

ORIGINAL ARTICLE

Surrogate endpoints for survival in KEYNOTE-585: neoadjuvant/adjvant pembrolizumab plus chemotherapy versus placebo plus chemotherapy for gastric or gastroesophageal junction adenocarcinoma [☆]

K. Shitara^{1*}, Y.-J. Bang², L. S. Wyrwicz³, S. Y. Rha⁴, T. Oshima⁵, F. Pietrantonio⁶, Y.-K. Park⁷, S. Lonardi⁸, P. Yañez⁹, C.-J. Yen¹⁰, J.-P. Metges¹¹, M. Garrido¹², M. Moehler¹³, S. Pelles-Avraham¹⁴, W. P. Yong¹⁵, A. Spallanzani¹⁶, E. Jensen¹⁷, R. Krishnan¹⁷, C.-S. Shih¹⁷ & S.-E. Al-Batran¹⁸

¹National Cancer Center Hospital East, Kashiwa; ²Seoul National University College of Medicine, Seoul, Republic of Korea; ³Maria Skłodowska-Curie National Cancer Research Institute, Warsaw, Poland; ⁴Yonsei University College of Medicine, Seoul, Republic of Korea; ⁵Kanagawa Cancer Center, Yokohama, Japan; ⁶Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ⁷Chonnam National University Medical School, Hwasun, Republic of Korea; ⁸Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; ⁹Universidad de La Frontera, James Lind Cancer Research Center, Temuco, Chile; ¹⁰National Cheng Kung University, Tainan, Taiwan; ¹¹CHU—Brest—Institut de Cancerologie et d’Hématologie ARPEGO Network, Brest, France; ¹²Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; ¹³Johannes-Gutenberg University Clinic, Mainz, Germany; ¹⁴Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; ¹⁵National University Cancer Institute Singapore (NCIS), Singapore; ¹⁶University Hospital of Modena, Modena, Italy; ¹⁷Merck & Co., Inc., Rahway, USA; ¹⁸Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany



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Background: In the randomized phase III KEYNOTE-585 trial, neoadjuvant/adjvant pembrolizumab plus chemotherapy was not superior to placebo plus chemotherapy for event-free survival (EFS) in participants with locally advanced gastric or gastroesophageal (GEJ) adenocarcinoma. However, pembrolizumab plus chemotherapy significantly improved pathologic complete response (pCR) versus placebo plus chemotherapy (difference 10.9%, 95% confidence interval (CI) 7.5% to 14.8%, $P < 0.00001$). This *post hoc* analysis evaluated whether pCR, major pathologic response (mPR), and pathologic downstaging (pDS) after neoadjuvant/adjvant pembrolizumab plus chemotherapy are associated with improved survival outcomes.

Patients and methods: Eligible participants had untreated, locally advanced gastric or GEJ adenocarcinoma (including Siewert type 2 or 3) and were scheduled for surgery after preoperative chemotherapy. The main cohort received pembrolizumab or placebo plus chemotherapy [cisplatin plus capecitabine (XP) or cisplatin plus 5-fluorouracil (FP)], whereas the safety cohort received pembrolizumab or placebo plus docetaxel, oxaliplatin, 5-fluorouracil, and leucovorin (FLOT). The outcomes for this *post hoc* analysis were the relationship between pCR, mPR, pDS to NO, or any pDS with EFS per RECIST v1.1 (by investigator) and overall survival (OS). We report outcomes in the main and FLOT cohorts combined. The data cut-off date was 9 February 2023.

Results: A total of 1007 participants were enrolled and randomly assigned ($n = 502$, pembrolizumab plus chemotherapy; $n = 505$, placebo plus chemotherapy); 221 (44.0%) and 172 (34.1%) participants, respectively, had pathologic nodal stage NO. The pCR rate was 13.9% with pembrolizumab plus chemotherapy and 2.8% with placebo plus chemotherapy; mPR rates were 31.5% and 22.2%, respectively. Among participants who experienced mPR ($\leq 10\%$ residual viable tumor), the hazard ratios for EFS and OS were 0.6 (95% CI 0.4-1.0) and 0.7 (95% CI 0.4-1.2), respectively, for pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

Conclusion: These findings suggest a potential association between pCR, mPR, or pDS and survival in patients with locally advanced gastric or GEJ adenocarcinoma, although further validation is needed.

