Clinical Trial Protocol

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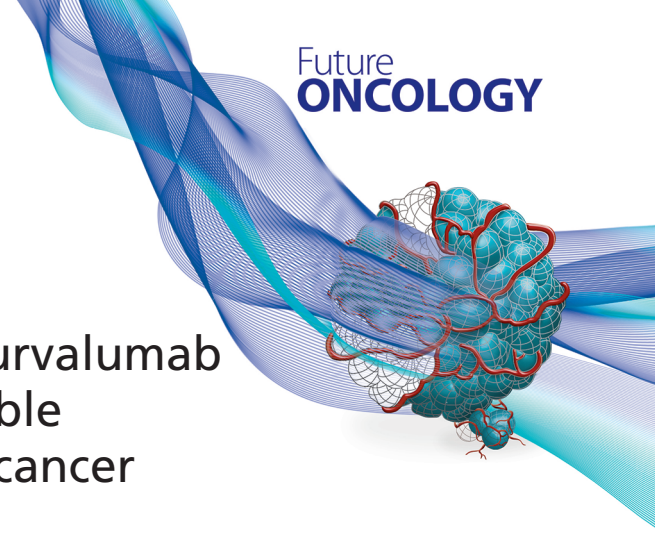

MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer

Yelena Y Janjigian*[1], Eric Van Cutsem[2], Kei Muro[3], Zev Wainberg[4], Salah-Eddin Al-Batran[5], Woo Jin Hyung[6], Daniela Molena[7], Michelle Marcovitz[8], Dario Ruscica[9], Scott H Robbins[10], Alejandra Negro[10] & Josep Tabernero[11]

[1]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[2]Department of Gastroenterology/Digestive Oncology, University Hospitals Leuven & KU Leuven, Leuven, 3000, Belgium
[3]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, 464-8681, Japan
[4]Department of Gastrointestinal Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90404, USA
[5]Institute of Clinical Cancer Research, Krankenhaus Nordwest, University Cancer Center, Frankfurt, 60488, Germany
[6]Department of Surgery, Yonsei University College of Medicine, Seoul, 03722, South Korea
[7]Esophageal Surgery Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[8]Statistics, AstraZeneca, Gaithersburg, MD 20878, USA
[9]Global Clinical Development, AstraZeneca, Cambridge, CB2 8PA, UK
[10]Global Clinical Development, AstraZeneca, Gaithersburg, MD 20878, USA
[11]Medical Oncology Department, Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, 08035, Spain
*Author for correspondence: Tel.: +1 646 497 9053; janjigiy@mskcc.org

Standard-of-care for resectable gastric/gastroesophageal junction cancer includes surgery and neoadjuvant-adjuvant 5-fluorouracil-leucovorin-oxaliplatin-docetaxel (FLOT) chemotherapy. Early-phase clinical studies support further clinical development of the immune checkpoint inhibitor (ICI); durvalumab, an anti-PD-L1 antibody, in patients with gastric/gastroesophageal junction cancer. Accumulating evidence indicates that ICIs combined with FLOT chemotherapy improve clinical outcomes in patients with advanced or metastatic cancer. We describe the rationale for and the design of MATTERHORN, a randomized, double-blind, placebo-controlled, phase III study investigating the efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable gastric/gastroesophageal junction cancer. The planned sample size is 900 patients, the primary end point is event-free survival and safety and tolerability will be evaluated.

Clinical trial registration: NCT04592913 (ClinicalTrials.gov)

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Stomach cancer, including gastric cancer/gastroesophageal junction cancer (GC/GEJC), is the fifth most common cancer type and the fourth leading cause of cancer-related deaths globally, accounting for approximately 1 million new cases and 769,000 deaths in 2020 [1]. Substantial geographic heterogeneity exists in the incidence of GC, with the highest incidence rates in Asia, whereas the incidence rates are generally low in North America (~75 vs 3% of all new cases, respectively) [1,2].

