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Original Research

Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325/KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma

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Abstract ***Background:*** The American Joint Committee on Cancer-8 (AJCC) classification of melanoma was implemented in January 2018. It was based on data gathered when checkpoint inhibitors were not used as adjuvant therapy in stage III melanoma. The European Organization for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 double-blind phase III trial evaluated pembrolizumab vs placebo in AJCC-7 stage IIIA (excluding lymph node metastasis ≤1 mm), IIIB or IIIC (without in-transit metastasis) patients after complete lymphadenectomy.

Patients, methods and results: Patients (n = 1019) were randomised 1:1 to pembrolizumab 200 mg or placebo every 3 weeks (total of 18 doses, ~1 year). At 1.25-year median follow-up, pembrolizumab prolonged relapse-free survival (RFS) in the total population (1-year RFS rate: 75.4% vs 61.0%; hazard ratio [HR] 0.57; logrank P < 0.0001) and consistently in the AJCC-7 subgroups. Prognostic and predictive values of AJCC-8 for RFS were evaluated in this study. Patient distribution according to the AJCC-8 stage subgroups was 8% (IIIA), 34.7% (IIIB), 49.7% (IIIC), 3.7% (IIID) and 3.8% (unknown). AJCC-8 classification was strongly associated with RFS (HRs for stage IIIB, IIIC and IIID vs IIIA were 4.0, 5.7 and 12.2, respectively) but showed no predictive importance for the treatment comparison regarding RFS (test for interaction: P = 0.68). The 1-year RFS rate for pembrolizumab vs placebo and the HRs (99% confidence interval) within each AJCC-8 subgroup were as follows: stage IIIA (92.7% vs 92.5%; 0.76 [0.11–5.43]), IIIB (79.0% vs 65.5%; 0.59 [0.35–0.99]), IIIC (73.6% vs 53.9%; 0.48 [0.33–0.70]) and IIID (50.0% vs 33.3%; 0.69 [0.24–2.00]).

Conclusions: AJCC-8 staging had a strong prognostic importance for RFS but no predictive importance: the RFS benefit of pembrolizumab was observed across AJCC-8 subgroups in resected high-risk stage III melanoma patients.
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1. Introduction

In concordance with results obtained with new drugs in advanced melanoma [1,2], adjuvant therapies with ipilimumab [3,4], nivolumab [5] and pembrolizumab [6] in melanoma patients at high risk for relapse regardless of BRAF mutation status, and with dabrafenib plus trametinib [7] in BRAF-mutant patients, demonstrated significant benefits that resulted in US Food and Drug Administration approvals for all and in European Medicine Agency (EMA) approvals for all but ipilimumab. The ipilimumab [2,3], pembrolizumab [6] and dabrafenib plus trametinib [7] trials were conducted in stage III patients with the restriction that among patients with stage IIIA the diameter of the micrometastasis had to be > 1 mm, according to the Rotterdam Criteria of sentinel node (SN) tumour load [8–10], to avoid that too many patients with a low risk of relapse would dilute the patient population and delay analysis because of a lack of events. The CheckMate-238 nivolumab trial was conducted in patients with stage IIIB-C/resected and stage IV patients [5]. All trials used the AJCC-7 staging system [11]. The AJCC-8 staging system has become operational recently [12]. It has introduced a number of changes regarding stage III, classifying the former substages A/B/C into the substages III A-B-C-D

based on the inclusion of thickness of the primary, number of positive nodes, microscopic or macroscopic nodal involvement and the presence of in transit metastases or satellites [12]. This new AJCC-8 staging system, therefore, leads to substage migrations compared with the AJCC-7, which may impact the outcome per substage in the adjuvant therapy trials.

We report here our analysis of the outcome in the stage III population in the EORTC1325/KEYNOTE-54 pembrolizumab trial according to the AJCC-8 staging system in comparison to the reported outcomes according to the AJCC-7 system [6].

2. Patients and methods

2.1. Patients

Patients aged 18 years or older with histologically confirmed cutaneous melanoma metastatic to regional lymph nodes were eligible to enter the study. Patients had either stage IIIA melanoma (patients with N1a or N2a had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases according to the AJCC-7 classification [11]. Complete regional lymphadenectomy was required within 13 weeks before the start of treatment. Exclusion criteria included Eastern Cooperative Oncology Group performance status score 2–4, presence of autoimmune disease and uncontrolled infections, the use of systemic corticosteroids and prior systemic therapy for melanoma. A tumour sample from melanoma-positive lymph nodes was required to be sent for central pathology evaluation of programmed death-1-ligand-1 receptor (PD-L1) expression. Membranous PD-L1 expression in tumour and tumour-associated immune cells was assessed by an immunohistochemistry assay and scored on a scale of 0–5; a score ≥2 (staining on > 1% of cells) was considered PD-L1 positive [13].

