## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Intraperitoneal irinotecan with concomitant FOLFOX and bevacizumab for patients with unresectable colorectal peritoneal metastases: protocol of the multicenter, open-label, phase II, INTERACT-II trial |
| **AUTHORS** | de Vlasakker, Vincent; Guchelaar, Niels; van den Heuvel, Teun; Lurvink, Robin; van Meerten, Esther; Bax, Ramon; Creemers, Geert-Jan; van Hellemond, Irene; Brandt-Kerkhof, Alexandra; Madsen, Eva; Nederend, Joost; Koolen, Stijn; Nienhuijs, Simon W.; Kranenburg, Onno; de Hingh, Ignace; Verhoef, Cornelis; Mathijssen, Ron; Burger, Jacobus |

## VERSION 1 – REVIEW

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| **REVIEWER** | Somashekhar, S. P.<br>Manipal Academy of Higher Education (MAHE), Surgical Oncology |
| **REVIEW RETURNED** | 28-Sep-2023 |

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| **GENERAL COMMENTS** | Overall Assessment:<br>The protocol submitted for review outlines a phase II study aimed at investigating the efficacy and safety of a novel treatment approach for patients with unresectable colorectal peritoneal metastases (CPM). The research question addressed in this study is of clinical relevance, as patients with CPM often face limited treatment options and a poor prognosis. Combining systemic chemotherapy with intraperitoneal irinotecan represents a potentially promising strategy to improve outcomes in this patient population.<br><br>1. Introduction:<br>The introduction provides essential context for the study by highlighting the significance of CPM and the limitations of current treatment options. It clearly states the research objective, which is to evaluate the overall survival of patients treated with intraperitoneal irinotecan in combination with mFOLFOX4 and bevacizumab. Mentioning the previously determined recommended phase II dose (RP2D) of intraperitoneal irinotecan (75 mg) from a phase I study strengthens the rationale for the chosen treatment regimen.<br><br>2. Materials and Methods:<br>a. Study Design:<br>- The study design, a single-arm phase II trial, is appropriate for assessing the efficacy and safety of the intervention in a relatively small cohort.<br>- Inclusion criteria (85 patients with unresectable CPM) are clearly defined, ensuring homogeneity within the study population. |

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| | - The use of diagnostic laparoscopy and the placement of peritoneal access ports are well-explained procedures that enhance the clarity of the protocol.<br><br>b. Treatment Regimen:<br>- The description of the treatment regimen, which includes intraperitoneal irinotecan, mFOLFOX4, and bevacizumab, is comprehensive and includes dosages and administration schedules.<br>- The rationale for using this combination of treatments is explained, providing a basis for the study's approach.<br><br>c. Outcome Measures:<br>- The primary outcome measure, overall survival, is clinically relevant and appropriate for assessing the efficacy of the intervention.<br>- Key secondary outcomes, including progression-free survival, safety, patient-reported outcomes, and pharmacokinetics, are relevant and add depth to the study's findings.<br><br>d. Hypothesis:<br>- The study's hypothesis is clearly stated, predicting a 4-month increase in overall survival as a result of the trial treatment.<br><br>3. Conclusion:<br>The submitted protocol for the journal is well-structured and addresses an important clinical question regarding the treatment of unresectable CPM. It provides a clear rationale, detailed methodology, and relevant outcome measures. Additionally, the protocol would benefit from a brief section on statistical methods to analyze the primary and secondary endpoints.<br><br>Overall, this protocol submission has the potential to contribute valuable insights into the management of colorectal peritoneal metastases and warrants consideration for publication after addressing the mentioned points. |

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| **REVIEWER** | Flood, Michael<br>Peter MacCallum Cancer Centre |
| **REVIEW RETURNED** | 11-Nov-2023 |

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| **GENERAL COMMENTS** | This is a very interesting concept and I wish the authors well in completing the trial.<br><br>My only query is with regards to IP port placement/irinotecan instillation in patients with metachronous peritoneal disease. Some of these patients will have dense adhesions at the time of laparoscopy due to their initial surgery for the colorectal primary. The study protocol should describe what would happen in these scenarios. If possible would full adhesiolysis occur at the time of diagnostic laparoscopy? Would some of these patients have to be excluded due to some quadrants of the abdominal cavity being inaccessible? Having already performed INTERACT I, have the authors encountered this problem in the initial 18 patients? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1:

