3-year follow-up analysis of disease-free survival in CheckMate 274 by PD-L1 expression using tumor cell and combined positive scoring algorithms

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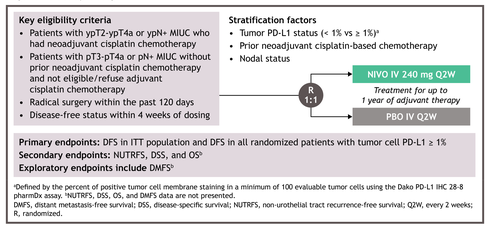
Background

- Nivolumab (NIVO) was approved by the US Food and Drug Administration in 2021 and the European Commission in 2022 for the adjuvant treatment of patients with muscle-invasive urothelial carcinoma (MIUC; regardless of tumor programmed death ligand 1 [PD-L1] expression in the United States and with tumor PD-L1 expression ≥ 1% in Europe) who are at high risk of recurrence after radical resection, based on the primary analysis of the phase 3 CheckMate 274 trial[1–4]
  - With minimum follow-up of 5.9 months (intent-to-treat [ITT] population), disease-free survival (DFS) was significantly improved with adjuvant NIVO versus placebo (PBO) both in the ITT population (hazard ratio [HR], 0.70; 98.22% confidence interval [CI], 0.55-0.90; *P* < 0.001) and in patients with tumor PD-L1 expression ≥ 1% as assessed by the tumor cell score (TC; HR, 0.55; 98.72% CI, 0.35-0.85; *P* < 0.001)[3]
    - In a subgroup analysis of DFS among the ITT population, patients benefitted from adjuvant NIVO irrespective of TC[3]
- Half of patients with MIUC are likely to develop disease recurrence within 2 years of radical resection.[6] Yet the DFS benefit with adjuvant NIVO versus PBO was maintained with extended minimum follow-ups of 11.0 months and 31.6 months, both in the ITT population and in patients with TC ≥ 1%[2,4]
- PD-L1 immunohistochemistry (IHC) testing has been widely implemented in clinical trials evaluating immune checkpoint inhibitors. However, interpreting PD-L1 data from tumor samples is challenging due to the multiple testing approaches used, which often includes differing scoring techniques (tumor cells vs immune cells)[5]
- To examine the relationship between the cell type expressing PD-L1 and outcomes with adjuvant NIVO, a post hoc exploratory analysis of DFS data from CheckMate 274 was performed based on PD-L1 expression levels as assessed by TC (ie, PD-L1 expression in tumor cells) or combined positive score (CPS; ie, PD-L1 expression in tumor cells and immune cells) with a minimum follow-up of 11.0 months (ITT population)[10,11]
  - More patients had CPS ≥ 1 than TC ≥ 1%, and most patients who had TC < 1% had CPS ≥ 1
  - DFS was improved with adjuvant NIVO versus PBO for patients with TC ≥ 1%, CPS ≥ 1, and for patients with both TC < 1% and CPS ≥ 1
- Here, we report an updated post hoc exploratory analysis of DFS by PD-L1 expression as assessed by both TC and CPS with extended 3-year follow-up from CheckMate 274

Methods

- CheckMate 274 (NCT02632409) is a phase 3, randomized, double-blind, multicenter trial of adjuvant NIVO versus PBO in patients with high-risk MIUC after radical surgery (**Figure 1**)
  - The secondary endpoint of overall survival (OS) is event-driven and will be assessed at a future database lock, per protocol

Figure 1. Study design



[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the Dako PD-L1 IHC 28-8 pharmDx assay. [b]NUTRFS, DSS, OS, and DMFS data are not presented.
DMFS, distant metastasis-free survival; DSS, disease-specific survival; NUTRFS, non-urothelial tract recurrence-free survival; Q2W, every 2 weeks; R, randomized.

