ETOP 9-15 PROMISE-meso

A multicentre randomised phase III trial comparing pembrolizumab versus standard chemotherapy for advanced pre-treated malignant pleural mesothelioma

PROMISE-meso*:* PembROlizuMab Immunotherapy versus Standard chemotherapy for advanced prE-treated malignant pleural mesothelioma

Sponsor: European Thoracic Oncology Platform (ETOP)

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ETOP c/o IBCSG Coordinating Centre, Effingerstrasse 40, CH- 3008 Bern
Phone: +41 31 511 94 00 Fax: +41 31 511 94 01

Version 1.0

Contacts

Trial Chair	Sanjay Popat, MD	Address Tel: Fax: Email:	Royal Marsden Hospital Fulham Road London SW3 6JJ, United Kingdom +44 207 808 2132 +44 207 808 2688 sanjay.popat@rmh.nhs.uk
Trial Chair	Alessandra Curioni-Fontecedro, MD	Address Tel: Fax: Email:	Clinic of Oncology University Hospital Zuerich CH-8044 Zürich, Switzerland +41 44 255 22 14 Alessandra.Curioni@usz.ch
Trial Co-Chair	Solange Peters, MD-PhD	Address Tel: Fax: Email:	Département d'Oncologie Centre Hospitalier Universitaire Vaudois 1011 Lausanne, Switzerland +41 79 556 01 92 +41 21 314 07 37 solange.peters@etop-eu.org
ETOP Chairman	Rolf Stahel, MD	Address Tel: Fax: Email:	Clinic of Oncology University Hospital Zuerich Raemistrasse 91 CH-8091 Zürich, Switzerland +41 44 255 22 19 +41 44 255 97 80 rolf.stahel@usz.ch
Translational Research Coordinator	Rosita Kammler	Address Tel: Fax: Email:	ETOP Coordinating Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 28 +41 31 511 94 01 rosita.kammler@ibcsg.org
Central Laboratory			CHUV - Department of oncology Center for Experimental Therapeutics (CTE) Hôpital Orthopédique HO 05/1552 Av. Pierre-Decker 4 CH-1011 Lausanne, Switzerland
Statistics	Urania Dafni, ScD Varvara Polydoropoulou	Address Tel: Fax: Email: Email:	Frontier Science Foundation – Hellas 116 Papadiamantopoulou Str. 15773, Zografou, Athens, Greece +30 2107710902 +30 2107710903 udafni@frontier-science.gr vpolydoropoulou@frontier-science.gr
Project Manager Data Management	Mark Finlayson, PhD Anne-Christine Piguet, PhD	Address Tel: Fax: Email: Tel: Email:	ETOP Coordinating Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 34 +41 31 511 94 01 PROMISE-meso@etop-eu.org +41 31 511 94 21 ETOPDataManagement@etop-eu.org

Drug supply	Barbara Ruepp, PharmD	Address Tel: Fax: Email:	ETOP Drug Supply Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 16 +41 31 389 92 29 drugsupply@etop-eu.org
Safety and Regulatory Affairs	Barbara Ruepp, PharmD	Address Tel: Fax: Email:	ETOP Safety and Regulatory Office c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 16 +41 31 389 92 29 regulatoryoffice@etop-eu.org
ETOP Medical Affairs	Manuela Rabaglio, MD	Address Tel. Fax : Email :	ETOP Medical Affairs c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 20 +41 31 511 94 01 medical.affairs@ibcsg.org
ETOP Coordinating Office	Anita Hiltbrunner Heidi Roschitzki, PhD	Address Tel: Fax: Email: Tel: Fax: Email:	c/o IBCSG Coordinating Centre Effingerstrasse 40 3008 Bern, Switzerland +41 31 511 94 42 +41 31 511 94 01 anita.hiltbrunner@etop-eu.org +41 31 511 94 18 +41 31 511 94 01 heidi.roschitzki@etop-eu.org
Electronic data capture (EDC) system	Anne-Christine Piguet, PhD Technical assistance	Email: Email:	ETOPDataManagement@etop-eu.org richard.king@etop-eu.org

In collaboration with Merck Sharp & Dohme Corp.

Protocol Signature Page

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ETOP 9-15 PROMISE-meso

Approved by:

Sanjay Popat
Trial Chair

11. Nov. 2016
Date

Alessandra Curioni
Trial Chair

10.11.16
Date

Rolf Stahel
ETOP Chairman

12.11.16
Date

Urania Dafni
Biostatistician

11/11/16
Date

Anita Hiltbrunner
ETOP Director

11.11.2016
Date

Principal Investigator Protocol Signature Page

A multicentre randomised phase III trial comparing pembrolizumab versus standard chemotherapy for advanced pre-treated malignant pleural mesothelioma

ETOP 9-15 PROMISE-meso

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by ETOP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator: _____

Institution’s name and place: _____

_____ _____

Signature Date

TABLE OF CONTENTS

Section **Page**

1. Protocol summary 9
2. Trial schedule 14
3. List of abbreviations 17
4. Background and rationale 20
   4.1. Disease background 20
   4.2. Treatment background 21
   4.3. Background pembrolizumab 21
   4.4. Choice of design and comparator 23
   4.5. Overall risk/benefit assessment 23
   4.6. Rationale for performing the trial 23
5. Objectives and endpoints 24
   5.1. Primary objective 24
   5.2. Secondary objectives 24
   5.3. Primary endpoint 24
   5.4. Secondary endpoints 24
   5.5. Correlative endpoints 24
6. Trial design, duration and termination 25
   6.1. Trial design 25
   6.2. Sample size and trial duration 25
7. Patient selection 26
   7.1. Inclusion criteria 26
   7.2. Exclusion criteria 27
8. Patient screening and randomisation 28
   8.1. Screening 28
   8.2. Randomisation and stratification 29
9. Investigational medicinal product 29
   9.1. Pembrolizumab 29
   9.2. Formulation 29
   9.3. Packaging and labeling 29
   9.4. Clinical supplies disclosure 29
   9.5. Storage and handling 30
10. Trial treatments 30
   10.1. Overview of trial treatment 30
   10.2. Treatment in the experimental arm 31
   10.3. Treatment in the control arm 40
   10.4. Treatment of pleural effusion 41
   10.5. Prohibited and restricted concomitant therapies during trial treatment (pembrolizumab, vinorelbine or gemcitabine) 42
   10.6. Contraception, nursing, pregnancy 42
11. Safety of trial treatments 43
   11.1. Adverse effects of pembrolizumab 43
   11.2. Immune-related adverse effects of pembrolizumab 44
   11.3. Adverse effects of chemotherapy in the control arm 44
12. Adverse event and serious adverse event reporting 45
   12.1. Adverse event (AE) 45
   12.2. Adverse reaction (AR) 45

12.3. Unexpected adverse reaction (UAR) 45
12.4. Serious adverse events (SAE) 45
12.5. Serious adverse reaction (SAR) 48
12.6. Suspected unexpected serious adverse reaction (SUSAR) 48
12.7. Severity / intensity of (serious) adverse events 48
12.8. Causality of adverse events 49
12.9. Duration of adverse events 49
12.10. Action taken 49
12.11. Reporting SAEs and ECIs 49
12.12. Pregnancy 50
12.13. Reference safety information 51
13. Response evaluation 52
13.1. CT schedule for response evaluation 52
13.2. Response evaluation criteria in solid tumours (RECIST version 1.1) 52
14. Endpoints definition 58
14.1. Progression-free survival 58
14.2. Objective response 58
14.3. Overall survival 58
14.4. Time to treatment failure 58
14.5. Toxicity 58
15. Biological material and translational research 58
15.1. Biobanking 58
15.2. Mandatory biomaterial 59
15.3. Optional biomaterial 60
15.4. Translational research 60
15.5. Submission of biomaterial 61
16. Trial procedures 62
16.1. Tumour assessment 62
16.2. Baseline evaluations before randomisation 62
16.3. Evaluations in the experimental arm (pembrolizumab treatment) 63
16.4. Evaluations in the control arm (chemotherapy treatment) 65
16.5. Evaluations at disease progression 65
16.6. Evaluations after cross-over to pembrolizumab treatment 66
16.7. Evaluations at the end of treatment visit 67
16.8. Evaluations in the follow-up phase (post treatment) before progression 68
16.9. Evaluations in the follow-up phase (post treatment) beyond progression 68
17. Case report forms and documentation 69
17.1. Case report forms schedule 69
18. Statistical considerations 71
18.1. Primary objective 71
18.2. Sample size determination 71
18.3. Trial duration 71
18.4. Analysis populations 71
18.5. Evaluation of primary and secondary objectives 72
18.6. Early safety evaluation 72
19. Criteria for termination of the trial 72
19.1. General criteria for termination of the trial 72
19.2. Discontinuation of protocol treatment for individual patients 73
19.3. Withdrawal of consent 73
20. Ethics aspects, regulatory approval, and patient informed consent 73

20.1. Ethical Review Board/Ethics Committee 74
20.2. Regulatory approval procedures 74
20.3. Informed consent 74
21. Governance and administrative issues 75
21.1. Final report 75
21.2. Steering Committee 75
21.3. Independent Data Monitoring Committee 75
21.4. Publication 76
21.5. Clinical trial insurance 76
21.6. Quality assurance 76
21.7. Protocol adherence 76
21.8. Data protection 76
21.9. Record retention 77
22. References 78

Appendices:

1. Template for patient information and informed consent form
2. ETOP publication guidelines

Index of tables

Table 1 Vinorelbine-based chemotherapy as second and beyond line therapy in MPM 21
Table 2 Overview of trial treatments 30
Table 3 Pembrolizumab infusion reaction treatment guidelines 32
Table 4 Treatment delay and supportive care guidelines for pembrolizumab-related adverse events 35
Table 5 Chemotherapy options 41
Table 6: Measurable disease - overall response 57
Table 7: Non-measurable Disease - Overall Response 57
Table 8: Overview of translational research studies 60
Table 9 Case report forms 69

1. Protocol summary

ETOP 9-15 PROMISE-*meso*

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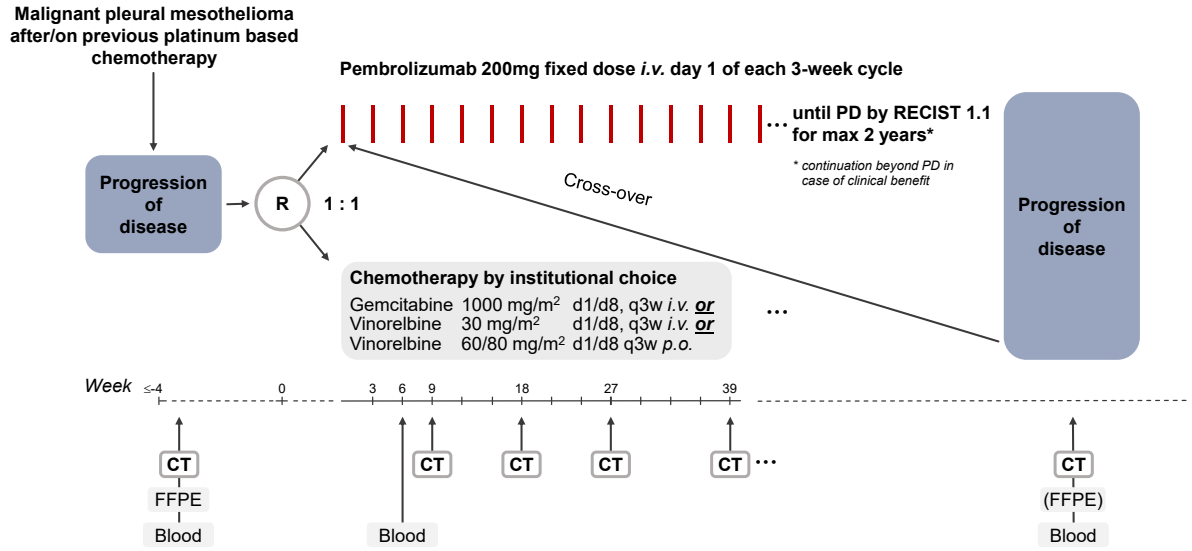
Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: Merck Sharp & Dohme Corp

Population: Advanced Malignant Pleural Mesothelioma

Design:

Randomised phase III multicentre clinical trial to demonstrate superiority of pembrolizumab versus standard, institutional-choice chemotherapy (gemcitabine or vinorelbine). Patients randomised to chemotherapy will be allowed to cross over to receive pembrolizumab at progression.



Sample size: 142 randomised patients

Randomisation: stratified by predominantly epitheloid vs non-epitheloid histological subtype

Rationale:

Mesothelioma is an aggressive malignancy usually affecting the surfaces of body coelomic cavities. It most commonly originates from the pleura with a propensity to the lower parietal pleura and costo-diaphragmatic recess, and is almost always caused by asbestos exposure, with a usual lag time of 30 years between exposure and presentation. Outcomes for most patients are invariably fatal, with median survival from presentation around 9-12 months in most series due to difficulties in achieving a complete microscopic surgical resection and tumour relative chemo-refractoriness. Whilst initially considered rare, due to the demand of asbestos of all varieties associated with industrialization following the Second World War, the background incidence of mesothelioma of 1/million has risen to 40/million in some countries. In the UK, where substantial asbestos exposure continued until the 1970s, the death rate is the highest in the world with a current epidemic of new cases, predicted to continue for another 5-10 years. Two main histological subtypes of mesothelioma are identified. The epitheliod subtype is the commonest, accounting for around 40% of cases, whilst the sarcomatoid subtype is observed in 20% of cases; the latter being typically aggressive and chemorefractory. Around 35% cases have features of both epitheliod and sarcomatoid subtypes and are termed biphasic subtype.

