Title: Clinical and palliative care outcomes for patients of poor performance status treated with anti-programmed death1 monoclonal antibodies for advanced melanoma

Short running Title: AntiPD1 Outcomes in Poor Performance Patients

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajco.12702](#).

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Abstract (250/250 words) and keywords

Background:

Anti-programmed death-1 antibodies (antiPD1) have response rates of 40% in metastatic melanoma. Patients with poor performance status (PS) were excluded from clinical trials, yet use of antiPD1 is widespread in clinical practice. Literature regarding clinical and palliative care outcomes in patients with poor PS treated with antiPD1 is lacking.

Methods:

Retrospective review of outcomes for all patients with advanced melanoma treated with antiPD1 between 2012 - June 2015 at Peter MacCallum Cancer Centre, a tertiary specialist cancer centre in Australia.

Results:

Between 2012 and 2015, 91 patients received antiPD1: median age 63, 65% males, 77% elevated LDH >1xULN (37/48 patients). 58 patients had baseline ECOG PS of 0-1 (64%), 24 patients ECOG PS 2-3 (26%) and ECOG PS was not recorded in 9 patients (10%).

Median overall survival (OS) for the ECOG PS 0-1 group was 19.5 months and 1.8 months for ECOG PS 2-3 (HR 5.5, 95% CI 9.1-50.3, p=0.0001). Tumor response was 23/58 (39%) in ECOG PS 0-1, 2/16 (12%) in ECOG PS 2, and 0/8 in ECOG PS 3. Toxicity did not differ between different groups. ECOG PS 2-3 patients were more likely to be treated and hospitalised within the last month of life compared to ECOG PS 0-1 patients, RR 1.75 (1.04-2.56, p= 0.019) and RR 1.73 (1.10-2.16, p = 0.009) respectively. ECOG PS 2-3 patients were more likely to die in an acute hospital RR 2.68 (1.17-6.51, p= 0.016).

Conclusions:

Patients with poor baseline PS have a significantly lower overall survival and reduced response to antiPD1. Further quality of life and palliative care research is needed.

Keywords: Melanoma; Palliative care; Immunotherapy; anti-programmed death1

Clinical and palliative care outcomes for patients of poor performance status treated with anti-programmed death1 monoclonal antibodies for advanced melanoma

Word count: 2462

Introduction

Immune checkpoint inhibitors such as anti-programmed death 1 antibodies (antiPD1) have rapidly entered clinical practice for many tumor types including melanoma(1-3), non-small cell lung cancer(4, 5), renal cancer(6) and Hodgkins lymphoma(7). Biomarkers which predict response to these treatments are under intensive investigation, although few have translated into clinical practice at the same pace as the treatments themselves. Traditional clinical biomarkers such as performance status (PS) have yet to be formally assessed, as patients with poor PS were excluded from the landmark clinical trials. Unlike cytotoxic chemotherapy, anti PD-1 antibodies are well tolerated and offer the prospect of durable benefit. As such, clinicians may be tempted to use these agents in patients with poor PS, with the hope they will salvage aggressive disease.

Traditional cytotoxic chemotherapy in patients with poor PS are associated with shorter survival and worse quality of life in some cancer types(8, 9), hence the American Society of Clinical Oncology have recommended against the use of chemotherapy in patients with European Cooperative Oncology Group (performance status (ECOG PS) score of 3 or more(10). However, antiPD1 antibodies have a distinct mechanism of action and toxicity profile compared to chemotherapy. Therefore it is important to review the efficacy and toxicity rates in patients with

poor PS treated with antiPD1 antibodies to determine if these agents are a therapeutic benefit in this subset of patients. Furthermore, there are some palliative care outcomes such as anti-PD1 treatment patterns in the last month of life and the place of death which may inform the palliative care needs for those with advanced malignancies. We sought to investigate the real-world outcomes of antiPD1 treatment in melanoma patients of both good and poor performance status.

Method:

All patients with advanced melanoma (unresectable stage IIIC or IV) who received at least one dose of anti-PD1 antibody at Peter MacCallum Cancer Centre, a specialist cancer centre in Australia were included in the study. Retrospective review of medical records was undertaken. Patient demographics, stage of melanoma, brain or leptomeningeal involvement, baseline lactate dehydrogenase (LDH), response rates, treatment related toxicities, and survival data were recorded. Tumor responses were performed on a range of modalities including computerised tomography (CT), positron emission tomography (PET/CT) and magnetic resonance imaging (MRI) and radiologists' assessment of response were recorded. Tumor response includes any radiological tumor reduction, progressive disease includes all enlarging lesions or new lesions and stable disease denotes neither tumor response nor progression. Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Immune related adverse events were defined as treatment related diarrhoea, colitis, endocrinopathy, hepatitis, pneumonitis, rash and other toxicities deemed by the treating oncologist.

