Addition of irinotecan to chemoradiotherapy as preoperative treatment for locally advanced rectal cancer (ARISTOTLE): a multicentre, open-label, phase 3, randomised controlled trial

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Summary

Background Locally advanced rectal cancer is routinely treated with neoadjuvant radiotherapy. Concomitant systemic anticancer therapy with standard fluoropyrimidines has not generally improved outcomes. Small studies reported high pathological complete response rates and acceptable toxicity using irinotecan and fluoropyrimidine chemoradiation. We aimed to explore the effect of the addition of concomitant irinotecan to standard-of-care chemoradiotherapy in patients with locally advanced rectal cancer.

Methods ARISTOTLE is a multicentre, open-label, parallel-design, phase 3, randomised controlled trial conducted at 75 UK hospital sites treating patients with rectal cancer. Patients were eligible if they were aged at least 18 years with MRI-defined, locally advanced rectal cancer threatening or involving resection margins without metastases. Patients were randomly assigned (1:1) to preoperative radiotherapy 45 Gy in 25 daily fractions, combined with either oral capecitabine 900 mg/m² alone twice daily on weekdays (standard-of-care group) or oral capecitabine 650 mg/m² twice daily on weekdays plus intravenous irinotecan 60 mg/m² once weekly in weeks 1–4 (irinotecan group). Randomisation was done centrally, with allocation concealed to investigators; masking of patients and treating clinicians was not feasible. Stratification was by radiotherapy centre, mesorectal fascia involvement, and presence or absence of equivocal metastatic disease. The primary endpoint was disease-free survival, with analysis done on a modified intention-to-treat basis (ie, all eligible patients who were randomly assigned to treatment). Safety analyses were conducted in all patients who started protocol treatment (as-treated population). For time-to-event endpoints, patients without an event were censored at the date they were last known to be alive; missing radiological and pathological response assessments were classified as non-response. The study is registered with EudraCT, 2008-005782-59, and is complete.

Findings Between Oct 25, 2011, and July 5, 2018, 589 patients were randomly assigned to treatment; after exclusions, 564 were included in the modified intention-to-treat population (284 in the standard-of-care group and 280 in the irinotecan group). 370 (66%) patients were male, 194 (34%) were female, and median age was 61 years (IQR 54–68); ethnicity data were not collected. Staging in both groups was similar: 223 (79%) patients in the standard-of-care group and 212 (76%) in the irinotecan group had mrT3 tumours; 44 (15%) and 45 (16%) had mrT4 tumours, respectively. Patients in the irinotecan group were less likely to receive 45 Gy radiotherapy than in the standard-of-care group (208 [75%] of 276 *vs* 251 [89%] of 283) or at least 90% of the planned capecitabine dose (187 [68%] of 276 *vs* 253 [89%] of 283). With a median follow-up was 78 months (95% CI 75–86), 36-month disease-free survival was 68% (95% CI 63–73) in the irinotecan group versus 67% (61–72) in the standard-of-care group (hazard ratio 0·91 [95% CI 0·68–1·23]; p=0·54). Deaths occurred in 88 (31%) patients in the irinotecan group and 92 (32%) in the standard-of-care group; rectal cancer was the leading cause, occurring in 59 (67%) patients in the irinotecan group and 67 (73%) in the standard-of-care group. There were five deaths related to protocol treatment: three in the irinotecan group (two had a thromboembolic event and one had multiorgan failure plus sepsis) and two in the standard-of-care group (one cardiac arrest and one febrile neutropenia). Grade 3 or worse were more frequent in patients receiving irinotecan than those receiving standard of care (215 [78%] *vs* 148 [52%]), including haematological investigations (235 [85%] *vs* 109 [39%]) and gastrointestinal events (57 [21%] *vs* 35 [12%]), notably diarrhoea (38 [14%] *vs* ten [4%]), lymphocyte count decreased (181 [66%] *vs* 100 [35%]), and neutrophil count decreased (27 [10%] *vs* three [1%]).

Interpretation For MRI-defined, high-risk, locally advanced rectal cancer, the addition of irinotecan to standard of care did not improve outcomes and should not be used in combination with radiotherapy plus capecitabine.

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Introduction

For locally advanced, non-metastatic rectal cancer, a meta-analysis of more than 8000 patients in 19 trials showed improved local control using preoperative radiotherapy.[1] The routine use of pelvic MRI to assess the circumferential resection margin of the cancer predicts disease-free survival and local recurrence. Pelvic MRI can define the disease as either unresectable or borderline resectable, due to the proximity of tumour to the mesorectal fascia, and thus stratify patients into risk groups for which neoadjuvant strategies can be selected. MRI is an accepted standard preoperative staging investigation of choice for rectal cancer.[2]

Phase 3, randomised controlled trials (RCTs) showed that preoperative concurrent chemoradiation significantly increases the histopathological complete response rate and local control in resectable stage II and III rectal cancer compared with long-course radiotherapy alone.[3–5] Together, these studies defined concurrent fluoropyrimidine preoperative chemoradiotherapy as a standard of care for T3 or T4 N+ rectal cancer. However, there remains an important need to further improve local control and reduce distant failure in patients at higher risk of relapse. Increasingly, international practice and clinical trials have focused on the possibilities for non-operative management of patients with rectal cancer, with a focus on clinical complete response rates. Although the ARISTOTLE trial was developed and delivered in the era preceding this focus on non-operative management, there is interest in strategies that influence histopathological complete response rates as proof of concept for improved rates of non-operative management. Notably, two phase 3 studies published in 2021 have informed clinical practice by showing that a total neoadjuvant therapy approach in which additional systemic therapy given after chemoradiotherapy (RAPIDO)[6] or before chemoradiotherapy (PRODIGE 23)[7] improved histopathological complete response rates and disease-free survival. Of note, PRODIGE 23 added the drug irinotecan as a component of the mFOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil) as induction chemotherapy but did not deliver irinotecan and chemoradiotherapy concurrently. Phase 2, mainly single-arm, trials using doublet concurrent chemotherapy agents reported higher histopathological complete response rates than achieved using fluoropyrimidine chemoradiotherapy with acceptable toxicity.[8] Irinotecan is a well established

Research in context

Evidence before this study

MRI-defined, locally advanced rectal cancer carries a significant risk of distant and local relapse. Evidence within the past 20 years has driven clinical practice towards more prolonged, multimodal therapy with combinations of additional systemic chemotherapy before or after radiotherapy. On April 5, 2026, we searched MEDLINE, Embase, Cochrane Library, and Google Scholar for randomised controlled trials reporting between Jan 1, 2000, and Feb 28, 2026, including the terms "rectal cancer" AND "neoadjuvant" AND "irinotecan" AND "clinical trial" AND "randomised". Our search, restricted to the English language, revealed 87 papers, 20 abstracts, and 28 registered clinical trials. On review, two more papers were identified. 24 of the trials recruited a total of 1298 patients but were all single-arm, non-randomised studies. We found four randomised controlled trials: three phase 2 trials that all indicated a non-significant benefit from the addition of irinotecan in a variety of approaches; and one phase 3 trial of an irinotecan-based approach that demonstrated an improvement in complete response rate, which was the primary outcome measure, but no improvement in disease-free survival or overall survival. Irinotecan has efficacy as a single agent or in combination with a fluoropyrimidine or anti-EGFR monoclonal antibody. It failed to show significant benefit in the adjuvant setting after resection of colorectal cancer. However, early data combining irinotecan with a fluoropyrimidine and radiotherapy showed acceptable toxicity and enhanced tumour response rates, justifying the ARISTOTLE trial.

Added value of this study

The ARISTOTLE phase 3 randomised controlled trial was a study recruiting patients with MRI-staged and MRI-defined, locally advanced rectal cancer, with central pathology review and a radiotherapy quality assurance programme to ensure delivery of a standardised radiotherapy outlining and planning protocol. To the best of our knowledge, this is the largest phase 3 randomised controlled trial in this setting, with 564 patients enrolled, and remains the only study to date to have prespecified disease-free survival as the primary outcome measure. Mature results indicate that irinotecan does not improve disease-free survival or complete response rate but adds additional toxicity.

Implications of all the available evidence

Irinotecan delivered concomitantly with neoadjuvant chemoradiotherapy for locally advanced rectal cancer does not improve disease-free survival and should not be used in this clinical setting. Contrary to the findings of one randomised controlled trial (CinClare), we found no evidence for an improvement in pathological complete response rate when irinotecan is added to standard neoadjuvant chemoradiotherapy in patients with MRI-defined, locally advanced rectal cancer.

chemotherapy agent with high activity in advanced colorectal cancer. Preclinical and early clinical data showed that irinotecan can enhance the radiosensitivity of rectal cancer, facilitated by intratumoural topoisomerase levels.[9,10] When the current trial was designed, several early phase studies had examined the addition of irinotecan to fluoropyrimidine chemoradiotherapy as neoadjuvant treatment for locally advanced rectal cancer with promising histopathological complete response rates and acceptable toxicity.[11–19]

In our randomised, phase 3 ARISTOTLE trial, we aimed to show the benefit of adding concurrent irinotecan to chemoradiotherapy compared with standard-of-care chemoradiotherapy in MRI-defined, locally advanced rectal cancer deemed at high risk of locoregional failure and distant relapse.