For patients with pleural mesothelioma, in whom surgery is not considered appropriate, systemic chemotherapy (platinum combined with pemetrexed) remains the international standard of care. Cisplatin/pemetrexed is associated with a response rate of 41% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma in Europe. Despite this, the median survival is 9-12 months from most series in unresectable cases. At relapse, after platinum-based chemotherapy, no anti-cancer systemic therapies are licensed. Whilst several small phase II studies and retrospective series have suggested potential efficacy for chemotherapy with agents including carboplatin/gemcitabine, or vinorelbine, none thus far have demonstrated efficacy benefit in a randomised study, with median PFS rates reported of about 3 months for both gemcitabine and vinorelbine. There is therefore a huge unmet need for effective therapy for patients with relapsed pleural mesothelioma. The largest trial ever performed of systemic therapy in relapsed pleural mesothelioma in 661 patients documented the natural outcome of this group of relapsed mesothelioma patients, reporting a median OS of 27.1 weeks (6 months) and median PFS for 6.1 weeks (1.5 months) for placebo.

Tremelimumab, a CTLA4-directed therapy, has shown some efficacy in two small single-arm phase II studies, reporting partial remissions in 7% of cases, disease control in 31% of cases, 6.2 months median PFS and 10.7 months median OS when delivered every 90 days. With an intensified tremelimumab schedule, immune-related ORR was 14%, with a 51% disease control rate, immune-related PFS was 6.2 months, and OS 11.3 months. Toxicity with this compound was as expected, with 90% patients reporting grade 1-2 toxicities and 7% grade 3-4 toxicities.

Programmed cell death-1 (PD-1) is a co-inhibitory molecule at the immunological synapse that acts as a major regulator of adaptive immunity, and is exploited by tumour cells to result in adaptive immune resistance (tolerance). This occurs when PD-1 binds to the ligands PD-L1 (B7H1) or PD-L2, which are expressed on many tumour types. High PD-L1 expression on tumours is associated with poorer outcomes. Mesothelioma has been shown to express PD-L1, with a small study identifying PDL1 expression in up to 40% of

mesotheliomas. Moreover, immunologically-mediated inflammation is known to be a key driver for mesothelioma development via the Nalp3 imflammasome.

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

In the phase I trial in unselected NSCLC, the objective response rate was 19.4%, the median duration of progression-free survival 3.7 months, and the median overall survival 12.0 months. Among patients with strong PD-L1 expression (at least 50% of positive cells) the response rate was 45.2, median progression-free survival was 6.3 months; median overall survival not reached in naive and 15.4 months in pretreated patients respectively [1, 2].

More recently, KEYNOTE-010 demonstrated that pembrolizumab improves overall survival (OS) over docetaxel in patients with previously treated NSCLC with membranous PD-L1 expression on ≥1% of tumour cells (hazard ratio [HR] 0.71, P = 0.0008 for pembrolizumab 2 mg/kg Q3W; HR 0.61, P < 0.0001 for pembrolizumab 10 mg/kg Q3W) [3].

Objectives and endpoints:

Primary objective:

To investigate whether treatment with pembrolizumab improves progression-free survival (PFS), as assessed by independent radiological review, compared to standard, institutional-choice chemotherapy (gemcitabine or vinorelbine).

Secondary objectives:

- To evaluate secondary measures of clinical efficacy including objective response (OR), investigator assessed PFS, overall survival (OS), and time to treatment failure (TTF)
- To assess the safety and tolerability of the treatment

Primary endpoint:

- Progression-free survival according to RECIST 1.1 criteria based on independent radiological review

Secondary endpoints:

- Objective response determined by RECIST 1.1 criteria
- Overall survival
- Time to treatment failure
- Investigator assessed progression-free survival determined according to RECIST 1.1 criteria
- Tolerability assessed by adverse events graded according CTCAE v4.0

Correlative endpoints:

- Responses according to PD-L1 expression levels, measured by IHC
- TILs analysis
- Mutation load

Most important eligibility criteria (see Section 7 for complete list)**:**

Inclusion criteria

- Histologically confirmed malignant pleural mesothelioma (all subtypes are eligible)
- Progressing after or on previous platinum based chemotherapy.
- Availability of tumour tissue for translational research
- Male and female patients aged ≥18 years
- ECOG performance status 0-1
- Life expectancy of at least 3 months
- Measurable or evaluable disease according to RECIST 1.1 criteria
- Adequate haematological, renal, and liver function

Exclusion criteria

- Prior therapy with an anti-PD-1, anti-PD-L1/L2, anti-CD137, or anti-CTLA-4 antibody
- Prior therapy with gemcitabine or vinorelbine
- Known active central nervous system metastases and/or carcinomatous meningitis.
- Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

Treatment arms:

Experimental arm:

Pembrolizumab, 200 mg fixed dose *i.v.* on day 1 of every 3-week (±3 days) cycle until progression of disease determined according to RECIST 1.1 criteria or lack of tolerability or until further protocol treatment is declined by the patient, for a maximum of 2 years.

In case of clinical benefit, with physician and patient agreement, pembrolizumab treatment can continue beyond documented disease progression according to RECIST 1.1 criteria until a maximum of 2 years on pembrolizumab treatment is reached. Patients need to meet the following criteria:

- ECOG performance status 0-1
- Absence of rapid progression of disease.
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Control arm:

For the control chemotherapy options, the choice of vinorelbine (*p.o.*) or vinorelbine (*i.v.*) or gemcitabine chemotherapy will be made on a per-patient basis prior to randomisation.

- Gemcitabine 1000 mg/m^2 *i.v.*, day 1 and day 8 of every 3-week (±3 days) cycle
- Vinorelbine *i.v.* 30 mg/m^2 *i.v.*, day 1 and day 8 of every 3-week (±3 days) cycle
- Vinorelbine 60/80 mg/m^2 *p.o.*, day 1 and day 8 of every 3-week (±3 days) cycle

At documented disease progression according to RECIST 1.1 criteria, patients in the control arm are allowed to receive pembrolizumab, if they meet the cross-over criteria:

- ECOG performance status 0-1
- Absence of progressive tumours at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Statistical considerations:

This is a 1:1 randomised phase III trial, designed to detect with 80% power, using a one-sided test at significance level of 0.025, an increase of the median PFS from 3.5 months on the chemotherapy arm to 6 months on pembrolizumab. This corresponds to a 6-month PFS of 30% vs 50% for the chemotherapy and the pembrolizumab group respectively (HR=0.58). A cumulative drop-out of 5% is assumed. A total of 110 events need to be observed to achieve the trial goal.

The expected accrual rate is 2 patients per month for the first 6 months, increasing to 10 patients per month thereafter. A total sample size of 142 patients accrued over a period of 19 months would be required to observe the total number of 110 events with a maximum total trial follow-up of 24 months.

The primary analysis is expected to be available 36 months after the inclusion of the first patient. The trial treatment phase will continue for a maximum of 2 years from the inclusion of the last patient and the trial is expected to end at all sites approximately 43 months after the inclusion of the first patient.

Total trial duration: 43 months from randomisation of the first patient

2. Trial schedule

	Before randomisation[1]	**Treatment Period**[2]				**PD**[7]	**End of Treatment visit**	**Post treatment visit** Every 12 (±2) weeks.	
		Experimental arm[3]	Control arm[4]	In addition on day 1 of cycle 3[5]	Beyond PD[4][6]			Before PD	After PD
Written informed consent: before any trial specific evaluations and intervention									
Medical history: smoking history, comorbidities and allergies									
Physical examination: PS, blood pressure, heart rate, temperature, body weight, height (only at baseline)		Within 72 hours before start of each treatment cycle							
Baseline symptoms									
Adverse events									
Concomitant medications									
Survival[8]									
Laboratory tests									
Thyroid function:[9] TSH, with reflex free T3/4		every 2nd treatment cycle			every 2nd treatment cycle				
HIV test									
Pregnancy test[10]	Repeated within 72 hours before treatment start	every 2nd treatment cycle			every 2nd treatment cycle		only for pembrolizumab		
Chemistry: serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH		Within 72 hours before start of each treatment cycle							
Haematology: haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count)		Within 72 hours before start of each treatment cycle							

	Before randomisation[1]	**Treatment Period**[2]				**PD**[7]	**End of Treatment visit**	**Post treatment visit** Every 12 (±2) weeks.	
		Experimental arm[3]	Control arm[4]	In addition on day 1 of cycle 3[5]	Beyond PD[4][6]			Before PD	After PD
Coagulation profile (INR)		every 2nd treatment cycle			every 2nd pembrolizumab cycle				
Liver function tests: total bilirubin, ALT, AST, ALP, GGT		Within 72 hours before start of each treatment cycle							
Renal function tests: urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockroft-Gault		Within 72 hours before start of each treatment cycle							
Urine analysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed		every 2nd treatment cycle							
Treatment									
Pembrolizumab[11]									
Chemotherapy[12]									
Further lines of treatment									
Disease evaluation									
Radiological tumour assessment[13]		First 6 months: every 9 weeks, then every 12 weeks					If not done within last 6 weeks		
Pulmonary function (FEV1 and FCV)[14]	**strongly encouraged**			**strongly encouraged**		**strongly encouraged**			
Biological material									
FFPE[15]						**optional**			
Blood samples[16]									

Mandatory evaluation / intervention

(1) Evaluations to be done within 5 weeks (35 days) before randomisation. If examinations were done prior to 5 weeks (35 days) before start of randomisation, they have to be repeated.
(2) Every 3 weeks (±3days).
(3) **Patients in the experimental arm (and patients in the control arm after cross-over):** assessments have to be done on day 1 of every treatment cycle (or within 3 days before these dates)
(4) **Patients in the control arm**: assessments have to be done on day 1 of every treatment cycle (or within 3 days before these dates). After cross-over to pembrolizumab treatment, biological material collection, examinations and documentation follow the schedule for the experimental arm (see footnote 3) starting at pembrolizumab cycle 1.
(5) On day 1 of treatment cycle 3 (or within 3 days before this date) for both experimental and control arm.
(6) In case of clinical benefit, with physician and patient agreement, pembrolizumab treatment can continue beyond progression until a maximum of 2 years on pembrolizumab treatment of therapy is reached.
(7) Disease progression: determined according to RECIST 1.1 criteria.
(8) Survival status: to be collected during the follow-up visits.
(9) Thyroid function test: TSH value. In case of abnormal TSH, free T3 and T4 also have to be measured.
(10) Pregnancy test: Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta HCG pregnancy test within 35 days before randomisation. The test has to be repeated 72 hours before pembrolizumab treatment start and then every 2nd cycle of pembrolizumab treatment and at end of treatment visit.
(11) Pembrolizumab is administrated at 200 mg fixed dose *i.v.* on day 1 (±3 days) of every 3-week cycle until progression of disease determined according to RECTIST 1.1 criteria or lack of tolerability for a maximum of 2 years. In case of clinical benefit, with physician and patient agreement, and if cross-over criteria are met, pembrolizumab treatment can continue beyond PD until a maximum of 2 years on pembrolizumab treatment is reached.
(12) Chemotherapy: for the control chemotherapy options, the choice of vinorelbine (*p.o.*) or vinorelbine (*i.v.*) or gemcitabine chemotherapy will be made on a per-patient basis prior to randomisation.
- Gemcitabine 1000 mg/m2 *i.v.*, day 1 and day 8 of every 3-week (±3 days) cycle or
- Vinorelbine 30 mg/m2 *i.v.*, day 1 and day 8 of every 3-week (±3 days) cycle or
- Vinorelbine 60/80 mg/m^2 *p.o.*, day 1 and day 8 of every 3-week (±3 days) cycle

At documented disease progression according to RECIST 1.1 criteria control arm patients that meet the cross-over criteria are allowed to receive pembrolizumab for a maximum of 2 years.
Examinations, blood sample collection and documentation for cross-over patients have to follow the schedule of the experimental arm and start at pembrolizumab cycle 1.
(13) Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively (and only after the first CT at baseline) CT of thorax and ultrasonography of upper abdomen, following the schedule indicated below; until tumour progression determined according to RECIST 1.1 criteria. If pembrolizumab treatment is continued beyond progression, radiological tumour assessment by CT has to continue until treatment stop. The same imaging technique, acquisition, and processing parameters should be used for each patient throughout the trial.

At baseline:	within 5 weeks before randomisation	
First 6 months (up to week 27):	every 9 weeks* (63 days)	at week 9, 18, 27 (±4 days)
Up to 2 years:	every 12 weeks* (84 days)	at week 39, 51, 63, …99 (±7 days)

* from start of trial treatment and during cross-over to pembrolizumab

(14) Pulmonary function: **strongly encouraged:** forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) at baseline, on day 1 of treatment cycle 3 and at disease progression.
(15) FFPE material: formalin-fixed, paraffin embedded (FFPE) archival tumour material from primary diagnosis. In addition, a fresh biopsy sample taken close to the start of trial treatment (after first-line therapy) should be submitted, if available. (A fresh FFPE biopsy sample is mandatory if the archival tumour material from diagnosis is fully depleted. If tumour tissue block is not available, 5 slides with FFPE tumour tissue sections of 4-5 µm thickness are an acceptable alternative). FFPE material has to be shipped to the central laboratory within 4 weeks after randomisation.
(16) Blood samples: 2.5 mL whole blood for DNA analysis at baseline, 2.5 mL RNA whole blood for RNA analysis and 5 mL serum samples will be collected at baseline, on day 1 of treatment cycle 3 and at disease progression.