2.2. Study design and treatment

Registration was carried out centrally at the EORTC headquarters. The randomisation was stratified by AJCC-7 staging (stage IIIA vs stage IIIB vs stage IIIC with 1–3 positive nodes vs stage IIIC with >3 positive nodes) and region. Only the local pharmacists were aware of trial group assignments.

Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses for (~1 year) or until disease recurrence, unacceptable toxicity, major protocol violation or withdrawal of consent (Supplementary Fig. 1).

The primary end-point was recurrence-free survival (RFS) in the overall population and in the subgroup of patients with PD-L1–positive tumours.

2.3. Assessments

Computed tomography and/or magnetic resonance imaging was performed every 12 weeks for the first 2 years, every 6 months through year 5. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed was taken into account.

Recurrence-free survival was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause. For patients without any event, the follow-up was censored at the latest disease evaluation performed according to the protocol.

2.4. Statistical analysis

Details regarding sample size computations, implementation of an interim analysis in an amended protocol and the dissemination of the treatment outcome results were provided in the original publication [6]. The RFS was assessed according to the intention-to-treat principle, all randomised patients being included in the analyses. At 1.25-year median follow-up, pembrolizumab prolonged RFS in the total population (hazard ratio [HR] stratified by stage provided at randomisation was 0.57, 98.4% confidence interval [CI] 0.43–0.74) [6].

Recurrence-free survival distribution was estimated using the Kaplan-Meier method, and the 95% CI for the 12- and 18-month rates were obtained via the Greenwood variance formula. For treatment comparison within AJCC-7 and AJCC-8 subgroups, the logrank test and the Cox model were used. The prognostic importance of AJCC-7 and AJCC-8 staging were assessed using the logrank test and the Cox model, both stratified by the treatment group.

We investigated the predictive importance of AJCC-7 and AJCC-8 staging classifications on the treatment differences regarding RFS. Forest plots were produced, and results of the test of interaction between each variable and the treatment group in a Cox model were indicated. For these subgroup analyses, the HRs were plotted along with their 99% CIs.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Distribution of AJCC-7 and AJCC-8, overall and by treatment group

The distribution of AJCC-7 and AJCC-8 staging classifications by treatment group is indicated in Table 1. AJCC-7 staging provided at randomisation, which was a stratification factor, was very well balanced in the 2

Table 1
Distribution of AJCC staging classifications by treatment group.

Staging classifications	Pembrolizumab (N = 514)	Placebo (N = 505)	Total (N = 1019)
	N (%)	N (%)	N (%)
AJCC-7 stage provided at randomisation			
III A	80 (15.6)	80 (15.8)	160 (15.7)
III B	237 (46.1)	230 (45.5)	467 (45.8)
III C (1–3 LN+)	95 (18.5)	93 (18.4)	188 (18.4)
III C (>3 LN+)	102 (19.8)	102 (20.2)	204 (20.0)
AJCC-7 staging based on CRFs			
Stage IIIA	77 (15.0)	76 (15.0)	153 (15.0)
Stage IIIB	240 (46.7)	232 (45.9)	472 (46.3)
Stage IIIC	197 (38.3)	197 (39.0)	394 (38.7)
Stage IIIC (1–3 positive lymph nodes)	87 (16.9)	95 (18.8)	182 (17.9)
Stage IIIC (>3 positive lymph nodes)	110 (21.4)	102 (20.2)	212 (20.8)
AJCC-8 staging based on CRFs			
Stage IIIA	42 (8.2)	40 (7.9)	82 (8.0)
Stage IIIB	163 (31.7)	191 (37.8)	354 (34.7)
Stage IIIC	267 (51.9)	239 (47.3)	506 (49.7)
Stage IIID	20 (3.9)	18 (3.6)	38 (3.7)
Unevaluable	22 (4.3)	17 (3.4)	39 (3.8)

CRF, case report form.
The collected information on CRFs was checked on site ("site data verification") by members of a clinical research organisation.

treatment groups. The AJCC-7 staging reviewed on-site ("site data verification"), and reported on case report forms, was well balanced in the two treatment groups as well: 15.0% of the patients were classified as stage IIIA, 46.3% as stage IIIB and 38.7% as stage IIIC. The distribution of the recent AJCC-8 staging was the following: 8.0% of the patients were classified as stage IIIA, 34.7% as stage IIIB, 49.7% as stage IIIC, 3.7% as stage IIID and 3.8% were unclassifiable because of the lack of essential information regarding Breslow thickness, ulceration status and/or number of lymph nodes involved. There was a small imbalance in disfavour of the pembrolizumab group: there were 51.9% patients with stage IIIC in the pembrolizumab group and 47.3% in the placebo group.

