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Use of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer
Initial Results From the Pembrolizumab Arm of a Phase 2 Randomized Clinical Trial

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IMPORTANCE Total neoadjuvant therapy (TNT) is often used to downstage locally advanced rectal cancer (LARC) and decrease locoregional relapse; however, more than one-third of patients develop recurrent metastatic disease. As such, novel combinations are needed.

OBJECTIVE To assess whether the addition of pembrolizumab during and after neoadjuvant chemoradiotherapy can lead to an improvement in the neoadjuvant rectal (NAR) score compared with treatment with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and chemoradiotherapy alone.

DESIGN, SETTING, AND PARTICIPANTS In this open-label, phase 2, randomized clinical trial (NRG-GI002), patients in academic and private practice settings were enrolled. Patients with stage II/III LARC with distal location (cT3-4 ≤ 5 cm from anal verge, any N), with bulky disease (any cT4 or tumor within 3 mm of mesorectal fascia), at high risk for metastatic disease (cN2), and/or who were not candidates for sphincter-sparing surgery (SSS) were stratified based on clinical tumor and nodal stages. Trial accrual opened on August 1, 2018, and ended on May 31, 2019. This intent-to-treat analysis is based on data as of August 2020.

INTERVENTIONS Patients were randomized (1:1) to neoadjuvant FOLFOX for 4 months and then underwent chemoradiotherapy (capecitabine with 50.4 Gy) with or without intravenous pembrolizumab administered at a dosage of 200 mg every 3 weeks for up to 6 doses before surgery.

MAIN OUTCOMES AND MEASURES The primary end point was the NAR score. Secondary end points included pathologic complete response (pCR) rate, SSS, disease-free survival, and overall survival. This report focuses on end points available after definitive surgery (NAR score, pCR, SSS, clinical complete response rate, margin involvement, and safety).

RESULTS A total of 185 patients (126 [68.1%] male; mean [SD] age, 55.7 [11.1] years) were randomized to the control arm (CA) (n = 95) or the pembrolizumab arm (PA) (n = 90). Of these patients, 137 were evaluable for NAR score (68 CA patients and 69 PA patients). The mean (SD) NAR score was 11.53 (12.43) for the PA patients (95% CI, 8.54-14.51) vs 14.08 (13.82) for the CA patients (95% CI, 10.74-17.43) (P = .26). The pCR rate was 31.9% in the PA vs 29.4% in the CA (P = .75). The clinical complete response rate was 13.9% in the PA vs 13.6% in the CA (P = .95). The percentage of patients who underwent SSS was 59.4% in the PA vs 71.0% in the CA (P = .15). Grade 3 to 4 adverse events were slightly increased in the PA (48.2%) vs the CA (37.3%) during chemoradiotherapy. Two deaths occurred during FOLFOX: sepsis (CA) and pneumonia (PA). No differences in radiotherapy fractions, FOLFOX, or capecitabine doses were found.

CONCLUSIONS AND RELEVANCE Pembrolizumab added to chemoradiotherapy as part of total neoadjuvant therapy was suggested to be safe; however, the NAR score difference does not support further study.

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Visual Abstract

Supplemental content

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Trimodality therapy of chemotherapy, chemoradiotherapy, and surgery has been considered the mainstay of treatment for stage II/III locally advanced rectal cancer (LARC).[1] Preoperative chemoradiotherapy is used for tumor downstaging, reducing local recurrence, and avoiding colostomies.[2] Total neoadjuvant therapy (TNT) is an emerging option to optimize successful delivery of chemotherapy. However, despite a low locoregional relapse rate of 6%, 5-year overall survival (OS) is 75%.[3,4] The TNT platform is a randomized clinical study to test novel agents with parallel, noncomparative experimental arms in LARC. The primary objective is to assess whether the addition of a novel agent during and after neoadjuvant chemoradiotherapy can lead to an improvement in the neoadjuvant rectal (NAR) score, which is a short-term surrogate end point proven to be more strongly associated with disease-free survival (DFS) and OS than pathological complete response (pCR).[5,6] The NAR score combines pathologic nodal status (ypN stage) with tumor downstaging (ypT minus baseline cT) to evaluate tumor response; it is calculated from 24

Key Points

Question Does the addition of pembrolizumab to neoadjuvant chemoradiotherapy improve efficacy compared with chemoradiotherapy alone for patients with locally advanced rectal cancer who have completed neoadjuvant FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin)?