3. List of abbreviations

AE	Adverse Event
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANC	Absolute Neutrophil Count
APC	Antigen presenting cell
AST	Aspartate transaminase
BID	Bis In Die (lat.), twice-daily
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BORR	Best Overall Response Rate
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
CTV	Clinical Target Volume
DLCO	Diffusing Capacity for Carbon Monoxide
DVH	Dose Volume Histogramm
EC	Ethics Committee
ECI	Event of Clinical Interest
ECL	Electrochemiluminescent
eCRF	Electronic Case Report Form
ED	Extensive Stage Disease
EDC	Electronic Data Capture
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EP	Etoposide - Cisplatinum
ERB	Ethical Review Board
FVC	Forced vital capacity
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GTV	Gross Tumour Volume
IA	Interim Analysis
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	Informed Consent
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial Lung Disease

INR	International Normalised Ratio
IMP	Investigational Medicinal Product
irAE	Immune-related Adverse Events
irPFS	Immune-related Progression Free Survival
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Hb	Hemoglobin
LD	Limited Stage Disease
LF	Lost to Follow-up
LFT	Liver Function Test
LLN	Lower Limit of Normal Lab Value
MIP	Maximum Intensity Projection
MLD	Mean Lung Dose
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NCCN	National Comprehensive Cancer Network
NSCC	Nonsquamous-Cell Carcinoma
NSCLC	Non-Small Cell Lung Carcinoma
OAR	Organs at Risk
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PIS	Patient Information Sheet
PK	Pharmacokinetics
PPK	Population Pharmacokinetic
PR	Partial Response
PS	Performance Status
QD	Quaque Die, once daily
PTV	Planning Target Volume
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SBRT	Stereotactic Body Radiation Therapy
SCC	Squamous-Cell Carcinoma
SCLC	Small cell lung carcinoma
SD	Stable Disease
SIAD	Syndrome of Inappropriate Diuresis
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standard uptake volume
Tc99mDTPA	Technetium-99m Diethyl Triamine Penta-Acetic Acid
TIL	Tumour Infiltrating Lymphocyte
Treg	Regulatory T-cells (CD4+CD25+)
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal lab value

VALG	Veterans Administration Lung Study Group
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell Count
WBRT	Whole Brain Radiotherapy
WC	Withdrawal of Consent

4 . Background and rationale

4.1. Disease background

Mesothelioma is an aggressive malignancy usually affecting the surfaces of body coelomic cavities. It most commonly originates from the pleura with a propensity to the lower parietal pleura and costo-diaphragmatic recess, and is almost always caused by asbestos exposure, with a usual lag time of 30 years between exposure and presentation [4]. Outcomes are invariably fatal, with median survival from presentation around 9-12 months in most series due to difficulties in achieving a complete microscopic surgical resection and tumour relative chemo-refractoriness [5]. Whilst initially considered rare, due to the demand of asbestos of all varieties associated with industrialization following the Second World War, the background incidence of mesothelioma of 1/million has risen to 40/million in some countries. In the UK, where substantial asbestos exposure continued until the 1970s, the death rate is the highest in the world with a current epidemic of new cases, predicted to continue for another 5-10 years [6]. Two main histological subtypes of mesothelioma are identified. The epitheliod subtype is the commonest, accounting for around 40% of cases, whilst the sarcomatoid subtype is observed in 20% of cases; the latter being typically aggressive and chemorefractory. Around 35% cases have features of both epitheliod and sarcomatoid subtypes and are termed biphasic subtype [7]. For patients with pleural mesothelioma, in whom surgery is not considered appropriate, systemic chemotherapy (platinum combined with pemetrexed) remains the international standard of care [5]. Cisplatin/pemetrexed is associated with a response rate of 41% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma [8].

Despite this, in unresectable cases, the median survival is 9-12 months from most series [4, 8]. At relapse, after platinum-based chemotherapy, no anti-cancer systemic therapies are licensed. Several small phase II studies and retrospective series have suggested potential efficacy for chemotherapy with agents including carboplatin/gemcitabine, or vinorelbine. There is therefore a huge unmet need for effective therapy for patients with relapsed pleural mesothelioma. The largest trial ever performed of systemic therapy in relapsed pleural mesothelioma in 661 patients [9] documented the natural outcome of this group of relapsed mesothelioma patients reporting a median OS of 27.1 weeks (6 months) and median PFS for 6.1 weeks (1.5 months) for placebo.

Tremelimumab, a CTLA4-directed therapy, has shown some efficacy in two small single-arm phase II studies, reporting partial remissions in 7% of cases, disease control in 31% of cases, 6.2 months median PFS and 10.7 months median OS when delivered every 90 days [10]. With an intensified tremelimumab schedule, immune-related ORR was 14%, with a 51% disease control rate, immune-related PFS was 6.2 months, and OS 11.3 months [11]. Toxicity with this compound was as expected, with 90% patients reporting grade 1-2 toxicities and 7% grade 3-4 toxicities [11]. There is a need to identify new ways for the systemic therapy of malignant mesothelioma and immune checkpoint inhibition is a promising way forward. Results from the proposed trial will contribute to overcoming tumour-specific immune suppression with immune checkpoint inhibition.

4.2. Treatment background

4.2.1. Gemcitabine

Gemcitabine (Gemzar; Eli-Lilly and Company, Indianapolis, IN) is a broadly active antifolate with acitivity and EMA license in a variety of solid tumours, including NSCLC, pancreatic cancer, and breast cancer. It has demonstrated activity in malignant mesothelioma with an activity as a single agent ranging from 0% to 31% [12] and it is not known to be cross-resistant with pemetrexed. Moreover, as a single agent or in combination, gemcitabine was the most commonly used agent in pre-treated patients who were treated in the phase III pemetrexed trial. It is therefore considered an active standard therapeutic option in the second-line setting after pemetrexed-based chemotherapy [13].

4.2.2. Vinorelbine

Vinorelbine (Navelbine; Pierre Fabre, Castres, France) is a vinca alkaloid cytotoxic chemotherapy that is available in intravenous and oral preparations with EMA licenses in lung cancer and breast cancer. It has been evaluated as single agent both in the first-line and second-line settings [14], both in prospective small phase II trials and also in retrospective cohorts (second or third-line) using either intravenous or oral formulations (see Table 1).

Table 1 Vinorelbine-based chemotherapy as second and beyond line therapy in MPM

Author [ref]	Regimen	# pts	Line	RR	DCR	mTTP/PFS	mOS
Stebbing [15][a)]	*i.v.* VNR	63	100% 2L	16%	84%	NR	9.6 mo
Sørensen [16][a)]	*p.o.* VNR	15	100% 2L	7%	NR	2.3 mo	2.5 mo
Zucali [17][b)]	*i.v.* VNR	59	58% 2L, 42% 3L	15%	49%	2.3 mo	6.2 mo
Zauderer [18, 19][b)]	*i.v.* VNR	45	53 2L 47% 3L	0%	52%	2.5 mo	5.0 mo
Zucali [13][a)]	*i.v.* VNR + GEM	30	100% 2L	10%	43%	2.8 mo	10.9 mo
Toyakawa [20][a)]	*i.v.* VNR + GEM	17	100% 2L	18%	82%	6.0 mo	11.2 mo

Ref = Reference; *i.v.* = intravenous; *p.o.* = oral; VNR = vinorelbine; GEM = gemcitabine; Line = line of therapy; RR = response rate; DCR = disease control rate (response rate + stable disease); mTTP/PFS = median time to progression or progression-free susrvival; mOS = median overall surial; mo = months. a) prospective studies; b) retrospective studies. Adapted from [14].

No randomised trials of vinorelbine have been performed for relapsed pleural mesothelioma. Responses observed to date have varied between 0-16%, and toxicities observed, are similar to those known for the compound. Despite these limitations, vinorelbine has gained popularity as an acceptable treatment option in the relapsed setting, as highlighted by several of the retrospective studies.

4.3. Background pembrolizumab

Programmed cell death-1 (PD-1) is a co-inhibitory molecule at the immunological synapse that acts as a major regulator of adaptive immunity, and is exploited by tumour cells to result in adaptive immune resistance (tolerance) [21]. This occurs when PD-1 binds to the ligands PD-L1 (B7H1) or PD-L2, which are expressed on many tumour types. High PD-L1 expression on tumours is associated with poorer outcomes. Mesothelioma has been shown to express PD-L1, with a small study identifying PD-L1 expression in up to 40% of mesotheliomas [22]. Moreover, immunologically-mediated inflammation is known to be a key driver for mesothelioma development via the Nalp3 imflammasome [23]. MK-3475

(pembrolizumab) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It has demonstrated activity in a number of different tumour types including melanoma and non-small cell lung cancer (NSCLC), with a favourable toxicity profile in NSCLC (9.5% grade 3-5 treatment-related adverse events, 0.6% diarrhoea, n=495), and marked efficacy with a 40% one-year PFS rate for previously treated patients with strong PD-L1 expression (>50%) (Garon 2015).

Pembrolizumab has also demonstrated superior efficacy to ipilimumab in metastatic melanoma [24]. Of major interest are the results of the KEYNOTE-028 basket trial, where 25 PD-L1 weak/strong positive (>1% PD-L1 expression) relapsed mesothelioma patients of all histological subtypes treated with pembrolizumab at 10 mg/kg q14 showed an unprecedented 76% disease control rate, supported by a 28% PR rate and a 48% SD rate. At time of reporting, 64% patients, including all responders, remained on treatment (duration 8+ to 24+ weeks) (Alley A, AACR 2015).

Additional data from KEYNOTE-028 presented at the World Lung Congress 2015 (Alley A, WCLC 2015) with a June 2015 data cut-off demonstrated that PD-L1 positivity (>1%) was observed in 45% of screened samples (newly obtained or archival) and that a 28% PR rate with a 48% SD rate had been maintained, supporting a 76% disease control rate. 61% of patients had evidence of tumour shrinkage, with duration of response ranging from 10.4 to 40.3+ weeks. Exploratory analyses demonstrated no relationship between magnitude of PD-L1 expression and presence/absence of response. Median PFS was 5.8 months.

4.3.1. Rationale for pembrolizumab fixed dosing

The choice of the 200 mg *i.v.* every 3 weeks as an appropriate dose for the fixed dosing, is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that *i)* are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, *ii)* will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and *iii)* will maintain individual patient's exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen, be more convenient for physicians and reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

The rationale for further exploration of 200 mg fixed doses of pembrolizumab in solid tumours is based on: *i)* similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg every 3 weeks in melanoma patients, *ii)* the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg to 10 mg/kg every 3 weeks, *iii)* the lack of effect of tumour burden on distribution of pembrolizumab (as assessed by the population PK model) and *iv)* the assumption that the dynamics of PD-1 target engagement will not vary meaningfully with tumour type. In addition, preliminary data from 45 previously treated, advanced or metastatic NSCLC patients treated at the 2 mg/kg every 3 weeks dose/schedule indicates a 20% BOR by RECIST 1.1 criteria (35% by irRECIST). This is in comparison to the 22.4% ORR observed at the 10 mg/kg every 2 weeks, suggesting lack of dose responsiveness and additional

justification for the inclusion of a fixed dose of 200 mg Q3W pembrolizumab in KEYNOTE 024 [NCT02142738; www.clinicaltrials.gov].

4.4. Choice of design and comparator

Gemcitabine represents a standard of treatment for mesothelioma in the second-line setting after treatment with pemetrexed [25]. This chemotherapy has shown a variable activity in first and second line. The EORTC-Lung Cancer Group (LCG) examined gemcitabine in mesothelioma at a dose of 1,250 mg/m2 i.v. over 30 minutes on days 1, 8, and 15 of each 28-day cycle. Here a response rate of 7% in 27 patients was observed [26]. The CALGB conducted a phase II multicenter trial evaluating the activity of gemcitabine in chemotherapy naïve patients with MPM, but among the 17 patients treated, there were no partial or complete responses and median survival was 4.7 months. Another phase II trial of gemcitabine in chemotherapy naïve patients with MPM demonstrated 2 objective responses among 27 patients (7%) and a median survival of 8 months [27].

4.5. Overall risk/benefit assessment

First-line chemotherapy is the standard treatment of patients not assessable for surgical interventions. Since palliative first-line chemotherapy results in a median overall survival of 12 months, new therapeutic approaches have to be developed. However, immunological approaches can be associated with the risk of off-target toxicity. Toxicity of immune checkpoint inhibitors is manageable and severe toxicities are rare. Moreover there is clear evidence that immune checkpoint inhibitors can be effective in advanced cancers, and pembrolizumab, especially in mesothelioma, has shown responses (partial responses and stable disease) in the vast majority of patients.

Taken together, for patients in a palliative setting with a median life expectancy of about 12 months the risk is reasonable in comparison to possible benefit. Moreover this trial is designed to let patients randomised to the chemotherapy arm cross over to receive pembrolizumab after progression, a treatment that would not be otherwise available for patients with incurable malignant pleural mesothelioma.

4.6. Rationale for performing the trial

Pembrolizumab has shown significant activity in a population of pre-treated mesothelioma patients. To date, no therapeutical treatments have shown an impact on the survival of patients in this setting. There is a need to identify new ways for the systemic therapy of malignant mesothelioma and immune checkpoint inhibition is a promising way forward.

5. Objectives and endpoints

5.1. Primary objective

To investigate whether treatment with pembrolizumab improves progression-free survival (PFS), as assessed by independent radiological review, compared to standard, institutional-choice chemotherapy (gemcitabine or vinorelbine).

5.2. Secondary objectives

5.2.1. To evaluate secondary measures of clinical efficacy including objective response (OR), investigator assessed PFS, overall survival (OS), and time to treatment failure (TTF).

5.2.2. To assess the safety and tolerability of the treatment.

5.3. Primary endpoint

5.3.1. Progression-free survival (PFS) according to RECIST 1.1 criteria based on independent radiological review. For definition, see Section 14.1.

