**IMPORTANCE** The effectiveness of immune checkpoint inhibitors (ICIs) and BRAF and MEK inhibitors has improved advanced melanoma recovery. However, it is unknown whether these novel therapies are cost-effective for newly diagnosed advanced melanoma with unknown *BRAF* status.

**OBJECTIVE** To compare the cost-utility of these novel agents and their combinations with or without *BRAF* gene testing guidance for treating newly diagnosed advanced melanoma with unknown *BRAF* status.

**DESIGN AND SETTING** A decision-analytic model was adopted to project the outcomes of 8 strategies containing different ICIs and BRAF and MEK inhibitors for newly diagnosed advanced melanoma with unknown *BRAF* pathogenic variant status. The key clinical data were derived from the CheckMate 067, KEYNOTE-006, COMBI-d, and COMBI-v trials, and the cost and health preference data were derived from the literature. Costs were estimated from the US payer perspective.

**MAIN OUTCOMES AND MEASURES** Costs, quality-adjusted life-years (QALYs), incremental cost-utility ratio (ICUR), and incremental net health benefits were calculated. Subgroup, 1-way, and probabilistic sensitivity analyses were performed.

**RESULTS** Of the 8 competing strategies, nivolumab plus ipilimumab without patient selection based on *BRAF* pathogenic variant testing yielded the most significant health outcome, and the nivolumab strategy was the cheapest option. The nivolumab, pembrolizumab, and nivolumab plus ipilimumab strategies formed the cost-effective frontier, which showed the ordered ICURs were $8593 (SD, $592 995)/QALY for pembrolizumab vs nivolumab and $125 593 (SD, $5 751 223)/QALY for nivolumab plus ipilimumab vs pembrolizumab. Other strategies, including the *BRAF* testing–guided strategies (*BRAF* pathogenic variant testing followed by corresponding regimens for *BRAF* wild and pathogenic variant tumors), were dominated or extended dominated. The most influential parameters were the treatment efficacy of these new regimens.

**CONCLUSIONS AND RELEVANCE** For newly diagnosed advanced melanoma with unknown *BRAF* pathogenic variant status, nivolumab plus ipilimumab and pembrolizumab strategies are likely to be the most cost-effective options. BRAF and MEK inhibitors might be productively placed in a second-line setting after *BRAF* pathogenic variant is confirmed.
Melanoma accounted for 0.71% of the disease burden of all neoplasms as reported by the Global Burden of Disease Study 2017, while the 5-year survival rate of melanoma was approximately 20% to 40% for those with advanced disease. In recent years, immunotherapies and BRAF and MEK inhibitors have dramatically influenced the treatment of advanced-stage melanoma. The overall survival (OS) of patients with advanced-stage melanoma has improved from approximately 9 months before 2011 to an undefined time frame, with more than 20% of patients having ongoing long-term disease control.

Recently, the long-term survival of patients treated with immune checkpoint inhibitors (ICIs) and BRAF and MEK inhibitors for advanced melanoma has been reported. In patients with previously untreated advanced melanoma, the CheckMate 067 trial showed the OS at 5 years was more than 50% in the nivolumab plus ipilimumab group and 44% in the nivolumab group, while the KEYNOTE-006 trial showed the median OS was 39% in the pembrolizumab group. In patients with previously untreated advanced melanoma anchoring a BRAF V600E or V600K pathogenic variant, the COMBI-d and COMBI-v trials showed the OS rates of dabrafenib plus trametinib treatment were 34% at 5 years.

