# Redefining Neoadjuvant Treatment in Rectal Cancers

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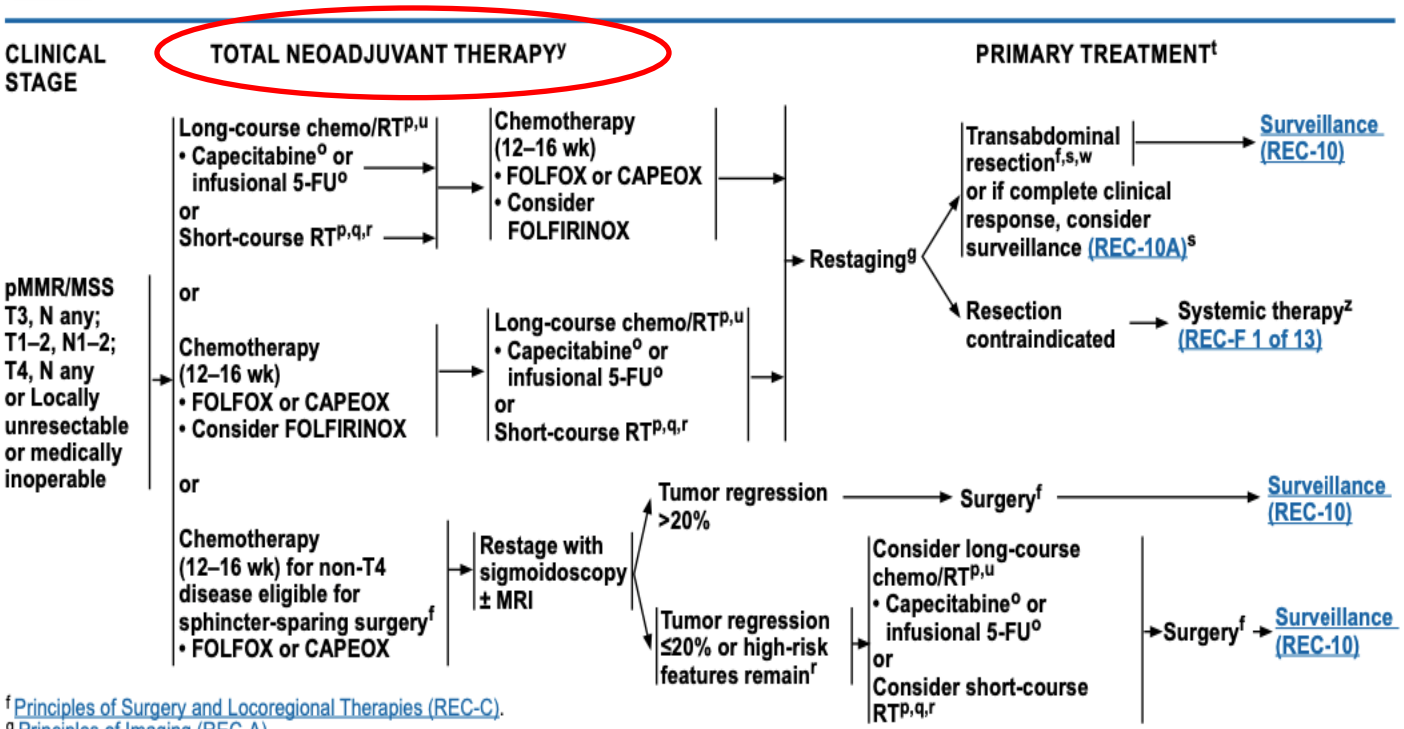



[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[r] While short-course RT can be considered for preoperative radiation, for high-risk rectal cancer (clinical tumor stage cT4a or cT4b, EMVI, clinical nodal stage cN2, involved MRF, or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.
[s] In those patients who achieve a complete clinical response with no evidence of residual disease on DRE, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for NOM should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).
[t] For stage II-III disease, if *PIK3CA* mutation, add aspirin 100-162 mg PO daily for 3 years following surgery.
[u] Principles of Perioperative Therapy (REC-D).
[w] For select patients who may be candidates for IORT, see Principles of Radiation Therapy (REC-E).
[y] In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.
[z] FOLFIRINOX is not recommended in this setting.

**Note: All recommendations are category 2A unless otherwise indicated.**

# TOTAL NEOADJUVANT THERAPY

- The introduction of TNT was with the premise that, with preoperative radiation and better quality surgery, local failures are no longer a problem and that they have reduced to ≤5%.

- The failures were now supposed to be largely distant that drive the overall survival.

# 2020

## Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

*Renu R Bahadoer*, Esmée A Dijkstra*, Boudewijn van Etten†, Corrie A M Marijnen†, Hein Putter, Elma Meershoek-Klein Kranenbarg, Annet G H Roodvoets, Iris D Nagtegaal, Regina G H Beets-Tan, Lennart K Blomqvist, Tone Fokstuen, Albert J ten Tije, Jaume Capdevila, Mathijs P Hendriks, Ibrahim Edhemovic, Andrés Cervantes, Per J Nilsson†‡, Bengt Glimelius†‡, Cornelis J H van de Velde†‡, Geke A P Hospers†‡, and the RAPIDO collaborative investigators§*

# Background – Treatment Landscape in Locally Advanced Rectal Cancer (LARC)

**1. Standard Management of Rectal Cancer (Pre-RAPIDO)**

- **Traditional approach for locally advanced rectal cancer (LARC)**:
  **Neoadjuvant chemoradiotherapy (CRT)**:
    Long-course radiation (45–50.4 Gy over 5–6 weeks)
    With concurrent chemotherapy (typically 5-FU or capecitabine)
  **Surgery**:
    **Total Mesorectal Excision (TME)** – gold standard for surgical resection
  **Adjuvant chemotherapy** (optional, depending on risk factors):
    Typically 6 months of FOLFOX or CAPOX

- Despite the standard treatment sequence: **High rates of distant metastases**
- Local control has improved significantly, but:
  **Systemic control remains a major challenge**
  Traditional adjuvant chemotherapy often underutilized due to:
    Poor postoperative recovery,Reduced compliance,Delayed initiation

- To overcome limitations of the traditional sequence, researchers proposed TNT, which involves:
- Delivering all systemic therapy (chemo) *before surgery*
- Can be combined with either:
  Long-course CRT or
  Short-course radiotherapy (SCRT) + chemotherapy
- Advantages of TNT:
  Earlier treatment of micrometastases
  Better chemotherapy compliance
  Increased tumor shrinkage (can help with organ preservation in select cases)
  Potentially higher pathologic complete response (pCR) rates

## RAPIDO Trial: Why Was It Needed?

Previous studies hinted at benefits of TNT but lacked large-scale randomized data.

**RAPIDO aimed to:**

**Evaluate efficacy and safety of TNT using short-course RT followed by chemo**
**Compare it directly against the standard CRT + surgery + adjuvant chemo**
**Determine if this new approach could reduce disease-related treatment failure, particularly distant metastases**

# Aim of the RAPIDO Trial

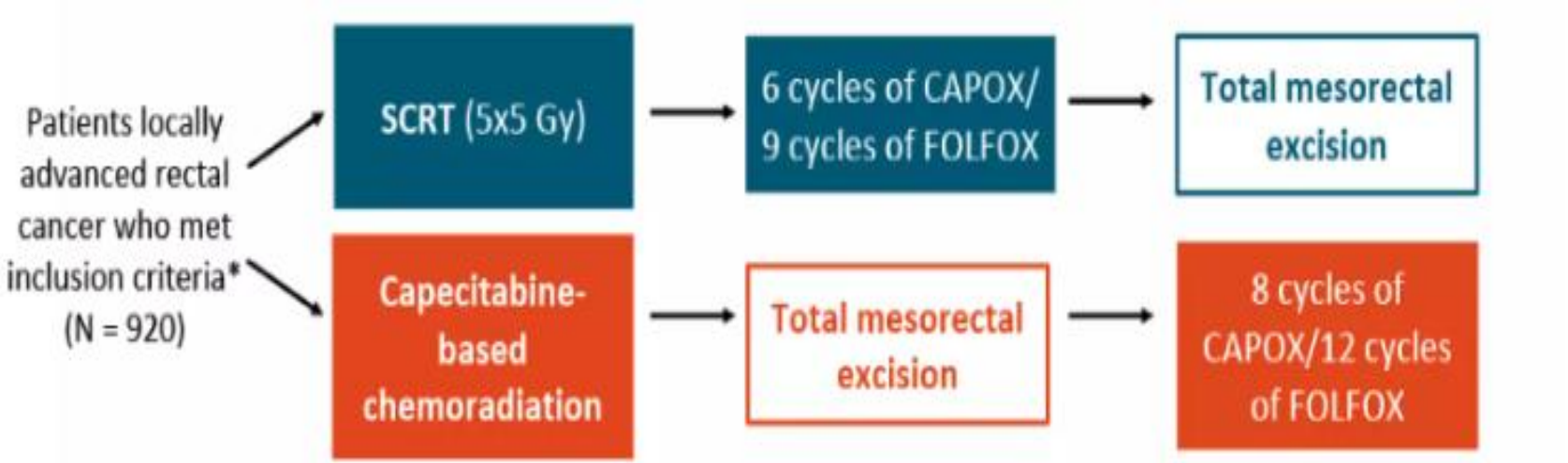
- **Primary Objective:**
  Compare **Total Neoadjuvant Therapy (TNT)** using **short-course radiotherapy (SCRT)** + consolidation chemotherapy before surgery vs. standard long-course CRT.

- **Primary Endpoint:**
  3-year disease-related treatment failure (DrTF).
  *(Composite of locoregional failure, distant metastasis, new primary colorectal tumor, and treatment-related death).*

- **Secondary Endpoints:**
  Distant metastasis-free survival (MFS)
  Pathologic complete response (pCR)
  Local relapse rate(LRR)
  Overall survival (OS)
  Treatment compliance & toxicity

# Methods: Trial Design

- **Type:** Phase III, multicenter, open-label randomized controlled trial.
- **Patients:** 912 patients with **high-risk LARC**:
  MRI features: cT4a/b, cN2, EMVI+, MRF+, lateral lymph nodes >7 mm.
- **Randomization:** 1:1 to TNT (SCRT + chemo) vs. standard CRT.
- **Follow-up:** Median 5.6 years.