The protocol submitted for review outlines a phase II study aimed at investigating the efficacy and safety of a novel treatment approach for patients with unresectable colorectal peritoneal metastases (CPM). The research question addressed in this study is of clinical relevance, as patients with CPM often face limited treatment options and a poor prognosis. Combining systemic chemotherapy with intraperitoneal irinotecan represents a potentially promising strategy to improve outcomes in this patient population. The submitted protocol for the journal is well-structured and addresses an important clinical question regarding the treatment of unresectable CPM. It provides a clear rationale, detailed methodology, and relevant outcome measures. Additionally, the protocol would benefit from a brief section on statistical methods to analyze the primary and secondary endpoints. Overall, this protocol submission has the potential to contribute valuable insights into the management of colorectal peritoneal metastases and warrants consideration for publication after addressing the mentioned points.
Response: We thank the reviewer for his thorough evaluation of our manuscript. The reviewer suggested the addition of a brief section on the statistical methods for the primary and secondary endpoints. The manuscript already contains a paragraph in which we describe statistical methods and tests we are planning to use to analyze the primary and secondary endpoints (page 12-14: paragraph 'statistical methods'). In our opinion, this section contains the required information for the reader to be informed about the statistical methods. We hope the reviewer agrees with this perspective. We have made an important adjustment in the exploratory analysis of the patient reported outcomes. Instead of choosing a pragmatical p-value of 0.01 to correct for multiple testing, we will perform a Bonferroni-correction per item.

Reviewer #2:
This is a very interesting concept and I wish the authors well in completing the trial.
My only query is with regards to IP port placement/irinotecan instillation in patients with metachronous peritoneal disease. Some of these patients will have dense adhesions at the time of laparoscopy due to their initial surgery for the colorectal primary. The study protocol should describe what would happen in these scenarios. If possible would full adhesiolysis occur at the time of diagnostic laparoscopy? Would some of these patients have to be excluded due to some quadrants of the abdominal cavity being inaccessible? Having already performed INTERACT I, have the authors encountered this problem in the initial 18 patients?
Response: We thank the reviewer for his comment. The reviewer makes an interesting point about patients who have dense adhesions and how to deal with those patients when placing the intraperitoneal port. However, within our experience with the INTERACT I trial, we have not encountered this problem. The placement of the diagnostic laparoscopy is a fairly easy procedure in which we lay the catheter into the peritoneal cavity, preferably with the tip in the pelvis. However, when some quadrant are deemed inaccessible, we can put the tip in another quadrant of the lower peritoneal cavity if that place is better accessible. Therefore, adhesions are no contra-indication for the placement of the IP port. We have added a sentence to the paragraph 'study treatment: port placement' that clarifies this (page 8).

Editor(s)' Comments to Author:
- Please amend the trial registration number in the manuscript
to NCT06003998.
Response: We have changed the trial registration number to the NCT number.
- Please place the "Strengths and limitations of this study" section after the abstract.
Response: We have moved the "Strengths and limitations of this study" section as requested.
- Inspired by the work of the patient partnership strategy at The BMJ
(https://www.bmj.com/campaign/patient-partnership), BMJ Open is encouraging active patient involvement in setting the research agenda. BMJ Open now require authors of all submissions to the journal to include a Patient and Public Involvement statement. The Patient and Public Involvement statement should be included as a sub-heading in the methods section of all manuscripts. It should

provide a brief description of any patient involvement in study design or conduct of the study, as well as any plans to disseminate the results to study participants. If patients and or public were not involved please state this. See our Instructions for Authors for further details: https://bmjopen.bmj.com/pages/authors/#reporting_patient_and_public_involvement_in_research
Response: We have added the “Patient and Public Involvement” statement under the method section.
- Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found (http://www.spirit-statement.org/)
Response: The SPIRIT checklist is included with our revised manuscript.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Flood, Michael<br>Peter MacCallum Cancer Centre |
| **REVIEW RETURNED** | 27-Nov-2023 |

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| **GENERAL COMMENTS** | I have no further comments or questions. Good luck to the authors |