The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2025 VOL. 393 NO. 3

Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer

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ABSTRACT

BACKGROUND

Perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) is a standard therapy for resectable gastric and gastroesophageal junction adenocarcinomas, but recurrence rates remain high. Immunotherapy plus chemotherapy may improve outcomes.

METHODS

In a phase 3, multinational, double-blind, randomized trial, we assigned participants with resectable gastric or gastroesophageal junction adenocarcinoma, in a 1:1 ratio, to receive durvalumab at a dose of 1500 mg or placebo every 4 weeks plus FLOT for 4 cycles (2 cycles each of neoadjuvant and adjuvant therapy), followed by durvalumab or placebo every 4 weeks for 10 cycles. The primary end point was event-free survival; secondary end points included overall survival and pathological complete response.

RESULTS

A total of 474 participants were randomly assigned to the durvalumab group, and 474 to the placebo group (median follow-up, 31.5 months; interquartile range, 26.7 to 36.6). Two-year event-free survival (Kaplan–Meier estimate) was 67.4% among the participants in the durvalumab group and 58.5% among those in the placebo group (hazard ratio for event or death, 0.71; 95% confidence interval [CI], 0.58 to 0.86; P<0.001). Two-year overall survival was 75.7% in the durvalumab group and 70.4% in the placebo group (piecewise hazard ratio for death during months 0 to 12, 0.99 [95% CI, 0.70 to 1.39], and during the period from month 12 onward, 0.67 [95% CI, 0.50 to 0.90]; P=0.03 by a stratified log-rank test [exceeding the significance threshold of P<0.0001]). The percentage of participants with a pathological complete response was 19.2% in the durvalumab group and 7.2% in the placebo group (relative risk, 2.69 [95% CI, 1.86 to 3.90]). Adverse events with a maximum grade of 3 or 4 were reported in 340 participants (71.6%) in the durvalumab group and in 334 (71.2%) in the placebo group. The percentage of participants with delayed surgery was 10.1% and 10.8%, respectively, and the percentage with delayed initiation of adjuvant treatment was 2.3% and 4.6%.

CONCLUSIONS

Perioperative durvalumab plus FLOT led to significantly better event-free survival outcomes than FLOT alone among participants with resectable gastric or gastroesophageal junction adenocarcinoma. (Funded by AstraZeneca; MATTERHORN ClinicalTrials.gov number, NCT04592913.)

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A complete list of investigators in the MATTERHORN trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 1, 2025, and updated on June 27, 2025, at NEJM.org.

N Engl J Med 2025;393:217-30.
DOI: 10.1056/NEJMoa2503701
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CME

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Gastric and gastroesophageal junction adenocarcinomas are among the leading causes of cancer-related death worldwide.[1] Although curative-intent surgery is the primary treatment for patients with resectable gastric or gastroesophageal junction adenocarcinoma, most of these patients have disease recurrence after resection[2,3]; therefore, additional therapy is recommended for disease that is at stage IB or higher.[3] The FLOT4 trial established perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) as treatment for locally advanced resectable gastric or gastroesophageal junction adenocarcinoma; FLOT was associated with better overall survival and disease-free survival outcomes than epirubicin and cisplatin plus either fluorouracil or capecitabine.[4] Despite this result, recurrence rates with FLOT remain high.[5]

The combination of anti–programmed death ligand 1 (PD-L1) therapy and chemotherapy has shown encouraging outcomes and is approved for the treatment of metastatic gastric and gastroesophageal junction adenocarcinomas.[6-10] Durvalumab, an anti–PD-L1 antibody, is approved for the treatment of a range of solid tumors.[11-16] In the phase 3, multinational MATTERHORN trial, we assessed whether adding durvalumab to FLOT as perioperative therapy could improve event-free survival in patients with resectable gastric or gastroesophageal junction adenocarcinoma.

Methods

Participants

We enrolled participants 18 years of age or older who had histologically documented resectable gastric or gastroesophageal junction adenocarcinoma (stage II through IVA[17] and eligible for radical surgery) and had not received anticancer therapy. The participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability), adequate organ and bone marrow function, and availability of a tumor sample before trial enrollment for the assessment of PD-L1 expression. The main exclusion criteria were the presence of peritoneal dissemination or distant metastasis, squamous-cell or adenosquamous-cell carcinoma, or gastrointestinal stromal tumor. Full eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

Trial Design and Interventions

The MATTERHORN trial was a phase 3, multinational, double-blind, randomized, placebo-controlled trial.[18] Participants were randomly assigned, in a 1:1 ratio, to receive durvalumab at a dose of 1500 mg or placebo, administered intravenously every 4 weeks on day 1 of each cycle, plus FLOT chemotherapy, administered intravenously every 2 weeks on day 1 and day 15 of each cycle for 4 cycles (2 cycles of neoadjuvant therapy and 2 cycles of adjuvant therapy), followed by durvalumab at a dose of 1500 mg or placebo, administered intravenously every 4 weeks on day 1 of each cycle for 10 additional cycles. Flexibility was permitted in the dosing of durvalumab (in accordance with the "dosing modification and toxicity management" guidelines listed in the protocol) and in the dosing of FLOT (in accordance with local standard clinical practice). Neoadjuvant therapy began after screening and randomization occurred. Participants underwent resection surgery 4 to 8 weeks after they received their last dose of neoadjuvant therapy. Adjuvant therapy began 4 to 12 weeks after surgery (according to each participant's recovery period). A surgical delay was defined as surgery occurring more than 8 weeks (56 days) after the last dose of neoadjuvant treatment.

