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LETTER TO THE EDITOR

Rationale and design of REGINA, a phase II trial of neoadjuvant regorafenib, nivolumab, and short-course radiotherapy in stage II and III rectal cancer

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Introduction

Standard treatment for stage II and III rectal cancer has long consisted of neoadjuvant long-course chemoradiotherapy (CRT) or short-course radiotherapy (SCRT) followed by total mesorectal excision (TME) plus or minus adjuvant chemotherapy [1]. Recently, results from the RAPIDO and PRODIGE-23 trials suggested superiority of the 'total neoadjuvant therapy' approach (i.e., systemic chemotherapy delivered before or after pre-operative (C)RT) over standard treatment in terms of pathological complete response (pCR), and disease-related treatment failure and disease-free survival, respectively [2,3]. Management of locally advanced rectal cancer, however, remains challenging, and despite the combined use of chemotherapy, radiotherapy and surgery, a substantial proportion of patients experience tumour recurrence (especially consisting of distant metastases) and ultimately die of this disease [4]. Therefore, novel treatment options are needed to further improve the survival outcomes of these patients.

Study rationale

While the vast majority of rectal cancers are DNA mismatch repair-proficient/microsatellite stable (pMMR/MSS) and therefore unlikely to benefit from currently available immunomodulatory strategies, there has been an increasing interest for the investigation of immunotherapy agents in combination with pre-operative (C)RT. RT, especially when delivered according to hypofractionated schedules, can mediate immunomodulation of the tumour microenvironment and enhance antitumoral immunity through a number of mechanisms including, among others, activation of T cells by immunogenic cell death, reprogramming of tumour-associated-macrophages (TAMs), and normalisation of aberrant neo-vascularisation [5–7]. Studies in rectal cancer also showed upregulation of PD-L1 expression in resection specimens following RT [8,9].

Recently, evidence has also emerged suggesting a synergistic effect between immune checkpoint inhibitors and multi-kinase inhibitors. In preclinical studies, combining an anti-PD-1 inhibitor with regorafenib induced superior tumour growth suppression as compared with either treatment alone. This synergistic effect is thought to be largely secondary to the anti-angiogenic effects of regorafenib, and its potential to reduce TAMs, promote M1-type macrophage conversion (possibly due to inhibition of the CSF1 receptor), and down-regulate expression of immunosuppressive factors through inhibition of oncogenic signalling pathways such as MAPK and JAK/STAT [10,11].

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Supplemental data for this article can be accessed here.

These preclinical findings have recently been supported by the results of a phase I trial conducted in Japan (REGONIVO, EPOC 1603) [12]. In this study, 50 patients with chemorefractory gastric ($n = 25$) or colorectal cancer ($n = 25$) were treated with regorafenib (80–160 mg, once daily for 21 on 7 days off) plus nivolumab (3 mg/kg every 2 weeks) in the dose-finding and dose-expansion phase. While the study population included heavily pre-treated patients, the objective response rate was 44% for gastric cancer and 36% for colorectal cancer. Notably, all responding patients except one had MSS tumours. The median progression-free survival (PFS) was 5.6 months and 7.9 months in the gastric and colorectal cancer cohort, respectively. The safety profile of the combination was manageable, and 80 mg was selected as the recommended dose for regorafenib to use in phase II trials. Less promising data have recently been reported by the investigators of a phase I/IB trial conducted in US, where the combination of regorafenib and nivolumab yielded a response rate of 6% and a median PFS of 5.7 months in a population of chemorefractory colorectal cancer patients [13]. These inconsistent results have been largely attributed to the high proportion of patients with unfavourable prognostic features and negative predictive factors for immunotherapy (such as right-sided tumour location and liver metastases). The potential of combining immune checkpoint inhibitors and multi-kinase inhibitors in the setting of gastrointestinal malignancies has indeed been confirmed by the impressive anti-tumour activity (objective response rate of 69%), which has recently been observed in a study of lenvatinib and pembrolizumab in chemorefractory gastric cancer [14].

