Long-term post-recurrence survival outcomes for stage IIB/C melanoma patients in real-world settings: analyses from a longitudinal electronic health record database in the United States

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Background

- Approximately 10%-26% of patients with stage IIB/C melanoma experience recurrence after complete resection[1]
- These outcomes suggest a high unmet need in this patient population, and little is known about post-recurrence treatment patterns and outcomes for patients with stage IIB/C melanoma who experience recurrence despite complete resection

Objectives

- Objectives of this study, which used individual-level patient data derived from nationwide, retrospective, longitudinal electronic health records (EHRs), were to evaluate the use of systemic anticancer treatment for first locoregional or distant recurrence and to generate long-term post-recurrence survival outcome projections for patients with stage IIB/C melanoma who did not receive systemic therapy following resection

Methods

Study design

- This retrospective observational study extracted information from the longitudinal Flatiron Health EHR-derived de-identified database for the period spanning January 2011 to November 2021 by applying the Enhanced Datamarts (EDMs) algorithm
  - The study cohort was derived from the Flatiron Health Advanced Melanoma Cohort, which consists of patients with advanced disease (stage III/IV) at initial diagnosis and patients with earlier disease stage (including stage IIB/C) who developed a locoregional or distant recurrence
  - The index date was the date of diagnosis of advanced melanoma
- This study cohort included patients with stage IIB/C melanoma who were eligible for, but did not receive, adjuvant treatment and progressed to advanced disease
- Patients were required to have an initial diagnosis of stage IIB/C melanoma (per American Joint Committee on Cancer, *Cancer Staging Manual*, Eighth Edition [AJCC-8]) and to have undergone complete surgical resection

Outcomes

- Outcomes were systemic anticancer treatment use for first locoregional or distant recurrence and post-recurrence survival outcomes (**Table 1**)

Table 1. Definition of post-recurrence survival outcomes[a]

Outcome	Description
Post-recurrence survival	• Time from locoregional or distant recurrence to death • Patients who were alive during their last follow-up were censored
Time from locoregional recurrence to a first subsequent, more severe event	• Time from locoregional recurrence to distant recurrence or death • Patients who were alive with no evidence of distant recurrence during their last follow-up were censored

[a]The database only captured 1 locoregional or distant recurrence for each patient; thus, second or subsequent locoregional or distant recurrences were not captured.

Data analysis

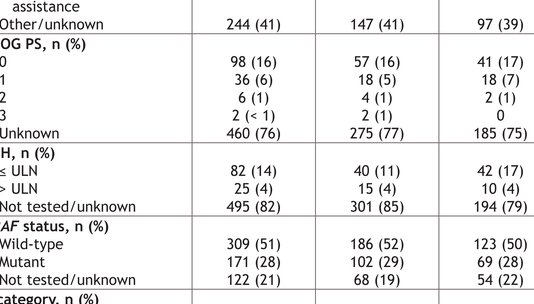
- Key baseline characteristics and systemic anticancer treatments for first locoregional or distant recurrence were analyzed descriptively
- Post-recurrence survival and time from locoregional recurrence to a first subsequent, more severe event (distant recurrence or death) were modeled separately
  - Post-recurrence survival and time from locoregional recurrence to a first subsequent, more severe event were characterized using observed Kaplan-Meier data (with 95% CIs) and best standard parametric fit (log-normal) and best spline fit (1-knot normal)
  - For each outcome, model selection was guided by commonly used statistical fit criteria and visual fit to the observed Kaplan-Meier curves
  - 5-, 10-, and 20-year rates for post-recurrence survival and patients remaining in locoregional recurrence as well as mean post-recurrence survival and mean time spent in locoregional recurrence were estimated across the selected models
  - Post-recurrence survival and proportion of patients remaining in locoregional recurrence were plotted separately for the extent of follow-up and a 30-year time horizon

Results

Sample selection

- A total of 602 patients were included, among whom 356 patients (59%) had stage IIB disease and 246 patients (41%) had stage IIC disease (**Figure 1**)

Figure 1. Sample selection according to prespecified inclusion and exclusion criteria



[a]Per AJCC-8. [b]Patients who received the following treatments at any time after surgical resection were excluded: interferon alfa-2B, peginterferon alfa-2B, ipilimumab, nivolumab, and pembrolizumab. SLNB, sentinel lymph node biopsy; WLE, wide local excision.

