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STUDY PROTOCOL

GRECCAR 14 – a multicentric, randomized, phase II–III study evaluating the tailored management of locally advanced rectal carcinoma after a favourable response to induction chemotherapy: Study protocol

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Abstract

Aim: Total neoadjuvant treatment (TNT) is becoming standard in patients with locally advanced rectal carcinoma (LARC). Preoperative chemoradiotherapy (CRT) has proven side effects on bowel and genitourinary function. An early tumoral response to induction chemotherapy demonstrates its high prognostic value. Tailored management could be used as an alternative to systematic CRT. The GRECCAR 14 trial will attempt to personalize treatment strategy according to the patient's early tumour response to intensive chemotherapy with the aim of achieving the best toxicity–efficiency ratio.

Method: GRECCAR 14 is a multicentric, randomized, two-arm, phase II–III noninferiority trial. Patients with mid or low LARC with a predictive circumferential resection margin ≤2 mm or T3c-d stage with extramural venous invasion will be included. Evaluation of the tumoral response will be performed after six courses of high-dose FOLFIRINOX chemotherapy. Good responders (GRs) will be defined by a 60% decrease in tumoral volume on magnetic resonance imaging. Patients will be randomized to CRT before surgery. The primary endpoints will be R0 resection for phase II and the 3-year disease-free survival (DFS) for phase III.

Results: Tailored management of LARC is becoming an exciting challenge for the modality of neoadjuvant treatment and for the type of surgery or its omission. Neoadjuvant FOLFIRINOX has established efficacy, with a significant increase in the 3-year DFS. Better control of systemic disease must be accompanied by the same locoregional control, with the lowest morbidity. Our previous GRECCAR 4 trial demonstrated the high value of the early tumoral response after induction chemotherapy and the long-term safety of tailored management for GRs.

Conclusion: If GRECCAR 14 demonstrates the ability to tailor TNT for LARC, this could lead to changes in clinical practice.

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INTRODUCTION

The standard treatment of locally advanced rectal carcinoma (LARC) consists of multimodal therapy including chemotherapy, chemoradiotherapy (CRT) and total mesorectal excision (TME) surgery. The use of chemotherapy before CRT has increased significantly over time, and is known as induction total neoadjuvant treatment (induction TNT). The French prospective randomized trial PRODIGE 23 confirmed that induction TNT (modified FOLFIRINOX) improved the pathological complete response (pCR) and 3-year disease-free survival (DFS) compared with classical induction CRT [1].

However, systematic use of the same neoadjuvant schedule exposes good responders (GRs) to chemotherapy to unnecessary radiotherapy-related toxicity [2, 3]. On the other hand, TNT increases the pCR and allows management by organ preservation [4–6]. Today, these strategies add complexity to the management of LARC. The two most important endpoints are overall survival and quality of life, with good long-term functional and sexual results; all other endpoints are surrogates.

The short- and long-term toxicity of pelvic radiation, with [7–10] or without [11] surgery, may be a compelling reason to reconsider systematic neoadjuvant CRT and to move towards a more individualized approach, particularly because the evolution of surgical techniques, especially minimally invasive surgery, has enhanced postoperative recovery [12, 13] and long-term functional and sexual outcomes [14].

A tailored strategy for LARC could potentially lead to omission of proctectomy in cases of complete or subcomplete response after TNT or to omission of CRT in GRs after neoadjuvant chemotherapy (NACT). The decision to proceed in one way or another is made by the patient (shared decision-making) or the surgeon (preoperative risk assessment). Magnetic resonance imaging (MRI) has become the indispensable cornerstone for assessing tumour response [15].

The US prospective noninferiority randomized trial (PROSPECT: NCT01515787) has evaluated the suppression of preoperative radiotherapy in selected patients. It concluded recently that preoperative FOLFOX was noninferior to preoperative CRT with respect to DFS [16]. Our previous phase II trial (GRECCAR 4) reported results in LARC patients treated with induction trichemotherapy (FOLFIRINOX) and tailored CRT (50/60 Gy), according to the tumoral volumetric response (cutoff 75%). Initial results [17] showed the high predictive prognostic value of the early tumoral response after induction chemotherapy, while long-term results [18] demonstrated the oncological safety of this management, especially locoregional control in GRs operated on without CRT.

