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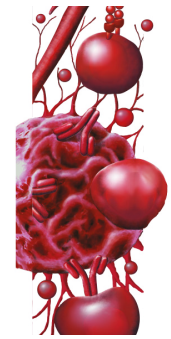

Sequential treatment approaches in the management of *BRAF* wild-type advanced melanoma: a cost–effectiveness analysis

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Aim: To evaluate the cost–effectiveness of treatment sequences with checkpoint inhibitors in patients with *BRAF* wild-type melanoma. **Materials & methods:** Using a discrete event simulation model, cost and health outcomes were estimated. Pooled data from CheckMate 067/069 trials were used to calculate survival outcomes including treatment-free interval extrapolated over a patient's lifetime. Costs accounted for treatment, administration, toxicity, and disease management. **Results:** First-line anti-PD-1 + anti-CTLA-4 initiating sequences had the highest estimated mean survival gain (7.6–7.7 years), driven by a longer estimated mean treatment-free interval (5.3 years). Incremental costs per incremental quality-adjusted life year gained for anti-PD-1 + anti-CTLA-4 followed by chemotherapy were US$30,955 versus anti-PD-1 initiating sequences, within the willingness-to-pay threshold. **Conclusion:** Anti-PD-1 + anti-CTLA-4 initiating sequences for *BRAF* wild-type melanoma are cost-effective versus anti-PD-1 .

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Keywords: economic models • ipilimumab • nivolumab

Melanoma is a common cancer in the USA, with more than 75,000 new cases and 10,000 deaths annually [1]. Although patients with localized early-stage melanoma have a 5-year survival rate of 98% [2], those with advanced melanoma historically have had a poor prognosis, with a 5-year survival rate of approximately 10% [3].

Patients with melanoma have a high mutation burden, with *BRAF* being the most commonly mutated gene. Although as many as 50% of patients with advanced melanoma have *BRAF* mutations, an equally substantial population of patients are reported to have normal or wild-type *BRAF* [2]. Regardless of *BRAF* status, immunotherapies can be effective for the treatment of advanced melanoma [4–6]. With the availability of antibody technology, immunotherapy has transitioned from a broad-based therapy to immune checkpoint inhibition that targets cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed death 1 (PD-1) receptors. These include ipilimumab (anti-CTLA-4) [7], nivolumab [4,8] and pembrolizumab (anti-PD-1) [8,9], as well as nivolumab plus ipilimumab in combination [10]. Targeted therapies that are specific to *BRAF* mutant melanoma are inhibitors of MAPK signaling, such as dabrafenib/vemurafenib (BRAF inhibitors) [11,12] and trametinib/cobimetinib (MEK inhibitors) [13,14].

With the availability of multiple therapeutic agents, there is a need to identify optimal sequencing strategies for both *BRAF* wild-type and *BRAF* mutant patient populations. Treatment sequences for *BRAF* mutant patients have to be considered separately, since these patients have an additional class of therapies that can be used in their treatment journey. An economic model assessing the clinical and economic outcomes of patients with *BRAF* mutant

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advanced melanoma reported that initiating first-line treatment with an anti-PD-1 + anti-CTLA-4 combination provided a longer survival benefit compared with BRAF + MEK inhibitors, leading to lower average cost per life year [15,16].

For *BRAF* wild-type patients, the only available effective options are immune checkpoint inhibitors. Whether to use these agents in combination upfront or sequentially is currently unknown from a cost–effectiveness perspective. A recent study concluded that first-line anti-PD-1 monotherapy followed by second-line ipilimumab was the most cost-effective treatment sequence for patients with *BRAF* wild-type advanced melanoma [17]. However, this analysis was confined to the summary end points of trials and did not adequately represent the properties of immunotherapies, such as treatment-free intervals and the resolution of adverse events with the use of immune-modulating agents like corticosteroids [18].

There is evidence that the use of checkpoint inhibitor therapies may be associated with sustained clinical benefit beyond treatment discontinuation [19], delaying subsequent treatment initiation and resulting in a long treatment-free intervals [20,21]. Pooled data from the CheckMate 067 and CheckMate 069 trials showed a longer treatment-free interval in patients on nivolumab + ipilimumab compared with those on nivolumab and ipilimumab alone [21]. Treatment-free interval is not captured by previously published cost–effectiveness analyses, therefore, potentially underestimating the benefit of these therapies. However, a long treatment-free interval and multiple lines of treatment will come at higher costs, influenced by the cost of treatments, associated adverse events and management of the condition. Given this perspective, there is a need to assess the cost–effectiveness of a sequence of treatments capturing the benefits and costs of each line of therapy explicitly. In this study, we used individual patient simulation to assess the overall quality-adjusted life years and total costs associated with relevant treatment sequences in patients with *BRAF* wild-type advanced melanoma. The costs are estimated from a US third-party payer's (such as commercial insurer, Medicaid and Medicare) perspective over the patient's lifetime.

Materials & methods

Model overview

The economic model presented here evaluated treatment sequences for patients with advanced melanoma and wild-type *BRAF* tumors naive to systemic therapies. Treatments approved by the US FDA and incorporated into treatment guidelines were included in sequences specified based on clinical relevance, as determined by market research data and expert opinion. These sources suggest that immunotherapies as monotherapy or in combination are the preferred choice for the first- and second-line treatment of patients with wild-type *BRAF* advanced melanoma. Chemotherapies are primarily used as salvage or palliative therapy in later lines of treatment. Therefore, the model considers sequences starting with an anti-PD-1, an anti-CTLA-4 or an anti-PD-1 + anti-CTLA-4 combination. Monotherapies are followed by an anti-PD-1 or an anti-CTLA-4 monotherapy, while an anti-PD-1 + anti-CTLA-4 combination is followed by chemotherapy or an anti-PD-1. The latter sequence is included because patients who experience benefit on an anti-PD-1 + anti-CTLA-4 combination, but discontinue due to toxicity and subsequently, experience disease progression, may reinitiate an anti-PD-1 monotherapy. Anti-PD-1 agents were represented in the model by nivolumab and pembrolizumab assuming an equal share, anti-CTLA-4 by ipilimumab, anti-PD-1 + anti-CTLA-4 by nivolumab + ipilimumab and chemotherapy by a mix of dacarbazine, temozolomide, paclitaxel and carboplatin + paclitaxel.