Treatment continued until withdrawal of consent or the investigator's decision to discontinue treatment or placebo because of confirmed disease progression or recurrence, unacceptable adverse effects, lack of adherence to the trial regimen or trial procedures, or another discontinuation criterion, or until the completion of 12 cycles of adjuvant durvalumab or at 1 year after the start of adjuvant therapy. Participants could continue treatment after progression (as defined by Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) occurred but only during the neoadjuvant treatment phase and if radical surgery was not precluded.

Participants were stratified according to geographic region (Asia or the rest of the world), clinical lymph-node status (positive or negative), and PD-L1 expression (≥1% or <1%, according to the Tumor Area Positivity score,[19] which is determined by visual aggregation and estimation of the area covered by PD-L1 positive tumor cells and tumor-associated immune cells relative to the total tumor area on the immunohistochemical slide). PD-L1 expression was assessed at a central

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laboratory with the investigational VENTANA PD-L1 [SP263] CDx assay [Roche Diagnostics]).

END POINTS

The primary end point was event-free survival, defined as the time from randomization until the date of one of the following events (whichever occurred first): disease progression according to RECIST, version 1.1, as assessed by blinded independent central review, that precluded surgery or that required nonprotocol therapy during the neoadjuvant treatment period; progression or recurrence according to RECIST, version 1.1, during the adjuvant treatment period; non-RECIST progression (according to investigator assessment or confirmed by biopsy) that precluded surgery or that required nonprotocol therapy during the neoadjuvant treatment period or that was discovered during surgery; progression or recurrence confirmed by biopsy after surgery; or death from any cause.

The key secondary end points were overall survival (defined as the time from randomization until the date of death from any cause) and pathological complete response (defined by no presence of residual viable tumor cells in the primary tumor and resected lymph nodes at surgery, corresponding to 100% pathological regression as assessed by blinded independent central review in accordance with modified Ryan criteria[20]). Other secondary end points were disease-free survival (defined as the time from the first postsurgery scan to the first documented disease recurrence [according to RECIST, version 1.1] or death, whichever occurred first), surgery (gastrectomy or gastroesophagectomy), and R0 resection (complete resection confirmed by pathological review). Results for additional secondary end points, including metastasis-free survival, disease-specific survival, and health-related quality of life are not provided here. Subgroup analyses of event-free survival that were prespecified in the statistical analysis plan were performed in subgroups defined according to sex, age at randomization (<65 or ≥65 years), geographic region (Asia or the rest of the world), clinical lymph-node status (positive or negative), PD-L1 expression (Tumor Area Positivity score ≥1% or <1%), tumor location (gastric or gastroesophageal junction), and ECOG performance-status score (0 or 1). Additional post hoc analyses of event-free survival were performed in subgroups defined according to histologic type (intestinal, diffuse, or indeterminate), microsatellite instability status (high, not high, not evaluable, or data missing), and PD-L1 expression (Tumor Area Positivity score ≥5% or <5% and ≥10% or <10%). Safety and adverse events were compared between the groups.

ASSESSMENTS

A baseline scan (by computed tomography or magnetic resonance imaging) was obtained for the neoadjuvant period (imaging performed ≤28 days before randomization) and for the adjuvant treatment period (imaging performed >4 weeks after the date of surgery and preferably ≤28 days before the start of adjuvant therapy). In addition, imaging was performed within 4 weeks after the last dose of neoadjuvant FLOT and before surgery was performed. After surgery and after adjuvant baseline imaging was performed, adjuvant tumor assessments were performed every 12 weeks (±1 week) for 2 years and then every 24 weeks (±1 week) thereafter until progression occurred. Pathological findings were reviewed to determine staging after surgery and to assess event-free survival. Details regarding microsatellite instability testing are provided in the Supplementary Appendix, available at NEJM.org. Adverse events were graded according to the revised National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

TRIAL OVERSIGHT

AstraZeneca sponsored the trial, supplied the durvalumab and placebo, and collaborated with the steering committee on the trial design and the collection, analysis, and interpretation of the data. FLOT was sourced locally or supplied centrally by AstraZeneca when local sourcing was not feasible. The trial was conducted in conformance with the International Council for Harmonisation guidelines for Good Clinical Practice and the ethical considerations of the Declaration of Helsinki. The trial protocol and amendments were approved by an institutional review board or independent ethics committee at each participating site. Written informed consent was obtained from the participants or their legal representatives (in Japan, participants <20 years of age were required to obtain consent from a guardian). An independent data monitoring committee reviewed unblinded safety data approximately every 6 months. All the investigators were responsible

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for data collection. All the authors participated in writing the manuscript. The authors and sponsor vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Medical writing assistance, including development of the initial draft of the manuscript under the direction of the authors, was funded by the sponsor.

STATISTICAL ANALYSIS

The protocol specified a plan to randomly assign approximately 900 participants in a 1:1 ratio to the two groups. Three formal analyses were prespecified: a pathological complete response analysis; an interim analysis of event-free survival and overall survival (referred to as the event-free survival analysis); and a final analysis of event-free survival, overall survival, or both, with overall survival to be formally tested only if the analysis of event-free survival showed statistical significance. The pathological complete response analysis was conducted after all the participants had undergone randomization and surgery or were deemed ineligible for resection; the pathological complete response results were final. The event-free survival analysis, with a data-cutoff date of December 20, 2024 (results reported here), was triggered after approximately 41% of the planned 385 events (event or death) had occurred across both treatment groups. The overall two-sided 5% alpha was initially allocated as 0.1% to the pathological complete response analysis and 4.9% to the event-free survival analysis. Because the pathological complete response analysis was positive, the 0.1% alpha was recycled. At the event-free survival analysis, a two-sided alpha of 2.39% was spent with the use of a Lan–DeMets alpha-spending function to approximate the O'Brien–Fleming boundary. An alpha of 0.01% was allocated to overall survival at this interim time point. The MATTERHORN trial is ongoing, with participants in active follow-up, and a final overall survival analysis has not yet been conducted.

