Study Title:	A randomized, phase IIb study of adju**V**ant durvalumab plus regorafenib vs untreated control in stage **IV** colorectal c**A**ncer patients with no evidence of disease (NED) **VIVA** trial
EudraCT Number:	2020-001588-10
Study Phase:	IIb
Study design	Randomized, open-label, crossover, multicentre
Indication:	Colorectal Cancer
Product Name:	Durvalumab Regorafenib
Sponsor:	IRCCS Ospedale Policlinico San Martino Largo Rosanna Benzi 10, 16132 Genova, Italy 
Principal investigator	Alberto Sobrero Medical Oncology Unit IRCCS Ospedale Policlinico San Martino Largo Rosanna Benzi 10, 16132 Genova, Italy
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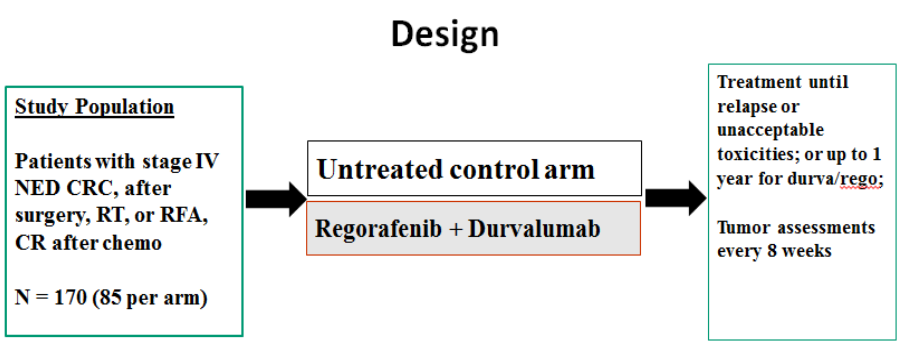
Study Site Contact	Fondazione GISCAD Gruppo Italiano per lo studio dei carcinomi dell'apparato digerente
Supporters	Astra Zeneca will provide Durvalumab Bayer will provide Regorafenib AIRC will provide funding to conduct the trial
Countries	Italy
Centers	39
Planned sample size (N)	170 patients 85 patients per arm (2 arms)
Planned study start/end dates	First Patient First Visit 2020 Q4 Last Patient Last Visit 2022 Q4 Study end date 2025 Q4
Recruitment period	~~24 months~~ 30 months
Rational and Objectives	To date, the introduction of new effective drugs, improvements in surgical and locoregional techniques and supportive care have led to a median overall survival of over 30 months in patients with metastatic colon-rectal cancer (CRC). Thanks to this survival prolongation, medical oncologists and patients are more and more attracted by the possibility to reach a non evidence of disease (NED) state not only under the classical favourable condition of a

	single or double liver metastases, but also under the less favourable conditions of multiple metastases even at different sites and even after 2 or 3 lines of treatment, whenever the clinical course allows. Therefore, this population of stage IV NED patients is growing. Previous studies showed that median relapse-free survival (RFS) ranges from 8 to 16-18 months in R0 patients, but up to 90% of these patients eventually relapse: hence, there is an unmet clinical need for effective systemic treatment to reduce the chances of recurrence in stage IV NED patients. After curative resection, international guidelines suggest regimens like FOLFOX, CAPOX, capecitabine or 5-FU/leucovorin alone as potential "adjuvant" therapy, but no standard treatments have been established and active surveillance with no treatment is the standard of care, especially if the patient has received prior chemotherapy as it will be the case for most of our patient population. A phase Ib trial (EPOC1603) tested safety and toxicity profile of Regorafenib combined with an immune-checkpoint inhibitor (ICI) (Nivolumab) in gastric and colorectal cancer. The rather promising results of the phase Ib study has been presented to the ASCO 2019 Annual Meeting, suggesting the activity of Regorafenib in combination with ICIs. The combination of Durvalumab and Tremelimumab showed to prolong median overall survival by 2.5 months compared with best supportive care alone in patients with advanced treatment-refractory colorectal cancer (phase II Canadian Cancer Trials Group (CCTG) CO.26 study). However, no data are available about the role of Durvalumab as adjuvant therapy together with a tyrosin-kinase inhibitor (TKI) like Regorafenib in CRC. Given the promising results of these drugs in the metastatic setting, the main objective of this study is to evaluate the efficacy (DFS) of Regorafenib plus Durvalumab versus untreated control in the adjuvant setting for stage IV NED CRC patients.
Design	 Control arm: no treatment. Crossover to Regorafenib + Durvalumab upon relapse Sperimental arm: Regorafenib 80mg d1-21 q28 + Durvalumab 1500mg q28 up to 1 year
Run-in phase	The combination of an immune-checkpoint inhibitor plus TKI anti-angiogenic agents has been extensively investigated in several trials (phase II and III) in different types of tumors, with no evidence of new safety signals. Although specific data are not available on the combination of durvalumab and regorafenib, we would not expect major toxicity issues. Therefore, a short run-in phase will be conducted on 4 patients using a starting dose of 40mg/die of regorafenib and 1500mg durvalumab to be escalated after two months to 80mg/die and 1500mg, respectively, if no problems arise. Should major toxicity issues arise at dose of 80mg/die of regorafenib, the run-in phase will be extended to additional 4 patients at the dose of 40mg/die of regorafenib plus 1500mg of durvalumab.

