Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

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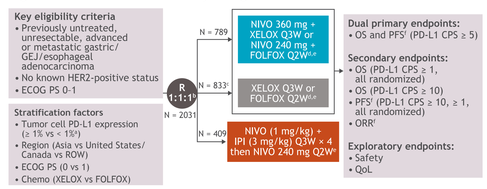
Introduction

- Standard first-line (1L) chemotherapy (chemo) for advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric cancer/gastroesophageal junction cancer (GC/GEJC) results in poor median overall survival (OS) of < 1 year[1-4]
- Nivolumab (NIVO) + chemo demonstrated superior OS vs chemo in advanced GC/GEJC/esophageal adenocarcinoma (EAC) after 12 months of minimum follow-up in CheckMate 649[5]
  - Superior OS was coupled with clinically meaningful progression-free survival (PFS) benefit, improved and durable responses, and an acceptable safety profile[5]
- NIVO + chemo is now approved as 1L treatment for patients with advanced or metastatic GC/GEJC/EAC in many countries, including the United States, based on these results[6]
- We report expanded analyses of efficacy and safety for NIVO + chemo vs chemo after 24-month follow-up

Methods

- CheckMate 649 (NCT02872116) is a randomized, open-label, global phase 3 study[5] (**Figure 1**)

Figure 1. CheckMate 649 study design



[a]Less than 1% includes indeterminate tumor cell PD-L1 expression; [b]After NIVO + chemo arm was added and before new patient enrollment in the NIVO + IPI arm was stopped early (June 5, 2018) based on DMC recommendation; patients already enrolled in the NIVO + IPI arm were allowed to remain on study; [c]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016–June 2018) and to NIVO + chemo (April 2017–April 2019); [d]XELOX: oxaliplatin 130 mg/m² IV (day 1) and capecitabine 1000 mg/m² orally twice daily (days 1–14); FOLFOX: oxaliplatin 85 mg/m², leucovorin 400 mg/m², and FU 400 mg/m² IV (day 1) and FU 1200 mg/m²/d IV daily (days 1–2); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [f]BICR assessed. BICR, blinded independent central review; CPS, combined positive score; DMC, data monitoring committee; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, fluorouracil; IPI, ipilimumab; IV, intravenous; ORR, objective response rate; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; QoL, quality of life; R, randomization; ROW, rest of world.

Results

- At data cutoff (May 27, 2021), the minimum follow-up (time from concurrent randomization of the last patient to clinical data cutoff) was 24.0 months in the NIVO + chemo arm
- Baseline characteristics were balanced across treatment arms (**Table 1**)

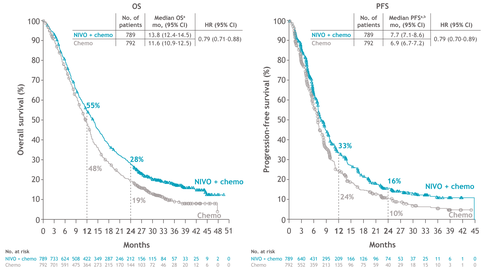
Table 1. Baseline characteristics

All randomized[a,b]	NIVO + chemo (n = 789)	Chemo (n = 792)
Median age (range), years	62 (18-88)	61 (21-90)
Male	68	71
Region[b]		
Asia	23	22
Non-Asian	77	78
ECOG PS 1[c]	59	57
Primary tumor location at initial diagnosis		
GC	70	70
GEJC	17	16
EAC	13	14
Baseline tumor burden < Q3[d]	57	57
Tumor cell PD-L1 status ≥ 1%[e]	16	16
Baseline albumin ≥ LLN[f]	73	73
Baseline NLR < 4[g]	60	58
Peritoneal metastases[h]	24	24
Liver metastases[h]	38	40
MSI status[i]		
MSS	88	86
MSI-H	3	3
FOLFOX/XELOX received on study[j]	54/46	53/47

