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Official Title: " A PHASE II SINGLE ARM CLINICAL TRIAL ASSESSING THE EFFICACY AND SAFETY OF BINTRAFUSP ALFA (M7824) IN PREVIOUSLY TREATED ADVANCED MALIGNANT PLEURAL MESOTHELIOMA" BIMES

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BIMES: BIntrafusp alfa (M7824) for the treatment of MESothelioma

Study Sponsor: Fundación GECP

EudraCT Number: 2020-004902-67
Sponsor code: [redacted]

Version 2.2

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Protocol Signature Page

A PHASE II SINGLE ARM CLINICAL TRIAL ASSESSING THE EFFICACY AND SAFETY OF BINTRAFUSP ALFA (M7824) IN PREVIOUSLY TREATED ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

BIMES: BIntrafusp alfa (M7824) for the treatment of MESothelioma

Sponsor code: [redacted]

Approved by:

Signature

_____

Dr. [redacted]
Trial Chair

Signature

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[redacted]

Principal Investigator Protocol Signature Page

Study Title: "A phase II single arm clinical trial assessing the efficacy and safety of BIntrafusp alfa (M7824) in previously treated advanced malignant pleural MESothelioma (BIMES)"

Sponsor protocol code: [redacted]
EudraCT Number: 2020-004902-67
Protocol version: v 2.2, 30th November 2021

As principal investigator of this site, I hereby confirm that:

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 Good Clinical Practice guidelines 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 the Fundación GECP, 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 25 years according to the Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator: _____

Institution's name and place: _____

Signature Date

TABLE OF CONTENTS

Section **Page**

1. Protocol summary 7
2. Trial schedule 15
3. Background and rationale 18
   3.1. Disease background 18
   3.2. Role of TGF-β in the tumor microenvironment 19
   3.3. Blocking TGF-β signaling pathway: Bintrafusp alfa (M7824) 19
   3.4. Rationale for trial design 22
4. Objectives and endpoints 24
   4.1. Primary objective and endpoint 24
   4.2. Secondary objectives and endpoints 24
   4.3. Exploratory objectives 24
5. Trial design, duration and termination 25
6. Patient selection 26
   6.1. Inclusion criteria 26
   6.2. Exclusion criteria 27
7. Patient enrollment 29
8. Trial procedures 29
   8.1. Overview of treatment sequence 29
9. Investigational Medicinal Product 34
   9.1. Packaging and labelling 35
   9.2. Receipt and storage of the IMP 35
   9.3. Unused trial drug supplies 35
10. Trial treatments description 35
   10.1. BINTRAFUSP alfa (M7824) 35
11. Dose modifications criteria 36
   11.1. General Notes Regarding Dose Modification 36
   11.2. BINTRAFUSP (M7824). Toxicity Management 36
12. Prohibited and permitted concomitant treatments 43
13. Adverse events and reporting 45
   13.1. Definition of an Adverse Event (AE) and AE's reporting 45
   13.2. Definition of Serious Adverse Event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) 48
   13.3. Adverse events of Special Interest for M7824 (Immediately reportable to the Sponsor) 50
   13.4. Overdose and secondary malignancies 50
   13.5. SAEs and SUSARs reporting 51
   13.6. Pregnancy 52
   13.7. Other safety considerations 52
14. Biological material and translational research 52
15. Case report forms and documentation 54
16. Statistical considerations 54
17. Criteria for termination of the trial 55
   17.1. General criteria for termination of the trial 55

