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Complete List of Authors:	van Kooten, Job; Erasmus MC Kanker Instituut, Surgical Oncology and Gastro-Intestinal Surgery Dietz, Michelle; Erasmus MC Kanker Instituut, Surgical Oncology Guchelaar, Niels; Erasmus Medical Center, Medical Oncology Brandt-Kerkhof, Alexandra; Erasmus MC Kanker Instituut, Department of Surgical Oncology Koolen, Stijn; Erasmus MC Cancer Institute, Department of Medical Oncology; Erasmus MC Cancer Institute, Department of Pharmacy Burger, Jacobus; Catharina Hospital, Department of Surgery Mathijssen, Ron; Erasmus MC Cancer Institute, Department of Medical Oncology Verhoef, Cornelis; Erasmus MC Kanker Instituut, Surgical Oncology and Gastro-Intestinal Surgery Aerts, Joachim; Erasmus MC Kanker Instituut, Pulmonary Medicine Madsen, Eva; Erasmus MC Kanker Instituut, Surgical Oncology
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Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma – a Phase I/II Dose Escalation and Safety Study: INTERACT MESO.

Job P. van Kooten (MD)[1#], Michelle V. Dietz (MD)[1#], Niels A.D. Guchelaar (BSc)[2], Alexandra R.M. Brandt-Kerkhof (MD)[1], Stijn L.W. Koolen (MD, PhD)[2,3], Jacobus W.A. Burger (MD, PhD)[4], Ron H.J. Mathijssen (MD, PhD)[2], Cornelis Verhoef (MD, PhD)[1], Joachim G.J.V. Aerts (MD, PhD)[5¶], Eva V.E. Madsen (MD, PhD)[1¶]

[1] Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[2] Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[3] Department of Hospital Pharmacy, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[4] Department of Surgery, Catharina Cancer Institute, Eindhoven, The Netherlands

[5] Department of Pulmonary Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[#] These authors contributed equally

[¶] These authors share the senior author position

Corresponding Author: Michelle Dietz

Email: m.dietz@erasmusmc.nl

Telephone: +31 107042125

Address: Room Na-2113, Department of Surgical Oncology
Erasmus MC Cancer Institute
Dr. Molewaterplein 40
3015 GD, Rotterdam, the Netherlands

Disclosures:

No conflicts of interests.

Abstract

Introduction. Malignant peritoneal mesothelioma (MPM) is a rare, aggressive tumor, arising primarily from the peritoneum. The only potentially curative treatment is cytoreductive surgery (CRS) with

hyperthermic intraperitoneal chemotherapy (HIPEC). However, the majority of patients are not eligible to undergo this treatment. The benefit of systemic treatment for these patients is limited, at the cost of considerable morbidity. Hence, there is need for appropriate palliative treatment options for MPM patients. As MPM rarely disseminates outside the abdominal cavity, these patients might benefit from local treatment. A higher, more effective dose of chemotherapy can directly be delivered at the site of disease. Systemic uptake will be limited, likely resulting in less toxicity. The aim of the INTERACT MESO trial is to determine the maximum tolerable dose (MTD) of intraperitoneal (IP) paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and toxicity, feasibility, and the pharmacokinetic profile of this treatment.

Methods and analysis. The INTERACT MESO trial is a prospective, open-label, single-center, phase-1 study with a classic three-plus-three dose escalation design. The study population consists of adult patients with primary MPM, without extra-abdominal disease, that are not eligible to undergo CRS-HIPEC. According to standard of care work-up for CRS-HIPEC, patients will undergo diagnostic laparoscopy (DLS) to determine the feasibility of CRS-HIPEC. In case CRS-HIPEC is not considered feasible, a peritoneal port-a-cath (PAC) system will be placed. Through this PAC, 8-16 weekly cycles of intraperitoneal chemotherapy will be administered.

Ethics and dissemination. The Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands) and the Research Ethics Committee (METC, Rotterdam, The Netherlands) have granted permission to carry out this study protocol. The results of this trial will be submitted for publication in a peer-reviewed scientific journal.
Trial registration number: Nederlands Trial Register: NL9718. EudraCT: 2021-003637-11.

Keywords: Malignant peritoneal mesothelioma, Intraperitoneal chemotherapy, Paclitaxel, Systemic chemotherapy, Palliative treatment, Dose-escalation study

Word count: 3711

Strengths and limitations of this study

- The INTERACT MESO trial may contribute to a more effective treatment with better quality of life for patients with malignant peritoneal mesothelioma (MPM) who are not eligible for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC).
- In patients with peritoneal metastases of ovarian cancer and small numbers of MPM patients who underwent CRS-HIPEC, (adjuvant) intraperitoneal (IP) chemotherapy with paclitaxel showed promising results.
- This study will provide clinicians and scientist important information about monotherapy with IP paclitaxel, by determination of the maximum tolerated dose (MTD), safety and feasibility of this treatment.
- In this phase I dose-escalation trial the value of IP paclitaxel on overall survival cannot be determined, when the MTD is determined, larger phase II and III clinical trials will be conducted to determine the effect on survival.

Introduction

Malignant Peritoneal Mesothelioma (MPM) is a rare, but aggressive neoplasm with a poor prognosis, arising primarily from the serosal lining of the peritoneal cavity.(1) Currently, the only possibly curative treatment is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).(2, 3) In the Netherlands, only a minority of patients undergo this treatment.(1) For patients that are not eligible to undergo CRS-HIPEC, the treatment options are limited. Overall response rates to systemic chemotherapy are low (20-25%), though morbidity rates are high, with a grade 3-4 hematological toxicity rate up to 38%.(4-6) Moreover, the two-year survival rate for these patients is only 20%.(1) Combination checkpoint-inhibition-therapy with nivolumab and Ipilimumab has been proposed as a new treatment option for MPM patients. However, this treatment has comparable morbidity rates to that of systemic chemotherapy, and its benefit for MPM patients is not proven.(7, 8) Because of the high morbidity rate, and the limited effectiveness of systemic treatment it is debatable whether these therapies are suitable as palliative treatment for patients with MPM. Due to lack of appropriate palliative treatment options, the majority of MPM patients in the Netherlands (63%) currently receives no anti-tumor treatment.(1)

For peritoneal metastases from several types of cancer, local treatment with intraperitoneal (IP) chemotherapy has been proposed as a palliative treatment option. This therapy can be delivered through an IP port-a-cath (PAC), and potentially has major advantages over systemic treatment. A higher, more effective dose of chemotherapy can directly be delivered at the site of disease, while

systemic uptake is limited, likely resulting in fewer toxicity. Paclitaxel is a chemotherapeutic agent that is considered extremely favorable for IP use.(9) Due to its large molecular weight and lipophilic properties, it is slowly cleared from the peritoneal cavity when administered locally. This results in an area under the curve (AUC) after IP- administration that is up to a 1000-fold (3-log) higher than that in plasma, while peritoneal concentrations persist up to 48 hours after administration.(10) This considerably increases drug activity.

Markman et al. presented the first phase-1 dose-escalation study of IP-paclitaxel in ovarian cancer patients, pre-treated with systemic chemotherapy.(10) They established the maximum-tolerable-dose (MTD) to be 175 mg/m^2 at a two-to-three week interval. Another dose-escalation study was performed by Francis et al., delivering a lower dose at a weekly frequency.(11) These patients were also pre-treated with systemic chemotherapy. Severe abdominal pain was uncommon and only low-grade leukopenia, fatigue and stomatitis was observed. Grade 3-4 gastro-intestinal complications were observed in 15% of patients. Francis et al. recommended a dose of 60-65 mg/m^2 IP-paclitaxel in weekly cycles. Markman et al. performed a phase-2 trial in 80 ovarian cancer patients, using 60 mg/m^2 of IP-paclitaxel, in 16 weekly cycles after pre-treatment with systemic chemotherapy.(12) The majority of patients (70%) received all planned 16 courses. Grade-3 complications were rare, with abdominal pain, neuropathy, and neutropenia in one, two and one patients respectively. Bowel perforation, a rare but potentially life-threatening complication, was observed once in the phase-1 trial (3%), but was not observed in the phase-2 trial. Five patients were removed from the study due to excessive toxicity, and three patients due to catheter malfunction. In total, 18 (24%) patients achieved a complete response.

As the effectiveness of systemic therapy is limit and MPM very rarely disseminates outside the abdominal-cavity, the use of IP paclitaxel monotherapy seems a logical and promising step. The group of Paul Sugarbaker utilizes long-term IP-administration of paclitaxel as an adjuvant treatment to CRS-HIPEC for patients with MPM. They use doses of 20 mg/m^2 daily for five consecutive days monthly, starting 4-6 weeks postoperatively. Some of these patients showed remarkable survival, despite incompleteness of cytoreduction at CRS-HIPEC.(13-15) Another major advantage of the suggested treatment is that ascites, a common MPM-symptom that causes major morbidity, can be drained through the same PAC-system.

Currently, there are no studies that investigate IP paclitaxel as non-adjuvant monotherapy in MPM patients. The main objective of this clinical trial is to determine the maximum tolerable dose (MTD) of

IP paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and toxicity, feasibility, and the pharmacokinetic profile of this treatment. When the MTD is determined, further research is needed to determine the effect on survival.

