JAMA Oncology | Original Investigation

Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

Alessandro Audisio, MD; Chiara Gallio, MD; Vaneja Velenik, MD, PhD; Hélène Meillat, MD; Erika Ruiz-Garcia, MD, MSc; Maria Carmen Riesco, MD; Javier Suárez Alecha, MD; Gertjan Rasschaert, MD; Carlos Carvalho, MD; Violaine Randrian, MD, PhD; Iva Kirac, MD, PhD; Jorge Hernando, MD, PhD; Mehmet Artaç, MD, PhD; Juan Manuel O'Connor, MD, MSc; Ithai Waldhorn, MD, PhD; Pètra M. Braam, MD, PhD; Ali Shamseddine, MD; Roberto Moretto, MD; Carolina De la Pinta, MD, PhD; Francesca De Felice, MD, PhD; Audrius Dulskas, MD, PhD; David Páez López-Bravo, MD, PhD; Alexander Vanden Bulcke, MD; Felix Bock, MD; Amélie Deleporte, MD; Marc Van Den Eynde, MD, PhD; Karen P. Geboes, MD, PhD; Mauro Loi, MD, PhD; Marco Messina, MD; Constance Houlzé-Laroye, MD; Alberto Puccini, MD, PhD; Alessandro Pastorino, MD; Demetris Papamichael, MD; Michele Fiore, MD; Daniel Sur, MD, PhD; Michal Eid, MD; Claire Antoun, MD; Massimiliano Salati, MD; Ingrid Garajovà, MD; Matas Jakubauskas, MD, PhD; Jiří Tomášek, MD, PhD; Cidália Maria Sousa Pinto, MD; Jerome Schwingel, MD; Federica Morano, MD; Richard A. Adams, MD; Alexandre Dermine, MD; Amélie Chau, MD; Muhammad Ahsan Javed, MD, PhD; Michele Ghidini, MD, PhD; Francesco Fiorica, MD, PhD; Paola Montenegro, MD; Angelica Petrillo, MD, PhD; Gaya Spolverato, MD; Núria Mulet Margalef, MD, PhD; Marie Diaz, MD; Chiara Baratelli, MD; Francesco Puleo, MD; Athanasios Karampeazis, MD, PhD; Fatma Sert, MD, PhD; Quentin Gilliaux, MD; Alfonso De Stefano, MD, PhD; Gabriel Liberale, MD, PhD; Luigi Moretti, MD, PhD; Philippe Martinive, MD, PhD; Vaiva Deltuvaite Thomas, PhD; Vincent Staggs, PhD; Everardo D. Saad, MD; Jean-Luc Van Laethem, MD, PhD; Francesco Sclafani, MD, PhD; for the International Real-World TNT Study Consortium

IMPORTANCE This was a clinical study of total neoadjuvant therapy (TNT) for rectal cancer.

OBJECTIVE To assess the use and outcomes of TNT in routine practice.

DESIGN, SETTING, AND PARTICIPANTS This international, multicenter study was conducted at 61 centers across 21 countries and included consecutive patients treated off trial with TNT for stage II/III rectal adenocarcinoma from September 2012 to December 2023. Data were analyzed between August and October 2024.

EXPOSURE TNT, defined as the delivery of radiotherapy and nonradiosensitizing chemotherapy before surgery or watch and wait.

MAIN OUTCOMES AND MEASURES The primary outcome was type of TNT administered. Secondary outcomes were patient characteristics, treatment adherence, safety, and efficacy overall and by type of TNT in the entire population and after propensity vector matching.

RESULTS A total of 1585 patients (588 female [37.1%]; median [IQR] age, 61 [53-68] years) were included, 1260 (79.5%) of whom had 1 or more high-risk features (eg, cT4, cN2, extramural venous invasion, threatened/involved mesorectal fascia, and lateropelvic lymphadenopathy). Patients were treated with the PRODIGE 23–like regimen (FOLFIRINOX/FOLFOXIRI followed by long-course chemoradiotherapy) (271 [17.7%]), RAPIDO-like regimen (short-course radiotherapy followed by consolidation FOLFOX/CAPOX) (529 [33.4%]), OPRA induction-like (induction FOLFOX/CAPOX followed by long-course chemoradiotherapy) (190 [12.0%]), OPRA consolidation-like (long-course chemoradiotherapy followed by consolidation FOLFOX/CAPOX) (257 [16.2%]), and other regimens (360 [22.7%]). After TNT, 192 (12.1%) underwent watch and wait, and 30 (1.9%) underwent local excision. Pathological or clinical complete response was reported in 23.2% of cases. At treatment failure, 8.5% was local and 16.4% was distant progression. Three-year event-free survival (EFS) was 68% (95% CI, 64%-71%), and 5-year overall survival (OS) was 79% (95% CI, 75%-83%). In the overall population, patients treated with the PRODIGE 23–like regimen were most likely to have serious adverse events (61 [23.5%]) but had better local control and survival outcomes than those treated with the RAPIDO-like (EFS: hazard ratio [HR], 0.68; 95% CI, 0.49-0.95; $P = .03$; OS: HR, 0.51; 95% CI, 0.27-0.97; $P = .04$), OPRA induction-like (EFS: HR, 0.66; 95% CI, 0.44-0.98; $P = .04$; OS: HR, 0.35; 95% CI, 0.18-0.70; $P = .003$), and OPRA consolidation-like (EFS: HR, 0.64; 95% CI, 0.44-0.93; $P = .02$; OS: HR, 0.50; 95% CI, 0.25-1.00; $P = .05$) regimens. In the matched population (928 patients [58.5%]), no differences in survival outcomes were observed between the TNT regimens.

CONCLUSIONS AND RELEVANCE The findings of this case series study show substantial variation in the choice of the TNT regimen and were overall aligned with those reported in clinical trials, suggesting the efficacy of TNT in a clinical setting regardless of the specific regimen.

JAMA Oncol. doi:10.1001/jamaoncol.2025.2026
Published online July 10, 2025.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Additional members of the International Real-World TNT Study Consortium appear in Supplement 2.

Corresponding Author: Francesco Sclafani, MD, PhD, Department of Gastrointestinal Oncology, Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, Institut Jules Bordet & Hôpital Erasme, Rue Meylemeersch 90 – 1070 Brussels, Belgium (francesco.sclafani@hubruxelles.be).

During the past few years, the management of locally advanced rectal cancer (LARC) has rapidly evolved.[1] Until recently, standard treatments included long-course chemoradiotherapy (LCCRT) or short-course radiotherapy (SCRT) followed by surgery (watch and wait [W&W] being an option in selected cases) with or without adjuvant chemotherapy, while in some countries, upfront surgery remained the preferred option for cT3a/b tumors of the mid-high rectum.[2]

In 2020, total neoadjuvant therapy (TNT) emerged as a new standard of care following the results of 2 randomized phase 3 clinical trials.[3] In RAPIDO, SCRT followed by 18 weeks of oxaliplatin-based chemotherapy yielded higher rates of pathologic complete response (pCR) and better 3-year disease-related treatment failure than LCCRT followed by surgery with or without adjuvant chemotherapy in high-risk LARC.[4,5] In PRODIGE 23, 12 weeks of modified folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) followed by LCCRT, surgery, and adjuvant chemotherapy improved the rates of pCR, 3-year disease-free survival, and 7-year overall survival (OS) compared with LCCRT followed by surgery and adjuvant chemotherapy in patients with stage II to III disease.[6,7] Despite being supported by lower-level evidence, other TNT regimens have increasingly gained traction in clinical practice. In the randomized, noncomparative phase 2 OPRA trial, the organ preservation rate at 5 years was higher with 16 weeks of oxaliplatin-based chemotherapy administered after rather than before LCCRT.[8,9] Finally, phase 3 trials testing other TNT regimens in Chinese populations have been reported, such as STELLAR and TNTCRT, that showed better 3-year OS or 3-year disease-free survival, respectively, than LCCRT.[10,11]

Limited information is available on the use and outcome of TNT in clinical practice. Also, to our knowledge, trials comparing these regimens are lacking, and according to international guidelines, any type, combination, and sequence of radiotherapy and chemotherapy are deemed acceptable.[12] With the intent to address this knowledge gap, and leveraging the potential of clinical data,[13] we launched the International Real-World Study of TNT in Rectal Cancer, an initiative designed to build the largest dataset of patients with LARC who were treated with TNT outside of clinical trials. In this article, we report the initial results.

