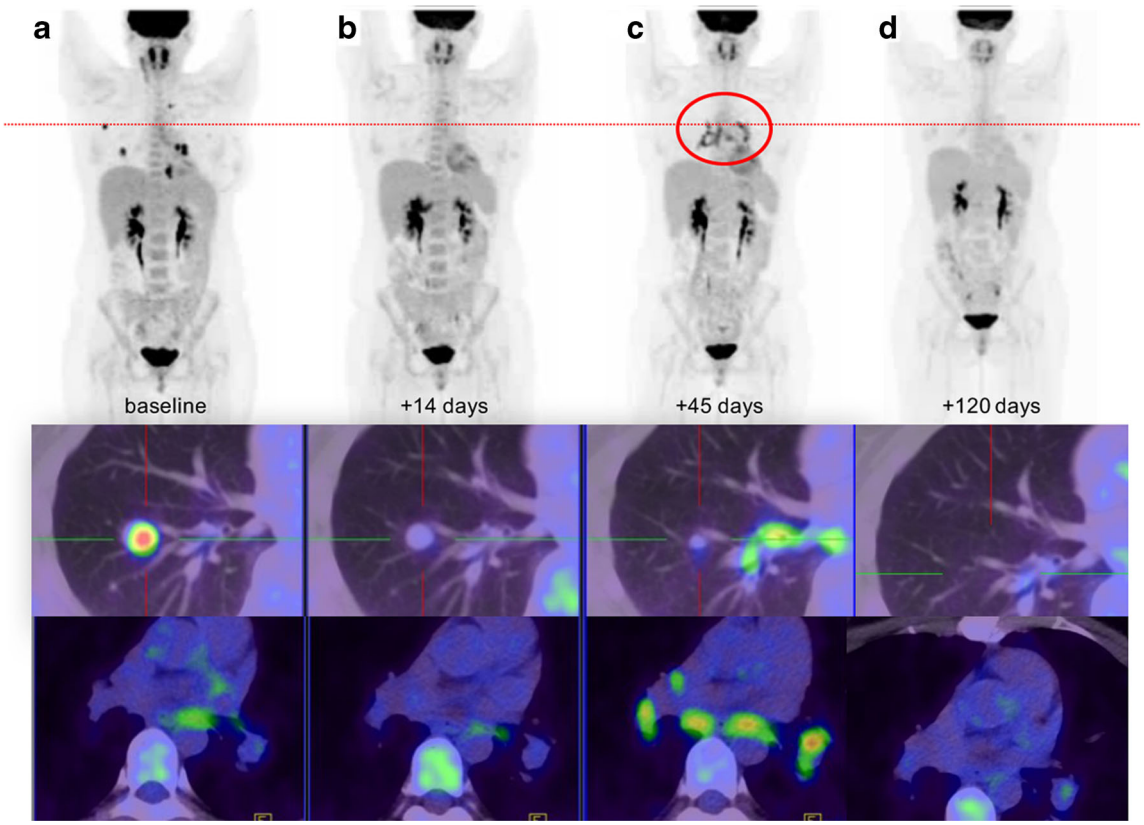

Fig. 3 **a**. This patient with multiple pulmonary metastasis commenced on combined BRAF and MEK inhibitors. **b**. After 14 days, there was an early complete metabolic response on PET despite little anatomic change on CT. **c**. At 45 days, there was new appearance of moderate-to-intense uptake in bilateral hilar and mediastinal nodes, which was interpreted as an immune-related inflammatory response in view of the symmetry and ongoing regression at sites of prior disease.
Note also the slight increase in splenic activity relative to hepatic uptake. **d**. By 120 days, the findings resolved and there was a complete response on CT, confirming an inflammatory aetiology

