Abstract

IMPORTANCE Melanoma accounts for most of the deaths due to skin cancer. In the past decade, effective US Food and Drug Administration (FDA)-approved therapies for melanoma have emerged.

OBJECTIVE To review changes in the long-term melanoma mortality rate (MMR) trends in the US and determine whether they have any temporal association with the FDA approval of new agents.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study used population data from the Surveillance, Epidemiology, and End Results (SEER) database and retrospectively reviewed the age-adjusted MMR trends in adult patients (aged ≥18 years) from 1975 to 2019 in the US population. The timeline of the FDA approvals for melanoma treatment was also reviewed. Data were analyzed from March 15 to August 15, 2022.

EXPOSURES Outcomes were assessed in association with FDA approval of drugs for the treatment of melanoma.

MAIN OUTCOMES AND MEASURES Mortality rates are from the SEER database, reported per 100,000 population and age-adjusted to the 2000 US standard population. The annual percent change (APC) has been used to report long-term trends.

RESULTS After the introduction of newer treatments in 2011 (most after 2013), a significant reduction in MMR was seen from 2013 to 2017 in the US for the first time in the past 40 years. Rates increased from 1975 to 1988 (APC, 1.65% [95% CI, 1.30%-2.00%]; P < .001). No statistically significant change in MMR was seen from 1988 to 2013 (APC, 0.01% [95% CI, −1.10% to 0.12%]; P = .85). The MMR decreased significantly from 2013 to 2017 (APC, −6.28% [95% CI, −8.52% to −3.97%]; P < .001).

CONCLUSIONS AND RELEVANCE These findings suggest a benefit associated with the availability of effective therapies in the past decade and further suggest that the use of new pharmacological therapies is associated with decreased MMR in the US population. These data are very encouraging and support the continued development of such therapies. Additionally, the accessibility of these treatments and the associated health care costs need to be addressed.


Key Points

Question Are new treatments for cutaneous melanoma associated with changes in melanoma mortality rate (MMR) trends among US adults?

Findings In this population-based cross-sectional study of patients with cutaneous melanoma from the Surveillance, Epidemiology, and End Results database from 1975 to 2019, the MMR decreased from 2013 to 2017, since the availability of new and effective treatment options after 2011.

Meaning These findings suggest the trend of decreased MMR is temporally associated with US Food and Drug Administration approval of new and effective treatment options for melanoma.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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In the past decade, new and effective therapies for melanoma have emerged, with US Food and Drug Administration (FDA) approval of multiple checkpoint inhibitors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors and multiple tyrosine kinase inhibitors targeting v-RAF murine sarcoma viral oncogene homologue B1 (BRAF)–mutated melanoma. These therapies have demonstrated remarkably improved overall survival in pivotal clinical trials.

Historically, the prognosis of metastatic melanoma with cytotoxic chemotherapy has been poor. However, with the use of novel therapies, the 5-year overall survival rate has increased from 5% to greater than 50%. A frequent cause of mortality in patients with metastatic melanoma is brain metastases, with more than 50% of patients developing these metastases in their lifetime. The median overall survival from the diagnosis of brain metastases historically has been approximately 5 months; however, current therapies have extended the median overall survival in these patients to approximately 3 years. The use of dual immunotherapy, such as ipilimumab-nivolumab, has shown an overall 5-year survival rate greater than 50%, albeit at the cost of high levels of treatment toxicity. Recently, the FDA approved nivolumab and relatlimab, a lymphocyte activation gene 3 (LAG-3)–blocking antibody, for patients with advanced melanoma, which seems to have a better toxicity profile.

Given the magnitude of benefit from these treatments compared with traditional chemotherapy, one can anticipate a potential association with improved mortality outcomes. This study used the Surveillance, Epidemiology, and End Results (SEER) database to identify trends in the melanoma mortality rate (MMR) in the US population during the past 4 decades (1975-2019) to determine whether a change in the epidemiology of melanoma (specifically MMR) is associated with the advent of these new and effective treatment options.