3.2. Relationship between AJCC-7 and AJCC-8 subgroups and other factors

A higher AJCC-7 stage category was associated with male sex and older age: in stage IIIA, IIIB and IIIC, the proportion of men was 60.1%, 60.0% and 64.2%, respectively, and the median age in these 3 subgroups was 51, 54 and 56 years, respectively (Table 2). As expected, there was a very strong correlation between the AJCC-7 subgroups and Breslow thickness, presence of ulceration, disease involvement and number of lymph nodes involved.

The same was true for the AJCC-8 staging: in stage IIIA, IIIB, IIIC and IIID, the proportion of men was 52.4%, 58.2%, 66.0% and 65.8%, respectively, and the median age in these 4 subgroups was 50, 55, 55 and 58.5 years, respectively (Table 3). AJCC-8 subgroups were strongly associated with the Breslow thickness, presence of ulceration, disease involvement and number of lymph nodes involved.

As expected, there was a strong correlation between the classification of patients according to the AJCC-7 and AJCC-8 staging classifications: the majority of patients were classified as stage IIIA, IIIB and IIIC according to both staging systems. However, AJCC-8 shifted a substantial group of patients from a lower AJCC-7 substage subgroup to a higher AJCC-8 substage subgroup (Table 3). This is mainly due to the classification of patients with a large Breslow thickness and/or presence of several clinically involved lymph nodes in higher stages.

3.3. Prognostic importance of AJCC-7 staging, subgroup analyses and its predictive importance

The AJCC-7 staging classification appeared to have a strong prognostic importance: the 1-year RFS rate, when considering both treatment groups combined, was 87.2% for stage IIIA, 69.2% for stage IIIB and 59.6% for stage IIIC patients, and the estimated HRs, stratified by treatment group, for stage IIIB and IIIC vs IIIA were 2.81 and 4.01, respectively (Fig. 1A). This prognostic importance was observed in each treatment group (Fig. 2): in the pembrolizumab group, the 1-year RFS rate was 93.4% in stage IIIA, 75.8% in stage IIIB and 67.7% in stage IIIC patients, whereas, in the placebo group, this rate was 81.1%, 62.4% and 51.5% in each of these subgroups, respectively. The subgroup analyses according to the AJCC-7 staging classification indicated that there was a consistent difference regarding RFS between the treatment groups: the estimated HR was 0.38, 0.57 and 0.58 in stage IIIA, IIIB and IIIC patients, respectively. The difference between these HRs was not

Table 2
Patient characteristics and relapse-free survival status by AJCC-7 staging.

