Cost-effectiveness of adjuvant nivolumab in adult patients with stage II/III carcinoma of the esophagus or gastroesophageal junction and residual disease after neoadjuvant chemo-radiotherapy following complete resection in Austria

Gerald Eichhober[1], Marco Voit[1], Evelyn Walter[1], Christian Boehler[2*]

[1]Institute for Pharmaeconomic Research [IPF], Vienna, Austria; [2]Bristol Myers Squibb, Vienna, Austria

*Corresponding author

Background

Esophageal carcinoma [EC] is a malignant tumor of the esophagus accounting for approximately 1% of all malignant cancers and about 2% of all cancer-related deaths in Austria [1, 2]. The gastroesophageal junction [GEJC], which connects the throat and the stomach, is also a potential carcinoma site [1].

More than 50% of patients with EC are over 65 at the time of diagnosis and the disease appears more often in men than in women [2]. Though age-standardized disease rates remain constant, the shift towards ageing societies has led the number of new cases and disease-related deaths to increase [2].

Few symptoms of both cancer types in early disease stages (stage I or II) often lead to late diagnosis (at stage III or IV) which is associated with a poor prognosis [2, 3].

Objectives

The aim of this analysis was to evaluate the cost-effectiveness of adjuvant nivolumab versus observation in adult patients with stage II/III EC or GEJC with residual disease after neoadjuvant chemo-radiotherapy [CRT] and being surgically rendered disease-free in Austria.

Methods

Overview

A discrete-time three-state Markov cohort model was adapted to the Austrian context. Clinical data stems from the phase 3 CheckMate 577 trial [4]. Resource utilization was identified by clinical experts and direct cost (2024 €) from an Austrian payers' perspective were taken from published sources (Table 1).

Cost were discounted at 5%, while 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. Both 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	Adult patients with stage II/III EC or GEJC who have residual disease after neoadjuvant CRT followed by complete resection: • Mean age: 60.50 years • Mean body surface: 1.85m^2 • Mean weight: 71.25kg • Proportion female: 15.00%
Intervention	Adjuvant treatment with nivolumab for a maximum of 52 weeks (240mg IV Q2W or 480mg IV Q4W each over 30 minutes in the first 16 weeks, following 480mg IV Q4W each over 30 minutes / Doses: Q2W: 8 or Q4W: 4, following Q4W: 9)
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	Discrete-time Markov cohort model with 3-health states
Perspective	Healthcare perspective
Health state utilities	Based on EQ-5D-3L data from Checkmate 577
Timing	2024
Time horizon	Lifetime (30 years)
Cycle length	1 month
Discount rate	• 5% for cost • 3% for LYs & QALYs
Sensitivity analysis	• Deterministic sensitivity analysis [DSA] • Probabilistic sensitivity analysis [PSA]

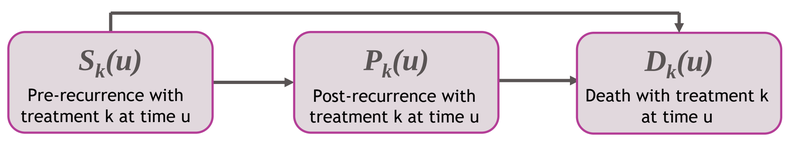
Model structure

A discrete-time Markov cohort model with 3-health states (pre-recurrence, post-recurrence, and death) was adapted to the Austrian context using a lifetime horizon (30 years) and a cycle length of one month (Figure 1).

All patients entered the model in the pre-recurrence state, and per cycle, they either remained in this health state, moved on to post-recurrence, or they entered the models' death state. Cost and QALYs in alive-states were then calculated for each alternative and each patient during each cycle.

Pre-recurrence to post-recurrence transition was informed by extrapolating observed data from disease-free survival [DFS] for nivolumab and observation from CheckMate 577 [4]. Transition from post-recurrence to death was modelled independent of treatment using real-world registry data matched to the CheckMate 577 population based on tumor staging, neoadjuvant therapy and surgery, resection status, and patients with residual pathological disease. Transition from pre-recurrence to death was based on general population mortality in accordance with Austrian national life tables [7].

Figure 1. Overview of discrete 3-state time Markov cohort model



Clinical data

The patient group modelled corresponds to patients included in the CheckMate 577 trial [4].