Key Points

Question What are the preferences of physicians and the outcomes of total neoadjuvant therapy (TNT) in routine practice?

Findings In this case series study of 1585 patients with rectal cancer, TNT was delivered via 12 weeks of folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX)/fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by long-course chemoradiotherapy, short-course radiotherapy followed by consolidation folinic acid, fluorouracil, and oxaliplatin (FOLFOX)/capecitabine and oxaliplatin (CAPOX), induction FOLFOX/CAPOX followed by long-course chemoradiotherapy, long-course chemoradiotherapy followed by consolidation FOLFOX/CAPOX, or other regimens. While better outcomes were observed with induction FOLFIRINOX/FOLFOXIRI followed by long-course chemoradiotherapy in the overall population, no statistically significant differences were found after a propensity vector matching analysis.

Meaning The results of this study suggest that substantial variation exists in the choice of TNT in routine practice, and efficacy outcomes in this setting are consistent with those from clinical trials and similar among the different regimens.

Methods

Study Design and Participants

The study was conducted according to the Declaration of Helsinki. Approval by institutional review boards and ethics committees, which advised on the need to obtain patient informed consent for study participation, was managed by the principal investigators at each center and according to the regulations from local authorities.

Eligibility was restricted to consecutive patients who fulfilled all the following criteria: histologically/cytologically confirmed adenocarcinoma, clinical stage II/III disease, distal tumor border within 15 cm of the anal verge and below the peritoneal reflection, and TNT according to local practice. TNT was defined as any treatment, including the delivery of radiotherapy and nonradiosensitizing chemotherapy before surgery (or W&W). Patients with metastatic disease, locally recurrent tumors, previous treatment for rectal cancer, receipt of TNT within a clinical trial, or a diagnosis of a second primary cancer within 2 years of initiating treatment were excluded.

Participating centers were invited through the Oncodinstinct Network and the European Organisation for Research and Treatment of Cancer or by direct contact with the local principal investigator. Data were entered into a password-protected REDCap database, and monitoring was conducted remotely by the study team at the Institut Jules Bordet (Brussels, Belgium). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE reporting guidelines.

Study Objectives and Outcome Measures

The primary objective was to describe clinical practice. TNT was analyzed by regimen (ie, PRODIGE 23-like vs RAPIDO-like vs OPRA induction-like vs OPRA consolidation-like), timing of chemotherapy (ie, induction vs consolidation vs sandwich), type of chemotherapy (ie, doublet vs triplet), and type of radiotherapy (ie, LCCRT vs SCRT). Secondary objectives included the evaluation of patient characteristics, treatment adherence, safety, and efficacy in the overall population and by type of TNT. Exploratory objectives included the investigation of prognostic/predictive biomarkers.

Analyses by the TNT regimen were done according to an intention-to-treat and a per-protocol (PP) basis. The former considered the type of radiotherapy (ie, LCCRT for PRODIGE 23-like, OPRA induction-like, and OPRA consolidation-like regimens and SCRT for RAPIDO-like regimens) and the type and timing of chemotherapy (ie, induction FOLFIRINOX/fluorouracil, leucovorin, oxaliplatin, and irinotecan [FOLFOXIRI] for PRODIGE 23-like, consolidation folinic acid, fluorouracil, and oxaliplatin [FOLFOX]/

Table. Patient Demographic and Baseline Characteristics in the Overall Population and by Total Neoadjuvant Therapy (TNT) Regimen

Variable	No. (%)					
	Overall population	PRODIGE 23-like[3]	RAPIDO-like[3]	OPRA induction-like[9]	OPRA consolidation-like[9]	Other
Age, median (IQR), y	61 (53-68)	60 (51-66)	62 (53-70)	64 (54-71)	59 (52-68)	61 (53-67)
Sex						
Female	588 (37.1)	107 (38.2)	202 (38.1)	63 (33.2)	97 (37.7)	119 (36.3)
Male	997 (62.9)	173 (61.8)	328 (61.9)	127 (66.8)	160 (62.3)	209 (63.7)
Date of diagnosis						
2012-2015	68 (4.3)	14 (5.0)	21 (4.0)	8 (4.2)	20 (7.8)	5 (1.5)
2016-2019	310 (19.6)	47 (16.8)	23 (4.0)	45 (23.7)	27 (10.5)	168 (51.2)
2020-2023	1207 (76.1)	219 (78.2)	486 (92.0)	137 (72.1)	210 (81.7)	155 (47.3)
ECOG/WHO performance status						
0	1026 (64.7)	212 (75.7)	277 (52.3)	134 (70.5)	162 (63.1)	241 (73.5)
≥1	495 (31.2)	64 (22.9)	225 (42.4)	47 (24.8)	80 (31.1)	79 (24.1)
Unknown	64 (4.1)	4 (1.4)	28 (5.3)	9 (4.7)	15 (5.8)	8 (2.4)
Tumor histotype						
Adenocarcinoma	1518 (95.8)	271 (96.8)	513 (96.8)	180 (94.7)	245 (95.3)	309 (94.2)
Mucinous carcinoma	48 (3.0)	7 (2.5)	12 (2.3)	7 (3.7)	8 (3.1)	14 (4.3)
Signet ring cell carcinoma	10 (0.6)	0	3 (0.5)	2 (1.1)	2 (0.8)	3 (0.9)
Other	8 (0.5)	2 (0.7)	1 (0.2)	1 (0.5)	2 (0.8)	2 (0.6)
Unknown	1 (0%)	0	1 (0.2%)	0	0	0
Tumor differentiation						
Grade 1-2	1012 (63.9)	195 (69.6)	356 (67.2)	93 (48.9)	154 (59.9)	214 (65.3)
Grade 3-4	111 (7.0)	14 (5.0)	42 (7.9)	18 (9.5)	13 (5.1)	24 (7.3)
Unknown	462 (29.1)	71 (25.4)	132 (24.9)	79 (41.6)	90 (35.0)	90 (27.4)

(continued)

capecitabine and oxaliplatin [CAPOX] for RAPIDO-like and OPRA consolidation-like, and induction FOLFOX/CAPOX for OPRA induction-like regimens). The latter also considered the radiotherapy dose and number of neoadjuvant chemotherapy cycles administered based on the regimens reported by the respective trials.[4,6,8] Adherence was evaluated by the proportion of patients who completed (chemo) radiotherapy and chemotherapy without modification/dose reduction or discontinuation. Safety was assessed based on the incidence of serious adverse events (SAEs) and grade 3 or higher perioperative complications according to the Clavien-Dindo classification.[14] Efficacy end points included pCR, complete response (CR), local (LP) or distant progression (DP) at the time of treatment failure (TTF), event-free survival (EFS), and OS. pCR was reported as the proportion of patients who had ypT0N0 tumors of those who initiated TNT, while CR also included those who had either ypT0Nx (after local excision) or ymrT0N0 tumors (if W&W) with no disease regrowth/progression for 15 months or longer after TNT completion. LP and DP were defined as intrapelvic and extrapelvic, respectively, tumor progression. EFS was calculated from TNT initiation to tumor progression or death, with censoring at the last imaging showing no progression. Isolated local regrowth during W&W was not considered an event for LP or EFS if followed by an R0/R1 salvage surgery. OS was calculated from TNT initiation to death, with censoring at the last follow-up. The methods for missing data imputation and propensity vector matching[15] are described in the eMethods in Supplement 1.

The statistical software used was R, version 4.3.1 (R Core Team 2023). Statistical significance was set at a $P < .05$.

