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Cost-Effectiveness of Nivolumab-Ipilimumab Combination Therapy Compared to Monotherapy for First-Line Treatment of Metastatic Melanoma in the United States

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Abstract

BACKGROUND—The approval of new immunotherapies has dramatically changed the treatment landscape of metastatic melanoma. These survival gains come with trade-offs in side effects and costs, as well as important considerations to third-party payer systems, physicians, and patients.

OBJECTIVE—Develop a Markov model to determine the cost-effectiveness of nivolumab, ipilimumab, and nivolumab-ipilimumab combination as first-line therapy in metastatic melanoma while accounting for differential effectiveness in PD-L1 positive and negative patients.

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PRIOR PEER-REVIEWED PRESENTATION AT A PROFESSIONAL/SCIENTIFIC CONFERENCE, IF APPLICABLE

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METHODS—A three-state Markov model ('PD-L1 positive stable disease', 'PD-L1 negative stable disease', and 'Progression and/or Death') was developed using a US societal perspective with a lifetime time horizon of 14.5 years. Transition probabilities were calculated from progression-free survival data reported in the CheckMate-067 trial. Costs were expressed in 2015 US dollars and were determined using national sources. Adverse event (AE) management was determined using immune-related AE (irAE) data from CheckMate-067, irAE management guides for nivolumab and ipilimumab, and treatment guidelines. Utilities were obtained from published literature, using melanoma-specific studies when available, and were weighted based on incidence and duration of irAEs. Base case, one-way sensitivity, and probabilistic sensitivity analyses were conducted.

RESULTS—Nivolumab-ipilimumab combination therapy is not the cost effective choice ($454,092 per progression-free quality-adjusted-life-year [PFQALY]) compared to nivolumab monotherapy in our base case analysis at a willingness-to-pay threshold of $100,000/PFQALY. Both combination therapy and nivolumab monotherapy were cost-effective choices compared to ipilimumab monotherapy. PD-L1 positive status, utility of nivolumab and combination therapy, and medication costs contributed the most uncertainty to the model. In a population of 100% PD-L1 negative patients, nivolumab was still the optimal treatment but combination therapy had an improved ICER of $295,903/PFQALY. Combination therapy became dominated by nivolumab when 68% of the sample was PD-L1 positive. In addition, the cost of ipilimumab would have to decrease to <$21,555 per dose for combination therapy to have an ICER <$100,000/PFQALY, and to <$19,151 (a 42% reduction) to be more cost-effective than nivolumab monotherapy.

CONCLUSIONS—Nivolumab-ipilimumab combination therapy is not cost-effective compared to nivolumab monotherapy, which is the most cost-effective option. Professionals in managed care settings should consider the pharmacoeconomic implications of these new immunotherapies as they make value-based formulary decisions and future cost-effectiveness studies are completed.

Introduction

In the United States, skin cancer is the most commonly diagnosed cancer with more than two million people diagnosed annually. In 2015, almost 74,000 new cases were due to melanoma, the most serious type of skin cancer that results in the most deaths.[1–3] The median age at diagnosis is 63 years old with the long-term survival rate of less than 10% for stage IV metastatic melanoma.[3, 4] With an increasing elderly population and the development of costly treatments, the estimated cost of healthcare treatment for melanoma in the U.S. was $2.8 billion in 2015, and this number is projected to increase.[5]

Before 2011, only two systemic therapies, dacarbazine and high-dose interleukin-2 (HD IL-2), were approved by the Food and Drug Administration (FDA) to treat metastatic melanoma, but neither treatment showed any benefit in overall survival while introducing severe dose limiting toxicities.[6] Beginning in 2011, the treatment landscape for metastatic melanoma changed with the approval of novel immunotherapies, such as ipilimumab (Yervoy®), and targeted therapies, such as vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), and trametinib (Mekinist®), all of which improved overall survival benefit.[6–11] In 2014, two additional immunotherapies, pembrolizumab (Keytruda®) and nivolumab (Opdivo®) were approved for the treatment of unresectable or metastatic melanoma. Both treatments were

associated with improvements in progression-free survival (PFS), overall survival (OS), and overall objective responses.[12–14]

In response to these FDA approvals, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) revised the melanoma treatment recommendations (version 3.2015) to include HD IL-2, nivolumab, ipilimumab, and pembrolizumab as first-line treatment options for patients with metastatic or unresectable melanoma with anticipated clinical stability of at least 12 weeks for both *BRAF* V600 mutant and wild types.[15] While nivolumab and ipilimumab were given Category 1 recommendations based upon uniform consensus and high-level evidence, no single treatment option was identified as the superior choice for first-line treatment.[4]

Most recently, in 2015, the FDA granted accelerated approval for the use of nivolumab in combination with ipilimumab (combination therapy) to treat unresectable or metastatic melanoma due to significant increases in objective response rate (60%) and PFS (median 11.5 months compared to median of 5 months for both pembrolizumab and nivolumab monotherapies) in phase II and III clinical trials, giving clinicians another first-line treatment option.[12, 16, 17] This combination therapy was included in version 2.2016 of the NCCN Guidelines® as another first-line option;[18] ipilimumab monotherapy was demoted to a second-line treatment or subsequent therapy option after the use of nivolumab, pembrolizumab, or combination therapy in version 3.2016 of the NCCN Guidelines®.[19]

The gains in response rates and survival come with trade-offs in adverse events (AE) and costs, which are important considerations for third party payer systems when determining the value of these new, innovative therapies. For a single dose of immunotherapy, the average wholesale price (AWP) from RED BOOK™ in 2015 for a 70kg patient was $5,732 for nivolumab, $33,162 for ipilimumab, and $35,073 for combination therapy. AE from these immunotherapies include immune-related reactions such as diarrhea, colitis, rash, endocrine disorders, hepatotoxicity, and pneumonitis.[20] Grade 3 or 4 AEs requiring hospitalization or urgent treatment are somewhat common, as 55% of patients in the combination group, 20–27% of patients in the ipilimumab monotherapy group, and 16% of patients in the nivolumab monotherapy group experienced these treatment-related AEs.[12, 14, 17] These are important considerations for oncologists and patients as treatment response, costs (both drug and AE management), and incidence of AEs may affect treatment decisions and patient quality of life. Therefore, it is uncertain whether one treatment provides true incremental cost-effectiveness value over the others in terms of efficacy, toxicity, and cost.

