Cost-effectiveness of nivolumab as an adjuvant treatment of muscle-invasive urothelial carcinoma at high risk of recurrence with tumour cell PD-L1 expression ≥ 1% in Sweden

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Introduction

Muscle-invasive urothelial carcinoma (MIUC)

- Urothelial carcinoma (UC) begins in the urothelial cells lining the mucosal surfaces of the lower urinary tract (including the urethra and bladder) and the upper urinary tract (including the ureter and renal pelvis)[1]
- In Sweden, the primary treatment of patients with MIUC (T2-T4a, N0-NX, M0) is radical cystectomy with lymph node excision preceded by neoadjuvant chemotherapy (if patients are eligible for chemotherapy). Routine use of adjuvant chemotherapy is not recommended. In cases in which neoadjuvant treatment was not given, adjuvant chemotherapy may be considered[2,3]

Nivolumab as an adjuvant treatment strategy

- Nivolumab monotherapy is the first and thus far the only immuno-oncology therapy to show through a phase 3 study (CheckMate 274) a statistically significant increase in disease-free survival (DFS) compared with placebo in patients with muscle-invasive urothelial carcinoma (MIUC) at high risk of recurrence[4,5]
- In patients whose tumour cells expressed at least ≥ 1% programmed death ligand-1 (PD-L1) level, the study demonstrated superiority of nivolumab over placebo in DFS (hazard ratio, 0.53; 95% confidence interval, [0.38-0.75]) and a safety profile consistent with previous clinical trials[4,5]
- Based on these results, nivolumab was granted marketing authorisation by European Commission approval on 1 April 2022 for adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection of MIUC[6-9]

Objective

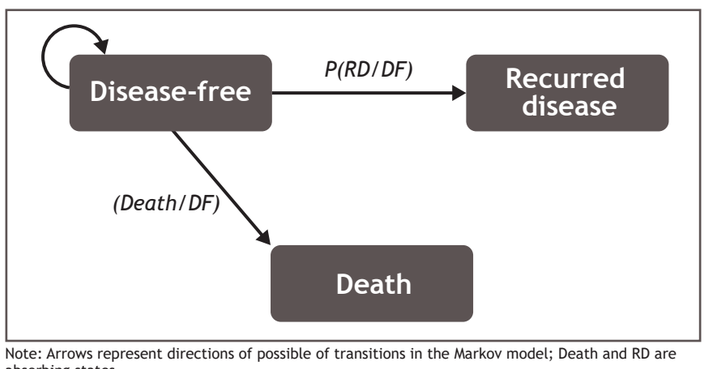
- To study the cost-effectiveness and cost-utility of nivolumab versus observation in Sweden for the adjuvant treatment of patients with MIUC at high risk of recurrence and tumour cell PD-L1 expression ≥ 1% who have undergone radical resection

Methods

Model structure

- A 3-state Markov model was developed to evaluate discounted total costs and quality-adjusted life-years (QALYs) for a 30-year time horizon from a healthcare payer perspective (**Figure 1**). Model states represent the evolution of MIUC and its different stages according to recurrence status as disease-free (DF), recurred disease (RD), which consists of both local recurrence and distant recurrence, and death
  - For patients in the RD health state, total cost and QALY are applied when entering the RD health state; therefore, no explicit transition is modelled from the RD health state to death

Figure 1. Overview of the 3-health-state model



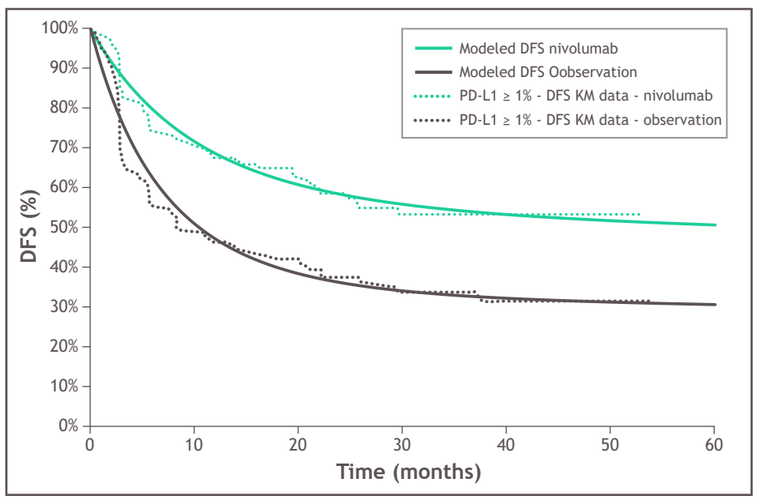
Note: Arrows represent directions of possible of transitions in the Markov model; Death and RD are absorbing states.

P(RD|DF) = probability of moving from DF to RD; P(Death|DF) = probability of death from DF.

