[EE209]

Cost-effectiveness of adjuvant nivolumab in adults with high-risk muscle-invasive urothelial carcinoma [MIUC] with tumor cell-PD-L1-expression ≥1% in Austria

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Background

One of the most common malignant tumors is urinary bladder carcinoma which accounts for approximately 3%-4% of all malignant cancers. It is three times more common in men than women with a mean age of onset greater than 70 years [1].

Urothelial carcinoma accounts for more than 90% of all bladder cancers and most commonly manifests as superficial non-muscle-invasive urothelial carcinoma [1]. Muscle-invasive urothelial carcinoma [MIUC] is a subtype of urinary bladder carcinoma and affects either the urinary bladder [MIBC] or the upper urinary tract [UTUC], consisting of the renal pelvis and ureter [2].

In Austria, standard-of-care treatment for most patients with MIUC are radical cystectomy and associated lymph node resection [3].

Objectives

The aim of this analysis was to evaluate the cost-effectiveness of adjuvant nivolumab versus observation in adult MIUC patients with tumor cell-PD-L1-expression ≥1% and with a high-risk of recurrence after radical resection of MIUC in Austria.

Methods

Overview

A Markov cohort model was adapted to the Austrian setting. Clinical data was taken from CheckMate 274, a phase 3 clinical trial [4]. Resource utilization and direct cost (2024 €) were derived from published sources, representing an Austrian payer perspective.

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 MIUC patients with tumor cell-PD-L1-expression ≥1% and with a high-risk of recurrence after radical resection of MIUC: • Mean age: 65.20 years • Mean body surface: 1.79m² • Mean weight: 73.90kg • Proportion female: 24.50% • Proportion PD-L1-expression ≥1%: 39.8%
Intervention	Adjuvant treatment with nivolumab for a maximum of 52 weeks (240mg IV Q2W / Mean doses: Q2W: 17.2)
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	3-health state Markov cohort model
Perspective	Healthcare perspective
Health state utilities	Based on EQ-5D-3L data from Checkmate 274
Timing	2024
Time horizon	Lifetime (30 years)
Cycle length	7 days
Discount rate	• 5% for cost • 3% for LYs & QALYs
Sensitivity analysis	• Deterministic sensitivity analysis [DSA] • Probabilistic sensitivity analysis [PSA]

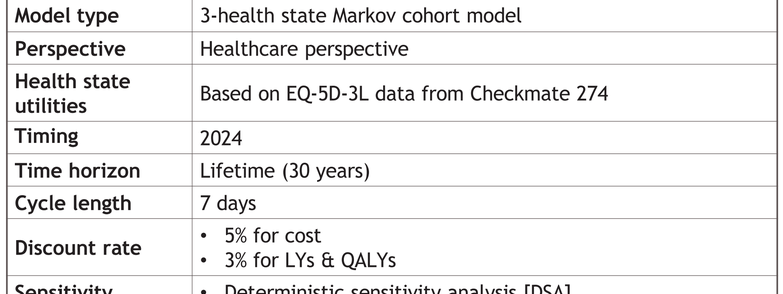
Model structure

A three-health state Markov cohort model (disease-free [DF]; recurred disease [RD]; and death) was adapted to the Austrian context using a lifetime horizon (30 years) and a cycle length of seven days (Figure 1).

All patients enter the model in the DF state following radical resection of MIUC. Per cycle, patients either remain in DF, move to RD, or enter the 'death' state. Cost and QALYs in alive-states are then calculated for each alternative and each patient during each cycle.

The proportion of patients staying in DF is based on the disease-free survival [DFS] endpoint from CheckMate 274 [4]. The risk of leaving DF was split into RD and death based on the observed total number of first events in Checkmate 274 [4]. Patients still in DF at 5 years and beyond are considered to be functionally cured so that the risk of death modelled is based on general population mortality in accordance with Austrian national life tables [7].

Figure 1. Overview of 3-health state Markov cohort model



Clinical data

The patient group modelled corresponds to patients included in the CheckMate 274 trial [4].

Checkmate 274 is a 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 urothelial carcinoma [4].

The study included high-risk patients (18 years or older) with completely resected MIBC or UTUC. A total of 709 patients were randomized to treatment with either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks [4].

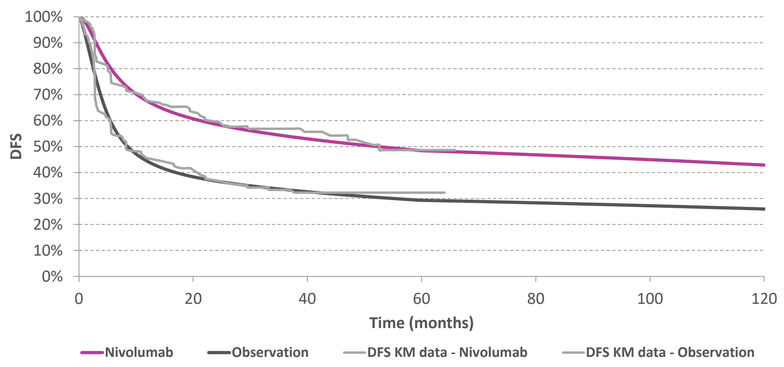
Treatment with nivolumab was continued until recurrence or unacceptable toxicity for a maximum duration of 1 year [4].

