European Journal of Cancer 110 (2019) 32–41

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Total neoadjuvant approach with FOLFOXIRI plus bevacizumab followed by chemoradiotherapy plus bevacizumab in locally advanced rectal cancer: the TRUST trial

Gianluca Masi [a,j,*], Caterina Vivaldi [a,j], Lorenzo Fornaro [a], Sara Lonardi [b], Piero Buccianti [c], Aldo Sainato [d], Lorenzo Marcucci [e], Angelo Martignetti [f], Emanuele Damiano Luca Urso [g], Maura Castagna [h], Gabriella Fontanini [h], Francesca Bergamo [b], Gianna Musettini [a], Lucio Urbani [c], Elisa Sensi [h], Riccardo Balestri [c], Sabrina Montrone [d], Francesco Pasqualetti [d], Chiara Cremolini [a,j], Antonello Di Paolo [i], Vittorina Zagonel [b], Alfredo Falcone [a,j]

[a] *Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Via Roma, 56126 Pisa, Italy*
[b] *Unit of Medical Oncology 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto, IRCCS, Via Luigi Pellizzo, 14, 35128 Padua, Italy*
[c] *Unit of General Surgery, Azienda Ospedaliero-Universitaria Pisana, Via Pietro Trivella, 56124 Pisa, Italy*
[d] *Division of Radiation Oncology, Azienda Ospedaliero-Universitaria Pisana, Via Roma, 56126 Pisa, Italy*
[e] *Division of Medical Oncology, Pontedera Hospital, Azienda Toscana Nord Ovest, Via Roma, 147, 56025 Pontedera, Italy*
[f] *Dipartimento oncologico usl sud-est toscana-area senese, Località Campostaggia s.n.c. 53036 Poggibonsi, Italy*
[g] *First Surgical Clinic, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Via Giustiniani 2, 35128 Padua, Italy*
[h] *Department of Surgical, Medical, Molecular Pathology and Critical Care, University of Pisa, Via Roma, 56126 Pisa, Italy*
[i] *Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 56126 Pisa, Italy*
[j] *Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, 56126 Pisa, Italy*

Received 16 October 2018; received in revised form 31 December 2018; accepted 6 January 2019
Available online 7 February 2019

* *Corresponding author*: Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, 56126 Pisa, Italy. Fax: +39 050 992069.

E-mail addresses: gl.masi@tin.it (G. Masi), caterinavivaldi@gmail.com (C. Vivaldi), lorenzo.fornaro@gmail.com (L. Fornaro), sara.lonardi@iov.veneto.it (S. Lonardi), p.buccianti@ao-pisa.toscana.it (P. Buccianti), aldo.sainato@alice.it (A. Sainato), lorenzo.marcucci@uslnordovest.toscana.it (L. Marcucci), angelo.martignetti@uslsudest.toscana.it (A. Martignetti), edl.urso@unipd.it (E.D. Luca Urso), maura.castagna@med.unipi.it (M. Castagna), gabriella.fontanini@med.unipi.it (G. Fontanini), francesca.bergamo@iov.veneto.it (F. Bergamo), g.musettini@gmail.com (G. Musettini), lucio.urbani.68@gmail.com (L. Urbani), elisasensi@tin.it (E. Sensi), r.balestri@ao-pisa.toscana.it (R. Balestri), sabri84na@gmail.com (S. Montrone), francep24@hotmail.com (F. Pasqualetti), chiaracremolini@gmail.com (C. Cremolini), antonello.dipaolo@med.unipi.it (A. Di Paolo), vittorina.zagonel@iov.veneto.it (V. Zagonel), alfredo.falcone@med.unipi.it (A. Falcone).

https://doi.org/10.1016/j.ejca.2019.01.006

KEYWORDS
Bevacizumab;
Chemotherapy;
FOLFOXIRI;
Locally advanced rectal cancer;
Radiotherapy

Abstract ***Background:*** Neoadjuvant chemoradiotherapy (CRT) in locally advanced rectal cancer (LARC) does not achieve effective control of distant metastases. Induction chemotherapy is a promising strategy, and bevacizumab (BV) could improve the results of CRT. 5-Fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) plus BV is a treatment option in metastatic colorectal cancer. We evaluate feasibility and efficacy of neoadjuvant treatment comprising induction FOLFOXIRI plus BV followed by CRT with fluoropyrimidines plus BV.

Methods: In this phase II single-arm trial, patients node-positive or clinical T4 or high-risk T3 LARC underwent 6 cycles of induction FOLFOXIRI plus BV, followed by CRT (50.4 Gy plus concomitant capecitabine) and BV (5 mg/kg on days 1, 15 and 28). Surgery was planned 8 weeks after completion of CRT. Primary end-point was 2-year disease-free survival (DFS).