Efficacy end points, including event-free survival, overall survival, and pathological complete response were evaluated in the full analysis population, which comprised all the participants who underwent randomization. Disease-free survival was analyzed in the R0 resection population, which included participants with margin-negative surgery and no evidence of disease on baseline imaging before the start of adjuvant therapy. Event-free survival, overall survival, and disease-free survival were analyzed with a stratified log-rank test, with adjustment for stratification factors. Hazard ratios and their confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Event-free survival, overall survival, and pathological complete response were the only end points that were part of the multiple testing procedure; therefore, the widths of the confidence intervals for the other end points and for the subgroups have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The incidence of events at fixed time points (18 months and 24 months) was summarized with the Kaplan–Meier method. Relative risk with respect to pathological complete response was analyzed with the use of a log-binomial regression model, with adjustment for the stratification factors.

For the time-to-event end point of event-free survival, if the participant had no tumor assessments by baseline imaging before the start of neoadjuvant therapy or after the completion of neoadjuvant therapy, data were censored at the randomization date unless the participant died or had non-RECIST progression later, in which case the participant was considered to have had an event on the date of death or progression. If there was no scan within the window after the date of surgery, no non-RECIST (confirmed by biopsy) progression or recurrence afterward, or the participant had not died, the data were censored at the surgery date. With respect to overall survival, data from participants who withdrew from the trial before they died were censored at the last date at which they were known to be alive. Among those participants, some could continue to be followed for survival status; if they could not be followed, survival status could be checked from publicly available death registries if permitted by local laws. When only a partial death date (the month and year or just the year) was available, the date of death was counted as the earliest possible date on the basis of the information available (first day of the month or first day of the year). With respect to pathological complete response, participants whose primary tumor and lymph nodes could not be evaluated by central pathological assessment or who did not have a surgical specimen were considered not to have had a response, and participants with a missing pathological complete response assessment were

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also considered not to have had a response. Further details on handling of missing data are provided in the Supplementary Appendix.

Safety data were summarized descriptively in the safety analysis population, which comprised all participants who received at least one dose of the trial treatment. Treatment-related adverse events were assessed by the investigator, who determined the relatedness to durvalumab or FLOT. Missing safety data were generally not imputed.

RESULTS

PARTICIPANTS

From November 17, 2020, to September 2, 2022, a total of 1258 participants were enrolled at 147 trial centers in 20 countries. The full analysis population comprised 948 participants; 474 participants were randomly assigned to receive durvalumab plus FLOT, and 474 to receive placebo plus FLOT (Fig. S1 in the Supplementary Appendix). The baseline demographic and clinical characteristics of the participants are shown in Table 1. A total of 68.4% of the participants in the durvalumab group and 66.7% of those in the placebo group had gastric cancer, and 19.0% of the participants in each group were treated at sites located in Asia (Table 1). The baseline demographic and clinical characteristics of the participants who had R0 resection are shown in Table S1. Black patients were underrepresented. Table S2 summarizes the representativeness of the MATTERHORN population.

At the data-cutoff date, the median duration of follow-up was 31.5 months (interquartile range, 26.7 to 36.6). A total of 458 participants (96.6%) in the durvalumab group and 449 participants (94.7%) in the placebo group completed all the assigned neoadjuvant durvalumab or placebo, 448 participants (94.5%) and 437 participants (92.2%), respectively, completed all the assigned neoadjuvant FLOT, 412 (86.9%) and 400 (84.4%) had surgery completed, 360 (75.9%) and 350 (73.8%) initiated the assigned adjuvant durvalumab or placebo, 353 (74.5%) and 346 (73.0%) initiated the assigned adjuvant FLOT, 248 (52.3%) and 245 (51.7%) completed all the assigned adjuvant durvalumab or placebo, and 229 (48.3%) and 245 (51.7%) completed all the assigned adjuvant FLOT (Fig. S1).

In the full analysis population, 48 participants (10.1%) in the durvalumab group had a delay in surgery and 11 participants (2.3%) had a delay in the initiation of adjuvant treatment; in the placebo group, 51 participants (10.8%) had a delay in surgery and 22 participants (4.6%) had a delay in the initiation of adjuvant treatment (Table S3). Subsequent therapy was received by 109 participants (23.0%) in the durvalumab group and by 153 participants (32.3%) in the placebo group; for a list of the anticancer therapies participants received after discontinuation of the trial regimens, see Table S4.

EFFICACY

Overall, 167 participants (35.2%) in the durvalumab group and 218 participants (46.0%) in the placebo group had disease progression or recurrence or died. Adding durvalumab to FLOT led to significantly better event-free survival outcomes than placebo (Fig. 1). The percentage of participants who remained event-free at 18 months was 73.2% in the durvalumab group and 63.6% in the placebo group, and the corresponding percentages at 24 months were 67.4% and 58.5% (hazard ratio for event or death, 0.71 [95% confidence interval {CI}, 0.58 to 0.86]; two-sided $P<0.001$ by stratified log-rank test) (Fig. 1). The proportional-hazards assumption for the analysis of event-free survival was assessed with a test of the interaction of time by treatment group and was satisfied (Fig. S2). Event-free survival in the population excluding participants with microsatellite instability–high status was consistent with that in the overall full analysis population (Fig. S3). The results of analyses in subgroups are shown in Figure 2 and Figure S4. Plots of log–log (event time) as compared with log (time) for event-free survival in participant subgroups are shown in Figure S5. The results of a sensitivity analysis of event-free survival that used modified censoring rules are shown in Table S5, and the reasons for censoring of data are shown in Table S6.

