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Post-adjuvant chemotherapy in ctDNA-positive patients with resected colorectal cancer: a randomized phase 3 trial

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Tumor-informed circulating tumor DNA (ctDNA) enables detection of molecular residual disease (MRD) after curative resection of colorectal cancer (CRC), but whether early intervention improves outcomes remains uncertain. ALTAIR was a randomized, double-blind, phase 3 trial embedded in the CIRCULATE-Japan platform evaluating a post-adjuvant ctDNA surveillance strategy with treatment initiation upon molecular recurrence. Patients with resected stage 0–IV CRC who became ctDNA positive after completion of standard-of-care therapy and had no radiological evidence of disease were randomly assigned (1:1) to receive trifluridine/tipiracil (FTD/TPI) or placebo for 6 months. The primary endpoint was investigator-assessed disease-free survival (DFS). Between July 2020 and June 2023, 243 patients were randomized to FTD/TPI ($n = 122$) or placebo ($n = 121$). Median DFS was 9.30 months with FTD/TPI and 5.55 months with placebo (hazard ratio = 0.79, 95% confidence interval: 0.60–1.05, $P = 0.107$), and the primary endpoint was not met. FTD/TPI increased grade 3 or higher hematologic adverse events (73.0% versus 3.3%) without new safety signals. These findings indicate that post-adjuvant intervention with FTD/TPI did not significantly improve DFS in ctDNA-positive patients without radiological disease. ClinicalTrials.gov identifier: NCT04457297.

CRC continues to be one of the leading causes of cancer-related mortality worldwide, with approximately 154,270 new cases expected in the United States in 2025 (ref. 1). The standard of care (SoC) for high-risk stage II and stage III CRC involves surgical resection followed by adjuvant chemotherapy (ACT), guided by clinicopathological risk factors[2,3]. For locally advanced mismatch repair-proficient rectal cancer, total neoadjuvant therapy with more than 4 months of oxaliplatin-based preoperative chemotherapy and/or chemoradiotherapy, selected based on risk factors such as T4 status and extramural invasion, is the preferred treatment approach. After this, surgery or non-operative management is chosen depending on the treatment response[4–6]. For mismatch repair-deficient stage II or stage III rectal cancer, immune checkpoint inhibitor-based therapy with curative intent has emerged as a highly effective strategy and is increasingly adopted as a non-operative treatment approach in selected patients[6,7]. In cases of resectable stage IV or recurrent CRC, neoadjuvant, perioperative or adjuvant chemotherapy,

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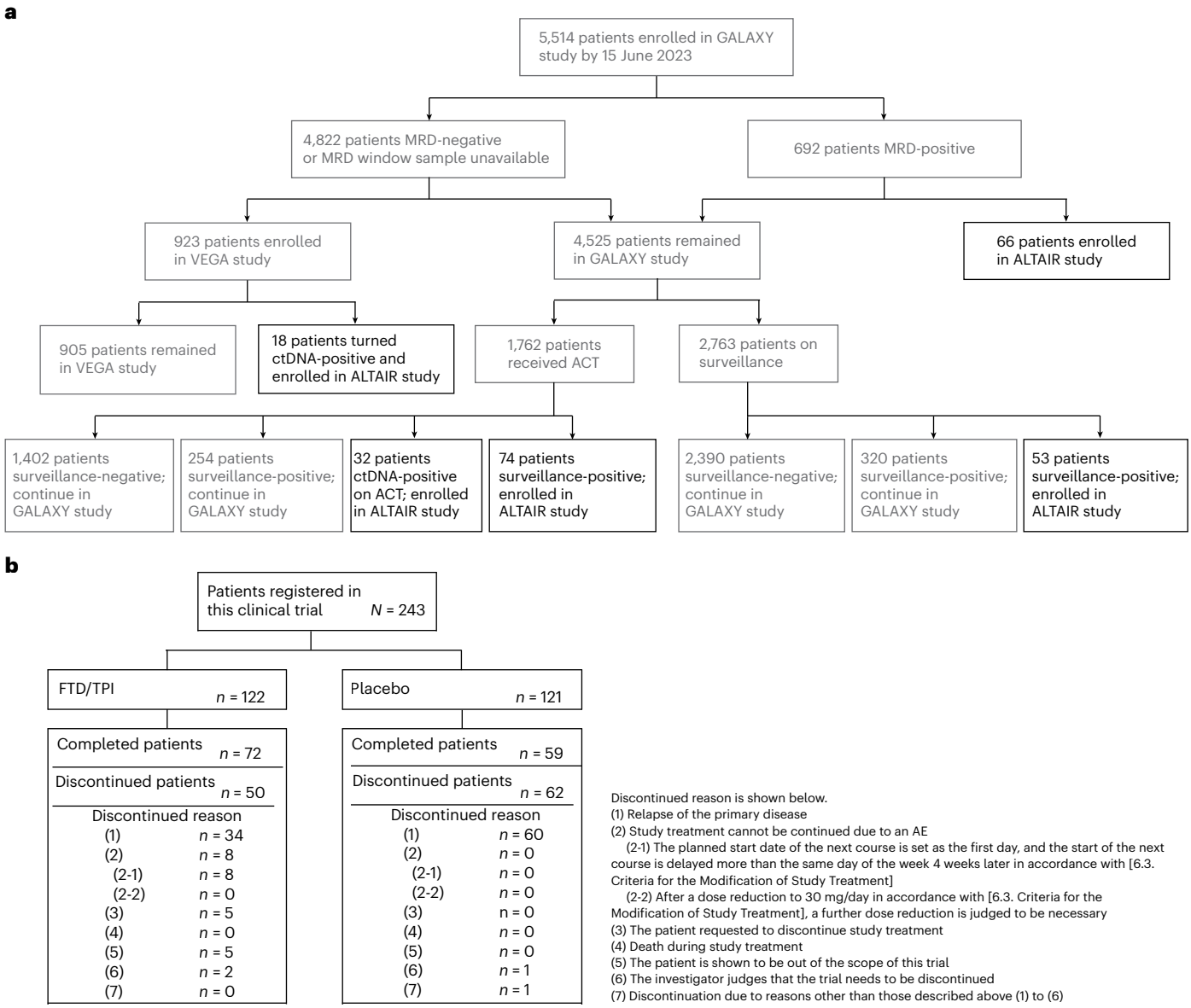

Fig. 1 | Patient inclusion and baseline characteristics. a, CONSORT diagram describing enrollment of patients with CRC (stage 0–IV, including unknown) in the ALTAIR trial during MRD, on-treatment (ACT) and surveillance enrollment windows. **b**, CONSORT diagram illustrating patients enrolled in the ALTAIR trial stratified by treatment received (placebo and FTD/TPI).

with or without targeted therapy, combined with metastasectomy or ablative therapy may also be considered[2,3].

Despite surgical intervention being largely curative, approximately 20% of patients with stage I–III CRC and 40–60% of resectable oligometastatic CRC experience disease recurrence. In high-risk stage II colon cancer, adjuvant therapy with single-agent 5-fluorouracil (5-FU) reduces mortality by an absolute 3–5%, whereas fluoropyrimidine-based therapy in stage III disease reduces mortality by 10–15%, with an additional 4–5% improvement observed when oxaliplatin is included[3]. Although the clinical benefits of ACT are limited to a minority of patients, systemic treatment is recommended for stage II patients with one or more high-risk clinicopathological features, for all stage III patients with colon cancer and for most patients with stage II and stage III rectal cancer[2,3]. For oligometastatic disease that is resectable or amenable to ablation, evidence supporting improved outcomes with perioperative or adjuvant systemic therapy remains limited[2,3,8].

ctDNA has emerged as a minimally invasive biomarker for MRD detection and disease monitoring after surgery, during surveillance and across treatment phases. Evidence from the CIRCULATE-Japan project has demonstrated the strong prognostic value of ctDNA for recurrence risk, with post-surgical ctDNA positivity being strongly associated with increased recurrence and shorter DFS and overall survival (OS), whereas ctDNA-negative patients have a substantially lower risk of relapse[9,10]. Evidence supporting ctDNA-guided ACT decision-making for stage II colon cancer has emerged from the randomized DYNAMIC-II trial, which demonstrated non-inferior recurrence-free survival with reduced chemotherapy use compared to standard management. However, the randomized DYNAMIC-III trial failed to demonstrate improved outcomes with ctDNA-guided treatment escalation or deescalation for stage III colon cancer[11,12]. In contrast to MRD window trials that guide adjuvant treatment decisions immediately after surgery, the ALTAIR trial evaluates a post-adjuvant ctDNA surveillance strategy with early intervention upon molecular recurrence. This strategy may offer the opportunity to introduce treatment in a previously underexplored setting and potentially increase the proportion of patients who can be cured. However, this approach targets a relatively small subset of patients with molecular recurrence (ctDNA positivity) and early clinical relapse, which may pose challenges for timely identification, patient accrual and trial feasibility.

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FTD/TPI has demonstrated antitumor activity in CRC cell lines and xenograft models resistant to 5-FU[13]. In the RECOURSE phase 3 trial, FTD/TPI significantly improved OS in patients with refractory metastatic CRC who had progressed after standard chemotherapy regimens, including 5-FU, oxaliplatin, irinotecan, bevacizumab and anti-EGFR antibodies (in *KRAS* wild-type tumors) (7.1 months versus 5.3 months with placebo; hazard ratio (HR) = 0.68, 95% CI: 0.58–0.81, $P < 0.001$)[14]. These results indicate the potential efficacy of FTD/TPI in patients with MRD after curative-intent surgery and SoC adjuvant therapies. Notably, multiple irinotecan-based adjuvant trials, including studies evaluating FOLFIRI in the postoperative setting, have failed to demonstrate a survival benefit, suggesting limited rationale for irinotecan-based regimens as MRD-directed therapy[15,16].

The ALTAIR trial, part of the CIRCULATE-Japan project, aims to evaluate the efficacy of FTD/TPI compared to placebo in patients with CRC who have undergone curative resection of primary and/or metastatic sites and SoC adjuvant treatment if indicated and have no recurrence on radiological imaging[17]. This phase 3, double-blind, randomized study seeks to determine whether FTD/TPI can improve outcomes in patients identified as high risk by ctDNA-based MRD assessment.

Results

Patient cohort

From 5 June 2020 to 15 June 2023, a total of 5,514 patients with resectable clinical stage 0–IV CRC across 152 sites in Japan and Taiwan were enrolled in the GALAXY observational study within the CIRCULATE-Japan platform. Among them, 1,104 patients were identified as ctDNA positive by Signatera at any timepoint after surgery, 243 of whom were enrolled in the ALTAIR trial (Fig. 1a and Extended Data Fig. 1). These 243 patients were randomly assigned to receive either FTD/TPI ($N = 122$) or placebo ($N = 121$). All 243 patients received at least one dose of their assigned treatment (FTD/TPI or placebo) and were included in the intention-to-treat (ITT), full analysis set (FAS) and safety population. The median follow-up for this analysis was 23.29 months (range, 18.43–23.52). A total of 72 patients in the FTD/TPI group and 59 patients in the placebo group completed the study treatment, whereas 50 and 62 patients, respectively, discontinued treatment. The primary reason for treatment discontinuation in both groups was disease relapse (Fig. 1b). Notably, when comparing ctDNA-positive patients enrolled in the ALTAIR trial with those in the non-ALTAIR population—defined as patients who were screened but did not participate in the ALTAIR trial—baseline ctDNA levels were significantly higher in the non-ALTAIR population (Extended Data Fig. 2).