Results: We enrolled 49 patients: All but one (withdrewing consent after enrolment) were included in the per-protocol analyses. The study met its primary end-point: 36 patients were free of recurrence at 2 years (2-y DFS: 80.45%, 95% confidence interval [CI]: 78.79–82.10). Forty-four patients underwent surgery; pathologic complete response rate was 36.4%. Forty-six patients completed induction: neutropenia (41.6%) and diarrhoea (12.5%) were main G3/4 toxicities. Forty-five patients received CRT, but the protocol was amended and the capecitabine schedule during CRT was slightly modified after 13 patients due to the incidence of G3 hand-foot syndrome and proctitis (23.1%). After amendment, no severe events during CRT were reported.

Conclusions: FOLFOXIRI plus BV followed by CRT plus BV is feasible and active. Results in terms of DFS suggest that this strategy may improve distant disease control in LARC.

1. Introduction

Rectal cancer represents a major need in clinical oncology as it covers one-third of all large bowel tumours [1]. Clinical stage II-III disease is generally referred to as locally advanced rectal adenocarcinoma (LARC): Over the last decade, several trials established neoadjuvant fluoropyrimidine-based chemoradiotherapy (CRT) followed by resection with total mesorectal excision (TME) as the standard of care [2]. This approach has led to a significant reduction of local recurrences but did not impact long-term outcome measures, with a progression-free survival (PFS) rate of 65%–70% at 3 years [3].

In the last few years, several attempts have been made to improve the results achieved with standard treatments, mainly by the addition of oxaliplatin to fluoropyrimidine-based CRT or by the administration of post-operative or induction (i.e. before neoadjuvant CRT) chemotherapy (CT) with more modern regimens. Randomised trials testing different strategies did not demonstrate a substantial benefit over standard CRT [3].

Interesting results have been reported with induction CT with capecitabine plus oxaliplatin [4,5]. Clinical trials available so far demonstrate that this strategy does not impair the delivery of neoadjuvant radiotherapy (RT), improves the exposure to systemic CT and is associated with a better safety profile compared with adjuvant CT. This possibly results in earlier and higher control of micrometastatic disease.

In metastatic colorectal cancer, a triplet regimen with 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) proved to be superior to a standard doublet [6] and confirmed its efficacy when added to bevacizumab (BV) [7]. FOLFOXIRI plus BV could represent an interesting therapy as induction strategy in LARC, in the attempt to maximise shrinkage of primary tumour and increase chances of eradication of distant disease possibly with an improved compliance if administered before neoadjuvant CRT.

Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis and resistance to RT [8]. Concomitant BV could therefore enhance the activity of RT by inhibiting VEGF-mediated signalling, increasing tumour blood flow, reducing interstitial pressure and decreasing mean vascular density [9]. BV combined with neoadjuvant CRT preliminarily confirmed signals of improved activity [9].

We conducted the phase II TRUST (TRiplet plus bevacizUmab followed by radiotherapy pluS bevacizumab in recTal cancer) study to evaluate the feasibility and efficacy of a neoadjuvant treatment comprising induction FOLFOXIRI plus BV followed by CRT with 5-fluorouracil or capecitabine plus BV and TME. To our knowledge, this is the first trial testing triplet CT in this setting and also the first evaluating preoperative BV with a more intensive induction CT.

2. Methods

2.1. Patients

Eligible patients had histologically proven locally advanced, resectable rectal adenocarcinoma defined by the presence of at least one of the following features: *i*) high-risk clinical T3 tumour, defined by magnetic resonance imaging (MRI) criteria of circumferential radial margin threatened or involved (i.e. tumour extending to within 1 mm of or beyond the mesorectal fascia); *ii*) lower third (i.e. $\leq$6 cm from anal verge); *iii*) tumour extending $\geq$5 mm into perirectal fat; *iv*) clinical T4 tumour; *v*) clinical stage III disease, with the definition of a clinically positive node being any node $\geq$1.0 cm at MRI. Distal border of the tumour had to be located <12 cm from the anal verge. We excluded patients with distant metastases. Other inclusion criteria were as follows: age 18–75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2 if age <70 years and = 0 if age 71–75 years. The study was conducted in accordance to the declaration of Helsinki and Good Clinical Practice guidelines. Approval was gained from the institutional review board of all participating centres, and written informed consent was obtained from each patient.

The study is registered on EUDRACT (2011-003340-45) and ClinicalTrials.gov (NCT03085992).

