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FDG-PET associations with pathological response and survival with neoadjuvant immunotherapy for melanoma

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ABSTRACT

Background Neoadjuvant immunotherapy has become the new standard of care for stage III melanoma. This study sought to describe the metabolic changes seen with fludeoxyglucose-18-positron emission tomography (FDG-PET) following neoadjuvant immunotherapy in patients with melanoma and explore associations with pathological response and recurrence-free survival (RFS).

Methods Data from patients with macroscopic stage III nodal melanoma treated with neoadjuvant checkpoint inhibitor therapy were pooled from five melanoma centers. All patients underwent baseline and preoperative FDG-PET and CT assessments, and all had surgery. Pathological response was determined using the International Neoadjuvant Melanoma Consortium criteria, radiological response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and FDG-PET response using European Organization for Research and Treatment of Cancer (EORTC) criteria. The primary endpoint was to explore the associations of metabolic and radiological responses with pathological response; secondary endpoints were RFS outcomes stratified by each response category.

Results 115 patients were included, 69% male, median age 59 years (27–92), 43% BRAF mutant, and median follow-up was 22.2 months (95% CI 13.7 to 26.4). 40 patients received anti-PD-1 monotherapy, 20 patients received pembrolizumab combined with lenvatinib, and 55 patients received ipilimumab and nivolumab. The major pathological response (MPR) rate was 62%, and the pathological complete response rate was 51%. RECIST response underestimated pathological response; patients achieving RECIST stable disease (38%) had a 50% chance of achieving MPR. The FDG-PET metabolic response rate was 73%, with most achieving an MPR (80%), especially in patients with a complete metabolic response (CMR, 96% MPR). A small proportion of patients (10%) had stable metabolic disease on FDG-PET, and all these patients were non-MPR. Patients with progressive metabolic disease were also in the majority non-MPR (79%). Patients with MPR, complete response/partial response on CT, and CMR/partial metabolic response on FDG-PET had a favorable 24-month RFS (95.6%, 97.3%, and 93.7%, respectively), with FDG-PET able to identify a greater proportion of patients with favorable progression-free survival (PFS) than pathology or CT (73%, 62%, and 43%, respectively).

Conclusion Neoadjuvant immunotherapy has high FDG-PET response rates in melanoma. FDG-PET response

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fludeoxyglucose-18-positron emission tomography (FDG-PET) response is an accurate predictor of survival in patients with advanced melanoma; however, it is currently unknown whether PET associates with pathological response or survival in the neoadjuvant setting.

WHAT THIS STUDY ADDS

⇒ This is the first study of FDG-PET in the neoadjuvant setting with immunotherapy for melanoma in over 100 patients from five International Neoadjuvant Melanoma Consortium centers. Our findings suggest that neoadjuvant immunotherapy has high FDG-PET response rates in melanoma, and that FDG-PET response associates with pathological response and survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ FDG-PET becomes an important tool for predicting immunotherapy response before surgery, potentially identifying patients for surgical de-escalation, or conversely, identifying those who would not have a pathological response and may benefit from alternative systemic treatment escalation prior to surgery.

associates with pathological response and confers impressive RFS, suggesting this could be an important clinical tool.

INTRODUCTION

Neoadjuvant immunotherapy has become a new standard of care for clinically detected stage III melanoma, superior to adjuvant therapy alone, with 1-year recurrence-free survival (RFS) of 73–84% vs 60–61%.[1 2] Neoadjuvant anti-PD-1-based regimens yield a 70% pathological response rate and a 48% pathological complete response (pCR) rate in the updated pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC).[3] Pathological response has been correlated with RFS and considered a reliable predictor of long-term outcomes. Those achieving major pathological response (MPR; ≤10% viable cells) have significantly improved outcomes, with recurrence being rare among these patients.[1–6] While patients with MPR have high event-free survival rates (93% at 2 years), the prognosis for patients with pathological partial response (pPR) or pathological non-response (pNR) is poorer, with RFS rates of 64% and 71% at 2 years, respectively. As such, the outcomes for individual patients in this situation are not clear.

CT imaging is a commonly used imaging modality in oncology. Similar to pathology, patients with a complete response (CR) or partial response (PR) have excellent RFS rates,[4] often with concurrent MPR. However, a large group of patients (36%) have stable disease (SD) which has uncertain outcomes (RFS 62% at 2 years).[4] Even patients with Response Evaluation Criteria in Solid Tumors (RECIST)[7] progressive disease (PD) occasionally have MPR and consequently experience long-term survival.[4] Therefore, neither pathology in those with non-MPR nor CT imaging is precise enough to accurately predict survival for patients with melanoma after neoadjuvant immunotherapy.

Functional imaging with fludeoxyglucose-18-positron emission tomography (FDG-PET) is a reliable tool for imaging patients with metastatic melanoma.[8 9] Studies have shown that metastatic patients achieving complete metabolic response (CMR) to immunotherapy have an excellent 5-year survival rate (90% progression free and 96% overall survival rate at 5 years), and many with only a RECIST PR have a CMR on FDG-PET.[8 9] However, it is currently unknown whether FDG-PET can predict pathological response nor whether it associates with RFS. If accurate, it could become an important tool for predicting immunotherapy response before surgery, potentially identifying patients for surgical de-escalation, or conversely, identifying those who would not have a pathological response and may benefit from systemic treatment escalation prior to surgery.