Feasibility: need for crossover	Any trial randomizing active treatments vs a no –treatment-control presents feasibility problems. In this setting, where the large majority of patients will relapse within few months, randomizing to an inactive control vs the possibility of receiving entirely innovative treatments will constitute a prohibitive feasibility obstacle. This may be overcome by offering the most innovative treatment (REGO DURVA) to patients randomized to control whenever they relapse. This will also provide an opportunity for the conduct of a "satellite" phase IIa trial among a patient population that should present very good conditions and with a not too bulky disease load. Because this crossover will not affect the primary endpoint of the study, this part of the study will be addressed and better specified only if the main protocol is approved. As to the amount of Durvalumab to be provided for this part, we may expect that 1/3 of patients will not be eligible for the cross over and we may postulate that among those starting palliative Durvalumab + Regorafenib, patients will receive a median of 4 months of therapy.
Primary Endpoint	Disease Free Survival (DFS) will be defined by Punt, JNCI 2007 In addition to the Punt definition, the following condition will be considered DFS event: Two consecutive increases in CEA levels above upper limit level (time gap decided by the clinical investigator).
Secondary Endpoints	● 18-months Disease Free Survival (DFS) ● Adverse events and Toxicity ● Overall Survival (OS) ● Compliance to the experimental treatment.
Exploratory Endpoints	● Association of translational research data (ctDNA, NGS) with outcome
Main Inclusion criteria	To be enrolled in this study each patient must meet all of the following criteria at the time of randomization: 1. Signed ICF, after oral as well as written information; 2. ≥ 18 years; 3. ECOG Performance Status ≤ 1; 4. Histologically confirmed diagnosis of colorectal adenocarcinoma; 5. Patients must be NED after completion of any treatments for stage IV CRC, including resections, RFA, RT with or without neoadjuvant/adjuvant therapies or CR after chemotherapy; 6. Patients must be randomized within 10 weeks since the achievement of the NED state. Those who have also received adjuvant therapy following the locoregional treatment are still eligible, provided they are randomized within 4 weeks since the last adjuvant chemotherapy cycle; 7. NED ascertained by means of CT scan and/or PET scan and/or MRI 8. CEA within normal limits 9. No highly suspicious lesion on imaging 10. Adequate organ function 11. Women of childbearing potential must use safe contraception.
Main Exclusion criteria	A patient who meets any of the following criteria at the time of randomization will be excluded from the study: 1. Any other active malignancy or prior history of malignancy within 5 years 2. Patients with microsatellite instability (MSI) or DNA Mismatch Repair Deficiency (dMMR) are not allowed.

	3. Any form of systemic disease that, in the opinion of the Investigator, would make the subject unsuitable for the study (including autoimmunity) or would prevent compliance with the study protocol.; 4. Serum creatinine > 2.0 x ULN; 5. Pregnant or lactating women; 6. Mental disease that could affect patient compliance in the study; 7. Participation in any other investigational study.
Investigational Treatments	Name - Dosage form - Dosage - Mode of administration - Schedule 1. Regorafenib – film-coated tablets – 80 mg – orally – once daily for the first 21 days of each 28-day cycle, up to 1 year 2. Durvalumab – vial – 1500mg – IV – infusion every four weeks up to 1 year
Justification of Sample Size	The study is set up as an exploratory phase 2B trial with sufficient patient numbers to broadly explore the differences between the experimental arm regimen and the control group. The randomisation plan is 1 to 1. Patients will be stratified by centre. The main aim of this study is to estimate the effect of the experimental arm relative to control group on the endpoint of interest: disease-free survival. In view of the treatment setting, disease-free survival is considered as the most sensitive clinical endpoint. The sample size is calculated according to a median DFS extimate of 6 months in the control group and to a forecast of 2 years duration of uniform accrual and 2 years of follow-up after the end of accrual. To achieve 90% power at a 0·05 two-sided significance level to detect a 40% fall in DFS event rate (corresponding to a median increase from 6 to 10 months), 160 patients have to be accrued and followed up for at least 2 year. Assuming an attrition rate of approximately 5%, a total of 170 patients (85 per arm) have to be randomized.
Statistical considerations	All randomised patients will be included in the primary assessment of efficacy (the intention-to-treat population). Safety analyses will include all treated patients (randomised patients receiving at least one dose of study drug). A log-rank test, will be used to assess disease-free survival and overall survival. A Cox proportional hazards model will be used to calculate HRs and 90% CIs). Sensitivity analysis of disease-free survival will be also done with a restricted mean survival time approach that does not assume the proportional hazards model, as outlined by Anderson and colleagues. For patients in the control group after progression, a cross-over is allowed. A descriptive summaries of the duration of this crossover treatment (overall and from the time of initial progression) will be done. The proportions of patients achieving an objective response or disease control will be compared with a logistic regression model adjusted for relevant covariates. Effect on survival of regorafenib plus durvalumab regimen within this crossover part of the study will be analysed by means of proportional hazard time depend analysis. Median progression-free survival will be calculated with the reverse Kaplan-Meier method. All statistical testing is two-sided at the nominal 10% significance level, with no adjustment for multiplicity. All patients who receive at least one regorafenib plus durvalumab dose will be included in the safety analysis.