Methods

Study design and participants

ARISTOTLE was a multicentre, open-label, parallel-group, phase 3 randomised trial conducted at 75 selected UK hospital sites delivering treatment for rectal cancer. Full details on eligibility criteria, study design, and methods are available in the trial protocol (appendix). In a deviation from the protocol which had specified an intention-to-treat analysis, efficacy analyses were conducted in the modified intention-to-treat population, defined as all eligible patients who were randomly assigned to treatment. This change was made during final data review, before the final comparative analyses were undertaken. The modified intention-to-treat population was considered the most appropriate efficacy population because it excluded patients who were found after randomisation not to meet eligibility criteria, and those who withdrew consent for use of their data. As this was an analysis-population decision only, with no change to trial treatment, follow-up, or data collection, separate Research Ethics Committee approval was not sought. The study was developed and overseen with input from patient representatives from the National Cancer Research Institute anorectal cancer subgroup and with membership of the Trial Management Group and Trial Steering Committee. Eligible patients were 18 years or older with histologically confirmed rectal adenocarcinoma, whose superior tumour extent was no higher than the S1–S2 junction on pelvic MRI, and with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. MRI-defined entry criteria included: mesorectal fascia directly involved or breached; mesorectal fascia threatened (tumour ≤1 mm from mesorectal fascia); or low tumours no further than 1 mm from the levator on two imaging planes; or involvement of the full thickness of muscularis propria at the level of puborectalis or below; or tumour involving the inter-sphincteric plane or external anal sphincter. Patients with involved pelvic sidewall nodes were eligible only if the primary tumour assessment met at least one of the above inclusion criteria. Additionally, patients were required to be fit to receive all trial treatments, have bowel function controlled with no more than 6 mg loperamide per day, be able to swallow oral medication, and have blood results indicating absolute neutrophil count greater than $1{\cdot}5\times10^9$/L, platelet count greater than 100×10^9/L, serum transaminase less than threefold higher than the upper limit of normal (ULN), adequate renal function (Cockcroft–Gault estimation ≥50 mL/min), and bilirubin less than 1·5-fold higher than ULN. Ethnicity data were not collected (as there were no data to indicate ethnic differences in outcome at the time of study inception) and sex data were captured from health-care records. Patients needed to be willing and able to give written informed consent and comply with treatment and follow-up schedule. Exclusion criteria included unequivocal metastatic disease on CT scanning, previous pelvic radiotherapy, a previous malignancy within 5 years, and known Gilbert's disease. Patients with uncontrolled cardiorespiratory comorbidity, major disturbance of bowel function, known dihydropyridine dehydrogenase deficiency, and those taking medications known to interact with the study drugs were also excluded.

See Online for appendix

The study followed Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All participants provided written informed consent. The trial was approved by the National Research Ethics Committee: Riverside (10/H0706/65), the Medicines and Healthcare Products Regulatory Agency (Clinical Trials Authorisation number 20363/0289/001), and each participating NHS Trust. The study is registered with EudraCT, 2008-005782-59, and is complete.

Randomisation and masking

Patients were randomly allocated (1:1) to either the standard-of-care group or irinotecan group using minimisation with a 90% random element. Stratification factors were radiotherapy centre, MRI assessment of mesorectal fascia involvement (yes or no), and the presence or absence of equivocal metastatic disease. Randomisation was conducted centrally by the UCL Clinical Trials Centre. The allocation sequence was concealed from investigators enrolling participants and assigning treatment by using a secure, central, web-based randomisation system. Given the nature of the interventions, masking of patients and treating clinicians was not feasible. However, efforts were made to minimise potential bias, including prespecification of postoperative chemotherapy decisions recorded at the time of randomisation.

Procedures

Patients were randomly assigned to receive preoperative pelvic radiotherapy at 45 Gy in 25 daily fractions over 5 weeks, combined with either oral capecitabine 900 mg/m² twice daily on radiotherapy days

(Monday–Friday, standard-of-care group) or oral capecitabine 650 mg/m² twice daily on radiotherapy days with intravenous irinotecan 60 mg/m² once weekly as a 30–60-min infusion during weeks 1–4 only (irinotecan group). Treatment commenced within 4 weeks of randomisation.

Radiotherapy was planned according to a standardised protocol, incorporating pretreatment imaging, target volume delineation, and quality assurance measures to ensure consistency across sites. Three-dimensional conformal planning was mandated. In the irinotecan group, if irinotecan was discontinued permanently due to toxicity, chemoradiotherapy could continue if deemed safe by the treating investigator. Patients could be removed from the study at any time if deemed reasonable by the investigator or if the patient withdrew consent. If this situation occurred, the circumstances of further data collection for follow-up would be discussed between the investigator and the patient.

All protocol-stipulated baseline assessments were required. Toxicity assessments were conducted before treatment initiation and weekly during treatment. Capecitabine compliance was monitored using patient diaries, reconciled with returned medication. Detailed chemotherapy toxicity dose modifications are included in the protocol (appendix).

Post-treatment assessments occurred 6–8 weeks after completion of chemoradiotherapy, including pelvic MRI and CT of the chest and abdomen (radiology was not centrally reviewed). Patients who could not undergo surgery for reasons other than radiological complete response (cT0N0M0) were classified as having residual disease. Surgery was recommended 8–10 weeks after completion of chemoradiotherapy, with multidisciplinary team review guiding the decision. A detailed pathology protocol was used to assess resected specimens, including the definition of histopathological complete response. All patients with documented histopathological complete response were centrally reviewed by a specialist pathologist (NW) who was masked to treatment group. Clinical assessments during follow-up were done every 6–12 months for 5 years, and MRI or CT scans were done every 12 months.

Safety was assessed through adverse events and serious adverse events reported from date of informed consent until 30 days post-treatment. Events were graded according to the Common Terminology Criteria for Adverse Events v4.02 and evaluated for causality. Postoperative adverse events were recorded at 4 months post-chemoradiotherapy.

Patient-reported outcomes were assessed using sex-specific pelvis structured questionnaires to evaluate bowel, urinary, and sexual function and their effect on daily functioning and quality of life, including pain. Assessments were completed at baseline and annually for 3 years post-chemoradiotherapy. Patients were considered not assessable at a given timepoint if the questionnaire was not returned.

Compliance with radiotherapy, capecitabine, and irinotecan was recorded. Surgery compliance was evaluated based on whether surgery was done, reasons for non-compliance, type of procedure, and time from radiotherapy completion to surgery.

Outcomes

The primary endpoint was disease-free survival, defined as the time from randomisation to the first disease-free survival event, including death, persistent locoregional disease following chemoradiotherapy, locoregional recurrence, or metastatic disease. Patients who never achieved a disease-free interval (eg, persistent loco-regional disease preventing resection or metastatic disease diagnosed before or during surgery) had their disease-free survival event time set to the date of randomisation. For those in whom disease recurred after an initial disease-free period, the disease-free survival event date was the earliest date of investigation confirming recurrence. In cases of death without previous evidence of residual or recurrent disease, the date of death was used as the disease-free survival event date. Patients without a disease-free survival event were censored at their last known date alive.

Secondary time-to-event endpoints included overall survival, cause-specific survival, time to locoregional failure, and time to distant metastasis. Time to treatment failure was protocol-specified but not reported separately, as its component events substantially overlap with the reported disease-free survival, treatment compliance, surgery compliance, withdrawal, and loss-to-follow-up outcomes. Overall survival was defined as the time from randomisation to death from any cause, with patients censored at the date they were last known to be alive. Cause-specific survival considered only deaths due to rectal cancer, censoring deaths from other causes. Time to locoregional failure and time to distant metastasis were defined as the time from randomisation to first confirmed locoregional failure or distant metastasis, respectively. For these reported endpoints, censoring occurred due to administrative end of follow-up or loss to follow-up and was assumed to be non-informative.

Secondary pathological outcomes included circumferential resection margin status and histo-pathological complete response. Histopathological tumour cell density was protocol-specified but is not reported with these main trial results because it requires detailed pathological analysis and will be reported separately. A circumferential resection margin-negative resection was defined as a microscopic tumour clearance of more than 1 mm from the radial non-peritonealised margin. Histopathological complete response (ypT0 ypN0) was confirmed when no viable tumour cells were identified in the specimen after

embedding the entire fibrotic scar and examining each block at three deeper levels. For resection status and pathological TNM staging, analyses were conducted among patients who were randomly assigned to treatment and underwent surgery, with missing assessments classified as non-response.

Other secondary endpoints were health-related quality of life and functional outcome, frequency and severity of adverse events, and compliance to trial treatment.

