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Efficacy and Safety of Two Neoadjuvant Strategies With Bevacizumab in MRI-Defined Locally Advanced T3 Resectable Rectal Cancer: Final Results of a Randomized, Noncomparative Phase 2 INOVA Study

Christophe Borg,[1] Georges Mantion,[1] Frank Boudghène,[2] Françoise Mornex,[3] François Ghiringhelli,[4] Antoine Adenis,[5] David Azria,[6] Jacques Balosso,[6] Meher Ben Abdelghani,[7] Jean Baptiste Bachet,[8] Véronique Vendrely,[9] Yves François,[10] Thierry Conroy,[11] Emmanuel Rio,[12] Bernard Roullet,[13] Dominique Spaëth,[14] Laurent Quero,[15] Zaher Lakkis,[1] Mathieu Coudert,[16] Miruna Ionescu-Goga,[16] Alexandre Tanang,[16] Thierry André[17]

Abstract

The INOVA randomized phase II study compared 2 neoadjuvant strategies for locally advanced rectal cancers. Final results up to 5 years of follow-up showed that neoadjuvant chemotherapy does not increase late toxicities and may have the potential to increase survival outcomes.

Background: Recurrence and distant metastases remain a significant issue in locally advanced rectal cancer (LARC). Several multimodal strategies are assessed in clinical trials. **Patients and Methods:** Patients with mid/low magnetic resonance imaging–defined high-risk LARC were randomized to arm A (12-week bevacizumab + FOLFOX-4 then bevacizumab–5-fluorouracil [5-FU]–radiotherapy [RT] before total mesorectal excision [TME]) or arm B (bevacizumab-5-FU–RT then TME). Long-term efficacy and safety up to 5 years' follow-up are reported. No comparison between arms was planned. **Results:** Overall, 91 patients (46 in arm A and 45 in arm B) were included. Main results have been presented previously. During the late follow-up period (> 4 weeks after surgery), 4 patients (8.7%) in arm A and 4 (8.9%) in arm B experienced grade 3/4 adverse events related to bevacizumab; the most frequent were 2 anastomotic fistulas (both in arm A) and abscesses (1 in arm A and 2 in arm B). At 5 years' follow-up, 9 (19.6%) and 11 (24.4%) patients in arms A and B developed a fistula in the year after surgery, and 2 (4.3%) in arm A at > 1 year after surgery. Most resolved before study end. Five-year disease-free survival was 70% and 64.3% in arms A and B, respectively. Five-year overall survival was 90.5% (95% confidence interval, 76.7, 96.3) in arm A and 72.7% (95% confidence interval, 56.0, 83.9) in arm B. **Conclusion:** Neoadjuvant bevacizumab + FOLFOX-4 may have the potential to increase

[1]Department of Medical Oncology, University Hospital of Besançon and CIC-BT506, Besançon, France
[2]Department of Radiology, Tenon Hospital, Paris, France
[3]Department of Radiotherapy, Lyon-Sud Hospital Center, Lyon, France
[4]Department of Medicine, Georges-François-Leclerc Center, Dijon, France
[5]Department of Medical Oncology, Oscar Lambret Center, Lille, France
[6]ICM Cancer Institute of Montpellier, Montpellier, France
[7]Gastroenterologist, Paul Strauss Center, Strasbourg, France
[8]Gastroenterologist, Pitié-Salpêtrière Hospital, Paris, France
[9]CHU Bordeaux, Bordeaux, France
[10]Department of Surgery, CHU Lyon Sud, Lyon, France
[11]Department of Medical Oncology, Lorraine Cancer Institute, Vandœuvre-lès-Nancy, France
[12]Department of Radiotherapy Oncology, Institut de Cancérologie de l'Ouest (ICO), Saint-Herblain, France
[13]Department of Radiotherapy Oncology, CHU Poitiers, Poitiers, France
[14]Department of Medical Oncology, Gentilly Oncology Center, Nancy, France
[15]Department of Radiotherapy Oncology, CHU Saint Louis, Paris, France
[16]Roche Laboratories, Boulogne-Billancourt, France
[17]Department of Medical Oncology, Saint Antoine Hospital and Pierre et Marie Curie University, UMPC Paris, Paris, France

Submitted: Oct 22, 2018; Revised: Apr 6, 2019; Accepted: Apr 26, 2019; Epub: May 3, 2019

Address for correspondence: Christophe Borg, MD, University Hospital Jean Minjoz and Center for Clinical Investigation in Biotherapy (CIC-BT 506), 2, Boulevard Fleming, 25030 Besançon, France
Fax: +33 (0) 3 81 61 56 17; e-mail contact: christophe.borg@efs.sante.fr

1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2019.04.006

survival outcomes when followed by bevacizumab−5-FU−RT and TME in LARC. Bevacizumab−5-FU−RT then TME was associated with a higher-than-projected rate of anastomotic fistulas. Further research of neoadjuvant strategies in LARC is encouraged.