Methods and analysis

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (supplementary appendix 1).(16)

Study design

Trial setting

The INTERACT MESO trial is a prospective, open-label, single-center, phase-1 study with a classic three-plus-three dose escalation design (figure 1). The defined dose levels are 100 mg, 150 mg, and 200 mg paclitaxel. This study is conducted in the Erasmus MC Cancer Institute, a tertiary referral hospital, located in Rotterdam, the Netherlands. Trial registration details are described in table 1.

Table 1. WHO trial registration data set

Primary registry and trial identifying number	EudraCT number: 2021-003637-11 Netherlands Trial Register: NL9718
Date of registration in primary registry	September 2021
Protocol version	Protocol version 4.0, date November 22th, 2021
SPIRIT guidelines data set for clinical trials	See supplementary file
Secondary Identifying Numbers	Dutch competent authority (CCMO): NL78373.078.21 Local medical ethics committee (METC): MEC-2021-0697
Source(s) of monetary or material support	Erasmus MC Foundation, Rotterdam, the Netherlands
Primary sponsor	Erasmus University Medical Center, Rotterdam, the Netherlands
Secondary sponsors	Not applicable
Contact for public queries	M.V. Dietz, study coordinator

	Department of surgical oncology Erasmus MC, Rotterdam, the Netherlands m.dietz@erasmusmc.nl, (+31)010-7042125
Contact for scientific queries	E.V.E. Madsen, principal investigator Department of surgical oncology Erasmus MC, Rotterdam, the Netherlands e.madsen@erasmusmc.nl, (+31)010-7041082
Public title	Treatment of abdominal mesothelioma with intra-abdominal chemotherapy: INTERACT MESO
Scientific title	Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma – a Phase I/II Dose Escalation and Safety Study: INTERACT MESO
Countries of recruitment	The Netherlands
Health conditions or problems studied	Malignant peritoneal mesothelioma
Interventions	Patients undergo a diagnostic laparoscopy (DLS) according to standard work-up for CRS-HIPEC. If the disease is considered not resectable, a peritoneal port-a-cath (PAC) will be placed. Through this PAC, intraperitoneal paclitaxel will be administered in weekly cycles.
Key inclusion and exclusion criteria	Key inclusion criteria: Confirmed diagnosis of malignant peritoneal mesothelioma, WHO-ECOG performance status 0-1, age ≥ 18 years old, and adequate organ function and bone marrow reserves. Key exclusion criteria:

	Extra-abdominal disease/metastatic disease, serious concomitant disease or active infections, any medical or psychological impediment to probable compliance with the protocol, and pregnant or lactating women.
Study type	Open label single center phase I/II study
Date of first enrolment	Planned February 2022
Target sample size	11 – 21 according to dose escalation
Recruitment status	Pending
Primary outcome	Maximum tolerable dose (MTD) of intraperitoneal (IP) paclitaxel monotherapy in patients with MPM
Key secondary outcome(s)	Safety and toxicity, feasibility, and the pharmacokinetic profile of intraperitoneal paclitaxel monotherapy

CRS, cytoreductive surgery; DLS, diagnostic laparoscopy; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; PAC, port-a-cath, SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

Study population

The study population consist of adult patients with primary MPM, without extra-abdominal disease, that are not eligible to undergo CRS-HIPEC. Potentially eligible patients will be referred by their local clinician or through self-referral to a medical specialist. A member of the study team will inform patients about the trial at the outpatient clinic, and an eligibility assessment will be performed. In order to be eligible to participate in the study, potential subjects must meet all of the following inclusion criteria:

- Histological confirmed diagnosis of malignant peritoneal mesothelioma
- Patients that are not eligible (or willing) to undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)
- Age ≥ 18 years
- Written informed consent by the patient according to the ICH-GCP and national/local regulations
- Patients must be ambulatory (WHO-ECOG performance status 0 or 1)

- Ability to return to the Erasmus MC for adequate follow-up as required by this protocol
- Patients must have normal organ function and adequate bone marrow reserve as assessed by the following laboratory requirements; absolute neutrophil count >1.5 * 10^9/l, platelet count >100*10^9/l and hemoglobin >6.0 mmol/l. Patients must have a bilirubin <1½ x upper limit of normal (ULN), serum AST and ALT <2.5 x ULN

A potential subject who meets any of the following exclusion criteria will be excluded from participation in the study:

- Incapacitated patients
- Extra-abdominal disease/metastatic disease established by preoperative CT-scan of thorax-abdomen and/or PET-scan. Imaging not older than two months at time of surgery
- Medical or psychological impediment to probable compliance with the protocol
- Serious concomitant disease or active infections
- History of auto-immune disease or organ allografts, or with active or chronic infection, including HIV and viral hepatitis
- Serious intercurrent chronic or acute illness such as pulmonary (COPD or asthma) or cardiac (NYHA class III or IV) or hepatic disease or other illness considered by the study coordinator to constitute an unwarranted high risk for participation in this study
- Pregnant or lactating women; for all women of child-bearing potential a negative urine pregnancy test will be required as well as the willingness to use adequate contraception during the study until 4 weeks after finishing treatment
- Absence of assurance of compliance with the protocol
- An organic brain syndrome or other significant psychiatric abnormality which would comprise the ability to give informed consent, and preclude participation in the full protocol and follow-up

Patient timeline and additional procedures

A flowchart of the study is shown in figure 2. A more detailed description of (additional) study procedures is presented in table 2.

	Before 1st visit	1st visit	2nd visit	DLS	1st post-op visit	IP-CTx								Response evaluation	IP-CTx 9-16th cycle[6]	Response evaluation	Last study visit
						1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle	7th cycle	8th cycle				
MTB[1]	X															X	
Medical history	X	X															
In- / exclusion criteria		X															
Provide information about the study		X	X														
Written informed consent			X														
Vital signs			X		X	X	X	X	X	X	X	X	X		X		
Physical examination (Incl. weight)[2]			X		X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		X[2]		
Operability check (Anesthetist)			X														
Hematology and blood chemistry			X		X[2]	X	X	X	X	X	X	X	X		X		
Viral serology			X														
Pregnancy test[2]			X														
Placement of peritoneal PAC[3]				X													
Visit medical oncologist			X		X									X		X	
CT-scan chest/abdomen	X[4]					X[5]								X		X	
Intraperitoneal chemotherapy						X	X	X	X	X	X	X	X		X		
Performance status			X		X	X	X	X	X	X	X	X	X	X	X	X	
Chemotherapy toxicity evaluation (CTCAE 5.0)						X	X	X	X	X	X	X	X	X	X	X	
Collection of blood and peritoneal fluid for PK analysis						X			X								

Removal of peritoneal PAC																X[8]

Table 2. Study procedures

[1)] Scans and reports of (referred) patients are first discussed in a multi-disciplinary tumor board. When patients are considered candidates for HIPEC-procedure, they are seen in the outpatient clinic.

[2)] If applicable.

[3)] In case complete cytoreduction is deemed impossible.

[4)] If not performed by referring center.

[5)] Maximum of four weeks before start of study treatment.

[6)] In case of no progression of disease (i.e. CR, PR or SD) and if patient is willing.

[7)] At cycle 16 if applicable.

[8)] Optional, according to patient preference and life expectancy

Screening

The multidisciplinary tumor board will review all referred patients who are possibly eligible to participate in the study. Potential candidates for CRS-HIPEC will visit the surgical oncology outpatient clinic, where they will be informed about the treatment options, including the study, and undergo standard screening procedures. The standard of care CRS-HIPEC screening procedure includes a CT scan of the thorax and abdomen (not older than two months before surgery), lab testing (including kidney and liver panels, and blood cell count), anesthetic assessment, and a diagnostic laparoscopy (DLS). If the disease is considered not resectable during DLS, and if the patient meets the inclusion/exclusion criteria, the patient is eligible for inclusion. Patients who are considered ineligible for CRS-HIPEC, based on parameters that were obtained before DLS, but have no contra-indication for IP chemotherapy, can also participate in the study.

Surgical procedures

Patients will be operated under general anesthesia, according to local hospital procedures. During the diagnostic laparoscopy, the extent of disease is assessed according to the 'peritoneal carcinomatosis index' (PCI). Ascites fluid will be collected for storage in the local MPM biobank. The surgeon will determine feasibility of complete cytoreduction. If it is deemed impossible to achieve complete cytoreduction, a port-a-cath (PAC) system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients may leave the hospital that same day, with careful (including written) instructions for e.g. hygiene. Patients are seen in the outpatient clinic approximately a week after surgery by a medical oncologist. The start date of the first treatment cycle of chemotherapy will be determined.

