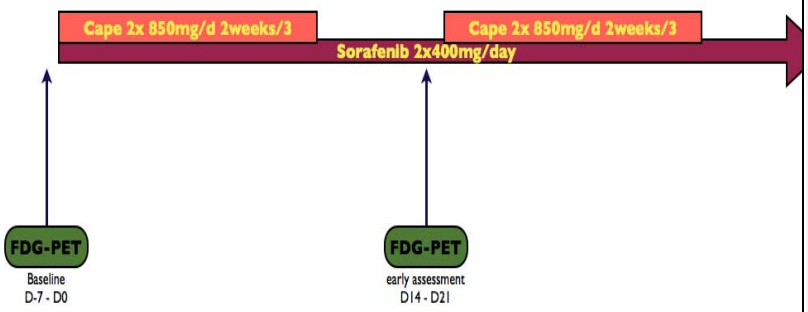
So More : Study Synopsis

Title of Study	**Sorafenib and Capecitabine in refractory Metastatic Colorectal Cancer : "So More" study**
Indication	Advanced chemorefractory colorectal cancer
Treatment line	**mCRC** 3d line mutated KRAS **or** 4th line wild-type KRAS
Study Coordinator/ Principal investigator for IJB	Alain Hendlisz MD, Unité d'Oncologie Digestive, Service de Médecine, Institut Jules Bordet, Université Libre de Bruxelles
Primary endpoint	a) To obtain a preliminary assessment about the activity of the combination by estimating overall survival of the study population at a fixed time point (6 months) b) To compare as an exploratory analysis the overall survival of metabolic responders versus non-responders.
Secondary endpoints	• To estimate the progression-free survival distribution of the study population • To determine the objective response rate of the study population as assessed by standard imaging. • To describe the adverse reactions associated with the study regimen in the study population. • To determine the correlation of early metabolic response, as assessed by FDG-PET/CT immediately before the first and the second cycles of treatment with the study regimen, with overall survival, progression-free survival, and response. • To determine the correlation of *growth modulation index* (GMI), defined as the time to progression under the study regimen over the time to progression under the latest prior regimen administered to the patient, with overall survival and progression-free survival.
Study design	Prospective non-randomized phase II study

	
Inclusion criteria	• Participants must have histologically confirmed colorectal cancer that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective. • All standard chemotherapy agents (fluoropyrimidines, irinotecan, and oxaliplatin) and monoclonal antibodies (bevacizumab, cetuximab, and panitumumab) are allowed as administered therapy before study entry. No more than two lines of treatment for metastatic or recurrent disease are allowed, except for patients with KRAS-wt tumors, for which third line with anti-EGFR agents is allowed. • Age over 18 years. • Life expectancy of greater than 12 weeks. • ECOG performance status ≤ 1. • Participants must have normal organ and marrow function as defined below: • Leukocytes ≥ 3,000/mcL • Absolute neutrophil count ≥ 1,500/mcL • Platelets ≥ 100,000/mcL • total bilirubin within 2 × normal institutional limits • AST/ALT/PAKL levels ≤ 5 × institutional upper limit of normal • creatinine within 2 × normal institutional limits or creatinine clearance ≥ 35mL/min • Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. • Ability to understand and the willingness to sign a written informed consent document.
Exclusion criteria	Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study. • Participants who have had chemotherapy or radiotherapy within 4 weeks prior

	to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. • Participants may not be receiving any other experimental agents. • Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. • History of allergic reactions attributed to compounds of similar chemical or biologic composition to sorafenib or capecitabine. • Bleeding diathesis, history of cardiovascular ischemic disease or cerebrovascular incident within the last six months, or major surgery within four weeks. • Uncontrolled concurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. • Pregnant women are excluded from this study because sorafenib and capecitabine are antitumor agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with sorafenib or capecitabine, breastfeeding should be discontinued if the mother is treated with sorafenib or capecitabine. These potential risks may also apply to other agents used in this study. • Uncontrolled Diabetes • Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.
Eligibility criteria	• Delay between assessment of screening criteria and first PET/CT < 21 days • FDG PET/CT positive and metabolically assessable lesions (>2cm diameter on baseline diagnostic CT) and lesions with a SUVmax x 2 superior to the SUVmax in normal liver or blood pool in cardiac cavities (if liver abnormal) at the baseline FDG PET/CT. • Blood glucose < 150 mg/dl at the time of FDG administration in diabetic patients. Insulin or oral anti-diabetic medication is not allowed on the days of PET/CT imaging. • Blood glucose <120 mg/dl at the time of FDG administration in NON diabetic patients • Respect of technical specifications to perform FDG PET/CT examinations from the Standard Procedures Imaging Manual (SPIM) • Delay between the first PET/CT imaging and the start of Sorafenib-