CheckMate 577 is a global, multicentre, randomized, placebo-controlled, double-blind phase 3 clinical study to investigate the efficacy and safety of nivolumab as monotherapy for the adjuvant treatment of carcinomas of the esophagus or gastroesophageal junction [4].

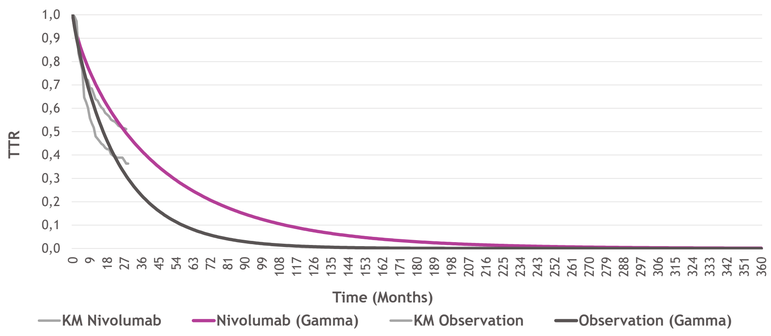
The study included adult patients independent of their tumor PD-L1 expression level with medically diagnosed residual EC or GEJC stage II or III and histologically confirmed adenocarcinoma or squamous cell carcinoma. Patients had received CRT followed by complete surgical resection within 16 weeks prior to randomization and had pathological residual disease of at least ypN1 or ypT1 after being surgically rendered disease-free [4].

794 patients were included and randomized in a 2:1 ratio to either nivolumab 240mg (n = 532) or placebo (n = 262). Patients received nivolumab intravenously over 30 minutes every 2 weeks for 16 weeks, followed by 480mg infused over 30 minutes every 4 weeks, starting at week 17 [4].

DFS was the primary efficacy endpoint in CheckMate 577 and defined as the time-to-recurrence [TTR] or death from any cause, whichever occurred first [4]. TTR was defined as the time between the date of randomization and the time of local, regional or distant recurrence from the primary resected site. TTR avoids double-counting of deaths and has been used to estimate the transition from pre-recurrence to post-recurrence in the model.

Kaplan-Meier [KM] curves of TTR for nivolumab and observation were extrapolated over a period of 360 months using Gamma distributions (Figure 2). The Gamma distribution has been identified as the appropriate extrapolation model with a good statistical and visual fit to the KM curves for both nivolumab and placebo (observation).

Figure 2. Observed and extrapolated TTR (Gamma models)



Utilities

CheckMate 577 collected patient reported outcomes using the EQ-5D-3L instrument [4].

Mean EQ-5D values for each health state of the economic model (i.e. pre-recurrence and post-recurrence) were based on the overall CheckMate 577 population using the EQ-5D index score [4].

Utility decrements due to adverse events [AE] were based on Nafees et al. (2008) [8]. Only grade 3 and 4 treatment-related AEs with ≥5% incidence were included in the analysis.

Resource use & costs

Direct cost components comprise treatment cost, monitoring cost, recurrence-free disease-related cost, post-recurrence disease-related cost, AE cost, subsequent treatment cost, and terminal care cost.

Treatment costs are based on Austrian ex-factory prices and reimbursement prices for 2024 [9].

The model also included AE costs with a severity grade of 3 or 4 and an incidence of at least 5%. Safety data were taken directly from the CheckMate 577 trial [4].

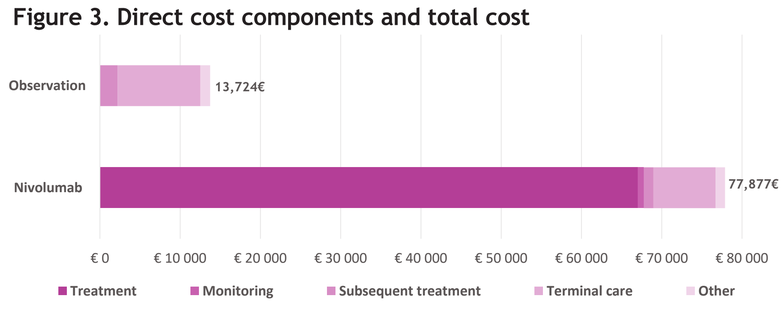
Results

Base-case results

Lifetime cost of adjuvant nivolumab therapy amount to 77,877€, compared to lifetime cost of 13,724€ for observation. Incremental cost of adjuvant nivolumab in adult patients with stage II/III carcinoma of the esophagus or gastroesophageal junction and residual disease after neoadjuvant chemo-radiotherapy following complete resection in Austria versus observation are therefore 64,153€ (Figure 3; Table 2).