ECOG PS scale was used to grade each patient's performance status prior to treatment(11).ECOG PS For patients in the cohort who died, additional palliative care data were collected, including treatment or hospitalisation within one month of death, admission to an intensive care unit, and place of death. Chi-square tests were used to compare differences in the proportion of patients receiving each measure according to ECOG PS status (ECOG PS 0-1 vs ECOG PS 2-3). Kaplan-Meier estimates of OS were calculated separately for patients grouped by

performance status and compared using a log-rank test, where P-values ≤ 0.05 were considered to be statistically significant. The median follow-up time was estimated from the inverse Kaplan-Meier method. Statistical analyses were performed using Graphpad Prism Version 6.0.5. This study was approved by the institutional research ethics committee.

Results:

Between 2012 and 2015, 91 patients were treated with antiPD1 antibodies for advanced melanoma. Fifty-eight (67%) patients had baseline ECOG PS of 0-1, 16 (13%) patients had ECOG PS 2 and 8 (9%) had ECOG PS 3. Nine (10%) patients without ECOG PS recorded were excluded from analysis. The baseline characteristics of patients are described in *Table 1*. The median follow-up from the start of antiPD1 treatment for all patients was 16.8 months. Tumor responses were assessed using positron emission tomography in 34 patients (41%), computerised tomography in 28 patients (34%), magnetic resonance imaging in 3 patients (4%), and clinical progression (not imaged) in 17 patients (21%) (*Table 2*).

Median overall survival (OS) for ECOG PS 0-1 group was 19.5 months versus 1.8 months for ECOG PS 2-3 group (HR 5.5, 95% CI 9.1 – 50.3, $p=0.0001$) (*Figure 1 top*). When the poor performance status group was subdivided into ECOG PS 2 versus ECOG PS 3, the median overall survival for ECOG PS 2 and ECOG PS 3 was 2.3 months v 0.7 months respectively (HR 2.4, 95% CI 1.1 – 10.6, $p=0.005$) (*Figure 1 bottom*).

Toxicity

The incidence of severe, life threatening or fatal (CTCAE version 4 grade 3-5) treatment related adverse events or immune-related adverse events did not differ significantly between the two groups (RR 0.30, $p=0.58$ and RR 2.04, $p=0.15$ respectively) (*Table 3*).

There was one patient in the ECOG PS 3 group where a treatment related death could not be excluded: a 62 year old woman with metastatic melanoma to lungs, bone, liver and lymph nodes. She presented with breathlessness and hypoxia after two doses of antiPD1 and was found to have an increase in pulmonary infiltrates, which did not respond to high dose corticosteroids or antibiotics. Although she had bilateral pulmonary metastases, an immune-related pneumonitis

could not be excluded. Of note, there were no other grade 2 to 4 immune-related adverse events in the poor performance group.

Patterns of health care in the last month of life

Fifty-two patients (57%) of the total cohort died. Of these, 26 had a baseline ECOG PS of 0-1, 21 were ECOG PS 2-3, and 5 had no baseline ECOG PS recorded and were excluded from analysis. 81% of the ECOG PS 2-3 group received antiPD1 antibody in the last month of life, compared with 46% of the ECOG PS 0-1 group (RR 1.75, $p=0.019$) (*Table 4*). Similarly, 90% of the patients of ECOG PS 2-3 were admitted to hospital in the last month of life, while only 52% of the ECOG PS 0-1 patients had hospital admissions (RR 1.73, $p=0.009$). All hospitalisation within the last month of life was for management of disease progression. The only apparent admission for treatment related toxicity was the aforementioned case of the patient with pulmonary infiltrates post anti-PD1. Patients of poor baseline performance status ECOG PS 2-3 were more likely to die in an acute setting compared to those with good baseline performance status (62% vs 23% respectively, RR 2.68, $p=0.016$). There was no significant difference in the proportion of patients who had an intensive care unit (ICU) stay in their last month of life between the ECOG PS 0-1 and ECOG PS 2-3 groups, with 2 patients in each group admitted to ICU in their last month of life.

Discussion

We conducted a retrospective study into the real world outcomes and end of life health care utilisation patterns of melanoma patients treated with antiPD1 antibodies. The ECOG PS 0-1 cohort included both patients naïve to systemic treatment and those heavily pre-treated but exhibited outcomes broadly similar to that of phase III trials with response rates of approximately 40%(2, 3, 12). However our outcomes for patients with baseline performance status of ECOG PS 2-3 were poor compared to those of ECOG PS 0-1. In particular, ECOG PS 3 patients did not exhibit any radiological tumor response and had a median overall survival of only 0.7 months. The historic survival data for melanoma patients of poor performance status is lacking, as these patients are routinely excluded from clinical trials. In general, untreated advanced melanoma is