The Academy of Managed Care Pharmacy (AMCP) has its own guidelines called the AMCP Format for Formulary Submission, which urges health plans to request a formal dossier from drug companies on a new drug's effectiveness and safety and its economic value relative to alternative therapies to inform value-based decisions in formulary management.[21, 22] However, healthcare decision makers have criticized the dossiers submitted by manufacturers as biased.[22] Previously, two separate analyses concluded that combination therapy and nivolumab monotherapy were respectively cost-effective compared to ipilimumab in an Australian population.[23, 24] Both analyses were published as abstracts by

industry authors based in Australia. Our cost-effectiveness study comparing combination therapy to both nivolumab and ipilimumab monotherapies in one analysis is meant to add value-based evidence without having ties to industry and therefore, better inform decision makers in assessing the value of new drugs by AMCP formulary guidelines. In addition, no analysis has been performed in the U.S. or has incorporated PD-L1 status when comparing the three therapies. These are notable differences because of the potential use of targeting treatment to PD-L1 status of patients, which is an emerging consideration as multiple subgroup analyses from clinical trials for PD-1 inhibitors suggest that the greatest benefit occurs in patients with PD-L1 positive tumors.[25] When drugs are better targeted to those that benefit, they are also more cost-effective. Additionally, the cost of the drugs and the willingness to pay (WTP) threshold varies by country so performing an analysis in the U.S. could lead to changes in the results and subsequent treatment decisions by U.S. decision makers.[26] Thus, our objective was to determine the cost-effectiveness of nivolumab-ipilimumab combination therapy compared to nivolumab and ipilimumab monotherapies as first-line treatments for patients with confirmed stage III or IV melanoma from a U.S. societal perspective. Managed care professionals can use these findings to better understand the comparative value of these treatments with respect to efficacy, toxicity, and cost, and make informed value-based formulary decisions on the role of each drug regimen in the treatment of melanoma.

Methods

We performed a cost-effectiveness analysis (CEA), which compare two or more alternative treatments to determine which one provides greater benefit at the same or lower costs, lower costs for the same or greater benefit, or both greater benefit and lower costs.[27] CEA results are expressed as the incremental cost-effectiveness ratio (ICER) in U.S. dollars (USD) per quality adjusted life years saved (QALYs). If the ICER is less than a WTP threshold (commonly $100,000 in U.S.)[28], then it is considered cost effective to adopt that treatment over the alternative.[27, 29] Our study and most CEA studies are Markov models based on efficacy outcomes from clinical trial literature and other published data to assess both the cost and benefit of each treatment and its side effects.[29] The steps include 1) defining our study population, 2) defining the health states of our Markov model as patients move from treatments to death, 3) determining the costs of moving from one health state to another, 4) determining the probability of patients transitioning from one health state to another, 5) calculating the ICER for each comparison for the base-case of assumptions, 6) determining which treatment is the most cost-effective (has the lowest ICER compared to the next costly alternative and under the $100,000 WTP threshold), 7) conduct sensitivity analysis on all factors of the model to see which factors change the CEA decision.[27, 29] Our methods adhered to both the recommendations of good research practices for model transparency and validation from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Society of Medical Decision Making, and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement from ISPOR Task Force.[27, 30, 31]

Study Population

The decision tree and Markov model for the CEA was based on the phase III, randomized controlled trial, CheckMate-067, for first-line treatment of confirmed stage III or IV, unresectable or metastatic melanoma.[12] Eligible patients were at least 18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance-status (PS) score of 0 or 1, measurable disease as assessed by computed tomography or magnetic resonance imaging, known PD-L1 status, and known *BRAF* V600 mutation status. There were no significant between-group differences at baseline. The mean age was 60 years old for all patients (59 in both nivolumab and combination arms and 61 in the ipilimumab arm). Sixty-four percent of the total sample was male, 73% had an ECOG PS of 0, 32% were positive for the *BRAF* V600 mutation, and 24% had positive PD-L1 status.[12]

Treatment options in our model reflected those in the CheckMate-067 clinical trial: i) combination therapy (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks); ii) nivolumab 3 mg/kg every 2 weeks; and iii) ipilimumab 3 mg/kg every 3 weeks for a total of 4 doses. The median number of doses was four for combination therapy, fifteen for nivolumab, and four for ipilimumab.[12] Treatment was discontinued if the disease progressed, unacceptable AEs developed, or patients withdrew consent.

Markov Model

The Markov model was developed using TreeAge Pro (TreeAge, Williamstown, MA) with three branches at the decision node to reflect the three drug treatments being compared: combination therapy, nivolumab monotherapy, and ipilimumab monotherapy (Figure 1a). The cycle length for the model was one month, and the time horizon was 175 months, which is consistent with the 10-year mortality rate of metastatic melanoma.[1] The health states after a patient received one of the treatment options was ‘Stable disease with positive PD-L1 status’, ‘Stable disease with negative PD-L1 status’, and ‘Progression and/or Death’ (Figure 1b). The model’s population started in the stable health state, separated by PD-L1 status based on the proportion of positive PD-L1 patients from CheckMate-067. In each simulation cycle, patients either stayed in the stable state or advanced to the terminal node of progression/death. The simulation continued until all patients entered the progression/death state.

For our base case analysis, we assessed effectiveness as months of PFS, and the ICER was expressed as USD per progression-free quality-adjusted life-year (PFQALY). Estimated treatment costs from our model results were ranked from lowest to highest. We assumed treatments were cost-effective based on a WTP threshold of $100,000 per PFQALY gained.