Complete surgical resection is the primary treatment option for patients with localized GC [3,4]. However, as the majority of patients with clinical stages II and III GC experience disease recurrence within 2 years following curative resection and neoadjuvant chemotherapy, multi-modality therapies including perioperative chemotherapy with a platinum and fluoropyrimidine combination, adjuvant chemotherapy or chemoradiotherapy are recommended for patients with resectable disease that is at least stage IB [3–5]. The standard-of-care for resectable GC/GEJC in

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Western countries consists of neoadjuvant-adjuvant 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) chemotherapy combined with surgery [4,6]. In east Asian countries, where patients often present with earlier-stage disease, the treatment approach generally includes surgery with extensive lymph node dissection and adjuvant chemotherapy, although neoadjuvant therapy is increasingly being used [7]. Although treatment advances have improved survival, the prognosis of patients with GC remains suboptimal, with a 5-year overall survival (OS) rate of 33% in the USA and 25% worldwide [8,9]. New treatment options are therefore required.

Immune checkpoint inhibitors (ICIs) have shown a significant benefit in survival when compared with standard therapies in prospective randomized clinical trials, for various tumor types [10–13]. The PD-1/PD-L1 pathway represents an adaptive immune-resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity [14]. PD-L1 expression is detected in approximately 50% of GCs and is associated with negative prognostic factors, including lymph node metastasis and depth of tumor invasion [14]. Immune checkpoint inhibition with an anti-PD-L1 antibody could therefore potentially enhance the anti-tumor immune response in patients with GC/GEJC [14].

The combination of docetaxel and 5-fluorouracil has been shown to promote T cell-dependent anti-tumor immunity by eliminating myeloid-derived suppressor cells *in vivo*, suggesting that the addition of an ICI to FLOT chemotherapy may enhance anti-tumor activity [15,16]. The combination of an ICI with platinum-based chemotherapy has shown significant anti-tumor activity in multiple other tumor types, and has become a standard-of-care first-line therapy for non-small-cell lung cancer (NSCLC) [17,18]. In patients with metastatic NSCLC and a PD-L1 tumor proportion score $\geq$1%, ICI monotherapy has replaced chemotherapy as first-line treatment [19]. Durvalumab, an anti-PD-L1 antibody, demonstrated significant clinical benefit when administered as a consolidation therapy after platinum-based chemoradiation therapy in patients with stage III NSCLC in the phase III PACIFIC study (NCT02125461): median progression-free survival (PFS) was 16.8 months (95% CI, 13.0–18.1) with durvalumab compared with 5.6 months (95% CI, 4.6–7.8) in the placebo group [20]. Recently updated results from the phase III CASPIAN study (NCT03043872) showed that durvalumab in combination with etoposide and cisplatin/carboplatin demonstrated a sustained OS benefit in patients with extensive-stage small-cell lung cancer (ES-SCLC) treated in the first-line setting, compared with etoposide and cisplatin/carboplatin therapy alone (hazard ratio [HR], 0.71, 95% CI, 0.60–0.86; nominal p = 0.0003) as well as a well-tolerated safety profile after >3 years of median follow-up [21]. In the phase III HIMALAYA study (NCT03298451) of patients receiving first-line treatment for unresectable hepatocellular carcinoma, a single, high priming dose of tremelimumab (anti-CTLA-4) plus durvalumab significantly improved OS versus sorafenib (HR, 0.78 [96% CI, 0.65–0.93]; p = 0.0035), and durvalumab monotherapy was noninferior to sorafenib for OS (HR, 0.86 [96% CI, 0.73–1.03]) [22].