Results

Baseline Characteristics

At the data cut-off date of December 31, 2023, 1585 patients who initiated treatment between September 2012 and December 2023 at 61 centers across 21 countries (eTable 1 and eFigure 1 in Supplement 2) were included. The median age was 61 years (IQR, 53-68), and most patients were males (62.9%) and had an Eastern Cooperative Oncology Group/World Health Organization performance status of 0 (1026 [64.7%]). The primary tumor was located in the distal rectum in 46% of cases. In almost all patients (93.9%), a pelvic MRI (± an endoscopic ultrasonography) was carried out for local staging, and 79.5% were found to have 1 or more high-risk features, including cT4 (25.3%), cN2 (47%), EMVI (32.4%), MRF+ (44.1%), and LPLN (3.8%) (**Table**).

Outcomes in the Entire Population, by Type/Timing of Chemotherapy, and Type of Radiotherapy

Chemotherapy was given as induction, consolidation, and sandwich treatment in 547 (34.5%), 809 (51.0%), and 229

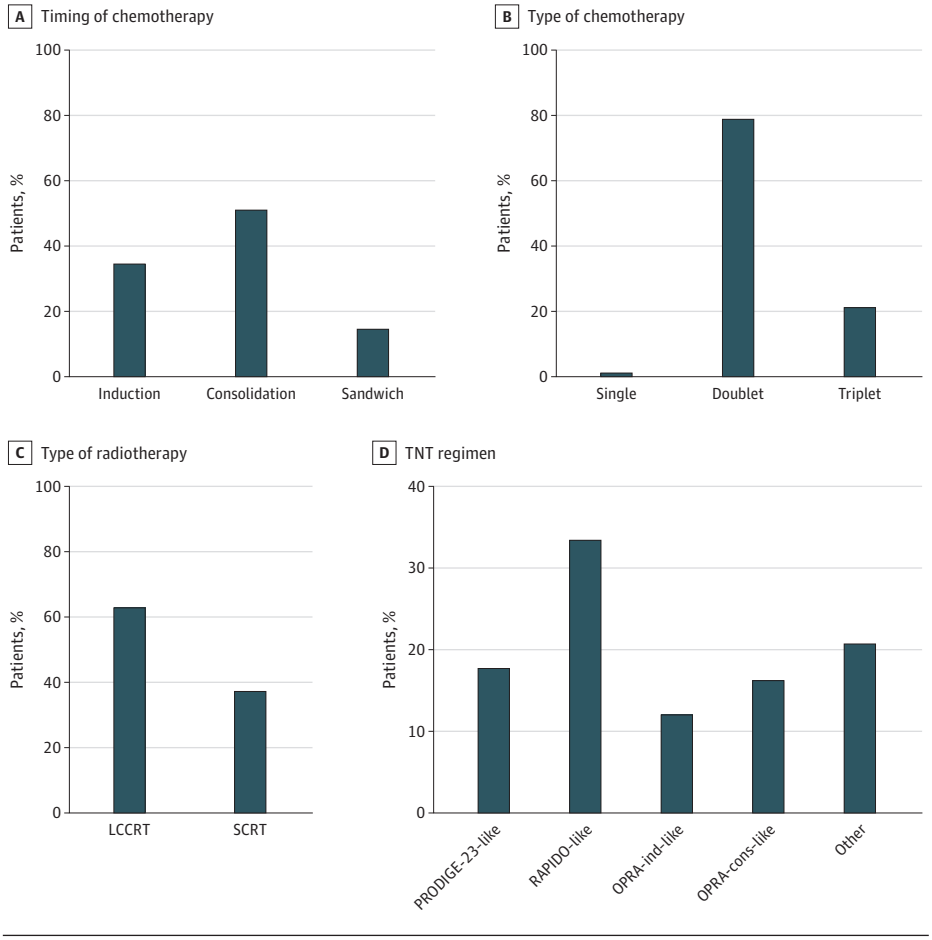
Table. Patient Demographic and Baseline Characteristics in the Overall Population and by Total Neoadjuvant Therapy (TNT) Regimen (continued)

Variable	No. (%)					
	Overall population	PRODIGE 23-like[3]	RAPIDO-like[3]	OPRA induction-like[9]	OPRA consolidation-like[9]	Other
MMR status						
pMMR/MSS	912 (57.5)	224 (80.0)	339 (64)	122 (64.2)	165 (64.2)	62 (18.9)
dMMR/MSI-high	34 (2.1)	5 (1.8)	10 (1.9)	3 (1.6)	13 (5.1)	3 (0.9)
Unknown	639 (40.4)	51 (18.2)	181 (34.1)	65 (34.2)	79 (30.7)	263 (80.2)
CEA						
Less than ULN	825 (52.0)	122 (43.6)	283 (53.)	91 (47.9)	142 (55.3)	187 (57)
Greater than ULN	559 (35.3)	71 (25.4)	199 (37.5)	80 (42.1)	88 (34.2)	121 (36.9)
Unknown	201 (12.7)	87 (31.0)	48 (9.1)	19 (10.0)	27 (10.5)	20 (6.1)
Pelvic MRI						
No	96 (6.1)	1 (0.4)	52 (9.8)	7 (3.7)	26 (10.1)	10 (3.0)
Yes	1489 (93.9)	279 (99.6)	478 (90.2)	183 (96.3)	231 (89.9)	318 (97.0)
Distance from the anal verge, cm						
≤5	729 (46.0)	150 (53.6)	221 (41.7)	89 (46.8)	132 (51.4)	137 (41.8)
>5 and ≤10	645 (40.7)	106 (37.8)	222 (41.9)	79 (41.6)	93 (36.2)	145 (44.2)
>10	191 (12.0)	23 (8.2)	74 (14.0)	22 (11.6)	27 (10.5)	45 (13.7)
Unknown	20 (1.3)	1 (0.4)	13 (2.4)	0	5 (1.9)	1 (0.3%)
cT stage						
cT1-2	78 (4.9)	12 (4.3)	25 (4.7)	5 (2.6)	19 (7.4)	17 (5.2)
cT3	1097 (69.2)	206 (73.6)	398 (75.1)	127 (66.8)	169 (65.8)	197 (60.0)
cT4	401 (25.3)	62 (22.1)	105 (19.8)	56 (29.5)	65 (25.3)	113 (34.5)
Unknown	9 (0.6)	0	2 (0.4)	2 (1.1)	4 (1.5)	1 (0.3)
cN stage						
cN0	178 (11.2)	53 (18.9)	57 (10.8)	8 (4.2)	36 (14.0)	24 (7.3)
cN1	638 (40.3)	131 (46.8)	200 (37.7)	79 (41.6)	116 (45.2)	112 (34.1)
cN2	745 (47.0)	90 (32.1)	267 (50.4)	100 (52.6)	99 (38.5)	189 (57.7)
Unknown	24 (1.5)	6 (2.2)	6 (1.1)	3 (1.6)	6 (2.3)	3 (0.9)
Lateropelvic lymph nodes						
No	1507 (95.1)	270 (96.4)	509 (96.1)	179 (94.2)	242 (94.2)	307 (93.6)
Yes	60 (3.8)	10 (3.6)	15 (2.8)	8 (4.2)	7 (2.7)	20 (6.1)
Unknown	18 (1.1)	0	6 (1.1)	3 (1.6)	8 (3.1)	1 (0.3)
Distance from the mesorectal fascia, mm						
≤1	699 (44.1)	155 (55.4)	208 (39.2)	81 (42.6)	86 (33.5)	169 (51.5)
>1	516 (32.6)	76 (27.1)	168 (31.7)	71 (37.4)	80 (31.1)	121 (36.9)
Unknown	370 (23.3)	49 (17.5)	154 (29.1)	38 (20.0)	91 (35.4)	38 (11.6)
Extramural venous invasion						
No	533 (33.6)	120 (42.9)	160 (30.2)	72 (37.9)	94 (36.6)	87 (26.5)
Yes	513 (32.4)	92 (32.9)	163 (30.8)	47 (24.7)	54 (21)	157 (47.9)
Unknown	539 (34)	68 (24.2)	207 (39.0)	71 (37.4)	109 (42.4)	84 (25.6)
RAPIDO high-risk features						
No	99 (6.2)	28 (10.0)	24 (4.5)	21 (11.1)	21 (8.2)	5 (1.5)
Yes	1260 (79.5)	222 (79.3)	418 (78.9)	146 (76.8)	171 (66.5)	303 (92.4)
Unknown	226 (14.3)	30 (10.7)	88 (16.6)	23 (12.1)	65 (25.3)	20 (6.1)