[a]All data are presented as % unless otherwise noted; [b]Percentages may not add up to 100 due to rounding; [c]Based on case report form. All randomly assigned patients had ECOG PS of 0 or 1 based on interactive response technology. ECOG PS 2: NIVO + chemo, n = 1; chemo, n = 3. Not reported: chemo, n = 1; [d]Per BICR. Q3 indicates third quartile. Not available: NIVO + chemo, n = 184; chemo, n = 185; [e]Tumor cell PD-L1 < 1% includes indeterminate tumor cell PD-L1 expression; [f]Not reported: NIVO + chemo, n = 32; chemo, n = 33; [g]Not available: NIVO + chemo, n = 9; chemo, n = 31; [h]Not reported: NIVO + chemo, n = 23; chemo, n = 26; [i]Not reported/invalid: NIVO + chemo, n = 71; chemo, n = 89; [j]Patients who received at least 1 dose of the assigned treatment: NIVO + chemo, n = 782; chemo, n = 767. LLN, lower limit of normal; MSI-H, microsatellite instability high; MSS, microsatellite stable; NLR, neutrophil to lymphocyte ratio. Adapted from Shitara K, et al.[7]

- Clinically meaningful improvement in OS and PFS with NIVO + chemo vs chemo was maintained with longer follow-up[7] (**Figure 2**)

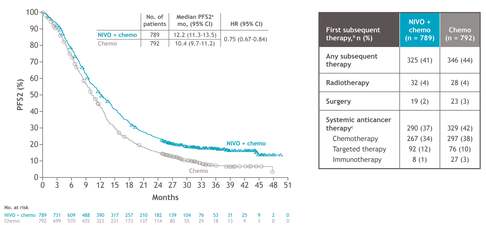
Figure 2. Overall survival and progression-free survival in all randomized patients



[a]Minimum follow-up, 24.0 months. [b]Per BICR assessment. CI, confidence interval; HR, hazard ratio; mo, months.

- Progression-free survival 2 (PFS2) favored NIVO + chemo vs chemo with a 25% reduction in risk of death or disease progression on subsequent therapy (**Figure 3**)

Figure 3. Progression-free survival 2 in all randomized patients

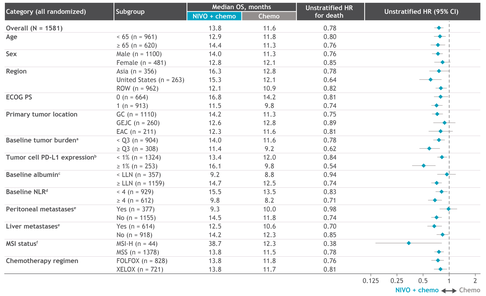


First subsequent therapy,[a] n (%)	NIVO + chemo (n = 789)	Chemo (n = 792)
Any subsequent therapy	325 (41)	346 (44)
Radiotherapy	32 (4)	28 (4)
Surgery	19 (2)	23 (3)
Systemic anticancer therapy[a]	290 (37)	329 (42)
Chemotherapy	267 (34)	297 (38)
Targeted therapy	92 (12)	76 (10)
Immunotherapy	8 (1)	27 (3)

[a]PFS2, progression-free survival on subsequent therapy (time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever was earlier); [b]Patients may have received more than 1 type of subsequent therapy; [c]Patients may receive multiple subsequent systemic therapies, out of which the first subsequent systemic therapies patients received are summarized in this table regardless of their timing relative to the subsequent radiotherapy and surgery.

- OS favored NIVO + chemo vs chemo across key subgroups in all randomized patients (**Figure 4**)

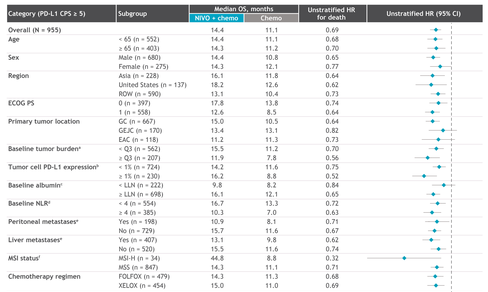
Figure 4. Overall survival subgroup analysis in all randomized patients



[a]Not available, n = 369. Q3 indicates third quartile; [b]Unknown, n = 4; [c]Not reported, n = 65; [d]Not available, n = 40; [e]Not reported, n = 49; [f]Invalid/not reported, n = 159. Adapted from Shitara K, et al.[7]