All these data provide a sound rationale for the investigation of regorafenib and nivolumab in combination with radiotherapy in non-metastatic rectal cancer. Also, they warrant the conduction of comprehensive correlative studies to better understand the mechanistic bases of response/resistance to this treatment, and to inform its development in future clinical trials.

Methods

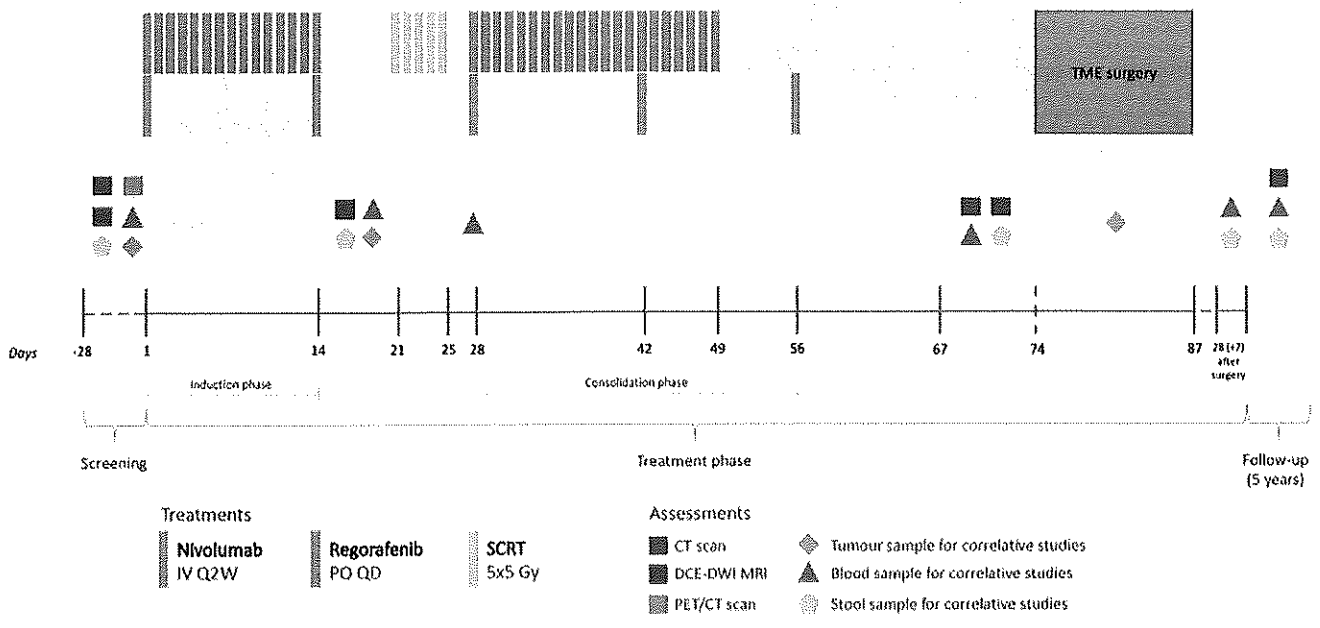
Study design

Neoadjuvant Regorafenib in Combination With Nivolumab and Short-course Radiotherapy in Intermediate-risk, Stage II-III Rectal Cancer (REGINA) is a Belgian, academic, multicentre, single-arm, phase II trial. The study is sponsored by the Institut Jules Bordet, and endorsed by the Belgian Group of Digestive Oncology (BGDO) and the Oncodistinct Network. The trial will be conducted in approximately 10 sites across Belgium.

Patients who sign the informed consent and are found to be eligible, will be treated according to the following treatment plan:

- Induction phase: nivolumab (240 mg intravenously, on days 1 and 14) and regorafenib (80 mg/day orally, from days 1 to 14).
- SCRT: 25 Gy delivered in 5 fractions (from days 21 to 25).
- Consolidation phase: nivolumab (240 mg intravenously, on days 28, 42, and 56) and regorafenib (80 mg/day orally, from days 28 to 49).
- Surgery (according to the principles of total mesorectal excision): between 7 and 8 weeks after completion of SCRT (*i.e.*, between days 74 and 87).