2.2. Procedures

Baseline staging: colonoscopy, contrast-enhanced computed tomography of chest and abdomen, endorectal ultrasound with rigid endoscope and contrast-enhanced pelvic MRI.

Neoadjuvant therapy: intravenous BV 5 mg/kg over 30 min, followed by irinotecan 165 mg/m^2 over 1 h, followed by oxaliplatin 85 mg/m^2 and folinate 200 mg/m^2 concomitantly over 2 h on day 1, followed by 5-fluorouracil 3200 mg/m^2 as a 48-h continuous infusion (ci) starting on day 1; cycles repeated every 2 weeks for 6 cycles.

Concomitant CRT plus BV: induction therapy was followed after 3 weeks by external-beam RT with 50.4 Gy in 28 daily fractions (over 5.5 weeks) with concomitant capecitabine 825 mg/m^2/bid for 7 days *per* week or 5-fluorouracil 225 mg/m^2/day ci. BV 5 mg/kg over 30 min was administered on day 1 of RT and then every 2 weeks (for up to 3 cycles). After the enrolment of 13 patients, the capecitabine dose was reduced to 800 mg/m^2/bid for 5 days *per* week.

Surgery: TME was performed between 7 and 9 weeks after the end of CRT plus BV. The choice between abdominoperineal and anterior resection was at the surgeon's discretion. No additional treatment was administered after surgery.

Treatment plan is summarised in Supplementary Figure 1.

Safety was assessed by the NCI Common Toxicity Criteria for Adverse Events, version 4.03.

Objective response rate (RR) was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1) by computed tomography of the thorax, abdomen and pelvis repeated after induction treatment and after at least 4 weeks from the end of CRT (when an MRI scan of the pelvis was also performed).

Histopathology was assessed as described by Quirke *et al.* [10], and pathologic Complete Response (pCR) was defined as the absence of residual tumour cells detected in the resected specimen. Pathologic features were assessed by tumour regression grade (TRG) according to Dworak *et al.* [11]. Follow-up procedures included testing for carcinoembryonic antigen every 3 months for the first year, every 6 months for the second and third years and annually thereafter. A total-body contrast-enhanced computed tomography was performed at 12, 24 and 36 months, whereas MRI was performed only if clinically indicated.

2.3. Translational analyses

Paraffin-embedded tissues of primary tumour and blood samples were stored for molecular analyses. A secondary end-point was the assessment of treatment outcome (DFS and pathological response) in relation to mutational status of *KRAS* (codons 12, 13, 59, 61, 117 and 146), *NRAS* (12, 13, 59, 61, 117 and 146) and *BRAF* (codons 594, 600 and 601) genes evaluated at the Unit of Pathology, University of Pisa, as previously described [12].

As *per* routine practice at the coordinating centre, patients were screened for common *DPD* variants (IVS14+1G > A, 2846A > T, 1679T > C) [13]. Moving from the preclinical role of methylenetetrahydrofolate reductase (MTHFR) in folate metabolism [14], we retrospectively correlated *MTHFR* single-nucleotide polymorphisms (SNPs) with adverse events during CRT.

Genomic DNA was obtained from whole blood using a commercial kit (QIAamp DNA Blood Mini Kit, Qiagen, Milan, Italy). *MTHFR* SNPs c.677C > T (rs1801133) and c.1298A > C (rs1801131) were evaluated by specific TaqMan assay, from Applied Biosystems (Life Sciences, Milan, Italy) on an ABI Prism 7900HT Sequence Detection System (Life Sciences). Genotypes were automatically identified using the Allelic Discrimination Sequence Detector Software (Life Sciences) [15]. The analyses were performed in duplicate, and concordance was absolute. Frequency of alleles, genotypes (according to Hardy–Weinberg law) and haplotypes (with linkage disequilibrium analysis) were obtained as described elsewhere [15].

2.4. Statistical considerations

TRUST was a phase II, single-arm, multicenter study. The primary end-point was DFS at 2 years, defined as the time from the start of treatment to local or distant progression, second primary tumour or death, whichever occurred first. Available data at the time of study design had shown that the 2-year DFS of patients with LARC treated with CRT and TME is about 65%. We regarded a 2-year DFS rate of 80% as of interest (p1) and a 2-year DFS of 65% as unacceptable (p0). According to the Fleming's single-stage design, considering an alpha error of 0.05 and a drop out of 10%, with a sample size of 49 patients, the study would have had an 80% power to reach the primary objective if 34 or more patients were free of progression at 2 years. Secondary end-points included the rate of clinical objective responses, rate of pCR and safety.

