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Original Research

Adjuvant nivolumab versus ipilimumab (CheckMate 238 trial): Reassessment of 4-year efficacy outcomes in patients with stage III melanoma per AJCC-8 staging criteria

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Stage 3

Abstract ***Purpose:*** Nivolumab was approved as adjuvant therapy for melanoma based on data from CheckMate 238, which enrolled patients per American Joint Committee on Cancer version 7 (AJCC-7) criteria. Here, we analyse long-term outcomes per AJCC-8 staging criteria compared with AJCC-7 results to inform clinical decisions for patients diagnosed per AJCC-8.
Patients and methods: In a double-blind, phase 3 trial (NCT02388906), patients aged ≥15 years with resected, histologically confirmed AJCC-7 stage IIIB, IIIC, or IV melanoma were randomised to receive nivolumab 3 mg/kg every 2 weeks or ipilimumab 10 mg/kg every 3 weeks for 4 doses and then every 12 weeks, both intravenously ≤1 year. Recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) were assessed in patients with stage III disease, per AJCC-7 and AJCC-8.
Results: Per AJCC-7 staging, 42.4% and 57.3% of patients were in substage IIIB and IIIC, respectively; per AJCC-8, 1.1%, 30.4%, 62.8%, and 5.0% were in IIIA, IIIB, IIIC, and IIID. After 4 years' minimum follow-up, the AJCC-7 superior efficacy of nivolumab over ipilimumab in patients with resected stage III melanoma was preserved per AJCC-8 analysis. No statistically significant difference in RFS between stage III substage hazard ratios was observed per AJCC-7 or -8 staging criteria (interaction test: AJCC-7, $P = 0.8115$; AJCC-8, $P = 0.1051$; $P = 0.8392$ ((AJCC-7) and $P = 0.8678$ (AJCC-8) for DMFS).
Conclusions: CheckMate 238 4-year RFS and DMFS outcomes are consistent per AJCC-7 and AJCC-8 staging criteria. Outcome benefits can therefore be translated for patients diagnosed per AJCC-8.
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1. Introduction

The checkpoint inhibitors pembrolizumab and nivolumab and the BRAF/MEK–targeted-therapy combination dabrafenib plus trametinib have been approved in many countries as adjuvant therapy for high-risk resected melanoma. Pivotal trials forming the basis for their use in this setting were CheckMate 238 [1], KEYNOTE-054 [2], and COMBI-AD [3] (in patients with *BRAF*-mutated tumours). Although ipilimumab was the only checkpoint inhibitor to show a survival benefit over placebo (EORTC 18071) [4], it has been replaced with newer therapies with improved safety profiles [5]. CheckMate 238 enrolled patients with completely resected American Joint Committee on Cancer version 7 (AJCC-7) stage IIIB–C or stage IV disease, while KEYNOTE-054 and COMBI-AD included patients with AJCC-7 stage IIIA–C disease, with the restriction that eligible patients with stage IIIA disease had sentinel node burden of at least one tumour >1 mm in diameter.

The AJCC staging criteria were revised (AJCC 8th edition [AJCC-8]) with the objective of improving prognostication and refining clinical trial patient stratification after the recruitment was completed for CheckMate 238, KEYNOTE-054, and COMBI-AD. Changes relevant to the study populations enrolled in these pivotal adjuvant trials included an increase in the number of prognostic stage III groupings (from three to four; i.e., to stages IIIA–D) based on updates in nodal burden and tumour thickness categories [6]. The improved prognostic accuracy of AJCC-8 for recurrence-free survival (RFS) in patients with stage III

melanoma was confirmed by investigators in an independent cohort of 156 patients [7].

Given the challenge of extrapolating efficacy outcomes for patients with AJCC-8 stage III subgroupings from these adjuvant trials enrolled under AJCC-7, updated analyses based on AJCC-8 staging have been performed. RFS results by AJCC-8 staging were reported for dabrafenib plus trametinib treatment after a minimum follow-up of 40 and 59 months in COMBI-AD [8]. Consistent with data analysed per the AJCC-7 staging criteria, patients staged per AJCC-8 criteria demonstrated similar RFS benefit versus placebo, with a marginal benefit in patients with stage IIIA disease. Similarly, with the AJCC-8 *post hoc* analysis of KEYNOTE-054 performed after a median follow-up of 15 months, pembrolizumab treatment demonstrated similar RFS improvement versus placebo, which was sustained up to 36 months [9,10]. AJCC-8 stage III substaging was strongly associated with RFS, with stages IIIB, IIIC, and IIID showing increasingly worse RFS outcomes versus stage IIIA. In addition, there was no significant difference between the pembrolizumab versus placebo RFS hazard ratios (HRs) across the stage III substages, indicating that the AJCC-8 classification was not predictive of a substage responding better to pembrolizumab (test for interaction: $P = 0.68$) [9]. Overall, the AJCC-8 staging analyses of these two clinical trials indicated that study results are largely consistent under the updated staging criteria; however, the RFS estimates for patients classified under each substage may differ.

The updated 4-year results of the CheckMate 238 study reinforced the long-term benefit of nivolumab over the active comparator ipilimumab in both RFS and distant metastasis-free survival (DMFS) [11]. Unlike the KEYNOTE-054 or COMBI-AD trials, CheckMate 238 did not enrol patients with stage IIIA disease. However, the staging exercise is important within the oncology community to understand if efficacy outcomes observed per AJCC-7 stage III subgroups hold when data are reanalysed per AJCC-8 stage IIIB, C, and D subgroups. Efficacy outcomes redrawn per AJCC-8 will also help support clinician discussions with patients who are currently staged per AJCC-8. Here, we analysed long-term RFS and DMFS outcomes per AJCC-8 staging criteria and compared them with AJCC-7 results.