Clinical Colorectal Cancer, Vol. 18, No. 3, 200-8 © 2019 Published by Elsevier Inc.
Keywords: Bevacizumab, Fistula, Neoadjuvant chemotherapy, Radiotherapy, Rectal cancer

Introduction

Preoperative chemoradiotherapy (CT-RT) followed by total mesorectal excision (TME) is the current standard multimodal treatment for locally advanced rectal cancer (LARC).[1] However, recurrences and distant metastases remain a significant issue,[2] and consequently long-term survival suffers as well.[3]

A preoperative oxaliplatin/fluoropyrimidine (FP) and radiotherapy (RT) strategy with or without adjuvant chemotherapy was evaluated in several phase 3 trials, with contradictory survival results.[4-8] Bevacizumab, an antiangiogenic agent active in various types of tumor, has been shown to improve survival of metastatic colorectal cancer patients,[9,10] but not in the adjuvant situation for stage II/III colon cancer.[11-13] The addition of oxaliplatin-based chemotherapies and bevacizumab to CT-RT is a potential solution to increase pathologic response rate, disease-free survival (DFS), and overall survival (OS). Unfortunately, results for trials that use bevacizumab in the treatment of LARC remain scarce, though the studies that have been published indicate promising results in phase 2 trials.[14-17]

The INOVA study assessed two different multimodal therapeutic approaches with bevacizumab combined with induction CT-RT for patients with high-risk T3 resectable rectal cancer. Interim results that included the primary end point of pathologic complete response (pCR) have already been published[18]; final results of the secondary end points including DFS and OS, among others, after 5-year follow-up are presented here.

Patients and Methods

Study Population

Eligible patients were between 18 and 75 years of age and had histologically confirmed rectal adenocarcinoma, magnetic resonance imaging (MRI)-defined T3 LARC within 10 cm from the anal margin (T3N0 1-2 in the lower rectum with distal tumor edge < 5 cm from the anal margin, or T3N0 in the midrectum with tumor spread > 5 mm into perirectal fat, or T3N1-N2), and Eastern Cooperative Oncology Group performance status of 0 or 1. Exclusion criteria and detailed information are provided in the initial publication.[18] All patients provided informed consent before initiation of the study. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use good clinical practice, and was registered at ClinicalTrials.gov (NCT00865189).

Treatment Plan

Eligible patients were allocated to treatment by balanced, centralized randomization, stratified by center, tumor site, and lymph node involvement. Patients in arm A received 12-week bevacizumab in addition to 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX-4), followed by bevacizumab−5-FU−RT before TME. Patients in arm B were treated with only bevacizumab−5-FU−RT before TME. The treatment allocation was not blinded. An outline of the study protocol is shown in Supplemental Figure 1 in the online version, while the detailed treatment plan and dosage guidelines have been published previously.[18]

Assessment

For initial disease staging, patients underwent pelvic MRI and thoracoabdominal computed tomographic scan.

After surgery, patients were scheduled for follow-up visits every 6 months for 5 years in order to collect long-term safety and efficacy data. Follow-up examinations included patient history, physical examination, hematologic and urinary analyses, abdominal and pelvic echography, and chest X-rays. Colonoscopies were performed at 6 months, 1 year, and 5 years.

Statistical Considerations

The primary end point was the proportion of patients who experienced pCR (ypT0-N0) according to local review. Secondary efficacy end points included compliance, tumor downstaging (ypT0-pT2), recurrence rate, and 5-year DFS and OS, while the incidences of adverse events (AEs) and serious AEs were safety end points.

Forty-one patients had to be included in each arm to show a difference between 10% (estimated as the minimum acceptable by the scientific committee) and the expected proportion of 25% with $\alpha = 0.05$ and a power of 80% using a binomial test.

Analyses were performed on the intent-to-treat population per treatment arm, which included all randomized and treated patients. DFS and OS from treatment onset were analyzed by the Kaplan-Meier method.

All the selected patients with at least one treatment dose were included in the safety population. A safety analysis was performed on the safety population per treatment period on all AEs and on AEs of special interest. AEs were graded and classified according to the Common Terminology Criteria for Adverse Events version 3.0 and the Medical Dictionary for Regulatory Activities (MedDRA version 18.1). Exploratory analyses of safety were performed for postsurgery and late fistulas, and for surgical and medical procedures carried out beyond 1 year after the surgery. Prognostic factors were also investigated for each treatment arm separately by a logistic regression model. No comparison between the arms was planned.