The model was developed as a discrete event simulation to estimate lifetime (30 years) cost and health outcomes, discounted at 3.0% per annum, from a US third-party payer's perspective. The model was developed using the discretely integrated condition event technique in Excel and Visual Basic for Applications [22]. Details of the modeling methods are presented below.

Model structure

The model used available clinical trial data to evaluate treatment sequences for a cohort of patients in which each patient has a unique set of baseline characteristics for each treatment sequence. Based on the characteristics and the correlation of outcomes, the model predicted the time to clinical events for each line of treatment in a sequence (Figure 1). These events were the start and the end of therapy lines, and the time of death during various disease stages.

At model initiation, patients start with first-line treatment and may discontinue treatment for any reason. After discontinuation, patients may remain treatment free for a variable amount of time before they start subsequent (second-line) therapy. Patients may progress while on first-line treatment or during the treatment-free interval.

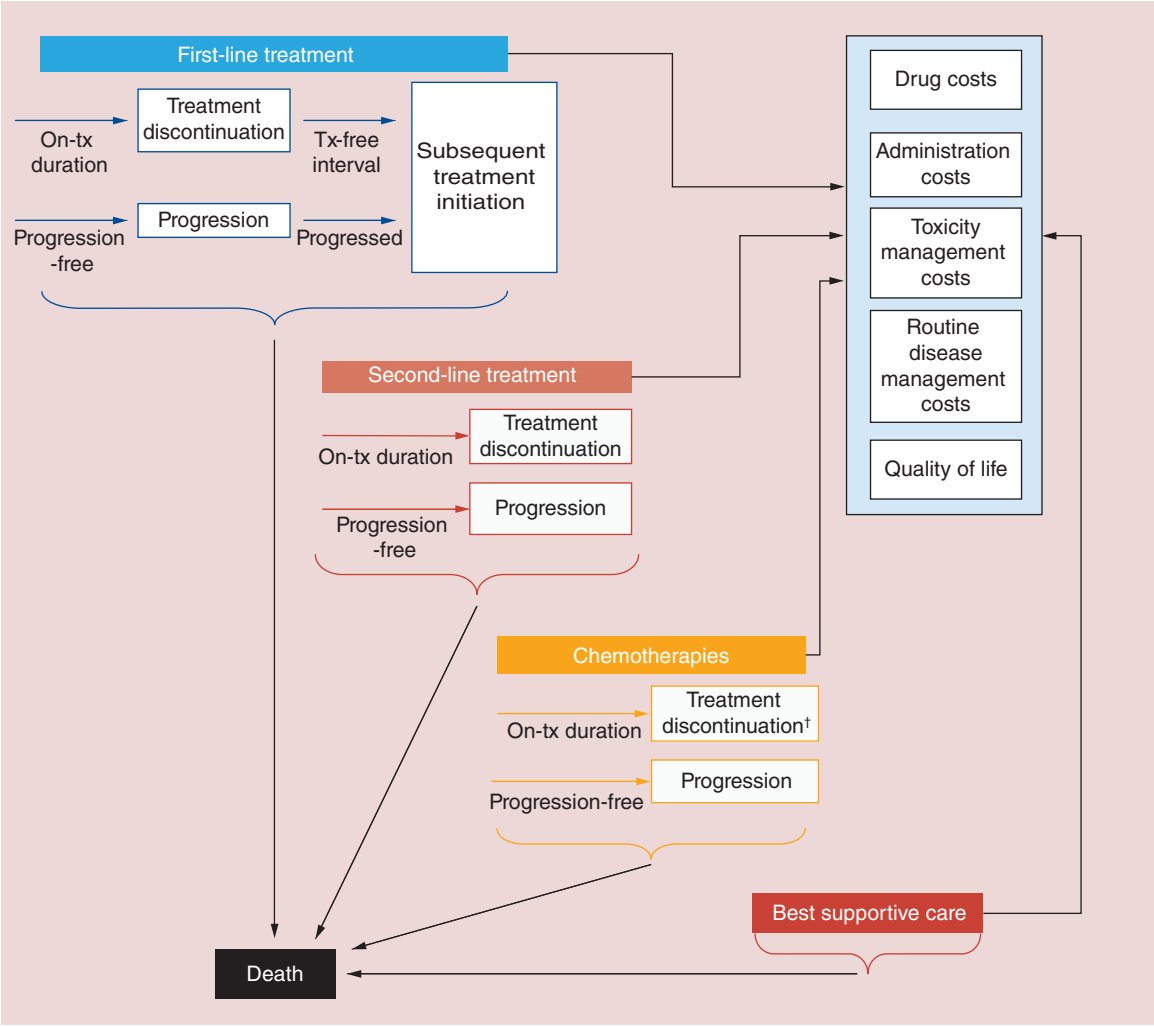

Figure 1. Schematic of the discrete event simulation developed to estimate lifetime cost and health outcomes.
†Progression used as a proxy for treatment duration.
Tx: Treatment.

Patients who progress, but remain alive, then start second-line treatment. A treatment-free interval following second-line treatment was not included in the model because of a lack of available data. Patients may start a third-line treatment upon second-line progression, including a blend of chemotherapies or best supportive care. Patients may die at any time in the model. Patients accrue costs for drug acquisition, administration and adverse events while on treatment, as well as disease management over their entire lifetime. Additionally, quality of life was accounted for based on disease phase, and disutility due to adverse events on the time to resolution of the adverse event experienced.