Abbreviations: CEA, carcinoembryonic antigen; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI-high, microsatellite instability high; MSS, microsatellite stability; pMMR, mismatch repair proficient; ULN, upper limit of normal; WHO, World Health Organization.

patients (14.5%), respectively (**Figure 1**). This consisted of single-agent (ie, fluoropyrimidine, 1.1%), doublet (ie, FOLFOX/CAPOX, 78.8%), and triplet (ie, FOLFOXIRI/FOLFIRINOX, 20.1%) regimens. In 2.1% of cases, antiangio-

Figure 1. Distribution of the Patient Population



Cons indicates consolidation; ind, induction; LCCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy; TNT, total neoadjuvant therapy.[3,9]

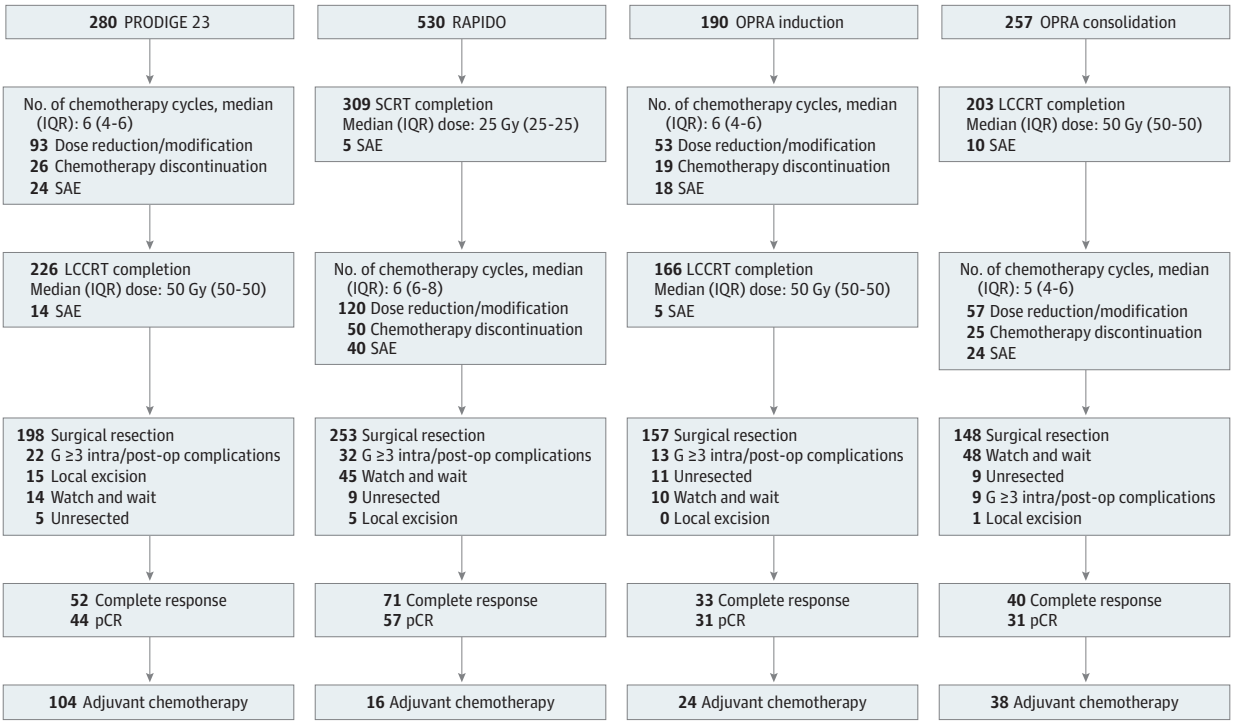
genic agents or anti-epidermal growth factor receptor monoclonal antibodies were added. Radiotherapy was delivered as SCRT in 37.2% and LCCRT in 62.8% of cases. Chemotherapy during LCCRT included fluoropyrimidine alone (94.6%) or fluoropyrimidine and oxaliplatin (4%). Following TNT, surgical resection was conducted for 82.3% of patients and local excision for 1.9%, while 12.1% of patients received W&W and 3.7% did not undergo surgery due to tumor unresectability, progression, toxic effects, or death. Adjuvant chemotherapy was administered to 19.4% of patients (eTables 2-4 in Supplement 1).

A total of 1514 patients (97.9%) completed radiotherapy as planned. Chemotherapy dose reductions and/or modifications were reported in 493 cases (31.9%) and discontinuation in 209 (13.5%). SAEs and grade 3 or higher perioperative complications were observed in 240 (15.5%) and 116 patients (8.9%), respectively. Adherence and safety data by type of treatment are available in eTables 5 to 7 in Supplement 1. Overall, pCR was achieved in 271 cases (21.3%) and CR in 335 (23.2%). After a median follow-up of 24 months (IQR, 14-35), 340 patients (23.6%) had progressive disease, and 150 (9.7%) died of any cause. LP and DP at the TTF occurred in 112 (7.0%) and 251 cases (16.2%), respectively. Three-year EFS was 68% (95% CI, 64%-71%), and 5-year OS was 79% (95% CI, 75%-83%) (eFigure 2 and eTable 4 in Supplement 1). LP was less frequent with triplet chemotherapy (odds ratio, 0.46; 95% CI, 0.24-0.83, $P = .01$), while patients treated with LCCRT (hazard ratio [HR], 0.77; 95% CI, 0.62-0.96; $P = .02$) and sandwich chemotherapy (HR, 0.67; 95% CI, 0.50-0.91; $P = .001$; compared with consolidation chemotherapy) had better EFS (eTable 8 and eFigure 3 in Supplement 1).

Outcomes by TNT Regimen in the Overall Population

Of the 1585 patients, 280 (17.7%), 530 (33.4%), 190 (12%), and 257 (16.2%) were treated according to the PRODIGE 23-like, RAPIDO-like, OPRA induction-like, and OPRA consolidation-like regimens, respectively. Demographic and baseline characteristics by TNT regimen are available in eTable 9 in Supplement 1, while adherence, toxic effects, surgical procedures, and outcomes are shown in eTables 10 to 12 in Supplement 1. Patients treated with the PRODIGE 23-like regimen were most likely to experience SAEs (61 [23.5%]) and require chemotherapy dose reduction and/or modification (109 [41.1%]). The median radiotherapy to surgery interval was 9.1 weeks (IQR, 7.8-10.4) for PRODIGE 23-like, 24.8 weeks (IQR, 21.3-28.7) for RAPIDO-like, 10.4 weeks (IQR, 9.1-13) for OPRA induction-like, and 24.3 weeks (IQR, 16.1-30.9) for OPRA consolidation-like regimens. The proportion of patients achieving pCR and

Figure 2. Details of Neoadjuvant Treatment, Safety, Surgical Procedures and Early Outcomes by Total Neoadjuvant Therapy (TNT) Regimen in the Matched Population



G, grade; Gy, gray; LCCRT, long-course chemoradiotherapy; op, operative; pCR, pathologic complete response; SAEs, serious adverse events; SCRT, short-course radiotherapy.[3,9]

CR, respectively, was 22.2% and 24.8% for PRODIGE 23-like, 21.7% and 24.4% for RAPIDO-like, 17.8% and 18.5% for OPRA induction-like, and 22.4% and 25.4% for OPRA consolidation-like regimens, respectively. Patients treated with the PRODIGE 23-like regimen were less likely to experience LP at the TTF than those treated with other regimens (3.9% vs 8.9% with RAPIDO-like regimens, 11.9% with OPRA induction-like regimens, and 10.1% with OPRA consolidation-like regimens), while no difference was observed for DP. Survival outcomes by TNT regimens are shown in eFigure 4 in Supplement 1. EFS and OS were longer with PRODIGE 23-like regimens than RAPIDO-like regimens (EFS: HR, 0.68; 95% CI, 0.49-0.95; P = .03; OS: HR, 0.51; 95% CI, 0.27-0.97; P = .04), OPRA induction-like regimens (EFS: HR, 0.66; 95% CI, 0.44-0.98; P = .04; OS: HR, 0.35; 95% CI, 0.18-0.70; P = .003), and OPRA consolidation-like regimens (EFS: HR, 0.64; 95% CI, 0.44-0.93; P = .02; OS: HR, 0.50; 95% CI, 0.25-1.00; P = .05). Associations between outcomes and prognostic factors estimated in multivariable analyses are listed in eTable 13a to f in Supplement 1, while outcomes in the PP population are presented in eTable 14 and eFigure 5 in Supplement 1.

