Cost-Effectiveness of Biomarker-Driven First-Line Immunotherapy in Advanced Melanoma: A Mathematical Modeling Approach

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have dramatically improved the prognosis of advanced melanoma, yet substantial heterogeneity in response and toxicity persists. Recent work by Tarantino et al. has shown that genomic heterogeneity and ploidy robustly predict intrinsic resistance to PD-1 blockade. We propose a simulation model to compare the cost-effectiveness of standard first-line treatment strategies versus a biomarker-based strategy that leverages genomic predictors.

Methods: We reconstructed individual patient data (IPD) from the published Kaplan–Meier curves of the CheckMate 067 trial and fitted parametric and spline survival models to derive monthly transition probabilities. A discrete-time Markov model—with three health states (stable disease, progressive disease, and death) and a 1-month cycle over a 10-year horizon—was constructed to simulate costs, quality-adjusted life-years (QALYs), and toxic effects. In an extended analysis, we incorporated the predictive performance (sensitivity, specificity, and PPV) reported by Tarantino et al. to simulate a biomarker-based treatment allocation strategy. Model inputs, including survival probabilities, utilities, and costs, were derived from published literature and calibrated against trial data.

Results: [Insert calibrated model results, cost-effectiveness outcomes, and sensitivity analyses here.]

Conclusions: Our initial results indicate that a biomarker-driven treatment allocation strategy may be cost-effective compared with a standard one-size-fits-all approach for first-line immunotherapy in advanced melanoma. These findings underscore the potential for personalized treatment strategies to improve clinical outcomes and resource utilization.

Keywords: cost-effectiveness, immunotherapy, melanoma, biomarker, mathematical model

1. Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced melanoma, leading to unprecedented long-term survival in a subset of patients. The CheckMate 067 trial demonstrated that both nivolumab monotherapy and the combination of nivolumab with ipilimumab offer superior overall survival (OS) and progression-free survival (PFS) compared with ipilimumab monotherapy. However, significant toxicities associated with combination therapy and the heterogeneous treatment response across patients necessitate a more personalized approach.

Recent work by Tarantino et al. has shown that genomic heterogeneity and ploidy can robustly predict intrinsic resistance to PD-1 blockade. These findings provide a basis for a biomarker-driven treatment strategy whereby patients predicted to be intrinsically resistant to single-agent PD-1 blockade may preferentially

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receive combination immunotherapy. In this study, we propose a simulation model to evaluate the cost-effectiveness of standard first-line treatment strategies versus a biomarker-based strategy that leverages genomic predictors.

Our objectives are to: - Calibrate a Markov model using reconstructed individual patient data from the CheckMate 067 trial. - Estimate monthly transition probabilities for OS and PFS based on parametric and spline survival models. - Compare the cost-effectiveness of nivolumab monotherapy and combination nivolumab plus ipilimumab. - Extend the model by incorporating the predictive performance of the genomic biomarker from Tarantino et al. to simulate a biomarker-based treatment allocation strategy.

2. Methods

2.1. Decision Model

We compared the cost-effectiveness of a biomarker-driven treatment allocation strategy versus a standard one-size-fits-all approach for first-line immunotherapy in advanced melanoma. The standard strategy involved treating all patients with nivolumab monotherapy, while the biomarker-driven strategy allocated patients to either nivolumab only or nivolmab plus ipilimumab based on their predicted response to single-agent PD-1 blockade. We created a Markov model to simulate treatments, adverse events, quality of life, costs, and survival among simulated patients. The state transition diagram (Figure 1) shows how patients move through the Markov model. The three main health states were stable disease, cancer progression, and death. Our cost-effectiveness model used a one-month cycle length extending over a 10-year time horizon, which is the length of time for the final follow-up in the CheckMate 067 trial (Wolchok et al., 2025). The Markov and survival models were constructed and analyzed in R (version 4.4.2). The design and reporting of this cost-effectiveness analysis follow standard guidelines published elsewhere (Sanders et al., 2016).

