Assessing the impact of additional follow-up data on disease-free survival projections of nivolumab and surveillance in high-risk, muscle-invasive urothelial carcinoma patients within the CheckMate-274 trial

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Introduction

Urothelial Carcinoma

- Urothelial carcinoma (UC) is the growth and spread of cancerous cells developing in the urothelial 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, where 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 immune-checkpoint inhibitors

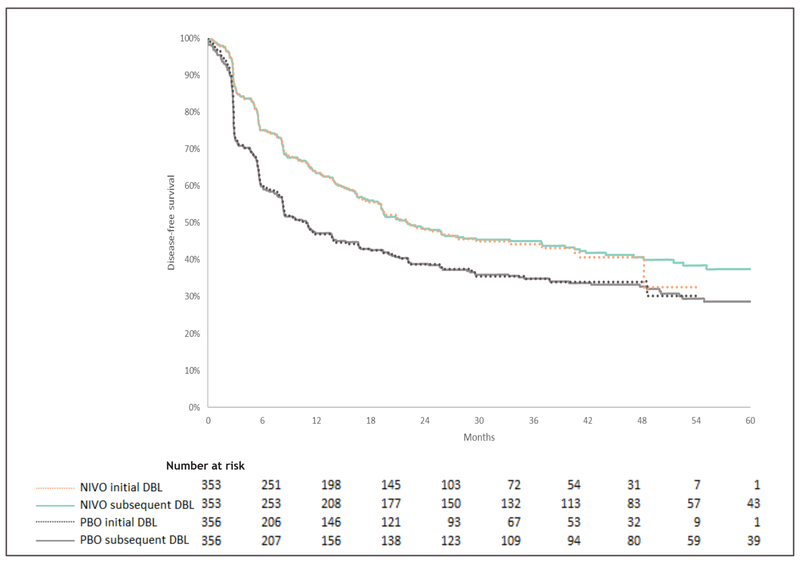
- In 2021, nivolumab (NIVO) became the first immuno-oncology agent to receive United States Food and Drug Administration approval for the adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection.[3]
- CheckMate-274 is a randomized (1:1), double blind, phase 3 clinical trial that compares NIVO with placebo (PBO) as 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] Disease-free survival (DFS) was the primary endpoint of the study.
- In the analysis of CheckMate-274 from the initial database lock (DBL) (with a minimum follow-up of 11.0 months) NIVO significantly improved DFS versus PBO with a hazard ratio (HR) of 0.70 (95% confidence interval (CI), 0.57-0.85) in the intention-to-treat (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. (**Table 1**).
- In the subsequent DBL of 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.
- **Figure 1** illustrates the comparison of DFS Kaplan-Meier (KM) curves of NIVO and PBO in the trial based on the initial DBL (11.0-month) and the subsequent DBL (31.6-month).

Table 1. Summary DFS data from the ITT population of CheckMate-274 across DBLs

	Initial DBL[5]		Subsequent DBL[6]	
	NIVO (N=353)	PBO (N=356)	NIVO (N=353)	PBO (N=356)
Median DFS (95% CI)	22.0 months (17.7, 36.9)	10.9 months (8.3, 14.0)	22.0 months (18.8,36.9)	10.9 months (8.3,15.2)
DFS HR NIVO versus PBO (95% CI)	0.70 (0.57, 0.85)		0.71 (0.58,0.86)	

Abbreviations: CI, confidence interval; DBL, database lock; DFS, disease-free survival; HR, hazard ratio; N, number of patients; NIVO, nivolumab; PBO, placebo.

Figure 1. DFS KM-curves across DBLs



Abbreviations: DBL, database lock; NIVO, nivolumab; PBO, placebo.

DFS extrapolations

- Longer-term follow-up data can offer additional certainty around long-term projections of efficacy outcomes from randomized controlled trials.
- For cost-effectiveness analysis, long-term predictions for DFS are needed to calculate the costs and effects of using NIVO instead of PBO for a lifetime horizon.
- Parametric models are typically fitted to the observed KM curves of the trial to obtain DFS predictions beyond the observed data.
- Parametric and spline-based models fitted DFS data from the initial DBL poorly and therefore a non-parametric approach leveraging external data (Sternberg et al., 2015[8]) was deployed.