5.4. Secondary endpoints

5.4.1. Objective response determined by RECIST 1.1 criteria

5.4.2. Overall survival

5.4.3. Time to treatment failure

5.4.4. Investigator assessed progression-free survival determined according to RECIST 1.1 criteria.

5.4.5. Adverse events graded according to CTCAE v4.0

5.5. Correlative endpoints

5.5.1. Responses according to PD-L1 expression levels, measured by IHC

5.5.2. TILs analysis

5.5.3. Mutation load

6. Trial design, duration and termination

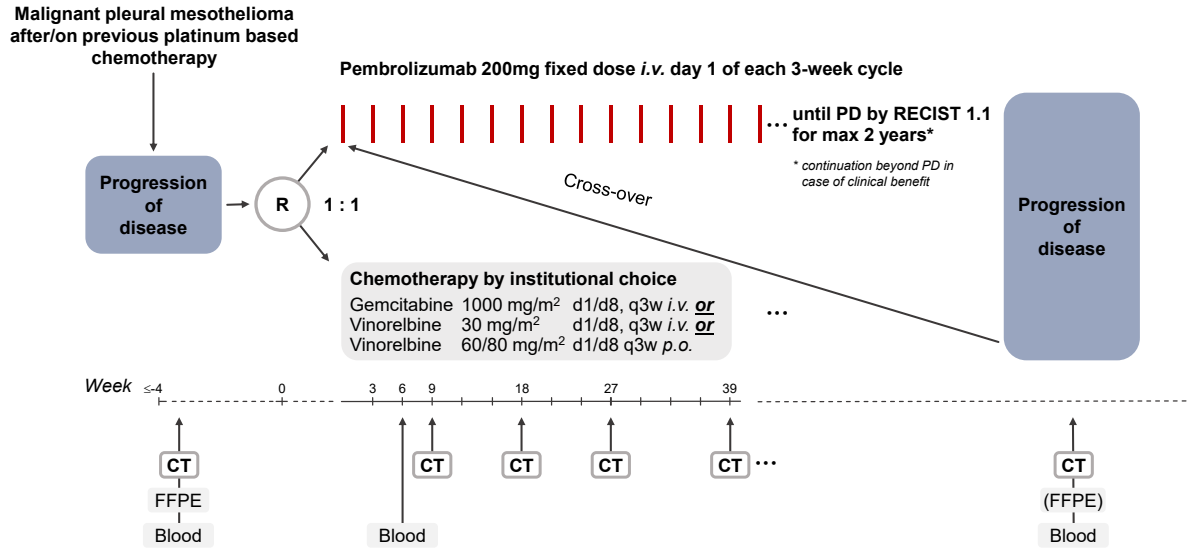
6.1. Trial design

This is a randomised phase III multicentre clinical trial designed to demonstrate superiority of pembrolizumab over institutional-choice standard chemotherapy (gemcitabine or vinorelbine), stratified by predominantly epitheloid vs non-epitheloid histological subtype.

Patients randomised to the control arm will be allowed to cross over to receive pembrolizumab at progression.

Patients will undergo CT imaging every 9 weeks for the first 6 months (until week 27) and every 12 weeks thereafter.

Cross-over: for patients in the control arm, at progression determined by RECIST 1.1 criteria according to local investigator assessment.



6.2. Sample size and trial duration

Patient accrual is expected to be completed within 19 months including a run-in period of 6 months. A total sample size of 142 patients will be required with a maximum total trial follow-up of 24 months.

Approximately 12 sites, including 7 from Switzerland and 5 from the United Kingdom, will participate in this trial.

Results of the primary analysis are expected to be available 36 months after the inclusion of the first patient. The trial treatment phase will continue for a maximum of 2 years from the inclusion of the last patient and the trial is expected to end at all sites approximately 43 months after the inclusion of the first patient.

7. Patient selection

Written informed consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention including the submission of mandatory biomaterial.

7.1. Inclusion criteria

7.1.1. Histologically confirmed MPM (all subtypes are eligible)

7.1.2. Progressing after or on previous platinum based chemotherapy.

7.1.3. Availability of tumour tissue for translational research (see Section 15.2.1)

7.1.4. Female and male patients aged ≥18 years

7.1.5. ECOG performance status 0-1

7.1.6. Life expectancy of at least 3 months

7.1.7. Measurable or evaluable disease according to RECIST 1.1 criteria (see Section 13.2)

7.1.8. Adequate renal function:

- Creatinine ≤1.5 × ULN OR
- Calculated creatinine clearance ≥40 mL/min (using the Cockroft-Gault formula below)

Cockroft-Gault formula Switzerland:

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{72 \times \text{Creatinine}_{\text{serum}} \left(\frac{\text{mg}}{\text{dL}}\right)} \ (\times 0.85 \text{ if female})$$

Cockroft-Gault formula UK:

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{\text{Creatinine}_{\text{serum}}\ [\mu\text{M}]} \times \text{A}$$

A= 1.23 [male] and 1.04 [female]

7.1.9. Adequate haematological function:

- Haemoglobin ≥90 g/L or ≥5.6 mmol/L
- WBC ≥1.0 × 10^9/L
- Lymphocytes ≥0.5 g/L
- Absolute neutrophils count (ANC) ≥1.5 × 10^9/L
- Platelet count ≥100 × 10^9/L

7.1.10. Adequate liver function:

ALT and AST ≤2.5 × ULN. If the patient has liver metastases, ALT and AST must be ≤5 × ULN

7.1.11. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 35 days before randomisation (the test has to be repeated 72 hours before pembrolizumab treatment start).

7.1.12. Written informed consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention including the submission of mandatory biomaterial.

7.2. Exclusion criteria

7.2.1. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

7.2.2. Prior therapy with gemcitabine or vinorelbine.

7.2.3. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to randomisation and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to randomisation. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

7.2.4. Known or suspected hypersensitivity to pembrolizumab or any of its excipients.

7.2.5. Known unstable or unresolved surgical or chemotherapy-related toxicity that would compromise the patient's capacity to participate in the trial.

7.2.6. Previous allogeneic tissue/solid organ transplant.

7.2.7. Live vaccines within 30 days prior to first dose of pembrolizumab.

7.2.8. Regular intake of immune-modulating drugs (such as interferon, methotrexate).

7.2.9. History of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease (ILD) or active, non-infectious pneumonitis.

7.2.10. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) or topical therapy (e.g., steroids) for psoriasis or eczema is not considered a form of systemic treatment.

7.2.11. Ongoing clinically serious infections requiring systemic antibiotic or antiviral, antimicrobial, or antifungal therapy.

7.2.12. HIV infection.

7.2.13. Known active hepatitis B or hepatitis C.

7.2.14. Known history of active tuberculosis.

7.2.15. Patients with diagnosed immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomisation.

7.2.16. Patients with other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical condition that could affect the patient's capacity to participate in the trial.

7.2.17. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial results.

7.2.18. Women who are pregnant or in the period of lactation.

7.2.19. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the trial and up to 120 days following cessation of trial treatment (see Section 10.6.1).

8. Patient screening and randomisation

This trial will use a web-based registration and randomisation system. Each participating centre will access the system directly to randomise patients into the trial. Specific details for the inclusion of patients are in the ***PROMISE-meso Procedures Manual*** which will be available on the trial documentation download section of the ETOP website (www.etop-eu.org).

8.1. Screening

Complete the following steps to screen and include a patient into this trial. Please consult the ***PROMISE-meso Procedures Manual*** for detailed instructions.

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention including the submission of mandatory biomaterial.

Verify eligibility and randomise the patient in the EDC system ETOPdata according to the information in the ***PROMISE-meso Procedures Manual***. The dates the informed consent form and the consent to the pathology material submission section of the informed consent form were signed by the patient and by the investigator are required to complete the eligibility checklist.

8.2. Randomisation and stratification

Patients with malignant pleural mesothelioma who have progressed after or during previous platinum based chemotherapy will be randomised to one of two treatment arms.

Patient eligibility must be checked before randomisation (see Section 7). Please complete and submit the Eligibility for randomisation eCRF (see Section 17). Then submit the randomisation eCRF in ETOPdata in order to randomise the patient.

Randomisation should take place at least 3 weeks after last dose of previous platinum based chemotherapy.

Trial treatment for both arms has to start within 7 days after randomisation.

Block stratified randomisation balanced by institution will be performed, stratified by histological subtype (predominantely epitheloid vs non-epitheloid) [28].

9. Investigational medicinal product

Pembrolizumab (MK-3475) is the investigational medicinal product (IMP) used in this trial. Merck will provide the IMP at no cost for this trial.

Complete details of the investigational medicinal product logistics, distribution, packaging, labeling and handling as well as accountability are described in the ***PROMISE-meso Drug Supply Manual***.

9.1. Pembrolizumab

Pembrolizumab (MK-3475) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and ultimately immune rejection.

9.2. Formulation

Refer to the current version of the pembrolizumab Investigator's Brochure (IB) for pharmaceutical formulation information.

Clinical supplies will be provided by Merck. For details please refere to the ***Drug Supply Manual***.

9.3. Packaging and labeling

Clinical supplies will be affixed with a clinical trial label in accordance with regulatory requirements.

9.4. Clinical supplies disclosure

This trial is open-label; therefore, the patient, the trial site personnel, ETOP and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

9.5. Storage and handling

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. The Principal Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10. Trial treatments

10.1. Overview of trial treatment

The treatments to be used in this trial are outlined in Table 2 below. The treatment in the experimental arm consists of 200 mg fixed dose pembrolizumab *i.v.* on day 1 (±3 days) of every 3-week cycle until progression of disease determined according to RECIST 1.1 criteria or lack of tolerability for a maximum of 2 years (expected maximum of 36 doses).

For the control chemotherapy options, the choice of vinorelbine (*p.o.*) or vinorelbine (*i.v.*) or gemcitabine chemotherapy must be made prior to randomisation.

Trial treatment for both arms should begin on the day of randomisation or as close as possible to this date (preferably within 7 days after randomisation).

Table 2 Overview of trial treatments

Drug	**Dose**	**Dose frequency**	**Route of administration**	**Regimen**
Experimental arm				
Pembrolizumab	200 mg	Q3W	*i.v.*	Day 1 (±3 days) of each 3-week cycle
Control arm				
Gemcitabine	1000 mg/m^2	Q3W	*i.v*	Day 1 & day 8 of each 3-week (±3 days) cycle
Vinorelbine	30 mg/m^2	Q3W	*i.v*	Day 1 & day 8 of each 3-week (±3 days) cycle
Vinorelbine	60 mg/m^2 (increase to 80 mg/m^2 from cycle 2 on if well tolerated)	Q3W	*p.o*	Day 1 & day 8 of each 3-week (±3 days) cycle

10.2. Treatment in the experimental arm

10.2.1. Pembrolizumab dose

Pembrolizumab is administrated at 200 mg fixed dose *i.v.* on day 1 of every 3-week (±3 days) cycle for a maximum or 2 years (expected maximum of 36 doses), or until progression of disease determined according to RECIST 1.1 criteria or lack of tolerability, or until the patient declines further treatment.

In case of clinical benefit, with physician and patient agreement, pembrolizumab treatment can continue beyond progression for a maximum of 2 years of therapy (see Section 10.2.7).

10.2.2. Dose delay criteria for pembrolizumab treatment

Note: There will be **no dose modifications for pembrolizumab allowed** for the management of toxicities of individual patients.

Pembrolizumab will be withheld for all grade ≥3 drug-related toxicities including laboratory abnormalities, and severe or life-threatening AEs.

If a dose of pembrolizumab is withheld for toxicity (other than those listed in Table 4 for which permanent discontinuation is required after the first occurrence of the toxicity), then patients may resume dosing with pembrolizumab when the toxicity has improved as described below:

- If toxicity does not resolve to grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the ETOP medical reviewer.
- Patients who require corticosteroids to manage drug-related adverse events must be at an equivalent dose of ≤10 mg per day of prednisone to resume dosing with pembrolizumab. If the corticosteroid dose to manage a drug-related adverse event cannot be reduced to the equivalent of ≤10 mg prednisone per day within 12 weeks of last pembrolizumab dose the investigator should contact the ETOP medical reviewer to discuss the continuation of trial treatment.
- With investigator and ETOP medical reviewer agreement, patients with a laboratory adverse event still at grade 2 after 12 weeks may continue trial treatment only if the toxicity is asymptomatic and controlled. This includes patients who experience drug induced hypothyroidism requiring replacement therapy. Resumption of pembrolizumab may occur once the patient is stable on adequate doses of replacement therapy and is clinically asymptomatic.
- For the occurrence and management of immune-related adverse effects, please refer to Section 10.2.4 and Table 4 in conjunction with the latest version of the pembrolizumab Investigator's Brochure.

10.2.3. Treatment of pembrolizumab related infusion reactions

Since pembrolizumab is a human immunoglobulin protein, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigours, headache, rash, pruritis, arthralgias,

hypo- or hypertension, bronchospasm, or other symptoms. All grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to CTCAE (version 4.0) guidelines.

Treatment recommendations are provided in Table 3 and may be modified based on local treatment standards and guidelines as appropriate:

Table 3 Pembrolizumab infusion reaction treatment guidelines

CTCAE grade	**Pembrolizumab Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, *i.v.* fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: - *i.v.* fluids - Antihistamines - NSAIDS - Acetaminophen - Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop second grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hours (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg *p.o.* (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms	**Stop Infusion.** **Patient is permanently discontinued from further trial treatment administration.** Additional appropriate medical	No subsequent dosing.

CTCAE grade	Pembrolizumab Treatment	Premedication at subsequent dosing
following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	therapy may include but is not limited to: - *i.v.* fluids - Antihistamines - NSAIDS - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids - Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For toxicity grading, please refer to the common terminology criteria for adverse events v4.0 (CTCAE V4.0)		

10.2.4. Treatment of immune-related adverse effects of pembrolizumab

An immune-related adverse effect (irAE) is defined as a clinically significant adverse event of any organ that is associated with trial drug exposure, is of unknown aetiology, and is consistent with an immune-related mechanism.

For the occurrence and management of immune-related adverse effects (which may include hypothyroidism, hyperthyroidism, pneumonitis or colitis), please refer to Table 4, in conjunction with the latest version of the pembrolizumab IB.

Potential immune-related adverse events (irAEs) are primary events of clinical interest (ECIs) and should be reported as SAEs (see Section 12.4.4 for details).

10.2.5. Supportive care during pembrolizumab treatment

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Table 4. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Table 3 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

For patients who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, a consultation between the ETOP medical reviewer and investigator should occur to determine whether the patient should continue in the trial. However, if a patient experiences a recurrence of the same Serious Adverse Event at the same grade or greater with rechallenge of pembrolizumab, the patient must discontinue trial medication. Refer to Table 4 and contact ETOP medical reviewer for guidance.

For the description and reporting of Events of Clinical Interest (ECI) see Section 12.4.4.

<u>Note</u>: Permanently discontinue for any grade 3 (grade 2 for pneumonitis) drug-related AE *that recurs*, or any life-threatening event.