2. Methods

2.1. Study design and procedures

The study design and full methodology of the double-blind, phase 3, randomised active-controlled CheckMate 238 (NCT02388906) trial have been reported previously [1,11]. Patients were ≥15 years of age with histologically confirmed stage IIIB, IIIC, or IV melanoma (based on AJCC-7). A complete resection of disease with no evidence of residual disease was required within 12 weeks before randomisation, as was an Eastern Cooperative Oncology Group performance status of 0–1. Randomisation (1:1) to nivolumab or ipilimumab was stratified by programmed death-ligand 1 status (positive [based on a 5% cut-off in tumour cells] versus negative or indeterminate) and AJCC-7 disease stage (stage IIIB/IIIC versus stage IV metastasis (M)1a/M1b versus stage IV M1c). Nivolumab 3 mg/kg was administered intravenously every 2 weeks and ipilimumab 10 mg/kg was administered intravenously every 3 weeks for 4 doses and then every 12 weeks; each treatment was administered with corresponding placebo for up to 1 year or until disease recurrence, unacceptable toxicity, or withdrawal of consent. Patients who discontinued therapy were followed until death or study conclusion.

The assessment of disease recurrence (by computed tomography or magnetic resonance imaging) was performed every 12 weeks for the first 2 years and every 6 months for the next 3 years [1,11]. The primary end-point was RFS by investigator assessment, defined as time from randomisation until the date of the first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause. In patients alive without disease recurrence, RFS was censored on the date of the last evaluable disease assessment. A key exploratory end-point was DMFS in patients with stage IIIB–C disease at study entry. DMFS was assessed in all patients and was defined as the time between the date of randomisation and the date of the first distant metastasis (including in those patients with an initial locoregional recurrence) or death from any cause. In addition, the incidence and location of distant metastases as a first recurrence were evaluated (i.e. distant recurrences occurring after the first distant recurrence were not evaluated for incidence and location).

In this analysis, RFS and DMFS were assessed in patients with stage III disease, per AJCC-7 and AJCC-8. Although a key secondary variable in the study [1], overall survival was not included in the current analysis because these data were immature at 4 years [11]. At data cut-off, only 211 of the 302 mortality events expected had occurred, yielding 73% statistical power opposed to the planned 88% power required for significance. In addition, patients with stage IV resected disease were excluded due to the resulting small sample sizes that would be created when remapped to the new AJCC-8 metastatic subcategories.

2.2. Statistical methods

RFS and DMFS were analysed using the Kaplan–Meier method, with 95% confidence intervals calculated using the Brookmeyer and Crowley method. The prognostic

importance of AJCC-7 and AJCC-8 was assessed using the log-rank test and Cox proportional hazards model. The predictive importance of AJCC-7 and AJCC-8 on treatment differences was assessed using a test of interaction in a forest plot.

3. Results

3.1. Patients and distribution

Of the 906 patients randomised in CheckMate 238 to treatment with nivolumab or ipilimumab (453 each), 736 patients had stage III disease [11]. Based on AJCC-7 staging, there were 312 (42.4%) patients in substage IIIB and 422 (57.3%) in substage IIIC; according to AJCC-8, there were 8 (1.1%) in IIIA, 224 (30.4%) in IIIB, 462 (62.8%) in IIIC and 37 (5.0%) in IIID (Table 1). Of AJCC-7 stage IIIB and IIIC patients, 58.7% and 81.8%, respectively, remained in Stage IIIB or Stage IIIC per AJCC-8 staging (Supplementary Fig. S1). Due to the small patient numbers in the stage IIIA subgroup (two per AJCC-7 and eight per AJCC-8), all investigations are restricted to stages IIIB–D.

Baseline demographics and characteristics by AJCC-8 and AJCC-7 stage III substage are provided in Table 2 and Supplementary Table S1, respectively. Baseline characteristics were generally consistent between the treatment arms in subgroups IIIB and IIIC except for ulcerated tumours that were more frequent in the nivolumab arm in patients with stage IIIC disease (46.6% versus 36.5%) for AJCC-8 (Table 2) and a higher frequency of primary versus recurrent tumours in nivolumab patients with stage IIIB melanoma (64.8% versus 54.4%) for AJCC-7 (Supplementary Table S1). The number of patients in the stage IIID subgroup was too small for meaningful comparison, but there appeared to be more patients in the nivolumab arm who were female, had macroscopic lymph node involvement, and had cutaneous melanoma, and more patients in the ipilimumab group with ulcerated primaries (Table 2).

3.2. RFS analysis

At 4 years' minimum follow-up, nivolumab continued to demonstrate RFS benefit versus ipilimumab across all stage III substages when patients were staged using AJCC-8 criteria (Supplementary Fig. S2). For both treatment groups, 4-year RFS rates were similar per subgroup when staged by AJCC-8 or AJCC-7, with nivolumab stage IIIB rates of 66.4% and 60.0% and stage IIIC rates of 47.1% and 46.1% for AJCC-8 and AJCC-7, respectively (Fig. 1). In addition, each treatment group demonstrated less favourable RFS with increasing stage III substage (HRs >1 for AJCC-8 stage IIIC and IIID and AJCC-7 stage IIIC, all versus stage IIIB). When comparing nivolumab to ipilimumab, one notable difference was that the stage IIIB HR according to AJCC-8 was lower than with AJCC-7 (0.56 versus 0.70) (Fig. 2). There was no statistically significant difference in the nivolumab to ipilimumab RFS HRs across the stage 3 substages per both the AJCC-8 and -7 criteria (test for interaction: AJCC-8, $P = 0.1051$; AJCC-7, $P = 0.8115$) (Fig. 2).