Methods

This cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Our analysis is derived from retrospective SEER data, which is publicly available and anonymized. The links to access these data are provided in the references. Therefore, institutional review board approval and patient consent were not required according to the Common Rule, as we used publicly available deidentified data under a data use agreement with the US National Cancer Institute.

Data Source

Long-term age-adjusted cutaneous MMR trends in the US using the SEER database from 1975 to 2019 were reviewed to determine any temporal association with the FDA approval of effective treatments. The inclusion criteria for patients consisted of being 18 years or older and having a diagnosis of cutaneous melanoma. Data for sex (men and women) and race and ethnicity (Black, White, and other race or ethnicity) were collected from the SEER database. Race and ethnicity data were collected to identify any racial or ethnic disparity trends for mortality outcomes. The National Cancer Institute's SEER Program publishes cancer statistics in the US. Cancer sites are defined using the SEER Cause of Death Recode 1969+ (04/16/2012).

Statistical Analysis

Data were analyzed from March 15 to August 15, 2022. Mortality rates reported in the SEER database are per 100 000 population and age-adjusted to the 2000 US standard population. The source of mortality data for SEER is the US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. The annual percent change (APC) with 95% CI and \( P \) value has been used to report long-term trends. The APC estimates reported in the SEER Explorer Program have been calculated from the underlying rates using the Joinpoint Trend Analysis Software, version 4.9.1.0. Two-sided \( P \leq .05 \) was considered to indicate a statistically significant difference. The
timeline for FDA approvals for melanoma treatment was reviewed to determine any temporal association with MMR trends.

Results

The MMR showed a downturn during the period between 2013 and 2017 for the first time in the past 40 years. The MMR rate per 100 000 US population was 2.07 (95% CI, 2.00-2.13) in 1975, 2.65 (95% CI, 2.61-2.72) in 2013, 2.09 (95% CI, 2.05-2.14) in 2017, and 2.01 (95% CI, 1.97-2.06) in 2019. The MMR increased from 1975 to 1988 (APC, 1.65% [95% CI, 1.30%-2.00%]; P < .001). In the 1970s, chemotherapy agents were introduced for melanoma but, with their marginal efficacy, no mortality benefit in the US population was seen. No statistically significant change in MMR was seen between 1988 and 2013 (APC, 0.01% [95% CI, −1.10% to 0.12%]; P = .85). During this period, no breakthrough treatment options emerged until the introduction of checkpoint inhibitors (ipilimumab) and BRAF inhibitors (vemurafenib) in 2011. Gradually, immunotherapy treatments became part of the treatment paradigm, given unprecedented responses in heavily pretreated patients who historically had a dismal prognosis. With the introduction of many more agents and combination treatments since 2013, the MMR significantly decreased from 2013 to 2017 (APC, −6.28% [95% CI, −8.52% to −3.97%]; P < .001). This statistically significant reduction in mortality during this period was seen across all the subgroups regardless of race, age group, or sex.19 No statistically significant decrease was seen from 2017 to 2019 (APC, −1.56% [95% CI, −6.41% to 3.55%]; P = .53); however, the trend was downward. The MMR trends are summarized in Table 1. We reviewed the timeline of FDA approvals for melanoma treatment, and the advent of new therapies appeared to have a temporal association with decreasing MMR trends. These results are summarized in Table 2 and Table 3.

Historically (before 2010), chemotherapy agents were sequenced to treat advanced cutaneous melanoma. The benefit was marginal, with rare complete responses and overall survival at 5 years ranging from 2% to 6%, and treatment was associated with significant toxic effects. Interleukin 2 was then approved in the 1990s with response rates less than 20%. In the early 2000s, different chemotherapeutic agents with some proven activity but without overall survival benefit were sequenced.23 No improvement in population mortality was seen during this period either.

Since 2011, several new agents have received FDA approval, more than ever before in melanoma. We will first discuss the timeline of drug approvals in metastatic disease and then the approvals in the adjuvant setting with a brief discussion about clinical data from the corresponding trials focusing primarily on overall survival.

