original reports

Prognosis of Patients With Stage III Melanoma According to American Joint Committee on Cancer Version 8: A Reassessment on the Basis of 3 Independent Stage III Melanoma Cohorts

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abstract

PURPOSE Three new therapies have been approved recently for the adjuvant treatment of stage III melanoma, substantially reducing the risk of tumor recurrences. This study evaluates 3 independent data sets to clarify the survival probabilities of patients with stage III melanoma.

PATIENTS AND METHODS The Central Malignant Melanoma Registry (CMMR) evaluated 1,553 patients with a primary diagnosis of stage III melanoma from 2000 to 2012. Studies from the European Organisation for Research and Treatment of Cancer (EORTC), of 573 patients in the observation arm of the 18991 study and 445 patients in the placebo arm of the 18071 study, were evaluated as reference cohorts. The survival outcomes were compared with the published American Joint Committee on Cancer version 8 (AJCCv8) stage III survival data.

RESULTS For the CMMR stage III cohort versus the AJCCv8 cohort, the melanoma-specific survival (MSS) rates at 5 years were 67% versus 77%, and at 10 years were 56% versus 69%, respectively. For stage IIIA, the MSS rates at 5 years were 80% versus 93%, and at 10 years were 71% versus 88%; for stage IIIB, the MSS rates at 5 years were 75% versus 83%, and at 10 years were 61% versus 77%. The MSS rates of the EORTC studies either overlapped with or were lower than, the CMMR data.

CONCLUSION The MSS rates in the CMMR and EORTC cohorts over the entire stage III are less favorable than those published in AJCCv8. This is particularly true for substages IIIA and IIIB.

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INTRODUCTION

The incidence of cutaneous melanoma has been increasing continuously for decades, and so far, no change in trend has been observed in Europe or the United States.[1] The proportion of metastatic melanomas is largely stable and shows an increasing trend in absolute numbers,[2] including patients with regional lymph node or skin metastasis classified as stage III in the 8th version of the American Joint Committee on Cancer (AJCC) classification (AJCCv8).

A new era of adjuvant therapy has begun for stage III melanoma.[3] Two immunotherapies and 1 targeted therapy were approved for stage III melanoma in 2018 in Europe and the United States on the basis of improved relapse-free, distant metastases-free, and in part overall survival (OS) benefits.[4] The exact prognostic outcomes should be taken into consideration in adjuvant treatment recommendations.[5]

The TNM classification of solid tumors, as established by the AJCC and the Union International Control Cancer, provides the backbone for prognostic classification and treatment decisions for solid tumors.[6] The first AJCC classification of melanoma was published in 1977 and was valid until 1983.[7] Starting with the AJCCv6 classification in 2002, Breslow's tumor thickness and ulceration were used for the T classification, and the distinction between micro- and macrometastasis and the number of nodes was used for the N classification.[8] The AJCCv7 classification of melanoma contained only small differences compared with the 6th classification.[9] The AJCCv8 of melanoma contains minor changes for the T classification, the N classification has been changed in several aspects, and substages of stage III disease have been newly defined.[10]

In the AJCCv8 classification, stage III melanoma is defined both by the N classification with 9 subgroups

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

Is the prognosis of patients with stage III melanoma, especially IIIA and IIIB, really as favorable as that published in the American Joint Committee on Cancer version 8 (AJCCv8) classification?

Knowledge Generated

In 3 independent cohorts of patients with stage III disease in the Central Malignant Melanoma Registry and the European Organisation for Research and Treatment of Cancer studies 18991 and 18071, we found significantly less favorable survival probabilities than those published in the AJCCv8 classification. The 5-year melanoma-specific survival rates were 73% to 80% in stage IIIA, instead of 93% according to AJCCv8, and 56% to 75% in stage IIIB, instead of 83% according to AJCCv8.

Relevance

The difference shown here should be taken into account in clinical decision making (eg, on initiation of adjuvant therapy) and in the planning of clinical trials.

and by the T classification, also with 9 subgroups, resulting in 81 different combination possibilities, which in 78 cases become relevant for the stage classification and makes staging complicated.[11] The combinations are presented in a field diagram and then assigned to the prognostically relevant substages of stage III: the 5- and 10-year melanoma-specific survival (MSS) rates for stage IIIA (combining 6 fields) were 93% and 88%, respectively; for stage IIIB (combining 19 fields), 83% and 77%, respectively; for stage IIIC (combining 48 fields), 69% and 60%, respectively; and for stage IIID (combining 3 fields), 32% and 24%, respectively. For the entire stage III population, the 5- and 10-year MMS rate were 77% and 69%, respectively.[10]

The favorable outcome in both stage IIIA and stage IIIB, as well as throughout stage III, in the AJCCv8 was considered surprising and can be explained partially by upstaging to stage III some patients who were classified previously as stage II. This has stirred vigorous discussions in the community regarding acceptable risk-benefit ratios and whether adjuvant therapy should be recommended at all to patients in stage IIIA or IIIB.[12,13]

Taking that into consideration, the current study examines the prognosis of patients with melanoma in stage III and its substages according to the definitions of the AJCCv8 classification. A database of the German Central Malignant Melanoma Registry (CMMR) containing patients with primary stage III melanoma diagnosed from 2000 to 2012 is used for this purpose. Furthermore, 2 databases from studies of the European Organisation for Research and Treatment of Cancer (EORTC) are analyzed, so that the prognostic course can be verified independently on the basis of 3 different data sets. The results of these analyses are of particular relevance because a thorough risk-benefit evaluation is of the utmost importance, especially in stages IIIA and IIIB, but also in stage III as a whole, for patient information and treatment recommendations, and also for future clinical study designs.

PATIENTS AND METHODS

Three Patient Cohorts

CMMR cohort. Between January 2000 and December 2012, 60,289 patients with melanoma were documented in the nationwide CMMR.[14] Only patients with cutaneous melanoma presenting with stage III at primary diagnosis were included in the current analysis. In the period from 2000 to 2012, patients with primary melanoma in stage IB and higher were staged with sentinel lymph node biopsy. Patients with ocular or mucosal melanoma and follow-up of less than 3 months were excluded. Follow-up was performed according to the valid version of the guidelines of the German Society of Dermatology. For stage III patients, physical examination, lymph node ultrasound, and blood testing including the tumor marker protein S100B, were performed every 3 months; whole-body computed tomography scans and brain magnetic resonance imaging were carried out every 6 months.

