

ESMO Research Fellowship (01/2020 – 09/2021)

Giacomo Bregni

FINAL REPORT

Host Institute: Institut Jules Bordet, Brussels (Belgium)

Mentor: Alain Hendlisz

Project title: A phase II trial of neoadjuvant regorafenib in combination with nivolumab and short-course radiotherapy in intermediate-risk, stage II-III rectal cancer (REGINA)

Home Institute: IRCCS AOU San Martino, Genoa (Italy)

Introduction

Alternative and more effective pre-operative treatment strategies are needed to improve the outcome of locally advanced rectal cancer patients. Further to the routine use of multimodal treatment approaches including pre-operative SCRT or CRT followed by TME, no additional improvement in survival has been observed. 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 [1,2]. 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 [3]. Therefore, novel treatment options are needed to further improve the survival outcomes of these patients.

Rationale and Aim

Rectal cancer represents approximately 35-40% of all colorectal cancers and is an important contributor to the global tumour burden [4]. Single agent or combination immunotherapy has been recently investigated in both early-stage and metastatic colorectal cancer with impressive outcome results for the small group of patients with dMMR/MSI tumours [5,6]. Despite the vast majority of rectal cancers are pMMR/MSS, there has been an increasing interest for the investigation of immune checkpoint inhibitors in combination with pre-operative (chemo)radiotherapy in this setting and a number of clinical trials are currently ongoing. Indeed, the immuno-modulatory effects secondary to the use of radiotherapy may increase the therapeutic potential of immunotherapy in the pMMR/MSS rectal cancer population [7]. Furthermore, as already demonstrated in other cancer types, combining immunomodulatory agents with anti-angiogenic therapies may have a synergistic effect [8]. The hypothesis that combining regorafenib with nivolumab may lead to a synergistic anti-tumor effect through the modification of the tumor microenvironment is supported by the results of preclinical studies in murine models where combination treatment was observed to induce superior tumor growth suppression compared to either treatment alone [9]. Further confirmation has been provided by the findings of a recently completed phase I trial. Objective tumour response was observed in 44% of gastric cancer subjects and in 36% of colorectal cancer subjects [10]. Of note, all responding subjects (apart from one subject in the colorectal cancer cohort) had MSS tumours. The aim of this clinical research project is to develop the study protocol and finalise the set-up of an academic, multicentre, phase II clinical trial investigating safety, efficacy and predictive/prognostic biomarkers of a novel immunotherapy-based combination treatment in the neoadjuvant setting of rectal cancer.

Experimental design

This is a multicenter, single arm, phase II study.

Eligible patients will be treated with neoadjuvant treatment consisting of induction treatment with nivolumab (240 mg, day 1 and 14) plus regorafenib (80 mg/day, day 1-15) followed by standard SCRT (25 Gy in 5 fractions, day 22-26) and further treatment with nivolumab (240 mg, day 29, 43 and 57) plus regorafenib (80 mg/day, day 29-49). Surgery according to the principles of total mesorectal excision (TME) will be performed 7 to 8 weeks after completion of SCRT. Use of adjuvant chemotherapy will be left to the discretion of the treating physician. At baseline and pre-defined time points during treatment patients will undergo imaging scans (including CT thorax-abdomen, DCE-DWI MRI pelvis and PET/CT scans) as well as collection of biological samples (including tumour tissue, blood and stool).

Results, Conclusions and Future Perspectives

The study set-up has been concluded. I have prepared all study documents, including the trial protocol, the informed consent form, the lab manual, and the medical monitoring plan. The first six study sites have been activated, while the remaining four will follow once the safety interim analysis is performed. The correlative analyses have been planned, and we have reached agreements with the labs that will be in charge of them.

The REGINA trial has started recruiting in Q2 2021, and the first 4 patients have completed treatment. Patient 5 has recently signed the informed consent to participate in the study, and a slot for a potential new patient has been booked by one of the study sites. Once the first 6 patients will complete their treatment period, enrolment will temporarily halt and the safety interim analysis will take place.

Sample collection for the enrolled patients is ongoing. While most correlative analyses will take place after study conclusion, single-cell transcriptomics analysis and patient-derived xenografts implantations have already begun.

We believe that the REGINA trial will help shed light on the potential role of immune checkpoint inhibitors-based combinations in the neoadjuvant treatment of rectal cancer, and support the development of effective strategies to overcome the resistance to immunotherapy in MSS colorectal cancers.

