original reports

Prognosis of Patients With Primary Melanoma Stage I and II According to American Joint Committee on Cancer Version 8 Validated in Two Independent Cohorts: Implications for Adjuvant Treatment

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abstract

PURPOSE The first randomized trial of adjuvant treatment with checkpoint inhibitor in stage II melanoma reported a significant reduction in risk of tumor recurrence. This study evaluates two independent data sets to further document survival probabilities for patients with primary stage I and II melanoma.

PATIENTS AND METHODS The Central Malignant Melanoma Registry (CMMR) in Germany evaluated 17,544 patients with a primary diagnosis of stage I and II melanoma from 2000 to 2015. The exploratory cohort consisted of 6,725 patients from the Center for Dermato-Oncology at the University of Tübingen, and the confirmatory cohort consisted of 10,819 patients from 11 other German centers. Survival outcomes were compared with published American Joint Committee on Cancer version 8 (AJCCv8) stage I and II survival data.

RESULTS For the two CMMR cohorts in stage IA compared with the AJCCv8 cohort, melanoma-specific survival rates at 10 years were 95.1%-95.6% versus 98%; 89.7%-90.9% versus 94% in stage IB; 80.7%-83.1% versus 88% in stage IIA; 72.0%-79.9% versus 82% in stage IIB; and 57.6%-64.7% versus 75% in stage IIC, respectively. Recurrence rates were approximately twice as high as melanoma-specific mortality rates in stages IA-IIA.

CONCLUSION The melanoma-specific survival rates in the two CMMR cohorts across stages I and II are less favorable than published in AJCCv8. This has important implications for the consideration of adjuvant treatment in this population.

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INTRODUCTION

In Western White populations, the incidence of cutaneous melanoma has been steadily increasing for decades, from approximately one case per 100,000 inhabitants/year in the 1950s to 30-50 cases today.[1] Ninety percent to 95% of this increase is due to UV exposure.[2] In recent decades, thin melanomas with tumor thickness up to 1 mm have been detected with increasing frequency at initial diagnosis.[3,4] In Western European countries and the United States, 60%-70% of all newly diagnosed melanomas now have a tumor thickness ≤ 1 mm.[5,6] There is no tumor thickness threshold at which metastasis cannot occur. Since the proportion of thin melanomas is very large, more patients die today from T1 tumors than from T4 tumors in absolute numbers.[7,8]

Systemic therapies with targeted *BRAF* and *MEK* inhibitors and with immune checkpoint inhibitors have significantly improved the treatment of melanoma. These drugs were initially used in the treatment of patients with distant metastatic or unresectable regional melanoma (stages III-IV) leading to 5-year survival rates between 30% and 50%. In adjuvant therapy, these new drugs have now been approved for resectable stage III melanoma.[9] In the three landmark stage III trials, adjuvant therapy with nivolumab or pembrolizumab, and in *BRAF*-mutant melanomas with the combination of dabrafenib plus trametinib, showed a reduction in the hazard ratio (HR) for recurrence to approximately 0.5 to approximately 0.6 in comparison to placebo in all trials.[10-12] Currently, large prospective randomized trials are underway testing

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

To reassess whether the prognosis of patients with stage I and II melanoma, particularly IB and IIA, are really as favorable as reported in the American Joint Committee on Cancer classification version 8 (AJCCv8)?

Knowledge Generated

In two independent cohorts of patients with stage I and II disease in the German Central Malignant Melanoma Registry, we found significantly less favorable survival probabilities than those published in the AJCCv8 classification. Melanoma-specific 10-year survival rates were 89.7%-90.9% in stage IB, instead of 94% according to AJCCv8, and 80.7%-83.1% in stage IIA, instead of 88% according to AJCCv8. Similar differences were found for the other substages.

Relevance

The difference shown here should be considered in clinical decision making such as the indication for adjuvant therapy and in the design of clinical trials.

adjuvant therapy for stage IIB and IIC melanoma, and in the first adjuvant trial of pembrolizumab versus placebo recently reported, the HR for recurrence was 0.65 after 12 months and 0.61 after 18 months of follow-up, and this agent received US Food and Drug Administration (FDA) approval in December 2021.[13,14]

The TNM classification of solid tumors published by the American Joint Committee of Cancer (AJCC) and the Union for International Cancer Control is an essential tool for decision making and discussion with patients; currently, the AJCC version 8 (AJCCv8) classification is used around the world.[15] Primary melanomas are classified into four substages T1-T4 on the basis of tumor thickness and substaged on the presence of ulceration. On the basis of tumor thickness and ulceration, primary melanomas without nodal metastases are classified into five substages IA/B and IIA/B/C.

In the 2017 AJCCv8 classification publication, melanoma-specific survival (MSS) probabilities for stages IA-IIC were presented on the basis of a multicenter database from 10 international centers with more than 46,000 cases, designated as the International Melanoma Database and Discovery Platform (IMDDP).[15] Evaluation of three independent stage III melanoma cohorts revealed significantly less favorable survival rates than presented in the AJCCv8 publication,[16] and similar results were reported for a stage III melanoma patient cohort from Germany.[17,18]

To determine the prognosis of primary melanomas in stages I and II, data from the Central Malignant Melanoma Registry (CMMR) in Germany were evaluated in this study, which were not part of the AJCC multicenter database. Patients were included with first diagnosis from 2000 to 2015 and melanoma stages IA-IIC. Melanoma patients with stages IB-IIC were only eligible if they had undergone a sentinel lymph node biopsy (SLNB). Two independent cohorts were evaluated. First, an exploratory data set was derived from the Center for Dermato-Oncology at the University Hospital Tübingen with more than 6,000 patients; subsequently, a confirmatory data set with more than 10,000 patients originating from 11 selected German university hospitals that had documented follow-up for more than 90% of patients. For these two cohorts, not only MSS but also recurrence-free survival (RFS) and overall survival (OS) were assessed. The survival probabilities were compared with MSS data from the AJCCv8 publication. In addition, the number needed to treat (NNT) to prevent a recurrence was modeled separately for each substage to provide a basis for discussion on adjuvant treatment.