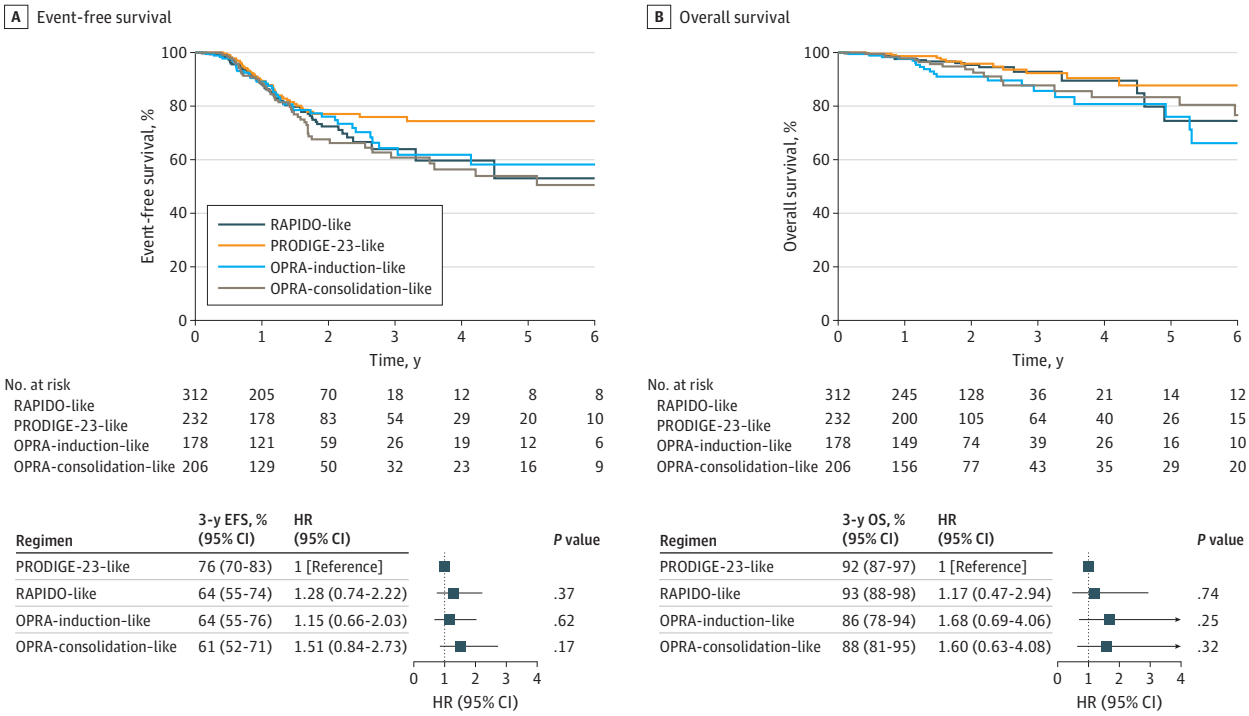
Outcomes by TNT Regimen in the Matched Population

After propensity vector matching, 928 patients (58.5%) were eligible for analysis. Demographic and baseline characteristics are shown in eTable 15 in Supplement 1, while treatment adherence, toxic effects, surgical procedures, and early outcome measures are shown in **Figure 2** (eTables 16-17 in Supplement 1). Patients treated with PRODIGE 23-like and RAPIDO-like regimens were most likely to require chemotherapy dose reduction and/or modification (40.8% and 40.4%, respectively), while SAEs were most commonly reported for patients treated with RAPIDO-like regimens (23.5%). When the OPRA consolidation-like regimen was used, more patients received W&W (23.3% vs 6.0% for PRODIGE 23-like, 14.4% for RAPIDO-like, and 5.6% for OPRA induction-like regimens). No statistically significant difference was observed between TNT regimens for any oncological outcome. At 3 years, the proportion of patients who were alive and free of progression was 76% (95% CI, 70%-83%) for PRODIGE 23-like, 64% (95% CI, 55%-74%) for RAPIDO-like, 64% (95% CI, 55%-76%) for OPRA induction-like, and 61% (95% CI, 52%-71%) for OPRA consolidation-like regimens. Five-year OS rates were 88% (95% CI, 80%-96%), 74% (95% CI, 59%-93%), 76% (95% CI, 64%-90%), and 83% (95% CI, 75%-93%), respectively (**Figure 3** and **Figure 4**; eTable 18 in Supplement 1).

Discussion

To our knowledge, this is the largest study to date on patients with LARC who were treated with TNT in a clinical setting. We found that TNT was mostly considered for high-risk tumors and delivered through various approaches. Safety and effi-

Figure 3. Event-Free Survival (EFS) and Overall Survival (OS) by Total Neoadjuvant Therapy (TNT) Regimen in the Matched Population[3,9]



Regimen	3-y EFS, % (95% CI)	HR (95% CI)	P value
PRODIGE-23-like	76 (70-83)	1 [Reference]	
RAPIDO-like	64 (55-74)	1.28 (0.74-2.22)	.37
OPRA-induction-like	64 (55-76)	1.15 (0.66-2.03)	.62
OPRA-consolidation-like	61 (52-71)	1.51 (0.84-2.73)	.17

HR (95% CI)

Regimen	3-y OS, % (95% CI)	HR (95% CI)	P value
PRODIGE-23-like	92 (87-97)	1 [Reference]	
RAPIDO-like	93 (88-98)	1.17 (0.47-2.94)	.74
OPRA-induction-like	86 (78-94)	1.68 (0.69-4.06)	.25
OPRA-consolidation-like	88 (81-95)	1.60 (0.63-4.08)	.32

HR (95% CI)

cacy outcomes were similar to those reported in clinical trials, and the latter were not consistently associated with the TNT regimen.

The recent TNT trial results have transformed the treatment landscape of LARC, enriching the therapeutic algorithm with options that improve pCR and long-term outcomes.[16] However, they have increased the complexity of decision-making. In addition to selecting patients who might benefit from neoadjuvant treatment intensification, physicians have to face the challenge of choosing among several regimens that were tested in different-risk populations and have not yet been compared against each other.[3,17,18] Evidence is needed to confirm the generalizability of trial results and address the question as to whether the available TNT regimens should be considered interchangeable or whether differences exist in either safety or efficacy that could guide treatment decisions for individual patients.