- OS favored NIVO + chemo vs chemo across key subgroups in patients with PD-L1 CPS ≥ 5 (**Figure 5**)

Figure 5. Overall survival subgroup analysis in patients with PD-L1 CPS ≥ 5



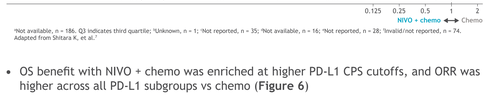
[a]Not available, n = 186. Q3 indicates third quartile; [b]Unknown, n = 1; [c]Not reported, n = 35; [d]Not available, n = 16; [e]Not reported, n = 28; [f]Invalid/not reported, n = 74. Adapted from Shitara K, et al.[7]

- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs, and ORR was higher across all PD-L1 subgroups vs chemo (**Figure 6**)

Figure 6. Efficacy subgroup analysis by PD-L1 CPS

Overall survival

Objective response rate

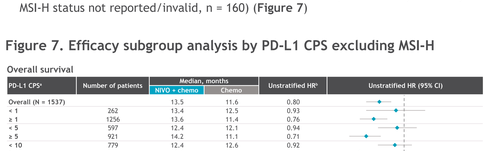


[a]PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 19; [b]Unstratified HR for death (OS); [c]Randomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 14; [d]Percentages may not reflect an exact difference due to rounding. Adapted from Shitara K, et al.[7]

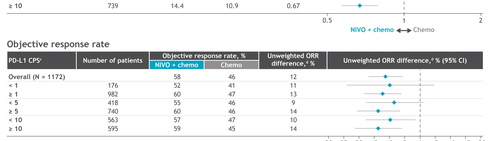
- OS and ORR benefits were consistent with the all randomized population when excluding patients with MSI-H tumors (MSI-H tumors, n = 44; MSS tumors, n = 1377; MSI-H status not reported/invalid, n = 160) (**Figure 7**)

Figure 7. Efficacy subgroup analysis by PD-L1 CPS excluding MSI-H

Overall survival



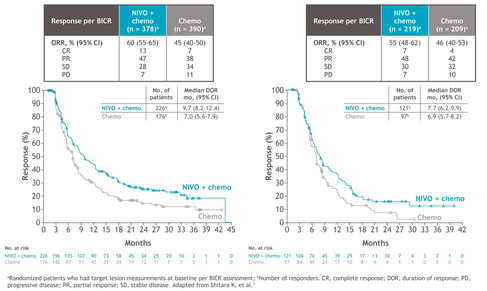
Objective response rate



[a]PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 19; [b]Unstratified HR for death (OS); [c]Randomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 14; [d]Percentages may not reflect an exact difference due to rounding.

- ORR was higher and responses were more durable with NIVO + chemo vs chemo regardless of PD-L1 CPS ≥ 5 or < 5 (**Figure 8**)

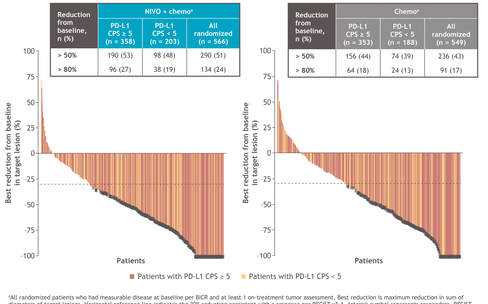
Figure 8. Response and duration of response



[a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]Number of responders. CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Shitara K, et al.[7]

- More deep responses were observed with NIVO + chemo vs chemo regardless of PD-L1 CPS ≥ 5 or < 5 (**Figure 9**)

Figure 9. Best percentage reduction in tumor burden



[a]All randomized patients who had measurable disease at baseline per BICR and at least 1 on-treatment tumor assessment. Best reduction is maximum reduction in sum of diameters of target lesions. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisk symbol represents responders. RECIST, Response Evaluation Criteria In Solid Tumors. Adapted from Shitara K, et al.[7]

Safety

- No new safety signals were identified with NIVO + chemo (**Table 2**)
- The most common grade 3/4 treatment-related adverse events (TRAEs) included:
  - NIVO + chemo: neutropenia (15%), decreased neutrophil count (11%), anemia (6%)
  - Chemo: neutropenia (13%), decreased neutrophil count (9%), diarrhea (3%)