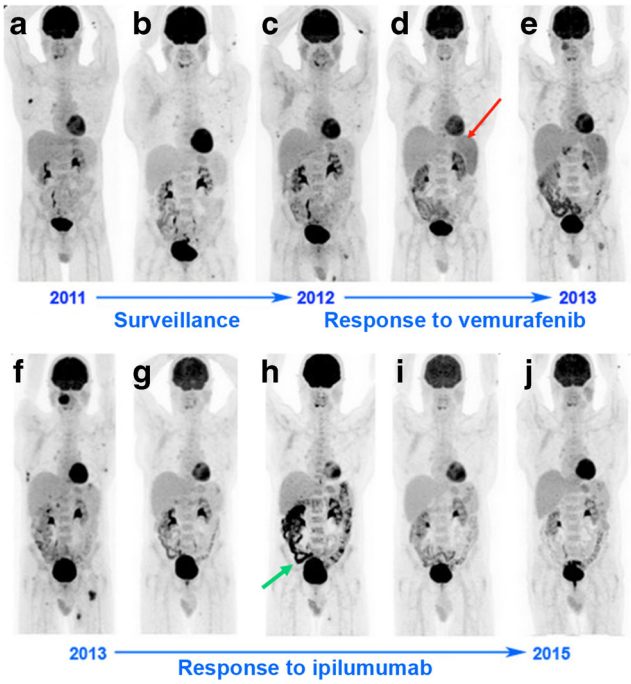

Fig. 4 **a**. Initial documentation of right axillary nodal disease in 2011 led to nodal basin dissection confirming BRAF V600E metastatic melanoma. **b**. However, following surgery (post-Sx), he developed widespread but asymptomatic subcutaneous nodules. **c**. These progressed along with development of small lung nodules in 2012. **d**. Within 1 month of introduction of vemurafenib (Vem), a BRAFi, there was a complete metabolic response accompanied by splenic activation (*red arrow*). **e**. Response was sustained for 12 months until recurrent disease became apparent at both prior and new sites of disease in 2013. **f**. An early apparent increase in uptake at sites of disease in response to ipilumumab, an anti-CTLA4 agent, was noted but the patient remained on therapy on the basis that this may have reflected an immunological flare response. **g**. Subsequent regression of abnormality confirmed this assumption. **h**. Shortly after this, the patient developed diarrhoea with increased activity in small (*green arrow*) and large bowel suggesting immune colitis. **i**. With introduction of steroids, his symptoms rapidly resolved with accompanying reduction in bowel activity. **j**. A sustained metabolic response was observed for over 18 months

Immunotherapy in melanoma

Immunotherapy has recently become a cornerstone of melanoma treatment. It has been long recognised that cancer and the immune system have a complex interaction, and there are some long-term survivors with melanoma who have gone into spontaneous remission. However, the translation of immune-targeted treatments to the clinic have been limited in the past, as vaccines and cytokine treatment have either been relatively ineffective or associated with significantly toxicity [2, 45]. The most recent advances in the field involve monoclonal antibodies that inhibit the physiological inhibitory checkpoints of immune activation. These treatments have shown remarkable responses in chemotherapy refractory tumours, and generally have been very well tolerated despite some immune-mediated toxicities. There are currently three approved immune checkpoint monoclonal antibodies for advanced melanoma, namely ipilimumab, an anti-CTLA4 monoclonal antibody; and, nivolumab and pembrolizumab, anti-programmed death 1 (anti-PD1) monoclonal antibodies [46].

Activation of the adaptive immune system requires antigen presentation to T-cells, as well as a co-stimulation signal from CD28 and cytokine receptor. CTLA4 is the physiological "off switch" which works by competing with CD28 and prevents an over-activation of the immune system. Ipilimumab, a monoclonal antibody targeting CTLA4, blocks this inhibitory process, which attenuates T-cell activation and, particularly, the expansion of cytotoxic T-cells in response to neoantigenic challenge. Anti-CTLA4 antibodies can also deplete T-regulatory cells, a cell type that inhibits antigen specific T-cell-mediated immune responses [47]. Accordingly, the anti-CTLA4 agents increase accumulation of tumour infiltrating lymphocytes (TILs) into sites of disease and increase germinal centre activity in draining lymph nodes. These aspects of the adaptive immune response are relevant to FDG PET/CT findings described below. Ipilimumab was the first immune checkpoint blockade to demonstrate a survival benefit compared to dacarbazine or vaccine [46]. Durable survival benefit was observed in approximately 20% of patients in a 10-year follow-up study of patients who have received ipilimumab for metastatic melanoma [48].

