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Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO *or elsewhere, for which the primary end point has already been reported.*

To assess long-term risk of local tumor regrowth, we report updated organ preservation rate and oncologic outcomes of the OPRA trial (ClinicalTrials.gov identifier: NCT02008656). Patients with stage II/III rectal cancer were randomly assigned to receive induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT). Patients who achieved a complete or near-complete response after finishing treatment were offered watch-and-wait (WW). Total mesorectal excision (TME) was recommended for those who achieved an incomplete response. The primary end point was disease-free survival (DFS). The secondary end point was TME-free survival. In total, 324 patients were randomly assigned (INCT-CRT, n = 158; CRT-CNCT, n = 166). Median follow-up was 5.1 years. The 5-year DFS rates were 71% (95% CI, 64 to 79) and 69% (95% CI, 62 to 77) for INCT-CRT and CRT-CNCT, respectively (P = .68). TME-free survival was 39% (95% CI, 32 to 48) in the INCT-CRT group and 54% (95% CI, 46 to 62) in the CRT-CNCT group (P = .012). Of 81 patients with regrowth, 94% occurred within 2 years and 99% occurred within 3 years. DFS was similar for patients who underwent TME after restaging (64% [95% CI, 53 to 78]) and patients in WW who underwent TME after regrowth (64% [95% CI, 53 to 78]; P = .94). Updated analysis continues to show long-term organ preservation in half of the patients with rectal cancer treated with total neoadjuvant therapy. In patients who enter WW, most cases of tumor regrowth occur in the first 2 years.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Protocol

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INTRODUCTION

A watch-and-wait (WW) strategy offers the possibility of organ preservation for patients with rectal cancer who achieve a clinical complete response to neoadjuvant therapy.[1,2] The initial results of the OPRA trial showed that many patients with locally advanced rectal cancer treated with total neoadjuvant therapy (TNT) achieved a complete or near-complete tumor response and were initially offered WW. However, almost one third of patients pursuing WW later developed local tumor regrowth and ultimately required total mesorectal excision (TME).[3] As the risk of tumor regrowth could have persisted or increased with time, longer follow-up was needed. Here, we report updated results from the OPRA trial after a median follow-up of 5 years.

METHODS

Study Design

The OPRA trial was a randomized, nonblinded phase II trial conducted at 18 institutions in the United States (ClinicalTrials.gov identifier: NCT02008656). The study design and eligibility criteria have previously been described.[3] All participants provided written informed consent. Patients with stage II or III rectal cancer were randomly assigned

to receive either induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT).

The trial Protocol (online only) was approved by the institutional review boards of each participating institute. All participants provided written informed consent.

Procedures

Induction and consolidation chemotherapy consisted of either eight 2-week cycles of infusional fluorouracil, leucovorin, and oxaliplatin chemotherapy or five 3-week cycles of capecitabine and oxaliplatin.[3] Radiation consisted of 4,500 centigray delivered to the pelvis over 25 fractions. Patients received a total dose of 5,000-5,600 centigray to the primary tumor and involved nodes with either a simultaneous integrated boost and/or a sequential boost. Per medical oncologist preference, patients received a continuous infusion of fluorouracil or oral capecitabine during radiotherapy.

Patients underwent reassessment for treatment response 8 ± 4 weeks after TNT. Those with incomplete clinical response (iCR) were recommended to undergo TME. Patients who achieved a clinical complete response (cCR) or a near-complete clinical response (nCR) were offered WW. WW consisted of digital rectal examination and flexible sigmoidoscopy every 4 months for the first 2 years, and every 6 months for the following 3 years. Rectal magnetic resonance imaging was to be performed every 6 months for the first 2 years and yearly for the following 3 years. Computed tomography scans of the abdomen, pelvis, and chest were performed yearly and colonoscopy was performed according to National Comprehensive Cancer Network guidelines.[4]