Accordingly, we designed GRECCAR 14 using the same philosophy of tailored management according to the early tumoral response after intensive induction chemotherapy. If GRECCAR 14 can demonstrate the ability to tailor TNT for LARC, this could change clinical practice and decrease long-term morbidity.

METHOD

The trial was validated by the scientific committee of the GRECCAR and PRODIGE groups, approved by the Comite de Protection des Personnes du Sud-Ouest and registered at ClinicalTrials.gov (NCT04749108) on 3 November 2021.

Study design

GRECCAR 14 is a national French, multicentre, open-label, randomized, phase II–III noninferiority clinical trial that will evaluate the de-escalation treatment in GR patients after induction chemotherapy. LARC with a predictive circumferential resection margin (CRM) ≤2 mm or T3c-d tumour (extending ≥5 mm beyond the muscularis propria) with extramural venous invasion or T4a-b tumours (except bone and sphincteric invasion) will be prescreened and treated by induction high-dose chemotherapy (six cycles of modified FOLFIRINOX). Ultra-low tumours (inferior tumour pole <1 cm from the upper part of the levator ani, which imposes radiotherapy for sphincter-saving management) will be excluded. GRs from a centralized review (volume regression ≥60% and CRM ≥1 mm) after neoadjuvant treatment will be randomized into two arms: (A) surgery alone or (B) CRT and surgery (Figure 1). Patients with a bad response after neoadjuvant treatment of six cycles of FOLFIRINOX will be followed out of the study and managed classically (CRT and surgery). Patients with a clinically proven complete response after neoadjuvant treatment will be managed by organ preservation.

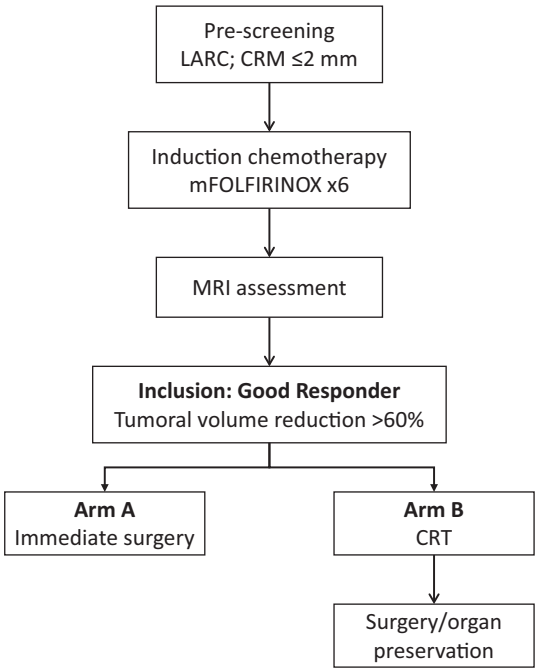

FIGURE 1 Study design (CRM, circumferential resection margin; CRT, chemoradiotherapy; LARC, locally advanced rectal carcinoma; MRI, magnetic resonance imaging).

In the first step, a phase II study will be conducted using a satisfactory R0 resection rate (90%) as the primary endpoint; in the second step, a phase III study will use the 3-year DFS as the primary endpoint in a noninferiority trial.

Participants

Study setting

Patients will be included from several departments (surgery, radiotherapy, medical oncology; $n=30$) in France. Before inclusion, all participating sites will obtain ethical approval from the institutional promoter (DRCI, Montpellier Cancer Institute).

The study will be coordinated by the investigator coordinators (PR, CL, TM, SN, CT) with responsibility for the selection and validation of participating centres. The Unité de Recherche Clinique of the Montpellier Cancer Institute (FC, SG) will monitor study inclusion and the methodological aspects (collection, management, analysis and data interpretation).

Screening of eligibility criteria (preinclusion)

Eligible patients will be screened and confirmed for eligibility after validation during a multidisciplinary meeting. All patients will be required to have a complete rectal cancer work-up, including clinical examination (previous history of colorectal cancer or other neoplasia, physical examination, assessment of WHO/ECOG performance status, assessment of digestive symptoms), complete colonoscopy with biopsy, rectal MRI, computed tomography (CT) of the chest, abdomen and pelvis, blood sample tests with tumour markers and a serum pregnancy test.

