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

Giacomo Bregni  

FINAL REPORT

Host Institute: Institut Jules Bordet, Brussels (Belgium)  
Mentor: Alain Hendiisz  
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)”


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

Publications

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


Selected presentations


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)

Acknowledgements

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References

10. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal

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