Disease-free survival with longer follow-up from the phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high-risk muscle-invasive urothelial carcinoma

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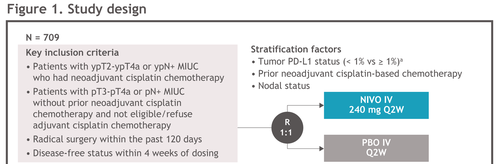
Introduction

- The standard of care for muscle-invasive urothelial carcinoma (MIUC) is surgery with or without cisplatin-based neoadjuvant chemotherapy[1]
  - Despite this treatment, most patients with high-risk MIUC experience recurrence[2]
  - There is currently no evidence supporting the use of adjuvant chemotherapy after neoadjuvant chemotherapy, and the level of evidence supporting the use of adjuvant cisplatin-based chemotherapy in patients who have not received neoadjuvant chemotherapy is low (except for urothelial carcinoma of the renal pelvis and ureter)[1,3-6]
  - Furthermore, many patients are ineligible for or decline cisplatin-based chemotherapy[7]
- In the phase 3 CheckMate 274 trial of adjuvant nivolumab (NIVO) versus placebo (PBO) in patients with MIUC at high risk of recurrence after radical surgery (minimum follow-up in the intent-to-treat [ITT] population, 5.9 months), disease-free survival (DFS) was significantly improved with NIVO versus 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 the population with tumor programmed death ligand 1 (PD-L1) expression ≥ 1% (HR, 0.55; 98.72% CI, 0.35-0.85; $P < 0.001$)[8]
  - The safety profile of NIVO monotherapy was consistent with that observed in previous trials[8-10]
- On the basis of primary results from CheckMate 274,[8,11] NIVO was approved in August 2021 in the United States as the first adjuvant immunotherapy for the treatment of patients with urothelial carcinoma at high risk of recurrence after radical resection
- Here, we report DFS outcomes from CheckMate 274 with approximately 5 months longer follow-up (minimum follow-up in the ITT population, 11.0 months)

Methods

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter trial of NIVO versus PBO in patients with high-risk MIUC (originating in the bladder, ureter, or renal pelvis; **Figure 1**)
- Patients were randomized 1:1 to NIVO 240 mg intravenously every 2 weeks (Q2W) or PBO for ≤ 1 year of adjuvant treatment, and stratified by nodal status, prior neoadjuvant cisplatin, and tumor PD-L1 status[8]
- Primary endpoints were DFS in all randomized patients (ITT population) and in patients with tumor PD-L1 expression ≥ 1%
  - DFS was also evaluated in prespecified subgroups
- Non-urothelial tract recurrence-free survival (NUTRFS) in ITT patients and in patients with tumor PD-L1 ≥ 1% was a secondary endpoint
- Distant metastasis-free survival (DMFS) and time to recurrence (TTR) were exploratory endpoints
- HRs and corresponding CIs for DFS, NUTRFS, and DMFS were estimated using a stratified Cox proportional hazards model

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]OS data were not mature at the time of this analysis. OS and DSS data are not presented.
DSS, disease-specific survival; IHC, immunohistochemistry; OS, overall survival; R, randomized.

Results

- Overall, 353 patients were randomized to NIVO (tumor PD-L1 ≥ 1%, n = 140) and 356 patients were randomized to PBO (tumor PD-L1 ≥ 1%, n = 142; **Table 1**)
- In this analysis, minimum follow-up was 11.0 months (median follow-up, 24.4 months [NIVO] and 22.5 months [PBO]) in the ITT population and 11.4 months (median follow-up, 25.5 months [NIVO] and 22.4 months [PBO]) in the population of patients with tumor PD-L1 ≥ 1%
- In the ITT population, the median (range) duration of therapy was 10.1 (0-12.5) months in the NIVO arm and 8.6 (0-12.6) months in the PBO arm
- With longer follow-up, DFS was improved with NIVO versus PBO in both the ITT population and in patients with tumor PD-L1 ≥ 1% (**Figure 2**)
  - In ITT patients, median DFS was 22.0 months with NIVO and 10.9 months with PBO
  - Among patients with tumor PD-L1 ≥ 1%, median DFS was NR with NIVO and 8.4 months with PBO