Statistical analysis

The trial aimed to detect a hazard ratio (HR) of 0·70 for disease-free survival, corresponding under the sample size assumptions to an absolute increase in 36-month disease-free survival from 65% in the standard-of-care group to 74% in the irinotecan group, as also used by Fu and colleague.[20] To achieve 80% power with a two-sided alpha of 0·05, assuming a 6-year recruitment period and a minimum of 3 years of follow-up, 247 disease-free survival events from 496 patients were required. During

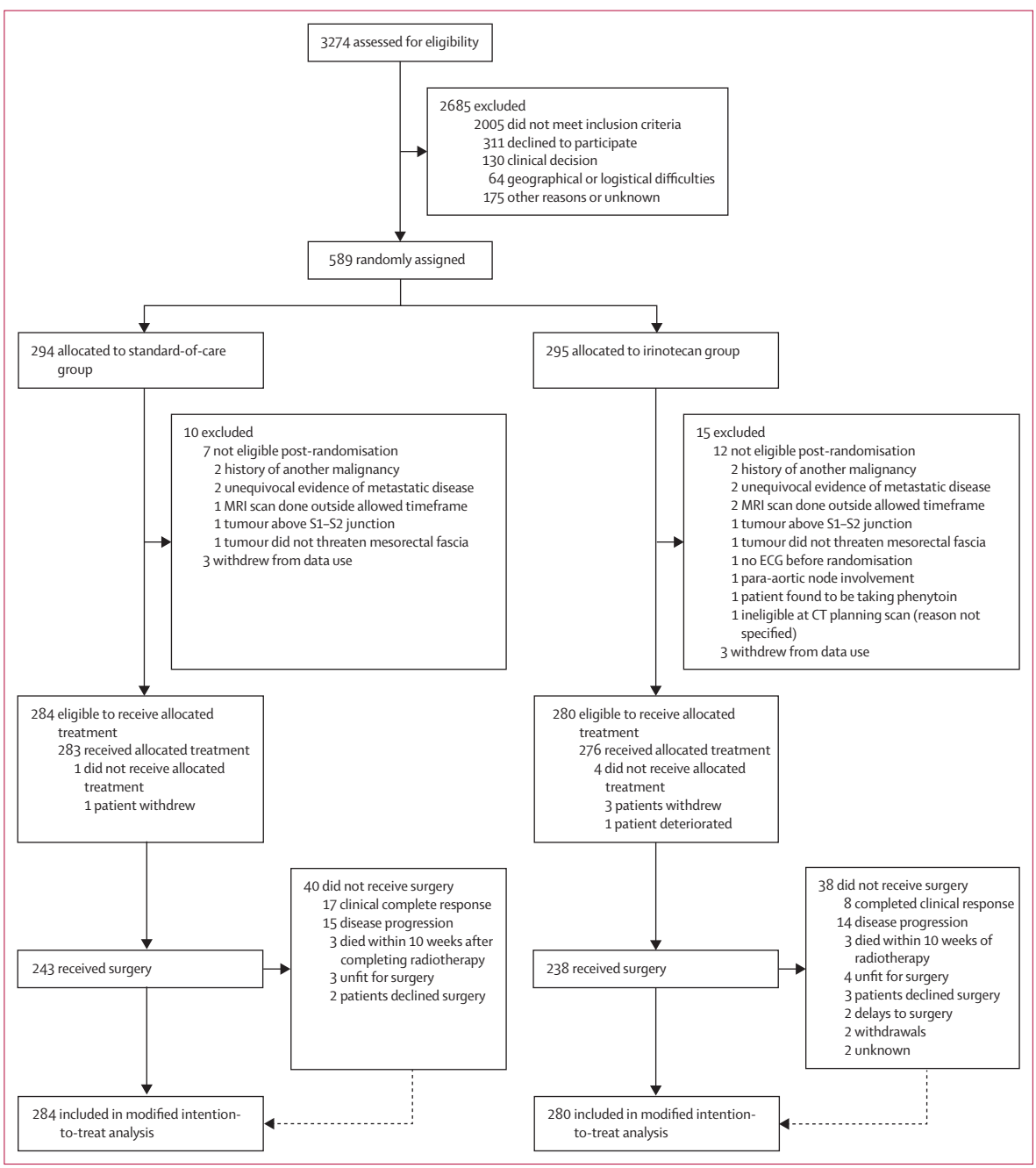

Figure 1: **Trial profile**

the trial, emerging data, including that from Fu and colleagues,[20] together with advances in pelvic MRI staging and updated information on event rates in similar trial populations, led to an adaptation of the original power calculations. To account for a potential decline in event rates beyond 3 years, the target recruitment was increased to 600 patients. The statistical analysis plan of the trial can be found in the appendix.

Confidential interim analyses were conducted annually by an independent data monitoring committee to review efficacy, safety, and trial conduct. A prespecified pragmatic futility analysis was planned after approximately 50 disease-free survival events, to allow early identification of a low probability of showing treatment benefit, to evaluate safety, and to inform recommendations to the trial steering committee and trial management group. Futility was assessed using conditional power at each independent data monitoring committee meeting.

The primary and secondary efficacy analyses were conducted in the modified intention-to-treat population. Safety analyses were conducted in all patients who started protocol treatment (as-treated population). Disease-free survival and overall survival were estimated using the Kaplan–Meier method. HRs and their 95% CIs were calculated using Cox proportional hazards models, both unadjusted and adjusted for prespecified stratification factors. Time to locoregional failure and time to distant metastasis were analysed separately in post-hoc exploratory competing-risk analyses as described in the appendix (p 31). Proportional hazards assumptions were assessed using Schoenfeld residuals, with tests conducted separately for disease-free survival (appendix p 10) and overall survival (appendix p 13). The 36-month event rates (with 95% CIs) were reported for each outcome, and Kaplan–Meier plots were presented. Descriptive statistics for categorical variables were presented as counts and percentages, and comparisons were made using Fisher's exact test, including adverse events, as appropriate. Continuous variables were presented as medians and IQRs. Quality-of-life and functioning outcomes were analysed by treatment group for each prespecified domain using logistic regression, with results reported as odds ratios, 95% CIs, and p values.

A planned sensitivity analysis of disease-free survival was done considering time to first evidence of suspected disease, confirmed disease, or death, whichever occurred first. A post-hoc sensitivity analysis for complete response was done in which patients with histopathological complete response or clinical complete response were classified as responders; patients who died within 10 weeks after completing radiotherapy, did not undergo surgery for reasons other than clinical complete response, or had surgery without resection due to disease deterioration were classified as non-responders.

	Irinotecan group (n=280)	Standard-of-care group (n=284)
Age, years		
Median (IQR)	60·5 (53·3–68·1)	60·9 (54·4–67·8)
Sex		
Male	173 (62%)	197 (69%)
Female	107 (38%)	87 (31%)
Tumour breached mesorectal fascia		
No	174 (62%)	173 (61%)
Yes	106 (38%)	111 (39%)
Metastases		
No metastases confirmed	268 (96%)	272 (96%)
Metastases equivocal	12 (4%)	12 (4%)
T stage (MRI defined)		
2	17 (6%)	16 (6%)
3	212 (76%)	223 (79%)
4	45 (16%)	44 (15%)
Not reported	6 (2%)	1 (<1%)
N stage (MRI defined)		
0	50 (18%)	81 (29%)
1	141 (50%)	119 (42%)
2	82 (29%)	83 (29%)
Not reported	7 (3%)	1 (<1%)
Primary tumour		
Semi-annular	129 (46%)	125 (44%)
Annular	101 (36%)	120 (42%)
Polypoidal	30 (11%)	31 (11%)
Not reported	20 (7%)	8 (3%)
ECOG performance status		
Fully active	217 (78%)	226 (80%)
Ambulatory (work able)	63 (23%)	58 (20%)
Stoma		
No	174 (62%)	194 (68%)
Yes	39 (14%)	22 (8%)
Not reported	67 (24%)	68 (24%)
CRM		
Directly involved (0 mm)	139 (50%)	138 (49%)
Threatened (≤1 mm)	108 (39%)	109 (38%)
CRM clear (>1 mm)	26 (9%)	34 (12%)
Not reported	7 (3%)	3 (1%)
Pre-MRI extramural venous invasion		
Absent	138 (49%)	147 (52%)
Present	133 (48%)	136 (48%)
Unknown	9 (3%)	1 (<1%)
Pre-MRI pelvic sidewall lymph nodes		
None	185 (66%)	214 (75%)
Benign or reactive	46 (16%)	28 (10%)
Malignant mixed signa	40 (14%)	39 (14%)
Unknown	9 (3%)	3 (1%)

Data are n (%) unless indicated otherwise. mrTRG staging was performed according to local systems and was expected to map to pathological TNM version 5. CRM=circumferential resection margin. ECOG=Eastern Cooperative Oncology group. mrTRG=magnetic resonance tumour regression grade. N stage=nodal stage. T stage=tumour stage.

Table 1: **Baseline patient and tumour characteristics**

Subgroup analyses for disease-free survival and overall survival were prespecified in the statistical analysis plan.

Treatment response on MRI was assessed post-chemoradiotherapy using magnetic resonance tumour regression grade (mrTRG) and analysed as a post-hoc outcome. mrTRG analyses were conducted in the full analysis population of randomly assigned patients, with missing assessments classified as non-response. Composite response was defined as mrTRG 1–2, and non-response as mrTRG 3–5, no protocol treatment, death or loss to follow-up within 10 weeks after radiotherapy, or missing or unreported post-treatment MRI assessment. Post-hoc exploratory analyses comprised competing-risk analyses of cancer-specific survival, locoregional failure, and distant metastasis; post-treatment response analyses, including the sensitivity analysis of complete response and mrTRG response analyses; sensitivity analyses of disease-free survival and overall survival restricted to patients receiving at least 90% of the planned radiotherapy dose; and cumulative incidence analysis of time to first grade 3–5 adverse event, with death as a competing event (appendix p 31).

All statistical tests were two-sided, and p values less than 0·05 were considered statistically significant. All analyses were done in STATA v18.0.