3. Results

3.1. Patients

Between April 2012 and May 2015, 49 patients were enrolled at 4 Italian centres. One patient withdrew consent after enrolment and received neoadjuvant CRT with capecitabine; hence, 48 patients are considered in the *per*-protocol analyses presented in this study. Baseline characteristics are summarised in Table 1.

3.2. Treatment

Fig. 1 shows patients' progress through the trial. Forty-six out of 48 patients (95.8%) considered in the *per*-protocol analyses received all 6 cycles of induction therapy, and 45 patients (93.7%) completed CRT plus BV: All patients received 50.4 Gy as planned. Median dose intensity for CT and BV during induction therapy was >90% of that planned for all agents (5-fluorouracil: 91.9%; oxaliplatin: 92.3%; irinotecan: 91.6%; BV: 92.7%).

Forty-four patients (91.7%) underwent surgery after completing treatment, whereas 1 was operated on primary tumour after induction therapy only. One patient experienced early systemic progression after the end of CRT and died without receiving any further therapy. Median time from the end of CRT to surgery was 66 days (range, 46–101). Surgery consisted in anterior resection of the rectum in 39 patients (88.6%) and abdominoperineal resection in 3 (7%). Two patients refused standard procedures and were allowed to undergo intersphincteric resection with TME and transanal excision (1 patient each [2.2%]). Radical (R0) resection was achieved in 97.8% of cases.

Table 1
Baseline patient demographics and clinical characteristics.

Characteristic	No. (48)	%
Gender		
Male	31	64.6
Female	17	35.4
Age, years		
Median	53	
Range	30–74	
ECOG performance status		
0	47	97.9
1	1	2.1
Clinical tumour category		
T3	31	64.6
T4	17	35.4
Clinical nodal category		
N0	8	16.7
N1-2	40	83.3
Clinical TNM stage		
II	8	16.7
III	40	83.3
Distance from anal verge		
>10 cm	3	6.25
5–10 cm	21	43.75
<5 cm	24	50
KRAS exon 2-3-4 mutations		
Wild-type	26	54.2
Mutant	17	35.4
Not available	5	10.4
NRAS exon 2-3-4 mutations		
Wild-type	39	81.3
Mutant	4	8.3
Not available	5	10.4
BRAF codon 600 mutation		
Wild-type	40	83.3
Mutant	3	6.3
Not available	5	10.4
MTHFR c.667C > T SNP		
CC	13	27.1
CT	24	50
TT	6	12.5
Not available	5	10.4
MTHFR c.1298A > C SNP		
AA	12	25
AC	26	54.2
CC	5	10.4
Not available	5	10.4

Abbreviations: No., number; %, percent; SNP, single-nucleotide polymorphism; ECOG, Eastern Cooperative Oncology Group; TNM, tumour-node-metastasis.

3.3. Activity

At a median follow-up of 37.6 months, 12 patients experienced disease progression, either as locoregional recurrence only (2 patients) or distant spreading (8 patients) or both (2 patients) and median DFS was not reached (Fig. 1). Thirty-six patients were free of progression at 2 years, for a 2-year DFS of 80.45% (95% CI: 78.79–82.10) (Fig. 2).

Objective RR was 82.6% after induction and 88.9% after CRT plus BV (Supplementary Table 1). A pCR was reached in 16 (36.4%) out of 44 patients (Supplementary Table 2). Overall, pathological