- Methods have been described previously.[10,11] Briefly, PD-L1 IHC was performed on formalin-fixed, paraffin-embedded tumor samples from the resected site of disease, obtained before randomization, using the Dako PD-L1 IHC 28-8 pharmDx assay and assessed by pathologist
  - Specimens with at least 100 evaluable tumor cells were eligible for PD-L1 scoring
- TC was determined from central laboratory testing before randomization and was calculated as the percentage of PD-L1 positive tumor cells in at least 100 evaluable tumor cells, divided by the total number of viable tumor cells in the evaluable tumor area multiplied by 100
- In this post hoc analysis, the CPS was determined retrospectively at a central laboratory from the previously stained IHC slides
- The CPS was calculated as the number of PD-L1 positive tumor and immune cells (lymphocytes and macrophages) divided by the total number of viable tumor cells in the evaluable tumor area multiplied by 100
- DFS was estimated using Kaplan-Meier methodology and compared between treatment groups using a 2-sided log-rank test
  - HRs and corresponding CIs were estimated using a stratified Cox proportional hazards model with the stratification factors prior neoadjuvant cisplatin chemotherapy and pathological nodal status

Results

- Of the 709 patients in the ITT population (minimum study follow-up, 31.6 months [time from clinical cutoff date to last patient's randomization date]; median follow-up, 36.1 months [time between randomization date and last known alive date, for patients who are alive, or death]), 630 (88.9%) had both quantifiable PD-L1 by TC and CPS at baseline (NIVO, n = 316; PBO, n = 314)
- Of these patients, 250 (39.7%) had TC ≥ 1% (NIVO, n = 125; PBO, n = 125), 380 (60.3%) had TC < 1% (NIVO, n = 191; PBO, n = 189), 558 (88.6%) had CPS ≥ 1 (NIVO, n = 282; PBO, n = 276), and 72 (11.4%) had CPS < 1 (NIVO, n = 34; PBO, n = 38)
  - In patients with TC < 1% (n = 380), 309 (81.3%) had CPS ≥ 1
- Baseline demographic and clinical characteristics in patients with a CPS ≥ 1 were generally balanced between treatment groups; however, a higher proportion of patients with NIVO versus PBO were aged < 65 years and had N0 with ≥ 10 nodes removed (**Table 1**)
  - A generally similar distribution of baseline demographic and clinical characteristics was observed in patients with CPS < 1 versus CPS ≥ 1. Nevertheless, differences in distribution between treatment arms in CPS < 1 included tumor origin at initial diagnosis, the presence of minor histological variants, pathologic tumor stage, and nodal status at resection. These differences should be interpreted with caution due to a low number of patients with CPS < 1

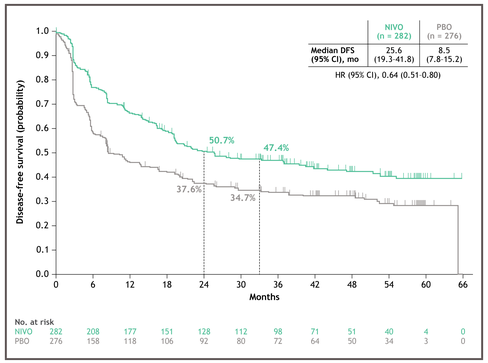
Table 1. Baseline demographic and clinical characteristics in patients by CPS (among all randomized patients with quantifiable CPS and TC at baseline)