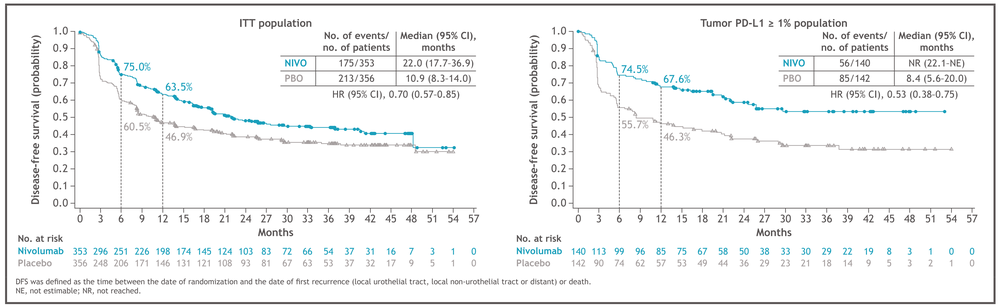
Table 1. Select baseline demographic and clinical characteristics[8]

	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)
Male, n (%)	265 (75.1)	275 (77.2)
Race or ethnic group, n (%)		
White	264 (74.8)	272 (76.4)
Asian	80 (22.7)	75 (21.1)
Black	2 (0.6)	3 (0.8)
Other	7 (2.0)	5 (1.4)
Unreported	0	1 (0.3)
ECOG PS,[a] n (%)		
0	224 (63.5)	221 (62.1)
1	122 (34.6)	125 (35.1)
2[b]	7 (2.0)	9 (2.5)
Tumor origin at initial diagnosis, n (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)
Tumor PD-L1 ≥ 1% as recorded at randomization by IVRS, %	140 (39.7)	142 (39.9)
Prior neoadjuvant cisplatin, %	153 (43.3)	155 (43.5)
Pathologic T stage at resection, %		
pTX	5 (1.4)	0
pT0	5 (1.4)	7 (2.0)
pTis	4 (1.1)	3 (0.8)
PT1	13 (3.7)	14 (3.9)
pT2	62 (17.6)	65 (18.3)
PT3	206 (58.4)	204 (57.3)
pT4a	57 (16.1)	62 (17.4)
Not reported	1 (0.3)	1 (0.3)
Nodal status at resection, %		
N+	167 (47.3)	168 (47.2)
N0/x with < 10 nodes removed	94 (26.6)	99 (27.8)
N0 with ≥ 10 nodes removed	91 (25.8)	88 (24.7)
Not reported	1 (0.3)	1 (0.3)

[a]Not reported for 1 patient in the PBO arm. [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice response system.

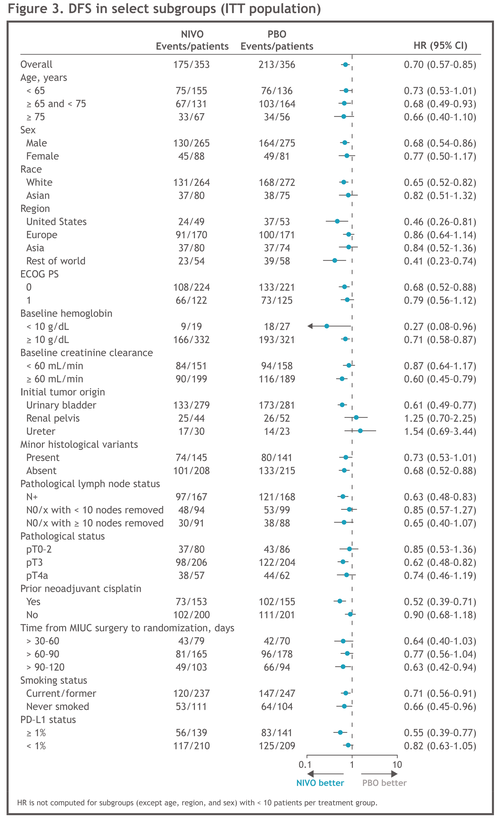
- In the subgroup analysis, improvement in DFS was observed with NIVO versus PBO for most subgroups analyzed, including age, sex, ECOG PS, nodal status, use of prior cisplatin-based chemotherapy, and tumor PD-L1 status (**Figure 3**)
- NUTRFS was improved with NIVO versus PBO in both ITT patients and those with tumor PD-L1 ≥ 1% (**Figure 4**)
  - In ITT patients, NUTRFS probabilities at 12 months were 65.8% in the NIVO arm and 50.6% in the PBO arm
  - In patients with tumor PD-L1 ≥ 1%, NUTRFS probabilities at 12 months were 69.2% in the NIVO arm and 47.1% in the PBO arm
- DMFS was also improved with NIVO versus PBO in both ITT patients and those with tumor PD-L1 ≥ 1% (**Figure 5**)
- In the ITT population, median (95% CI) TTR was 25.8 (19.6-NE) months in the NIVO arm and 11.1 (8.3-19.4) months in the PBO arm
- In the tumor PD-L1 ≥ 1% population, median (95% CI) TTR was NR (25.8-NE) in the NIVO arm and 10.9 (5.8-22.2) months in the PBO arm