Ipilimumab, an anti–CTLA-4 antibody, was approved by the FDA in 2011 for metastatic melanoma.12 The approval was based on results of a phase 3 trial involving patients with pretreated metastatic melanoma and showed an overall survival benefit compared with the glycoprotein 100 peptide vaccine (ie, 10.1 months with ipilimumab [3 mg/kg intravenously every 3 weeks] vs 6.4 months with glycoprotein 100; hazard ratio [HR], 0.66; P = .003).12

Vemurafenib, a BRAF kinase inhibitor, was approved by the FDA for metastatic melanoma with a BRAF V600E mutation in 2011 based on results of a phase 3 BRIM-3 trial comparing vemurafenib against dacarbazine.22 Overall survival was 84% (95% CI, 78%-89%) with vemurafenib and 64% (95% CI, 56%-73%) with dacarbazine. Even with the crossover to vemurafenib after progression with
| Therapy                        | FDA approval year | Dose                      | Comparator      | Trial name   | Study phase | Primary end point | Statistically significant OS benefit | Indication or line of treatment in patients with metastatic or unresectable melanoma | Statistically and clinically significant outcomes from trials |
|--------------------------------|-------------------|---------------------------|-----------------|--------------|-------------|-------------------|---------------------------------------|----------------------------------------------------------------------------------|
| Ipilimumab12                   | 2011              | 3 mg/kg body weight IV every 3 wk | Gp100           | NA           | 3           | OS                | Yes                                   | First line                                                                      | Median OS 10.1 mo with ipilimumab vs 6.4 mo with Gp100                          |
| Vemurafenib22                  | 2011              | 960 mg PO BID             | Dacarbazine     | BRIM-3       | 3           | OS and PFS       | Yes                                   | Melanoma with BRAF V600E mutation (first line)                                    | Median OS 13.6 mo with vemurafenib vs 9.7 mo with dacarbazine                  |
| Dabrafenib mesylate23-25       | 2013              | 150 mg PO BID             | Dacarbazine     | BREAK-3      | 3           | ORR and OS       | Yes                                   | Metastatic melanoma with BRAF V600E mutation (first line)                           | 5-y OS 24% with dabrafenib vs 22% with dacarbazine, but crossover to dabrafenib was allowed |
| Trametinib dimethyl sulfoxide26 | 2013              | 2 mg PO once a day        | Dacarbazine or paclitaxel | METRIC       | 3           | PFS and OS       | Yes                                   | Melanoma with BRAF V600E mutation (first line)                                    | 6-mo OS 81% with trametinib vs 67% with dacarbazine or paclitaxel, including 47% patients with crossover to trametinib after progression |
| Pembrolizumab27,28             | 2014              | 10 mg/kg body weight every 2 or 3 wk | Ipilimumab (3 mg/kg) every 3 wk for 4 doses | KEYNOTE 006   | 3           | PFS and OS       | Yes                                   | First line                                                                        | Median OS 32.7 mo with pembrolizumab vs 19.9 mo with ipilimumab                 |
| Nivolumab monotherapy29,30     | 2014              | 3 mg/kg body weight IV every 2 wk | Investigator’s choice chemotherapy (dacarbazine, 1000 mg/m² every 3 wk, or paclitaxel, 175 mg/m², combined with carboplatin [area under the curve, 6] every 3 wk) | CheckMate 037 | 3           | Objective response | No                                    | Approval based on better response rate 32% with nivolumab vs 11% with chemotherapy |                                                                                  |
| Nivolumab monotherapy31,32     | 2015              | 3 mg/kg body weight IV every 2 wk | Dacarbazine     | CheckMate 066 | 3           | PFS and OS       | Yes                                   | Metastatic melanoma (first line)                                                   | 5-y OS 39% with nivolumab vs 17% with dacarbazine                              |
| Nivolumab with ipilimumab33,34 | 2015              | Nivolumab, 1 mg/kg every 2 wk, plus ipilimumab, 3 mg/kg every 2 wk, for 4 doses, followed by nivolumab, 3 mg/kg every 2 wk | Nivolumab (3 mg/kg every 2 or 3 wk) or ipilimumab (3 mg/kg every 3 wk for 4 doses) | CheckMate 067 | 3           | PFS and OS       | Yes                                   | Metastatic melanoma (first line)                                                   | Median OS 72.1 mo in combination vs 36.9 mo with nivolumab vs 19.9 mo with ipilimumab |
| Dabrafenib with trametinib35-37 | 2015              | Dabrafenib, 150 mg PO BID with trametinib, 2 mg once a day | Dabrafenib      | COMBI-d      | 3           | PFS              | Yes                                   | Melanoma with BRAF V600E mutation (first line)                                    | Median OS 25.1 mo with combination vs 18.7 mo with dabrafenib; 3-y OS 45% with combination vs 32% with vemurafenib          |
| Vemurafenib plus cobimetinib fumarate38,39 | 2015              | Vemurafenib, 960 mg PO BID, and cobimetinib fumarate, 60 mg once a day | Vemurafenib     | coBRIM       | 3           | PFS              | Yes                                   | Melanoma with BRAF V600E mutation (first line)                                    | 5-y OS 31% with combination vs 26% with vemurafenib                           |
| Talimogene laherparepvec40-42   | 2015              | Intralensial first dose, 10⁶ pfu/mL, then 10⁵ pfu/mL every 2 wk starting 3 wk after first dose | GM-CSF          | OPTIM        | 3           | OS and DRR       | No                                    | Unresectable stage III or IV melanoma (first line)                               | DRR (>6 mo) 16.3% with talimogene laherparepvec vs 2.1% with GM-CSF               |
| Encorafenib plus binimetinib43  | 2018              | Encorafenib, 450 mg PO once a day, plus binimetinib, 45 mg PO BID | Vemurafenib     | COLUMBUS     | 3           | PFS              | Yes                                   | Metastatic or unresectable melanoma with BRAF V600E mutation (first line)         | Median OS 33.6 mo with combination vs 16.7 mo with vemurafenib                 |
chemotherapy, the updated analysis continued to show overall survival benefit in the vemurafenib group (median, 13.6 vs 9.7 months; HR, 0.70; \(P < .001\)).