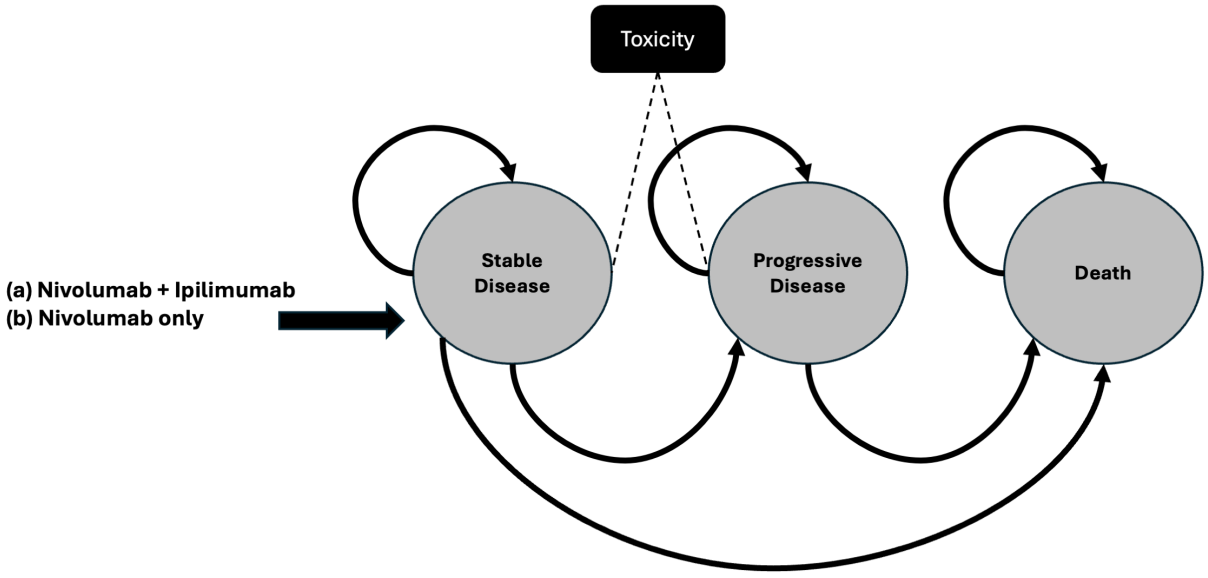

Figure 1: State-transition diagram of the Markov model

Note: Patients transition between stable disease, progressive disease, and death. Adverse events are modeled as temporary events with associated cost and utility decrements.

2.2. Treatment Details

We used the CheckMate 067 trial as a construct to model the different treatment groups. Patients in the nivolumab group received treatment every two weeks at a dose of 3 mgkg. The optimal length of nivolumab treatment among long-term responders is unknown; therefore, we evaluated different scenarios and assessed how these assumptions impacted the cost-effectiveness of this treatment. Our base case analysis followed the CheckMate 067 protocol, whereby patients received nivolumab until disease progression. We also tested scenarios

2.3. Model Structure

We developed a discrete-time Markov model to simulate a cohort of patients with advanced melanoma receiving first-line ICI. The model includes three primary health states:

- **Stable Disease (Progression-Free):** Patients receiving treatment without disease progression.
- **Progressive Disease:** Patients with disease progression.
- **Death:** An absorbing state.

A one-month cycle length was used over a 10-year time horizon. Patients may also experience treatment-related adverse events, which incur additional costs and temporary utility decrements. The model was implemented in R (version 4.0.2) using custom code and packages such as **heemod** for cost-effectiveness analysis.

The evolution of the cohort is mathematically defined by the following equations:

$$\begin{aligned} S(t+1) &= S(t) \times (1 - p_{\text{prog}} - p_{\text{death}}), \\ P(t+1) &= S(t) \times p_{\text{prog}} + P(t) \times (1 - q_{\text{death}}), \\ D(t+1) &= D(t) + S(t) \times p_{\text{death}} + P(t) \times q_{\text{death}}, \end{aligned}$$

where:

- p_{prog} is the monthly probability of progression from the stable state,
- p_{death} is the monthly probability of death from the stable state,
- q_{death} is the monthly probability of death from the progressive state.