Key words: chemotherapy, gastric cancer, major pathologic response, pathologic complete response, pembrolizumab, pathologic downstaging

*Correspondence to: Dr Kohei Shitara, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan. Tel: +81-4-7133-1111

E-mail: kshitara@east.ncc.go.jp (K. Shitara).

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INTRODUCTION

The addition of pembrolizumab to standard-of-care therapy has improved overall survival (OS) for patients with unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.¹⁻⁴ However, it remains unclear

whether inhibition of the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis could also improve OS for patients with resectable gastric or GEJ adenocarcinoma in the neoadjuvant setting. Achieving pathologic complete response (pCR), major pathologic response (mPR), or pathologic downstaging (pDS) after neoadjuvant immunotherapy has been shown to improve survival across a range of tumor types.⁵⁻⁷ Similar findings have also been reported for patients with gastric or GEJ adenocarcinoma treated with neoadjuvant chemotherapy.⁸⁻¹⁰ However, there is no consensus on the relationship between these surrogate efficacy endpoints and survival in the neoadjuvant immunotherapy gastric or GEJ adenocarcinoma setting.^{11,12}

In the KEYNOTE-585 study, treatment with neoadjuvant and adjuvant pembrolizumab plus cisplatin-based chemotherapy significantly improved the pCR rate compared with placebo plus chemotherapy [12.9% versus 2.0%, respectively; difference 10.9%, 95% confidence interval (CI) 7.5-14.8, $P < 0.00001$].¹³ However, this did not result in a statistically significant difference in event-free survival (EFS) with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy for participants with locally advanced gastric or GEJ adenocarcinoma [44.4 months (95% CI 33.0 months to not reached) versus 25.3 months (95% CI 20.6-33.9 months), respectively, hazard ratio (HR) 0.81, 95% CI 0.67-0.99, $P = 0.0198$].¹³

We report the results of a *post hoc* analysis of pCR, mPR, and pDS as surrogate endpoints of survival in KEYNOTE-585, including a cohort of participants treated with pembrolizumab or placebo plus docetaxel-based chemotherapy.

METHODS

Study design and participants

KEYNOTE-585 (NCT03221426) was a multicenter, double-blind, randomized, placebo-controlled, phase III study designed to evaluate the efficacy and safety of neoadjuvant or adjuvant pembrolizumab (or both) or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo in locally advanced gastric or GEJ adenocarcinoma. Eligible participants had a T3 or greater primary lesion or the presence of any positive nodes without evidence of metastatic disease, including participants with Siewert type 2 or 3 tumors [per the American Joint Committee on Cancer (AJCC) 8th Edition staging system]. Participants had treatment-naïve disease and were to proceed to surgical intervention following preoperative chemotherapy. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent. The complete study methodology was previously published.¹³

Randomization and treatment

In the main study cohort, participants were randomly assigned 1 : 1 to receive 3 cycles of neoadjuvant pembrolizumab 200 mg or placebo (saline) intravenously plus

chemotherapy every 3 weeks (Q3W), followed by 3 cycles of adjuvant pembrolizumab or placebo plus chemotherapy Q3W after gastrectomy, and then an additional 11 cycles of pembrolizumab or placebo monotherapy Q3W. Chemotherapy regimens were decided by the investigator before random assignment and included cisplatin 80 mg/m² intravenously on day 1 of each cycle plus capecitabine 1000 mg/m² intravenously twice daily from days 1 to 14 of each cycle (XP) or cisplatin plus 5-fluorouracil 800 mg/m² per day intravenously from days 1 to 5 of each cycle (FP). In a smaller safety cohort, participants who were randomly assigned 1 : 1 to receive the same schedule of pembrolizumab or placebo Q3W as the main study cohort were enrolled, with FLOT (docetaxel 50 mg/m², oxaliplatin 85 mg/m², 5-fluorouracil 2600 mg/m², and leucovorin 200 mg/m² intravenously) Q2W for four cycles in the neoadjuvant and adjuvant phases.

Outcomes

The outcomes for this *post hoc* analysis were the relationship between pCR, mPR, pDS to NO, or any pDS with EFS per RECIST v1.1 (by investigator) and OS in the combined cohorts [intention-to-treat (ITT) population of all randomly assigned participants]. pCR was defined as the absence of residual invasive cancer on evaluation of the complete resected specimen and all sampled regional lymph nodes. mPR was defined as a reported Mandard tumor regression grade of 1 or 2 ($\leq 10\%$ residual viable tumor).¹⁴ pDS was derived by comparing clinical and pathologic tumor and nodal staging at diagnosis with pathologic tumor and nodal staging after treatment; participants could have tumor pDS, nodal pDS, or both.