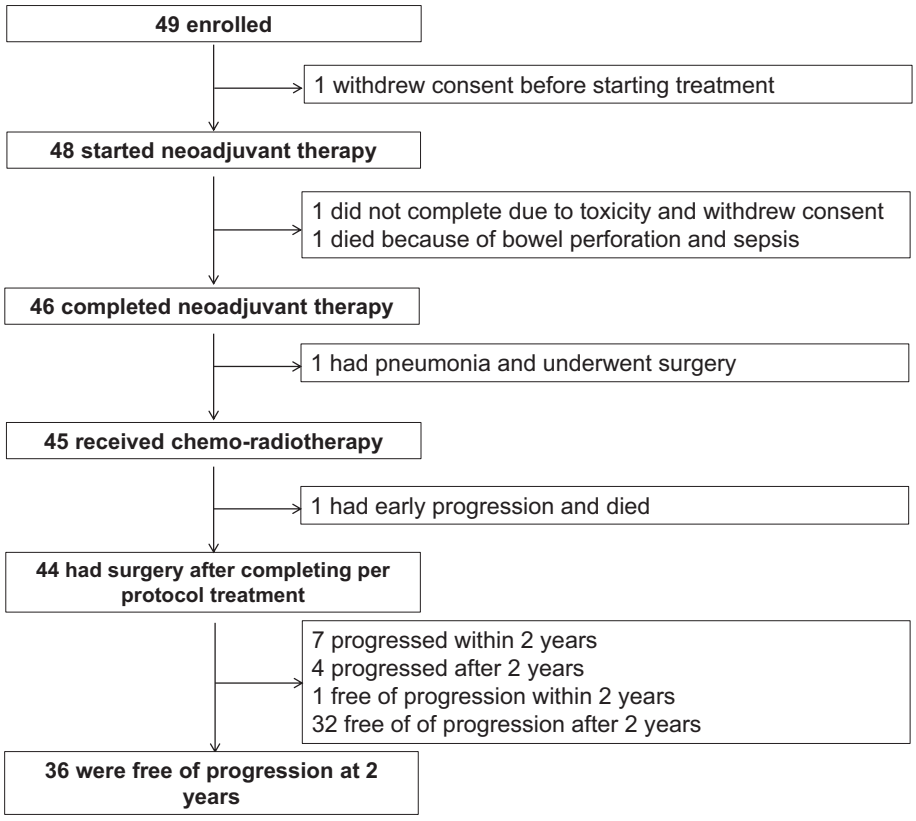

Fig. 1. Consort diagram.

downstaging was obtained in 26 (65%) patients (Supplementary Table 3).

3.4. Safety

Toxicities reported during induction treatment are summarised in Table 2. Two patients treated before amendment did not complete therapy: 1 patient died due to bowel perforation and sepsis related to study treatment after the first cycle of FOLFOXIRI plus bevacizumab, and 1 patient discontinued induction treatment after acute kidney injury (followed by complete recovery). Another patient had pneumonia at the end of induction and underwent immediate surgery.

Before amendment, a high rate of grade (G) 3 diarrhoea, mucositis and hand-foot syndrome (HFS) was reported during CRT (Table 2). After amendment, all patients completed CRT with few G3 toxicities (Table 2).

Early post-surgical complication rate was 32%, with 18% (8 patients) of anastomotic dehiscences. Two months after surgery, all these complications recovered and none required reintervention.

Long-term adverse events were reported in 9 out of 44 resected patients. In particular, pelvic pain was reported in 6.6% of patients; incidence of chronic diarrhoea, constipation and sexual dysfunction was 4.5%; fecal incontinence, urinary incontinence and urinary frequency were reported in 2.2% of patients.

3.5. Molecular analyses

RAS-BRAF analyses were performed in 43 patients. There was insufficient tissue in 5 patients (as a result of pCR, tumour regression or inadequate tumour tissue in pretreatment biopsy). Results are summarised in Table 1. Neither *RAS* nor *BRAF* status was associated with DFS ($p = 0.75$ and $p = 0.74$, respectively) or pCR ($p = 0.74$ and $p = 1.000$, respectively).

3.6. Pharmacogenetic variant analyses

None of the enrolled patients had *DPYD* variants associated with increased toxicity from fluoropyrimidines. Results of *MTHFR* SNPs are available for 43 patients, of whom 40 completed treatment (Table 1). Minor allele frequency was 0.419 for both c.677C > T c.1298A > C *loci*, and their genotype distribution did not deviate from Hardy–Weinberg equilibrium. Furthermore, the investigated *loci* were in linkage disequilibrium ($D' = 1.000$, $r^2 = 0.518$).

MTHFR c.1298A > C seems to be significantly related to G3-4 diarrhoea, mucositis and HFS both among patients treated before protocol amendment and in the entire study population ($p = 0.037$)

