Cost-effectiveness analysis of nivolumab as an adjuvant treatment of muscle-invasive urothelial carcinoma at high risk of recurrence in Greece

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Introduction

Muscle-Invasive Urothelial Carcinoma

- Urothelial cancer is growth of abnormal tissue, known as a tumour, that develops in the urothelial cells lining the renal pelvis, ureters, or urinary bladder. Bladder cancer is the ninth most common cancer worldwide with 430,000 new cases diagnosed annually, resulting in approximately 145,000 deaths globally each year[1]
- Muscle-invasive urothelial carcinoma (MIUC) is a serious, life-threatening disease that occurs predominantly (90%-95% of cases) in the bladder (muscle-invasive bladder cancer) but can also occur in the upper excretory tract in 5%-10% of cases (upper tract urothelial carcinoma)[2-4]
- The management strategy for MIUC is based on radical surgery. For patients eligible for cisplatin-based chemotherapy, neoadjuvant cisplatin-based combination chemotherapy is recommended. After surgery and prior to CheckMate 274, no active therapy is recommended when patients are ineligible for cisplatin-based adjuvant chemotherapy. Only active surveillance is recommended[5-6]

Nivolumab

- Nivolumab monotherapy is the first and 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 MIUC at high risk of recurrence[7-8]
- In patients whose tumour cells expressed programmed death ligand-1 (PD-L1) at a threshold ≥ 1%, the study demonstrated the superiority of nivolumab over placebo on DFS (hazard ratio: 0.53; 95% confidence interval, 0.38-0.75) and a safety profile consistent with previous clinical trials involving patients with metastatic urothelial carcinoma and other cancers.[9-11] Based on these results, nivolumab was granted European marketing authorization on 1 April 2022[12]

Objective

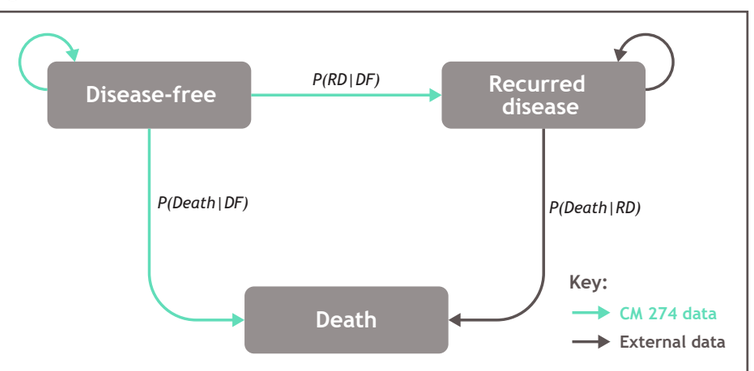
- To assess the cost-effectiveness of nivolumab versus surveillance, a proxy of placebo, in MIUC for patients with tumour cell PD-L1 ≥ 1% (expressed as tumour proportion score) in Greece

Methods

Model Structure

- A 3-state Markov model was developed comprising disease-free (DF) and recurred disease (RD), which consists of both local recurrence and distant recurrence, and finally death. The model was developed to evaluate discounted total costs and quality-adjusted life-years (QALYs) over a 30-year time horizon (**Figure 1**)

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



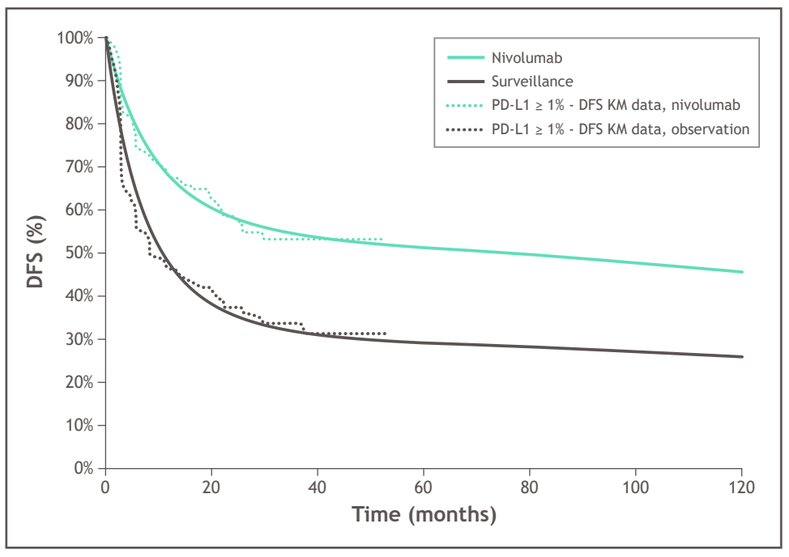
Note: Arrows represent possible directions of transitions in the Markov model; death is an absorbing state