Figure 2. Disease-free survival



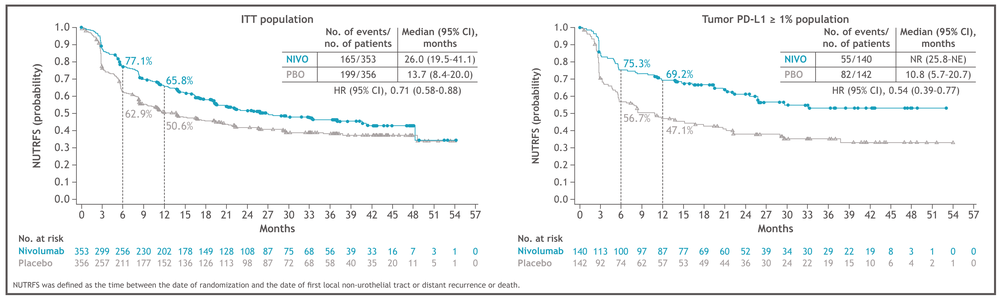
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
NE, not estimable; NR, not reached.

Figure 3. DFS in select subgroups (ITT population)



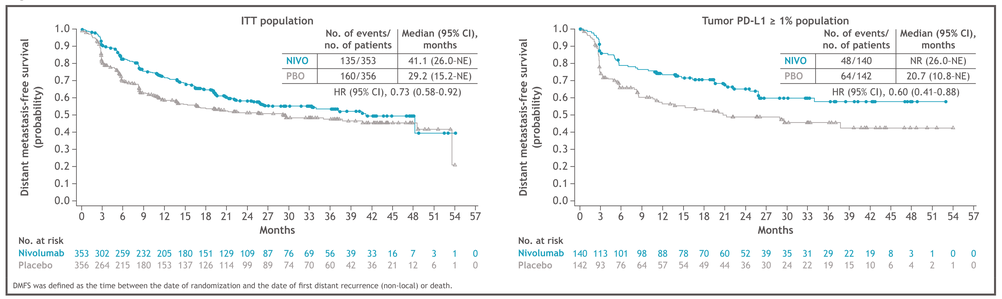
HR is not computed for subgroups (except age, region, and sex) with < 10 patients per treatment group.

Figure 4. Non-urothelial tract recurrence-free survival



NUTRFS was defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death.

Figure 5. Distant metastasis-free survival



DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or death.

- A summary of subsequent anticancer therapy received by patients in the study is shown in **Table 2**
  - DFS results accounted for subsequent cancer therapy

Table 2. Subsequent anticancer therapy

Subsequent therapy, n (%)	NIVO (N = 353)	PBO (N = 356)
Patients who received any subsequent therapy[a]	35.1	40.7
Subsequent radiotherapy	6.2	8.1
Subsequent surgery	4.0	4.2
Subsequent intravesical chemotherapy[b]	2.5	3.6
Subsequent systemic therapy	30.0	37.6
Subsequent platinum-based chemotherapy	20.4	18.3
Subsequent immunotherapy[c]	7.9	23.9

DFS results accounted for subsequent cancer therapy.
[a]Patients may have received more than 1 type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (or the randomization date if the patient was never treated).
[b]Includes patients who received 1 single dose and those who received more than 1 single dose of intravesical chemotherapy.
[c]The most frequent subsequent immunotherapies were pembrolizumab, atezolizumab, and NIVO.

Conclusions

- With longer follow-up, NIVO continued to demonstrate clinically meaningful improvement in DFS versus PBO for patients with high-risk MIUC after radical surgery
  - This DFS benefit was observed both in ITT patients and in patients with tumor PD-L1 ≥ 1%
- A DFS benefit was observed in most prespecified clinical subgroups
- NUTRFS, DMFS, and TTR were also improved with NIVO compared with PBO in both ITT patients and those with tumor PD-L1 ≥ 1%
- These results support adjuvant NIVO as a standard-of-care treatment for patients with high-risk MIUC after radical resection

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