Treatment costs for nivolumab are the most notable cause of cost differences between the two alternatives, whilst terminal care costs and subsequent treatment costs are higher for observation. Other cost components make a minor contribution to overall cost differences (Figure 3; Table 2).

Figure 3. Direct cost components and total cost



In the pre-recurrence state, adjuvant therapy leads to a considerable QALY gain of 6.07, whilst observation is associated with 3.71 QALYs. Also taking QALYs in the post-recurrence state into account, this results in a total QALY gain of 6.38 for nivolumab whilst observation leads to total QALYs of 4.14. The incremental QALY gain of nivolumab versus observation is therefore 2.25.

Incremental costs of 64,153€ and incremental QALYs of 2.25 lead to an ICUR of 28,519€ for nivolumab versus observation.

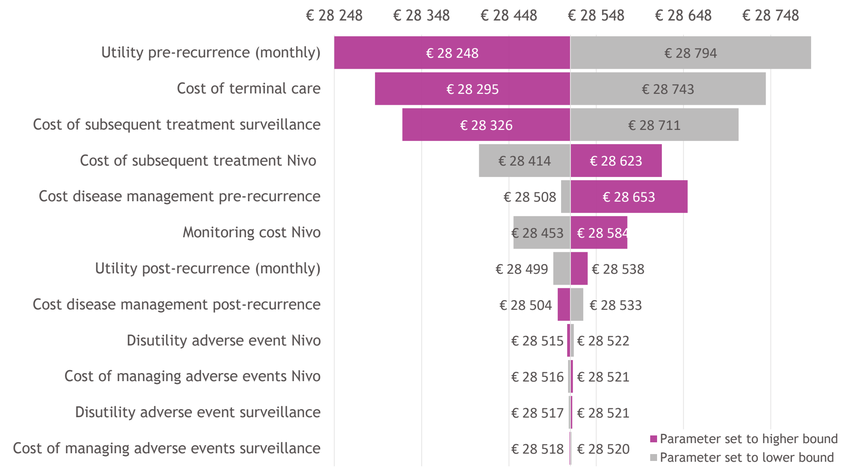
Table 2. Base-case results

Parameters	Nivolumab	Observation	Difference
Treatment cost	67,008.86€	0.00 €	67,008.86 €
Monitoring cost	748.19€	0.00€	748.19 €
AE cost	31.40€	12.66€	18.74 €
Recurrence-free disease-related cost	640.38€	516.59€	123.78 €
Post-recurrence disease-related cost	505.53€	673.87€	-168.34 €
Subsequent treatment cost	1,202.33€	2,210.67€	-1,008.34 €
Terminal care cost	7,740.20€	10,309.79€	-2,569.59 €
Total cost	**77,876.89 €**	**13,724.34 €**	**64,152.55 €**
Total LYs	**6.33**	**4.79**	**1.55**
LYs pre-recurrence	5.95	4.26	1.69
LYs post-recurrence	0.39	0.53	-0.14
ICER per LY gained		**41,451.10 €**	
Total QALYs	**6.38**	**4.14**	**2.25**
QALYs pre-recurrence	6.07	3.71	2.36
QALYs post-recurrence	0.32	0.42	-0.11
ICUR per QALY gained		**28,518.66 €**	

Sensitivity analysis

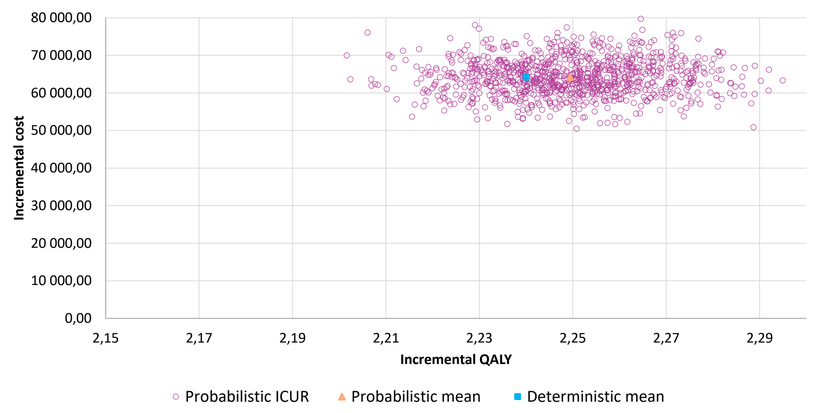
DSA and PSA were performed to assess input parameters' impact on model outcomes and uncertainty in incremental cost, health effects, and cost-utility. Figure 4 shows DSA results.