Objectives

- Primary objective: To evaluate the impact of additional follow-up (>20 months) on the DFS data on its long-term predictions.
- Secondary objective: To compare the long-term DFS projections obtained from the parametric and non-parametric approaches using the longer-term follow-up data.

Methods

- Patient-level DFS data from the two successive database-locks (DBLs) of CheckMate-274 with 11.0-month and 31.6-month of minimum follow-up for the ITT population were used.

Base case: non-parametric modelling approach

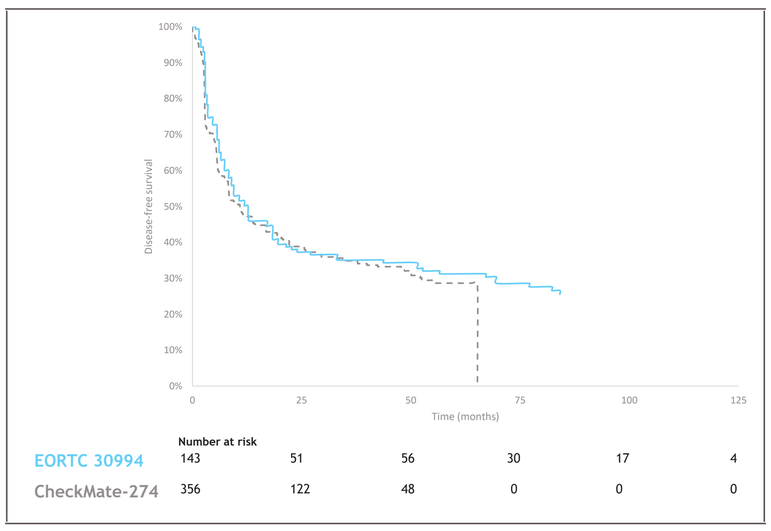
- In the base case, NIVO and PBO DFS were modelled using the reported DFS KM curves from CheckMate-274 (up to year 3) and the control arm from EORTC-30994[8] (with 7-year median follow-up) from 3 to 5 years, followed by general mortality after 5 years.
- The 3-year point was selected based on comparison of smoothed hazards, and most recurrences and disease-related deaths have already occurred at 3 years in MIUC (based on CheckMate-274 data and expert opinion), therefore providing a robust time point to switch to EORTC 30994 hazards. Between 3 and 5 years the CheckMate-274 DFS curves were adjusted using the EORTC 30994 hazards.
- The most appropriate source of external data was deemed to be the EORTC 30994 study (Sternberg et al., 2015[8]), which is an intergroup, open-label, randomized, phase 3 trial that recruited patients from hospitals in 12 European countries and Canada between 2002 and 2008.
- Longer follow-up was reported from EORTC 30994 compared to CheckMate-274, which had a median follow-up 7.2 years [interquartile range 5.6-8.7] in the deferred chemotherapy group.
- The EORTC 30994 study was also chosen as the main source of external data as it had a similar patient population to that of CheckMate-274 trial (**Table 2**).
- **Figure 2** shows how the EORTC 30994 data (deferred chemotherapy arm) are almost identical to the PBO DFS KM data from CheckMate-274 and can therefore be used as an extension of the CheckMate-274 KM curve to predict DFS from CheckMate-274 in the initial DBL up to 5 years after which point DFS is estimated based on UK life table hazards.
- When the underlying hazards for the progression-free survival (PFS) data in the deferred chemotherapy arm of EORTC 30994 study were analyzed, they further supported the functional cure assumption starting from 5 years, indicating very low risk of recurrence or death around and beyond 5 years.