Chemotherapy

Patients will receive intraperitoneal paclitaxel (dose according to current dose-level) dissolved in 1 liter of saline (0.9% NaCl), pre-warmed to 37°C through the PAC that was placed during laparoscopy. Patients will receive all necessary pre-medications prior to infusion, according to the local standard protocol for intravenous administration of paclitaxel. If present, prior to infusion, ascites will be drained through the PAC, and stored in the MPM biobank. Administration of IP-chemotherapy will take about 1.5-2 hours. After infusion, patients are instructed to switch position frequently to maximize distribution of chemotherapy in the peritoneal cavity. Patients will be observed for two hours after chemotherapy administration. If no adverse events occur during this period, patients will be discharged with careful instructions to contact the hospital if any alarming symptoms do develop. During the first and the fourth cycle of IP-chemotherapy, additional blood samples and IP-fluid

samples will be collected for pharmacokinetic (PK) analysis. The 24-hour AUC will be calculated for systemic and IP-paclitaxel. Other pharmacokinetic parameters such as the maximum concentration (Cmax) and the elimination half-life ($t_{1/2}$) will also be determined.

Patients will initially receive eight weekly cycles of IP-chemotherapy. After the start of the first cycles, following cycles can be delayed, at the discretion of the medical oncologist in case of a medical indication (e.g. neutropenia). If a cycle is delayed for more than two weeks, this is considered a dose limiting toxicity. After the first eight cycles, response evaluation will take place. Depending on this outcome, another eight cycles can be initiated. In case of ongoing therapy response, there is no limit to the number of cycles.

Follow-up

As the current proposal is a phase-1 trial, long-term follow-up is not applicable. However, (PET-)CT scans are performed at baseline, during response evaluation and every four months after the last treatment. By doing so, valuable preliminary data on the effectiveness of this treatment can be acquired. Also, in case of treatment response after 16 cycles, a second diagnostic laparoscopy can be performed to definitively assess response and possibly assess eligibility for surgical treatment.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Should a patient or the study coordinator decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Patients will receive treatment according to standard of care. Three patients within a dose level must be observed for 2 weeks (2 cycles of chemotherapy) before proceeding to the next higher dose level. If a patient is withdrawn from the study prior to completing 2 cycles of therapy and 1 week of follow-up without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. The investigators also have the right to withdraw patients from the study if one of more of the following events occur:

- Significant protocol violation or noncompliance on the part of the patient or investigator
- Refusal of the patient to continue treatment or observations
- Any change in the condition of the patient that justifies discontinuation of treatment
- Decision by the study coordinator that termination is in the patient's best medical interest
- Unrelated medical illness or complication.

Objectives and analysis

Primary objective

The primary objective is to determine the maximum tolerable dose (MTD) of intraperitoneal paclitaxel monotherapy for patients with MPM that are ineligible to undergo CRS-HIPEC. The MTD will be determined during the first eight cycles of IP-chemotherapy by a classic three-plus-three dose escalation design with three dose-levels (i.e. 100 mg, 150 mg, and 200 mg flat dose paclitaxel; see figure 1). To determine the MTD, dose limiting toxicities (DLTs) are predefined. DLTs are graded according to the CTCAE version 5.0. If less than 33% of subject in a dose-cohort experience DLT (i.e. one subject out of a maximum of six subjects in a dose-cohort), the next higher dose cohort will be assessed. Dose levels higher than 200 mg will not be assessed. If ≥ 33% of subjects experience DLT in the first dose-cohort (i.e. 100 mg), a dose-de-escalation to 80 mg will be assessed. There will be no dose-escalation within patients. The following events will be considered DLTs:

Hematologic:

- Absolute neutrophil count (ANC) $<0.5*10^9$/l (grade 4), lasting longer than 7 days
- Febrile neutropenia (ANC $<1.0*10^9$/l with fever ≥38.5°C) (grade 3-4)
- Platelet count $<25*10^9$/l (grade 4)

Non-hematologic

- Grade ≥3 non-hematological adverse-events, except nausea/vomitus, diarrhea, or fatigue, for which the following DLT definition will apply:
    - Nausea grade ≥3, despite optimal anti-emetic use
    - Diarrhea grade ≥3, despite optimal loperamide use
    - Fatigue grade ≥3 lasting longer than 7 days
    - Delay of next cycle by >2 weeks due to any medical reason

Secondary Objective(s):

Secondary objectives are to assess the safety, toxicity, and feasibility of this treatment, and to establish the pharmacokinetic profile of IP-paclitaxel. During the study, ascites and tumor material will be systematically collected, processed, and stored for translational research purposes.

Sample size calculation and statistical analysis

Because of the dose escalation design, the needed number of participants depends on data obtained during different dose levels (see figure 1). The minimum number of patients is four, if the first two patients in the first dose cohort immediately experience DLT, as well as the first two patients in the dose-de-escalation cohort. The minimum number of patients required to reach the primary endpoint (i.e. to find the MTD) is 11. If the first three patients experience no DLT, but the first two patients in the

second dose-cohort both experience DLT. Then five patients were already included, after which an additional six patients have to be included at the first dose level, to come to nine patients treated at the MTD. The maximum number of patients that can possibly be required to reach the primary endpoint is 21. If there are six patients required in each dose cohort to reach the MTD, after which an additional three patients have to be included in the final dose cohort, to come to nine patients treated at the MTD.

The statistical analyses/data summaries will be performed using R and Rstudio. Other tools may be used for exploratory summaries and graphical presentations. Descriptive statistics will be used to describe paclitaxel pharmacokinetics, dose linearity, and its relation to paclitaxel related side effects. Systemic bioavailability of peritoneal administration will be analyzed by comparing the AUC with the results of our many other pharmacological studies with paclitaxel. Relationship between toxicity and paclitaxel exposure will be explored graphically and with logistic regression (two sided and $P < 0.05$).

Harms and auditing

All adverse events (AE), serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSARs) will be recorded. All (S)AEs and SUSARs as a related to the administration of intraperitoneal paclitaxel will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States. The sponsor (Erasmus MC Cancer Institute, the Netherlands) is insured to provide cover for any patients who suffer harm from study participation.

Since this is a phase I dose escalation study, all (S)AEs and SUSARs will be evaluated by the study team before the decision will be made to continue with the next dose-level. Therefore, no data safety monitoring board will be installed.

Patient and public involvement

There was no patient or public involvement in the design, conduct, reporting, or dissemination plans of the INTERACT MESO trial. However, the design of this trial has been shared with the Asbestos Victims Association of the Netherlands (in Dutch ‘Asbestslachtoffers Vereniging Nederland’, AVN), and they support this research.

Ethics and dissemination

This study will be conducted in agreement with both the Declaration of Helsinki (latest amendment: 64th WMA General Assembly, Fortaleza, Brazil, October 2013), the Dutch laws and regulations with the WMO ("Wet Medisch-wetenschappelijk Onderzoek met mensen") in particular. In case of protocol modifications, the research medical ethics committee (METC) and the Dutch competent authority (CCMO) will be informed. The new protocol has to be approved by the METC, and CCMO, before it can be implemented. Data collection, data assessment and data analysis will be performed according to the local guidelines for data management of the Erasmus MC.

The sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

The results of this clinical trial will be submitted for publication in a peer-reviewed scientific journal.

Discussion

The main objective of the INTERACT MESO trial is to determine the maximum tolerable dose (MTD) of IP paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and toxicity, feasibility, and the pharmacokinetic profile of this treatment. To our knowledge, the INTERACT MESO trial is the first clinical trial that investigates intraperitoneal (IP) paclitaxel as non-adjuvant monotherapy in MPM patients that are not eligible for CRS-HIPEC.

Currently, the majority of MPM patients in the Netherlands receive no anti-tumor treatment.(1) The morbidity of systemic treatment is high, and the effectiveness is limited.(4-8) Hence, there is a lack of appropriate palliative treatment for patients with MPM. As MPM rarely disseminates outside the abdominal-cavity, the use of intraperitoneal (IP) chemotherapy seems a logical and promising step. This has major advantages over systemic treatment, as a higher, more effective dose of chemotherapy can directly be delivered at the site of disease, while systemic uptake is limited. This will likely result in fewer systemic toxicity, and thus an increase in quality of life. In rare cases where metastases do develop, a switch can be made to systemic treatment. By first applying local treatment, most patients will be spared a toxic and often ineffective systemic therapy. The placement of the intraperitoneal PAC is performed during standard of care diagnostic laparoscopy, thus not associated with extra visits or procedures. The Erasmus MC Cancer Institute is experienced with the placements of intraperitoneal PACs and the administration of intraperitoneal chemotherapy. The INTERACT trial,

a phase I, dose-escalation study with concomitant intraperitoneal irinotecan combined with FOLFOX in patients with peritoneal metastases from colorectal carcinoma, was conducted in the Erasmus MC Cancer Institute.(17) This trial recently finished and shows promising results. Another advantage of the peritoneal PAC is that ascites, a common symptom of MPM, causing major morbidity, can repeatedly be drained through the PAC system.

