PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	First-line palliative systemic therapy alternated with electrostatic pressurized intraperitoneal aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases: protocol of a multicenter, single-arm, phase II study (CRC-PIPAC-II)
AUTHORS	Lurvink, Robin; Rauwerdink, Paulien; Rovers, Koen; Wassenaar, Emma; Deenen, Maarten; Nederend, Joost; Huysentruyt, Clément; van 't Erve, Iris; Fijneman, Remond; van der Hoeven, Erik; Seldenrijk, Cornelis; Constantinides, Alexander; Kranenburg, Onno; Los, Maartje; Herbschleb, Karin; Thijs, Annemarie; Creemers, Geert-Jan; Burger, Jacobus; Wiezer, Marinus; Nienhuijs, Simon W.; Boerma, Djamila; de Hingh, Ignace

VERSION 1 – REVIEW

REVIEWER	Paolo Sammartino MD PhD Department of Surgery "Pietro Valdoni" Sapienza University of Rome Italy
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	The Authors face a real problem represented by the standardization of treatment including PIPAC and systemic chemotherapy in patients with peritoneal metastases from colorectal cancer not amenable of cytoreduction and HIPEC. The Authors rightly represent as a limitation of the study the common evaluation of colorectal and appendicular cancer and the analysis of histotypes with different clinical behaviour. In the continuation of the study after overcoming problems related to safety and feasibility of the trial it will be appropriate to analyze more homogeneous classes. Another aspect that should be taken into consideration in the future concerns the definition of unresectable peritoneal metastases. The adoption of a cutoff according to PCI would seem appropriate.

REVIEWER	REYMOND MA National Center for Pleura and Peritoneum, University of Tübingen, Germany I am the inventor of PIPAC and of ePIPAC, holder of several patents on PIPAC and related technologies, and a shareholder of Capnomed GmbH, Zimmern o.R., Germany.
REVIEW RETURNED	26-Nov-2020

GENERAL COMMENTS	This is a valuable, solid study protocol. Design is fine for Phase I-II, the focus is on safety, which is correct since bevacizumab is known to cause bowel perforations with no PIPAC. Thus, some bowel perforations have to be expected. Indeed, it might be

	difficult to determine the causality of CTCAE Grade 3+ using a bidirectional protocol, and the absolute incidence in the absence of a control group with systemic chemo alone. There is a significant risk is to record a high rate of adverse events in a difficult population of patients with advanced, non-resectable peritoneal metastasis. The incidence of severe CTCAE after combined palliative systemic chemotherapy + bevacizumab has not been evaluated so far in comparative studies in this population of patients. Since efficacy is only an explorative outcome criterion, the detection of an additional anticancer effect, and the evaluation of the risk-benefit balance will be challenging. Of course, if there is a low rate of CTCAE 3+, this study might pave the way for a randomized trial that could show a benefit of bidirectional, chemo for patients with no true therapy option. The technical aspects of the therapy protocol are OK for me. It would have been nice to cite the first in-human use of ePIPAC (PMID: 30911614) but this is not essential.

REVIEWER	Jan Franko MercyOne Medical Center, Des Moines, IA, USA
REVIEW RETURNED	29-Nov-2020

GENERAL COMMENTS	Lurvink et al. provide a description of planned prospective trial of PIPAC in addition to first-line systemic therapy for colorectal peritoneal metastases. They explore an important question of combining regionally delivered and systemically delivered therapy among patients with most unfavorable mCRC (Stage IVc) featuring peritoneal metastases. This study is likely to bring an important information for design of future therapy and will inform about early response/non-response by direct observation and sampling. It is well thought of and well written. I have a few comments and questions only. Comments: 1. Rationale for oxaliplatinum PIPAC, with or without systemic 5-FU should be better elucidated. While PIPAC with oxaliplatinum is best studied, PRODIGE-7 (ASCO 2018 abstract) does not suggest clinical activity of such “bidirectional” dosing. 2. What do authors think about omission of prolonged infusion of 5-FU as opposed to a single infusion? Single infusion is known to have lesser efficacy. 3. Is even dose of 5-FU during PIPAC in this study any meaningful? 4. Sequencing of ePIPAC-OX and systemic therapy and radiological restaging should be re-thought. This is obviously not in purview of the reviewer, but of the authors. Please consider radiologic re-evaluation prior to any PIPAC, so radiologic, operative, and molecular sampling can be correlated at the same time. 5. There is no mention of serum CEA level, or other markers such as CTC, or cf-DNA. 6. There is no mention of relevant molecular markers in this small sample: RAS, BRAF, MSI/MSS, Her2, ALK, etc. At least BRAF is prognostic enough (Jones 2018).