17.2. Discontinuation of protocol treatment and from the study for individual patients 55
18. Ethics aspects, regulatory approval, and Patient Informed Consent 56
18.1. Ethical Review Board/Ethics Committee/Health Authority 56
18.2. Informed consent 57
19. Governance and administrative issues 57
19.1. Study documentation 57
19.2. Protocol non-compliances/deviations 58
19.3. Protocol amendment 58
19.4. Final report 58
19.5. Independent Data Monitoring Committee (IDMC) 58
19.6. Publication 58
19.7. Financial disclosure 58
19.8. Clinical trial insurance 59
19.9. Quality assurance 59
19.10. Data protection 59
19.11. Study monitoring team 60
19.12. Record retention 60
20. References 61
1. Supplementary Data: Proposed Radiology Guidelines for Inclusion in Clinical Trial Protocols 65
1.1. *Definition of measurability* 65
1.2. *Measurement sites at baseline* 65
2. Measurement of disease at subsequent time points: 72
3. Definitions of objective response: 72

Appendices:

1. Common Terminology criteria for Adverse Events (CTCAE)
2. Modified RECIST (mRECIST) criteria version 1.1 for malignant pleural mesothelioma
3. SAE Form
4. Pregnancy Form
5. Mesothelioma TNM definitions according to the 8th edition

1. Protocol summary

A PHASE II SINGLE ARM CLINICAL TRIAL ASSESSING THE EFFICACY AND SAFETY OF BINTRAFUSP ALFA (M7824) IN PREVIOUSLY TREATED ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

BIMES: BIntrafusp alfa (M7824) for the treatment of MESothelioma

Sponsor: Fundación GECP

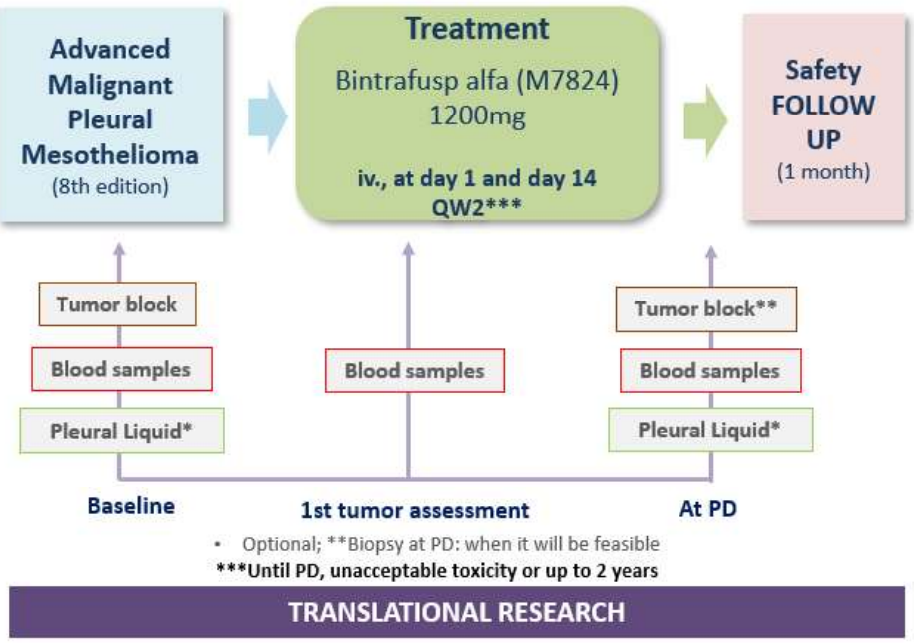
Trial Chair: [redacted]

Protocol code: [redacted]

Population: advanced malignant pleural mesothelioma patients previously treated with platinum-based chemotherapy

Design: Open-label, non-randomized, phase II, single arm, multi-center controlled clinical trial

Study schema:



Sample size: 47 patients

Rationale:

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy arising from the mesothelial surface of the pleura. In Europe, the incidence is about 20 per million and is almost always caused by asbestos exposure, with a usual lag time of 30 years between exposure and presentation.[1] Histologic subtypes of MPM include epithelioid (about 60%), and non-epithelioid (around 40%) including sarcomatoid, biphasic and others. Disease is considered resectable in only 10-15% of MPM patients.[2] The prognosis in unresectable cases remains very poor, with median overall survival (OS) of 9 to 12 months.[1,3] The disease is invariably fatal, due to anatomical limitations preventing the achievement of a complete microscopic surgical resection and tumor relative chemo-refractoriness.[4]