Dabrafenib mesylate, a \(BRAF\) inhibitor, was approved by FDA in 2013 for the treatment of metastatic melanoma with a \(BRAF\) \(V600E\) mutation after results from the BREAK-3 study.\(^{23,24}\) Even after crossover to dabrafenib after progression with dacarbazine, dabrafenib has a slightly superior 5-year overall survival rate of 24% vs 22% after 5 years.\(^{25}\)

Trametinib dimethyl sulfoxide, an allosteric inhibitor of MEK1 and MEK2 kinases, was approved in 2013 after the results of the METRIC trial for \(BRAF\) \(V600E\)- or \(BRAF\) \(V600K\)-positive advanced melanoma.\(^{26}\) Trametinib vs chemotherapy (paclitaxel or dacarbazine) showed a 6-month overall survival of 81% with trametinib vs 67% with chemotherapy (HR, 0.54; \(P = .01\)), even with 47% of patients receiving chemotherapy crossing over to trametinib treatment.\(^{26}\)

In 2014, pembrolizumab, an anti–PD-1 antibody, was approved for treatment of advanced melanoma after showing superior progression-free survival (PFS) as well as overall survival and less high-grade toxicity in comparison with ipilimumab (3 mg/kg every 3 wk for 4 total doses) in the randomized phase 3 trial KEYNOTE 006.\(^{27,28}\) Updated results after 5 years of follow-up showed a median overall survival of 32.7 months in the pembrolizumab groups and 15.9 months in the ipilimumab group (HR, 0.73 [\(P < .001\)]).\(^{27,28}\)

In 2014, nivolumab was approved as second-line therapy among patients with disease refractory to ipilimumab or a \(BRAF\) inhibitor for advanced melanoma after the positive results of the CheckMate 037 trial based on higher rates of response compared with the investigator’s choice of chemotherapy (ie, 32% vs 11%).\(^{29,30}\) The updated analysis published later does not show overall survival benefit.\(^{29,30}\)