Reference cohorts: EORTC 18991 and 18071 trials. To estimate the validity and reliability of the CMMR survival data, we used 2 reference cohorts from EORTC studies conducted in patients with stage III melanoma over the past 15 years. The first reference cohort consisted of patients from the observation arm of the EORTC 18991 study (recruitment period, June 2000 through August 2003), in which adjuvant treatment with pegylated interferon-alpha was tested.[15,16] The second reference cohort consisted of patients from the placebo arm of the EORTC 18071 study (recruitment period from July 2008 to August 2011), which tested adjuvant treatment with ipilimumab.[17-19] In both studies, eligible patients underwent complete regional lymphadenectomy and had not received previous systemic therapy for melanoma. Patients with in-transit metastasis (EORTC 18991 and 18071) and those with 1-3 lymph node micrometastases $\leq$ 1 mm in diameter (EORTC 18071) were excluded. Both patient cohorts are described in detail in the original publications.[16,18]

Outcomes

The outcomes of interest were MSS and OS. MSS was defined as the time between the date of primary diagnosis of stage III cutaneous melanoma and the date of death from melanoma; the follow-up of patients still alive was censored at the last date to be alive, and of those who died as a result

TABLE 1. Clinical and Histopathologic Characteristics of the CMMR Cohort and the EORTC 18991 and 18071 Cohorts of Patients With Stage III Melanoma, and Their Follow-Up

Patient and Tumor Characteristics and Follow-Up	CMMR (2000-2012; n = 1,553)	EORTC 18991, Observation Group (n = 573)	EORTC 18071, Placebo Group (n = 445)
Sex			
Male	884 (56.9)	333 (58.1)	275 (61.8)
Female	669 (43.1)	240 (41.9)	170 (38.2)
Age, years			
Median (IQR)	61.0 (47.0-71.0)	50.0 (39.0-59.0)	52.2 (42.7-62.0)
≤ 50	480 (30.9)	303 (52.9)	209 (47.0)
51-70	684 (44.0)	270 (47.1)	209 (47.0)
> 70	389 (25.0)	0 (0)	27 (6.1)
Breslow thickness, mm			
Median (IQR)	2.80 (1.70-4.20)	2.2 (1.5-4.0)	2.2 (1.3-4.0)
< 0.8	41 (2.9)	29 (5.1)	38 (8.5)
≥ 0.8-1	50 (3.2)	38 (6.6)	32 (7.2)
> 1-2	390 (25.1)	188 (32.8)	135 (30.3)
> 2-4	583 (37.5)	169 (29.5)	128 (28.8)
> 4	374 (24.1)	113 (19.7)	112 (25.2)
Unknown	115 (7.4)	36 (6.3)	
Ulceration			
Yes	718 (46.2)	176 (30.7)	196 (44.0)
No	699 (45.0)	328 (57.2)	230 (51.7)
Not known	136 (8.8)	69 (12.0)	19 (4.3)
Stage, AJCCv7			
IIIA	394 (25.4)	151 (26.4)	83 (18.7)
IIIB	682 (43.9)	208 (36.3)	198 (44.5)
IIIC	477 (30,7)	159 (27.7)	164 (36.9)
Unknown	0 (0)	55 (9.6)	0 (0)
Stage, AJCCv8			
IIIA	293 (18.9)	81 (14.1)	38 (8.5)
IIIB	576 (37.1)	228 (39.8)	159 (35.7)
IIIC	642 (41.3)	254 (44.3)	232 (52.1)
IIID	42 (2.7)	10 (1.7)	16 (3.6)
Survival status			
Alive	1046 (67.4)	262 (45.7)	238 (53.5)
Dead	507 (32.6)	311 (54.3)	207 (46.5)
Melanoma	441 (28.4)	297 (51.8)	200 (44.9)
Other cause	66 (4.2)	14 (2.4)	7 (1.6)
Follow-up, months			
Median (IQR)	58.0 (34.0-93.0)	90.5 (84.7-99.4)	86.4 (64.4-97.2)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: AJCCv7, American Joint Committee on Cancer version 7; AJCCv8, American Joint Committee on Cancer version 8; CMMR, Central Malignant Melanoma Registry; EORTC, European Organisation for Research and Treatment of Cancer; IQR, interquartile range.

of other causes, at the date of death. OS was calculated from the date of primary diagnosis of stage III cutaneous melanoma to the date of last follow-up (censored observation) or the date of death as a result of any cause. For the EORTC trials, the starting point of these end points was the date of random assignment.

Statistical Analysis

Quantitative clinical and histopathologic data were expressed as medians with interquartile ranges (IQRs), and categoric data were presented as absolute numbers and proportions. The Kaplan-Meier method was used to estimate MSS and OS, and differences between the substages IIIA, IIIB, IIIC, and IIID were assessed by means of the log-rank test. Estimated survival rates were expressed as percentages with standard errors. Cumulative incidences of death as a result of melanoma and not as a result of melanoma were estimated using competing risk methods.

All statistical tests were 2 sided, with a P value $< .05$ considered statistically significant. Statistical calculations were performed with IBM SPSS Statistics Version 25.0 (IBM SPSS, Chicago, IL) or SAS Version 6.4 (Cary, NC) statistical software.

In sensitivity analyses, we compared the MSS curves for stage III patients classified according to AJCCv8 with those classified according to AJCCv7. For this purpose, Kaplan-Meier survival curves were identified from 2 publications describing the AJCCv7[9,20] and the AJCCv8.[10] The curves were scanned, extracted, and digitized manually using an interactive digitizing software[21] as described previously.[22,23] This software creates sampling points and allows curve construction by linear interpolation between these points.

