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

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Abstract

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 MRI-defined high risk LARC were randomized to Arm A (12-week bevacizumab + Folfox-4 then bevacizumab–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-year follow-up (FU) are reported. No comparison between the arms was planned.

Results: Overall, 91 patients (Arm A: 46; Arm B: 45) were included. Main results were presented previously. During the late FU period (>4 weeks after the surgery), 4 (8.7%) patients in Arm A and 4 (8.9%) Arm B experienced grade 3-4 adverse events related to bevacizumab, the most frequent were 2 anastomotic fistulas in Arm A and abscesses (Arm A, n=1; Arm B, n=2). At 5-year FU, 9 patients (19.6%) and 11 (24.4%) in Arms A and B developed a fistula in the year following surgery, and 2 (4.3%) in Arm A, > one year post-surgery. Most resolved before study end. 5-year DFS were 70% and 64.3% in Arms A and B, respectively. 5-year OS were 90.5% [95% CI 76.7, 96.3] in Arm A, and 72.7% [95% CI 56.0, 83.9] in Arm B.

Conclusions: Neo-adjuvant bevacizumab-Folfox-4 may have the potential to increase survival outcomes when followed with bevacizumab-5-FU-RT and TME in LARC. Bevacizumab-5-FU-RT then TME was associated with a higher rate of anastomotic fistulas than projected. Further research of neoadjuvant strategies in LARC is encouraged.

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]

Preoperative oxaliplatin/fluoropyrimidine (FP) and radiotherapy strategy with or without adjuvant chemotherapy was evaluated in several phase III trials and showed contradicting 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 adjuvant situation for stage II/III colon cancer.[11-13] The addition of oxaliplatin-based chemotherapies and bevacizumab to chemoradiotherapy is a potential solution to increase pathological response rate, disease-free survival (DFS) and overall survival (OS). Unfortunately, results for trials utilizing bevacizumab in the treatment of LARC patients remain scarce, though the studies that have been published indicate promising results in phase II trials.[14-17]

The INOVA study assessed two different multimodal therapeutic approaches with bevacizumab combined with induction chemoradiotherapy, for patients with high-risk T3 resectable rectal cancer. Interim results that included the primary endpoint of pathologic complete response (pCR) have already been published; [18] final results of the secondary endpoints including disease-free survival and overall survival, 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, 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 mid-rectum with tumor spread >5 mm into perirectal fat or T3N1-N2, and 0-1 ECOG performance status. Exclusion criteria and detailed information are available in the initial publication.[18] All patients provided informed consent before study start. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and ICH GCP and registered on www.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 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 Figure S1, while the detailed treatment plan and dosage guidelines were published previously.[18]

Assessment

For initial disease staging, patients underwent pelvic MRI and thoracoabdominal CT-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, hematological 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 endpoint was the proportion of patients achieving pCR (ypT0-N0) according to local review. Secondary efficacy endpoints included compliance, tumor downstaging (ypT0-pT2), recurrence rate, and 5-year DFS and OS, while the incidences of adverse events (AEs) and serious AEs (SAEs) were safety endpoints.

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 (ITT) population per treatment arm, which included all randomized and treated patients. DFS and OS from treatment onset were analyzed using 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 (see Table 2). AEs were graded and classified according to the Common Terminology Criteria for Adverse Events version 3.0 (CTC AE v 3.0) and the Medical Dictionary for Regulatory Activities (MedDRA version 18.1). Exploratory analyses of safety were performed for post-surgery 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, via a logistic regression model. No comparison between the arms was planned.

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 which completed the study: 34 patients (73.9%) in Arm A and 26 (57.8%) in Arm B.[18] The 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 (n=12 in Arm A; n=19 in Arm B). The main reasons were lost to follow-up (n=6 in each arm) and death (n=4 in Arm A; n=11 in Arm B). Patient and disease characteristics are presented in Table 1. 18 (39%) and 24 (53.3%) of the patients included in ARM A and B respectively received an adjuvant chemotherapy (FOLFOX/XELOX for 17 and 22 patients in ARM A and B).

Safety

The safety analysis including the 8 weeks period following rectal surgery was previously reported.[18] The final analysis of the clinical outcomes collected during the 5 year follow-up period is reported hereafter with specific emphasis on AEs that occurred during the "early" post-surgery period (date between the 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 start of the study until 8-weeks post-surgery. Incidence of adverse events 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 bevacizumab-related in 4 patients (8.7%) including anastomotic fistula (n=2), pelvic abscess (n=1), 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 deaths (6.5%) due to disease progression and 1 death (2.2%) from lung cancer.