Through the participation of many centers worldwide, we managed to gather individual data from several series of patients with LARC treated with TNT according to local practice. The inclusion period spanned more than a decade, with most patients being treated during the last few years. Yet, in approximately 25% of cases, TNT was administered before 2020, which highlights the adoption of this strategy in some centers before the positive results of phase 3 trials became available. As expected, we observed a substantial variation in the choice of TNT. The RAPIDO-like was the most used regimen, while fewer patients were treated with other regimens. However, virtually all patients were treated before the latest trial readouts (showing worse local control for RAPIDO, better overall survival for PRODIGE 23, and prolonged organ preservation for OPRA consolidation),[5,7,9] and a shift over time in the adoption of the different TNT regimens cannot be excluded. What appears clear from the characteristics of this population is that TNT was generally regarded as an option for high-risk tumors, as originally proposed by the RAPIDO and TNTCRT trials.[4,11] However, the choice of the regimen was largely independent of the individual risk profile or eligibility criteria of the corresponding study, with the proportion of high-risk patients treated with RAPIDO-like, PRODIGE 23-like, and OPRA-like regimens being similar and ranging from 67% to 79%. This suggests that TNT regimens are generally considered similar and broadly applicable to the entire spectrum of patients with LARC.

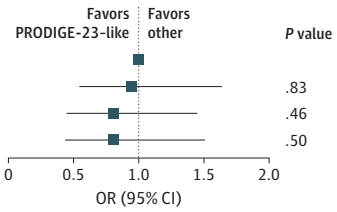
Based on the higher rates of pCR compared with LCCRT, TNT is assumed to also be associated with an increased likelihood of pursuing organ-preservation approaches.[8,9,19] In our series, 14% of the patients were treated either with local excision or W&W. The former was mostly offered to patients treated with PRODIGE 23-like regimens, while the latter was especially considered for those treated with OPRA consolidation-like regimens. These findings likely reflect systematic preferences in some centers for certain strategies when an organ-sparing approach is intentionally pursued.[8,9] The rate of pCR did not differ substantially among regimens. This was 21.3% in the entire population, which was overall consistent with clinical trials,[4,6,10,11] especially considering that an additional 2% had sustained cCR more than 1 year after treatment completion.

Some of the uncertainty regarding the choice of the TNT regimen is derived from the variable association that neoadjuvant treatment intensification may have with long-term outcomes. While none of the available phase 3 TNT trials were

Figure 4. Pathologic Complete Response (pCR), Complete Response (CR), Local Progression (LP), and Distant Progression (DP) by Total Neoadjuvant Therapy Regimen in the Matched Population

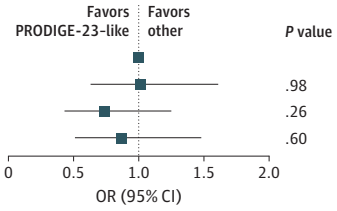
A pCR

Regimen	pCR rate, %	OR (95% CI)	P value
PRODIGE-23-like	21.9	1 [Reference]	
RAPIDO-like	21.9	0.94 (0.54-1.64)	.83
OPRA-induction-like	18.7	0.8 (0.44-1.45)	.46
OPRA-consolidation-like	19.9	0.8 (0.43-1.51)	.50



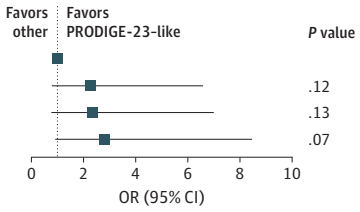
B CR

Regimen	CR rate, %	OR (95% CI)	P value
PRODIGE-23-like	24.0	1 [Reference]	
RAPIDO-like	24.9	1.01 (0.63-1.61)	.98
OPRA-induction-like	19.4	0.74 (0.43-1.25)	.26
OPRA-consolidation-like	22.3	0.87 (0.51-1.48)	.60



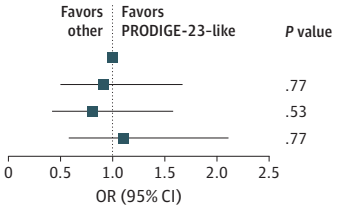
C LP

Regimen	LP rate, %	OR (95% CI)	P value
PRODIGE-23-like	3.6	1 [Reference]	
RAPIDO-like	8.5	2.29 (0.8-6.58)	.12
OPRA-induction-like	11.3	2.34 (0.78-6.99)	.13
OPRA-consolidation-like	10.6	2.8 (0.93-8.45)	.07



D DP

Regimen	DP rate, %	OR (95% CI)	P value
PRODIGE-23-like	15.7	1 [Reference]	
RAPIDO-like	14.8	0.91 (0.50-1.67)	.77
OPRA-induction-like	13.7	0.81 (0.42-1.58)	.53
OPRA-consolidation-like	18.7	1.10 (0.58-2.11)	.77



OR indicates odds ratio.[3,9]

powered to primarily address OS, the PRODIGE 23 and STELLAR trials were the only to suggest an OS advantage with TNT.[7,10] Also, only the RAPIDO trial reported a detrimental effect of TNT on local control.[5] The long-term outcomes of this population met the expectations overall. Patients treated with the PRODIGE 23-like regimen had a reduced risk of LP at TTF and better survival outcomes compared with those treated with other regimens. However, these findings were not confirmed in the matched analysis, in which only a numerical but not statistically significant difference in favor of the PRODIGE 23-like regimen was observed. The median follow-up of our study was relatively short, making estimations highly uncertain at this stage. Investigators from the PRODIGE 23 trial reported an OS advantage for TNT only after prolonged follow-up and using the restricted mean survival time.[6,7] Regarding local failure, the rate observed with the RAPIDO-like regimen (8.9%) did not appear different compared with that observed with the OPRA induction-like or OPRA consolidation-like regimens (12.5% and 10.1%, respectively). The long duration of the consolidation chemotherapy in the RAPIDO trial and risk of tumor repopulation were proposed to explain the unexpectedly worse local control.[20,21] In our study, the LP rate among patients with the RAPIDO-like regimens was similar between the intention-to-treat and PP populations (ie, 8.9% vs 9.7%). However, the pattern of progression was captured only at the TTF, and the overall rate of LP (as well as DP) could have been underestimated.

Confirming the feasibility and safety of TNT in a clinical population is one of the requisites for the wide adoption of this strategy in routine practice. In line with clinical trials, the adherence with radiotherapy in our study was very high regardless of the type of TNT. Regarding chemotherapy, early discontinuation occurred in 13.5% of cases (compared with 8%-23% from clinical trials),[6,8] and this was more commonly reported with the RAPIDO-like regimen, possibly due to the longer treatment duration. On the other hand, chemotherapy dose reductions/modifications occurred for 32% (compared with 44%-47% from clinical trials)[4,6] and were expectedly more frequent among patients treated with the PRODIGE 23-like regimen, who also appeared to have an increased risk of SAE. Re-

assuringly, the incidence of grade 3 or higher postoperative complications was low (8.9%) and in accordance with the 4% to 14% range from TNT trials.[10,11]

Limitations

Our study had several limitations. First, the retrospective design was inherently associated with data collection errors/biases and missing information, which were only partially addressed with the remote monitoring and data imputation. Second, this was a nonrandomized study, and despite running a propensity vector matching analysis, the comparison between TNT regimens remained subject to treatment selection biases due to unknown confounders. Furthermore, variations in treatment delivery, staging methods, and supportive care across institutions further complicated direct comparisons. Third, the relatively short follow-up might have precluded us from detecting differences in long-term outcomes between TNT regimens. Fourth, the lack of comprehensive molecular testing did not allow us to evaluate the prognostic effect of certain tumor biomarkers. Fifth, no correction methods for multiple testing were applied, and the possibility of chance findings could not be excluded. Finally, despite the high number of countries involved, most patients were treated in Europe, limiting the generalizability of our results to other populations.

Conclusions

This case series study illuminates the applicability of TNT to clinical practice. Recruitment of additional centers is ongoing, and further analyses are planned with larger numbers and longer follow-up. Meanwhile, according to our initial findings, we believe that TNT decisions should be made based on the individual risk profile and following an accurate discussion about the positives and negatives of each option while considering patient preferences and expectations.

ARTICLE INFORMATION

Accepted for Publication: April 16, 2025.