Overall, 145 participants (30.6%) in the durvalumab group and 176 participants (37.1%) in the placebo group died from any cause (Fig. 3A). Overall survival at 18 months was 81.1% among the participants in the durvalumab group and 77.1% among those in the placebo group; overall survival at 24 months was 75.7% in the durvalumab group and 70.4% in the placebo group (Fig. 3A). The P value by a stratified log-rank test for the between-group comparison of overall

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Table 1. Baseline Demographic and Clinical Characteristics in the Full Analysis Population.*

Characteristic	Durvalumab plus FLOT (N = 474)	Placebo plus FLOT (N = 474)	Total (N = 948)
Age			
Median (range) — yr	62 (26–84)	63 (28–83)	62 (26–84)
Distribution — no. (%)			
<50 yr	86 (18.1)	57 (12.0)	143 (15.1)
≥50 to <65 yr	205 (43.2)	208 (43.9)	413 (43.6)
≥65 to <75 yr	146 (30.8)	166 (35.0)	312 (32.9)
≥75 yr	37 (7.8)	43 (9.1)	80 (8.4)
Sex — no. (%)			
Male	326 (68.8)	356 (75.1)	682 (71.9)
Female	148 (31.2)	118 (24.9)	266 (28.1)
Region — no. (%)			
Asia	90 (19.0)	90 (19.0)	180 (19.0)
Rest of the world	384 (81.0)	384 (81.0)	768 (81.0)
Race or ethnic group — no. (%)†			
White	321 (67.7)	322 (67.9)	643 (67.8)
Asian	96 (20.3)	97 (20.5)	193 (20.4)
American Indian or Alaska Native	18 (3.8)	20 (4.2)	38 (4.0)
Black or African American	7 (1.5)	3 (0.6)	10 (1.1)
Other	8 (1.7)	8 (1.7)	16 (1.7)
Not reported	24 (5.1)	24 (5.1)	48 (5.1)
ECOG performance-status score — no. (%)‡			
0	337 (71.1)	366 (77.2)	703 (74.2)
1	137 (28.9)	108 (22.8)	245 (25.8)
Primary tumor location — no. (%)			
Gastric	324 (68.4)	316 (66.7)	640 (67.5)
Gastroesophageal junction	150 (31.6)	158 (33.3)	308 (32.5)
Siewert classification — no. (%)§			
Type 1	44 (9.3)	55 (11.6)	99 (10.4)
Type 2	72 (15.2)	68 (14.3)	140 (14.8)
Type 3	34 (7.2)	35 (7.4)	69 (7.3)
Primary tumor stage — no. (%)¶			
Non-T4	357 (75.3)	357 (75.3)	714 (75.3)
T0	1 (0.2)	0	1 (0.1)
Tis	1 (0.2)	0	1 (0.1)
T1	7 (1.5)	4 (0.8)	11 (1.2)
T2	41 (8.6)	32 (6.8)	73 (7.7)
T3	307 (64.8)	321 (67.7)	628 (66.2)
T4	117 (24.7)	117 (24.7)	234 (24.7)
T4a	101 (21.3)	103 (21.7)	204 (21.5)
T4b	16 (3.4)	14 (3.0)	30 (3.2)
Positive clinical lymph-node status — no. (%)‖	329 (69.4)	330 (69.6)	659 (69.5)

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Table 1. (Continued.)

Characteristic	Durvalumab plus FLOT (N=474)	Placebo plus FLOT (N=474)	Total (N=948)
PD-L1 expression, according to TAP — no. (%)**			
<1%	48 (10.1)	47 (9.9)	95 (10.0)
≥1%	426 (89.9)	427 (90.1)	853 (90.0)
Microsatellite instability status — no. (%)††			
High	25 (5.3)	24 (5.1)	49 (5.2)
Not high	301 (63.5)	310 (65.4)	611 (64.5)
Not evaluable	69 (14.6)	52 (11.0)	121 (12.8)
Data missing	79 (16.7)	88 (18.6)	167 (17.6)
Histologic type — no. (%)			
Intestinal	245 (51.7)	238 (50.2)	483 (50.9)
Diffuse	130 (27.4)	119 (25.1)	249 (26.3)
Unspecified adenocarcinoma or mixed or other	99 (20.9)	117 (24.7)	216 (22.8)

* FLOT denotes fluorouracil, leucovorin, oxaliplatin, and docetaxel.
† Race or ethnic group was reported by the patient. The category "Other" included any patient-reported race or ethnic group that did not fit in any of the categories specified on the basis of definitions from the Food and Drug Administration.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Siewert type 1 indicates an adenocarcinoma of the lower esophagus with the center located within 1 to 5 cm above the anatomical gastroesophageal junction; Siewert type 2 indicates a true carcinoma of the cardia at the gastroesophageal junction, with the tumor center within 1 cm above and 2 cm below the gastroesophageal junction; and Siewert type 3 indicates a subcardial carcinoma with the tumor center between 2 cm and 5 cm below the gastroesophageal junction, which infiltrates the gastroesophageal junction and lower esophagus from below.
¶ Tumor staging was performed according to the eighth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual*.[17]
‖ The lymph-node status was recorded at randomization with the use of the interactive response technology system or the randomization and trial supply management system.
** Programmed death ligand 1 (PD-L1) expression (assessed according to the Tumor Area Positivity [TAP] score,[19] which is determined by visual aggregation and estimation of the area covered by PD-L1 positive tumor cells and tumor-associated immune cells relative to the total tumor area on the immunohistochemical slide) was measured by the VENTANA PD-L1 (SP263) CDx assay and recorded at randomization with the use of the interactive response technology system, randomization and trial supply management system, or an electronic case-report form or with data from an external vendor from samples collected on or before randomization.
†† Microsatellite instability was measured by a clinical trial assay based on FoundationOne CDx in a research use only capacity.