Patient characteristics	Stage IIIA (N = 153)	Stage IIIB (N = 472)	Stage IIIC (N = 394)	Total (N = 1019)
	N (%)	N (%)	N (%)	N (%)
Sex				
Male	92 (60.1)	283 (60.0)	253 (64.2)	628 (61.6)
Female	61 (39.9)	189 (40.0)	141 (35.8)	391 (38.4)
Age at randomisation (years)				
< 50	72 (47.1)	179 (37.9)	128 (32.5)	379 (37.2)
50-<65	49 (32.0)	183 (38.8)	157 (39.8)	389 (38.2)
>=65	32 (20.9)	110 (23.3)	109 (27.7)	251 (24.6)
Median	51.0	54.0	56.0	54.0
Range	19.0–83.0	19.0–85.0	19.0–88.0	19.0–88.0
Primary localisation				
Head–neck	14 (9.2)	51 (10.8)	56 (14.2)	121 (11.9)
Trunk	79 (51.6)	168 (35.6)	141 (35.8)	388 (38.1)
Extremities	59 (38.6)	181 (38.3)	166 (42.1)	406 (39.8)
Unknown	1 (0.7)	72 (15.3)	31 (7.9)	104 (10.2)
Breslow (mm)				
< 0.8	2 (1.3)	44 (9.3)	24 (6.1)	70 (6.9)
>=0.8–1	11 (7.2)	27 (5.7)	31 (7.9)	69 (6.8)
>1–2	55 (35.9)	93 (19.7)	54 (13.7)	202 (19.8)
> 2–4	58 (37.9)	127 (26.9)	122 (31.0)	307 (30.1)
> 4	23 (15.0)	91 (19.3)	122 (31.0)	236 (23.2)
Unknown	4 (2.6)	90 (19.1)	41 (10.4)	135 (13.2)
Presence of ulceration[a]				
No	152 (99.3)	231 (48.9)	98 (24.9)	481 (47.2)
Yes	0 (0.0)	153 (32.4)	252 (64.0)	405 (39.7)
Not reported	1 (0.7)	88 (18.6)	44 (11.2)	133 (13.1)
Lymph node involvement[a]				
Microscopic	153 (100.0)	159 (33.7)	36 (9.1)	348 (34.2)
Macroscopic	0 (0.0)	313 (66.3)	358 (90.9)	671 (65.8)
Number of lymph nodes involved[a]				
1	98 (64.1)	281 (59.5)	85 (21.6)	464 (45.5)
2–3	55 (35.9)	191 (40.5)	97 (24.6)	343 (33.7)
4+	0 (0.0)	0 (0.0)	212 (53.8)	212 (20.8)
RFS status				
No RFS events	132 (86.3)	313 (66.3)	223 (56.6)	668 (65.6)
LR recurrence	12 (7.8)	56 (11.9)	64 (16.2)	132 (13.0)
LR/DM or DM w/o LR recurrence	8 (5.2)	102 (21.6)	106 (26.9)	216 (21.2)
Death without recurrence	1 (0.7)	1 (0.2)	1 (0.3)	3 (0.3)

RFS, relapse-free survival; LR, locoregional; LR/DM, locoregional recurrence and distant metastasis; DM w/o LR, distant metastasis without locoregional.
[a] As indicated on the case report forms.

statistically significant (test for interaction: P = 0.69), indicating no evidence of a predictive importance of AJCC-7 staging regarding RFS (Supplementary Fig. 2).

By splitting AJCC-7 stage IIIC patients in those with 1–3 positive lymph nodes (n = 182) and those with >3 positive lymph nodes (n = 212), two subgroups emerged, who had a different outcome: the 1-year RFS rates were 66.4% and 53.9%, respectively (Supplementary Fig. 3). The 4-categorical AJCC-7 staging variable (IIIA, IIIB, IIIC with 1–3 positive lymph nodes, IIIC with >3 positive lymph nodes) had a stronger prognostic importance than the usual 3-categorical AJCC-7 classification (data not shown). A Cox model stratified by treatment showed that this 4-categorical variable retained its strong prognostic importance even after adjustment by sex and age and that sex and age had no significant impact on RFS adjusting for stage (data not shown). The treatment comparison stratified by this 4-categorical AJCC-7 staging variable yielded an estimated HR of 0.56 and 98.4% CI 0.43–0.73, which was in line with the one reported in the main analysis (HR 0.57) [6].

3.4. Prognostic importance of AJCC-8 staging, subgroup analyses and its predictive importance

The AJCC-8 staging was of strong prognostic importance: the 1-year RFS rate, when considering both treatment groups combined, was 92.6%, 71.7%, 64.3% and 42.1% in stage IIIA, IIIB, IIIC and IIID patients, respectively, and the estimated HRs, stratified by treatment group, for stage IIIB, IIIC and IIID vs IIIA were 4.0, 5.7 and 12.2, respectively (Fig. 1B). This prognostic importance was observed in each treatment group

Table 3
Patient characteristics and relapse-free survival status by AJCC-8 staging.