Baseline demographic and clinical characteristics were well balanced between the treatment groups. Overall, 96.3% of patients received guideline-concordant postoperative management, defined as either observation alone or ACT according to disease stage and Japanese clinical practice guidelines; the remaining nine patients had stage III disease but did not receive ACT after surgery, per physician's discretion (Table 1). Most patients were male ($n = 142$, 58.4%) and under 70 years of age ($n = 155$, 63.8%). The primary tumor site was located in the left-sided colon or rectum in 173 patients (71.2%). Disease stage at diagnosis was distributed as follows: stage I (10/243, 4.1%), stage II (58/243, 23.9%), stage III (109/243, 44.9%) and stage IV (66/243, 24.2%). A total of 112 patients (46.1%) received ACT. Patients were enrolled at three distinct time windows: during the MRD window (58/243, 23.9%), defined as 2–10 weeks after surgery and prior to the initiation of adjuvant therapy (if administered); on-treatment (during ACT) (33/243, 13.6%); and during the surveillance window after definitive therapy (152/243, 62.6%) (Table 1). The median time from surgery to the baseline pre-enrollment ctDNA positivity was 255 days (range, 72–687 days; interquartile range (IQR), 171 days) in the surveillance group.

Table 1 | Patient and tumor characteristics ($N = 243$)

Characteristic	All	By ALTAIR arm	
	$N = 243$[a]	Placebo, $N = 121$[a]	FTD/TPI, $N = 122$[a]
Age, years			
<70	155 (64%)	78 (64%)	77 (63%)
>70	88 (36%)	43 (36%)	45 (37%)
Sex			
Male	142 (58%)	71 (59%)	71 (58%)
Female	101 (42%)	50 (41%)	51 (42%)
Primary site			
Right-sided colon	60 (26%)	29 (24%)	31 (25%)
Left-sided colon	127 (52%)	64 (53%)	63 (52%)
Rectum	46 (19%)	22 (18%)	24 (20%)
Unknown	10 (4%)	6 (5%)	4 (3%)
Stage			
I	10 (4.1%)	3 (2.5%)	7 (5.7%)
II	58 (24%)	30 (25%)	28 (23%)
III	109 (45%)	56 (46%)	53 (43%)
IV	66 (27%)	32 (26%)	34 (28%)
Neoadjuvant treatment	87 (36%)	41 (34%)	46 (38%)
Adjuvant treatment	112 (46%)	56 (46%)	56 (46%)
Recurrence events	198 (81.48%)	99 (81.15%)	99 (81.82%)
ctDNA 1 month postoperative			
Negative	113 (47%)	56 (46%)	57 (47%)
Positive	130 (53%)	65 (54%)	65 (53%)
Enrollment timepoint			
MRD window[b]	58 (24%)	30 (25%)	28 (23%)
On-treatment	33 (14%)	19 (16%)	14 (11%)
Surveillance	152 (63%)	72 (60%)	80 (66%)
BRAF			
$BRAF^{wt}$	234 (96%)	118 (98%)	116 (95%)
$BRAF^{V600E}$	9 (3.7%)	3 (2.5%)	6 (4.9%)
RAS			
RAS^{wt}	148 (61%)	79 (65%)	69 (57%)
RAS^{mut}	95 (39%)	42 (35%)	53 (43%)
MSI			
MSS	238 (98%)	118 (98%)	120 (98%)
MSI-high	5 (2.1%)	3 (2.5%)	2 (1.6%)

[a]*n* (%). [b]The MRD window was defined as 2–10 weeks after surgery and before the start of any adjuvant therapy. All statistical tests, where applicable, were two-sided. MSI, microsatellite instability; MSS, microsatellite stable; mut, mutant; wt, wild-type.

Treatment efficacy

The median DFS was 9.30 months (range, 7.92–10.84) in the FTD/TPI group and 5.55 months (range, 4.17–7.33) in the placebo group. Although this result demonstrated a numerical advantage for the FTD/TPI group, the difference did not reach statistical significance in the primary population, including all stages (HR = 0.79, 95% CI: 0.60–1.05, $P = 0.107$) (Fig. 2a). Thus, the trial did not meet its protocol-defined primary endpoint of improving investigator-assessed DFS at a two-sided α level of 0.05, and all subsequent analyses are exploratory, including subgroup analyses and the post hoc blinded central radiology review. A notable benefit of FTD/TPI over placebo in the overall population was observed at 6-month DFS of 70.5% (61.5–77.7) versus 45.5% (36.4–54.0) for placebo. Additionally, stage IV disease alone appeared to derive significant benefit from FTD/TPI versus placebo (HR = 0.53, $P = 0.012$) (Fig. 2b),

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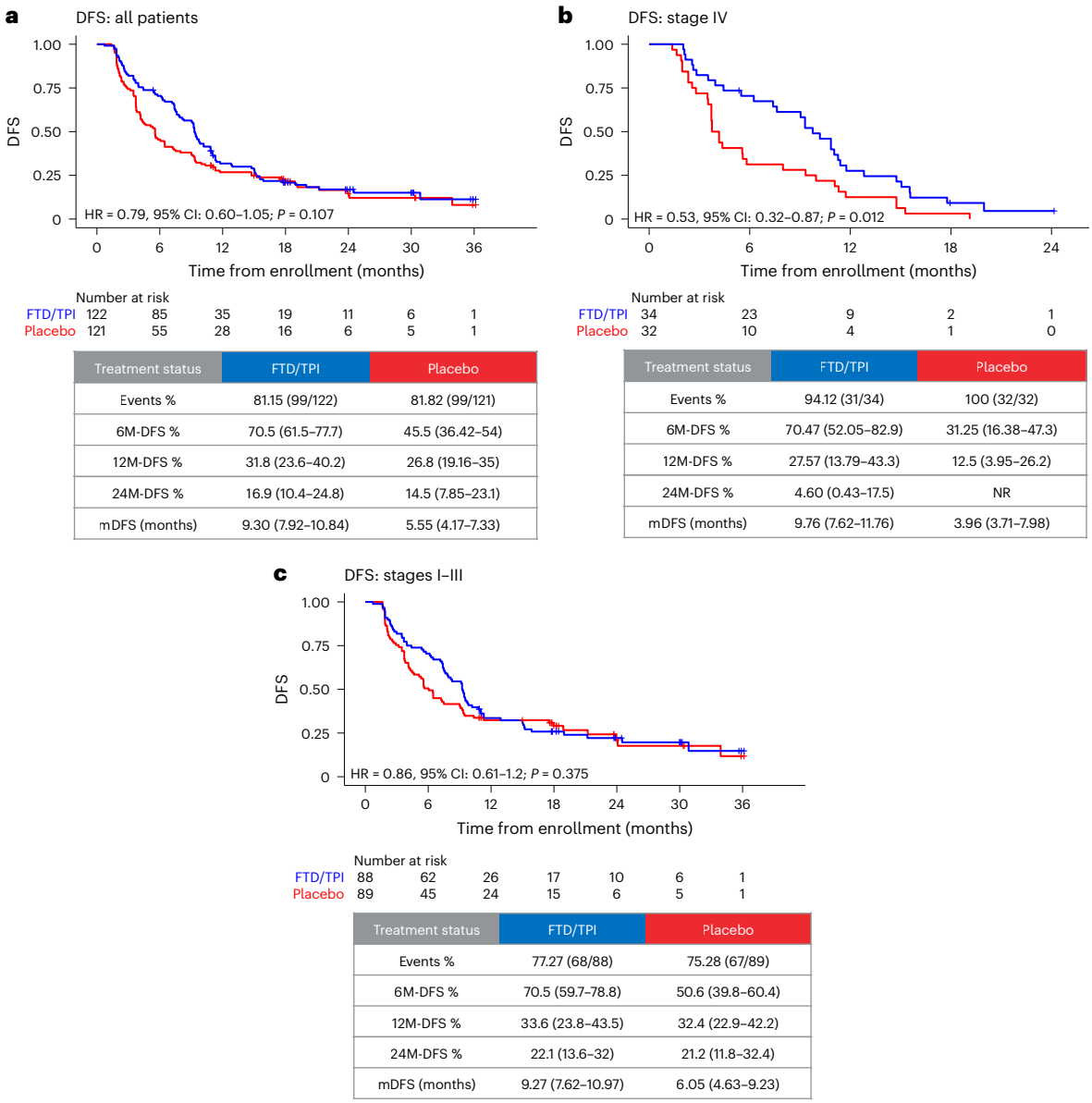

Treatment status	FTD/TPI	Placebo
Events %	81.15 (99/122)	81.82 (99/121)
6M-DFS %	70.5 (61.5–77.7)	45.5 (36.42–54)
12M-DFS %	31.8 (23.6–40.2)	26.8 (19.16–35)
24M-DFS %	16.9 (10.4–24.8)	14.5 (7.85–23.1)
mDFS (months)	9.30 (7.92–10.84)	5.55 (4.17–7.33)

Treatment status	FTD/TPI	Placebo
Events %	94.12 (31/34)	100 (32/32)
6M-DFS %	70.47 (52.05–82.9)	31.25 (16.38–47.3)
12M-DFS %	27.57 (13.79–43.3)	12.5 (3.95–26.2)
24M-DFS %	4.60 (0.43–17.5)	NR
mDFS (months)	9.76 (7.62–11.76)	3.96 (3.71–7.98)

Treatment status	FTD/TPI	Placebo
Events %	77.27 (68/88)	75.28 (67/89)
6M-DFS %	70.5 (59.7–78.8)	50.6 (39.8–60.4)
12M-DFS %	33.6 (23.8–43.5)	32.4 (22.9–42.2)
24M-DFS %	22.1 (13.6–32)	21.2 (11.8–32.4)
mDFS (months)	9.27 (7.62–10.97)	6.05 (4.63–9.23)

Fig. 2 | Association of ctDNA status with DFS in patients stratified by clinical stage. a–**c**, Kaplan–Meier estimates for DFS for FTD/TPI versus placebo in all patients ($n = 243$, $P = 0.107$) (**a**), in stage IV ($n = 66$, $P = 0.012$) (**b**) and in stages I–III ($n = 177$, $P = 0.375$) (**c**). HRs and 95% CIs were calculated using the Cox proportional hazards model; *P* values were calculated using the two-sided log-rank test. For **a**, the HR was stratified by stage (stage II or lower versus stage III or M1) and ctDNA status at 1 month after surgery (positive versus negative/unmeasured). M, month; NR, not reached; mDFS, median disease-free survival.

whereas no significant clinical benefit was detected in patients with stage I–III disease (HR = 0.86, $P = 0.375$) (Fig. 2c). Because these subgroup analyses were not adjusted for multiplicity, the apparent benefit in stage IV disease should be considered exploratory and hypothesis generating. Furthermore, we evaluated DFS stratified by treatment arm at different enrollment windows (MRD, on-treatment and surveillance). Although there was no significant overall difference in DFS between the two treatment arms by enrollment window (Extended Data Fig. 3a–c), we observed a numerical improvement in 6-month DFS for FTD/TPI patients enrolled during the MRD and surveillance windows ($P = 0.035$ and $P < 0.001$, respectively) (Extended Data Fig. 3a,c). Notably, among patients enrolled during the on-treatment window, DFS was numerically worse with FTD/TPI than with placebo, although numbers were small. These comparisons were exploratory and unadjusted for multiplicity and should, therefore, be interpreted with caution. Likewise, no significant differences were observed in the ctDNA mean tumor molecules per milliliter (MTM/ml) levels between the treatment arms at different