PATIENTS AND METHODS

Exploratory and Confirmatory Cohort

Between January 2000 and December 2015, 79,425 patients with melanoma were documented in the CMMR. Seventeen thousand five hundred forty-four patients with invasive cutaneous melanoma with stage IA-IIC (according to AJCCv8) at primary diagnosis were included in the present analysis. Six thousand seven hundred twenty-five patients were sourced from the CMMR database of Tübingen, which served as an exploratory cohort. The remaining sample of 10,819 patients derived from 11 selected German dermato-oncology centers documented into the CMMR were used as a confirmatory cohort.

Outcomes

The outcomes of interest were MSS, OS, and RFS. Survival was defined as the time between date of diagnosis of the primary melanoma and the date of first recurrence (RFS), date of death from melanoma (MSS), or date of death from any cause (OS); the follow-up of patients still alive was censored at the last date known to be alive.

Statistical Analyses

The Kaplan-Meier method was used to estimate MSS, OS, and RFS. Differences between the substages were assessed by means of the log-rank test. Estimated survival

TABLE 1. Clinical and Histopathologic Characteristics of the CMMR Exploratory and Confirmatory Cohorts of Patients With Stage I and II Melanoma

Patient and Tumor Characteristics, Follow-Up	CMMR Exploratory Cohort (2000-2015), N = 6,725 (%)	CMMR Confirmatory Cohort (2000-2015), N = 10,819 (%)
Sex		
Male	3,412 (50.7)	5,362 (49.6)
Female	3,313 (49.3)	5,457 (50.4)
Age, years		
Median (IQR)	57.0 (45.0-68.0)	59.0 (45.0-69.0)
≤ 50	2,453 (36.5)	3,645 (33.7)
51-70	2,920 (43.4)	4,905 (45.3)
> 70	1,352 (20.1)	2,269 (21.0)
Breslow thickness, mm		
Median (IQR)	0.75 (0.42-1.47)	0.7 (0.4-1.24)
< 0.8	3,463 (51.5)	5,875 (54.3)
≥ 0.8 to 1	787 (11.7)	1,616 (14.9)
> 1 to 2	1,377 (20.5)	1,791 (16.6)
> 2 to 4	779 (11.6)	1,069 (9.9)
> 4	319 (4.7)	468 (4.3)
Ulceration		
Yes	788 (11.7)	1,007 (9.3)
No	5,157 (76.7)	8,708 (80.5)
Not known	780 (11.6)	1,104 (10.2)
Stage (AJCCv8)		
Stage IA	4,250 (63.2)	7,491 (69.2)
Stage IB	1,152 (17.1)	1,550 (14.3)
Stage IIA	714 (10.6)	940 (8.7)
Stage IIB	436 (6.5)	580 (5.4)
Stage IIC	173 (2.6)	258 (2.4)
Survival status		
Alive	6,022 (89.5)	10,142 (93.7)
Dead	703 (10.5)	677 (6.3)
Melanoma	467(66.4)	300 (44.3)
Other cause	236 (33.6)	377 (55.7)
Recurrence		
Yes	930 (13.8)	930 (8.6)
No	5,795 (86.2)	9,889 (91.4)
Follow-up, months		
Median (IQR)	72.0 (44.0-112.0)	37.0 (17.0-63.0)

Abbreviations: AJCCv8, American Joint Committee on Cancer version 8; CMMR, Central Malignant Melanoma Registry; IQR, interquartile range.

rates were expressed as percentages with 95% CIs. Cumulative incidences of death resulting from melanoma and from other causes were estimated using competing risk methods.

To discuss the indication for adjuvant therapies, we calculated the NNT to prevent a recurrence. On the basis of HRs published in adjuvant therapy trials in patients with stage III and stage II melanoma, we derived absolute risk reduction estimates. The absolute risk reduction is the product of the event rate and 1 – HR. The NNTs were then calculated according to the following formula:

$$\mathrm{ARR} = \mathrm{ER} \times (1 - \mathrm{HR}),$$

$$\mathrm{NNT} = 1/\mathrm{ARR}.$$

All statistical tests were two-sided, with a P value $< .05$ considered statistically significant. Statistical calculations were performed with IBM SPSS Statistics Version 27.0 (IBM SPSS, Chicago, IL) and STATA Version 15 statistical software (StataCorp LLC, College Station, TX).

RESULTS

Patient Characteristics

The clinical and histopathologic characteristics are summarized in Table 1. Two independent cohorts of the CMMR database are the exploratory cohort with 6,725 patients and the confirmatory cohort of 10,819 patients. Median patient age at diagnosis was 57 years (interquartile range [IQR], 45.0-68.0 years) for the exploratory cohort and 59 years (IQR, 45.0-69.0 years) for the confirmatory cohort. Median tumor thickness was 0.75 mm and 0.7 mm, 11.7% and 9.3% of the melanomas were ulcerated, and 20% and 16.5% of the patients were classified into tumor stage II.

At a median follow-up of 72 months (IQR, 44.0-112.0 months), 703 (10.5%) patients in the exploratory cohort had died, 467 (66.4%) of those due to melanoma and 236 (33.6%) of other causes. Recurrences occurred in 930 (13.8%) patients. In the confirmatory cohort, median follow-up was 37 months (IQR, 17.0-63.0 months) and 677 (6.3%) patients had died. Three hundred deaths (44.3%) were melanoma-specific and 377 (55.7%) due to other causes. Recurrences were noted in 930 (8.6%) patients.

Survival Analysis

We compared the MSS rates for both cohorts with data from the IMDDP analysis (Table 2). Overall, the stage-specific MSS probabilities calculated for the CMMR cohorts were less favorable than those of the IMDDP cohort.

In the IMDDP cohort, the 5- and 10-year stage-specific MSS were 99% and 98% in stage IA, and 97% and 94% in stage IB (Table 2). The 5- and 10-year stage-specific MSS rates for the exploratory cohort were 98.4% and 95.1% in stage IA, and 96% and 90.9% in stage IB. Corresponding 5- and 10-year MSS in the confirmatory cohort were 98.5% and 95.6% in stage IA, and 96.1% and 89.7% in stage IB (Table 2 and Figs 1A and 1B). For both cohorts, the 10-year cumulative incidence of death caused by melanoma was about 10% (8.9%-10%) in stage IB and is therefore almost twice as high as in the IMDDP collective (6%; Appendix Table A1, online only).