Statistical analysis

Reported HRs and corresponding 95% CIs for EFS and OS were estimated using an unstratified Cox regression model, with treatment as a covariate. Event rates over time were estimated within each treatment group using the Kaplan–Meier method. The data cut-off date was 9 February 2023 and statistical analysis was conducted using SAS 9.3.

RESULTS

Participants

Overall, 1007 participants were randomly assigned to receive pembrolizumab plus chemotherapy ($n = 502$) or placebo plus chemotherapy ($n = 505$). Median time from random assignment to database cut-off was 46.3 months (range 24.2-63.5 months). Baseline characteristics were largely well-balanced between treatment groups (Table 1).

Efficacy

The pCR rate was 13.9% with pembrolizumab plus chemotherapy and 2.8% with placebo plus chemotherapy; the mPR rates were 31.5% and 22.2%, respectively (Table 2). Participants who experienced pCR, mPR, pDS to NO, or any tumor or nodal pDS were observed to have longer EFS (Figure 1) and

Table 1. Baseline characteristics of the KEYNOTE-585 ITT population

Characteristic	Pembrolizumab + chemotherapy (n = 502)	Placebo + chemotherapy (n = 505)
Age, median (range), years	64.0 (22.0-90.0)	63.0 (25.0-84.0)
Age ≥65 years, n (%)	237 (47.2)	220 (43.6)
Male sex, n (%)	366 (72.9)	358 (70.9)
Primary tumor location, n (%)		
Stomach	376 (74.9)	386 (76.4)
GEJ	126 (25.1)	118 (23.4)
Missing	0 (0)	1 (0.2)
Clinical tumor stage ^a , n (%)		
T1	3 (0.6)	2 (0.4)
T2	27 (5.4)	17 (3.4)
T3	289 (57.6)	302 (59.8)
T4	181 (36.1)	182 (36.0)
TX	2 (0.4)	1 (0.2)
Missing	0 (0)	1 (0.2)
Clinical nodal stage ^a , n (%)		
N0	105 (20.9)	102 (20.2)
N1	210 (41.8)	219 (43.4)
N2	142 (28.3)	150 (29.7)
N3	39 (7.8)	31 (6.1)
NX	6 (1.2)	2 (0.4)
Missing	0 (0)	1 (0.2)
Pathologic tumor stage ^b , n (%)		
T0	79 (15.7)	18 (3.6)
T1	52 (10.4)	49 (9.7)
T2	45 (9.0)	68 (13.5)
T3	169 (33.7)	177 (35.0)
T4	83 (16.5)	108 (21.4)
TX	0 (0)	1 (0.2)
Missing	74 (14.7)	84 (16.6)
Pathologic nodal stage ^b , n (%)		
N0	221 (44.0)	172 (34.1)
N1	81 (16.1)	78 (15.4)
N2	54 (10.8)	73 (14.5)
N3	72 (14.3)	98 (19.4)
Missing	74 (14.7)	84 (16.6)
PD-L1 expression ^c , n (%)		
CPS ≥1	366 (72.9)	384 (76.0)
CPS <1	91 (18.1)	91 (18.0)
Not evaluable	32 (6.4)	21 (4.2)
MSI status ^d , n (%)		
MSI-H	43 (8.6)	38 (7.5)
Non-MSI-H	390 (77.7)	382 (75.6)
Not evaluable	49 (9.8)	70 (13.9)
Missing	20 (4.0)	15 (3.0)
Chemotherapy backbone, n (%)		
XP	292 (58.2)	314 (62.2)
FP	107 (21.3)	86 (17.0)
FLOT	100 (19.9)	103 (20.4)
Missing	3 (0.6)	2 (0.4)

CPS, combined positive score; FLOT, docetaxel 50 mg/m² plus oxaliplatin 85 mg/m² plus fluorouracil 2600 mg/m² plus leucovorin 200 mg/m² administered every 2 weeks; FP, cisplatin 80 mg/m² on day 1 of each 3-week cycle plus 5-fluorouracil 800 mg/m² per day from days 1 to 5 of each cycle; GEJ, gastroesophageal junction; ITT, intention-to-treat; MSI, microsatellite instability; MSI-H, microsatellite instability-high; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand 1; XP, cisplatin 80 mg/m² on day 1 of each 3-week cycle plus capecitabine 1000 mg/m² twice daily from days 1 to 14 of each cycle.