Patient characteristics	Stage IIIA (N = 82)	Stage IIIB (N = 354)	Stage IIIC (N = 506)	Stage IIID (N = 38)	Stage III unknown (N = 39)
	N (%)	N (%)	N (%)	N (%)	N (%)
Sex					
Male	43 (52.4)	206 (58.2)	334 (66.0)	25 (65.8)	20 (51.3)
Female	39 (47.6)	148 (41.8)	172 (34.0)	13 (34.2)	19 (48.7)
Age at randomisation (yrs)					
< 50 yrs	41 (50.0)	128 (36.2)	177 (35.0)	14 (36.8)	19 (48.7)
50-<65 yrs	30 (36.6)	143 (40.4)	193 (38.1)	13 (34.2)	10 (25.6)
>=65 yrs	11 (13.4)	83 (23.4)	136 (26.9)	11 (28.9)	10 (25.6)
Median	50.0	55.0	55.0	58.5	50.0
Range	24.0–77.0	19.0–88.0	19.0–84.0	21.0–81.0	19.0–79.0
Primary localisation					
Head–neck	5 (6.1)	45 (12.7)	57 (11.3)	10 (26.3)	4 (10.3)
Trunk	51 (62.2)	125 (35.3)	191 (37.7)	11 (28.9)	10 (25.6)
Extremities	26 (31.7)	143 (40.4)	197 (38.9)	17 (44.7)	23 (59.0)
Unknown	0 (0.0)	41 (11.6)	61 (12.1)	0 (0.0)	2 (5.1)
Breslow (mm)					
< 0.8 mm	8 (9.8)	50 (14.1)	12 (2.4)	0 (0.0)	0 (0.0)
>=0.8–1 mm	19 (23.2)	35 (9.9)	15 (3.0)	0 (0.0)	0 (0.0)
>1–2 mm	55 (67.1)	114 (32.2)	33 (6.5)	0 (0.0)	0 (0.0)
> 2–4 mm	0 (0.0)	114 (32.2)	192 (37.9)	0 (0.0)	1 (2.6)
> 4 mm	0 (0.0)	0 (0.0)	193 (38.1)	38 (100.0)	5 (12.8)
Unknown	0 (0.0)	41 (11.6)	61 (12.1)	0 (0.0)	33 (84.6)
Presence of ulceration[a]					
No	74 (90.2)	250 (70.6)	141 (27.9)	0 (0.0)	16 (41.0)
Yes	8 (9.8)	56 (15.8)	298 (58.9)	38 (100.0)	5 (12.8)
Not reported	0 (0.0)	48 (13.6)	67 (13.2)	0 (0.0)	18 (46.2)
Lymph node involvement[a]					
Microscopic	82 (100.0)	79 (22.3)	173 (34.2)	8 (21.1)	6 (15.4)
Macroscopic	0 (0.0)	275 (77.7)	333 (65.8)	30 (78.9)	33 (84.6)
Number of lymph nodes involved[a]					
1	58 (70.7)	222 (62.7)	168 (33.2)	0 (0.0)	16 (41.0)
2–3	24 (29.3)	132 (37.3)	176 (34.8)	1 (2.6)	10 (25.6)
4+	0 (0.0)	0 (0.0)	162 (32.0)	37 (97.4)	13 (33.3)
AJCC 2009[a]					
Stage IIIA	68 (82.9)	58 (16.4)	23 (4.5)	0 (0.0)	4 (10.3)
Stage IIIB	14 (17.1)	247 (69.8)	192 (37.9)	0 (0.0)	19 (48.7)
Stage IIIC	0 (0.0)	49 (13.8)	291 (57.5)	38 (100.0)	16 (41.0)
RFS status					
No RFS events	75 (91.5)	245 (69.2)	310 (61.3)	14 (36.8)	24 (61.5)
LR recurrence	4 (4.9)	36 (10.2)	77 (15.2)	9 (23.7)	6 (15.4)
LR/DM or DM w/o LR recurrence	3 (3.7)	72 (20.3)	117 (23.1)	15 (39.5)	9 (23.1)
Death without recurrence	0 (0.0)	1 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)

RFS, relapse-free survival; LR, locoregional; LR/DM, locoregional recurrence and distant metastasis; DM w/o LR: distant metastasis without locoregional.
[a] As indicated on the case report forms.

(Fig. 3): in the pembrolizumab group, the 1-year RFS rate was 92.7% for stage IIIA, 79.0% for stage IIIB, 73.6% for stage IIIC and 50.0% for stage IIID patients, whereas, in the placebo group, these rates were 92.5%, 65.5%, 53.9% and 33.3%, respectively. These subgroup analyses according to the AJCC-8 staging indicated that there was a consistent difference regarding RFS between the treatment groups. The estimated treatment HR was 0.76 in stage IIIA, 0.59 in stage IIIB, 0.48 in stage IIIC and 0.69 in stage IIID patients. The difference between these HRs was not statistically significant (test for interaction: P = 0.68), indicating no evidence of predictive importance of AJCC-8 stage regarding RFS (Supplementary Fig. 2).

Considering only patients with a known AJCC-8 subgroup (n = 980), the prognostic importance of AJCC-8 staging was very similar to the one of the 4-categorical AJCC-7 staging.

The analysis stratified by the AJCC-8 staging (IIIA-IIIB-IIIC-IIID-unknown) yielded an estimated HR of 0.54 and 98.4% CI 0.42–0.71, which was slightly lower than the one obtained in the main analysis (HR 0.57), as the imbalance of AJCC-8 Stage IIIC disfavoured the pembrolizumab group.