Cytotoxic chemotherapy remains one of the few therapeutic options that has been proven to improve survival in advanced MPM in a randomized controlled trial.[5] The combination of cisplatin and pemetrexed has become standard first-line therapy worldwide for patients who are not suitable for aggressive surgery or in whom chemotherapy is recommended as part of a multimodality regimen.[4] Cisplatin/pemetrexed is associated with a response rate of 30-40% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma.[3] Carboplatin is often substituted for cisplatin, due to simpler and shorter administration and assumption of a more favorable toxicity profile based on experience in other diseases. Although carboplatin use is not supported by randomized evidence, and there has been no direct comparison between the two platinum agents, phase I and II studies have demonstrated similar activity of either carboplatin or cisplatin with pemetrexed, with objective radiological response rates between 20% and 30%.[6,7] Maintenance with pemetrexed is not considered standard of care. The addition of bevacizumab to chemotherapy modestly improved overall survival, but this treatment is not available in all countries.[8]

Dual immune checkpoint inhibition of PD1 and CTLA-4 with nivolumab plus ipilimumab has recently demonstrated superiority to platinum plus pemetrexed in the first line setting in the CheckMate-743 study.[9] Dual immune ckeckpoint blockade showed larger OS benefit in patients with non-epithelioid tumors and those with positive PD-L1 expression.

However, no treatment has yet been shown to improve OS in patients who progressed to prior platinum-based chemotherapy, resulting in a high unmet need for effective therapies in previously treated patients with MPM. Single agent immunotherapy has demonstrated limited efficacy in the relapsed setting in the PROMISE-meso trial, which compared pembrolizumab with gemcitabine or vinorelbine. [10]

As a therapeutic strategy, neutralization of TGFβ activity has the potential to control tumor growth by restoring effective antitumor immunity, blocking metastasis, and inhibiting angiogenesis. Inhibition of TGFβ by soluble TGFβRII reduced malignant mesothelioma in a manner that was associated with increases in CD8+ T cell antitumor effects. [17] The absence of TGFβ1 produced by

activated CD4+ T cells and regulatory T (Treg) cells has been shown to inhibit tumor growth and protect mice from spontaneous cancer. [18] Thus, TGFβ appears to be important for tumor immune evasion. Furthermore, because the upregulation of TGFβ signaling-associated genes has been linked to anti-PD-1 resistance in metastatic melanoma,[19] blockade of TGFβ signaling may target mechanisms of resistance and sensitize tumor to anti-PD-1/PD-L1 therapies.

Bintrafusp alfa is being developed as an immuno-oncology agent for treatment in a number of tumor types, including nonsmall cell lung cancer (NSCLC), biliary tract cancer (BTC), cervical cancer, and triple-negative breast cancer (TNBC). Bintrafusp alfa was shown to have full biological activity in vitro including the ability to block PD-L1 and neutralize TGFβ simultaneously. Durable clinical activity of bintrafusp alfa was observed in a number of tumor types in the 2 Phase I studies (EMR200647-001 and MS200647-0008).

Prior clinical trials with immune checkpoint inhibitors with anti-PD1 and anti-PD-L1 in previously treated MPM showed modest efficacy probably due to the predominantly immune suppressive tumor microenvironment, the generally low tumor mutational burden as well as the high aneuploidy which is characteristic of this tumor. In the PROMISE-Meso study, pembrolizumab was not superior to single chemotherapy in the second line setting in a non-selected population of MPM[29].