survival was 0.03, which was greater than the threshold for significance (P<0.0001) (Fig. 3A and Supplementary Results). A late separation between the groups in the Kaplan–Meier curves was observed for overall survival (Fig. 3A). The proportional-hazards assumption for the analysis of overall survival was assessed with a test of the interaction of time by treatment group and was not satisfied (Fig. S6). The results of a piecewise analysis showed that the hazard ratio for death in the durvalumab group as compared with the placebo group was 0.99 (95% CI, 0.70 to 1.39) for those at risk at the beginning of the 0-to-12-month interval, and 0.67 (95% CI, 0.50 to 0.90) among those still at risk at 12 months onward (Fig. 3A and Supplementary Results). The restricted mean survival time was 37.6 months (95% CI, 36.1 to 39.1) in the durvalumab group and 35.4 months (95% CI, 33.9 to 36.9) in the placebo group (difference in restricted mean survival time, 2.2 months [95% CI, 0.0 to 4.3]). The percentage of participants who had a pathological complete response was 19.2% (95% CI, 15.7 to 23.0) in the durvalumab group and 7.2% (95% CI, 5.0 to 9.9) in the placebo group (relative risk, computed with a log-binomial regression model with adjustment for stratification factors, 2.69 [95% CI, 1.86 to 3.90]) (Fig. 3B). The percentages of participants with missing data for pathological complete response are shown in Table S7.

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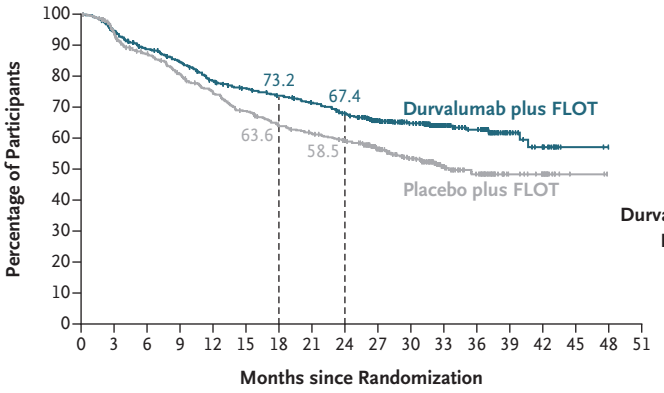

	No. of Participants with Event/ Total No. of Participants (%)	Median Event-free Survival (95% CI)
		mo
Durvalumab plus FLOT	167/474 (35.2)	NR (40.74–NR)
Placebo plus FLOT	218/474 (46.0)	32.8 (27.86–NR)

Stratified hazard ratio for event or death, 0.71 (95% CI, 0.58–0.86)
P<0.001 by stratified log-rank test

No. at Risk

Durvalumab plus FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0
Placebo plus FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0

Figure 1. Kaplan–Meier Estimates of Event-free Survival (Full Analysis Population).

The threshold of significance for this analysis was 0.0239. The analysis was based on blinded independent central review assessments, on local pathological testing (if it was clinically required), or both. The hazard ratio and corresponding confidence interval were estimated from a Cox proportional-hazards model, with adjustments for geographic region, clinical lymph-node status, and programmed death ligand 1 (PD-L1) expression. The confidence interval for the hazard ratio was calculated with the use of a profile likelihood approach. A hazard ratio of less than 1 favored durvalumab. A two-sided P value was calculated with a stratified log-rank test with adjustments for geographic region, clinical lymph-node status, and PD-L1 expression. At the data-cutoff date, in the event-free survival analysis, data from three participants (0.6%) in the durvalumab group and seven participants (1.5%) in the placebo group were censored at the randomization date because of a missing disease assessment before or after the start of neoadjuvant treatment (surgery was not attempted, and they did not die or have a non-RECIST progression); data from three participants (0.6%) and six participants (1.3%), respectively, were censored at the surgery date because of a missing adjuvant postsurgery baseline assessment; and data from eight participants (1.7%) and six participants (1.3%) who withdrew consent were censored at the last disease assessment available before withdrawal from the trial (Table S6). Tick marks indicate censored observations. CI denotes confidence interval, FLOT fluorouracil, leucovorin, oxaliplatin, and docetaxel, and NR not reached.

The percentages of participants with a pathological complete response across subgroups are shown in Figure S7.

Pathological staging of disease in participants in whom surgery was attempted (i.e., participants in whom surgery was successful as well as those in whom surgery was started but not completed because the surgeon deemed that it was no longer feasible to complete the surgery) is shown in Table S8. Among the participants in whom surgery was completed, 377 of 412 participants (91.5%) in the durvalumab group and 369 of 400 participants (92.3%) in the placebo group had R0 resection. Among these participants, in whom no evidence of disease at the postsurgery adjuvant baseline scan was observed (R0 resection population), disease-free survival at 24 months was 75.2% in the durvalumab group and 66.2% in the placebo group (hazard ratio for disease recurrence or death, 0.70 [95% CI, 0.53 to 0.93]; Fig. S8).