Despite the promising results of ICIs and BRAF plus MEK inhibitors for advanced melanoma, a few issues still need to be resolved: (1) whether patient selection that uses BRAF pathogenic variant testing should be implemented for tailoring the first-line treatment, and (2) which treatment regimen optimally balances the factors of health benefit and financial burden for making the opportunity cost of the alternative uses of resources explicit. A 2017 study evaluated the economic outcomes of ICIs in patients with treatment-naive BRAF wild-type advanced melanoma. However, few studies have investigated the economic outcomes of currently available novel therapies for newly diagnosed advanced melanoma with unknown BRAF status. Thus, the present analysis, from a US payer perspective, investigates the health and economic outcomes of 8 potential up-line novel treatment regimens for newly diagnosed advanced melanoma with unknown BRAF status by using the latest long-term survival data.

Methods

Analytic Overview

A partitioned-survival model with 3 health states was constructed for an initial decision measuring the lifetime clinical and economic outcomes of 8 treatment strategies for previously untreated unresectable stage III or stage IV melanoma with unknown BRAF pathogenic variant status. As shown in Figure 1, the 3 mutually exclusive states were progression-free disease (PFD), progressed disease (PD), and death. In the 3-health-state model, the proportion of OS is partitioned into those alive and with PFD and those alive and with PD. The proportion alive at cycle t (1-week cycle) was estimated by the area under the OS curve, and the proportion alive and with PFD was estimated by the area under the PFS curve. The proportion alive and with PD was estimated by the difference between the OS and PFS curves. The proportions of PFS and OS were based on the results of clinical trials. All patients received 1 of 8 front-line interventions: (1) ipilimumab, (2) nivolumab, (3) nivolumab plus ipilimumab, (4) pembrolizumab every 3 weeks, (5) BRAF pathogenic variant testing followed by nivolumab for BRAF wild-type tumor and nivolumab plus ipilimumab for confirmed BRAF pathogenic variant (BRAF-guided Pem-DT strategy), (6) BRAF pathogenic variant testing followed by pembrolizumab every 3 weeks for BRAF wild-type tumor and dabrafenib plus trametinib for confirmed BRAF pathogenic variant (BRAF-guided Niv-DT strategy), (7) BRAF pathogenic variant testing followed by nivolumab for BRAF wild-type tumor and dabrafenib plus trametinib for confirmed BRAF pathogenic variant (BRAF-guided Niv-DT strategy), and (8) BRAF pathogenic variant testing followed by pembrolizumab every 3 weeks for BRAF wild-type tumor and nivolumab plus ipilimumab for confirmed BRAF pathogenic variant (BRAF-guided Niv-Di-Pem strategy). This study was based on a literature review and modeling techniques and did not require approval by an institutional research ethics board based on the Common Rule.

Clinical Data Inputs

The latest reports informed the clinical data of the CheckMate 067, KEYNOTE-006, COMBI-d, and COMBI-v trials. The virtual patient-level progression-free survival (PFS) and OS data were generated by using standard statistical analyses described by Guyot et al and Ouwens et al. Owing to comparable trial eligibility criteria and patient baseline characteristics (eTable 1 in the Supplement) between the CheckMate 067 and KEYNOTE-006 trials, we pooled the PFS and OS data of the ipilimumab strategy in the 2 trials. These reconstructed virtual patient-level PFS and OS data were adopted to extrapolate over the model time horizon by fitting the potential survival distributions according to the value of the Akaike information criterion. The survival distributions are summarized in Table 1, and results of goodness-of-fit tests are summarized in eTable 2 in the Supplement. The validation plot, survival distribution, and hazard ratios (HRs) in the subgroups are shown in eFigures 2, 3, 4, and 5 in the Supplement. The survival rates of ipilimumab in the subgroups with BRAF pathogenic variant and no BRAF pathogenic variant were...
calculated by multiplying the survival rates of ipilimumab in the full cohort vs the HRs of the subgroups vs the full cohort. The HRs are shown in eTable 3 in the Supplement, which were estimated by using the Cox proportional hazards model after pooling the virtual patient-level data of the whole population and the 2 subgroups with BRAF pathogenic variant and no BRAF pathogenic variant in the CheckMate 067 trial (eFigure 1 in the Supplement). The HRs of nivolumab plus ipilimumab, and nivolumab and pembrolizumab vs ipilimumab in the full cohort and the subgroups with BRAF pathogenic variant and no BRAF pathogenic variant were directly taken from the CheckMate 067 and KEYNOTE-006 trials (Table 1). In the BRAF-guided strategies, the outcomes were combined by the 2 subgroups with BRAF pathogenic variant and no BRAF pathogenic variant. The prevalence of BRAF V600 pathogenic variant was approximately 35% (range, 31%-39%) in advanced melanoma, which was estimated by averaging the reported data of the CheckMate 067 and KEYNOTE-006 trials.4,6 The sensitivity analysis would check the effect of the prevalence of BRAF V600 pathogenic variant (range, 14.3%-60%).11,12 As done in previous reports,7 the alive proportion during each cycle was defined as the minimum value of OS and the background alive proportion. The background alive proportion for each age group was estimated from US Life Tables (2017).13 The data of patients who received second-line active treatment were extracted from the trials.4-6

