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ORIGINAL ARTICLE

FDG-PET response and outcome from anti-PD-1 therapy in metastatic melanoma

A. C. Tan[1,2], L. Emmett[1,3,4], S. Lo[1], V. Liu[3], R. Kapoor[5,6], M. S. Carlino[1,7], A. D. Guminski[1,2,6], G. V. Long[1,2,6] & A. M. Menzies[1,2,6]*

[1]Melanoma Institute Australia and The University of Sydney, Sydney; [2]Department of Medical Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, Sydney; [3]Department of Nuclear Medicine, St Vincent's Hospital, Sydney; [4]The University of New South Wales, Sydney; [5]Department of Radiology, Royal Prince Alfred Hospital, Sydney; [6]Mater Hospital, Sydney; [7]Department of Medical Oncology, Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Sydney, Australia

Correspondence to: Prof. Alexander M. Menzies, Department of Medical Oncology, Melanoma Institute Australia, 40 Rocklands Rd, North Sydney, NSW 2060, Australia. Tel: +61-2-9911-7258;
E-mail: alexander.menzies@sydney.edu.au

Background: Immune checkpoint inhibitor therapy has resulted in impressive and durable clinical activity for many cancers including melanoma; however, there remain few reliable predictors for long-term response. This study investigated whether [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG-PET) imaging may better predict long-term outcomes compared with standard computed tomography (CT) response criteria.

Patients and methods: Retrospective analysis of metastatic melanoma patients treated with anti-PD-1-based immunotherapy with baseline and 1-year FDG-PET and CT imaging at Melanoma Institute Australia. One-year response was determined using RECIST for CT and EORTC criteria for PET, coded as complete response (CR or CMR), partial response (PR or PMR), stable disease (SD or SMD) or progressive disease (PD or PMD). Progression-free survival (PFS) was determined from the 1-year landmark.

Results: Patients ($n = 104$) were evaluated with median follow-up 30.1 months and 98% remain alive. Most received anti-PD-1 as monotherapy (67%) or combined with ipilimumab (31%). At 1 year, 28% had CR, 66% had PR and 6% had SD on CT, while 75% had CMR, 16% PMR and 9% SMD/PMD on PET. CMR was observed in 68% of patients with PR on CT. RECIST PFS post 1-year landmark was similar in patients with CR versus PR/SD, but improved in patients with CMR versus non-CMR {median not reached [NR] versus 12.8 month; hazard ratio [HR] 0.06 [95% confidence interval (CI) 0.02–0.23]; $P < 0.01$}. In patients with PR on CT, PFS was improved in patients with PR + CMR versus PR + non-CMR (median NR versus 12.8 months; HR 0.07 [95% CI 0.02–0.27]; $P < 0.01$). In the 78 CMR patients, 78% had discontinued treatment and 96% had ongoing response.

Conclusions: Whilst only a small proportion of patients have a CR at 1 year, most patients with a PR have CMR on PET. Almost all patients with CMR at 1 year have ongoing response to therapy thereafter. PET may have utility in predicting long-term benefit and help guide discontinuation of therapy.

Key words: anti-PD-1 therapy, immunotherapy, PD-1, melanoma, PET, positron emission tomography

Introduction

Anti-PD-1-based immune checkpoint inhibitor therapy has resulted in durable clinical activity for many patients with metastatic melanoma and other cancers [1–5]. Currently, there remain few reliable predictors of long-term response. Patients with complete response (CR) based on standard response criteria using computed tomography (CT) imaging have excellent long-term outcomes with immunotherapy; however, many more patients with partial response (PR) or stable disease (SD) also do well long term [6]. Additionally, the optimal duration of therapy is unknown. It appears that discontinuation of therapy after 2 years has a low risk of subsequent progression for melanoma and that the best response as determined by CT does not appear to impact the risk of progression or death after discontinuation [6, 7]. One hypothesis for this is that many patients with incomplete responses on CT may not have residual disease.