RESULTS

Patient Characteristics

Clinical and histopathologic characteristics are summarized in Table 1. The CMMR cohort comprised 1,553 stage III patients according to the AJCCv8, of whom 41.3% were classified as stage IIIC. Only patients with data for AJCCv8 classification were selected. Because of incomplete information, 664 patients from a total of 2,217 patients were excluded, which corresponds to 30% of the whole stage III CMMR collective. There were no differences in terms of age and sex between the patients included and excluded. There was a statistically significant difference in tumor

TABLE 2. Estimated MSS Rates at 5, 7, and 10 Years Corresponding to IMDDP and CMMR Databases and EORTC 18991 and EORTC 18071 Trials, in Patients With Stage III Melanoma According to the AJCCv8 Classification

	MSS Rate (SE%)			
MSS	IMDDP[10] (n = 4,708)	CMMR (n = 1,553)	EORTC 18991, Observation Group (n = 573)	EORTC 18071, Placebo Group (n = 445)
All stage III patients				
5 year	77.0 (n.a.)	67.0 (1.4)	52.7(2.1)	55.5 (2.4)
7 year	—	61.1 (1.6)	47.7 (2.1)	53.1 (2.5)
10 year	69.0 (n.a.)	55.6 (2.0)	—	—
Stage IIIA				
5 year	93.0 (n.a.)	80.0 (2.8)	80.4 (4.5)	72.5 (7.5)
7 year	—	75.7 (3.3)	74.4 (5.1)	72.5 (7.5)
10 year	88.0 (n.a.)	70.6 (3.9)	—	—
Stage IIIB				
5 year	83.0 (n.a.)	74.5 (2.2)	56.2 (3.3)	65.8 (3.9)
7 year	—	68.8 (2.6)	50.5 (3.4)	62.2 (4.0)
10 year	77.0 (n.a.)	60.6 (3.5)	—	—
Stage IIIC				
5 year	69.0 (n.a.)	55.9 (2.4)	41.8 (3.2)	47.6 (3.4)
7 year	—	48.7 (2.7)	38.1 (3.2)	45.4 (3.5)
10 year	60.0 (n.a.)	44.9 (3.0)	—	—
Stage IIID				
5 year	32.0 (n.a.)	29.9 (8.8)	20.0 (12.7)	27.5 (11.6)
7 year	—	29.9 (8.8)	10.0 (9.5)	27.5 (11.6)
10 year	24.0 (n.a.)	29.9 (8.8)	—	—

Abbreviations: AJCCv7, American Joint Committee on Cancer version 7; AJCCv8, American Joint Committee on Cancer version 8; CMMR, Central Malignant Melanoma Registry; EORTC, European Organisation for Research and Treatment of Cancer; IMDDP, International Melanoma Database and Discovery Platform; MSS, melanoma-specific survival; n.a., not assessed; SE%, standard error in %.

characteristics: patients excluded from the analysis had a median tumor thickness of 4.95 mm compared with 2.80 mm in patients included ($P < .001$). A higher proportion of patients excluded had stage IIIC (AJCCv7) disease compared with patients included in the analysis (65.2% *v* 30.7%; $P < .001$).

The stage III melanoma cohort of the EORTC 18991 trial comprised 573 patients from the observation arm, and the stage III cohort of the EORTC 18071 trial consisted of 445 patients from the placebo arm. In both studies, only patients with complete data were included in this analysis. A total of 56 patients (8.9%) in the EORTC 18991 study and 31 patients (6.5%) in the EORTC 18701 study were excluded. There was no significant difference in terms of age and sex between the 2 groups of excluded and included patients. Tumor thickness was slightly higher in the excluded patients compared with the included patients: in the EORTC 18991 study, 2.8 mm versus 2.2 mm, and in the EORTC 18701 study, 2.5 mm versus 2.2 mm, respectively.

In the CMMR cohort, melanoma-specific death occurred in 441 patients (28.4%) and death from other cause in 66 patients (4.2%). The median follow-up time was 58.0 months (IQR, 34.0-93.0 months). In the EORTC studies 18991 and 18071, melanoma-specific deaths occurred in 297 patients (51.8%) and in 200 patients (44.9%), respectively. In the 18991 study, 14 patients (2.4%), and in the 18071 study, 7 patients (1.6%), died as a result of other causes. The median follow-up time was 90.5 months (IQR, 54.5-99.4 months) in the EORTC 18991 cohort and 86.4 months (IQR, 64.4-97.2 months) in the EORTC 18071 cohort.

Survival Analysis

We compared the MSS rates for all 3 cohorts with data from the International Melanoma Database and Discovery Platform (IMDDP) analysis presented in the publication of the AJCCv8 classification (Table 2).[10] In the IMDDP analysis, the 5- and 10-year MSS rates for all stage III patients were 77% and 69%, higher than those calculated for all our collectives. In the CMMR cohort, the 5- and 10-year MSS rates were 67% and 56%. In the EORTC 18991 and 18071 studies, the 5-year MSS rates were even lower (52.7% and 55.5%, respectively), whereas the 10-year MSS rates were not available.

The 5-year stage-specific MSS in the IMDDP cohort was 93% in stage IIIA, 83% in stage IIIB, 69% in stage IIIC, and 32% in stage IIID. The 5-year MSS rates in the CMMR cohort and in EORTC cohorts 18991 and 18071 were systematically lower: in stage IIIA, 80% (18991: 80%; 18071: 73%); in stage IIIB, 75% (18991: 56%; 18071: 66%); in stage IIIC, 56% (18991: 42%; 18071: 48%); and in stage IIID, 30% (18991: 20%; 18071: 28%; Table 2, Figs 1-3).