Acceptability curves are a method for summarizing information on uncertainty around a cost-effectiveness ICER.[27, 29] These curves show the probability that an intervention is cost-effective compared with an alternative for a range of maximum thresholds that a decision maker would be willing to pay for a particular unit change in outcome. One-way and probabilistic sensitivity analyses (PSA) were used to examine the uncertainties surrounding the model’s assumptions, including characteristics of baseline population PD-L1 status,

treatment efficacy, utilities, costs, and uncertainty in other model parameters (Table 1). PSA was performed with 10,000 Monte Carlo simulations to simultaneously account for uncertainty in all utility and cost parameters, including transition probabilities at each cycle (Table 1).[32] We assigned beta distributions to probability and utility estimates as both are bounded by zero at the lower end and one at the upper end.[29] Zero represents the worst possible health state and one represents perfect health in the utility estimates. For cost estimates, we assigned gamma distributions as cost data is often highly skewed and represented by infinity at the upper end.[29]

Transition Probabilities

Transition probabilities represent the proportion of the population that would move from one health state into another health state after one cycle.[29] For example, if one patient from a population of 100 patients in the 'Stable PD-L1' state moved into the 'Progression and/or Death' state after one cycle, then the transition probability would be 0.01. To calculate monthly transition probabilities, PFS data for all three treatments, separated by PD-L1 status, were extracted from the published Kaplan-Meier curves in the CheckMate-067 clinical trial using a validated graphical digitizer (WebPlotDigitizer version 3.9; Ankit Rohatgi, Austin, TX) (Appendix Figure 1).[12] The extracted data was used to calculate the survival function, hazard function, and transition probabilities. We assumed patients who survived through the end of the clinical trial have longer survival and might be different than those who had died from their malignancy, as the tail of the Kaplan-Meier curve from Checkmate-067 appeared to level off.[12] In order to preserve the treatment effect and extrapolate the tail of Kaplan-Meier curves to zero, we carried forward the last observed transition probability rather than using the Declining Exponential Approximation of Life Expectancy (DEALE) method, which overestimates mortality rate in the tails.[33] PFS data was used since OS data had not been published at the time of this analysis.

Costs and Utilities

Costs of drug treatment, drug administration, and treatment-related AE management were applied upfront as an initial cost while the costs associated with the progression/death health state were applied as a final cost. National registries were used to determine costs when available. All costs were adjusted to 2015 USD, and drug costs were discounted at 3% annually (Table 1).[27, 29] Drug costs were taken from RED BOOK™ Online 2015 as AWP in 2015 USD and were discounted by 17% to account for contract pricing and to be consistent with estimates for Medicare reimbursement.[34] The costs of drug treatment were calculated using a standard average patient weight in the U.S. of 74.4kg rounded down to 70kg for weight loss effects of cancer stage[35] and were weighted based on the dosing regimen and median duration of treatment from CheckMate-067.[12]

Treatment-associated costs were determined using Current Procedural Terminology codes, the 2015 Medical Fee Book, and the 2015 Clinical Laboratory Fee Schedule and included physician fees, outpatient office visits, laboratory tests, infusion costs, and imaging tests to monitor disease progression. Treatment-associated costs were calculated based on the recommended schedule from the study protocol and median duration of each treatment.

The probabilities for organ-specific AEs were taken from CheckMate-067, and grade 1 and 2 AEs were separated from grade 3 and 4 AEs (Table 2). All non-immune-related AEs were excluded. We explicitly accounted for costs and utilities only associated with immune-related AEs (irAEs) reported by at least 5% of patients in any of the treatment groups as these irAEs are most concerning to clinicians and most likely to cause severe episodes resulting in costly hospitalizations.[12] Costs and utilities for the management of irAEs were weighted based on the percentage of patients experiencing that irAE and the median time to resolution (two months) for irAEs as reported in Checkmate-067.

Costs for irAE management included drugs used to treat irAEs, consultations needed while hospitalized, and laboratory and imaging tests used to diagnose and monitor the irAE. Management of irAEs was determined using the study protocol, AE management guides supplied by the manufacturer, treatment guidelines, and expert clinical knowledge.[12] The model assumed that all patients with an irAE that required steroid treatment would receive oral prednisone as per consensus management[36] and with dosing based off of the average dose as listed and recommended in the manufacturer's AE management guide, a patient weight of 70kg, and the median time to resolution of the irAE.[12] Per consensus management, prednisone tapers occur with a 10mg dose decrease every week until a 5mg dose was achieved.[36] The model also assumed that all grade 3 and 4 irAEs would incur a hospitalization charge, and once discharged from the hospital, patients would receive follow-up outpatient visits to monitor the irAE every two weeks. Grade 1 and 2 irAEs would not require hospitalization and thus just follow-up outpatient visits to monitor the irAE would occur monthly.

Baseline utility estimates for stable and progression/death health states and utility values for irAEs grouped by organ system were obtained from previously published health preferences studies based on patients with advanced melanoma or other malignancies.[37–42] Methodologies for these health preference studies included standard gamble and time trade-off. Utilities for stable and progression/death health states for each treatment arm were calculated as an annual (12 month) weighted utility. Thus, the weighted utility values for irAEs were multiplied by 2/12 (median time of two months to resolution) and then subtracted from the baseline utility value of stable and progressive disease that was multiplied by 10/12 (remaining 10 months without the irAE). The use of weighted utility values allowed for more accurate estimations of the utilities given the varying timeframe that a patient may experience an irAE. The utility value for the progression/death health state was divided in half to account for both the utility during the time in the progressed state and during the time in a dead state when the utility would be zero. Utility values were applied upfront in the model at the decision node prior to initiation of nivolumab monotherapy, ipilimumab monotherapy, or combination therapy (Figure 1a).

Results

Cost-Effectiveness Analysis

In the base case analysis, which represents our best available estimates, nivolumab monotherapy had the lowest overall cost at $169,320, followed by ipilimumab monotherapy at $213,763, and combination therapy, which was the most expensive at $228,352 (Table 3).

