Assessing the impact of additional follow-up from the CheckMate-274 trial on the cost-effectiveness (CE) profile of nivolumab versus surveillance in high-risk muscle-invasive urothelial carcinoma (MIUC)

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Background

Urothelial carcinoma

- Urothelial carcinoma (UC) refers to the growth and spread of cancerous cells lining the renal pelvis, ureters, or urinary bladder.
- UC is the ninth most common cancer worldwide, with 430,000 new cases diagnosed annually, resulting in 145,000 deaths globally each year.[1]
- In some cases, the tumor spreads beyond the lining, into the surrounding bladder muscle . In such cases it is referred to as muscle-invasive urothelial carcinoma (MIUC).
- MIUC is associated with a higher risk of recurrence compared with non-muscle invasive UC and has a poorer prognosis.[2]

Adjuvant treatment of MIUC with nivolumab

- In 2021, nivolumab (NIVO) became the first immuno-oncology agent to receive United States Food and Drug Administration approval for the adjuvant treatment of MIUC who are at high risk of recurrence after undergoing radical resection.[3]
- CheckMate-274 is a randomized (1:1), double blind, phase 3 clinical trial that compares NIVO with placebo (PBO) as an adjuvant treatment in adults (aged ≥ 18 years) who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.[4]
- One of the primary endpoints of the CheckMate-274 trial was disease-free survival (DFS) in the intention-to-treat (ITT) population. In the analysis of the initial database lock (DBL) from CheckMate-274, with a minimum follow-up of 11.0, months NIVO significantly improved DFS versus PBO with a hazard ratio (HR) of 0.70 (95% CI, 0.57-0.85) in the-ITT population.[5] Median DFS for the ITT population was 22.0 months (95% CI, 17.7-36.9) for NIVO compared with 10.9 months (95% CI, 8.3-14.0) for PBO.
- In a subsequent DBL from CheckMate-274 with a minimum follow-up of 31.6 months, NIVO maintained the significant improvement in DFS with a HR of 0.71 (95% CI, 0.58-0.86) in the ITT population.[6] Median DFS for the ITT population was 22.0 months (95% CI, 18.8-36.9) for NIVO compared with 10.9 months (95% CI, 8.3-15.2) for PBO.

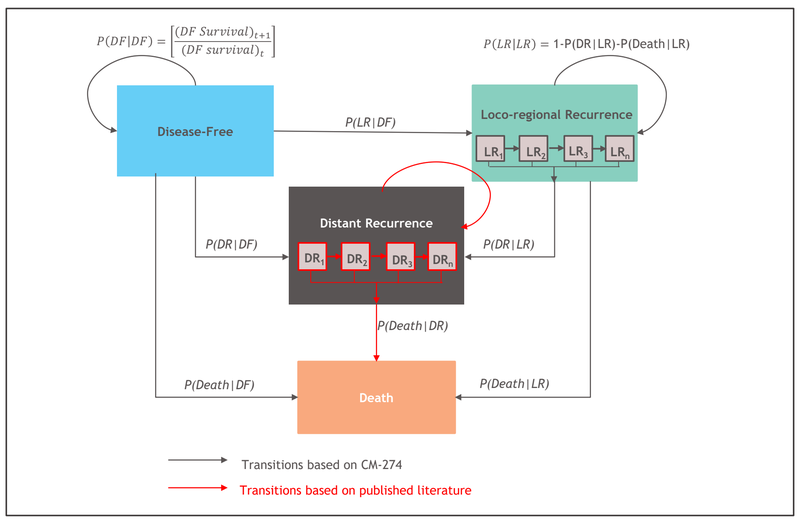
Objectives

- To assess the sensitivity of the cost-effectiveness (CE) of NIVO versus PBO with respect to the duration of follow-up on the DFS data for the treatment of high-risk MIUC patients from a United Kingdom (UK) payer perspective.