TABLE 2. Estimated MSS Rates at 5 and 10 Years in the IMDDP Cohort, the CMMR Exploratory Cohort, and the CMMR Confirmatory Cohort for Patients With Stage I and II Melanoma According to the American Joint Committee on Cancer Version 8 Subgroups

MSS	IMDDP (since 1998), N = 15,691	CMMR Exploratory Cohort (2000-2015), N = 6,725	CMMR Confirmatory Cohort (2000-2015), N = 10,819
Stage IA			
5-year rate (95% CI)	99.0 (NA)	98.4 (98.0 to 98.8)	98.5 (98.1 to 98.9)
10-year rate (95% CI)	98.0 (NA)	95.1 (94.1 to 96.1)	95.6 (94.2 to 97.0)
Stage IB			
5-year rate (95% CI)	97.0 (NA)	96.0 (94.8 to 97.2)	96.1 (94.9 to 97.3)
10-year rate (95% CI)	94.0 (NA)	90.9 (88.7 to 93.1)	89.7 (86.4 to 93.0)
Stage IIA			
5-year rate (95% CI)	94.0 (NA)	88.7 (86.2 to 91.2)	92.6 (90.4 to 94.8)
10-year rate (95% CI)	88.0 (NA)	80.7 (77.0 to 84.4)	83.1 (78.4 to 87.8)
Stage IIB			
5-year rate (95% CI)	87.0 (NA)	82.8 (78.9 to 86.7)	86.5 (82.6 to 90.4)
10-year rate (95% CI)	82.0 (NA)	72.0 (66.7 to 77.3)	79.9 (74.2 to 85.6)
Stage IIC			
5-year rate (95% CI)	82.0 (NA)	70.0 (62.6 to 77.4)	76.6 (68.8 to 84.4)
10-year rate (95% CI)	75 0 (NA)	57.6 (48.4 to 66.8)	64.7 (51.6 to 77.8)

Abbreviations: CMMR, Central Malignant Melanoma Registry; IMDDP, International Melanoma Database, and Discovery Platform; MSS, melanoma-specific survival; NA, not available.

Even larger divergence between the IMDDP cohort and the CMMR cohorts became visible in patients with stage II melanoma. In the IMDDP cohort, the 5- and 10-year stage-specific MSS were 94% and 88% in stage IIA, 87% and 82% in stage IIB, and 82% and 75% in stage IIC, respectively (Table 2). The 5- and 10-year stage-specific MSS rates in the CMMR cohorts were systematically lower. For the exploratory cohort, the 5- and 10-year stage-specific MSS rates were 88.7% and 80.7% in stage IIA, 82.8% and 72% in stage IIB, and 70% and 57.6% in stage IIC, respectively. In the confirmatory cohort, corresponding 5- and 10-year stage-specific MSS rates were 92.6% and 83.1% in stage IIA, 86.5% and 79.9% in stage IIB, and 76.6% and 64.7% in stage IIC, respectively (Table 2, Figs 1A and 1B).

There are no data available for the OS and RFS rates from the IMDDP collective. The OS data from both CMMR cohorts are presented in Table 3 and shown in Figures 1C and 1D. OS survival rates are slightly less favorable than MSS survival rates.

The unfavorable prognosis for stage I and II patients with respect to the survival probability is even more evident in the RFS rates. In the exploratory cohort, the 10-year RFS was 90.7% for stage IA, 80.3% for stage IB, 64.1% for stage IIA, 55.8% for stage IIB, and 33.3% for stage IIC. Corresponding rates in the confirmatory cohort were 88.3% for stage IA, 78.6% for stage IB, 62% for stage IIA, 55.5% for stage IIB, and 49.3% for stage IIC (Table 4, Figs 1E and 1F).

DISCUSSION

Using two independent cohorts, the present analysis of survival probabilities for patients with primary melanoma shows that MSS is significantly less favorable than presented for the IMDDP AJCCv8 cohort as illustrated in Figure 2. This finding is particularly relevant to discussions and decision making with patients in stages IA, IB, and IIA regarding surveillance imaging and consideration for future adjuvant trial interventions.

The probability of dying from melanoma within 10 years is 2% in the IMDDP cohort versus 4%-5% in the CMMR cohorts for patients in stage IA, 6% in the IMDDP cohort versus 9%-10% in the CMMR cohorts for stage IB, and 12% in the IMDDP cohort versus 17%-19% in the CMMR cohorts for stage IIA.

In this context, the comparison of survival probabilities for primary melanomas in the AJCCv7 and AJCCv8 publications is particularly interesting.[15,20] The classifications differ only marginally for stages I-II from the AJCCv7 classification, where a mitotic rate of 1 per mm^2 or higher led to upstaging from IA to IB; in the AJCCv8 classification, this criterion for upstaging was omitted. The probability of dying from melanoma for stage IA within 10 years is 2% in the AJCCv8 cohort versus 8% in the AJCCv7 cohort, for stage IB 6% in the AJCCv8 cohort versus 20% in the AJCCv7 cohort, and for stage IIA 12% in the AJCCv8 cohort versus 28% in the AJCCv7 cohort. These differences are again much larger than those between the IMDDP cohort and the CMMR cohorts.