Nivolumab, an anti-PD-1 antibody, in combination with chemotherapy demonstrated significant improvements in OS (HR, 0.71 [98.4% CI, 0.59–0.86]; p < 0.0001), PFS benefit (HR, 0.68 [98% CI, 0.56–0.81]; p < 0.0001), with an acceptable safety profile, versus chemotherapy alone in previously untreated patients with advanced GC/GEJC/esophageal adenocarcinoma and a PD-L1 combined positive score (CPS) $\geq$5 in the phase III CheckMate 649 study (NCT02872116) [23]. Nivolumab in combination with chemotherapy also provided significant improvement in OS in patients with PD-L1 CPS $\geq$1 (HR, 0.77 [99.3% CI, 0.64–0.92]; p < 0.0001) and all randomized patients versus chemotherapy (HR, 0.80 [99.3% CI, 0.68–0.94]; p = 0.0002) [23]. In the phase III CheckMate 577 study (NCT02743494), adjuvant nivolumab significantly prolonged disease-free survival (22.4 months [95% CI, 16.6–34.0]) compared with patients who received placebo (11.0 months [95% CI, 8.3–14.3]) [24]. The KEYNOTE-059 study (NCT02335411) has demonstrated additive activity of pembrolizumab, an anti-PD-1 antibody, plus chemotherapy versus pembrolizumab alone in patients with advanced GC/GEJC [25]. The objective response rate was 60.0% (95% CI, 39.0–79.0) in the pembrolizumab plus chemotherapy group versus 25.8% (95% Cl, 11.9–44.6) in the pembrolizumab-alone group in patients with previously untreated recurrent or metastatic GC/GEJC [25]. The phase III KEYNOTE-062 study (NCT02494583) demonstrated that pembrolizumab was noninferior to chemotherapy for OS with fewer grade $\geq$3 treatment-related adverse events (TRAEs) and that pembrolizumab plus chemotherapy was not superior to chemotherapy for OS or PFS as first-line therapy for patients with advanced GC/GEJC and PD-L1 CPS $\geq$1 [26].

An improved response to immunotherapies in the presence of chemotherapy supports the evaluation of durvalumab combined with FLOT for the treatment of patients with resectable GC/GEJC [17,18,23,25].

We present the methodology for MATTERHORN (Assessing Durvalumab and FLOT Chemotherapy in Resectable Gastric and Gastroesophageal Junction Cancer), a randomized, double-blind, placebo-controlled, phase III

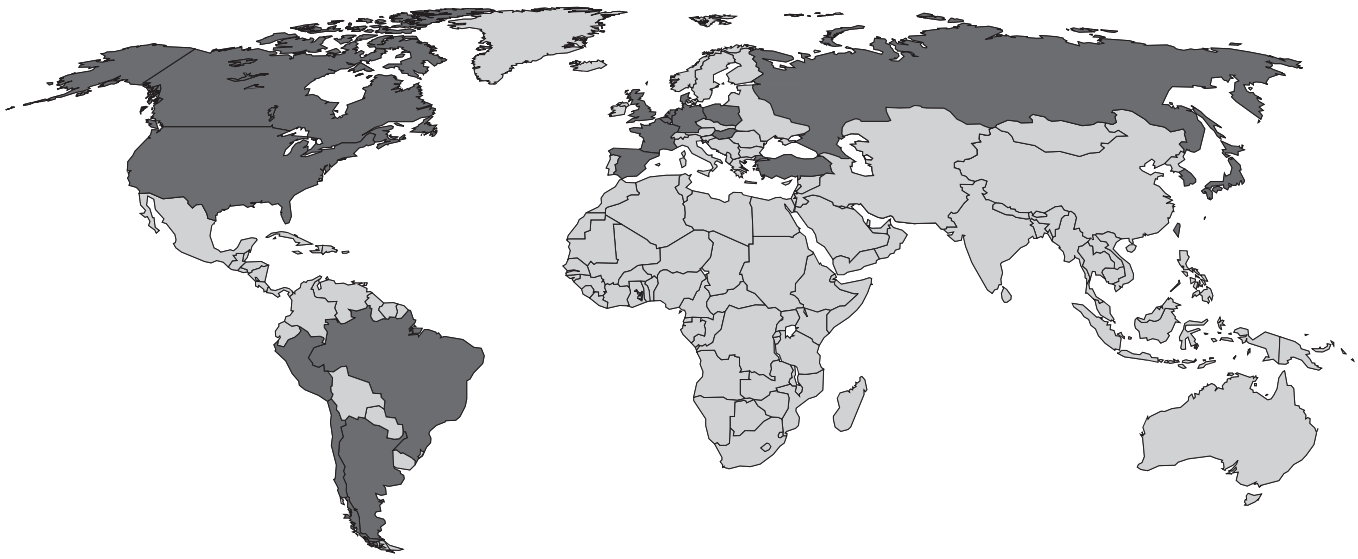

Figure 1. Planned study sites. There are currently 20 countries and regions participating in the MATTERHORN study.

study of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab in patients with resectable GC/GEJC (ClinicalTrials.gov; NCT04592913) [27]. This study is funded by AstraZeneca.