For the study cohorts CMMR and EORTC 18991 and 18071, the estimated OS rates and OS curves are presented in the Appendix Table A1 and Appendix Figs A1-A3 (online only). Because the rates of nonmelanoma causes of death were < 5% (Table 1), the OS and MSS rates were

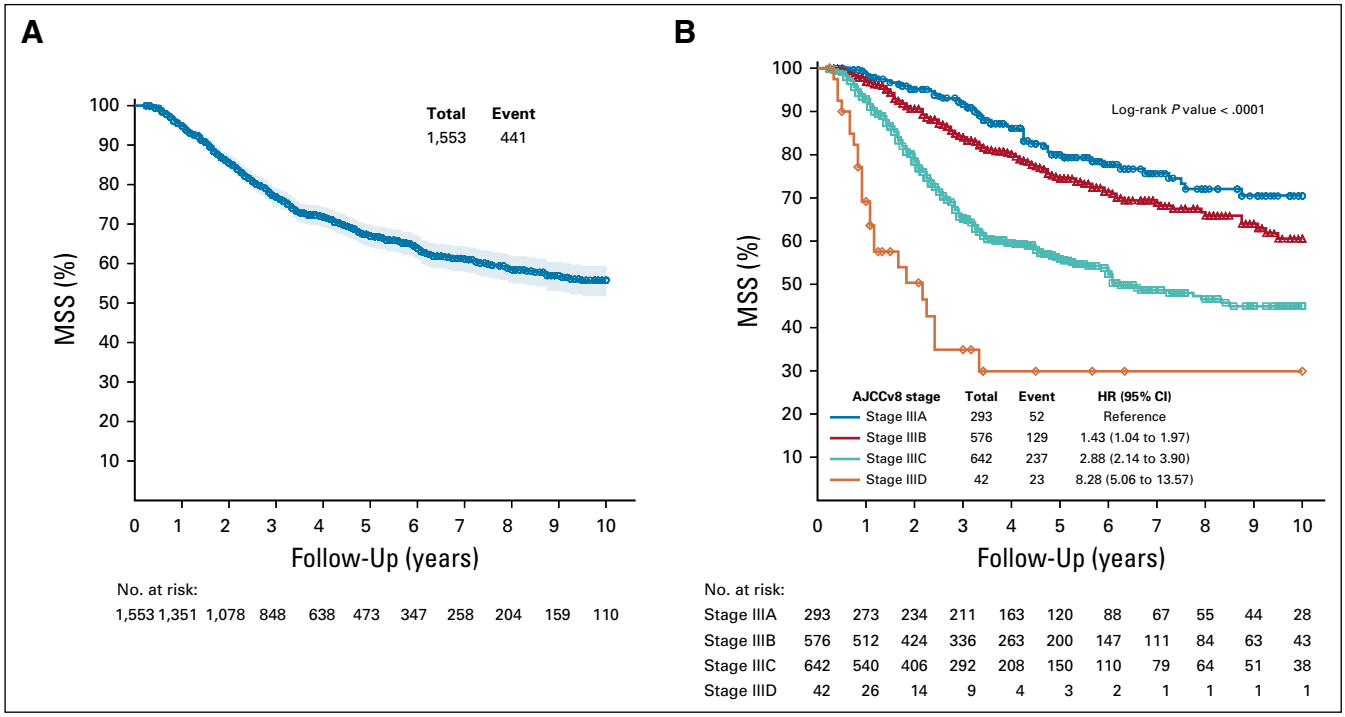

FIG 1. Kaplan-Meier curves for melanoma-specific survival (MSS) in the Central Malignant Melanoma Registry cohort. (A) In all stage III patients. (B) According to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

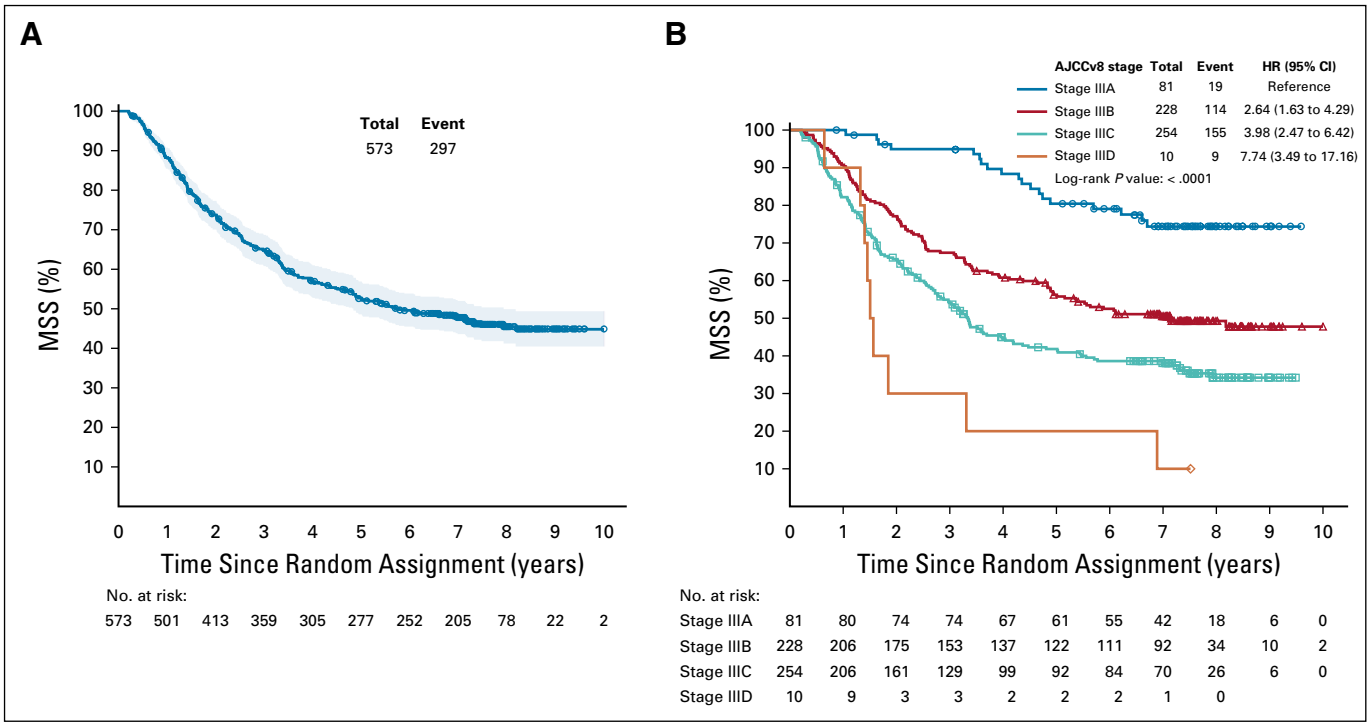

FIG 2. Kaplan-Meier curves for melanoma-specific survival (MSS) in European Organisation for Research and Treatment of Cancer cohort 18991, observation group. (A) In all stage III patients. (B) According to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

similar; the difference was between 2% and 5%. The 5-, 7-, and 10-year cumulative incidences of death as a result of melanoma and not as a result of melanoma are indicated in the Appendix (Table A2, online only). For the CMMR cohort, the 10-year cumulative incidence of death as a result of melanoma was 28.8% for stage IIIA patients and 37.7% for stage IIIB patients.