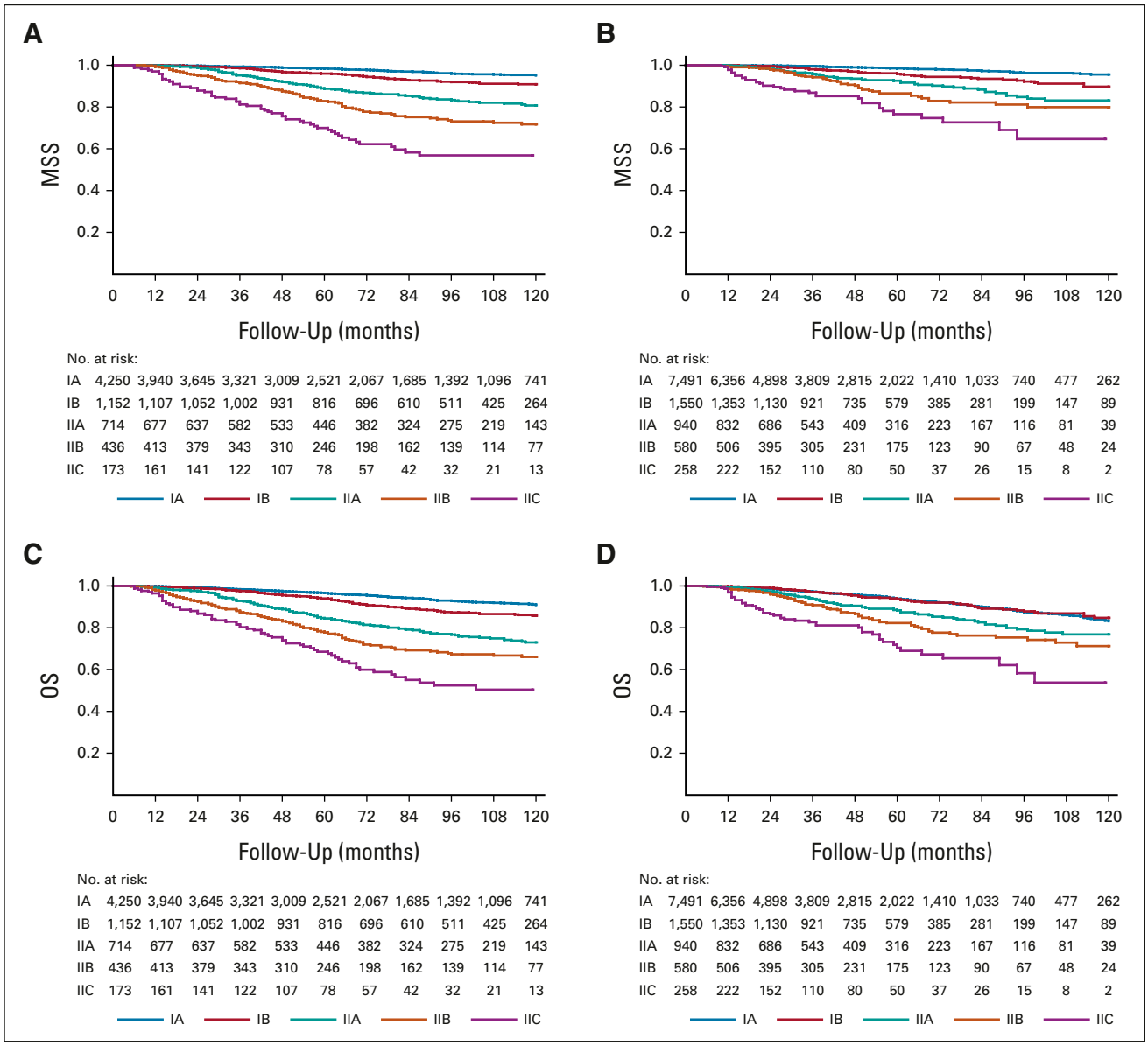

FIG 1. Survival rates and patient number at risk for stage I and II melanoma, according to American Joint Committee on Cancer version 8: (A) MSS, CMMR exploratory cohort; (B) MSS, CMMR confirmatory cohort; (C) OS, exploratory cohort; (D) OS, confirmatory cohort; (E) RFS, exploratory cohort; and (F) RFS, confirmatory cohort. CMMR, Central Malignant Melanoma Registry; MSS, melanoma-specific survival; OS, overall survival; RFS, recurrence-free survival. (continued on following page)

One possible reason for the differences in survival between AJCCv7 and AJCCv8 may be the introduction of SLNB, which was not yet fully established for the AJCCv7 cohort. However, this does not explain the large difference in stage IA, where SLNB would not have been performed. Overall, the differences in survival are probably less because of the composition of the cohorts in terms of prognostic factors than by differences in recording. Here, the median duration of follow-up plays a role that may be responsible for explaining the differences between the two CMMR cohorts (exploratory cohort 72 months *v* confirmatory cohort 37 months, not published for IMDDP). Furthermore, the recording of deaths from melanoma plays a role, and in this context, how unclear causes of death were handled. Here, some control can be achieved by comparing MSS with OS (not published for IMDDP), which should not differ too much. A larger discrepancy could be due to under-reporting of deaths from melanoma and may be recognized by the comparison to OS. Differences in center size/configuration may contribute to differences in the two data sets. Large expert centers often treat patients with high risk and less favorable prognosis. However, all CMMR and IMDDP centers are among the large expert centers.

Others have also reported lower stage II MSS probabilities than for the IMDDP cohort in the AJCCv8 publication. In a