Statistical analyses & efficacy modeling

The engine of the model was a set of statistical risk equations for anti-PD-1, anti-CTLA-4 and anti-PD-1 + anti-CTLA-4 initiating sequences, estimated using the pooled patient-level dataset for nivolumab, ipilimumab and nivolumab + ipilimumab from the Phase III CheckMate 067 [6] and Phase II CheckMate 069 [5] clinical trials and extensive discussions with clinicians. For each patient in the model, these equations predict time on first-line treatment, time between discontinuing first-line therapy and initiation of subsequent treatment (i.e., the length of treatment-free interval), time on second-line treatment and risk of death at any specific treatment phase. More details about the statistical analyses and the covariates included in the various risk equations are provided in the supplement and Supplementary Table 1. The internal clinical validity of the risk equations was established

Table 1. Estimated drug, administration, adverse event management and disease management costs per month.

	Anti-CTLA-4	Anti-PD-1		Anti-PD-1 + anti-CTLA-4	Chemotherapy			
	Ipilimumab	Nivolumab	Pembrolizumab	Nivolumab + Ipilimumab[†]	Dacarbazine	Temozolomide	Paclitaxel	Carboplatin + Paclitaxel
Drug cost[‡]	$50,463[§]	$13,280	$13,083	$13,280	$261	$1,748	$280	$412
Administration cost	$363[§]	$456	$304	$456	$1518	$0	$911	$607
Grade 3/4 management cost								
First-line	$138	$36	$30	$414	–	–	–	–
Second-/third-line	$247	$4	$7	–	$474	$298	$988	$1546
Grade 3/4 immune-related AE management								
First-line	$106	$26	$26	$170	–	–	–	–
Second-/third-line	$107	$0	$0	–	–	–	–	–
Disease management cost: first-line								
On-treatment, progression-free	$844	$482	$482	$798	–	–	–	–
On-treatment, progressed	$1071	$1176	$1176	$1230	–	–	–	–
Off-treatment, progression-free	$730	$188	$188	$263	–	–	–	–
Off-treatment, progressed	$1622	$1608	$1608	$1298	–	–	–	–
Disease management cost: second- and third-line								
On-treatment	$351	$395	$395	–	$826	$826	$826	$826
Off-treatment	$741	$688	$688	–	$760	$760	$760	$760

[†]Induction drug cost was $54,152 for 2.76 months and induction administration cost was $667 for 2.76 months.
[‡]For drug cost calculations, a mean weight of 82.8 kg and a mean body surface area of 1.91 m^2 were used based on the CheckMate 069 and CheckMate 067 trials.
[§]Induction drug cost was $50,463 for 2.76 months and induction administration cost was $363 for 2.76 months.
AE: Adverse event; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed death 1.

by comparing the model-simulated outcomes with observed trial data from the two CheckMate studies [5,6,10] (Supplementary Figures 1–5). Statistical analyses and their validation are reported in detail elsewhere.

The efficacy of pembrolizumab first-line therapy was assumed to be equivalent to nivolumab. This was supported by clinical opinion, similar overall survival (OS) reported in a network meta-analysis (hazard ratio = 1.08; 95% CI: 0.69–1.68) of pembrolizumab versus nivolumab [Bristol-Myers Squibb, Unpublished Data], and similar median treatment duration for pembrolizumab and nivolumab in the KEYNOTE-006 [8] and CheckMate 067 [10] trials, respectively. CheckMate trials allowed immuno-oncology treatment receipt until progression, toxicity, or physician discretion; therefore, an early stopping rule (e.g., 2 years as mandated by KEYNOTE-006 [23]) was considered only as a scenario.

To generate results, real patient profiles based on baseline characteristics from the *BRAF* wild-type patient pool of the CheckMate 067 and CheckMate 069 trials [5,6,10,24] were run through the simulation. The summary of baseline characteristics is provided in Supplementary Table 2. Most patient characteristics included in this model were assumed to be constant over time. The following four characteristics were considered time-dependent and, hence, had to be updated during the simulation: age, time since diagnosis, Eastern Cooperative Oncology Group score, and lactate dehydrogenase level.

Costs

The drug and administration costs per month were estimated using drug acquisition cost, route of administration, unit costs for administration (payer reimbursement for intravenous drug administration in the hospital outpatient setting), recommended dose, and dosing frequency based on publically available sources [25–27], US FDA labels [28–30] and clinical trials (Table 1 and Supplementary Tables 3–6) [31–33]. The model considers grade 3/4 treatment-related and immune-related adverse events reported in the trials. Only grade 3/4 adverse events were included, as they incur higher resource use, such as outpatient and inpatient hospitalizations, and affect patients' quality of life

compared with grade 1/2 adverse events. Adverse event management costs based on the inpatient and outpatient settings were obtained from published literature [34–36] (Table 1 and Supplementary Tables 7–11). Unit costs, which were not in 2016 dollars, were inflated using the medical consumer price index from the USA. Treatment-related costs, including drug, administration and adverse event management, were applied for the entire duration of treatment. All costs are varied 20% around the mean.

Routine disease management costs were estimated from the CheckMate 067 and CheckMate 069 trial data. Annual rates of resource use were analyzed by treatment arm, for being on-treatment or treatment-free, and being progression-free or progressed (Table 1 & Supplementary Tables 12–18). Unit costs for concomitant drugs, hospitalization events, surgeries, laboratory tests and procedures associated with the management of the disease were obtained from published sources [26,37–39]. The annual cost of disease management was applied for the patient's entire lifetime. Hospitalization and surgery costs during the treatment-free interval identified from the trials were applied for 28 months after treatment initiation.

Quality of life

The model considered measures of health-related quality of life for progression-free and progressed health states (0.79 and 0.75, respectively), estimated from responses to a generic and regularly reported health utility measure collected in CheckMate 067, the EuroQoL-5 dimensions [40]. These were combined with progression-free survival data to estimate quality-adjusted life years.

Adverse event-related utility decrements or disutilities were considered, depending on the setting of care (outpatient, -0.13; inpatient, -0.17), with the probability of incidence obtained from clinical trials (Supplementary Table 19) and setting of care derived from the sources listed for the cost of adverse events above. The duration of disutility related to adverse events is based on time to resolution of events reported in CheckMate 067. For adverse events not reported in CheckMate 067, published literature was used.