DISCUSSION

In this investigation, we show that MSS in AJJCv8 stage III is less favorable in 3 independent databases than as reported by the IMDDP database leading to the AJCCv8 classification of melanoma. This is true for the prognosis of the entire stage III cohort and is particularly true for the substages IIIA and IIIB. According to the IMDDP data, on which the survival calculations of the AJCCv8 classification of melanoma are based, the 5- and 10-year MSS rates in stage IIIA were 93% and 88%, and in stage IIIB, 83% and 77%. Corresponding MSS rates from the CMMR at 5 and 10 years in stage IIIA were 80% and 71%, respectively, and in stage IIIB, 75% and 61%, respectively. Therefore, the Kaplan-Meier estimation of the 10-year rate of dying as a result of melanoma in stage IIIA was 12% according to AJCCv8 data and 29% according to CMMR data. In stage IIIB, it was 23% according to AJCCv8 data and 38% according to CMMR data. The CMMR outcomes in stage III melanoma were similar to the data from the EORTC 18991 and 18071 studies. The data of the CMMR, as well as both EORTC cohorts, are also well in line with 2 German cohorts published recently that reported 5-year MSS rates of 89% for stage IIIA, 73% for stage IIIB, 56% for stage IIIC, and 52% for stage IIID.[24] Moreover, another study, by the Swedish cancer registry in 2,067 patients, reported 5- and 10-year MSS rates of 87% and 80% for stage IIIA, 69% and 55% for stage IIIB, and 50% and 43% for stage IIIC.[25]

Three adjuvant stage III therapies for melanoma have been approved since 2018, all of which are effective in extending relapse-free survival, distant-metastases–free survival and (in part) OS.[26] First, it was shown that adjuvant treatment with ipilimumab versus placebo in stage III melanoma resulted in a hazard ratio for relapse-free survival of 0.76, and another study comparing nivolumab and ipilimumab for relapse-free survival showed a hazard ratio of 0.65 (product value of both hazard ratios = 0.49).[4,18,27] Nivolumab was subsequently approved in both the United States and Europe for the adjuvant treatment of stage III melanoma.[5,] The estimated hazard ratio for relapse-free survival comparing the programmed cell death protein 1 antibody pembrolizumab with placebo was 0.57, and for the targeted therapy (with the combination of dabrafenib and trametinib) with placebo was 0.47. Both therapies were approved for adjuvant treatment in the United States, Europe, and many other countries.[28,29] The estimated hazard ratios for distant-metastasis–free survival were generally in the same range as for relapse-free survival. At

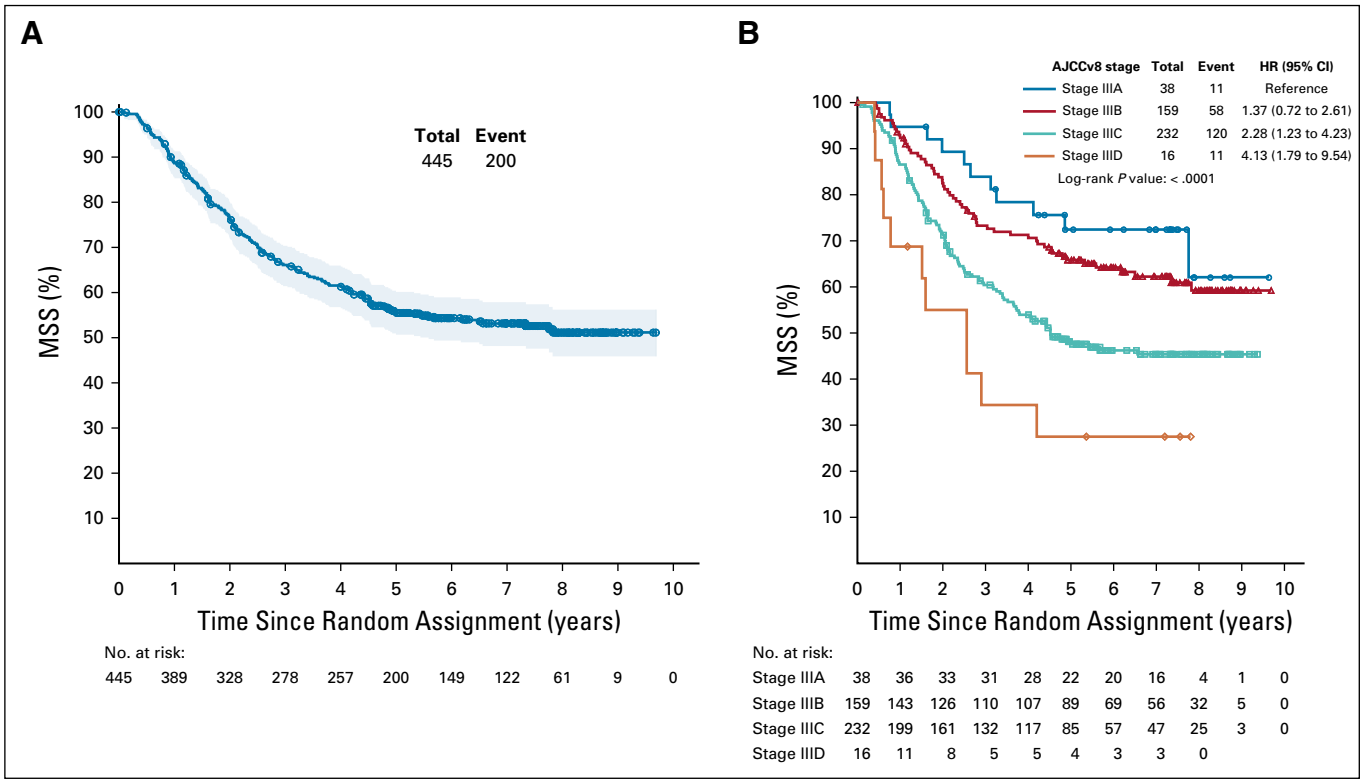

FIG 3. Kaplan-Meier curves for melanoma-specific survival (MSS) in European Organisation for Research and Treatment of Cancer cohort 18071, placebo group. (A) In all stage III patients. (B) According to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