Key points for eligibility include: histologically confirmed diagnosis of rectal adenocarcinoma; distal part of the tumour 1–10 cm from the upper part of the levator ani (dynamic rectal examination); no unequivocal evidence of established metastatic disease on CT and MRI evaluation of the locally advanced tumour; predictive CRM ≤2 mm or T3c-d with extra mural venous invasion or T4a-b (except bone and sphincteric invasion). Patients should be suitable for radical pelvic surgery and systemic therapy with FOLFIRINOX.

Criteria for ineligibility include nonmeasurable rectal tumour assessed by MRI, ultra-low rectal tumour that precludes radiotherapy (inferior tumour pole <1 cm from the upper part of the levator ani), patient with a history of chemotherapy or pelvic radiotherapy and contraindication to chemotherapy and/or radiotherapy.

Prescreened patients will receive a modified FOLFIRINOX regimen, i.e. one cycle every 14 days during six cycles according to the following procedure: oxaliplatin 85 mg/m^2 intravenous (IV) infusion over 2 h, immediately followed by folinic acid 400 mg/m^2 or calcium levofolinate 200 mg/m^2 administered as a 2-h IV infusion; after 30 min, irinotecan 180 mg/m^2 administered as a 90-min IV infusion through a Y-connector, immediately followed by a 90-min IV infusion of 5-fluorouracil 2400 mg/m^2 over 46 h of continuous infusion. The use of prophylactic granulocyte colony-stimulating factor from day 5 to day 10 is advised whenever a cycle has been postponed for a week or more due to neutropenia.

Inclusion criteria

For study inclusion, a patient must show tumoral regression ≥60% and CRM ≥1 mm from postchemotherapy MRI after NACT. Criteria will be validated in a centralized review performed in the Montpellier Cancer Institute.

Exclusion criteria

Patients with a bad tumoral response (tumoral volume regression <60% or CRM <1 mm) will not be randomized and will receive classical management (CRT and surgery). They will be followed out of the GRECCAR 14 study according to the protocol of each team.

Inclusion and randomization

Inclusion and randomization will be centralized to the Biometrics Unit (ICM), CTD INCa using eCRF (EnnovClinical® software). The screening procedure will only concern patients who sign the informed consent form and complete all initial assessment examinations to validate all criteria for inclusion and exclusion. The procedural use of eCRF will be explained to investigators at the opening of each centre. An identification number will be allocated to each patient, which will be retained for the whole duration of the trial.

Randomization using the minimization method with a 1:1 ratio will be performed at inclusion according to the following known prognostic factors as stratification parameters: topography (1–6 cm vs. 6–12 cm), stage (T3 vs. T4) and centre.

Experimental arm

Arm A: surgery alone (proctectomy TME), preferably performed 4 weeks after randomization but always within 6 weeks. Complete tumoral response will be checked by MRI (tumour regression grade 1), rectal examination and endoscopy. An organ-preservation strategy is not the standard in such management. It could be proposed after shared decision-making and after having been requested by the patient.

Control arm

Arm B: CRT using the Cap 50 protocol [50 Gy radiotherapy, conventional 3D or intensity-modulated radiotherapy (2 Gy/fraction, five

fractions/week for 5 weeks/44 Gy in minipelvis, and 6 Gy boost on reduced peritumoral volume) with concomitant oral capecitabine at 800 mg/m^2 twice a day, delivered during radiotherapy] plus surgery or organ preservation, according to the patient's response.

Surgery

Surgical resection will be scheduled 6–8 weeks after the end of the preoperative treatment in both groups. Rectal resection will be performed with respect to French clinical guidelines for oncological surgery. TME will be performed using the laparotomy, laparoscopic, robotic or transanal approach. In case of complete response, rectal preservation management will be allowed using a watch-and-wait procedure. Complete tumoral response will be checked by MRI (tumour regression grade 1), rectal examination and endoscopy. An organ-preservation strategy can be employed, and the patient will be considered successful.

Postoperative treatment and follow-up

Postoperative adjuvant chemotherapy will be the investigator's choice, depending on the final pathological results and the practices of each centre. Recommendations issued by the scientific steering committee are as follows: surveillance for complete pathological responses (ypCR) or ypT1N0 tumours; chemotherapy with six cycles of FOLFOX for ypT ≥2 or ypN ≥1.

