Cost-effectiveness of adjuvant nivolumab for patients with stage III and IV melanoma who have undergone complete resection in Austria

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Background

Various types of melanoma affect people of all age groups and socioeconomic backgrounds, and compared to other cancers, this disease often affects individuals at a younger age [1]. Across EU-27 countries, it is estimated that melanoma accounts for 4% of all new cancer diagnoses in 2020 (all cancers, excluding non-melanoma skin cancers) and for 1.3% of all deaths due to cancer [2]. The disease is associated with substantial burden on patients as well as their caregivers [1].

Standard-of-care treatment for most patients with stage III melanoma and some patients with resectable stage IV melanoma are tumor and associated lymph node resection [1].

Objectives

The aim of this analysis was to evaluate the cost-effectiveness of adjuvant nivolumab versus observation in patients with stage III and IV melanoma who have undergone complete resection in Austria.

Methods

Overview

A partitioned survival model [PSM] was adapted to the Austrian context to assess the cost-effectiveness and cost-utility of adjuvant nivolumab versus observation for patients with stage III and IV melanoma who have undergone complete resection in Austria (Table 1).

Clinical data were taken from the phase 3 CheckMate 238 [3] trial and the CA 184-029 trial [4] to create an indirect treatment comparison [ITC] between observation and nivolumab for resected stage III to IV melanoma. Resource utilization and direct cost (2024 €) from an Austrian payer perspective were derived from published sources.

While cost were discounted at 5%, quality-adjusted life years [QALYs] and life-years [LYs] were discounted at 3% annually. A willingness-to-pay [WTP] threshold of 40,000€ per QALY gained was applied. Deterministic and probabilistic sensitivity analyses were performed to assess input parameters' impact on model outcomes and to address uncertainty in incremental cost, health effects, and cost-utility.

The economic analysis was performed in accordance with the "ISPOR Good Research Practices Task Force Report" guidelines [5] and the Austrian guidelines for health economic evaluation [6].

Table 1. Methods

Parameters	Model settings
Population	Melanoma patients with fully resected stage IIIB to IV disease: • Mean age: 53.11 years • Stages: IIIB: 34.48%; IIIC: 46.78%; IV: 18.74% • Mean weight: 80.0kg • Proportion female: 39.9% • Proportion BRAF V600 positive: 48.1%
Intervention	Adjuvant treatment with nivolumab up to 12 months (3mg/kg once every two weeks as per CheckMate 238)
Comparator	Observation
Outcomes	LYs saved; QALYs saved; total cost; incremental cost-effectiveness ratio [ICER]; incremental cost-utility ratio [ICUR]
Study type	• Cost-effectiveness analysis [CEA] • Cost-utility analysis [CUA]
Model type	Partitioned survival model [PSM]
Perspective	Healthcare perspective
Health state utilities	Based on EQ-5D-3L data from Checkmate 238
Timing	2024
Time horizon	Lifetime (60 years)
Cycle length	28 days
Discount rate	• 5% for cost • 3% for LYs & QALYs
Sensitivity analysis	• Deterministic sensitivity analysis [DSA] • Probabilistic sensitivity analysis [PSA]

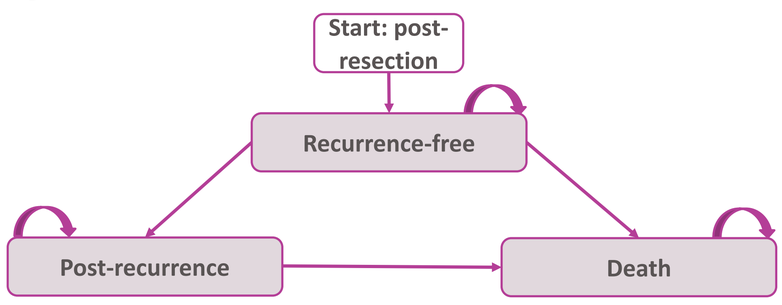
Model structure

A three-health state PSM (recurrence-free [RF], post-recurrence [PR], and death) with a lifetime horizon of 60 years and a cycle length of 28 days was adapted to the Austrian setting (Figure 1).

The model uses overall survival [OS] and recurrence-free-survival [RFS] curves to estimate health state occupancy of RF, PR and death. RF corresponds to the area below the RFS curve, PR to the area between the RFS and OS curves, and death to the area above OS curve, respectively.