Outcomes

The primary outcome was disease-free survival (DFS), defined as the interval from random assignment to the first occurrence of locoregional failure, distant recurrence, a new invasive colorectal primary cancer, or death.[3] Locoregional failure was defined as either an unresectable rectal primary tumor after neoadjuvant treatment, an R2 resection for the rectal primary tumor, or recurrence in the primary tumor bed after an R0-R1 resection. Tumor regrowth after a cCR or nCR and a period of WW was not considered a locoregional failure if it was followed by an R0-R1 resection. The secondary outcome was rate of organ preservation (TME-free survival), measured in the intention-to-treat population. TME-free survival was calculated from random assignment date to (first) TME surgery, local excision date, date of restaging for patients with iCR who refused surgery/had

TABLE 1. Baseline Demographics and Clinical Characteristics of the Full Cohort

Characteristic	INCT-CRT Group (n = 158)	CRT-CNCT Group (n = 166)
Age, year, median (IQR)	59 (51-68)	56 (49-67)
Female, No. (%)	55 (35)	64 (39)
Race, No. (%)		
White	130 (82)	143 (86)
Black	10 (6)	8 (5)
Asian	10 (6)	7 (4)
Other	3 (2)	1 (1)
Unknown	5 (3)	7 (4)
Ethnicity, No. (%)		
Hispanic or Latino	7 (4)	11 (7)
Non-Hispanic	151 (96)	154 (93)
Unknown	0 (0)	1 (1)
cT classification, No. (%)		
cT1-2	11 (7)	21 (13)
cT3	124 (78)	126 (76)
cT4	23 (15)	19 (11)
cN classification, No. (%)		
cN-negative	47 (30)	47 (28)
cN-positive	111 (70)	119 (72)
Tumor distance from anal verge, cm, median (IQR)	4.3 (3.0-6.3)	4.5 (3.0-6.5)
High-grade tumor, No. (%)	7 (4)	8 (5)

NOTE. Percentages may not total 100 because of rounding. There were no significant differences between the two groups with respect to the baseline patient characteristics.
Abbreviations: cN, clinical nodal classification; CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; cT, clinical tumor classification; INCT-CRT, induction chemotherapy followed by chemoradiotherapy.

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disease progression, regrowth date for patients on WW who refused surgery/had disease progression, or last follow-up date. Other end points included rate of tumor regrowth in patients who entered WW, local recurrence-free survival (LRFS) after TME (interval from random assignment to the first occurrence of locoregional failure or last follow-up date), distant metastasis-free survival (DMFS; interval from random assignment to distant recurrence or last follow-up date), and overall survival (OS; interval from random assignment to date of death). We also compared DFS between patients who underwent TME after restaging and patients who underwent TME after tumor regrowth, which was calculated from date of surgery.

Statistical Analysis

Survival curves were estimated using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. All analyses followed the intention-to-treat principle unless otherwise noted. Statistical methods have been previously reported.[3]

RESULTS

Of the 324 patients randomly assigned, 158 were assigned to the INCT-CRT group and 166 to the CRT-CNCT group (CONSORT diagram in Appendix Fig A1, online only). Baseline and tumor characteristics are summarized in Table 1. The data for all outcomes were available up to April 24, 2023. Median follow-up for patients who were alive and event-free at the time of analysis was 5.1 years (IQR, 3.5-5.7).

In total, 89 DFS events were observed. The estimated 5-year DFS rates were 71% (95% CI, 64 to 79) for the INCT-CRT group and 69% (95% CI, 62 to 77) for the CRT-CNCT group (Fig 1A). The estimated 5-year OS rates were also similar in