<table>
<tr><td></td><td>Capecitabine < 7 days
• Second PET/CT imaging performed on D21 (range: D19-D23, with D1 as the first day of chemo administration)</td></tr>
<tr><td>Treatment doses</td><td>
<table>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th></tr>
<tr><td>Sorafenib</td><td>200mg in the morning, 400mg in the evening; escalation to 400mg twice daily after 1 cycle</td><td>Oral</td><td>Continuous dosing</td><td>21 days (3 weeks)</td></tr>
<tr><td>Capecitabine</td><td>850mg/m^2 twice daily</td><td>Oral</td><td>Days 1-14, weeks 1-2</td><td></td></tr>
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<tr><td>Sample size justification/statistical analysis</td><td>Sample size has been estimated in order to be able to test the null hypothesis that the overall survival rate at 6 months is less than 30%. This hypothesis will be tested using a binomial distribution. The study should be able to reject the null hypothesis, using a 1-sided test with α = 0.025, with a power of 90% in case of a true overall survival ≥ 50% (rate at 6 months). The sample size required is 66 eligible patients (to be followed for 6 months minimum). Analysis will be done on all registered patients using an ITT approach on all eligible patients.

A co-primary endpoint is to compare the overall survival of patients assessed as early PET responders and of patients assessed as early PET non responders (the clinicians will remain blinded for PET response assessment). For this primary analysis, patients who will undergo the second PET assessment will be eligible and time zero for measuring survival will be the date of this second PET examination. It is anticipated that 95% of the patients will be eligible for the analysis with a 50% expected rate of early PET non-responders (result obtained from an unpublished study conducted at Jules-Bordet Institute). With 66 patients registered, we anticipate then that 63 patients will be available for the co-primary endpoint. With 63 patients and our assumption that the HR for the comparison between the survival distributions will be around 0.385 (based on the previously mentioned unpublished study), we will need using a two-sided logrank test at the 2.5% level (2.5% chosen because of the existence of 2 co-primary endpoints), 54 events (power of 90%). With 63 patients and a follow-up after accrual of 1 year, we should reach this number of 54 events. However, to account for another possible 5% drop-out (patient's refusal for undergoing the second PET examination for instance), sample size should be increased to 70 eligible patients.

The study is designed as a single-arm phase II study, with all patients accrued in</td></tr>
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	one stage. No early stopping rules will be used. However, our estimation of 50% expected rate of early PET responders is coming from a prospective unicentric cohort of 38 patients undergoing chemotherapy for 1st line or 2nd line treatment of advanced colorectal cancer with a few of them having received biological agents together with chemotherapy. Our estimation may then not be reliable due to small sample size and different patients population. If this rate of early PET responders proves to be higher, we should be prepared to increase our sample size for targeting the same power of 90%. For instance, if the rate is 67% instead of 50%, the required number of events would be 62 instead of 54. If the rate is 75%, the number of events should be increased to 73. The number of patients would have then to be adapted according to the rate of evaluable patients for this PET objective and the rate of patients lost to follow-up. For reassessing the required numbers of events, we did not change our hypothesis of detecting, if true, a hazard ratio of 0.385 in favour of early PET responders. We plan, during the course of accrual, to assess the rate of patients evaluable for the PET objective, of early PET responders and, if possible the rate of patients lost to follow-up in order to check whether we need to review our planned sample size. However, no interim analysis will be done on the primary endpoints.
Number of sites	4 Belgian sites (referring to PEPITA network PET centers in Belgium)
Study duration	2.5 years recruitment + 6 months follow-up = 3 years total