In 2015, the FDA approved nivolumab in untreated patients with metastatic melanoma without a \(BRAF\) mutation. Approval was based on the results of CheckMate 066 showing the overall survival and PFS benefit of nivolumab compared with dacarbazine.\(^{31}\) Updated 5-year overall survival rates continued to show superiority (ie, 39% vs 17%).\(^{32}\)

In 2015, the results of the CheckMate 067 study led to the approval of the combination of nivolumab plus ipilimumab in patients with untreated advanced melanoma with and without \(BRAF\) \(V600\) mutation.\(^{33}\) This trial compared the combination regimen vs nivolumab or ipilimumab monotherapy as the frontline treatment for these patients. The toxicity of the combination therapy,

<table>
<thead>
<tr>
<th>Therapy</th>
<th>FDA approval year</th>
<th>Dose</th>
<th>Comparator</th>
<th>Trial name</th>
<th>Study phase</th>
<th>Primary end point</th>
<th>Statistically significant OS benefit</th>
<th>Indication or line of treatment in patients with metastatic or unresectable melanoma</th>
<th>Statistically and clinically significant outcomes from trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab plus cobimetinib and vemurafenib(^{44})</td>
<td>2020</td>
<td>Cobimetinib, 60 mg PO once a day (d 1-21), plus vemurafenib, 720 mg PO BID plus IV atezolizumab, 840 mg, d 1 plus 15 d in 28-d cycles Placebo with cobimetinib and vemurafenib</td>
<td>IMspire150</td>
<td>3</td>
<td>OS and PFS</td>
<td>No</td>
<td>Metastatic melanoma with (BRAF) (V600) mutation (first line)</td>
<td>OS data not mature yet, approval based on PFS of 15.1 mo with combination vs 10.6 mo with placebo and cobimetinib and vemurafenib</td>
<td></td>
</tr>
<tr>
<td>Relatlimab and nivolumab(^{18})</td>
<td>2022</td>
<td>Relatlimab, 160 mg IV, and nivolumab, 480 mg IV in a fixed dose combination every 4 wk</td>
<td>Nivolumab, 480 mg IV every 4 wk</td>
<td>RELATIVITY-047</td>
<td>2/3</td>
<td>PFS</td>
<td>No</td>
<td>Unresectable stage III(^{a}) or metastatic melanoma (first line)</td>
<td>OS data not mature yet; median PFS 10.1 mo with combination vs 4.6 mo with nivolumab</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; \(BRAF\), v-RAF murine sarcoma viral oncogene homologue B1; DRR, durable response rate; FDA, US Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gp100, glycoprotein 100; IV, intravenously; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pfu, plaque-forming unit; PO, orally.

\(^{a}\) The stage of melanoma is per American Joint Committee on Cancer staging system for cancers.
however, raised concerns. Drug-related adverse events (DRAE) of grade 3 or 4 occurred in 16.3% of patients in the nivolumab group and 55.0% of those in the nivolumab plus ipilimumab group. Updated results from a 6.5-year follow-up from this study showed a median overall survival of 72.1 months in the combination group, 36.9 months in the nivolumab group, and 19.9 months in the ipilimumab group.34

Also in 2015, results of 2 other phase 3 trials comparing dabrafenib plus trametinib (BRAF and MEK inhibitors) with dabrafenib monotherapy (COMBI-d) and vemurafenib monotherapy (COMBI-v) for the treatment of advanced melanoma with \textit{BRAF} V600E or V600K mutations led to the approval of the combination therapy.35,36 In COMBI-d, the median overall survival was 25.1 months with the combination therapy and 18.7 months with dabrafenib monotherapy.35 In the COMBI-v study, the reported 3-year follow-up overall survival was 45% with combination therapy vs 32% with vemurafenib monotherapy.36 Pooled data from the COMBI-d and COMBI-v trials to report extended survival results showed overall survival of 34% at 5 years.37