Analyses

The model estimated total life years, quality-adjusted life years and lifetime costs for each treatment sequence, as well as the incremental cost per incremental life year and cost per quality-adjusted life year gained. To estimate uncertainty in results, sensitivity analyses were conducted where inputs were varied as per the standard guidelines by the International Society for Pharmacoeconomics and Outcomes Research — Society for Medical Decision Making task force. The impact of each varied input on the model outcomes was presented as a tornado graph. Probabilistic analyses, based on 1000 Monte Carlo simulations, were presented as cost–effectiveness acceptability curves to capture the impact of uncertainty around the input parameters on the probability of individual sequences being the most cost-effective strategy under various willingness-to-pay thresholds.

Results

The estimated total life years, quality-adjusted life years and lifetime costs for each treatment sequence, as well as the estimated cost per life year and cost per quality-adjusted life year gained, are presented in Table 2. Sequences starting with anti-PD-1 + anti-CTLA-4 combination were estimated to have the highest number of life years (7.6–7.7 years) as well as quality-adjusted life years (5.8–5.9 years). The main driver of additional life years and quality-adjusted life years gained for first-line anti-PD-1 + anti-CTLA-4 initiating sequences was a longer treatment-free interval with the first-line treatment anti-PD-1 + anti-CTLA-4 combination (mean of 5.3 years) compared with first-line anti-PD-1 (mean of 3.5 years) and first-line anti-CTLA-4 (mean of 2.4 years) alone. Total costs are also highest for anti-PD-1 + anti-CTLA-4 initiating sequences.

Examining the costs and benefits associated with sequences incrementally, first-line anti-PD-1 + anti-CTLA-4 followed by chemotherapy produced the largest gain in life years and quality-adjusted life years, associated with a minor addition in costs, making it a cost-effective strategy compared with first-line anti-CTLA-4 followed by anti-PD-1 and anti-PD-1 followed by anti-CTLA-4 (Table 3). Incremental cost–effectiveness of anti-PD-1 + anti-CTLA-4 followed by anti-PD-1 compared with anti-CTLA-4 initiating sequences or anti-PD-1 initiating sequences was higher, but well within the willingness-to-pay threshold of $150,000/quality-adjusted life year [41].

Running a scenario with a maximum of 2-year treatment duration did not impact overall results (Supplementary Table 20). The probabilistic analyses, representing the uncertainty in the input parameter estimates (Figure 2), resulted in a cost–effectiveness acceptability curve showing that above a willingness-to-pay value of $32,500, anti-PD-1 + anti-CTLA-4 followed by chemotherapy is the most cost-effective treatment strategy (Figure 3). Univariate

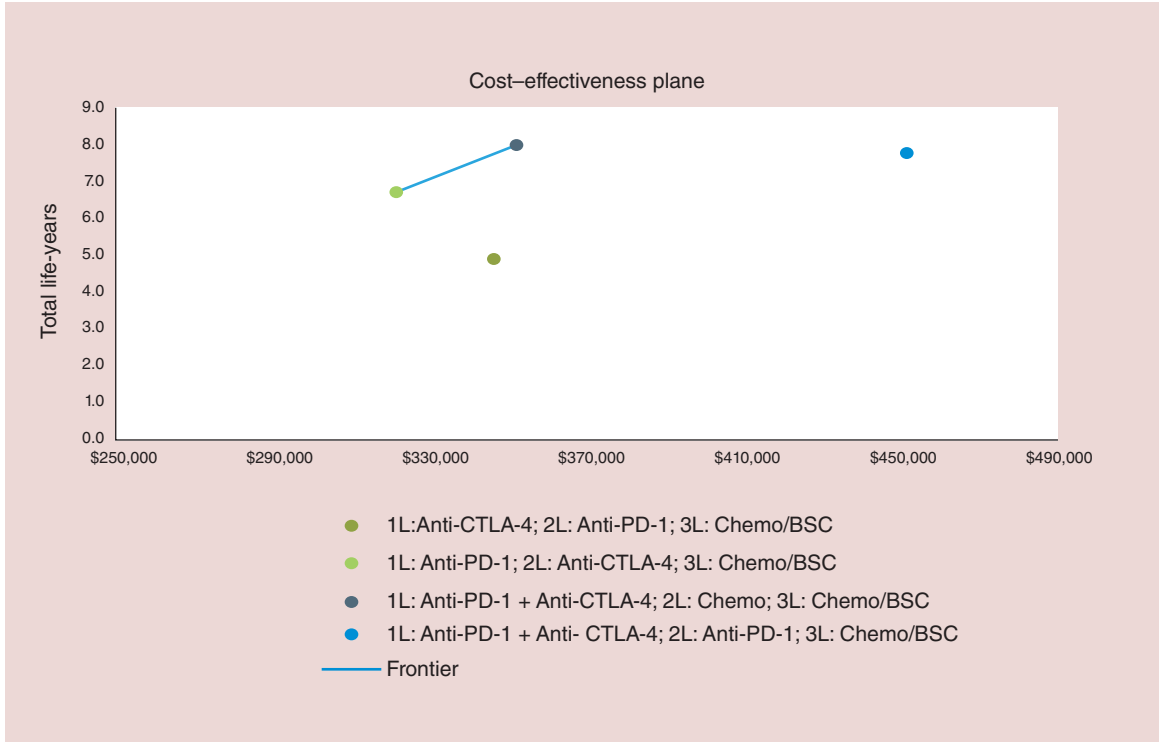

Figure 2. Probabilistic sensitivity analysis showing the cost–effectiveness frontier for checkpoint inhibitor therapies.
1L: First-line; 2L: Second-line; 3L: Third-line; BSC: Best supportive care; Chemo: Chemotherapy; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed death 1.