*Inclusion criteria: biopsy-proven primary adenocarcinoma of the rectum, 18 years or older, absence of distant metastases, MRI with high-risk features (T4a/b, extramural vascular invasion +N2, mesorectal fascia + enlarged lymph nodes).

# RESULTS

| | Experimental Arm | Standard Arm | p- value |
|---|---|---|---|
| **Disease related t/t failure** | **23.7%** | **30.4%** | **0.019** |
| **Distant mets** | **20%** | **26.8%** | **0.0048** |
| **LR failure** | **8.3%** | **6%** | **0.12** |
| **Pathological CR** | **28%** | **14%** | **<0.0001** |
| **T/t related death** | **3%** | **3%** | **-** |

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# RAPIDO Trial

## *Randomised Study of Preoperative Radiotherapy & Chemotherapy for High-Risk Rectal Cancer*

ORIGINAL ARTICLE

OPEN

### Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery

*A 5-Year Follow-up of the RAPIDO Trial*

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# ❑ Results: Primary Endpoint

- 920 patients were enrolled and randomly assigned to a treatment between June 21, 2011, and June 2, 2016, 906 (460 in the EXP and 446 patients in the STD group) were eligible

- Median follow-up was 5·6 years (IQR 3·5–5·5).

- At **5 years**, the cumulative probability of **DrTF** was 27.8% (95% CI, 23.7–31.8) in the EXP group and 34.0% (95% CI, 29.6–38.4) in the STD group (HR: 0.79 (95% CI, 0.63–1.00);P= 0.0480).

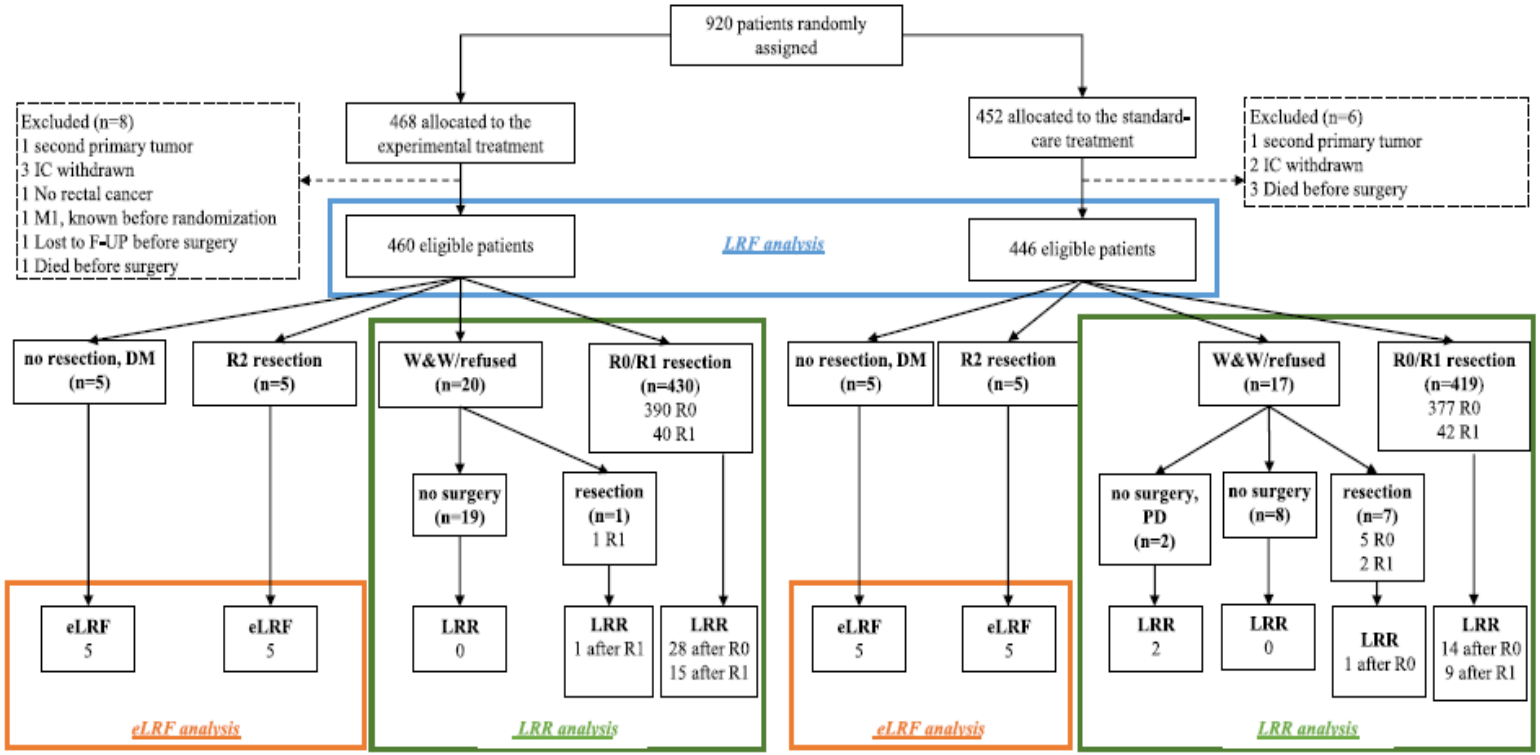


**FIGURE 1.** Consort diagram. Patients entering a W&W program or who "refused surgery" according to the case record forms were grouped together since the predominant reason for the refusers was no remaining tumor/no need for surgery. These patients were included in the LRR analysis. The 2 patients who initially entered a W&W strategy/refused surgery but later developed regrowth without having surgery were scored as LRR. When W&W patients with tumor regrowth underwent a curative resection, this was not scored as LRR. However, when regrowth was subsequent to a radical resection in W&W patients, this was scored as LRR. F-UP indicates follow-up; IC, informed consent; PD progressive disease.

- An **LRF** was detected in **54/460 (11.7%)** and **36/446 (8.1%)** patients in the **EXP** and **STD groups**, respectively (P=0.07).

- EXP patients were more often treated with 3-dimensional-conformed radiotherapy (P=0.029).

- In the EXP group, LRR was detected more often [44/431 (10%) vs. 26/428 (6%); P=0.027], with more often a breached mesorectum (9/44 (21%) vs. 1/26 (4); P=0.048).

- The EXP treatment, enlarged lateral lymph nodes, positive circumferential resection margin, tumor deposits, and node positivity at pathology were the significant predictors for developing LRR.

- Location of the LRRs was similar between groups.

- Overall survival after LRF was comparable [hazard ratio: 0.76 (95% CI, 0.46–1.26); P=0.29].

- The cumulative probability of DM at 5 years in the EXP group was 23.0% (95% CI, 19.2–26.8) and 30.4% (95% CI,26.1–34.7) in the STD group (HR: 0.73 (95% CI, 0.57–0.93); P= 0.011).

## High-risk criteria, radiation, surgical and pathological characteristics of patients who developed a locoregional recurrence

| | Experimental (n=44) | | Standard-care (n=26) | | P-value |
|---|---|---|---|---|---|
| **High-risk criteria at baseline†** | | | | | |
| cT4 | 14 | (32) | 7 | (27) | 0.66 |
| cN2 | 33 | (75) | 20 | (77) | 0.86 |
| Enlarged lateral nodes | 9 | (21) | 7 | (27) | 0.53 |
| EMVI + | 14 | (32) | 13 | (50) | 0.13 |
| MRF + | 30 | (68) | 21 | (81) | 0.25 |
| **Radiation technique** | | | | | 0.14 |
| 3D-CRT | 37 | (84) | 18 | (69) | |
| IMRT/VMAT | 7 | (16) | 8 | (31) | |
| **Type of resection** | | | | | 0.18 |
| Anterior resection, PME | - | | - | | |
| Low anterior resection, TME | 23 | (52) | 9 | (35) | |
| Abdominoperineal resection | 12 | (27) | 11 | (42) | |
| Hartmann's procedure | 8 | (18) | 3 | (12) | |
| Other | 1 | (2) | 1 | (4) | |
| Refused surgery | - | | 2 | (8) | |
| **Resection status (distance to distal margin, according to Wittekind)** | | | | | 0.93§ |
| R0 > 1 mm | 28 | (64) | 15 | (58) | |
| R1 ≤ 1 mm | 16 | (36) | 9 | (35) | |
| Refused surgery | | | 2 | (8) | |
| **Pathological complete response** | | | | | 0.19§ |
| No | 40 | (91) | 23 | (88) | |
| Yes | 3 | (7) | - | | |
| Unknown | 1 | (2) | 3 | (12) | |
| **Mesorectum** | | | | | |
| Intact | 29 | (66) | 22 | (85) | 0.048§ |
| Breached | 9 | (21) | 1 | (4) | |
| Missing | 6 | (14) | 3 | (12) | |

Continued..

| | | | | | |
|---|---|---|---|---|---|
| **Differentiation grade** | | | | | **0.92§** |
| Well | 9 | (21) | 7 | (27) | |
| Moderate | 22 | (50) | 9 | (35) | |
| Poor | 8 | (18) | 6 | (23) | |
| Not assessed/unknown | 5 | (11) | 2 | (8) | |
| **Pathological T-stage** | | | | | 0.38§ |
| ypT0 | 3 | (7) | - | | |
| ypTis | - | | - | | |
| ypT1 | - | | - | | |
| ypT2 | 5 | (11) | 4 | (15) | |
| ypT3 | 30 | (68) | 16 | (62) | |
| ypT4 | 6 | (14) | 4 | (15) | |
| Unknown/refused surgery | - | | 2 | (8) | |
| **Pathological N-stage** | | | | | 0.26§ |
| ypN0 | 21 | (48) | 9 | (35) | |
| ypN1 | 14 | (32) | 7 | (27) | |
| ypN2 | 9 | (21) | 8 | (31) | |
| Unknown/refused surgery | - | | 2 | (8) | |
| **Distance to circumferential resection margin of the tumor** | | | | | 0.67§ |
| CRM- (>1 mm) | 28 | (64) | 14 | (54) | |
| CRM+ (≤1 mm) | 16 | (36) | 10 | (39) | |
| Unknown/refused surgery | | | 2 | (8) | |
| **Tumor size at baseline MRI** | | | | | 0.44§ |
| <40mm | 4 | (9) | 4 | (15) | |
| ≥40mm | 38 | (86) | 20 | (78) | |
| Unknown | 2 | (5) | 1 | (4) | |
| **Tumor size at histopathology** | | | | | 0.12§ |
| <40mm | 33 | (75) | 14 | (54) | |
| ≥40mm | 10 | (23) | 10 | (38) | |
| Unknown/refused surgery | 1 | (2) | 2 | (8) | |

Data is presented as locoregional recurrence/population in numbers and percentages. Percentages may not equal 100% due to rounding

LRR Locoregional recurrence; EMVI extramural vascular invasion; MRF mesorectal fascia; IMRT intensity-modulated radiation therapy; VMAT volumetric-modulated arc therapy; CRM circumferential resection margin.