3.3. DMFS analysis

At a minimum follow-up of 4 years, nivolumab continued to demonstrate DMFS benefit versus ipilimumab across all AJCC-8 stage III substages (nivolumab: 142 events per 370 patients, ipilimumab:160 events per 366 patients; Supplementary Fig. S3). In both treatment groups, 4-year DMFS rates were similar per subgroup when staged by AJCC-8 or AJCC-7, with nivolumab stage IIIB rates of 70.0% and 67.0% and stage IIIC rates of 55.7% and 52.5%, respectively. Each treatment group demonstrated less favourable DMFS trends with increasing stage III substage (HRs >1 for AJCC-8 stage IIIC and IIID and AJCC-7 stage IIIC, all versus stage IIIB; Fig. 3). There was no statistically significant difference between the substage HRs comparing nivolumab with ipilimumab (test for

Table 1
AJCC stage III substages by treatment arm.

Staging classification	*n* (%)		
	Nivolumab ($n = 370$)	Ipilimumab ($n = 366$)	Total ($N = 736$)
AJCC-7 stage			
IIIB	165 (44.6)	147 (40.2)	312 (42.4)
IIIC	203 (54.9)	219 (59.8)	422 (57.3)
Other[a]	2 (0.5)	0 (0)	2 (0.3)
AJCC-8 stage			
IIIA[b]	3 (0.8)	5 (1.4)	8 (1.1)
IIIB	117 (31.6)	107 (29.2)	224 (30.4)
IIIC	232 (62.7)	230 (62.8)	462 (62.8)
IIID	17 (4.6)	20 (5.5)	37 (5.0)
Unevaluable	1 (0.3)	4 (1.1)	5 (0.7)

AJCC, American Joint Committee on Cancer.
[a] Stage IIIA.
[b] Two patients with stage IIIB melanoma (per AJCC-8 staging criteria) were recorded in the database as having stage IIIA melanoma and were therefore included in the IIIA group.

Table 2
Baseline characteristics by AJCC-8 stage III substage.

	AJCC-8					
	Stage IIIB, *n* (%)		Stage IIIC, *n* (%)		Stage IIID, *n* (%)	
	Nivolumab (*n* = 117)	Ipilimumab (*n* = 107)	Nivolumab (*n* = 232)	Ipilimumab (*n* = 230)	Nivolumab (*n* = 17)	Ipilimumab (*n* = 20)
Age, median years (range)	55 (20–83)	55 (25–81)	56 (19–83)	53 (18–86)	62 (38–71)	55 (26–74)
Sex						
Male	64 (54.7)	61 (57.0)	141 (60.8)	134 (58.3)	9 (52.9)	13 (65.0)
Female	53 (45.3)	46 (43.0)	91 (39.2)	96 (41.7)	8 (47.1)	7 (35.0)
Tumour ulceration status						
Absent	79 (67.5)	69 (64.5)	115 (49.6)	139 (60.4)	4 (23.5)	1 (5.0)
Present	33 (28.2)	31 (29.0)	108 (46.6)	84 (36.5)	13 (76.5)	19 (95.0)
Not reported	5 (4.3)	7 (6.5)	9 (3.9)	7 (3.0)	0	0
Lymph node involvement						
Microscopic	32 (27.4)	31 (29.0)	88 (37.9)	85 (37.0)	6 (35.3)	13 (65.0)
Macroscopic	75 (64.1)	69 (64.5)	129 (55.6)	134 (58.3)	11 (64.7)	7 (35.0)
Not reported	10 (8.5)	7 (6.5)	15 (6.5)	11 (4.8)	0	0
Tumour origin						
Primary	62 (53.0)	43 (40.2)	143 (61.6)	124 (53.9)	12 (70.6)	16 (80.0)
Recurrent	55 (47.0)	63 (58.9)	88 (37.9)	106 (46.1)	5 (29.4)	4 (20.0)
Not reported	0	1 (0.9)	1 (0.4)	0	0	0
Melanoma subtype						
Mucosal	1 (0.9)	4 (3.7)	13 (5.6)	5 (2.2)	1 (5.9)	1 (5.0)
Cutaneous	108 (92.3)	90 (84.1)	189 (81.5)	197 (85.7)	15 (88.2)	14 (70.0)
Acral	2 (1.7)	2 (1.9)	12 (5.2)	10 (4.3)	0	3 (15.0)
Ocular/uveal	0	0	0	0	0	0
Other	6 (5.1)	11 (10.3)	18 (7.8)	18 (7.8)	1 (5.9)	2 (10.0)
ECOG performance status						
0	109 (93.2)	98 (91.6)	207 (89.2)	205 (89.1)	16 (94.1)	19 (95.0)
1	8 (6.8)	9 (8.4)	25 (10.8)	25 (10.9)	1 (5.9)	1 (5.0)
LDH expression						
≤ULN	106 (90.6)	98 (91.6)	214 (92.2)	211 (91.7)	14 (82.4)	18 (90.0)
>ULN	9 (7.7)	7 (6.5)	14 (6.0)	16 (7.0)	3 (17.6)	2 (10.0)
Not reported	2 (1.7)	2 (1.9)	4 (1.7)	3 (1.3)	0	0
PD-L1 expression						
<5%	71 (60.7)	64 (59.8)	141 (60.8)	149 (64.8)	10 (58.8)	11 (55.0)
≥5%	40 (34.2)	41 (38.3)	80 (34.5)	74 (32.2)	5 (29.4)	7 (35.0)
Indeterminate	6 (5.1)	2 (1.9)	11 (4.7)	7 (3.0)	2 (11.8)	2 (10.0)
BRAF status						
Mutant	48 (41.0)	54 (50.5)	96 (41.4)	100 (43.5)	5 (29.4)	5 (25.0)
Wild-type	47 (40.2)	46 (43.0)	99 (42.7)	104 (45.2)	10 (58.8)	13 (65.0)
Not reported	22 (18.8)	7 (6.5)	37 (15.9)	26 (11.3)	2 (11.8)	2 (10.0)