Background & rationale

Durvalumab is a human, immunoglobulin G1 monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1, resulting in enhanced effector T-cell function and tumor cell elimination [20,28]. Durvalumab has demonstrated favorable clinical activity and a manageable safety profile in multiple tumor types, including NSCLC [29], small-cell lung cancer [30] and urothelial carcinoma [31]. The clinical development of durvalumab in patients with resectable GC/GEJC is supported by preliminary data from two early-phase clinical studies in patients with metastatic or recurrent GC/GEJC [32,33].

In the phase II Study 1108 (NCT01693562), durvalumab monotherapy 10 mg/kg intravenously every 2 weeks (Q2W), administered for a maximum of 12 months, demonstrated a confirmed overall response rate (ORR) of 3.9% (n = 2) in a cohort of 51 patients with GC/GEJC [32]. Of those who responded to treatment, one patient with prior neoadjuvant fluorouracil/leucovorin/oxaliplatin showed a complete response with a duration of response of more than 9.7 months, and the other patient with prior trastuzumab/capecitabine/cisplatin, trastuzumab/MM-111/paclitaxel, and paclitaxel showed a partial response (PR) with a duration of response of more than 27.0 months [32]. Among the GC/GEJC patient cohort, 69 and 39% of patients had second-line or greater and third-line or greater prior therapies, respectively [32]. TRAEs were experienced by 56.9% of patients, and led to dose delays or interruptions in 7.8% of patients [32]. Nevertheless, there were no serious TRAEs or TRAEs leading to discontinuation or death [32]. In the phase Ib/II Study 21 (NCT02340975), durvalumab monotherapy (10 mg/kg Q2W) demonstrated a median PFS of 1.6 months and a median OS of 3.4 months in 24 pre-treated patients with metastatic or recurrent GC/GEJC [33]. Based on these early-phase studies in patients with metastatic or recurrent GC/GEJC and observations in other tumor types, durvalumab in combination with FLOT chemotherapy has the potential to improve clinical outcomes in patients with resectable GC/GEJC.

Design

Study design

MATTERHORN is a randomized, double-blind, placebo-controlled, multicenter, global phase III study to assess the efficacy and safety of neoadjuvant-adjuvant durvalumab in combination with FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable GC/GEJC. Countries with participating centers are shown in Figure 1. Eligible patients will be randomized in a 1:1 ratio to receive durvalumab 1500 mg or placebo every 4 weeks (Q4W) on day 1 plus FLOT every 2 weeks (Q2W) on days 1 and 15 for four cycles (two cycles neoadjuvant and two cycles adjuvant), followed by durvalumab 1500 mg or placebo on day 1 Q4W for 10