We hypothesize that dual targeting of PD-L1 and TGF-β by bintrafusp alfa (M7824) may reduce tumor aggressiveness in MPM, can reverse the suppressive tumor microenvironment and extend progression-free survival (PFS). We propose a single-arm phase II clinical trial to assess the efficacy and the safety of M7824 in a cohort of patients with previously treated advanced MPM. We also hypothesize that selection of patients based on the TGF-β pathway activation in tissue or in the blood and stratification of patients based on immune groups will be helpful to identify MPM patients who are more likely to benefit from immunotherapy.

Objectives and endpoints:

Primary objective:

- To determine the efficacy of M7824 in terms of the Progression Free Survival (PFS) assessed by the investigator according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) Version 1.1.
  PFS is defined as the time from administration of first dose of bintrafusp alfa until objective tumor progression or death.

Secondary objectives:

- To determine the ORR of the treatment as measured by investigator-assessed overall response rate (ORR) with M7824 according to modified RECIST v1.1.
- To determine the PFS assessed by an independent review committee by revised modified RECIST criteria v1.1.

- To evaluate secondary measures of clinical efficacy including duration of response, disease control rate and the Overall survival (OS).
- To evaluate the safety and tolerability of the treatment assessed by adverse events graded according CTCAE v5.0

Exploratory Objectives:

- To correlate efficacy endpoints (PFS and ORR) with PD-L1 expression. This will be measured by PD-L1 immunohistochemistry in the central laboratory.
- To correlate efficacy endpoints (PFS and ORR) with activation of TGF-β pathway in tumor biopsies obtained at baseline and at tumor progression. This will be measured by SMAD2/3 and phosphor-SMAD2/3 immunohistochemistry in tumor biopsies obtained at baseline and at tumor progression.
- To correlate efficacy endpoints (PFS and ORR) with TGF-β levels along with additional cytokines measured in serum obtained prior to initiation of immunotherapy and cytokines at tumor progression.
- To correlate efficacy endpoints (PFS and ORR) with TGF-β levels along with additional cytokines measured in pleural effusion obtained prior to initiation of immunotherapy and at tumor progression. To determine the immune cell subpopulations harvested in the pleural effusion at baseline and at tumor progression using flux cytometry in a subset of patients included in the study.
- To determine the predictive value of the immune groups based on the expression of cytotoxic T cells and Th2 cells signature measured in the tumor sample at baseline by using gene expression panels from NanoString technologies.

Eligibility criteria:

Inclusion criteria:

1. Male or female subjects aged $\geqslant$ 18 years and capable of giving signed informed consent or requirement per local legislation.
2. ECOG performance status of 0-1.
3. Histologically confirmed malignant pleural mesothelioma (all histological subtypes are eligible), unresectable advanced or metastatic.
4. Patients that progressed or be intolerant to ≤ 2 regimens of chemotherapy, including platinum-based chemotherapy with pemetrexed. Prior bevacizumab treatment given during chemotherapy are allowed.
5. Evaluable disease or measurable disease as assessed according to the modified RECIST v1.1 criteria.
6. Availability of tumor tissue for translational research (at least 10 slides); Archival tumor tissue at diagnosis can be sent if it was obtained less than 18 months ago.
7. Life expectancy of at least 3 months.

8. Adequate hematologic and organ function defined by the following laboratory results obtained within 14 days prior to enrollment:

   Hematologic: Absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, and hemoglobin $\geqslant$ 9 g/dL

   Hepatic: Total bilirubin level $\leqslant$ the upper limit of normal (UNL) range, AST and ALT levels $\leqslant$ 1.5 x ULN and ALP $\leqslant$ 2.5 x ULN. For participants with liver involvement in their tumor, AST $\leqslant$5 x ULN, ALT $\leqslant$ 5 x ULN, and bilirubin $\leqslant$ 3.0 x ULN.

   Renal: Creatinine level $\leqslant$1.5 x ULN or estimated creatinine clearance $\geqslant$ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method) (may be modified to a higher creatinine clearance threshold, e.g. $\geqslant$ 50 ml/min or $\geqslant$ 60 ml/min as appropriate based on the target population or other drugs used in a combination regimen). For participants with Creatinine > 1.5 x ULN, glomerular filtration rate (GFR) can also be used.