Paclitaxel is a well-known chemotherapeutic agent and is considered extremely favorable for IP use.(9) Due to its large molecular weight and lipophilic properties, it is slowly cleared from the peritoneal cavity when administered locally. This results in an area under the curve (AUC) after IP-administration that is up to a 1000-fold (3-log) higher than that in plasma, while peritoneal concentrations persist up to 48 hours after administration.(10) Based on earlier studies, intraperitoneal paclitaxel is expected to be a more effective treatment for patients with extensive peritoneal mesothelioma, compared to the current available systemic chemotherapy. Though systemic administration has not shown to result in survival benefit for MPM patients, the fact that up to a 1000-fold AUC can be achieved by peritoneal administration, provides the rationale for the hypothesis that intraperitoneal treatment can be effective.

The starting dose in this dose escalation study will be a 100 mg flat-dose. In earlier phase-1 and 2 studies that investigated the use of IP-paclitaxel in ovarian cancer patients in weekly cycles, the MTD was 60-65 mg/m2.(11, 12) This translates to a 120-130 mg flat-dose. The ovarian cancer patients in these studies were heavily pre-treated with systemic chemotherapy. As IP-paclitaxel will be used as first line monotherapy in the current study, a higher MTD is anticipated. Currently, the systemic effective dosage is 175-200 mg (flat-dose). As IP-administration can reach up-to a 1000-fold higher AUC, there is no clinical rationale to pursue a dose escalation beyond a 200 mg flat-dose.

Earlier studies have shown that intraperitoneal administration of paclitaxel causes mild toxicity. Common toxicities that occur from systemic administration, such as neuropathy, were not observed after intraperitoneal administration.(10-12) Bowel perforation is a rare, but potentially serious complication from intraperitoneal treatment. This was extremely rare in previous studies that investigated a similar treatment strategy.

During this study, ascites and tumor material will also be collected, processed, and stored for translational research purposes. As MPM is a rare disease, this could result in valuable information for all MPM patients.

If the MTD for IP-paclitaxel in the current study population is determined, and the treatment is found to be safe, a larger phase III clinical trial should be conducted to determine the effect on survival outcomes. Because the incidence of MPM in the Netherlands alone is low, a phase III clinical trial would have to be conducted internationally.

Author contributions: JPvK and MVD drafted this manuscript. All authors drafted the original study protocol and revised the manuscript. EVEM, JGJVA, CV and RHJM initiated the trial and supervised the drafting of the study protocol and manuscript. EVEM acquired funding for implementation of the trial protocol and is the primary clinical investigator. All authors approved the final manuscript.

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Competing interests: none declared.

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Figure legends

Figure 1. Three-plus-three dose escalation design. *DLT, dose limiting toxicity; MTD, maximum tolerable dose.*

Figure 2. Study workflow: *After patients are diagnosed with MPM, they will undergo a DLS, as a part of standard care. If the disease is deemed resectable, patients will undergo CRS-HIPEC as part of standard care. If the disease is considered not resectable during DLS, patients are eligible for inclusion in the currents study. A PAC system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients will receive weekly cycles of IP-chemotherapy. PAC, port-a-cath; CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal.*

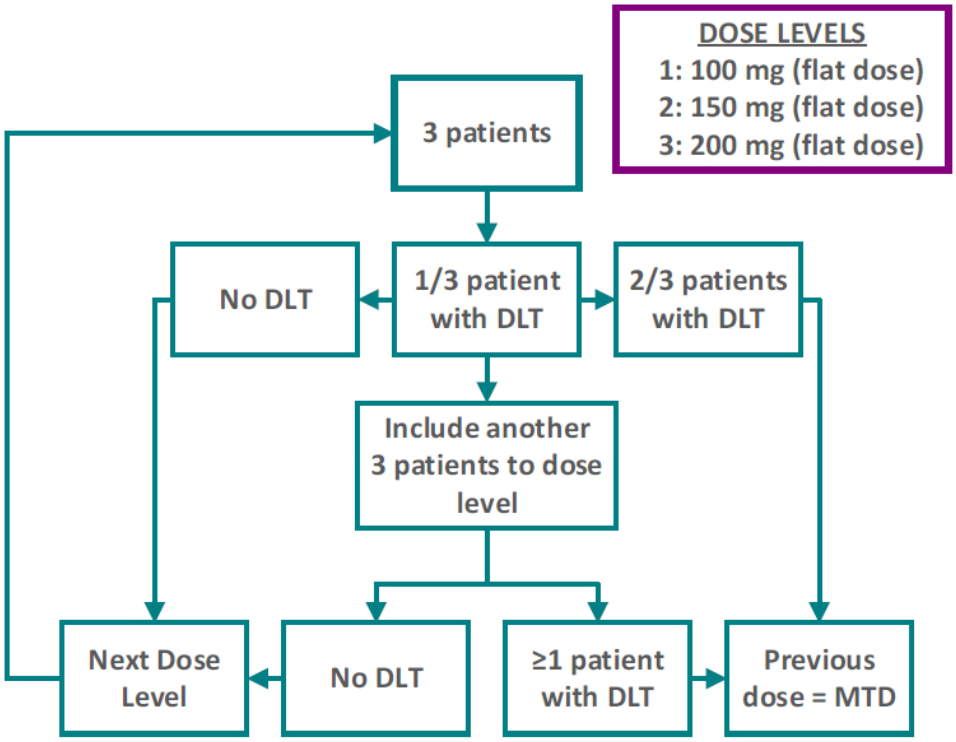

Figure 1. Three-plus-three dose escalation design. DLT, dose limiting toxicity; MTD, maximum tolerable dose.

207x168mm (96 x 96 DPI)

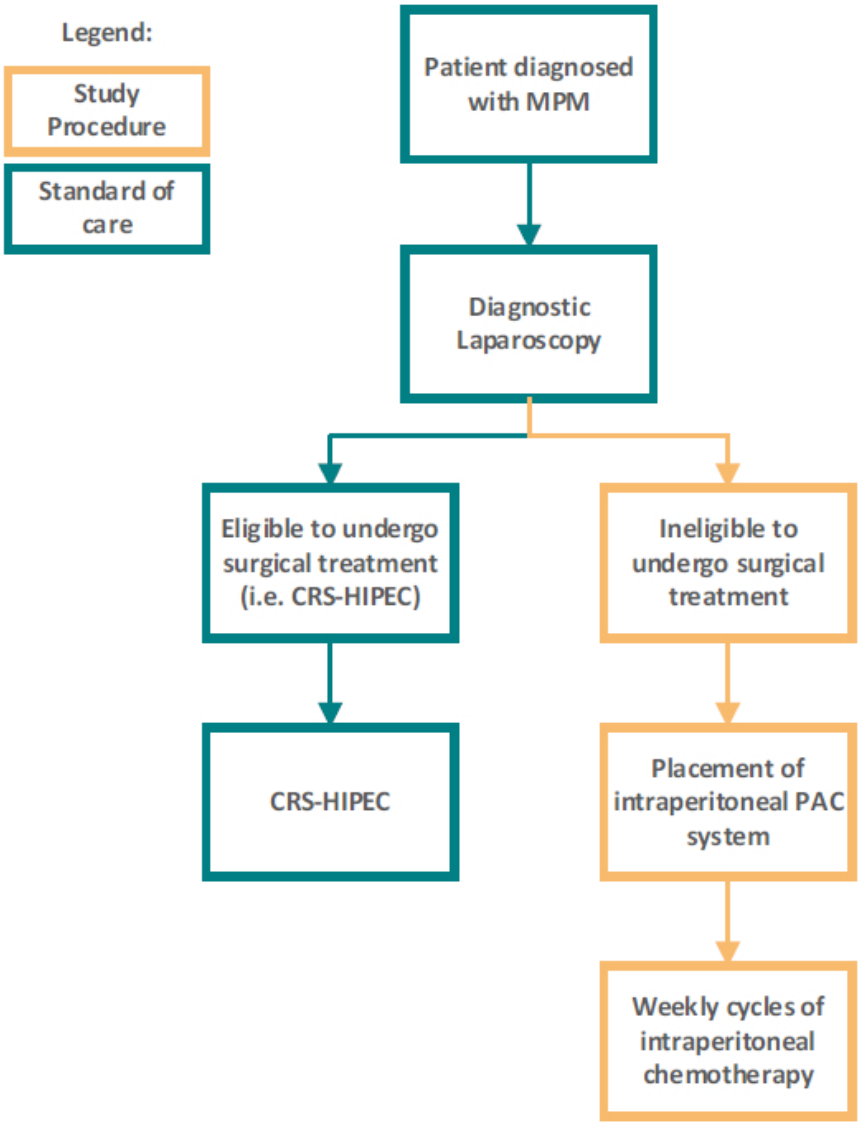

Figure 2. Study workflow: After patients are diagnosed with MPM, they will undergo a DLS, as a part of standard care. If the disease is deemed resectable, patients will undergo CRS-HIPEC as part of standard care. If the disease is considered not resectable during DLS, patients are eligible for inclusion in the currents study. A PAC system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients will receive weekly cycles of IP-chemotherapy. PAC, port-a-cath; CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal.