Primary outcome

Phase II

To assess for patients with a GR to NACT, a de-escalation treatment strategy will have the primary outcome of a satisfactory R0 resection rate (90%; CRM ≥1 mm). The excision limits will be precisely determined after exhaustive sampling of the maximum tumour extension zones and containing the surface of the inked mesorectum. No resection of the primary tumour because of clinical complete response will be considered a success, whatever the group. No resection of the primary tumour because of local progression or the patient being unfit for surgery will be considered as a failure.

Phase III

To assess for patients who have a GR to NACT, a de-escalation treatment strategy will have the primary outcome of 3-year DFS rate in a noninferiority trial. DFS is defined as the time interval between randomization and the occurrence of the first event, such as local or metastatic recurrence, the development of a second cancer or death from any cause. Locoregional failure includes locally progressive disease leading to an unresectable tumour, local R2 resection or local recurrence after an R0–R1 resection. Patients without events at the time of analysis will be censored on the date of the last informative follow-up.

Secondary outcome for phases II–III

Oncological

Compliance rate of the therapeutic schedule, pCR rate, Dworak grading, TME grading (Quirke), distal margin, 3-year metastasis recurrence, 3-year local-recurrence-free survival rate, 3-year metastasis-recurrence-free survival rate, 3-year DFS, 3- and 5-year overall survival.

Safety

The safety of NACT and radiochemotherapy will be evaluated using version 5.0 of the NCI-CTCAE scale until the end of the postlegal surgery period.

Morbidity

Clavien–Dindo grades 3 and 4, definitive stoma rate, sphincter-saving surgery rate, second surgery rate, rehospitalization rate.

Functional results

Digestive [low anterior resection syndrome (LARS)] and quality of life evaluated by the EORTC QLQ-C30+CR29 questionnaires (baseline, before surgery and 1 year after surgery).

Ancillary studies

First, to explore the prognostic value of baseline 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT and its power to predict the response to NACT. Second, to develop a radiomic-specific programme to predict the early tumoral response from the MRI database.

Statistical analysis

A total of 1075 patients will be included to randomize a total of 430 patients for the phase II–III trials, according to a good response rate of 40%. Sample size is based on the following calculations.

Phase II: a two-stage Simon design, $\alpha = 5\%$, $\beta = 5\%$, p0 (maximum inefficiency/R0 rate) = 85% and p1 (minimum efficiency/R0

rate) = 95%, results in 100 (35 + 65) patients in each arm; thus, 200 patients (100 per arm) will be required for phase II.

Phase III: at the end of phase II, the sample size calibration for the phase III study will be performed again to adapt to the hypothesis if necessary. A noninferiority design will be used to demonstrate that the 3-year-DFS rate is not lower by >10% (i.e. if the 3-year-DFS is 80% in the control arm, then the experimental arm should not be <70%); this corresponds to a hazard ratio of 1.62 and 430 patients (ratio 1:1) to observe 145 events ($1-\beta = 80\%$, one-sided $\alpha = 0.025\%$).

An interim analysis on the primary endpoint is planned after the observation of 50% of the expected events. According to the phase II/III design, patients included in phase II will be considered in phase III in case of a successful phase II, i.e. inclusion of 200 patients in phase II and 230 additional patients for phase III.

A statistical analysis plan will be written before the locked database. The baseline characteristics and compliance to induction chemotherapy will be described for the full analysis set and intention-to-treat (ITT) populations. Compliance with CRT will be described in the ITT and per-protocol populations, as will the primary endpoint analysis (the main analysis for the phase III noninferiority study). The safety analyses will be performed on the safety populations.

The Independent Scientific Committee will meet at different times during the study to evaluate enrolment, safety and efficacy of the administered treatment. The planned scheduled timepoints will be phase II interim analysis, phase II final analysis, phase III interim analysis and phase III final analysis.

Study period

Inclusion began in January 2022. The duration of inclusion will be 36 months in phase II and 36 months in phase III. The duration of follow-up will be 36 months. The total study duration will be 108 months.