Figure 1 displays the state-transition diagram of the model.

2.4. Model Probabilities and Calibration

Transition probabilities for OS and PFS were estimated by reconstructing individual patient data (IPD) from the published Kaplan–Meier curves in CheckMate 067. We digitized the curves for both the nivolumab monotherapy and the combination (nivolumab plus ipilimumab) arms using GetData Graph Digitizer, then generated pseudo-IPD with the **IPDfromKM** package in R. Parametric models (e.g., exponential, Weibull, log-logistic) and natural cubic spline models were fitted to the reconstructed data. The best-fitting models, selected based on the Akaike information criterion (AIC), provided the monthly probabilities of disease progression and death. Figure 2 shows the overlay of our model predictions with the published Kaplan–Meier curves.

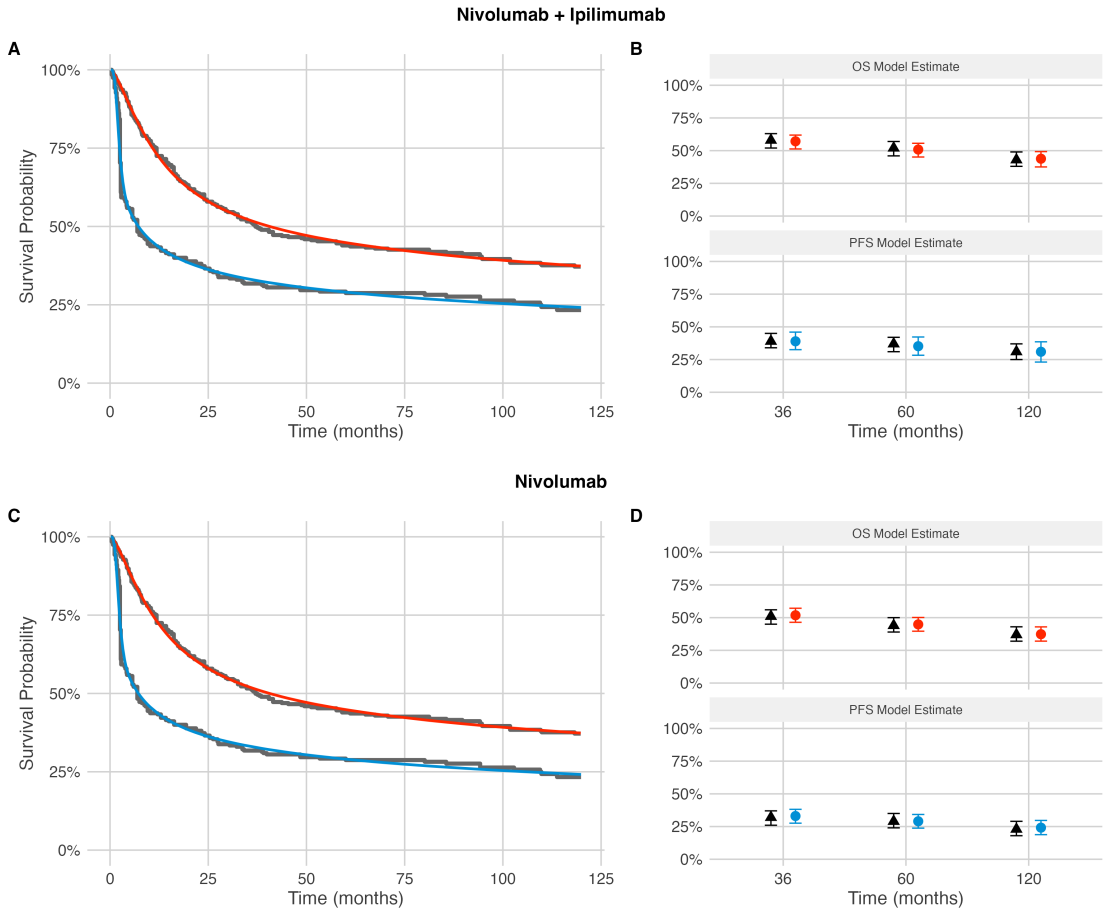

Figure 2: Model validation. (A) and (C) display the reconstructed Kaplan–Meier curves overlaid with the predicted OS and PFS curves for the combination and nivolumab monotherapy arms, respectively. (B) and (D) compare model estimates at 30, 60, and 120 months with the published data. The smooth curves represent the model predictions, while the superimposed points with error bars denote published estimates and their confidence intervals.