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). Four events were bevacizumab-related grade 3-4 AEs 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 a single patient each (2.2%), and three-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 a 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 following 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 three years following the surgery and the other patient had a pelvic abscess complicated by fistula more than 2 years after rectal surgery.

Efficacy

The primary end-point (pCR) and tumor downstaging were described in the previous publication.[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% CI 10.9, 36.4]), 8 of whom (17.4% [95% CI 7.8, 31.4]) had a distant recurrence and 3 (6.5% [95% CI 0.1, 14.8]) had a 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 a 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, 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. Altogether, 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 AIO-4 trial and 8.8% in the PRODIGE 02 trial[5,19] and 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 INOVA trial confirmed that exposition to a 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 in comparison with 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 III ACCORD 12 (72.7%), STAR-01 (74.2%), CAO/ARO/AIO-04 (75.9%) and PETACC-6 (75.4%),[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.[6,8] The combination of oxaliplatin

and FP was also assessed as a neoadjuvant sequence in phase II studies before FP-RT.[25-28] DFS and OS results, when assessed were inconsistent, showing no impact or promising results. In the phase II trials of neoadjuvant oxaliplatin, the estimated 5-year DFS of 62%[29] and 63.1%[27] were close but slightly lower to those of Arm A of INOVA.

The 5-year survival rate of 90.5% in Arm A of INOVA compares favorably with those of oxaliplatin-based chemoradiotherapy arm in the phase III STAR-01 (84.4%) and NSABP R-04 (81.3%). Similar trend in phase II trials with this combination was observed for estimated 5-year survival rate ranging from 66.7% to 80%.[25, 27, 39, 30]

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

Altogether, 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 I/II trials.[14,15,31-35] Actuarial DFS rate with such strategy was reported by Crane et al. to be 77.3% at 2 years. No OS outcomes or survival rates were reported in these studies.

One of the main strength of INOVA trial was a long term follow-up with the monitoring of 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 the surgery) were reported for 6.6% of Arm A patients and 4.4% of Arm B patients. The incidence of postoperative fistula is about two times higher when compared with a maximum of 8% observed after bevacizumab-oxaliplatin-FP-RT and surgery for LARC in clinical trials.[36] Due to differences in post-surgery 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 post-surgery complications should be included in trials. Other parameters such as preparation for surgery, surgery procedures and others need to be taken into account. The incidence of fistula and anastomotic leakage varies substantially between phase III trials. In the French ACCORD 12/0405-Prodige 2 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 following surgery was 15%.[37] In a meta-analysis including 14 randomized trials conducted by the Cochrane Collaboration, the rate of anastomotic leakage following laparoscopic or open TME for rectal cancer was estimated at 7.7% and 6.3% respectively.[38] Asteria et al reported a rate of 15.2% of anastomotic leakage in 520 patients who had undergone low anterior resection in 2005.[39] A rate of 12.6% of anastomotic leakage was reported in a series of 2,085 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 II INOVA study reveals that induction bevacizumab–Folfox-4 followed by bevacizumab–5-FU–RT and TME for locally advanced rectal cancer may have the potential to increase survival outcomes. The role of bevacizumab cannot be established because combined with neo-adjuvant FOLFOX4. The use of bevacizumab–5-FU–RT before TME was associated with a high rate of anastomotic fistulas compared to known 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.

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Conflict of interest Disclosure

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Tables

Table 1: Patients and disease characteristics – ITT (*n*=91)

	Arm A ***n*=46**	**Arm B** ***n*=45**
Median age, years (range)	60.6 (40.2 ; 73.7)	60.1 (24.3 ; 76.0)
Male *	31 (67.4%)	30 (66.7%)
ECOG performance status at selection*		
0	40 (87.0%)	38 (84.4%)
1	6 (13.0%)	7 (15.6%)
Histological 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%)
Radiological TNM stage[a] *		
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 to 3	27 (58.7%)	30 (66.7%)
≥4	7 (15.2%)	7 (15.6%)
Vascular invasion (embolus) - MRI		
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%)