Combination therapy provided an additional 0.69 PFQALYs with an incremental cost of $14,589 compared to ipilimumab and an additional 0.13 PFQALYs with an incremental cost of $59,032 compared to nivolumab. The model demonstrated that nivolumab was less expensive and more effective than ipilimumab, thus nivolumab dominated and was the cost-effective choice compared with ipilimumab. Combination therapy was not cost-effective when compared to nivolumab at a WTP threshold of $100,000/PFQALY because its ICER of $454,092/PFQALY gained is greater than the WTP threshold. However, combination therapy was cost-effective compared to ipilimumab at the same WTP threshold, with an ICER of $21,143/PFQALY gained. The drivers of this difference were both the higher costs and shorter PFS time of ipilimumab compared with nivolumab. Based on our base-case analysis, it would be cost-effective to choose nivolumab over ipilimumab for monotherapy decisions alone. However, combination therapy is not a cost-effective choice compared with nivolumab (the least costly option), but combination therapy is cost-effective compared to ipilimumab (the costlier monotherapy). Therefore, combination therapy can remain a cost-effective option in some cases.

Sensitivity Analyses

The acceptability curve (Figure 2a) confirmed the findings from our base case analysis with nivolumab as the optimal treatment below a WTP threshold of approximately $450,0000/PFQALY. With increasing WTP thresholds, the probability that combination therapy was the optimal treatment increased, whereas the probability for nivolumab as optimal treatment decreased. Ipilimumab was not a viable treatment option for any WTP threshold between zero and $800,000 since it was dominated by both nivolumab and combination therapy throughout this range.

The tornado analysis (Appendix Figure 2) showed that PD-L1 positive status, utility of nivolumab in progressive disease adjusted for irAEs, and utility of combination therapy in progression adjusted for irAEs contributed the most uncertainty to our model, justifying additional exploratory one-way and probabilistic sensitivity analyses to identify how our decision changes if all patients are assumed PD-L1 positive or negative in our model. In the one-way sensitivity analysis that examined a population of 100% PD-L1 negative patients in all treatment groups, nivolumab was still the optimal treatment as combination therapy had an ICER of $295,903/PFQALY, exceeding the WTP threshold of $100,000/PFQALY (Table 3). When the entire population was 100% PD-L1 positive, both the combination therapy and ipilimumab were dominated by nivolumab, further supporting the baseline case findings. Combination therapy became dominated by nivolumab when 68% of the sample was PD-L1 positive and the effectiveness of nivolumab and combination therapy was equal at 4.42 PFQALYs (Figure 2b).

Because the duration and intensity of the AEs differed among the three treatment choices, their utility may have affected the outcome of the CEA. When utility values were changed to reflect only values for stable (0.80) and progressive disease/death (0.26) without any adjustments for irAEs, ipilimumab continued to be dominated by nivolumab, and combination therapy had an ICER of $18,947/PFQALY when compared to ipilimumab. Compared to nivolumab, combination therapy had an additional cost of $275,544/PFQALY,

which still exceeded the $100,000/PFQALY WTP threshold, so nivolumab remained the optimal treatment (Table 3).

In assessing only the cost variables, the ICER was most sensitive to the total drug cost of ipilimumab, though the optimal treatment decision of nivolumab did not change. Thus, we varied the drug cost of ipilimumab from $1 to $132,649 (base case value). Ipilimumab was no longer dominated by nivolumab when the total drug cost of ipilimumab (four doses) decreased to approximately $88,000. However, nivolumab remained cost-effective compared to ipilimumab with an ICER of $59/PFQALY, while combination therapy had an ICER of $114,858/PFQALY compared to nivolumab monotherapy (Table 3). Combination therapy became a viable treatment option (ICER of combination therapy compared to nivolumab was less than the WTP threshold of $100,000/PFQALY) when the total drug cost of ipilimumab was approximately $86,272. Combination therapy became the optimal treatment dominating nivolumab when the total drug cost of ipilimumab was approximately $73,520 (Table 3).

Discussion

Based on our CEA and a WTP of $100,000/PFQALY, nivolumab monotherapy is cost-effective compared to both ipilimumab monotherapy and combination therapy for patients as first-line treatment for unresectable or metastatic melanoma, regardless of PD-L1 status. Furthermore, if a patient has a PD-L1 negative status, combination therapy is not cost-effective at a WTP of $100,000/PFQALY; however, combination therapy could still be considered as a treatment option when compared only to ipilimumab or compared to nivolumab if 100% of patients are PD-L1 negative. Also combination therapy could be cost-effective if decision makers are willing to pay a higher maximum cost per QALY saved. There is some discussion that the WTP especially for anticancer drugs should be increased to at least $160,000/QALYs and some have suggested increasing this to as high as $300,000/QALY.[28] However, our analysis shows that even at this higher WTP threshold combination therapy would not be cost-effective compared to nivolumab. Additionally, due to the lack of consensus in interpreting PD-L1 tests for metastatic melanoma and varying thresholds of PD-L1 expression for a positive test, we cannot confidently recommend combination therapy as a cost-effective choice compared to nivolumab for PD-L1 negative patients at this time.

This result is similar to the findings of the cost-effectiveness analyses completed in Australia which resulted in an ICER of $44,867/QALYS when comparing combination therapy with ipilimumab resulting in the same cost-effectiveness decision as we did for this comparison.[23, 24] They did not compare combination therapy with nivolumab.[23] Leaving out ipilimumab in our model, however, demonstrated that combination therapy also was not cost-effective compared to nivolumab monotherapy, with an ICER of $454,092/PFQALY gained. Nivolumab is a better comparator with combination therapy as it is the next least costly alternative.

In the sensitivity analyses, our model was robust to all variables as there were no changes in the preferred treatment when parameters for all inputs were varied across a plausible range. Nivolumab remained more cost-effective than combination therapy as combination therapy

consistently had a higher ICER than the $100,000 WTP threshold, and ipilimumab was consistently dominated by nivolumab.