2.5. Biomarker-Based Strategy

In addition to the standard treatment strategies, we simulated a biomarker-driven approach. Based on the results of Tarantino et al., genomic heterogeneity and ploidy can predict intrinsic resistance to PD-1 blockade with a reported positive predictive value (PPV) of 90%, sensitivity of 33%, and specificity of 97%. In our model, all patients undergo a one-time genomic test (cost: $5,000), and based on the test's performance characteristics, patients are probabilistically assigned to either:

- **Combination Therapy (nivolumab + ipilimumab)** if predicted resistant, or
- **Nivolumab Monotherapy** if predicted sensitive.

This biomarker-based strategy is then compared with the standard, non–biomarker-based approach.

2.6. Counterfactual Survival Estimates

To further elucidate the heterogeneity in survival outcomes among patients receiving single-agent anti–PD-1 therapy, we derived counterfactual survival functions that delineate the extremes of patient response. Our underlying hypothesis is that the overall survival (OS) and progression-free survival (PFS) observed

in the nivolumab monotherapy arm represent a composite of two distinct subpopulations: patients who respond favorably to anti–PD-1 therapy and those who are intrinsically resistant. We assumed that the survival experience of responders is upper-bounded by that observed under combination therapy (Nivolumab + Ipilimumab), while the survival outcomes for intrinsically resistant patients are markedly lower.

Mathematically, we express the monotherapy survival model function as a weighted average:

$$S_{\text{mon}} = w \times S_{\text{comb}} + (1 - w) \times S_{\text{resistant}},$$

where S_{mon} is the survival probability in the nivolumab monotherapy arm, S_{comb} represents the survival probability for responders (assumed to match the combination therapy survival), and $S_{\text{resistant}}$ is the counterfactual survival probability for intrinsically resistant patients. In our base-case analysis, we assumed that 60% of patients are responders (i.e., $w = 0.6$) and 40% are intrinsically resistant. An analogous procedure was applied to the PFS curves. Counterfactual survival curves are presented in Figure 3.