* n (%); [a] pelvic MRI + thoracoabdominal CT-Scan

Table 2: Summary of emerging adverse events by period according to treatment arm – Safety population (*n*=91)

	n events	n pts (%)	n events	n pts (%)
During the 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 the post-surgery 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 the 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%)

*Hypertension; gastrointestinal perforation; fistulas; wound healing complication; congestive heart failure; bleeding / hemorrhage; thromboembolism events (venous and arterial); proteinuria; reversible posterior leukoencephalopathy syndrome (RPLS)

Table 3: Grade 3-4 bevacizumab-related adverse events according to treatment arm during the entire study period – Safety population

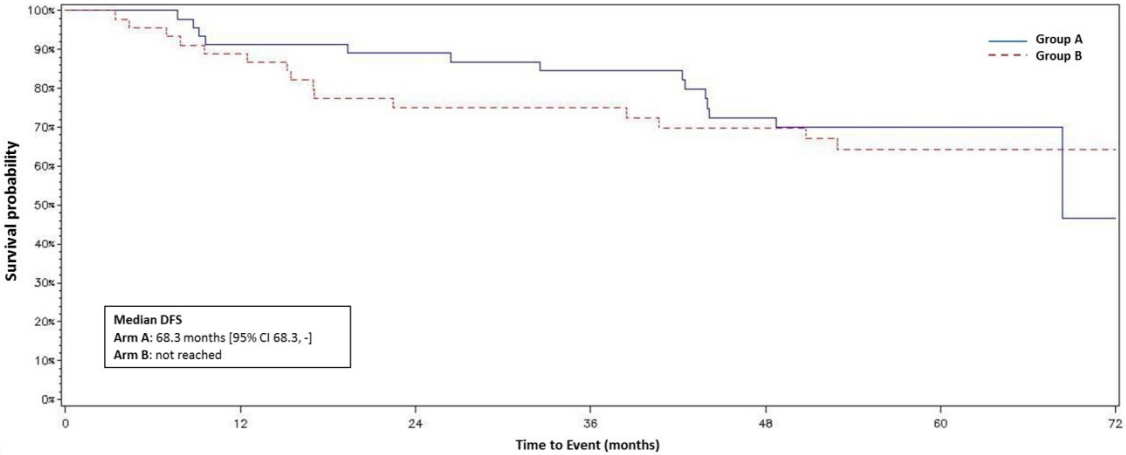
	Arm A (N=46)		Arm B (N=45)		Total (N=91)	
SOC / preferred term	**n**	**%**	**n**	**%**	**n**	**%**
Total	19	41.3	11	24.4	30	33.0
Injury, poisoning and procedural complications	6	13.0	7	15.6	13	14.3
Anastomotic fistula	3	6.5	5	11.1	8	8.8
Wound dehiscence	0	0.0	2	4.4	2	2.2
Catheter site infection	1	2.2	0	0.0	1	1.1
Gastrointestinal anastomotic complication	1	2.2	0	0.0	1	1.1
Intestinal anastomosis complication	1	2.2	0	0.0	1	1.1
Wound complication	0	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	0.0	1	2.2	1	1.1
Embolism venous	0	0.0	1	2.2	1	1.1
Phlebitis deep	1	2.2	0	0.0	1	1.1
Shock haemorrhagic	1	2.2	0	0.0	1	1.1
Thrombophlebitis	1	2.2	0	0.0	1	1.1
Venous thrombosis	0	0.0	1	2.2	1	1.1
Gastrointestinal disorders	5	10.9	2	4.4	7	7.7
Diarrhoea	2	4.3	0	0.0	2	2.2
Colitis ischaemic	0	0.0	1	2.2	1	1.1
Enteritis	1	2.2	0	0.0	1	1.1
Gastrointestinal perforation	1	2.2	0	0.0	1	1.1
Intra-abdominal haematoma	1	2.2	0	0.0	1	1.1
Nausea	1	2.2	0	0.0	1	1.1
Rectal haemorrhage	0	0.0	1	2.2	1	1.1
Vomiting	1	2.2	0	0.0	1	1.1
Infections and infestations	1	2.2	3	6.7	4	4.4
Abdominal wall abscess	0	0.0	1	2.2	1	1.1
Pelvic abscess	1	2.2	0	0.0	1	1.1
Perineal abscess	0	0.0	1	2.2	1	1.1
Postoperative abscess	0	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	0.0	1	1.1
Female genital tract fistula	0	0.0	1	2.2	1	1.1
Rectoprostatic fistula	1	2.2	0	0.0	1	1.1
Vaginal fistula	1	2.2	0	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	0.0	2	2.2
Neutrophil count decreased	2	4.3	0	0.0	2	2.2
Metabolism and nutrition disorders	2	4.3	0	0.0	2	2.2
Decreased appetite	2	4.3	0	0.0	2	2.2
Musculoskeletal and connective tissue disorders	1	2.2	0	0.0	1	1.1
Osteonecrosis	1	2.2	0	0.0	1	1.1
Nervous system disorders	1	2.2	0	0.0	1	1.1
Ruptured cerebral aneurysm	1	2.2	0	0.0	1	1.1
Renal and urinary disorders	0	0.0	1	2.2	1	1.1
Proteinuria	0	0.0	1	2.2	1	1.1