	CPS < 1		CPS ≥ 1	
	NIVO (n = 34)	PBO (n = 38)	NIVO (n = 282)	PBO (n = 276)
Age, years				
Median (range)	66.5 (34-83)	68.0 (47-81)	66.5 (33-92)	67.0 (42-88)
< 65, n (%)	15 (44.1)	10 (26.3)	122 (43.3)	105 (38.0)
≥ 65, n (%)	19 (55.9)	28 (73.7)	160 (56.7)	171 (62.0)
Sex, n (%)				
Male	23 (67.6)	29 (76.3)	214 (75.9)	211 (76.4)
Female	11 (32.4)	9 (23.7)	68 (24.1)	65 (23.6)
Race or ethnic group, n (%)				
White	25 (73.5)	33 (86.8)	237 (84.0)	234 (84.8)
Asian	6 (17.6)	5 (13.2)	39 (13.8)	33 (12.0)
Other/not reported	3 (8.8)	0	6 (2.1)	9 (3.3)
PD-L1 expression of ≥ 1% based on clinical source, n (%)	0	1 (2.6)	125 (44.3)	124 (44.9)
Tumor origin at initial diagnosis, n (%)				
Urinary bladder	19 (55.9)	26 (68.4)	237 (84.0)	222 (80.4)
Renal pelvis	9 (26.5)	11 (28.9)	25 (8.9)	32 (11.6)
Ureter	6 (17.6)	1 (2.6)	20 (7.1)	22 (8.0)
Minor histological variants present, n (%)				
Yes	14 (41.2)	8 (21.1)	122 (43.3)	121 (43.8)
No	20 (58.8)	30 (78.9)	160 (56.7)	155 (56.2)
Previous cisplatin-based therapy, n (%)	12 (35.3)	20 (52.6)	134 (47.5)	126 (45.7)
ECOG PS, n (%)				
0	23 (67.6)	23 (60.5)	180 (63.8)	176 (63.8)
1	11 (32.4)	15 (39.5)	96 (34.0)	90 (32.6)
2	0	0	6 (2.1)	9 (3.3)
Not reported	0	0	0	1 (0.4)
Time from initial diagnosis to randomization, n (%)				
< 1 year	32 (94.1)	35 (92.1)	261 (92.6)	251 (90.9)
≥ 1 year	2 (5.9)	3 (7.9)	21 (7.4)	25 (9.1)
Pathologic tumor stage at resection, n (%)				
pTX	0	0	5 (1.8)	0
pT0	0	0	5 (1.8)	7 (2.5)
pTis	0	1 (2.6)	3 (1.1)	2 (0.7)
pT1	5 (14.7)	2 (5.3)	7 (2.5)	10 (3.6)
pT2	3 (8.8)	9 (23.7)	56 (19.9)	53 (19.2)
pT3	23 (67.6)	17 (44.7)	158 (56.0)	161 (58.3)
pT4A	2 (5.9)	9 (23.7)	48 (17.0)	42 (15.2)
Not reported	1 (2.9)	0	0	1 (0.4)
Nodal status at resection, n (%)				
N0 or NX with < 10 nodes removed	15 (44.1)	12 (31.6)	64 (22.7)	72 (26.1)
N0 with ≥ 10 nodes removed	3 (8.8)	8 (21.1)	80 (28.4)	65 (23.6)
N1	4 (11.8)	7 (18.4)	58 (20.6)	56 (20.3)
N2	12 (35.3)	7 (18.4)	68 (24.1)	66 (23.9)
N3	0	3 (7.9)	11 (3.9)	17 (6.2)
Not reported	0	1 (2.6)	1 (0.4)	0

ECOG PS, Eastern Cooperative Oncology Group performance status; N+, node; p, pathologic; T, tumor; Tis, tumor in situ; X, cannot be assessed.

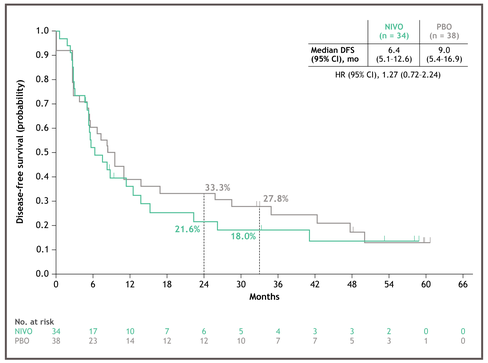
- In patients with CPS ≥ 1, median DFS was 25.6 months with NIVO and 8.5 months with PBO (**Figure 2**; **Table 2**)

Figure 2. DFS in patients with CPS ≥ 1



- In patients with CPS < 1, median DFS was 6.4 months with NIVO and 9.0 months with PBO (**Figure 3**; **Table 2**)

Figure 3. DFS in patients with CPS < 1



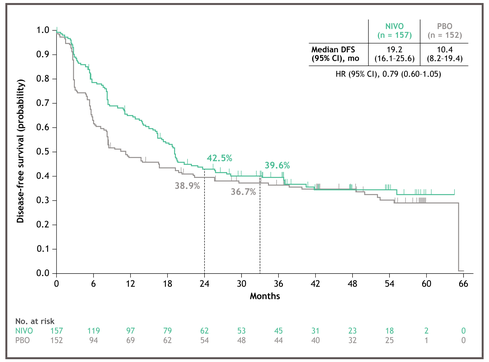
- In patients with TC < 1% and CPS ≥ 1, median DFS was 19.2 months with NIVO and 10.4 months with PBO (**Figure 4**; **Table 2**)
- In patients with TC ≥ 1%, median DFS was 52.6 months with NIVO and 8.4 months with PBO (**Table 2**)
- In patients with TC < 1%, median DFS was 17.1 months with NIVO and 9.7 months with PBO (**Table 2**)