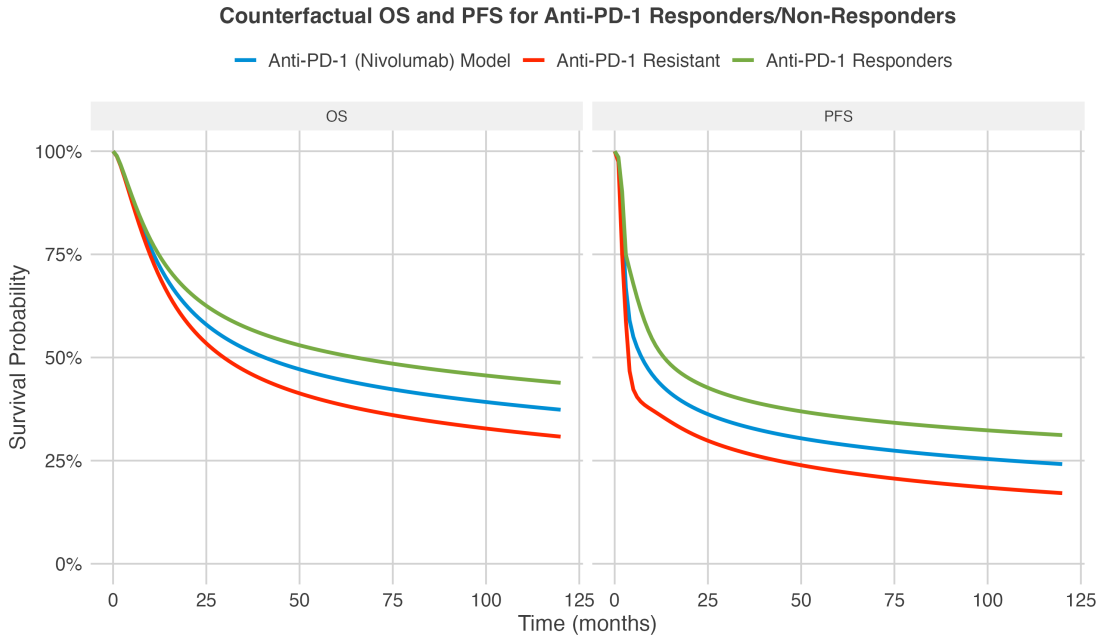

Figure 3: Counterfactual survival estimates. The solid lines represent the observed Kaplan–Meier curves for the nivolumab monotherapy arm, while the dashed lines denote the derived counterfactual survival functions for responders and intrinsically resistant patients.

We generated predictions over a common time vector (0–120 months) from our fitted survival models—namely. These predictions allowed us to compute the counterfactual survival functions for the intrinsically resistant and responsive subgroups. In effect, our approach provides bounds on the survival outcomes under single-agent therapy: the best-case scenario (for responders) is upper-bounded by the combination therapy survival curve, while the worst-case scenario is represented by the derived counterfactual for intrinsically resistant patients.

Furthermore, to assess the robustness of our findings, we incorporated these counterfactual estimates into our probabilistic sensitivity analysis. In this analysis, we varied the weighting parameter w as well as the limits of the survival bounds to account for uncertainty in the classification of responders versus non-responders. This sensitivity analysis enables us to evaluate how deviations from our base-case assumptions might influence the cost-effectiveness of a biomarker-based treatment allocation strategy.

2.7. Model Parameters

Table 1 summarizes the key model parameters, including survival probabilities, health utilities, costs, and genomic test characteristics. To ensure the table fits within the text width, we use the LaTeX `\resizebox` command.

Table 1: Model Parameters

Parameter	**Value**	**Source / Comments**
Cycle Length (months)	1	Assumed
Time Horizon (years)	10	Assumed
$\text{Utility}_{\text{PF}}$	0.85	Literature/Assumption
$\text{Utility}_{\text{PD}}$	0.65	Literature/Assumption
Cost_{PF} (per cycle)	\$1,000	Assumed
Cost_{PD} (per cycle)	\$3,000	Assumed
Cost of Genomic Test	\$5,000	Tarantino et al. (adjusted)
Transition Prob. (Death) – Nivo Monotherapy	0.02 (monthly)	Derived from CheckMate 067 calibration
Transition Prob. (Death) – Nivo+Ipi	0.015 (monthly)	Derived from CheckMate 067 calibration
Transition Prob. (Progression) – Nivo Monotherapy	0.04 (monthly)	Derived from CheckMate 067 calibration
Transition Prob. (Progression) – Nivo+Ipi	0.03 (monthly)	Derived from CheckMate 067 calibration
Biomarker Sensitivity	33%	Tarantino et al.
Biomarker Specificity	97%	Tarantino et al.
Biomarker PPV	90%	Tarantino et al.
Prevalence of Intrinsic Resistance	20%	Assumed

Note: Transition probabilities were estimated by fitting parametric and spline models to the reconstructed IPD from the CheckMate 067 trial. Costs and utilities are based on published literature and expert opinion.

2.8. Cost-Effectiveness Analysis

Using our calibrated Markov model, we simulated three treatment strategies over a 10-year horizon:

1. **Nivolumab Monotherapy**
2. **Combination Nivolumab + Ipilimumab**
3. **Biomarker-Based Strategy:** Patients first undergo genomic testing and are then assigned to combination therapy (if predicted resistant) or nivolumab monotherapy (if predicted sensitive).