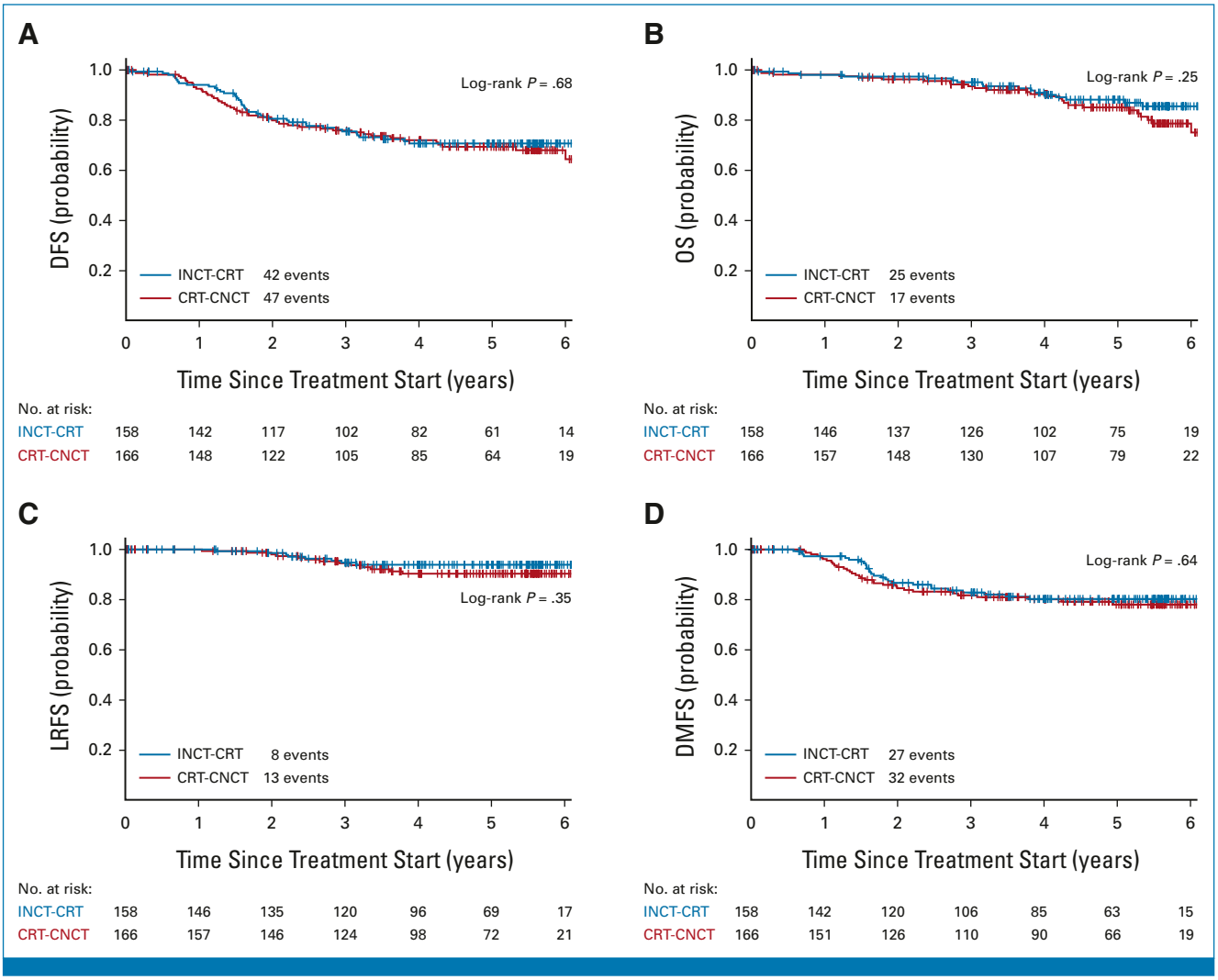

FIG 1. Kaplan-Meier estimates of (A) DFS, (B) OS, (C) LRFS, and (D) DMFS in the intention-to-treat population by treatment group. CRT-CNCT, chemoradiation followed by chemotherapy; DFS, disease-free survival; DMFS, distant metastasis-free survival; INCT-CRT, chemotherapy followed by chemoradiation; LRFS, local recurrence-free survival; OS, overall survival.

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both groups; 88% (95% CI, 83 to 94) for INCT-CRT and 85% (95% CI, 79 to 91) for CRT-CNCT (Fig 1B). Estimated 5-year LRFS rates (94% [95% CI, 90 to 98] for INCT-CRT and 90% [95% CI, 85 to 96] for CRT-CNCT) and DMFS rates (80% [95% CI, 74 to 87] for INCT-CRT and 78% [95% CI, 71 to 85] for CRT-CNCT) were similar in both groups (Figs 1C and 1D).