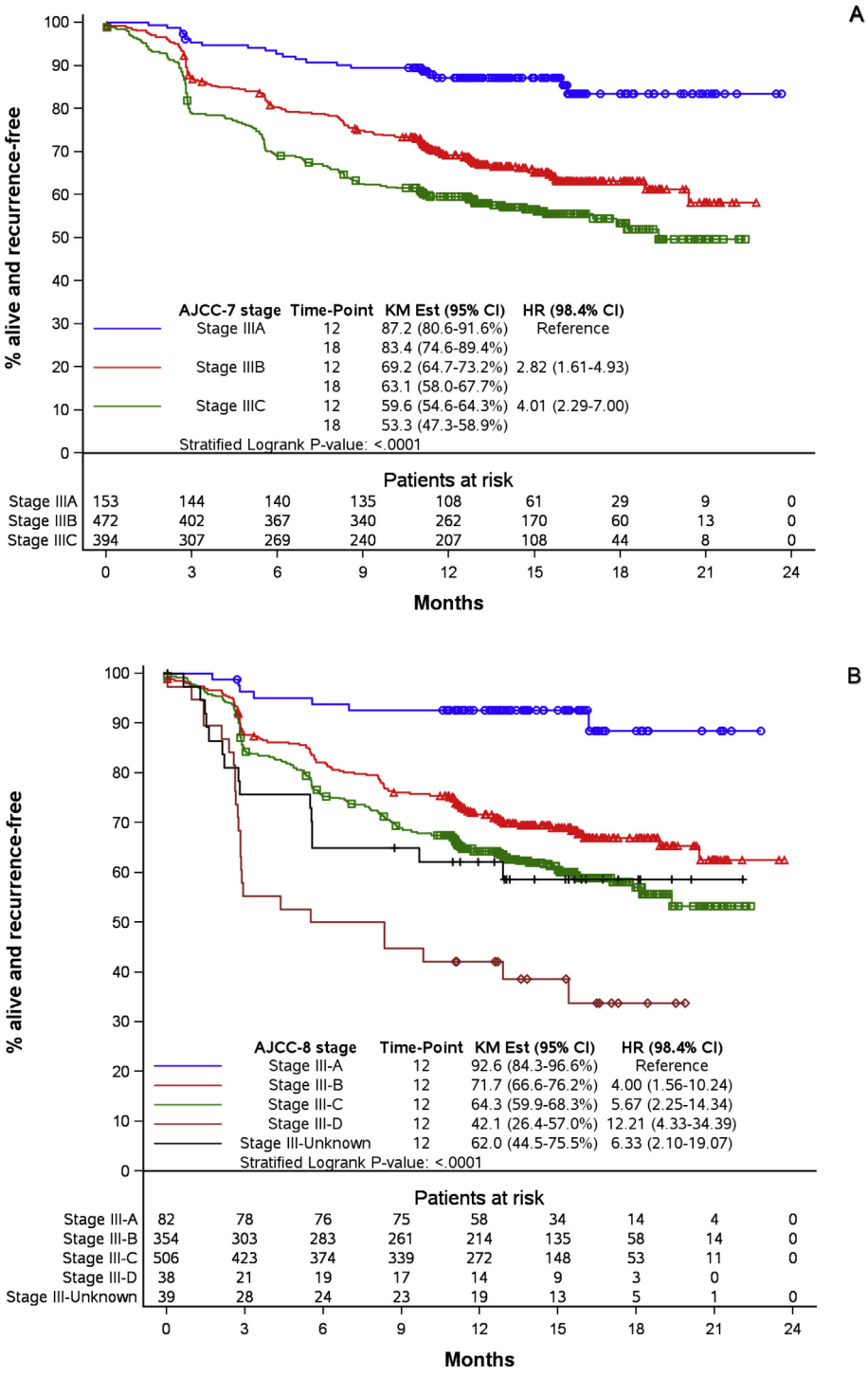

Fig. 1. Relapse-free survival by (A) AJCC-7 staging and (B) AJCC-8 staging. KM, Kaplan-Meier; Est, estimate; HR, hazard ratio; CI, confidence interval.