Table 1 Patients and Disease Characteristics in 91 ITT Patients

Characteristic	Arm A (N = 46)	Arm B (N = 45)
Age (years), median (range)	60.6 (40.2-73.7)	60.1 (24.3-76.0)
Male sex	31 (67.4%)	30 (66.7%)
ECOG PS at Selection		
0	40 (87.0%)	38 (84.4%)
1	6 (13.0%)	7 (15.6%)
Histologic Type		
Adenocarcinoma	46 (100.0%)	45 (100.0%)
Well differentiated	29 (63.0%)	24 (53.3%)
Moderately differentiated	13 (28.3%)	18 (40.0%)
Missing	4 (8.7%)	3 (6.7%)
Tumor Localization		
Middle rectum (5-10 cm)	28 (60.9%)	27 (60.0%)
Low rectum (< 5 cm)	18 (39.1%)	18 (40.0%)
Radiologic TNM Stage		
T3N0M0	10 (21.7%)	8 (17.8%)
T3N1M0	31 (67.4%)	28 (62.2%)
T3N2M0	5 (10.9%)	9 (20.0%)
Node Involvement (MRI)		
Node positive	34 (73.9%)	37 (82.2%)
1-3	27 (58.7%)	30 (66.7%)
≥4	7 (15.2%)	7 (15.6%)
Type of Surgery Planned		
Resection/anastomosis	30 (65.2%)	31 (68.9%)
Abdominoperineal resection	9 (19.6%)	6 (13.3%)
Other	5 (10.9%)	6 (13.3%)
Missing	2 (4.3%)	2 (4.4%)

Data are presented as n (%) unless otherwise indicated. Arm A refers to 12-week bevacizumab + FOLFOX-4 then bevacizumab—5-FU—RT before TME; and arm B, bevacizumab—5-FU—RT then TME.
Abbreviations: 5-FU = 5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; ITT = intention to treat; MRI = magnetic resonance imaging; RT = radiotherapy; TNM = tumor, node, metastasis classification system.

Results

Study Population and Follow-up

A total of 91 patients (46 in arm A and 45 in arm B) were included between October 2007 and July 2010, 60 of whom completed the study: 34 patients (73.9%) in arm A and 26 (57.8%) in arm B.[18] The duration of follow-up was 5 years for both arms. The majority of withdrawals in both arms occurred during the late period of the follow-up period (12 in arm A, 19 in arm B). The main reasons were loss to follow-up (6 in each arm) and death (4 in arm A, 11 in arm B). Patient and disease characteristics are presented in Table 1. Eighteen (39%) and 24 (53.3%) of the patients included in arms A and B, respectively, received an adjuvant chemotherapy (FOLFOX/capecitabine and oxaliplatin for 17 and 22 patients in arms A and B).

Safety

The safety analysis including the 8-week period after rectal surgery has been previously reported.[18] The final analysis of the clinical outcomes collected during the 5-year follow-up period is reported here, with specific emphasis on AEs that occurred during the early postsurgery period (time between surgery and 4 weeks after) and late AEs (AEs that occurred more than 4 weeks after surgery but before the end of the study).

As reported previously, no deaths occurred from the start of the study until 8 weeks after surgery. Incidence of AEs by arm and by period is summarized by severity and relationship in Table 2. The 51 related grade 3/4 AEs reported during the entire study period in 30 patients (33.0%) are described in Table 3.

Of the AEs reported during the late follow-up period in arm A, 10 were grade 3/4 AEs in 9 patients (19.6%). The most frequent grade 3/4 late AEs were anastomotic fistula, diarrhea, incisional hernia, and intestinal anastomosis complication (2 patients each). Five grade 3/4 events were related to bevacizumab in 4 patients (8.7%), including anastomotic fistula (n = 2), pelvic abscess (n = 1), and erectile dysfunction (n = 1). There were 4 late fistulas occurring in 3 patients (6.5%); all recovered but one with sequelae. There were 4 deaths (8.7%) reported in arm A during the follow-up period, 3 (6.5%) due to disease progression and 1 (2.2%) from lung cancer.