Table 4 Treatment delay and supportive care guidelines for pembrolizumab-related adverse events

Toxicity	Grade	Action to be taken	Timing for restarting treatment	Dose/schedule for restarting treatment	Permanent discontinuation[1)]	Supportive care
Pneumonitis	any grade	N/A	N/A	N/A	N/A	Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
	1	continue treatment	N/A	N/A	N/A	
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion and prednisone or equivalent was reduced to ≤10 mg/day within 12 weeks.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with systemic corticosteroids[(2)]. Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper.
	3-4	hold treatment	N/A	N/A	**Permanently discontinue treatment**.	Immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
Diarrhea/ colitis	any grade	N/A	N/A	N/A	N/A	Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via *i.v.* infusion. For grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
	1	continue treatment	N/A	N/A	N/A	
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion and prednisone or equivalent was reduced to ≤10 mg/day within 12 weeks.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Administer oral corticosteroids[(2)]. 1–2 mg/kg/day prednisone or equivalent followed by a taper.

Toxicity	Grade	Action to be taken	Timing for restarting treatment	Dose/schedule for restarting treatment	Permanent discontinuation[1)]	Supportive care
	3	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion and prednisone or equivalent was reduced to ≤10 mg/day within 12 weeks.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with intravenous steroids followed by high dose oral steroids[(1)]. 1–2 mg/kg/day prednisone or equivalent followed by a taper.
	4	hold treatment	N/A	N/A	**Permanently discontinue**.	Treat with intravenous steroids followed by high dose oral steroids[(1)]. 1–2 mg/kg/day prednisone or equivalent followed by a taper.
Hepatic toxicity (AST, ALT, increased bilirubin)	1	continue treatment	N/A	N/A	N/A	N/A
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Monitor liver function tests more frequently until returned to baseline values (consider weekly) Treat with *i.v.* or oral corticosteroids[(1)]. Initial dose of 0.5–1 mg/kg/day prednisone or equivalent followed by a taper.
	3-4	hold treatment	N/A	N/A	**Permanently discontinue[(3)]**	Treat with intravenous corticosteroids for 24 to 48 hours[(1)]. 1–2 mg/kg/day prednisone or equivalent followed by a taper.
Haematological Toxicity	1 & 2	continue treatment	N/A	N/A	N/A	
	3	hold treatment **<u>Exception</u>**: grade 1-3 neutropenia	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion and for any severe event**	
	4	hold treatment	N/A	N/A	**Permanently discontinue**	
Diabetes mellitus type I (T1DM) including	T1DM and DKA	hold treatment	When patient is clinically and metabolically stable.	Same dose and schedule	N/A	Insulin replacement therapy is recommended for Type I diabetes mellitus and for grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Toxicity	Grade	Action to be taken	Timing for restarting treatment	Dose/schedule for restarting treatment	Permanent discontinuation[1)]	Supportive care
ketoacidosis [DKA] or grade ≥3 hyper-glycemia[(4)]	3-4	hold treatment	When patient is clinically and metabolically stable.	Same dose and schedule	N/A	Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
Hypophysitis	1	continue treatment	N/A	N/A	N/A	N/A
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
	3-4	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with an initial dose of *i.v.* corticosteroids followed by oral corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
Hyperthyroidism	1	continue treatment	N/A	N/A	N/A	N/A
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy.
	3	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with an initial dose of *i.v.* corticosteroid followed by oral corticosteroids[1] Replacement of appropriate hormones may be required as the steroid dose is tapered.
	4	hold treatment	N/A	N/A	**Permanently discontinue[3)]**	Treat with an initial dose of *i.v.* corticosteroid followed by oral corticosteroids[(1)] Replacement of appropriate hormones may be required as the steroid dose is tapered.

Toxicity	Grade	Action to be taken	Timing for restarting treatment	Dose/schedule for restarting treatment	Permanent discontinuation[1)]	Supportive care
Hypothyroidism	1	continue treatment	N/A	N/A	N/A	N/A
	2-4	continue treatment	Treatment can continue while thyroid replacement therapy is instituted	Same dose and schedule	N/A	Thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
Infusion reaction	any grade	N/A	N/A	N/A	N/A	Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 3 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patients should be premedicated for the next scheduled dose. Please refer to Table 3 "Infusion reaction treatment guidelines" for further management details.
	3-4	hold treatment	N/A	N/A	**Permanently discontinue**	
Renal failure or nephritis	1	continue treatment	N/A	N/A	N/A	N/A
	2	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion and prednisone or equivalent was reduced to ≤10 mg/day within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	Treat with corticosteroids[1]. Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper.
	3-4	hold treatment	N/A	N/A	**Permanently discontinue**	Treat with systemic corticosteroids[(1)]. Initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper.
All other drug-related toxicites	1	continue treatment	N/A	N/A	N/A	N/A

Toxicity	Grade	Action to be taken	Timing for restarting treatment	Dose/schedule for restarting treatment	Permanent discontinuation[1)]	Supportive care
	2	hold treatment	At physician discretion until toxicity resolves to 0-1 within 12 weeks of last infusion.	Same dose and schedule	**Permanenty discontinue** for persistent grade 2 adverse reaction for which trial treatment has been held.	N/A
	≥3	hold treatment	Toxicity resolves to grade 0-1 within 12 weeks of last infusion and prednisone or equivalent was reduced to ≤10 mg/day within 12 weeks of last infusion.	Same dose and schedule	**Permanently discontinue if toxicity does not resolve within 12 weeks of last infusion**.	N/A
	4	hold treatment	N/A	N/A	**Permanently discontinue**	N/A
Note: Patients who experience a recurrence of the same event (all grade 3; grade 2 for pneumonitis) at the same grade or greater after rechallenge of pembrolizumab should be discontinued from trial treatment						

N/A: not applicable
1) After consultation with ETOP medical reviewer
2) When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.
3) Exception: patients with liver metastasis who begin treatment with grade 2 AST or ALT can resume treatment, if AST or ALT increases by less than 50% relative to baseline and for less than 1 week.
4) If associated with ketosis (ketonuria) or metabolic acidosis (DKA)

10.2.6. Dose administration for pembrolizumab

Please refer to the ***PROMISE-meso Drug Supply Manual*** for specific instructions regarding preparation of the infusion fluid, and administration.

Pembrolizumab 200 mg fixed dose will be administered as a 30 minute *i.v.* infusion on day 1 (±3 days) of every 3-week cycle until progression of disease determined according to RECIST 1.1 criteria or lack of tolerability for a maximum of 2 years. Sites should make every effort to target infusion duration to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of minus 5 minutes and plus 10 minutes is permitted (i.e. infusion time is 25-40 minutes). Please refer to Table 3 for the management of infusion reaction.

Planning the time of trial drug infusion (e.g., time of the week for first administration; time of the day for each administration) should take trial visit procedures into consideration. All trial treatments will be administered on an out-patient basis (hospitalization <24h).

10.2.7. Criteria to continue pembrolizumab treatment in case of progression

Disease progression is determined according to local investigator assessment by RECIST 1.1 criteria. Patients in the experimental arm with progression of disease may still benefit from the continuation of pembrolizumab treatment. This includes patients who develop new symptomatic brain lesions without extracranial progression. Continuation of pembrolizumab treatment (until a maximum of 2 years is completed) for such patients must be discussed with ETOP medical reviewer (please contact PROMISE-meso@ETOP-eu.org).

Patients in the experimental arm need to be stable and have to meet the following criteria to continue pembrolizumab treatment:

- ECOG performance status 0-1
- Absence of rapid progression of disease.
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Any patient deemed clinically unstable should be discontinued from trial treatment at radiologic evidence of progressive disease.

10.2.8. Stop of pembrolizumab treatment

Patients will receive pembrolizumab treatment for a maximum of 2 years (calculated from the date of the first dose), until progression of disease (see Section 10.2.7 above), lack of tolerability, or until further protocol treatment is declined by the patient.

10.3. Treatment in the control arm

10.3.1. Dose administration for gemcitabine or vinorelbine chemotherapy

A control chemotherapy drug (either gemcitabine or vinorelbine) will be chosen on a per-patient basis. Systemic therapy treatment will be delivered according to local standards and can consist either of gemcitabine (*i.v.*) or vinorelbine (*i.v.* or *p.o.*). Chemotherapy will be administered on days 1 and 8 of every 3-week (21 ±3 days) cycle (see Table 5).

A maximum number of treatment cycles is not mandated. Patients are not allowed to switch between vinorelbine and gemcitabine chemotherapy for any reason. Patients may, however, switch between oral and intravenous formulations of vinorelbine if clinically indicated. Chemotherapy options should be administered according to local practice.

For additional details regarding dispensing or reconstitution, preparation of the infusion fluid, and administration for each of the standard of care chemotherapy regimens, please refer to the approved product labels and local policies for gemcitabine and vinorelbine.

Table 5 Chemotherapy options

Option	Compound	Dose	Schedule
1	Gemcitabine *i.v.*	1000 mg/m^2	d1 and d8, q3w (±3 days)
2	Vinorelbine *i.v.*	30 mg/m^2	d1 and d8, q3w (±3 days)
3	Vinorelbine *p.o.*	60/80 mg/m^2 (increase to 80 mg/m^2 on cycle 2 in case of good tolerability)	d1 and d8, q3w (±3 days)

10.3.2. Dose modification and delay criteria for gemcitabine or vinorelbine chemotherapy

Dose modification, reductions and holds should be performed according to local practice. Please refer to approved product labels for patients receiving these regimens.

10.3.3. Cross-over to pembrolizumab treatment for patients in the control arm

At documented disease progression according to RECIST 1.1 criteria, patients in the control arm are allowed to receive pembrolizumab, if they meet the cross-over criteria:

- ECOG performance status 0-1.
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

10.3.4. Pembrolizumab treatment after cross-over

Administration of pembrolizumab will follow the same schedule as for patients in the experimental arm, i.e. 200 mg fixed dose as a 30 minute *i.v.* infusion on day 1 of every 3-week (±3 days) cycle for a maximum of 2 years or until trial termination. Please refer to Section 16.6 for details. Tumour assessment and biological sample collection after cross-over follows the same schedule as the experimental arm (see Sections 13.1 and 15).

10.4. Treatment of pleural effusion

Puncture of the thoracic effusion and installation of a tunnelled drainage catheter are allowed whenever clinically indicated. Talc- or fibrin-pleurodesis are not allowed during trial treatment. Further surgical interventions for the treatment of mesothelioma, including pleurectomy decortication or pleuro-pneumonectomy, are not allowed during trial treatment.

In case of a local infection and especially in case of an abscess, local treatment including decortication of the abscess is allowed. However, the patient is not allowed to commence or continue trial treatment until a complete resolution of the infection is documented.

10.5. Prohibited and restricted concomitant therapies during trial treatment (pembrolizumab, vinorelbine or gemcitabine)

Locoregional therapy is left to the investigator's discretion according to medical need (for treatment of pleural effusions see Section 10.4) with the exception of prohibited therapies listed below.

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Cytoreductive surgery (e.g., pleurectomy, extra-pleural pneumonectomy, or radiofrequency ablation).
- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Live vaccines within 30 days prior to the first dose of trial treatment and while on trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids (more than 10 mg prednisolone equivalent) for any purpose other than for management of events of clinical importance, as pre-medication for the control chemotherapies, and/or a premedication for *i.v.* contrast allergies or reactions. The use of physiologic doses of corticosteroids (prednisone 10 mg orally daily or equivalent) is at the discretion of the investigator.

Note: Palliative doses of radiation therapy and SBRT to a symptomatic solitary lesion or to the brain is allowed. Pembrolizumab treatment needs to be interrupted during palliative radiotherapy.

10.6. Contraception, nursing, pregnancy

10.6.1. Contraception

Female patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential.

Women of childbearing potential and sexually active men must use highly effective contraception from the start of trial treatment until 120 days after the last dose of any trial

treatment (pembrolizumab, vinorelbine or gemicitabine). The following contraception methods are considered highly effective:

- Hormonal (estrogen and progesterone) contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation
- Progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- Intrauterine deviced (IUD) or intrauterine hormone releasing systems (IUS)
- Bilateral tubal occlusion
- Vasectomy

Women who become pregnant while participating in the trial must discontinue trial treatment immediately. The pregnancy must be reported following procedures detailed in Section 12.7. Also any pregnancy that occurs in a female partner of a male trial participant must be reported.

Patients should be informed that taking the trial medication may involve unknown risks to the fetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above) for the duration of the trial up to 120 days after the last dose of any trial treatment. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

10.6.2. Use in pregnancy

If a patient inadvertently becomes pregnant while on any trial treatment, trial treatment will be stopped immediately for the patient and the event reported immediately, see Section 12.12. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to ETOP without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to ETOP.

10.6.3. Use in nursing women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for randomisation.

11. Safety of trial treatments

11.1. Adverse effects of pembrolizumab

As of 30 June 2015, 9400 patients had been treated with pembrolizumab at several dose schedules. The safety of pembrolizumab has been evaluated in 1012 patients across three

doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies. Most common adverse reactions (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. The majority of adverse reactions reported were of grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

As of 14 August 2015, data of 409 patients treated with 200 mg fixed dose were reviewed. The adverse events reviewed were consistent with the known adverse event profile for pembrolizumab; no new significant findings were evident.

11.2. Immune-related adverse effects of pembrolizumab

An immune-related adverse effect (irAE) is defined as a clinically significant adverse event of any organ that is associated with trial drug exposure, is of unknown aetiology, and is consistent with an immune-related mechanism.

Immune-related adverse reactions are presented based on 2117 patients with melanoma and with NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. The most commonly reported irAEs across the dose-schedules are hypothyroidism (7.8%), hyperthyroidism (2.9%), pneumonitis (2.4%), and colitis (1.7 %).

For the occurrence and management of immune-related adverse effects, please refer to section 10.2.2 in conjunction with the latest version of the pembrolizumab IB.

Based on literature review and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are primary events of clinical interest (ECIs) and should be reported as SAEs (see Section 12.4.4 for details).

11.3. Adverse effects of chemotherapy in the control arm

11.3.1. Adverse effects of vinorelbine

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis and constipation. Fatigue and fever were also reported very commonly. The most commonly system organ classes involved are: 'Blood and lymphatic system disorders', 'Gastrointestinal disorders', 'Infections and infestations' and 'General disorders and administration site conditions'. This information is consistent with the pre-marketing experience (from SPC).