Methods

- Patient-level data corresponding to the initial and subsequent DBLs (with 11.0- and 31.6-months of minimum follow-up) were used to populate a 4-health state semi-Markov model (**Figure 1**) consisting of disease-free (DF), local recurrence (LR), distant recurrence (DR), and death states. (**Table 1**)
- Post-recurrence stratified by type of recurrence, LR and DR, was clinically more appropriate and important from an economic standpoint according to clinical experts and health economists consulted because:
  - — As reported in the literature, the two recurrences have different prognoses.[5]
  - — Treatment options may vary between the two types of recurrences with implications on costs and quality of life.

Figure 1. Overview of the 4-health state semi-Markov model



- For the estimation of transitions from the DF state, DFS from CheckMate-274 was used from 0-3 years, the control arm from the EORTC-30994 trial was used from 3-5 years, after which DF patients were assumed to be cured.
- Transitions from the LR and DR states to the subsequent states were estimated via tunnel health states due to the time-varying nature of the hazards. Transitions from LR and DR states were informed by the data from CheckMate-274 and published literature in MIUC, respectively.
- Between the two DBLs, all trial-specific model inputs relevant for the DFS transitions were updated without changing modelling assumptions (**Table 2**).

Table 1. Summary of economic model

Aspect	Details	Comment
Analytical method	4-health state semi-Markov model	Analytical technique that has been applied in previous technology appraisals for anti-cancer treatments in adjuvant setting
Treatment arms	NIVO PBO	The key treatment comparator (PBO) is based on the comparator in the CheckMate-274 clinical trial
Time horizon	30-year time horizon	Captures differences in expected costs and QALYs between treatment strategies and provides lifetime estimates for the subset of patients who are expected to be in long-term remission and have a mortality risk like the general population.
Cycle length	Weekly	Weekly cycles to better reflect possible transitions between health states and capture the impact different health states can have on QoL
Discounting options	Costs and health outcomes	Both costs and outcomes are subject to annual discounting in the evaluation (3.5% as per UK NICE reference case)
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle

Abbreviations: NICE, national institute for health and care excellence; QALY, quality adjusted life year; QoL, quality of life; UK, United Kingdom.

- Results reflect the health care payer perspective across a 30-year time horizon and encompass the following costs: disease management, drug acquisition, drug administration and monitoring, adverse events (AE), subsequent treatment, and end-of-life (EoL). Costs were sourced from UK public sources referencing the year 2019/2020.
- Expected costs and quality-adjusted life-years (QALY) were calculated for the ITT population over a 30-year time horizon.
- Utility scores were calculated from the three-level version of EuroQol five dimensions (EQ-5D-3L) data collected in CheckMate-274 for both DBLs. However, for this study, to isolate the impact of the updated DFS data, the subsequent DBL utility set was used.

Table 2. Model inputs between two DBLs

Model input	Initial DBL	Subsequent DBL
DFS (up to 5 years)	CheckMate-274 Kaplan-Meier (KM) data from 0 to 3 years, EORTC 30994 hazards adjustments from 3 to 5 years	Updated CheckMate-274 KM data from 0 to 3 years, EORTC 30994 hazards adjustments from 3 to 5 years
DFS from 5 years onwards	General UK population mortality (2018-2020)	
Survival from LR [a]	Pooled data from both treatment arms fitted to an exponential model applied to the proportion of patients moving to LR from disease-free	Updated pooled data from both treatment arms fitted to a generalized gamma model [a] applied to the updated proportion of patients moving to LR from disease-free
Survival from DR – cisplatin-eligible	Independent, 2 knot spline hazard model to estimate post-DR survival for patients receiving cisplatin + gemcitabine and HRs applied to this curve to estimate post-DR survival for patients receiving either MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin)[7] or high dose (HD)-MVAC[8]	
Survival from DR – cisplatin-ineligible	Independent, 1 knot spline normal model to estimate post-DR survival for patients receiving carboplatin + gemcitabine and HRs applied to this curve to estimate post-DR survival for patients receiving either pembrolizumab[9] or atezolizumab[10]	
Distribution of subsequent treatments [b]	Post-NIVO / Post-PBO	Post-NIVO / Post-PBO
Gemcitabine + cisplatin	51% / 33%	30% / 26%
Gemcitabine + carboplatin	41% / 23%	49% / 25%
Pembrolizumab	8% / 34%	16% / 35%
Atezolizumab	0% / 10%	6% / 15%
Costs (drug acquisition, administration, disease management, subsequent treatments, end-of-life)	Costs were sourced from UK public sources referencing the year 2019/2020	
Utility by health state [b]		
Disease-free	0.840	0.824
Local recurrence	0.725	0.724
Distant recurrence	0.708	0.696

[a] Exponential distribution was used for comparison with initial DBL. [b] For this model setting data from subsequent DBL was used because the interest lied in researching the isolated effect of updated DFS data.