To investigate this, we conducted this INMC study to explore the changes seen with FDG-PET following neoadjuvant immunotherapy in patients with melanoma and explore associations with RECIST response, pathological response and survival.

METHODS

Patients and treatment

Patients commencing neoadjuvant immunotherapy between July 2018 and May 2024 from five INMC centers, including Australia (Melanoma Institute Australia and Peter MacCallum Cancer Centre), USA (Moffitt Cancer Center), Brazil (A C Camargo Cancer Center), and Russia (N N Blokhin NMRC of Oncology, Ministry of Health), were enrolled. All patients had American Joint Committee on Cancer 8th Edition (AJCC v8[10]) IIIB-IV resectable and measurable melanoma per RECIST criteria and received either anti-PD-1 monotherapy (pembrolizumab or prolgolimab[11]), combination nivolumab 3 mg/kg and ipilimumab 1 mg/kg or pembrolizumab+lenvatinib via the NeoTrio and NeoPele clinical trials,[12 13] or non-trial treatments. Adjuvant therapy, including anti-PD-1 or targeted therapy, was used based on physicians' choice or trial protocol. Patients treated with neoadjuvant targeted therapy (alone or in combination or sequence with immunotherapy) were intentionally excluded as FDG-PET responses are high, yet associations with pathological response are less clear, and recurrences are frequent.[14 15]

Response evaluation criteria

Radiological response was assessed using RECIST criteria.[7] Pathological response was determined per INMC criteria as follows: MPR, which includes pCR (0% viable tumor) and near-complete pathological response (npCR, >0% to ≤10% residual tumor), pPR (>10% to ≤50% residual tumor), and pNR (>50% residual tumor).[16] Metabolic responses (MR) were evaluated based on the European Organization for Research and Treatment of Cancer (EORTC) criteria,[17] which included CMR, partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD). For patients with multiple involved lymph nodes, the most avid node on FDG-PET was selected for assessment. All response outcomes (CT, FDG-PET, and pathology) were performed blinded to the other response outcome and survival data. For clinical trial patients, the images were reviewed by the clinical trial radiologists or nuclear medicine physicians as part of the trial protocol. For non-trial patients, the data were collected from the reports available in the clinical notes.

Data collection and recurrence assessment

The following clinical data were retrospectively collected from the clinical notes: baseline demographics (age and sex), anatomic location of the nodal disease, BRAF V600 mutational status, stage (by AJCC v8 for cutaneous melanoma), treatment regimen, RECIST response, pathological response, MR, maximum voxel value of standardized uptake value (SUVmax) of the most avid node on baseline and preoperative FDG-PET scans, adjuvant therapy, recurrence pattern, and RFS from surgery. Disease recurrence was determined by the treating physician. The data cut-off date was in July 2024. The primary endpoint was to explore the associations of metabolic

and radiological responses with pathological response; secondary endpoints were RFS outcomes stratified by each response category.

Statistical analysis

Patient characteristics and clinical features were summarized using median (range) for continuous variables and frequency (proportion) for categorical variables for the pooled cohort. RFS time was calculated as the time from surgery until the date of first recurrence or metastasis or death from any cause, whichever occurred first. The Kaplan-Meier method was used to describe RFS outcome stratified by response category within each modality (pathology, CT, and FDG-PET). RFS differences between groups were assessed using the log-rank test. The association between SUVchange and pathological response was evaluated using the Wilcoxon rank test. The ability to predict RFS among the three modalities was compared using area under the curve (AUC). Statistical analysis was carried out using R (V.4.3.2). A two-sided p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and neoadjuvant treatment

A total of 115 patients were included from five melanoma centers (online supplemental figure S1, table 1). The majority of patients were male (69%), with a median age of 59 years (range: 27–92). BRAF V600 mutations were present in 49 (43%) patients. 62 patients had AJCC v8 IIIB (54%) and 45 had IIIC (39%) disease, with a small proportion of IIID and IV (3% each). Lymph node metastases were located in the neck (30%), axilla (40%), and groin (27%). The median baseline lesion SUVmax was 14.4 (range: 2.3–80). Patients received a median of two (range: 1–6) cycles of neoadjuvant immunotherapy. 40 patients (35%) received anti-PD-1 monotherapy (pembrolizumab 200 mg once every 3 weeks or prolgolimab 1 mg/kg once every 2 weeks), including both clinical trial (NeoTrio trial) and non-trial settings, 20 patients (17%) received pembrolizumab combined with lenvatinib (NeoPele trial—pembrolizumab 200 mg once every 3 weeks combined with lenvatinib 20 mg once per day), and 55 patients (48%) received dual immunotherapy (nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg once every 3 weeks) outside of trials. All patients underwent surgery and 39 (34%) received adjuvant therapy, among whom 11 with BRAF mutations switched to adjuvant targeted therapy. Median follow-up was 22.2 months (95% CI 13.7 to 26.4).