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

Efficacy and Survival

- Efficacy measures for nivolumab versus surveillance were based on 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 following the National Institute for Health and Care Excellence methods guidance[13]
- A dependent Gompertz extrapolation model was chosen as the base-case model as it was the second best fit in terms of Akaike information criteria and Bayesian information criteria, but it had superior visual fit to both the trial Kaplan-Meier (KM) curves and the underlying smoothed hazards (Figure 2) compared with the best-fit model (generalized gamma), which resulted in clinically implausible DFS estimates:
  - DFS from 5 years onward was further adjusted using Greek life table data supported by CheckMate 274 DFS hazards converging with Greek life table hazards before year 5 in both arms. Thus, patients who are still disease free at 5 years are assumed to be functionally cured of disease. This is supported by other studies showing minimum risk of recurrence or death from this point[14,15] and clinical expert opinion
  - The model applies the proportions of recurrence events to the DFS curve to weight transitions from DF to RD and death states
  - The first recurrence events are reported in the CheckMate 274 data over the whole follow-up period and are applied in the model as constant weights up to year 5, after which patients are at risk only of dying and not recurrence

Figure 2. Extrapolated DFS



- As overall survival data were not available from CheckMate 274 at time of model development to inform transitions from the RD health state, survival data from the first-line metastatic UC setting (1L mUC) were used as a proxy for patients entering the RD health state:
  - Transition probabilities for the RD health state were based on survival data from the 1L mUC literature[16,17] fitted with exponential distribution, representing 1L mUC survival for cisplatin-eligible and -ineligible patients, respectively, and further informed by Greek clinical expert opinion
  - Scenario analysis showed limited impact of survival estimation following disease recurrence on the incremental model results (**Table 3**)
- No extrapolation was required for time to discontinuation given that trial data were fully mature due to the 1-year treatment-stopping rule in the trial

Inputs and Settings

- The analyses were performed from a Greek healthcare system perspective
- The model included costs of drug acquisition, administration, monitoring, adverse events (AE), disease management, subsequent treatment, subsequent surgery and radiotherapy, and terminal care
- Costs for drug acquisition, administration, monitoring, subsequent therapy, and AE management were sourced from published prices, literature review, and clinical expert input
- Disease management resource use (urology consultant, urethroscopy, computed tomography scan, and blood tests) was based on clinical expert input
- 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 trial treatment-stopping rule
- Utility values assigned to model health states were estimated from the EQ-5D-3L questionnaire administered to patients in the CheckMate 274 study.[18] QALY losses due to AEs were also included
- An annual discount of 3.5% was applied to costs and utilities per National Institute for Health and Care Excellence guidelines
- The key base-case settings are presented in **Table 1**

Table 1. Key Model Settings

Parameters	Base-case values
Time horizon	30 years
Cycle length	Weekly
Discounting	Annual 3.5% for both costs and outcomes (QALYs, LYs)
Patient characteristics (age, gender)	65.2 years, 75.5% male[7]
Survival extrapolation	
DF	Parametric model (Gompertz); dependent
RD	Exponential
Health state utilities	
DF	0.820
RD	0.692
Adverse events	Grade ≥ 3 (grades 3 and 4) of treatment-emergent AEs with at least 2% incidence based on CheckMate 274
Resource use	Based on clinical expert opinion

LY = life-year.

Note: Patient characteristics derived from the CheckMate 274 study.

Results

Base Case

- Survival was predicted to be higher for nivolumab, with a 2.777 LY difference (total LYs: 8.275 vs. 5.498, respectively) compared with surveillance over a 30-year time horizon
- Treatment with nivolumab was associated with greater total QALYs compared with surveillance (total QALYs: 6.739 vs. 4.436, respectively), resulting in an incremental QALY gain of 2.303
- Most QALYs were generated from the DF health state (94% for nivolumab and 87% for surveillance)
  - This was largely driven by the functional cure assumption applied in the DF health state and poor survival outcomes following disease recurrence
  - Therefore, a complex analysis of subsequent treatment for patients in the RD health state was not required as it would have little effect on the overall model results
- Although total treatment costs were higher for nivolumab, cost savings were observed in terms of subsequent treatment, subsequent surgery and radiotherapy, and terminal care
- The corresponding incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) amounted to €7,500/LY gained and €9,042/QALY gained, respectively
- The discounted base-case results are presented in **Table 2**