151x192mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	9, 10
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	8, 9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8, 9

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	4, 5

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5, 6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4 – 6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4, 5, 11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4 – 6

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	6, 7

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5 – 7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6, 7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5, 6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	7

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *This is described in the patient information folder that patients will receive (approved by the* research ethics committee*). This information folder is in Dutch since this is a single center study, performed in the Netherlands. Therefore, the folder is not added to the manuscript.*	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6, 7

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6, 7
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6, 7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *This is described in the patient information folder that patients will receive (approved by the* research ethics committee*). This information folder is in Dutch since this is a single center study, performed in the Netherlands. Therefore, the folder is not added to the manuscript.*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7

BMJ Open

Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma – a Phase I/II Dose Escalation and Safety Study: INTERACT MESO.

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Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma – a Phase I/II Dose Escalation and Safety Study: INTERACT MESO.

Job P. van Kooten (MD)[1#], Michelle V. Dietz (MD)[1#], Niels A.D. Guchelaar (BSc)[2], Alexandra R.M. Brandt-Kerkhof (MD)[1], Stijn L.W. Koolen (MD, PhD)[2,3], Jacobus W.A. Burger (MD, PhD)[4], Ron H.J. Mathijssen (MD, PhD)[2], Cornelis Verhoef (MD, PhD)[1], Joachim G.J.V. Aerts (MD, PhD)[5¶], Eva V.E. Madsen (MD, PhD)[1¶]

[1] Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[2] Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[3] Department of Hospital Pharmacy, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[4] Department of Surgery, Catharina Cancer Institute, Eindhoven, The Netherlands

[5] Department of Pulmonary Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[#] These authors contributed equally

[¶] These authors share the senior author position

Corresponding Author: Michelle Dietz

Email: m.dietz@erasmusmc.nl

Telephone: +31 107042125

Address: Room Na-2113, Department of Surgical Oncology
Erasmus MC Cancer Institute
Dr. Molewaterplein 40
3015 GD, Rotterdam, the Netherlands

Disclosures:

No conflicts of interests.

Abstract

Introduction. Malignant peritoneal mesothelioma (MPM) is a rare, aggressive tumor, arising primarily from the peritoneum. The only potentially curative treatment is cytoreductive surgery (CRS) with

hyperthermic intraperitoneal chemotherapy (HIPEC). However, the majority of patients are not eligible to undergo this treatment. The benefit of systemic treatment for these patients is limited, at the cost of considerable morbidity. Hence, there is need for appropriate palliative treatment options for MPM patients. As MPM rarely disseminates outside the abdominal cavity, these patients might benefit from local treatment. A higher, more effective dose of chemotherapy can directly be delivered at the site of disease. Systemic uptake will be limited, likely resulting in less toxicity. The aim of the INTERACT MESO trial is to determine the maximum tolerable dose (MTD) of intraperitoneal (IP) paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and toxicity, feasibility, and the pharmacokinetic profile of this treatment.

Methods and analysis. The INTERACT MESO trial is a prospective, open-label, single-center, phase-1 study with a classic three-plus-three dose escalation design. The study population consists of adult patients with primary MPM, without extra-abdominal disease, that are not eligible to undergo CRS-HIPEC. According to standard of care work-up for CRS-HIPEC, patients will undergo diagnostic laparoscopy (DLS) to determine the feasibility of CRS-HIPEC. In case CRS-HIPEC is not considered feasible, a peritoneal port-a-cath (PAC) system will be placed. Through this PAC, 8-16 weekly cycles of intraperitoneal chemotherapy will be administered.

Ethics and dissemination. The Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands) and the Research Ethics Committee (METC, Rotterdam, The Netherlands) have granted permission to carry out this study protocol. The results of this trial will be submitted for publication in a peer-reviewed scientific journal.
Trial registration number: Nederlands Trial Register: NL9718. EudraCT: 2021-003637-11.

Keywords: Malignant peritoneal mesothelioma, Intraperitoneal chemotherapy, Paclitaxel, Systemic chemotherapy, Palliative treatment, Dose-escalation study

Word count: 3744

Strengths and limitations of this study

- The INTERACT MESO trial is the first trial that investigates paclitaxel monotherapy in patients with malignant peritoneal mesothelioma (MPM) who are not eligible for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC).
- In this phase I dose-escalation trial the maximum tolerated dose (MTD), safety and feasibility of this treatment will be determined.
- This trial will also determine the pharmacokinetic profile of intraperitoneal paclitaxel monotherapy.
- Due to the nature of this trial, the efficacy of IP paclitaxel cannot be determined, when the MTD is determined, larger phase II and III clinical trials will be conducted to determine the efficacy.

Introduction

Malignant Peritoneal Mesothelioma (MPM) is a rare, but aggressive neoplasm with a poor prognosis, arising primarily from the serosal lining of the peritoneal cavity.(1) Currently, the only possibly curative treatment is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).(2, 3) In the Netherlands, only a minority of patients undergo this treatment.(1) For patients that are not eligible to undergo CRS-HIPEC, the treatment options are limited. Overall response rates to systemic chemotherapy are low (20-25%), though morbidity rates are high, with a grade 3-4 hematological toxicity rate up to 38%.(4-6) Moreover, the two-year survival rate for these patients is only 20%.(1) Combination checkpoint-inhibition-therapy with nivolumab and Ipilimumab has been proposed as a new treatment option for MPM patients. However, this treatment has comparable morbidity rates to that of systemic chemotherapy, and its benefit for MPM patients is not proven.(7, 8) Because of the high morbidity rate, and the limited effectiveness of systemic treatment it is debatable whether these therapies are suitable as palliative treatment for patients with MPM. Due to lack of appropriate palliative treatment options, the majority of MPM patients in the Netherlands (63%) currently receives no anti-tumor treatment.(1)

For peritoneal metastases from several types of cancer, local treatment with intraperitoneal (IP) chemotherapy has been proposed as a palliative treatment option. This therapy can be delivered through an IP port-a-cath (PAC), and potentially has major advantages over systemic treatment. A higher, more effective dose of chemotherapy can directly be delivered at the site of disease, while systemic uptake is limited, likely resulting in fewer toxicity. Paclitaxel is a chemotherapeutic agent that is considered extremely favorable for IP use.(9) Due to its large molecular weight and lipophilic

properties, it is slowly cleared from the peritoneal cavity when administered locally. This results in an area under the curve (AUC) after IP- administration that is up to a 1000-fold (3-log) higher than that in plasma, while peritoneal concentrations persist up to 48 hours after administration.(10) This considerably increases drug activity.

Markman et al. presented the first phase-1 dose-escalation study of IP-paclitaxel in ovarian cancer patients, pre-treated with systemic chemotherapy.(10) They established the maximum-tolerable-dose (MTD) to be 175 mg/m^2 at a two-to-three week interval. Another dose-escalation study was performed by Francis et al., delivering a lower dose at a weekly frequency.(11) These patients were also pre-treated with systemic chemotherapy. Severe abdominal pain was uncommon and only low-grade leukopenia, fatigue and stomatitis was observed. Grade 3-4 gastro-intestinal complications were observed in 15% of patients. Francis et al. recommended a dose of 60-65 mg/m^2 IP-paclitaxel in weekly cycles. Markman et al. performed a phase-2 trial in 80 ovarian cancer patients, using 60 mg/m^2 of IP-paclitaxel, in 16 weekly cycles after pre-treatment with systemic chemotherapy.(12) The majority of patients (70%) received all planned 16 courses. Grade-3 complications were rare, with abdominal pain, neuropathy, and neutropenia in one, two and one patients respectively. Bowel perforation, a rare but potentially life-threatening complication, was observed once in the phase-1 trial (3%), but was not observed in the phase-2 trial. Five patients were removed from the study due to excessive toxicity, and three patients due to catheter malfunction. In total, 18 (24%) patients achieved a complete response.

As the effectiveness of systemic therapy is limit and MPM very rarely disseminates outside the abdominal-cavity, the use of IP paclitaxel monotherapy seems a logical and promising step. The group of Paul Sugarbaker utilizes long-term IP-administration of paclitaxel as an adjuvant treatment to CRS-HIPEC for patients with MPM. They use doses of 20 mg/m^2 daily for five consecutive days monthly, starting 4-6 weeks postoperatively. Some of these patients showed remarkable survival, despite incompleteness of cytoreduction at CRS-HIPEC.(13-15) Another major advantage of the suggested treatment is that ascites, a common MPM-symptom that causes major morbidity, can be drained through the same PAC-system.

Currently, there are no studies that investigate IP paclitaxel as non-adjuvant monotherapy in MPM patients. The main objective of this clinical trial is to determine the maximum tolerable dose (MTD) of IP paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and

toxicity, feasibility, and the pharmacokinetic profile of this treatment. When the MTD is determined, further research is needed to determine the effect on survival.

Methods and analysis

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (supplementary appendix 1).(16)

Study design

Trial setting

The INTERACT MESO trial is a prospective, open-label, single-center, phase-1 study with a classic three-plus-three dose escalation design (figure 1). The defined dose levels are 100 mg, 150 mg, and 200 mg paclitaxel. This study is conducted in the Erasmus MC Cancer Institute, a tertiary referral hospital, located in Rotterdam, the Netherlands. Trial registration details are described in table 1. The study started recruitment in February 2022, and as of 17 May 2022 one patient has been enrolled. The end of the study is planned in February 2026.