All patients enter the PSM in the RF state and may either remain in this state after each model cycle, or transition to PR or death. Cost and QALYs in alive-states are calculated for each alternative and each patient during each cycle.

Figure 1. Overview of the PSM



Clinical data

Patients considered in the model correspond to those included in CheckMate 238 [3] and CA 184-029 [4].

CheckMate 238 is a two-arm, multicentre, randomized, double-blind, phase III clinical trial which investigated the efficacy and safety of nivolumab monotherapy versus ipilimumab in patients with completely resected stage IIIB-C or stage IV melanoma and high-risk for recurrence, for maximum treatment duration of 12 months [3].

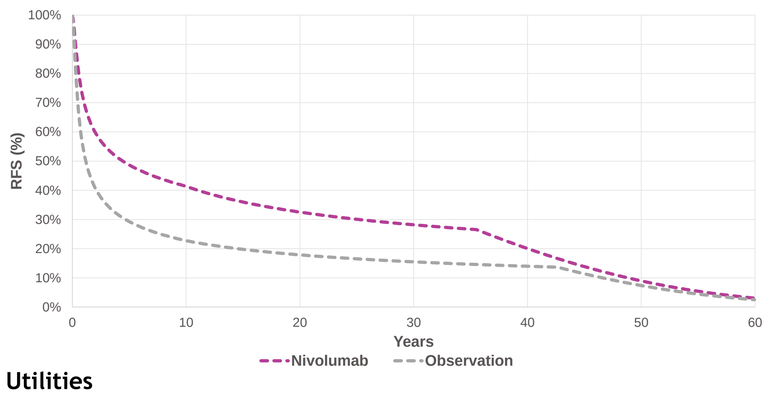
CA 184-029 is a two-arm, randomized, double-blind, phase III clinical study in patients with stage III melanoma after complete resection to determine if ipilimumab versus placebo is effective in preventing or delaying recurrence and to prolong survival [4].

In CheckMate 238 [3] and in CA 184-029 [4], the primary endpoint was RFS in the intention-to-treat [ITT] population, defined as the time between randomization and first recurrence, new primary melanoma or death. In CheckMate 238, secondary efficacy endpoints included OS, safety and side-effect profiles, RFS according to tumor PD-L1 expression, and health-related quality of life [HRQoL] [3]. In CA 184-029, secondary efficacy endpoints included OS and adverse events [AE] [4].

Key clinical inputs for the model were derived from OS and RFS data taken from an ITC performed with CheckMate 238 [3] and CA184-029 data [4]. The parametric ITC provided parametric survival curves to allow treatment comparisons between nivolumab and observation for RFS and OS using CheckMate 238 [3] and CA184-029 [4]. The Bucher ITC provided Hazard Ratios [HR] in relation to treatment comparisons in CheckMate 238 [3] and CA184-029 [4] and estimated the indirect treatment HR between nivolumab and placebo. Distributions offering the best visual and statistical fit (determined by the Akaike information criterion [AIC] and Bayesian information criterion [BIC]) for long-term extrapolation were spline one-knot odds for RFS and spline one-knot normal for OS.

Figure 2 shows the adjusted efficacy curves for nivolumab and observation in the partitioned survival approach for RFS.

Figure 2. RFS over 60 years (odds, 1-knot)



Utilities

A mixed effects regression model with covariate adjustment was used to estimate mean utility values from observed EQ-5D-3L data collected within CheckMate 238 [3]. As this trial compared nivolumab against ipilimumab, all treatments within the model are conservatively assumed to have the same utility within each health state.

Utility decrements for AE were based on published sources [7]. The proportions of patients experiencing immune-related AEs, diarrhoea, or other AEs and their average duration were based on CheckMate 238 and used to estimate a weighted utility decrement.

Resource use & costs

Direct cost components comprise treatment cost, administration cost, monitoring cost, AE cost, subsequent treatment cost, and end of life cost.

Treatment cost are based on Austrian ex-factory prices and reimbursement prices for 2024 [8].

The model also includes hospital bed and outpatient cost for each type of AE considered, i.e. immune-related AEs, diarrhoea (grade ≥2), or other AEs (grade ≥3). Austrian unit cost for AEs (2024) are based on published sources [9, 10].