Table 1 Demographic and clinical characteristics at baseline

Characteristics	Total (n=115)
Center	
MIA	44 (38%)
ACCCC	34 (30%)
MCC	17 (15%)
PMCC	14 (12%)
NMRCO	6 (5%)
Sex	
Male	79 (69%)
Age	
Years, median (range)	59 (27–92)
BRAF status, n (%)	
BRAF V600 mutant	49 (43)
AJCC v8 stage*	
IIIB	62 (54%)
IIIC	45 (39%)
IIID	4 (3%)
IV	3 (3%)
Nodal disease sites	
Neck	34 (30%)
Axilla	46 (40%)
Groin	31 (27%)
Others	4† (3%)
Baseline SUVmax value	
Median (range)	14.4 (2.3–80)
Treatment modality	
Pembrolizumab or prolgolimab‡	40 (35%)
Pembrolizumab+lenvatinib	20 (17%)
Nivolumab+ipilimumab	55 (48%)
Treatment setting	
Trial	35 (30%)
Non-trial	80 (70%)
Adjuvant therapy	39 (34%)
Targeted therapy	11 (10%)

*Data not available n=1.
†One epitrochlear, two in transit with groin nodes, and one unavailable.
‡n=6.
ACCCC, A C Camargo Cancer Center; AJCC v8, American Joint Committee on Cancer 8th Edition; MCC, Moffitt Cancer Center; MIA, Melanoma Institute Australia; NMRCO, N N Blokhin NMRC of Oncology; PMCC, Peter MacCallum Cancer Centre; SUVmax, maximum voxel value of standardized uptake value.

Response rates by modality and associations with each other

86 of 115 (75%) patients had a pathological response. MPR and pCR rates were 71/115 (62%) and 59/115 (51%), respectively (table 2). Response rates by different modalities are shown in figure 1A–C. 49 (43%) patients had a RECIST response. The RECIST response underestimated pathological response. For instance, while patients with a RECIST CR (17%) and PR (26%) had high rates of MPR (95% and 87%, respectively), patients with SD (38%) still had a 50% chance of achieving MPR. Furthermore, of the 22 patients with RECIST PD, five (23%) exhibited an MPR.

Table 2 Correlations of radiological and pathological responses

	Pathological response				
RECIST response	**pCR**	**npCR**	**pPR**	**pNR**	**Total**
CR	17	1	1	0	19 (17%)
PR	22	4	2	**2**	30 (26%)
SD	**16**	**6**	9	13	44 (38%)
PD	**4**	**1**	**3**	14	22 (19%)
Total	59 (51%)	12 (10%)	15 (13%)	29 (25%)	115

Bold indicates discordant response cases.
CR, complete response; npCR, near-complete pathological response; pCR, pathological complete response; PD, progressive disease; pNR, pathological non-response; pPR, pathological partial response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

84 patients (73%) had an FDG-PET MR (table 3). CMR occurred in 26 (23%) patients and 25 (96%) of these achieved MPR. PMR patients (50%) also often achieved MPR (72%, 42/58). A small proportion of patients were evaluated as SMD (10%) and all were categorized as non-MPR (100%, 12/12). Patients with PMD (17%) were mostly pNR (63%, 12/19), although four (21%) did have an MPR. Furthermore, the extent of SUVmax decrease correlated with pathological response. Patients with MPR had more significant SUVmax reduction than those with non-MPR (−76.6% vs −6.1%, p<0.0001, online supplemental figure S2). Stratified analysis showed no significant differences in the MR rates across the different treatment modalities (online supplemental table S1).

Response modalities and RFS

The landmark 24-month RFS rate for patients receiving neoadjuvant immunotherapy was 82.2% (95% CI 73.9% to 91.3%). Stratified analysis by treatment modality showed that the MPR rate and pCR rate were 67% vs 57.5% vs 55% and 56% vs 50% vs 40% for nivolumab plus ipilimumab, anti-PD-1 monotherapy, and pembrolizumab combined with lenvatinib, respectively, with no significant difference in RFS among the three groups, although the