Table 2. Comparison of baseline patient characteristics between CheckMate-274 and EORTC 30994

CheckMate-274, PBO (n=356)		EORTC 30994, deferred chemotherapy (n=143)	
Age		**Age**	
< 65	136 (38.2%)	< 60	70 (49%)
≥ 65	220 (61.8%)	≥ 60	73 (51%)
Median	67	Median	61
Sex: Female	81 (22.8%)	**Sex: Female**	27 (19%)
Time from cystectomy (days)		**Time from cystectomy (days)**	
≤ 30	3 (0.8%)	≤ 30	15 (10%)
31-60	70 (19.7%)	31-60	47 (33%)
61-90	177 (49.7%)	61-90	81 (57%)
91-120	95 (26.7%)		
> 120	11 (3.1%)		
pT category		**pT category**	
< pT2	21 (5.9%)	pT1	4 (3%)
pT2	65 (18.3%)	pT2	27 (19%)
pT3	204 (57.3%)	pT3	87 (61%)
pT4a	62 (17.4%)	pT4a	24 (17%)
pT4b		pT4b	1 (<1%)
pN category		**pN category**	
N0 < 10 nodes removed	99 (27.8%)	N0	44 (31%)
N0 ≥ 10 nodes removed	88 (24.7%)	N1	55 (38%)
N1	72 (20.2%)	N2	44 (31%)
N2	76 (21.3%)	N3	0 (0%)
N3	20 (5.6%)		

Abbreviations: pN, pathological N classification (regional lymph nodes); pT, pathological T classification (primary tumor).

Figure 2. Comparison of KM-curves between PBO of CheckMate-274 and deferred chemotherapy of EORTC 30994



Parametric modelling approach

- Standard parametric and spline-based models (with up to two knots) were fitted to the DFS KM-curves from the two DBLs.
- Model selection was based on the Akaike Information Criterion (AIC),-the Bayesian Information Criterion (BIC), visual comparison of the predicted hazards with the observed hazards and clinical plausibility of the projections.
- The long-term extrapolations were also visually assessed against reported long-term data from EORTC 30994.

Functional cure

- Patients who were disease-free by year 5 were assumed as functionally cured as also seen in the EORTC 30994 data. Cured patients experienced no recurrence and died only from non-disease related causes in the extrapolated DFS.
- Similarly, Cagiannos et al.[7] show in their study that only 2-3% of patients relapsed between 5 and 10 years.
- In addition, the NCCN guidelines (Version 1.2022) no longer recommend monitoring patients after 5 years following radical resection if they have not experienced disease recurrence.
- Age- and sex-adjusted non-disease related mortality rates were derived from UK lifetables.

Performance measures

- The performance measures comparing the predictive performances of parametric and non-parametric approaches from the two DBLs were landmark DFS rates and restricted mean (RM) DFS at 5, 10 and 30 years.

Results

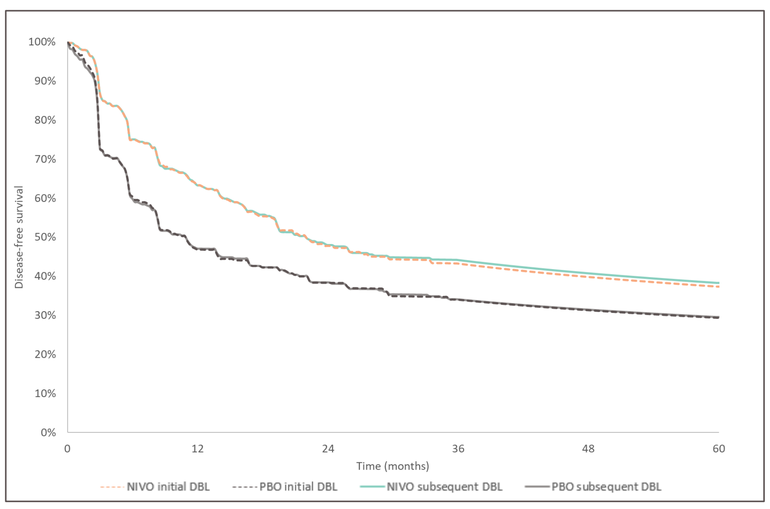
Parametric approach

- With the longer follow-up in the subsequent DBL, the parametric models fitted better to the data. Therefore, parametric extrapolation using the 1-knot spline odds model for both NIVO and PBO DFS up to 5 years was explored.