† MRI defined

§ p-value calculated in patients in which the value was known.

* Distance was missing in 4 patients of the experimental group and in 1 patient of the standard-care group.

**TABLE 1.** Univariate and Multivariate Cox Regression Analyses for Locoregional Recurrence Regarding Allocation Group, Distance From the Anal Verge and High-risk Factors at Baseline in Patients Who Underwent an R0 or an R1 Resection

| | | Univariate analyses | | | Multivariate analyses | | |
|---|---|---|---|---|---|---|---|
| Variable | Category | n | HR (95% CI) | *P* | n | HR (95% CI) | *P* |
| Treatment | Standard-care | **426** | **1** | — | **426** | **1** | — |
| | Experimental | **431** | **1.84 (1.12–3.02)** | **0.017** | **431** | **1.87 (1.14–3.07)** | **0.014** |
| Distance from anal verge (endoscopy)* | < 5 cm | 196 | 1 | 0.829 | — | — | — |
| | 5–10 cm | 318 | 1.19 (0.63–2.27) | — | — | — | — |
| | ≥ 10 cm | 282 | 1.094 (0.53–2.04) | — | — | — | — |
| Clinical T4 | No | 582 | 1 | — | — | — | — |
| | Yes | 275 | 0.99 (0.59–1.65) | 0.959 | — | — | — |
| Clinical N2 | No | 267 | 1 | — | — | — | — |
| | Yes | 590 | 1.38 (0.80–2.39) | 0.252 | — | — | — |
| Clinical ELLN | No | **723** | **1** | — | **723** | **1** | — |
| | Yes | **134** | **1.74 (0.99–3.04)** | **0.053** | **134** | **1.79 (1.02–3.13)** | **0.042** |
| Clinical EMVI+ | No | 557 | 1 | — | — | — | — |
| | Yes | 300 | 1.13 (0.69–1.85) | 0.621 | — | — | — |
| Clinical MRF+ | No | 271 | 1 | — | — | — | — |
| | Yes | 586 | 1.25 (0.74–2.12) | 0.412 | — | — | — |

Bold values indicate statistical significance $p \leq 0.05$.
Test for interaction is $P = 0.89$.
*In 61 patients, the distance from the anal verge was unknown.
MRF indicates mesorectal fascia.

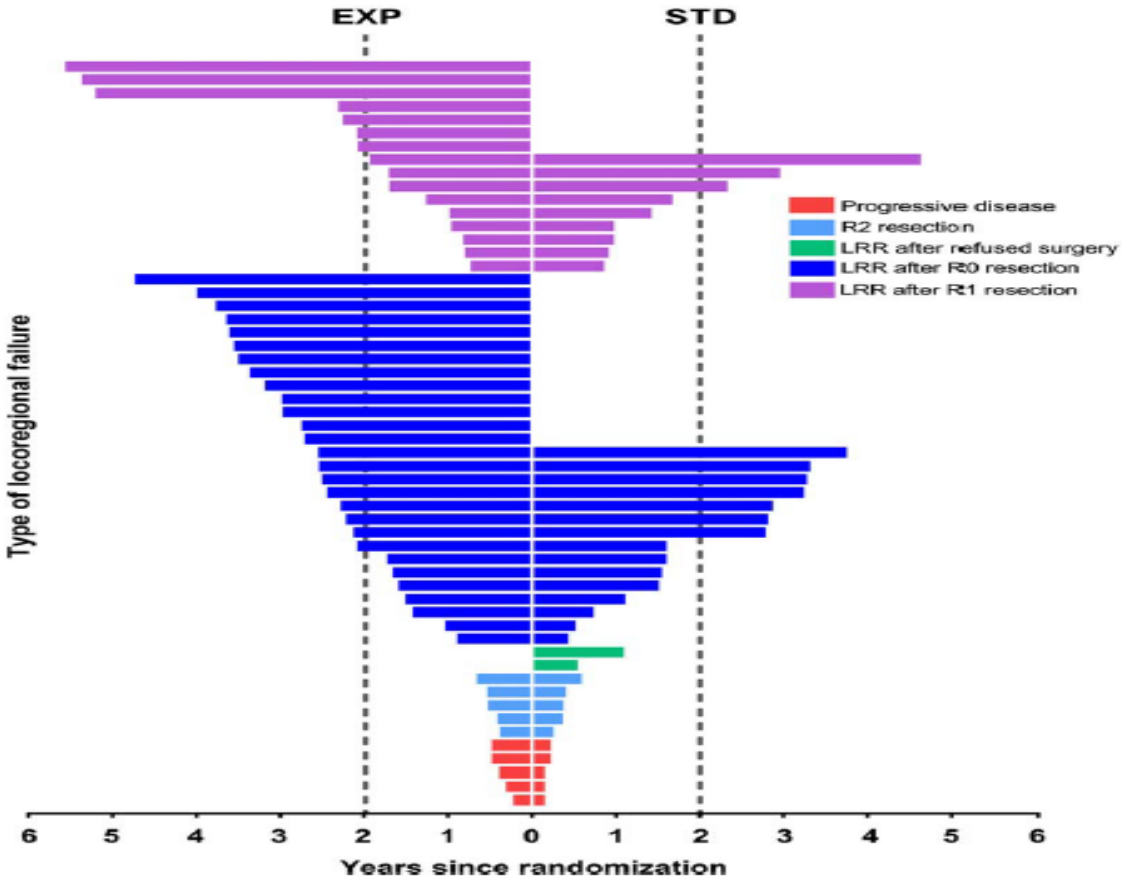


**FIGURE 2.** Plot development of locoregional failure against time in years after randomization. Red: no resection surgery for other reasons than entering a W&W strategy (5 vs. 5). Light blue: R2 (residual tumor locally (all these patients also had distant metastases) (5 vs. 5). Green: locoregionally progressive disease after having refused surgery (0 vs. 2, referred to the LRR group) Dark blue: LRR after an R0 resection (28 vs. 15). Pink: LRR after an R1 resection (16 vs. 9).

## Conclusions:

The EXP treatment was associated with an increased risk of LRR, whereas the reduction in disease-related treatment failure and distant metastases remained after 5 years.

# UNICANCER-PRODIGE 23

## Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial

*Thierry Conroy, Jean-François Bosset, Pierre-Luc Etienne, Emmanuel Rio, Éric François, Nathalie Mesgouez-Nebout, Véronique Vendrely, Xavier Artignan, Olivier Bouché, Dany Gargot, Valérie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Clotilde Morand, Christelle de la Fouchardière, Najib Lamfichekh, Béata Juzyna, Claire Jouffroy-Zeller, Eric Rullier, Frédéric Marchal, Sophie Gourgou, Florence Castan, Christophe Borg, on behalf of the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group**

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## Rationale:

- Total neoadjuvant therapy (TNT) — giving systemic chemotherapy before surgery — aims to: improve systemic control (reduce metachronous metastases), increase pathological complete response (pCR), and improve compliance with systemic therapy.

- PRODIGE-23 tested whether intensifying induction chemotherapy with **modified FOLFIRINOX (mFOLFIRINOX)** before standard long-course CRT improves disease-free survival (DFS) vs standard preop CRT.

# Objective:

- Main objective :- to determine if neo-adjuvant Chemotherapy (NAC) before surgery improves Disease-free survival (DFS)compared with standard preoperative chemoradiotherapy in patients with locally advanced rectal cancer.

- Fluorouracil/leucovorin, oxaliplatin plus irinotecan (FOLFIRINOX) was selected as the neoadjuvant regimen based on

-high response rates (66– 86%)
- disease control rates (94%) in metastatic disease
- 5-FU-oxaliplatin doublets have failed to increase PathCR or to reduce metastatic progression in this setting
-Bolus 5-FU omitted- to reduce febrile neutropenia and the occurrence of neutropenia

# Study Design

- Multicenter, randomized, open-label phase III trial

*Stratified by treatment center, tumor stage (cT3 vs cT4), nodal status (cN0 vs cN+), extramural extension (≥ 5 vs < 5 mm), tumor location (cm from anal verge)*

Patients aged 18-75 yrs with resectable cT3/cT4 rectal adenocarcinoma < 15 cm from anal verge; WHO PS 0/1; no metastatic disease; no prior pelvic RT or CT; no PN > grade 1 (N = 461)

