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**ARTICLE DETAILS**

<table>
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<th>Regorafenib Assessment in Refractory advanced Colorectal Cancer: RegARd-C study protocol.</th>
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<td>AUTHORS</td>
<td>Hendlisz, Alain; Deleporte, Amelie; Vandeputte, Caroline; Charette, Nicolas; Paesmans, Marianne; Guiot, Thomas; Garcia, Camilo; Flamen, Patrick</td>
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**VERSION 1 - REVIEW**

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<th>REVIEWER</th>
<th>Sharlene Gill</th>
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<td>BC Cancer Agency</td>
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<td>Vancouver, BC Canada</td>
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<td>REVIEW RETURNED</td>
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**GENERAL COMMENTS**

This is a protocol submission describing a planned single arm phase II study to evaluate whether early FDG PET response is a predictor of treatment response in patients with refractory MCRC on regorafenib therapy.

Interesting study question. My main concern is that the objectives are over-stated for the given study design. For instance, the wording of the primary objective as stated is confusing – "To identify in a population of patients bearing advanced, refractory CRC, those who draw no benefit from treatment with regorafenib. OS will be used as primary endpoint". This is a single arm, non-randomized study and all subjects are receiving regorafenib – in the absence of a placebo-controlled arm, a determination of 'no benefit' cannot be made. Are the investigators trying to state that the primary objective is to determine whether day 14 FDG-PET based metabolic response assessment is a predictive correlate for OS in patients treated with regorafenib?

In addition to non-randomized design, study limitations should also address that the treatment discontinuation rate for regorafenib is often high - how will this be addressed? Are dose modifications permitted? Is a starting dose of 160mg/day mandated (as many pts actually start on 120mg/day).

Has study feasibility been considered? What are the expected accrual timelines?
REVIEWER
Masato Nakaura
Aizawa Hospital

REVIEW RETURNED
27-Jan-2015

GENERAL COMMENTS
This is a study design paper about metabolic response assessment using PET and genomic and epigenetic biomarker analysis in regorafenib treatment. It is very interesting and meaningful trial. I have two concern.

1) There are no criteria to asses the FDG-PET results. What is the primary endpoint in FDG-PET study? What is the definition of target region(s) in FDG-PET study? How do you define the anti-tumor effect (CR or PR or SD or PD)?

2) And how do you analyze the relationship of results of FDG-PET and clinical parameters (OS, PFS, and etc)? Statistical method was described only about genomic research. But in this study, to identify non-responders to regorafenib, FDG-PET study seems to be more important.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Sharlene Gill

• This is a protocol submission describing a planned single arm phase II study to evaluate whether early FDG PET response is a predictor of treatment response in patients with refractory MCRC on regorafenib therapy.

Interesting study question. My main concern is that the objectives are over-stated for the given study design. For instance, the wording of the primary objective as stated is confusing – “To identify in a population of patients bearing advanced, refractory CRC, those who draw no benefit from treatment with regorafenib. OS will be used as primary endpoint”. This is a single arm, non-randomized study and all subjects are receiving regorafenib – in the absence of a placebo-controlled arm, a determination of ‘no benefit’ cannot be made. Are the investigators trying to state that the primary objective is to determine whether day 14 FDG-PET based metabolic response assessment is a predictive correlate for OS in patients treated with regorafenib?

Authors’ reply: We agree with the reviewer, that in absence of randomization, the certitude of “no-benefit” cannot be made formally as the discrimination between a predictive and a prognostic effect of metabolic non-response is not possible, even in case of an otherwise proven effective treatment. We therefore have made the following change in the sentence (page 9):

“To identify in a population of patients bearing advanced, refractory CRC, those who draw no benefit from treatment with regorafenib”, which becomes:

“To identify in a population of patients bearing advanced, refractory CRC, those unlikely to draw a substantial benefit from treatment with regorafenib.”

• In addition to non-randomized design, study limitations should also address that the treatment discontinuation rate for regorafenib is often high - how will this be addressed? Are dose modifications permitted? Is a starting dose of 160mg/day mandated (as many pts actually start on 120mg/day).

Authors’ reply: The discontinuation rate is indeed high during a treatment with regorafenib, especially considering that the start dose was fixed at 160mg/day, the company’s recommended dose, and despite a rather liberal doses modifications authorization. This issue had been anticipated as
described in the statistics section (page 15) and copied hereunder: “In order to reach this number of evaluable patients, the overall sample size of registered patients will be adapted during the study accrual. Taking into account an expected 20-25% drop-out rate between registration and the time of further examinations, between 124 and 140 patients will be accrued.”

We made no changes in the manuscript for this part.

• Has study feasibility been considered? What are the expected accrual timelines?
Authors’ reply: The study feasibility has been considered, and the study has run accordingly in 16 clinical centers referring patients to 5 EARL-accredited PET/CT centers. At the time of this reply, an accrual of 141 patients in 11 months has been achieved. No clinical or metabolic analysis has however been conducted up to now, except for the patients’ safety issues.

Reviewer Name Masato Nakaura
This is a study design paper about metabolic response assessment using PET and genomic and epigenetic biomarker analysis in regorafenib treatment. It is very interesting and meaningful trial. I have two concern.

1) There are no criteria to asses the FDG-PET results. What is the primary endpoint in FDG-PET study? What is the definition of target region(s) in FDG-PET study? How do you define the anti-tumor effect (CR or PR or SD or PD)?

• Authors’ reply: the primary endpoint of RegARd-C is to identify in a population of patients bearing advanced, refractory CRC, those unlikely to draw a substantial benefit from treatment with regorafenib. Overall Survival (OS) will be used as primary endpoint. The metabolic assessment has been previously described in references 13 and 15, which report also the selection of target lesions. Otherwise, the inclusion criteria report also the definition of a target lesion (page 11): “Presence of at least one metabolically measurable tumoral lesion on FDG PET/CT fulfilling following criteria: Size ≥ 1.5cm and FDG uptake above the background liver uptake.”
Among secondary objectives is the validation of this assessment methodology in the study’s population.
In order to clarify this point, the references explaining the assessment methodology have been expressively pointed out by a sentence added in page 14: “The results of the metabolic assessment remains blinded for the clinical investigator, and will follow a predetermined 3-step methodology previously described.[13,15]”

2) And how do you analyze the relationship of results of FDG-PET and clinical parameters (OS, PFS, and etc)? Statisticial method was described only about genomic research. But in this study, to identify non-responders to regorafenib, FDG-PET study seems to be more important.

Authors’ reply: We will use a binary assessment of PET metabolic response based on previous results obtained from another trial in the same patients population and with an early metabolic assessment too (ref.15). We will define OS and PFS from the time of of second PET and analyze the relationship with PET metabolic response with univariate and multivariate Cox regression models.
Regorafenib assessment in refractory advanced colorectal cancer: RegARd-C study protocol

Alain Hendilisz, Amélie Deleporte, Caroline Vandeputte, Nicolas Charette, Marianne Paesmans, Thomas Guiot, Camilo Garcia and Patrick Flamen

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