Published Online: July 10, 2025. doi:10.1001/jamaoncol.2025.2026

Author Affiliations: Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, Institut Jules Bordet–Hôpital Erasme, Brussels, Belgium (Audisio, Gallio, Liberale, Moretti, Martinive, Van Laethem, Sclafani); Azienda Ospedaliera S.Croce e Carle, Cuneo, Italy (Audisio); Institute of Oncology Ljubljana, Ljubljana, Slovenia (Velenik); Institut Paoli-Calmettes, Marseille, France (Meillat); Instituto Nacional de Cancerología, Mexico City, Mexico (Ruiz-Garcia); Hospital Universitario 12 de Octubre, Madrid, Spain (Riesco); Hospital Universitario de Navarra, Pamplona, Spain (Alecha); University Hospitals Leuven–Campus Gasthuisberg, Leuven, Belgium (Rasschaert); Champalimaud Clinical Centre, Lisbon, Portugal (Carvalho); CHU de Poitiers, Poitiers, France (Randrian); Institute for Gastroenterological Tumours, and University Hospital for Tumors, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia (Kirac); Vall d'Hebron University Hospital, Barcelona, Spain (Hernando); Necmettin Erbakan University, Faculty of Medicine, Konya, Turkey (Artaç); Instituto Alexander Fleming, Buenos Aires, Argentina (O'Connor); Rambam Health Care Campus, Haifa, Israel (Waldhorn); Radboud University Medical Centre, Nijmegen, the Netherlands (Braam); American University of Beirut Medical Center, Beirut, Lebanon (Shamseddine); Azienda Ospedaliera Universitaria Pisana, Pisa, Italy (Moretto); Ramón y Cajal University Hospital, IRYCIS, Madrid, Spain (De la Pinta); Policlinico Umberto I Sapienza University of Rome, Rome, Italy (De Felice); Vilnius University Hospital National Cancer Institute, Vilnius University, Vilnius, Lithuania (Dulskas); Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (Páez López-Bravo); AZ Groeninge, Kortrijk, Belgium (Vanden Bulcke); Rostock University Medical Center, Rostock, Germany (Bock); Saint-Pierre University Hospital, Brussels, Belgium (Deleporte); Institut Roi Albert II, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium (Van Den Eynde); Ghent University Hospital, Ghent, Belgium (Geboes); Azienda Ospedaliero Universitaria Careggi, Firenze, Italy (Loi); ARNAS Civico, Palermo, Italy (Messina); Claude Huriez Hospital, CHU Lille, Lille, France (Houlzé-Laroye); Humanitas University, Pieve Emanuele, Milan, Italy and IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Rozzano, Milan, Italy (Puccini); Ospedale Policlinico San Martino–IRCCS, Genoa, Italy (Pastorino); Bank of Cyprus Oncology Centre, Nicosia, Cyprus (Papamichael); Università Campus Bio–Medico di Roma and Fondazione Policlinico Universitario Campus Bio–Medico, Rome, Italy (Fiore); University of Medicine and Pharmacy Iuliu Haţieganu, Cluj-Napoca, Romania (Sur); University Hospital Brno, Faculty of Medicine, Masaryk University, Brno, Czech Republic (Eid); University Hospital of Besançon, Besançon, France (Antoun); University Hospital Modena, Modena, Italy (Salati); University Hospital of Parma, Parma, Italy (Garajovà); Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania (Jakubauskas); Masaryk Memorial Cancer Institute, Brno, Czech Republic (Tomášek); Centro Hospitalar Universitário do Algarve-Hospital de Faro, Faro, Portugal (Sousa Pinto); Caritasklinikum St. Theresia, Saarbruecken, Germany (Schwingel); Istituto Nazionale dei Tumori di Milano, Milan, Italy (Morano); Cardiff University and Velindre Cancer Centre, Cardiff, Wales (Adams); CHU Helora Hospital La Louvière Site Jolimont, La Louvière, Belgium (Dermine); Polyclinique Hénin-Beaumont, Group Ahnac, Haut-de-France, France (Chau); Liverpool University Hospitals Foundation Trust, Liverpool, England (Javed); Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (Ghidini); AULSS Scaligera, Verona, Italy (Fiorica); Auna-Oncosalud, Lima, Peru (Montenegro); Ospedale del Mare, Naples, Italy (Petrillo); University of Padova, Padova, Italy (Spolverato); Institut Català d'Oncologia - Badalona, Badalona, Spain (Mulet Margalef); Centre Hospitalier Universitaire Ambroise Paré, Mons, Belgium (Diaz); University of Turin, San Luigi Hospital Orbassano, Italy (Baratelli); Chirec Delta Hospital, Brussels, Belgium (Puleo); 401 Army General Hospital, Athens, Greece (Karampeazis); Ege University Faculty of Medicine, Izmir, Turkey (Sert); Centre Hospitalier Universitaire UCL Namur, Site Godinne, Yvoir, Belgium (Gilliaux); Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, Napoli, Italia (De Stefano); International Drug Development Institute, Louvain-la-Neuve, Belgium (Deltuvaite Thomas, Staggs, Saad).

Author Contributions: Dr Sclafani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Audisio, Spolverato, Sert, Sclafani.
Acquisition, analysis, or interpretation of data: Audisio, Gallio, Velenik, Meillat, Ruiz-Garcia, Riesco-Martínez, Suárez Alecha, Gertjan Rasschaert, Carvalho, Randrian, Kirac, Hernando, Artaç, O'Connor, Waldhorn, Braam, Shamseddine, Moretto, De la Pinta, De Felice, Dulskas, Paez, Vanden Bulcke, Bock, Deleporte, Van den Eynde, Geboes, Loi, Messina, Piessen, Puccini, Pastorino, Papamichael, Fiore, Sur, Eid, Borg, Salati, Garajova, Jakubauskas, Tomasek, Pinto, Schwingel, Morano, Adams, Dermine, Chau, Javed, Ghidini, Fiorica, Montenegro Beltran, Petrillo, Mulet Margalef, Diaz, Baratelli, Puleo, Karampeazis, Gilliaux, De Stefano, Liberale, Moretti, Martinive, Deltuvaite Thomas, Staggs, Saad, Van Laethem, Sclafani.
Drafting of the manuscript: Audisio, O'Connor, Paez, Loi, Sur, Tomasek, Pinto, Fiorica, Montenegro Beltran, Baratelli, Sert, Staggs, Sclafani.
Critical review of the manuscript for important intellectual content: Audisio, Gallio, Velenik, Meillat, Ruiz-Garcia, Riesco-Martínez, Suárez Alecha, Gertjan Rasschaert, Carvalho, Randrian, Kirac, Hernando, Artaç, Waldhorn, Braam, Shamseddine, Moretto, De la Pinta, De Felice, Dulskas, Paez, Vanden Bulcke, Bock, Deleporte, Van den Eynde, Geboes, Messina, Piessen, Puccini, Pastorino, Papamichael, Fiore, Sur, Eid, Borg, Salati, Garajova, Jakubauskas, Pinto, Schwingel, Morano, Adams, Dermine, Chau, Javed, Ghidini, Montenegro Beltran, Petrillo, Spolverato, Mulet Margalef, Diaz, Baratelli, Puleo, Karampeazis, Gilliaux, De Stefano, Liberale, Moretti, Martinive, Deltuvaite Thomas, Saad, Van Laethem, Sclafani.
Statistical analysis: Audisio, Messina, Eid, Pinto, Deltuvaite Thomas, Staggs, Saad.
Obtained funding: Van den Eynde.
Administrative, technical, or material support: Audisio, Gallio, Velenik, Ruiz-Garcia, Riesco-Martínez, Gertjan Rasschaert, Kirac,

Hernando, Artaç, O'Connor, Waldhorn, Braam, De la Pinta, Dulskas, Bock, Deleporte, Van den Eynde, Piessen, Puccini, Pastorino, Sur, Eid, Salati, Garajova, Jakubauskas, Pinto, Morano, Javed, Montenegro Beltran, Mulet Margalef, Diaz, Puleo, Sclafani.
Supervision: Meillat, Riesco-Martínez, Artaç, O'Connor, Shamseddine, Paez, Deleporte, Loi, Messina, Pastorino, Papamichael, Fiore, Sur, Javed, Ghidini, Spolverato, Mulet Margalef, Martinive, Van Laethem, Sclafani.
Other: Carvalho, De Felice.