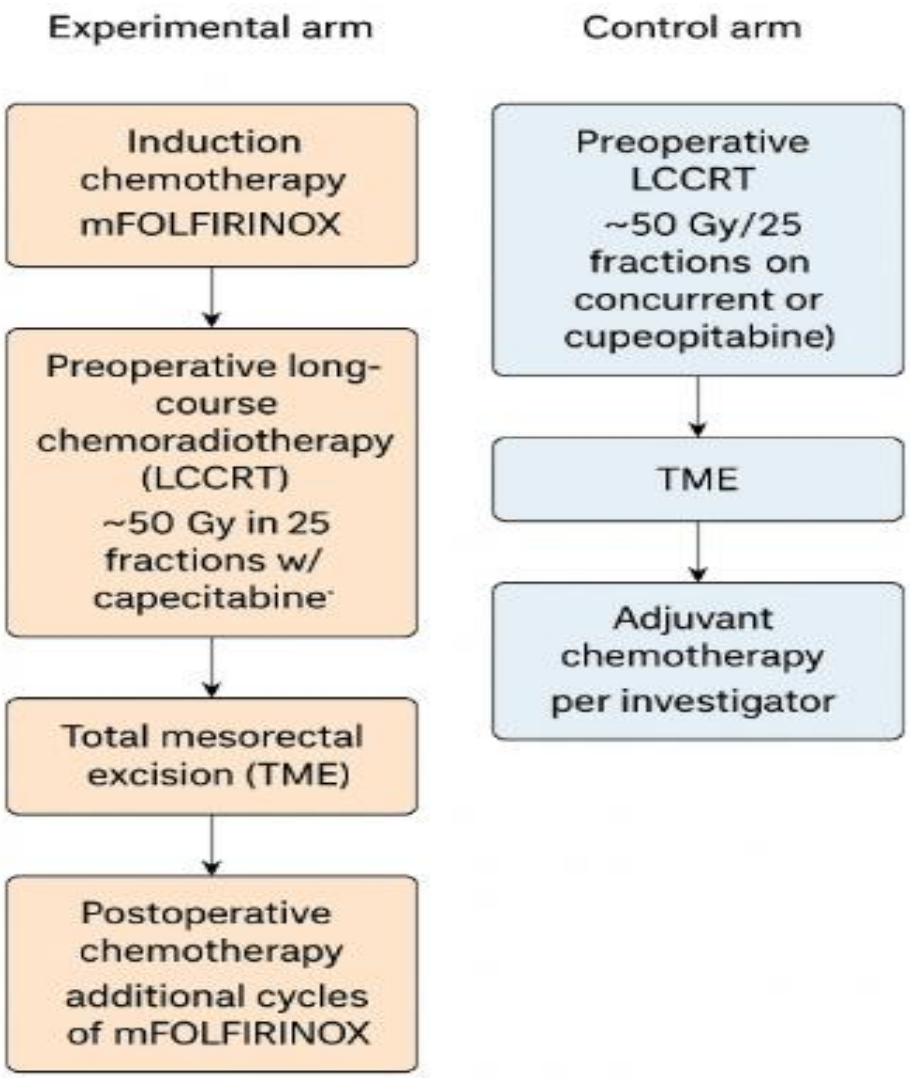
→ **mFOLFIRINOX + CRT + TME**, followed by adjuvant CT for 3 mos (n = 231)

→ **CRT + TME**, followed by adjuvant CT for 6 mos (n = 230)

mFOLFIRINOX administered for 6 cycles over 3 months. CRT = RT 50.4 Gy over 5 wks + capecitabine. TME performed 7 wks after completion of CRT. Adjuvant CT = mFOLFOX6 or capecitabine.

- Primary endpoint: DFS
- Median follow-up: 46.5 mos
- Secondary endpoints: pCR, MFS, OS, safety, QoL

# Treatment Regimen




- FOLFIRINOX consisted of oxaliplatin 85 mg/m2 and leucovorin 400 mg/m² delivered as a 2-hour intravenous infusion followed by irinotecan 180 mg/m² as a 90-minute intravenous infusion, and fluorouracil 2400 mg/m² by continuous intravenous infusion over 46 hours every 14 days for 6 cycles.

- Chemoradiotherapy consisted of 50 Gy over 5 weeks (2 Gy 5-times/week, with a reduction in fields after 44 Gy) and concurrent oral capecitabine 800 mg/m2 twice daily 5 days/week.

- Surgery was mandatory and was planned 6–8 weeks after chemoradiotherapy

- Adjuvant chemotherapy was started 5–12 weeks following surgery regardless of ypTN stage, and consisted of 6-12 cycles of FOLFOX 6 (mFOLFOX6) or 4-8 cycles capecitabine depending on randomisation arm

## Randomisation :

- Patients randomly assigned (1:1) to either neoadjuvant chemo arm or standard care group within 14 days of enrolment

- Randomization done using NKI software- random element of 80% , with stratification :
  - -Center
  - -extramural extension of tumor(≤5mm or ≥5mm)
  - -tumor location from anal verge
  - -stage (cT3 vs cT4, cN0 vs cN+)

- Participants and Investigators were not masked to treatment allocation

## Statistical Analysis:

- Survival rates were estimated using the Kaplan-Meier method and compared using a stratified log-rank test

- A stratified Cox proportional-hazard model according to stratification factors was used to estimate HRs with 95% confidence intervals (CI).

# Results:-

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## Baseline Characteristics: PRODIGE -23

| Characteristic | mFOLFIRINOX + CRT + TME (n = 231) | CRT + TME (n = 230) |
|---|---|---|
| Median age, yrs (range) | 61 (34-77) | 62 (26-75) |
| Male, % | 64.9 | 67.8 |
| WHO PS 0/1, % | 77.7/22.3 | 80.5/19.5 |
| Distance to anal verge, % | | |
| ▪ ≤ 5 cm | 37.7 | 36.1 |
| ▪ 5.1-10 cm | 49.3 | 51.3 |
| ▪ 10.1-15 cm | 13.0 | 12.6 |
| T stage | | |
| ▪ T2 | 1.3 | 0.9 |
| ▪ T3 | 80.9 | 83.6 |
| ▪ T4 | 17.8 | 15.6 |
| cN+, % | 89.1 | 90.0 |
| Predicted lateral margin ≤ 1 mm, % | 26.0 | 27.7 |

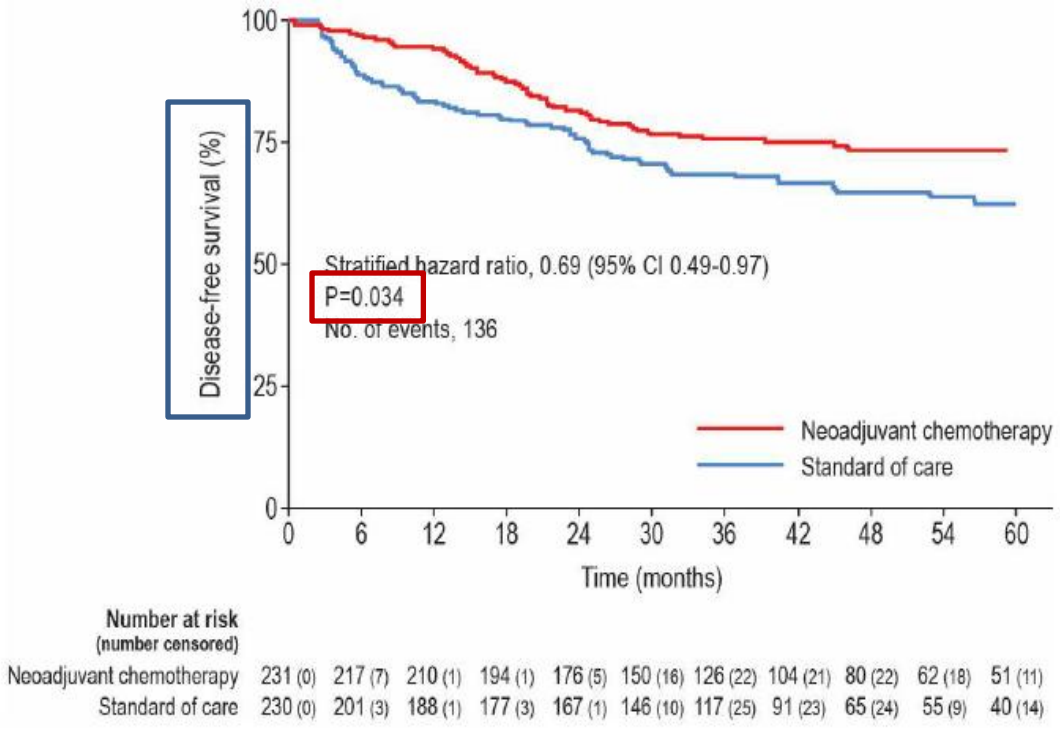
# Treatment Compliance:

| Treatment Received | mFOLFIRINOX + CRT + TME | CRT + TME | *P* Value |
|---|---|---|---|
| Completed 6 cycles neoadjuvant mFOLFIRINOX, n/N (%) | 207/226 (91.6) | -- | |
| CRT | (n = 219) | (n = 227) | |
| ▪ Radiotherapy ≥ 48 Gy, % | 98.2 | 98.7 | NS |
| ▪ Capecitabine discontinuation, % | 8.3 | 3.1 | < .02 |
| Surgery | (n = 213) | (n = 218) | |
| ▪ Median time between CRT and surgery, wks | 7.9 | 7.9 | NS |
| ▪ Nontherapeutic laparotomy, % | 0 | 3.7 | .007 |
| Adjuvant CT | (N = 231) | (N = 230) | |
| ▪ Received, % | 70.6 | 68.7 | NS |
| – mFOLFOX6 | 82.8 | 85.4 | NS |
| – Capecitabine | 17.2 | 14.6 | NS |
| – Completed all cycles | 80.4 | 75.3 | NS |

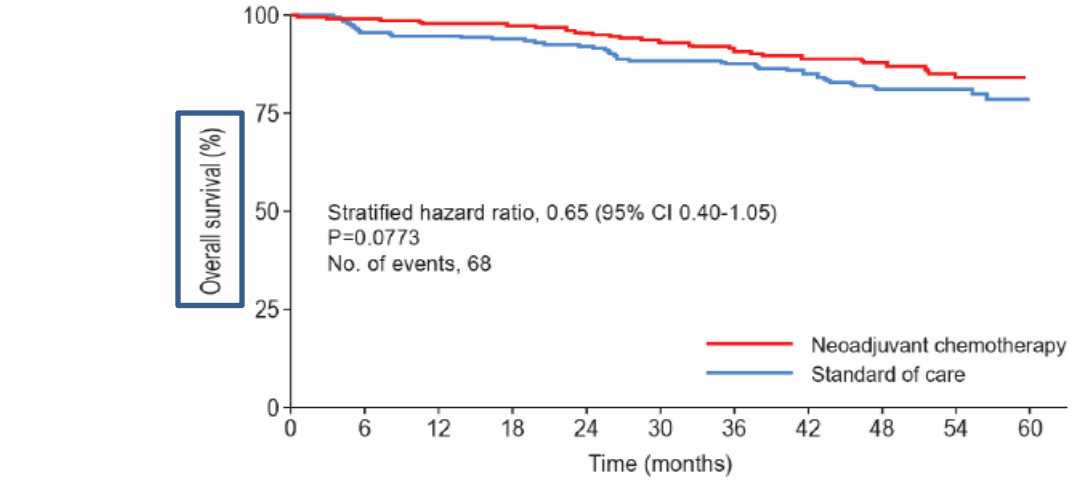
# Primary and Key Secondary Endpoints

| Efficacy Outcome (ITT), % | mFOLFIRINOX + CRT + TME (n = 231) | CRT + TME (n = 230) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| 3-yr DFS | 75.7 | 68.5 | 0.69 (0.49-0.97) | .034 |
| 3-yr MFS | 78.8 | 71.7 | 0.64 (0.44-0.93) | .017 |
| Local relapse | 4.8 | 7.0 | -- | NS |
| Resection status | (n = 213) | (n = 218) | | |
| ▪ ypT0 | 28.3 | 12.6 | -- | < .001 |
| ▪ ypN0 | 82.6 | 67.4 | -- | < .001 |
| ▪ ypT0N0 | 27.8 | 12.1 | -- | < .001 |
| Grade 1 modified Dworak's tumor regression* | (n = 213) 47.6 | (n = 218) 31.8 | -- | .003 |