Cost and Utility Inputs
This analysis adopted the third-party payer perspective in the US, which considers only direct medical costs (eTable 4 in the

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**Figure 1. Model Structure for Previously Untreated Unresectable Stage III or Stage IV Melanoma With Unknown BRAF Pathogenic Variant Status**

- **All patients: ipilimumab (reference strategy)**
- **All patients: nivolumab (nivolumab strategy)**
- **All patients: nivolumab plus ipilimumab (nivolumab plus ipilimumab strategy)**
- **All patients: pembrolizumab (pembrolizumab strategy)**

**BRAF pathogenic variant testing**
- **BRAF pathogenic variant positive: nivolumab plus ipilimumab**
- **BRAF pathogenic variant negative: nivolumab**
- **BRAF pathogenic variant positive: dabrafenib plus trametinib**
- **BRAF pathogenic variant negative: pembrolizumab every 3 wk**
- **BRAF pathogenic variant positive: dabrafenib plus trametinib**
- **BRAF pathogenic variant negative: pembrolizumab every 3 wk**
- **BRAF pathogenic variant positive: nivolumab plus ipilimumab**
- **BRAF pathogenic variant negative: pembrolizumab every 3 wk**

**Newly diagnosed advanced melanoma with unknown BRAF pathogenic variant status**

**Partitioned-survival model**

- **Progression-free disease**
- **Progressed disease**
- **Death**

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The costs are reported in 2019 US dollars and were inflated to 2019 values according to the Medical-Care Inflation.\textsuperscript{14}

Based on prescribing information from the US Food and Drug Administration (FDA), the prescription information was as follows: nivolumab at a dose of 1 mg/kg of body weight every 3 weeks plus ipilimumab at a dose of 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab at a dose of 240 mg every 2 weeks (nivolumab plus ipilimumab strategy); nivolumab at a dose of 240 mg every 2 weeks (nivolumab strategy); ipilimumab at a dose of 3 mg/kg every 3 weeks for 4 doses (ipilimumab strategy); and pembrolizumab at a dose of 200 mg every 3 weeks (pembrolizumab strategy). Medication costs were calculated by using a base-case patient with a weight of 70 kg.\textsuperscript{7}