^aClinical tumor staging was carried out before enrollment per the American Joint Committee on Cancer staging guidelines.

^bLauren histologic classification was required at baseline.

^cPD-L1 expression was determined using PD-L1 IHC 22C3 pharmDx (Agilent, Santa Clara, CA). CPS was calculated as the total number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

^dMSI status was established centrally by PCR using the MSI Analysis System, version 1.2 (Promega, Madison, WI) and characterized as high if ≥2 tumor microsatellite loci were changed compared with normal controls.

Table 2. Participants achieving surrogate efficacy outcomes by treatment group in the ITT population

Outcome, n (%)	Pembrolizumab + chemotherapy (n = 502)	Placebo + chemotherapy (n = 505)
pCR	70 (13.9)	14 (2.8)
mPR	158 (31.5)	112 (22.2)
Tumor pDS	234 (46.6)	176 (34.9)
Nodal pDS	203 (40.4)	146 (28.9)
Any tumor or nodal pDS	291 (58.0)	241 (47.7)

ITT, intention-to-treat; mPR, major pathologic response; pCR, pathologic complete response; pDS, pathologic downstaging.

OS (Figure 2) compared with participants who did not experience those outcomes. More participants in the pembrolizumab plus chemotherapy group experienced any pDS compared with participants in the placebo plus chemotherapy group (58.0% versus 47.7%; Table 2 and Figure 3). Participants who experienced mPR had an EFS HR of 0.6 (95% CI 0.4-1.0) (Figure 1B) and an OS HR of 0.7 (95% CI 0.4-1.2) (Figure 2B), comparing participants in the pembrolizumab plus chemotherapy group with participants in the placebo plus chemotherapy group.

DISCUSSION

In this *post hoc* analysis of KEYNOTE-585, participants who experienced pCR, mPR, pDS to N0, or any tumor or nodal pDS were observed to have numerically improved EFS and OS compared with participants who did not experience these surrogate outcomes, although sample sizes were inadequate for definitive findings. Additionally, participants who experienced mPR had numerically improved EFS and OS with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Although results of KEYNOTE-585 showed significant improvement in pCR with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy, the difference in EFS was not statistically significant, and OS was not statistically tested.¹³ The discordance between the two primary endpoints and the exploratory nature of this analysis underscore the need for cautious interpretation. However, the magnitude of benefit in pCR and EFS was comparable, with both an 11% difference for pCR and 3-year EFS. There was also a 9% difference in mPR; however, these trends should be considered hypothesis-generating rather than confirmatory.

To the best of our knowledge, this analysis is the first in which early surrogate endpoints and survival are assessed for participants treated with neoadjuvant immunotherapy in the locally advanced resectable gastric or GEJ adenocarcinoma setting. Previous studies in the chemotherapy-only setting have demonstrated that histopathological tumor regression and nodal downstaging are strongly associated with survival outcomes. A study that summarized 480 cases of gastric adenocarcinoma found that greater histopathologic regression after neoadjuvant