REVIEWER	Aditi BHATT Zydus Hospital, Ahmedabad, India
REVIEW RETURNED	30-Nov-2020

GENERAL COMMENTS	This is the protocol of an ongoing phase 2 study that aims to study the safety, feasibility, anti-tumor activity, patient-reported outcomes, costs, and systemic pharmacokinetics of first-line e-PIPAC and systemic chemotherapy in patients with isolated unresectable CPM. The manuscript is well written and covers all the details of the study, its strengths and limitations well. Some minor clarifications/changes could be helpful 1. The study will enroll patients with unresectable disease which could include those with a high PCI (>20 as per the Dutch national guidelines) or disease that cannot be completely resected due to its anatomical location. As stated in the ancillary and post-study care, some of these patients may become eligible for further curative treatment and hence I would suggest that the term 'palliative' is dropped from the title of the manuscript and text both. That patients will receive further supportive, palliative or curative intent treatment could also be added in the section on 'evaluation' on page 11. 2. It should be specified if patients who are responding will receive further cycles of PIPAC or continue systemic treatment alone once the 3 sessions of PIPAC are over 3. The date (proposed) of commencement of the study is missing in the manuscript 4. The authors could add some explanation for selecting bevacizumab and not anti-EGFR therapy 5. Though the targetted therapy is uniform, there is still heterogeneity in the systemic chemotherapy, specifically as FOLFOXIRI and bevacizumab may produce a greater response than the other regimens. The sample size of 20 may be small to address this heterogenity and this could be a limitation of the study 6. On page 13, line 1, is it grade < 2 or grade > 2? 7. The results of the PIPOX trial (ref 35) were recently published and showed a dose limiting toxicity at 90m/m2 of oxaliplatin. Some comment on these results could be added to the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Paolo Sammartino, Umberto I Policlinico di Roma Comments to the Author:
The Authors face a real problem represented by the standardization of treatment including PIPAC and systemic chemotherapy in patients with peritoneal metastases from colorectal cancer not amenable of cytoreduction and HIPEC. The Authors rightly represent as a limitation of the study the common evaluation of colorectal and appendicular cancer and the analysis of histotypes with different clinical behaviour. In the continuation of the study after overcoming problems related to safety and feasibility of the trial it will be appropriate to analyze more homogeneous classes. Another aspect that should be

taken into consideration in the future concerns the definition of unresectable peritoneal metastases. The adoption of a cutoff according to PCI would seem appropriate.

After exploring the safety and feasibility of bidirectional therapy in this histopathologically heterogeneous, yet clinically homogeneous population of patients (a homogeneity that contrasts other PIPAC-studies), future randomized trials can indeed be designed with more homogeneous histopathological patient groups. The definition of 'unresectable peritoneal metastases' is adjusted and defined in line 10-11 of page 8.

Reviewer: 2
Dr. Marc Reymond, Eberhard Karls Universität Tübingen Comments to the Author:
This is a valuable, solid study protocol. Design is fine for Phase I-II, the focus is on safety, which is correct since bevacizumab is known to cause bowel perforations with no PIPAC. Thus, some bowel perforations have to be expected. Indeed, it might be difficult to determine the causality of CTCAE Grade 3+ using a bidirectional protocol, and the absolute incidence in the absence of a control group with systemic chemo alone. There is a significant risk is to record a high rate of adverse events in a difficult population of patients with advanced, non-resectable peritoneal metastasis. The incidence of severe CTCAE after combined palliative systemic chemotherapy + bevacizumab has not been evaluated so far in comparative studies in this population of patients. Since efficacy is only an explorative outcome criterion, the detection of an additional anticancer effect, and the evaluation of the risk-benefit balance will be challenging. Of course, if there is a low rate of CTCAE 3+, this study might pave the way for a randomized trial that could show a benefit of bidirectional, chemo for patients with no true therapy option.

The technical aspects of the therapy protocol are OK for me.

It would have been nice to cite the first in-human use of ePIPAC (PMID: 30911614) but this is not essential.

We agree that the addition of bevacizumab to systemic chemotherapy and PIPAC-oxaliplatin potentially could lead to an increased risk of gastro-intestinal complications, such as bleeding or perforations. We agree with the reviewer that using a bidirectional treatment in a single-arm study complicates the interpretation of causes of adverse events, that the risk of adverse events is high in this population with advanced colorectal peritoneal metastases, and that the interpretation of anti-tumor effect is difficult in a single-arm study. However, we believe this study is the appropriate first step to prospectively investigate the feasibility and safety of first-line systemic chemotherapy and bevacizumab, alternated with PIPAC in patients with unresectable colorectal peritoneal metastases. As mentioned by the reviewer, this study might pave the way for future (phase 2/3) randomized trials assessing the value of this first-line bidirectional regimen.