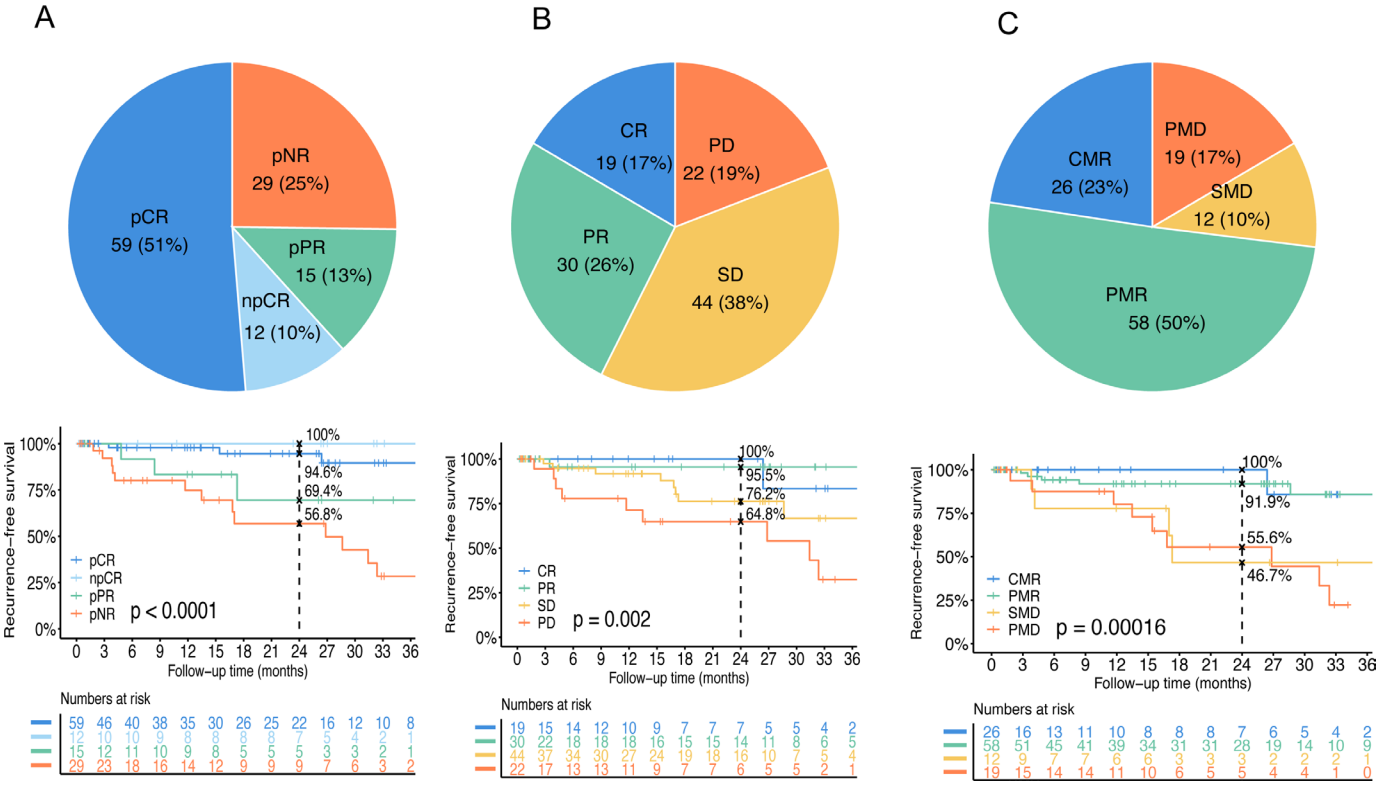

Figure 1 Response rates and recurrence-free survival (RFS) by (A) pathology, (B) CT, and (C) fludeoxyglucose-18-positron emission tomography (FDG-PET). CMR, complete metabolic response; CR, complete response; npCR, near-complete pathological response; pCR, pathological complete response; PD, progressive disease; PMD, progressive metabolic disease; PMR, partial metabolic response; pNR, pathological non-response; pPR, pathological partial response; PR, partial response; SD, stable disease; SMD, stable metabolic disease.

Table 3 Correlations of metabolic and pathological responses

	Pathological response				
FDG-PET response	**pCR**	**npCR**	**pPR**	**pNR**	**Total**
CMR	23	2	0	**1**	26 (23%)
PMR	33	9	8	**8**	58 (50%)
SMD	0	0	4	8	12 (10%)
PMD	**3**	**1**	**3**	12	19 (17%)
Total	59 (52%)	12 (10%)	15 (13%)	29 (25%)	115

Bold indicates discordant response cases.
CMR, complete metabolic response; EORTC, European Organization for Research and Treatment of Cancer; FDG-PET, fludeoxyglucose-18-positron emission tomography; npCR, near-complete pathological response; pCR, pathological complete response; PMD, progressive metabolic disease; PMR, partial metabolic response; pNR, pathological non-response; pPR, pathological partial response; SMD, stable metabolic disease.

response rate and the 2-year RFS rate were higher in the dual immunotherapy group (p=0.65, online supplemental figure S3).

Pathological response was associated with RFS; the 24-month RFS rates for patients with pCR, npCR, pPR, and pNR were 94.6% (95% CI 87.7% to 100%), 100% (95% CI 100% to 100%), 69.4% (95% CI 44.8% to 100%), and 56.8% (95% CI 38.3% to 84.2%), respectively (p<0.0001) (figure 1A). RFS for patients with MPR was notably superior to that of patients with non-MPR, with 2-year RFS rates of 95.6% vs 60.9%, respectively (p<0.0001) (figure 2A). 11 out of 17 patients with BRAF V600 mutations and pathological pNR received adjuvant targeted therapy. In patients with pNR and BRAF V600 mutations, the recurrence rates within 2 years were 9% (1/11) and 50% (3/6) for those who did and did not receive adjuvant targeted therapy, respectively.

Using RECIST criteria, CT response was also associated with RFS; the 24-month RFS rates for patients with CR, PR, SD, and PD were 100% (95% CI 100% to 100%), 95.5% (95% CI 87.1% to 100%), 76.2% (95% CI 62.0% to 93.7%), and 64.8% (95% CI 45.5% to 92.3%), respectively (p=0.002) (figure 1B). Two-year RFS rates were