More recently, anti-PD1 immune checkpoint antibodies have demonstrated activity in a number of different tumour types including melanoma [4, 5, 49], non-small cell lung cancer [50], Hodgkin lymphoma [51], renal cell carcinoma [52], Merkel cell carcinoma [53], and mismatch repair deficit colorectal cancer [54]. PD1 is another immune checkpoint receptor which is upregulated on activated T-cells. T-cells produce interferon which induces the upregulation of programmed death ligand 1 (PDL1) on tumour cells and other tissues. The binding of PDL1 to PD1 inhibits T-cells and subsequent adaptive immune response to the tumour, particularly cell killing. Accordingly, the mechanism of action of anti-PD1 and anti-PDL1 agents has some similarities to conventional cytotoxic therapies that predominantly induce tumour cell death. This is clearly important to recognise in understanding PET imaging characteristics of response. The phase III clinical trial for nivolumab demonstrated that 73% of patients with metastatic melanoma are alive at 1 year with an objective response rate by RECIST criteria of 40% [5]. KEYNOTE 002, a phase II randomised study that compared pembrolizumab to chemotherapy in ipilimumab refractory patients [55], demonstrated objective response by RECIST of 21–26% for different dose regimens of pembrolizumab compared to 4% for chemotherapy. KEYNOTE-006, a phase III study randomised of 834 patients, demonstrated objective response rates of 36% for pembroluzimab compared to 13% for ipilimumab [49], conferring an OS benefit. Attempts have been made to combine different immune checkpoint blockades with success observed in the combination of nivolumab and ipilimumab.

This combinbation demonstrated an increased response rate compared to monotherapy with either agent in a phase III study but significantly higher toxicity as discussed below [56]. There are a great number of clinical trials in the drug development pipeline investigating anti-PD1 in combination with different agents, including other immune checkpoint blockades, injectable immune stimulating agents, chemotherapy and radiation. Although these treatments may serve to modulate FDG PET responses, either locally or distantly, a detailed history of prior and recent treatments are vital to scan interpretation.

Immune-mediated toxicities

Immune checkpoint blockades have unique immune-related adverse events including dermatitis, enterocolitis, hepatitis, endocrinopathies, and other immune toxicities. Ipilimumab is more likely to be associated with severe or life-threatening toxicities compared to the anti-PD1 antibodies, rates of 10–15% compared to approximately 5%, respectively. Combination of immunotherapy agents increases toxicity further, such as the combination of nivolumab and ipilimumab which resulted in 55% severe or life-threatening toxicity [56]. Mild immune-related adverse events can mostly be managed conservatively, whereas severe or life-threatening toxicities need to be managed with treatment discontinuation, high dose corticosteroids or other immune-suppressing agents such as tumour necrosis factor (TNF) antagonists. It is important that clinicians are able to recognise these toxicities early and initiate appropriate treatment [57]. Most immune toxicities from ipilimumab had an early onset after treatment initiation with a median onset of 6–8 weeks [58, 59]. Occasionally, some of these immune-related adverse events can be asymptomatic but diagnosed on imaging performed for routine follow-up. Hence, it is important that imaging specialists recognise some of the imaging features of these toxicities and liaise promptly with the treating clinician [60, 61]. Enterocolitis can present with diarrhoea and abdominal pain and typically occurs about 6 weeks after the start of treatment [58]. Rarely, this can result in colonic bleeding, perforation and death. Severe colitis is more common with anti-CTLA4 than with anti-PD1, 5–10% compared to 1–2%, respectively. Radiologically, there can be signs of colonic inflammation with colonic wall thickening, pericolonic fat stranding, and possible intestinal perforation and free fluid. Hepatitis most commonly manifests as asymptomatic elevations in liver enzymes of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This occurred in 10% with ipilimumab, and 5% in anti-PD1 studies. Radiological features of immune-mediated hepatitis can include mild hepatomegaly, peri-portal lymphadenopathy and peri-portal oedema [62]. Pneumonitis presents with dyspnoea or cough but can be asymptomatic [63]. This serious potential toxicity which can occur months after treatment has been initiated. Radiological findings on CT can include ARDS-pattern pneumonitis in severe cases, with diffuse ground-glass opacities, reticular opacities, consolidation, and traction bronchiectasis [64]. Endocrinopathies such as hypophysitis, thyroiditis, and adrenalitis can be challenging to diagnose clinically given its non-specific symptoms that include fatigue and headache. The endocrine axis should be monitored routinely and replacement hormones should be initiated as necessary. More uncommon immune related toxicities can include neuropathies, nephrotoxicities, myopathies, ocular toxicities such as anterior uveitis or chorioretinitis. The management of these toxicities require a multi-disciplinary approach, and clinicians need to be aware of these novel immune-mediated side effects as the use of these immunotherapies become more widespread in oncology practice [65, 66]. Importantly, many of these immune-related toxicities can be observed on PET. Amongst the most common is auto-immune thyroiditis [67] but the pituitary fossa, adrenals, lungs, liver, pancreas and bowel can all demonstrate increased uptake due to immune cell infiltrates.