Table 2 | Baseline MTM/ml levels at enrollment timepoints

	Number	Baseline MTM/ml (median)
Primary population	243	0.40
Stage at diagnosis		
Stage I	10	0.19
Stage II	58	0.29
Stage III	109	0.38
Stage IV	66	0.68
Enrollment timepoint		
MRD window	58	0.97
On-treatment	33	0.82
Surveillance window	152	0.24

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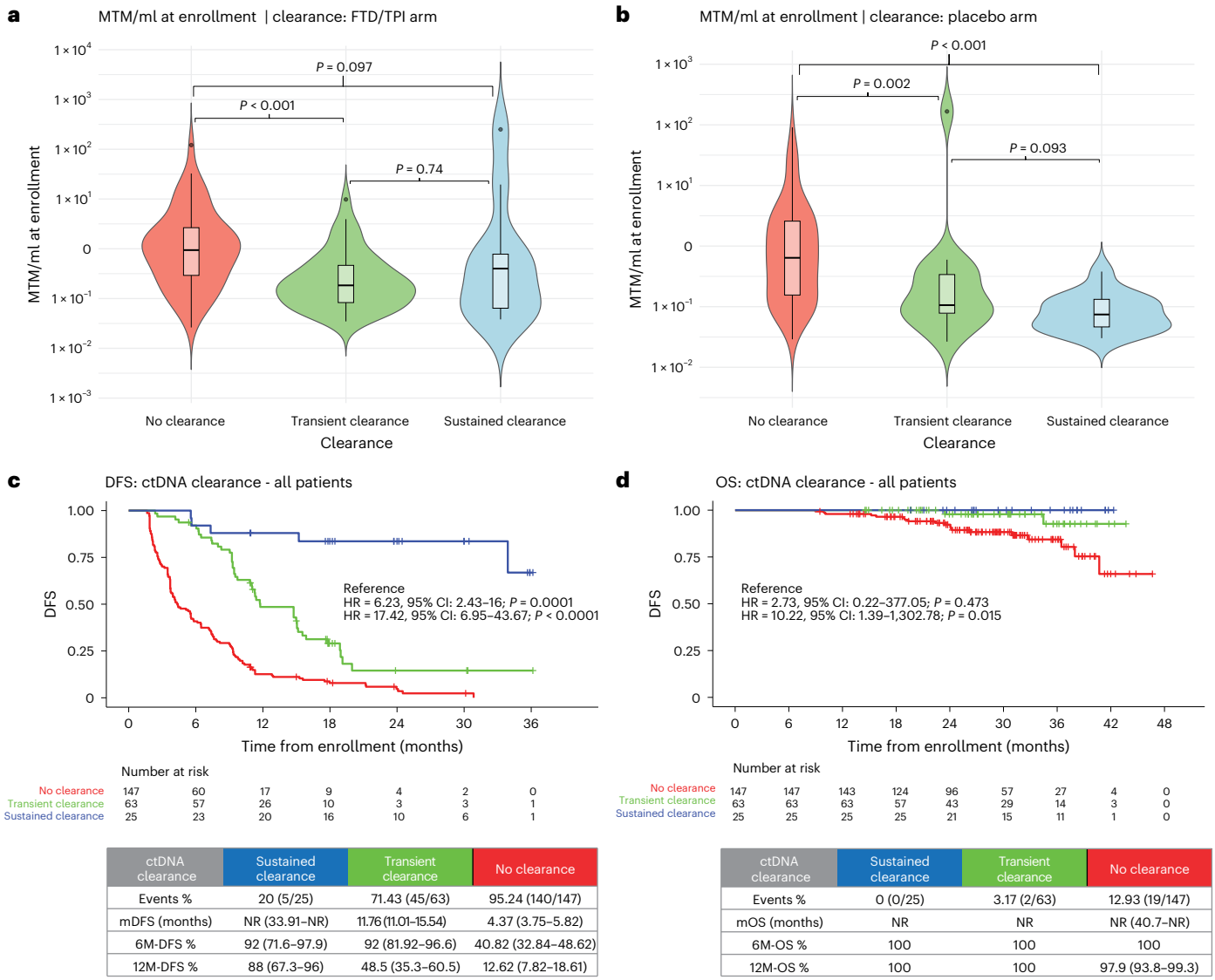

ctDNA clearance	Sustained clearance	Transient clearance	No clearance
Events %	20 (5/25)	71.43 (45/63)	95.24 (140/147)
mDFS (months)	NR (33.91–NR)	11.76 (11.01–15.54)	4.37 (3.75–5.82)
6M-DFS %	92 (71.6–97.9)	92 (81.92–96.6)	40.82 (32.84–48.62)
12M-DFS %	88 (67.3–96)	48.5 (35.3–60.5)	12.62 (7.82–18.61)

ctDNA clearance	Sustained clearance	Transient clearance	No clearance
Events %	0 (0/25)	3.17 (2/63)	12.93 (19/147)
mOS (months)	NR	NR	NR (40.7–NR)
6M-OS %	100	100	100
12M-OS %	100	100	97.9 (93.8–99.3)

Fig. 3 | Association of ctDNA clearance with clinical outcomes. a,**b**, Violin plots showing MTM/ml levels according to ctDNA clearance status (transient, sustained, no clearance) in the FTD/TPI (**a**; $n = 122$) and placebo (**b**; $n = 121$) arms at enrollment. The violin plots represent the distribution of the data. The center line indicates the median, the box indicates the IQR (25th–75th percentiles), whiskers extend to the most extreme data points within 1.5× IQR, and points beyond this range are shown as outliers. *P* values were calculated using the two-sided Wilcoxon rank-sum test. **c**,**d**, Kaplan–Meier estimates for DFS (**c**) and OS (**d**) according to ctDNA clearance status (sustained, transient, no clearance; $n = 235$). HRs and 95% CIs were calculated using the Cox proportional hazards model; *P* values were calculated using the two-sided log-rank test. mOS, median overall survival.

enrollment windows (Extended Data Fig. 3d). The MTM/ml values shown in Fig. 3d represent baseline ctDNA burden measured at the time of trial enrollment rather than longitudinal changes in ctDNA levels.

The mean ± s.d. of treatment completion rates was 77.87 ± 30.26% in the FTD/TPI group and 78.79 ± 25.46% in the placebo group, indicating similar treatment completion rates between the two groups ($P = 0.798$). The median DFS2, defined as the time to DFS events plus the occurrence of secondary cancers other than CRC, was 9.30 months in the FTD/TPI group and 5.55 months in the placebo group (HR = 0.78, 95% CI: 0.58–1.02, $P = 0.073$). OS data remain immature, with only 24 events reported across both treatment arms at a median follow-up of 23.29 months.

Post hoc independent blinded central radiological review (exploratory sensitivity analysis)

To assess the robustness of the primary endpoint to potential interobserver variability, we performed a post hoc, independent, blinded central radiological review of baseline and follow-up imaging in 242 of 243 patients. This analysis was not prespecified in the original statistical analysis plan and was undertaken after database lock as a sensitivity analysis. Local and central assessments were generally concordant, with only 10 patients reclassified (four from non-recurrence to recurrence and six from recurrence to non-recurrence); overall agreement was 95.9% with a Cohen's κ of 0.866 (Extended Data Table 1). Based on the centrally adjudicated events, median DFS was 9.23 months with FTD/TPI and 5.55 months with placebo (HR = 0.75, 95% CI: 0.55–0.98, $P = 0.0406$) (Extended Data Fig. 4).

An influence (tipping-point) analysis restricted to these discordant cases showed that statistical significance was lost only after reverting multiple reclassified events, indicating that the result was not driven by a single discrepant case. Notably, this exploratory sensitivity analysis yielded an HR similar in magnitude to the protocol-defined primary analysis and does not alter the overall conclusion that ALTAIR did not meet its primary endpoint in the ITT population.

Association of post-surgical ctDNA status and levels with DFS

We evaluated the benefit of FTD/TPI in patients stratified by ctDNA status in the MRD window. No significant difference in DFS was observed

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Table 3 | Safety and AEs

Item	FTD/TPI		Placebo	
Number of patients in the analysis population	122		121	
	n (%)		*n* (%)	
AEs	120 (98.4)		69 (57.0)	
AEs of grade 3 or higher	89 (73.0)		4 (3.3)	
Serious AEs	6 (4.9)		0 (0.0)	
AEs leading to study discontinuation	8 (6.6)		0 (0.0)	
AEs leading to death	0 (0.0)		0 (0.0)	
	All grades	Grade 3 or higher	All grades	Grade 3 or higher
	n (%)	*n* (%)	*n* (%)	*n* (%)
Neutrophil count decreased	91 (74.6)	69 (56.6)	5 (4.1)	0 (0.0)
White blood cell count decreased	78 (63.9)	21 (17.2)	4 (3.3)	0 (0.0)
Platelet count decreased	15 (12.3)	2 (1.6)	4 (3.3)	0 (0.0)
Lymphocyte count decreased	10 (8.2)	5 (4.1)	1 (0.8)	0 (0.0)
Leading to dose skipping	116 (95.1)	77 (63.1)	14 (11.6)	1 (0.8)
Leading to dose reduction	46 (37.7)	32 (26.2)	1 (0.8)	0 (0.0)

n, number of incidence patients (%), incidence rate (*n*/number of patients in the analysis population×100).

in both the ctDNA-positive (HR = 0.72, 95% CI: 0.5–1.04, $P = 0.079$) and the ctDNA-negative (HR = 0.91, 95% CI: 0.59–1.4, $P = 0.662$) patient population with FTD/TPI versus placebo (Extended Data Fig. 5).

However, ctDNA levels stratified based on baseline (enrollment) timepoint revealed distinct patterns. The median baseline MTM/ml levels for patients with stage I, stage II, stage III and stage IV disease were 0.19 MTM/ml, 0.29 MTM/ml, 0.38 MTM/ml and 0.68 MTM/ml (Kruskal–Wallis rank-sum test, $P = 0.07264$), respectively (Table 2), indicating a substantially higher molecular tumor burden with higher stage.

ctDNA clearance and its association with DFS

The ctDNA clearance rate, defined as the proportion of patients who tested negative for ctDNA at the first assessment after completion of the study treatment, was 17.2% (95% CI: 11.0–25.1) in the FTD/TPI group and 12.4% (95% CI: 7.1–19.6) in the placebo group ($P = 0.367$). We then stratified ctDNA dynamics into three categories: sustained clearance, defined as serial ctDNA negativity after study treatment; transient clearance, defined as ctDNA negativity during or after study treatment followed by ctDNA positivity at one or more timepoints; and no clearance, where ctDNA remained persistently positive after the initiation of study treatment.

When evaluating ctDNA dynamics across the cohort, patients with no clearance or transient clearance had significantly worse DFS (no clearance ($N = 147$): HR = 17.42, 95% CI: 6.95–43.67, $P < 0.0001$; transient clearance ($N = 63$): HR = 6.23, 95% CI: 2.43–16, $P = 0.0001$) compared to patients with sustained clearance ($N = 25$). The corresponding median DFS values for no clearance, transient clearance and sustained clearance were 4.37 months, 11.76 months and not reached, respectively (Fig. 3c). Similar results were observed for OS (no clearance: HR = 10.22, 95% CI: 1.39–1,302.78, $P = 0.015$; transient clearance: HR = 2.73, 95% CI: 0.22–377.05, $P = 0.473$) (Fig. 3d).