SAFETY

The safety analysis population comprised 475 participants in the durvalumab group and 469 participants in the placebo group. The median duration of exposure to the trial treatment is shown in Table S9. Adverse events of any grade occurred in 471 participants (99.2%) in the durvalumab group and in 463 participants (98.7%) in the placebo group (Table 2). Adverse events with a maximum grade of 3 or 4 occurred in 340 participants (71.6%) in the durvalumab group and in 334 participants (71.2%) in the placebo group; among these participants, 283 (59.6%) and 277 (59.1%), respectively, had adverse events that were possibly related to any component of the trial regimens (Table 2). A total of 24 participants (5.1%) in the durvalumab group and 20 participants (4.3%) in the placebo group had adverse events that led to death (Table 2). Immune-mediated adverse events occurred in 110 participants (23.2%) in the durvalumab group and in

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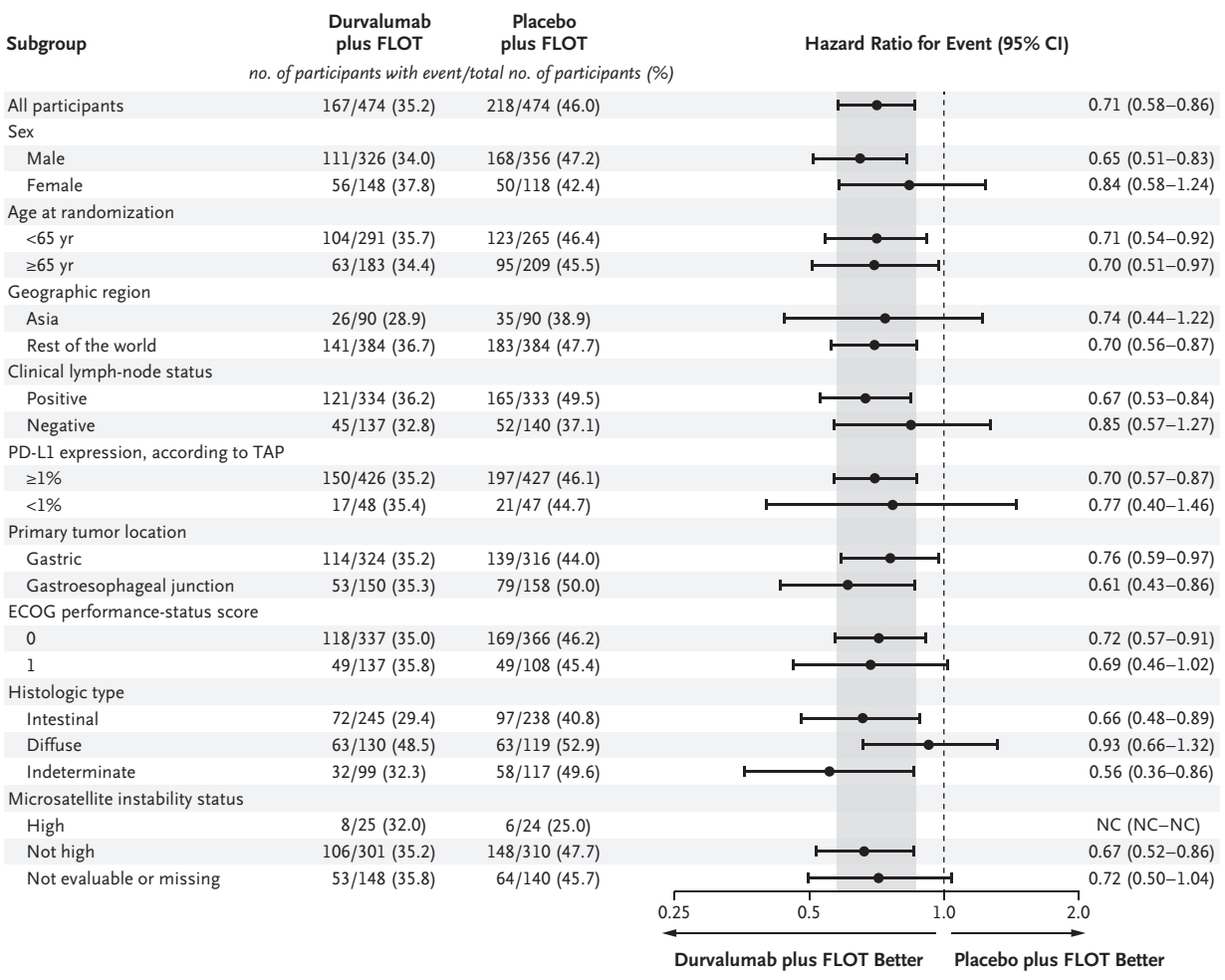

Figure 2. Event-free Survival in Participant Subgroups (Full Analysis Population).

Subgroups defined according to sex, age at randomization, geographic region, clinical lymph-node status, PD-L1 expression, tumor location, and Eastern Cooperative Oncology Group (ECOG) performance-status score were prespecified in the protocol. ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability. The analysis was performed with a Cox proportional-hazards model with treatment as the only covariate. A hazard ratio of less than 1 favored durvalumab. The confidence interval was calculated with the use of a profile likelihood approach. Because event-free survival, overall survival, and pathological complete response were the only end points that were part of the multiple testing procedure, the widths of the confidence intervals for other end points or subgroups have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The gray band represents the 95% confidence interval for the hazard ratio calculated for all participants. The analysis was based on blinded independent central review assessment, on local pathological testing (if clinically required), or both. The proportional-hazards assumption that included the interaction of time by treatment in general was tested and was satisfied for most event-free survival subgroups (see Fig. S5 in the Supplementary Appendix). PD-L1 expression was assessed according to the Tumor Area Positivity (TAP) score,[19] which is determined by visual aggregation and estimation of the area covered by PD-L1 positive tumor cells and tumor-associated immune cells relative to the total tumor area on the immunohistochemical slide. NC denotes not calculable.

34 participants (7.2%) in the placebo group (Table 2). Adverse events that led to surgery not being performed or to delayed surgery were rare across the groups: surgery was not performed because of adverse events in 3 participants (0.6%) in the durvalumab group and in 2 participants (0.4%) in the placebo group and was delayed because of adverse events in 11 (2.3%) and 12 (2.6%), respectively; Table 2). Adverse events that were possibly related to surgery are

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Figure 3. Kaplan–Meier Estimates of Overall Survival and Pathological Complete Response (Full Analysis Population).

