Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: 14-month follow-up of CheckMate 577

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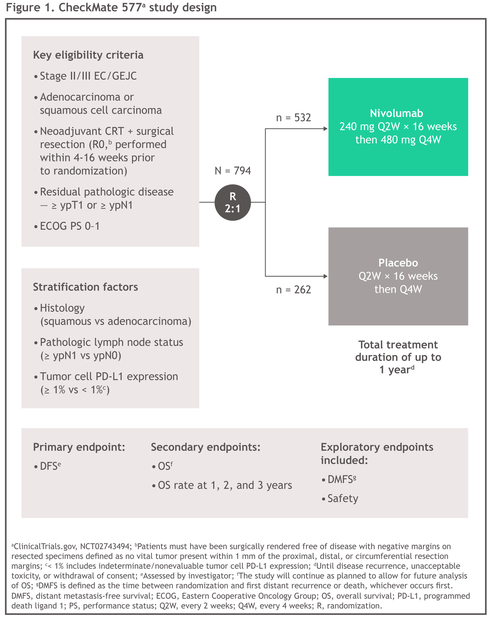
Introduction

- Neoadjuvant chemoradiotherapy (CRT) followed by surgery (trimodality therapy) is a well-established standard of care for patients with resectable locally advanced esophageal cancer (EC) and gastroesophageal junction cancer (GEJC)[1-4]
- The risk of recurrence following trimodality therapy remains high, particularly in patients with residual pathologic disease[1-5]
- CheckMate 577 is the first global, phase 3, randomized, double-blind study for EC/GEJC to evaluate an immune checkpoint inhibitor in the adjuvant setting following trimodality therapy
- In CheckMate 577, nivolumab demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) versus placebo (median 22.4 vs 11.0 months, respectively; hazard ratio [HR], 0.69; 96.4% confidence interval [CI], 0.56-0.86; $P < 0.001$) with a well-tolerated safety profile[6]
  - Based on these results, nivolumab received US Food and Drug Administration and European Commission approval for the adjuvant treatment of patients with resected EC/GEJC and residual pathologic disease following neoadjuvant CRT[7,8]
- Here we present efficacy and safety data from CheckMate 577 with an additional 8 months of follow-up

Methods

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled study (**Figure 1**)

Figure 1. CheckMate 577[a] study design



[a]ClinicalTrials.gov, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and first distant recurrence or death, whichever occurs first. DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD-L1, programmed death ligand 1; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomization.

Results

- At data cutoff (January 4, 2021), the median follow-up (time from randomization date to clinical data cutoff) was 32.2 months (range, 14.0-52.7 months)
- Baseline characteristics were balanced between treatment arms (**Table 1**)

Table 1. Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62 (26-82)	61 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	59	58
GEJC	41	42
Histology,[b] %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[c,d] %		
≥ 1%	17	15
< 1%	70	75
Time from complete resection to randomization, %		
< 10 weeks	34	28
≥ 10 weeks	66	72

In a post hoc analysis, a baseline PD-L1 combined positive score (CPS) of 5 or higher was observed in 246 of 435 patients (57%) in the nivolumab arm and in 125 of 231 patients (54%) in the placebo arm.

[a]Other races not shown; [b]< 1% had other histology in the nivolumab arm; [c]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which, for most patients, was obtained after completion of chemoradiotherapy; [d]14% and 10% of patients had tumor cell PD-L1 expression indeterminate or nonevaluable in the nivolumab and placebo arms, respectively.

- The median duration of treatment was almost 2 months longer in the nivolumab arm compared to the placebo arm (**Table 2**)
- Treatment completion was the most common reason for treatment discontinuation in the nivolumab arm, while treatment completion and disease progression were the most common reasons for discontinuation in the placebo arm (**Table 2**)

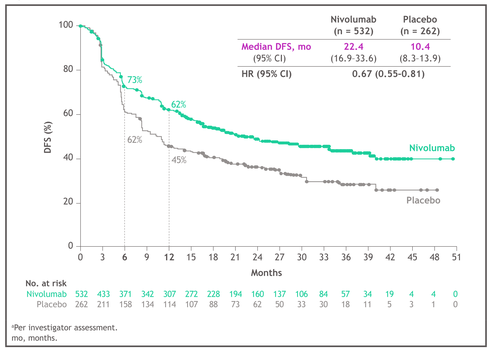
Table 2. Exposure and disposition

	Nivolumab[a] (n = 532)	Placebo[a] (n = 260)
Median duration of treatment (range), months	10.8 (< 0.1-14.2)	9.0 (< 0.1-15.0)
Discontinued treatment, n (%)[b]	532 (100)	260 (100)
Reasons for treatment discontinuation, n (%)		
Treatment completion	259 (49)	115 (44)
Disease progression	149 (28)	114 (44)
AEs related to treatment	57 (11)	8 (3)
AEs not related to treatment	16 (3)	9 (3)
Patient request	42 (8)	9 (3)
Other[c]	9 (2)	5 (2)

[a]Patients who received ≥ 1 dose of study treatment; [b]All patients completed 100 days of follow-up after the last dose of study treatment; [c]Included poor/non-compliance (n = 2), death (n = 2), maximum clinical benefit (n = 2), lost to follow-up (n = 1), and additional reasons (n = 7).
AE, adverse event.

