nature portfolio

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Reporting Summary

Nature Portfolio 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 Portfolio 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	no commercial, open source and custum code
Data analysis	*Provide a description of all commercial, open source and custom code used to analyse the data in this study, specifying the version used OR state that no software was used.*

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The minimum datasets necessary to interpret this research have been provided within the article and supplementary data file. ctDNA results are available at https://datadryad.org/stash/share/9gJRvMke6AE0V4IWHc9Gt-nFBYhntTLzXTImefQIdmg (doi:10.5061/dryad.fn2z34v47). ctDNA sequencing data are available at the FCCD under restricted access for ethical and privacy concerns. Applicants may also directly contact the corresponding author (DT).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex was collected based on self-reporting and analyzed as prognostic marker of survival
Population characteristics	Sex, age and ECOG PS were analyzed
Recruitment	Patients were included and randomized in this prospective phase II trial
Ethics oversight	Comité de Protection des Personnes Nord-Ouest II, number 2018-002014-13 on April 16, 2019

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

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	Median PFS with FOLFIRI as a second-line chemotherapy in gastric/GEJ adenocarcinoma is between 2 and 4 months. Given this and using the binomial exact method to calculate sample size, the hypotheses were H0: 50% of patients alive and without progression at 4 months was not acceptable and H1: 70% of patients alive and without progression at 4 months was expected. With a risk α of 5%, a power of 85% and according to the binomial exact method, 44 evaluable patients were needed by arm. Assuming 5% of non-evaluable or lost to follow-up patients, 47 patients were included by arm.
Data exclusions	No data was excluded.
Replication	ctDNA quantification were replicated but the first analysis used a triplex assay to target two methylated cancer-specific genes (MSC Antisense RNA 1 (MSC-AS1) called « MSC » and (Potassium Voltage-Gated Channel Subfamily A Member 3 (KCNA3)) as well as a methylation-insensitive target on the albumin (ALB) gene used as the reference (assay called Triplex MSC/KCNA3/ALB in the manuscript). In the second step, for the negative or weakly positive samples, a new analysis was carried out, this time targeting the methylation of a sequence of the Zinc Finger Protein 790 Antisense RNA 1 (ZNF790-AS1) (assay referred to as Duplex ZNF790/ALB).
Randomization	Randomisation was carried out using the minimisation technique according to a 1:1 ratio to receive FOLFIRI Durvalumab or FOLFIRI Durvalumab, Tremelimumab and stratified on centre and duration of disease control during first-line chemotherapy (no disease control versus < 3 months versus ≥ 3 months).
Blinding	Open-label trial.

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
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

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

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	NCT03959293
Study protocol	Provided as supplementary data
Data collection	Between August 27, 2020 and June 4, 2021, 96 patients in 37 centres were randomised. Blood samples were prospectively collected before the first cycle at baseline (C0) and at 4 weeks just before the third cycle of treatment (C3). Tubes were centrifuged for 20 minutes at 1,600g, and plasma was transferred into cryotubes and stored at -80°C until ctDNA analysis.
Outcomes	We assessed the value of adding ctDNA to known prognostic factors for predicting PFS and OS in patients with advanced gastric/GEJ adenocarcinoma. Analyses were conducted on the modified intention-to-treat population (mITT population, defined as all patients who received at least one treatment dose in the study regardless of their eligibility criteria). The primary endpoint was the relationship between baseline ctDNA levels and PFS at 4 months based on RECIST 1.1 criteria as evaluated by the investigator. PFS was defined as the time from randomization to disease progression or death from any cause. Alive patients without progression were censored on the date of the last news.