Panel A shows Kaplan–Meier estimates of overall survival calculated with an unstratified Cox proportional-hazards model. A hazard ratio of less than 1 favors durvalumab plus FLOT. The threshold of significance for this analysis was P<0.0001. Tick marks indicate censored observations. The two-sided P value was calculated with a stratified log-rank test with adjustments for geographic region, clinical lymph-node status, and PD-L1 expression. Data from 9 participants (1.9%) in the durvalumab group and 17 participants (3.6%) in the placebo group were censored because the participants withdrew from the trial before death; the data were censored at the last date at which the participants were known to be alive (Table S6). Some of these participants were able to be followed for survival status after having withdrawn from the trial; if not, where applicable, survival status was checked from publicly available death registries. Panel B shows the percentages of participants in each group who had a pathological complete response. The threshold of significance for this analysis was P=0.001 . The analysis for relative risk was performed with a log-binomial regression model with adjustment for stratification factors, which included geographic region, clinical lymph-node status, and PD-L1 expression at randomization. For pathological complete response, 43 participants (9.1%) in the durvalumab group and 46 participants (9.7%) in the placebo group did not have surgery attempted and did not provide a surgical specimen for central assessment of pathological response and were classified as not having had a response; 19 participants (4.0%) and 28 participants (5.9%) in the durvalumab and placebo groups, respectively, had surgery attempted but had a missing sample; and 24 participants (5.1%) and 24 participants (5.1%) had surgery attempted but did not have evaluable samples and were classified as not having had a response (Table S7).

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listed according to the preferred term in the *Medical Dictionary for Regulatory Activities*, version 27.1, in Table S10.

The most common adverse events of any grade and the adverse events with a maximum grade of 3 or 4 are listed in Table 2. Diarrhea was the most common adverse event, occurring in 296 participants (62.3%) in the durvalumab group and in 270 participants (57.6%) in the placebo group (Table 2). Adverse events are listed according to the preferred term in Table S11.

DISCUSSION

The MATTERHORN trial showed significantly better event-free survival outcomes with perioperative durvalumab plus FLOT than with placebo plus FLOT among participants with resectable gastric or gastroesophageal junction adenocarcinoma. At 24 months, 67.4% of the participants in the durvalumab and 58.5% of those in the placebo group remained event-free, and the sustained separation of the Kaplan–Meier curves indicated durable benefit with durvalumab plus FLOT. The difference between the groups in overall survival has not reached statistical significance.

The FLOT4 trial showed better disease-free survival and overall survival outcomes with perioperative FLOT than with epirubicin and cisplatin plus either fluorouracil or capecitabine in resectable gastric and gastroesophageal junction cancers.[4] Furthermore, although preoperative chemoradiotherapy was associated with better survival outcomes in patients with potentially curable esophageal or esophagogastric junction cancer than surgery alone,[21] the TOPGEAR trial showed that perioperative chemotherapy plus neoadjuvant chemoradiotherapy did not lead to better overall survival outcomes than perioperative chemotherapy alone among patients with resectable gastric or gastroesophageal junction cancer,[22] and the ESOPEC trial showed better overall survival outcomes with perioperative FLOT plus surgery than with neoadjuvant chemoradiotherapy plus surgery among patients with resectable esophageal cancer.[23] These findings further support perioperative FLOT as the chemotherapy backbone of choice.

Outside Asia, perioperative FLOT plus surgery has become standard therapy in resectable gastric and gastroesophageal junction cancers,[4,5] whereas use of perioperative chemotherapy is increasing in Asia,[24-26] including alternative triplet regimens.[27] In Asia, studies have shown better efficacy with perioperative chemotherapy than with adjuvant chemotherapy alone.[27,28] Moreover, neoadjuvant chemotherapy is now recommended for selected patients with locally advanced gastric or gastroesophageal junction cancer in Asia.[29] Furthermore, in a Japanese population with gastric and gastroesophageal junction cancers, the safety and efficacy of perioperative FLOT were generally similar to those in the FLOT4 trial, which suggested feasibility of the use of this therapy in Asia.[4,26]

A key strength of the MATTERHORN trial was its global reach, which reflected the global population with gastric or gastroesophageal junction adenocarcinoma eligible for perioperative FLOT, including participants across Europe, the Americas, and East Asia with stage II to IVA disease. Of note, the median event-free survival in the placebo group of the MATTERHORN trial (32.8 months) was consistent with the median disease-free survival in the FLOT group of the FLOT4 trial (30 months).[4] Recent studies suggest that event-free survival is a good surrogate end point for overall survival in patients with gastric or gastroesophageal junction adenocarcinoma in the context of neoadjuvant therapy with or without adjuvant therapy.[30] In patients with metastatic gastric or gastroesophageal junction adenocarcinoma, PD-L1 expression and microsatellite instability status are established predictors of response to immunotherapy.[6,31] In this study of resectable disease, however, an analysis of these biomarkers showed no difference in benefit between durvalumab and placebo, a finding possibly due to the low prevalence of PD-L1–negative and microsatellite instability–high tumors in this unselected cohort.