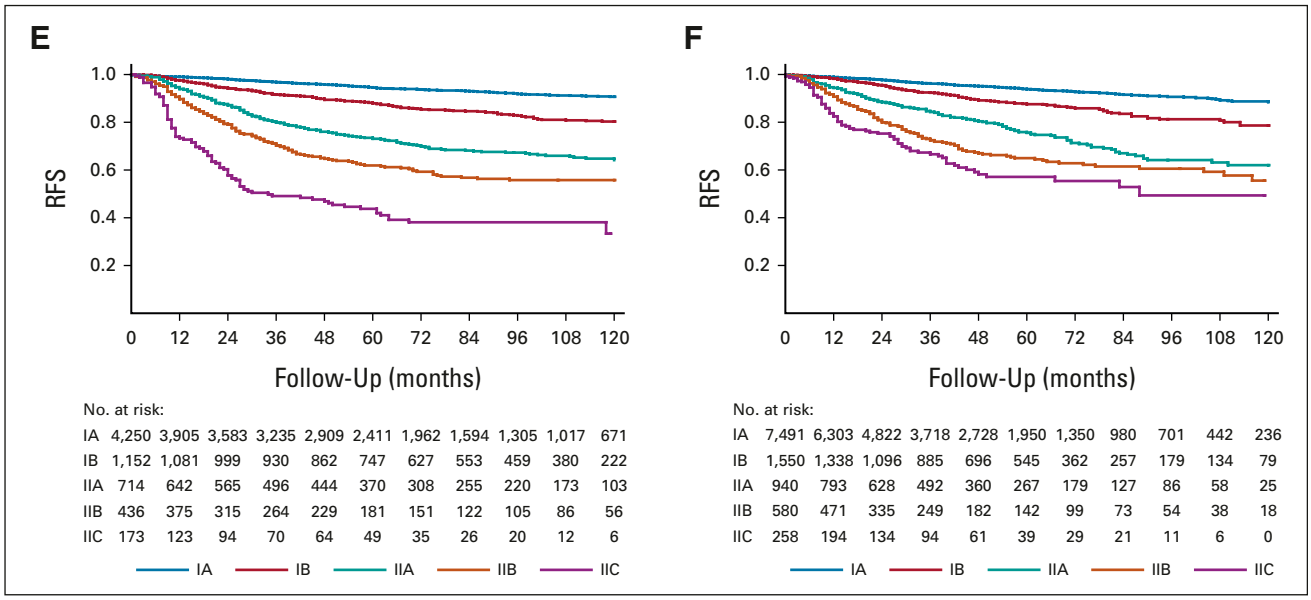

FIG 1. (Continued).

German cohort, 10-year MSS probabilities were found to be 64% in stage IIA (IMDDP: 88%), 51% in stage IIB (IMDDP: 82%), and 30% in stage IIC (IMDDP: 75%).[17] In a stage II cohort from the University of Utah Huntsman Cancer Institute, 10-year MSS probabilities were 80% in stage IIA, 70% in stage IIB, and 60% in stage IIC, also considerably lower than IMDDP survival rates.[21]

TABLE 3. OS Rates at 5 and 10 Years in the CMMR Exploratory Cohort and the CMMR Confirmatory Cohort for Patients With Stage I and II Melanoma According to the American Joint Committee on Cancer Version 8 Subgroups

OS	CMMR Exploratory Cohort, N = 6,725	CMMR Confirmatory Cohort, N = 10,819
Stage IA		
5-year rate (95% CI)	96.7 (96.1 to 97.3)	94.1 (93.3 to 94.9)
10-year rate (95% CI)	91.1 (89.7 to 92.5)	83.1 (80.7 to 85.5)
Stage IB		
5-year rate (95% CI)	94.0 (92.4 to 95.6)	94.0 (92.4 to 95.6)
10-year rate (95% CI)	85.8 (83.3 to 88.3)	84.8 (80.8 to 88.6)
Stage IIA		
5-year rate (95% CI)	84.4 (81.5 to 87.3)	88.3 (85.6 to 91.0)
10-year rate (95% CI)	73.9 (68.9 to 77.1)	76.8 (71.7 to 81.9)
Stage IIB		
5-year rate (95% CI)	77.7 (73.6 to 81.8)	82.3 (78.0 to 86.6)
10-year rate (95% CI)	66.0 (60.7 to 71.3)	71.2 (64.1 to 78.3)
Stage IIC		
5-year rate (95% CI)	68.5 (61.1 to 75.9)	70.4 (62.6 to 78.2)
10-year rate (95% CI)	50.4 (40.6 to 60.2)	53.7 (39.4 to 68.0)

Abbreviations: CMMR, Central Malignant Melanoma Registry; OS, overall survival.

Considering the large differences in prognosis in stage I and II in AJCCv7 and AJCCv8 classifications with very favorable prognosis in AJCCv8 classification, CMMR data also indicate less favorable survival probabilities and should be used for surveillance strategy and adjuvant clinical trial planning.

A substantial number of recurrences and melanoma-related deaths occur more than 5 years after initial surgery. In stage I patients, the risk of melanoma death is almost equally distributed in the first and second 5-year periods, whereas in stage II patients, significantly more die in the first 5-year period, but still a significant proportion die in the second 5-year period (Appendix Fig A1A, online only). These late recurrences and deaths should be considered in planning follow-up and surveillance strategies for patients with stage I and II melanoma. The hazard of dying from other causes than melanoma is equally manifest in stages I and II (Appendix Fig A1B).

An accurate estimation of MSS and RFS is important in discussing prognosis with patients, but critically, also in considering the risk-to-benefit ratio of adjuvant therapy in early-stage melanoma. In the Keynote-716 study (KN716), 17% of patients in the placebo arm experienced recurrences during the first year of follow-up. For the cohorts studied here, the recurrence rates in stages IIB and IIC were, respectively, 11% and 26% in the exploratory cohort and 10% and 20% in the confirmatory cohort, that is, in the same range as in the placebo arm of KN716. Half the RFS events in KN716 were local recurrences, and these can be treated surgically and then given adjuvant therapy; so, the link between RFS and OS is even less certain.

The European Society for Medical Oncology formulated in an expert meeting under the auspices of the European Society for Medical Oncology Guidelines Committee: an absolute survival

TABLE 4. RFS Rates at 5 and 10 Years in the CMMR Exploratory Cohort and the CMMR Confirmatory Cohort for Patients With Stage I and II Melanoma According to the American Joint Committee on Cancer Version 8 Subgroups

RFS	CMMR Exploratory Cohort, N = 6,725	CMMR Confirmatory Cohort, N = 10,819
Stage IA		
5-year rate (95% CI)	94.5 (93.7 to 95.3)	93.3 (93.1 to 94.7)
10-year rate (95% CI)	90.7 (89.5 to 91.9)	88.3 (86.5 to 90.1)
Stage IB		
5-year rate (95% CI)	87.9 (85.9 to 89.9)	87.6 (85.4 to 89.9)
10-year rate (95% CI)	80.3 (77.6 to 83.0)	78.6 (74.5 to 82.7)
Stage IIA		
5-year rate (95% CI)	73.1 (69.6 to 76.6)	75.6 (72.1 to 79.1)
10-year rate (95% CI)	64.1 (59.8 to 68.4)	62.0 (56.3 to 67.7)
Stage IIB		
5-year rate (95% CI)	61.9 (57.0 to 66.8)	65.0 (60.1 to 69.9)
10-year rate (95% CI)	55.8 (50.5 to 61.1)	55.5 (48.1 to 62.9)
Stage IIC		
5-year rate (95% CI)	43.7 (35.9 to 51.5)	57.1 (49.5 to 64.7)
10-year rate (95% CI)	33.3 (22.1 to 44.8)	49.3 (38.5 to 60.1)

Abbreviations: CMMR, Central Malignant Melanoma Registry; RFS, recurrence-free survival.

benefit of 5% at 5 years would be considered strong evidence to recommend adjuvant therapy in stage III melanoma.[22] Additionally, as half of all patients with primary melanoma are diagnosed under the age 60 years, the question of whether it would not be better to use the 10-year survival benefit arises, particularly for stage I melanoma.