Treatment response assessment with conventional imaging techniques

Given the distinct mechanisms of action of immunotherapy compared to traditional chemotherapy, novel responses have been observed on imaging after these agents. In addition to survival benefit noted for patients who experience a reduction or stability of tumour lesions, there are patients whose tumours enlarge prior to a subsequent reduction, i.e. 'pseudo-progression'. These atypical immune response have been associated with improved survival compared to those patients who would have been misclassified as having progressive disease by traditional classifications such as the WHO or RECIST [68]. In the phase II study of ipilimumab, 9.7% (22 of 227) of the treated patients experienced an atypical response. Biopsies of such enlarging lesions have confirmed inflammatory cell infiltration or necrosis rather than tumour cell proliferation as the cause of the radiological enlargement of lesions. Patients with such atypical response have comparable survival to patients experiencing complete response, partial response or stable disease by WHO Criteria. Hence, the Immune-related Response Criteria (IrRC) and subsequently the Immune-related Response Evaluation Criteria In Solid Tumor (IrRECIST) were proposed (Table 1). These reclassifications seek to avoid premature cessation of treatment for patients who may be deriving benefit. Similar atypical responses have been observed in the phase 1b study of pembrolizumab, where approximately 13% (84 of 655) of treated patients experienced a progressive disease by RECIST version 1.1 but atypical response by IrRC [69]. The

Table 1 Summary of the major differences between WHO, RECIST v1.1, irRC and IrRECIST classification

	WHO	RECIST v1.1	irRC	IrRECIST
Measurement of tumour burden	Bidimensional	Unidimensional	Bidimensional	Unidimensional
Maximum number of target lesions	10	5	10 visceral, 5 cutaneous	5
Classification of new lesions	PD	PD	Added to tumour burden	Added to tumour burden
CR	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions
PR	≥50% decrease in the tumour burden	≥30% decrease in the tumour burden	≥50% decrease in tumour burden	≥30% decrease in the tumour burden
SD	Neither PR nor PD	Neither PR nor PD	Neither PR or PD	Neither PR or PD
PD	≥25% increase in tumour burden New lesions	≥20% increase and ≥5mm absolute increase in tumour burden New lesions	≥25% increase in tumour burden	≥20% increase and ≥5mm absolute increase in tumour burden

Abbreviations: *WHO*, World Health Organisation; *RECIST v1.1*, Response Evaluation Criteria In Solid Tumours version 1.1; *irRC*, Immune-related Response Criteria; *IrRECIST*, Immune-related Response Evaluation Criteria In Solid Tumours; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

2-year OS rates were 77.6% in patients with non-progressive disease per both criteria (n = 331), 37.5% in patients with progressive disease per RECIST v1.1 but non-progressive disease by IrRC (n = 84), and 17.3% in patients with progressive disease by both criteria (n = 177). IrRC has been reported in very few studies, and in these studies, the additional immune-mediated response is approximately 4% [70].