Analysis

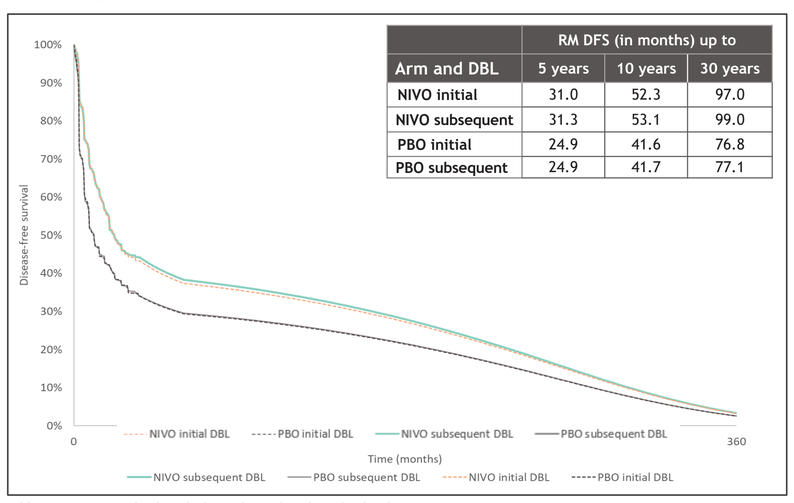
- For PBO both DBLs resulted in similar 30-year RM DFS [77-months for the initial versus 77-months the subsequent DBL]. (**Figure 4** and **Figure 6**)
- For NIVO the initial DBL predictions resulted in lower 30-yr RM DFS versus the subsequent DBL: mean DFS increased from 97 to 99-months in the non-parametric approach **(Figure 4)** versus an increase from 91 to 96-months in the parametric approach **(Figure 6).**
- Non-parametric and parametric approaches estimated similar RM DFS at 5-years for both arms. (**Figure 3** and **Figure 5**)
- The parametric approach resulted in lower 10-year RM DFS than the non-parametric approach in both DBLs for both arms (**Figure 4** and **Figure 6**).

Figure 3. Modelled DFS curves using non-parametric approach over a 5-year time horizon



- The DFS curves estimated from the non-parametric approach showed that the DFS estimates obtained from the initial DBL were comparable to those obtained from subsequent DBL for both arms of CheckMate-274, but slightly more conservative for NIVO. **(Figure 3)**
- With the parametric approach, DFS curves estimated from the subsequent DBL showed a larger DFS differential between the arms of CheckMate-274 compared to the DFS differential obtained from the initial DBL. Specifically, the DFS estimates from the initial DBL were less (more) conservative for PBO (NIVO). (**Figure 5** and **Figure 6**)

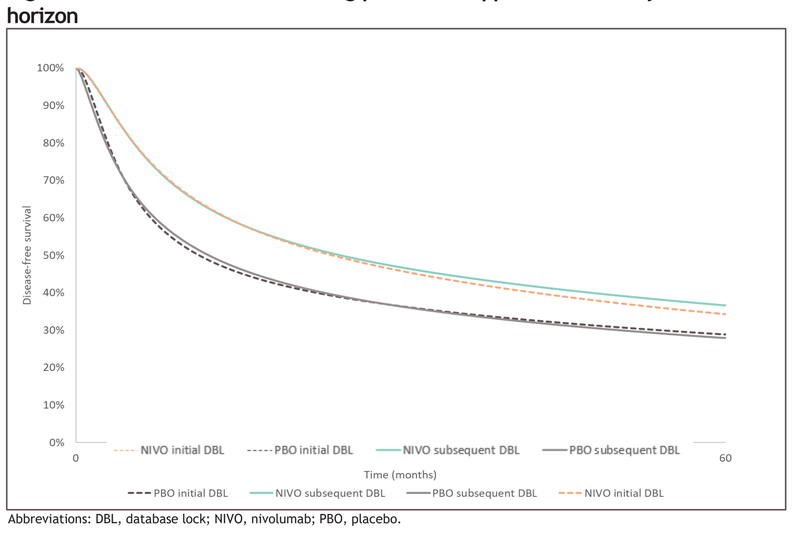
Figure 4. Modelled DFS curves using non-parametric approach over a 30-year time horizon