DISCUSSION

Recently, TNT was recommended in the National Comprehensive Cancer Network guidelines as the preferred treatment strategy in LARC [19]. It has been reported to increase the rate of pCR and to be related to improved oncological outcomes. However, treating all LARC patients with the same neoadjuvant schedule exposes GRs to chemotherapy to unnecessary radiotherapy-related toxicity [2]. Therefore, it is still necessary to select patients who will obtain some oncological benefit from radiotherapy at the cost of radiotoxicity. On the other hand, TNT increases the pCR and allows organ preservation, with the risk of regrowth and completion of TME [20]. GRECCAR 14 will attempt to personalize the treatment strategy according to the patient's early tumour response to intensive chemotherapy, with the aim of achieving the best toxicity–efficiency ratio.

Oncological and functional rationale for omitting pelvic irradiation in a tailored treatment strategy for LARC

For low-risk rectal cancer, MRI risk stratification is accepted when tailoring neoadjuvant therapy. The UK National Institute for Health and Care Excellence changed their guidelines on the inescapable role of radiotherapy due to improvements in initial MRI staging and TME standardization [21], similar to the changes in the ASTRO guidelines for tumours with good prognosis [22]. Following this, research has questioned the usefulness of radiotherapy after induction chemotherapy even for LARC [23, 24].

Despite interest in improving local control, preoperative CRT has never been shown to decrease the risk of metastatic recurrence or improve survival in rectal cancer patients undergoing TME, regardless of the pathological tumour stage [25, 26]. A CRT strategy could instead be considered in a watch-and-wait approach, with the omission of radical surgery. Although the rates of clinical complete remission (cCR) are reportedly higher in moderately advanced rectal cancer than in more advanced rectal cancer, most patients do not achieve cCR and tumour regrowth occurs in 25%–40% of patients with cCR after CRT. Therefore, even if the watch-and-wait approach after neoadjuvant CRT is an option in early tumours to avoid proctectomy, radical surgery is still the standard treatment for later tumours. In patients with moderately advanced rectal cancer, omission of CRT is considered to be oncologically safer than omission of radical surgery [27].

Despite the oncological benefits of CRT for local control, irradiation induces tissue oedema and fibrosis, disturbs surgical procedures, impairs wound healing and increases the rate of anastomotic leakage and stricture [27]. Long-term functional results have reported that CRT is associated with considerable adverse effects on anorectal and social function and a significant decrease in quality of life [7, 8, 28]. In the first study to demonstrate the impact of CRT alone on anorectal function after the watch-and-wait strategy, one-third of patients had major LARS and the most frequently reported complaints were clustering and faecal urgency [11].

New data supporting NACT alone

In a meta-analysis of 12 812 patients in six studies (NACT $n = 677$; neoadjuvant CRT $n = 12\,135$) [23], there were no significant differences between groups in terms of pCR [odds ratio (OR) = 0.62], N downstaging rate (OR = 1.20), R0 resection rate (OR = 1.24) or local relapse rate (OR = 1.12). Another meta-analysis of 60 870 patients in 19 studies [24] found no significant difference in overall survival ($p = 0.19$) or pCR ($p = 0.086$) between the NACT and neoadjuvant CRT groups. However, the incidences of anastomotic fistula ($p = 0.001$) and temporary colostomy ($p = 0.001$) were significantly lower in the NACT group, with a simultaneous increase in the sphincter preservation rate ($p = 0.029$). There was no significant difference in the tumour downstaging rate or overall and urinary complications. These

two analyses highlighted the lower postoperative morbidity in the NACT group and noninferiority to neoadjuvant CRT in terms of pCR, N downstaging, R0 resection, local relapse and distant metastasis.

Phase II trials have used different types of NACT alone to study the pCR rate, which varied from 12% [29] to 17% [30]. The first results published from the phase II NEO trial [31] included patients with clinical T1-T3ab N0 low- or mid-rectal adenocarcinoma eligible for endoscopic resection, who were treated with 3 months of chemotherapy alone (capecitabine–oxaliplatin). Of the 58 patients enrolled, 33 (57%) had tumour downstaging and organ preservation. The 2-year locoregional relapse-free survival was 90%, and there were no distant recurrences or deaths.