Efficacy and survival

- For each treatment, efficacy measures (coprimary endpoint: DFS), were based on the reported PD-L1 ≥ 1% subgroup data from the CheckMate 274 trial
- To estimate the cumulative DFS over a 30-year time horizon, parametric survival curves were fitted to the CheckMate 274 data based on methods guidance from the Decision Support Unit at the National Institute for Health and Care Excellence[10,11]
- The best fit to the data based on raw statistical criteria (i.e., Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) was the independent generalised gamma model, but it generated clinically implausible DFS estimations and therefore was not considered in the cost-effectiveness evaluations. The second-best statistical fit based on AIC and BIC (independent Gompertz model) was chosen for the base-case analysis due to its superior visual fit to Kaplan-Meier (KM) curves reported from the trial as well as the underlying smoothed hazards (**Figure 2**)
- The Gompertz distribution also generated long-term survival rates that were well aligned with the long-term data from the deferred chemotherapy arm of EORTC 30994 study[12] in a similar MIUC population
- External data shows steadily declining DFS hazards with time[12,13] which converge with the general population mortality rates. Therefore, DFS extrapolations from the Gompertz model were adjusted using Swedish life table data to ensure that DFS hazards estimated from the trial data never exceed the general population mortality rates
- The model utilised the proportions of first recurrence events along with the estimated DFS rates from the Gompertz model to derive the transitions from DF to RD and death states
- The distribution of first recurrence events applied in the model was assumed to be constant for PD-L1 ≥ 1% subgroup based on the distribution of events over the whole follow-up period in the CheckMate 274 trial
- Post-recurrence cost and health outcomes in the RD health state were modelled as one-off composite parameters of the model. Treatment-specific total discounted costs and QALYs were aggregated using the local shares of first-line therapies available for the treatment of metastatic UC (mUC) in Sweden

Figure 2. Modelled DFS Using Independent Gompertz Distribution Over 60 Months



  - Survival data to estimate the one-off costs and QALYs associated with the entrance to the RD health state was based on the analysis and extrapolations of published survival data from first-line mUC literature
    - In this analysis, patients first-line mUC patients were classified as cisplatin-eligible using trial data Bellmunt et al. (2012)[14] and -ineligible using trial data from De Santis et al. (2012)[15]
    - Incremental QALY gains with avelumab treatment compared with chemotherapy were also considered in the model according to reported data from the health technology assessment conducted by the Statens legemiddelverk[16] in Norway

Inputs and settings

- The analyses were performed from a healthcare payer perspective
- The model included costs of drug acquisition, administration, monitoring, adverse events (AE), disease management, subsequent treatment, surgery and radiotherapy, and terminal care. Drug acquisition cost for each treatment was sourced from Swedish national sources
- Healthcare resource use (urology consultant, urethroscopy, computerised tomography scan, and blood tests) to estimate disease management costs was based on clinical expert opinion
- Costs associated with mUC treatments were based on either their published durations and survival data, or prior health technology appraisals reporting their total estimated costs
- Safety data were taken directly from the CheckMate 274 trial. For nivolumab arm, the model included all causality AEs with grade 3 and 4 that have incidence rates ≥ 15%
  - No AEs were assumed for the observation arm in the analysis as a conservative assumption
- Drug acquisition cost for nivolumab was calculated using the mean number of doses reported from CheckMate 274. Due to 1-year treatment cap in the trial, all acquisition costs were incurred within the first year after first dose implying the maturity of the time on treatment data as the minimum follow-up for the trial was 11.4 months
- For each health state in the model, EQ-5D-5L utility values were derived from the questionnaire administered to patients in the CheckMate 274 study[17]
- Utility decrements due to AEs were based on estimates from Nafees et al.[18] which reported utility values in patients with metastatic non small cell lung cancer
- An annual discount rate of 3.0% was applied for both costs and QALYs in line with TLV (Swedish Dental and Pharmaceutical Benefits Agency) guidelines
- The base-case parameter settings are presented in **Table 1**

Table 1. Key model settings

Parameters	Base-case values
Time horizon	30 years
Perspective	Healthcare payer
Cycle length	Weekly (half-cycle correction applied)
Discounting	Annual 3.0% for both costs and outcomes (QALYs, LYs)
Patient characteristics (baseline mean age, gender distribution, mean BSA)[19,20]	CheckMate 274 RCT 65.2 years, 75.5% male, 1.79 m^2
Survival extrapolation	
DF	Gompertz model; independent fit to arms of CheckMate-274
RD	One-off outcomes derived from first-line mUC literature
Health state utilities (SE)	
DF	0.820 (0.013)
RD	0.692 (0.009)
AEs	All causality grade 3 and 4 AEs with at least 15% incidence rate based on ITT population in CheckMate 274
Resource use	Clinical expert input[21]
Unit cost for resource use	Swedish public sources and the published literature

BSA = body surface area; ITT = intent to treat; LY = life-year; RCT = randomised controlled trial; SE = Standard error.