11.3.2. Adverse effects of gemcitabine

The most commonly reported adverse drug reactions associated with Gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients (from SPC).

12. Adverse event and serious adverse event reporting

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the CTCAE version 4.0. The CTCAE is available for downloading on the internet at http://evs.nci.nih.gov/ftp1/CTCAE/About.html. An interactive version can be found at https://safetyprofiler-ctep.nci.nih.gov/.

12.1. Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of signature of informed consent until 30 days after all trial treatment discontinuation, regardless of whether it is considered related to a medication.

Any grade of any observed AE should be reported on the AE eCRFs.

12.2. Adverse reaction (AR)

An adverse reaction (AR) is defined as “any noxious and unintended response to an IMP related to any dose administered”.

All adverse events judged by either the reporting investigator or the ETOP medical reviewer as having a reasonable causal relationship (see Section 12.8) to an IMP qualify as adverse reactions. The expression “suspected/related” means to convey in general that there is evidence or argument to suggest a causal relationship to the trial treatment.

12.3. Unexpected adverse reaction (UAR)

An unexpected adverse reaction (UAR) is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

When the outcome of the adverse reaction is not consistent with the IB or summary of product characteristics (SPC), this adverse reaction should be considered as unexpected.

12.4. Serious adverse events (SAE)

A serious adverse event (SAE) is defined as any undesirable medical occurrence/adverse drug experience that at any dose:

- results in death (any cause, except progression of cancer under study)
- is life-threatening
- requires or prolongs inpatient hospitalisation (see Section 12.4.1)
- results in persistent or significant disability/incapacity
- constitutes an important medical event
- is a congenital anomaly or birth defect (including neonatal deaths)
- is a secondary malignancy (see Section 12.4.3)

- is an event of clinical interest (see Section 12.4.4)

12.4.1. Inpatient hospitalisation

A hospital stay equal to, or greater than, 24 hours. Hospitalisations occurring under the following circumstances are **not** considered to be SAEs:

- elective surgery
- occur on an outpatient basis and do not result in admission (hospitalisation <24h)
- are part of the normal treatment or monitoring of the studied treatment

12.4.2. Important medical events

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalisation, or disability, but may jeopardise the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

12.4.3. Secondary malignancies

Primary malignancy

A second primary malignancy is one that is unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

12.4.4. Events of clinical interest (ECI)

The following events of clinical interest (ECIs) are not necessarily SAEs, but should be reported as such on the SAE eCRFs (***SAE Initial Reports***) by indicating that this is an "event of clinical interest".

- **Drug induced liver injury (DILI):** AST or ALT elevations ≥3x ULN with concurrent elevation of total bilirubin ≥2× ULN and, at the same time, alkaline phosphatase (AP) <2 × ULN.
- **Overdose**: All overdoses with and without an AE must be reported by the investigator to ETOP safety office within 24 hours.

12.4.5. Pembrolizumab overdose

An overdose of pembrolizumab is defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is associated with ("results from") the overdose of pembrolizumab, the AE is reported as SAE, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported reported on the ***SAE Initial Report*** **eCRF** as ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 24 hours of awareness.

12.4.6. Exceptions to the SAE definition

The following situations do not need to be reported as SAEs:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalisation which was planned before the patient consented for trial participation and where admission did not take longer than anticipated (see section 12.4.1).
- A hospitalisation planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an (serious) AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen significantly.
- Progression of cancer under study:

  By convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

12.5. Serious adverse reaction (SAR)

A serious adverse reaction (SAR) is defined as any SAE which is considered related to the protocol treatment.

12.6. Suspected unexpected serious adverse reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) occurring in clinical investigations qualify for expedited reporting to the appropriate regulatory authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

12.7. Severity / intensity of (serious) adverse events

The (serious) AE severity grade provides a qualitative assessment of the extent or intensity of a specific event, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g., severe nausea, mild seizure), and does not reflect the relationship to trial drug. A severe event may be of relatively minor medical significance (such as severe headache). The term "severe" **not** the same as "serious" which is based on patient/event **outcome** or **action criteria** associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

Severity grade for other adverse events not covered in the toxicity grading scale:

- **Grade 1** = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- **Grade 2** = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- **Grade 3** = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible
- **Grade 4** = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
- **Grade 5** = Death – the event results in death

12.8. Causality of adverse events

The investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE following the definitions indicated below:

Not suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Relationship to the protocol treatment	
Not suspected	**Suspected / related to trial treatment**
- unrelated - unlikely	- possible - probable - definite

12.9. Duration of adverse events

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

12.10. Action taken

The investigator will report the action taken with trial drug(s) because of an AE or SAE, as applicable (e.g., discontinuation of trial drug(s), medication needed for the treatment of an AE) and in case of an SAE report if concomitant and/or additional treatments were given for the event.

12.11. Reporting SAEs and ECIs

Any SAE and any ECI, whether related to trial drug or not, occurring in a patient after providing written informed consent (IC) within 90 days after last dose of trial treatment or within 30 days following cessation of trial treatment, if the patient initiates a new anticancer therapy, must be reported. Information about all such events will be collected and recorded on the SAE eCRFs (***SAE Initial Reports***).

After completion of trial treatments, report all SAEs beyond 90 days (or beyond 30 days following cessation of trial treatment, if the patient initiates new anticancer therapy) that are considered at least possibly related to previous trial treatment. Cases of secondary (non-pleura) malignancies and congenital abnormalities and neonatal deaths are to be cosidered

as SAEs, regardless of whether they occur during or after trial treatment. These events should be reported during the whole trial duration on the serious adverse event eCRFs (***SAE Initial Reports***)

To ensure patient safety, ETOP must be informed of each SAE and each ECI using the procedures described below:

- The investigator/MD responsible for the patient must complete an ***SAE Initial Report*** eCRF in English within 24 hours of awareness in the EDC system ETOPdata.
- Queries may be issued by the ETOP safety office; a timely response by the investigator to all SAE-related queries is crucial.
- The SAE outcome must be reported within 15 days after initial reporting by online submitting the ***SAE Follow-up Report*** eCRF. In case the SAE is reported as ongoing after 15 days, a second follow-up report has to be submitted with the final outcome.

Submission of SAE is done via the EDC system, or in case of unavailability, by sending the SAE form by fax to the ETOP Safety Office:

+41 31 389 92 29

As soon as the EDC system is available again, the SAE eCRF has to be completed and submitted by the site.

The ETOP safety office will inform **Merck Global Safety** and other appropriate persons about all SAEs and ECIs within 24 hours of receipt at the ETOP safety office.

The ETOP Safety Office will record the SAE/ECI and prepare a summary report of all SAEs/ECIs received. Listings of SAEs will be prepared as required.

12.12. Pregnancy

Please refer to section 10.6 for information on contraception, nursing, pregnancy and highly effective contraception methods.

12.12.1. Maternal exposure

In the case of pregnancy occurring during the course of the trial or within 120 days after treatment discontinuation, the investigator shall immediately (within 24 hours after awareness of pregnancy) notify ETOP by completing the pregnancy eCRF in ETOPdata in accordance with the SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported (within 14 days) by submitting a second pregnancy eCRF in ETOPdata. All neonatal deaths that occur within 28 days of birth should be reported, irrespective of causality, as SAEs. In addition, any infant death after 28 days, irrespective of causality should also be reported within 24 hours of the investigator's knowledge of the event using the SAE forms.

12.12.2. Paternal exposure

Pregnancy that occurs in a female partner of a male trial participant is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to during the course of the trial or within 120 days after treatment discontinuation by completing the pregnancy eCRF in ETOPdata.

12.13. Reference safety information

The pembrolizumab IB edition 10 Section 7 served as reference document for the determination of the expectedness of the serious adverse events of pembrolizumab.

The currently EU approved summary of product characteristics (SPC) of vinorelbine and gemcitabine serve as reference safety information to assess the expectedness of vinorelbine and gemcitabine related serious adverse events.

13. Response evaluation

13.1. CT schedule for response evaluation

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively (and only after the first CT at baseline) CT of thorax and ultrasonography of upper abdomen following the schedule indicated below; until tumour progression determined according to RECIST 1.1 criteria. If pembrolizumab treatment is continued beyond progression, radiological tumour assessment by CT has to continue until pembrolizumab treatment stop. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

At baseline:	within 5 weeks before randomisation	
First 6 months (up to week 27):		
	every 9 weeks* (63 days)	at week 9, 18, 27 (±4 days)
Up to 2 years:	every 12 weeks* (84 days)	at week 39, 51, 63, …99 (±7 days)

* from start of pembrolizumab/chemotherapy treatment

CT schedule after cross-over

Patients in the control arm are allowed to cross over to receive pembrolizumab beyond determined progression determined according to RECIST 1.1 criteria, for a maximum of 2 years from start of pembrolizumab treatment. Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done according to the schedule indicated below, until further tumour progression determined according to RECIST 1.1 criteria or until a maximum of 2 years from start of pembrolizumab treatment, or trial termination. If pembrolizumab treatment is continued beyond further progression, radiological tumour assessment by CT has to continue until pembrolizumab treatment stop.

First 6 months (up to week 27):		
	every 9 weeks* (63 days)	at week 9, 18, 27 (±4 days)
Up to 2 years:	every 12 weeks* (84 days)	at week 39, 51, 63, …99 (±7 days)

* from start of pembrolizumab

13.2. Response evaluation criteria in solid tumours (RECIST version 1.1)

13.2.1. Introduction

All included patients will be evaluated for disease response and progression according to the revised response evaluation criteria in solid tumours (RECIST version 1.1) [29].

In this trial, patients must have **measurable or evaluable** disease (see definitions below).

13.2.2. Methods of assessment

In this trial, CT scans will be used to evaluate response.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan should generally be performed using a ≤5 mm contiguous reconstruction algorithm. MRI is acceptable for certain situations, e.g., body scans.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules) and ≥10 mm. In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

Ultrasound is not useful in assessment of lesion size and is not accepted as a method of assessment.

FDG-PET is not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a PET/CT scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT scan performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT scan (with i.v. and oral contrast), then the CT scan portion of the PET/CT can be used for RECIST measurements.

13.2.3. Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray

  Reminder: A lesion in a previously irradiated area is not eligible for measurable disease.

- **Malignant lymph nodes**: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan, assuming the slice thickness is ≤5 mm. At baseline and in follow-up, only the short axis will be measured.

13.2.4. Non-measurable disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured.

Non-measurable lesions/sites of disease and special considerations:

- Small non-nodal lesions (longest diameter <10 mm in CT scan)
- Small lymph nodes (short axis ≥10 and <15 mm). Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.
- Bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions
- Tumour lesions situated in a previously irradiated area, or subjected to other locoregional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion
- Abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

13.2.5. Selection of target lesions

Target lesions should be identified, measured and recorded at baseline. At baseline, there can be up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. **Lymph nodes** selected as target lesions should always have the **short axis** recorded. All **other lesions** should always have their **longest diameters** recorded. The sum of diameters will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

13.2.6. Selection of non-target lesions

All other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

For non-target lesions, measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the eCRF.

Note: pleural effusion is a non-target lesion.

13.2.7. Evaluation of target lesions

All target lesions will be measured at each tumour assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete response (CR): Disappearance of all target lesions. Lymph nodes selected as target lesions must each have reduction in the short axis to <10 mm in order for the response to be considered complete. In this case, the sum of diameters may be > 0.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions (see section 13.2.9) denotes disease progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on study.

Note: All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a target lesion is thought likely to have disappeared, use "0 mm."

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

13.2.8. Evaluation of non-target lesions

- Complete response (CR): Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (<10 mm).
- Non-CR/non-PD: Persistence of one or more non-target lesions (non-CR).
- Progression (PD): unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease, or an overall substantial increase in tumour burden that merits treatment discontinuation.

When no imaging is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesions are evaluated at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the

contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

13.2.9. Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumour. If a new lesion is equivocal, e.g., because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan when the lesion was discovered.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g., brain metastases) are considered new lesions. The detection of new lesions is not restricted to the examination methods used at baseline.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

13.2.10. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.2.11. When the patient has only non-measurable disease

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable).

A useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumour burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’ or an increase in lymphangitic disease from localised to widespread. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II of reference [29].

If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-

measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

13.2.12. Determination of time point response

Based on the responses of target lesions, non-target lesions, and the presence or absence of new lesions, the overall response will be determined at each tumour evaluation time point, according to the table below.

13.2.13. For patients with measurable disease

Table 6: Measurable disease - overall response

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR / non-PD*	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

13.2.14. For patients with non-measurable disease

Table 7: Non-measurable Disease - Overall Response

Non-target lesions	**New lesions**	**Overall response**
CR	No	CR
Non-CR / non-PD*	No	Non-CR / non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

13.2.15. Determination of best overall response

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial.

13.2.16. Storage of images

All CT images must be stored locally in electronic format for later central review, please consult the ***PROMISE-meso Procedures Manual*** for details.

14. Endpoints definition

14.1. Progression-free survival

PFS is defined as the time from the date of randomisation until documented progression, or death, if progression is not documented. Censoring will occur at the last tumour assessment only if patient is lost to follow-up or refuses further documentation of follow-up.

14.2. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from randomisation to termination of trial treatment. Objective response to pembrolizumab treatment will be determined using RECIST 1.1 criteria (see Section 13.2).

14.3. Overall survival

OS is defined as time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

14.4. Time to treatment failure

Defined as time from the date of randomisation to discontinuation of treatment for any reason (including progression of disease, treatment toxicity, refusal and death). Censoring will occur at the last follow-up date.

14.5. Toxicity

Adverse events classified according to CTCAE version 4.0.

15. Biological material and translational research

15.1. Biobanking

A biobank for all biological material collected from every patient randomised in this trial will be created with centralised samples for translational research, integral to the trial. The required pathological material (described below) is submitted to, catalogued, and maintained at the central laboratory: Tumour tissue blocks, whole blood, and serum samples will be centrally collected and biobanked at the Center for Experimental Therapeutics CTE, CHUV Lausanne, Switzerland. The material will be centrally archieved and subjected to central histology review and biomarker testing. Eventually, the biological material will be made available for translational research, following completion of the primary trial translational research objectives.