4. Discussion

We carried out a study comparing AJCC-7 staging vs AJCC-8 staging in the population of stage III melanoma patients that participated in the EORTC1325/KEYNOTE-054 trial. We already demonstrated in this study that at 1.25-year median follow-up, pembrolizumab prolonged RFS in the total population (1-year RFS rate: 75.4% vs 61.0%; HR 0.57, 98.4% CI 0.43–0.74; $P < 0.0001$), and the PD-L1-positive subgroup as well [6]. Prognostic and predictive values of AJCC-7 and AJCC-8 stagings for RFS were evaluated in the present study.

Patient distribution according to the AJCC-7 stage III subgroups was 15.0% (IIIA), 46.3% (IIIB) and 38.7% (IIIC) and according to the AJCC-8 stage III subgroups,

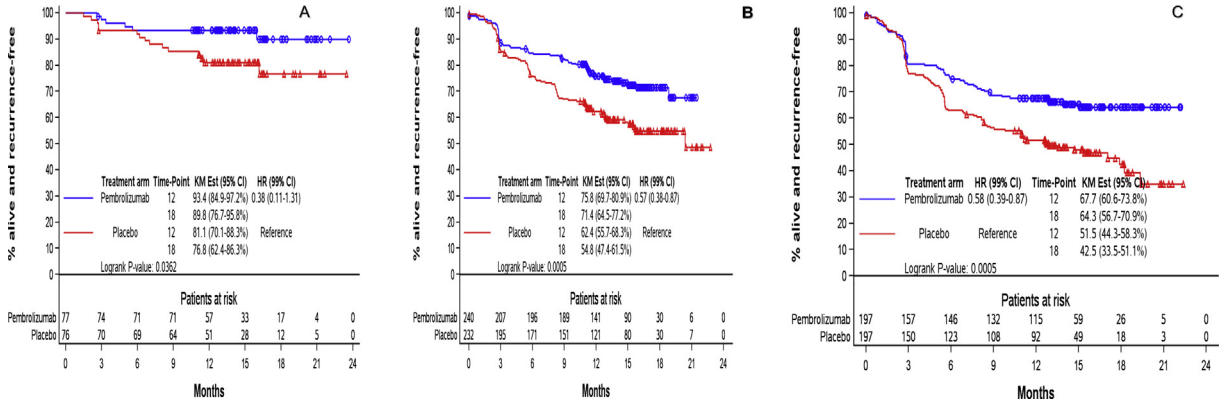

Fig. 2. Relapse-free survival by treatment group according to AJCC-7 staging: (A) stage IIIA, (B) stage IIIB and (C) stage IIIC. KM, Kaplan-Meier; Est, estimate; HR, hazard ratio; CI, confidence interval.

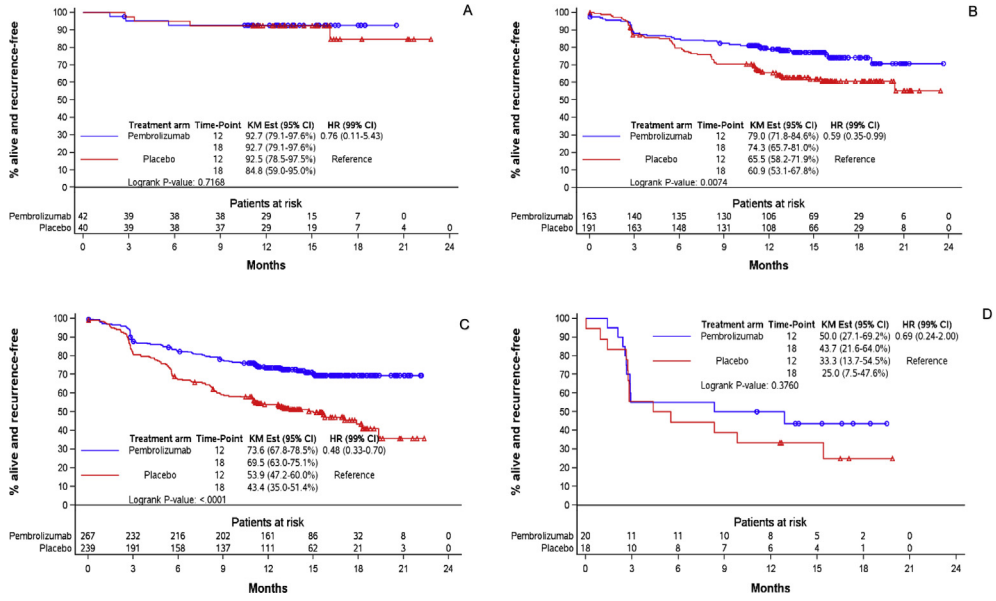

Fig. 3. Relapse-free survival by treatment group according to AJCC-8 staging: (A) stage IIIA, (B) stage IIIB, (C) stage IIIC and (D) stage IIID. KM, Kaplan-Meier; Est, estimate; HR, hazard ratio; CI, confidence interval.