The mechanism of action of immune checkpoint inhibitors, in contrast to traditional cytotoxic chemotherapy or targeted therapies, means response evaluation using conventional CT response criteria is challenging. Newer immune-related response criteria (irRC) have been developed to account for phenomena such as pseudoprogression [8]. However, irRC and conventional RECIST criteria both fail to identify which patients without CR will have good long-term outcomes.

[^{18}F]2-fluoro-2-deoxy-D-glucose (FDG-PET) imaging, which provides functional information to complement standard anatomic imaging, may therefore have an important role in the assessment and evaluation of treatment response. We hypothesised that PET will distinguish residual lesions in patients with PR or SD that may be free of viable tumour, and that patients with a complete metabolic response (CMR) will have better outcomes than those without. This study aimed to investigate whether PET imaging could better predict long-term outcomes compared with standard CT response and provide guidance on potential timing of discontinuation of therapy.

Materials and methods

Patient selection

A prospectively assembled cohort of consecutive patients treated with anti-PD-1-based immunotherapy between May 2013 and April 2018 at Melanoma Institute Australia were examined. All patients received baseline and 1-year FDG-PET/CT imaging, alongside diagnostic extracranial CT and magnetic resonance imaging (MRI) every 3 months. Key eligibility criteria for this study included patients with unresectable or metastatic melanoma treated with anti-PD-1-based immunotherapy that had not progressed at 1 year on CT by RECIST or on clinical grounds. Anti-PD-1-based therapy consisted of nivolumab or pembrolizumab either as monotherapy or in combination with any other drug treatment. Patients who received any subsequent systemic therapy before the 1-year follow-up imaging were excluded. Patients who discontinued therapy without RECIST/clinical progression, for toxicity or other reasons, before the 1-year imaging and had not received any other subsequent therapy remained eligible. One-year imaging was defined as 12 months (±3 months) from time point of commencing anti-PD-1-based therapy. Patients without baseline metabolically avid disease on PET or measurable disease on CT were excluded. Patient demographics, disease features, treatment details and patient outcomes were collected from the medical records. The study was approved by the Human Ethics Review Committee (protocols X10-0300, HREC/10/RPAH/530 and MIA 2015/146).

Response evaluation criteria

PET images were reviewed and analysed using a modified EORTC criteria, by two independent nuclear medicine physicians, blinded to the CT results or patient outcomes [9]. The standardized uptake value (SUV max) of the top five most intense metastatic lesions were measured at baseline and on the 1-year PET, in addition to any new metabolically active lesions on the 1-year PET. All metastatic lesions were coded for anatomic site. Responses by PET assessment were coded as CMR, partial metabolic response, stable metabolic disease or progressive metabolic disease. PET intensity at or below mediastinal blood-pool was considered the cutoff for CMR. The presence of bilateral reactive mediastinal or hilar lymphadenopathy on PET was documented but not coded as 'consistent with melanoma' in the assessment of response and may represent a benign sarcoid-like pattern seen in patients receiving immune checkpoint inhibitor therapy [10]. Contrast-enhanced CT images were reviewed and analysed using RECIST 1.1 criteria [11], and accordingly, responses were coded as CR, PR, SD or progressive disease (PD). PET and CT correlation, based on the above response criteria, were analysed using cross tabulation.

Statistical analysis

Patient characteristics were summarised using descriptive statistics. Kaplan–Meier survival analysis was carried out to determine progression-free survival (PFS) from the 1-year landmark. Progression events were based on CT (RECIST) imaging response evaluation or clinical progression. Survival performance based on type of responses (CT, PET or both) was tested using Cox proportional hazard model. Hazard ratio with its 95% confidence intervals are displayed along with the associated log-rank *P*-value. Statistical analysis was carried out using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and treatment details

There were 104 patients treated with anti-PD-1-based therapy who had not progressed at 1 year (Table 1). The median age was 65 years (range 32–88 years), 70 (67%) patients were male, 34 (33%) had *BRAF* mutation positive melanoma, 64 (61%) had AJCC v7 M1c disease (anatomical), 16 (15%) had prior/current brain metastases, 82 (79%) had normal serum lactate dehydrogenase and 73 (70%) had an ECOG performance status 0. Nine (9%) patients had received prior neoadjuvant or adjuvant therapy for early stage disease, and 29 (28%) patients had received prior systemic therapy in the metastatic setting. Most received anti-PD-1 monotherapy (67%), or anti-PD-1 combined with ipilimumb (31%). At time of analysis, median duration of treatment was 21 months and 77% of patients had discontinued treatment, 45% for toxicity.