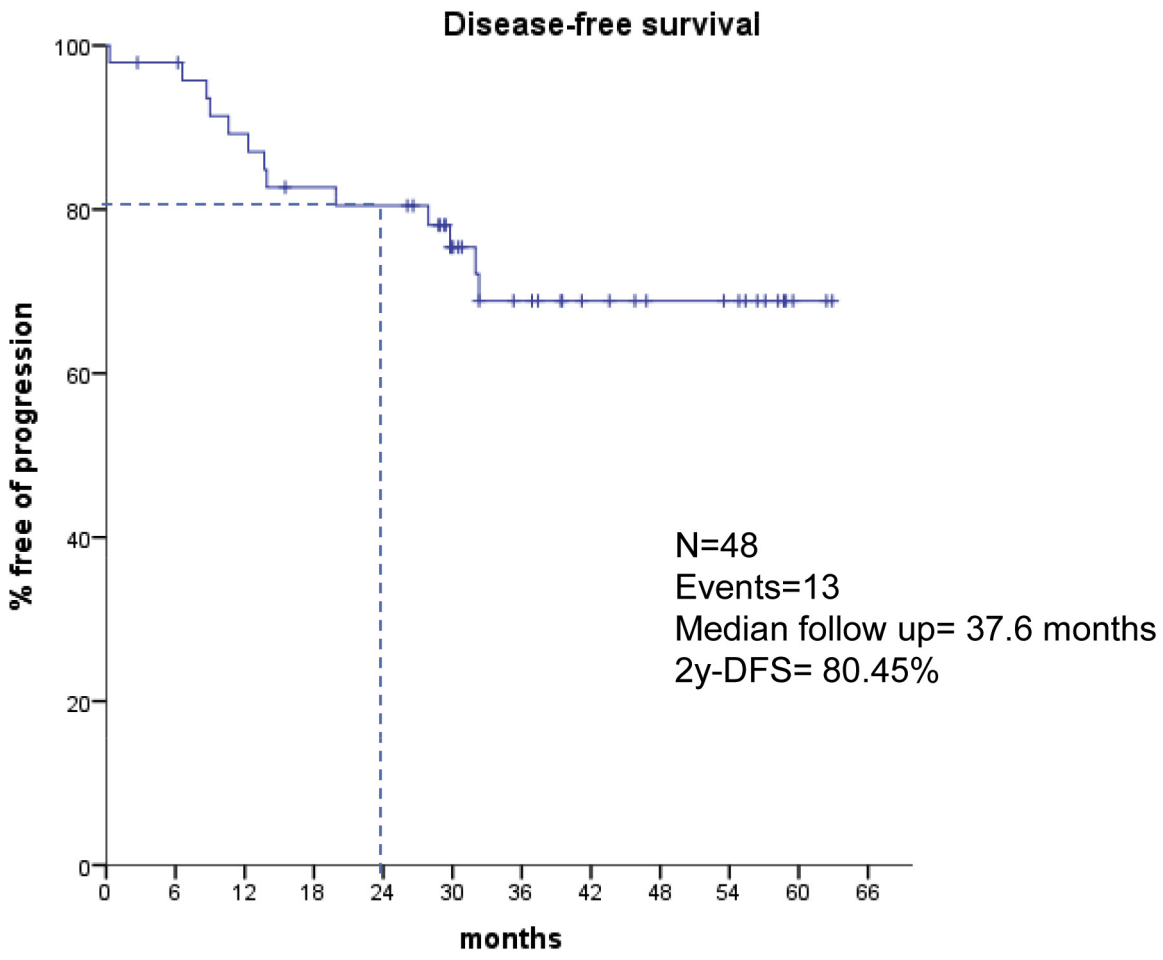

Fig. 2. Disease-free survival (DFS).

(Supplementary Table 4). Only a trend towards significance was observed for the association of c.677C > T SNP and severity of toxicities.

4. Discussion

TRUST trial met its primary end-point with a DFS rate at 2 years of 80.45%, suggesting potential effects of this strategy against distant disease. Furthermore, the study demonstrates that an intensive induction therapy is feasible with a toxicity rate consistent with the safety profile previously reported in metastatic colorectal cancer [7]. Most of the enrolled patients (89.8%) were able to complete the program of a total neoadjuvant approach followed by surgery, confirming that the strategy of administering systemic therapy before CRT maximises exposure to active agents (as proved by the dose intensity above 90% for all agents) without compromising safety.

Pathologic complete response has been largely used as an early end-point in rectal cancer trials, although its role of surrogate of overall survival (OS) in this setting is controversial [16]. In TRUST, results in terms of pCRs (36.4%) are interesting [3], and considering that most of the enrolled patients had T4 and/or N+ disease (recognised poor prognostic features in LARC), the TRUST strategy resulted in even more valuable results in terms of pCR and DFS. In our opinion, alternative end-points to better estimate the treatment impact on long-term survival should be developed in non-metastatic rectal cancer. Therefore, for the present trial, we chose DFS as a primary end-point. After induction treatment, CRT was associated with a slightly higher-than-expected mucocutaneous toxicity rate, mainly attributable to concomitant capecitabine and possibly due to the accumulation of intracellular folates during induction CT. Of note, the adjusted capecitabine schedule (800 mg/m^2/bid for 5 days *per* week) was superimposable with that used in a recent randomised study [17], and in our trial, it did not seem to impair CRT activity (pCRs before and after amendment: 38.5% and 31.4%, respectively).

Susceptibility to fluoropyrimidines might be related to individual differences in folate metabolism [18], and different studies have shown increased toxicity with capecitabine administered after fluorouracil and leucovorin, suggesting a sequence-specific interaction [14,19].