Table 2 Summary of Emerging AEs by Period According to Treatment Arm, Safety Population (N = 91)

Characteristic	Arm A		Arm B	
	No. of Events	Patients, N (%)	No. of Events	Patients, N (%)
During Entire Study Period				
All events	571	46 (100)	256	44 (97.8)
Bevacizumab-related events	196	44 (95.7)	63	30 (66.7)
Grade 3/4 AEs	68	29 (63.0)	41	17 (37.8)
Grade 3/4 bevacizumab-related AEs	30	19 (41.3)	21	11 (24.4)
SAE	39	21 (45.7)	38	18 (40.0)
Bevacizumab-related SAEs	19	16 (34.8)	14	9 (20.0)
AE of special interest	106	40 (87.0)	68	32 (71.1)
During Postsurgery Period				
All events	34	21 (45.7)	35	24 (53.3)
Bevacizumab-related events	15	13 (28.3)	18	14 (3.1)
Grade 3/4 AEs	14	10 (21.7)	16	11 (24.4)
Grade 3/4 bevacizumab-related AEs	6	5 (10.9)	11	8 (17.8)
SAE	13	10 (21.7)	16	11 (24.4)
Bevacizumab-related SAEs	7	6 (13.0)	9	7 (15.6)
AE of special interest	16	13 (28.3)	21	15 (33.3)
During Late Period				
All events	17	13 (28.3)	14	14 (31.1)
Bevacizumab-related events	9	8 (17.4)	10	8 (17.8)
Grade 3/4 AEs	10	9 (19.6)	12	6 (13.3)
Grade 3/4 bevacizumab-related AEs	5	4 (8.7)	4	4 (8.9)
SAE	9	7 (15.2)	14	7 (15.6)
Bevacizumab-related SAEs	4	3 (6.5)	4	4 (8.9)
AE of special interest	10	9 (19.6)	12	9 (20.0)

Arm A refers to 12-week bevacizumab + FOLFOX-4 then bevacizumab—5-FU—RT before TME; and arm B, bevacizumab—5-FU—RT then TME. AE of special interest refers to hypertension, gastrointestinal perforation, fistulas, wound healing complication, congestive heart failure, bleeding, hemorrhage, thromboembolism events (venous and arterial), proteinuria, reversible posterior leukoencephalopathy syndrome.
Abbreviations: 5-FU = 5-fluorouracil; AE = adverse event; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; RT = radiotherapy; SAE = serious adverse event; TME = total mesorectal excision.

Late-period AEs reported in arm B included 12 grade 3/4 AEs in 6 patients (13.3%). The most frequent grade 3/4 late AE was postoperative abscess (2 patients). Grade 3/4 AEs were related to bevacizumab in 4 patients (8.9%) including perineal abscess (n = 1), postoperative abscess (n = 1), ischemic colitis (n = 1), and deep-vein thrombosis (n = 1). Three fistulas occurred in 3 patients (6.7%); 2 fistulas resolved. Deaths were reported for 11 patients (24.4%) in arm B due to disease progression in 7 patients (15.6%), secondary cancer in 2 patients (4.4%), acute pulmonary edema and congestive heart failure in 1 patient each (2.2%), and 3-branch coronary artery disease in a patient with poor general health status.

From treatment initiation to the end of the 5-year follow-up period, 11 events of fistulas were reported in 9 patients (19.6%) in arm A; 7 fistulas in 6 patients were serious and 5 required surgical management. More than half (54.4%) resolved without sequelae, and 27.3% resolved with sequelae. Ten fistulas were recorded in 10 patients (22.2%) in arm B, including 7 in 7 patients classified as serious AE. The majority (80%) resolved without sequelae.

Overall, all fistulas but one were anastomotic. Nearly all fistulas developed within the year after the surgery, except 3 cases reported as occurring later in 2 patients (4.3%) in arm A; one patient developed anastomotic fistula with pelvic abscess more than 3 years after the surgery, and the other had a pelvic abscess complicated by fistula more than 2 years after rectal surgery.

Efficacy

The primary end point (ie, pCR) and tumor downstaging have been previously described.[18] Key efficacy results are presented in Table 4.

In arm A, during the 5-year follow-up, recurrences were reported in 10 patients (21.7%; 95% confidence interval [CI], 10.9, 36.4), 8 of whom (17.4%; 95% CI, 7.8, 31.4) had distant recurrence and 3 (6.5%; 95% CI, 0.1, 14.8) local recurrence. Median DFS was 68.3 months (95% CI, 68.3, −) with 14 DFS-related events observed, resulting in a 3-year DFS rate of 84.6% (95% CI, 70.3, 92.3) and a 5-year DFS rate of 70.0% (95% CI, 53.9, 81.4) (Figure 1). Four deaths occurred in arm A; subsequently the median OS was not reached, and the OS rates were 90.5% (95% CI, 76.7, 96.3) at 5 years (Figure 1).