We added the citation of the first in-human use of ePIPAC to the Introduction, on line 18 of page 6.

Reviewer: 3
Dr. Jan Franko, Mercy Medical Center
Comments to the Author:
Lurvink et al. provide a description of planned prospective trial of PIPAC in addition to first-line systemic therapy for colorectal peritoneal metastases. They explore an important question of combining regionally delivered and systemically delivered therapy among patients with most unfavorable mCRC (Stage IVc) featuring peritoneal metastases. This study is likely to bring an important information for design of future therapy and will inform about early response/non-response by direct observation and sampling. It is well thought of and well written. I have a few comments and questions only.

Comments:
1. Rationale for oxaliplatinum PIPAC, with or without systemic 5-FU should be better elucidated. While PIPAC with oxaliplatinum is best studied, PRODIGE-7 (ASCO 2018 abstract) does not suggest clinical activity of such "bidirectional" dosing.

3. Is even dose of 5-FU during PIPAC in this study any meaningful?

Combined reply for comment 1 and 3;

The present study was initiated almost a year before the recent publication of the PRODIGE-7 trial. At the time of initiation, we decided to administer PIPAC with oxaliplatin and an intraoperative intravenous bolus of 5-fluorouracil and leucovorin with the aim to enhance intraperitoneal oxaliplatin activity. However, we agree with the reviewer that the rationale for this regimen could be questioned by the recently published PRODIGE-7 trial, which questions the role of the addition of oxaliplatin-based HIPEC to (near-) complete cytoreductive surgery in heavily pretreated patients with CPM. Before trial participation, the majority of the patients received preoperative systemic therapy, mainly consisting of oxaliplatin-containing chemotherapy. This may have resulted in an acquired resistance of the remaining intraperitoneal cancer cells to oxaliplatin. Furthermore, no mandatory wash-out period of prior systemic therapy was required before commencing trial treatment.
In contrast, patients in the current CRC-PIPAC-II study are either chemotherapy-naïve or have undergone a >6 months wash-out period. Therefore, we hypothesize that tumor cells in this setting may be more sensitive to oxaliplatin than in the PRODIGE 7 trial.

Moreover, the settings of both studies significantly differ, as patients in the present study undergo palliative instead of curative intent treatment and receive repetitive instead of a single administration of intraperitoneal oxaliplatin. In a palliative setting, oxaliplatin with 5-fluorouracil and leucovorin is internationally recommended as first-line systemic therapy in the treatment of metastatic colorectal cancer.

Finally, oxaliplatin (with or without intraoperative intravenous 5-fluorouracil and leucovorin) is the most used and best studied PIPAC-drug for patients with CPM, and is frequently combined with first-line systemic chemotherapy and bevacizumab in many centers worldwide. Nevertheless, the safety and feasibility of bidirectional therapy have never been prospectively investigated in clinical trials. Altogether, it remains important to address this evidence gap and to assess the safety and feasibility of the combination of first-line palliative systemic therapy and repetitive PIPAC in the present study.

We added these arguments in line 8-21 of page 18.

2. What do authors think about omission of prolonged infusion of 5-FU as opposed to a single infusion? Single infusion is known to have lesser efficacy.

The intraoperative intravenous bolus of 5-fluorouracil and leucovorin prior to PIPAC-oxaliplatin is merely used as a chemo-sensitizer, similar to the Dutch CRS-HIPEC protocol.

4. Sequencing of ePIPAC-OX and systemic therapy and radiological restaging should be re-thought. This is obviously not in purview of the reviewer, but of the authors. Please consider radiologic re-evaluation prior to any PIPAC, so radiologic, operative, and molecular sampling can be correlated at the same time.

We agree that performing more frequent radiological restaging could reduce potential bias when radiologic re-evaluations are compared to other evaluations (e.g. intra-operative PCI, histopathological sampling). In our previous study (CRC-PIPAC, NCT03246321), assessing repetitive PIPAC-OX monotherapy for unresectable CPM, radiological restaging was performed after each PIPAC. However, radiological response of CPM was not observed in any patient (Rovers et al., Ann Surg Oncol, 2021, in press). These findings question the value of such frequent radiological response assessment in this setting. Therefore, we chose to perform less radiological evaluations in the present study.