Conflict of Interest Disclosures: Dr Ruiz-Garcia reported personal fees from Roche/Genentech, Amgen, BMS, Astellas, and Merck Serono and nonfinancial support from Bayer and Gilead outside the submitted work. Dr Riesco-Martínez reported personal fees from Servier and Mundipharma and nonfinancial support from Amgen and Merck outside the submitted work. Dr Gertjan Rasschaert reported personal fees from Agenus, GSK, Medimix, MSD, and Neapolis Pharma, grants from GSK, and nonfinancial support from MSD, Ipsen, Esmo, and Servier outside the submitted work. Dr Randrian reported personal fees from Takeda, MSD, Merck Serono, Amgen, and Servier during the conduct of the study. Dr Moretto reported personal fees from Takeda and Amgen outside the submitted work. Dr Paez reported grants from Merck, personal fees from Amgen, Novartis Support, Esteve, and MSD outside the submitted work. Dr Deleporte reported personal fees from Servier and travel feeds from Amgen and Merckx outside the submitted work. Dr Geboes reported personal fees from BMS, MSD, Servier, Ipsen, Beigene, AstraZeneca, Amgen, and Meck Darmstadt and grants from Incyte outside the submitted work. Dr Piessen reported personal fees from BMS, Nestle, Astellas Pharma, Medtronic, MSD, Daiichi, Elivie, and Stryker outside the submitted work. Dr Puccini reported personal fees from GlaxoSmithKline, Takeda, Bayer, Daiichi Sankyo, MSD, Pierre Fabre, Servier, Amgen, and BMS and grants from GlaxoSmithKline and Amgen outside the submitted work. Dr Papamichael reported grants from Roche and Merck and institutional fees Merck Serono, Ipsen, and Servier outside the submitted work. Dr Eid reported personal fees from Merck, Ipsen, Roche, and Servier during the conduct of the study. Dr Borg reported grants from Bayer, Boehringer, and Merck Serono and personal fees from Molecular, Pierre Fabre, MSD, and Servier outside the submitted work. Dr Morano reported personal fees from Pierre Fabre, Accademia della Medicina, and Servier, grants from Incyte, and nonfinancial support from Amgen and Pierre Fabre outside the submitted work. Dr Petrillo reported personal fees from MSD, BMS, Merck Serono, Servier, Amgen, AstraZeneca, Roche, and Bayer outside the submitted work. Dr De Stefano reported nonfinancial support from Pierre Fabre and Servier outside the submitted work. Dr Sclafani reported personal fees from AMAL Therapeutics, Amgen, Bayer, BMS, Dragonfly Therapeutics, GKS, Nordic Pharma, Roche, and Servier; grants from Astellas, AstraZeneca, MSD, Pierre-Fabre, Sanofi, Amgen, Bayer, BMS, Merck, Roche, and Servier; and nonfinancial support from Lilly, Amgen, AstraZeneca, Bayer, Merck, Roche, and Servier outside the submitted work, as well as being the secretary of the European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Group. No other disclosures were reported.

Funding/Support: The study was sponsored by the Institut Jules Bordet and endorsed by the Oncodistinct Network. Statistical support was provided by the International Drug Development Institute.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: Additional members of the International Real-World TNT Study Consortium appear in Supplement 2.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Scott AJ, Kennedy EB, Berlin J, et al. Management of locally advanced rectal cancer: ASCO Guideline. *J Clin Oncol*. 2024;42(28):3355-3375. doi:10.1200/JCO.24.01160

2. Glynne-Jones R, Wyrwicz L, Tiret E, et al; ESMO Guidelines Committee. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv22-iv40. doi:10.1093/annonc/mdx224

3. Giunta EF, Bregni G, Pretta A, et al. Total neoadjuvant therapy for rectal cancer: making sense of the results from the RAPIDO and PRODIGE 23 trials. *Cancer Treat Rev*. 2021;96:102177. doi:10.1016/j.ctrv.2021.102177

4. Bahadoer RR, Dijkstra EA, van Etten B, et al; RAPIDO Collaborative Investigators. 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. *Lancet Oncol*. 2021;22(1):29-42. doi:10.1016/S1470-2045(20)30555-6

5. Dijkstra EA, Nilsson PJ, Hospers GAP, et al; Collaborative Investigators. 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. *Ann Surg*. 2023;278(4):e766-e772. doi:10.1097/SLA.0000000000005799

6. Conroy T, Bosset JF, Etienne PL, et al; Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive Group. 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. *Lancet Oncol*. 2021;22(5):702-715. doi:10.1016/S1470-2045(21)00079-6

7. Conroy T, Castan F, Etienne PL, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiotherapy in patients with locally advanced rectal cancer: long-term results of the UNICANCER-PRODIGE 23 trial. *Ann Oncol*. 2024;35(10):873-881. doi:10.1016/j.annonc.2024.06.019

8. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J Clin Oncol*. 2022;40(23):2546-2556. doi:10.1200/JCO.22.00032

9. Verheij FS, Omer DM, Williams H, et al. Long-term results of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: the randomized phase II OPRA trial. *J Clin Oncol*. 2024;42(5):500-506. doi:10.1200/JCO.23.01208

10. Jin J, Tang Y, Hu C, et al. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). *J Clin Oncol*. 2022;40(15):1681-1692. doi:10.1200/JCO.21.01667

11. Wang X, Liu P, Xiao Y, et al. Total neoadjuvant treatment with long-course radiotherapy versus concurrent chemoradiotherapy in local advanced rectal cancer with high risk factors (TNTCRT): a multicenter, randomized, open-label, phase 3 trial. *J Clin Oncol*. 2024;42(suppl 17):LBA3511. doi:10.1200/JCO.2024.42.17_suppl.LBA3511

12. National Comprehensive Cancer Network. NCCN Guidelines, rectal cancer, version 4.2024. Accessed December 14, 2024. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

13. Saesen R, Van Hemelrijck M, Bogaerts J, et al. Defining the role of real-world data in cancer clinical research: the position of the European Organisation for Research and Treatment of Cancer. *Eur J Cancer*. 2023;186:52-61. doi:10.1016/j.ejca.2023.03.013

14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae

15. Lopez MJ, Gutman R. Estimation of causal effects with multiple treatments: a review and new ideas. *Stat Sci*. 2017;32(3):432-454. doi:10.1214/17-STS612

16. Zwart WH, Hotca A, Hospers GAP, Goodman KA, Garcia-Aguilar J. The multimodal management of locally advanced rectal cancer: making sense of the new data. *Am Soc Clin Oncol Educ Book*. 2022;42:1-14. doi:10.1200/EDBK_351411

17. Aref A, Abdalla A. Total neoadjuvant therapy for locally advanced rectal cancer: induction or consolidation chemotherapy? *J Clin Oncol*. 2022;40(23):2515-2519. doi:10.1200/JCO.22.00506

18. Sclafani F, Conti C, Gallio C, Hendlisz A. Beyond 'the good, the bad and the ugly': let us put rectal cancer patients at the centre of the decision making. *Curr Opin Oncol*. 2024;36(4):305-307. doi:10.1097/CCO.0000000000001044

19. van der Valk MJM, Hilling DE, Bastiaannet E, et al; International Watch & Wait Database Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391(10139):2537-2545. doi:10.1016/S0140-6736(18)31078-X

20. Glynne-Jones R, Hollingshead J. TNT and local recurrence in the RAPIDO trial—untangling the puzzle. *Nat Rev Clin Oncol*. 2023;20(6):357-358. doi:10.1038/s41571-023-00751-4

21. Socha J, Bujko K. Repopulation of rectal cancer may explain worse local control after short-course radiation therapy in the RAPIDO trial. *Dis Colon Rectum*. 2024;67(3):e204-e205. doi:10.1097/DCR.0000000000003178