   Coagulation: normal international normalized ratio (INR), PT $\leqslant$ 1.5 x ULN and activated partial thromboplastin time (aPTT) $\leqslant$ 1.5 x ULN.

9. For patients with HIV infection, it needs to be a stable HIV infection on ART for at least 4 weeks, no documented evidence of multi-drug resistance, viral load of < 400 copies/ml and CD4+ T-cells $\geqslant$ 350 cells/µL.
10. For patients with HBV/HCV infection, it needs to be a controlled HBV/HCV infection on a stable dose of antiviral therapy, HBV viral load below the limit of quantification. HCV viral load below the limit of quantification.

11. All patients are notified of the investigational nature of this study and signed a written informed consent in accordance with institutional and national guidelines, including the Declaration of Helsinki prior to any trial-related intervention.
12. For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly throughout the study and for at least 2 months after last bintrafusp alfa treatment administration.
13. For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly.
14. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drugs. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom. For male patients the duration of contraception after the last dose of bintrafusp alfa is 4 months.
15. Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 8 days prior to initiation of study drug.

Exclusion criteria:

1. Prior immune checkpoint therapy with an anti-PD-1, anti-PD-L1, anti-CD137, or anti-CTLA-4 antibody.
2. Known severe hypersensitivity [Grade $\geqslant$ 3 NCI CTCAE 5.0]) to investigational product or any component in its formulations, any history of anaphylaxis, or recent, within 5 months, history of uncontrollable asthma.
3. Previous malignant disease (other than the target malignancy to be investigated in this study) within the last 3 years. Participants with a history of cervical carcinoma in situ, superficial or noninvasive bladder cancer, localized prostate cancer or basal cell or squamous cell carcinoma in situ previously treated with curative intent and endoscopically resected GI cancers limited to the mucosal layer without recurrence in > 1 year are NOT excluded.
4. Active central nervous system (CNS) metastases and/or carcinomatous meningitis that require therapeutic intervention or are causing clinical symptoms. Patients with previously treated brain metastases may participate provided they are stable and are not using steroids for at least 7 days prior to randomization.
5. Prior major surgery within 4 weeks prior to the first dose of study intervention.
6. Unstable or unresolved surgical or chemotherapy-related toxicity that would compromise the patient's capacity to participate in the trial. Persisting Grade > 1 NCI CTCAE 5.0 toxicity (except alopecia and vitiligo) related to prior therapy; however, sensory neuropathy Grade $\leqslant$ 2 is acceptable.
7. Prior organ transplantation including allogenic stem-cell transplantation, except transplants that do not require immunosuppression.
8. Live vaccines given 30 days prior to first dose of protocol treatment (M7824). Seasonal flu vaccines that do not contain a live virus are permitted. Also, COVID-19 vaccines approved by the authorities that do not contain live virus are permitted.
9. Drug-induced interstitial lung disease (ILD) or participant has had a history of drug-induced pneumonitis that has required oral or IV steroids, and/or other diseases, which in the opinion of the Investigator might impair the participant's tolerance for the study or ability to consistently participate in study procedures.
10. Active and serious autoimmune disease that might deteriorate upon treatment with immunotherapy. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. 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.
11. Ongoing clinically serious infections requiring systemic antibiotic or antiviral, antimicrobial, or antifungal therapy.
12. Known history of active tuberculosis or any active infection requiring systemic therapy.
13. Patients with diagnosed immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment, EXCEPT for the

following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ⩽ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

14. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (⩾ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
15. History of bleeding diathesis or recent major bleeding events within 12 months prior to enrollment (i.e. Grade ⩾ 2 bleeding events in the month prior treatment)
16. History of abdominal or tracheoesophageal fistula, active gastrointestinal ulcer or gastrointestinal perforation within 12 months prior to enrollment
17. Patients with any serious underlying medical condition that might impair patient's capacity to participate in the trial.
18. Substance or alcohol abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial results.
19. Women who are pregnant or in the period of lactation.