it was 8.0% (IIIA), 34.7% (IIIB), 49.7% (IIIC), 3.7% (IIID) and 3.8% (unknown). As the AJCC-8 staging classification considers more variables to categorise patients than AJCC-7, it resulted in defining two extreme groups including a small proportion of patients: stage IIIA (only 1–3 sentinel lymph node involved and Breslow thickness≤1 mm or 1.01–2 mm and without ulcerated melanoma) and stage IIID (≥4 lymph nodes involved, or presence of matted nodes, or ≥2 lymph nodes involved and/or presence of matted nodes or presence of in-transit metastases, and Breslow thickness≥4 mm and ulcerated melanoma). They had a very different prognosis: the 1-year RFS rate was 92.6% for stage IIIA patients and 42.1% for stage IIID patients (both treatment groups combined). In contrast, the previous AJCC-7 classification resulted in larger subgroups, with a less extreme prognosis: the 1-year RFS rate was 87.2% for stage IIIA and 59.6% for stage IIIC patients. By splitting the latter group according to the number of lymph nodes involved, those with >3 lymph nodes involved, representing 20.8% of the entire population, had the worst prognosis: 1-year RFS rate was 53.9%. This was also observed in the previous EORTC 18071 study [3]. In both EORTC studies (18071 and 1325), the randomisation was stratified by the 4-categorical AJCC-7 staging (IIIA, IIIB, IIIC 1–3 positive lymph nodes, IIIC and >3 positive lymph nodes). In the previous EORTC 18952 and 18991 interferon studies, randomisation was stratified by sex and by several variables that were considered in the AJCC-7 staging [14–18].

We demonstrated that, just like the AJCC-7 classification, the AJCC-8 classification was strongly associated with RFS: HRs for stage IIIB, IIIC and

IIID vs IIIA were 4.0, 5.7 and 12.2, respectively. Importantly, we observed no predictive importance for the treatment comparison regarding RFS, the treatment HRs (99% CI) being consistently less than 1 (test for interaction: P = 0.68) within each AJCC-8 subgroup: IIIA (0.76 [0.11–5.43]), IIIB (0.59 [0.35–0.99]), IIIC (0.48 [0.33–0.70]) and IIID (0.69 [0.24–2.00]). The largest CIs were observed in stages IIIA and IIID because these stages had the smallest numbers of patients. The estimated HR of 0.76 in stage IIIA patients indicates a potentially lesser important benefit in a patient population with thin and/or non-ulcerated primaries, having an expected low rate of relapse but persisting beyond 5-year follow-up. This observation may impact the discussion with especially elderly patients to choose or forego adjuvant therapy.

The results of this trial are not changed, by applying the AJCC-8 staging rules, and using AJCC-8 staging does not change the validity of the approval of pembrolizumab across the substages of stage III melanoma patients. Some have been critical of the AJCC-8 staging system which has introduced multiple changes regarding stage III, mainly because of the inclusion of Breslow thickness of the primary, and of an increased survival rates for stage IIIA patients that have not been observed before [19]. Others have emphasised that AJCC-8 represents another improved staging system bringing additional granularity and precision to prognosis-driven discussions and decisions with patients in daily practice [20].

Although completion lymph node dissection (CLND) has been a mandatory component in all reported adjuvant phase III trials to date, it is no longer considered mandatory based on the results of the Deutsche Cooperative Oncology Group (DeCOG) and multicenter selective lymphadenectomy trial-II (MSLT) CLND trials [21,22] and can be further simplified by combining sentinel node tumour load information and the (non) ulcerated status of the primary melanoma [23].

In conclusion, we have shown that with a 1.25-year median follow-up, both AJCC-7 and AJCC-8 classifications had a strong prognostic importance regarding RFS. This was true overall, and in both treatment groups. In addition, these classifications showed no predictive importance regarding the treatment difference: the magnitude of the advantage of pembrolizumab over placebo regarding RFS was quite similar between the different subgroups defined by either the AJCC-7 or AJCC-8 classifications. Of course, these findings should be confirmed when longer follow-up will be available. This is particularly important in the stage IIIA subgroup, either according to the AJCC-7 or AJCC-8 classification, as one expects a lower risk of relapse but for a longer period than in the higher stage subgroups. This is important for all further adjuvant trial reporting.

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Conflict of interest statement

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.020.

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