a median follow-up of 2.8 years, the combined treatment with dabrafenib and trametinib showed promising results regarding OS (estimated hazard ratio, 0.57), but more mature follow-up results are required to draw conclusions.[29] Overall, there is no other cancer for which such effective adjuvant therapies are available.

The survival curves generated from the IMDDP database leading to the AJCC classification have a great impact on the clinical management of patients with melanoma.[20,30] They are used for patient information, risk calculation, and decision making, including risk-benefit evaluations of therapeutic measures (eg, adjuvant therapies). Furthermore, the AJCC survival estimates are of great value because they are used for sample size calculations in the planning of clinical studies. Survival curves are critically dependent on the completeness and length of the follow-up of all patients. Therefore, loss of follow-up is a critical quality parameter that is not reported in the IMDDP publication.

Interesting in this context is the comparison of the MSS rates of the entire stage III patients from the AJCCv7 and AJCCv8 publications. Despite the fact that the definitions of the entire stage III remained unchanged between AJCCv7 and AJCCv8, a large difference was observed regarding MSS between these 2 versions. For stage III, the 5-year MSS rates were 60% for AJCCv7 and 77% for AJCCv8, and the 10-year MSS rates were 45% for AJCCv7 and 69% for AJCCv8 (Appendix Fig A4, online only). These differences in MSS cannot be explained by any therapeutic progress.

How could these apparently favorable survival data in the IMPDD cohort come into existence? The most likely explanation is an underreporting of melanoma-related deaths. The IMDDP database consists of a total of 10 clinical registry data sets going back to 1998, collected in different centers, under different national and cultural conditions, which also implicates different follow-up schedules. In such data sets, the recording of deaths is a critical matter, because many patients do not die in hospitals. For future evaluations of relevant survival data, not only MSS should be calculated, but also OS, which includes all different causes of death. If there are significant differences between the 2 curves, it is likely that melanoma-specific deaths have been under-recorded.

The databases of the CMMR and of the EORTC studies were created using a prospective data collection. The clinical trials are particularly carefully controlled for deaths. The CMMR also systematically identifies deaths by asking residents' registration offices. In this respect, a high quality of the evaluated data can be assumed.

One disadvantage of these databases is that they do not contain population-related data, but this is also the case for

the IMDDP data set used for the AJCCv8 classification of melanoma. Regarding the EORTC data, 1 limitation is that there was a trial-specific selection; however, this probably excluded only a small proportion of patients. In the EORTC 18071 study, stage IIIA patients with a more favorable prognosis (1-3 micrometastases, ≤ 1 mm in the greatest diameter) were excluded, which may explain in part the less favorable prognosis of this collective in comparison with the CMMR data.

In conclusion, the data presented here may indicate that MSS in stage III according to the AJCCv8 classification of melanoma is less favorable than that published for the IMDDP cohort. This is particularly true for stages IIIA and IIIB.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prognosis of Patients With Stage III Melanoma According to American Joint Committee on Cancer Version 8: A Reassessment on the Basis of 3 Independent Stage III Melanoma Cohorts