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

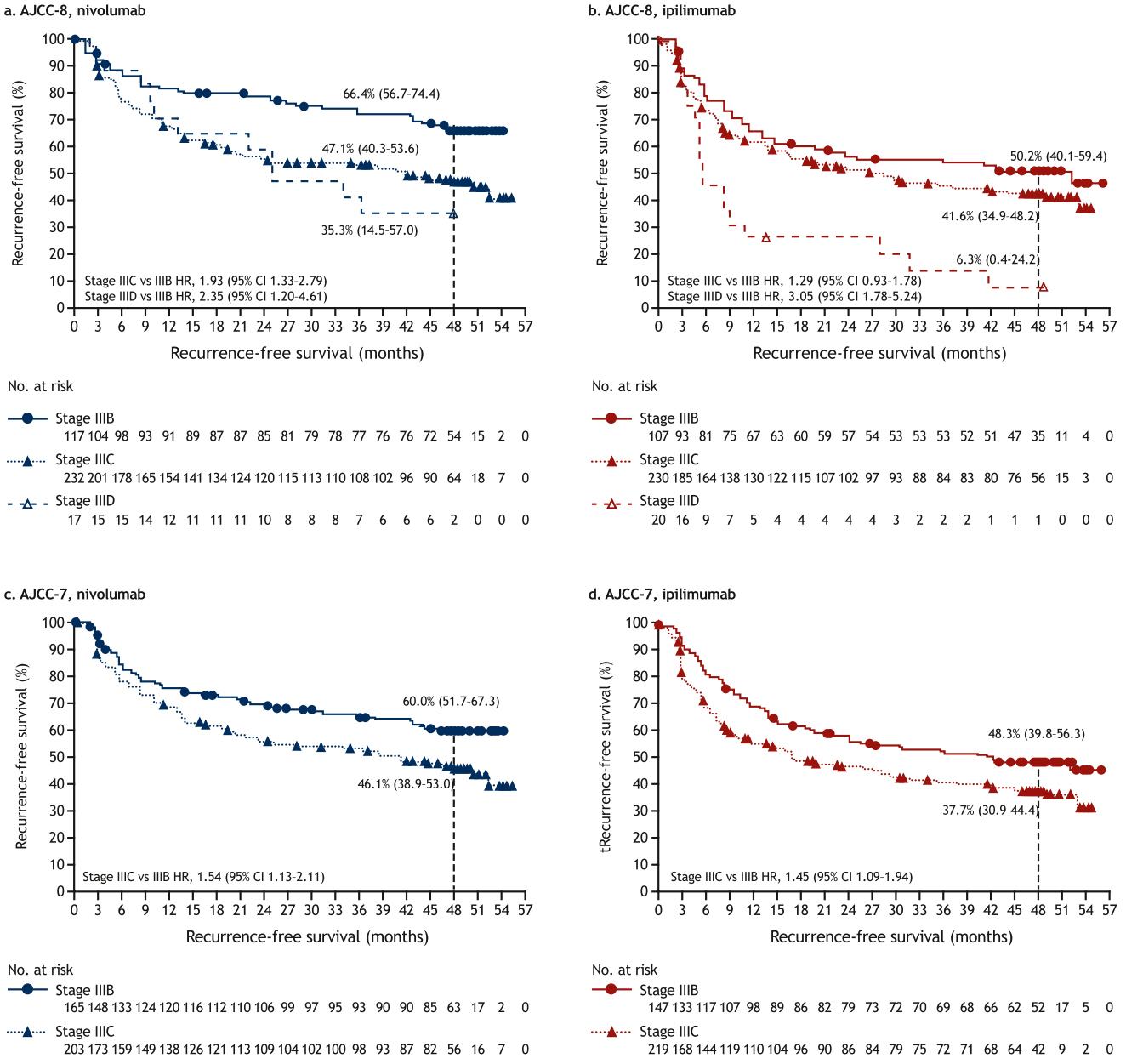


Fig. 1. Recurrence-free survival by AJCC-8 in stage III substage patients treated with (a) nivolumab or (b) ipilimumab and by AJCC-7 in stage III substage patients treated with (c) nivolumab or (d) ipilimumab; patients were followed for a minimum of 48 months (dotted line). AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio.

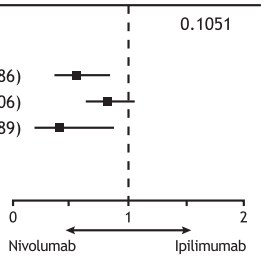
interaction: AJCC-8, $P = 0.8678$; AJCC-7, $P = 0.8392$) and substage HRs were similar for both AJCC-8 and AJCC-7 (Fig. 4).

Among stage III patients at first recurrence (nivolumab, 167; ipilimumab, 194), 96 (57.5%) nivolumab-treated patients and 111 (57.2%) ipilimumab-treated patients had distant metastasis as their first recurrence, with or without a concurrent local/regional recurrence (Supplementary Table S2). In each treatment group, the proportion of patients in stage IIIB and stage IIIC with distant recurrences were similar per AJCC-8 or AJCC-7. Per AJCC-8, out of patients who had a recurrence, a higher proportion of stage IIIB and IIID patients in the nivolumab arm had distant recurrences relative to the ipilimumab arm (70.3% versus 57.1% and 72.7% versus 50.0%), whereas a lower proportion of stage IIIC nivolumab-treated patients had a distant recurrence (52.1% versus 59.0%). Per AJCC-7, similar distant metastasis trends for nivolumab versus ipilimumab were observed in stage IIIB (66.1% versus 56.3%) and IIIC (52.4% versus 57.7%) patients.