The coBRIM trial compared the combination of vemurafenib and cobimetinib fumarate (BRAF and MEK inhibitors) with vemurafenib monotherapy for the treatment of \textit{BRAF} V600–positive advanced melanoma and led to the approval of this combination in 2015 as well.38 The median PFS was better with the combination treatment (12.3 vs 7.2 months). The 5-year overall survival was also better with the combination treatment (31% vs 26%).39

In 2015, the OPTiM trial led to the approval of intralesional talimogene laherparepvec in patients with surgically unresectable stage III or IV melanoma.40-42 The durable response rate (lasting >6 months) was 16.3% in the talimogene laherparepvec group compared with 2.1% in the group receiving granulocyte-macrophage colony-stimulating factor. Median overall survival increased with longer follow-up to 23.3 months with talimogene laherparepvec and 18.9 months with granulocyte-macrophage colony-stimulating factor (HR, 0.79; \textit{P} = .051).40-42

### Table 3. FDA-Approved Adjuvant Therapies for Melanoma Since 2011 and Summary of Pivotal Trials Leading to Corresponding FDA Approval

<table>
<thead>
<tr>
<th>Therapy</th>
<th>FDA approval year</th>
<th>Dose (duration as mentioned below or until disease recurrence or medication toxicity)</th>
<th>Comparator</th>
<th>Trial</th>
<th>Phase</th>
<th>Primary end point</th>
<th>OS benefit (yes/no)</th>
<th>Indication/line of treatment</th>
<th>Statistically significant and clinically significant outcomes from trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon alfa-2b</td>
<td>2011</td>
<td>6 μg/kg body weight SC weekly for 8 wk then 3 μg/kg SC weekly for 5 y</td>
<td>Placebo</td>
<td>EORTC 18991</td>
<td>3</td>
<td>RFS and OS</td>
<td>No</td>
<td>Stage III melanoma, microscopic or gross nodal involvement after surgery*</td>
<td>4-y RFS 45.6% with pegylated interferon alfa-2b vs 38.9% with placebo</td>
</tr>
<tr>
<td>Ipilimumab monotherapy</td>
<td>2015</td>
<td>10 mg/kg body weight IV every 3 wk for 4 doses</td>
<td>Placebo</td>
<td>EORTC 18071</td>
<td>3</td>
<td>RFS and OS</td>
<td>Yes</td>
<td>Stage III melanoma, pathologic involvement of regional lymph nodes &gt;1 mm after surgery</td>
<td>7-y OS rate of 60.0% with ipilimumab vs 51.3% with placebo; 1% deaths in ipilimumab group related to DRAE</td>
</tr>
<tr>
<td>Nivolumab monotherapy</td>
<td>2017</td>
<td>3 mg/kg body weight IV every 3 wk for 4 doses</td>
<td>Ipilimumab</td>
<td>CheckMate 238</td>
<td>3</td>
<td>RFS and OS</td>
<td>No</td>
<td>Resected stage IIIC and IV melanoma</td>
<td>4-y RFS of 52% with nivolumab vs 41% with ipilimumab</td>
</tr>
<tr>
<td>Dabrafenib plus trametinib</td>
<td>2017</td>
<td>Dabrafenib, 150 mg PO BID, plus trametinib, 2 mg PO BID for 12 mo</td>
<td>Placebo</td>
<td>COMBI-AD</td>
<td>3</td>
<td>OS</td>
<td>Yes</td>
<td>Stage III melanoma with \textit{BRAF} V600E/V600K mutations</td>
<td>3-y OS rate of 86% with combination vs 77% with placebo</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2019</td>
<td>200 mg IV every 3 wk for 18 cycles</td>
<td>Placebo</td>
<td>KEYNOTE-054</td>
<td>3</td>
<td>RFS</td>
<td>No</td>
<td>Completely resected stage III melanoma</td>
<td>3.5-y RFS 59.8% with pembrolizumab vs 41.1% with placebo</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2021</td>
<td>200 mg IV every 3 wk for 17 cycles</td>
<td>Placebo</td>
<td>KEYNOTE-716</td>
<td>3</td>
<td>RFS and OS</td>
<td>No</td>
<td>Completely resected high-risk stage II melanoma</td>
<td>21-mo Follow-up for first recurrence of disease or mortality 15% with pembrolizumab vs 24% with placebo</td>
</tr>
</tbody>
</table>