In arm B, 9 patients (20.0; 95% CI, 9.6, 34.6) experienced recurrence, with distant recurrences occurring in 6 patients (13.3; 95% CI, 5.1, 26.8) and local recurrences in 4 (8.9; 95% CI, 0.1,

Table 3 Grade 3/4 Bevacizumab-Related Adverse Events According to Treatment Arm During Entire Study Period, Safety Population

Characteristic	Arm A (N = 46)		Arm B (N = 45)		Total (N = 91)	
	N	%	N	%	N	%
Total	19	41.3	11	24.4	30	33.0
Injury, Poisoning, and Procedural Complications	6	13.0	7	15.6	13	14.3
Anastomotic fistula	3	6.5	5	11.1	8	8.8
Wound dehiscence	0	0	2	4.4	2	2.2
Catheter site infection	1	2.2	0	0	1	1.1
Gastrointestinal anastomotic complication	1	2.2	0	0	1	1.1
Intestinal anastomosis complication	1	2.2	0	0	1	1.1
Wound complication	0	0	1	2.2	1	1.1
Vascular Disorders	5	10.9	4	8.9	9	9.9
Hypertension	3	6.5	2	4.4	5	5.5
Deep vein thrombosis	0	0	1	2.2	1	1.1
Embolism venous	0	0	1	2.2	1	1.1
Phlebitis deep	1	2.2	0	0	1	1.1
Shock hemorrhagic	1	2.2	0	0	1	1.1
Thrombophlebitis	1	2.2	0	0	1	1.1
Venous thrombosis	0	0	1	2.2	1	1.1
Gastrointestinal Disorders	5	10.9	2	4.4	7	7.7
Diarrhea	2	4.3	0	0	2	2.2
Colitis ischemic	0	0	1	2.2	1	1.1
Enteritis	1	2.2	0	0	1	1.1
Gastrointestinal perforation	1	2.2	0	0	1	1.1
Intra-abdominal hematoma	1	2.2	0	0	1	1.1
Nausea	1	2.2	0	0	1	1.1
Rectal hemorrhage	0	0	1	2.2	1	1.1
Vomiting	1	2.2	0	0	1	1.1
Infections and Infestations	1	2.2	3	6.7	4	4.4
Abdominal wall abscess	0	0	1	2.2	1	1.1
Pelvic abscess	1	2.2	0	0	1	1.1
Perineal abscess	0	0	1	2.2	1	1.1
Postoperative abscess	0	0	1	2.2	1	1.1
Reproductive System and Breast Disorders	3	6.5	1	2.2	4	4.4
Erectile dysfunction	1	2.2	0	0	1	1.1
Female genital tract fistula	0	0	1	2.2	1	1.1
Rectoprostatic fistula	1	2.2	0	0	1	1.1
Vaginal fistula	1	2.2	0	0	1	1.1
General Disorders and Administration site Conditions	1	2.2	1	2.2	2	2.2
Asthenia	1	2.2	1	2.2	2	2.2
Investigations	2	4.3	0	0	2	2.2
Neutrophil count decreased	2	4.3	0	0	2	2.2
Metabolism and nutrition disorders	2	4.3	0	0	2	2.2
Decreased appetite	2	4.3	0	0	2	2.2
Musculoskeletal and connective tissue disorders	1	2.2	0	0	1	1.1
Osteonecrosis	1	2.2	0	0	1	1.1
Nervous system disorders	1	2.2	0	0	1	1.1

Table 3 Continued

Characteristic	Arm A (N = 46)		Arm B (N = 45)		Total (N = 91)	
	N	%	N	%	N	%
Ruptured cerebral aneurysm	1	2.2	0	0	1	1.1
Renal and urinary disorders	0	0	1	2.2	1	1.1
Proteinuria	0	0	1	2.2	1	1.1

Arm A refers to 12-week bevacizumab + FOLFOX-4 then bevacizumab—5-FU—RT before TME; and arm B, bevacizumab—5-FU—RT then TME. AE of special interest refers to hypertension, gastrointestinal perforation, fistulas, wound healing complication, congestive heart failure, bleeding, hemorrhage, thromboembolism events (venous and arterial), proteinuria, reversible posterior leukoencephalopathy syndrome.
Abbreviations: 5-FU = 5-fluorouracil; AE = adverse event; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; RT = radiotherapy; SAE = serious adverse event; TME = total mesorectal excision.

18.3). Median DFS was not reached, 15 DFS-related events occurred, and the 3- and 5-year DFS rates were 75.1 (95% CI, 59.5, 85.4) and 64.3 (95% CI, 47.6, 76.9), respectively (Figure 1). Median OS was also not reached in arm B; 11 deaths resulted in 3- and 5-year OS rates of 88.4 (95% CI, 74.3, 95.0) and 72.7 (95% CI, 56.0, 83.9), respectively (Figure 1).