In the FTD/TPI group, the median baseline ctDNA levels for patients with no clearance, transient clearance and sustained clearance were 0.95, 0.18 and 0.4 MTM/ml, respectively (Fig. 3a). By contrast, the median baseline ctDNA levels in the placebo group were 0.64, 0.11 and 0.07 MTM/ml, respectively (Fig. 3b). Notably, 9.6% (11/115) of placebo-treated patients met the definition of ctDNA clearance, suggesting that low-level biological fluctuation or non-persistent ctDNA positivity may account for some baseline positive results. On further evaluating clearance patterns for each arm, in the FTD/TPI arm, sustained, transient and no clearance were observed in 11 of 120 (9.2%), in 47 of 120 (39.2%) and in 62 of 120 (51.7%) patients, respectively; in the placebo arm, the corresponding numbers were 14 of 115 (12.2%), 16 of 115 (13.9%) and 85 of 115 (73.9%) patients (Extended Data Fig. 6a,b), indicating that ctDNA dynamics function as a post-baseline prognostic marker.

Safety and adverse events

Adverse events (AEs) of any grade were reported in 120 patients (98.4%) in the FTD/TPI arm and in 69 patients (57.0%) in the placebo arm. Grade 3 or higher AEs occurred in 89 patients (73.0%) in the FTD/TPI arm compared to four patients (3.3%) in the placebo arm. Among grade 3 or higher AEs exceeding an incidence of 10% in the FTD/TPI arm, a decrease in the neutrophil count was observed in 69 patients (56.6%), and a decrease in white blood cell count was seen in 21 patients (17.2%). Dose reduction due to AEs was required in 37.7% of patients in the FTD/TPI group, and 95.1% of those patients skipped at least one dose, compared to 0.8% and 11.6%, respectively, in the placebo group. No treatment-related deaths were reported in either arm, and no new safety signals were identified (Table 3). Given that the trial did not meet its primary endpoint, these toxicity findings underscore the importance of weighing the high incidence of grade 3 or higher hematologic AEs against the modest, non-statistically significant, exploratory differences in DFS observed between treatment arms.

Patient-reported outcomes

In the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) assessment, Global Health Status/Quality of Life (QoL) scores significantly worsened in the FTD/TPI group during the treatment period, with a notable difference observed at week 8 ($P = 0.028$). However, after treatment completion (week 24 onward), the difference between the two groups was minimal. Improvements from baseline that were significantly greater in the FTD/TPI group compared to the placebo group were observed in the following functional scales: Physical Functioning (week 16), Role Functioning (week 8), Cognitive Functioning (week 32) and Social Functioning (weeks 8, 24 and 32). Regarding symptom scales, a significant improvement was observed only in Appetite Loss at week 40 in the FTD/TPI group (Supplementary Table 1).

In the EuroQol 5-Dimension, 5-Level (EQ-5D-5L) assessment, baseline scores were similar between groups. Throughout the study period (excluding week 48), the placebo group consistently showed a trend of greater improvement. Similarly, Visual Analog Scale (VAS) scores revealed no significant baseline differences, yet the placebo group demonstrated more consistent improvement across almost all timepoints, except for week 40, compared to the FTD/TPI group (Supplementary Table 2).

Discussion

The ALTAIR trial, conducted as part of the CIRCULATE-Japan project, is, to our knowledge, the first phase 3 study to evaluate and report results on the efficacy of interventional therapy with FTD/TPI in patients identified as high risk through ctDNA-based MRD assessment. Previously, Mayer et al.[14] demonstrated that FTD/TPI significantly improved OS among patients with refractory metastatic CRC who had progressed despite standard chemotherapy regimens. Based on these findings, we sought to evaluate the efficacy of FTD/TPI in MRD-positive patients after curative-intent surgery for CRC and SoC adjuvant therapy if indicated.

Our study demonstrates, again to our knowledge, the first randomized phase 3 trial of treat on molecular recurrence (TOMR) to

successfully complete enrollment. In the protocol-defined primary analysis, however, FTD/TPI did not significantly improve DFS (median DFS of 9.3 months versus 5.5 months; HR = 0.79, $P = 0.107$), and, thus, the trial did not meet its primary endpoint. All subsequent analyses—including central imaging review, subgroup analyses and ctDNA burden analyses—are exploratory and not adjusted for multiplicity. In exploratory analyses, a statistically significant benefit in DFS was observed with FTD/TPI compared to placebo in patients with oligometastatic stage IV disease (median DFS of 9.7 months versus 3.9 months; HR =0.53, $P = 0.012$), a subgroup with higher baseline ctDNA burden. In addition, a post hoc blinded central review demonstrated a significant DFS advantage with FTD/TPI across all patients (median DFS 9.23 months versus 5.55 months; HR =0.75, $P = 0.0406$). Additional follow-up of this cohort, which includes OS data, may provide valuable insights into the potential role of FTD/TPI in improving survival outcomes among patients with CRC after curative resection.

More recently, in the DYNAMIC-III trial, the ctDNA-positive cohort was evaluated within a phase 2 exploratory escalation component, and ctDNA-guided treatment escalation did not demonstrate an improvement in recurrence-free survival compared to standard chemotherapy in stage III CRC[12]. This trial randomized patients to different escalation strategies, including singlet, doublet and triplet chemotherapy, and different durations, which makes it difficult to isolate the effect of any single agent. By contrast, ALTAIR was designed to evaluate a uniform intervention—FTD/TPI—against placebo after completion of SoC treatment, allowing a clearer assessment of drug-specific efficacy in the MRD-positive setting. This difference in trial design may partially account for the distinct DFS patterns observed in ALTAIR compared to DYNAMIC-III. Early PEGASUS data similarly suggest that irinotecan-based escalation may achieve ctDNA clearance without convincing evidence of sustained clinical benefit[18]. In the refractory metastatic setting, the addition of bevacizumab to FTD/TPI has been shown to improve survival outcomes compared to FTD/TPI alone[19]. Although bevacizumab has not demonstrated efficacy in the adjuvant setting[20], these data raise the hypothesis that combining FTD/TPI with antiangiogenic agents could be explored in future TOMR trials. Taken together, these findings indicate that, although ctDNA-guided treatment intensification is biologically appealing, its clinical utility depends critically on the choice of therapeutic agent and the consistency of the treatment strategy being evaluated. Although ALTAIR did not meet its primary endpoint, the data support the feasibility of MRD-guided approaches for adjuvant and post-adjuvant therapy selection and administration, and future randomized trials using consistent MRD-directed interventions will be essential.

For the target population of ctDNA-positive, clinically disease-free patients, the FTD/TPI toxicity profile is a critical consideration. Although the decline in the EORTC QLQ-C30 Global Health Status/QoL scores during treatment was temporary and resolved after cessation, the high incidence of grade 3 or higher hematologic toxicities (including grade 3 or higher neutropenia in approximately 57% of patients), contrasted with the modest, non-statistically significant absolute differences in DFS in the overall population, highlights the need to carefully weigh the exploratory efficacy signals against the treatment burden.

This study has several limitations. The primary analysis did not reach statistical significance, despite the FTD/TPI group having a numerically longer DFS of 9.30 months compared to 5.55 months for placebo. A post hoc central radiological review identified 10 discordant cases and demonstrated a statistically significant DFS benefit, but these non-prespecified findings must be interpreted as an exploratory sensitivity analysis. Future ctDNA-guided CRC trials should incorporate a prespecified blinded independent central radiological review for a more standardized evaluation. Finally, heterogeneity in the enrolled population with patients entering at different timepoints (MRD, on-treatment and surveillance windows), and some having received ACT prior to enrollment, may have confounded the study outcomes. In particular, no benefit—and a numerically worse DFS—was observed among patients enrolled after ctDNA positivity during ACT, although the sample size was limited. OS data remain immature at a median follow-up of 2 years, with only 24 death events observed. Consequently, OS findings should be considered exploratory, and our data likely reflect earlier treatment of subclinical metastatic disease rather than a durable survival benefit, as a detailed OS analysis would be underpowered. Additionally, our study did not prospectively collect data on systemic therapies administered after completion of the study treatment. As a result, we cannot formally assess whether early use of FTD/TPI in the MRD setting influenced subsequent treatment sequencing or access to later-line SoC therapies, including combination regimens with bevacizumab. Future MRD-guided interventional trials should prospectively capture post-progression treatment patterns to enable a more comprehensive evaluation of downstream clinical impact.

Our findings suggest that patients with a higher baseline molecular tumor burden appeared to derive greater benefit from FTD/TPI; however, patients with high anatomic tumor burden and radiological recurrence were excluded from the study design, which confounded the overall observable treatment effect in this study population. This underscores the clinical heterogeneity inherent in the study population and highlights the challenge of fully capturing the therapeutic potential of FTD/TPI within a selectively lower-risk trial cohort.

Furthermore, the study's design anticipated a one-third reduction in recurrence risk (median DFS of 8 months for placebo and 12 months for FTD/TPI). Although initial median DFS results (5.55 months versus 9.30 months) seemed promising, the efficacy did not confer a durable disease control and waned by 24 months, with the difference in DFS narrowing (HR of 0.921) (as calculated by dividing the negative natural logarithm of the 24-month DFS in the FTD/TPI and placebo arms: HR = 0.772 / 0.839 = 0.921). This pattern is consistent with a recurrence-delaying, rather than curative, effect, as also reflected in restricted mean survival time (RMST) and milestone analyses (Extended Data Table 2A). It is also noted that the initial assumptions about treatment benefit for ctDNA-positive patients were based on limited understanding as data from the GALAXY observational study—part of the CIRCULATE-Japan project—were immature at the time of trial design.

In conclusion, although the ALTAIR study did not demonstrate a statistically significant difference in efficacy, ctDNA-based analyses suggest that the administration of FTD/TPI may help delay recurrence in patients with CRC who have undergone curative resection, received SoC adjuvant treatment and have shown no evidence of recurrence on radiological imaging. Appropriate trial designs and statistical plans should account for real-world time to recurrence after MRD positivity, heterogeneity of enrollment across treatment settings, the potential for spontaneous ctDNA clearance and the statistical impact of excluding patients with overt metastatic disease.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-026-04428-0.

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Methods

Ethical approval and consent

This trial was conducted in accordance with Good Clinical Practice (GCP) guidelines and adhered strictly to the study protocol. The protocol received approval from the institutional review board (IRB) or independent ethics committee (IEC) at each participating study site. All patients provided written informed consent, and the trial was performed in line with the ethical principles of the Declaration of Helsinki. A full list of IRBs/IECs is provided in Supplementary Information.

Patients

We enrolled patients aged 20 years or older with histopathologically diagnosed CRC (stage II or lower, stage III or oligometastatic stage IV) who had undergone radical resection of the primary and/or metastatic tumors. Enrollment required a positive ctDNA test result using Signatera from blood samples collected within 3 months of any timepoint between 1 month and 24 months after surgery. Additional inclusion criteria included eligibility for postoperative ACT as per national guidelines or medical practice, no radiographic evidence of relapse, ability to ingest medication orally, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and absence of major organ disorders, diarrhea or stomatitis. In Japanese clinical practice, ACT is generally recommended for patients with high-risk stage II and stage III colon cancer. For rectal cancer, stage II–III disease is typically managed with multimodal treatment strategies, including neoadjuvant therapy based on individual risk factors. By contrast, postoperative adjuvant therapy is not clearly recommended for patients with oligometastatic stage IV disease after curative resection. Accordingly, patients for whom standard perioperative therapy was indicated received such treatment prior to randomization, and only those who became ctDNA positive after completing the appropriate SoC were eligible for enrollment.