Response evaluation and correlation of PET and CT scans

At 1 year, 69 (66%) patients had a PR as per CT assessment, but the majority of these patients ($n = 47$, 68%) had a CMR on PET scan, with 78 (75%) of all 104 patients in CMR at 1 year (Table 2). Similar results were seen in the subgroups treated with anti-PD-1 monotherapy and combination therapy (supplementary Table S1, available at *Annals of Oncology* online), and in those who had discontinued therapy within 1 year and those who remained on treatment at 1 year (supplementary Table S2, available at *Annals of Oncology* online). In the 49 patients with CMR at 1 year and PR/SD on CT, lung lesions (59%) and lymph nodes (33%) were the most common residual sites on CT that were not avid on PET (supplementary Table S3, available at *Annals of Oncology* online).

Of the 78 patients with CMR at 1 year, 27 patients (35%) had follow-up of >24 months from treatment commencement, thus also had a PET and CT scan at 2 years. All 27 patients remained in CMR on PET. On CT correlation, 13 patients were in CR, 13 in PR and 1 had SD. No patient had RECIST disease progression. Four patients improved from PR to CR, with the other patients having no change in CT response. Nine patients with sufficient follow-up, also had a PET and CT scan at 3 years, with all nine

Table 1. Baseline patient and tumour characteristics and treatment details

Characteristic	*n* (%)
Number of patients	104
Age (median, range)	65 years (32–88)
Sex	
Female	34 (33)
Male	70 (67)
Mutation status	
BRAF	34 (33)
NRAS	17 (16)
BRAF/NRAS wild-type	53 (51)
Primary	
Cutaneous	90 (86)
Acral	2 (2)
Occult	12 (12)
Stage[a]	
Unresectable IIIC	5 (5)
M1a	8 (8)
M1b	27 (26)
M1c	64 (61)
LDH at baseline	
Normal	82 (79)
1× ULN	19 (19)
2× ULN	3 (3)
ECOG	
0	73 (70)
1	31 (30)
Presence of brain metastases	
No	88 (85)
Yes	16 (15)
Neoadjuvant or adjuvant drug treatment of early stage disease	
No	95 (91)
Yes	9 (9)
Dabrafenib/trametinib	3 (3)
Vemurafenib	1 (1)
Ipilimumab	2 (2)
Interferon	3 (3)
Prior systemic therapy for advanced disease	
No	75 (72)
Yes	29 (28)
Binimetinib/ribociclib	1 (1)
Dabrafenib/trametinib	14 (13)
Lenvatinib	1 (1)
Vemurafenib	1 (1)
Ipilimumab	14 (13)
Ipilimumab/nivolumab	1 (1)
Nivolumab	2 (2)
Dacarbazine	1 (1)
Anti-PD-1-based therapy	
Nivolumab	14 (14)
Nivolumab + ipilimumab	13 (13)
Pembrolizumab	55 (53)
Pembrolizumab + ipilimumab	20 (18)
Pembrolizumab + TVEC	2 (2)
Time on treatment (median, range)	21.1 months (1.4-58.9)
Discontinued treatment	
No	24 (23)
Yes	80 (77)
Reason for anti-PD-1 discontinuation	
Completed 2 years	28 (27)
Toxicity	36 (35)
Progressive disease	5 (5)
Other	11 (11)
Subsequent therapy	
No	98 (94)
Yes	6 (6)

[a]AJCC version 7, excluding lactate dehydrogenase (LDH).

remaining in CMR. CT response was either the same ($n = 7$) or better ($n = 2$) than the 1-year CT.