Abbreviations: \textit{BRAF}, v-RAF murine sarcoma viral oncogene homologue B1; DRAE, drug-related adverse events; EORTC, European Organisation for Research and Treatment of Cancer; FDA, US Food and Drug Administration; IV, intravenously; OS, overall survival; RFS, recurrence-free survival; SC, subcutaneously. * Stage of melanoma is per American Joint Committee on Cancer staging system for cancers.
In 2018, the third combination of BRAF and MEK inhibitors—encorafenib and binimetinib—were approved for unresectable or metastatic melanoma based on the result of the COLUMBUS trial.43 The results of this phase 3 study found the median overall survival of the group receiving combination therapy to be 33.6 months compared with 16.7 months for vemurafenib (HR, 0.54 [95% CI, 0.40-0.71]).

In 2019, the CheckMate 511 study was conducted to address the toxicity of checkpoint inhibitor combination.55 This study compared FDA-approved nivolumab, 1 mg/kg, plus ipilimumab, 3 mg/kg, with nivolumab, 3 mg/kg, plus ipilimumab, 1 mg/kg. The latter combination demonstrated an improved safety profile, and there were no meaningful efficacy differences between the groups, even in the updated 3-year follow-up data. Although this dose is not yet FDA approved, it has been clinically adapted in various institutes as a preferred combination dose due to its better toxicity profile.

In 2020, atezolizumab (immunotherapy consisting of a programmed cell death ligand 1 [PD-L1] inhibitor) in combination with cobimetinib and vemurafenib was given to patients with BRAF V600 mutation–positive melanoma.44 Based on the results of the IMspire150 study, the FDA approved the combination of atezolizumab, vemurafenib, and cobimetinib therapy for metastatic melanoma. The phase 3 study found the triplet combination therapy to have a better median PFS of 15.1 vs 10.6 months (HR, 0.78; P = .02). The median overall survival was not mature.

Most recently, in March 2022, the FDA approved nivolumab and relatlimab, a LAG-3–blocking antibody for patients with unresectable or metastatic melanoma.18 The approval was based on results of the randomized phase 3 RELATIVITY-047 clinical trial (combination group vs nivolumab) in patients with previously untreated advanced melanoma. The median PFS was 10.1 months with relatlimab and nivolumab compared with 4.6 months with nivolumab (HR, 0.75; P = .006). The overall survival data are not mature yet. Grade 3 or 4 DRAE occurred in 18.9% of patients in the relatlimab-nivolumab group and in 9.7% of patients in the nivolumab group.

Unlike metastatic therapy approvals that began around the 1970s, adjuvant therapies for melanoma were not approved until 2011. Pegylated interferon alfa-2b was the first drug to be approved in the adjuvant setting for American Joint Committee on Cancer stage III melanoma in 2011 based on recurrence-free survival (RFS) advantage of 45.6% vs 38.9% at 4 years.46 No overall survival advantage was seen. With more effective immunotherapy approvals since, this therapy is not typically used.

In 2015, ipilimumab monotherapy (10 mg/kg for 4 doses) was approved in the adjuvant setting for patients with pathologic involvement of regional lymph nodes (>1 mm) after surgery.46 This approval was based on the EORTC (European Organisation for Research and Treatment of Cancer) 18071 trial that showed a longer median RFS with ipilimumab (26.1 vs 17.1 months; P = .001). At a high dose, adjuvant ipilimumab therapy was associated with significant toxicity; a 53% discontinuation rate was reported, and 5 patients (1%) died owing to DRAE. This was not readily used due to toxicity.46 Longer-term follow-up showed a better 7-year overall survival rate of 60.0% with ipilimumab vs 51.3% with placebo.47 Reducing the dose from 10 mg/kg to 3 mg/kg of body weight lowered the discontinuation rate while maintaining similar efficacy.48