Discussion

Various types of preoperative therapy were and continue to be assessed in LARC patients. INOVA was designed to evaluate two different preoperative multimodal therapies in patients with high-risk LARC. Taken together, these final results provide long-term efficacy outcomes (DFS and OS) and show a potential safety signal related to the occurrence of anastomotic fistula and late complications related to bevacizumab.

Regarding efficacy, in arm A, local recurrences were uncommon (6.5%), which compared favorably with previous clinical trials: 6% in the AIO-4 trial and 8.8% in the PRODIGE 02 trial.[5,19] Distant recurrences occurred in 17.4% of the patients. In arm B, local and distant recurrences occurred in 8.9% and 13.3% of the patients, respectively. The long-term follow-up of patients included in the INOVA trial confirmed that exposure to neoadjuvant chemotherapy did not worsen the risk of local failure.

In the literature, surgery alone compared to preoperative RT followed by surgery reduced local recurrence and distant metastasis.[20] Preoperative FP-RT reduced local recurrence compared to preoperative RT alone,[21,22] and resulted in a reduced local recurrence rate.[3,23]

In arm A of INOVA, the 3-year DFS of 84.6% reported compares favorably with those of the preoperative oxaliplatin—FP—RT arms in the phase 3 ACCORD 12 (72.7%), STAR-01 (74.2%), CAO/ARO/AIO-04 (75.9%), and PETACC-6 (75.4%) trials,[4-6,8,24] while the 5-year DFS of 70% was similar with 69.2% in the STAR-01 and in the NSABP R-04 trials.[6,8] The combination of oxaliplatin and FP was also assessed as a neoadjuvant sequence in phase 2 studies before FP-RT.[25-28] DFS and OS results, when assessed, were inconsistent, showing no impact or promising results. In the phase 2 trials of neoadjuvant oxaliplatin, the estimated 5-year DFS values of 62%[29] and 63.1%[27] were close to but slightly lower than those of arm A of the INOVA study.

The 5-year survival rate of 90.5% in arm A of INOVA compares favorably with those of oxaliplatin-based CT-RT arm in the phase 3 STAR-01 (84.4%) and NSABP R-04 (81.3%) studies. A similar trend in phase 2 trials with this combination was observed, for an estimated 5-year survival rate ranging from 66.7% to 80%.[25,27,30,31]

Survival outcomes with preoperative bevacizumab—oxaliplatin—FP—RT were reported for only one phase 2 trial with a 5-year survival rate of 80%.[16]

All together, efficacy outcomes in arm B were lower than those observed in arm A. The DFS rates were 75.1% at 3 years, and the survival rate at 5 years was 72.7%. Preoperative bevacizumab—FP—RT was assessed in several phase 1/2 trials.[14,15,32-36] The actuarial DFS rate with such a strategy was reported by Crane et al[17] to be 77.3% at 2 years. No OS outcomes or survival rates were reported in these studies.

One of the main strengths of the INOVA trial was long-term follow-up that included monitoring AEs of special interest, which included fistulas and bevacizumab-related toxicities as well as the involvement of a data safety monitoring board. After the surgery and up to 5 years' follow-up, 19.6% of patients in arm A and 22.2% of patients in arm B developed a fistula. Late fistulas (beyond 4 weeks after surgery) were reported for 6.6% of arm A patients and 4.4% of arm B patients. The incidence of postoperative fistula is about 2 times higher compared to a maximum of 8% observed after bevacizumab—oxaliplatin—FP—RT and surgery for LARC in clinical trials.[37] As a result of differences in postsurgery AEs reporting and analysis, comparison between trials may lead to incorrect interpretation. To allow comparison between multimodal strategies for the management of LARC, the use of standardized criteria for the definition and the evaluation of surgery and postsurgery complications should be included in trials. Other parameters, including preparation for surgery as well as surgical procedures, must be taken into account.

The incidence of fistula and anastomotic leakage varies substantially between phase 3 trials. In the French ACCORD 12/0405-Prodige 2 study with oxaliplatin—FP—RT, the incidence of anastomotic fistula was approximately 4%. In the randomized GRECCAR 5 trial, with 2 parallel arms (drain vs. no drain), the rate of anastomotic leakage within the 30 days after surgery was 15%.[38] In a meta-analysis including 14 randomized trials conducted by the Cochrane Collaboration, the rate of anastomotic leakage after laparoscopic or open TME for rectal cancer was estimated at 7.7% and 6.3%, respectively.[39] Asteria et al[31] reported a rate of 15.2% of anastomotic leakage in 520 patients who had undergone low anterior resection in 2005. A rate of 12.6% of anastomotic leakage was reported in a series of 2085 patients who underwent TME surgery between January 2005 and December 2007, with or without preoperative 5-FU—RT in Germany.[40]