Our sensitivity analyses demonstrated that multiple factors prevented combination therapy from being cost-effective against nivolumab. Primarily, the overall cost of combination therapy is naturally more expensive than either nivolumab or ipilimumab alone due to the combination of two drugs and lengthier treatment duration. Although our model showed that immunotherapies achieve remarkable improvements in survival and response, the health state utility of the treatment AEs may still be a huge burden for patients, even under the most favorable assumptions. During Checkmate-067, 36% of patients in the combination arm discontinued treatment due to treatment-related AEs compared to 8% in the nivolumab arm and 15% in the ipilimumab arm.[12] While the higher discontinuation rate for combination therapy may suggest there is a potential reduction in the overall treatment cost, Checkmate-067 also reported patients on the combination treatment were administered a median of four nivolumab doses and four ipilimumab doses.[12] Therefore, patients who discontinued combination therapy likely accounted for a majority of treatment cost relatively early in their course. Additionally, altering AE utilities did not change the recommendation for nivolumab monotherapy.

Much has been written on the unsustainable, rising prices of cancer drugs and value-based pricing.[43, 44] The innovative nature of these therapies, specifically combination therapy and its effect on lengthening PFS and increasing response rate, must be acknowledged by a higher price. However, the utility may not be high enough to offset the current price set by the manufacturer in the U.S. The use of ipilimumab monotherapy has already been reassessed in the newest NCCN Guidelines® (v.3.2016), which now recommend ipilimumab monotherapy solely for second-line or subsequent therapy.[19] While the price of these immunotherapies will most likely not be reevaluated, health plans must be aware of their benefit and toxicities when examining the value, safety, and affordability of these therapies. Both ipilumumab and nivolumab are produced and marketed by the same manufacturer. While nivolumab is priced much lower than ipilumumab, combination therapy would allow continued presence of both drugs on the market even as ipilimumab is moved to second-line or subsequent therapy. Similar drugs from other manufacturers (e.g. atezolizumab (Tecentriq™)) are in development, and subsequent market pressures for the price of these drugs may decrease these drug’s prices.

We also considered the impact of targeting treatment to PD-L1 status of a patient on our ICER analysis.[25] Emerging evidence indicates that those who are PD-L1 positive may respond more favorably to combination therapy compared to PD-L1 negative patients.[25, 45] If this is the case, combination therapy may be considered as a targeted treatment for metastatic melanoma patients with PD-L1 positive tumors. However, since no standardized method for assessing PD-L1 expression exists and the threshold to define PD-L1 status as positive differs between clinical trials (e.g. at least 5% of tumor cells showing PD-L1 staining for combination therapy or nivolumab trials versus 1% for pembrolizumab trials), it may be premature to target treatment in melanoma based on PD-L1 status.[12, 14] Our sensitivity analysis demonstrated that in a population of 100% PD-L1 negative patients, combination therapy, despite having a lower ICER than the base case, was still not cost-

effective (ICER= $295,903/PFQALY) compared to nivolumab and ipilimumab monotherapies at WTP of $100,000/PFQALY.

The biomarker testing process could affect treatment decisions and patient access to anti-PD-L1 therapies. First, it is not clear if detection of tumor cells truly characterizes PD-L1-positive samples. Second, effectiveness and clinical outcomes between different investigational drugs may not be compared as different companion diagnostic assays with independent definitions of PD-L1 positivity are used.[46] Clinical trials and any future CEAs that compare new treatments, such as pembrolizumab to combination therapy or nivolumab monotherapy need to take into consideration the staining thresholds and the fact that PD-L1 assays are not currently interchangeable.

Limitations

Our model had several limitations. First, our Markov model required several assumptions. For example, when micro-costing AEs, we estimated the frequency of follow-up visits, frequency of diagnostic and monitoring labs, and duration of the steroid taper. However, these assumptions were based on the clinical protocol for CheckMate-067 combined with clinical knowledge, treatment guidelines, and corroboration from a physician who is an expert in the treatment and management of melanoma, giving us confidence in their accuracy. Efficacy and AE data were taken directly from Checkmate-067 and thus, while a deterministic Markov model is based on the evolution of a hypothetical cohort of patients, the PSA simulates the evolution of real-life, individual patients. In addition, we varied costs of treating and managing AEs by ±25% to account for uncertainty, but this did not change our decision. Furthermore, we used PFS as our only outcome since OS was not yet available at the time of the analysis. However, even when PFS is weakly correlated with OS, PFS provides a useful indicator on the quality of a drug product to the manufacturer and to practicing physicians.[43] In using PFS as our outcome, we assumed that OS would follow the PFS Kaplan Meier curve. Other methods for estimating the relationship between PFS and OS include assuming that an incremental benefit in PFS for treatment A and B leads to a proportional gain in OS for each treatment, or one could model independent curves for PFS and OS for each treatment. However, both options have weaknesses and this study, as any study based on PFS outcomes should be followed up with further studies when OS is available.[47] As the use of PFS will likely underestimate the life-years gained, we mitigated this by including PFS in the sensitivity analysis, assigning a final utility to the progression/death health state and dividing that utility in half to adjust for those who died. Moreover, we varied the utility of the progression/death health state by ±25%, which still resulted in nivolumab monotherapy dominating the other treatments. We also used ICD-9 codes and utility values for AE that were not always exactly correlated to irAEs, as direct results for general health status and quality of life were not published at the time of the analysis. This is not uncommon in CEAs and the ICD-9 codes were closely matched to the description of the irAE being treated and utility values were carefully selected based on the closest representation of the published literature.[37–42] Additionally, when we ran the model without utility, our results did not change.

Finally, this analysis focused on the cost effectiveness combination therapy, nivolumab, and ipilimumab as first-line therapies; the cost associated with the progression/death health state did not include the cost of any second- or third-line treatments for metastatic melanoma since these data were not available and would change the nature of our question. This study was initiated when the NCCN Guidelines still recommended ipilimumab, nivolumab, and pembrolizumab as first line treatment options. Pembrolizumab was not included as a comparator in this analysis because of the differences in the clinical trial study designs and patient populations from our comparators. Considering the updated versions of the NCCN guidelines, pembrolizumab should ideally become one of the comparators of any further cost-effectiveness studies for melanoma.

