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 Denmark

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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 90%-95% of cases, UC develops in the bladder. In approximately 5%-10% of cases, it develops in the upper urinary tract[2,3]
- According to the Danish Multidisciplinary Cancer Group, the primary treatment of patients with muscle-invasive bladder cancer (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

Nivolumab as an adjuvant treatment strategy

- Nivolumab monotherapy is the first and thus far the only immuno-oncology treatment 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 UC (MIUC) at high risk of recurrence[4,5]
- In patients whose tumour cells expressed programmed death ligand-1 (PD-L1) level at least ≥ 1%, the study demonstrated superiority of nivolumab over placebo for the DFS endpoint (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 European Commission approval on 1 April 2022 to be used as an 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

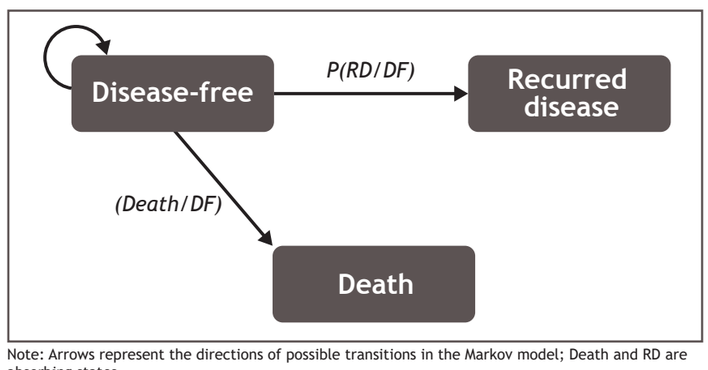
- To assess the cost-effectiveness and cost-utility of nivolumab versus observation in Denmark for the adjuvant treatment of patients with MIUC with high risk of recurrence and tumour cell PD-L1 expression ≥ 1% who have undergone radical resection

Methods

Model structure

- A 3-state Markov model was developed to evaluate discounted total costs and quality-adjusted life-years (QALYs) for a 20-year time horizon from a limited societal perspective (**Figure 1**). The model represents evolution of MIUC disease in different states according to recurrence status as disease-free (DF), recurred disease (RD), which consists of both local recurrence and distant recurrence, and death
  - RD state is considered as an absorbing state. Therefore, total costs and QALYs associated with this state are applied as one-off upon patients' entrance to the state without having to model explicit transitions from this state to death

Figure 1. Overview of the 3-Health-State Model



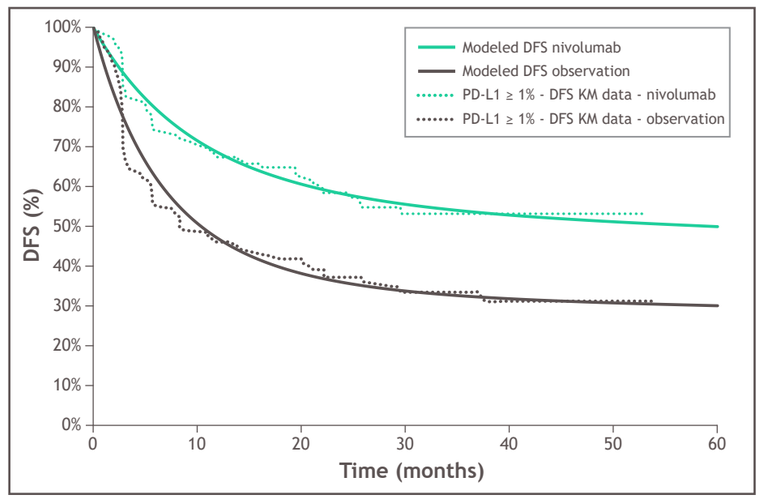
Note: Arrows represent the directions of possible transitions in the Markov model; Death and RD are absorbing states.

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) for nivolumab versus observation were based on PD-L1 ≥ 1% subgroup data from the CheckMate 274 trial
- To estimate DFS over a 20-year time horizon, parametric survival curves were fitted to the CheckMate 274 DFS data based on methods guidance from the Danish Medicines Council (DMC)[10] and the Decision Support Unit at the National Institute for Health and Care Excellence[11,12]
- 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. 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 the corresponding Kaplan-Meier (KM) curves reported from the trial and the underlying smoothed hazards (**Figure 2**)
- The long-term extrapolations from Gompertz distribution were also well aligned with long-term data from the deferred chemotherapy arm of EORTC 30994 study[13] in a similar MIUC population
- External data showed steady declines in DFS hazards over time[13,14] converging with the general population mortality rates. Therefore, DFS extrapolations were adjusted using Danish life table data to ensure that DFS hazards estimated from the trial data can never go below the general population mortality
- The model leveraged 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 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 local shares of first-line therapies available for the treatment of metastatic UC (mUC) in Denmark

Figure 2. Modelled DFS from independent Gompertz models 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 from Bellmunt et al.[15] and -ineligible using trial data from De Santis et al.[16]
    - 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[17] in Norway