PFS analysis

At time of data collection, with median follow-up of 30.1 months from the commencement of treatment, 102 (98%) patients were alive and 2 (2%) patients had died. Ninety (87%) patients were progression free, 12 (12%) had extracranial progression, 1 (1%) had intracranial progression and 1 (1%) had concurrent intracranial and extracranial progression as per RECIST.

PFS from the 1-year landmark was not statistically different in patients with CR on CT compared with PR/SD {median not reached [NR] in both groups; hazard ratio [HR] 0.18 [95% confidence interval (CI) 0.06–0.56] $P = 0.06$; Figure 1A} although approached significance. No patient with a CR on CT had progressed, while 51 (86%) patients with PR/SD on CT were progression-free at 1 year post imaging. There was a significant difference in PFS in patients with CMR on PET compared with non-CMR [median NR versus 12.8 months; HR 0.06 (95% CI 0.02–0.23); $P < 0.01$; Figure 1B], with 100% and 57% progression free at 1 year post imaging, respectively. In the subset of patients with CMR on PET, PFS was not different between patients with CMR + CR compared with CMR+PR/SD [median NR in both groups; HR 0.72 (95% CI 0.07–7.2); $P = 0.47$; supplementary Figure S1, available at *Annals of Oncology* online), but in patients with PR on CT, PFS post 1-year imaging was improved in patients with PR + CMR compared with PR + non-CMR [median NR versus 12.8 months; HR 0.07 (95% CI 0.02–0.27); $P < 0.01$; Figure 1C), with 100% and 58% progression free at 1 year post imaging, respectively.

For the 78 patients with CMR at 1 year, median time on treatment was 20.7 months, 78% had discontinued treatment with median follow-up post discontinuation of 14.5 months, and 75 (96%) remained progression free. Of the three patients who progressed, one had CMR + PR at 1 year, was on treatment for 28 months until intracranial only progression and died 2 months later. The second patient had 8 months of anti-PD-1 therapy (pembrolizumab with reduced-dose ipilimumab on clinical trial Keynote-029), CMR + CR at 1 year, progressed 29 months after cessation of therapy with in-transit and nodal metastases and recommenced single-agent anti-PD-1 treatment. The third

Table 2. Correlation of computed tomography (CT) and ^{18}F-FDG PET response at 1-year

^{18}F-FDG PET response at 1-year	Number of patients (%)			
	CT response at 1 year			
	CR	PR	SD	Total
CMR	29 (28)	47 (45)	2 (2)	78 (75)
PMR	0 (0)	15 (14)	2 (2)	17 (16)
SMD	0 (0)	1 (1)	0 (0)	1 (1)
PMD	0 (0)	6 (6)	2 (2)	8 (8)
Total	29 (28)	69 (66)	6 (6)	

CMR, complete metabolic response; CR, complete response; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; SD, stable disease; SMD, stable metabolic disease.

patient had CMR + PR at 1 year with a residual 18-mm lung lesion that grew after 27 months and was treated with radiotherapy, with ongoing pembrolizumab therapy.

In the overall cohort, 27 patients had discontinued therapy before the 1-year landmark due to toxicity, and none had progressed at the time of data collection. Rates of discontinuation of therapy before the 1-year landmark were 36% and 15% in patients with CMR and non-CMR, respectively ($P = 0.06$). Similarly, rates of discontinuation of therapy before the 1-year landmark were 32% and 18% in those with PR + CMR and PR + non-CMR, respectively ($P = 0.37$).