In total, 304 patients were restaged after a median of 7.8 weeks (IQR, 5.9-9.4) after finishing TNT and 79 (26%) of them were recommended TME: 41/146 (28%) in the INCT-CRT group and 38/158 (24%) in the CRT-CNCT group. A total of 225 (74%) were offered WW: 105/146 (72%) in the INCT-CRT group (54/105 [51%] with cCR, 47/105 [45%] with nCR, and 4/105 [4%] with iCR) and 120/158 (76%) in the CRT-CNCT group (69/120 [58%] with cCR, 47/120 [39%] with nCR, and 4/120 [3%] with iCR). Of the patients who entered WW, 81 (36%) developed a tumor regrowth: 46/105 (44%) in the INCT-CRT group and 35/120 (29%) in the CRT-CNCT group. Regrowth occurred in 27 (22%) of 123 patients with cCR (INCT-CRT 15/54 [28%] and CRT-CNCT 12/69 [17%]), 49 (52%) of 94 patients with nCR (INCT-CRT 27/47 [57%] and CRT-CNCT 22/47 [47%]), and five (63%) of eight patients with iCR (INCT-CRT 4/4 [100%] and CRT-CNCT 1/4 [25%]). Of all cases of tumor regrowth, 76 (94%) occurred within

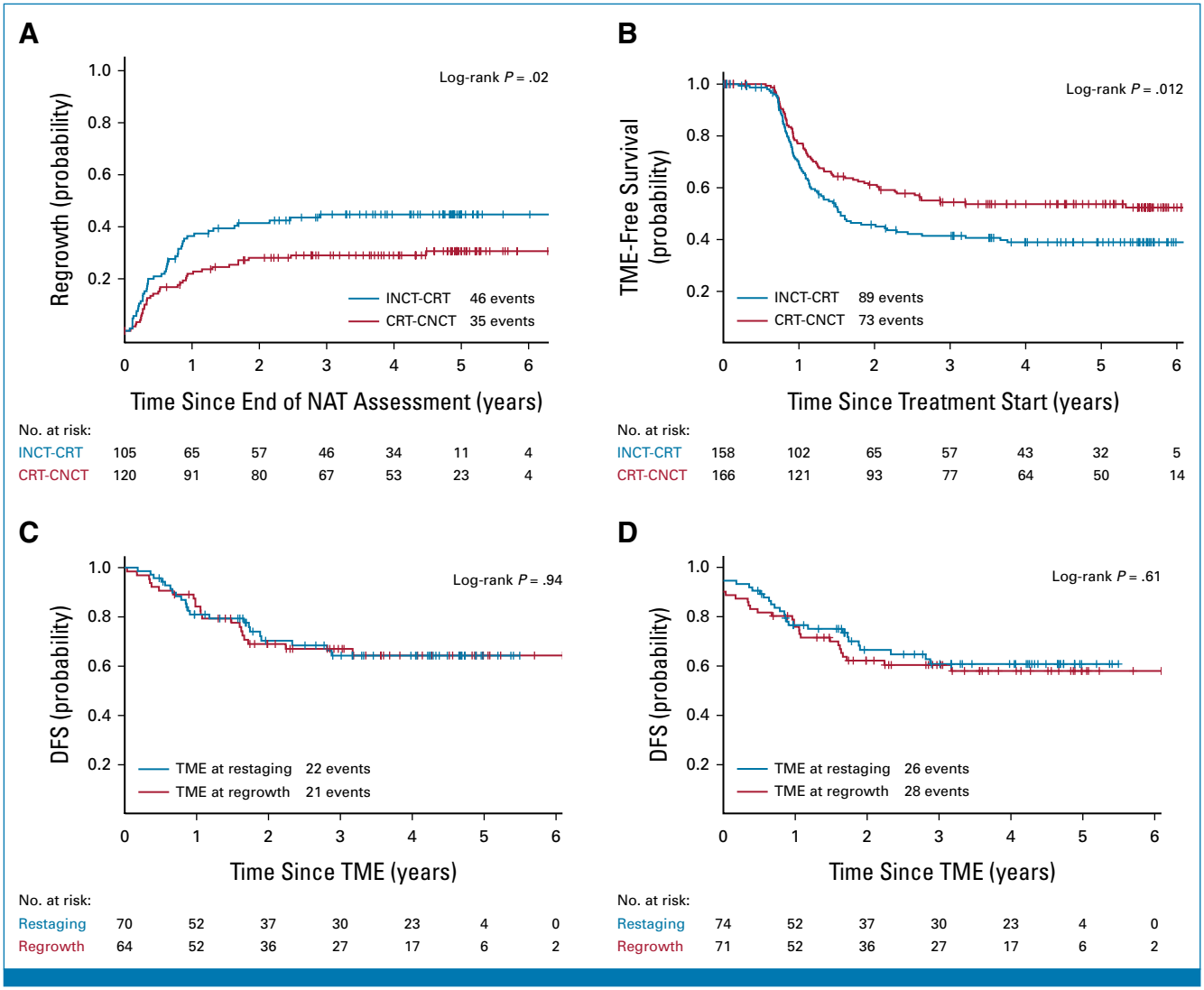

FIG 2. Kaplan-Meier estimates of (A) time to regrowth in watch-and-wait patients, (B) TME-free survival by intention-to-treat, (C) DFS for patients who were recommended TME after restaging and patients who were recommended TME after regrowth, and (D) DFS for patients who were recommended TME after restaging and patients who were recommended TME after regrowth by intention-to-treat. Patients who developed distant metastasis before TME was recommended (three at restaging and six at regrowth) and patients in whom TME was not performed because of disease progression found at surgery (one at restaging and two at regrowth) are not included in the analysis. Three patients were lost to follow-up after TME (two patients with TME after restaging and one patient with TME after regrowth). A total of 11 patients refused TME and were censored as having an event at the time of refusal in the intention-to-treat analysis. CRT-CNCT, chemoradiation followed by chemotherapy; DFS, disease-free survival; INCT-CRT, chemotherapy followed by chemoradiation; NAT, neoadjuvant therapy; TME, total mesorectal excision.