Results from randomized phase II/III trials are demonstrative

The FOWARC trial [32] randomized 495 LARC patients into three arms: two CRT with or without oxaliplatin versus six courses of FOLOX6 alone. The pCR rate was 14.0%, 27.5% and 6.6%, respectively, while downstaging (ypT0-1) was achieved in 37.1%, 56.4% and 35.5% of patients. Higher toxicity and a greater rate of postoperative anastomotic leakage (20.2%, 23.6%, 8.5%; $p=0.007$) were observed in patients who received radiotherapy [9]. With a median follow-up of 40.2 months, 54% of the entire population reported major LARS [7], with a greater proportion of major LARS (64.4% vs. 38.6%; $p<0.001$) and worse quality of life in the neoadjuvant CRT group.

The phase III CONVERT trial [33] included 663 LARC patients with uninvolved mesorectal fascia randomly assigned to NACT (four cycles of CapOx) or neoadjuvant CRT (Cap 50) before TME. The pCR rate (11% vs. 13.8%, respectively; $p=0.333$) and the downstaging rate (40.8% vs. 45.6%; $p=0.256$) were similar in both treatment arms. However, the rate of perioperative distant metastases was significantly lower with NACT (0.7% vs. 3.1%; $p=0.034$), as was the rate of preventative ileostomy (52.2% vs. 63.6%; $p=0.008$). The authors concluded that NACT achieved similar pCR and downstaging rates with a lower incidence of perioperative distant metastasis and preventive ileostomy compared with neoadjuvant CRT.

Very few trials tailored preoperative management according to tumour response

In 106 LARC patients with neoadjuvant mFOLFOXIRI chemotherapy [34], patients with mesorectal fascia-positive or ycT4a/b after re-evaluation received radiation before surgery (14%), whereas responders had immediate TME. Among 103 patients who completed at least four cycles of preoperative chemotherapy, 14 (14%) received radiation before TME and 89 (86%) received immediate TME; the pCR was 20.4%.

Predicting the tumour response to NACT is feasible at an early treatment phase [35]. After two cycles of CAPOX for Stage II/III rectal cancer of low and intermediate risk, none of the 61 patients included was converted to neoadjuvant CRT because of tumour progression; the pCR was 21%.

The Bacchus phase II trial [36] tested intensive chemotherapy (FOLFOXIRI with bevacizumab) for aggressive LARC. Patients stopped treatment if they failed to respond after four cycles (defined as a ≥30% decrease in standardized uptake value compared with baseline PET/CT). The trial stopped early because of poor accrual. Despite a pCR of 10% and morbidity, the authors concluded that FOLFOXIRI and bevacizumab could be a novel arm in a future trial.

GRECCAR 4 [17, 18] was a prospective, randomized, multicentre French study that tailored CRT based on the tumour response to intensive induction chemotherapy (FOLFIRINOX). GRs (≥75% tumour volume reduction) were randomly assigned to immediate surgery or standard CRT (Cap 50) plus surgery; poor responders were assigned to Cap 50 or intensive CRT (Cap 60 Gy) before surgery. Overall, 206 LARC patients (CRM <1 mm at diagnosis) were enrolled between 2011 and 2014. Thirty patients (15%) were classified as GRs. The primary objective was a R0 resection rate, which was 100% for GR (with or without CRT); in poor responders, the rate was 83% with 50 Gy and 88% with 60 Gy. At the 5-year follow-up, overall survival was 90% for surgery alone in GR, 93.3% for GR with CRT, 84.3% for poor responders with 50 Gy and 86.1% for poor responders with 60 Gy. Local recurrence did not occur in GR, but was 2.1% for poor responders with 50 Gy and 9.3% for those with 60 Gy; the metastasis rate was 20% in the four arms. The main limitation was due to the small number of patients randomized in the GR arms, especially those without radiotherapy. We concluded that this first study of tailored management of LARC confirms the promising prognostic value of the early tumoral response after high-dose chemotherapy and the ability to avoid radiotherapy in GR without impacting local control with the same oncological prognosis. Late morbidity was higher with CRT (30% vs. 50%). At the same time, the pCR was 60% in GR, which paves the way for organ preservation. We must consider the operative risk to specify the surgical management. With an early good tumour response, high-risk surgical patients can be candidates for an organ preservation strategy, while less risky surgical patients can avoid long-term morbidity from radiotherapy using a minimally invasive surgical approach after chemotherapy.