Discussion

There is increasing evidence that patients with metastatic melanoma treated with anti-PD-1 based therapy who are in CR on CT have excellent long-term outcomes and can safely cease therapy with low risk of relapse [7, 12–14]. Many patients with PR on CT also have durable response to anti-PD-1-based therapy; however identifying which patients will subsequently progress remains a challenge and the optimal duration of therapy is unknown [7]. Updated analysis from the Keynote-006 trial illustrated in patients with CR and PR who completed 2 years of pembrolizumab therapy, 18-month PFS rates of 95.8% and 91.3%, respectively [7]. In this study, we demonstrate that FDG-PET imaging reveals that the majority of patients in PR by conventional CT response evaluation at 1 year have had a CMR, with excellent medium-term outcomes, mirroring those with CR on CT, but those with residual ^{18}F-FDG avidity fare less well. Longer term follow-up in this cohort will be crucial; however, such information is prognostic and may inform discussions regarding duration of therapy.

FDG-PET has been well validated to monitor treatment, assess response and predict prognosis in many subtypes of lymphoma, and more recently has been incorporated into response-adapted treatment in Hodgkin lymphoma [15]. For melanoma, it has strong evidence for use in staging to detect distant metastases [16, 17]. The value of FDG-PET in assessing response to therapy for

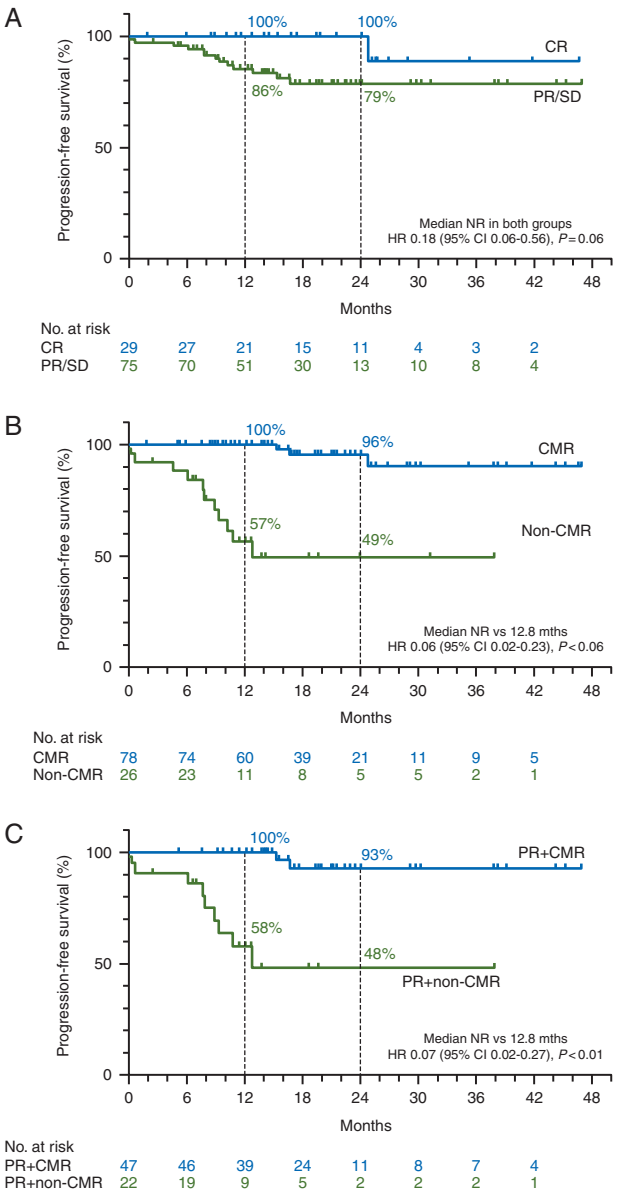

Figure 1. Progression free survival post 1-year imaging by computed tomography (CT) response (A), [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG-PET) response (B) and ^{18}F-FDG PET response in patients with partial response (PR) on CT (C) at 1 year. CMR = complete metabolic response.

metastatic melanoma is less well established. With the advent of immune checkpoint inhibitors and targeted therapies that improve survival [1, 2, 18, 19], there is a growing need for evidence for the utility of FDG-PET in monitoring response and outcome with therapy. With targeted therapies, early FDG-PET scans at day 15 in patients on phase I trials demonstrated early complete or partial metabolic responses, potentially with prognostic significance [20, 21]. In patients treated with immune checkpoint inhibitors, there have only been reports of small cohorts, with FDG-PET scans early in the treatment course [22, 23]. These studies did not provide evidence for the prognostic value of FDG-PET for long-term patient outcome, particularly in patients with durable clinical response.