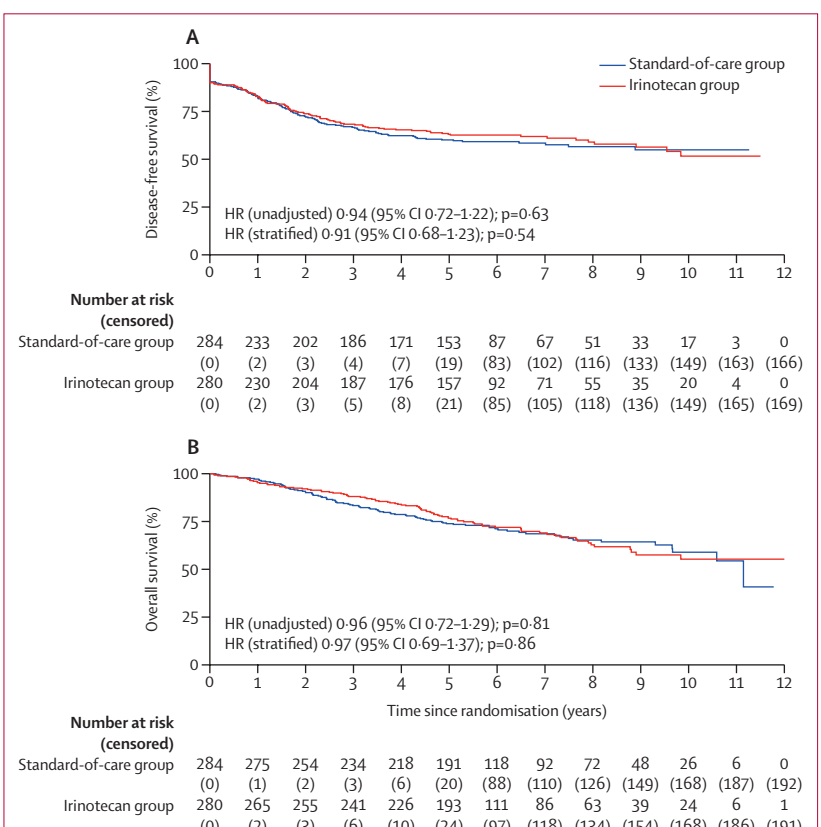

Figure 2: **Disease-free survival (A) and overall survival (B)**
Cox regression was stratified by radiotherapy centre, tumour breach of the fascia (yes *vs* no), and metastatic status (no confirmed metastases *vs* equivocal metastases).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 25, 2011, and July 5, 2018, 3274 patients were screened across 75 centres in the UK (appendix pp 32–34). Of these, 589 patients were randomly assigned to receive treatment (295 in the irinotecan group and 294 in the standard-of-care group). After randomisation, 25 patients were excluded due to ineligibility (ten in the standard-of-care group and 15 in the irinotecan group) and six patients withdrew consent for data use. The modified intention-to-treat population included 564 eligible patients: 280 in the irinotecan group and 284 in the standard-of-care group (figure 1). Baseline characteristics are shown in table 1. The median age was 61 years (IQR 54–68), 370 (66%) patients were male, and 194 (34%) were female. A total of 435 (77%) patients had T3 MRI-defined tumours (212 [76%] in the irinotecan group and 223 [79%] in the standard of care group) and 89 (16%) had T4 tumours (45 [16%] *vs* 44 [15%]). Radiologically, 24 (4%) patients had equivocal metastases and evidence of lymph node involvement was present in 425 (75%) patients. The MRI-defined circumferential resection margin was directly involved (0 mm) in 277 (49%) patients, threatened (≤1 mm) in 217 (38%), and clear in 60 (11%).

Overall, 559 (99%) patients started protocol treatment: 276 in the irinotecan group and 283 in the standard-of-care group. Of the five patients who did not start treatment (four in the irinotecan group and one in the standard-of-care group), four withdrew from the study and one had disease progression. 208 (75%) of 276 patients in the irinotecan group received the full 45 Gy radiotherapy as scheduled, compared with 251 (89%) of 283 in the standard-of-care group. A reduced radiotherapy dose (<90% of the intended dose) was delivered in 16 (6%) patients in the irinotecan group and four (1%) patients in the standard-of-care group (appendix pp 1–2). Capecitabine dose reductions were also more common in the irinotecan group: 187 (68%) patients received at least 90% of the planned dose, compared with 253 (89%) in the standard-of-care group (appendix pp 3–5).

A total of 205 (74%) patients received at least 90% of the intended irinotecan dose (appendix pp 6–7). Following neoadjuvant therapy, 238 (86%) patients in the irinotecan group and 243 (86%) in the standard-of-care group underwent surgery (appendix p 8). 38 patients in the irinotecan group and 40 in the standard-of-care group did not undergo surgery. Among these, the most common reasons for not undergoing surgery were clinical complete response (eight [21%] patients in the irinotecan group *vs* 17 [43%] patients in the standard-of-care group) and disease progression (14 [37%] patients *vs* 15 [38%]

patients; appendix p 8). The median interval between completion of neoadjuvant radiotherapy and surgery was 10·6 weeks in both groups (IQR 9·3–13·4 in the irinotecan group; 9·6–12·9 in the standard-of-care group). Among patients who had surgery, abdominoperineal resection was done in 130 (55%) of 238 patients in the irinotecan group versus 134 (55%) of 243 in the standard-of-care group, and anterior resection in 100 (42%) patients versus 94 (39%) patients (figure 1; appendix p 8). Similar percentages of patients in the irinotecan and standard-of-care groups received subsequent anticancer therapies, including systemic treatments and locoregional interventions (appendix p 9).

By data cutoff on Oct 17, 2024, median follow-up was 78 months (95% CI 75–86), with similar duration in both treatment groups (78 months [71–88] in the irinotecan group *vs* 79 months [74–88] in the standard-of-care group). Disease-free survival events were reported in 111 (40%) patients in the irinotecan group and 118 (42%) in the standard-of-care group. The 36-month disease-free survival rates were 68% (95% CI 63–73) for the irinotecan group and 67% (61–72) for the standard-of-care group (figure 2A, appendix p 10).

	Events/patients, n/N (%)		Disease-free survival at 36 months, % (95% CI)		Hazard ratio (95% CI)	$p_{interaction}$
	Irinotecan group	Standard-of-care group	Irinotecan group	Standard-of-care group		
Overall population	**111/280 (40%)**	**118/284 (42%)**	**68·3% (62·5–73·4)**	**66·7% (60·8–71·8)**	**0·94 (0·72–1·22)**	**0·63**
Age, years						
≤60	49/137 (36%)	45/128 (35%)	69·3% (60·8–76·3)	72·3% (63·6–79·2)	1·04 (0·69–1·56)	0·54
>60	62/143 (43%)	73/156 (47%)	67·4% (59·0–74·4)	62·1% (54·0–69·2)	0·88 (0·63–1·23)	
Sex						
Male	69/173 (40%)	79/197 (40%)	68·1% (60·6–74·5)	67·8% (60·8–73·9)	0·97 (0·70–1·33)	0·77
Female	42/107 (39%)	39/87 (45%)	68·7% (58·9–76·7)	64·1% (53·0–73·2)	0·89 (0·58–1·38)	
Tumour breached fascia						
No	59/174 (34%)	66/173 (38%)	72·6% (65·3–78·7)	69·4% (61·9–75·7)	0·88 (0·62–1·25)	0·55
Yes	52/106 (49%)	52/111 (47%)	61·3% (51·4–69·8)	62·4% (52·6–70·8)	1·02 (0·70–1·50)	
Metastases						
No metastases confirmed	104/268 (39%)	115/272 (42%)	68·8% (62·8–74·0)	65·6% (59·6–70·9)	0·89 (0·69–1·17)	0·085
Metastases equivocal	7/12 (58%)	3/12 (25%)	58·3% (27·0–80·1)	91·7% (53·9–98·8)	2·86 (0·74–11·08)	
T stage (MRI defined)						
2	8/17 (47%)	3/16 (19%)	58·8% (32·5–77·8)	81·2% (52·5–93·5)	2·92 (0·77–11·04)	0·090
3	75/212 (35%)	94/223 (42%)	72·5% (65·9–78·0)	67·5% (60·9–73·3)	0·80 (0·59–1·09)	
4	25/45 (56%)	21/44 (48%)	51·1% (35·8–64·5)	56·1% (40·1–69·3)	1·12 (0·62–2·02)	
N stage (MRI defined)						
0	18/50 (36%)	30/81 (37%)	70·0% (55·3–80·7)	70·3% (59·1–79·0)	0·94 (0·52–1·68)	0·57
1	57/141 (40%)	56/119 (47%)	67·9% (59·4–74·9)	58·5% (49·1–66·8)	0·79 (0·55–1·15)	
2	33/82 (40%)	32/83 (39%)	67·0% (55·7–76·0)	74·4% (63·5–82·5)	1·11 (0·68–1·80)	
Primary tumour						
Annular	44/101 (44%)	50/120 (42%)	67·1% (57·0–75·4)	66·5% (57·2–74·2)	1·07 (0·72–1·61)	0·55
Semi-annular	47/129 (36%)	53/125 (42%)	69·6% (60·9–76·8)	62·0% (52·9–69·9)	0·79 (0·53–1·16)	
Polypoidal	11/30 (37%)	12/31 (39%)	66·7% (46·9–80·5)	77·4% (58·4–88·5)	0·96 (0·42–2·18)	
ECOG performance status						
Ambulatory (work able)	27/63 (43%)	35/58 (60%)	67·9% (54·8–78·0)	48·3% (35·0–60·3)	0·59 (0·36–0·99)	0·045
Fully active	84/217 (39%)	83/226 (37%)	68·5% (61·8–74·2)	71·4% (65·0–76·9)	1·08 (0·79–1·46)	
Stoma						
No	66/174 (38%)	69/194 (36%)	67·4% (59·9–73·9)	71·5% (64·6–77·3)	1·12 (0·80–1·57)	0·012
Yes	19/39 (49%)	19/22 (86%)	59·0% (42·0–72·5)	31·8% (14·2–51·1)	0·45 (0·23–0·85)	
MRI CRM						
Threatened (≤1 mm)	35/108 (32%)	38/109 (35%)	76·7% (67·5–83·6)	72·3% (62·9–79·8)	0·86 (0·54–1·36)	0·87
Involved (0 mm)	61/139 (44%)	65/138 (47%)	62·4% (53·8–69·9)	61·9% (53·2–69·5)	0·94 (0·66–1·33)	
CRM clear	11/26 (42%)	13/34 (38%)	65·4% (44·0–80·3)	67·6% (49·2–80·6)	1·12 (0·50–2·51)	