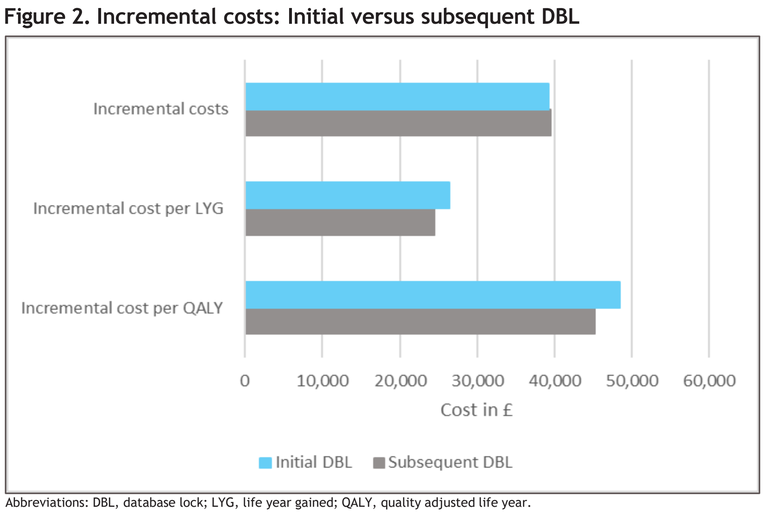
Sensitivity analysis

- To test the sensitivity of the changed inputs between DBLs, the subsequent DBL data impacting aspects of the model other than DFS and LR were set to the initial DBL input to identify the most sensitive parameter of the model in terms of the incremental cost-utility ratio (ICUR).

Results

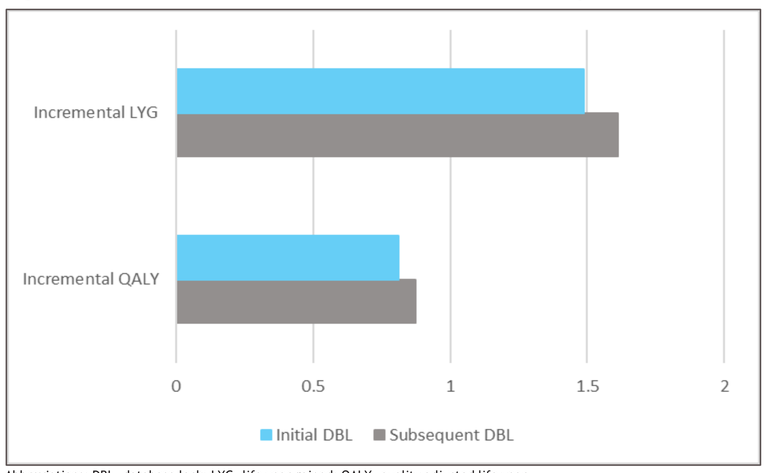
- The ICUR of NIVO versus PBO marginally improved from £48,407/QALY to £45,200/QALY (Δ = 7%) with the use of data from the subsequent DBL compared to the initial DBL. (**Figure 2**)
- The difference between incremental QALYs and costs across the arms was modest-to-negligible (Δ < 1% in costs, Δ < 10% in QALYs) between the two DBLs. Total (and DF) QALYs increased by 0.07 (and 0.08) for NIVO and by 0.01 (and 0.01) for PBO. (**Figure 3**)

Figure 2. Incremental costs: Initial versus subsequent DBL



Abbreviations: DBL, database lock; LYG, life year gained; QALY, quality adjusted life year.