### Table 1. Key Clinical Inputs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical inputs</strong></td>
<td></td>
</tr>
<tr>
<td>Survival model of PFS in the full cohort</td>
<td>gamma0 = −2.1172; gamma1 = 0.9218; gamma2 = −0.5233; gamma3 = 0.3493</td>
</tr>
<tr>
<td>MCM with log-logistic for nivolumab plus ipilimumab \textsuperscript{6}</td>
<td>theta = 0.3505; shape = 1.455; scale = 21.6629</td>
</tr>
<tr>
<td><strong>Survival model of OS in the full cohort</strong></td>
<td></td>
</tr>
<tr>
<td>Spline model for nivolumab (knot = 2) \textsuperscript{6}</td>
<td>gamma0 = −12.6277; gamma1 = 6.0451; gamma2 = 1.302; gamma3 = −0.7823</td>
</tr>
<tr>
<td>MCM with lognormal for nivolumab plus ipilimumab \textsuperscript{6}</td>
<td>theta = 0.438; meanlog = 4.0933; sdlog = 1.3611</td>
</tr>
<tr>
<td><strong>Survival model of PFS in BRAF pathogenic variant</strong></td>
<td></td>
</tr>
<tr>
<td>Spline model for ipilimumab (knot = 2) \textsuperscript{4,6}</td>
<td>gamma0 = −2.6989; gamma1 = 0.1587; gamma2 = −0.1046; gamma3 = 0.1478</td>
</tr>
<tr>
<td>Spline model for nivolumab (knot = 2) \textsuperscript{6}</td>
<td>gamma0 = −11.5176; gamma1 = 4.7603; gamma2 = 1.2352; gamma3 = −0.7906</td>
</tr>
<tr>
<td><strong>Survival model of OS in BRAF pathogenic variant</strong></td>
<td></td>
</tr>
<tr>
<td>Spline model for ipilimumab (knot = 1) \textsuperscript{5}</td>
<td>gamma0 = −5.4308; gamma1 = 3.2751; gamma2 = 0.0947</td>
</tr>
<tr>
<td>Spline model for nivolumab (knot = 2) \textsuperscript{6}</td>
<td>gamma0 = −11.8106; gamma1 = 5.1428; gamma2 = 1.1102; gamma3 = −0.7594</td>
</tr>
<tr>
<td><strong>Survival model of PFS in no BRAF pathogenic variant</strong></td>
<td></td>
</tr>
<tr>
<td>Spline model for ipilimumab (knot = 1) \textsuperscript{2}</td>
<td>gamma0 = −6.4446; gamma1 = 3.5309; gamma2 = 0.0783</td>
</tr>
<tr>
<td>Spline model for nivolumab (knot = 2) \textsuperscript{6}</td>
<td>gamma0 = −8.5331; gamma1 = 3.5396; gamma2 = 0.6453; gamma3 = −0.4492</td>
</tr>
<tr>
<td><strong>Survival model of OS in no BRAF pathogenic variant</strong></td>
<td></td>
</tr>
<tr>
<td>Gompertz model for ipilimumab (knot = 1) \textsuperscript{6}</td>
<td>shape = −0.0057; rate = 0.0104</td>
</tr>
<tr>
<td>MCM with lognormal for nivolumab \textsuperscript{6}</td>
<td>theta = 0.2401; meanlog = 4.4362; sdlog = 1.6392</td>
</tr>
<tr>
<td><strong>HR of pembrolizumab vs ipilimumab in subgroups</strong></td>
<td></td>
</tr>
<tr>
<td>PFS in no BRAF pathogenic variant (pembrolizumab every 3 wk) \textsuperscript{4}</td>
<td>Expected value (range): 0.57 (0.43 to 0.75); lognormal distribution (log-mean = −0.562; log-se = 2.508)</td>
</tr>
<tr>
<td>OS in no BRAF pathogenic variant (pembrolizumab every 3 wk) \textsuperscript{4}</td>
<td>Expected value (range): 0.73 (0.58 to 0.93); lognormal distribution (log-mean = −0.315; log-se = 2.416)</td>
</tr>
<tr>
<td>PFS in BRAF pathogenic variant (pembrolizumab every 2 wk) \textsuperscript{4}</td>
<td>Expected value (range): 0.54 (0.32 to 0.91); lognormal distribution (log-mean = −0.616; log-se = 1.894)</td>
</tr>
<tr>
<td>OS in BRAF pathogenic variant (pembrolizumab every 2 wk) \textsuperscript{4}</td>
<td>Expected value (range): 0.70 (0.44 to 1.11); lognormal distribution (log-mean = −0.357; log-se = 1.767)</td>
</tr>
<tr>
<td>Prevalence of BRAF pathogenic variant \textsuperscript{4,6,11,12}</td>
<td>Expected value (range): 0.35 (0.143 to 0.6); beta distribution (α = 5.9; β = 10.9)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; MCM, mix cure model; OS, overall survival; PFS, progression-free survival.