15.2. Mandatory biomaterial

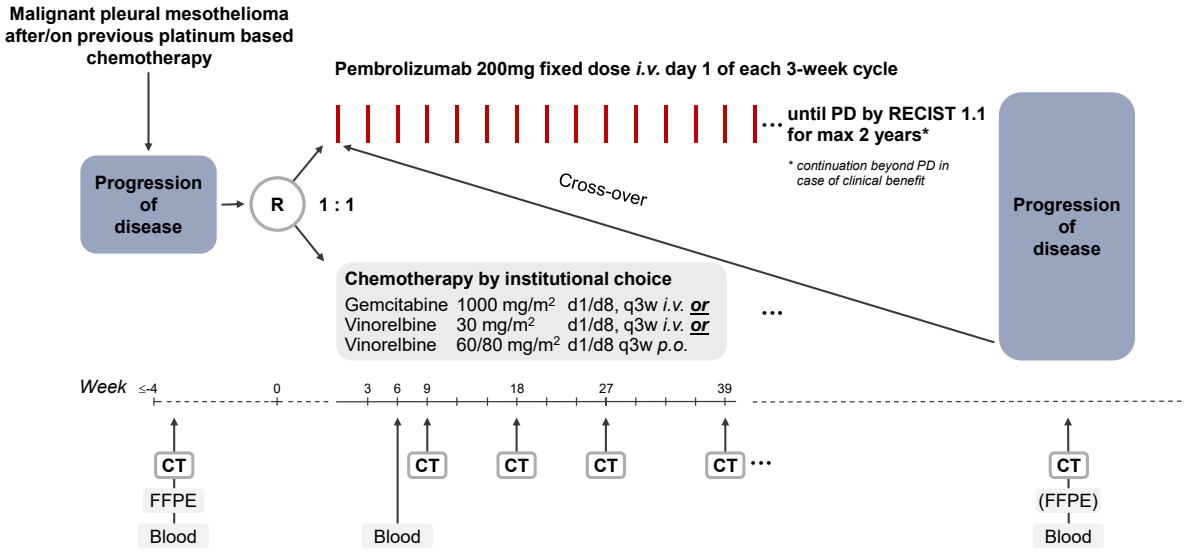
15.2.1. FFPE-material

FFPE tumour tissue availability must be confirmed at time of randomisation and material shipped within 4 weeks thereafter.

- Formalin-fixed, paraffin embedded (FFPE) archival tumour material from primary diagnosis must be submitted centrally. In addition, a fresh biopsy sample taken close to the start of trial treatment (after first-line therapy) should be submitted, if available. A fresh FFPE biopsy sample is mandatory if the archival tumour material from diagnosis is fully depleted.
- Submission of an FFPE tumour tissue block is strongly preferred but, if not available, 5 slides with FFPE tumour tissue sections of 4-5 µm thickness are an acceptable alternative. All slides should be freshly cut and shipped to the central reference laboratory within 1 week of sectioning.
- Cytological specimens are not accepted in this trial.

15.2.2. Blood and serum samples

- 2.5 mL whole blood will be collected in PAXgene RNA tubes (for RNA profiling) at baseline, on day 1 of treatment cycle 3, and at disease progression.
- 2.5 mL whole blood will be collected in PAXgene DNA tubes (for germline mutation assessment as a reference for tumour somatic mutation analysis) at baseline.
- Serum samples from 5 mL blood taken at baseline, on day 1 of treatment cycle 3 (week 6), and at disease progression.
- All samples should be immediately frozen at -80ºC.



15.3. Optional biomaterial

15.3.1. FFPE-material

FFPE tumour block (preferred) or alternatively 5 tissue sections of 4-5 µm thickness, and 10-15 tumour tissue sections of 15-20 µm thickness from re-biopsy at disease progression. If blocks were not submitted, an additonal 10-15 tumour tissue sections of 15-20 µm thickness from archival tumor and/or fresh biopy, if feasible.

15.4. Translational research

The following table gives an overview of all biological material collected during the trial and the associated translational research projects under consideration. These projects will be continuously adapted according to the growing knowledge about immunological modification and potential biomarkers of immune checkpoint inhibitor therapy. Translational research studies will be conducted by ETOP-internal and -external collaborators in line with the ETOP iBiobank policy.

Table 8: Overview of translational research studies

Sample	**Time point**				**Potential analyses**
	Diagnosis (archival)	**Baseline**	**Day 1 of cycle 3[(1)]**	**PD**	
FFPE (To be shipped to the central laboratory within 4 weeks after randomisation)					
- Tumour block **OR**	X	X		optional	- IHC/mutational analyses listed below
- min. 5 sections of 4-5 µm	X	X		optional	- PD-L1 (IHC) - TILs analysis (H&E)
- 5-10 sections of 15-20 µm	optional	optional		optional	- Mutation load - PD-L2 (IHC) - PD-L1 (IHC) with different antibody? - DNA/RNA (NGS)
Archival tumour material from primary diagnosis must be submitted. In addition, a fresh biopsy sample taken close to the start of trial treatment (after first-line therapy) should be submitted, if available. (A fresh FFPE biopsy sample is **mandatory** if the archival tumour material from diagnosis is fully depleted).					
Blood samples (Frozen samples kept at site at -80°C until centrally arranged shipment)					
Whole blood – RNA Whole blood – DNA		2.5 mL 2.5 mL	2.5 mL	2.5 mL	- RNA profiling - Germline mutation reference (HLA haplotype)
Serum		5 mL	5 mL	5 mL	- Cytokines - ctDNA - IL6 - Mesothelin - CRP

(1) For patients in the control arm and crossing over to pembrolizumab, these samples will be collected twice, on day 1 of cycle 3 and at PD on chemotherapy as well as on day 1 of cycle 3 and at PD on pembrolizumab treatment.

15.5. Submission of biomaterial

All biological samples collected during the conduct of the trial must be marked with the patient identifier issued by the EDC system and registered in the system. FFPE tumour tissue and blood samples will be shipped to the central reference laboratory in Lausanne (Ludwig Institute for Cancer Research, University of Lausanne, Switzerland).

15.5.1. Submission of FFPE material

- FFPE tumour material as defined in Section 15.2.1. and Section 15.3.1.
- Pathology report from diagnostic biopsy and from biopsy after first-line therapy (all information allowing identification of the patient, e.g., patient name, day and month of birth, must be removed).
- Pathology report from re-biopsy at progression (all information allowing identification of the patient, e.g., patient name, day and month of birth, must be removed).

Tumour material should be submitted as soon as obtained (but not no later than 4 weeks after patient randomisation), and documented in the ***Biological Material Tracking*** eCRF in the database. On request, blocks can be returned to the submitting site within a reasonable time frame (est. 3 months) and after slides for the planned analyses have been cut.

All reports, slides, and blocks must be marked with the patient identification number issued by the EDC system.

Please ensure that the blocks and/or slides are carefully packaged according to the ***PROMISE-meso Procedures Manual***, as otherwise they could easily get damaged during transport.

Samples have to be sent to:

CHUV - Department of Oncology
Center for Experimental Therapeutics (CTE)
Hôpital Orthopédique, HO 05/1552
Av. Pierre-Decker 4
CH-1011 Lausanne, Switzerland

Anonymised pathology reports should be uploaded via the EDC system. Please consult the ***PROMISE-meso Procedures Manual*** for specific instructions.

15.5.2. Submission of blood samples

For blood collection and serum preparation see ***PROMISE-meso procedures manual***.

Blood samples as defined in Sections 15.2.2. and 15.3.2.

Blood samples must be stored locally at -80ºC and will be kept at the participating site until shipment. Shipments will be arranged centrally once a site has collected all blood samples after the inclusion of the last patient. Samples have to be sent to the same address as indicated above.

16. Trial procedures

This section gives an overview of procedures, clinical and laboratory evaluations and follow-up investigations.

16.1. Tumour assessment

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done as indicated in section 13.1.

16.2. Baseline evaluations before randomisation

The following examinations should be done within 5 weeks (35 days) before randomisation. If examinations were done prior to 5 weeks (35 days) before start of randomisation, they have to be repeated.

16.2.1. Written informed consent:

before any trial specific evaluations or interventions

16.2.2. Radiological tumour assessment

by CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included)

16.2.3. Medical history:

including baseline symptoms, smoking history, medications, comorbidities and allergies

16.2.4. Physical examination:

including, ECOG performance status, blood pressure, heart rate, temperature, body weight, height.

16.2.5. HIV test

16.2.6. Thyroid function:

TSH value. In case of abnormal TSH, free T3 and T4 have also to be measured.

16.2.7. Chemistry:

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.2.8. Haematology:

haemoglobin, platelet count, white blood cell (WBC) count including differential (lymphocytes and absolute neutrophil count).

16.2.9. Coagulation profile (INR)

16.2.10. Liver function tests:

total bilirubin, ALT, AST, ALP, GGT

16.2.11. Renal function tests:

urea, uric acid, serum creatinine and and creatinine clearance calculated according to Cockroft-Gault.

16.2.12. Urine analysis:

specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed.

16.2.13. Pregnancy test:

Women of childbearing potential, including women who had their last menstrual period within the last 2 years, must have a negative serum or urine beta-HCG pregnancy test within 35 days before randomisation. The test has to be repeated within 72 hours before pembrolizumab treatment start and then every 2nd cycle of pembrolizumab treatment.

16.2.14. Pulmonary function:

FEV1 and FVC (strongly encouraged)

16.2.15. Biological material (see Section 15.2 and 15.3 for details):

FFPE material: archival tumour material from primary diagnosis. In addition, a fresh biopsy sample taken close to the start of trial treatment (after first-line therapy) if available.

Note: A fresh biopsy sample is mandatory if the archival tumour material from diagnosis is fully depleted.

Blood samples: 2 x 2.5 mL whole blood for RNA and DNA analysis and 5 mL serum samples.

16.3. Evaluations in the experimental arm (pembrolizumab treatment)

At each treatment cycle

The following evaluations have to be done on day 1 of every treatment cycle (or within 3 days before these dates):

16.3.1. Recording of symptoms, adverse events and concomitant medications.

16.3.2. Physical examination:

including ECOG performance status, blood pressure, heart rate, temperature, body weight.

16.3.3. Chemistry:

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.3.4. Haematology:

haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

16.3.5. Liver function tests:

total bilirubin, ALT, AST, ALP, GGT

16.3.6. Renal function tests:

urea, uric acid, serum creatinine and and creatinine clearance calculated according to Cockroft-Gault.

At every 2nd treatment cycle

The following additional evaluations have to be done on day 1 (or within 3 days before these dates) of every other treatment cycle, (i.e. cycle 1, 3, 5, 7, 9, etc):

16.3.7. Thyroid function:

TSH value. In case of abnormal TSH, free T3 and T4 have also to be measured.

16.3.8. Coagulation profile (INR)

16.3.9. Urine analysis:

specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed.

16.3.10. Pregnancy test:

Women of childbearing potential, including women who had their last menstrual period within the last 2 years, must have a negative serum or urine beta-HCG pregnancy test. The test has to be repeated within 72 hours before pembrolizumab treatment start and then every 2nd cycle of pembrolizumab treatment.

At treatment cycle 3

The following additional evaluations have to be done on day 1 of treatment cycle 3 (or within 3 days before this date):

16.3.11. Pulmonary function:

relative FEV1 and FVC (strongly encouraged)

16.3.12. Biological material (see Section 15.2 and 15.3 for details):

Blood samples:

- 2.5 mL whole blood for RNA analysis

- 5 mL serum samples.

16.4. Evaluations in the control arm (chemotherapy treatment)

At each treatment cycle

The following evaluations have to be done within 3 days before day 1 of each chemotherapy treatment cycle:

16.4.1. Recording of symptoms, adverse events and concomitant medications.

16.4.2. Physical examination:

ECOG performance status, blood pressure, heart rate, temperature, body weight.

16.4.3. Chemistry:

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH

16.4.4. Haematology:

haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

16.4.5. Liver function tests:

total bilirubin, ALT, AST, ALP, GGT

16.4.6. Renal function tests:

urea, uric acid, serum creatinine and and creatinine clearance calculated according to Cockroft-Gault.

At treatment cycle 3

The following evaluations have to be done on day 1 of treatment cycle 3 (or within 3 days before this date):

16.4.7. Pulmonary function:

relative FEV1 and FVC (strongly encouraged)

16.4.8. Biological material (see Section 15.2 and 15.3 for details):

Blood samples:

- 2.5 mL whole blood for RNA analysis

- 5 mL serum samples.

16.5. Evaluations at disease progression

At progression, the following assessments are required:

16.5.1. Pulmonary function:

relative FEV1 and FVC (strongly encouraged)

16.5.2. Biological material (see Section 15.2 and 15.3 for details):

FFPE: tumour re-biopsy is strongly encouraged

Blood samples:

- 2.5 mL whole blood for RNA analysis

- 5 mL serum samples.

16.6. Evaluations after cross-over to pembrolizumab treatment

At documented disease progression according to RECIST 1.1 criteria, patients in the control arm are allowed to receive pembrolizumab, if they meet the cross-over criteria (see Section 10.3.3). The following evaulations have to be performed during pembrolizumab treatment:

At each treatment cycle

The following evaluations have to be done on day 1 of every pembrolizumab treatment cycle (or within 3 days before these dates):

16.6.1. Recording of symptoms, adverse events and concomitant medications.

16.6.2. Physical examination:

including ECOG performance status, blood pressure, heart rate, temperature, body weight.

16.6.3. Chemistry:

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH.

16.6.4. Haematology:

haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

16.6.5. Liver function tests:

total bilirubin, ALT, AST, ALP, GGT.

16.6.6. Renal function tests:

urea, uric acid, serum creatinine and and creatinine clearance calculated according to Cockroft-Gault.