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2 years and 80 (99%) occurred within 3 years after restaging (Fig 2A). The proportion of patients who achieved organ preservation at 5 years for the intention-to-treat population was 39% (95% CI, 32 to 48) for the INCT-CRT group and 54% (95% CI, 46 to 62) for the CRT-CNCT group (P = .012; Fig 2B). Of the 144 patients who had a sustained cCR in the rectum at last follow-up, 13 (9%) developed distant metastases after a median of 1.5 years from random assignment: 6/59 (10%) of patients in the INCT-CRT group and 7/85 (8%) of patients in the CRT-CNCT group. R0 resection rates (local excisions excluded) were similar in patients who had TME after restaging (64/71 [90%]) and patients who had TME after tumor regrowth (58/64 [91%]; P = 1.0). The proportion of patients who had sphincter-preserving surgery was also similar between patients who had TME after restaging (39/71 [55%]) and patients who had TME after tumor regrowth (28/64 [44%]; P = .23). Five-year DFS was similar for patients who underwent TME after restaging (64% [95% CI, 53 to 78]) and patients who underwent TME after tumor regrowth (64% [95% CI, 53 to 78]; P = .94, Fig 2C). The intention-to-treat analysis comparing DFS between patients who had TME after restaging and patients who had TME after tumor regrowth is shown in Figure 2D.

DISCUSSION

In this updated analysis of the OPRA trial, we found that nearly all tumor regrowth in WW patients occurs during the first 2 years after restaging, and that half of the patients with rectal cancer treated with TNT preserved their rectum after 5 years of follow-up. Organ preservation rates at 5 years were higher in patients treated with CRT-CNCT compared with INCT-CRT. Salvage TME for tumor regrowth during WW appears to offer similar outcome to immediate TME after incomplete response to TNT. The 5-year DFS rate in the entire cohort was similar between both treatment groups.

To our knowledge, this study provides the largest prospective cohort and the longest follow-up for patients with locally advanced rectal cancer on WW surveillance after TNT.[5] Consistent with the literature, our study shows that most cases of local tumor regrowth occur during the first 2 years after initiation of WW, and that regrowth after 3 years is extremely rare.[1,5,6] Our results support the recommendation that patients with rectal cancer offered WW after neoadjuvant therapy should have very close surveillance during the first 3 years.