* The range is the reported or estimated 95% CI.
Based on previous reports, the maximum treatment duration of ICI treatment was 2 years. Dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily was administered on a continuous dosing schedule. The prices of ipilimumab, nivolumab, pembrolizumab, and dabrafenib plus trametinib in the US (average wholesale price) were collected from public databases and the literature. The overall costs related to administration, subsequent therapy, and supportive and terminal care were collected from the published literature. In the US, the price of ipilimumab, nivolumab, pembrolizumab, and dabrafenib plus trametinib was discounted at 17% to account for contract pricing. In the BRAFT-guided strategy, BRAFT pathogenic variant testing cost was considered. The analysis included the costs related to managing grade 3 or greater adverse events, which were extracted from the literature.

The mean health utility scores for the PFD and PD states were derived from the published literature (eTable 4 in the Supplement), which were measured by standard gamble technique. The disutility value-related adverse drug reactions, specifying the decrease in the valued quality of life for a given adverse drug reaction, were adopted for 1 week for each incident event throughout treatment.

**Analysis**

The probabilistic sensitivity analyses were conducted for calculating the incremental cost-utility ratio (ICUR), which was expressed as the incremental cost per additional quality-adjusted life-year (QALY) gained in terms of next-best non-dominated option. A strategy would be termed as a dominated strategy if it is more costly, yet less effective than an alternative, or termed as an extended dominated strategy if it has a higher ICUR than the next more effective strategy. Costs and QALYs were discounted at an annual rate of 3%. We also estimated the incremental net health benefit (INHB, QALY) and incremental net monetary benefit (INMB, $) in terms of next-best non-dominated option based on the following formulas:

\[
\text{INHB}(\lambda) = \frac{(E_a - E_b) - (C_a - C_b)}{\lambda} = \Delta E - \Delta C/\lambda
\]

INMB(\lambda) = \frac{(E_a - E_b) \times \lambda - (C_a - C_b)}{\lambda} = \Delta E \times \lambda - \Delta C

where C and E are the cost and effectiveness of the next-best non-dominated option (a) or the last-best dominated option (b), respectively, and \( \lambda \) is the willingness-to-pay (WTP) threshold ($150 000/QALY). Subgroup analyses were performed in the prespecified subgroups as reported in the trials by varying the HRs of OS.

One-way sensitivity analyses were conducted for all parameters, and the estimated range of each parameter was either based on the reported or estimated 95% CIs in the referenced studies or determined by assuming a 25% change from the base-case value (Table 1). For checking effect of the price of nivolumab, ipilimumab, pembrolizumab, dabrafenib, and trametinib, a 50% reduction of their price would be assumed in the 1-way sensitivity analysis. In the probabilistic sensitivity analyses, a Monte Carlo simulation of 10 000 iterations was generated by simultaneously sampling the critical model parameters from the prespecified distributions. Gamma distribution was selected for the cost parameters, log-normal distribution for the HRs, and beta distribution for the probability, proportion, and preference value parameters. Based on the data from 1000 iterations, a cost-effectiveness acceptability curve was created to represent the likelihood that a competing option would be considered cost-effective at various WTP levels for health gains (QALYs).

