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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All study data were captured in InForm version 4.6 (Oracle).
Data analysis	SAS version 9.4 (SAS Institute) was used for all statistical analyses. Power and interim analysis calculations were performed using the gsDesign R package version 3.0.1.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (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: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. 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 US and EU or after product development is

discontinued; an exception will be made for this ongoing trial such that data will be made available for request after the protocol-specified primary endpoint analyses have been reported. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to a SAS portal so that the requestor can perform the proposed analyses.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Approximately 692 participants will be randomly allocated in a 1:1 ratio between the pembrolizumab and placebo arms. This calculation was based on the following assumptions: (1) the enrollment period is 28 months and the ramp-up period of enrollment is 6 months; (2) the duration of PFS and OS follow exponential distribution; (3) median PFS is 6.7 months in the control group and the true HR is 0.7; (4) median OS is 13.8 months in the control group and the true HR ratio is 0.75 [Bang, Y. J., et al 2010]
Data exclusions	No data from the specified efficacy and as-treated populations were excluded from analysis.
Replication	This is a randomized clinical trial of participants with HER2-positive gastric or gastroesophageal adenocarcinoma and it is therefore not possible to replicate the data.
Randomization	Participants are randomly allocated in a 1:1 ratio to receive either pembrolizumab or placebo by means of an integrated interactive voice-response and Web-response system. Randomization is stratified by geographic region (Australia/Europe/Israel/North America vs Asia vs rest of world), PD-L1 combined positive score (≥1 vs <1), and investigator's choice of chemotherapy (5-fluorouracil plus cisplatin vs capecitabine plus oxaliplatin).
Blinding	This is a double-blind trial where the investigator, participant, and sponsor were all blinded to treatment assignment.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Key eligibility criteria include age 18 years or older; previously untreated, unresectable or metastatic, histologically or cytologically confirmed adenocarcinoma of the stomach or gastroesophageal junction that is HER2-positive (either immunohistochemistry [IHC] 3+ or IHC 2+ with positive in situ hybridization or fluorescence in situ hybridization); measurable disease per RECIST, version 1.1 as assessed by the investigator; have ECOG performance-status score of 0 or 12; have life expectancy of more than 6 months; have adequate organ function; and have provided a tumour sample adequate for assessment of PD-L1 and MSI status. Extended data table 2 summarizes the baseline demographics and disease characteristics for the efficacy and intention-to-treat populations.
Recruitment	Investigators at 168 medical centres in Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan,

Recruitment	New Zealand, Poland, Russia, South Korea, Spain, Turkey, the United Kingdom, and the United States recruit participants according the full eligibility criteria outlined in the study protocol without bias
Ethics oversight	The study protocol and all amendments were approved by the appropriate ethics body at each participating study centre, the names of which are found in the Supplementary Information.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov, NCT03615326
Study protocol	The protocol is available as part of the Supplemental Information
Data collection	Data were collected at 168 medical centres in Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Turkey, the United Kingdom, and the United States (Supplementary Information). This first interim analysis included the 434 participants randomly allocated to treatment between October 5, 2018, and the data cutoff date of June 17, 2020.
Outcomes	Tumour imaging by computed tomography (preferred) or magnetic resonance imaging is scheduled for week 6 and every 6 weeks thereafter. Response to treatment is assessed according to RECIST, version 1.1, by blinded independent central review (BICR). Adverse events and laboratory abnormalities are collected regularly during study treatment and for up to 30 days thereafter (up to 90 days for serious adverse events), classified according to the Medical Dictionary for Regulatory Affairs, version 23.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Following treatment discontinuation, participants are assessed for survival every 12 weeks. The protocol-specified dual primary endpoints are progression-free survival (i.e., time from randomization to disease progression assessed according to RECIST v1.1 by BICR or death, whichever occurred first) and overall survival (i.e., the time from randomization to death) and the secondary efficacy endpoints are objective response rate (i.e., percentage of participants with a best overall response of complete or partial response assessed according to RECIST v1.1 by BICR) and duration of response (i.e., time from first assessment of complete or partial response to disease progression assessed per RECIST v1.1 by BICR or death, whichever occurred first); these standard endpoints in oncology clinical trials are accepted by global regulatory authorities. Per the statistical analysis plan outlined in the protocol, only objective response rate and duration of response were assessed at the first interim analysis reported in our article.