Findings In this randomized clinical trial, which included 185 patients with stage II/III locally advanced rectal cancer, the mean neoadjuvant rectal score was 11.53 for the pembrolizumab arm compared with 14.08 for the control arm.

Meaning The results do not support combining neoadjuvant pembrolizumab with chemoradiotherapy after FOLFOX treatment of locally advanced rectal cancer.

Table. Patient and Tumor Characteristics at Baseline: NRG-GI002 Study

Patient or tumor characteristic	No. (%) of patients			*P* value
	CA (n = 95)	PA (n = 90)	Total (n = 185)	
Sex				
Female	29 (30.5)	30 (33.3)	59 (31.9)	.75
Male	66 (69.5)	60 (66.7)	126 (68.1)	
Age, y				
<50	30 (31.6)	25 (27.8)	55 (29.7)	.76
50-59	28 (29.5)	33 (36.7)	61 (33.0)	
60-69	30 (31.6)	27 (30.0)	57 (30.8)	
≥70	7 (7.4)	5 (5.6)	12 (6.5)	
Race				
White	77 (81.1)	77 (85.6)	154 (83.2)	.22
American Indian or Alaska Native	2 (2.1)	1 (1.1)	3 (1.6)	
Asian	4 (4.2)	3 (3.3)	7 (3.8)	
Black or African American	6 (6.3)	2 (2.2)	8 (4.3)	
Not reported	3 (3.2)	4 (4.4)	7 (3.8)	
Unknown	3 (3.2)	3 (3.3)	6 (3.2)	
Ethnicity				
Hispanic or Latino	5 (5.3)	9 (10.0)	14 (7.6)	.28
Not Hispanic or Latino	83 (87.4)	78 (86.7)	161 (87.0)	
Not reported	4 (4.2)	2 (2.2)	6 (3.2)	
Unknown	3 (3.2)	1 (1.1)	4 (2.2)	
Distal location				
No	27 (28.4)	25 (27.8)	52 (28.1)	>.99
Yes	68 (71.6)	65 (72.2)	133 (71.9)	
Bulky disease				
No	40 (42.1)	30 (33.3)	70 (37.8)	.23
Yes	55 (57.9)	60 (66.7)	115 (62.2)	
High risk of metastatic disease				
No	58 (61.1)	55 (61.1)	113 (61.1)	>.99
Yes	37 (38.9)	35 (38.9)	72 (38.9)	
Not a candidate for SSS				
No	44 (46.3)	41 (45.6)	85 (45.9)	>.99
Yes	51 (53.7)	49 (54.4)	100 (54.1)	
N stage				
N0	22 (23.2)	20 (22.2)	42 (22.7)	>.99
N1	36 (37.9)	35 (38.9)	71 (38.4)	
N2	37 (38.9)	35 (38.9)	72 (38.9)	
T stage				
T1/T2	5 (5.3)	4 (4.4)	9 (4.9)	.90
T3	68 (71.6)	67 (74.4)	135 (73.0)	
T4	22 (23.2)	19 (21.1)	41 (22.2)	

Abbreviations: CA, control arm; PA, pembrolizumab arm; SSS, sphincter-sparing surgery.

items on a pseudo-continuous scale from 0 (pCR from cT4) to 100 (ypN2 and progression from cT1 to ypT4), with lower scores indicating better prognosis.[5,6] Chemoradiotherapy can increase the immunogenic properties of tumor cells, thereby increasing their vulnerability to cytotoxic lymphocytes[7,8] and inducing expression of programmed death-ligand 1 on tumor cells, which can lead to an immunosuppressive microenvironment.[9,10] We hypothesized that the addition of anti-programmed death 1 therapy to neoadjuvant chemoradiotherapy could increase $CD8^+$ T cells, leading to better pCR and improved NAR score. In this article, we present the primary end point (NAR score) results of the experimental pembrolizumab arm (PA) vs the control arm (CA). Results from the other experimental arm have been previously presented.[11]