The ATTRACTION-5 trial evaluated adjuvant nivolumab plus chemotherapy in patients with gastric or gastroesophageal junction cancer, and the results did not show longer relapse-free survival (the primary end point) with the intervention than with chemotherapy alone.[32] These data, together with results shown here, suggest that the greatest benefit may be derived from a treatment regimen that incorporates neoadjuvant and adjuvant therapy (i.e., an anti–PD-L1 therapy plus chemotherapy). The KEYNOTE-585 trial evaluated this perioperative approach, focusing primarily on cisplatin-based chemotherapy instead of FLOT

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Table 2. Adverse Events in the Safety Analysis Population.*

Adverse Event	Durvalumab plus FLOT (N=475)†	Placebo plus FLOT (N=469)	Total (N=944)
	number of participants (percent)		
Any grade	471 (99.2)	463 (98.7)	934 (98.9)
Possibly related to any trial treatment	453 (95.4)	444 (94.7)	897 (95.0)
Maximum grade 3 or 4 adverse event	340 (71.6)	334 (71.2)	674 (71.4)
Possibly related to any trial treatment	283 (59.6)	277 (59.1)	560 (59.3)
Serious adverse event	229 (48.2)	207 (44.1)	436 (46.2)
Adverse event leading to discontinuation of any trial regimen	142 (29.9)	107 (22.8)	249 (26.4)
Leading to discontinuation of durvalumab or placebo	48 (10.1)	30 (6.4)	78 (8.3)
Leading to discontinuation of any component of FLOT	121 (25.5)	95 (20.3)	216 (22.9)
Adverse event with outcome of death	24 (5.1)	20 (4.3)	44 (4.7)
Possibly related to durvalumab or placebo	3 (0.6)	1 (0.2)	4 (0.4)
Possibly related to FLOT	3 (0.6)	2 (0.4)	5 (0.5)
Immune-mediated adverse event of any grade‡	110 (23.2)	34 (7.2)	144 (15.3)
Maximum grade 3 or 4 immune-mediated adverse event	34 (7.2)	17 (3.6)	51 (5.4)
Serious immune-mediated adverse event, including events with outcome of death	23 (4.8)	13 (2.8)	36 (3.8)
Immune-mediated adverse event with outcome of death	2 (0.4)	0	2 (0.2)
Any adverse event leading to surgery not being performed	3 (0.6)	2 (0.4)	5 (0.5)
Any adverse event leading to a delay in surgery§	11 (2.3)	12 (2.6)	23 (2.4)
Any adverse event possibly related to surgery	182 (38.3)	173 (36.9)	355 (37.6)
Most common adverse events of any grade occurring in ≥30% of participants in either group			
Diarrhea	296 (62.3)	270 (57.6)	566 (60.0)
Nausea	241 (50.7)	237 (50.5)	478 (50.6)
Neutropenia	153 (32.2)	155 (33.0)	308 (32.6)
Alopecia	145 (30.5)	149 (31.8)	294 (31.1)
Decreased appetite	145 (30.5)	141 (30.1)	286 (30.3)
Fatigue	137 (28.8)	146 (31.1)	283 (30.0)
Anemia	119 (25.1)	147 (31.3)	266 (28.2)
Most common adverse events of maximum grade 3 or 4 occurring in ≥5% of participants in either group			
Neutropenia	101 (21.3)	104 (22.2)	205 (21.7)
Neutrophil count decreased	93 (19.6)	105 (22.4)	198 (21.0)
Diarrhea	30 (6.3)	28 (6.0)	58 (6.1)
White-cell count decreased	25 (5.3)	28 (6.0)	53 (5.6)
Anemia	24 (5.1)	24 (5.1)	48 (5.1)

* Included are adverse events reported during the overall treatment period that had an onset date on or after the first dose of investigational treatment, as well as adverse events that had an onset date before the first dose but that increased in severity on or after the first dose up to and including 90 days after the last dose or until initiation of the first subsequent anticancer therapy (excluding palliative radiotherapy), whichever occurred first.
† One participant in the placebo group received a single dose of durvalumab and was therefore included in the durvalumab group for the safety analysis.
‡ This category excludes infusion or hypersensitivity reactions.
§ A surgical delay was defined as surgery occurring more than 8 weeks (56 days) after the last dose of neoadjuvant treatment.

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in patients with resectable gastric or gastroesophageal junction cancer.[24] The trial showed better pathological complete response with pembrolizumab plus chemotherapy than with placebo plus chemotherapy but did not show a significant event-free survival benefit.[24] Thus, a FLOT chemotherapy backbone combined with immune checkpoint inhibitor therapy appears to be critical to the efficacy observed in the MATTERHORN trial.

The safety profile of perioperative durvalumab plus FLOT was consistent with the safety profiles for each individual agent, which indicates that this combination did not exacerbate the toxic effects. The incidence of adverse events with a maximum grade of 3 or 4 and of adverse events that led to death was similar in the two groups. A higher incidence of immune-mediated adverse events was reported in the durvalumab group than in the placebo group, a finding consistent with the durvalumab mechanism of action.[33] Moreover, combining durvalumab and FLOT did not prevent participants from receiving surgery or adjuvant treatment.

Trial limitations include the fact that the design did not include a separate evaluation of the neoadjuvant and adjuvant contributions; further investigation is warranted. Variability in surgical techniques and postoperative management and the absence of a mandated diagnostic laparoscopy may have affected outcomes despite centralized review of pathological results. In addition, the trial did not enroll participants from several countries and regions, such as China, that have a high incidence of these cancers, and Black patients were underrepresented. These factors may limit generalizability.[1] An analysis of overall survival after longer follow-up has occurred is warranted to determine whether the current numerical difference translates into a statistically significant benefit.

Perioperative durvalumab plus FLOT was associated with significantly better event-free survival outcomes than placebo plus FLOT. No new safety signals were observed. These findings support the use of perioperative durvalumab combined with FLOT as a potential first-line treatment for patients with resectable gastric or gastroesophageal junction adenocarcinoma.

Supported by AstraZeneca. Dr. Janjigian's work was supported by a Cancer Center Support grant (P30 CA008748, to the Memorial Sloan Kettering Cancer Center) from the National Cancer Institute of the National Institutes of Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in this trial and their caregivers, the trial site personnel, the members of the independent data monitoring committee, and Lauren Hogarth, M.Sc., and Claire Tinderholm, Ph.D., at CMC Connect, a division of IPG Health Medical Communications, for medical writing support (funded by AstraZeneca).

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