In our study, the rate of organ preservation is higher than the rates of pathologic complete response in patients treated with TNT and TME.[7-11] These differences are probably related to the use of TNT, the overall treatment length, and the assessment of tumor response at almost 8 weeks from the end of TNT. Offering organ preservation to patients with a nCR may have also contributed to the high rate of organ preservation. However, offering WW to patients with nCR resulted in a higher rate of tumor regrowth compared with the international WW registry that offered WW only to patients with cCR.[1] When compared with patients with cCR exclusively, the regrowth rates of the OPRA trial are in line with the international WW registry.[1,12]

Consistent with the literature, the OPRA trial also suggests that WW patients requiring TME after tumor regrowth have equivalent survival to patients recommended to undergo TME after TNT for incomplete response.[13,14] The long-term DFS in this study was similar to the 5-year DFS and disease-related treatment failure rate reported in clinical trials of patients with rectal cancer treated with neoadjuvant therapy and TME.[15,16]

In conclusion, TNT for patients with rectal cancer resulted in long-term organ preservation in half of the patients. Local tumor regrowth occurs mostly within the first 2 years. Although the order of TNT did not result in a difference in survival, CRT-CNCT resulted in higher organ preservation at 5 years compared with INCT-CRT. Future research should focus on more effective and less toxic neoadjuvant treatment regimens to further drive up cCR rates.

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DISCLAIMER

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

PRIOR PRESENTATION

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

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Consulting or Advisory Role: Baxter, Stryker, Medtronic

Blase Polite
Honoraria: American Journal of Managed Care, Genzyme
Consulting or Advisory Role: Janssen Oncology, Cellicon Biotechnologies
Speakers' Bureau: Natera
Travel, Accommodations, Expenses: Tapestry Pharmaceuticals
Open Payments Link: https://openpaymentsdata.cms.gov/physician/1196539

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Consulting or Advisory Role: Olympus Medical Systems, Davol
Research Funding: Merck (Inst), Freenome (Inst)

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Honoraria: Intuitive Surgical
Consulting or Advisory Role: Virtual Incisions Inc
Travel, Accommodations, Expenses: Intuitive Surgical

Andrew L. Coveler
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Research Funding: XBiotech (Inst), Newlink Genetics (Inst), Taiho Pharmaceutical (Inst), Immunomedics (Inst), Onconova Therapeutics (Inst), Lilly (Inst), Gilead Sciences (Inst), Genentech (Inst), Seagen (Inst), AbGenomics International (Inst), Halozyme (Inst), Novocure (Inst), Amgen (Inst), Actuate Therapeutics (Inst), Surface Oncology (Inst), Nucana (Inst), Nextrast (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Halozyme, AbbVie, Nucana

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John Krauss
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Other Relationship: National Cancer Institute

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Research Funding: Bristol Myers Squibb, Pfizer, Roche/Genentech, Merck, Immunocore, AstraZeneca, Regeneron (Inst), PureTech (Inst), Agenus (Inst)
Travel, Accommodations, Expenses: AstraZeneca/MedImmune, Regeneron

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Stock and Other Ownership Interests: Haystack Oncology
Consulting or Advisory Role: Bayer, GlaxoSmithKline, Incyte, Merck, Janssen, Seagen, G1 Therapeutics, Daiichi Sankyo/AstraZeneca
Research Funding: Seagen, GlaxoSmithKline
Patents, Royalties, Other Intellectual Property: Neoadjuvant PD1 blockade in mismatch repair deficient solid tumors (Inst), Hepatic arterial infusion with FUDR for colorectal liver metastases with DPD (Inst)

Rona Yaeger
Honoraria: Zai Lab
Consulting or Advisory Role: Mirati Therapeutics
Research Funding: Boehringer Ingelheim (Inst), Pfizer (Inst), Mirati Therapeutics (Inst), Daiichi Sankyo/UCB Japan (Inst)

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Open Payments Link: https://openpaymentsdata.cms.gov/physician/851428

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Other Relationship: Johnson & Johnson/Janssen

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Consulting or Advisory Role: AstraZeneca, MORE Health, NanoVi
Research Funding: CivaTech Oncology
Travel, Accommodations, Expenses: CivaTech Oncology
Open Payments Link: https://openpaymentsdata.cms.gov/physician/368691

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No other potential conflicts of interest were reported.