*CR or near CR.




| Number at risk (number censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neoadjuvant chemotherapy | 231 (0) | 217 (7) | 210 (1) | 194 (1) | 176 (5) | 150 (16) | 126 (22) | 104 (21) | 80 (22) | 62 (18) | 51 (11) |
| Standard of care | 230 (0) | 201 (3) | 188 (1) | 177 (3) | 167 (1) | 146 (10) | 117 (25) | 91 (23) | 65 (24) | 55 (9) | 40 (14) |




| Number at risk (number censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neoadjuvant chemotherapy | 231 (0) | 221 (8) | 217 (1) | 215 (1) | 205 (6) | 180 (20) | 151 (25) | 124 (24) | 99 (24) | 73 (22) | 54 (19) |
| Standard of care | 230 (0) | 215 (5) | 212 (1) | 207 (3) | 201 (2) | 182 (11) | 151 (30) | 117 (30) | 82 (30) | 71 (11) | 51 (18) |

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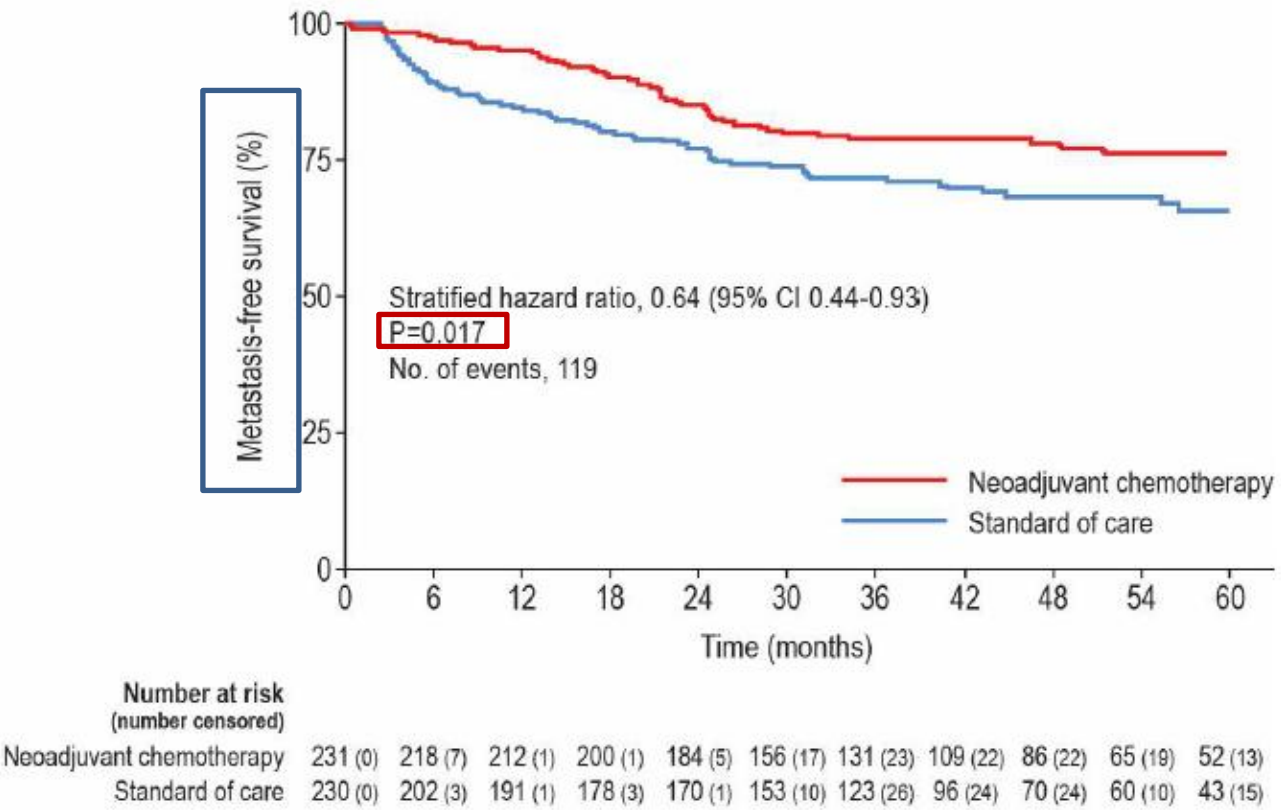
- DFS at 3 years was 76% vs 69%
- OS at 3 years was NS




Metastasis Free Survival (MFS) at 3 years - 79% vs 72%

# DFS Prognostic factors and QOL

| Variable | Unstratified Univariate Analysis | | Stratified Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| mFOLFIRINOX + CRT + TME (vs CRT + TME) | 0.69 (0.49-0.97) | .033 | 0.68 (0.48-0.97) | .03 |
| TNM stage | | < .001 | | < .001 |
| ▪ Stage III | 1.03 (0.57-1.87) | | 1.44 (0.62-3.32) | |
| ▪ Stage IV | 16.64 (6.87-40.00) | | 17.12 (5.49-53.38) | |
| Tumor location | | < .002 | | |
| ▪ Middle rectum | 0.53 (0.37-0.75) | | | |
| ▪ Upper rectum | 0.70 (0.41-1.20) | | | |
| T stage | | | | |
| ▪ mrT3+ CRM > 1 mm | 0.70 (0.42-1.16) | .03 | | |
| ▪ mrT4a/b | 1.93 (1.24-3.02) | .013 | | |
| Baseline cT4 stage | 1.75 (1.12-2.75) | .02 | | |

- Both study arms showed significant improvements in overall global health status/QoL over time ($P < .001$); trend toward greater improvements in QoL with mFOLFIRINOX + CRT + TME ($P = .076$)

# Safety:

| Grade 3/4 AEs With mFOLFIRINOX, % | Patients (n = 226) |
|---|---|
| Neutropenia | 16.9 |
| Diarrhea | 11.1 |
| Fatigue | 7.1 |
| Nausea | 6.2 |
| Vomiting | 4.9 |
| Thromboembolic event | 2.7 |
| Peripheral neuropathy | 2.2 |
| Febrile neutropenia | 2.2 |
| Thrombocytopenia | 1.3 |
| Anemia | 0.9 |
| Sudden death | 0.4 |

| Grade 3/4 AEs With CRT, % | mFOLFIRINOX + CRT + TME (n = 219) | CRT + TME (n = 227) | *P* Value |
|---|---|---|---|
| Neutropenia | 2.8 | 0 | < .02 |
| **Events With Surgery** | **mFOLFIRINOX + CRT + TME (n = 213)** | **CRT + TME (n = 218)** | ***P* Value** |
| ▪ Median hospital stay, days (range) | 11 (3-78) | 12 (2-99) | NS |
| ▪ Postoperative morbidity, % | 29.3 | 31.2 | NS |
| ▪ Postoperative mortality, % | 0 | 2.8 | .03 |

| Grade 3/4 AEs With Adjuvant CT, % | mFOLFIRINOX + CRT + TME, 3 Mos (N = 163) | CRT + TME, First 3 Mos (N = 158) | *P* Value* | CRT + TME, All 6 Mos (N = 158) | *P* Value* |
|---|---|---|---|---|---|
| Overall incidence | 44.4 | 52.5 | .03 | 74.1 | < .001 |
| Neutropenia | 5.6 | 11.6 | .07 | 18.1 | < .001 |
| Lymphopenia | 11.2 | 20.0 | .03 | 27.1 | < .001 |
| Peripheral neuropathy | 11.7 | 5.2 | .04 | 20.7 | .033 |

**P* value vs mFOLFIRINOX + CRT + TME, 3 mos.

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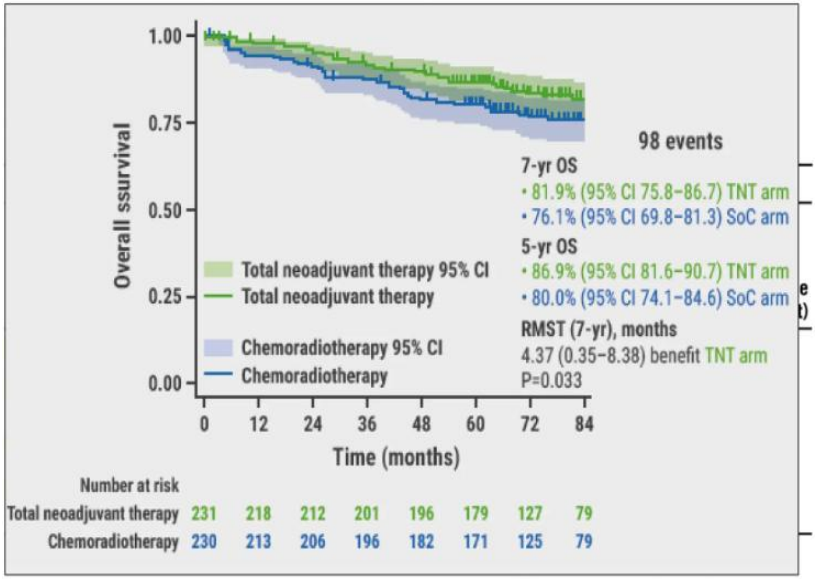
# Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

Survival results.

| | Arm A: CRT 7-year estimate [95% CI] | Arm B: mFOLFIRINOX + CRT 7-year estimate [95% CI] | Stratified HR [95%CI] (Cox Model) | Difference between RMST in mos (Arm B - Arm A) [95%CI] | p-value (Difference RMST test) |
|---|---|---|---|---|---|
| **DFS** | 62.5% [55.6-68.6] | 67.6% [60.7-73.6] | 0.80 [0.58-1.11] | | |
| **RMST*** | 60.4 mos [56.2-64.7] | 66.2 mos [62.4-69.9] | | 5.7 [0.05-11.4] | 0.048 |
| **MFS** | 65.4% [58.7-71.3] | 73.6% [67.0-79.2] | 0.73 [0.51-1.02] | | |
| **RMST*** | 62.1 mos [57.9-66.3] | 69.3 mos [65.7-72.8] | | 7.1 [1.7-12.6] | 0.011 |
| **OS** | 76.1% [69.8-81.3] | 81.9% [75.8-86.7] | 0.73 [0.48-1.09] | | |
| **RMST*** | 71.9 mos [68.8-75.1] | 76.3 mos [73.8-78.8] | | 4.3 [0.4-8.4] | 0.033 |
| **CSS** | 79.6% [73.5-84.4] | 84.9% [79.1-89.2] | 0.66 [0.42-1.05] | | |
| **RMST*** | 73.4 mos [70.3-76.4] | 77.2 mos [74.8-79.6] | | 3.8 [-0.02-7.7] | 0.051 |

CI= Confidence Interval * at 84 mos F/U.