5. There is no mention of serum CEA level, or other markers such as CTC, or cf-DNA.

Biochemical tumor response was stated as a secondary outcome measure in the section 'Outcomes', yet not specified for the type of tumor marker. We have specified the carcinoembryonic antigen (CEA) tumor marker in line 18 of page 13.

Blood is collected regularly during the trial participation for translational research (at baseline and before each ePIPAC; as mentioned in line 11-13 on page 12). These samples will be used for the analysis of CTC and cf-DNA.

6. There is no mention of relevant molecular markers in this small sample: RAS, BRAF, MSI/MSS, Her2, ALK, etc. At least BRAF is prognostic enough (Jones 2018).

We agree that these molecular markers are relevant in the treatment of metastatic colorectal cancer. Though not an official baseline variable according to the study protocol, these molecular markers are frequently determined in metastatic colorectal cancer patients in the Netherlands, we aim to report the mutation status in the final trial report.

Reviewer: 4
Dr. Aditi Bhatt, Zydus Hospital
Comments to the Author:
This is the protocol of an ongoing phase 2 study that aims to study the safety, feasibility, anti-tumor activity, patient-reported outcomes, costs, and systemic pharmacokinetics of first-line e-PIPAC and systemic chemotherapy in patients with isolated unresectable CPM. The manuscript is well written and covers all the details of the study, its strengths and limitations well. Some minor clarifications/changes could be helpful

1. The study will enroll patients with unresectable disease which could include those with a high PCI (>20 as per the Dutch national guidelines) or disease that cannot be completely resected due to its anatomical location. As stated in the ancillary and post-study care, some of these patients may become eligible for further curative treatment and hence I would suggest that the term 'palliative' is dropped from the title of the manuscript and text both. That patients will receive further supportive, palliative or curative intent treatment could also be added in the section on 'evaluation' on page 11.

We agree that, according to currently available literature on PIPAC-oxaliplatin for (initially) unresectable CPM, some patients may become eligible for curative-intent treatment after receiving bidirectional treatment. Unfortunately, both in currently available literature and in the results from our previous study (CRC-PIPAC, NCT03246321), this only applies to a very small group of patients, as most patients have diffuse and extensive peritoneal metastases. Thus, bidirectional therapy is given with palliative-intent. To prevent unrealistic expectations, we prefer to keep the term 'palliative' in the title and the manuscript, but we do not rule out additional curative-intent treatment when considered feasible.

2. It should be specified if patients who are responding will receive further cycles of PIPAC or continue systemic treatment alone once the 3 sessions of PIPAC are over

We agree that this was insufficiently clarified, and have specified this in line 17-20 of page 11.

3. The date (proposed) of commencement of the study is missing in the manuscript

The date of study commencement was indeed missing, thus we have added this issue in line 15 of page 14.

4. The authors could add some explanation for selecting bevacizumab and not anti-EGFR therapy

We agree that the rationale for bevacizumab as targeted therapy was insufficiently documented. According to the ESMO guideline for metastatic colorectal cancer, bevacizumab and anti-EGFR therapy can be added to first-line palliative systemic therapy when disease control is the main goal of treatment. According to the Dutch guideline, bevacizumab is the first-choice biological agent in the palliative treatment of metastatic colorectal cancer, since it can be administered to patients with both wildtype KRAS and patients with mutated KRAS.

We have added this clarification and additional references in line 19-24 of page 9.

5. Though the targetted therapy is uniform, there is still heterogeneity in the systemic chemotherapy, specifically as FOLFOXIRI and bevacizumab may produce a greater response than the other regimens. The sample size of 20 may be small to address this heterogenity and this could be a limitation of the study

We agree that the incorporation of different first-line systemic regimens (including FOLFOXIRI) could result in clinical heterogeneity, and that the sample size of 20 patients will be too small to address this issue. Although the heterogeneity in systemic regimens could impede the interpretation of preliminary efficacy outcomes, this is not the major focus of the present study.

We have added this potentially relevant clinical heterogeneity as a limitation in our discussion, in line 4-6 of page 18.

6. On page 13, line 1, is it grade < 2 or grade > 2?

The primary outcome of the study is the number of CTCAE adverse events grade 3 or higher (≥3), as described on line 18-21, page 12. A secondary outcome, as described on line 4-6, page 13, is the number of CTCAE adverse events grade 2 or lower (i.e. grade ≤2).

7. The results of the PIPOX trial (ref 35) were recently published and showed a dose limiting toxicity at 90m/m2 of oxaliplatin. Some comment on these results could be added to the discussion.

Thank you for this notification. As the results of the PIPAC-OX and PIPOX trials were indeed recently published, we updated this section of the discussion in line 22-26 of page 18 and line 1-4 of page 19.