Patients were enrolled at one of three predefined time windows based on the timing of ctDNA positivity relative to surgery and adjuvant therapy: (1) the MRD window, defined as ctDNA positivity detected 2–10 weeks after surgery and prior to initiation of adjuvant chemotherapy when administered; (2) the on-treatment window, defined as ctDNA positivity detected during ACT, typically within the first 3 months after surgery; and (3) the surveillance window, defined as ctDNA positivity detected after completion or omission of all definitive SoC therapy during postoperative surveillance. For patients enrolled in the on-treatment window, enrollment in ALTAIR was considered at the discretion of the treating physician, and ACT was required to be discontinued prior to initiation of study treatment. No concurrent administration of ACT and study treatment was permitted.

Exclusion criteria included prior treatment with FTD/TPI; history of treatment with two or more postoperative chemotherapeutic regimens; presence of a malignancy other than CRC; active local or systemic infections requiring intervention; active hepatitis B, hepatitis C or HIV; poorly controlled diabetes or other comorbidities; history of interstitial lung disease requiring treatment; serious illnesses; or continuous systemic steroid administration. Additional inclusion and exclusion criteria are detailed in Supplementary Information. Only patients meeting all inclusion criteria and none of the exclusion criteria were enrolled in the study.

Trial design and interventions

ALTAIR is a randomized, double-blind, multinational (Japan and Taiwan) phase 3 trial comparing FTD/TPI versus placebo in patients with stage I–IV CRC who were positive for ctDNA after curative intent surgery. Patients with resected stage I–IV CRC in the GALAXY study who were found to be ctDNA positive by Signatera at any timepoint (1 month to 24 months) after surgery were evaluated for enrollment in the ALTAIR trial. Patients enrolled in ALTAIR were randomly assigned in a 1:1 ratio to receive a 28-day course of either FTD/TPI (administered orally at a dose of 35 mg m^{-2} per dose) or placebo twice daily for five consecutive days, followed by a 2-day withdrawal. This regimen was repeated twice, followed by a 14-day withdrawal from study treatment. Administration of FTD/TPI continued until the completion of six treatment courses or until discontinuation. Additional trial design methods are detailed in Supplementary Information.

Trial oversight

The ALTAIR study is an investigator-initiated trial. Although Taiho Pharmaceutical provided the study drug and funding, it did not act as the trial sponsor. The study design, implementation and conduct were carried out independently by the investigators. The study was registered with ClinicalTrials.gov (NCT04457297). Additionally, drug safety and efficacy data were monitored by an independent data monitoring committee. Enrollment for patients with no radiographic evidence of relapse was determined based on assessments conducted at local institutions; however, independent central imaging review was performed for sensitivity analysis.

Sex was recorded as a biological variable based on clinical records at enrollment. Age and other baseline demographic characteristics are summarized in Table 1. All participants provided written informed consent prior to enrollment. No financial compensation was provided to participants. Sex was considered as a baseline demographic variable; however, no prespecified sex-based subgroup analyses were performed, as the study was not designed or powered to detect differences by sex.

Personalized ctDNA analysis

ctDNA analysis was performed using a clinically validated, personalized, tumor-informed 16-plex polymerase chain reaction (PCR) next-generation sequencing (NGS) assay (Signatera; Natera). In brief, whole-exome sequencing (WES) was performed on tumor tissue and matched normal DNA. After the evaluation of quality metrics and sample concordance, WES data were used for somatic variant calling, enabling the omission of germline and mutations of clonal hematopoiesis of indeterminate potential. Up to 16 somatic single-nucleotide variants (SNVs) were selected, and PCR amplicons were developed to track these variants in the corresponding patient's plasma samples. Plasma samples with two or more SNVs were defined as ctDNA positive, and ctDNA concentration was reported in MTM/ml.

Endpoints

The primary endpoint was DFS, defined as the time from randomization to relapse, the development of a secondary CRC lesion other than a relapse (with intramucosal lesions not considered as events) or death, whichever occurred first. Recurrence was defined as the appearance of one or more new lesions, whether local, regional or distant from the primary resected site, confirmed by radiological or pathological evaluation. The study assumed a median DFS of 8 months in the placebo group, an HR of 0.667 for the FTD/TPI group, a significance level of 0.05 and a power of 0.80. With a planned 2-year enrollment period and 1-year follow-up, the trial required 240 patients and 190 events to achieve its objectives.

Secondary endpoints included the ctDNA clearance rate, DFS2, OS, incidence of AEs, treatment completion rate and QoL. Patients were followed for 1 year from the enrollment date of the last patient. After the trial period, patients were followed for approximately 5 years.

The ctDNA clearance rate was defined as the proportion of patients who tested negative for ctDNA at the first assessment conducted immediately after the completion of study treatment. DFS2 was defined as the time from randomization to the first occurrence of any of the following events: recurrence of the index CRC, development of a second primary malignant tumor (excluding intramucosal colorectal lesions) or death from any cause. This composite endpoint was selected to capture clinically meaningful events that may plausibly be influenced by systemic therapy. OS was defined as the time from the date of

enrollment to the date of death from any cause. AEs were documented throughout the trial treatment period from the first dose of study treatment to 30 days after the last dose, with severity graded according to Common Terminology Criteria for Adverse Events version 5.0. The treatment completion rate was calculated for each patient using the following formula: treatment completion rate (%) = (number of treatment courses completed / 6) × 100. QoL was assessed using the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

Statistical analysis

Efficacy analyses were conducted on the FAS, which comprised all patients who received at least one dose of the protocol-defined treatment and fulfilled the eligibility criteria. For MRD analysis, ctDNA timepoints within 2–10 weeks after surgery (MRD window) and prior to adjuvant therapy (if administered) were included. The on-treatment analysis was defined as ctDNA timepoints during ACT. Surveillance analysis comprised ctDNA timepoints, after ACT or after MRD timepoint if no ACT was given, until documented progression/recurrence. For each group, DFS was estimated using the Kaplan–Meier method, with DFS rates calculated at 3-month intervals along with their 95% CIs. The median DFS and its corresponding 95% CI were also determined. A stratified log-rank test was employed to compare DFS between the two groups under the null hypothesis that the DFS curves are identical. If the *P* value from this test was below the significance threshold of 0.05, the null hypothesis was rejected, indicating a statistically significant difference between the groups. Proportional hazard assumptions for DFS were evaluated using Schoenfeld residuals and global tests. Given the visual suggestion of a waning treatment effect over time, we also conducted exploratory analyses of restricted mean survival time (RMST) up to 24 months and milestone DFS at 6 months, 12 months, 18 months and 24 months with 95% CIs (Extended Data Table 2B,C).

The originally planned stratification factors for the primary DFS analysis were age, institution, disease classification, primary tumor location and ctDNA status 1 month after curative resection. Before unblinding, and based on a blinded review of the event distribution and model stability, the stratification set was narrowed to disease stage classification and 1-month ctDNA status, which were retained for the primary analysis. To address potential concerns regarding post hoc modification of stratification, we additionally performed sensitivity analyses of DFS in the FAS, including (1) a Cox/log-rank analysis stratified by the original full stratification set and (2) an unstratified analysis. These analyses yielded HRs and *P* values highly consistent with the primary analysis (HRs ≅ 0.79, $P = 0.0956–0.131$; Extended Data Table 3), supporting the robustness of the primary efficacy conclusions.

The analysis of ctDNA clearance rates was conducted using the FAS. The proportion of patients achieving ctDNA clearance at their most recent assessment after treatment completion was estimated for each group, with the corresponding 95% CI calculated. Group comparisons were performed using Fisher's exact test, and the odds ratio with its 95% CI was estimated using a logistic regression model. For time to ctDNA clearance, cumulative incidence curves were estimated for each group while accounting for competing risks. The cumulative incidence rates at 3-month intervals, along with their 95% CI, were calculated. Group differences were evaluated using the Gray test, and the HR with its 95% CI was estimated using the Fine–Gray model.

Based on ctDNA status (negative/positive) during and after treatment but before a DFS event, patients were classified into three groups. To be included in this analysis, patients were required to have at least one ctDNA assessment after starting treatment and before or on the same day as a DFS event. Patients categorized as having 'no clearance' were those who remained ctDNA positive at all timepoints up to a DFS event. Patients classified as having 'sustained clearance' were those who converted from ctDNA positive to ctDNA negative and remained negative at all subsequent timepoints. To meet the criteria for 'sustained clearance', at least one negative ctDNA result after treatment completion was required. The third category, 'transient clearance', included patients who converted from ctDNA positive to ctDNA negative during or after treatment but subsequently reverted to ctDNA positive at later timepoints. This category also included patients who converted from ctDNA positive to ctDNA negative during treatment but did not have a post-treatment ctDNA assessment available.

This classification system ensures a clear and consistent interpretation of ctDNA dynamics in relation to treatment outcomes. OS analysis was conducted using the Kaplan–Meier method. OS rates at 3-month intervals, along with their 95% CI, were calculated for each group. The median OS and its 95% CI were also determined. A log-rank test was used to compare OS curves under the null hypothesis of no difference between the two groups. For treatment completion rates, summary statistics were calculated for each group, and comparisons were performed using Student's *t*-test.

Safety analysis was conducted on the safety population. The incidence of AEs was summarized, including stratification by system organ class and preferred term. The analysis also included incidence rates of risk-based AEs, a summary of causes of death, subgroup analyses of AE incidence rates and a listing of AEs with an incidence of at least 10%. Additionally, differences in AE incidence rates of at least 5% between intrinsic factor subgroups were evaluated. Summary statistics for QoL variables were calculated for each group at each assessment timepoint. Longitudinal comparisons between groups were performed using a linear mixed-effects model, enabling the analysis of changes over time and differences between groups.

Statistical analyses were performed using both SAS software (version 9.4; SAS Institute) and R software (version 4.4.0). The data cutoff date for the analyses was 18 July 2024. This statistical approach ensures a comprehensive evaluation of efficacy, safety and QoL outcomes, providing robust evidence for the assessment of FTD/TPI in patients with high-risk CRC identified through ctDNA-based MRD assessment.

Post hoc independent blinded central radiological review

A post hoc independent blinded central radiological review was conducted by a panel of four independent radiological experts, according to the predefined review charter. Although this review was not prespecified in the original statistical analysis plan and was initiated after database lock, it was performed as an exploratory sensitivity analysis to assess the robustness and consistency of recurrence assessment between local investigators and centralized review.

For each patient, the baseline scan, the scan at the time of recurrence as determined by the local investigator and other scans deemed necessary for evaluation were reviewed. Each case was initially reviewed by one independent radiologist (single-reader approach). When findings were discordant with the local investigator's assessment, or when consensus was deemed necessary, additional review by another radiologist and panel discussion were undertaken to reach a final determination. All reviewers were blinded to clinical information other than the prespecified imaging data as well as to ctDNA results and treatment allocation.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The minimum dataset necessary to interpret, verify and extend the findings of this study is available within the article and its Supplementary Information. Individual participant-level clinical data are not publicly available due to patient privacy considerations and ethical restrictions under the Japanese Act on the Protection of Personal Information. Deidentified individual participant data may be made available from the corresponding author (T.Y., tyoshino@east.ncc.go.jp) upon reasonable request, subject to approval by the CIRCULATE-Japan study

steering committee and relevant IRBs and execution of a data-sharing agreement in accordance with institutional and regulatory policies. Requests will be evaluated to ensure compliance with ethical, legal and confidentiality requirements. Source data are provided with this paper.