For treatment decisions, RFS should be considered, as time without disease is highly valued by patients. RFS is accepted as a primary end point for adjuvant trials by regulatory agencies (FDA in the United States and in Europe the European Medicines Agency). RFS data are not available for the IMDDP cohort but were calculated in this study. The 10-year RFS in the CMMR cohorts was 88%-91% in stage IA, 79%-80% in stage IB, 62%-64% in stage IIA, 56% in stage IIB, and 33%-49% in stage IIC. In stages IA-IIA, almost twice as many recurrences occur as melanoma-specific deaths.

When considering who should be considered for adjuvant treatment, it is useful to know the NNT to avoid recurrence (Appendix Table A2, online only). For adjuvant interferon-alpha, the NNT was 13:1 for relapse-free survival (10-year survival rate, 30%; HR, 0.89).[23] Patient preference surveys showed that the majority of patients were willing to accept moderate toxicity lasting 1 year for a 5-year benefit in RFS of 4%. RFS ranks highly among patients.[24,25]

The NNT for stage IB and IIA can be modeled for the new adjuvant therapies if the previously observed HRs of 0.5 for stage III and 0.61 in stage IIB/C are taken as a basis. With a HR of 0.5-0.61, in stage IB, 10-13 patients would need to be treated to avoid one recurrence, and in stage IIA, 5-7 patients. These data suggest that stage IB and IIA should also be considered for adjuvant therapy clinical trials. Stages IIB/C account for 7.8%-9.1% of all primary melanomas in the two independent cohorts of CMMR, with a 10-year recurrence rate of 44%-67%. Stages IB/IIA make up a much larger proportion of patients with melanoma, accounting for 23%-27.7% of all primary melanomas, and with a 10-year recurrence rate of 20%-37%.

When considering adjuvant therapy, the potential toxicity of the treatment must also be considered, particularly if the risk of

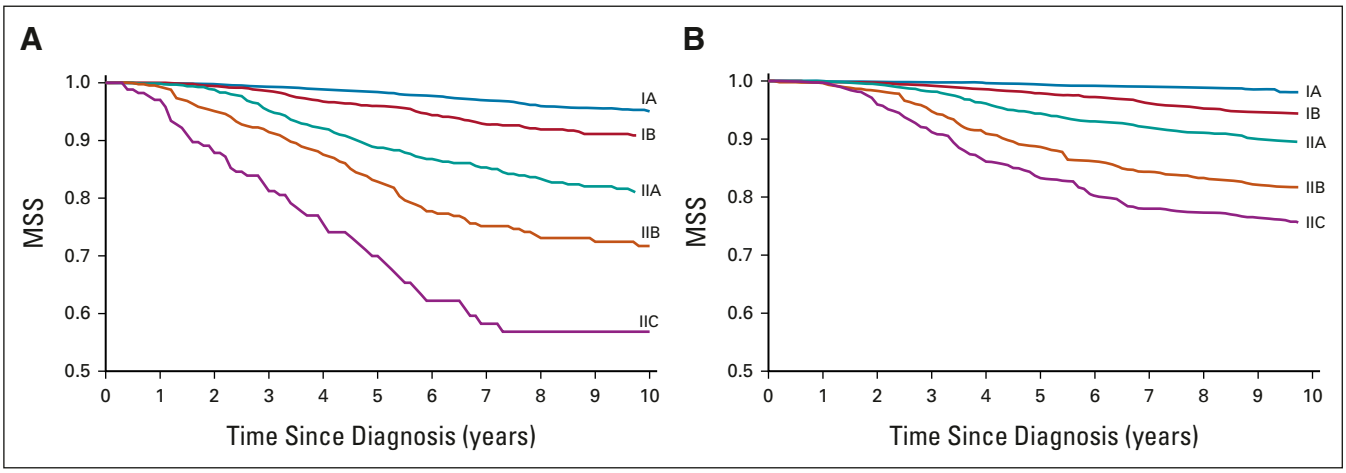

FIG 2. The MSS of patients with primary melanoma staged according to the AJCC classification version 8 was substantially lower in the CMMR in Germany compared with the IMDDP published with the AJCC classification version 8. Patients with stage IB and above are sentinel lymph node biopsy staged. Curves were generated using an interactive digitizing software program (DigitizeIt[19]) on the basis of the originals. (A) Patients in the exploratory cohort of the CMMR with first diagnosis in 2000-2015 (n = 6,725). (B) Patients in the IMDDP diagnosed since 1998 (n = 15,691). AJCC, American Joint Committee on Cancer; CMMR, Central Malignant Melanoma Registry; IMDDP, International Melanoma Database and Discovery Platform; MSS, melanoma-specific survival.

recurrence and mortality is relatively low. Within the pivotal European Organisation for Research and Treatment of Cancer 1325/Keynote 054 study, treatment-related toxicity of all grades was recorded in 77%-99% of patients, with grade 3 and 4 (G3/4) toxicities observed in approximately 15% of patients.[26] Lifelong substitution treatment may be needed in case of endocrine toxicities—hypothyroidism (0.8%-14.3%), hypophysitis (1.5%-2.2%), and type I diabetes (1.0%)—and these can potentially affect fertility and life expectancy. The rate and the type of toxicity do not differ between patients treated with adjuvant pembrolizumab in stage II and stage III.[10,14]

Emerging prognostic biomarkers may improve individual risk prediction in the near future. Gene expression profiling (GEP) involves analyzing the genetic features of a tumor at the transcriptional level.[27] The development and adoption of GEP assays for melanoma treatment is likely to improve the stratification of patients according to the risk of recurrence. Currently, there are a number of different GEP assays in development, although these are not validated as standard of care.[28]

A limitation of this study is that it deals with historical cohorts, a good part of which could not benefit from the new therapeutic options of targeted therapy or immune checkpoint inhibitor therapy at the onset of distant metastasis. Therefore, the survival prognosis of currently diagnosed patients might be better. Another limitation may be that selection bias cannot be reliably excluded for the cohorts studied. In the exploratory cohort, 66% of deaths were attributable to melanoma, whereas in the confirmatory cohort, only 44% were. A possible reason for this could be that in the region of Tübingen, many patients in early stages of melanoma are operated on in private offices and are not registered in the clinical center. So, a higher-risk population may have been recorded with more melanoma-attributable deaths here.