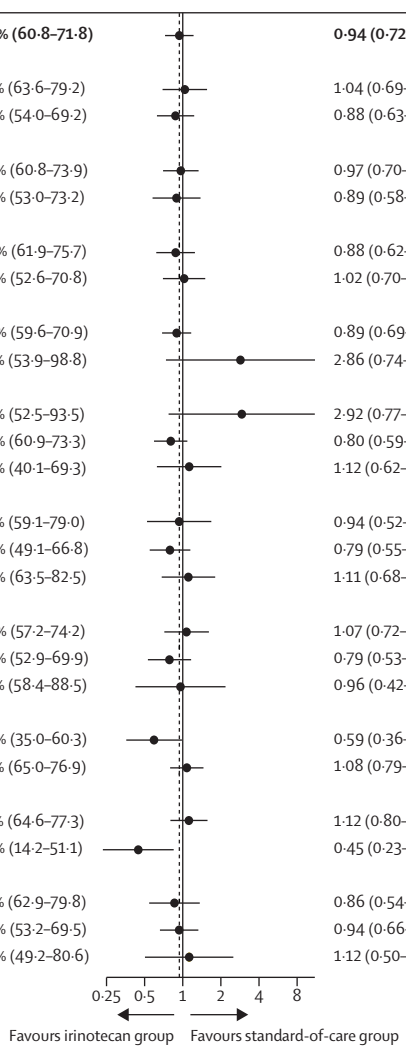

Figure 3: **Subgroup analysis of treatment effect (unadjusted) on disease-free survival**
The solid vertical line indicates the null treatment effect (HR 1·00); the dashed line indicates the estimated overall treatment effect (HR 0·94, p=0·63). The $p_{interaction}$ value was obtained from a likelihood-ratio test comparing Cox proportional hazard models with and without the treatment-by-baseline variable interaction. Results shown were a preplanned exploratory analysis and not adjusted for multiple testing. CRM=circumferential resection margin. ECOG=Eastern Cooperative Oncology Group.

Irinotecan was not associated with a statistically significant benefit in disease-free survival compared with standard of care (stratified HR 0·91 [0·68–1·23]; p=0·54).

Subgroup analyses for disease-free survival showed relatively weak evidence of an interaction at the 5% level between treatment and ECOG performance status ($p_{interaction}$=0·045) and between treatment and stoma status ($p_{interaction}$=0·012); p values would exceed 0·05 if adjusted for multiple comparisons. There appeared to be benefit from irinotecan in ambulatory patients (HR 0·59 [95% CI 0·36–0·99]) and in patients with a stoma (0·45 [0·23–0·85]). No evidence of treatment effect heterogeneity was seen across other subgroups (all interactions p>0·05; figure 3). Locoregional failure was uncommon, occurring in 16 (6%) patients in the irinotecan group and 19 (7%) in the standard-of-care group (appendix pp 11, 24). Distant metastases occurred in 81 (29%) of 280 patients in the irinotecan group and 91 (32%) of 284 in the standard-of-care group. Adjusted model-based 36-month cumulative incidence rates for distant metastases were 27·7% (95% CI 22·5–33·0) in the irinotecan group and 25·3% (20·6–29·9) in the standard-of-care group (adjusted subdistribution HR 0·90 [95% CI 0·67–1·20]; p=0·47; appendix pp 12, 25).

There were 88 (31%) deaths in the irinotecan group and 92 (32%) deaths in the standard-of-care group. The most common cause of death was rectal cancer, which occurred in 59 (67%) in the irinotecan group and 67 (73%) in the standard-of-care group (appendix p 13).

The 36-month overall survival rate was 88% (95% CI 84–91) in the irinotecan group versus 83% (78–87) in the standard-of-care group. No evidence of a significant treatment effect was observed for overall survival (stratified HR 0·97 [0·69–1·37]; p=0·86; figure 2B and appendix p 13) or for cause-specific survival (adjusted subdistribution HR 0·89 [0·62–1·26]; p=0·50; appendix pp 14 and 26). No evidence of a treatment effect on overall survival was observed across patient subgroups at the 5% significance level, except for MRI-defined T stage ($p_{interaction}$=0·0036, but the number of patients and events in the T2 subgroup was small) and stoma status ($p_{interaction}$=0·015; appendix p 27).

Treatment response on MRI was similar between groups (table 2). Among patients with an evaluable MRI, 38 (14%) of 280 in the irinotecan group and 39 (14%) of 284 in the standard-of-care group were reported to have mrTRG 1 (p=0·96). mrTRG 1 or 2 was observed in 128 (46%) patients in the irinotecan group and 126 (44%) in the standard-of-care group. Protocol deviations and missing post-treatment MRI data were infrequent and balanced.

Surgical excision specimens were available for 469 (98%) of 481 patients who had undergone surgery. Among patients who underwent surgery, pR0 resection was achieved in 207 (87%) of 238 in the irinotecan group and 212 (87%) of 243 in the standard-of-care group (p=0·93). There were similar rates between groups in terms of pR1 resection: 23 (10%) in the irinotecan group versus 24 (10%) in the standard-of-care group. One patient in the irinotecan group and two in the standard-of-care group had a pR2 resection. Histopathological complete response (ypT0N0) was observed in 46 (19%) patients in the irinotecan group and 42 (17%) in the standard-of-care group (p=0·56). In a post-hoc sensitivity analysis in which patients with a clinical complete response were classified as responders, and those who died within 10 weeks of completing radiotherapy, did not undergo surgery, or had surgery without resection due to disease deterioration were classified as non-responders, complete response was

	Irinotecan group	Standard-of-care group	p value*
mrTRG			
Patients included in mrTRG analysis, n	280	284	..
TRG1	38 (14%)	39 (14%)	0·96
TRG2	90 (32%)	87 (31%)	..
TRG3	63 (23%)	69 (24%)	..
TRG4	49 (18%)	51 (18%)	..
TRG5	19 (7%)	24 (8%)	..
Did not have protocol treatment	4 (1%)	1 (<1%)	..
Died ≤10 weeks after end of radiotherapy	3 (1%)	3 (1%)	..
Lost to follow-up ≤10 weeks after radiotherapy	1 (<1%)	0	..
Not reported	13 (5%)	10 (4%)	..
Resection status			
Patients who had surgery, n	238	243	..
pR0	207 (87%)	212 (87%)	0·93
pR1 (0 mm)	13 (5%)	13 (5%)	..
pR1 (≤1 mm)	10 (4%)	11 (5%)	..
pR2	1 (<1%)	2 (1%)	..
Resection not performed due to advanced or metastatic disease	3 (1%)	2 (1%)	..
Not reported	4 (2%)	3 (1%)	..
Pathological TNM staging			
Patients who had surgery, n	238	243	..
Stage 0 (ypT0N0, pCR)	46 (19%)	42 (17%)	0·56
Stage I	63 (26%)	49 (20%)	..
Stage IIA	46 (19%)	64 (26%)	..
Stage IIB or C	8 (3%)	7 (3%)	..
Stage IIIA	12 (5%)	16 (7%)	..
Stage IIIB	55 (23%)	60 (25%)	..
Stage IIIC	1 (<1%)	1 (<1%)	..
Resection not peerformed due to advanced or metastatic disease	3 (1%)	2 (1%)	..
Not reported	4 (2%)	2 (1%)	..

Data are n/N (%). mrTRG=magnetic resonance tumour regression grade. pCR=pathological complete response. *p values from difference in proportions tests (χ^2 test).

Table 2: **Radiological, pathological, and surgical outcomes**

observed in 54 (21%) of 259 patients in the irinotecan group and 59 (21%) of 276 in the standard-of-care group (p=0·88). Subgroup analyses showed no evidence of a differential treatment effect on histopathological complete response, except for age ($p_{interaction}$=0·023; appendix p 28).