Administration of adjuvant chemotherapy will be left to the discretion of the treating physician, who will also decide on the type and duration of the same (Figure 1).



Abbreviations: *DCE-DWI, diffusion-weighted and dynamic contrast-enhanced; EOT, end of treatment; Gy, gray; IV, intravenously; PO, per os, Q2W, once every 2 weeks; QD, every day; TME, total mesorectal excision.*

Figure 1. Study design.

Baseline imaging scans for staging and confirmation of study eligibility will include a diffusion-weighted and dynamic contrast-enhanced (DCE-DWI) MRI of the pelvis, a CT scan of the thorax and abdomen, and a ^{18}F-FDG-PET/CT scan. Response to treatment will be assessed with repeat DCE-DWI MRI at the end of the induction phase and before TME. All patients will undergo serial collection of tumour, blood, and stool samples at pre-specified time points at baseline, during treatment and follow-up for exploratory correlative studies (Figure 1). The REGINA trial is registered on clinicaltrials.gov (NCT04503694).

Eligibility criteria

The main inclusion criteria include age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, histologically or cytologically confirmed adenocarcinoma of the rectum, tumour with distal border below the peritoneal reflection and within 15 cm from the anal verge, intermediate-risk, stage II or III tumour (as defined by the following criteria on baseline pelvic MRI: cT3/T4aN$_{any}$ or cT1-2N+, no involvement/threatening of the mesorectal fascia, no involvement of lateral pelvic lymph nodes), adequate haematological, hepatic, and renal function. Complete inclusion and exclusion criteria are listed in Table 1.

Table 1. Study eligibility criteria.

Inclusion criteria

1. Age ≥ 18 years old
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
3. Histologically or cytologically verified adenocarcinoma of the rectum
4. Tumour with distal border below the peritoneal reflection and within 15 cm from the anal verge
5. Intermediate-risk rectal cancer as defined by the following criteria on baseline pelvic MRI:
   - cT3/T4a and Nany or cT1-2 and N+
   - No involvement/threatening of the mesorectal fascia (i.e., no evidence of cancer cells ≤ 1 mm from the mesorectal fascia)
   - No involvement of lateral pelvic lymph nodes
6. Absence of distant metastases as shown by baseline computed tomography (CT) of the thorax-abdomen or CT scan of the thorax and MRI of the abdomen and positron emission tomography (PET)/CT scan
7. Adequate haematological function as defined by absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and haemoglobin ≥ 9 g/dL
8. Adequate hepatic function as defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range (excluding subjects with known Gilbert's syndrome), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN
9. Adequate renal function as defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault or Wright formula
10. Negative serum pregnancy test at screening (up to 28 days before treatment start) for women of childbearing potential
11. Women of childbearing potential must agree to use of one highly effective method of contraception prior study entry, during the course of the study and at least 5 months after the last administration of study treatment
12. Men with childbearing potential partner must agree to use condom during the course of this study and for at least 5 months after the last administration of the study treatment
13. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
14. Absence of clinical conditions that, in the opinion of the investigator, would contraindicate neoadjuvant therapy and/or surgery
15. Life expectancy of at least 3 months
16. Completion of all necessary screening procedures within 28 days prior to enrolment
17. Signed Informed Consent form obtained prior to any study related procedure