Role of FDG PET in immunotherapy treatment response assessment

The role of FDG PET in chemotherapy response assessment for tumours such as Hodgkin lymphoma is well established with good evidence suggesting the adverse prognostic implications of a positive interim FDG PET scan [71]. Multiple trials are ongoing to evaluate salvage treatment strategies to abrogate the poor prognosis generally associated with a positive interim response scan. Tumour response assessment for immunotherapy using FDG PET is also under investigation but published results vary preliminary. In a study in which 22 patients receiving ipilumumab were assessed after 2 and cycles of treatment, early progression of disease on FDG PET/CT carried an adverse prognosis compared to that for patients with stable metabolic disease, although 2/15 patients with progressive metabolic disease did not eventually demonstrate clinical progression, suggesting that the changes on PET may have reflected a metabolic flare [67]. Kong et al. investigated the use of FDG PET in 27 patients with residual disease after anti-PD1 therapy for melanoma [72]. They found that 56% of patients had residual FDG-avid lesions when scans were performed at a median interval of 15.2 months after initiation of treatment. Eight of the patients with residual avid lesions proceeded to a biopsy of the avid lesions, and 62% (5 out of 8) confirmed melanoma while 38% (3 out of 8) confirmed an inflammatory infiltrate. The melanoma lesions had a higher median SUVmax compared to the positive results due to a presumed local immune response (SUVmax = 18 versus 7.1, respectively). Lesions that have very similar SUV results before and after treatment are more suspicious than those that are altered, unless the lesion was or becomes subject to partial volume effects due to small size or development of extensive central necrosis. Even though this is a small cohort, this highlights that an avid lesion months after therapy may represent an immune infiltrate. Of the 12 patients with a negative FDG PET scan, none of the patients have recurred in 6–10 months follow-up period. Currently, the optimal duration of therapy for anti-PD1 antibodies is not known, and future prospective studies may clarify whether a negative FDG PET scan can identify patients who can stop treatment, which is a particularly relevant question in patients suffering secondary autoimmune toxicity but also has significant cost-saving implications.

Given that both melanoma and immune infiltrates can be FDG-avid, it is challenging for FDG PET to differentiate patients with progression from those experiencing ‘pseudo-pro-

gression'. With experience, however, signs of immune-related inflammatory responses may be visualised on FDG PET/CT. If these features are seen, we caution reporting other findings as progression and recommend a follow-up scan to assess for temporal change before defining progression. Patterns of an inflammatory response include (Figs. 3, 4 and 5):

- Symmetric hilar and mediastinal nodal uptake in a pattern similar to sarcoidosis. This is more commonly seen in patients with pulmonary metastatic disease, and can also be seen following BRAF and MEK inhibition
- Reactive nodal uptake in the drainage basin of metastases, e.g. porta hepatitis nodal activity in the setting of hepatic metastases
- Diffuse splenic uptake

In our experience, inflammatory changes, which could be considered an "immune flare" response, are significantly more frequently observed with anti-CTLA4 compared to anti-PD1 agents, congruent with the higher incidence of autoimmune side effects seen with anti-CTLA4 agents. These tend to occur relatively early after introduction of treatment and are often associated with increased splenic activity. Since anti-PD1/PDL1 agents are thought to activate established anti-tumour cytotoxic T-cells to facilitate rapid cell killing, the most common response, in our experience, is a progressive reduction in %ID and MTV, which is like the response seen with conventional chemotherapy, although sometimes over a much-protracted time scale. With early imaging, progression on anti-PD1/PDL1 agents is very seldom a manifestation of immune flare response unless the patients is on a combination with anti-CTLA4 treatment.

Further investigation into these PET parameters in larger prospective studies will allow capture of the true incidence of these immune responses on PET versus pseudo-progression on radiologic criteria and how they can be best incorporated into the existing treatment response assessment criteria. More specific receptor antibodies targeted at imaging the CD8 receptor may hold promise to resolve this clinical dilemma, and some of these have been validated in preclinical studies [73] and are now entering clinical trials.

As mentioned above, it is important to carefully consider immune toxicities as a cause for abnormalities that develop early during treatment, especially if these new abnormalities are not associated with progression at prior sites of disease and especially if most disease sites are regressing [74].