**Results**

**Probabilistic Sensitivity Analyses**

Examining all treatment strategies incrementally (Table 2), nivolumab, pembrolizumab, and nivolumab plus ipilimumab strategies constituted the cost-effective frontier (eFigure 6 in the Supplement). By virtue of its lower cost and greater effectiveness, the cheapest nivolumab strategy dominated the ipilimumab and BRAFT-guided Pem-DT strategy. Compared with the nivolumab strategy, the pembrolizumab strategy yielded an additional 2.088 (SD, 1.311) QALYs with an
incremental cost of $5029 (SD, $13 696), which resulted in an ICUR of $8593 (SD, $592 995)/QALY and dominated the BRAF-guided Niv-DT and BRAF-guided NivIpi-Pem strategies. The BRAF-guided NivIpi-Niv strategy was extended dominated by the first-line nivolumab plus ipilimumab strategy, which gained the greatest health outcomes with an additional 2.66 (SD, 2.44) QALYs and $166 110 (SD, $36 093) compared with the pembrolizumab strategy. The ICUR of the first-line nivolumab plus ipilimumab over pembrolizumab strategy was $125 593 (SD, $5 751 223)/QALY. The deterministic results showed comparable ICURs (eTable 5 in the Supplement). At the threshold of $150 000/QALY, the first-line nivolumab plus ipilimumab strategy produced the greatest INHBs and INMBs, followed next by the nivolumab strategy.

At the WTP thresholds of $50 000, $100 000, and $150 000/QALY (Figure 2), the cost-effectiveness acceptability curve showed nearly 54%, 33% and 25% and 33%, and 55% and 64% probabilities of pembrolizumab and nivolumab plus ipilimumab strategies being cost-effective options in the simultaneous competition of the 8 strategies.

One-Way Sensitivity Analyses
In the comparison between pembrolizumab and nivolumab strategies, the 1-way sensitivity analyses revealed that the model outcomes were substantially influenced by the HR of OS of pembrolizumab, time horizon, and the cost related to nivolumab and pembrolizumab (eFigure 7A in the Supplement). In the comparison between the nivolumab plus ipilimumab and pembrolizumab strategies, the HRs of OS of pembrolizumab and nivolumab plus ipilimumab, time horizon, and the cost related to nivolumab, pembrolizumab, and ipilimumab played a considerable role in the model outcomes (eFigure 7B in the Supplement). The remaining parameters, such as the cost-utility values related to adverse drug reactions, had a moderate or small influence on the outcomes.

With the increase of the prevalence of BRAF pathogenic variant, the INHBs of BRAF-guided NivIpi-Niv and NivIpi-Pem strategies were augmented in comparison with the ipilimumab strategy, and the INHBs of BRAF-guided Pem-DT and Niv-DT strategies were reduced (eFigure 8 in the Supplement). However, the INHBs of nivolumab plus ipilimumab and pembrolizumab strategies were always higher than the 4 BRAF-guided strategies across the range of prevalence of BRAF pathogenic variant (14.3%-60%).

Subgroup Analyses
Because the nivolumab plus ipilimumab strategy gained the greatest health outcomes (Table 2), a subgroup analysis related to nivolumab plus ipilimumab treatment was performed (eFigure 9 in the Supplement). By varying the HRs of OS between the nivolumab plus ipilimumab and ipilimumab strategies, the INHBs in the subgroups with respect to the health benefit varied from 2.08 (range, 1.54-2.78; probabilities of cost-effectiveness, 100%) in more than 3 lesion sites to 2.84 (range, 2.21-3.33; probabilities of cost-effectiveness, 100%) in 1 lesion site.

Discussion
Our analysis yielded 4 key findings. First, of the 8 competing strategies examined, an up-front use of nivolumab plus ipilimumab without BRAF pathogenic variant testing could maximize the health outcome, followed by BRAF-guided NivIpi-Niv and pembrolizumab strategies. Second, as indicated in the economic analysis, the pembrolizumab, nivolumab, and nivolumab plus ipilimumab strategies were found to be the potentially most cost-effective options in the cost-effective frontier, and the other competing options were dominated because of their relatively higher cost and lower health outcomes or for not being cost-effective as a result of the ICUR far exceeding the WTP threshold. Third, BRAF pathogenic variant testing did not show the value of improving the cost-effectiveness and generating more favorable health outcomes in BRAF-guided strategies, which were dominated by the strategies in the cost-effective frontier. Fourth, the most influential parameters driving our model were the treatment efficacy of these new regimens. The results indicated that those with longer OS would have more favorable economic outcomes.