List of Publications and Presentations Resulting from the Translational Research Project “A phase II trial of neoadjuvant regorafenib in combination with nivolumab and short-course radiotherapy in intermediate-risk, stage II-III rectal cancer (REGINA)”

Bregni G, et al. Rationale and design of REGINA, a phase II trial of neoadjuvant regorafenib, nivolumab, and short-course radiotherapy in stage II and III rectal cancer. *Acta Oncol* 2021; 60(4):549-553.

Bregni G, et al. 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). *ESMO Annual Meeting 2021* (poster presentation).

List of Publications and Presentations resulting from other projects during the fellowship period (if applicable)

Publications

Saude Conde R, Bregni G, Saad ED, Hendlisz A, Sclafani F. JCOG0603: are we really sure this was a negative trial? *J Clin Oncol* 2022 [Accepted for publication].

Personeni N, Smiroldo V, Giunta EF, Prete MG, Rimassa L, Bregni G, Sclafani F. Tackling Refractory Metastatic Colorectal Cancer: Future Perspectives. *Cancers (Basel)*. 2021 Sep 7;13(18):4506. doi: 10.3390/cancers13184506. PMID: 34572729; PMCID: PMC8472765.

Vandeputte C, Bregni G, Gkolfakis P, Guiot T, Pretta A, Kehagias P, Senti C, Reina EA, Van Bogaert C, Deleporte A, Geboes K, Delaunoit T, Demolin G, Peeters M, D'Hondt L, Janssens J, Carrasco J, Holbrechts S, Goeminne JC, Vergauwe P, Van Laethem JL, Flamen P, Hendlisz A, Sclafani F. Sex and Regorafenib Toxicity in Refractory Colorectal Cancer: Safety Analysis of the RegARd-C Trial. *Clin Colorectal Cancer*. 2021 Jul 24:S1533-0028(21)00071-2. doi: 10.1016/j.clcc.2021.07.006. Epub ahead of print. PMID: 34404621.

Giunta EF, Bregni G, Hendlisz A, Sclafani F. Anal squamous cell carcinoma: standards of care, new data and ongoing clinical trials. *Curr Opin Oncol.* 2021 Jul 1;33(4):372-377. doi: 10.1097/CCO.0000000000000748. PMID: 33882526.

Giunta EF, Bregni G, Pretta A, Deleporte A, Liberale G, Bali AM, Moretti L, Troiani T, Ciardiello F, Hendlisz A, Sclafani F. Total neoadjuvant therapy for rectal cancer: Making sense of the results from the RAPIDO and PRODIGE 23 trials. *Cancer Treat Rev.* 2021 May;96:102177. doi: 10.1016/j.ctrv.2021.102177. Epub 2021 Mar 16. PMID: 33798955.

Camera S, Akin Telli T, Woff E, Vandeputte C, Kehagias P, Guiot T, Critchi G, Wissam Y, Bregni G, Trevisi E, Pretta A, Senti C, Leduc S, Gkolfakis P, Hoerner F, Rothé F, Sclafani F, Flamen P, Deleporte A, Hendlisz A. Prognostic Value of the Pace of Tumor Progression as Assessed by Serial 18F-FDG PET/CT Scan and Liquid Biopsy in Refractory Colorectal Cancer: The COROLAN Trial. *Cancers (Basel).* 2020 Sep 24;12(10):2752. doi: 10.3390/cancers12102752. PMID: 32987838; PMCID: PMC7601470.

Bregni G, Sticca T, Camera S, Akin Telli T, Craciun L, Trevisi E, Pretta A, Kehagias P, Leduc S, Senti C, Deleporte A, Vandeputte C, Saad ED, Kerger J, Gil T, Piccart-Gebhart M, Awada A, Demetter P, Larsimont D, Hendlisz A, Aftimos P, Sclafani F. Feasibility and clinical impact of routine molecular testing of gastrointestinal cancers at a tertiary centre with a multi-gene, tumor-agnostic, next generation sequencing panel. *Acta Oncol.* 2020 Dec;59(12):1438-1446. doi: 10.1080/0284186X.2020.1809704. Epub 2020 Aug 21. PMID: 32820683.

Pretta A, Trevisi E, Bregni G, Deleporte A, Hendlisz A, Sclafani F. Treatment compliance in early-stage anal cancer. *Ann Oncol.* 2020 Oct;31(10):1282-1284. doi: 10.1016/j.annonc.2020.07.006. Epub 2020 Jul 22. PMID: 32707167.