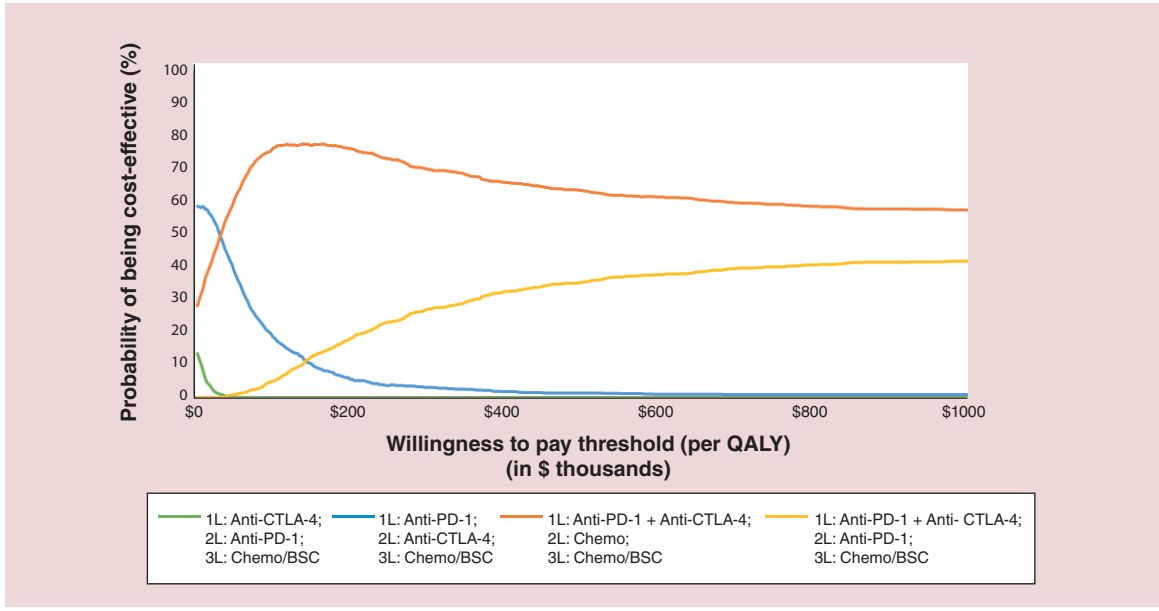

Figure 3. Cost–effectiveness acceptability curves.
1L: First-line; 2L: Second-line; 3L: Third-line; BSC: Best supportive care; Chemo: Chemotherapy; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed death 1; QALY: Quality-adjusted life year.

Table 2. Cost and health outcomes as estimated life years, total LYs, total QALYs and lifetime costs.

Sequence	1L Anti-CTLA-4; 2L Anti-PD-1; 3L Chemo/BSC	1L Anti-PD-1; 2L Anti-CTLA-4; 3L Chemo/BSC	1L Anti-PD-1 + anti-CTLA-4; 2L Chemo; 3L Chemo/BSC	1L Anti-PD-1 + anti-CTLA-4; 2L Anti-PD-1; 3L Chemo/BSC
1L On-treatment LYs	0.65	1.30	1.05	1.05
1L Treatment-free LYs	2.36	3.47	5.27	5.27
2L On-treatment LYs	1.15	0.46	0.46	0.73
3L On-treatment LYs	0.06	0.08	0.05	0.04
Post 3L LYs	0.53	1.11	0.90	0.56
Total LYs	4.75	6.42	7.72	7.64
Total QALYs	3.64	4.91	5.90	5.84
First-line costs	$142,981[†]	$257,609	$322,664	$322,664
Second-line costs	$193,441	$48,279[†]	$16,868	$121,478
Third-line costs	$7120	$13,193	$10,175	$6402
Total cost	$343,542	$319,082	$349,707	$450,544
Average cost per LY	$72,255	$49,732	$45,272	$58,982
Average cost per QALY	$94,268	$65,040	$59,320	$77,189

[†]Includes only drug cost per month of $50,463 for 2.76 months and administration cost per month was $363 for 2.76 months.
1L: First-line; 2L: Second-line; 3L: Third-line; BSC: Best supportive care; Chemo: Chemotherapy; CTLA-4: Cytotoxic T-lymphocyte antigen 4; LY: Life year; PD-1: Programmed death 1; QALY: Quality-adjusted life year.

Table 3. Incremental cost per incremental effectiveness ratio (per quality-adjusted life years).

	ICER vs 1L Anti-CTLA-4 2L Anti-PD-1	ICER vs 1L Anti-PD-1 2L Anti-CTLA-4	ICER vs 1L Anti-PD-1 + anti-CTLA-4 2L Chemo	ICER vs 1L Anti-PD-1 + anti-CTLA-4 2L Anti-PD-1
1L Anti-CTLA-4 2L Anti-PD-1 3L Chemo/BSC	–	Dominated	$**2739**	$**48,802**
1L Anti-PD-1 2L Anti-CTLA-4 3L Chemo/BSC	Dominant	–	$**30,955**	$**141,213**
1L Anti-PD-1 + anti-CTLA-4 2L Chemo 3L Chemo/BSC	$*2739*	$*30,955*	–	Dominant
1L Anti-PD-1 + anti-CTLA-4 2L Anti-PD-1 3L Chemo/BSC	$*48,802*	$*141,213*	Dominated	–

Italic costs = more costly, more effective; bold costs = less costly, less effective.
1L: First-line; 2L: Second-line; 3L: Third-line; BSC: Best supportive care; Chemo: Chemotherapy; CTLA-4: Cytotoxic T-lymphocyte antigen 4; ICER: Incremental cost per incremental effectiveness ratio; PD-1: Programmed death 1.

sensitivity analyses (Supplementary Figure 6) showed that model outcomes were sensitive to the treatment effect coefficient of the risk equations for time on first-line treatment, time to subsequent treatment, time on second-line treatment, survival during treatment-free interval and survival after second-line treatment. Furthermore, the analysis results were influenced by utilities (pre- and post-progression), drug costs and disease management costs. Both costs and quality-adjusted life years were sensitive to the mortality rate during the treatment-free interval and the time to second-line treatment initiation. Costs and quality-adjusted life years were determined by the duration of the treatment-free interval where patients did not incur costs but accumulated health benefits.

Discussion

Despite the improved outcomes with immunotherapies and targeted therapies, most patients with advanced melanoma continue to receive multiple lines of therapy, due to disease progression or toxicity. The increasing number of treatment options poses a considerable economic impact in the management of advanced melanoma, although the bigger challenges are to determine an optimal first-line therapy and whether there is an optimal sequence or combination [42]. In this regard, economic models that assess cost–effectiveness of various treatments

in a specific line of treatment [15–18] often do not consider sequential treatments and optimal positioning of various treatments.