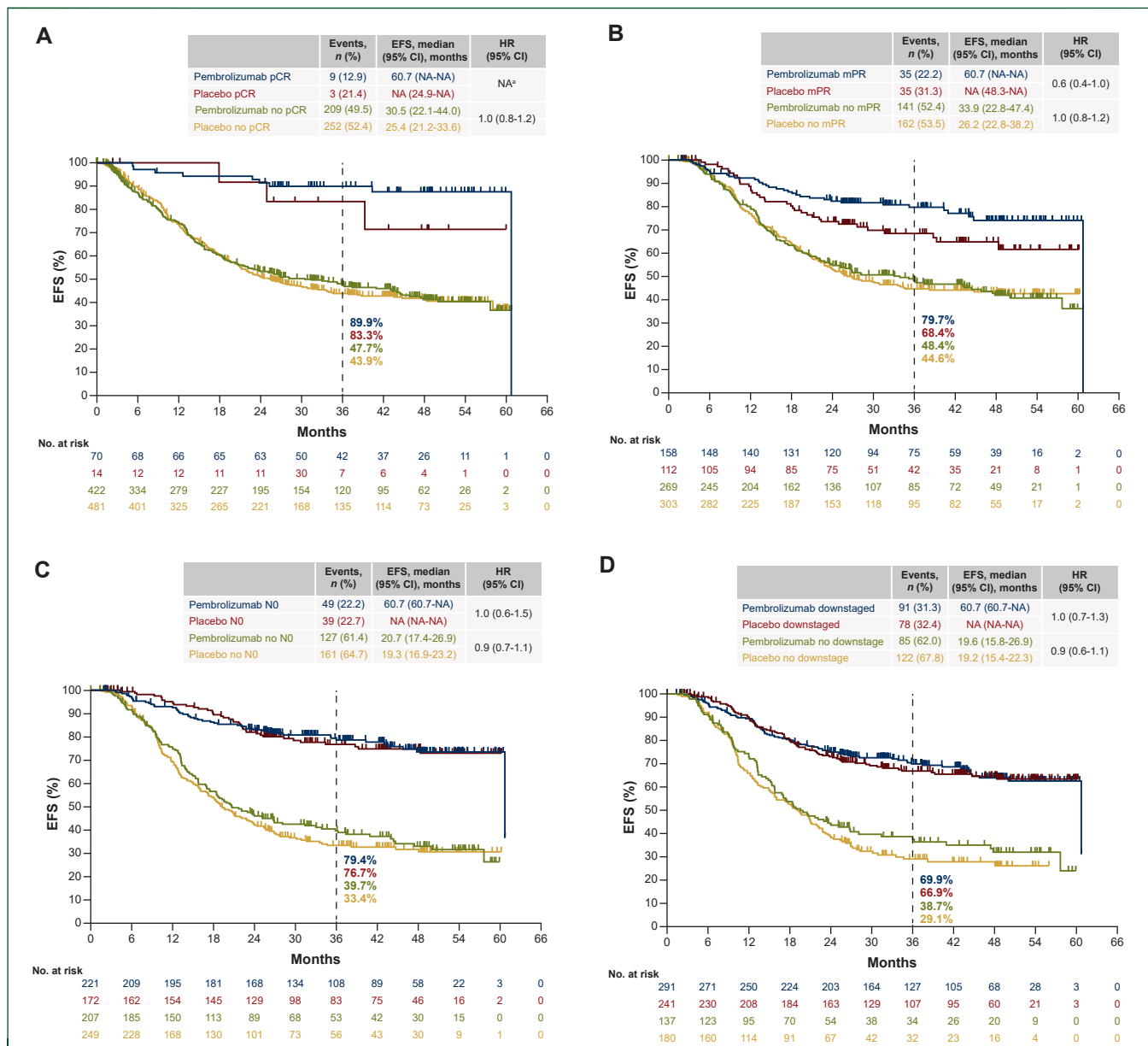


Figure 1. Kaplan–Meier estimates in the ITT population. EFS in participants with and without pCR (A), mPR (B), nodal pDS to NO (C), and any pDS (D). ^aNot calculated due to insufficient data. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; mPR, major pathologic response; NA, not applicable; pCR, pathologic complete response; pDS, pathologic downstaging.

chemotherapy correlated with improved prognosis.¹⁵ Similarly, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial reported that pathologic tumor response and nodal status were independent predictors of survival.¹⁶ These findings underscore the biological plausibility of using pCR, mPR, and pDS as surrogate endpoints. One limitation of the current analysis is that mPR was derived from Mandard regression grade and was not scored directly as in other reported studies. Notably, results of a retrospective study in China showed that the Mandard system may be more useful than other tumor regression grading systems in gastric cancer for prediction of survival.¹⁷ This observation is consistent with findings from an analysis of patients with locally advanced

esophagogastric adenocarcinoma who received neoadjuvant chemotherapy followed by surgery.¹⁸ This analysis demonstrated that regression grading systems, including Mandard, provide prognostic information beyond conventional staging. However, further validation of this approach is needed to comprehensively conclude whether trial-level and patient-level correlation exists between these surrogate endpoints and survival.