Exclusion criteria

1. Any prior or concurrent surgery, chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for rectal cancer. Concurrent use of hormones for noncancer-related conditions (i.e., insulin for diabetes and hormone replacement therapy) is acceptable
2. Any contraindication to pelvic irradiation as evaluated by the investigator
3. Prior organ transplantation, including allogeneic stem cell transplantation
4. Clinically significant acute or chronic infections including, among others:
   - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
   - Known history of testing positive for hepatitis B virus surface antigen or anti-hepatitis C virus antibody and confirmatory HCV RNA test
5. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent (subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible)
6. Systemic corticosteroids administered as hormone replacement or as immunosuppressants at doses exceeding 10 mg/day of prednisone or equivalent. Other immunosuppressive medications including, but not limited to methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of treatment-related AEs or in subjects with contrast allergies is acceptable. A temporary period of steroids is allowed for different indications, at the discretion of the investigator (i.e., chronic obstructive pulmonary disease, radiation, nausea, etc.). Administration of steroids through a route known to result in a minimal systemic exposure [topical, intranasal, intro-ocular, or inhalation] is acceptable
7. Known severe hypersensitivity reactions to the investigational treatments, or any excipients or non-investigational medicinal products or concomitant medications
8. Pregnant and/or lactating women
9. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure, or serious cardiac arrhythmia requiring medication
10. Prior myocarditis
11. Known history of immune colitis, immune pneumonitis, pulmonary fibrosis or other medical conditions (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment
12. Vaccination within 28 days of the first dose of study treatment and while on trial (except for administration of inactivated vaccines)
13. Other invasive malignancy within 2 years except for non-invasive malignancies such as cervical carcinoma *in situ*, non-melanomatous carcinoma of the skin or ductal carcinoma *in situ* of the breast that has/have been surgically cured. Anti-neoplastic treatment received in the past for malignancies cured 2 or more years before enrolment are permitted
14. Any investigational anti-cancer therapy other than the protocol specified therapies
15. Strong inhibitors of CYP3A4 activity (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole), strong UGT1A9 inhibitors (e.g., mefenamic acid, diflunisal, and niflumic acid), and strong inducers of CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital and St. John's wort) from 28 days before study enrolment up to the end of study treatment

Study objectives

The primary objective of the study is to demonstrate that administering combination treatment with nivolumab plus regorafenib before and after standard, neoadjuvant SCRT is associated with a higher pCR rate than historical controls. Secondary objectives include assessment of the safety of the investigational treatment in terms of toxicity during and after completion of neoadjuvant therapy and intra-/post-operative complications, evaluation of the feasibility of combining regorafenib with nivolumab in the setting of locally advanced rectal cancer as demonstrated by subject compliance with the investigational strategy, SCRT and surgery, and assessment of other efficacy outcome measures including R0 resection rate, pathological tumour regression grade, objective response rate, tumour downstaging/downsizing, event-free survival, and overall survival. Exploratory objectives include the evaluation of changes throughout treatment of the immune contexture and tumour microenvironment, gene expression, inflammatory/immunomodulatory cytokines and chemokines, angiogenic factors, mutated and/or methylated circulating tumour (ct)DNA, gut microbiome, and the establishment of patient derived xenografts. Details of collection and processing of biological samples as well as description of the planned exploratory correlative analyses will be included in the study laboratory manual.

Study endpoints

The primary endpoint of the study is pCR. This is defined as ypT0N0 and will be assessed locally according to the recommendations from the Royal College of Pathologists [15]. For the purpose of the primary endpoint assessment, patients who are managed by watch & wait and have a sustained clinical complete response (cCR) lasting for at least 12 months will be considered as having achieved pCR. Secondary endpoints include toxicity, compliance to treatment, R0 resection, pTRG according to Dworak et al. [16], objective response by RECIST v1.1, event-free survival, and overall survival (OS).

Statistical analysis

The trial has been designed according to the Simon's two-stage design. The null hypothesis that the true pCR rate is 12% (based on the results of the Stockholm III trial) [4] will be tested against a one-sided alternative. In the first stage, 36 patients will be enrolled. After the enrolment of these, the pCR rate will be evaluated in order to decide on the continuation of the study (efficacy interim analysis). If there are $\leq$4 pCRs, study recruitment will be stopped. Otherwise, 24 additional patients will be accrued for a total of 60. The null hypothesis will be rejected if $\geq$12 pCRs are observed overall. This design yields a type I error rate of 5% and power of 80% when the true pCR rate is 24%.