For each strategy, we calculated total costs, QALYs, and the incremental cost-effectiveness ratio (ICER), applying a 3% annual discount rate. Deterministic one-way sensitivity analyses and probabilistic sensitivity analyses (using Monte Carlo simulation with 100,000 iterations) were performed to evaluate parameter uncertainty.

3. Results

[Insert the calibrated model results here. For example, report the simulated total costs, QALYs, and ICERs for each treatment strategy. Provide details on the sensitivity analyses—both deterministic and probabilistic—to illustrate the robustness of the findings.]

4. Discussion

Our analysis indicates that both nivolumab monotherapy and combination nivolumab plus ipilimumab yield favorable long-term survival outcomes relative to historical controls. However, the higher toxicity and cost associated with combination therapy underscore the need for a more refined treatment allocation strategy. By incorporating genomic predictors of intrinsic resistance, our biomarker-based strategy potentially allocates combination therapy only to those patients most likely to benefit, while sparing others from unnecessary toxicity and cost.

The close alignment between our reconstructed Kaplan–Meier curves and the published CheckMate 067 data supports the robustness of our survival models. Furthermore, our sensitivity analyses suggest that even under parameter uncertainty, the biomarker-driven strategy remains cost-effective—assuming a willingness-to-pay threshold of $100,000 per QALY.

Several limitations warrant discussion. First, our survival models are extrapolated beyond the observed trial data, and long-term outcomes may differ. Second, while the genomic test parameters are promising, they require further prospective validation. Finally, our cost inputs—derived from published literature and expert opinion—may not capture all regional or temporal variations in treatment expenses.

Future research should integrate real-world data to further refine these estimates and explore the inclusion of additional biomarkers and treatment modalities. Nonetheless, our findings provide a strong rationale for personalized treatment strategies in advanced melanoma, with the potential to improve clinical outcomes and optimize resource allocation.

Table 2: Base-Case Parameters for the Cost-Effectiveness Model: NIVO vs. NIVO+IPI

Parameter	**Base-Case Value**	**PSA (Distribution/Range)**	**Source**
Model Time Horizon and Discounting			
Time horizon (years)	10 (monthly cycles)	–	User-defined
Discount rate (% per year)	3%	–	Standard guide
Survival Inputs (CheckMate 067 Fitted Models)			
NIVO OS/PFS model	Parametric or K–M fit	–	Trial / user fits
NIVO+IPI OS/PFS model	Parametric or K–M fit	–	Trial / user fits
Drug Acquisition Costs (Per Cycle)			
Nivolumab cost	$14,975	Gamma (95% CI: 9,703–21,417)	AWP**?**
Ipilimumab cost	$11,450	Gamma (7,413–16,296)	AWP**?**
NIVO+IPI combination	$26,425	Gamma (17,089–37,662)	AWP**??**
Adverse Events (AE)			
Probability G3–4 AE (NIVO) per cycle	0.05	Beta (0.03–0.07)	Derived from tr
Probability G3–4 AE (NIVO+IPI) p/cycle	0.15	Beta (0.10–0.20)	Derived from tr
Cost per severe AE (NIVO)	$1,185	Gamma (767–1,695)	**??**
Cost per severe AE (NIVO+IPI)	$6,384	Gamma (4,139–9,127)	**??**
AE disutility (NIVO) per cycle	0.017	Beta (0.011–0.024)	**??**
AE disutility (NIVO+IPI) per cycle	0.019	Beta (0.012–0.027)	**??**
AE duration (cycles)	1	–	Placeholder ass
Health-State Costs (Per Cycle)			
Stable disease cost	$2,166	Gamma (1,397–3,098)	**?**
Progressed disease cost	$4,000	Gamma (2,575–5,512)	**?**
Palliative care (one-time)	$15,957	Gamma (10,335–23,818)	**?**
Utilities (Annual)			
Progression-free utility	0.754	Beta (0.47–0.97)	**??**
Progressed utility	0.180	Beta (0.11–0.37)	**??**
Death	0	–	Standard assum

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