In this study, we have quantified the overall economic burden of managing patients with *BRAF* wild-type advanced melanoma with sequential treatments, estimated the optimal positioning of anti-PD-1 + anti-CTLA-4 in the treatment algorithm and quantified the added benefit of anti-PD-1 + anti-CTLA-4 compared with other therapies in overall health and economic benefit.

In the CheckMate 067 trial, although median OS had not been reached in the combination treatment group, long-term survival outcomes were superior in the nivolumab-containing groups compared with the ipilimumab alone group [6]. Descriptive analyses suggest numerically higher survival rates with nivolumab + ipilimumab than nivolumab alone at 3 years (58 and 52%, respectively) [6]. In the current analysis, when clinical outcomes are extrapolated over a patient's lifetime, first-line anti-PD-1 + anti-CTLA-4 was estimated to offer an additional 1.2–3.0 life years compared with sequences starting with first-line anti-PD-1 or anti-CTLA-4, respectively.

The survival advantage estimated with the use of nivolumab + ipilimumab in the first line was primarily driven by a significant extension in the treatment-free interval after patients discontinue first-line treatment [21] (Supplementary Figure 2). This level of clinically meaningful increase in treatment-free interval is a hallmark of immunotherapy and is rarely seen with other forms of advanced cancer therapy. While most clinical trials in melanoma focus primarily on progression-free survival gains, the possibility for a patient to achieve durable disease control without the need for continuously receiving cancer treatment is a highly valued clinical benefit. We argue that such long-term clinical gains need to be taken into account in estimating the most optimal treatment sequences. Furthermore, in addition to our modeling analysis, it is important that long-term follow-up data from the CheckMate studies be investigated in order to confirm the treatment-free interval and life years predictions of our model.

The extension in life years seen in our model also translated to an increase in quality-adjusted life years. Anti-PD-1 + anti-CTLA-4 initiating sequences were associated with an additional 0.9–2.3 quality-adjusted life years compared with anti-PD-1 or anti-CTLA-4 monotherapy initiating sequences. Further, it is also important to acknowledge that the anti-PD-1 + anti-CTLA-4 combination was associated with a higher probability of grade 3/4 adverse events, although most of these adverse events tend to resolve within a limited period of time. In CheckMate 067, except for endocrine adverse events that may lead to long-term hormone replacement therapy, most treatment-related adverse events of grade 3/4 resolved within 2–3 months [6]. Therefore, the incidence of higher-grade adverse events tends to have a small impact on the quality-adjusted life years that were estimated over a patient's lifetime.

Anti-PD-1 + anti-CTLA-4 initiating sequences were associated with high first-line treatment costs, primarily driven by drug and disease management costs. Rather than assuming patients are treated until progression, as many cost–effectiveness analyses do [17], first-line treatment costs in this analysis were accrued based on the actual treatment duration observed in the CheckMate trials. Combination immunotherapy (nivolumab + ipilimumab) has high drug costs; however, only 10–20% of patients in the CheckMate studies received second or later lines of treatment, hence the treatment-free interval benefit with the combination immunotherapy. This is well supported in this analysis with the nivolumab + ipilimumab initiating treatment sequences.

Avoiding later lines of treatment was estimated to lead to a total cost savings of approximately $100,000 over the entire lifetime, which may offset the higher expenditures accrued by the first-line combination treatment. Overall, the cost per life year and cost per quality-adjusted life year for anti-PD-1 + anti-CTLA-4 followed by chemotherapy were the lowest compared with other treatment sequences.

A cost-effective analysis by Kohn *et al.* examined different immunotherapy sequencing strategies for the treatment of patients with *BRAF* wild-type advanced melanoma, utilizing a distinct modeling strategy [17]. They concluded that first-line anti-PD-1 followed by second-line anti-CTLA-4 was the most cost-effective sequencing strategy for the treatment of metastatic melanoma. Kohn *et al.* used a cohort-based model that assumes patients are homogeneous with respect to their baseline characteristics and that baseline characteristics have no explicit impact on clinical outcomes. In addition, they used trial-reported Kaplan–Meier curves and combined data from various first-line and second-line trials. In our analysis, patient-level data were used and patient-level simulation was conducted to model the impact of patient characteristics and the correlation of disease milestones on clinical outcomes. Further, where the Kohn *et al.* study used a Weibull distribution to model survival outcomes, we applied a set of sequential risk equations and piecewise fitting of the survival data to reflect the unique mechanism of action for immunotherapies, which show reduction in hazards over time resulting in Kaplan–Meier curve plateaus [43,44]. Finally, the analysis by

Kohn *et al.* did not take into account key features of immunotherapy, such as the impact of the contribution of treatment-free periods to life year and cost outcomes, which is unique to our analysis to the best of our knowledge, and allows a closer approximation of real-world patient experience.

Our study has several limitations that should be considered when interpreting the results. A general limitation was that the results were limited to the patient cohorts enrolled in CheckMate 067 and CheckMate 069 and, therefore, may not represent the general advanced melanoma population. Due to the nature of the data, family, employer and societal perspectives were not incorporated into the value-based model. In addition, potential treatment-free interval or progression after second-line treatment was not modeled because the data were not available from clinical trials. The analysis uses second-line progression based on published second-line trials [7,9,31,45–47] due to lack of data for progression on subsequent therapies in the CheckMate trials. Notably, chemotherapy was used as a second-line option after anti-PD-1 + anti-CTLA-4 or as a third-line option after second-line treatment, given limited options available for patients with *BRAF* wild-type advanced melanoma. However, the impact of chemotherapy on the observed findings is expected to be minor because chemotherapy is relatively inexpensive and nonefficacious. Another assumption in the study was made for pembrolizumab, for which data were based on ipilimumab trials (except for treatment-related costs and adverse event incidences) due to the lack of patient-level clinical trial data on pembrolizumab. Further analyses will need to confirm similarities of outcomes for the two treatments. Grade 1/2 adverse events were not included in the analysis as they are expected to have minor cost or quality-of-life implications.