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APPENDIX

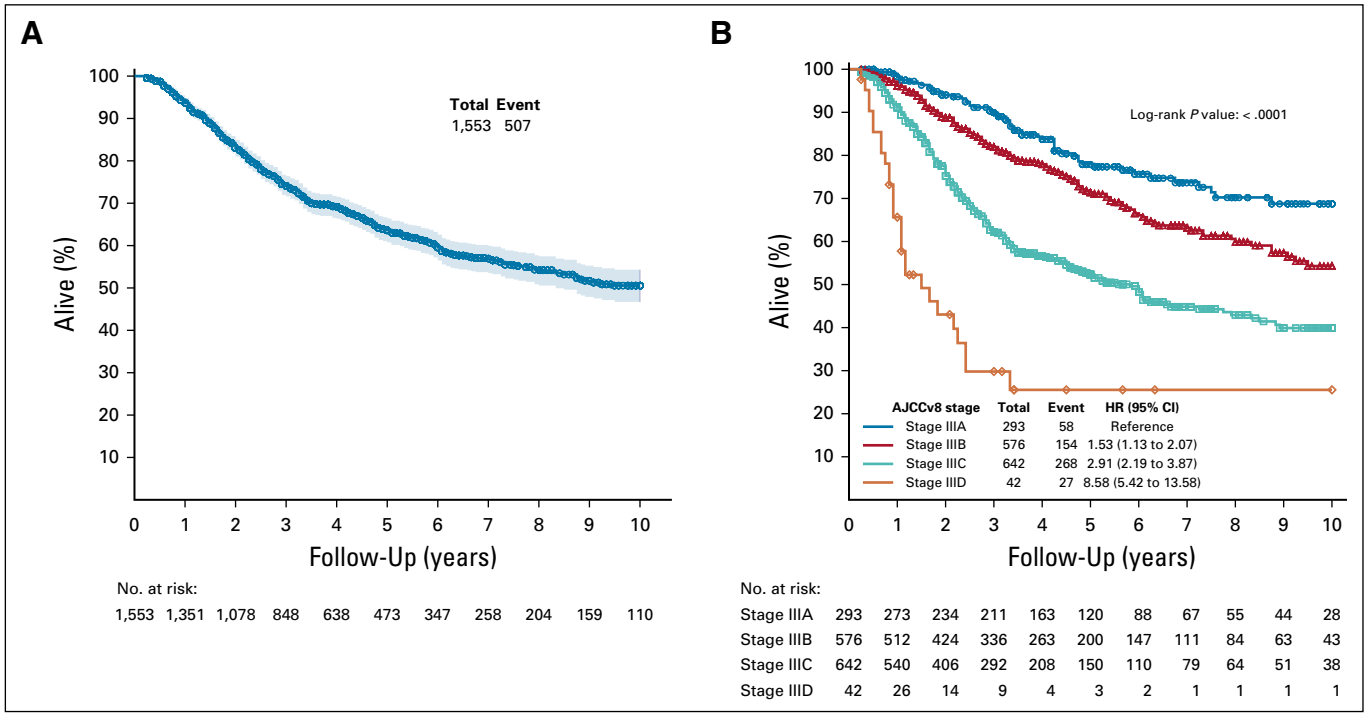

FIG A1. Kaplan-Meier curves for overall survival in the Central Malignant Melanoma Registry cohort. (A) In all stage III patients. (B) According to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

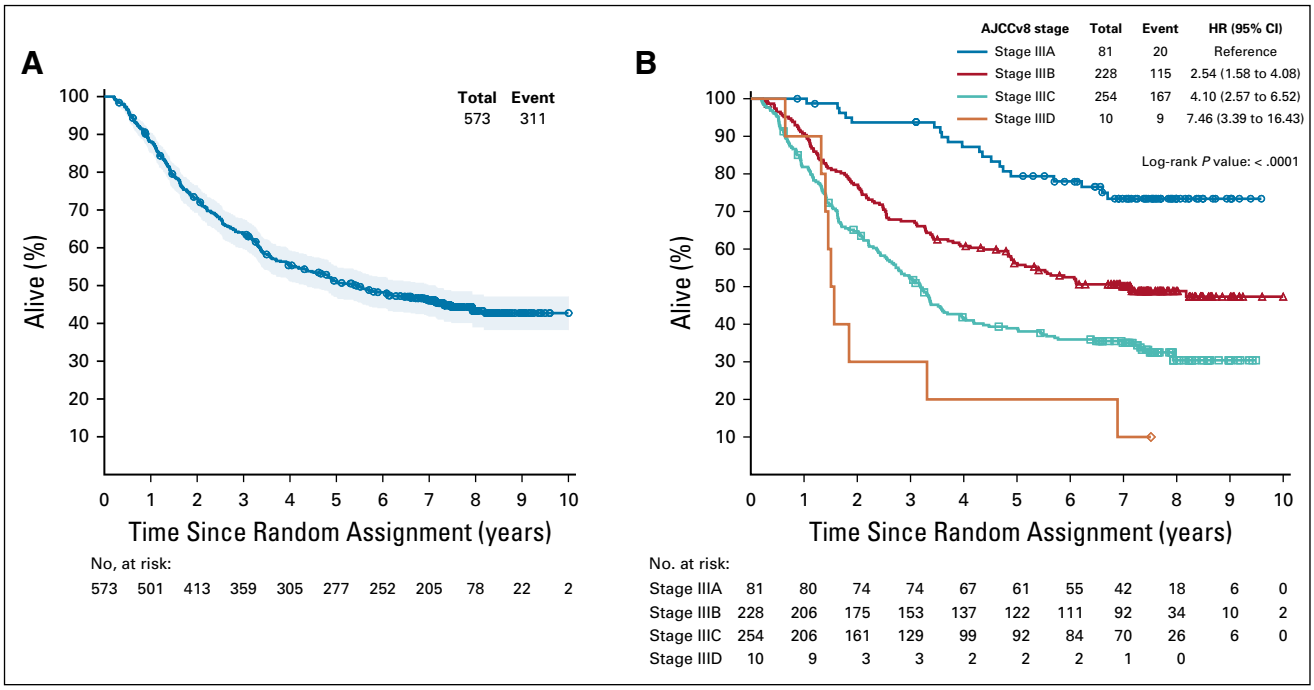

FIG A2. Kaplan-Meier curves for overall survival in the European Organisation for Research and Treatment of Cancer cohort 18991, observation group. (A) In all stage III patients. (B) According to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