Among all stage III patients in whom distant metastasis sites were reported at first recurrence (75 for nivolumab and 98 for ipilimumab), the most common sites (≥10% patients) for nivolumab and ipilimumab were, respectively, brain (12.0% and 15.3%), liver (16.0%

a. AJCC-8

	N	Nivolumab		Ipilimumab		Unstratified RFS hazard ratio (95% CI)	Interaction test
		n of events (*n* of patients)	mRFS (95% CI)	*n* of events (*n* of patients)	mRFS (95% CI)		
AJCC-8 Stage							0.1051
Stage IIIA	8	1 (3)	NR (21.65-NR)	2 (5)	NR (2.99-NR)		
Stage IIIB	224	37 (117)	NR	52 (107)	52.11 (17.08-NR)	0.56 (0.37-0.86)	
Stage IIIC	462	120 (232)	41.56 (21.32-NR)	128 (230)	26.51 (16.56-41.63)	0.83 (0.65-1.06)	
Stage IIID	37	11 (17)	25.07 (9.56-NR)	18 (20)	5.60 (3.91-11.07)	0.42 (0.20-0.89)	
Not reported	5	1 (1)	0.26 (NR-NR)	3 (4)	14.98 (14.09-18.56)		



b. AJCC-7

	N	Nivolumab		Ipilimumab		Unstratified RFS hazard ratio (95% CI)	Interaction test
		n of events (*n* of patients)	mRFS (95% CI)	*n* of events (*n* of patients)	mRFS (95% CI)		
AJCC-7 Stage							0.8115
Stage IIIB	312	62 (165)	NR	74 (147)	41.66 (21.82-NR)	0.70 (0.50-0.98)	
Stage IIIC	422	108 (203)	41.46 (23.26-NR)	129 (219)	16.82 (10.81-29.60)	0.74 (0.57-0.95)	
Other	2	0 (2)	NR				

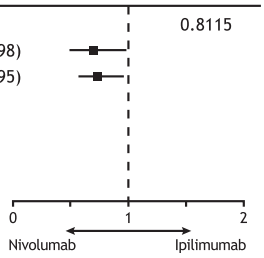


Fig. 2. Forest plot of treatment effect and interaction test on RFS by AJCC-8 (a) and AJCC-7 (b). AJCC, American Joint Committee on Cancer; CI, confidence interval; mRFS, median RFS; NR, not reached; RFS, recurrence-free survival.

and 14.3%), lung (32.0% and 39.8%), and lymph nodes (26.7% and 33.7%; Fig. 5 and Supplementary Table S3). These site-specific patterns and frequencies of distant metastases were also generally observed when the data were analysed by either an AJCC-8 or -7 stage III substage.

4. Discussion

This *post hoc* analysis of CheckMate 238 demonstrates that the superior efficacy of nivolumab over ipilimumab in patients with resected stage III melanoma previously observed per AJCC-7 staging was preserved when reanalysed per AJCC-8 staging. Longer RFS and DMFS favoured nivolumab regardless of the staging criteria and across substages.

In this first report of restaging CheckMate 238 patients per AJCC-8, redistribution was most prominent in the AJCC-7 stage IIIB subgroup, with 36.9% of patients redistributing into the AJCC-8 stage IIIC subgroup. Most patients (81.8%) in the AJCC-7 stage IIIC subgroup continued to be classified as AJCC-8 stage IIIC, with less than 10% each reclassified as AJCC-8 stage IIIB or IIID. This redistribution pattern was expected due to the reclassification of patients with thicker melanomas and/or more extensive nodal involvement into a higher stage subgroup per AJCC-8. The trial did not enrol stage IIIA patients per AJCC-7, and only eight patients were reclassified as stage IIIA per AJCC-8, preventing a meaningful analysis of efficacy outcomes for this small number of AJCC-8 stage IIIA patients on CheckMate 238. Other studies have previously shown high rates of RFS in this subgroup [9,12]. However, given the limited nature of these data, guidelines recommend treating these patients on an individualised basis [5,13].

The RFS superiority of nivolumab over ipilimumab per AJCC-7 across all stage III subgroups was preserved when analysed per AJCC-8. In addition, RFS rates decreased with increasing stage III substage (per AJCC-7 or -8) in both treatment arms, as expected, since the staging systems were developed primarily to identify prognostically different subgroups of patients. Rates in the stage IIIB substage were slightly higher when analysed per AJCC-8 versus AJCC-7 (66.4% versus 60%). In addition, per AJCC-8, the difference in nivolumab to ipilimumab HRs between stage IIIB and IIIC patients is more pronounced (0.56 versus 0.83) versus the difference noted per AJCC-7 analysis (0.70 versus 0.74). The stronger treatment effect in stage IIIB patients per AJCC-8 may have been due to a relatively large shift of higher risk patients from AJCC-7 stage IIIB to AJCC-8 stage IIIC. Nevertheless, there was no statistical difference among HRs across stage III subgroups per either AJCC-8 ($P = 0.1051$) or AJCC-7 ($P = 0.8115$). Overall, the results indicate a similar treatment effect for nivolumab across the substages, keeping in mind that the trial was not powered to detect