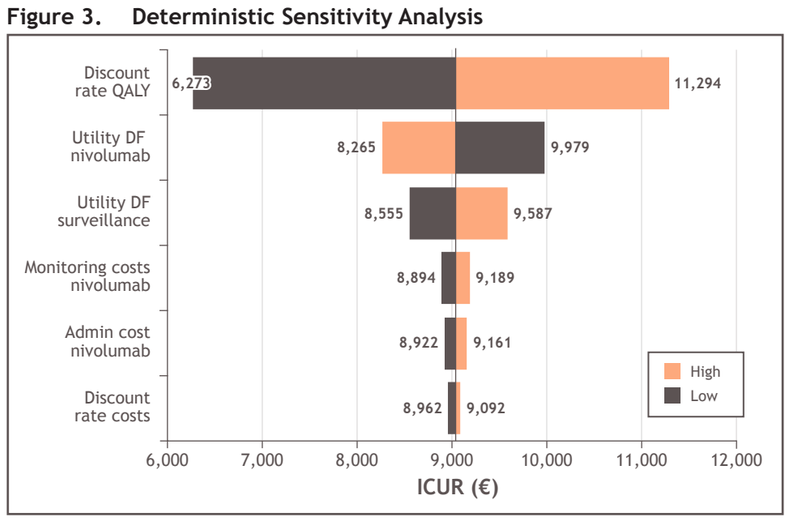
Table 2. Base-Case Results

Settings	Nivolumab	Surveillance
Total cost	**€48,658**	**€27,834**
Total QALYs	**6.739**	**4.436**
DF health state	6.361	3.853
RD health state	0.380	0.584
Disability due to AEs	(0.001)	(0.001)
Total LYs	**8.275**	**5.498**
DF health state	7.757	4.699
RD health state	0.518	0.799
ICER vs. surveillance	**€7,500**	
ICUR vs. surveillance	**€9,042**	

Sensitivity Analysis

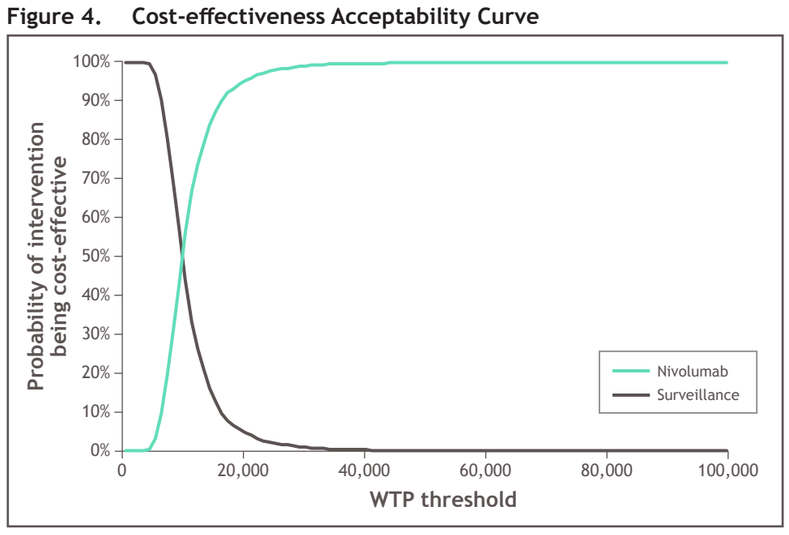
- Deterministic sensitivity analysis showed that the parameters with the largest uncertainty included the discount rate for QALYs (approximately −31% to +25% change) followed by the utility value for DF nivolumab (approximately −9% to +10%) and the utility value for DF surveillance (approximately −5% to 6%). The remaining parameters resulted in the ICUR varying by less than 2% (**Figure 3**)

Figure 3. Deterministic Sensitivity Analysis



- The probabilistic sensitivity analysis confirmed the robustness of the model results, with nivolumab having an estimated average ICER of €7,741/LY gained, an estimated average ICUR of €9,337/QALY gained, and a 99.6% probability of being cost-effective at a willingness-to-pay (WTP) threshold of €35,000 (**Figure 4**)
- Nivolumab has a positive net monetary benefit compared with surveillance after a WTP threshold of €9,500/QALY

Figure 4. Cost-effectiveness Acceptability Curve



- The following scenario analysis was undertaken (**Table 3**): (1) doubling the exponential rate in the post-recurrence survival (PRS) analysis, (2) halving the exponential rate in the PRS analysis, and (3) shortening the time horizon:
  - Doubling or halving the exponential rate in the PRS altered the ICUR by −4.1% and 8.6%, respectively, which shows the RD health state's limited impact on cost-effectiveness results
  - A shortened time horizon resulted in an increased ICUR
- All scenarios and sensitivity analyses tested resulted in ICURs well below a WTP threshold of €35,000/QALY

Table 3. Scenario Analysis Results

Settings	ICUR	Difference from base case (%)
Base case	€9,042	
PRS double exponential rate	€8,674	−4.1%
PRS half exponential rate	€9,822	8.6%
25-year time horizon	€9,295	2.8%
20-year time horizon	€10,500	11.2%
15-year time horizon	€11,874	31.3%

Conclusions

- Over 30 years, with a deterministic ICER of €7,500/LY gained and a deterministic ICUR of €9,042/QALY gained, nivolumab is estimated to be a cost-effective treatment strategy at a WTP of €35,000/QALY
- Nivolumab is cost-effective compared with surveillance beyond a WTP threshold of €9,500/QALY
- The results were robust to uncertainties in key parameters as demonstrated in sensitivity analyses, including shortening the time horizon and halving/doubling the survival following disease recurrence
- Nivolumab as adjuvant therapy is estimated to be a life-extending and cost-effective for adjuvant treatment in patients with MIUC who are at high risk of recurrence following radical resection with PD-L1 expression ≥ 1% in Greece. It could improve the distribution of resources of the Greek healthcare system, providing a considerable health benefit for patients

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