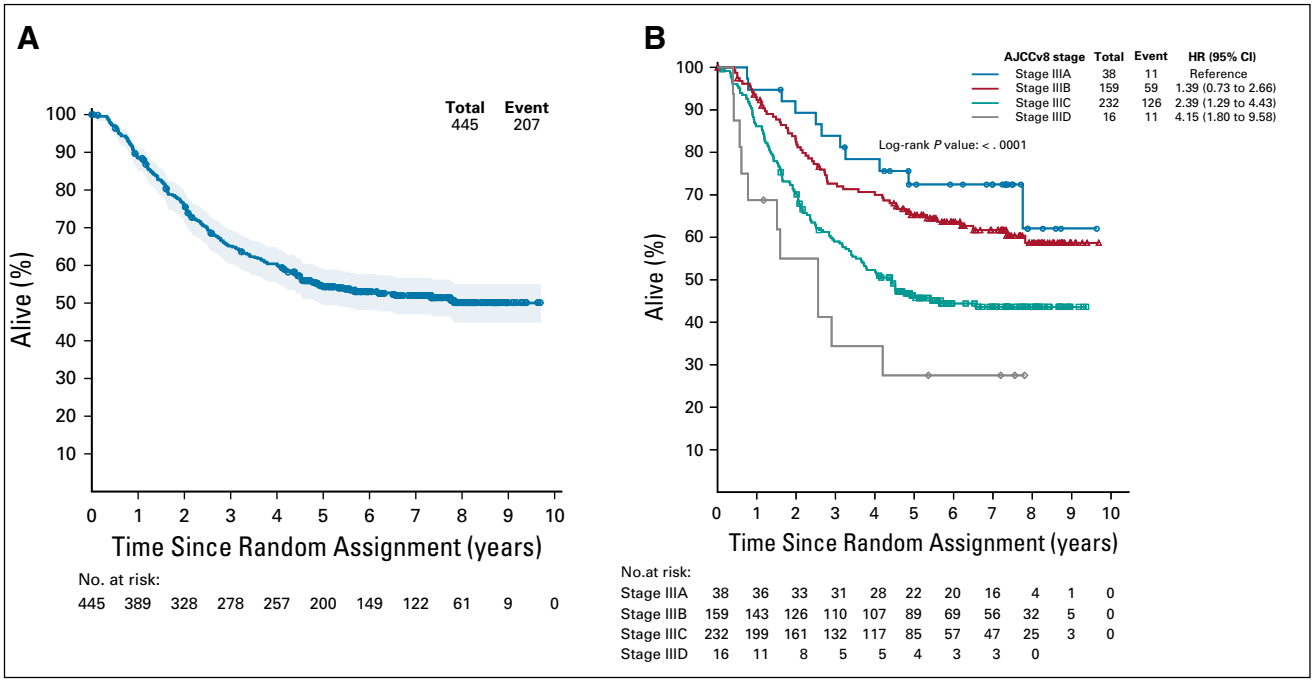

FIG A3. Kaplan-Meier curves for overall survival in the European Organisation for Research and Treatment of Cancer cohort 18071, placebo group. (A) In all stage III patients. (B) according to American Joint Committee on Cancer version 8 (AJCCv8) classification: stage IIIA, IIIB, IIIC, and IIID. HR, hazard ratio.

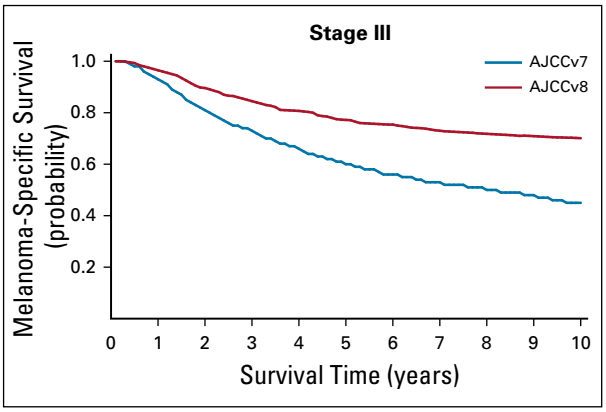

FIG A4. Reconstructed melanoma-specific survival curves for patients staged according to American Joint Committee on Cancer version 7 (AJCCv7) and American Joint Committee on Cancer version 8 (AJCCv8) for all stage III patients.

TABLE A1. Estimated OS Rates at 5, 7, and 10 Years of CMMR Database and EORTC 18991 and EORTC 18071 Trials in Patients With Stage III Melanoma According to AJCCv8 Classification

	OS Rate (SE%)		
OS	CMMR (2000-2012; n = 1,553)	EORTC 18991, Observation Group (n = 573)	EORTC 18071, Placebo Group (n = 445)
All stage III patients			
5 year	63.7 (1.4)	51.2 (2.1)	54.3 (2.4)
7 year	56.8 (1.6)	46.0 (2.1)	52.0 (2.5)
10 year	50.6 (1.9)	—	—
Stage IIIA			
5 year	78.0 (2.9)	79.4 (4.6)	72.5 (7.5)
7 year	73.8 (3.3)	73.4 (5.1)	72.5 (7.5)
10 year	68.8 (3.9)	—	—
Stage IIIB			
5 year	71.4 (2.3)	56.2 (3.3)	65.3 (3.9)
7 year	63.1 (2.7)	50.1 (3.4)	61.7 (4.0)
10 year	54.3 (3.4)	—	—
Stage IIIC			
5 year	52.3 (2.3)	38.9 (3.1)	45.7 (3.3)
7 year	44.9 (2.6)	35.0 (3.1)	43.6 (3.4)
10 year	39.9 (2.9)	—	—
Stage IIID			
5 year	25.5 (7.8)	20.0 (12.7)	27.5 (11.6)
7 year	25.5 (7.8)	10.0 (9.5)	27.5 (11.6)
10 year	25.5 (7.8)	—	—

Abbreviations: AJCCv8, American Joint Committee on Cancer version 8; CMMR Central Malignant Melanoma Registry; EORTC European Organisation for Research and Treatment of Cancer; OS, overall survival; SE%, standard error in %.

TABLE A2. Estimated Cumulative Incidence of Death as a Result of Melanoma and as a Result of Another Cause at 5, 7, and 10 Years for the CMMR Database and EORTC 18991 and EORTC 18071 Trials in Patients With Stage III Melanoma

Cause of Death	Death Rate (95% CI)		
	CMMR (2000-2012; n = 1,553)	EORTC 18991, Observation Group (n = 573)	EORTC 18071, Placebo Group (n = 445)
Death as a result of melanoma			
All stage III patients			
5 year	32.2 (29.4 to 34.9)	46.8 (42.6 to 50.9)	44.1 (39.3 to 48.7)
7 year	37.6 (34.5 to 40.7)	51.7 (47.4 to 55.7)	46.4 (41.5 to 51.2)
10 year	42.7 (39.0 to 46.3)	—	—
Stage IIIA			
5 year	19.6 (14.5 to 25.3)	19.4 (11.4 to 28.9)	27.5 (14.1 to 42.8)
7 year	23.8 (17.8 to 30.3)	25.4 (16.1 to 35.7)	27.5 (14.1 to 42.8)
10 year	28.8 (21.5 to 36.6)	—	—
Stage IIIB			
5 year	25.0 (20.8 to 29.3)	43.8 (37.2 to 50.1)	34.1 (26.6 to 41.6)
7 year	30.3 (25.4 to 35.3)	49.5 (42.7 to 55.8)	37.7 (29.7 to 45.5)
10 year	37.7 (31.3 to 44.1)	—	—
Death as a result of another cause			
All stage III patients			
5 year	4.2 (3.2 to 5.4)	2.0 (1.0 to 3.4)	1.6 (0.7 to 3.2)
7 year	5.6 (4.3 to 7.2)	2.3 (1.3 to 3.9)	1.6 (0.7 to 3.2)
10 year	6.8 (5.1 to 8.7)	—	—

Abbreviations: CMMR, Central Malignant Melanoma Registry; EORTC, European Organisation for Research and Treatment of Cancer.