Treatment:

Bintrafusp alfa (M7824): 1200mg, over 60 minutes IV infusion

The treatment will start within 1-5 days from enrollment. The treatment will be administered at day 1 and day 14 (2 weeks ±3days) of 28 days cycle.

Treatment will be administered until unacceptable toxicity, loss of clinical benefit, disease progression or completion of 2 years of therapy. If the patient has benefit after 2 years, the trial chair and the sponsor must be consulted to evaluate how to continue with the treatment.

If pseudoprogression is suspected, patients can continue with the study therapy until loss of clinical benefit as judged by the principal investigator. Prior to continuing with the study therapy, the trial chair of the study must be informed.

Statistical considerations:

This study is designed to show that experimental treatment will achieve a median PFS of 4.5 months (expected median for standard scheme is 3 months which is equivalent to consider an improvement of 0.66 in terms of hazard ratio), with a statistical power of 90% and a one-sided type I error of 10%. On these bases and considering Lachin design, 45 pts are needed (44 or more events for null hypothesis and 43 or less events for alternative hypothesis) over a period of 18 months with a minimum median follow-up of 12 months to perform an exponential test. Considering a 5 % of drop-out patients and a hazard of 0.04 for dropouts a total sample size of 47 patients will be needed. In

case of having 43 or less events during follow-up alternative hypothesis will be concluded and experimental treatment will be declared as promising.

The expected accrual rate is 2 patients per month for the first 6 months, increasing to 4-5 patients per month thereafter. Primary analysis is expected to be available 18 months after the inclusion of the first patient. In order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, they will be replaced by a new one subject that fulfil them, this replacement will ensure that the sample size will be the one calculated initially.

Total trial duration: 3.5 years (1.5 years of recruitment, approximately 2 years of treatment and 1 month for the safety follow up)

Translational research:

Blood samples, tumor biopsy and malignant pleural effusion will be collected prior to initiating M7824 and when possible at tumor progression for the correlative studies.

The main objective is to assess whether the activation of the TGF-β pathway in the tumor or the levels of TGF-β in the baseline blood and in the pleural effusion are correlated with the efficacy of M7824 and also to explore the predictive value of the immune group classification identified by our group to identify patients who benefit from immunotherapy.

Endpoints for the translational research:

-To correlate PFS and ORR with activation of TGF-β pathway measured by SMAD2/3 and phosphor-SMAD2/3 immunohistochemistry in tumor biopsies obtained at baseline and at tumor progression.
-To correlate efficacy PFS and ORR with TGF-β levels and cytokines measured by ELISA in serum obtained prior to initiation of immunotherapy and cytokines at tumor progression.
- To correlate efficacy PFS and ORR with TGF-β levels along with additional cytokines in pleural effusion , if the patient has pleural effusion. A pleural tap will be performed to measure TGF-β levels and cytokines measured by ELISA at baseline and at tumor progression.
-To determine the immune cell subpopulations by flux cytometry in the pleural effusion at baseline and at tumor progression. These results will be correlated with TGF-β levels measured in pleural effusion by ELISA and with clinical benefit from M7824.
-To stratify patients according to the immune groups by gene-expression profiling using nanostring to cover cytotoxic T cells and Th2 cells signatures and a panel of immune checkpoints (PD1, PD-L1, PD-L2, TIM3, B7-H3) and correlate whether immune groups have distinct clinical outcome when treated with M7824.

- To correlate efficacy endpoints (PFS and ORR) with PD-L1 expression. This will be measured by PD-L1 immunohistochemistry in the central laboratory.