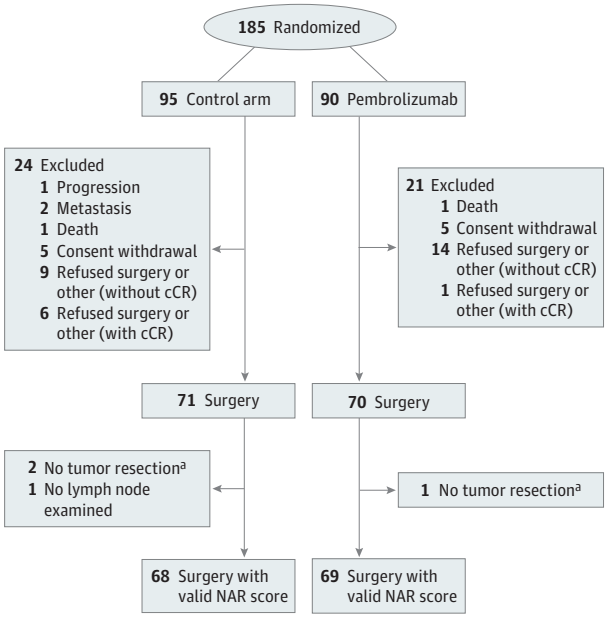
Methods

This study is a prospective, open-label, phase 2 randomized clinical trial, with equal allocation to each trial arm by permuted block method. Trial accrual opened on August 1, 2018, and ended on May 31, 2019. A total of 185 patients were concurrently randomized, with 95 randomized to the CA and 90 to the PA. This intent-to-treat analysis is based on data as of August 2020. The trial protocol can be found in Supplement 1. Written informed consent was provided by the study participants. Data were not deidentified. The NRG-GI002 study was approved by local human investigations committees with assurances filed with the US Department of Health and Human Services.

Patients were randomized to receive 6 cycles of FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) followed by chemoradiotherapy (825 mg/m^2 of capecitabine twice daily concurrently with 4500 cGy in 25 fractions for 5 weeks plus a 540-cGy boost in 3 fractions) starting 3 to 4 weeks after FOLFOX (CA) or the same dosage of FOLFOX followed by the same chemoradiotherapy regimen in combination with 200 mg of pembrolizumab every 3 weeks starting on day 1 of chemoradiotherapy for up to 6 doses (PA). Surgery was performed 8 to 12 weeks after the last dose of radiotherapy (eFigure in Supplement 2).

Stratification factors included clinical tumor stage (T1 or T2, T3, or T4) and clinical nodal stage (N0, N1, or N2). Inclusion criteria included stage II or III LARC that met at least 1 of the following criteria: distal location (cT3-4 ≤ 5 cm from the anal verge), bulky disease (any cT4 or evidence that the tumor is within 3 mm of the mesorectal fascia), high risk of metastatic disease with 4 or more involved regional lymph nodes (cN2), or not a candidate for sphincter-sparing surgery (SSS) at presentation. The sample size of 79 evaluable patients per arm was calculated based on targeting an NAR score reduction of 4.70 points for the PA (mean reduction in NAR score from 14.32 to 9.62) compared with a mean NAR score from similarly eligible patients derived from the GCR-3 and Complete Neoadjuvant Treatment for Rectal Cancer (CONTRE) studies,[3,4] with 1-sided type 1 error of $\alpha = .10$ and a type 2 error of $\beta = 0.20$ (power of 80%). Secondary objectives include pCR, SSS rate, DFS, and OS. Mean NAR scores were compared in a linear model that controlled for baseline cT stage, and binary outcomes were compared by the Fisher exact test.

Figure 1. CONSORT Diagram of Patients in the NRG-GI002 Study



cCR indicates clinical complete response; NAR, neoadjuvant rectal.

[a] Patients underwent surgery but had no tumor resection (without cCR).