Conclusions

This analysis, which demonstrated that nivolumab is more cost-effective than nivolumab-ipilimumab combination therapy and ipilimumab monotherapy, contributes to the discussion surrounding value-based and indication-specific pricing in the oncology space. Additionally, it has implications for formulary and reimbursement decisions, as well as treatment decisions by physicians and patients. Insurers, health systems, and physicians must consider these results in the context of patient outcomes and efficient care. Future research includes updating the decision tree and Markov model to reflect OS data once made available, which would more accurately make the comparison between combination therapy and both nivolumab and ipilimumab monotherapies and allow for more informed cost-effective decisions to be made regarding their use. Despite the weakness of using PFS as an outcome in this CEA, our results are supported by the only other CEA analyses for the comparison they had in common. We found that combination therapy is not cost-effective using PFS, compared with nivolumab, but is cost-effective compared with ipilimumab. One could still consider the use of combination treatments until OS data becomes available to provide better long-term outcomes. In addition, future clinical trials and CEAs should compare pembrolizumab to nivolumab and combination therapy according to the updated NCCN Guideline recommendations. Furthermore, CEA of nivolumab and combination therapy in other disease states is warranted as these therapies may have broader clinical uses and varying effectiveness. Since the AWP of nivolumab and ipilimumab may change due to further competition and possible FDA approval of additional indications for nivolumab and combination therapy, further work is needed to understand the clinical benefits and value of these therapies. In the meantime, this work can support the information in the dossier of a health plan when examining the value of formulary recommendation of these combinations or monotherapies as suggested by the AMCP format for formulary submissions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY BULLETS

What is already known about this subject

- The Food and Drug Administration recently approved nivolumab in combination with ipilimumab and nivolumab monotherapy as first-line treatment options to treat unresectable or metastatic melanoma.
- The gains in response rates and survival come with trade-offs in side effects and costs, which are important considerations to third party payer systems when determining the value of new, innovative therapies.
- The true incremental value of one treatment over the other treatments in terms of efficacy, toxicity, and cost was unknown prior to this analysis.

What this study adds

- In the base case analysis, ipilimumab monotherapy was dominated by nivolumab monotherapy while nivolumab-ipilimumab combination therapy had an incremental cost-effectiveness ratio (ICER) of $454,092 per progression-free quality-adjusted life-year gained compared to nivolumab.
- PD-L1 positive status, utility of nivolumab and combination therapy, and medication costs contributed the most uncertainty to the model; these three factors are important to consider when determining the pharmacoeconomic implications of nivolumab monotherapy, ipilimumab monotherapy, and combination therapy.
- At a willingness-to-pay threshold of $100,000/PFQALY, nivolumab monotherapy is the most cost-effective option compared to combination therapy and ipilimumab monotherapy.

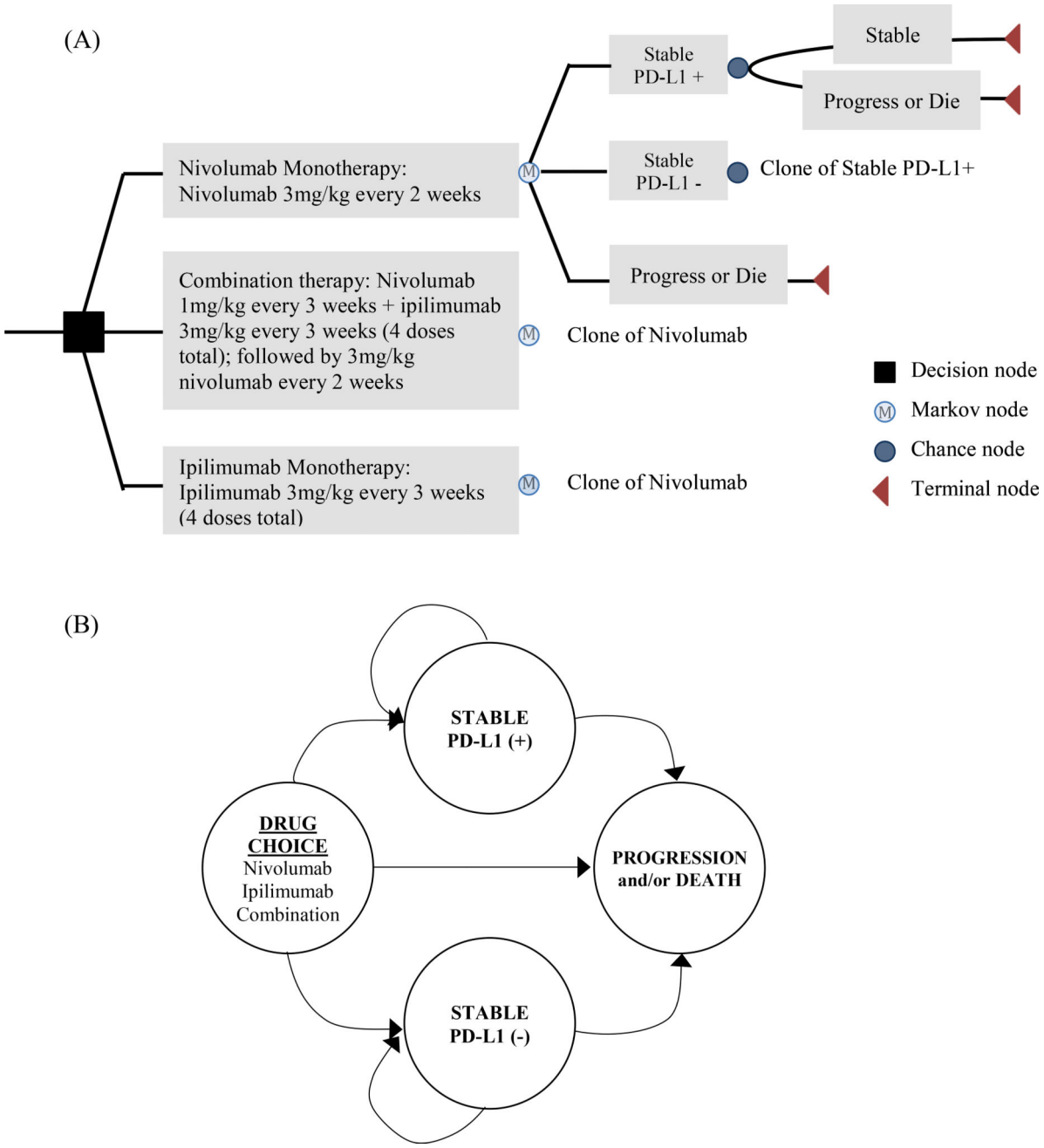

Figure 1.