2. Trial schedule

	Baseline (-28 days before enrollment)	Treatment Bintrafusp alfa (M7824) Cycles[16]	Progression Disease (PD)	End of Treatment[17]	Follow up[18]
					up

[1]

).

[redacted]

The other follow ups CT-SCANs after progression will be done as per local standard.

[13] Tumor sample (or at least 10 slides) is mandatory at baseline (it might be the archival tissue biopsy obtained when diagnosed with mesothelioma) and a rebiopsy at progression disease is strongly recommended.

[14]Blood samples for correlative studies will be drawn at:

- Baseline or before day 1-week 1 of treatment
- First tumor assessment
- At disease progression

[15] Pleural Liquid at baseline and at progression disease are strongly recommended.

[16] Cycles will be administered every 2 weeks (±3 days). Day 1 of week 1 treatment will start within 1-5 days from enrollment. If pseudoprogression is shown it is allowed to continue with study treatment until progression disease will be confirmed. A confirmation from the trial chair/sponsor has to be granted to continue treatment.

Blood pressure must be taken always before the drug administration. Blood pressure should be routinely measured before every infusion after a resting period of 10 min. If baseline record is performed more than 3 days before first study dose, they must be repeated on day 1 week 1.

[17] *End of treatment* is defined as the day of discontinuation of the treatment.

[18] A safety follow up visit must be done within 30 days (±3 days) after the last dose the treatment or immediately before the initiation of any other anticancer therapy. See section 8.1.5 for more details about safety follow up visit procedures.

3. Background and rationale

3.1. Disease background

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy arising from the mesothelial surface of the pleura. In Europe, the incidence is about 20 per million and is almost always caused by asbestos exposure, with a usual lag time of 30 years between exposure and presentation.[1] Histologic subtypes of MPM include epithelioid (about 60%), and non-epithelioid (around 40%) including sarcomatoid, biphasic and others. Disease is considered resectable in only 10-15% of MPM patients.[2] The prognosis in unresectable cases remains very poor, with median overall survival (OS) of 9 to 12 months.[1,3] The disease is invariably fatal, due to anatomical limitations preventing the achievement of a complete microscopic surgical resection and tumor relative chemo-refractoriness.[4]

Cytotoxic chemotherapy remains one of the few therapeutic options that has been proven to improve survival in advanced MPM in a randomized controlled trial.[5] The combination of cisplatin and pemetrexed has become standard first-line therapy worldwide for patients who are not suitable for aggressive surgery or in whom chemotherapy is recommended as part of a multimodality regimen.[4] Cisplatin/pemetrexed is associated with a response rate of 30-40% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma.[3] Carboplatin is often substituted for cisplatin, due to simpler and shorter administration and assumption of a more favorable toxicity profile based on experience in other diseases. Although carboplatin use is not supported by randomized evidence, and there has been no direct comparison between the two platinum agents, phase I and II studies have demonstrated similar activity of either carboplatin or cisplatin with pemetrexed, with objective radiological response rates between 20% and 30%.[6,7] Maintenance with pemetrexed is not considered standard of care. The addition of bevacizumab to chemotherapy modestly improved overall survival, but this treatment is not available in all countries.[8]

Dual immune checkpoint inhibition of PD1 and CTLA-4 with nivolumab plus ipilimumab has recently demonstrated superiority to platinum plus pemetrexed in the first line setting in the CheckMate-743 study.[9] Dual immune ckeckpoint blockade showed larger OS benefit in patients with non-epithelioid tumors and those with positive PD-L1 expression.