Table 4: Overview of efficacy – Key results – ITT population

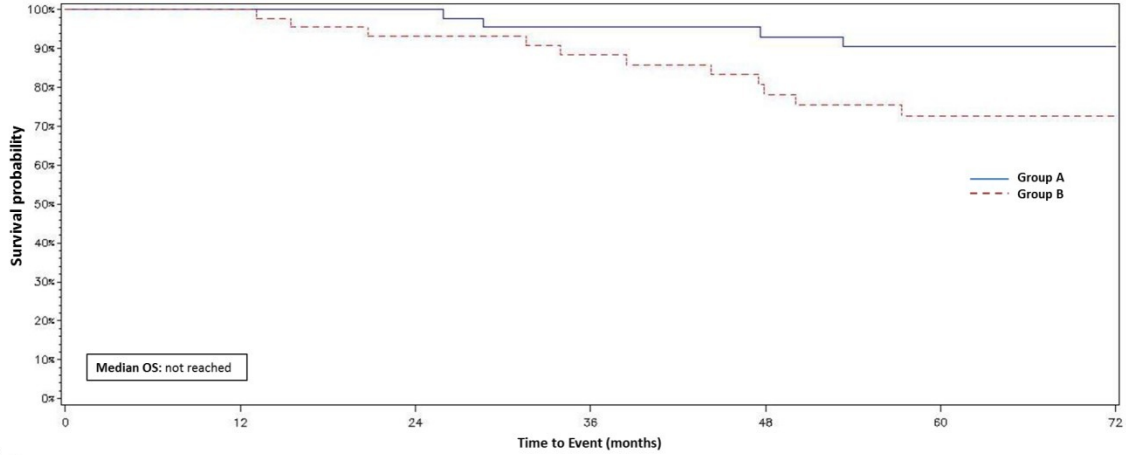
	Arm A N=46	**Arm B N=45**
	n (%) - [95%CI]	n (%) - [95%CI]
	N=42	N=44
Sterilization of the tumor piece (Local review)	10 (23.8%) - [12.1, 39.5]	5 (11.4%) - [3.8, 24.6]
Binomial test	0.015	0.906
	N=41	N=44
Downstaging (Local review)	27 (65.9%) - [51.3, 80.4]	24 (54.5%) - [39.8, 69.3]
	N=45	N=44
Adherence/infiltration of the 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 a recurrence	10 (21.7%) - [10.9, 6.4]	9 (20.0%) - [9.6, 34.6]
Patient with a local recurrence	3 (6.5%) - [0.1, 14.8]	4 (8.9%) - [0.1, 18.3]
Patient with a distant recurrence	8 (17.4%) - [7.8, 31.4]	6 (13.3%) - [5.1, 26.8]
SURVIVAL RESULTS		
	N=46	N=45
DFS Events, 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]
	N=46	N=45
OS events, 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]

Figures

Figure 1: Disease-free survival curve and Overall survival curve according to the Kaplan-Meier method – ITT population



Time at risk / Events	0	12	24	36	48	60	72
Group A	46/0	42/4	40/5	36/7	29/12	25/13	0/14
Group B	45/0	40/5	31/11	30/11	26/13	22/15	0/15



Time at risk / Events	0	12	24	36	48	60	72
Group A	46/0	46/0	45/0	41/2	38/3	34/4	0/4
Group B	45/0	45/0	39/3	36/5	30/9	26/11	0/11