# Conclusion :

- PRODIGE-23 demonstrated feasibility of administering neoadjuvant mFOLFIRINOX in stage II/III rectal cancers
  - -Increased probability of CR
  - - Decreased probability of surgery with non curative intent
  - - Improved DFS and MFS and OS at 7 years

- Investigators Concluded that TNT with mFOLFIRINOX should now be considered standard of care fpr initial treatment of cT3/T4 rectal camcers

# Limitations :

- Trial was open label, which may introduce bias as neither participant nor investigator were blinded
- Some patients had cT3N0 tumors without predicted involved radial margin and might have been overrated
- Serious adverse events were reported , with notable incidence of grade 3-4 toxicities , raising concern with treatment safety profile

# RAPIDO vs PRODIGE-23

Baseline Patient Characteristics

| Characteristics | RAPIDO | PRODIGE 23 |
|---|---|---|
| Number of patients | 912 | 461 |
| Median age (years) | 62 | 61 |
| Distance from anal verge | | |
| <5 cm | 25.7% | 36.9% |
| 5-10 cm | 39.3% | 50.3% |
| 10-15 cm | 35.0% | 12.8% |
| Clinical T stage | | |
| cT3 | 65.8% | 82.2% |
| cT4 | 31.1% | 12.8% |
| Clinical N stage | | |
| cN0 | 8.4% | 10.4% |
| cN1 | 26.1% | 89.6%(N+) |
| cN2 | 65.5% | |
| Other high-risk features | | |
| EMVI + | 29.9% | NR |
| MRF + | 61% | 27% |
| Lateral N + | 14.8% | NR |

*EMVI, extramural venous invasion; MRF, mesorectal fascia invasion; NR, not reported*

Comparison of outcomes from RAPIDO and PRODIGE-23

| Outcome | RAPIDO (TNT vs. CRT) | PRODIGE 23 (TNT vs. CRT) |
|---|---|---|
| Primary endpoint | 3-year DrTF<br>23.7% vs. 30.4% | 3-year DFS<br>75% vs. 68.5% |
| pCR rate | 28.4% vs. 14.3%<br>P<0.001 | 27.8% vs. 12.1%<br>P<0.001 |
| Locoregional failure (at 3 years) | 8.3% vs. 6.0%<br>P=0.12 | NR |
| Distant metastasis (at 3 years) | Cumulative probability<br>20.0% vs. 26.8% | Metastasis-free survival<br>78.8% vs. 71.7% |
| OS (at 3 years) | 89.1% vs. 88.8%<br>P=0.59 | 90.8% vs. 87.7%<br>P=0.07 |

*TNT, total neoadjuvant therapy; CRT, chemoradiation therapy; DFS, disease-free survival; DrTF, disease-related treatment failure; pCR, pathological complete response; OS, overall survival; NR, not reported*

# PROSPECT Trial (Alliance N1048)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Preoperative Treatment of Locally Advanced Rectal Cancer

Deborah Schrag, M.D., M.P.H., Qian Shi, Ph.D., Martin R. Weiser, M.D., Marc J. Gollub, M.D., Leonard B. Saltz, M.D., Benjamin L. Musher, M.D., Joel Goldberg, M.D., Tareq Al Baghdadi, M.D., Karyn A. Goodman, M.D., Robert R. McWilliams, M.D., Jeffrey M. Farma, M.D., Thomas J. George, M.D., Hagen F. Kennecke, M.D., Ardaman Shergill, M.D., Michael Montemurro, M.D., Garth D. Nelson, M.S., Brian Colgrove, B.S., Vallerie Gordon, M.D., Alan P. Venook, M.D., Eileen M. O'Reilly, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Amylou C. Dueck, Ph.D., Ethan Basch, M.D., George J. Chang, M.D., and Harvey J. Mamon, M.D., Ph.D.

This article was published on June 4, 2023, at NEJM.org.

# Rationale

- FOLFOX chemotherapy (fluorouracil, Leucovorin, and Oxaliplatin) has shown efficacy when used preoperatively; early pilot data suggested radiation might be avoidable in responsive

- PROSPECT was designed to test whether neoadjuvant FOLFOX—with radiation reserved only for poor responders—would be noninferior in disease-free survival (DFS) while potentially reducing radiation toxicity

# Methods

- A randomized, phase II/III, unblinded, multicenter trial across North America , Canada and Switzerland

- **Inclusion Criteria**: -18 years of age or older
  -ECOG performance score 0,1 or2
  - previously untreated
  -pathologically confirmed
  - locally advanced rectal cancer that had been clinically staged as T2 node-positive, T3 node-negative, or T3 node-positive

- **Exclusion criteria**: -Patients with T4 tumors
  -four or more pelvic lymph nodes with a short axis larger than 10 mm
  - tumor visible within 3 mm of the radial margin seen on baseline pelvic imaging

- **Randomized** -1:1on the basis of a dynamic randomization scheme with stratification according to ECOG performance-status score

## Treatment Arms :-

- **Control Arm:** Standard 5-FUCRT (5040 cGy over 5.5 weeks + capecitabine or 5FU), then total mesorectal excision (TME).

- **Intervention Arm:** Six cycles of modified FOLFOX 6, restage; if tumor regression ≥20%, proceed to TME; if <20%, administer Chemoradiotherapy before TME.

*Postoperative Chemotherapy was suggested in both arms but not mandated*

- In both treatment groups, the choice between three-dimensional conformal radiotherapy or intensity-modulated radiotherapy was at the discretion of the radiation oncologist.

- The surgical approach (open resection vs. laparoscopic or robot-assisted) was chosen at the surgeon's discretion.

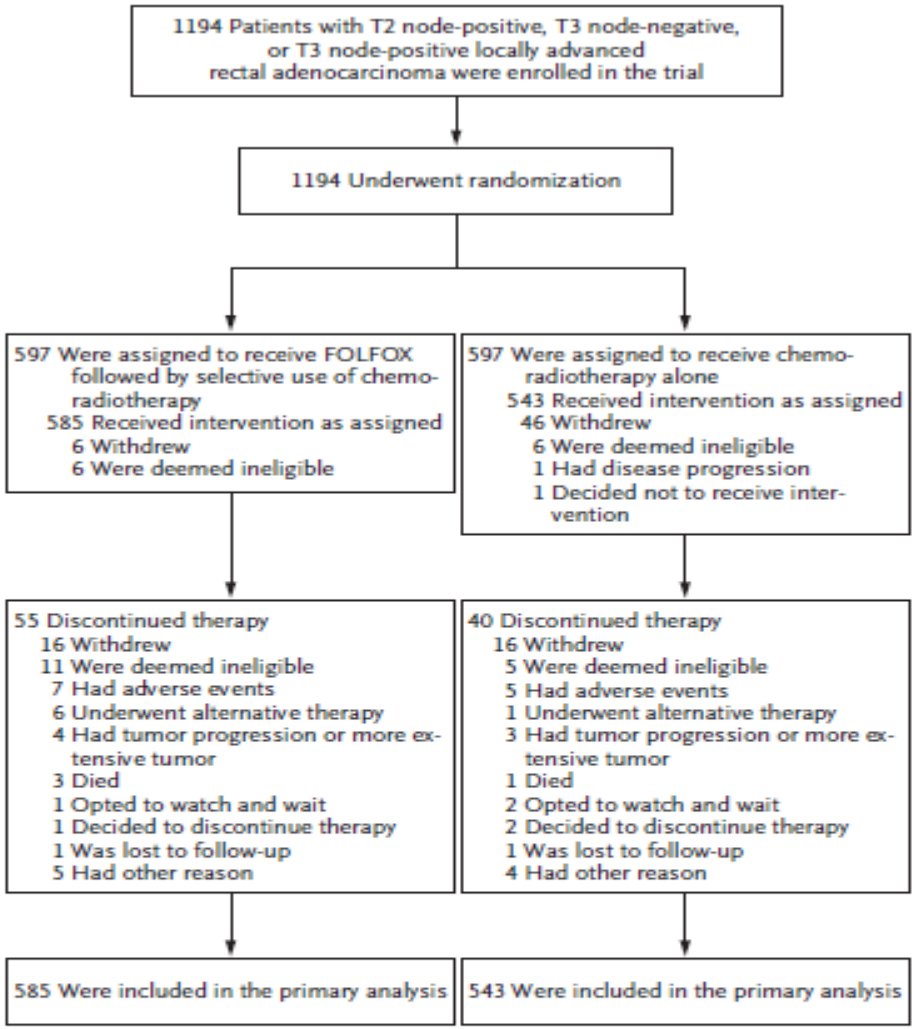



**Figure 1. Enrollment, Randomization, and Follow-up.**

Sites were not required to provide screening logs during the recruitment phase, and therefore the number of patients assessed for eligibility is not available. FOLFOX consists of fluorouracil, leucovorin, and oxaliplatin; the chemoradiotherapy used in the trial consisted of pelvic radiation therapy plus sensitizing chemotherapy with a fluoropyrimidine. Patients in the FOLFOX group received six cycles of FOLFOX, with chemoradiotherapy given only if the primary tumor decreased in size by less than 20% or if FOLFOX was discontinued because of side effects; patients in the chemo-radiotherapy group received chemoradiotherapy alone.