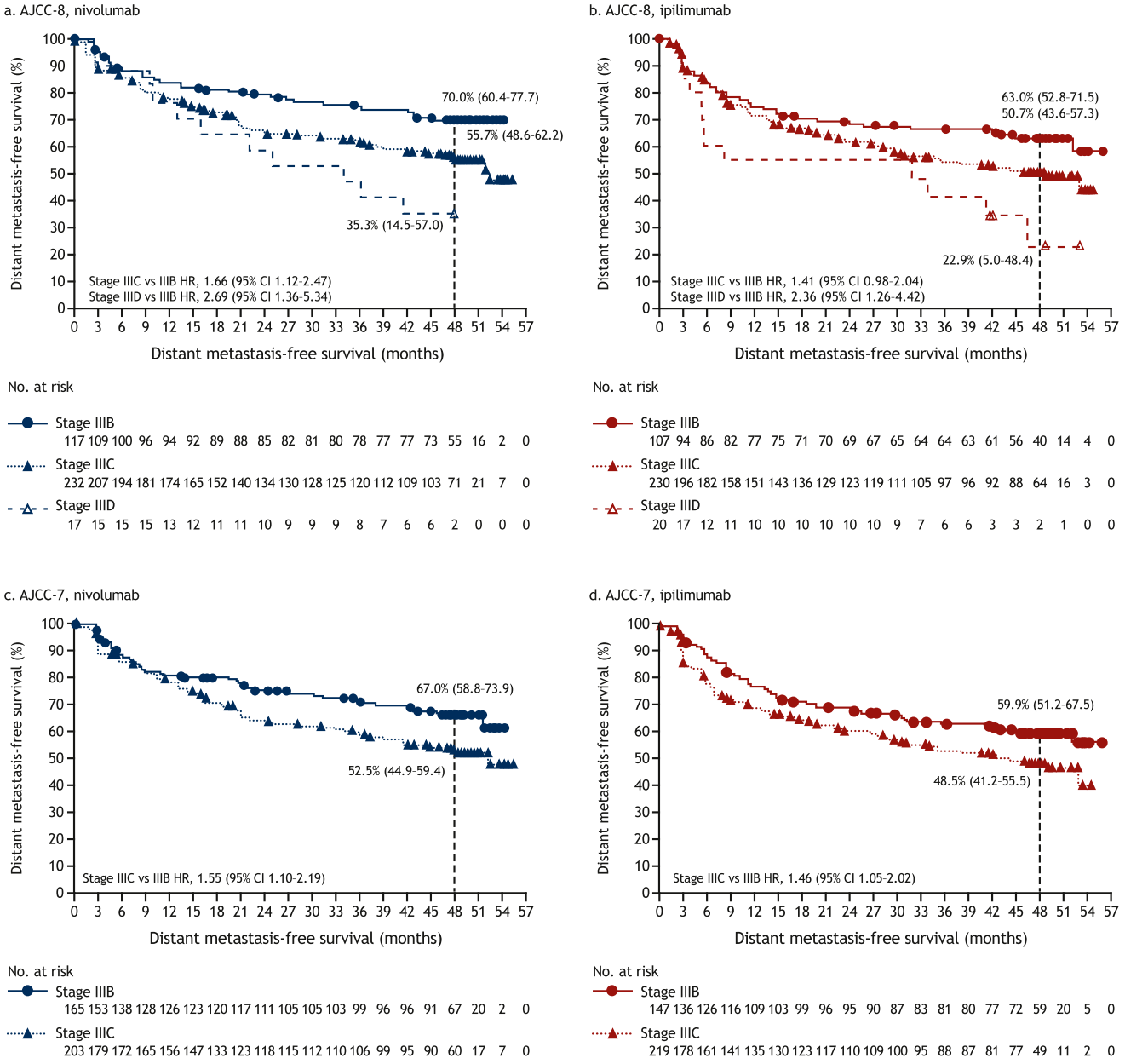


Fig. 3. Distant metastasis-free survival[a] by AJCC-8 in stage III substage patients treated with (a) nivolumab or (b) ipilimumab and by AJCC-7 in stage III substage patients treated with (c) nivolumab or (d) ipilimumab; patients were followed for a minimum of 48 months (dotted line). AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio. [a]DMFS analysis accounted for all distant recurrences, including those that occurred beyond a locoregional recurrence.

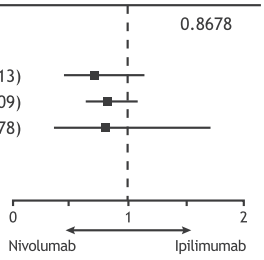
such differences. Similar trends were reported for adjuvant pembrolizumab versus placebo in KEYNOTE-054, with the caveat that the use of a placebo as a comparator in KEYNOTE-054 led to a stronger treatment effect than observed in CheckMate 238, with AJCC-8 Stage IIIB, IIIC and IIID RFS HRs of 0.57, 0.50 and 0.62, respectively, for pembrolizumab and 0.56, 0.83 and 0.42 for nivolumab [10].

Similar to the RFS data, DMFS rates decreased with the increasing stage for both AJCC-7 and AJCC-8 analyses in both arms. The CheckMate 238 DMFS analysis accounted for all distant recurrences, including those that occurred beyond a locoregional recurrence, an approach also used in KEYNOTE-054 [14]. Indeed, 4-year DMFS rates (per AJCC-7) for nivolumab in our study and 3.5-year rates for pembrolizumab in KEYNOTE-054 were similar (CheckMate 238 versus KEYNOTE-054: stage IIIB, 67.0% versus 68%; stage IIIC, 52.5% versus 56%).