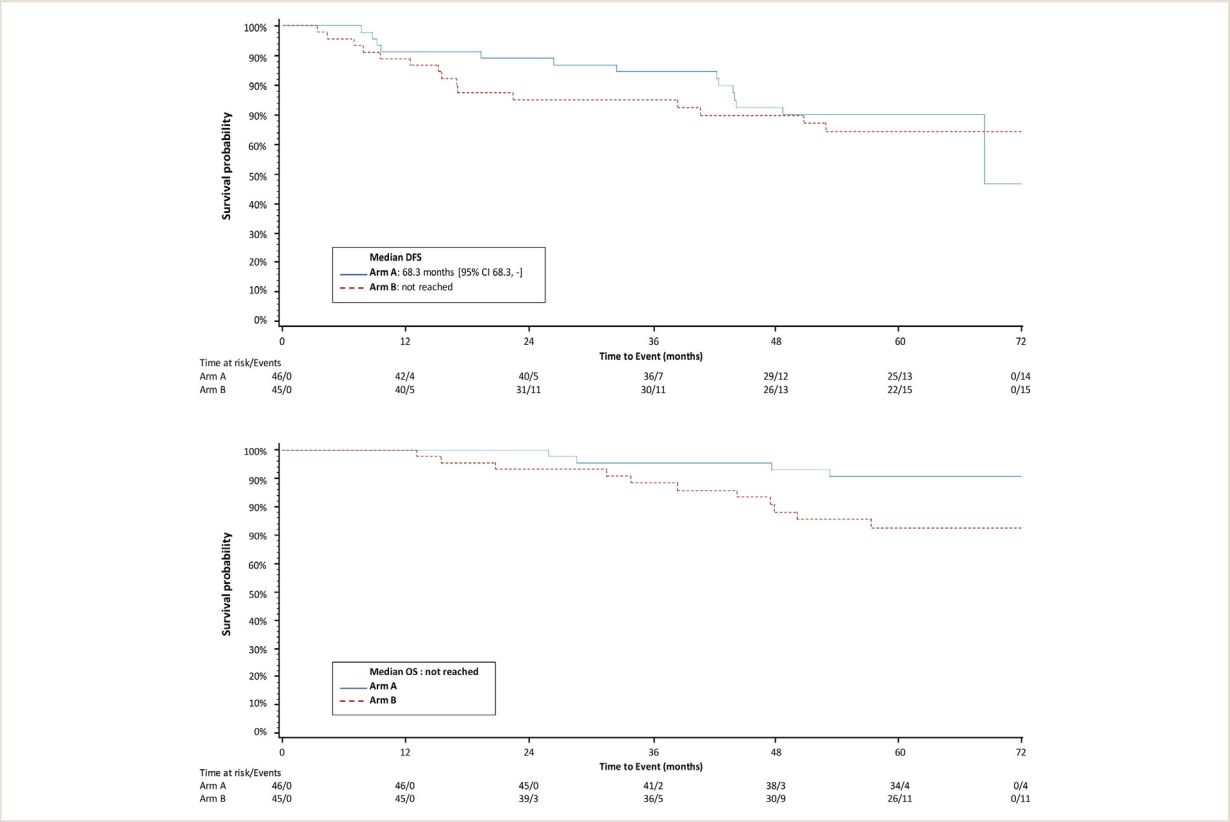
In conclusion, the final results of the phase 2 INOVA study reveal that induction bevacizumab—FOLFOX-4 followed by