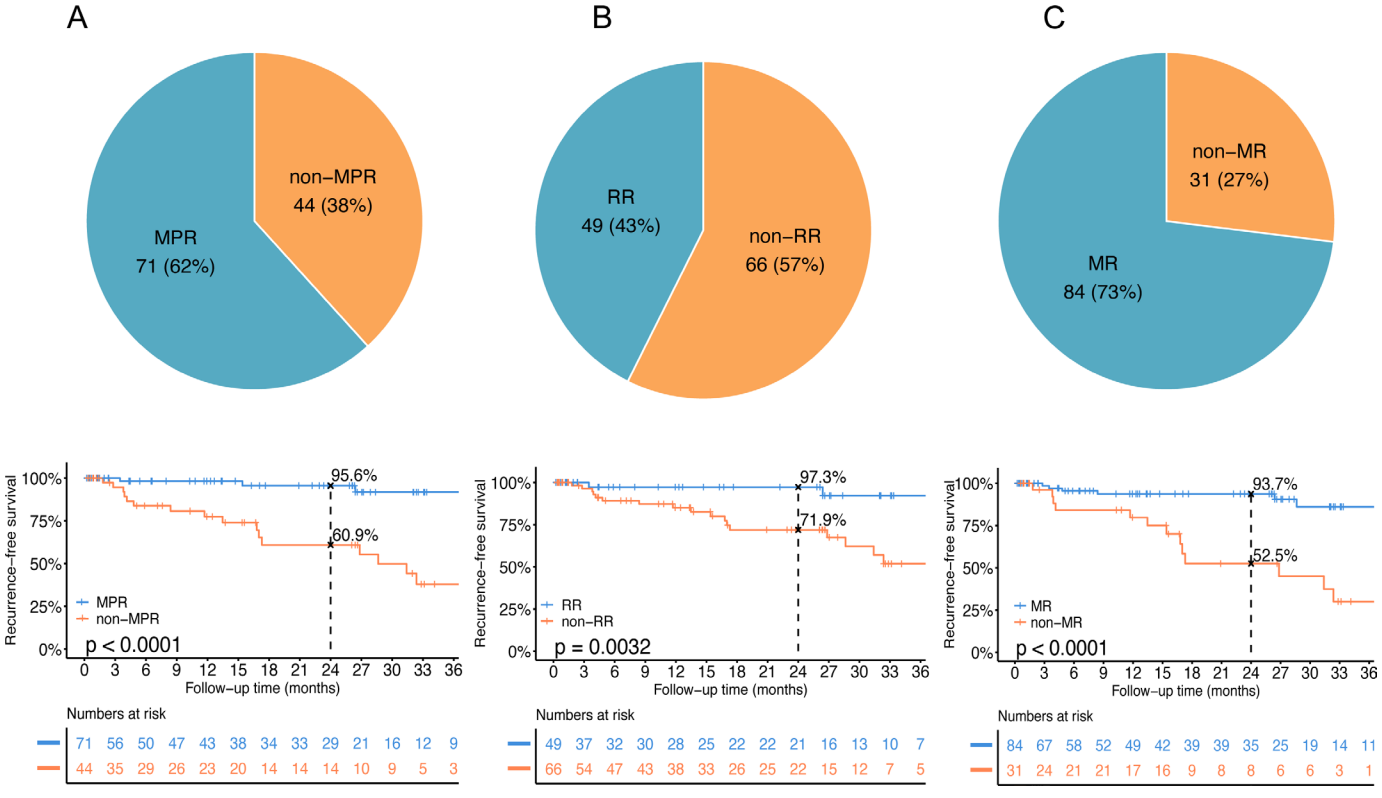

Figure 2 Categorical response rates and recurrence-free survival (RFS) by (A) pathology, (B) CT, and (C) fludeoxyglucose-18-positron emission tomography (FDG-PET). MPR, major pathological response (≤10% tumor cells); MR, metabolic response (complete metabolic response (CMR)+partial metabolic response (PMR)); RR, radiological response (complete response (CR)+partial response (PR)).