Table 2. Treatment-related adverse events

All treated,[a] n (%)	NIVO + chemo (n = 782)		Chemo (n = 767)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[b]	739 (95)	471 (60)	682 (89)	344 (45)
Serious TRAEs[b]	175 (22)	133 (17)	94 (12)	77 (10)
TRAEs leading to discontinuation[b,c]	300 (38)	141 (18)	188 (25)	70 (9)
Treatment-related deaths[d]	16 (2)[e]		4 (< 1)[f]	

[a]Patients who received ≥ 1 dose of study drug; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]TRAEs leading to discontinuation of any drug in the regimen; [d]Treatment-related deaths were reported regardless of timeframe; [e]Included 4 events of pneumonitis, 2 events of febrile neutropenia or neutropenic fever, and 1 event each of acute cerebral infarction, disseminated intravascular coagulation, GI bleeding, GI toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, septic shock, and stroke; [f]Included 1 event each of asthenia and severe hypoxexia, diarrhea, pneumonitis, and pulmonary thromboembolism. GI, gastrointestinal. Adapted from Shitara K, et al.[7]

- TRAEs with potential immunologic etiology
  - Grade 3/4 events occurred in ≤ 5% of patients with NIVO + chemo across organ categories (**Table 3**)
  - The majority of non-endocrine events with NIVO + chemo resolved (62%-88% across organ categories) with a median time to resolution of 1.6-23.4 weeks (**Table 3**)

Table 3. TRAEs with potential immunologic etiology[a,b]

All treated,[a,c] n (%)	NIVO + chemo (n = 782)					
	Any grade	Grade 3/4[d]	Median time to onset (range), weeks	Median time to resolution (range), weeks	Resolved, n (%)	Patients receiving IMM, n (%)
Endocrine	109 (14)	6 (< 1)	15.3 (2.0-124.3)	NR (0.4 to 191.3+)	41 (38)	17 (16)
Gastrointestinal	266 (34)	43 (5)	4.3 (0.1-97.3)	1.6 (0.1 to 155.7+)	233 (88)	29 (11)
Hepatic	207 (26)	31 (4)	8.0 (0.1-193.7)	10.1 (0.4 to 203.7+)	156 (76)	24 (12)
Pulmonary	41 (5)	14 (2)	24.0 (1.6-96.9)	10.4 (0.3+ to 174.4+)	30 (73)	31 (76)
Renal	29 (4)	7 (< 1)	18.9 (1.7-65.7)	2.9 (0.1 to 67.7+)	22 (76)	7 (24)
Skin	218 (28)	27 (3)	9.9 (0.1-139.4)	23.4 (0.1 to 206.7+)	135 (62)	85 (39)

[a]TRAEs with potential immunologic etiology that require frequent monitoring/intervention; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]Patients who received ≥ 1 dose of study drug; [d]The most common grade 3/4 events (≥ 2%) in the NIVO + chemo arm were diarrhea (n = 35), aspartate aminotransferase increased (n = 13), palmar-plantar erythrodysesthesia syndrome (n = 12), and pneumonitis (n = 12). There were no grade 5 events. IMM, immune modulating medication; NR, not reached. Adapted from Shitara K, et al.[7]

Conclusions

- NIVO + chemo continued to demonstrate clinically meaningful improvement in efficacy vs chemo with an acceptable safety profile with longer follow-up in previously untreated patients with advanced GC/GEJC/EAC
  - Favorable PFS2
  - OS benefit across key subgroups and enriched at higher PD-L1 CPS cutoffs
  - Higher ORR across all evaluated PD-L1 CPS subgroups
  - More deep and more durable responses regardless of PD-L1 CPS ≥ 5 or < 5
  - OS and ORR benefit across PD-L1 CPS subgroups consistent with the all randomized population when excluding patients with MSI-H tumors
  - No new safety signals; TRAEs with potential immunologic etiology resolved in most patients with the use of established management algorithms
- These data further support the use of NIVO + chemo as standard 1L treatment in patients with advanced GC/GEJC/EAC

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