Code availability

The fully documented code for the R statistical computing environment for analyses related to this paper is deposited in the GitHub repository and can be accessed at https://github.com/Natera-TMED/Bando-et-al_ALTAIR-Clinical-analysis.git.

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Author contributions

H.B., J.W., Y.N., H.T., T.K. and T.Y. conceived and designed the study. H.B., J.W., T.K. and T.Y. supervised the trial and were responsible for its overall conduct. H.B., J.W., Y.T., M.K., N.M., E.O., Y.K., M.S., K.H., Y.M., M.T., K.Y., D.M., A.K., Y.-H.L., K.-H.Y., I.T., D.K., Y.N., H.T. and T.K. enrolled patients and collected clinical data. Y.Y., T.M. and Q.S. performed the statistical analyses. H.B., J.W., S.S., V.N.A., A.J., M.R., M.C.L., A.A., Y.N., T.K. and T.Y. interpreted the data. H.B. and J.W. drafted the paper. All authors critically revised the paper for important intellectual content and approved the final version for submission.

Competing interests

H.B. reports research funding from Ono Pharmaceutical and honoraria from Ono Pharmaceutical, Taiho Pharmaceutical and Guardant Health. J.W. reports honoraria for lectures from Johnson & Johnson, Covidien Japan, Eli Lilly, Terumo and Takeda Pharmaceutical, and research funding from Covidien Japan, Terumo and Stryker Japan, all outside the submitted work. Y.T., K.H., Y.M., M.T., D.M., A.K., M.F., I.T. and D.K. declare no competing interests. M.K. reports honoraria from Chugai Pharmaceutical, Eli Lilly Japan and Takeda Pharmaceutical. N.M. reports honoraria from multiple companies, including Abbott, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly, Guardant Health, Johnson & Johnson, Kyowa Kirin, Merck, MSD, Novartis, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical and others, and research funding to the institution from Covidien Japan, Johnson & Johnson, Taiho Pharmaceutical, Terumo and others. E.O. reports research funding from Guardant Health and honoraria from Ono Pharmaceutical, Takeda Pharmaceutical, Bayer, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly Japan and Bristol Myers Squibb. Y.K. reports research funding from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, Amgen, MSD, Daiichi Sankyo, Eisai, Sysmex and Takeda Pharmaceutical, and honoraria from Bayer, Chugai Pharmaceutical, Taiho Pharmaceutical, Merck, MSD, Ono Pharmaceutical, Daiichi Sankyo, Eisai, Guardant Health, Astellas and Takeda Pharmaceutical. M.S. reports honoraria from Eli Lilly, Takeda Pharmaceutical, Merck Serono, Ono Pharmaceutical and Taiho Pharmaceutical. M.T. reports research funding from Ono Pharmaceutical and Nippon Boehringer Ingelheim, and honoraria from Chugai Pharmaceutical, MSD, Taiho Pharmaceutical, Ono Pharmaceutical and Bristol Myers Squibb. K.Y. reports honoraria from Ono Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo, Takeda Pharmaceutical, Eli Lilly, MSD and Bristol Myers Squibb. Y.-H.L. reports honoraria from Amgen, Bayer, Bristol Myers Squibb, Merck, Ono Pharmaceutical and Takeda Pharmaceutical. K.-H.Y. reports honoraria from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, MSD, Merck, Novartis, Ono Pharmaceutical, Pierre Fabre, Pfizer, Roche and Takeda Pharmaceutical. Y.W. and Y.Y. are employees of EPS Corporation. S.S., V.N.A., A.J., M.R., M.C.L. and A.A. are employees of Natera. A.S reports research funding to the institution from Taiho Pharmaceutical, Boehringer Ingelheim, Bayer, Chugai Pharmaceutical, Ono Pharmaceutical, Takeda Pharmaceutical, Pentax Medical Devices, MSD, Daiichi Sankyo/UCB Japan, Merck Pharmaceutical FerroptoCure and Shionogi Pharmaceutical, all outside the submitted work. Y.N. reports advisory roles for Guardant Health; research funding from Exact Sciences, Pfizer and Shionogi; and speaker fees from MSD, Merck Biopharma, Daiichi Sankyo, Chugai Pharmaceutical and Guardant Health Japan. Q.S. reports consulting or advisory roles for Bayer, Boehringer Ingelheim, Regeneron, Genmab, AbbVie, Exelixis and others, and research funding to the institution from Regeneron, Bristol Myers Squibb, Roche/Genentech, Janssen and Novartis. H.T. reports honoraria from Ono Pharmaceutical, Merck Biopharma, Eli Lilly Japan, Chugai Pharmaceutical and Takeda Pharmaceutical, and research funding from Takeda Pharmaceutical, Daiichi Sankyo and Ono Pharmaceutical. T.Y. reports research funding from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, MSD, Bristol Myers Squibb, Caris MPI, Daiichi Sankyo, Eisai, Exact Sciences, FALCO Biosystems, Medical & Biological Laboratories, Merus N.V., Miyarisan Pharmaceutical, Natera, Nippon Boehringer Ingelheim, Pfizer, Sysmex and Takeda Pharmaceutical; honoraria from Chugai Pharmaceutical, Merck Biopharma, Ono Pharmaceutical and Takeda Pharmaceutical; and consulting fees from Sumitomo and Indivumed. T.K. reports honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Ono Pharmaceutical and Eli Lilly.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-026-04428-0.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-026-04428-0.

Correspondence and requests for materials should be addressed to Takayuki Yoshino.

Peer review information *Nature Medicine* thanks Filippo Pietrantonio and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available. Primary Handling Editor: Ulrike Harjes, in collaboration with the *Nature Medicine* team.

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Extended Data Table 1 | Details of cases with discordant recurrence assessment between local and central review

Case number	Local diagnosis	Central review	Detail
1	Yes	No	No evidence of recurrence was identified on central review.
2	No	Yes	Recurrence was identified in lymph nodes posterior to the portal vein on central review.
3	Yes	No	The lesion in the descending colon was considered residual disease and remained radiologically stable without progression.
4	Yes	No	Pulmonary and hepatic lesions were considered pre-existing findings on baseline CT.
5	No	Yes	Metastatic lymph nodes were identified in the right para-aortic and retrocaval regions.
6	Yes	No	A pulmonary nodule detected on baseline CT showed progressive changes.
7	Yes	No	No evidence of recurrence was identified on central review.
8	No	Yes	Metastatic involvement was identified in the internal iliac lymph node.
9	No	Yes	Metastatic involvement was identified in the portal lymph node.
10	Yes	No	No evidence of recurrence was identified on central review.

https://doi.org/10.1038/s41591-026-04428-0

Extended Data Table 2 | Assessment of proportional hazards, milestone DFS, and restricted mean survival time (RMST)

A) Proportional hazards (PH) assumption tests			
Test			p-value
Schoenfeld residual test for treatment effect			0.0027
Global Schoenfeld residual test			0.0027
B) Milestone disease-free survival (DFS)			
Time (months)		Control DFS (95% CI)	FTD/TPI DFS (95% CI)
6		0.46 (0.37–0.55)	0.71 (0.63–0.79)
12		0.27 (0.20–0.36)	0.32 (0.24–0.41)
18		0.22 (0.15–0.31)	0.21 (0.15–0.30)
24		0.15 (0.09–0.25)	0.17 (0.11–0.26)
C) Restricted mean survival time (RMST)			
Analysis	Estimate (months)	95% CI	p-value
RMST difference (FTD/TPI – Control)*	1.93	−0.95 to 4.82	0.189

*RMST was calculated up to 23.69 months, corresponding to the maximum common follow-up time across treatment groups. Proportional hazards were assessed using Schoenfeld residual–based tests. Significant p-values indicate violation of the PH assumption and a time-varying treatment effect. Milestone DFS rates were estimated using the Kaplan–Meier method with corresponding 95% confidence intervals. RMST was estimated as the area under the DFS curve up to the truncation time. The RMST difference represents the average delay in recurrence over the first approximately 24 months of follow-up.

https://doi.org/10.1038/s41591-026-04428-0

Extended Data Table 3 | Sensitivity analyses of treatment effect using different stratification approaches

Analysis	Stratification	HR (95% CI)	Log-rank P
(a) Original	Age, stage, tumor site, 1-mo ctDNA	0.79 (0.58–1.07)	0.131
(b) Primary	Stage, 1-mo ctDNA	0.79 (0.60–1.05)	0.107
(c) Unstratified	None	0.79 (0.60–1.04)	0.0956

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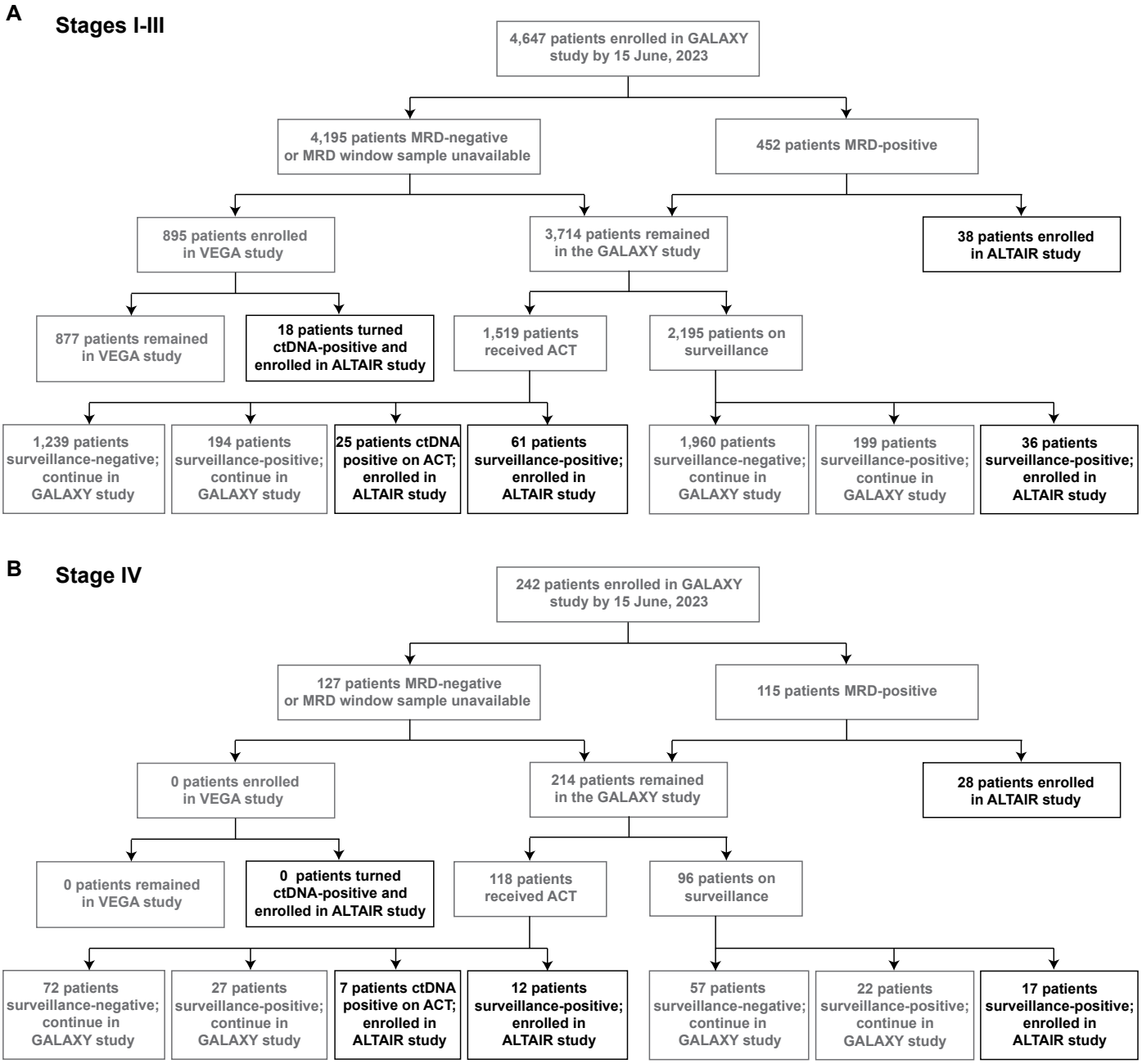

Extended Data Fig. 1 | Patient inclusion and baseline characteristics. CONSORT diagram describing enrollment of CRC patients (**A**) stages I-III and (**B**) stage IV in the ALTAIR trial during MRD, on-treatment (adjuvant chemotherapy), and surveillance enrollment windows.