Conclusion

Treatment sequences initiating with anti-PD-1 + anti-CTLA-4 combination followed by either chemotherapy or anti-PD-1 monotherapy seem to be cost effective and provide important OS gains as well as quality-adjusted survival gains to patients with *BRAF* wild-type advanced melanoma. These improvements were driven by a longer mean treatment-free interval before patients require subsequent therapy.

Summary points

- Multiple checkpoint inhibitors have been approved for the treatment of advanced melanoma in the past several years. Thus, creating more options in the treatment of this fatal disease, but also leading to difficult treatment decisions.
- A cost–effectiveness analysis was conducted to distinguish between various treatment sequences used in treating *BRAF* wild-type advanced melanoma.
- A patient-level simulation was developed using discretely integrated condition event structure to evaluate cost and health outcomes over a patient's lifetime.
- The analysis is based on patient-level data from Phase III CheckMate 067 and Phase II CheckMate 069 clinical trials and takes into account several relationships between patient characteristics and outcomes (treatment duration, treatment-free interval, progression and survival).
- First-line anti-PD-1 + anti-CTLA-4 initiating sequences had the highest estimated mean survival gain (7.6–7.7 years), driven by estimated mean treatment-free interval (5.3 years).
- Incremental costs per incremental quality-adjusted life year gained for anti-PD-1 + anti-CTLA-4 followed by chemotherapy were US$30,955 versus anti-PD-1 initiating sequences, within the willingness-to-pay threshold.
- Anti-PD-1 + anti-CTLA-4 initiating sequences for *BRAF* wild-type melanoma are cost-effective versus anti-PD-1 or anti-CTLA-4 initiating sequences.

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Authors' contributions

Study conceptualization: A Tarhini, A Benedict, A Ambavane and S Rao. Methodology: A Benedict and A Ambavane. Formal analysis: V Aponte-Ribero. Investigation: all authors. Writing of original draft, review, and editing: all authors.

Availability of data & materials

BMS policy on data sharing may be found at https://www.bms.com/researchers-andpartners/independent-research/data-sharing-request-process.html

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at www.futuremedicine.com/doi/suppl/10.2217/imt-2018-0085

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J. Clin.* 67(1), 7–30 (2017).
2. American Cancer Society. Cancer treatment & survivorship facts & figures 2016–2017 (2016). www.cancer.org/acs/groups/content/@research/documents/document/acspc-048074.pdf
3. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist* 16(1), 5–24 (2011).
4. Weber JS, D'Angelo SP, Minor D *et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, Phase 3 trial. *Lancet Oncol.* 16(4), 375–384 (2015).
5. Hodi FS, Chesney J, Pavlick AC *et al.* Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, Phase 2 trial. *Lancet Oncol.* 17(11), 1558–1568 (2016).
6. Wolchok JD, Chiarion-Sileni V, Gonzalez R *et al.* Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N. Engl. J. Med.* 377(14), 1345–1356 (2017).

•• **The CheckMate 067 study demonstrated that, among patients with advanced melanoma, significantly longer overall survival occurred with nivolumab plus ipilimumab combination therapy or with nivolumab monotherapy than with ipilimumab alone.**

7. Hodi FS, O'Day SJ, McDermott DF *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363(8), 711–723 (2010).
8. Robert C, Schachter J, Long GV *et al.* KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
9. Ribas A, Puzanov I, Dummer R *et al.* Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, Phase 2 trial. *Lancet Oncol.* 16(8), 908–918 (2015).

• **Findings from this randomized Phase II trial established pembrolizumab as a new standard of care for the treatment of ipilimumab refractory melanoma.**

10. Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(1), 23–34 (2015).
11. Chapman PB, Hauschild A, Robert C *et al.* BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* 364(26), 2507–2516 (2011).
12. Hauschild A, Grob JJ, Demidov LV *et al.* Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, Phase 3 randomised controlled trial. *Lancet* 380(9839), 358–365 (2012).

13. Flaherty KT, Robert C, Hersey P *et al.* METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N. Engl. J. Med.* 367(2), 107–114 (2012).

14. Larkin J, Ascierto PA, Dréno B *et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N. Engl. J. Med.* 371(20), 1867–1876 (2014).

15. Atkins MB, McDermott D, Tarhini A *et al.* Matching-adjusted indirect comparison of nivolumab + ipilimumab and BRAF + MEK inhibitors for the treatment of *BRAF*-mutant treatment-naive advanced melanoma. Presented at: *American Association for Cancer Research Annual Meeting.* Chicago, IL, USA, 14–18 April 2018 (Abstract 9538).

•• **Analysis demonstrated that, after adjusting for baseline characteristics, the nivolumab + ipilimumab combination had a significant overall survival benefit over BRAF + MEK inhibitors for the treatment of patients with *BRAF*-mutant advanced melanoma.**

16. Tarhini A, McDermott DF, Ambavane A *et al.* Clinical and economic outcomes associated with sequential treatment in *BRAF* mutant advanced melanoma patients. Presented at: *American Society of Clinical Oncology Annual Meeting.* Chicago, IL, USA, 1–5 June 2018.

•• **Cost–effectiveness analysis showed that, in patients with *BRAF*-mutant advanced melanoma, starting with first-line anti-PD-1 + anti-CTLA-4 combination treatment provided a longer survival benefit compared with BRAF + MEK inhibitors, leading to a lower average cost per life year.**

17. Kohn CG, Zeichner SB, Chen Q, Montero AJ, Goldstein DA, Flowers CR. Cost-effectiveness of immune checkpoint inhibition in *BRAF* wild-type advanced melanoma. *J. Clin. Oncol.* 35(11), 1194–1202 (2017).

• **For patients with treatment-naive *BRAF* wild-type advanced melanoma, immune-based therapies were cost-effective treatment strategies.**

18. Benedict Á, Ambavane A, Tarhini A. Comprehensive reporting in cost-effectiveness modeling. *J. Clin. Oncol.* 35(26), 3085–3086 (2017).