Recruitment will be temporarily halted after accrual of the first 6 patients to allow a safety interim analysis. Data from these patients will be analysed by an Independent Data Monitoring Committee (IDMC) that will advise on the continuation of the study.

Discussion

Despite the recently reported better outcomes with 'total neoadjuvant therapy' in locally advanced rectal cancer, there is still scope for improvement. In the RAPIDO and PRODIGE-23 trials, approximately one fourth of patients treated with an intensified neoadjuvant treatment strategy including 12–18 weeks of doublet or triplet systemic chemotherapy delivered either before or after (C)RT, experienced tumour recurrence within 3 years of treatment [2,3]. It is clear that any further survival gain in this setting is likely to be achieved with alternative treatment strategies, the combination of chemotherapy and radiotherapy having now reached a ceiling effect.

Based on a sound biological rationale and promising preliminary findings, we have designed a trial that will investigate for the first time the combination of standard SCRT with an immune checkpoint inhibitor and a multi-kinase inhibitor. Immune checkpoint inhibition has so far failed to exert significant anti-tumour activity in pMMR/MSS or low tumour mutational burden colorectal cancers, which account for the vast majority of all colorectal tumours. Therefore, identification of novel treatment strategies that could overcome the inherent immune-resistance of these tumours has become one of the most pressing priorities of cancer research. The available data suggest that the therapeutic potential of immune checkpoint inhibitors may be enhanced by the concurrent delivery of multi-kinase inhibitors and radiotherapy through a variety of immunomodulatory effects. Our study will address this hypothesis, building on the data from ongoing studies of immune checkpoint inhibitors with radiotherapy plus or minus standard chemotherapy.

While the primary objective of the trial is to demonstrate that combining nivolumab and regorafenib with standard neoadjuvant SCRT is feasible and associated with a higher rate of pCR as compared to historical controls, the robust translational component will allow exploring alterations of the tumour and microenvironment as well as modulation of the host immune response against the tumour following the administration of the investigational treatment. In particular, the sequential treatment strategy (*i.e.*, nivolumab plus regorafenib administered before and after SCRT) along with the collection of biological samples at key time points, will provide an optimal *in vivo* platform for correlative biomarker analyses aiming to identify potential mechanisms of response or resistance to treatment. Running co-clinical trials with patient derived xenografts will also allow testing hypotheses regarding potential strategies to overcome inherent treatment resistance.

Further to the results of the RAPIDO and PRODIGE 23 trials, one could argue the legitimacy of proposing a chemotherapy-free treatment for stage II/III rectal cancer patients. Nevertheless, it should be noted that participation to our trial will be restricted to patients with intermediate-risk tumours, those with high-risk features (who are also the

most likely to benefit from total neoadjuvant therapy) being excluded. Therefore, no issues in terms of patients' and investigators' compliance to the study design, and overall recruitment are foreseen.

Conclusion

The REGINA trial is the first prospective study to investigate the combination of an immune checkpoint inhibitor and a multi-kinase inhibitor with standard SCRT in the setting of intermediate-risk, stage II/III rectal cancer. The study is expected to start recruiting in January 2021, and accrual is anticipated to be completed after approximately 30 months. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist is available as supplementary file.

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Disclosure statement

Marc Van den Eynde – Consultancy, advisory board: Amgen, Eli Lilly, Merck, Pierre Fabre, Servier, MSD. Research funding: Merck, Roche. Travel grants: Amgen, Eli Lilly, Merck, Roche, Servier. Amelie Deleporte – Travel grants: Amgen, Ipsen. Alain Hendlisz – Consultancy, advisory board: Amgen, Bayer, Eli Lilly, Merck, Pierre Fabre, Servier, Sirtex. Research funding: Amgen, AstraZeneca, Ipsen, Leo Pharma, Merck, Roche, Sanofi, Teva Pharma. Travel grant: Merck, Roche, Sirtex. Francesco Sclafani – Consultancy, advisory board: Bayer. Research funding: AstraZeneca, Bayer, BMS, Roche. Travel grants: Bayer, Lilly. All other authors do not have any conflicts of interests.

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