505TiP - REGINA: a phase II trial of neoadjuvant regorafenib (Rego) in combination with nivolumab (Nivo) and short-course radiotherapy (SCRT) in intermediate-risk, stage II-III rectal cancer (RC)

Giacomo Bregni, Chiara Senti, Elena Acedo Reina, Luigi Moretti, Ana Veron, Pieter Demetter, Gabriel Liberale, Patrick Flamen, Javier Carrasco, Lionel D'Hondt, Karen Geboes, Yeter Gokburun, Marc Peeters, Marc Van den Eynde, Jean-Luc Van Laethem, Philippe Vergauwe, Marc Buyse, Amelie Deleporte, Alain Hendlisz, Francesco Sclafani

BACKGROUND

- Despite recent improvements, management of locally advanced rectal cancer (LARC) remains challenging, and many patients still experience recurrence.
- In preclinical models, combining regorafenib with an anti-PD-1 inhibitor led to superior tumour growth suppression as compared with either treatment alone.
- In a phase I clinical trial, remarkable results were reported for the combination of regorafenib and nivolumab in advanced MSS colorectal cancer. This synergistic effect is thought to be secondary to the anti-angiogenic effects of regorafenib and its potential to reduce TAMs, promote M1 macrophage conversion, and down-regulate expression of immunosuppressive factors.
- Building on these data, we designed a trial of regorafenib and nivolumab with standard short-course radiation therapy (SCRT) in the neoadjuvant setting of RC.

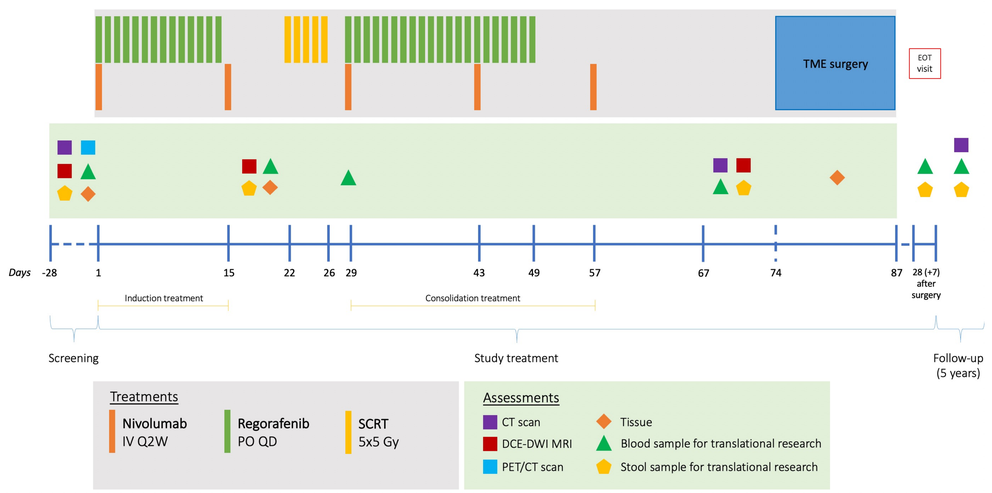
OBJECTIVES

- 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 promising pathological complete response (pCR) rate.
- Secondary objectives include:
  - Feasibility
  - Safety
  - R0 resection rate
  - Pathological tumour regression grade (pTRG)
  - Objective response rate
  - Tumour downstaging/downsizing
  - Event-free survival
  - 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, single-cell transcriptomics analysis, and the establishment of patient derived xenografts

TRIAL DESIGN

- REGINA is an academic, multicentre, single-arm, phase II trial.
- Eligible patients are treated according to the following plan:
  - **Induction treatment**
    - Nivolumab 240 mg IV days 1 and 15, and regorafenib 80 mg PO days 1 to 14
  - **SCRT**
    - Days 22 to 26
  - **Consolidation treatment**
    - Nivolumab 240 mg IV days 29, 43, and 57, and regorafenib 80 mg PO days 29 to 49
  - **Surgery**
    - 7-8 weeks after SCRT
- The study follows a Simon's two-stage design (null hypothesis pCR=12%, alternative hypothesis pCR=24%; α=5%, β=20%) with a maximum of 60 pts to be enrolled. A safety interim analysis is planned after the first 6 pts have completed treatment.
- Serial collection of tumour, blood, and stool samples is mandatory at pre-specified time points for exploratory correlative biomarker analyses.

Figure. REGINA trial schema



ENDPOINTS

- The **primary endpoint** is pathological complete response (**pCR**).
- Secondary endpoints include:
  - Toxicity
  - Compliance to treatment
  - R0 resection rate
  - pTRG
  - Objective response rate before surgery
  - Local recurrence rate
  - Distant recurrence rate
  - Event-free survival
  - Overall survival.

MAIN ELIGIBILITY CRITERIA

- Age ≥ 18 years old
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Histologically or cytologically verified adenocarcinoma of the rectum
- Tumour with distal border below the peritoneal reflection and within 15 cm from the anal verge
- 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
- Absence of distant metastases

SPONSORSHIP, FUNDING, AND TIMELINES

- The REGINA trial is sponsored by the Institut Jules Bordet and funded by Bayer
- The trial is registered at ClinicalTrials.gov (NCT04503694)
- The trial is planned to be run in 8-10 centres across Belgium. Study recruitment started in Q1 2021 and is anticipated to complete in Q3 2023.

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DISCLOSURES

GB declares no conflict of interest.

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Corresponding author: Dr. Francesco Sclafani (francesco.sclafani@bordet.be)