(A) Abbreviated Markov model decision tree comparing nivolumab-ipilimumab combination therapy, nivolumab monotherapy, and ipilimumab monotherapy for first-line therapy for metastatic melanoma while incorporating PD-L1 status, and (B) Schematic representation of the Markov model showing disease states and transitions between them.

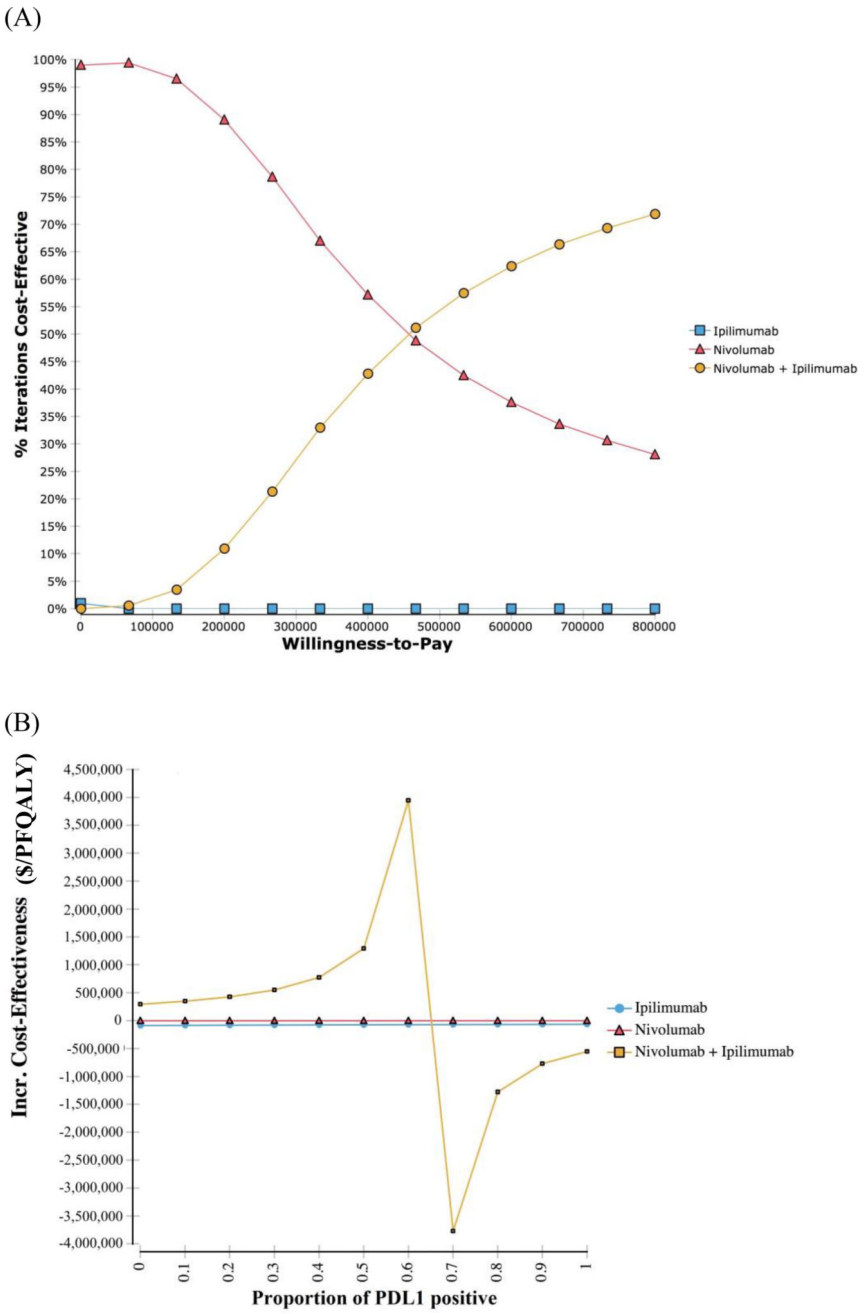

Figure 2.

(A) Acceptability curve for nivolumab-ipilimumab combination therapy, ipilimumab monotherapy, and nivolumab monotherapy, and (B) one-way sensitivity analysis for proportion of PD-L1 positive patients.

Table 1

Model input parameters, distribution, and range.

Parameter	Base case	Range		Source
		Low	High	
Drug costs[a] ($) (γ distribution)				
Nivolumab	$85,983	$64,487	$107,478	RED BOOK, ±25%
Ipilimumab	$132,649	$99,487	$165,811	
Combination therapy: Nivolumab; Ipilimumab	$7,643; $132,649	$5,732; $99,487	$9,554; $165,811	
Total treatment-associated costs[b] ($) (γ distribution)				
Nivolumab	$12,036	$9,027	$15,045	Medical Fee Book 2015, CLFS 2015; ±25%
Ipilimumab	$5,219	$3,914	$6,524	
Combination therapy: nivolumab; ipilimumab	$5,219; $253	$3,914; $190	$6,524; $316	
Cost of managing adverse events ($) (γ distribution)				
Nivolumab	$2,688	$2,015	$3,359	HCUP, ±25%
Ipilimumab	$7,049	$5,286	$8,811	
Combination therapy	$14,415	$10,811	$18,019	
Cost of Disease Progression/Death (γ distribution)	$68,849	$34,424	$137,697	[48]
Utilities[c] (β distribution)				
Stable disease, base case	0.667	0.5	0.833	[37–42], ±25%
Progressive disease, base case	0.433	0.325	0.542	
Nivolumab stable	0.131	0.098	0.164	
Nivolumab progression/death	0.084	0.063	0.106	
Ipilimumab stable	0.129	0.097	0.162	
Ipilimumab progression/death	0.082	0.062	0.104	
Combination stable	0.119	0.089	0.149	
Combination progression/death	0.072	0.054	0.091	