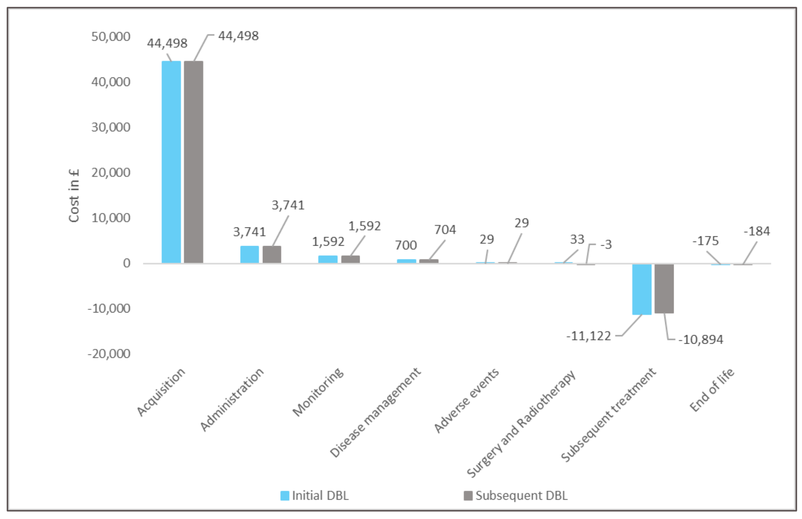
Figure 3. Incremental effects results: Initial versus subsequent DBL



Abbreviations: DBL, database lock; LYG, life year gained; QALY, quality adjusted life year.

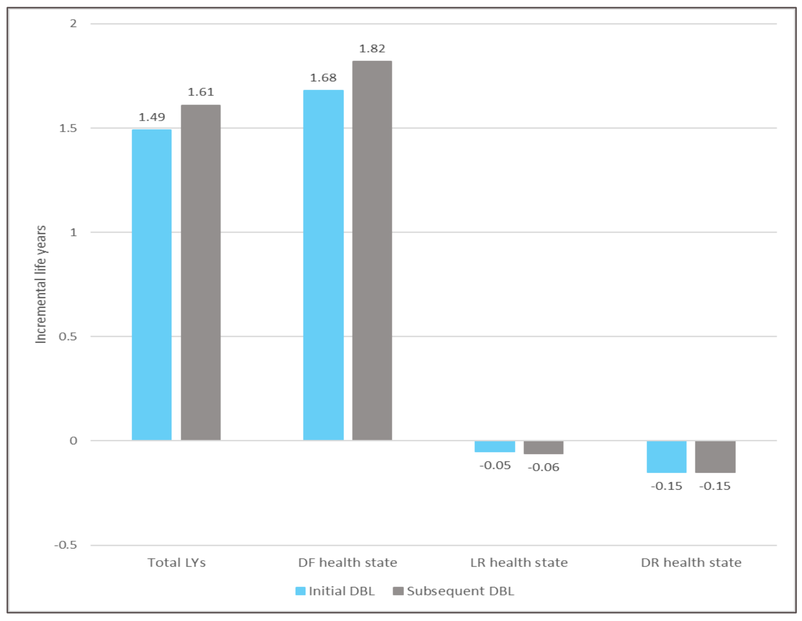
- The total cost between DBLs (from initial to subsequent DBL) decreased slightly from £74,310 to £73,764 for NIVO, and from £35,049 to £34,281 for PBO.
- Cost changes between the two DBLs were driven by a decrease in subsequent treatment costs and a minor decrease in terminal care costs. (**Figure 4**)
- A larger increase of LYs was observed for NIVO in the subsequent DBL compared to the increase observed for PBO. This is attributed to the longer stay in DF state compared to the initial DBL. A larger increase of QALYs was observed for NIVO in the subsequent DBL compared to the increase observed for PBO. This is attributed to the longer stay in DF state compared to the initial DBL. (**Figure 5** and **Figure 6**)
- When using the subsequent treatment distribution seen in the initial DBL the ICUR decreased to £44,763/QALY (-£3644), because more patients received IOs (i.e., pembrolizumab and atezolizumab) after NIVO. IO therapies are more costly and the subsequent DBL distribution was more realistic than seen in the initial DBL.
- The probability of NIVO being CE at a willingness-to-pay threshold of £50,000/QALY increased from 48% to 54% with the subsequent DBL. (**Figure 7**)