DFS was the primary efficacy endpoint for all randomized patients and for randomized patients with tumor cell-PD-L1 expression ≥1%. Secondary efficacy endpoints included overall survival [4].

DFS was defined as the time between the date of randomization and the date of first documented recurrence as assessed by the investigator (local recurrence within the urinary tract, recurrence outside the urinary tract or distant metastasis) or death (of any cause), whichever occurred first [4].

In this analysis, the Kaplan-Meier [KM] curves of nivolumab and placebo (observation) of DFS were extrapolated over a period of 120 months using the Gompertz distribution up to 60 months (Figure 2) and thereafter Austrian life table adjustment to the DFS curves. The Gompertz 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 DFS (Gompertz models)



Utilities

Mean EQ-5D-3L values for each health state were based on data collected within Checkmate 274 to which linear mixed-effects repeated measures models with random intercepts were applied to estimate the impact of recurrence and treatment status on changes in EQ-5D-3L health utility scores from baseline.

Utility decrements due to grade 3 and 4 adverse events [AE] with an incidence rate of ≥2% for all treatments in the analyses were based on Nafees et al. (2008) [8].

Resource use & costs

Direct cost components comprise drug acquisition cost, drug administration cost, monitoring cost, disease management cost, AE cost, subsequent treatment cost, and end of life cost.

Drug acquisition cost are based on Austrian ex-factory prices for 2024 [9].

The model included AE cost with a severity grade of 3 or 4 and an incidence of at least 2%. Safety data were taken directly from CheckMate 274 [4]. Conservatively, no AEs were assumed in the analysis in the observation arm.

The proportion of patients receiving subsequent treatment was also informed by Checkmate 274 data [4].

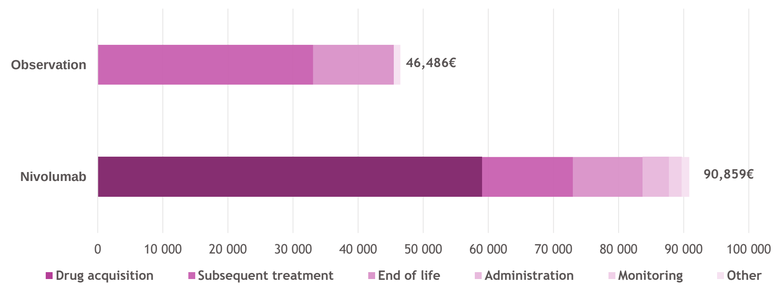
Results

Base-case results

Over a lifetime horizon, nivolumab results in total cost of 90,859€. In contrast, observation causes total cost of 46,486€, resulting in incremental cost of 44,373€ for nivolumab versus observation in Austria (Figure 3; Table 2).

Unsurprisingly, drug acquisition cost for nivolumab are the most notable cause of cost differences between the two alternatives, whilst subsequent treatment cost are significantly higher in the observation group. Other cost, including 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 cost



In the DF state, adjuvant therapy leads to a considerable QALY gain of 6.31, whilst observation is associated with 3.96 QALYs in DF. Taking the RD state into account, this results in a total QALY gain of 6.79 for nivolumab whilst observation leads to total QALYs of 4.68. The incremental QALY gain of nivolumab versus observation is therefore 2.11.

For nivolumab versus observation, incremental cost of 44,373€ and incremental QALYs of 2.11 lead to an ICUR of 21,046€ in Austria.