- Nivolumab continued to demonstrate clinically meaningful benefit in DFS with a 33% reduction in the risk of recurrence or death, a doubling in median DFS versus placebo, and sustained separation of the curves (**Figure 2**)
  - Compared with earlier results,[6] the HR numerically decreased with longer follow-up (HR, 0.67 [95% CI, 0.55-0.81] from 0.69 [96.4% CI, 0.56-0.86])

Figure 2. Disease-free survival[a]



[a]Per investigator assessment.
mo, months.

- DFS benefit was observed with nivolumab versus placebo across multiple subgroups (**Figure 3**)
  - Compared with earlier results,[6] there was a numerical reduction in HR for multiple subgroups, including GEJC (HR, 0.80 [95% CI, 0.59-1.08] from 0.87 [95% CI, 0.63-1.21]) and adenocarcinoma (HR, 0.73 [95% CI, 0.58-0.91] from 0.75 [95% CI, 0.59-0.96])

Figure 3. Disease-free survival subgroup analysis

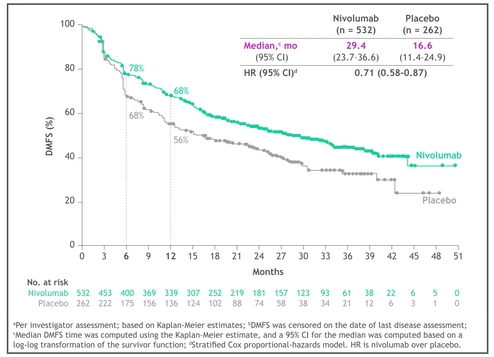
Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
	Nivolumab	Placebo		
Overall (N = 794)	22.4	10.4	0.68	
Age, years				
< 65 (n = 507)	25.1	9.3	0.63	
≥ 65 (n = 287)	19.4	13.9	0.79	
Sex				
Male (n = 671)	21.3	10.3	0.70	
Female (n = 123)	29.3	11.0	0.62	
Race				
White (n = 648)	21.3	10.8	0.69	
Asian (n = 117)	29.7	9.7	0.71	
ECOG PS				
0 (n = 464)	26.6	11.1	0.71	
1 (n = 330)	18.5	9.3	0.64	
Tumor location at initial diagnosis				
Esophagus (n = 465)	23.4	8.3	0.61	
Gastroesophageal junction (n = 329)	21.4	16.8	0.80	
Histologic type				
Adenocarcinoma (n = 563)	19.6	10.4	0.73	
Squamous cell carcinoma (n = 230)	29.7	10.6	0.60	
Tumor cell PD-L1 expression[a]				
≥ 1% (n = 129)	28.3	10.2	0.68	
< 1% (n = 567)	20.8	11.0	0.70	
Indeterminate/nonevaluable (n = 98)	26.6	9.9	0.64	
PD-L1 CPS[a,b]				
≥ 5 (n = 371)	29.3	8.5	0.60	
< 5 (n = 295)	15.3	11.1	0.85	
Indeterminate/nonevaluable/NR (n = 128)	26.6	10.8	0.64	
Pathologic lymph node status				
ypN0 (n = 337)	Not reached	27.0	0.71	
≥ ypN1 (n = 457)	14.8	7.6	0.65	
Pathological tumor status[c]				
ypT0[d] (n = 45)	34.0	5.2	0.40	
ypT1 or ypT2 (n = 311)	29.3	9.2	0.59	
ypT3 or ypT4 (n = 436)	18.5	11.5	0.80	
Time from complete resection to randomization				
< 10 weeks (n = 256)	24.0	12.7	0.85	
≥ 10 weeks (n = 538)	21.3	9.3	0.63	

0.25 0.5 1 2
Nivolumab better ← → Placebo better

[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which, for most patients, was obtained after completion of CRT; [b]Post hoc analysis; [c]2 patients had unknown pathological tumor status in the nivolumab arm; [d]The lower bound of the 95% CI for this subgroup is 0.18.
NR, not reported.