Conclusion

The treatment landscape for advanced melanoma has changed markedly over the past few years. Novel agents including molecularly targeted therapies and immunotherapies have

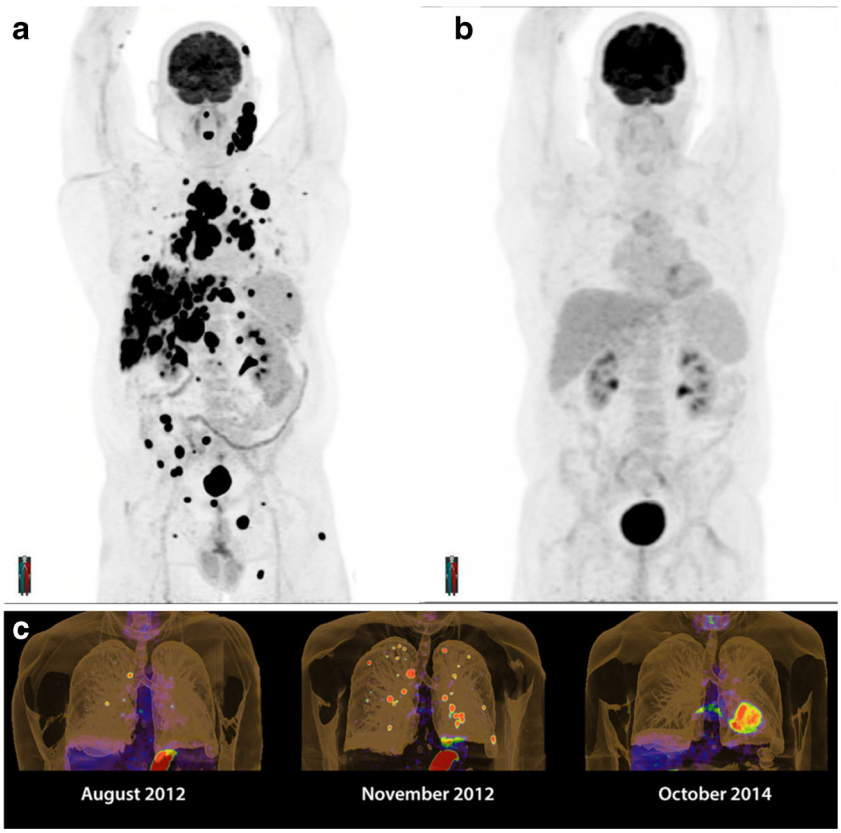

Fig. 5 **a**. This patient presented with a scalp melanoma associated with very extensive nodal and systemic metastasis. **b**. Three months after commencing anti-PD1 therapy there was an almost complete metabolic response. **c**. In another patient without a targetable mutation, following radiotherapy of a large and unresectable left adrenal mass, there was small volume but progressive pulmonary metastatic disease. Introduction of anti-PD1 therapy led to gradual regression of pulmonary nodules over the next 2 years, which was accompanied by reducing size and metabolic activity of the pulmonary metastases and mildly increased mediastinal nodal uptake suggesting immune activation. Activity in the left lower thorax in the final image is in the myocardium. The left adrenal mass almost completely resolved. This patient remains alive more than 4 years after commencing this therapy

rapidly entered clinical practice as new standards of care. FDG PET/CT remains an invaluable modality in the evaluation of responses and monitoring for toxicities for these agents. Understanding the FDG PET characteristics of the immune response to the new immunotherapies may also lead to a deeper understanding of the mechanism by which these agents are exerting their effect. Because of differing mechanisms of action, the optimal timing of scans after commencement of treatment is likely to vary and the interpretation criteria are also likely to be different. Therefore, is it vital to obtain details of the type, commencement and duration of treatment. For targeted agents, assessment very early in treatment may allow identification of primary refractory disease whereas with anti-CTLA4, early imaging may be compromised by immune flare responses but enable early detection and treatment of immune-related toxicities. For anti-PD1/PDL1 therapy, imaging later in treatment may provide better assessment of benefit. While this is an exciting era in which to be involved in cancer therapy response assessment, much work is still needed to define and refine response assessment guidelines as it is unlikely that a one-size-fits-all approach will be effective, despite the attractions of standardised criteria like RECIST and PERCIST.

Compliance with ethical standards This review does not report any previously unpublished studies with human participants or animals performed by any of the authors. Therefore, ethics committee approval is not applicable.

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Conflicts of interest None of the authors has a conflict of interest to report.

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