Table 1. WHO trial registration data set

Primary registry and trial identifying number	EudraCT number: 2021-003637-11 Netherlands Trial Register: NL9718
Date of registration in primary registry	September 2021
Protocol version	Protocol version 4.0, date November 22th, 2021
SPIRIT guidelines data set for clinical trials	See supplementary file
Secondary Identifying Numbers	Dutch competent authority (CCMO): NL78373.078.21 Local medical ethics committee (METC): MEC-2021-0697
Source(s) of monetary or material support	Erasmus MC Foundation, Rotterdam, the Netherlands
Primary sponsor	Erasmus University Medical Center, Rotterdam, the Netherlands
Secondary sponsors	Not applicable

Contact for public queries	M.V. Dietz, study coordinator Department of surgical oncology Erasmus MC, Rotterdam, the Netherlands m.dietz@erasmusmc.nl, (+31)010-7042125
Contact for scientific queries	E.V.E. Madsen, principal investigator Department of surgical oncology Erasmus MC, Rotterdam, the Netherlands e.madsen@erasmusmc.nl, (+31)010-7041082
Public title	Treatment of abdominal mesothelioma with intra-abdominal chemotherapy: INTERACT MESO
Scientific title	Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma – a Phase I/II Dose Escalation and Safety Study: INTERACT MESO
Countries of recruitment	The Netherlands
Health conditions or problems studied	Malignant peritoneal mesothelioma
Interventions	Patients undergo a diagnostic laparoscopy (DLS) according to standard work-up for CRS-HIPEC. If the disease is considered not resectable, a peritoneal port-a-cath (PAC) will be placed. Through this PAC, intraperitoneal paclitaxel will be administered in weekly cycles.
Key inclusion and exclusion criteria	Key inclusion criteria: Confirmed diagnosis of malignant peritoneal mesothelioma, WHO-ECOG performance status 0-1, age ≥ 18 years old, and adequate organ function and bone marrow reserves.

	Key exclusion criteria: Extra-abdominal disease/metastatic disease, serious concomitant disease or active infections, any medical or psychological impediment to probable compliance with the protocol, and pregnant or lactating women.
Study type	Open label single center phase I/II study
Date of first enrolment	Planned February 2022
Target sample size	11 – 21 according to dose escalation
Recruitment status	Pending
Primary outcome	Maximum tolerable dose (MTD) of intraperitoneal (IP) paclitaxel monotherapy in patients with MPM
Key secondary outcome(s)	Safety and toxicity, feasibility, and the pharmacokinetic profile of intraperitoneal paclitaxel monotherapy

CRS, cytoreductive surgery; DLS, diagnostic laparoscopy; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; PAC, port-a-cath, SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

Study population

The study population consist of adult patients with primary MPM, without extra-abdominal disease, that are not eligible to undergo CRS-HIPEC. Potentially eligible patients will be referred by their local clinician or through self-referral to a medical specialist. A member of the study team will inform patients about the trial at the outpatient clinic, and an eligibility assessment will be performed. In order to be eligible to participate in the study, potential subjects must meet all of the following inclusion criteria:

- Histological confirmed diagnosis of malignant peritoneal mesothelioma
- Patients that are not eligible (or willing) to undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)
- Age ≥ 18 years

- Written informed consent by the patient according to the ICH-GCP and national/local regulations
- Patients must be ambulatory (WHO-ECOG performance status 0 or 1)
- Ability to return to the Erasmus MC for adequate follow-up as required by this protocol
- Patients must have normal organ function and adequate bone marrow reserve as assessed by the following laboratory requirements; absolute neutrophil count >1.5 * 10^9/l, platelet count >100*10^9/l and hemoglobin >6.0 mmol/l. Patients must have a bilirubin <1½ x upper limit of normal (ULN), serum AST and ALT <2.5 x ULN

A potential subject who meets any of the following exclusion criteria will be excluded from participation in the study:

- Incapacitated patients
- Extra-abdominal disease/metastatic disease established by preoperative CT-scan of thorax-abdomen and/or PET-scan. Imaging not older than two months at time of surgery
- Medical or psychological impediment to probable compliance with the protocol
- Serious concomitant disease or active infections
- History of auto-immune disease or organ allografts, or with active or chronic infection, including HIV and viral hepatitis
- Serious intercurrent chronic or acute illness such as pulmonary (COPD or asthma) or cardiac (NYHA class III or IV) or hepatic disease or other illness considered by the study coordinator to constitute an unwarranted high risk for participation in this study
- Pregnant or lactating women; for all women of child-bearing potential a negative urine pregnancy test will be required as well as the willingness to use adequate contraception during the study until 4 weeks after finishing treatment
- Absence of assurance of compliance with the protocol
- An organic brain syndrome or other significant psychiatric abnormality which would comprise the ability to give informed consent, and preclude participation in the full protocol and follow-up

Patient timeline and additional procedures

A flowchart of the study is shown in figure 2. A more detailed description of (additional) study procedures is presented in table 2.

	Before 1st visit	1st visit	2nd visit	DLS	1st post-op visit	IP-CTx								Response evaluation	IP-CTx 9-16th cycle[6]	Response evaluation	Last study visit
						1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle	7th cycle	8th cycle				
MTB[1]	X															X	
Medical history	X	X															
In- / exclusion criteria		X															
Provide information about the study		X	X														
Written informed consent			X														
Vital signs			X		X	X	X	X	X	X	X	X	X		X		
Physical examination (Incl. weight)[2]			X		X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		X[2]		
Operability check (Anesthetist)			X														
Hematology and blood chemistry			X		X[2]	X	X	X	X	X	X	X	X		X		
Viral serology			X														
Pregnancy test[2]			X														
Placement of peritoneal PAC[3]				X													
Visit medical oncologist			X		X									X		X	
CT-scan chest/abdomen	X[4]					X[5]								X		X	
Intraperitoneal chemotherapy						X	X	X	X	X	X	X	X		X		
Performance status			X		X	X	X	X	X	X	X	X	X	X	X	X	
Chemotherapy toxicity evaluation (CTCAE 5.0)						X	X	X	X	X	X	X	X	X	X	X	
Collection of blood and peritoneal fluid for PK analysis						X			X								

Removal of peritoneal PAC																X[8]

Table 2. Study procedures

[1)] Scans and reports of (referred) patients are first discussed in a multi-disciplinary tumor board. When patients are considered candidates for HIPEC-procedure, they are seen in the outpatient clinic.

[2)] If applicable.

[3)] In case complete cytoreduction is deemed impossible.

[4)] If not performed by referring center.

[5)] Maximum of four weeks before start of study treatment.

[6)] In case of no progression of disease (i.e. CR, PR or SD) and if patient is willing.

[7)] At cycle 16 if applicable.

[8)] Optional, according to patient preference and life expectancy

Screening

The multidisciplinary tumor board will review all referred patients who are possibly eligible to participate in the study. Potential candidates for CRS-HIPEC will visit the surgical oncology outpatient clinic, where they will be informed about the treatment options, including the study, and undergo standard screening procedures. The standard of care CRS-HIPEC screening procedure includes a CT scan of the thorax and abdomen (not older than two months before surgery), lab testing (including kidney and liver panels, and blood cell count), anesthetic assessment, and a diagnostic laparoscopy (DLS). If the disease is considered not resectable during DLS, and if the patient meets the inclusion/exclusion criteria, the patient is eligible for inclusion. Patients who are considered ineligible for CRS-HIPEC, based on parameters that were obtained before DLS, but have no contra-indication for IP chemotherapy, can also participate in the study.

Surgical procedures

Patients will be operated under general anesthesia, according to local hospital procedures. During the diagnostic laparoscopy, the extent of disease is assessed according to the 'peritoneal carcinomatosis index' (PCI). Ascites fluid will be collected for storage in the local MPM biobank. The surgeon will determine feasibility of complete cytoreduction. If it is deemed impossible to achieve complete cytoreduction, a port-a-cath (PAC) system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients may leave the hospital that same day, with careful (including written) instructions for e.g. hygiene. Patients are seen in the outpatient clinic approximately a week after surgery by a medical oncologist. The start date of the first treatment cycle of chemotherapy will be determined.

Chemotherapy

Patients will receive intraperitoneal paclitaxel (dose according to current dose-level) dissolved in 1 liter of saline (0.9% NaCl), pre-warmed to 37°C through the PAC that was placed during laparoscopy. Patients will receive all necessary pre-medications prior to infusion, according to the local standard protocol for intravenous administration of paclitaxel. If present, prior to infusion, ascites will be drained through the PAC, and stored in the MPM biobank. Administration of IP-chemotherapy will take about 1.5-2 hours. After infusion, patients are instructed to switch position frequently to maximize distribution of chemotherapy in the peritoneal cavity. Patients will be observed for two hours after chemotherapy administration. If no adverse events occur during this period, patients will be discharged with careful instructions to contact the hospital if any alarming symptoms do develop. During the first and the fourth cycle of IP-chemotherapy, additional blood samples and IP-fluid

samples will be collected for pharmacokinetic (PK) analysis. The 24-hour AUC will be calculated for systemic and IP-paclitaxel. Other pharmacokinetic parameters such as the maximum concentration (Cmax) and the elimination half-life ($t_{1/2}$) will also be determined.