In our study, among all stage III patients at their initial recurrence, distant metastases occurred in 57.5% and 57.2% of nivolumab and ipilimumab patients, respectively, with or without a concomitant local/regional recurrence. Remapping from AJCC-7 to AJCC-8 did not result in appreciable changes within each treatment arm on the proportion of patients with

a. AJCC-8

	N	Nivolumab		Ipilimumab		Unstratified DMFS hazard ratio (95% CI)	Interaction test
		n of events (*n* of patients)	mDMFS (95% CI)	*n* of events (*n* of patients)	mDMFS (95% CI)		
AJCC-8 Stage							0.8678
Stage IIIA	8	1 (3)	NR (21.65-NR)	0 (5)	NR		
Stage IIIB	224	33 (117)	NR	39 (107)	NR (52.11-NR)	0.71 (0.45-1.13)	
Stage IIIC	462	96 (232)	52.37 (47.67-NR)	105 (230)	48.56 (30.49-NR)	0.83 (0.63-1.09)	
Stage IIID	37	11 (17)	34.04 (9.99-NR)	13 (20)	31.77 (5.32-46.26)	0.80 (0.36-1.78)	
Not reported	5	1 (1)	0.72 (NR-NR)	3 (4)	18.56 (14.09-28.71)		



b. AJCC-7

	N	Nivolumab		Ipilimumab		Unstratified DMFS hazard ratio (95% CI)	Interaction test
		n of events (*n* of patients)	mDMFS (95% CI)	*n* of events (*n* of patients)	mDMFS (95% CI)		
AJCC-7 Stage							0.8392
Stage IIIB	312	51 (165)	NR (51.58-NR)	57 (147)	NR (52.11-NR)	0.78 (0.54-1.14)	
Stage IIIC	422	91 (203)	52.37 (38.90-NR)	103 (219)	44.32 (28.78-NR)	0.82 (0.62-1.09)	
Other	2	0 (2)	NR				

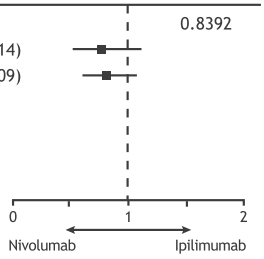


Fig. 4. Forest plot of treatment effect and interaction test on DMFS[a] by AJCC-8 (a) and AJCC-7 (b). AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; mDMFS, median DMFS. [a]DMFS analysis accounted for all distant recurrences, including those that occurred beyond a locoregional recurrence.

distant metastases in the stage IIIB and IIIC subgroups. This information will help clinicians to have a more meaningful dialogue with patients on the risk of distant metastases based on the current AJCC-8 stage III substages. The observed frequency of distant metastases is like that reported in a 2015–2018 retrospective study of patients with resected stage III/IV melanoma treated with adjuvant PD-1 therapy [15] and in the KEYNOTE-054 study (57%–68%), including patients with concurrent locoregional recurrences [14]. The similarity of these rates to the 51% reported in a retrospective study of 340 patients with melanoma followed for recurrence before the approval of checkpoint inhibitors [16] demonstrates a need for novel therapeutics in the adjuvant setting. Notably, 52% of patients received adjuvant treatment in that retrospective study (16% with high-dose interferon alfa and 23% with experimental vaccines) [16].

Commonly reported sites of distant metastases at initial recurrence in patients treated with nivolumab included the skin, liver, lungs, brain, bone, and lymph nodes. There did not seem to be an appreciable (≥10%) difference in the anatomic sites or frequencies of distant recurrences between the nivolumab and ipilimumab arms nor between AJCC-7 and AJCC-8 analyses. Given the relatively lower number of patients (nivolumab, 75; ipilimumab, 98) with reported sites of distant metastases spread across different target organs, conclusions regarding any difference in patterns between the arms cannot be easily drawn. The pattern of metastases was generally consistent with reports published before [16] and after [14,15] the introduction of checkpoint inhibitors. Data from the KEYNOTE-054 trial indicated that, among patients who recurred, the involved organs and proportion of patients with distant metastases were similar between placebo and pembrolizumab arms [14]. These findings underscore the continued need for improved therapeutic modalities to prevent the distant dissemination of disease, especially to visceral organs. In addition, the common observance of brain metastases highlights the need for early detection of brain involvement through imaging during treatment as well as follow-up.

A limitation of our study was the small number of patients with stage IIIA disease per AJCC-8, as a result of the exclusion of AJCC-7 stage IIIA patients. However, adjuvant immunotherapy in melanoma is administered less often and on a case-by-case basis in patients with stage IIIA melanoma and typically in patients with a sentinel node tumour burden >1 mm in diameter, after discussing the risks and benefits with the patient [13]. In addition, data in patients with stage IV disease were not analysed per AJCC-8 because of the small sample sizes created from remapping to AJCC-8 subcategories. Any meaningful analyses per AJCC-8 were limited in this subgroup since very few patients had M1c disease or elevated lactate dehydrogenase [1,17], two categories that can cause differences in stage IV substaging per AJCC-8 [6].