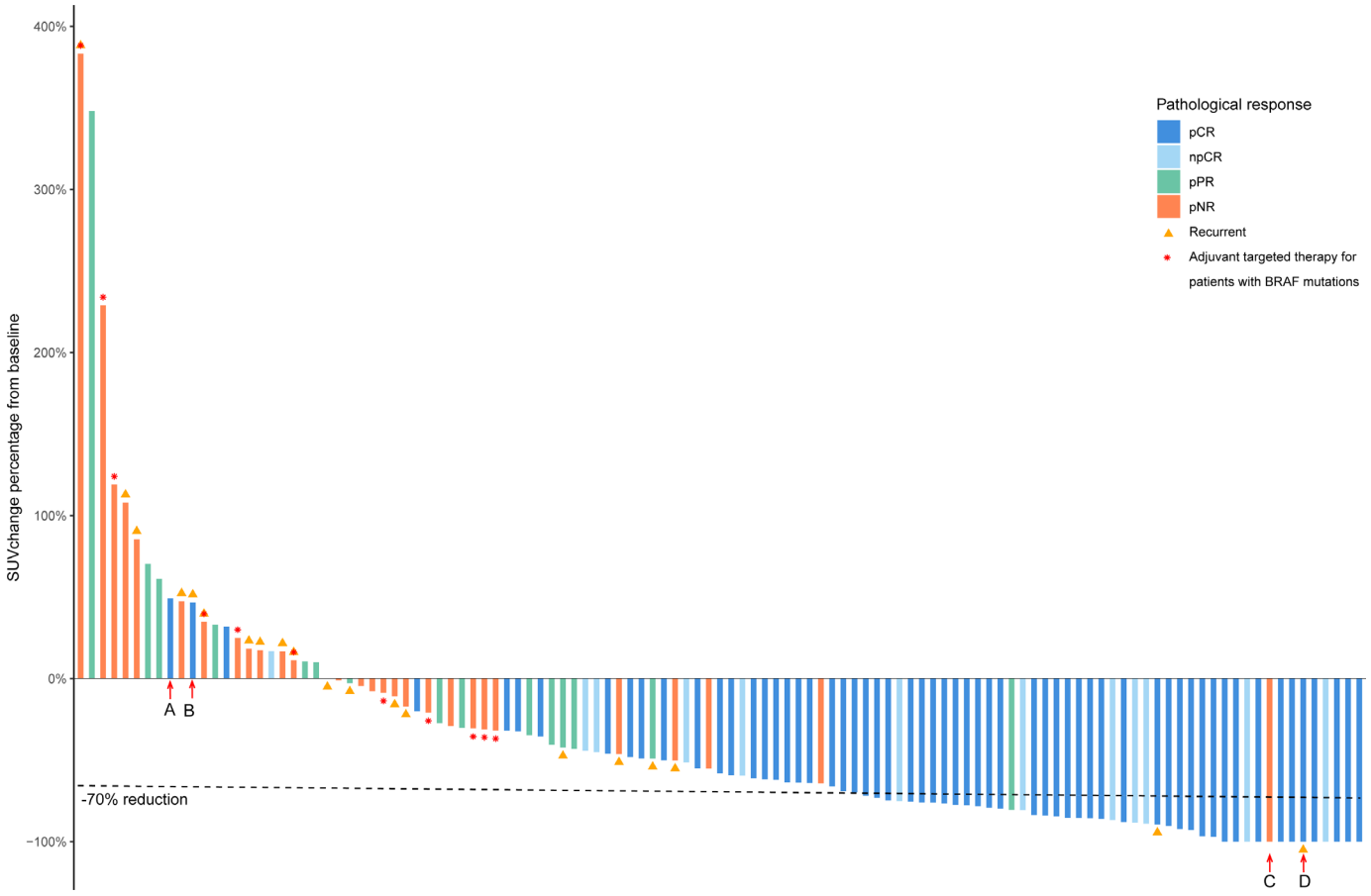

Figure 3 Waterfall plot by SUVchange associated with pathological response and recurrence. Cases A–D details are shown in figure 4. npCR, near-complete pathological response; pCR, pathological complete response; pNR, pathological non-response; pPR, pathological partial response; SUV, standardized uptake value.

97.3% vs 71.9% for patients with objective responses and those without (p=0.0032) (figure 2B).

Similar to pathology and CT, FDG-PET response was also associated with RFS; the 24-month RFS rates for patients with CMR, PMR, SMD, and PMD were 100% (95% CI 83.6% to 100%), 91.9% (95% CI 87% to 100%), 46.7% (95% CI 21% to 100%), and 55.6% (95% CI 37.8% to 91.5%), respectively (p=0.00016) (figure 1C). Patients with an FDG-PET response (CMR/PMR, 73%) demonstrated better RFS than those without (SMD/PMD) (2-year RFS rates: 93.7% vs 52.5%, p<0.0001) (figure 2C). When examining the waterfall plots of SUV, we observed that the vast majority of patients with >70% reduction had an MPR (43/45, 96%) and recurrences were rare (2/45, 4.4%) (figure 3).

Across all assessment modalities, 'good responders' (pathology=MPR, CT=CR/PR, FDG-PET=CMR/PMR) had excellent outcomes (2-year RFS between 93.7% and 97.3%); however, FDG-PET identified the highest proportion of such patients (84/115, 73%), more than pathology (71/115, 62%) or CT (49/115, 43%) (figure 2A–C). Pathological response demonstrated the most accurate predictive performance for RFS, with an overall AUC of 77.7% (95% CI 68.3% to 87.1%), compared with 72.6% (95% CI 62.0% to 83.2%) for FDG-PET response and an AUC of 72.0% (95% CI 59.9% to 84.2%) for CT response.

Combining different modalities to predict RFS

A model combining MR and pathological response did not provide additional predictive value beyond pathology or FDG-PET alone (online supplemental figure S4). Notably, 21 of 115 (18%) patients with either an MR or MPR (not both) still had uncertain RFS within this model (2-year RFS 71.3%). We also divided RECIST SD/PD patients into those with and without MR; patients with SD/PD and MR demonstrated markedly better outcomes compared with those without MR (2-year RFS 89.6% vs 51.5%, p=0.0052, online supplemental figure S5).