Table 2
Toxicity during induction therapy with FOLFOXIRI plus bevacizumab and during chemoradiotherapy plus bevacizumab (before and after amendment).

Induction therapy					
Adverse event	No. 48 (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Anaemia	32 (67)	3 (6)	–	–	35 (73)
Thrombocytopenia	9 (19)	–	1 (2)	–	10 (21)
Neutropenia	5 (10)	13 (27)	11 (23)	9 (19)	38 (79)
Febrile neutropenia	–	–	–	2 (4)	2 (4)
Nausea	23 (48)	13 (27)	–	–	36 (75)
Vomiting	8 (17)	4 (8)	–	–	12 (25)
Diarrhoea	17 (35)	9 (19)	4 (8)	2 (4)	32 (67)
Hand-foot syndrome	4 (8)	5 (10)	–	–	9 (19)
Stomatitis	17 (35)	8 (16)	2 (4)	–	27 (57)
Rectal bleeding	1 (2)	2 (4)	–	–	3 (6)
Asthenia	13 (27)	12 (25)	3 (6)	–	28 (58)
Hypertension	5 (10)	–	1 (2)	–	6 (12)
Neurotoxicity	25 (52)	7 (15)	–	–	32 (67)
Aminotransferases elevation	–	–	1 (2)	–	1 (2)
Rectovaginal fistula	–	–	1 (2)	–	1 (2)
Proctitis	3 (6)	2 (4)	–	–	5 (10)

Concomitant chemoradiotherapy								
Adverse event	Before amendment: No. 13 (%)				After amendment: No. 32 (%)			
	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total
Anaemia	9 (69)	–	–	9 (69)	15 (47)	–	–	15 (47)
Neutropenia	6 (46)	–	–	6 (46)	13 (41)	5 (16)	–	18 (56)
Thrombocytopenia	5 (38)	–	–	5 (38)	9 (28)	–	–	9 (28)
Hand-foot syndrome	–	6 (46)	3 (23)	9 (69)	7 (22)	2 (6)	–	9 (28)
Neurotoxicity	2 (15)	3 (23)	–	5 (38)	11 (34)	–	–	11 (34)
Stomatitis	–	–	–	–	1 (3)	–	–	1 (3)
Hypertension	1 (8)	2 (15)	–	3 (23)	1 (3)	–	–	1 (3)
Nausea	2 (15)	–	–	2 (15)	7 (22)	–	–	7 (22)
Vomiting	1 (8)	–	–	1 (8)	2 (6)	–	–	2 (6)
Astenia	6 (46)	4 (31)	1 (8)	11 (85)	17 (53)	3 (9)	–	20 (62)
Cystitis	1 (8)	5 (38)	–	6 (46)	9 (28)	2 (6)	–	11 (34)
Radiation dermatitis	7 (54)	5 (38)	1 (8)	13 (100)	16 (50)	6 (19)	–	22 (69)
Diarrhoea	4 (31)	2 (15)	2 (15)	8 (62)	18 (56)	2 (6)	–	20 (62)
Rectal bleeding	3 (23)	7 (54)	–	10 (77)	11 (34)	–	–	11 (34)
Proctalgia	3 (23)	5 (38)	3 (23)	11 (85)	16 (50)	3 (9)	1 (3)	20 (62)
Proctitis	2 (15)	8 (62)	3 (23)	13 (100)	20 (62)	2 (6)	2 (6)	24 (75)

Abbreviations: No., number.

On the basis of this hypothesis, we retrospectively tested MTHFR SNPs and found a significant correlation of MTHFR c.1298A > C genotype with G3-4 toxic events during CRT both in patients treated before protocol amendment and in the entire study population. This finding suggests a contribution of decreased MTHFR enzyme activity in determining capecitabine toxicity. Prospective studies are needed to determine if the dose of capecitabine administered after fluorouracil and leucovorin should be reduced in patients with MTHFR c.1298A > C genotype to lessen toxicity and if this modification could impact clinical efficacy of treatment.

Phase I-II evidence indicates that when added to concomitant CRT, BV could increase the rate of toxicities during CRT and early post-operative complications [9], in particular regarding the increased risk of anastomotic leak [20,21]: Our results are in line with those of previous studies. The fatal bowel perforation that occurred during induction CT is in the spectrum of known but serious BV-related adverse reactions. Notably, TRUST did not report an increase in post-operative mortality rate, and all possibly surgical BV-related complications resolved without sequelae. Furthermore, the rate of sphincter-preserving surgery in this trial is worth noting (93%).