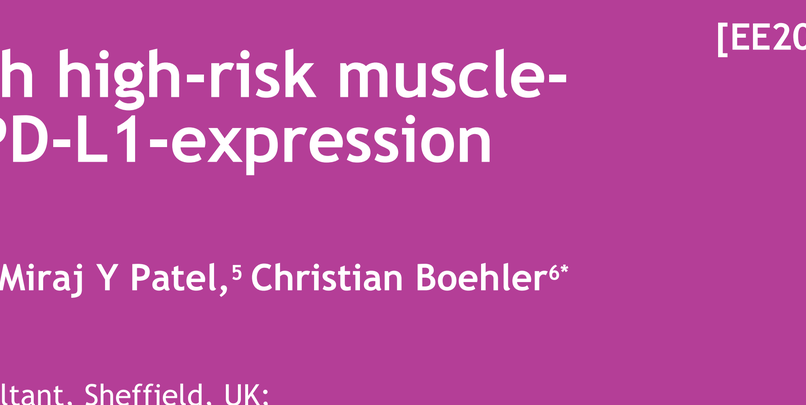
Table 2. Base-case results

Parameters	Nivolumab	Observation	Difference
Disease management cost	785.46€	551.43€	234.03€
Drug acquisition cost	59,030.40€	0.00€	59,030.40€
Drug administration cost	4,042.00€	0.00€	4,042.00€
Monitoring cost	1,933.28€	0.00€	1,933.28€
AE cost	112.83€	0.00€	112.83€
Surgery & radiotherapy cost	276.97€	434.13€	-157.17€
End of life cost	10,721.79€	12,423.53€	-1,701.75€
Subsequent treatment cost	13,955.86€	33,076.62€	-19,120.77€
Total cost	**90,858.58€**	**46,485.72€**	**44,372.86€**
Total LYs	**8.41**	**5.89**	**2.52**
DF health state	7.70	4.83	2.87
RD health state	0.71	1.06	-0.35
ICER per LY gained		**17,619.32€**	
Total QALYs	**6.79**	**4.68**	**2.11**
DF health state	6.31	3.96	2.35
RD health state	0.49	0.72	-0.24
ICUR per QALY gained		**21,046.25€**	

Sensitivity analysis

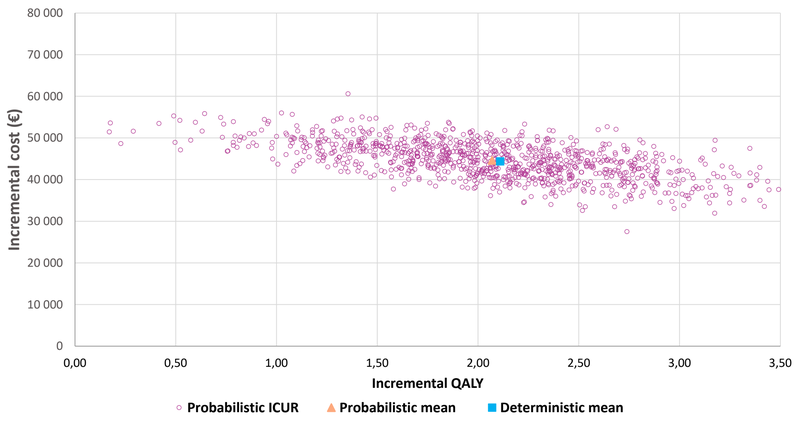
DSA and PSA were performed to assess input parameters' impact on model outcomes and uncertainty in incremental cost, health effects, and cost-utility. The DSA varied mean parameter values by their respective standard error, 95% confidence interval or ± 20% of the expected values (Figure 4).

Figure 4. DSA: nivolumab versus observation



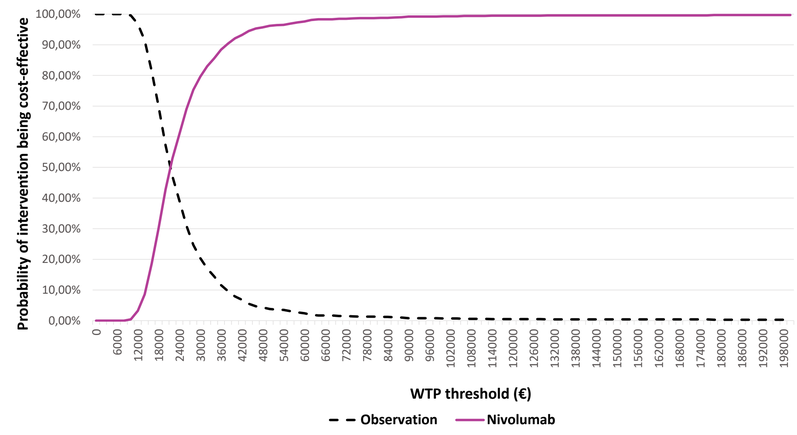
Monte Carlo PSA results of 1,000 second-order simulations plotting incremental cost versus incremental effects are depicted in Figure 5.

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 92% of simulations (Figure 6).

Figure 6. CEAC: nivolumab versus observation



Discussion

Adjuvant treatment with nivolumab in adult MIUC patients with tumor cell-PD-L1-expression ≥1% and with a high-risk of recurrence after radical resection of MIUC leads to a significantly longer DFS compared to observation.

Improving DFS using adjuvant treatment with nivolumab increases both life expectancy and QALYs. In addition, subsequent treatment costs are significantly reduced by extending DFS and OS.

The benefits of adjuvant therapy using nivolumab in terms of DFS, OS and QALYs are also very likely to impact the indirect costs of the disease, such as productivity loss, work loss or need for long-term care. Further research should therefore quantify these costs 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 MIUC patients with tumor cell-PD-L1-expression ≥1% and with a high-risk of recurrence after radical resection of MIUC is a cost-effective therapy option compared to observation in Austria.

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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. Lei Ni is employee of RTI Health Solutions and Christopher Knight is a former employee of RTI Health Solutions. RTI Health solutions was a paid consultant to Bristol Myers Squibb responsible for developing the global parmacoeconomic model and validating the local adaptation the Austrian setting. Siguroli Teitsson, Miraj Y Patel, and Christian Boehler are employees and shareholders of Bristol Myers Squibb.

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