Key baseline characteristics

- Patients with stage IIB and stage IIC disease had similar key baseline characteristics (**Table 2**)
  - In patients with stage IIB and stage IIC disease, respectively, median age was 68.5 and 67.0 years, 66% and 71% were male, 84% and 87% were White, and 79% and 77% were treated at a community practice
  - Among patients with available data, most had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, normal lactate dehydrogenase (LDH) levels, and *BRAF* wild-type status

Table 2. Key baseline characteristics

	Stage IIB/C (n = 602)	Stage IIB (n = 356)	Stage IIC (n = 246)
Median age, years (range)	68.0 (19.0-84.0)	68.5 (19.0-83.0)	67.0 (24.0-84.0)
Male, n (%)	409 (68)	235 (66)	174 (71)
Race, n (%)			
White	513 (85)	299 (84)	214 (87)
Other/unknown	89 (15)	57 (16)	32 (13)
Median BMI, kg/m² (range)	29.0 (16.1-59.4)	28.5 (18.5-59.4)	29.6 (16.1-51.9)
Practice type, n (%)			
Community	471 (78)	281 (79)	190 (77)
Academic	128 (21)	73 (21)	55 (22)
Community and academic	3 (< 1)	2 (1)	1 (< 1)
Insurance type, n (%)[a]			
Commercial	248 (41)	142 (40)	106 (43)
Medicare/Medicaid/other governmental	229 (38)	143 (40)	86 (35)
Out-of-pocket/patient assistance	11 (2)	6 (2)	5 (2)
Other/unknown	244 (41)	147 (41)	97 (39)
ECOG PS, n (%)			
0	98 (16)	57 (16)	41 (17)
1	36 (6)	18 (5)	18 (7)
2	6 (1)	4 (1)	2 (1)
3	2 (< 1)	2 (1)	0
Unknown	460 (76)	275 (77)	185 (75)
LDH, n (%)			
≤ ULN	82 (14)	40 (11)	42 (17)
> ULN	25 (4)	15 (4)	10 (4)
Not tested/unknown	495 (82)	301 (85)	194 (79)
***BRAF* status, n (%)**			
Wild-type	309 (51)	186 (52)	123 (50)
Mutant	171 (28)	102 (29)	69 (28)
Not tested/unknown	122 (21)	68 (19)	54 (22)
T category, n (%)			
T3b	221 (37)	221 (62)	0
T4a	135 (22)	135 (38)	0
T4b	246 (41)	0	246 (100)

[a]Patients could have had ≥ 1 type of insurance. BMI, body mass index; T, tumor; ULN, upper limit of normal.

Systemic anticancer treatment for first locoregional or distant recurrence

- In the overall study cohort with stage IIB/C melanoma, 64% (383/602) initiated systemic anticancer treatment for first locoregional or distant recurrence, whereas 36% (219/602) did not initiate systemic anticancer treatment (**Table 3**)
  - Systemic treatment was used for the first locoregional and distant recurrence in 12% (46/383) and 88% (337/383) of patients, respectively

Table 3. Systemic anticancer treatment for first locoregional or distant recurrence

	Stage IIB/C (n = 602)	Stage IIB (n = 356)	Stage IIC (n = 246)
Any systemic treatment for first locoregional or distant recurrence, n (%)[a]	383 (64)	229 (64)	154 (63)
Treatment for first locoregional recurrence	46 (12)	31 (14)[b]	15 (10)
Nivolumab	17 (37)	11 (36)	6 (40)
Pembrolizumab	12 (26)	9 (29)	3 (20)
Ipilimumab	1 (2)	0	1 (7)
Nivolumab plus ipilimumab	6 (13)	3 (10)	3 (20)
Dabrafenib plus trametinib	3 (7)	3 (10)	0
Other	7 (15)	5 (16)	2 (13)
Treatment for first distant recurrence	337 (88)	198 (87)[b]	139 (90)
Nivolumab plus ipilimumab	93 (28)	56 (28)	37 (27)
Pembrolizumab	80 (24)	53 (27)	27 (19)
Nivolumab	64 (19)	38 (19)	26 (19)
Ipilimumab	38 (11)	21 (11)	17 (12)
Dabrafenib plus trametinib	24 (7)	11 (6)	13 (9)
Temozolomide	7 (2)	2 (1)	5 (4)
Other	31 (9)	17 (9)	14 (10)

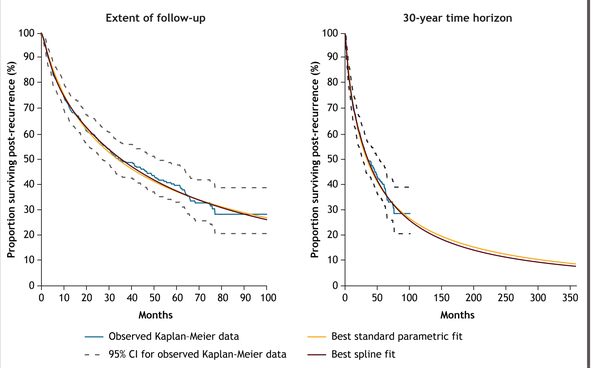
[a]Percentages were calculated based on the number of patients in each category. [b]Percentages may not total to 100 because of rounding.