In 2017, nivolumab (3 mg/kg) was approved based on favorable results seen in CheckMate 238 study compared with ipilimumab (10 mg/kg). The 12-month RFS was 70.5% with nivolumab and 60.8% with ipilimumab (HR, 0.65; P < .001).49 In a 4-year update from the study, no overall survival advantage was seen. However, a continued RFS benefit of 52% vs 41% (HR, 0.71; P < .001) was seen.50

Soon after, in 2017, the combination of dabrafenib plus trametinib was approved based on the results of the COMBI-AD trial as adjuvant therapy for patients with BRAF V600 mutation–positive stage III melanoma.51 The 3-year RFS was 58% with the combination therapy and 39% with placebo. The combination also improved overall survival at 3 years (86% vs 77%; HR, 0.57 [95% CI, 0.42-0.79]).51
Pembrolizumab was first approved by the FDA for use as adjuvant therapy for melanoma in 2019 for patients with stage III melanoma after complete resection based on the results of the Keynote-054 study. The 1-year RFS rate was 75.4% with pembrolizumab vs 61.0% with placebo (HR 0.57; P < .001). The benefit was seen regardless of PD-L1 status. Follow-up at 3.5 years continued to show RFS in favor of pembrolizumab at 59.8% vs 41.1% (HR, 0.59 [95% CI, 0.49-0.70]).

More recently in 2021, pembrolizumab was approved as adjuvant monotherapy for completely resected high-risk stage II disease (stage IIB or IIC melanoma) after results of the phase 3 KEYNOTE-716 study. In a second interim analysis of this study at 21 months, RFS was not reached in either group, but fewer patients treated with pembrolizumab had a first recurrence of disease or mortality (15%) when compared with placebo (24%) (HR, 0.61 [95% CI, 0.45-0.82]). In patients with melanoma and BRAF V600 mutation, the most effective sequence of melanoma treatment using targeted therapy and immunotherapy continues to be investigated.

Discussion
In this study, we reviewed MMR trends in the US population during the last 4 decades, specifically 1975 to 2019, focusing on MMR with the changing melanoma treatment paradigm. After the introduction of newer treatments in 2011 (mostly after 2013), a significant reduction in MMR was seen from 2013 to 2017 in the US. This likely reflects a benefit from the availability of effective therapies in the last decade. The fact that even the elderly population (eg, those aged >75 years) was living longer with melanoma supports these therapies being well tolerated and successfully used in an elderly population.

Despite all these important advances in the treatment of melanoma, barriers to optimal care and accessibility to treatments remain an issue for many patients (eg, in rural areas). Also, the cost of modern therapies can be prohibitive for universal treatment access. Future directions need to address treatment access issues in addition to the development of new agents.

Strengths and Limitations
The strength of our study is its large sample size from the publicly available SEER database, which is generalizable to the US population. These data include older and socioeconomically disadvantaged patients who are not very well represented in most randomized clinical trials.

This study, however, has limitations. Being a retrospective study, it is prone to unaddressed confounders as well as inherent selection bias from the SEER database and lacks a control population. The SEER database does not have information on clinical and chemotherapeutic data for individual patients that, if available, could be used to draw more definitive conclusions.

Conclusions
The effectiveness of new and innovative therapeutics for melanoma is likely represented by the remarkable and statistically significant drop in population-level melanoma mortality in the last decade. These are very encouraging data and support the continued development of such therapies. Ways to address the accessibility of these treatments and the health care costs need to be supported.
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Data Sharing Statement: See the Supplement.

Additional Information: Most updated information in the SEER database was reviewed on or before July 23, 2022, and has been discussed. All the information and materials in the manuscript are original. The statistical data have been generated using the publicly available SEER Explorer Application.

REFERENCES


**SUPPLEMENT.**

Data Sharing Statement