Discordant cases

Four patients with PMD achieved MPR, one with a clinical inflammatory presentation. Figure 4A,B show two patients with PMD who achieved pCR. Patient 6 with PMD and pCR (20% necrosis and 80% fibrosis/melanosis) recurred with brain metastasis (figure 4B). All patients with CMR had pathological response except one with pNR (figure 4C). Among patients with CMR, two relapsed (one local and distant, one local), both after a

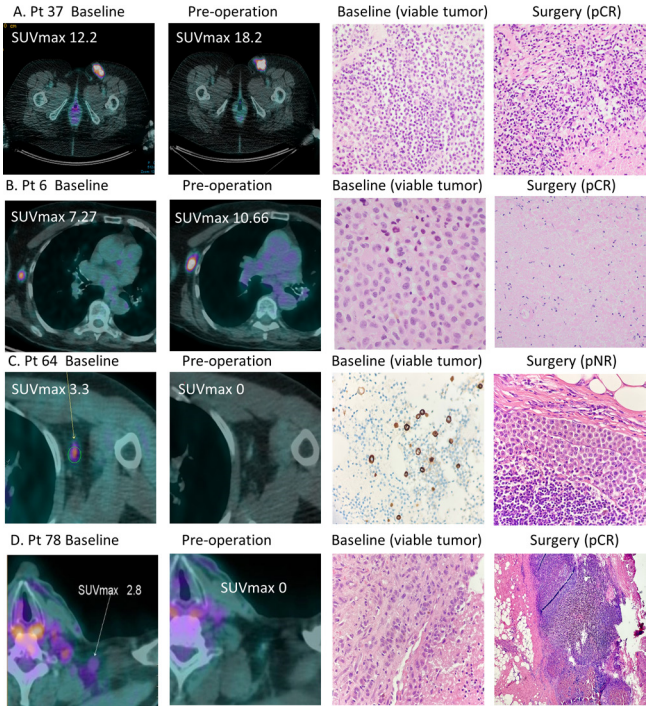

Figure 4 Representative discordant cases with images of fludeoxyglucose-18-positron emission tomography (FDG-PET) and pathology. (A) Patient (Pt) 37 treated with two cycles of pembrolizumab with progressive metabolic disease (PMD) (a new avid node while the initial node was also more avid) developed redness, warmth, and tenderness over the inguinal fossa, suggestive of an inflammatory process. This patient achieved a pathological complete response (pCR) (necrosis 40%, melanosis 10%, and 50% fibrosis) and did not have any adjuvant therapy. (B) Pt 6 treated with pembrolizumab plus lenvatinib had PMD with pCR (20% necrosis and 80% fibrosis/melanosis) and no adjuvant therapy, recurring with brain metastasis 15.4 months later. (C) Pt 64 treated with nivolumab and ipilimumab had a complete metabolic response (CMR) with pathological non-response (pNR) (subcapsular intact neoplastic cells) and received adjuvant immunotherapy afterwards. Immunohistological chemistry (IHC) images: HMB45 Ventana antibody. (D) Pt 78 treated with nivolumab and ipilimumab had both a CMR and pCR without adjuvant therapy and recurred locally 5 months later. SUVmax, maximum voxel value of standardized uptake value.

pCR (one is shown in figure 4D). These patients are also noted in figure 3.

DISCUSSION

Neoadjuvant immunotherapy has become the new standard of care for stage III melanoma. While pathological response is a surrogate for survival, whether FDG-PET associates with pathological response or survival in the neoadjuvant setting is unknown. This study represents the first study of FDG-PET in the setting of neoadjuvant immunotherapy for patients with melanoma. Our findings indicate that MR assessed by FDG-PET occurs early and often and associates with pathological response and relapse-free survival, thus making it an important tool for clinicians using neoadjuvant immunotherapy.

FDG-PET is widely known to define tumor response to treatment in many tumor types. In lymphoma, FDG-PET is routinely employed to evaluate therapeutic efficacy.[18] For advanced melanoma treatment, FDG-PET imaging has been shown to predict long-term outcomes and can direct clinical decision-making regarding duration of therapy and follow-up schedules.[8 9 19] While pathological response is currently the best surrogate for survival after neoadjuvant therapy in melanoma,[2 4 6] it is not a perfect biomarker (eg, some patients with pCR still recur, and many with pNR do not), and it requires an invasive procedure (ie, surgery) to obtain data. CT response (by RECIST) is less useful, as response rates are low, and some patients (38%) with SD can have a pathological response and do not recur. FDG-PET, therefore, is an attractive non-invasive option.

This study demonstrates that FDG-PET scans with neoadjuvant immunotherapy in melanoma have high response rates (73%), correlate with pathological response, and are associated with survival (2-year RFS 93.7% responders vs 52.5% in non-responders). Data suggest that patients who are shown to have an MR prior to surgery have a high likelihood of pathological response. Such patients may benefit from surgical de-escalation, including as an index node biopsy rather than a full lymphadenectomy,[6] or potentially no surgery altogether (as with mismatch repair-deficient colorectal cancer).[20] This approach may reduce morbidity and reduce healthcare costs. By contrast, patients with metabolic progression, who have low rates of pathological response and poor survival outcomes, may be considered for an alternative, additional 'second neoadjuvant' systemic therapy, prior to surgery, or a more extensive surgical approach, such as therapeutic lymph node dissection, may be warranted. While the precise threshold of MPR to determine the surgical approach remains undefined, MR data could play a crucial role in tailoring surgery to individual patient needs.

No significant difference in response rates or RFS was observed among the different treatment modalities. The impact of treatment on response rates needs further prospective investigation in a larger sample. We did observe a minority of patients with discordant responses based on FDG-PET and pathology. One scenario was that a few patients experienced dramatic SUVmax increase (PMD) yet had MPR at surgery. Here, one patient exhibited a marked clinically inflammatory presentation, similar to the pseudoprogression phenomenon seen in metastatic patients, whereby immune cell infiltration and tumor inflammation occur early in the course of treatment.[21 22] By contrast, another scenario was observed where one patient with excellent MR (CMR) had no response on surgical pathology (pNR), received adjuvant radiotherapy and further immunotherapy, and has not recurred after 7.6 months. Finally, a small proportion of patients (two) with both a CMR and pCR recurred after surgery. Such cases have been occasionally observed

through neoadjuvant trials in melanoma; for example, in the OpACIN and OpACIN-neo trials, two patients with MPR developed distant metastases.[4] This small group of patients, who have pCR (and likely CMR) and later recur, warrants further investigation.