19. Schadendorf D, Wolchok JD, Hodi FS *et al.* Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized Phase II and III trials. *J. Clin. Oncol.* 35(34), 3807–3814 (2017).

•• **Pooled data from nivolumab plus ipilimumab combination therapy showed that efficacy outcomes were similar between patients who discontinued treatment because of adverse events during the induction phase and those who did not. Patients may continue to derive benefit from combination therapy even after treatment discontinuation.**

20. Kaufman HL, Kirkwood JM, Hodi FS *et al.* The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. *Nat. Rev. Clin. Oncol.* 10(10), 588–598 (2013).

21. Postow M, Larkin J, Wolchok JD *et al.* Pooled 3-year overall survival data from Phase II and Phase III trials of nivolumab (NIVO) combined with ipilimumab (IPI) in advanced melanoma. Presented at: *Society for Immunotherapy of Cancer Annual Meeting.* National Harbor, MD, USA, 10–12 November 2017.

• **Pooled data demonstrated that the nivolumab plus ipilimumab combination resulted in a longer treatment-free interval than nivolumab or ipilimumab alone and that combination treatment leads to a higher percentage of patients alive and treatment free at 3 years compared with the monotherapies.**

22. Caro JJ, Möller J. Adding events to a Markov model using DICE simulation. *Med. Decis. Making.* 38(2), 235–245 (2018).

23. Robert C, Ribas A, Hamid O *et al.* Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J. Clin. Oncol.* 36(17), 1668–1674 (2018).

24. Postow MA, Chesney J, Pavlick AC *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006–2017 (2015).

25. Truven Health Analytics, an IBM Company. Micromedex red book: a comprehensive, consistent drug pricing resource (2018). http://truvenhealth.com/products/micromedex/product-suites/clinical-knowledge/red-book

26. Centers for Medicare & Medicaid Services. Physician fee schedule look-up tool. National payment amount (non-facility fee) by HCPCS code (2017). www.cms.gov/medicare/medicare-fee-for-service-payment/pfslookup/index.html

27. Centers for Medicare & Medicaid Services. 2017 Hospital outpatient PPS file. Payment by HCPCS code (2018). www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/index.html?redirect=/hospitaloutpatientpps/

28. OPDIVO® (nivolumab), prescribing information. Bristol-Myers Squibb Company, Princeton, NJ, USA https://packageinserts.bms.com/pi/pi_opdivo.pdf

29. YERVOY® (ipilimumab), prescribing information. Bristol-Myers Squibb Company, Princeton, NJ, USA https://packageinserts.bms.com/pi/pi_yervoy.pdf

30. KEYTRUDA® (pembrolizumab), prescribing information. Merck & Co. Inc., Whitehouse Station, NJ, USA www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

31. Middleton MR, Lorigan P, Owen J *et al.* A randomized Phase III study comparing dacarbazine, BCNU, cisplatin and tamoxifen with dacarbazine and interferon in advanced melanoma. *Br. J. Cancer* 82(6), 1158–1162 (2000).

32. Hauschild A, Agarwala SS, Trefzer U *et al.* Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J. Clin. Oncol.* 27(17), 2823–2830 (2009).
33. Hersh EM, O'Day SJ, Ribas A *et al.* A Phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naive patients with metastatic melanoma. *Cancer* 116(1), 155–163 (2010).
34. Barzey V, Atkins MB, Garrison LP, Asukai Y, Kotapati S, Penrod JR. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. *J. Med. Econ.* 16(2), 202–212 (2013).
35. Bilir SP, Ma Q, Zhao Z, Wehler E, Munakata J, Barber B. Economic burden of toxicities associated with treating metastatic melanoma in the United States. *Am. Health Drug Benefits* 9(4), 203–213 (2016).
36. Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Overview of the national (nationwide) inpatient sample (NIS) (2018). www.hcup-us.ahrq.gov/nisoverview.jsp
37. Hauschild A, Agarwala SS, Trefzer U *et al.* Results of a Phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J. Clin. Oncol.* 27(17), 2823–2830 (2009).
38. Centers for Medicare & Medicaid Services. Clinical laboratory fee schedule (2018). www.cms.gov/medicare/medicare-fee-for-service-payment/clinicallabfeesched/
39. Paly VF, Colby C, Sabater J, Kotapati S. Predictors of utility over time among patients with treatment-naive advanced melanoma from the Phase III CheckMate 067 trial. Presented at: *International Society for Pharmacoeconomics and Outcomes Research 21st Annual International Meeting.* Washington, DC, USA, 23–25 May 2016.
40. Rosner S, Bogatch K, Postow MA. Outcomes of patients with melanoma who discontinue immunotherapy. *J. Clin. Oncol.* 35(15 Suppl.), 9548 (2017).
41. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness: the curious resilience of the $50,000-per-QALY threshold. *N. Engl. J. Med.* 371(9), 796–797 (2014).
42. Expert insights on strategies for managing advanced melanoma with Ryan J. Sullivan, MD. *Am. J. Manag. Care* December(Suppl.), 29–32 (2017).
43. Ishak KJ, Muszebek N, Proskorovsky I, Zhang Y. Projecting survival with immuno-oncology therapies: new challenges and new approaches. Presented at: *International Society for Pharmacoeconomics and Outcomes Research 19th Annual European Congress.* Vienna, Austria, 29 October–2 November 2016.
44. Othus M, Bansal A, Koepl L, Wagner S, Ramsey S. Accounting for cured patients in cost-effectiveness analysis. *Value Health* 20(4), 705–709 (2017).
45. Weber JS, Gibney G, Kudchadkar R *et al.* Phase I/II study of metastatic melanoma patients treated with nivolumab who had progressed after ipilimumab. *Cancer Immunol. Res.* 4(4), 345–353 (2016).
46. Weber JS, Gibney G, Sullivan RJ *et al.* Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, Phase 2 trial. *Lancet Oncol.* 17(7), 943–955 (2016).
47. Weber JS, Samlowski WE, Gonzalez R *et al.* A Phase 1–2 study of imexon plus dacarbazine in patients with unresectable metastatic melanoma. *Cancer* 116(15), 3683–3691 (2010).