Inputs and settings

- The analyses were performed from the Danish limited societal perspective as per Danish Medicines Council (DMC) guidelines[18]
- The model included costs of drug acquisition, administration, monitoring, adverse events (AE), disease management, subsequent treatment, surgery and radiotherapy, and terminal care. Drug acquisition list price for each treatment was sourced from Danish national sources[19]
- Healthcare resource use (urology consultant, urethroscopy, computerised tomography scan, and blood tests) to estimate disease management costs was based on inputs from national clinical treatment guidelines for bladder tumours in Denmark[20]
- 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 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
- Time on treatment for nivolumab was informed by the mean number of doses from CheckMate 274 with all acquisition costs incurred within the first year in line with the treatment-stopping rule in the trial and licensed indication
- In line with DMC guidelines[18], EQ-5D-5L utility values assigned to model health states were mapped from the EQ-5D-3L data which were derived from the questionnaire administered to patients in the CheckMate 274 study[21]
- Utility decrements due to AEs were based on estimates by Nafees et al.[22] which reported utility values in patients with metastatic non small cell lung cancer
- An annual discount rate of 3.5% was applied for both costs and QALYs in line with DMC guidelines[18]
- Base-case parameter settings are summarised in Table 1

Table 1. Base-case model settings

Parameters	Base-case values
Time horizon	20 years
Perspective	Limited societal
Cycle length	Weekly (half-cycle correction applied)
Discounting	Annual 3.5% for both costs and outcomes (QALYs, LYs)
Patient characteristics (baseline mean age, gender distribution, mean BSA)[23,24]	Average characteristics of CheckMate 274 population 65.2 years, 75.5% male, 1.89 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	0.854 (0.011)
RD	0.752 (0.006)
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[25] and national clinical treatment guidelines for bladder tumours in Denmark[20]
Unit cost for resource use	Danish public sources and the published literature

BSA = body surface area; LY = Life-years; RCT = randomised controlled trial; SE = standard error.

Results

Base case (discounted)

- Estimated survival was substantially higher for nivolumab compared with observation, with a resulting 2.08 LY differential (total LYs: 7.99 vs. 5.91 for nivolumab and observation, respectively) over a 20-year time horizon
- Treatment with nivolumab was associated with greater total QALYs compared with observation (total QALYs: 6.60 vs. 4.82 for nivolumab and observation, respectively), resulting in a QALY gain of 1.78
- 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
- The corresponding incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were DKK 157,446/LY gained and DKK 184,626/QALY gained, respectively
- The base-case results are presented in Table 2

Table 2. Base-case results

Settings	Nivolumab	Observation
Total costs[a]	**960,174**	**632,370**
Drug acquisition	378,464	–
Drug administration	40,575	–
Monitoring	25,975	–
AEs	DKK 220	–
Disease management	124,209	79,071
Subsequent treatment	362,900	521,483
Patient transport and loss of time costs incurred per visit	29,086	16,832
Terminal care	27,590	31,391
Total QALYs		
DF health state	5.81	3.69
RD health state	0.79	1.14
Disability due to AEs	0.00	0.00
Total LYs		
DF health state	6.94	4.40
RD health state	1.05	1.51
ICER	**DKK 157,446**	
ICUR	**DKK 184,626**	

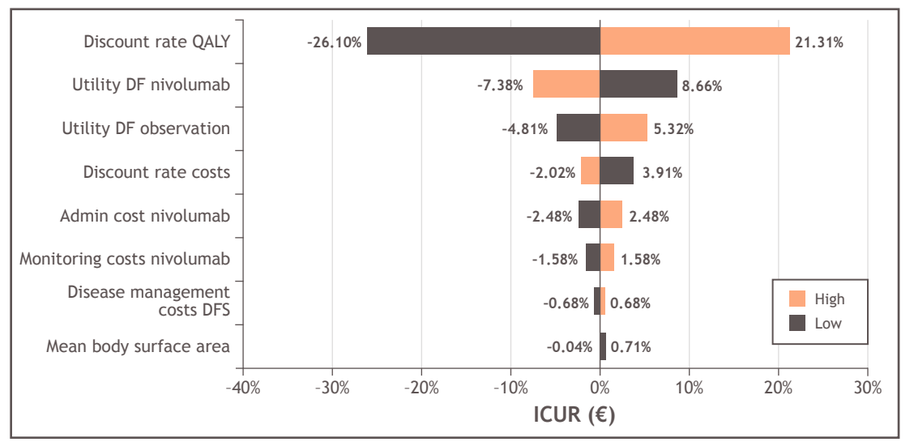
[a] Costs were reported in 2022 Danish krone (DKK).

Note: Results presented differ slightly from those presented in the abstract due to updates implemented in the cost-effectiveness analysis during the health technology assessment phase in Denmark.

Sensitivity analysis

- Deterministic sensitivity analysis showed that the parameters with the largest impact on the ICUR results were the annual discount rate for QALYs (approximately −27% to +22% impact) followed by the utility value for the DF nivolumab (approximately −8% to +9% impact) and the utility value for the DF Observation (approximately −5% to 6% impact). Pre-specified variations in other parameters resulted in < 4% change in ICURs (Figure 3)
- Probabilistic sensitivity analyses confirmed the robustness of the model results (average ICUR DKK 192,817/QALY), with nivolumab having 95%, 98%, and 99% probability of being cost-effective at willingness-to-pay thresholds of DKK 500,000/QALY, DKK 800,000/QALY, and DKK 1,000,000/QALY, respectively

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 a 4-health-state Markov model
- Results from scenario analyses are presented in **Table 3**. All tested scenarios resulted in 10% or less change from the base-case ICUR

Table 3. Results from scenario analyses

Settings	ICUR (DKK)	Difference from the base case (%)
Base case	184,626	–
20% increase in subsequent treatment costs	166,763	−10%
20% decrease in subsequent treatment costs	202,490	10%
4-health-state Markov model	202,108	9%

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 Denmark
- 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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