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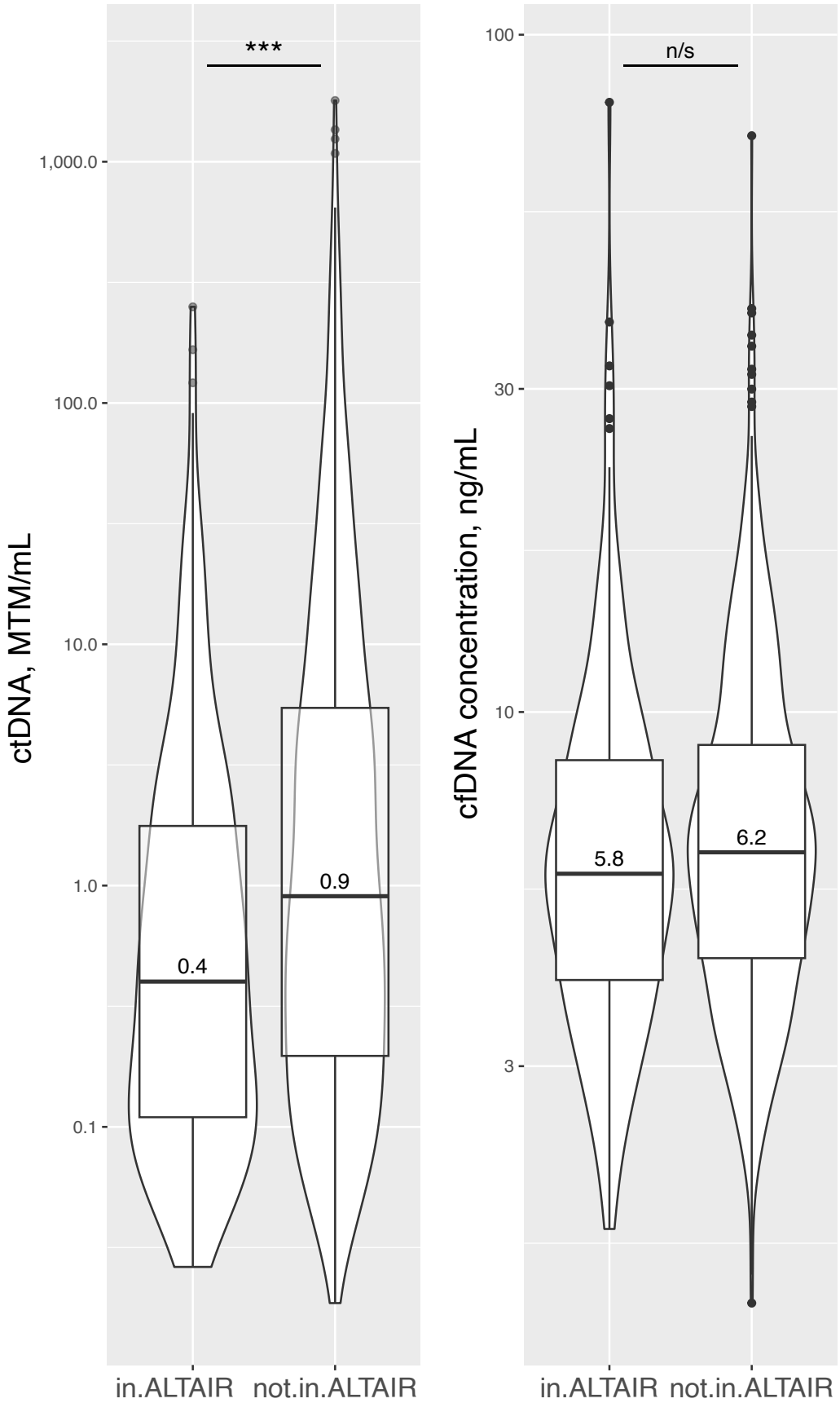

Extended Data Fig. 2 | Violin and box plots showing baseline ctDNA and cfDNA concentration levels in ALTAIR (n = 243) versus non-ALTAIR (n = 786) populations. Baseline levels were defined as the ctDNA or cfDNA measurements obtained at the time of enrollment into the ALTAIR study. Box plots were generated using the ggplot2 package (v3.3.6) in R (v4.2.1). The center line represents the median; the box indicates the interquartile range (25th–75th percentiles); points represent outliers. P values were calculated using the two-sided t-test.

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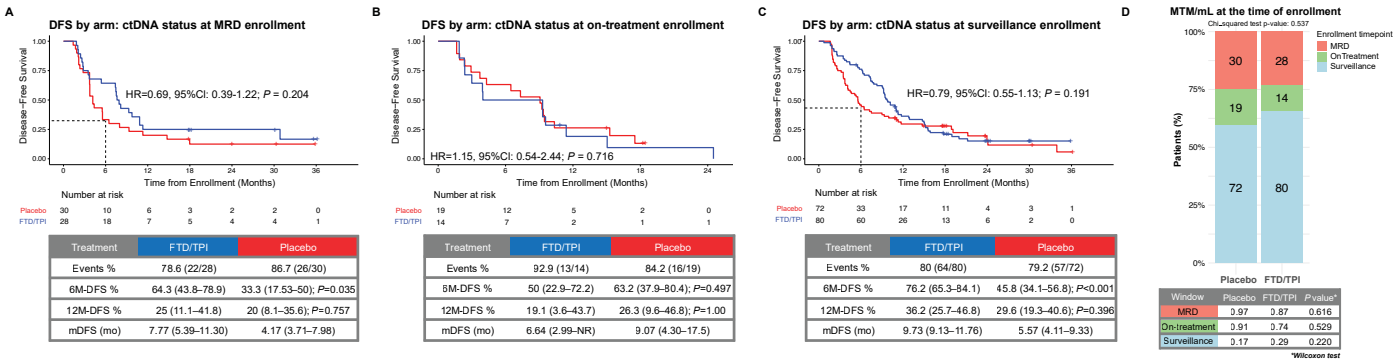

Treatment	FTD/TPI	Placebo
Events %	78.6 (22/28)	86.7 (26/30)
6M-DFS %	64.3 (43.8–78.9)	33.3 (17.53–50); *P*=0.035
12M-DFS %	25 (11.1–41.8)	20 (8.1–35.6); *P*=0.757
mDFS (mo)	7.77 (5.39–11.30)	4.17 (3.71–7.98)

Treatment	FTD/TPI	Placebo
Events %	92.9 (13/14)	84.2 (16/19)
6M-DFS %	50 (22.9–72.2)	63.2 (37.9–80.4); *P*=0.497
12M-DFS %	19.1 (3.6–43.7)	26.3 (9.6–46.8); *P*=1.00
mDFS (mo)	6.64 (2.99–NR)	9.07 (4.30–17.5)

Treatment	FTD/TPI	Placebo
Events %	80 (64/80)	79.2 (57/72)
6M-DFS %	76.2 (65.3–84.1)	45.8 (34.1–56.8); *P*<0.001
12M-DFS %	36.2 (25.7–46.8)	29.6 (19.3–40.6); *P*=0.396
mDFS (mo)	9.73 (9.13–11.76)	5.57 (4.11–9.33)

Window	Placebo	FTD/TPI	*P* value*
MRD	0.97	0.87	0.616
On-treatment	0.91	0.74	0.529
Surveillance	0.17	0.29	0.220

*Wilcoxon test

Extended Data Fig. 3 | Association of ctDNA status with DFS at the time of enrollment stratified by treatment arm. Kaplan–Meier estimates for DFS for FTD/TPI versus placebo. Association of ctDNA status with DFS at the time of enrollment stratified by treatment arm. Kaplan–Meier estimates for DFS for FTD/TPI versus placebo in patients enrolled at (**A**) MRD (n = 58; P = 0.204), (**B**) on-treatment (n = 33; P = 0.716), and (**C**) surveillance (n = 152; P = 0.191). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model; P values were calculated using the two-sided log-rank test. (**D**) Contingency plot showing the percentage of patients enrolled at MRD, on-treatment, and surveillance time points stratified by treatment arm (n = 243). MTM/mL levels are shown for each treatment arm within the respective enrollment windows. P value was calculated using the two-sided chi-square test (P = 0.537). Abbreviations: CI, confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio.

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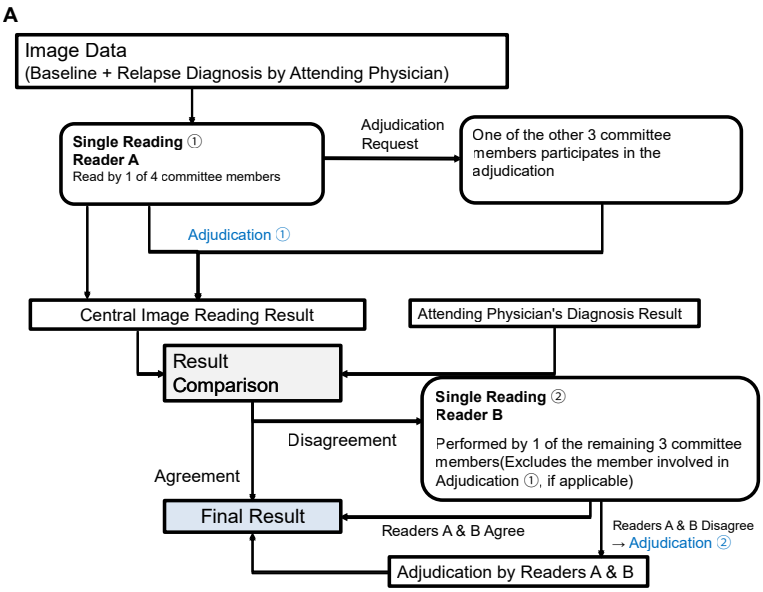