Our study represents the largest cohort to date of patients treated with immune checkpoint inhibitors, specifically anti-PD-1-based therapy, who underwent later serial FDG-PET (at 1 year) with ongoing follow-up. Immunotherapy induces an immune cell infiltrate and inflammation of tumours early during the treatment course, sometimes resulting in the phenomena of pseudo-progression, which may confound interpretation of early FDG-PET scans [24, 25]. Other inflammatory reactions, such as sarcoid-like reactions, may also occur early during treatment, manifesting as new lesions on CT and PET [26]. Therefore later FDG-PET, for example, at 1–year, may provide the most useful prognostic information. The correlation of CT and FDG-PET responses is also vital. Residual lesions in patients with PR on CT may represent scarring and this may be particularly prevalent in residual lung and nodal lesions, common sites in our study of persistent lesions without FDG-avidity. Furthermore, case reports have documented the histopathology of lesions biopsied that were free of viable tumour [27, 28]. Crucially, our study highlighted that almost all patients with PR on CT and CMR on FDG-PET had ongoing response to therapy, and outcomes were essentially equivalent to patients with CR on CT. Our one patient who progressed with intracranial only progression, also emphasises the poor ability of FDG-PET in assessing cerebral metastases, and the additional importance of MRI.

An earlier study we conducted investigated 27 patients with prolonged response to anti-PD-1-based therapy [29]. An FDG-PET scan was carried out, at a median 15.2 months, with CMR predicting good ongoing response, consistent with our current cohort of patients. The optimal duration of therapy with anti-PD-1-based therapy, particularly in longer term responders, is also an increasingly important question that remains to be answered. Initial trials of anti-PD-1 therapy continued treatment indefinitely, however, subsequent trials have predefined cessation at 2 years of treatment. In our cohort, 60% had discontinued treatment at time of data collection and 36% had less than 12 months of treatment. Similar proportions of patients with CMR had discontinued therapy within 12 months than those without CMR, and yet they still had superior PFS. Our results therefore suggest that as with the previous long-term analysis of the Keynote-001 trial that demonstrated cessation of therapy after CR on CT was safe [13], cessation of therapy after CMR on FDG-PET may similarly be safe. Prospective evaluation of FDG-PET scans is warranted, and the best timing of PET is yet to be determined.

The application of these findings in other cancers is also of significance. There have been limited studies in other cancers assessing the role of FDG-PET in response evaluation to immune checkpoint inhibitor therapy. A phase II study of nivolumab in classical Hodgkin lymphoma after autologous stem cell transplantation and brentuximab vedotin failure demonstrated CMR was associated with durable response [30]. Immunotherapy can induce long-term responses in a subgroup of patients across most cancer types, and whether FDG-PET may play an important role in response evaluation should be explored.

In this study of patients who did not progress within the first year with anti-PD-1-based immune checkpoint inhibitor therapy on CT, almost all patients with CMR on FDG-PET had ongoing response to therapy thereafter. Whilst only a small proportion of patients on CT had a CR, most patients have a CMR on PET, including the majority with a CT PR. Therefore, PET may have utility in predicting long-term benefit and help guide discontinuation of therapy. Prospective evaluation using PET at earlier intervals is warranted.

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Disclosure

ADG has served on advisory boards to BMS, Eisai, Merck KgA, Pfizer, Regeneron, Roche and Sun Pharma. AMM and MSC have served on advisory boards for BMS, MSD Merck, Novartis, Roche and Pierre-Fabre. GVL has served on advisory boards to Amgen, Array, BMS, MSD Merck, Novartis, Oncosec, Roche and Pierre-Fabre. LE has served on advisory boards to Oncosil. All remaining authors have declared no conflicts of interest.

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