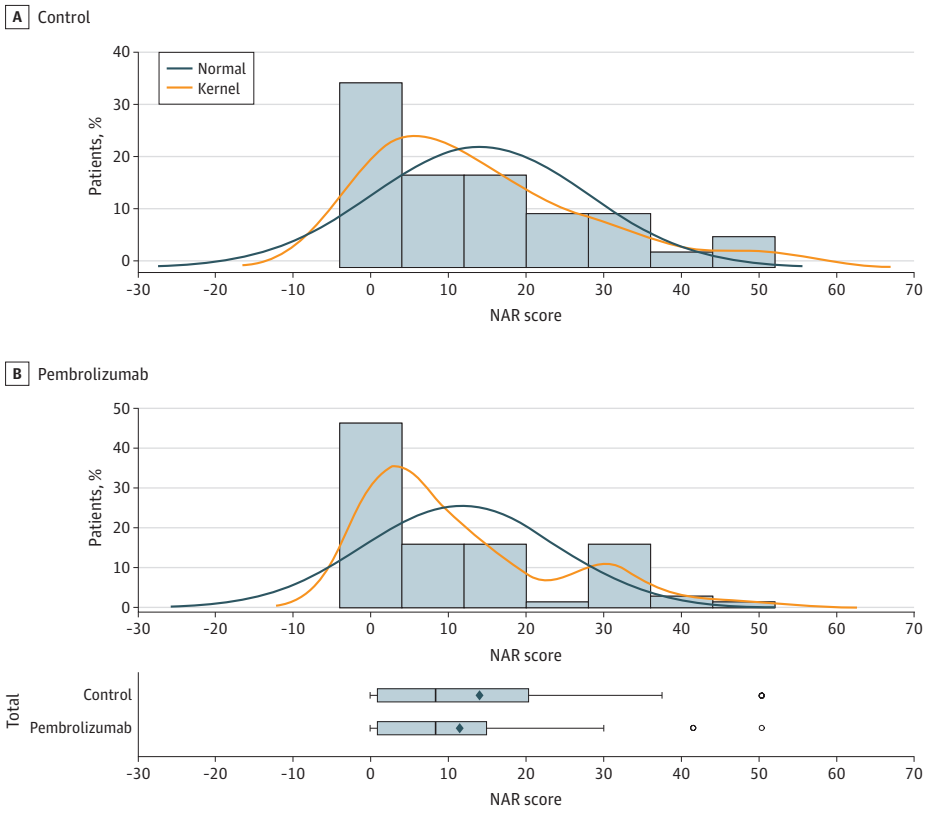
Results

A total of 185 patients (126 [68.1%] male; mean [SD] age, 55.7 [11.1] years) were concurrently randomized to the CA (n = 95) and PA (n = 90). Patient and tumor characteristics are reported in the **Table**. More patients in the PA had bulky disease vs the CA patients (60 [66.7%] vs 55 [57.9%]), whereas more patients in the CA vs the PA had T4 disease (22 [23.2%] vs 19 [21.1%]). Thirty-seven of 81 patients (45.7%) who started radiotherapy in the PA received 6 doses of pembrolizumab, whereas 21 patients (25.9%) received 5 doses, 21 (25.9%) received 1 to 4 doses, and 2 (2.5%) did not receive any pembrolizumab.

Clinical and Pathological Outcomes

Patient disposition is summarized in **Figure 1**. Of the 138 patients with resected tumor, 137 had complete pathologic assessment and a valid NAR score. The mean (SD) NAR scores were 11.53 (12.43) (95% CI, 8.54-14.51) in the PA (n = 69) vs 14.08 (13.82) (95% CI, 10.74-17.43) in the CA (n = 68). The difference of 2.55 was not statistically significant ($P = .26$) (**Figure 2**). Twelve patients with invalid NAR scores because of missing pathologic assessment underwent clinical staging immediately before surgery. The evaluable sample size per arm was

Figure 2. Neoadjuvant Rectal (NAR) Score of Patients in the NRG-GI002 Study



This histogram displays the distribution of the NAR scores along with the best fit normal (gaussian distribution) and kernel (smoothed nonparametric) distributions.

less than our targeted 79 patients per arm, resulting in a reduced power of 75.7% instead of 80.0%. We created an exploratory modified NAR score by substituting presurgical ycT and ycN in place of ypT and ypN for the patients with clinical staging but no pathologic staging. The mean (SD) mNAR scores were 11.52 (12.85) (95% CI, 8.59-14.46) for the PA (n = 76) vs 13.70 (14.21) (95% CI, 10.47-16.93) for the CA (n = 77). The difference of 2.17 was not statistically significant (P = .32). Although there was a slightly higher pCR rate in the PA of 31.9% (22 of 69; 95% CI, 21.2%-44.2%) vs 29.4% (20 of 68; 95% CI, 19.0%-41.7%) in the CA, this finding was not statistically significant (P = .75). The clinical complete response rate, based on presurgical staging as an exploratory end point, was 13.9% (11 of 79; 95% CI, 7.2%-23.6%) in the PA and 13.6% (11 of 81; 95% CI, 7.0%-23.0%) in the CA (P = .95). The R0 resection rate was 94% in the PA vs 89.4% in the CA (P = .36). In patients who underwent tumor resection, the SSS rate was lower in the PA (41 of 69 [59.4%]; 95% CI, 46.9%-71.1%) vs the CA (49 of 69 [71.0%]; 95% CI, 58.8%-81.3%), which was not statistically significant (P = .15). Analyses of longer-term outcomes, including DFS and OS, remain ongoing.