Emerging evidence from perioperative immunotherapy trials, such as the MATTERHORN trial of durvalumab in gastric and GEJ cancer, suggests that integrating immune checkpoint inhibitors may enhance the depth of response and potentially improve long-term outcomes.¹⁹ This aligns with the trends observed in KEYNOTE-585, where

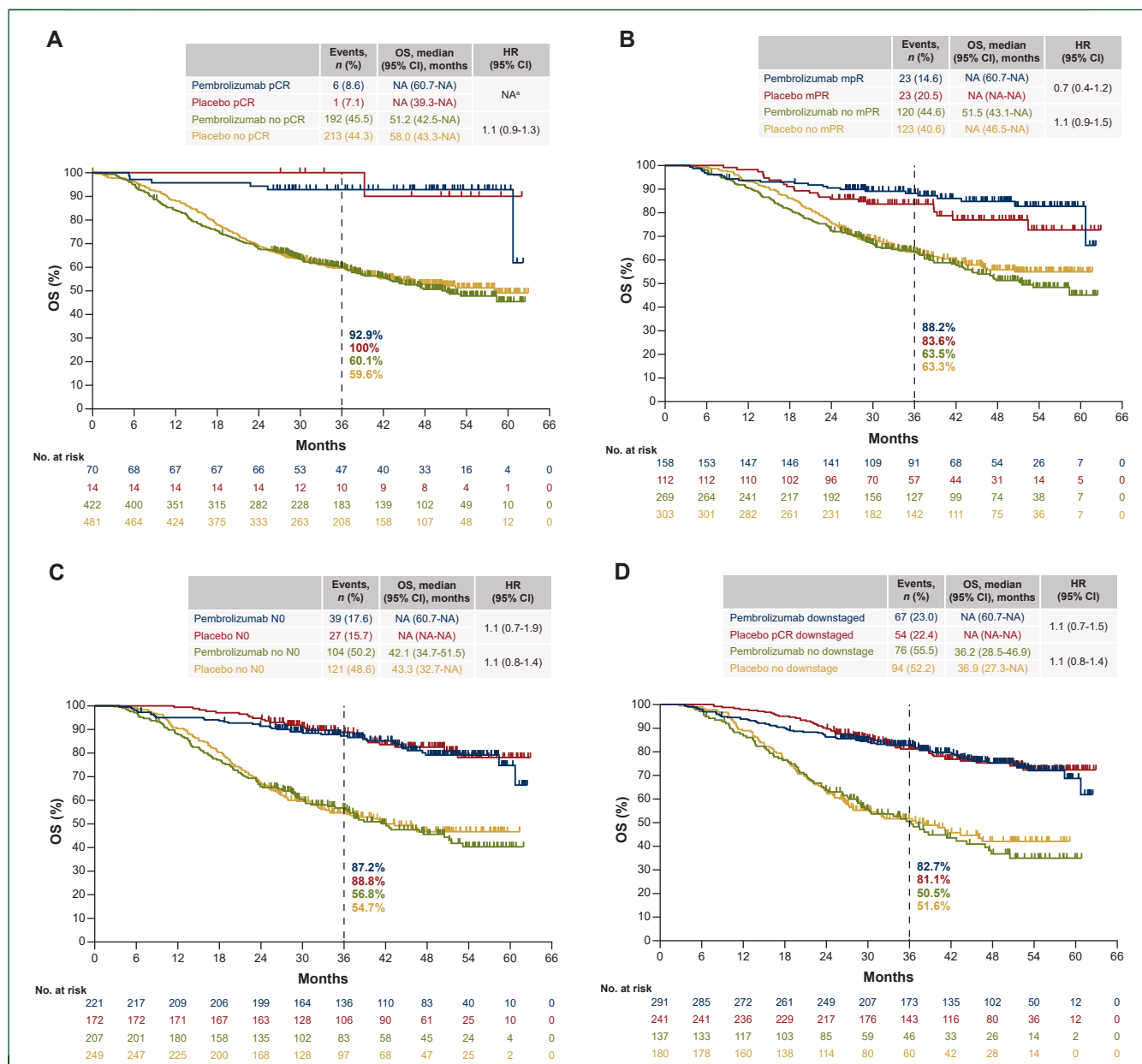


Figure 2. Kaplan–Meier estimates in the ITT population. OS in participants with and without pCR (A), mPR (B), nodal pDS to N0 (C), and any pDS (D). ^aNot calculated due to insufficient data. CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPR, major pathologic response; NA, not applicable; OS, overall survival; pCR, pathologic complete response; pDS, pathologic downstaging.

pembrolizumab plus chemotherapy increased rates of pCR and mPR compared with chemotherapy alone. The *post hoc* nature, limited population size in some of the analytical subgroups, and lack of multiplicity adjustments limit the strength of a causal inference between surrogate endpoints and survival. Additionally, 15% of the population was missing microsatellite instability status, information relevant to the interpretation of these data. These analyses provide a basis for further exploration and validation of these early surrogate endpoints.