	Irinotecan group (n=276)				Standard-of-care group (n=283)			
	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade 1–2	Grade 3	Grade 4	Grade 5*
Any adverse event	61 (22%)	184 (67%)	28 (10%)	3 (1%)	135 (48%)	133 (47%)	13 (5%)	2 (1%)
Blood and lymphatic system disorders	70 (25%)	9 (3%)	1 (<1%)	..	34 (12%)	4 (1%)	..	1 (<1%)
Anaemia	70 (25%)	8 (3%)	..	..	34 (12%)	4 (1%)	..	..
Febrile neutropenia	..	2 (1%)	1 (<1%)	..	..	..	..	1 (<1%)
Disseminated intravascular coagulation	..	1 (<1%)	..	..	..	..	..	..
Cardiac disorders	16 (6%)	3 (1%)	1 (<1%)	..	16 (6%)	3 (1%)	..	1 (<1%)
Chest pain—cardiac	6 (2%)	1 (<1%)	..	..	4 (1%)	2 (1%)	..	..
Acute coronary syndrome	2 (1%)	..	..	..	2 (1%)	1 (<1%)	..	..
Cardiac arrest	..	..	1 (<1%)	..	..	..	..	1 (<1%)
Myocardial infarction	..	1 (<1%)	..	..	..	..	..	..
Restrictive cardiomyopathy	..	1 (<1%)	..	..	..	..	..	..
Gastrointestinal disorders	209 (76%)	56 (20%)	1 (<1%)	..	221 (78%)	27 (10%)	8 (3%)	..
Diarrhoea	184 (67%)	37 (13%)	1 (<1%)	..	165 (58%)	8 (3%)	2 (1%)	..
Nausea	129 (47%)	9 (3%)	..	..	113 (40%)	1 (<1%)	..	..
Abdominal pain	125 (45%)	13 (5%)	..	..	106 (37%)	1 (<1%)	..	..
Constipation	82 (30%)	..	..	..	53 (19%)	..	..	..
Rectal pain	41 (15%)	4 (1%)	..	..	43 (15%)	2 (1%)	..	..
Mucositis oral	49 (18%)	1 (<1%)	..	..	33 (12%)	..	..	..
Proctitis	34 (12%)	3 (1%)	..	..	38 (13%)	4 (1%)	..	..
Anal pain	30 (11%)	2 (1%)	..	..	43 (15%)	3 (1%)	..	..
Vomiting	46 (17%)	4 (1%)	..	..	23 (8%)	2 (1%)	..	..
Gastrointestinal pain	24 (9%)	..	..	..	19 (7%)	1 (<1%)	..	..
Dyspepsia	28 (10%)	..	..	..	14 (5%)	..	..	..
Rectal haemorrhage	19 (7%)	..	..	..	21 (7%)	1 (<1%)	..	..
Bloating	8 (3%)	2 (1%)	..	..	6 (2%)	..	..	..
Ileus	4 (1%)	2 (1%)	..	..	..	2 (1%)	1 (<1%)	..
Other gastrointestinal disorders	3 (1%)	..	..	..	5 (2%)	1 (<1%)	..	..
Small intestinal obstruction	1 (<1%)	2 (1%)	..	..	..	2 (1%)	3 (1%)	..
Colitis	4 (1%)	3 (1%)	..	..	..	..	..	..
Colonic obstruction	..	2 (1%)	..	..	1 (<1%)	1 (<1%)	1 (<1%)	..
Dysphagia	2 (1%)	..	..	..	..	1 (<1%)	..	..
Enterocolitis	..	2 (1%)	..	..	..	1 (<1%)	..	..
Rectal obstruction	2 (1%)	1 (<1%)	..	..	..	..	..	..
Toothache	..	..	..	..	2 (1%)	1 (<1%)	..	..
Pancreatitis	..	..	..	..	..	2 (1%)	..	..
Colonic perforation	..	..	..	..	..	..	1 (<1%)	..
Gastric ulcer	..	..	1 (<1%)	..	..	..	..	..
Ileal obstruction	..	..	..	..	..	1 (<1%)	..	..
Small intestinal mucositis	..	1 (<1%)	..	..	..	..	..	..
General disorders and administration-site conditions	220 (80%)	19 (7%)	..	1 (<1%)	206 (73%)	9 (3%)	1 (<1%)	.
Fatigue	219 (79%)	17 (6%)	..	..	205 (72%)	8 (3%)	..	..
Pain	10 (4%)	2 (1%)	..	..	11 (4%)	1 (<1%)	..	..
Oedema, limbs	12 (4%)	1 (<1%)	..	..	4 (1%)	..	..	..
Infusion-related reaction	2 (1%)	1 (<1%)	..	..	..	..	..	..
Localised oedema	..	..	..	..	..	..	1 (<1%)	..
Multiorgan failure	..	..	..	1 (<1%)	..	..	..	..

(Table 3 continues on next page)

The rate of any grade 3–5 adverse event was higher in the irinotecan group than in the standard-of-care group (215 [78%] of 276 patients *vs* 148 [52%] of 283; p<0·0001; table 3 and appendix pp 14–21). Grade 3–5 laboratory test abnormalities were more common with irinotecan than with standard of care (191 [69%] *vs* 104 [37%]), with the most frequent events including lymphocyte count decreased (181 [66%] *vs* 100 [35%]), neutrophil count decreased (27 [10%] *vs* three [1%]), and white blood cell count decreased (26 [9%] *vs* five [2%]). Grade 3–5 gastrointestinal events were also reported more often in the irinotecan group (57 [21%] *vs* 35 [12%]), particularly diarrhoea (38 [14%] *vs* ten [4%]), and abdominal pain (13 [5%] *vs* one [<1%]). Five patients had a reported adverse event that led to death (grade 5) and all were related to protocol treatment: three patients in the irinotecan group (two had thromboembolic event and one had multiorgan failure plus sepsis) and two in the standard-of-care group (one with cardiac arrest and one with febrile neutropenia with acidosis). We undertook a post-hoc cumulative

	Irinotecan group (n=276)				Standard-of-care group (n=283)			
	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade 1–2	Grade 3	Grade 4	Grade 5*
(Continued from previous page)								
Infections and infestations	50 (18%)	25 (9%)	3 (1%)	1 (<1%)	50 (18%)	22 (8%)	5 (2%)	..
Wound infection	13 (5%)	6 (2%)	..	..	20 (7%)	10 (4%)	1 (<1%)	..
Urinary tract infection	16 (6%)	4 (1%)	..	..	12 (4%)	1 (<1%)	1 (<1%)	..
Other infections and infestations	3 (1%)	7 (3%)	..	..	5 (2%)	2 (1%)	..	..
Pelvic infection	2 (1%)	5 (2%)	..	..	2 (1%)	6 (2%)	..	..
Anorectal infection	6 (2%)	1 (<1%)	..	..	6 (2%)	1 (<1%)	..	..
Lung infection	2 (1%)	1 (<1%)	..	..	4 (1%)	5 (2%)	..	..
Sepsis	..	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	..	2 (1%)	..
Skin infection	3 (1%)	1 (<1%)	..	..	2 (1%)	2 (1%)	..	..
Abdominal infection	2 (1%)	..	..	..	..	1 (<1%)	..	..
Catheter-related infection	1 (<1%)	..	..	..	..	..	1 (<1%)	..
Enterocolitis infectious	..	..	..	..	..	1 (<1%)	..	..
Hepatic infection	..	1 (<1%)	..	..	..	..	..	..
Peritoneal infection	..	..	..	..	..	..	1 (<1%)	..
Soft tissue infection	..	1 (<1%)	..	..	..	..	..	..
Injury, poisoning, and procedural complications	52 (19%)	10 (4%)	3 (1%)	..	57 (20%)	10 (4%)	1 (<1%)	..
Dermatitis radiation	26 (9%)	4 (1%)	..	..	29 (10%)	3 (1%)	..	..
Wound dehiscence	14 (5%)	3 (1%)	2 (1%)	..	15 (5%)	5 (2%)	1 (<1%)	..
Radiation recall reaction (dermatological)	5 (2%)	..	..	..	8 (3%)	1 (<1%)	..	..
Gastrointestinal anastomotic leak	4 (1%)	1 (<1%)	..	..	6 (2%)	1 (<1%)	..	..
Other injury, poisoning, and procedural complications	3 (1%)	3 (1%)	..	..	2 (1%)	..	..	..
Wound complication	1 (<1%)	1 (<1%)	..	..	2 (1%)	..	..	..
Burn	..	..	..	..	1 (<1%)	1 (<1%)	..	..
Hip fracture	..	1 (<1%)	..	..	..	..	..	..
Intraoperative haemorrhage	..	..	1 (<1%)	..	..	..	..	..
Large intestinal anastomotic leak	..	..	..	..	..	1 (<1%)	..	..
Investigations (laboratory test abnormalities)	83 (30%)	166 (60%)	25 (9%)	..	175 (62%)	101 (36%)	3 (1%)	..
Other investigations	255 (92%)	2 (1%)	..	..	258 (91%)	..	..	..
Lymphocyte count decreased	77 (28%)	161 (58%)	20 (7%)	..	156 (55%)	99 (35%)	1 (<1%)	..
Neutrophil count decreased	60 (22%)	19 (7%)	8 (3%)	..	28 (10%)	1 (<1%)	2 (1%)	..
GGT increased	62 (22%)	3 (1%)	..	..	49 (17%)	1 (<1%)	..	..
Alanine aminotransferase increased	76 (28%)	2 (1%)	..	..	35 (12%)	..	..	..
White blood cell decreased	56 (20%)	21 (8%)	5 (2%)	..	25 (9%)	4 (1%)	1 (<1%)	..
Platelet count decreased	45 (16%)	1 (<1%)	..	..	46 (16%)	1 (<1%)	..	..
Creatinine increased	46 (17%)	..	..	..	41 (14%)	..	..	..
Blood bilirubin increased	28 (10%)	1 (<1%)	..	..	22 (8%)	..	..	..
Alkaline phosphatase increased	28 (10%)	..	..	..	21 (7%)	1 (<1%)	..	..