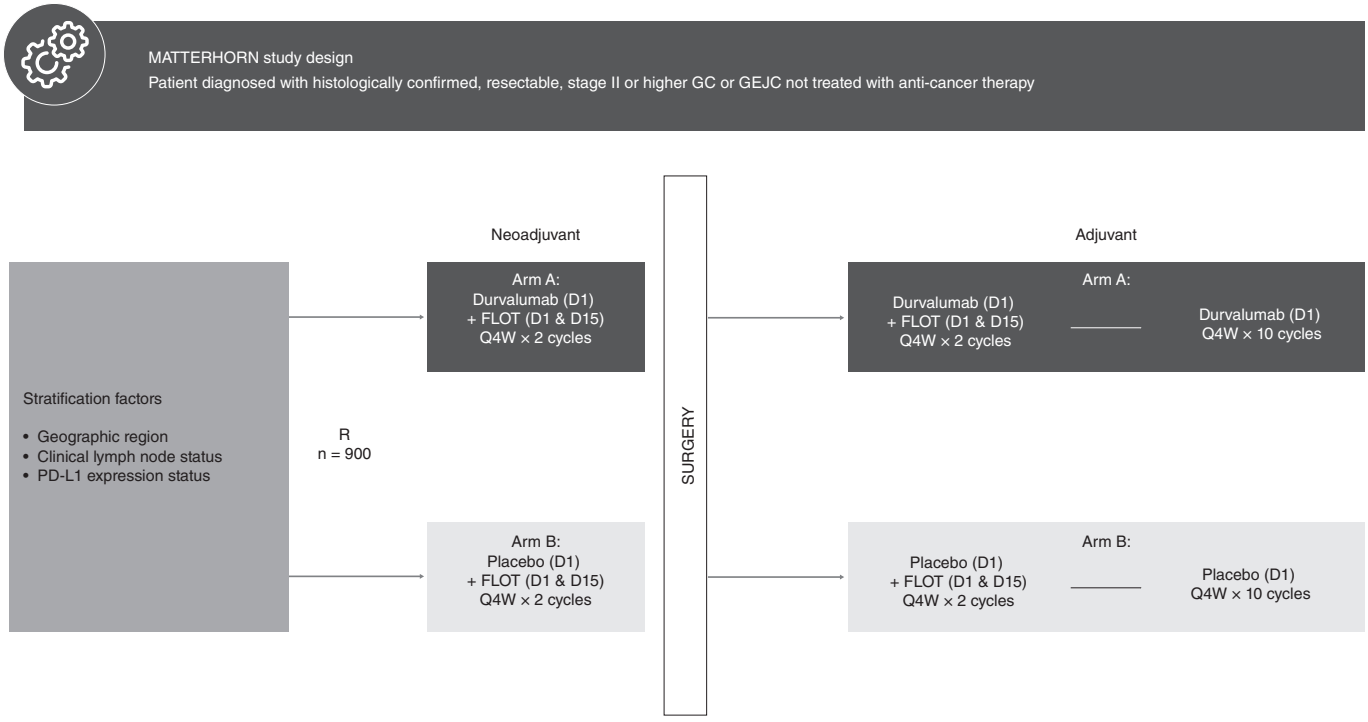

Figure 2. MATTERHORN study design. A schematic of the study design, population, stratification, and dosage information. Durvalumab was dosed at 1500 mg. FLOT comprised 5-fluorouracil 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2 and docetaxel 50 mg/m^2. D: Day; FLOT: 5-Fluorouracil + leucovorin + oxaliplatin + docetaxel; GC: Gastric cancer; GEJC: Gastroesophageal junction cancer; Q4W: Every 4 weeks; R: Randomization.

Table 1. MATTERHORN key eligibility criteria.

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years (≥20 years in Japan) • Histologically confirmed, resectable, stage ≥II GC or GEJC not treated with anti-cancer therapy • Complete surgical resection of the primary tumor must be achievable • WHO/Eastern Cooperative Oncology Group performance status of 0 or 1 • Adequate organ and marrow function • Availability of tumor sample prior to study entry	• Any prior immune-mediated therapy • Peritoneal dissemination or distant metastasis • (Adeno)squamous cell carcinoma, or gastrointestinal stromal tumor • Any concurrent chemotherapy, investigational product, biologic or hormonal therapy for cancer treatment • Contraindication to any of the study drugs

GC: Gastric cancer; GEJC: Gastroesophageal junction cancer.

additional cycles (Figure 2). Neoadjuvant therapy will begin following completion of screening and randomization, and patients should undergo resection surgery 4–8 weeks after the last dose of neoadjuvant therapy. Adjuvant therapy will begin 4–12 weeks post-surgery (based on the patient's recovery period). Treatment will continue until confirmed disease progression or recurrence, unacceptable toxicity, withdrawal of consent, non-compliance with treatment or trial procedures, another discontinuation criterion is met, or completion of 12 cycles of adjuvant durvalumab treatment.

Randomization will be performed centrally using an interactive trial management system. Patients will be stratified according to geographic region, clinical lymph node status and PD-L1 expression status. Patients will provide a tumor sample at screening to determine PD-L1 status for stratification. Durvalumab or placebo assignment will be masked to both patients and investigators.

After final analysis of this study, patients may roll over to another study for purposes of OS follow-up only.