In conclusion, participants with locally advanced gastric or GEJ adenocarcinoma achieving pCR, mPR, or pDS after neoadjuvant treatment had numerically prolonged EFS and OS compared with participants who did not achieve these

surrogate outcomes. Participants who received pembrolizumab plus chemotherapy had a higher incidence of nodal pDS to N0, as well as any tumor or nodal pDS, compared with placebo plus chemotherapy. To establish a definitive surrogacy relationship between these endpoints, additional meta-analyses (including data from ongoing trials) are warranted.

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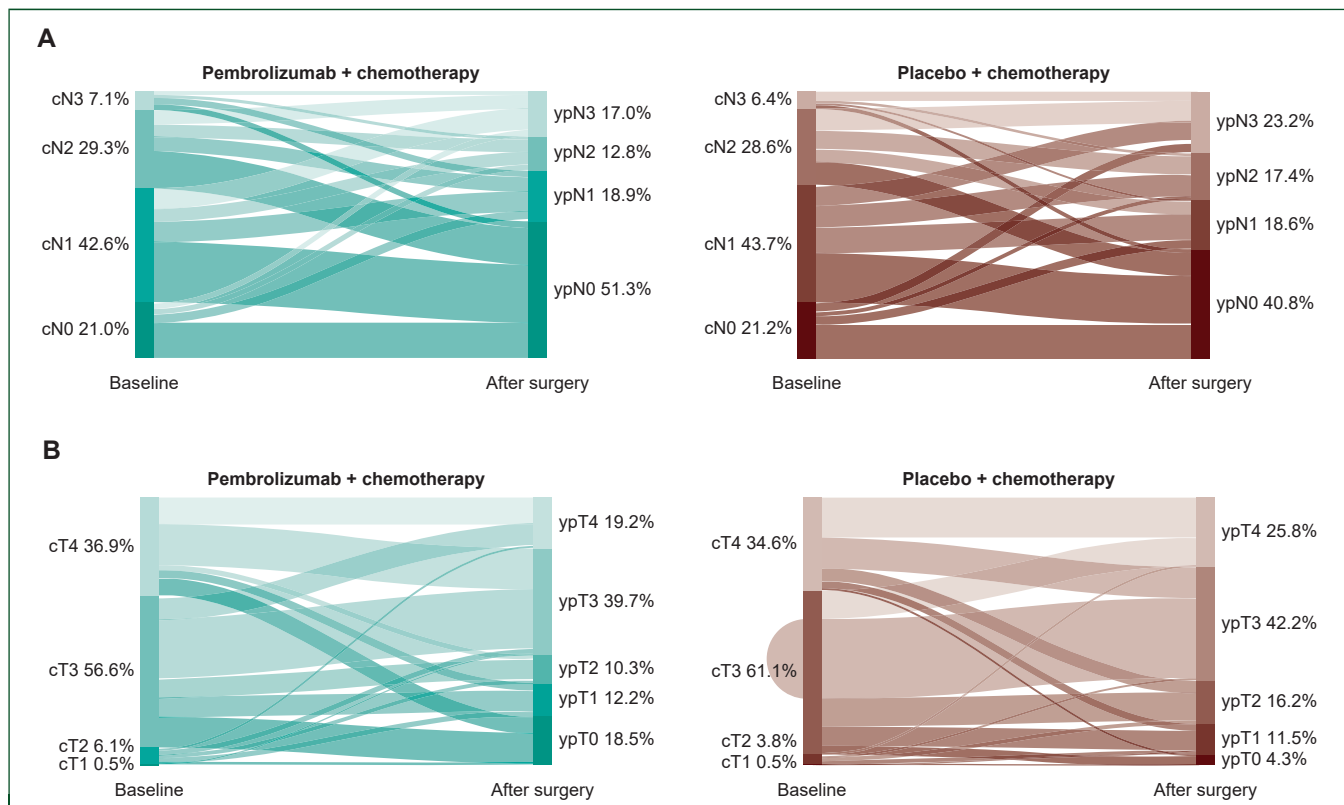


Figure 3. Sankey plots. Nodal status (A) and tumor status (B) at baseline and after surgery in the surgical population per the AJCC 8th Edition staging system.

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DISCLOSURE

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DATA SHARING

Merck Sharp and Dohme LLC, a subsidiary of Merck and Co., Inc., Rahway, NJ (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: <https://externaldatasharing-msd.com/>) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are

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