- Nivolumab showed a 29% reduction in the risk of distant recurrence or death versus placebo (**Figure 4**)
  - Compared with earlier results,[6] the HR numerically decreased with longer follow-up (HR, 0.71 [95% CI, 0.58-0.87] from 0.74 [95% CI, 0.60-0.92])

Figure 4. Distant metastasis-free survival[a,b]



[a]Per investigator assessment; based on Kaplan-Meier estimates; [b]DMFS was censored on the date of last disease assessment; [c]Median DMFS time was computed using the Kaplan-Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function; [d]Stratified Cox proportional-hazards model. HR is nivolumab over placebo.

- Similar overall incidences of any AEs and serious AEs were reported for nivolumab and placebo, both for low- and high-grade events (**Table 3**)
- The majority of treatment-related AEs (TRAEs) were grade 1 or 2 (**Table 3**)

Table 3. Safety summary

Patients, n (%)	Nivolumab[a] (n = 532)		Placebo[a] (n = 260)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AEs[b,c]	513 (96)	186 (35)	243 (93)	84 (32)
Serious AEs[c]	160 (30)	109 (20)	80 (31)	53 (20)
AEs leading to discontinuation[d]	71 (13)	39 (7)	21 (8)	16 (6)
Any TRAEs[b]	379 (71)	74 (14)	122 (47)	16 (6)
Serious TRAEs	41 (8)	31 (6)	7 (3)	3 (1)
TRAEs leading to discontinuation	49 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm[b]				
Fatigue	92 (17)	6 (1)	29 (11)	1 (< 1)
Diarrhea	89 (17)	2 (< 1)	39 (15)	2 (< 1)
Pruritus	53 (10)	2 (< 1)	9 (3)	0
Rash	51 (10)	4 (< 1)	10 (4)	1 (< 1)
Hypothyroidism	51 (10)	0	4 (2)	0

[a]Patients who received ≥ 1 dose of study treatment; [b]Events reported between first dose and 30 days after last dose of study drug; [c]There were 8 and 7 grade 5 AEs in the nivolumab and placebo arms, respectively; [d]There were 3 and 2 grade 5 AEs leading to discontinuation in the nivolumab and placebo arms, respectively.

- The majority of select TRAEs (those with potential immunologic etiology) were grade 1 or 2 (**Table 4**)
- Grade 3-4 select TRAEs occurred in ≤ 1% of patients in the nivolumab arm (**Table 4**), and there were no grade 5 select TRAEs

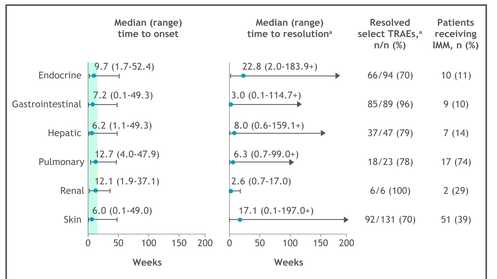
Table 4. Select TRAEs

Select TRAEs,[b,c] n (%)	Nivolumab[a] (n = 532)		Placebo[a] (n = 260)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine	94 (18)	5 (< 1)	6 (2)	0
Gastrointestinal	92 (17)	4 (< 1)	40 (15)	3 (1)
Hepatic	50 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (< 1)
Renal	7 (1)	1 (< 1)	2 (1)	0
Skin	131 (25)	7 (1)	28 (11)	1 (< 1)

[a]Patients who received ≥ 1 dose of study treatment; [b]Select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention; [c]Events reported between first dose and 30 days after last dose of study drug.

- Select TRAEs in the nivolumab arm occurred early (median time to onset, 6-13 weeks) and resolved for most patients (70%-100% across organ categories) with the use of established management algorithms (median time to resolution, 3-23 weeks) (**Figure 5**)

Figure 5. Onset and resolution of select TRAEs



Shaded area indicates first 13 weeks of treatment. ● indicates the median time. → indicates ongoing events. + indicates a censored value.
[a]Events without a stop date or with a stop date equal to the death, as well as grade 5 events, are considered unresolved; events without worsening from baseline were excluded.
IMM, immune modulating medication.

Conclusions

- Adjuvant nivolumab continued to demonstrate clinically meaningful efficacy versus placebo in patients with resected EC/GEJC following neoadjuvant CRT with longer follow-up
  - 33% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple subgroups
  - 29% reduction in the risk of distant recurrence or death and a 13-month improvement in median DMFS
- Longer follow-up suggests directionally improved HRs for DFS, DMFS, and DFS across multiple subgroups, including GEJC and adenocarcinoma
- Adjuvant nivolumab was well tolerated, no new safety signals were identified, and the frequencies of AEs were consistent with earlier results
- These findings further support adjuvant nivolumab as a new standard of care for patients with resected EC/GEJC who received neoadjuvant CRT and have residual pathologic disease

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