(Table 3 continues on next page)

incidence analysis to better describe the accumulation of grade 3–5 adverse events, using the Fine and Gray model,[21] with death as a competing event. The adjusted stratified HR was 2·27 (95% CI 1·83–2·80, p<0·0001; appendix p 29), indicating a statistically significant increase in the subdistribution hazard of experiencing a grade 3–5 adverse event in the irinotecan group compared with the standard-of-care group.

Rates of post-surgical complications were similar between the two groups, including any complication (94 [39%] of 238 in the irinotecan group *vs* 91 [37%] of 243 in the standard-of-care group), re-admission after

	Irinotecan group (n=276)				Standard-of-care group (n=283)			
	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade 1–2	Grade 3	Grade 4	Grade 5*
(Continued from previous page)								
Metabolism and nutrition disorders	142 (51%)	39 (14%)	1 (<1%)	..	110 (39%)	9 (3%)	..	1 (<1%)
Hypoalbuminaemia	114 (41%)	13 (5%)	..	..	51 (18%)	1 (<1%)	..	..
Anorexia	92 (33%)	6 (2%)	..	..	73 (26%)	2 (1%)	..	..
Hyponatraemia	2 (1%)	23 (8%)	1 (<1%)	..	..	6 (2%)	..	..
Hyperkalaemia	10 (4%)	..	..	..	14 (5%)	1 (<1%)	..	..
Hypokalaemia	1 (<1%)	10 (4%)	..	..	..	2 (1%)	..	..
Dehydration	1 (<1%)	10 (4%)	..	..	..	1 (<1%)	..	..
Hypocalcaemia	2 (1%)	1 (<1%)	..	..	..	1 (<1%)	..	..
Acidosis	..	..	..	..	..	..	..	1 (<1%)
Other metabolism and nutrition disorders	..	1 (<1%)	..	..	..	..	..	..
Musculoskeletal and connective tissue disorders	29 (11%)	2 (1%)	..	..	34 (12%)	2 (1%)	1 (<1%)	..
Back pain	14 (5%)	..	..	..	20 (7%)	1 (<1%)	..	..
Myalgia	1 (<1%)	1 (<1%)	..	..	3 (1%)	..	..	..
Other musculoskeletal and connective tissue disorders	1 (<1%)	..	..	..	..	1 (<1%)	1 (<1%)	..
Generalised muscle weakness	..	1 (<1%)	..	..	1 (<1%)	..	..	..
Soft tissue necrosis, lower limb	..	1 (<1%)	..	..	..	..	..	..
Soft tissue necrosis, upper limb	..	1 (<1%)	..	..	..	..	..	..
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6 (2%)	1 (<1%)	..	..	5 (2%)	..	..	..
Tumour pain	5 (2%)	1 (<1%)	..	..	5 (2%)	..	..	..
Nervous system disorders	66 (24%)	6 (2%)	..	..	62 (22%)	..	..	..
Dysgeusia	32 (12%)	..	..	..	21 (7%)	..	..	..
Headache	18 (7%)	1 (<1%)	..	..	12 (4%)	..	..	..
Dizziness	16 (6%)	1 (<1%)	..	..	13 (5%)	..	..	..
Syncope	..	2 (1%)	..	..	1 (<1%)	..	..	..
Cerebrospinal fluid leakage	..	1 (<1%)	..	..	..	..	..	..
Encephalopathy	..	1 (<1%)	..	..	..	..	..	..
Psychiatric disorders	26 (9%)	1 (<1%)	..	..	30 (11%)	1 (<1%)	..	..
Depression	6 (2%)	1 (<1%)	..	..	10 (4%)	1 (<1%)	..	..
Renal and urinary disorders	117 (42%)	3 (1%)	2 (1%)	..	121 (43%)	3 (1%)	1 (<1%)	..
Urinary frequency	92 (33%)	1 (<1%)	..	..	88 (31%)	..	..	..
Cystitis non-infective	19 (7%)	..	..	..	29 (10%)	..	..	..
Urinary retention	11 (4%)	..	..	..	6 (2%)	1 (<1%)	..	..
Acute kidney injury	3 (1%)	1 (<1%)	2 (1%)	..	2 (1%)	2 (1%)	..	..
Urinary incontinence	5 (2%)	..	..	..	2 (1%)	..	1 (<1%)	..
Haematuria	1 (<1%)	1 (<1%)	..	..	3 (1%)	..	..	..
Reproductive system and breast disorders	26 (9%)	..	..	..	23 (8%)	1 (<1%)	..	..
Vaginal pain	3 (1%)	..	..	..	3 (1%)	1 (<1%)	..	..
Respiratory, thoracic, and mediastinal disorders	36 (13%)	4 (1%)	..	..	26 (9%)	1 (<1%)	..	..
Dyspnoea	13 (5%)	3 (1%)	..	..	7 (2%)	..	..	..
Adult respiratory distress syndrome	1 (<1%)	1 (<1%)	..	..	4 (1%)	1 (<1%)	..	..

(Table 3 continues on next page)

	Irinotecan group (n=276)				Standard-of-care group (n=283)			
	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade 1–2	Grade 3	Grade 4	Grade 5*
(Continued from previous page)								
Skin and subcutaneous tissue disorders	123 (45%)	3 (1%)	..	..	116 (41%)	8 (3%)	..	..
Skin ulceration	58 (21%)	2 (1%)	..	..	59 (21%)	4 (1%)	..	..
Palmar-plantar erythrodysesthesia syndrome	39 (14%)	..	..	..	45 (16%)	..	..	..
Pain of skin	7 (3%)	..	..	..	7 (2%)	2 (1%)	..	..
Pruritus	7 (3%)	..	..	..	7 (2%)	1 (<1%)	..	..
Telangiectasia	..	1 (<1%)	..	..	1 (<1%)	..	..	..
Photosensitivity	..	..	..	..	..	1 (<1%)	..	..
Vascular disorders	31 (11%)	10 (4%)	1 (<1%)	2 (1%)	26 (9%)	7 (2%)	1 (<1%)	..
Thromboembolic event	17 (6%)	6 (2%)	1 (<1%)	2 (1%)	11 (4%)	2 (1%)	1 (<1%)	..
Hypertension	4 (1%)	3 (1%)	..	..	6 (2%)	4 (1%)	..	..
Haematoma	3 (1%)	..	..	..	..	1 (<1%)	..	..
Hypotension	..	1 (<1%)	..	..	..	..	..	..
Phlebitis	..	..	..	..	..	1 (<1%)	..	..

For each event type, data are shown as the number of patients as a percentage of the total of eligible patients who received treatment (n [%]). A patient may be counted in more than one row. Further detail and all grade toxicities are provided in the appendix (pp 14–21). GGT=γ-glutamyl transferase. *Grade 5 adverse events (ie, adverse events leading to death) were reported in three patients in the irinotecan group (one with multiorgan failure with sepsis; two with a thromboembolic event) and two patients in the standard-of-care group (one with febrile neutropenia with acidosis; one with cardiac arrest).

Table 3: **Any grade 3–5 adverse events and grade 1–2 adverse events in at least 10% of patients**

discharge (33 [14%] *vs* 34 [14%]), and second operation within 30 days (27 [11%] *vs* 26 [11%]). There was one death related to surgery in the standard-of-care group (appendix pp 21–22).

Completion rates for questionnaires relating to patient-reported outcomes for the pelvis were high in both treatment groups, with more than 95% of patients providing data at least once (appendix p 23). Follow-up completion declined over time yet remained broadly similar between irinotecan and standard-of-care groups and across male and female subgroups, with no meaningful differences in long-term questionnaire return beyond 12 months, 24 months, or 36 months. Self-reported moderate-to-severe adverse events at 12 months, 24 months, or 36 months after completion of standard-of-care therapy are summarised in the appendix (p 30). Most events occurred at similar frequencies in both treatment groups, with no statistically significant differences. Pain when opening the bowels and vaginal bleeding were significantly more common in the irinotecan group than in the standard-of-care group.

A planned sensitivity analysis of disease-free survival, which included any suspected or confirmed disease recurrence or death, was consistent with the primary analysis, with 120 events reported in the irinotecan group and 127 in the standard-of-care group (stratified HR 0·84 [95% CI 0·62–1·12], p=0·24). A post-hoc exploratory sensitivity analysis assessed disease-free survival and overall survival only in patients who received more than 90% of the radiotherapy dose. The stratified HRs were 0·89 (0·65–1·20; p=0·44) and 0·96 (0·67–1·37; p=0·83), respectively, and these findings did not alter our conclusions.

Discussion

There is no evidence that the addition of weekly concurrent irinotecan to standard-of-care capecitabine chemoradiotherapy improved histopathological complete response or disease-free survival in patients with MRI-defined, locally advanced rectal cancer. Adding irinotecan resulted in decreased radiotherapy and capecitabine compliance, and a higher rate of adverse events including diarrhoea and neutropenia. Patients in the irinotecan group were less likely to receive the full 45 Gy radiotherapy as scheduled, compared with those in the standard-of-care group, suggesting that additional gastrointestinal toxicity from irinotecan might have contributed to this difference.