The strengths of this study are that it is the first study of FDG-PET in neoadjuvant immunotherapy, conducted across several centers of the INMC, including clinical trial patients, using validated FDG-PET criteria (EORTC) and with pathological and radiological response rates similar to those reported in previous clinical trials. While a validation cohort would be ideal, this study includes all patients from INMC centers who had neoadjuvant immunotherapy with FDG-PET response data to date. Regardless, confirmation of these findings is required. More detailed stratification of pathological response and MR to better correlate with survival outcomes is needed. FDG-PET, in combination with other biomarkers such as novel PET tracers (eg, CD8[23 24]), liquid biopsy (ctDNA[25]), and other biomarkers within the tumor microenvironment, could provide a more effective approach for predicting outcomes, particularly if they can be determined early and via non-invasive means. Studies with larger cohorts should be conducted to confirm these findings.

CONCLUSION

Neoadjuvant immunotherapy has high response rates on FDG-PET in melanoma, and FDG-PET demonstrates significant clinical utility in predicting pathological response and RFS. FDG-PET may become an important tool for predicting immunotherapy response before surgery, potentially identifying patients for surgical de-escalation, or conversely, identifying those who would not have a pathological response and may benefit from alternative systemic treatment escalation prior to surgery.

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Contributors AMM, LZ, and MBeS conceptualized and designed the study. GVL, AMM, ZE, SS, IS, MSC, GA-Y, MG, AJS, TP, KFS, RK, JD, RBdP, DEG, RPMS, SC, RVR, IPdS, ACJvA, and RAS collected the data. LZ, AMM, EH, SNL, and MBeS carried out the analysis and interpretation of results. LZ drafted the paper. AMM is acting as guarantor. All authors reviewed the results and approved the final version of the paper.

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Competing interests AMM has served on advisory boards for BMS, MSD, Novartis, Roche, Pierre Fabre and QBiotics. RAS has received fees for professional services from SkylineDx BV, IO Biotech ApS, MetaOptima Technology Inc, F Hoffmann-La Roche Ltd, Evaxion, Provectus Biopharmaceuticals Australia, QBiotics, Novartis, Merck Sharp & Dohme, NeraCare, Amgen Inc, Bristol Myers Squibb, Myriad Genetics, and GlaxoSmithKline. DEG has served on advisory boards for BMS, MSD and Skyline Dx. ZE has been on advisory boards for Regeneron, Pfizer, Replimune, Natera, Sun Pharma, and Incyte, with institutional research funding from Boehringer Ingelheim and Pfizer. RPMS has received honoraria for advisory board participation from MSD and Clinical Laboratories Pty Ltd. RVR has received honoraria from MSD for advisory board participation and educational activities. ACJvA: advisory board and consultancy honoraria: 4SC AG, Amgen, Bristol Myers Squibb, Merck Serono-Pfizer, MSD-Merck, NeraCare, Novartis, Pierre Fabre, Sanofi, Sirius Medical, SkylineDx; research grants: Amgen, Merck Serono-Pfizer, SkylineDx. SS reported paid advisory board roles with Bristol Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Novartis, and Merck Serono (funds go to a research fund at the Peter MacCallum Cancer Centre), and institutional research grants for an investigator-initiated trial from Novartis, Genentech, Amgen, AstraZeneca, Merck Serono, Merck Sharp & Dohme, and Pfizer. IS reported paid advisory board roles for Novartis, Roche, Pierre Fabre, Biocad, R-Pharm, and Swixx Biopharma, and institutional research grants for an investigator-initiated trial from Novartis and Roche. SNL has received fees for professional services from SkylineDx BV and an honorarium for editorial duties from the British Association of Dermatologists. IPdS: travel support: BMS, MSD; speaker fees: Roche, BMS, MSD, Novartis, Pierre Fabre; advisory board: MSD, Regeneron, STX-001. GVL is consultant advisor for Agenus, Amgen, Array Biopharma, AstraZeneca, Bayer, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, GI Innovation, Hexal AG (Sandoz Company), Highlight Therapeutics SL, Immunocore, Innovent Biologics USA, IOBiotech, Iovance Biotherapeutics, MSD, Novartis, PHMR Ltd, Pierre Fabre, Regeneron, Scancell, and SkylineDx BV. CB has advisory roles for BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, and Third Rock Ventures; received research funding from BMS, Novartis, NanoString, 4SC; stock ownership: co-founder of Flindr Therapeutics to develop TNF sensitizers to clinic, co-founder of Signature Oncology to develop IFN-sign algorithm to clinic, and patents (including submitted): WO 2021/177822 A1, N2027907, P091040NL2, all unrelated to this work here.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Sydney Local Health District Human Research Ethics Committee (Protocol No X15-0454 and HREC/11/RPAH/444). This study was conducted in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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