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APPENDIX

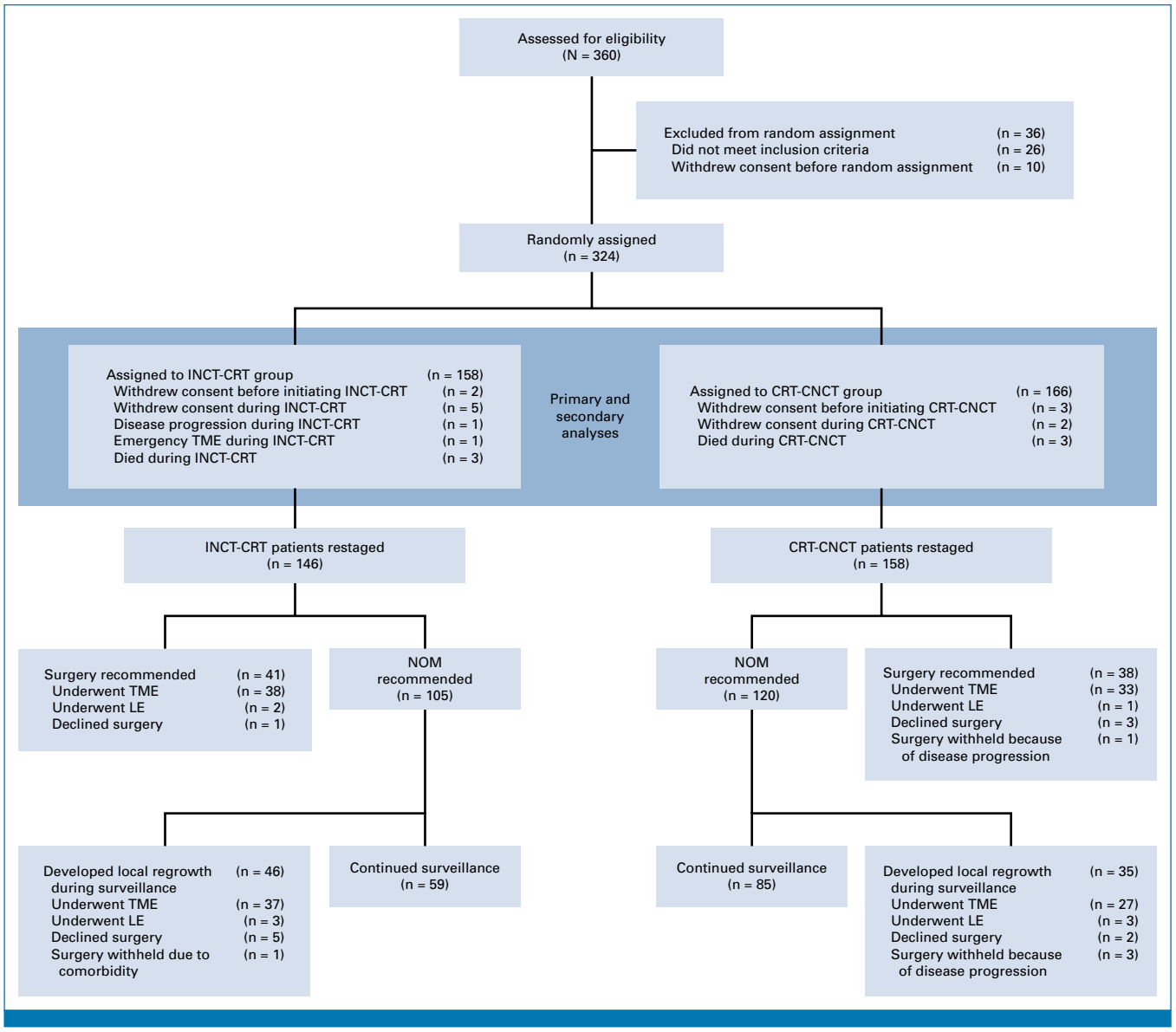

FIG A1. CONSORT diagram illustrating the eligibility, random assignment, outcomes, and follow-up of the trial cohort. A total of 158 INCT-CRT and 166 CRT-CNCT patients represent the intention-to-treat population, and were used for primary and secondary analyses. CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; INCT-CRT, induction chemotherapy followed by chemoradiotherapy; LE, local excision; NOM, nonoperative management; TME, total mesorectal excision.

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