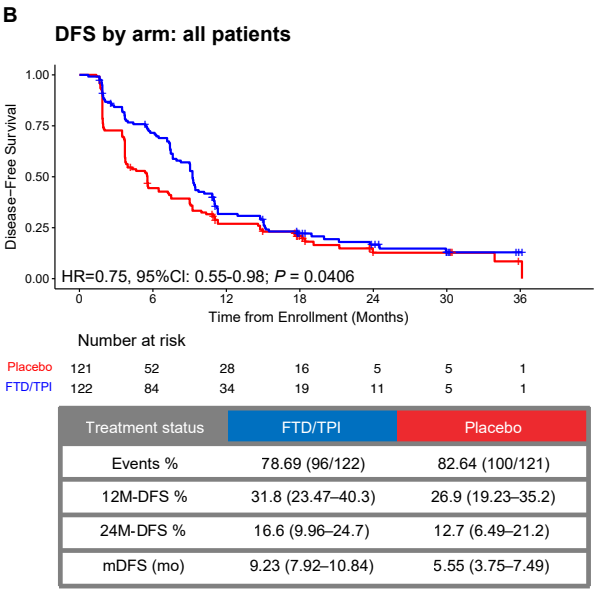

Treatment status	FTD/TPI	Placebo
Events %	78.69 (96/122)	82.64 (100/121)
12M-DFS %	31.8 (23.47–40.3)	26.9 (19.23–35.2)
24M-DFS %	16.6 (9.96–24.7)	12.7 (6.49–21.2)
mDFS (mo)	9.23 (7.92–10.84)	5.55 (3.75–7.49)

Extended Data Fig. 4 | Central review schema and Kaplan–Meier estimates for disease-free survival for FTD/TPI versus placebo in all patients. (**A**) Central review schema. A post-hoc independent blinded central review was conducted to ensure objective and consistent radiological assessment. (**B**) Kaplan–Meier estimates for disease-free survival (DFS) for FTD/TPI versus placebo in all patients (n = 243). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model; P values were calculated using the two-sided log-rank test. Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.

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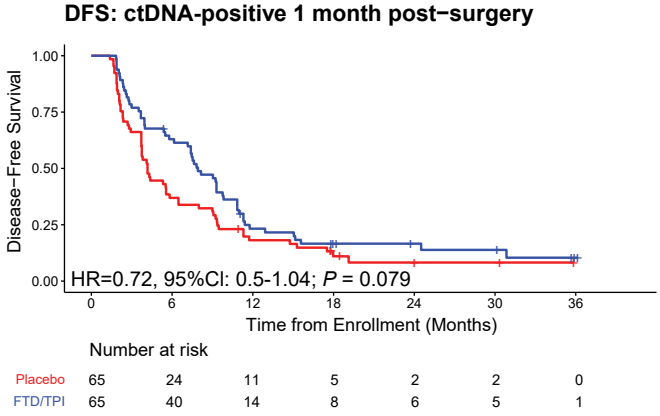
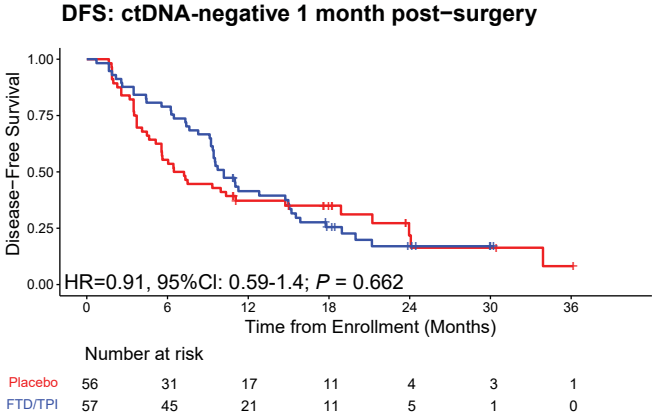
A



Treatment status	FTD/TPI	Placebo
Events %	84.62 (55/65)	89.23 (58/65)
12M-DFS %	23.3 (13.74–34.3)	18.13 (9.85–28.4)
24M-DFS %	16.6 (8.63–26.9)	8.24 (2.7–17.8)
mDFS (mo)	7.92 (7.16–10.84)	4.17 (3.71–6.47)

B



Treatment status	FTD/TPI	Placebo
Events %	77.2 (44/57)	73.2 (41/56)
12M-DFS %	41.4 (28.48–53.9)	37.2 (24.72–49.7)
24M-DFS %	17 (7.71–29.4)	21.8 (9.43–37.4)
mDFS (mo)	10.18 (9.23–15)	6.85 (5.55–18.9)

Likelihood-Ratio Interaction: *P* = 0.3931

Extended Data Fig. 5 | Association of ctDNA status with DFS stratified by ctDNA status 1 month post-surgery. Kaplan–Meier estimates for DFS for FTD/TPI versus placebo in patients who were (**A**) ctDNA-positive (n = 130; P = 0.079) and (**B**) ctDNA-negative (n = 113; P = 0.662). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model; P values were calculated using the two-sided log-rank test. Abbreviations: CI, confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio.

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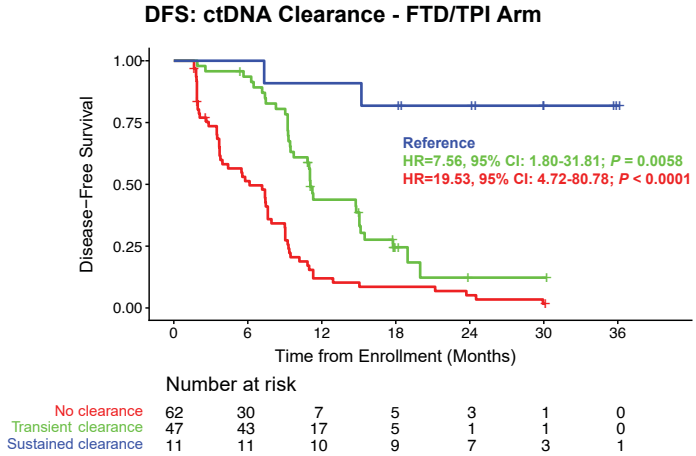
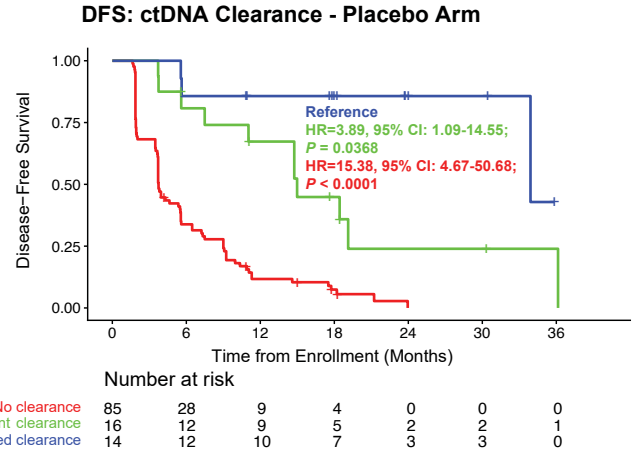
A



ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	18.18 (2/11)	72.34 (34/47)	93.54 (58/62)
mDFS (mo)	NR	11.07 (9.73–15.15)	6.14 (3.78–7.92)
6M-DFS %	100	93.6 (81.37–97.9)	51.31 (37.98–63.1)
12M-DFS %	90.9 (50.8–98.7)	43.8 (28.84–57.8)	11.97 (5.26–21.6)
24M-DFS %	81.8 (44.7–95.1)	12.3 (2.76–29.3)	5.13 (1.35–12.9)

B



ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	21.4 (3/14)	68.75 (11/16)	94.12 (80/85)
mDFS (mo)	33.91 (33.91–NR)	14.98 (11.04–NR)	3.75 (3.71–5.55)
6M-DFS %	85.7 (53.9–96.2)	80.8 (51.40–93.4)	33.83 (23.98–43.9)
12M-DFS %	85.7 (53.9–96.2)	67.3 (38.29–84.9)	11.71 (5.87–19.7)
24M-DFS %	85.7 (53.9–96.2)	23.9 (4.76–51.1)	NR

Extended Data Fig. 6 | Association of ctDNA clearance with DFS by treatment arm. (exploratory analysis). Kaplan–Meier estimates for DFS in the FTD/TPI (**A**; n = 120) and placebo (**B**; n = 115) arms according to ctDNA clearance status (transient, sustained, no clearance). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model; P values were calculated using the two-sided log-rank test. Abbreviations: CI, confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio; MTM, mean tumor molecules; OS, overall survival.

nature portfolio

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Last updated by author(s): Mar 20, 2026

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☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
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☐	☒ A description of all covariates tested
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☐	☒ 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	Statistical analyses performed with SAS version 9.4 (SAS/STAT 15.2) and R version 4.1.2. Code used for analysis is available in a public repository (GitHub).
Data analysis	Custom R scripts used for statistical analyses are available in a public GitHub repository (link provided).

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.

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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

Clinical trial registration: ClinicalTrials.gov NCT04457297.
The full study protocol (version 10.1, July 10, 2024) and Statistical Analysis Plan are provided as Supplementary Information.

Data sharing: De-identified participant-level data will be available upon reasonable request to the corresponding author, subject to institutional and regulatory approval and execution of a data sharing agreement.

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	Both male and female patients with colorectal cancer were eligible and enrolled. Sex-specific analyses were not pre-specified, and outcomes were not stratified by sex.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were not collected as study variables. The study was conducted in Japan and Taiwan, where the majority of participants are East Asian.
Population characteristics	Baseline demographic and clinical characteristics, including age, sex, ECOG performance status, and disease stage, are summarized in Table 1 of the manuscript.
Recruitment	Patients with stage II–IV colorectal cancer who were ctDNA-positive following curative resection (± adjuvant therapy) were recruited at 152 academic and community hospitals in Japan and Taiwan between June 2020 and June 2023.
Ethics oversight	The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review boards or ethics committees at each participating site (listed in Supplementary Appendix). Written informed consent was obtained from all patients before enrollment. The trial was prospectively registered at ClinicalTrials.gov (NCT04457297).

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	Sample size was determined based on 240 patients (190 DFS events required) to detect a hazard ratio of 0.667 with 80% power and a two-sided α of 0.05.
Data exclusions	No patients were excluded after randomization. Exclusions were limited to screening failures before randomization, as specified in the protocol.
Replication	This was a single phase III trial. Replication in an independent cohort has not yet been performed.
Randomization	Eligible patients were randomized 1:1 to FTD/TPI or placebo using a central web-based RTSM system. Randomization was stratified by disease stage, adjuvant chemotherapy status, and country.
Blinding	Patients, investigators, treating physicians, study staff, radiologists, and statisticians were blinded to treatment allocation. Placebo tablets were identical in appearance to FTD/TPI tablets.

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	ClinicalTrials.gov Identifier: NCT04457297
Study protocol	The full study protocol (EPOC1905, Version 10.1, July10, 2024) and Statistical Analysis Plan are provided as supplementary materials and are available upon request from the corresponding author.
Data collection	Patients were enrolled at 152 hospitals in Japan and Taiwan between June 2020 and June 2023. Data were collected prospectively from electronic case report forms (eCRFs), imaging records, and laboratory results. Serial plasma samples were collected for ctDNA analysis at baseline and scheduled follow-up visits.
Outcomes	Primary outcome: Disease-free survival (DFS1), defined as the time from randomization to recurrence or death from any cause, whichever occurred first.Secondary outcomes: ctDNA clearance rate, DFS2, overall survival (OS), safety (adverse events per CTCAE v5.0), and quality of life (EORTC QLQ-C30).All outcomes were pre-specified in the protocol.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a