Results

Base case (discounted)

- Estimated survival was substantially higher for nivolumab compared with observation, with a resulting 3.16 LY difference (total LYs: 9.70 vs. 6.54 for nivolumab and observation, respectively) over a 30-year time horizon
- Treatment with nivolumab was associated with greater total QALYs compared with observation (total QALYs: 6.25 vs. 4.26 for nivolumab. and observation, respectively), resulting in a QALY gain of 1.99
- Although nivolumab was associated with higher total treatment acquisition costs than observation, it led to savings from subsequent treatment and terminal care by reducing the rates of recurrences and deaths simultaneously
- The corresponding incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were SEK 167,919/LY gained and SEK 266,834/QALY gained, respectively
- The discounted base-case results are presented in **Table 2**

Table 2. Base-case results

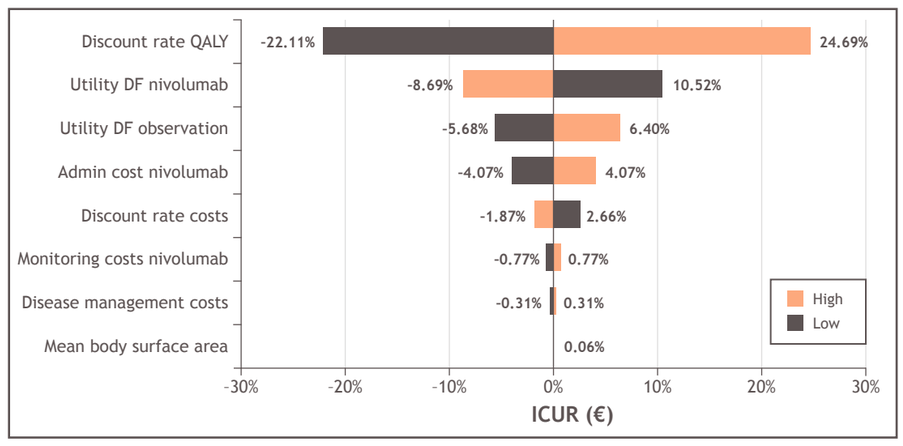
Settings	Nivolumab	Observation
Total costs[a]	**1,247,051**	**716,044**
Drug acquisition	538,042	–
Drug administration	107,982	–
Monitoring	20,465	–
AEs	174	–
Disease management	115,616	72,743
Subsequent treatment	410,629	589,121
Total QALYs		
DF health state	5.87	3.71
RD health state	0.38	0.55
Disability due to AEs	0.00	0.00
Total LYs		
DF health state	9.12	5.72
RD health state	0.58	0.82
ICER	**SEK 167,919**	
ICUR	**SEK 266,834**	

[a] Costs were reported in 2022 Swedish krone (SEK).

Sensitivity analyses

- Deterministic sensitivity analysis showed that the parameters with the largest impact on the ICUR results were the annual discount rate for QALYs (approximately −23% to +25% impact) followed by the utility value for nivolumab patients in DF state (approximately −9% to +11% impact) and the utility value for the observation in DF state (approximately −6% to 7% impact). Pre-specified variations in other parameters resulted in < 4% change in ICURs (**Figure 3**).
- Probabilistic sensitivity analyses resulted in an average ICUR of SEK 274,961/QALY, with nivolumab having a 98% probability of being cost-effective at a willingness-to-pay threshold of SEK 1,000,000/QALY gained

Figure 3. Deterministic sensitivity analysis showing the percentage change in ICURs from baseline estimate



Scenario analyses with respect to subsequent treatments and model structure

- Scenario analyses explored variation in ICURs with respect to:
  - (1) Changes in overall cost of subsequent treatments:
    - (1a) 20% increase in subsequent treatment costs
    - (1b) 20% decrease in subsequent treatment costs
  - (2) Changes in model structure by splitting RD state into 2 separate states as local and distant recurrence and correspondingly using 4-health-state Markov model
- All tested scenarios resulted in ≤ 7% changes from the base-case ICUR. Results from scenario analyses are presented in **Table 3**

Table 3. Scenario results

Settings	ICUR (SEK)	Difference from the base case (%)
Base case	266,834 SEK	–
20% increase in subsequent treatment costs	248,896 SEK	−7%
20% decrease in subsequent treatment costs	284,773 SEK	7%
4-health-state Markov model	276,620 SEK	4%

Conclusions

- Nivolumab is estimated to be a life-extending and a cost-effective adjuvant treatment for patients with MIUC who are at high risk of recurrence following radical resection with PD-L1 expression ≥ 1% in Sweden
- Modelling of early lines of therapy, such as adjuvant therapy, has some inherent challenges due to the long-term survival (e.g., in relation to later lines of metastatic treatment) and impact of subsequent therapies on survival
- In this study key benefits of nivolumab are composed of where trial data are available (DF health state) and not where assumptions have been needed regarding modelling of subsequent treatment (RD health state)

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