Post-recurrence survival

- In the overall study cohort (stage IIB: n = 356; stage IIC: n = 246), estimated post-recurrence survival rates ranged from 37.3%-37.9% at 5 years, 23.4%-24.7% at 10 years, and 11.8%-14.4% at 20 years (**Figure 2**)
  - The estimated mean post-recurrence survival ranged from 7.50-8.34 years

Figure 2. Post-recurrence survival

Post-recurrence survival rate, %			Mean post-recurrence survival,[a] years
5-year	10-year	20-year	
37.3–37.9	23.4–24.7	11.8–14.4	7.50–8.34



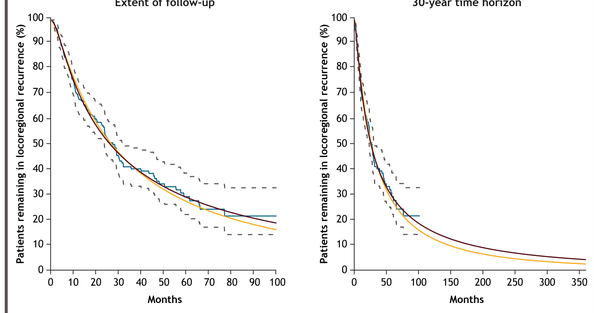
[a]Calculated as the area under the curve for the 30-year time horizon.

Time from locoregional recurrence to a first subsequent, more severe event (distant recurrence or death)

- Among patients with an initial locoregional recurrence (n = 249), mean age was 67 years, and 65% were male, 87% were White, and 63% had stage IIB disease
- Among patients with stage IIB disease (n = 156), 49 patients had distant recurrence before death, and there were 25 deaths before distant recurrence
- Among patients with stage IIC disease (n = 93), 35 patients had distant recurrence before death, and there were 16 deaths before distant recurrence
- Estimated rates of patients remaining in locoregional recurrence ranged from 27.6%-29.3% at 5 years, 13.1%-15.8% at 10 years, and 4.9%-7.3% at 20 years (**Figure 3**)
  - The estimated mean time spent in locoregional recurrence ranged from 4.97-5.71 years

Figure 3. Time from locoregional recurrence to a first subsequent, more severe event (distant recurrence or death)

Patients remaining in locoregional recurrence, %			Mean time spent in locoregional recurrence,[a] years
5-year	10-year	20-year	
27.6–29.3	13.1–15.8	4.9–7.3	4.97–5.71



[a]Calculated as the area under the curve for the 30-year time horizon.

Strengths and limitations

- Strengths of this study included the use of a large, national database that enabled real-world characterization of outcomes in a population with unmet medical needs
- The study was limited by potential errors in data entry and/or patient misclassification
- This study selected patients with stage II melanoma who developed advanced disease; therefore, survival estimates are for a relatively higher-risk population and may not be generalizable to the broader population of patients with recurrent, stage IIB/C melanoma in real-world or clinical trial settings

Conclusions

- Findings from this study highlight the unmet need for effective adjuvant treatments for patients with stage IIB/C melanoma
- This modeling study offers stage IIB/C-specific post-recurrence survival estimates from a recent longitudinal cohort and can mitigate some of the limitations borne by the lack of overall survival data in clinical trials for health technology assessment submissions
- Along with the distributions of systemic treatments received upon recurrence, estimated long-term post-recurrence survival from the Flatiron Health database can be used as a test-bed to evaluate the predictive performance of first-line network meta-analyses in predicting post-recurrence survival
- Nivolumab (an anti-programmed death-1 antibody) was recently approved as an adjuvant treatment for resected stage IIB/C melanoma in the United States and the European Union based on the phase 3 CheckMate 76K trial (NCT04099251), demonstrating a 58% reduction in the risk of recurrence or death versus placebo (hazard ratio, 0.42; 95% CI, 0.30-0.59)[2]
- Future research should examine how recently approved adjuvant therapies, such as nivolumab, influence post-recurrence survival in patients with melanoma who experience recurrence

References

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