Notably, the ARISTOTLE trial included important components to enhance the quality of its outputs. The use of MRI was mandated for all patients to define the high-risk population studied. The protocol included detailed radiotherapy and pathology guidance driving multidisciplinary management. The standardised radiotherapy protocol was developed through a series of national workshops, and ARISTOTLE used centralised radiotherapy quality assurance through a national body. The radiotherapy protocol was subsequently adopted in the UK as standard of care, so even though the trial did not show a treatment benefit, it still had an effect on routine clinical care for this patient group. Centralised, blinded pathology quality assurance was used for the assessment of histopathological complete response. Low

rates of circumferential resection margin involvement and local relapse were observed in both groups, indicating high-quality surgery and multidisciplinary care.

There are three main strategies to the intensification of therapy for locally advanced rectal cancer: (1) intensification of systemic anticancer therapy concomitantly with radiotherapy; (2) radiotherapy dose intensification; and (3) addition of sequential systemic anticancer therapy concomitantly with radiotherapy, the so-called total neoadjuvant therapy approach, which has gained traction with phase 3 clinical trials in the last 5 years.

Reviews in 2018 by Clifford and colleagues,[22] in 2019 by Hüttner and colleagues,[19] and in 2021 by Des Guetz and colleagues[23] assessed the addition of a second systemic agent in combination with chemoradiotherapy. These conclude little or no benefit using this approach with chemoradiotherapy. The 2018 review looked at a range of agents and suggested that there was no consistent increase in efficacy in randomised trials for any agent, including oxaliplatin.[22]

To our knowledge, ARISTOTLE is the largest phase 3 study globally that has evaluated irinotecan in combination with capecitabine, and the only study done in high-income countries. One other phase 3 RCT has been done in China. The smaller CinClare study of 360 patients investigated the addition of irinotecan to capecitabine-based chemoradiotherapy for rectal cancer among patients who had *UGT1A1* genotype **1/*1* or **1/*28*.[24] The authors of the CinClare study reported an improvement in histopathological complete response from 15% to 30% (risk ratio 1·96 [95% CI 1·30–2·97]; p<0·001). The longer-term follow-up paper[25] reported improvements in disease-free survival and overall survival that were not statistically significant, with HRs of 0·71 (p=0·10) and 0·73 (p=0·17), respectively. The CinClare trial concluded that irinotecan might have benefit as a potential contemporary treatment option. However, ARISTOTLE provides important contrasting evidence based on more patients (564 instead of 360) and more events. Disease-free survival rates in the control groups of these two studies are subtly different, with 3-year disease-free survival of 67% in ARISTOTLE and 5-year disease-free survival of 71% in CinClare. It is difficult to compare populations directly, as CinClare did not provide high-risk baseline features of MRI-defined lymphovascular invasion and pelvic sidewall lymph node involvement. However, when baseline characteristics of ARISTOTLE were matched to those of the two major practice-informing total neoadjuvant therapy trials, RAPIDO and PRODIGE-23,[6,7] high-risk features are similar, including circumferential resection margin status, T4, N+, pelvic sidewall lymph nodes, and lymphovascular invasion. There are also similarities in the disease-free survival rates reported in the control groups: 67% in ARISTOTLE, 69% 3-year disease-free survival in PRODIGE-23, and 70% 3-year disease-free survival in RAPIDO.

In terms of treatment tolerability, the CinClare study used *UGT1A1*-guided dosing to reduce irinotecan-related toxicity, a strategy not adopted in ARISTOTLE. There are pronounced differences in *UGT1A1* variants between Chinese and European populations that might affect irinotecan-related toxicities in the two studies. Neither trial evaluated *DPYD* status to inform capecitabine dosing. Irinotecan remains a debated component of neoadjuvant treatment. In rectal cancer, the PRODIGE-23 trial incorporated irinotecan during the induction chemotherapy phase before chemoradiotherapy in the investigational group. This approach has since become a standard of care, although the role of irinotecan remains controversial, in part due to the absence of a FOLFOX (folinic acid, fluorouracil, and oxaliplatin) comparator group, with other studies now assessing strategies that omit it. Within the context of total neoadjuvant therapy, the results of ARISTOTLE do not support the addition of concurrent irinotecan to capecitabine chemoradiotherapy when combined with doublet or triplet neoadjuvant chemotherapy. The ongoing phase 3 JANUS/NRG GI010 (NCT05610163) RCT explores FOLFOX versus mFOLFIRINOX as consolidation neoadjuvant chemotherapy after chemoradiotherapy and should report in 2–3 years.

There are other notable differences between ARISTOTLE and CinClare: ARISTOTLE used a lower radiotherapy dose (45 Gy *vs* 50 Gy) and, in the standard-of-care group, a higher capecitabine dose (900 mg/m² *vs* 825 mg/m²). Additionally, in CinClare, a single cycle of oxaliplatin and capecitabine was given after completion of chemoradiotherapy, but the histopathological complete response rates in the control group were similar at 18% (ARISTOTLE) and 15% (CinClare). Comparing the investigational groups, whereas the standard dose of weekly irinotecan 60 mg/m² was used for weeks 1–4 in ARISTOTLE, in CinClare the irinotecan dosing was guided by *UGT1A1* evaluation, with weekly irinotecan 80 mg/m² for patients with *UGT1A1* genotype **1*1* or 65 mg/m² for patients with *UGT1A1* genotype **1*28* (heterozygous). Thus, 25% of patients had the lower dose during weeks 1–5, and notably, no patients with *UGT1A1 *28*28* were included; the incidence was about 1% in Chinese populations and 12% in the UK population.[26] Capecitabine doses were similar, at 650 mg/m² and 625 mg/m², but in the interventional group of CinClare a single cycle of irinotecan and capecitabine was given after chemoradiotherapy as consolidation. The histopathological complete response rate in the interventional group was 19·9% in ARISTOTLE, lower than the 30% in CinClare.[6,7]

The main limitation of the current study was a lower number of expected disease-related events compared with our initial assumption, which had been supported by the evidence available at the time of trial design. The target effect size might have been overestimated, as subsequent phase 3 RCTs in rectal cancer have reported

only modest incremental benefits, suggesting that the study might be underpowered to detect smaller but clinically relevant differences.

Within ARISTOTLE, about 30% of patients relapsed with distant metastases, highlighting that this remains an important issue in rectal cancer management. Evidence published since 2021 indicates that sequential use of systemic anticancer therapy concomitantly with radiotherapy within a total neoadjuvant therapy approach can significantly reduce distant metastatic relapse.[6,7]

In conclusion, the ARISTOTLE trial shows no evidence of a benefit from the addition of irinotecan to standard chemoradiotherapy in either short-term or long-term oncological outcomes. Evaluation of patients by *UGT1A1* might be of value to further interrogate subgroups gaining a significant benefit from the use of irinotecan. Samples and data from ARISTOTLE have informed publications from 2024 that identify subgroups of patients with a high chance of histopathological complete response or clinical complete response, and those in whom intensification strategies are needed, either through a 33 gene signature or digital imaging of haematoxylin and eosin-stained sections from diagnostic biopsies.[27–29] We anticipate that future RCTs will look to further subdivide patients into biomarker-defined groups that can predict the likelihood of clinical complete response or disease-free survival (local and distant) with the potential to inform patient-based treatment decision strategies as to the benefit or otherwise of neoadjuvant or definitive non-surgical approaches.

Contributors

Concept and design: DS-M, SG, LMS, RA, AL, NW, PQ, ASM, and RG-J. Acquisition of data: DS-M, RA, SG, LMS, and NW. Verification of data: DS-M and AL. Drafting of the manuscript: AL, RA, SG, LMS, RB, DS-M, and NW. Critical revision of the manuscript for important intellectual content: all authors. Data analysis: AL, RA, DS-M, LMS, SG, RB, and EC. All authors had access to all the data reported in the study. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

DS-M was the chief investigator and received a study grant from Cancer Research UK to conduct the ARISTOTLE trial. NW received institutional payment from Cancer Research UK to conduct the ARISTOTLE study and received further institutional support from Yorkshire Cancer Research, GSK, Pierre Fabre, Roche Diagnostics, and the National Institute of Health Research (NIHR); payment from Bristol-Myers Squibb, Astellas, Pfizer, GSK, Amgen, Servier, and Beigene for consultation services; honoraria from Amgen; and has a patent with Roche Diagnostics. NB received consultancy fees from Eli Lilly for taking part in an advisory board, payment for honoraria from Pfizer, financial support for attending meetings or travel from AstraZeneca and Roche, and is the Chair of the Medicines Management Committee at Calderdale and Huddersfield NHS Foundation Trust. PQ received institutional support from the Yorkshire Cancer Research Programme and NIHR Leeds Biomedical Research Centre, and was previously the President of the Pathological Society of Great Britain and Ireland. RA has received payment for consultation services and honoraria from Takeda, Servier, and Bristol-Myers Squibb, payment for honoraria from Amgen and Seagen, and payment for consulting fees from Nordic Pharma. RGJ received payment for consultancy fees from Incyte Biosciences and Nanobiotix. SG received funding from Yorkshire Cancer Research and the Cancer Research UK Prospective Sample Collection Award. All other authors declare no competing interests.

Data sharing

De-identified individual participant data collected for this study, together with a data dictionary defining each field in the dataset, will be made available to others subject to approval of a proposal and a signed data sharing agreement. Related documents, including the study protocol and statistical analysis plan, will also be available. Data will be available from publication. Data sharing requests should be submitted to ctc.aristotle@ucl.ac.uk.

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