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	Study data were collected and managed using REDCap electronic data capture tools (Version 14.6.7) hosted at the Walter and Eliza Hall Institute.
Data analysis	All statistical analyses were performed using R version 3.6.1 (R Core Team, Vienna, Austria) and SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC).

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

Qualified external researchers may request access to anonymized individual patient-level clinical data based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Data requests should be sent to WEHI (the sponsor) study chair at tie.j@wehi.edu.au.

Approval of such requests is at WEHI and the trial steering committee's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data to ensure analyses performed on the data are in line with the ethically approved study protocol. We will attempt to respond to data requests within 2 months, but this timeframe may vary depending on the requesters availability to respond to comments. Once approved, a data transfer agreement will be required prior to any data transfer.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Aggregated sex data reported in baseline characteristics table
Reporting on race, ethnicity, or other socially relevant groupings	No race/ethnicity or socially relevant groupings were collected in this study
Population characteristics	Patients with curatively resected stage II colon cancer who have not received prior chemotherapy or radiation. Other population characteristics are reported in Table 1.
Recruitment	Patients with stage II colon cancer were recruited from clinics at 23 participating institutions in Australia. These participating sites were selected based on factors such as patient population availability and investigator expertise. Patients were recruited and enrolled at the discretion of the investigator based on their clinical judgment and patient's ability to comply with study procedures. All ctDNA testing was performed centrally in a single lab. Attempts were made to limit selection bias through study design (e.g. no upper age limit, allowing both single agent fluoropyrimidine and oxaliplatin based doublet to be used at clinician's discretion) and site selection (including both metropolitan and regional sites) to create a representative population of patients with stage II colon cancer who are fit for adjuvant chemotherapy.
Ethics oversight	Melbourne Health Human ethics committees is the lead IRB approving the master protocol. IRB from all of the participating centers also approved the protocol

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	The overall sample size was developed to ensure a minimum of 30 patients would yield a ctDNA-positive result in the ctDNA-guided arm and an acceptable non-inferiority margin for 2-year recurrence-free survival of 8.5%, to exclude the largest absolute benefit that could be derived from adjuvant oxaliplatin-based chemotherapy for high-risk stage II patients. A total sample size of 450 patients, provides 80% power to demonstrate non-inferiority between the two study arms, assuming a type-I error of 5%, 2-year recurrence-free survival with standard management of 84% and ctDNA-guided management of 85%, and allowing 10% drop-out rate.
Data exclusions	Patients who withdrew consent, who did not have both week 4 and 7 blood collections, or found to have stage IV disease post enrolment were excluded
Replication	Replication is not applicable to a clinical trial as this study is conducted in human participants
Randomization	Patients were randomized in a 2:1 ratio to be managed according to ctDNA results (ctDNA-guided management) or to be managed by the treating clinician according to standard clinico-pathologic criteria (standard management). Individual patients were assigned to study arms using block randomization stratified by the participating center location (regional or metropolitan) and T stage (T3 or T4).
Blinding	Not blinded to the study arm given one arm will receive ctDNA results and the other arm not.

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
☒	☐ Plants

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	Australian New Zealand Clinical Trials Registry ACTRN12615000381583
Study protocol	Can be accessed via the primary NEJM publication
Data collection	Data was collected at 23 participating hospitals and clinics in Australia, between August 10, 2015, and January 17, 2024. Investigators and study coordinators at the clinical trial sites collected and recorded data into EDC system.
Outcomes	The primary efficacy endpoint was the recurrence-free survival rate at 2 years. This analysis focuses on the long-term survival outcomes according to management arm, post-op ctDNA status, T stage or MMR status. The analysed outcomes included recurrence free interval (RFI), recurrence free survival (RFS), disease specific survival (DSS) and overall survival (OS). RFI time was calculated from the date of randomization to the date of recurrence confirmation or the last date at which the patient was known to be free of disease (censoring time). Recurrence-free survival time was calculated from the date of randomization to the date of recurrence confirmation or death from any cause (whichever occurred earlier), or the last date at which the patient was known to be free of disease (censoring time). OS was measured from the date of randomisation until death from any cause. DSS time was measured from the date of randomisation until disease-specific death date or the last date at which patients was known to be alive.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*