associated with a prognosis of 6 to 10 months(13-15). Pooled survival data from EORTC melanoma trials prior to the era of anti-PD1 antibodies reported that patients with ECOG PS ≥ 1 with liver or gastrointestinal metastases had a median survival of 2.9 months(16). Our dataset suggests that ECOG PS performance status remains a useful predictor of clinical outcome in the era of anti-PD1 treatment, in keeping with previous studies with chemotherapy. The paucity of responses in ECOG PS 2-3 patients might be reflective of the aggressiveness of their disease and the majority of this cohort possessed both M1c staging and elevated LDH which conferred a worse outcome. Our findings show that patients of ECOG PS 3 had a very short survival after treatment with antiPD1 antibodies and this is consistent with ASCO guidelines that recommend against the use of chemotherapy for patients with ECOG PS 3.

Overall this study provides some real-world data to enable clinicians to have a more realistic discussion with their patients about the use of these agents in patients with poor performance status. This in turn may facilitate advanced care planning and discussions about end of life care, given the context of short survival and low response rate. In our cohort the rate of severe or life threatening toxicities did not differ greatly between ECOG PS 0-1 and ECOG PS 2-3. It is important to note that the toxicity rate is low in the poor performance group, although this could potentially be explained by the short duration on treatment and short survival. There is a perception that immunotherapy agents have lower toxicity rates than chemotherapy, and hence less likely to do harm even if the response rate is low. However, commencing immunotherapy may restrict the use of supportive medications such as corticosteroids because of concerns of reducing the efficacy of immunotherapy. This may pose a dilemma in management of cancer-related symptoms such as anorexia, nausea or lethargy, which are likely to benefit from corticosteroids. Importantly, corticosteroids can also rapidly palliate symptoms from brain metastases, which can present in up to 75% of advanced melanoma patients. Withholding steroids potentially impairs symptomatic management in these patients. Corticosteroid use patterns in the last month of life was not feasible in this study as patient received their end of life care in different locations (home, hospice or inpatient), however this would be an important parameter to consider in future studies.

Furthermore, the atypical immune-related responses seen with immunotherapy agents compound the complexity of providing palliative care to patients with advanced cancers(17, 18). Clinicians may feel compelled to continue immunotherapy and intensive supportive treatment despite such radiological progression even though only a minority of patients will have a delayed immune response. This poses challenges in decision making as to the appropriate level of aggressive supportive medical management that should be offered given a minority of patients may indeed derive a durable response. However our data suggests that patients with ECOG PS 3 are unlikely to derive clinical benefit from antiPD1 antibodies, and therefore may provide some framework for establishing the ceiling of care prior to embarking on such treatments.

Given the short survival of patients with ECOG PS 2-3 we then sought to examine end of life care outcomes. Patients with ECOG PS 2-3 experienced a higher rate of hospitalisations in the last month preceding death and were more likely to die in an acute hospital setting. Part of the palliative care and hospice movement's concern around the use of chemotherapies at the end of life is that they may interfere with achieving a 'good death'(19, 20) Consensus themes about good death raised three important indicators namely details of the death scene and preparation for death, pain-free status, and emotional wellbeing. Given the poor survival with immunotherapy in ECOG PS 2-3 patients, clinicians may be encouraged to discuss end of life care preferences in these patients. However, this remains as always, a sensitive exploration of patient and family wishes, understanding and goals of care.

Our study is limited by its single site retrospective design, heterogeneous imaging modality for tumor assessment and small patient numbers particularly in the ECOG PS 2 and 3 groups. However this study, to our knowledge, is the first to report on outcome, toxicity and health resource utilisation in patients with poor performance status treated with anti-PD1 antibodies. This study highlights the need for ongoing research in this patient group as these exciting agents enter into routine oncology practice.

Conclusion

Patients with poor baseline performance status have a significantly lower overall survival and reduced chance of response to antiPD1 antibodies compared to patients with good performance status. The findings from this study provide real-world data to enable clinicians to have realistic discussions with their patients about the use of these agents in patients with poor performance status. This in turn may facilitate advanced care planning and discussions about end of life care, given the context of short survival and low response rate. Further studies of the quality of life outcomes and palliative care needs of patients with poor performance status undergoing immunotherapy compared to those who opt for symptom management alone are required.

Disclosures:

Annie Wong: nil

Molly Williams: nil

Donna Milne: Advisory role for Merck, Novartis. Honoraria from Merck, Novartis and Bristol Myers Squibb

Kortnye Morris: nil

Peter Lau: Honoraria from Bristol Myers Squibb

Odette Spruyt: nil

Sonia Fullerton: nil

Grant McArthur: Research funding from Pfizer, Celgene, Ventana. Advisory role for Provectus

Funding: This work did not have specific funding.