In conclusion, for patients with stage IIB/C melanoma, for whom the first new immunotherapy has been approved in the adjuvant setting, there are now additional RFS/OS/MSS data for stage IIB/IIC melanoma that allow us to refine the discussion about the implications of this new FDA approval for adjuvant pembrolizumab. However, patients with stage IB/IIA disease also have a significant risk of recurrence, and clinical trials of adjuvant therapy in this setting should be undertaken.

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REFERENCES

1. Garbe C, Keim U, Gandini S, et al: Epidemiology of cutaneous melanoma and keratinocyte cancer in white populations 1943-2036. Eur J Cancer 152:18-25, 2021
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3. Garbe C, Leiter U: Melanoma epidemiology and trends. Clin Dermatol 27:3-9, 2009
4. Leiter U, Keim U, Garbe C: Epidemiology of skin cancer: Update 2019. Adv Exp Med Biol 1268:123-139, 2020
5. Armstrong A, Powell C, Powell R, et al: Are we seeing the effects of public awareness campaigns? A 10-year analysis of Breslow thickness at presentation of malignant melanoma in the South West of England. J Plast Reconstr Aesthet Surg 67:324-330, 2014
6. van der Leest RJ, Zoutendijk J, Nijsten T, et al: Increasing time trends of thin melanomas in the Netherlands: What are the explanations of recent accelerations? Eur J Cancer 51:2833-2841, 2015
7. Claeson M, Baade P, Marchetti M, et al: Comparative performance of predictors of death from thin (≤ 1.0 mm) melanoma. Br J Dermatol 185:849-851, 2021
8. Whiteman DC, Baade PD, Olsen CM: More people die from thin melanomas (≤1 mm) than from thick melanomas (>4 mm) in Queensland, Australia. J Invest Dermatol 135:1190-1193, 2015
9. Curti BD, Faries MB: Recent advances in the treatment of melanoma. N Engl J Med 384:2229-2240, 2021
10. Eggermont AMM, Blank CU, Mandala M, et al: Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 378:1789-1801, 2018
11. Long GV, Hauschild A, Santinami M, et al: Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 377:1813-1823, 2017
12. Weber J, Mandala M, Del Vecchio M, et al: Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 377:1824-1835, 2017
13. Luke JJ, Ascierto PA, Carlino MS, et al: KEYNOTE-716: Phase III study of adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma. Future Oncol 16:4429-4438, 2020
14. Luke JJ, Rutkowski P, Queirolo P, et al: Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Ann Oncol 32:S1283-S1346, 2021
15. Gershenwald JE, Scolyer RA, Hess KR, et al: Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 67:472-492, 2017
16. Garbe C, Keim U, Suciu S, et al: 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. J Clin Oncol 38:2543-2551, 2020
17. Kanaki T, Stang A, Gutzmer R, et al: Impact of American Joint Committee on Cancer 8th edition classification on staging and survival of patients with melanoma. Eur J Cancer 119:18-29, 2019
18. Isaksson K, Katsarelias D, Mikiver R, et al: A population-based comparison of the AJCC 7th and AJCC 8th editions for patients diagnosed with stage III cutaneous malignant melanoma in Sweden. Ann Surg Oncol 26:2839-2845, 2019
19. DigitizeIt. http://www.DigitizeIt.de/
20. Balch CM, Gershenwald JE, Soong SJ, et al: Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27:6199-6206, 2009
21. Bleicher J, Swords DS, Mali ME, et al: Recurrence patterns in patients with stage II melanoma: The evolving role of routine imaging for surveillance. J Surg Oncol 122:1770-1777, 2020
22. Michielin O, van Akkooi A, Lorigan P, et al: ESMO consensus conference recommendations on the management of locoregional melanoma: Under the auspices of the ESMO Guidelines Committee. Ann Oncol 31:1449-1461, 2020
23. Suciu S, Eggermont AMM, Lorigan P, et al: Relapse-free survival as a surrogate for overall survival in the evaluation of stage II-III melanoma adjuvant therapy. J Natl Cancer Inst 110, 2018
24. Kilbridge KL, Weeks JC, Sober AJ, et al: Patient preferences for adjuvant interferon alfa-2b treatment. J Clin Oncol 19:812-823, 2001
25. Schadendorf D, Hauschild A, Santinami M, et al: Patient-reported outcomes in patients with resected, high-risk melanoma with BRAF(V600E) or BRAF(V600K) mutations treated with adjuvant dabrafenib plus trametinib (COMBI-AD): A randomised, placebo-controlled, phase 3 trial. Lancet Oncol 20:701-710, 2019
26. Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378:158-168, 2018
27. Bollard SM, Casalou C, Potter SM: Gene expression profiling in melanoma: A view from the clinic. Cancer Treat Res Commun 29:100447, 2021
28. Grossman D, Okwundu N, Bartlett EK, et al: Prognostic gene expression profiling in cutaneous melanoma: Identifying the knowledge gaps and assessing the clinical benefit. JAMA Dermatol 156:1004-1011, 2020

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Prognosis of Patients With Primary Melanoma Stage I and II According to American Joint Committee on Cancer Version 8 Validated in Two Independent Cohorts: Implications for Adjuvant Treatment