Table 4 Overview of Efficacy for Key Results, Intention-To-Treat Population

Characteristic	Arm A (N = 46) N (%) [95% CI]	Arm B (N = 45) N (%) [95% CI]
	N = 42	N = 44
Sterilization of tumor piece (local review)	10 (23.8%) [12.1, 39.5]	5 (11.4%) [3.8, 24.6]
Binomial test	0.015	0.906
	N = 41	N = 44
Downstaging (local review)	27 (65.9%) [51.3, 80.4]	24 (54.5%) [39.8, 69.3]
	N = 45	N = 44
Adherence/infiltration of other organ	1 (2.2%)	4 (9.1%)
	N = 46	N = 43
Tumoral Embolus	8 (17.4%)	9 (20.9%)
Venous	1 (12.5%)	2 (22.2%)
Lymph Node Involvement	N = 44	N = 44
N0	30 (68.2%)	23 (52.3%)
N1	12 (27.3%)	18 (40.9%)
N2	2 (4.5%)	3 (6.8%)
R Stage	N = 43	N = 42
R0	37 (86.0%)	40 (95.2%)
R1	4 (9.3%)	1 (2.4%)
Rx	2 (4.7%)	1 (2.4%)
	N = 46	N = 45
Patient with recurrence	10 (21.7%) [10.9, 6.4]	9 (20.0%) [9.6, 34.6]
Patient with local recurrence	3 (6.5%) [0.1, 14.8]	4 (8.9%) [0.1, 18.3]
Patient with distant recurrence	8 (17.4%) [7.8, 31.4]	6 (13.3%) [5.1, 26.8]
Survival Results		
DFS Events	N = 46	N = 45
N (%)	14 (30.4%)	15 (33.3%)
Censored, n (%)	32 (69.6%)	30 (66.7%)
Q3 [95% CI]	– [68.3, –]	– [–, –]
Median DFS [95% CI]	68.3 [68.3, –]	– [53.0, –]
Q1 [95% CI]	44.0 [26.4, –]	38.5% [12.5, –]
DFS rate at 12 months [95% CI]	91.3% [78.5, 96.6]	88.9% [75.3, 95.2]
DFS rate at 24 months [95% CI]	89.1% [75.7, 95.3]	75.1% [59.5, 85.4]
DFS rate at 36 months [95% CI]	84.6% [70.3, 92.3]	75.1% [59.5, 85.4]
DFS rate at 48 months [95% CI]	72.5% [56.6, 83.4]	69.9% [53.7, 81.3]
DFS rate at 60 months [95% CI]	70.0% [53.9, 81.4]	64.3% [47.6, 76.9]
OS Events	N = 46	N = 45
N (%)	4 (8.7%)	11 (24.4%)
Censored, n (%)	42 (91.3%)	34 (75.6%)
Q3 [95% CI]	—	—
Median OS [95% CI]	—	—
Q1 [95% CI]	—	57.3 [34.0, –]
OS rate at 12 months [95% CI]	100% [100, 100]	100% [100, 100]
OS rate at 24 months [95% CI]	100% [100, 100]	93.2% [80.3, 97.7]
OS rate at 36 months [95% CI]	95.5% [83.2, 98.9]	88.4% [74.3, 95.0]
OS rate at 48 months [95% CI]	93.1% [80.0, 97.7]	78.1% [62.1, 88.0]
OS rate at 60 months [95% CI]	90.5% [76.7, 96.3]	72.7% [56.0, 83.9]

Arm A refers to 12-week bevacizumab + FOLFOX-4 then bevacizumab—5-FU—RT before TME; and arm B, bevacizumab—5-FU—RT then TME.
Abbreviations: 5-FU = 5-fluorouracil; CI = confidence interval; DFS = disease-free survival; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; OS = overall survival; Q = quadrant; RT = radiotherapy; TME = total mesorectal excision.

Figure 1 Kapan-Meier Disease-Free and Overall Survival Curves for Intention-to-Treat (ITT) Population



bevacizumab−5-FU−RT and TME for LARC may have the potential to increase survival outcomes. The role of bevacizumab cannot be established because it is combined with neoadjuvant FOLFOX-4. The use of bevacizumab−5-FU−RT before TME was associated with a high rate of anastomotic fistulas compared to the published data. Further research of neoadjuvant strategies in LARC should be encouraged. Long-term safety follow-up using standardized criteria for the definition and assessment of surgery and post-surgery complications of rectal surgery needs to be implemented.

Clinical Practice Points

- Two neoadjuvant strategies with bevacizumab were assessed in high-risk LARC.
- Bevacizumab−FOLFOX-4 then bevacizumab−5-FU−RT and TME may potentially increase survival in LARC.
- Bevacizumab−5-FU−RT only before TME was associated with a high rate of anastomotic fistulas.

Acknowledgments

Supported in part by Roche SAS France. The authors are grateful to the physicians, patients and their families who participated in this study. The authors would like to thank the study project team and Eltium for writing and editing support.

Disclosure

C.B. received honoraria and consulting fees from Roche, and sat on advisory boards from Bayer, Sanofi and Servier. G.M., F.B., J.B.B. and V.V. received honoraria from Roche. F.G. received honoraria from Lilly, Sanofi, Amgen, and Roche, and sat on advisory boards for Merck Serano, Amgen, Sanofi, and Roche. D.A. received honoraria from Roche and Astellas. M.B.A. received honoraria and consulting fees from Amgen, Merck, Sanofi, and Bayer. M.C., MI.-G., and A.T. are employees of Roche. T.A. received honoraria and played a consulting/advisory role for Roche and Sanofi, and received travel funds for Roche. The other authors have stated that they have no conflict of interest.

Supplemental Data

A supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.04.006.

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Supplemental Data

Supplemental Figure 1 Outline of Study Protocol