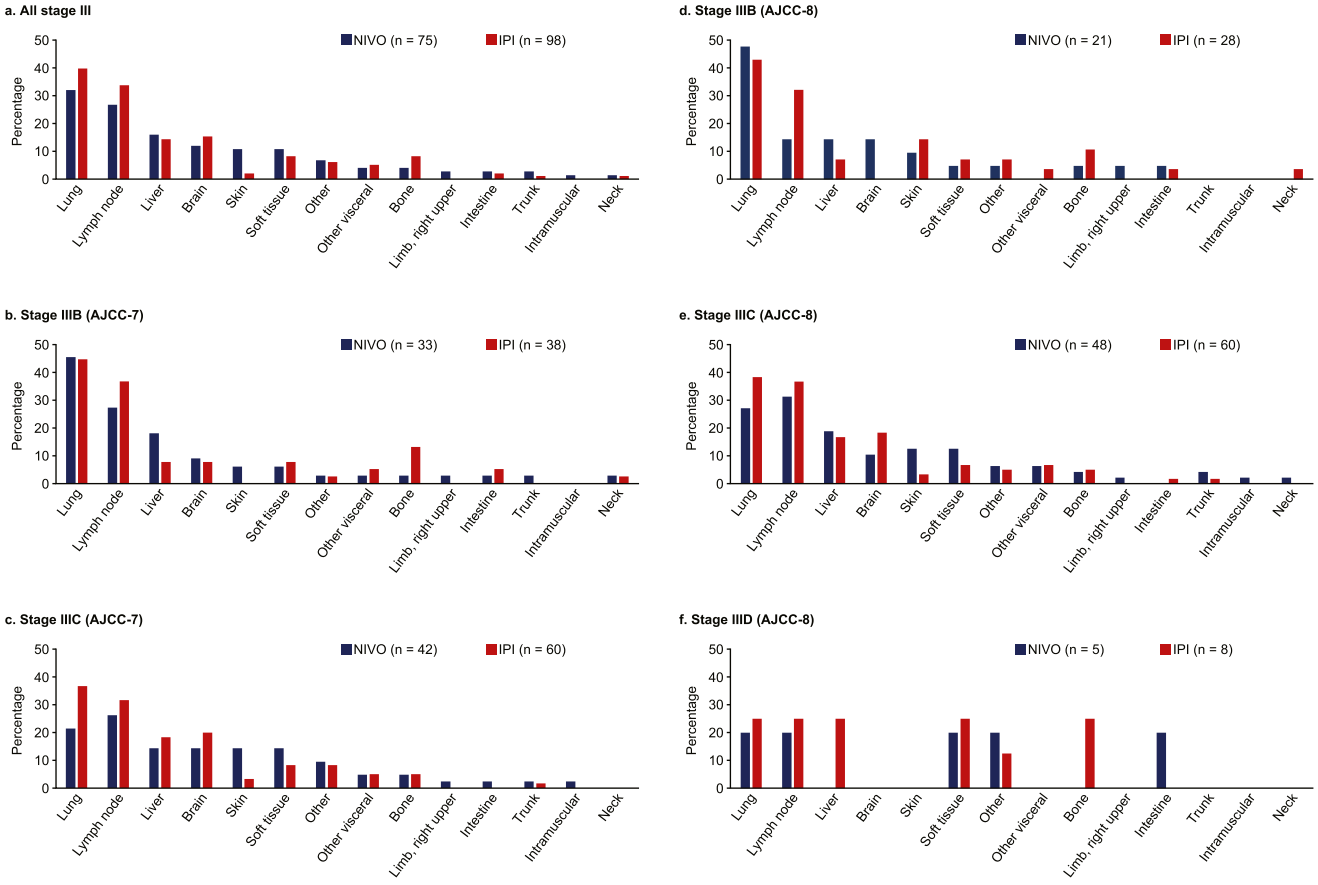


Fig. 5. Distant metastatic site[a] by all stage III (a), AJCC-7 (b), (c), and AJCC-8 (d), (e), (f) substage in patients with distant metastases at the time of first recurrence. AJCC, American Joint Committee on Cancer; IPI, ipilimumab; NIVO, nivolumab. [a]Patients may have been counted in more than one site.

In conclusion, this *post hoc* analysis shows that the RFS and DMFS outcomes per AJCC-7 translated similarly to the newer AJCC-8 staging subcategories. The results should reassure medical professionals and help facilitate discussions on the benefits and risks of adjuvant nivolumab with patients diagnosed per AJCC-8.

Author contributions

Conception or design: JL, ML, PA, MMandala. Data acquisition: JL, JW, MDV, HG, AA, SD, CLC, MS, JG, VC, IM, MB, AMDG, MMiddleton, LC, PA, VA, AH, LF, MMillward, NK, PQ, GVL, PA, MMandala. Data analysis: ML, MA. Data interpretation: All authors. Manuscript writing, reviewing, and approval: All authors.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **JLa** has worked in a consulting/advisory role for iOnctura, Apple Tree, Merck, Bristol Myers Squibb (BMS), Eisai, Debipharm, and Incyte; has received honoraria from AstraZeneca, BMS, Eisai, EUSA Pharma, GlaxoSmithKline (GSK), Incyte, Ipsen, Merck, touchEXPERTS, Royal College of Physicians, Cambridge Healthcare Research, Royal College of General Practitioners, VJOncology, Agence Unik, Merck Sharp & Dohme (MSD), Novartis, Aptitude, Pierre Fabre, Pfizer, Roche, Seagen, Inselgruppe, eCancer, Ultimovacs, Calithera, and Goldman Sachs; and has received research/grant support from Achilles Therapeutics, BMS, Immunocore, Aveo, Pharmacyclics, MSD, Nektar Therapeutics, Covance, Novartis, Pfizer, and Roche.

JW has worked in a consulting/advisory role for, received honoraria from, and received institutional

research/grant support from BMS; and is named on a patent for a PD-1 biomarker not used in the current trial.

MDV has worked in a consulting/advisory role for and received honoraria from BMS, MSD, Novartis, and Pierre Fabre.

HG has worked in a consulting/advisory role for Amgen, BMS, MSD, and Replimune; has received honoraria from BMS, MSD, Novartis, Sanofi, and Pierre Fabre; and has received research/grant support from Amgen, BMS, Iovance, MSD, Pfizer, and Replimune.

AMA has worked in a consulting/advisory role for, and received honoraria from Pierre Fabre, Novartis, BMS, Merck, Roche, MSD, and Sanofi; and has served as a speaker/provided expert testimony for BMS, Merck, Pierre Fabre, Novartis, MSD, Sanofi, and Roche.

SD has received research/grant support from BMS and MSD; has received travel/congress support from BMS; and has worked in an advisory role for MSD.
CLC has worked in a consulting/advisory role for Merck, Novartis, Pfizer, Sanofi, and Eisai.

MS has received research/grant support from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, BeiGene, Bioven, Clovis Pharmaceutical, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Merck Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sanofi, and Tesaro.

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MMan has worked in a consulting/advisory role for BMS, MSD, Novartis, Pierre Fabre, Sanofi, and Sun Pharma; has received honoraria from Novartis, BMS, MSD, Pierre Fabre, Sanofi, and Sun Pharma; and has received research/grant support from Novartis. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.041.

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