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APPENDIX

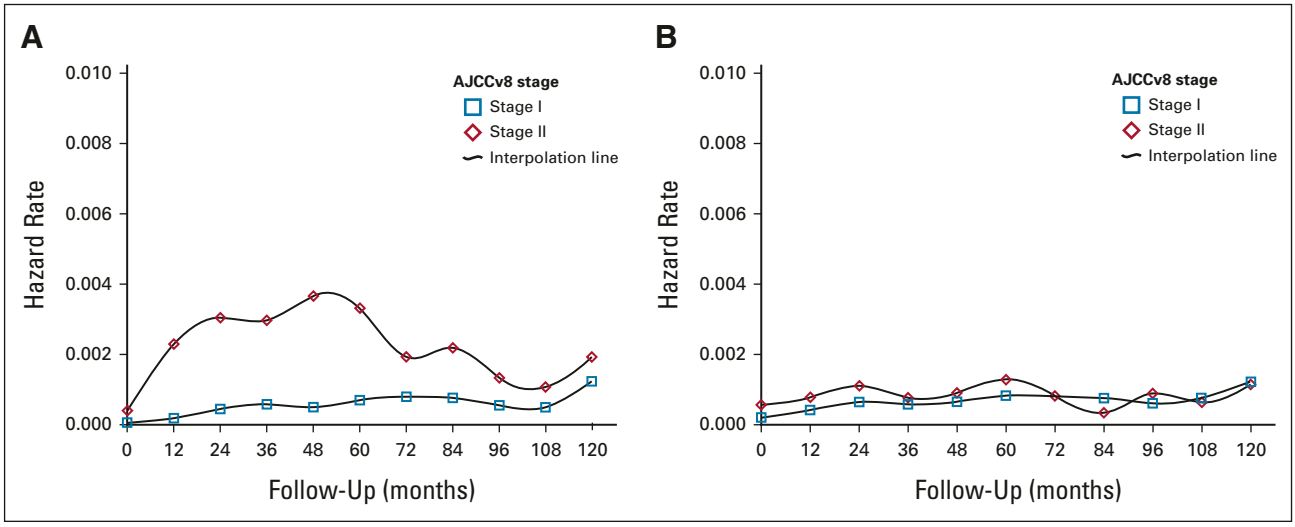

FIG A1. Hazard rates for stage I and II melanoma, according to AJCCv8 for total collective (N = 17,544): (A) death due to melanoma and (B) death due to other causes. AJCCv8, American Joint Committee on Cancer version 8.

TABLE A1. Melanoma-Specific Death/Recurrence Rate and NNT to Avoid One Event Within 10 Years in Patients With Stage I and II Melanoma (Central Malignant Melanoma Registry data: exploratory plus confirmatory cohort, N = 17,544)

	Melanoma-Specific Death		Recurrence	
AJCCv8 Substages	Rate, %	NNT HR 0.5/HR 0.75[a]	Rate, %	NNT HR 0.5/HR 0.75[a]
IA	5	40/80	10	20/40
IB	10	20/40	20	10/20
IIA	18	11/22	37	6/11
IIB	24	8/17	44	5/9
IIC	38	6/11	59	4/7

Abbreviations: AJCCv8, American Joint Committee on Cancer version 8; HR, hazard ratio; NNT, number of patients needed to treat to avoid one event (melanoma-specific death or recurrence); RFS, recurrence-free survival.

[a]Three independent phase III studies in stage III determined a HR of approximately 0.5 for RFS with adjuvant therapy with immune checkpoint inhibitors and with targeted therapy, respectively.[10-12] In stage II, one study determined a HR 0.61 for RFS with adjuvant therapy with pembrolizumab.[13,14] For the NNT calculations, the range of HR 0.5-0.75 was chosen.

TABLE A2. Estimated Cumulative Incidence of Death as a Result of Melanoma and as a Result of Another Cause at 5 and 10 Years in the CMMR Exploratory Cohort and the CMMR Confirmatory Cohort for Patients With Stage I and II Melanoma According to the American Joint Committee on Cancer Version 8 Subgroups

	Death Rate (95% CI)	
Cause of Death	**CMMR Exploratory Cohort, N = 6,725**	**CMMR Confirmatory Cohort, N = 10,819**
Death due to melanoma		
Stage IA		
5-year	1.7 (1.3 to 2.2)	1.4 (1.1 to 1.9)
10-year	4.6 (3.7 to 5.7)	4.1 (3.1 to 5.4)
Stage IB		
5-year	4.0 (2.9 to 5.3)	3.8 (2.7 to 5.2)
10-year	8.9 (7.0 to 11.0)	10.0 (7.0 to 13.5)
Stage IIA		
5-year	10.8 (8.5 to 13.4)	7.3 (5.4 to 9.6)
10-year	18.4 (15.0 to 22.0)	16.2 (12.0 to 20.9)
Stage IIB		
5-year	16.5 (12.9 to 20.4)	13.1 (9.6 to 17.1)
10-year	26.8 (21.9 to 31.9)	19.2 (14.2 to 24.9)
Stage IIC		
5-year	29.6 (22.5 to 37.1)	22.5 (15.6 to 30.3)
10-year	42.3 (33.2 to 51.0)	33.2 (21.5 to 45.4)
Death due to another cause		
Stage IA		
5-year	1.8 (1.3 to 2.2)	4.4 (3.8 to 5.1)
10-year	4.3 (3.5 to 5.3)	12.4 (10.4 to 14.6)
Stage IB		
5-year	2.0 (1.3 to 3.0)	2.1 (1.3 to 3.3)
10-year	5.4 (3.9 to 7.2)	5.3 (3.3 to 8.0)
Stage IIA		
5-year	4.6 (3.2 to 6.5)	4.2 (2.7 to 6.1)
10-year	8.7 (6.3 to 11.4)	7.0 (4.4 to 10.3)
Stage IIB		
5-year	5.5 (3.5 to 8.0)	4.7 (2.8 to 7.3)
10-year	7.2 (4.8 to 10.1)	9.5 (5.3 to 15.3)
Stage IIC		
5-year	1.9 (0.5 to 5.0)	5.6 (2.7 to 10.0)
10-year	7.4 (3.0 to 14.5)	13.0 (5.2 to 24.5)

Abbreviation: CMMR, Central Malignant Melanoma Registry.