Table 2. Summary of DFS outcomes by CPS and TC status with 3-year follow-up

		Median DFS (95% CI), months	DFS probability at 24 months (95% CI), %	DFS probability at 33 months (95% CI), %	HR (95% CI) for disease recurrence or death
CPS ≥ 1	NIVO n = 282	25.6 (19.3-41.8)	50.7 (44.5-56.5)	47.4 (41.3-53.3)	0.64 (0.51-0.80)
	PBO n = 276	8.5 (7.8-15.2)	37.6 (31.8-43.5)	34.7 (28.9-40.5)	
CPS < 1	NIVO n = 34	6.4 (5.1-12.6)	21.6 (9.1-37.6)	18.0 (6.8-33.6)	1.27 (0.72-2.24)
	PBO n = 38	9.0 (5.4-16.9)	33.3 (18.9-48.4)	27.8 (14.6-42.6)	
TC ≥ 1%	NIVO n = 125	52.6 (25.8-NE)	61.6 (52.1-69.8)	57.8 (48.2-66.3)	0.48 (0.34-0.69)
	PBO n = 125	8.4 (5.6-17.9)	35.8 (27.1-44.5)	31.9 (23.6-40.6)	
TC < 1%	NIVO n = 191	17.1 (13.4-19.4)	38.8 (31.8-45.9)	35.9 (29.0-42.9)	0.84 (0.65-1.07)
	PBO n = 189	9.7 (8.2-16.7)	38.0 (31.0-44.9)	35.0 (28.2-42.0)	
TC < 1% and CPS ≥ 1	NIVO n = 157	19.2 (16.1-25.6)	42.5 (34.5-50.2)	39.6 (31.8-47.4)	0.79 (0.60-1.05)
	PBO n = 152	10.4 (8.2-19.4)	38.9 (31.0-46.6)	36.7 (28.9-44.4)	

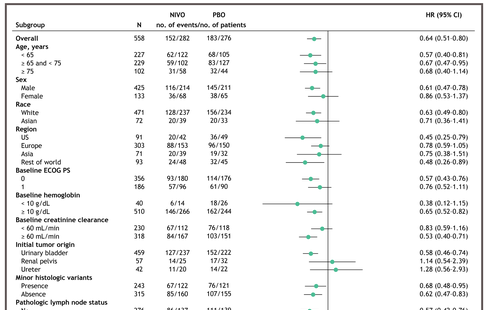
NE, not estimable.

Figure 4. DFS in patients with TC < 1% and CPS ≥ 1



- In an analysis of DFS by subgroup in patients with CPS ≥ 1, DFS HRs generally favored NIVO over PBO in most of the subgroups analyzed, including those based on age, sex, ECOG PS, nodal status, and prior cisplatin-based chemotherapy (**Figure 5**)

Figure 5. DFS by clinical and demographic subgroups in patients with CPS ≥ 1



HR calculated with stratified Cox proportional hazards model. HR was not computed for subgroup (except age, region, and sex) category with fewer than 10 patients per treatment group.

Conclusions

- This post hoc exploratory analysis of PD-L1 expression by TC and CPS from the CheckMate 274 trial showed that most patients with TC < 1% had CPS ≥ 1, as noted previously[11]
- With extended follow-up (minimum, 31.6 months; median, 36.1 months), a DFS benefit with NIVO versus PBO continued to be observed in the CPS ≥ 1, TC ≥ 1%, and TC < 1% populations, and across most clinically relevant subgroups within the CPS ≥ 1 population, consistent with previous reports in this subgroup and the ITT population in earlier follow-ups[3,11]
- In patients with TC < 1% and CPS ≥ 1, median DFS with NIVO was nearly double that with PBO, with a 21% reduction in the risk of disease recurrence or death with NIVO (DFS HR, 0.79)
- The small proportion of patients with CPS < 1 precludes definitive conclusions
- These results support the interpretation that most patients with high-risk MIUC after radical surgery and with a TC < 1% also benefit from adjuvant NIVO

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Declaration of interests

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