Arm and DBL	RM DFS (in months) up to 5 years	10 years	30 years
NIVO initial	31.0	52.3	97.0
NIVO subsequent	31.3	53.1	99.0
PBO initial	24.9	41.6	76.8
PBO subsequent	24.9	41.7	77.1

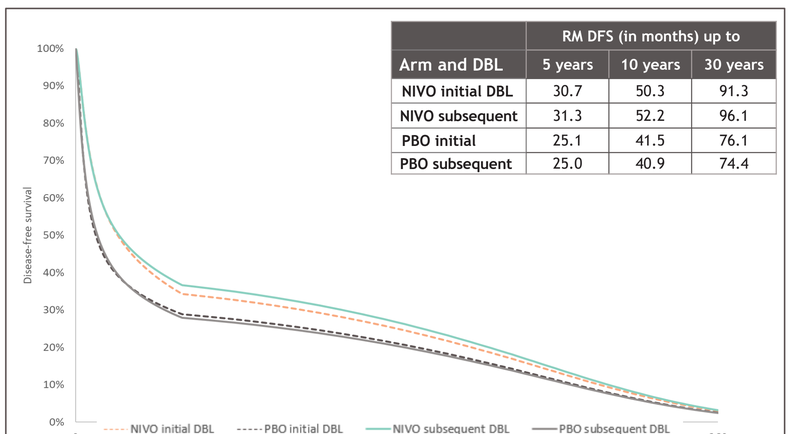
Abbreviations: DBL, database lock; NIVO, nivolumab; PBO, placebo.

Figure 5. Modelled DFS curves using parametric approach over a 5-year time horizon



Abbreviations: DBL, database lock; NIVO, nivolumab; PBO, placebo.

Figure 6. Modelled DFS curves using reported data from both DBLs over a 30-year horizon



Arm and DBL	RM DFS (in months) up to 5 years	10 years	30 years
NIVO initial DBL	30.7	50.3	91.3
NIVO subsequent	31.3	52.2	96.1
PBO initial	25.1	41.5	76.1
PBO subsequent	25.0	40.9	74.4

Abbreviations: DBL, database lock; NIVO, nivolumab; PBO, placebo.

- In the non-parametric approach, because the initial DBL from CheckMate-274 had reported KM-curves extending up to 3-years, external data from EORTC 30994 was incorporated into DFS extrapolations starting from year 3 until functional cure.
- In a sensitivity analysis using the extended follow-up data from CheckMate-274, external data from EORTC 30994 trial was incorporated into DFS extrapolations starting from month 54. Results of this sensitivity analysis showed that earlier incorporation of external data had limited impact on DFS extrapolations which indicates the robustness of the results from the initial DBL. (**Table 3**)

Table 3. Estimated landmark DFS rates applying adjustment with external data from EORTC 30994 trial at 4.5 years (54 months)

Arm and DBL	Mean (months)	Median (months)	DFS rate 6 months	1 year	2 years	3 years	4 years	5 years	10 years	20 years	30 years
NIVO initial	83	22	75%	63%	48%	43%	39%	30%	27%	15%	3%
NIVO subsequent	94	22	75%	63%	48%	44%	39%	36%	32%	18%	3%
PBO initial	74	11	60%	47%	38%	34%	33%	28%	25%	14%	2%
PBO subsequent	73	11	59%	47%	38%	34%	32%	27%	24%	14%	2%

Conclusion

- Based on the reported results from CheckMate-274, with longer follow-up, NIVO continued to demonstrate clinical meaningful improvement in DFS versus PBO for patients with high-risk MIUC after radical surgery.
- The previously employed non-parametric approach to predict longer-term DFS was shown to be robust compared to more mature observed data and the parametric approach explored in this study.
- Across a life-time horizon, DFS projections obtained from the subsequent DBL confirmed that the predictions for NIVO from the initial DBL were marginally conservative.

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