Patients will initially receive eight weekly cycles of IP-chemotherapy. After the start of the first cycles, following cycles can be delayed, at the discretion of the medical oncologist in case of a medical indication (e.g. neutropenia). If a cycle is delayed for more than two weeks, this is considered a dose limiting toxicity. After the first eight cycles, response evaluation will take place. Depending on this outcome, another eight cycles can be initiated. In case of ongoing therapy response, there is no limit to the number of cycles.

Follow-up

As the current proposal is a phase-1 trial, long-term follow-up is not applicable. However, (PET-)CT scans are performed at baseline, during response evaluation (if possible according to RECIST-criteria), and every four months after the last treatment. By doing so, valuable preliminary data on the effectiveness of this treatment can be acquired. Also, in case of treatment response after 16 cycles, a second diagnostic laparoscopy can be performed to definitively assess response and possibly assess eligibility for surgical treatment.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Should a patient or the study coordinator decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Patients will receive treatment according to standard of care. Three patients within a dose level must be observed for 2 weeks (2 cycles of chemotherapy) before proceeding to the next higher dose level. If a patient is withdrawn from the study prior to completing 2 cycles of therapy and 1 week of follow-up without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. The investigators also have the right to withdraw patients from the study if one of more of the following events occur:

- Significant protocol violation or noncompliance on the part of the patient or investigator
- Refusal of the patient to continue treatment or observations
- Any change in the condition of the patient that justifies discontinuation of treatment
- Decision by the study coordinator that termination is in the patient's best medical interest
- Unrelated medical illness or complication.

Objectives and analysis

Primary objective

The primary objective is to determine the maximum tolerable dose (MTD) of intraperitoneal paclitaxel monotherapy for patients with MPM that are ineligible to undergo CRS-HIPEC. The MTD will be determined during the first eight cycles of IP-chemotherapy by a classic three-plus-three dose escalation design with three dose-levels (i.e. 100 mg, 150 mg, and 200 mg flat dose paclitaxel; see figure 1). To determine the MTD, dose limiting toxicities (DLTs) are predefined. DLTs are graded according to the CTCAE version 5.0. If less than 33% of subject in a dose-cohort experience DLT (i.e. one subject out of a maximum of six subjects in a dose-cohort), the next higher dose cohort will be assessed. Dose levels higher than 200 mg will not be assessed. If ≥ 33% of subjects experience DLT in the first dose-cohort (i.e. 100 mg), a dose-de-escalation to 80 mg will be assessed. There will be no dose-escalation within patients. The following events will be considered DLTs:

Hematologic:

- Absolute neutrophil count (ANC) <0.5*10^9/l (grade 4), lasting longer than 7 days
- Febrile neutropenia (ANC <1.0*10^9/l with fever ≥38.5°C) (grade 3-4)
- Platelet count <25*10^9/l (grade 4)

Non-hematologic

- Grade ≥3 non-hematological adverse-events, except nausea/vomitus, diarrhea, or fatigue, for which the following DLT definition will apply:
    - Nausea grade ≥3, despite optimal anti-emetic use
    - Diarrhea grade ≥3, despite optimal loperamide use
    - Fatigue grade ≥3 lasting longer than 7 days
    - Delay of next cycle by >2 weeks due to any medical reason

Secondary Objective(s):

Secondary objectives are to assess the safety, toxicity, and feasibility of this treatment, and to establish the pharmacokinetic profile of IP-paclitaxel. During the study, ascites and tumor material will be systematically collected, processed, and stored for translational research purposes.

Sample size calculation and statistical analysis

Because of the dose escalation design, the needed number of participants depends on data obtained during different dose levels (see figure 1). The minimum number of patients is four, if the first two patients in the first dose cohort immediately experience DLT, as well as the first two patients in the dose-de-escalation cohort. The minimum number of patients required to reach the primary endpoint

(i.e. to find the MTD) is 11. If the first three patients experience no DLT, but the first two patients in the second dose-cohort both experience DLT. Then five patients were already included, after which an additional six patients have to be included at the first dose level, to come to nine patients treated at the MTD. The maximum number of patients that can possibly be required to reach the primary endpoint is 21. If there are six patients required in each dose cohort to reach the MTD, after which an additional three patients have to be included in the final dose cohort, to come to nine patients treated at the MTD.

The statistical analyses/data summaries will be performed using R and Rstudio. Other tools may be used for exploratory summaries and graphical presentations. Descriptive statistics will be used to describe paclitaxel pharmacokinetics, dose linearity, and its relation to paclitaxel related side effects. Systemic bioavailability of peritoneal administration will be analyzed by comparing the AUC with the results of our many other pharmacological studies with paclitaxel. Relationship between toxicity and paclitaxel exposure will be explored graphically and with logistic regression (two sided and $P < 0.05$).

Harms and auditing

All adverse events (AE), serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSARs) will be recorded. All (S)AEs and SUSARs as a related to the administration of intraperitoneal paclitaxel will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States. The sponsor (Erasmus MC Cancer Institute, the Netherlands) is insured to provide cover for any patients who suffer harm from study participation.

Since this is a phase I dose escalation study, all (S)AEs and SUSARs will be evaluated by the study team before the decision will be made to continue with the next dose-level. Therefore, no data safety monitoring board will be installed.

Patient and public involvement

There was no patient or public involvement in the design, conduct, reporting, or dissemination plans of the INTERACT MESO trial. However, the design of this trial has been shared with the Asbestos

Victims Association of the Netherlands (in Dutch 'Asbestslachtoffers Vereniging Nederland', AVN), and they support this research.

Ethics and dissemination

This study will be conducted in agreement with both the Declaration of Helsinki (latest amendment: 64th WMA General Assembly, Fortaleza, Brazil, October 2013), the Dutch laws and regulations with the WMO ("Wet Medisch-wetenschappelijk Onderzoek met mensen") in particular. In case of protocol modifications, the research medical ethics committee (METC) and the Dutch competent authority (CCMO) will be informed. The new protocol has to be approved by the METC, and CCMO, before it can be implemented. Data collection, data assessment and data analysis will be performed according to the local guidelines for data management of the Erasmus MC.

The sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

The results of this clinical trial will be submitted for publication in a peer-reviewed scientific journal.

Discussion

The main objective of the INTERACT MESO trial is to determine the maximum tolerable dose (MTD) of IP paclitaxel monotherapy in patients with MPM. Secondary endpoints are to assess safety and toxicity, feasibility, and the pharmacokinetic profile of this treatment. To our knowledge, the INTERACT MESO trial is the first clinical trial that investigates intraperitoneal (IP) paclitaxel as non-adjuvant monotherapy in MPM patients that are not eligible for CRS-HIPEC.

Currently, the majority of MPM patients in the Netherlands receive no anti-tumor treatment.(1) The morbidity of systemic treatment is high, and the effectiveness is limited.(4-8) Hence, there is a lack of appropriate palliative treatment for patients with MPM. As MPM rarely disseminates outside the abdominal-cavity, the use of intraperitoneal (IP) chemotherapy seems a logical and promising step. This has major advantages over systemic treatment, as a higher, more effective dose of chemotherapy can directly be delivered at the site of disease, while systemic uptake is limited. This will likely result in fewer systemic toxicity, and thus an increase in quality of life. In rare cases where metastases do develop, a switch can be made to systemic treatment. By first applying local treatment, most patients will be spared a toxic and often ineffective systemic therapy. The placement of the intraperitoneal PAC is performed during standard of care diagnostic laparoscopy, thus not associated

with extra visits or procedures. The Erasmus MC Cancer Institute is experienced with the placements of intraperitoneal PACs and the administration of intraperitoneal chemotherapy. The INTERACT trial, a phase I, dose-escalation study with concomitant intraperitoneal irinotecan combined with FOLFOX in patients with peritoneal metastases from colorectal carcinoma, was conducted in the Erasmus MC Cancer Institute.(17) This trial recently finished and shows promising results. Another advantage of the peritoneal PAC is that ascites, a common symptom of MPM, causing major morbidity, can repeatedly be drained through the PAC system.

Paclitaxel is a well-known chemotherapeutic agent and is considered extremely favorable for IP use.(9) Due to its large molecular weight and lipophilic properties, it is slowly cleared from the peritoneal cavity when administered locally. This results in an area under the curve (AUC) after IP-administration that is up to a 1000-fold (3-log) higher than that in plasma, while peritoneal concentrations persist up to 48 hours after administration.(10) Based on earlier studies, intraperitoneal paclitaxel is expected to be a more effective treatment for patients with extensive peritoneal mesothelioma, compared to the current available systemic chemotherapy. Though systemic administration has not shown to result in survival benefit for MPM patients, the fact that up to a 1000-fold AUC can be achieved by peritoneal administration, provides the rationale for the hypothesis that intraperitoneal treatment can be effective.