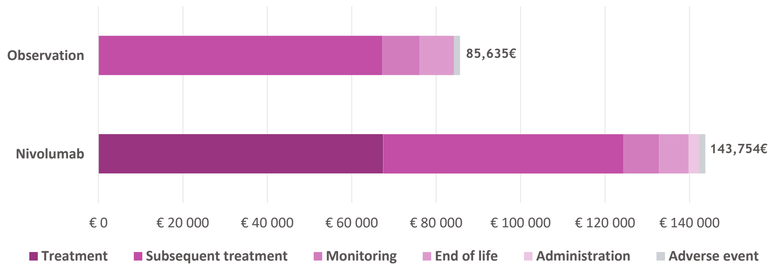
Results

Base-case results

Lifetime cost of nivolumab and observation amount to 143,754€ and 85,635€, respectively (Figure 3; Table 2). Incremental cost of adjuvant nivolumab in patients with stage III and IV melanoma who have undergone complete resection versus observation amount to 58,119€ in Austria (Table 2).

Treatment cost for nivolumab are the most notable cause of total cost differences between the two alternatives. Subsequent treatment cost, on the other hand, are significantly higher in the observation group. AE cost over the remaining lifetime make a minor contribution to overall cost differences (Figure 3; Table 2).

Figure 3. Direct cost components and total costs



Adjuvant therapy leads to a considerable QALY gain of 8.11 in the recurrence-free health state, compared to 5.02 QALYs gained for observation. Also taking post-recurrence QALYs into account, nivolumab is associated with a total QALY gain of 11.41 compared to 9.63 for observation. The incremental QALY gain of nivolumab versus observation is 1.79.

Incremental cost of 58,119€ and incremental QALYs of 1.79 lead to an ICUR of nivolumab versus observation of 32,551€ per QALY gained in Austria.

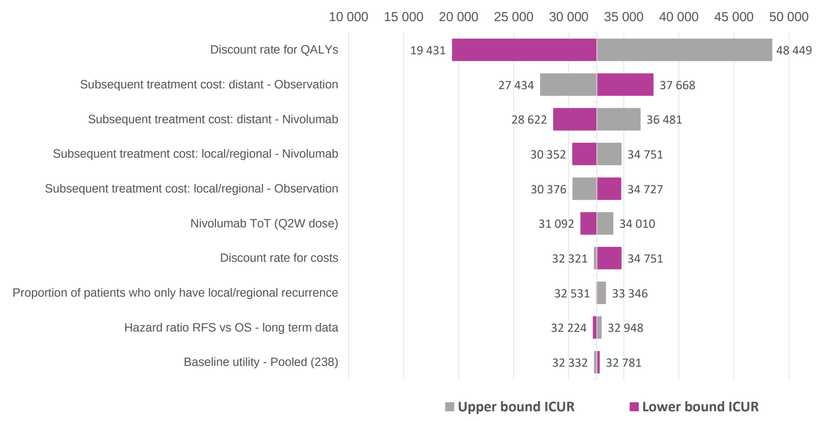
Table 2. Base-case results

Parameters	Nivolumab	Observation	Difference
Treatment cost	67,438.28€	0.00€	67,438.28€
Administration cost	2,425.55€	0.00€	2,425.55€
Monitoring cost	8,505.54€	8,837.61€	-332.07€
AE cost	1,529.54€	1,397.75€	131.79€
Subsequent treatment cost	56,864.56€	67,261.88€	-10,397.32€
End of life cost	6,990.54€	8,138.17€	-1,147.63€
Total cost	**143,754.01€**	**85,635.41€**	**58,118.60€**
Total LYs	**14.54**	**12.50**	**2.04**
Recurrence-free state	10.02	6.19	3.83
Post-recurrence state	4.52	6.31	-1.79
ICER per LY gained		**28,462.90€**	
Total QALYs	**11.41**	**9.63**	**1.79**
Recurrence-free state	8.11	5.02	3.09
Post-recurrence state	3.31	4.61	-1.30
ICUR per QALY gained		**32,551.34€**	