Figure 4. Incremental costs per category: Initial versus subsequent DBL



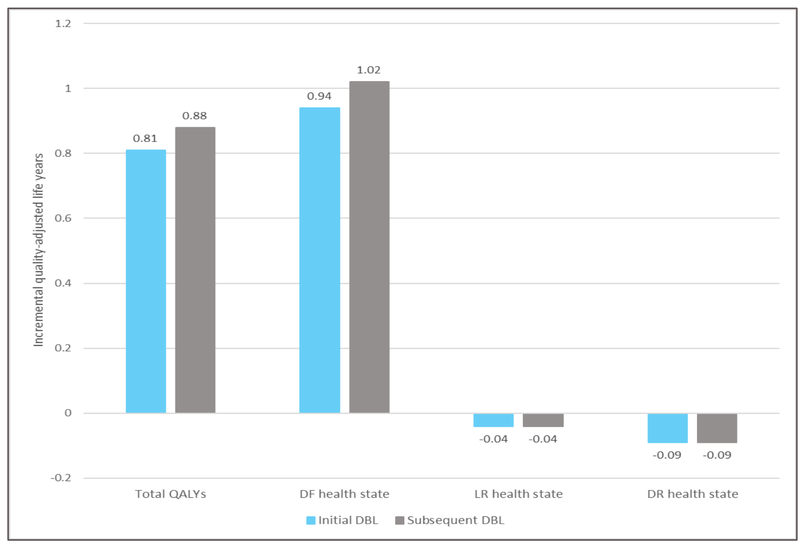
Abbreviations: DBL, database lock.

Figure 5. Incremental life years per health state: Initial versus subsequent DBL



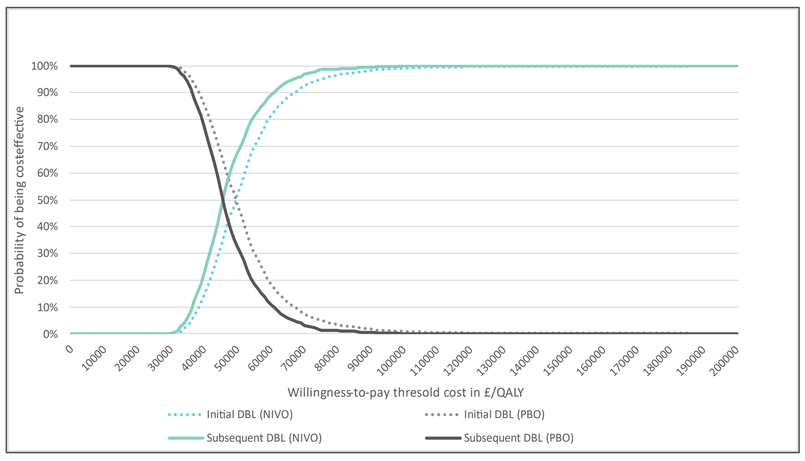
Abbreviations: DBL, database lock; DF, disease-free; DR, distant recurrence; LR, local recurrence; LY, life years.

Figure 6. Distribution of incremental QALYs across health states: Initial versus subsequent DBL



Abbreviations: DBL, database lock; DF, disease-free; DR, distant recurrence; LR, local recurrence; QALY, quality-adjusted life years

Figure 7. CEAC: Initial versus subsequent DBL



Abbreviations: DBL, database lock; CEAC, cost-effectiveness acceptability curve; QALY, quality adjusted life year.

Conclusion

- Analyses based on the earlier DBL were conservative and underestimated the DF QALY benefit of NIVO versus PBO and thereby the CE profile of NIVO versus PBO.
- The longer follow-up data from the CheckMate-274 study had a marginal impact on the original CE of NIVO versus PBO, confirming the robustness of the initial DBL informing its CE profile and its long-term economic value for the adjuvant treatment of MIUC.

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