Key eligibility criteria

Eligibility criteria are described in Table 1. Briefly, adults will be eligible if they have a histologically documented gastric or gastroesophageal junction adenocarcinoma with resectable disease, i.e., radical-surgery eligible; stage II or higher (>T2 N0–3 M0 or T0–4N1–3 M0) per American Joint Committee on Cancer 8th edition.

Planned sample size

Approximately 900 patients will be randomized at approximately 180 sites globally.

Planned study period

The first patient was enrolled into the study in November 2020, and the estimated date of study completion is February 2025.

Outcome measures/end points

The primary end point is event-free survival (EFS), defined as the time from randomization to the following, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 per blinded independent central review assessment and/or local pathology testing: progression that precludes surgery or requires non-protocol therapy; local or distant recurrence or progression of disease; or death due to any cause. EFS is considered an appropriate registrational end point in an early disease setting [34,35] and is also used as a primary end point in the ongoing phase III study of neoadjuvant-adjuvant pembrolizumab plus chemotherapy in GC/GEJC (NCT03221426). Key secondary end points include OS, defined as the length of time from randomization until death due to any cause, and the pathological complete response (pCR) rate, defined as the proportion of patients who have no residual viable tumor in the resected specimens as determined by pathology review. Safety and tolerability will be evaluated.

Study procedures

EFS will be assessed according to RECIST version 1.1 and/or local pathology testing. Patients will undergo baseline assessments for both the neoadjuvant treatment period and the adjuvant treatment period. On-study adjuvant tumor assessments will occur regularly. Pathology reviews will be conducted to determine staging after surgery, EFS and pCR.

Safety data will be collected and recorded throughout the study until the follow-up period is complete. Adverse events will be graded using the revised National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. An independent data monitoring committee will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study and the integrity of the study, and to oversee the planned interim efficacy analyses.

Statistics

The primary objective of the study is to assess the efficacy of durvalumab plus FLOT compared with placebo plus FLOT in terms of EFS according to RECIST version 1.1 per blinded independent central review assessment and/or locally by pathology testing in patients with resectable GC/GEJC. Efficacy data will be assessed in the full analysis set, which will include all randomized patients. The primary end point, EFS and the key secondary end point of OS, will be summarized using Kaplan–Meier curves plotted by treatment arm. EFS and OS will be analyzed using a stratified log-rank test adjusting for the stratification factors of geographic region, clinical lymph node status and PD-L1 expression status. The other key secondary end point, pCR, will be analyzed using a stratified Cochran–Mantel–Haenszel test, adjusting for the same stratification factors as EFS and OS. Safety data will be summarized descriptively from the safety analysis set, which will include all randomized patients who have received at least one dose of the study medication.

Conclusion

Although treatment advances have improved survival for patients with resectable GC/GEJC, the 5-year OS rate remains suboptimal and new treatment options are required. Durvalumab, an immune checkpoint inhibitor, has demonstrated encouraging anti-tumor activity in early-phase clinical studies in patients with metastatic or recurrent GC/GEJC. The anti-tumor activity of durvalumab in combination with FLOT cytotoxic chemotherapy in patients with resectable GC/GEJC may improve patient outcomes. Here, we have described the methodology of the MATTERHORN study, which will assess the efficacy and safety of perioperative (neoadjuvant-adjuvant) durvalumab in combination with FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable GC/GEJC. The results of this study will help define the role of neoadjuvant-adjuvant immune checkpoint inhibitors in combination with chemotherapy for this population.

Executive summary

- Patients with resectable gastric cancer/gastroesophageal junction cancer (GC/GEJC) have a poor prognosis, and standard-of-care surgery plus neoadjuvant-adjuvant chemotherapy offers limited survival.

Background & rationale

- Accumulating evidence indicates that combining immunotherapy with standard-of-care chemotherapy can improve clinical outcomes in patients with advanced and/or metastatic cancer.
- Data from two early-phase clinical studies of durvalumab in patients with metastatic or recurrent GC/GEJC support further investigation into the use of neoadjuvant-adjuvant durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy in patients with resectable GC/GEJC.