Figure 4. DSA: nivolumab versus observation



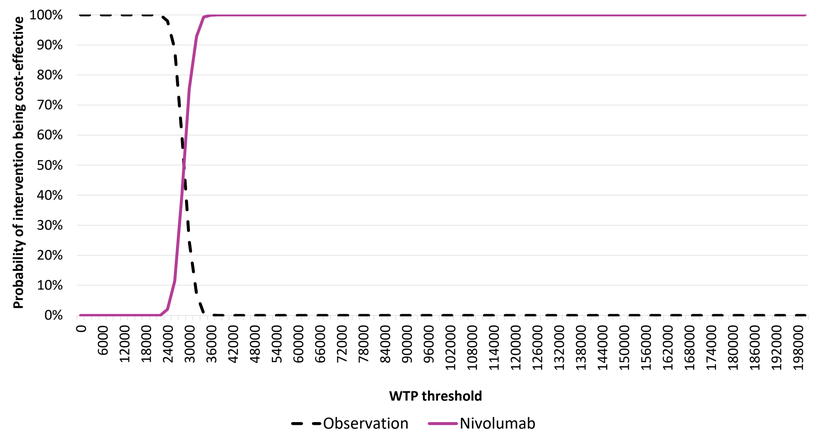
Monte Carlo PSA results of 1,000 second-order simulations plotting incremental cost versus incremental effects are depicted in Figure 5.

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 about 100% of simulations (Figure 6).

Figure 6. CEAC: nivolumab versus observation



Discussion

Results from CheckMate 577 indicate that adjuvant treatment with nivolumab in adult patients with stage II/III EC or GEJC who have residual disease after neoadjuvant CRT followed by complete resection leads to significantly longer DFS compared to observation. Improving DFS also increases life expectancy and QALYs. In addition, adjuvant therapy may reduce future healthcare spending by avoiding or at least suspending potential recurrence to an active disease state.

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

Conclusion

Adjuvant therapy with nivolumab in adult patients with stage II/III EC or GEJC who have residual disease after neoadjuvant CRT followed by complete resection is a cost-effective therapy in Austria, which significantly improves DFS compared to observation.

References

1. Kade B, Görling U, Höfler H, Körber J, Messmann H, Porschen R, Schidberger H, Vanhöfer U, Wullstein C. Cancer of the oesophagus: A guideline for patients. 2016.
2. Stahl M, Al-Batran SE, Borner M, Gockel I, Grenacher L, Hass H, Köberle D, Möhler M, Porschen R, Pritzkuleit R, Rumpold H, Stuschke M, Sinn M. Onkopedia guideline: Oesophageal carcinoma. German Society for Haematology and Medical Oncology (DGHO) e.V. Berlin, 2021.
3. Federal Joint Committee [GBA] Module 3P. Dossier for the benefit assessment § 35a SGB V: Nivolumab (Opdivo®) Module 3P: Adjuvant treatment of adult patients with carcinoma of the oesophagus or gastro-oesophageal junction with pathological residual disease after previous neoadjuvant chemoradiotherapy. 2021
4. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, Uronis H, Elimova E, Grootscholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM, Moehler M; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 384(13):1191-1203. 2021. DOI: 10.1056/NEJMoa2032125.
5. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sclpher M, Severens J. Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. 12 (4): 409-418. 2009.
6. Walter E. Österreichische Guidelines zur gesundheitsökonomischen Evaluation [Guidelines for health-economic evaluations in Austria]. Pharmaco Econ Ger Res Art. 4(2):55–63. German. 2006. DOI:10.1007/BF03321566.
7. Statistics Austria. Austrian life tables 2022. 2023.
8. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes;6:84. 2008. DOI: 10.1186/1477-7525-6-84.
9. Österreichischer Apothekerverlag. Warenverzeichnis I [Austrian classified index of goods I]. 2024 Feb. German.

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.

This study was funded by Bristol Myers Squibb. All authors contributed to and approved the presentation.

Presented at ISPOR Europe 2024; November 17-20, 2024; Barcelona, Spain

E-Mail: <christian.boehler@bms.com>