Sensitivity analysis

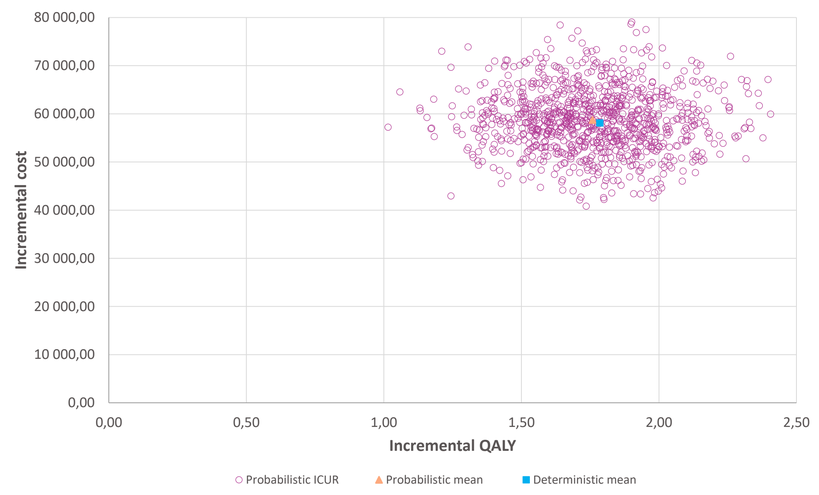
DSA and PSA were performed to assess input parameters' impact on model outcomes and uncertainty in incremental cost, health effects, and cost-utility. Figure 4 shows DSA results.

Figure 4. DSA: nivolumab versus observation



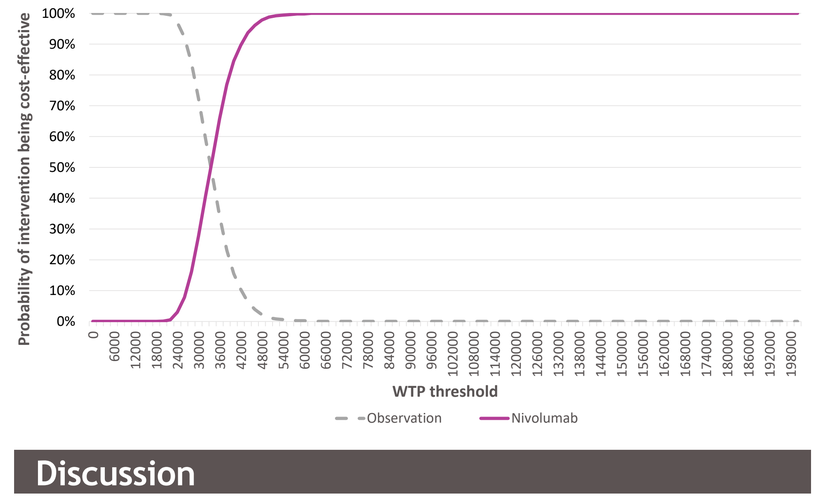
Monte Carlo PSA results of 1,000 second-order simulations plotting incremental cost versus incremental effects are depicted in Figure 5.

Figure 5. Cost-effectiveness plane: nivolumab versus observation



The cost-effectiveness acceptability curve (CEAC) shows that, at a WTP threshold of 40,000€/QALY, nivolumab was cost-effective versus observation in around 85% of simulations (Figure 6).

Figure 6. CEAC: nivolumab versus observation



Discussion

Adjuvant treatment with nivolumab for patients with completely resected stage III and IV melanoma leads to a significantly longer RFS compared to observation.

Improving RFS using adjuvant treatment with nivolumab directly improves health outcomes and increases both life expectancy and QALYs. In addition, subsequent treatment cost and end of life cost are being significantly reduced by avoiding or at least suspending potential recurrence into an active disease state.

The benefits of adjuvant therapy using nivolumab in terms of RFS, life expectancy and QALYs are also very likely to impact the indirect cost of the disease, such as productivity loss, work loss or need for long-term care. Further research should therefore quantify these cost and their potential impact on the cost-effectiveness of adjuvant therapy using nivolumab from an Austrian societal perspective.

Conclusion

Adjuvant treatment with nivolumab in malignant melanoma patients who have undergone complete resection is a cost-effective therapy option in Austria, compared to observation.

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Disclosures

Evelyn Walter, Gerald Eichhober, and Marco Voit are employees of the Institute for Pharmaeconomic Research [IPF]. IPF was a paid consultant to Bristol Myers Squibb in connection with the local adaptation of the global pharmacoeconomic model as well as the development of this abstract and poster. Christian Boehler is an employee and shareholder of Bristol Myers Squibb.

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