The starting dose in this dose escalation study will be a 100 mg flat-dose. In earlier phase-1 and 2 studies that investigated the use of IP-paclitaxel in ovarian cancer patients in weekly cycles, the MTD was 60-65 mg/m2.(11, 12) This translates to a 120-130 mg flat-dose. The ovarian cancer patients in these studies were heavily pre-treated with systemic chemotherapy. As IP-paclitaxel will be used as first line monotherapy in the current study, a higher MTD is anticipated. Currently, the systemic effective dosage is 175-200 mg (flat-dose). As IP-administration can reach up-to a 1000-fold higher AUC, there is no clinical rationale to pursue a dose escalation beyond a 200 mg flat-dose.

Earlier studies have shown that intraperitoneal administration of paclitaxel causes mild toxicity. Common toxicities that occur from systemic administration, such as neuropathy, were not observed after intraperitoneal administration.(10-12) Bowel perforation is a rare, but potentially serious complication from intraperitoneal treatment. This was extremely rare in previous studies that investigated a similar treatment strategy.

During this study, ascites and tumor material will also be collected, processed, and stored for translational research purposes. As MPM is a rare disease, this could result in valuable information for all MPM patients.

If the MTD for IP-paclitaxel in the current study population is determined, and the treatment is found to be safe, a larger phase III clinical trial should be conducted to determine the effect on survival outcomes. Because the incidence of MPM in the Netherlands alone is low, a phase III clinical trial would have to be conducted internationally.

Author contributions: JvK and MD drafted this manuscript. All authors drafted the original study protocol and revised the manuscript. EM, JA, CV and RM initiated the trial and supervised the drafting of the study protocol and manuscript. NG, ABK, SK, and JB contributed in the study conceptualization and development of the study protocol. EM acquired funding for implementation of the trial protocol and is the primary clinical investigator. All authors approved the final manuscript.

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Competing interests: none declared.

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Figure legends

Figure 1. Three-plus-three dose escalation design. *DLT, dose limiting toxicity; MTD, maximum tolerable dose.*

Figure 2. Study workflow: *After patients are diagnosed with MPM, they will undergo a DLS, as a part of standard care. If the disease is deemed resectable, patients will undergo CRS-HIPEC as part of standard care. If the disease is considered not resectable during DLS, patients are eligible for inclusion in the currents study. A PAC system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients will receive weekly cycles of IP-chemotherapy. PAC, port-a-cath; CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal.*

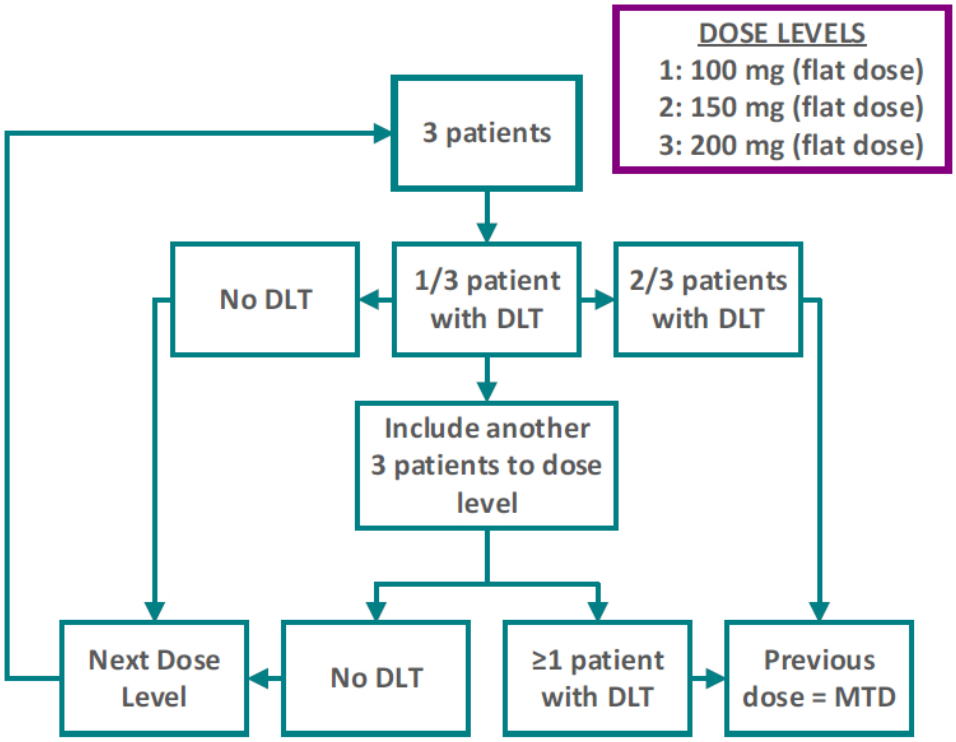

Figure 1. Three-plus-three dose escalation design. DLT, dose limiting toxicity; MTD, maximum tolerable dose.

207x168mm (96 x 96 DPI)

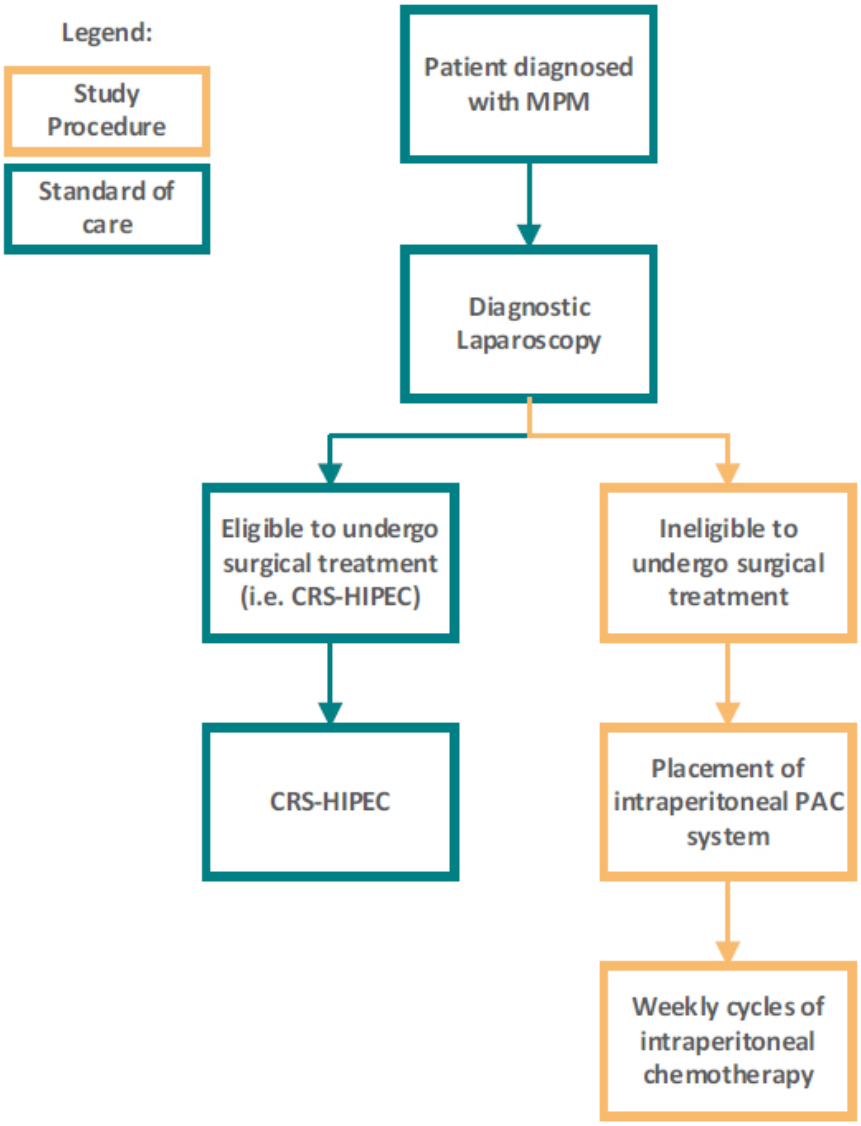

Figure 2. Study workflow: After patients are diagnosed with MPM, they will undergo a DLS, as a part of standard care. If the disease is deemed resectable, patients will undergo CRS-HIPEC as part of standard care. If the disease is considered not resectable during DLS, patients are eligible for inclusion in the currents study. A PAC system will be placed subcutaneously, while the catheter tip is placed inside the peritoneal cavity. After surgery, patients will receive weekly cycles of IP-chemotherapy. PAC, port-a-cath; CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; DLS, diagnostic laparoscopy; IP, intraperitoneal.

151x192mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	9, 10
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	8, 9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8, 9

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	4, 5

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5, 6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4 – 6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4, 5, 11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4 – 6

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	6, 7

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5 – 7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6, 7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5, 6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	7

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *This is described in the patient information folder that patients will receive (approved by the* research ethics committee*). This information folder is in Dutch since this is a single center study, performed in the Netherlands. Therefore, the folder is not added to the manuscript.*	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6, 7

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6, 7
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6, 7
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *This is described in the patient information folder that patients will receive (approved by the* research ethics committee*). This information folder is in Dutch since this is a single center study, performed in the Netherlands. Therefore, the folder is not added to the manuscript.*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7