Our findings are consistent with those of another economic study published by Oh and colleagues, which determined the cost-effectiveness of nivolumab, ipilimumab, and nivolumab plus ipilimumab as frontline therapies in metastatic melanoma from a US societal perspective. They found that nivolumab plus ipilimumab and nivolumab monotherapy were cost-effective in comparison with ipilimumab monotherapy, and nivolumab plus ipilimumab was not cost-effective in comparison with the nivolumab strategy. A 2017 economic study revealed that the ICUR of pembrolizumab vs
iipilimumab strategy was $81,091/QALY. This finding indicated pembrolizumab to be cost-effective for the treatment of patients with advanced melanoma from a US health system perspective, which is different from the cost-saving results found in the current study. The potential reason for this is that perhaps the lower cost of overall subsequent therapy in the study by Wang and colleagues. In February 2018, the FDA modified weight-based doses of pembrolizumab given as monotherapy to fixed doses (200 mg every 3 weeks), which might further reduce the costs related to pembrolizumab compared with the study by Wang and colleagues. In Norwegian patients with the BRAF pathogenic variant, Pike and colleagues found that none of 7 new drugs (cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib, or vemurafenib) can be considered cost-effective when compared with chemotherapy. However, chemotherapy was dominated by pembrolizumab in the US patients with the BRAF pathogenic variant. Because the Norwegian and US studies focused on patients with confirmed BRAF status and used chemotherapy as the reference strategy, our results are not comparable with these studies.

Strengths and Limitations

The strengths of this study are worth highlighting. First, to our knowledge, our analysis provides the most comprehensive evaluation to date that compares different treatment strategies for newly diagnosed advanced melanoma with unknown BRAF pathogenic variant status; our analysis also addresses the BRAF pathogenic variant testing value for directing immunotherapy and targeted treatment. Second, the current analysis adopted the latest long-term survival data from the CheckMate 067, KEYNOTE-006, COMBI-d, and COMBI-v trials, which could more credibly track the health and economic outcomes. Finally, we accounted for the advanced melanoma with unknown BRAF pathogenic variant information, rather than a confirmed BRAF pathogenic variant status, which emulates the real-world diagnostic and treatment pathway.

Several weaknesses should also be noted. First, owing to the lack of head-to-head data, an indirect comparison was conducted; this presents a weakness because the comparison relies on the assumption that the included studies did not differ in terms of patient characteristics, especially the COMBI-d and COMBI-v trials, which included more metastatic tumors than the CheckMate 067 and KEYNOTE-006 trials. Fortunately, by using the base-case PFS and OS data of dabrafenib plus trametinib for BRAF pathogenic variant tumors as the reference and adjusting the HRs of PFS and OS, the 2-way sensitivity analyses showed that the nivolumab strategy still dominated the BRAF-guided Pem-DT and Niv-DT strategies (eFigure 10 in the Supplement). Second, the current analysis did not include other new competing agents, such as encorafenib plus binimetinib, because long-term survival data of these treatments are not yet available. Finally, owing to the theoretical challenges associated with aggregating the costs and effects that fall on different sectors and individuals, we did not adopt a societal perspective, which included the costs related to the informal health care and non–health care sectors.

Conclusions

In summary, for newly diagnosed advanced melanoma, the first-line treatment approaches of nivolumab plus ipilimumab and pembrolizumab were the more cost-effective alternatives on the basis of currently accepted WTP thresholds. The up-front use of BRAF and MEK inhibitors for the subgroup with the BRAF pathogenic variant was not found to be cost-effective, which indicates that BRAF and MEK inhibitors might be able to play an active role in the second-line setting.