MATTERHORN study design & eligibility criteria

- MATTERHORN is a randomized, double-blind, placebo-controlled, phase III study that aims to evaluate the efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy, followed by adjuvant durvalumab monotherapy compared with placebo plus chemotherapy in patients with resectable GC/GEJC.
- An estimated 900 patients with histologically documented, resectable, stage II or higher GC/GEJC not previously treated with anti-cancer therapy will be enrolled.
- Eligible patients will be randomly assigned 1:1 to receive neoadjuvant-adjuvant durvalumab or placebo in combination with FLOT chemotherapy, followed by adjuvant durvalumab or placebo monotherapy.

Outcomes

- The primary end point is event-free survival; secondary end points include overall survival and the pathological complete response rate.
- Safety and tolerability will be evaluated.

Conclusion

- The results of MATTERHORN will help define the role of neoadjuvant-adjuvant durvalumab plus FLOT chemotherapy as a treatment option for patients with resectable GC/GEJC.

Author contributions

All authors contributed to the conception or design of the study. All authors critically reviewed the manuscript and approved the final version for submission.

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Financial & competing interests disclosure

This study is sponsored by AstraZeneca. Y Janjigian has stock or ownership interest in RGENIX; has a consulting or advisory role with AstraZeneca, Basilea Pharmaceutica, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Imugene, Merck Serono, Merck, Michael J. Hennessy Associates, Paradigm Medical Communications, Pfizer, RGENIX, Seagen and Zymeworks Inc.; and has received research funding from Bayer, Bristol Myers Squibb, Cycle for Survival, Department of Defense, Eli Lilly, Fred's Team, Genentech/Roche, Merck, NCI and RGENIX. E Van Cutsem has received research funding from Amgen (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Lilly (Inst), Merck Serono (Inst), Novartis (Inst), Roche (Inst), and Sanofi (Inst). K Muro has received personal fees from AstraZeneca during the conduct of the study; grants from Solasia Pharma, Merck Serono, Daiichi Sankyo, Parexel International, Pfizer, and MSD; grants and personal fees from Amgen, Ono, Sanofi, Taiho, and AstraZeneca; and personal fees from Chugai, Takeda, Eli Lilly, Bristol Myers Squibb and Bayer, outside the submitted work. Z Wainberg has served as a consultant or an advisor for Array BioPharma, AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, Five Prime Therapeutics, Genentech, Lilly, Merck, Merck KGaA, and Novartis; has received research funding from Five Prime Therapeutics (Inst), Merck (Inst), Novartis (Inst), Pfizer (Inst), Plexxikon (Inst); and has received travel, accommodations and expenses from Genentech. S Al-Batran has served as an advisor for Lilly, Bristol Myers Squibb, MacroGenics, Immutep, and MSD Sharp & Dohme; as a speaker for Bristol Myers Squibb, Lilly, AIO Studien gGmbH, and MCI Deutschland GmbH; and as CEO/founder of the Institute of Clinical Cancer Research IKF at Northwest Hospital; and has received research grants from Sanofi, Roche, Celgene, Vifor, Medac, Hospira, Lilly, Eurozyto, Immutep, Ipsen, Bristol Myers Squibb, MSD Sharp & Dohme, AstraZeneca, German Cancer Aid (Krebshilfe), German Research Foundation, and the Federal Ministry of Education and Research. WJ Hyung is an employee in a leadership role and shareholder of Hutom; has served as a consultant or advisor for with Ethicon; and has received research funding from Medtronic and GC Pharma. D Molena reports participation on a steering committee with AstraZeneca, during the conduct of the study; and has received other travel reimbursement from Intuitive and consultant fees from UroGen, Johnson & Johnson, and Boston Scientific, outside the submitted work. M Marcovitz, D Ruscica, SH Robbins and A Negro are employees and shareholders of AstraZeneca. J Tabernero reports personal financial interest

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Ethical conduct of research

The study protocol was approved by the appropriate ethics committee or institutional review board at each participating center. The study will be conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. In addition, all participants will provide written informed, consent for the inclusion of their medical and treatment history within this work.

Data sharing statement

Data underlying the methodology described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Open access

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