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Table 1. Baseline Demographic and Disease Characteristics

Characteristics	ECOG PS		ECOG PS		ECOG PS 3	
	0-1 (N=58)	%	2 (N=16)	%	(N=8)	%
Median age (range) – yr	60 (30-88)		73.5 (36-88)		54.5 (36-79)	
Male sex - no. (%)	36	(62)	13	(81)	4	(50)
Elevated LDH>1xULN	22/33	(67)	10/10	(100)	5/5	(100)
LDH Not recorded	25		6		3	
Metastasis stage - no. (%)						
IIIC	2	(3)	0	(0)	0	(0)
M1a	4	(7)	1	(6)	0	(0)
M1b	14	(24)	2	(13)	1	(13)
M1c	38	(66)	13	(81)	7	(88)
Central Nervous System						
Metastases – no. (%)						
Brain	9	(16)	6	(38)	0	(0)
Leptomeningeal	2	(3)	1	(6)	0	(0)
Subtype						
Cutaneous	37	(64)	11	(68)	6	(75)
Mucosal	7	(12)	2	(13)	0	(0)
Acral	1	(2)	0	(0)	1	(13)
Ocular	5	(9)	0	(0)	0	(0)
Unknown primary	8	(14)	3	(19)	1	(13)

Line of previous systemic therapy					
0	7	(12)	1	(6)	1 (13)
1	26	(45)	8	(50)	2 (25)
2	12	(21)	3	(31)	5 (63)
3 or more	13	(22)	4	(25)	0 (0)

Table 2. Tumor Responses After antiPD1 Treatment

	ECOG PS 0-1 (%) N=58	ECOG PS 2 (%) N=16	ECOG PS 3 (%) N=8
Tumor Response	23 (40)	2 (12)	0 (0)
Stable disease	7 (12)	0 (0)	1 (12)
Progressive disease	28 (48)	14 (88)	7 (88)
Total	58	16	8

Table 3. Maximum Grade of Treatment Related Adverse Event and Immune-related Adverse Event

CTCAE v4 Adverse Event	ECOG PS 0-1 (%) (N=58)	ECOG PS 2 (%) (N=16)	ECOG PS 3 (%) (N=8)	CTCAE Immune-related Adverse Event	ECOG PS 0-1 (%) (N=58)	ECOG PS 2 (%) (N=16)	ECOG PS 3 (%) (N=8)
Grade 0	30 (52)	10 (63)	8 (100)	Grade 0	37 (61)	15 (94)	7 (88)
Grade 1	19 (33)	3 (19)	0 (0)	Grade 1	12 (20)	1 (6)	0 (0)

Grade 2	6 (10)	1 (6)	0 (0)	Grade 2	2 (3)	0 (0)	0 (0)
Grade 3	3 (5)	2 (13)	0 (0)	Grade 3	9 (15)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)	Grade 5	0 (0)	0 (0)	1 (13)
Total	58	16	8	Total	58	16	8

Table 4. Treatment and Hospitalization Within One Month of Life; Place of Death.

	Patients, no. (%)		RR (95% CI)	P value ^a
	ECOG PS 0-1	ECOG PS 2-3		
	N=26	N =21		
Treatment in the last month of life				
Yes	12 (46)	17 (81)	1.75 (1.04-2.56)	0.019
No	14 (54)	4 (19)		
Hospital admission in the last month of life				
Yes	13 (52)	18 (90)	1.73 (1.10-2.16)	0.009
No	12 (48)	2 (10)		
Place of death				
Acute hospital	6 (23)	13 (62)	2.68 (1.17-6.51)	0.016
Not acute hospital	20 (77)	8 (38)		

a: Determined using the Chi-square test for the difference in proportions between ECOG PS 0-1 and ECOG PS 2-3 patients.

Figure 1. Overall Survival after antiPD1 for patients with metastatic melanoma

Overall survival of patients with advanced melanoma with ECOG PS 0-1 compared to ECOG PS 2-3 (Fig 1.top); overall survival of patients with advanced melanoma divided into subgroups of ECOG PS 2 compared to ECOG PS 3 (Fig 1.bottom).

Figure 1.

Overall survival of patients with advanced melanoma with ECOG 0-1 compared to ECOG 2-3 (Fig 1.top); overall survival of patients with advanced melanoma divided into subgroups of ECOG 2 compared to ECOG 3 (Fig 1.bottom).

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Title:

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Date:

2017-12-01

Citation:

Wong, A., Williams, M., Milne, D., Morris, K., Lau, P., Spruyt, O., Fullerton, S. & McArthur, G. (2017). Clinical and palliative care outcomes for patients of poor performance status treated with antiprogrammed death-1 monoclonal antibodies for advanced melanoma. ASIA-PACIFIC JOURNAL OF CLINICAL ONCOLOGY, 13 (6), pp.385-390. <https://doi.org/10.1111/ajco.12702>.

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