Adverse Events

Grade 3 to 4 adverse events were slightly increased on the PA during and after chemoradiotherapy (39 [48.2%] vs 31 [37.3%]). No grade 5 adverse events were reported during and after chemoradiotherapy. Immune-related adverse events were reported in 35 patients (43.2%) on in the PA, including only 3 (3.7%) with grade 3 events and no grade 4 or 5 events. Immune-related adverse events were consistent with the pembrolizumab safety profile (eTable in Supplement 2).

Discussion

The addition of pembrolizumab to chemoradiotherapy as part of TNT in LARC did not demonstrate our prespecified improvement in the primary end point of NAR score compared with FOLFOX and chemoradiotherapy alone. Although the pCR rate was higher in the PA, it did not reach statistical significance. The DFS and OS data are not mature and will be presented in future publications. The combination was well tolerated without new safety concerns raised.

Although the efficacy of programmed cell death 1 blockade has been impressive in microsatellite-instable tumors,[12] the microsatellite-stable tumors (which account for >95% of rectal cancers) remain resistant to immune checkpoint inhibitors. This resistance may be attributable to many factors, including major histocompatibility complex 1 downregulation, low tumor mutation burden, the immune desert or excluded phenotypes, and the immune suppressive microenvironment.[13] Whether additional immune checkpoint inhibitors or immune agonists are needed to overcome the resistance to programmed cell death 1 blockade remains

to be determined.[14,15] The ongoing genomic (including microsatellite status) and immune correlatives from the NRG-GI002 trial will further explore the mechanisms of immune resistance and inform future LARC studies.

Limitations

Although patients in both arms had similar exposures to chemoradiotherapy, 44 (54.3%) did not receive all 6 doses of pembrolizumab and 23 (28.4%) received fewer than 5 doses. The NRG-GI002 study had slightly less power than originally planned (75.7% vs 80.0%).

Conclusions

These results suggest that pembrolizumab added to chemoradiotherapy as part of total neoadjuvant therapy is safe; however, the NAR score difference does not support further study.

ARTICLE INFORMATION

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Author Contributions: Drs Rahma and Yothers had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, as well as the work as a whole, from inception to published article.
Concept and design: Rahma, Yothers, Hong, Russell, You, Jacobs, Colangelo, Hall, Kachnic, Sigurdson, Wolmark, George.
Acquisition, analysis, or interpretation of data: Rahma, Yothers, You, Parker, Colangelo, Lucas, Gollub, Vijayvergia, O'Rourke, Faller, Valicenti, Schefter, Moxley, Kainthla, Stella, George.
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Supervision: Rahma, Yothers, Gollub, Hall, Kachnic, Faller, George.

Conflict of Interest Disclosures: Dr Rahma reported receiving personal fees from the Sobi Advisory Board, the Genentech Advisory Board, the Bayer Advisory Board, the GSK Advisory Board, the Imvax Advisory Board, the Maverick Advisory Board, and the Puretech Advisory Board outside the submitted work; in addition, Dr Rahma had a patent for DFCI 2386.010 pending. Dr Yothers reported receiving grants from the NRG Oncology Statistical and Data Management Center during the conduct of the study and serving on the Orbus Pharmaceuticals Data Monitoring Committee outside the submitted work. Dr Hong reported serving as a consultant for Merck, Novocure, and Synthetic Biologics outside the submitted work. Dr Russell reported serving as a consultant for the American College of Surgeons. Dr Colangelo reported receiving grants from NRG Oncology during the conduct of the study. Dr Lucas reported stock ownership in Amgen and having a spouse who received speaker honorarium from Schrodinger outside the submitted work. Dr Hall reported receiving institutional research support from Elekta AB outside the submitted work. Dr Kachnic reported receiving honorarium from UpToDate outside the submitted work. Dr Vijayvergia reported serving on advisory boards for Lexicon, Halio Dx, and QED Therapeutics, serving as a consultant for Novartis, and receiving grants from Merck and Bayer outside the submitted work. Dr George reported receiving institutional support from BMS, Merck, AstraZeneca, Genentech, Tesaro/GSK, Ipsen, Bayer, and Lilly outside the submitted work. No other disclosures were reported.

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