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# Endpoints

**Primary endpoint:** Disease-free survival (DFS).

**Secondary endpoints:** -Overall survival (OS)
-local recurrence–free survival,
-R0 resection
-pathologic complete response (CR)
-toxicity

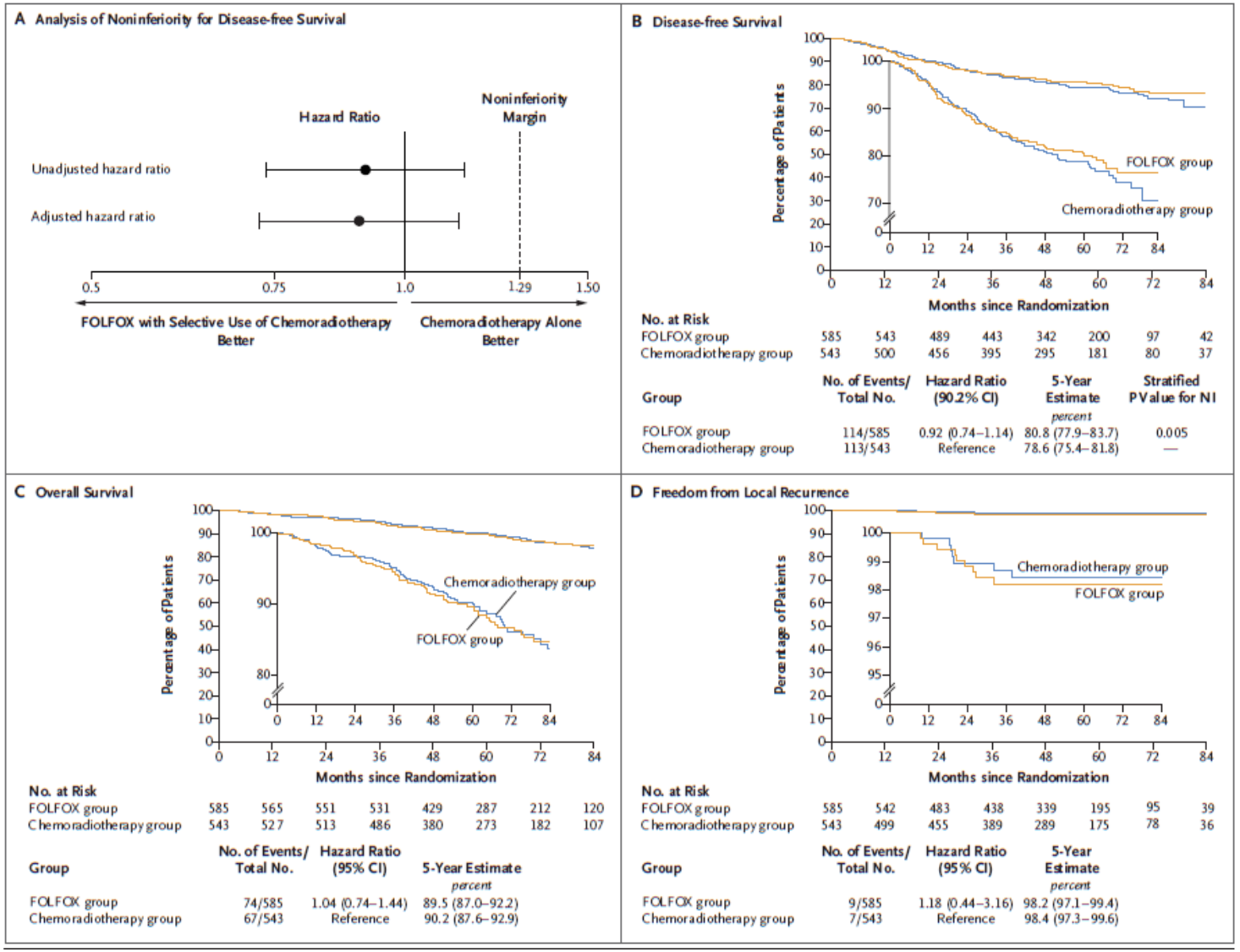
# ▪ Results

- From June 2012 through December 2018, a total of 1194 patients with pathologically confirmed rectal adenocarcinoma that had been clinically staged as T2 node-positive, T3 node-negative, or T3 node-positive were randomly assigned to the FOLFOX group (597 patients) or the chemoradiotherapy (597 patients)

- At a median follow-up of 58 months, FOLFOX was noninferior to chemoradiotherapy for disease-free survival (hazard ratio for disease recurrence or death, 0.92; 90.2% confidence interval [CI], 0.74 to 1.14; P = 0.005 for noninferiority).

- Five-year disease-free survival was 80.8% (95% CI, 77.9 to 83.7) in the FOLFOX group and 78.6% (95% CI, 75.4 to 81.8) in the chemoradiotherapy group.

- The groups were similar with respect to overall survival (hazard ratio for death, 1.04; 95% CI, 0.74 to 1.44) and local recurrence (hazard ratio, 1.18; 95% CI, 0.44 to 3.16).




In Panel A, the dashed line at a hazard ratio of 1.29 indicates the noninferiority margin.

**Table 2. Surgical and Pathological Secondary and Exploratory End Points in Patients in the Per-Protocol Population Who Underwent Surgery.**

| End Point | FOLFOX Group (N=535) | Chemoradiotherapy Group (N=510) |
|---|---|---|
| **Secondary end points** | | |
| Completeness of rectal resection — no. (%)* | | |
| R0 | 529 (98.9) | 495 (97.1) |
| R1 | 6 (1.1) | 14 (2.7) |
| R2 | 0 | 1 (0.2) |
| Pathological complete response — no. (%)† | | |
| Yes | 117 (21.9) | 124 (24.3) |
| No | 418 (78.1) | 386 (75.7) |
| **Other surgical and pathological end points** | | |
| Median time from randomization to surgery (interquartile range) — wk | 19.0 (17.1–21.1) | 15.6 (14.6–17.0) |
| Median time from end of preoperative therapy to surgery (interquartile range) — wk‡ | 4.6 (3.1–6.3) | 7.7 (6.9–9.0) |
| Type of surgery — no. (%) | | |
| Abdominal perineal resection | 13 (2.4) | 10 (2.0) |
| Low anterior resection | 522 (97.6) | 500 (98.0) |
| Histologic grade — no./total no. (%)§ | | |
| G1 or G2 | 396/535 (74.0) | 344/504 (68.3) |
| G3 or G4 | 22/535 (4.1) | 27/504 (5.4) |
| GX | 117/535 (21.9) | 133/504 (26.4) |
| Radial margin category — no./total no. (%)¶ | | |
| ≤1 mm | 6/509 (1.2) | 7/469 (1.5) |
| >1 mm but ≤3 mm | 26/509 (5.1) | 31/469 (6.6) |
| >3 mm | 477/509 (93.7) | 431/469 (91.9) |
| Pathological tumor stage after neoadjuvant therapy — no./total no. (%) | | |
| ypT0 | 121/534 (22.7) | 125/506 (24.7) |
| ypT1 | 56/534 (10.5) | 50/506 (9.9) |
| ypT2 | 183/534 (34.3) | 156/506 (30.8) |
| ypT3 | 169/534 (31.6) | 173/506 (34.2) |
| ypT4 | 5/534 (0.9) | 2/506 (0.4) |
| Pathological node status after neoadjuvant therapy — no. (%) | | |
| ypN0 | 400 (74.8) | 390 (76.5) |
| ypN1 | 108 (20.2) | 104 (20.4) |
| ypN2 | 27 (5.0) | 16 (3.1) |

Table 2. (Continued.)

| End Point | FOLFOX Group (N=535) | Chemoradiotherapy Group (N=510) |
|---|---|---|
| Pathological metastatic status — no./total no. (%) | | |
| M0 | 520/521 (99.8) | 494/499 (99.0) |
| M1a | 1/521 (0.2) | 5/499 (1.0) |
| Tumor regression grade — no./total no. (%) | | |
| Pathological complete response or grade 0 | 123/533 (23.1) | 127/510 (24.9) |
| Grade 1 | 161/533 (30.2) | 200/510 (39.2) |
| Grade 2 | 146/533 (27.4) | 151/510 (29.6) |
| Grade 3 | 103/533 (19.3) | 32/510 (6.3) |

# Safety Profile:

- Clinician-reported toxic effects during neoadjuvant therapy incidence of severe (grade ≥3) adverse events in the FOLFOX group than in the chemoradiotherapy group (41.0% vs. 22.8%).
- Neuropathy was more frequent and severe in the FOLFOX group than in the chemoradiotherapy group
- Diarrhea was more frequent and severe in the chemoradiotherapy group than in the FOLFOX group.

# Conclusion:

- FOLFOX with selective chemoradiation is noninferior to standard 5FUCRT in terms of DFS, OS, and local control.
- Distinct toxicity and symptom profiles allow personalized treatment decisions, particularly when considering patient preferences, access to radiation, or potential side–effect management.
- Both options are validated; radiation is not automatically omitted, but FOLFOX-first is a viable alternative strategy

# Limitations:

- Patient selection: Exclusion of high-risk tumors limits applicability; study population is largely moderate-risk, early/intermediate LARC.
- Population representation: Primarily North American and white patients—results may not generalize to more diverse populations.
- Evolution of treatments: New strategies—like total neoadjuvant therapy or nonoperative management—were emerging during trial's conduct. Long-term toxicity and HRQL beyond 18 months remain pending.

Meeting Abstract: 2020 ASCO Annual Meeting I

FREE ACCESS | Gastrointestinal Cancer—Colorectal and Anal | May 25, 2020

# ARISTOTLE: A phase III trial comparing concurrent capecitabine with capecitabine and irinotecan (Ir) chemoradiation as preoperative treatment for MRI-defined locally advanced rectal cancer (LARC).

**Authors**: David Sebag-Montefiore, Richard Adams, Simon Gollins, Leslie M. Samuel, Robert Glynne-Jones, Robert Harte, Nicholas West, ... SHOW ALL ... ,

**Background:** Phase II studies reported high pathological complete response (pCR) rates and acceptable toxicity using irinotecan and fluoropyrimidine chemoradiation in LARC

# Methods:

- Phase III, multicentre, open-label trial funded by Cancer Research UK
- randomly assigned (1:1) patients with MRI defined LARC threatening or involving resection margins without metastases, to pre-operative radiotherapy (RT) 45Gy/25 fractions combined with either capecitabine 900mg/$m^2$(CRT) or 650 mg/m2 bd weekdays with Irinotecan iv once-weekly 60mg/m2 weeks 1-4 (IrCRT)
- Primary endpoint - disease-free survival (DFS)
- Secondary endpoints -treatment compliance, safety and pCR.