The lack of a control arm and the limited number of patients represent potential limitations. Our trial does not definitively prove the value of a total neoadjuvant approach over preoperative CRT, nor allows the identification of the best candidates to an intensive approach. The number of patients is limited, and larger randomised series are needed to adequately define safety of efficacy of such an approach. However, TRUST places in a new scenario in LARC management. Indeed,

disparate strategies have been extensively investigated in the last few years: i) intensified CRT with oxaliplatin, which failed to demonstrate an advantage compared to standard CRT in different randomised trials [22]; ii) adjuvant CT with combination regimens [23,24]; iii) short course of RT followed by consolidation CT [25] and iv) preoperative CT without RT [26]. Despite interesting results, none of these strategies have yet overcome standard fluoropyrimidine-based CRT, and further research is therefore needed to optimise different treatment options.

One of the key issues in LARC management is indeed represented by the identification of the optimal window for the administration of systemic therapy. As adjuvant CT after neoadjuvant CRT has not convincingly demonstrated an OS advantage in phase III trials, a total neoadjuvant approach may represent a valuable alternative.

One could argue if a very active induction therapy should be followed by CRT in all cases or CRT should be better reserved to non-responsive patients. This personalised approach could increase the safety of a total neoadjuvant therapy reducing the acute and long-term toxicities of RT. However, omitting RT in LARC should currently be considered exploratory, and trials are ongoing to address this issue [26,27].

Our study does not allow concluding that all the components of this strategy are needed. However, even taking into account the biases of cross-study comparisons, the triplet plus BV we tested resulted in more pCRs than neoadjuvant capecitabine and oxaliplatin (CAPOX) (36.4% and 14.3%, respectively) [4]. FOLFOXIRI is currently being tested in LARC, with promising results in terms of activity [28]. Results of Prodige23 (NCT01804790), a French phase 3 study comparing preoperative CRT versus neoadjuvant 5-fluorouracil, leucovorin, Irinotecan and oxaliplatin (FOLFIRINOX) followed by preoperative CRT in patients with LARC, are expected in the near future. Regarding metastatic setting, Federation Francophone de Cancerologie Digestive (FFCD)1102 phase II trial recently explored the efficacy of 5-fluorouracil, leucovorin, Irinotecan and Oxaliplatin (FOLFIRINOX) as induction treatment in rectal cancer with synchronous metastases and demonstrated that triplet chemotherapy is effective in control of primary tumour and distant metastases [29].

With regards to BV, targeting VEGF may improve pathological response of colorectal cancer liver metastases [30] and may provide significant benefit when added to FOLFOXIRI [7,31]. Rectal cancer has a peculiar biology compared with colon cancer [32], and VEGF inhibitors could increase CRT efficacy acting as radiosensitisers by enhancing tumour blood flow, reducing interstitial pressure and decreasing vessel density [33]. In single-arm phase II trials, induction therapy with oxaliplatin-based doublets plus BV has been associated with variable pCR rates (from 20% to 36%), although reports for DFS are not conclusive due to short follow-up, small number of patients enrolled and non-randomised study design [20,34]. In a retrospective study, BV seems to improve the rate of objective responses and pCRs of neoadjuvant CT [33], and these findings have been confirmed by a recent meta-analysis [35]. Despite the preclinical rationale and the interesting results of phase II trials, no phase III study is currently testing bevacizumab in LARC and the phase II BACCHUS trial evaluating a total neoadjuvant approach with FOLFIXIRI plus BV and FOLFOX plus BV before surgery with TME stopped early because of poor accrual [36]. Therefore, the added value of bevacizumab in this setting is still questionable.

It is arguable that future studies in such a heterogeneous patient population will clarify *i*) if triplet CT is superior to doublet CT as induction treatment, *ii*) if BV is needed during induction CT and/or CRT and *iii*) if CRT is necessary in all patients.

Waiting for a tailored treatment strategy, TRUST demonstrates that induction with FOLFOXIRI plus BV followed by CRT plus BV is feasible and active and should be further tested in trials focussing on high-risk LARC.

Acknowledgements

The trial was supported by Fondazione ARCO (Associazione Ricerche e Cure in Oncologia) Onlus. Roche provided bevacizumab but was not involved in study design, data collection and analysis, results interpretation and manuscript writing.

Additional contributions

The authors want to thank all the patients, their families and their caregivers, as well as the investigators from participating institutions in Italy.

Conflict of interest statement

Prof. G. Masi reported receiving personal fees from Amgen, F. Hoffman–La Roche, Bayer, Merk Serono and Sirtex. Prof. A. Falcone reported receiving grants and personal fees from F. Hoffman–La Roche, Amgen and Merck Serono as well as personal fees from Celgene, Bayer and Sanofi Aventis. No other disclosures were reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.01.006.

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