At first treatment cycle and then every 2nd cycle

The following evaluations have to be done on day 1 (or within 3 days before these dates) of every other pembrolizumab treatment cycle, (i.e. cycle 1, 3, 5, 7, 9, etc):

16.6.7. Thyroid function:

TSH value. In case of abnormal TSH, free T3 and T4 have also to be measured.

16.6.8. Coagulation profile (INR)

16.6.9. Urine analysis:

specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed.

16.6.10. Pregnancy test:

Women of childbearing potential, including women who had their last menstrual period within the last 2 years, must have a negative serum or urine beta-HCG pregnancy test within 35 days before randomisation. The test has to be repeated within 72 hours before pembrolizumab treatment start and then every 2nd cycle of pembrolizumab treatment.

At treatment cycle 3

The following evaluations have to be done on day 1 of pembrolizumab treatment cycle 3 (or within 3 days before this date):

16.6.11. Pulmonary function:

relative FEV1 and FVC (strongly encouraged)

16.6.12. Biological material (see Section 15.2 and 15.3 for details):

Blood samples:

- 2.5 mL whole blood for RNA analysis

- 5 mL serum samples.

16.7. Evaluations at the end of treatment visit

At the end of the trial treatment and **irrespective of the reason for stopping treatment**, a post treatment visit at the centre is to be scheduled within 30 days following the decision to stop trial treatment. The following procedures should be performed:

16.7.1. Recording of symptoms, adverse events and concomitant medications.

16.7.2. Physical examination:

including ECOG performance status, blood pressure, heart rate, temperature, body weight.

16.7.3. Chemistry:

serum albumin, glucose, potassium, sodium, calcium, amylase, lipase and LDH.

16.7.4. Haematology:

haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

16.7.5. Liver function tests:

total bilirubin, ALT, AST, ALP, GGT.

16.7.6. Renal function tests:

urea, creatinine and uric acid, serum creatinine and creatinine clearance calculated according to Cockroft-Gault.

16.7.7. Pregnancy test (pembrolizumab treatment only).

16.7.8. Radiological tumour assessment

by CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included), if not done within the last 6 weeks.

16.8. Evaluations in the follow-up phase (post treatment) before progression

Patients who completed pembrolizumab treatment (after 2 years, this corresponds to an expected maximum of 36 doses) or discontinue trial treatment before progression should have the following examinations documented every 12 weeks (±2 week) starting from date of end of treatment visit/last dose of treatment received up to 2 years after the randomisation of the last patient.

16.8.1. Physical examination:

including ECOG performance status, blood pressure, heart rate, temperature, body weight.

16.9. Evaluations in the follow-up phase (post treatment) beyond progression

Patients with progression will end trial treatment (exceptions see Section 10.2.7) and will be followed up every 12 weeks (±2 week) starting from date of progression up to 2 years after the randomisation of the last patient.

They should have documented:

16.9.1. Survival

16.9.2. Further lines of treatment

17. Case report forms and documentation

17.1. Case report forms schedule

eCRFs will only be available on-line at the electronic data capture (EDC) facility ETOPdata. No paper forms will be used, with the exception of a paper SAE form and pregnancy form in case of system unavailability.

Table 9 Case report forms

CRF in ETOPdata	**To be completed**
1 - Eligibility Check and Randomisation	Within 35 days of start of baseline evaluations.
2 - Baseline	Within 14 days after randomisation.
3 - Tumour Assessments	Baseline before randomisation: within 14 days after randomisation; During trial: within 14 days of date of each imaging; After cross-over: within 14 days of date of each imaging; At end of treatment visit if not done within the last 6 weeks.
4 - Concomitant Medications	Continuously from date of randomisation to 30 days after end of trial treatment. To be updated: - within 14 days after randomisation; - within 14 days of start of each Experimental; Arm/Control Arm cycle; - within 14 days of End of Treatment visit; - within 14 days of Follow-up visits.
5 - Experimental Arm / Control Arm	Within 14 days of start of each treatment cycle.
6 - Adverse Events	Continuously from date of Informed Consent signature until 30 days after trial treatments discontinuation. To be updated: - within 14 days of randomisation (baseline symptoms); - within 14 days of start of each Experimental Arm/Control Arm cycle; - within 14 days after End of Treatment visit; - within 14 days of Follow-up visits.
7 - Serious Adverse Event Initial Reports	Within 24h of awareness of SAE. Must be submitted via ETOPDdata, submission via fax to ETOP safety office only in case of inavailability of ETOPdata.

CRF in ETOPdata	To be completed
8 - Serious Adverse Event Follow-up Reports	Within 15 days of completion of initial report. If event was not resolved after 15 days, submit an additional report within 7 days of resolution of event.
9 - End of Treatment	Within 14 days after End of Treatment visit (which is to take place within 30 days following the decision to stop initial trial treatment).
10 - Cross-Over to Pembrolizumab Treatment	Only for patients in Control Arm
11 - End of Treatment after Cross-Over	Only for patients in Control Arm after cross-over Within 14 days after End of Treatment visit (which is to take place within 30 days following the decision to stop trial treatment).
12 - Follow-up	Follow-up before/after progression: Within 14 days of clinical follow-up visits. Follow-up on death: Within 14 days upon awareness of death.
13 - Pregnancy	Within 24h of first documentation of pregnancy; Within 14 days of end of pregnancy.
14 - Biological Material Tracking	This eCRF is to be completed incrementally. Entries are to be made: - within 4 weeks of randomisation: for information pertaining to "Tumour material from primary diagnosis" (archival) and/or fresh biopsy taken close to the start of trial treatment (at randomization, after disease progression on first-line therapy); - immediately after local storage of blood samples (on same day): for information pertaining to "Date of blood draw"; - immediately (on same day) after submission of material (FFPE and blood) for central biobanking: for "Date Sent to Central Laboratory"; - within 4 weeks of progression: for information pertaining to "Tumour material from re-biopsy at progression" (after trial treatment, optional).
15 - WC/LFU	Within 14 days of awareness of withdrawal of consent or loss to follow-up.

18. Statistical considerations

18.1. Primary objective

This randomised phase III trial will evaluate the potential of pembrolizumab to provide PFS benefit (based on independent radiological review) over standard institutional-choice chemotherapy (gemcitabine or vinorelbine monotherapy) in patients with advanced pre-treated malignant mesothelioma. Patients randomised to chemotherapy will be allowed to cross over to receive pembrolizumab at progression.

18.2. Sample size determination

This is a 1:1 randomised phase III trial, designed to detect an increase in median PFS from 3.5 months in the control arm to 6 months in the experimental arm. This corresponds to a 6-month PFS of 30% vs 50% for the control and the experimental group respectively (HR=0.58). Using 80% power and a one-sided type I error of 2.5%, a total of 110 events need to be observed to achieve the trial goal. Assuming an accrual rate of 2 patients per month for the first 6 months and 10 patients per month thereafter, a total sample size of 142 patients accrued over a period of 19 months would be required to observe the above number of events with a maximum total trial follow-up of 24 months.

18.3. Trial duration

Assuming a cumulative drop-out rate of 5%, the total trial duration from randomisation of the first patient to the date of the primary analysis is estimated to be 36 months, allowing for a start-up period of 6 months.

All calculations are performed using the EAST package [30].

18.4. Analysis populations

18.4.1. Intention-to-treat (ITT) population

All randomised patients will be analysed in the arm they were allocated by randomisation.

18.4.2. Censored population

All randomised patients will be analysed in the arm they were allocated by randomisation but in addition, patients in the control arm that will selectively cross over to receive pembrolizumab after progression, will be censored at the time point of cross-over when evaluating OS.

18.4.3. Safety population

All patients who have started trial treatment (at least one dose of the trial drug/s).

A patient will be considered to be eligible if he/she did not have any major deviation from the patient entry criteria listed in section 7 of the protocol. Potential eligibility problems will be assessed by the ETOP medical reviewer.

18.5. Evaluation of primary and secondary objectives

18.5.1. Primary analysis

The analysis of the primary and secondary endpoints will be performed on all randomised patients according to the ITT principle.

Time to event endpoints (PFS, OS, TTF) will be estimated by the Kaplan Meier method and compared between the two treatment arms by a stratified logrank test. In addition, stratified (by the randomisation stratification factors) and multivariate Cox models will be used for exploring the association of the primary (investigator assessed PFS) and secondary endpoints (irPFS, OS and TTF) with treatment in the presence of prognostic factors.

Clinical efficacy will be further described by objective response rate (ORR; complete or partial response) for all eligible patients according to the treatment assigned at randomisation (ITT analysis population). ORR will be compared between the two treatment groups by the Fisher's exact test.

The safety and tolerability of pembrolizumab treatment will be assessed through analysis of toxicity, based on the safety population. The worst grade of toxicity/ adverse events observed over the whole treatment period according to CTCAE version 4.0 will be displayed. No formal statistical analysis will be performed to compare toxicity between the two arms.

18.5.2. Sensitivity analysis

For the secondary endpoints OS and TTF, censored analysis and the inverse probability weighting (IPW) approach will be applied as sensitivity analyses to the ITT approach. These methods aim to account for disruptions in randomisation due to selective cross-over at progression and will be performed on the censored population.

Statistical analysis for the primary and secondary endpoints will be described in detail in the statistical analysis plan (SAP) document.

18.6. Early safety evaluation

In order to exclude an exacerbation of adverse events by pembrolizumab treatment, a safety evaluation will take place when 33% of the patients will have reached 6 months from randomisation. This first safety evaluation will be submitted to the IDMC for advice. Recruitment into the trial will continue while safety is evaluated. Safety evaluations will be performed at least yearly and submitted to the IDMC at their regular bi-annual meetings.

19. Criteria for termination of the trial

19.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the IMP leads to doubt as to the benefit/risk ratio, by decision of ETOP upon recommendation of the ETOP 9-15 PROMISE-meso Steering Committee and IDMC. Specific considerations will be based on the interim safety and efficacy evaluations.

The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

19.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression according to RECIST 1.1 criteria.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation of protocol therapy. **Note**: Diagnosis of another neoplastic disease (second malignant tumour) does not mandate a stop of trial therapy, patients may continue to receive protocol treatment after appearance of a second primary tumour, stopping protocol treatment is determined by the medical judgment of the treating physician.
- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.

  Note: Patients randomised to the control arm who refuse further chemotherapy may only cross over to pembrolizumab treatment after progressive disease has been diagnosed.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

The decision for discontinuation of protocol treatment of individual patients is taken by the treating physician based on his medical evaluation and taking into account the patient's individual situation.

19.3. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue to be evaluated in the trial. The investigator should ask the patient for consent to continue to collect information on her/his disease and survival status.

It should be documented in both the medical records and in the eCRF, according to the instructions in the ***ETOP 9-15 PROMISE-meso CRF completion guidelines***, if the patient accepts to be contacted for survival status despite withdrawing the trial consent. For the patient's safety, an end of treatment visit should be performed and documented in the eCRF if the patient agrees to this.

20. Ethics aspects, regulatory approval, and patient informed consent

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in

which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in “Guideline for Good Clinical Practice (GCP)” ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

20.1. Ethical Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The Ethical Review Board/Institutional Review Board (ERB/IRB) written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP coordinating office prior to randomisation of the first patient.

Any modifications made to the protocol must be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to health authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the health authorities (if required), the investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

20.2. Regulatory approval procedures

If applicable, in addition to the approval of the ethics committee according to national legislation, the protocol, protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP coordinating office prior to participating centre activation.

20.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “patient information and informed consent" (see Appendix 1). One signed and dated, a copy of the informed consent must be given to each patient and the original copy must be retained in the investigator’s trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for randomisation into this trial.

The “Declaration of Helsinki” recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material

from her/his tumour and blood and serum samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e. a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with GCP and the "Declaration of Helsinki".

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (appendix 1), which can be edited to incorporate information specific to your institution. The template patient information sheet and informed consent has been written according to ICH guidelines which state the informed consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki". The final version should receive the IRB / local EC approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their ethics committee.

21. Governance and administrative issues

21.1. Final report

A final clinical trial report will be written and distributed to health authorities as required by applicable regulatory requirements

21.2. Steering Committee

A steering committee will be constituted for this trial. The steering committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial chairs and co-chairs, trial statisticians, ETOP officials, representatives from participating institutions and a representative from Merck Sharp & Dohme Corp.

21.3. Independent Data Monitoring Committee

The ETOP IDMC is a standing committee of independent experts. Its role is the systematic review of the accumulating data from all ongoing ETOP sponsored trials including accrual, safety and efficacy. The primary mandate of the IDMC is to safeguard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Details of the particular responsibilities and procedures within the ETOP 9-16 PROMISE-meso trial are summarised in the ETOP IDMC Guidelines and the trial-specific IDMC charter.

The trial will be presented for review to the ETOP IDMC at each of their bi-annual meetings. Based on this review, the IDMC recommends to the trial Steering Committee whether to continue, modify or stop the trial.

21.4. Publication

The results of the trial will be published according to the ETOP publication guidelines (appendix 3).

21.5. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP coordinating office.

21.6. Quality assurance

ETOP conducts trials according to the ICH GCP guidelines. The Trial data manager reviews each eCRF as it is received. In addition, the ETOP medical reviewer reviews each case at specific time points. ETOP conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The investigator should ensure that source documents are made available to appropriately qualified personnel from ETOP or its designees, or to ethics committee and health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the centre will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review trial progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing IMP, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood and serum samples.

21.7. Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact ETOP or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any deviations to the sponsor and to the EC concerned in accordance with the applicable EC policies and procedures. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by the sponsor and approved by the IRB/IEC/ERB it cannot be implemented. All protocol deviations will be recorded.

21.8. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the EDC facility ETOPdata. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central labs.

Biological material will be transferred outside the treating institution for central screening and review. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and pertinent ethics committees (IRB/ERB) may have access to patient data on-site. ETOP audit or monitoring personnel will also have access to such data on-site.

21.9. Record retention

The centre must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. ETOP guarantees access and availability of the data entered into ETOPdata for at least 15 years after the termination of the trial.

Longer retention may be required for participating centres according to national regulations.

In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to ETOP and the local ethics committee at least 1 month in advance.

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