# Results:

- UK sites randomised 564 eligible patients from Oct/11 to July/18 284 to CRT and 280 to IrCRT
- Staging in both arms was similar: mrT3 (432/564(77%), mrT4 (89/564(16%); mrCRM involved (275/564(49%); threatened ≤1mm (215/564(38%).
- Compared with CRT, IrCRT patients were less likely to receive 45Gy RT (207/276(75%) vs 251/283(89%), $p < 0.001$) or receive ≥90% capecitabine dose in 188/276(68%) vs 253/283(89.4%)$p < 0.001$
- The grade 3-4 gastrointestinal adverse event rate was 21%(58/276) with IrCRT and 12%(34/283) with CRT ($p = 0.004$).
- Patients receiving IrCRT had significantly more diarrhoea 38/276(13.8%) vs 10/283(3.5%)$p < 0.001$) and neutropenia 27/276(9.8%) vs 3/283 (1.1%) $p < 0.001$).

# Conclusion:

- For patients with MRI defined high risk LARC low rates of CRM involvement were observed in both arms reflecting high quality multidisciplinary care.
- The addition of irinotecan did not significantly improve the pCR rate, was associated with a decrease in the RT and capecitabine compliance and a higher rate of adverse events.
- Surgical procedure or complications were unaffected.
- Longer follow-up is required to assess DFS and translational data.

Hanna et al. Radiat Oncol (2021) 16:163
https://doi.org/10.1186/s13014-021-01888-1

Radiation Oncology

STUDY PROTOCOL Open Access

# Durvalumab (MEDI 4736) in combination with extended neoadjuvant regimens in rectal cancer: a study protocol of a randomised phase II trial (PRIME-RT)

Catherine R. Hanna[1*], Sean M. O'Cathail[2], Janet S. Graham[2], Mark Saunders[4], Leslie Samuel[5], Mark Harrison[6], Lynsey Devlin[3], Joanne Edwards[7], Daniel R. Gaya[8], Caroline A. Kelly[1], Liz-Anne Lewsley[1], Noori Maka[9], Paula Morrison[10], Louise Dinnett[1], Susan Dillon[1], Jacqueline Gourlay[1], Jonathan J. Platt[11], Fiona Thomson[12], Richard A. Adams[13] and Campbell S. D. Roxburgh[14]

**Background:** Advances in multi-modality treatment of locally advanced rectal cancer (LARC) have resulted in low local recurrence rates, but around 30% of patients will still die from distant metastatic disease.

- In parallel, there is increasing recognition that with radiotherapy and systemic treatment, some patients achieve a complete response and may avoid surgical resection, including in many cases, the need for a permanent stoma.

- The inclusion of immunotherapy in the neoadjuvant setting has the potential to further enhance this strategy by priming the local immune microenvironment and engaging the systemic immune response.

# Methods:

PRIME-RT is a multi-centre, open label, phase II, randomised trial for patients with newly diagnosed LARC.

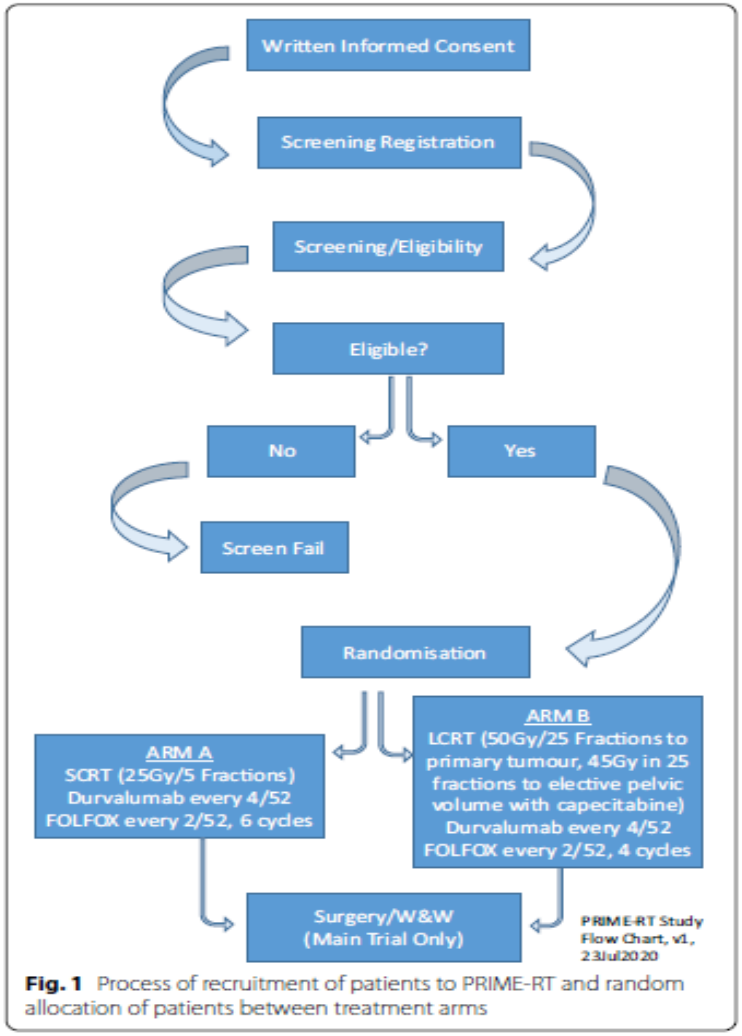



**Fig. 1** Process of recruitment of patients to PRIME-RT and random allocation of patients between treatment arms

**primary endpoint**
is complete response rate in each arm.

**Secondary endpoints** include treatment compliance, toxicity, safety, overall recurrence, proportion of patients with a permanent stoma, and survival.

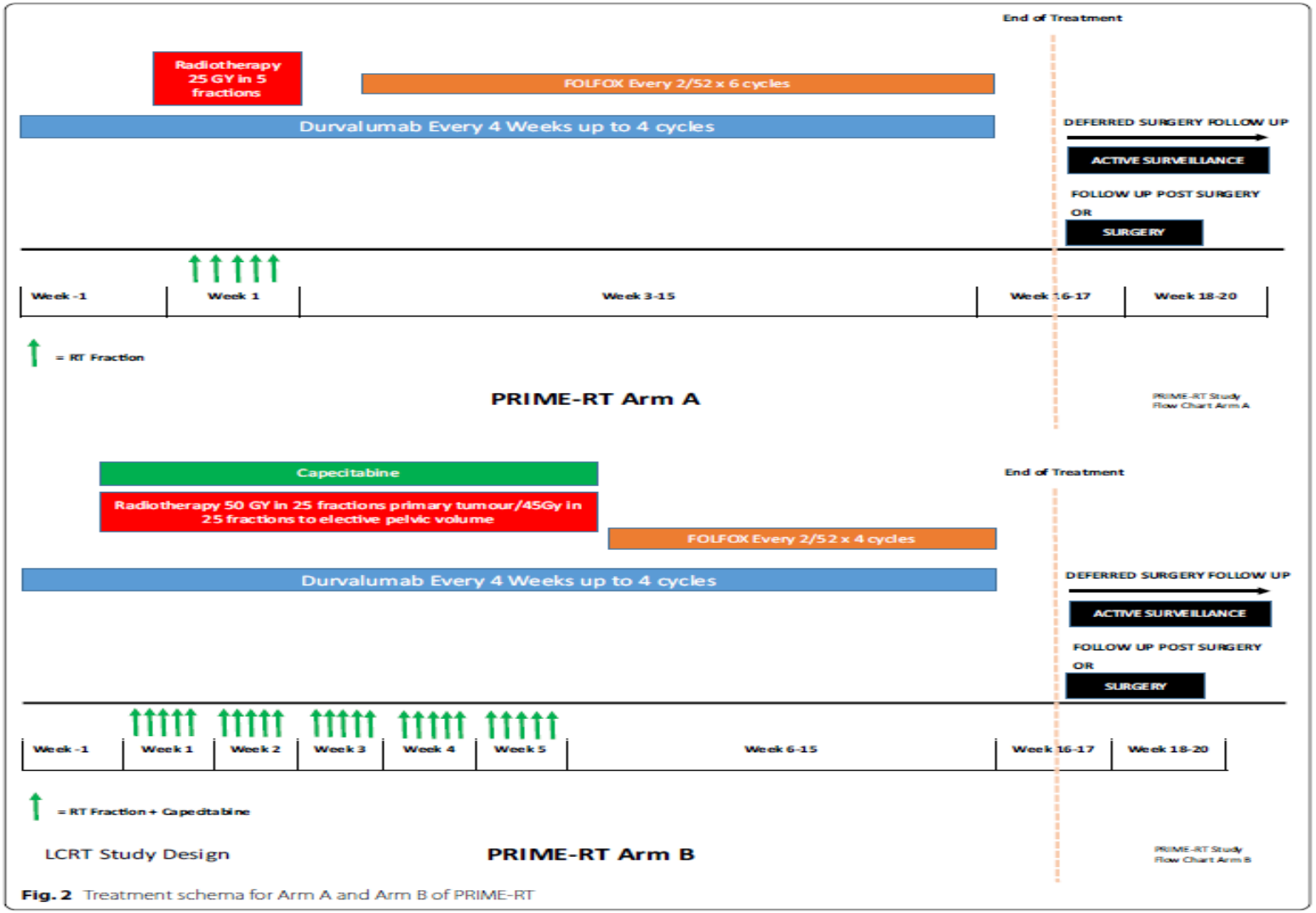



**Fig. 2** Treatment schema for Arm A and Arm B of PRIME-RT

The trial opened and the first patient was recruited in January 2021.

The main trial will recruit up to 42 patients with LARC and commence after completion of a safety run-in that will recruit at least six patients with LARC or metastatic disease.

# SUMMARY

- RAPIDO & PRODIGE 23 → TNT is superior to traditional CRT → surgery.

- PROSPECT → Selected intermediate-risk patients may skip RT and do well with chemo-first.

- PRIME-RT → The future lies in immunotherapy + TNT/RT, especially in MSI-H tumors, with potential for non-operative management (organ preservation).

# TAKE HOME MESSAGE

- Overall – TNT (RAPIDO, PRODIGE 23) improves systemic control; PROSPECT challenges routine RT.

- Future – Immunotherapy ( PRIME-RT) may transform TNT and enable non-operative management.