CLFS = Clinical Laboratory Fee Schedule; **HCUP** = Healthcare Cost and Utilization Project

[a] Cost for complete course corresponds to median number of doses. All drug prices are average wholesale price minus 17%

[b] Includes cost of outpatient initial visit, follow-up visits, lab draws, and follow-up imaging as recommended by the manufacturer of nivolumab and ipilimumab, treatment guidelines, and expert opinion; total cost is based on number of procedures for each visit and median number of doses for each treatment

[c] Utilities from the literature were based on standard gamble and time trade-off; utility values are listed after weighting 10/12 for stable and progression and 2/12 for treatment with irAEs

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Table 2

Proportion of patients from CheckMate-067 experiencing immune-related adverse events (irAEs) and utility estimate by organ system.

% of patients experiencing the irAEs	Nivo (n=313)		Combo (n=313)		Ipi (n=311)		Utility[38–42]
	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	
Skin	1.6	40.3	5.8	53.4	2.9	51.1	
Pruritis	0.0	18.8	1.9	31.3	0.3	35.0	−0.057
Rash	0.3	21.4	2.9	25.6	1.6	19.3	
Rash maculo-papular	0.3	3.8	1.9	9.9	0.3	11.6	
Vitiligo	0.3	7.0	0.0	6.7	0.0	3.9	
Gastrointestinal	2.2	17.3	14.7	31.6	11.6	25.1	
Diarrhea	2.2	16.9	9.3	34.8	6.1	27.0	−0.116
Colitis	0.6	0.6	7.7	4.2	8.7	2.9	
Hepatic	2.6	3.8	18.8	11.2	1.6	5.5	
Increase in ALT	1.3	2.6	8.3	9.3	1.6	2.3	−0.308
Increase in AST	1.0	2.9	6.1	9.3	0.6	2.9	
Endocrine	0.6	13.7	4.8	25.2	2.3	8.7	
Hypothyroidism	0.0	8.6	0.3	14.7	0.0	4.2	−0.115
Hyperthyroidism	0.0	4.2	1.0	8.9	0.0	1.0	
Hypophysitis	0.3	0.3	1.6	6.1	1.9	1.9	
Pulmonary	0.3	1.3	1.0	6.1	0.3	1.6	
Pneumonitis	0.3	1.0	1.0	5.4	0.3	1.3	−0.159

irAE = immune-related adverse event

Table 3

Summary of cost-effectiveness of nivolumab, ipilimumab, and combination as first-line treatment of metastatic melanoma and one-way deterministic sensitivity analysis from the Markov model.

Treatment	Total Cost[a] (95% CI)	Total Effectiveness, PFQALY (95% CI)	Incremental cost (95% CI)	Incremental effect, PFQALY (95% CI)	ICER, per PFQALY
Base Case Analysis (PD-L1 status unknown)					
Nivolumab	$169,320	4.24	---	---	---
Ipilimumab	$213,763	3.68	$44,443	-0.57	(dominated)
Combo vs. ipilimumab	$228,352	4.37	$14,589	0.69	$21,143
Combo vs. nivolumab	$228,352	4.37	$59,032	0.13	$454,092
PD-L1 status known (100% PD-L1 negative)					
Nivolumab	$169,449	4.14	---	---	---
Ipilimumab	$213,765	3.62	$44,316	-0.52	(dominated)
Combo vs. ipilimumab	$228,387	4.34	$14,622	0.72	$20,308
Combo vs. nivolumab	$228,387	4.34	$58,937	0.20	$295,903
PD-L1 status known (100% PD-L1 positive)					
Nivolumab	$168,900	4.57	---	---	---
Ipilimumab	$213,757	3.86	$44,857	-0.72	(dominated)
Combo vs. ipilimumab	$228,241	4.46	$14,484	0.6	$24,140
Combo vs. nivolumab	$228,241	4.46	$59,342	-0.11	(dominated)
Utilities Unadjusted for Adverse Events					
Nivolumab	$169,320	4.26	---	---	---
Ipilimumab	$213,763	3.70	$44,444	-0.55	(dominated)
Combo vs. ipilimumab	$228,352	4.47	$14,589	0.77	$18,947
Combo vs. nivolumab	$228,352	4.47	$59,033	0.21	$275,544
Ipilimumab monotherapy = $73,520					

Treatment	Total Cost[a] (95% CI)	Total Effectiveness, PFQALY (95% CI)	Incremental cost (95% CI)	Incremental effect, PFQALY (95% CI)	ICER, per PFQALY
Ipilimumab	$154,636	3.68	---	---	---
Combo	$169,226	4.37	$14,589	0.69	$21,090
Nivolumab	$169,320	4.24	$94.06	-0.13	(dominated)
Ipilimumab monotherapy = $86,272					
Ipilimumab	$167,387	3.68	---	---	---
Nivolumab	$169,320	4.24	$1,932	0.57	$3,420
Combo	$181,976	4.37	$12,657	0.13	$99,872
Ipilimumab monotherapy = $88,171					
Ipilimumab	$169,286	3.68	---	---	---
Nivolumab	$169,320	4.24	$33.27	0.57	$58.88
Combo	$183,876	4.37	$14,556	0.13	$114,858
Ipilimumab monotherapy = $88,443					
Nivolumab	$169,320	4.24	---	---	---
Ipilimumab	$169,558	3.68	$238.03	-0.57	(dominated)
Combo vs. ipilimumab	$184,147	4.37	$14,589	0.69	$21,143
Combo vs. nivolumab	$184,147	4.37	$14,827	0.13	$116,999

[a] In 2015 USD

CI = confidence interval; **ICER** = incremental cost-effectiveness ratio; **PFQALY** = progression-free quality-adjusted life year

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