The PROSPECT trial

One of the first teams to publish gave results for NACT alone (FOLFOX 6-bevacizumab) for LARC with omission of radiotherapy [37] based on tumour response. All patients achieved R0 resection (CRM >1 mm) and 25% had a pCR with an 84% DFS at 4 years, without local recurrence. This pilot study inspired the PROSPECT noninferiority, randomized trial of neoadjuvant FOLFOX 6 with CRT given only if the primary tumour decreased in size by <20%. A total of 1128 patients were evaluable: rectal adenocarcinoma with a mean location from anal verge 8.6 cm, staged T2N1 (10%) or T3 N0 (40%)–1 (50%). Recent published data [16] showed that FOLFOX

was noninferior to CRT for DFS at 5 years, DFS being 80.8% in the FOLFOX group and 78.6% in the CRT group (HR 0.92; 90.2%; $p=0.005$). The groups were similar with respect to overall survival (HR 1.04) and local recurrence (HR 1.18).

PROSPECT highlights the evaluation of tumoral response, particularly the cutoff to determine a GR. This notion is crucial to the quality of oncological results. The tumour volumetric analysis obtained using MRI has been correlated with DFS in patients with advanced rectal cancer who underwent preoperative CRT [38]. The tumour volume reduction ratio with a cutoff of 60% ($p=0.009$), CRM ($p=0.008$) and tumour regression grade ($p=0.002$) were significantly associated with DFS. Multivariate analysis showed that the tumour volume reduction ratio was the only variable associated with DFS ($p=0.003$). In a retrospective analysis of 102 LARC patients treated by NACT [39], multivariate analysis demonstrated that extramural venous invasion on MRI and a tumour volume reduction rate <60% were significantly and independently associated with worse recurrence-free survival. We also reviewed the results of the GRECCAR 4 trial and found that a reduction of ≥60% was sufficient to define a GR [40]. These findings explain the cutoff of 60% chosen to define GR in GRECCAR 14.

CONCLUSIONS

Both the inherent heterogeneity in LARC and observed range of different responses underline the need for response biomarkers to individually tailor therapy, rather than a 'one size fits all' approach. PD-1 blockade in mismatch repair-deficient LARC is the most demonstrative example [41].

In the era of personalized medicine, the treatment of LARC must be tailored. For patients who are not suitable for radical surgery because of their underlying condition or comorbidity, or for high-risk operative patients, TNT need to be considered first to try and achieve a cCR. For patients whose rectal cancer had an early and good response to chemotherapy, with safe CRMs after induction therapy, radical surgery and omission of radiotherapy can be considered in a trial.

Recent results of the PROSPECT trial have clearly demonstrated this possibility for selected patients.

In the meantime, an early good tumoral response after induction intensive chemotherapy should be used to tailor strategy, either to promote minimally invasive TME without radiotherapy for low-risk operative patients or organ preservation with radiotherapy for high-risk operative patients.

AUTHOR CONTRIBUTIONS

Philippe Rouanet: Conceptualization; funding acquisition; writing – original draft; validation; writing – review and editing; supervision; resources; investigation; visualization; methodology. **Florence Castan:** Methodology; validation; conceptualization; formal analysis; supervision. **Thibault Mazard:** Conceptualization; investigation; methodology. **Claire Lemanski:** Conceptualization; investigation; methodology. **Stephanie Nougaret:** Conceptualization; investigation; methodology. **Emmanuel Deshayes:** Conceptualization; investigation; methodology. **Patrick Chalbos:** Methodology; project administration; data curation; supervision; investigation. **Sophie Gourgou:** Conceptualization; investigation; methodology; formal analysis; project administration; data curation; supervision; writing – original draft. **Christophe Taoum:** Conceptualization; investigation; supervision; writing – original draft; writing – review and editing; validation; data curation; formal analysis.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Trial in progress data not yet available.

ETHICS STATEMENT

This study was approved by all ethics committees at all study centres and written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

PATIENT CONSENT STATEMENT

At inclusion, all patients signed a free, informed consent form (validated by the ethics committee SOOM IV on 07/15/2021), including for the publication of de-identified data in a peer-reviewed journal.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT04749108 (3 November 2021).

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