Camera S, Deleporte A, Bregni G, Trevisi E, Pretta A, Telli TA, Polastro L, Gombos A, Kayumba A, Ameye L, Piccart-Gebhart M, Awada A, Sclafani F, Hendlisz A. MOMENTUM: A Phase I Trial Investigating 2 Schedules of Capecitabine With Aflibercept in Patients With Gastrointestinal and Breast Cancer. *Clin Colorectal Cancer.* 2020 Dec;19(4):311-318.e1. doi: 10.1016/j.clcc.2020.05.007. Epub 2020 May 29. PMID: 32631787.

Bregni G, Akin Telli T, Camera S, Deleporte A, Moretti L, Bali AM, Liberale G, Holbrechts S, Hendlisz A, Sclafani F. Adjuvant chemotherapy for rectal cancer: Current evidence and recommendations for clinical practice. *Cancer Treat Rev.* 2020 Feb;83:101948. doi: 10.1016/j.ctrv.2019.101948. Epub 2019 Dec 10. PMID: 31955069.

Bregni G, Akin Telli T, Camera S, Baratelli C, Shaza L, Deleporte A, Moretti L, Bali MA, Liberale G, Hendlisz A, Sclafani F. Grey areas and evidence gaps in the management of rectal cancer as revealed by comparing recommendations from clinical guidelines. *Cancer Treat Rev.* 2020 Jan;82:101930. doi: 10.1016/j.ctrv.2019.101930. Epub 2019 Nov 11. PMID: 31756591.

Akin Telli T, Bregni G, Camera S, Deleporte A, Hendlisz A, Sclafani F. PD-1 and PD-L1 inhibitors in oesophago-gastric cancers. *Cancer Lett.* 2020 Jan 28;469:142-150. doi: 10.1016/j.canlet.2019.10.036. Epub 2019 Oct 25. PMID: 31669518.

Selected presentations

Bregni G, Trevisi E, Senti C, et al. Prognostic value of baseline and early changes of circulating cell-free (cf)DNA in the neoadjuvant setting of early stage colon cancer (CC). *AACR Annual Meeting 2021* [Oral presentation].

Puccini A, Damiani A, Varesco L, Zupo S, Battistuzzi L, Bregni G, et al. Universal Screening for Lynch Syndrome : reflex testing to improve appropriateness of genetic counseling and diagnosis. *World Congress on Gastrointestinal Cancer 2020* [Poster discussion].

Bregni G, Sticca T, Akin Telli T, et al. Feasibility and clinical impact of routine molecular testing of gastrointestinal (GI) cancers at a tertiary centre with a multi-gene, next generation sequencing (NGS) panel. *Gastrointestinal Cancers Symposium 2020* [Poster presentation].

Bregni G, Akin Telli T, Camera S, et al. Grey areas and evidence gaps in the management of rectal cancer as revealed by the comparison of recommendations from national and international clinical guidelines. Gastrointestinal Cancers Symposium 2020 [Poster presentation].

Bregni G, Sticca T, Akin Telli T, et al. Feasibility and clinical impact of routine molecular testing of gastrointestinal (GI) cancers at a tertiary centre with a multi-gene, next generation sequencing (NGS) panel. Belgian Week of Gastroenterology 2020 [Oral presentation].

Distinctions

Conquer Cancer Foundation Merit Award – Gastrointestinal Cancers Symposium 2020

Conquer Cancer Foundation Merit Award – ASCO Annual Meeting 2021

Selection of Courses and Workshops Attended During the Fellowship

HarvardX - Data Science: R basics (01/2020)

Cours intensif de cancérologie digestive – BGDO/FFCD (05/2021)

Data Scientist with R – DataCamp (ongoing)

Pharmaceutical Bioinformatics – Uppsala University (ongoing)

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References

1. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22(1):29-42.
2. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22(5):702-715.
3. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a Multicentre, Randomised, Non-Blinded, Phase 3, Non-Inferiority Trial. *Lancet Oncol* 2017; 18(3):336-346.
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68:394-424.
5. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020;26(4):566-576.
6. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020;383(23):2207-2218.
7. Galluzzi L, Buqué A, Kepp O, et al. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol* 2017;17(2):97-111.
8. Wu RY, Kong PF, Xia LP, et al. Regorafenib Promotes Antitumor Immunity via Inhibiting PD-L1 and IDO1 Expression in Melanoma. *Clin Cancer Res* 2019;25(14):4530-4541.
9. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603). *J Clin Oncol* 2019;no. 15_suppl:2522.
10. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal



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Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). J Clin Oncol 2020;38(18):2053-2061.

SIGNATURES

Award Recipient full name

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28/1/2022

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HENDLISZ Alvin

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