However, no treatment has yet been shown to improve OS in patients who progressed to prior platinum-based chemotherapy, resulting in a high unmet need for effective therapies in previously treated patients with MPM. Single agent immunotherapy has demonstrated limited efficacy in the relapsed setting in the PROMISE-meso trial, which compared pembrolizumab with gemcitabine or vinorelbine. [10]

3.2. Role of TGF-β in the tumor microenvironment

The TGF-β cytokine is overexpressed in various cancer types with correlation to tumor stage.[11,12] Many types of cells in the tumor microenvironment produce TGF-β, including the tumor cells themselves, immature myeloid cells, Treg cells, and stromal fibroblasts; these cells collectively generate a large reservoir of TGF-β in the extracellular matrix including apoptotic neutrophils, myeloid-derived suppressor cells (MDSCs), T cells, and tumor cells. [13,14]

The tumorigenic effect of TGF-β relies on its effect on the tumor cell and the tumor microenvironment. It has been shown that TGF-β supports the self-renewal and prevents differentiation of CD44 high/Id1 high cancer-initiating cells that promote tumor initiation, relapse, and resistance to standard treatments. Moreover, TGF-β can induce cancer-associated fibroblasts and cooperate with vascular endothelial growth factor, hypoxia-inducible factor, platelet-derived growth factor, and other growth factors to modulate angiogenesis. [15] TGF-β signaling contributes to tumor progression by promoting metastasis, stimulating angiogenesis, and suppressing innate and adaptive antitumor immunity.[11]

Indeed, TGF-β is one of the most potent immune suppressive cytokines and negatively regulates both innate and adaptive immune responses. As a broadly immunosuppressive factor, TGF-β directly downregulates the effector function of activated cytotoxic T cells and NK cells and potently induces the differentiation of naïve CD4+ T cells to the immunosuppressive Treg phenotype. [12] In addition, TGF-β polarizes macrophages and neutrophils to a wound-healing phenotype that is associated with production of immunosuppressive cytokines. [16]

As a therapeutic strategy, neutralization of TGF-β activity has the potential to control tumor growth by restoring effective antitumor immunity, blocking metastasis, and inhibiting angiogenesis. Inhibition of TGF-β by soluble TGF-βRII reduced malignant mesothelioma in a manner that was associated with increases in CD8+ T cell antitumor effects. [17] The absence of TGF-β1 produced by activated CD4+ T cells and regulatory T (Treg) cells has been shown to inhibit tumor growth and protect mice from spontaneous cancer. [18] Thus, TGF-β appears to be important for tumor immune evasion. Furthermore, because the upregulation of TGF-β signaling-associated genes has been linked to anti-PD-1 resistance in metastatic melanoma,[19] blockade of TGF-β signaling may target mechanisms of resistance and sensitize tumor to anti-PD-1/PD-L1 therapies.

3.3. Blocking TGF-β signaling pathway: Bintrafusp alfa (M7824)

Bintrafusp alfa (M7824, MSB0011359C) is a first-in-class, bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-βRII or TGF-β Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin G1 (IgG1) antibody blocking programmed death ligand 1 (anti-PD-L1).

Bintrafusp alfa is designed to simultaneously target 2 pathways that have independent and complementary immunosuppressive functions in the tumor microenvironment. PD-L1 signaling plays a key role in the immunosuppressive network that dampens T cell activity and TGF-β functions as an autocrine or paracrine signal within the local tumor microenvironment, where it promotes tumor progression. Preclinical studies showed that dual blockade of TGF-β and PD-L1 triggers a strong immune response through the combined inhibition of TGF-β-mediated epithelial-to-mesenchymal transition, stimulation of the cytotoxic activity of natural killer cells and CD8+ lymphocytes, and the suppression of Tregs.

Bintrafusp alfa was shown to have full biological activity in vitro including the ability to block PD-L1 and neutralize TGF-β simultaneously. In experiments investigating the combination of bintrafusp alfa with standard of care therapies in mouse tumor models, bintrafusp alfa separately enhanced the antitumor effects of standard of care therapies including targeted therapies (in combination with receptor tyrosine kinase inhibitor pazopanib or anti-VEGF antibody), immune-oncology therapies (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]), of radiation therapy, and in combination with chemotherapy such as 5-fluorouracil and oxaliplatin (FOLFOX), gemcitabine, cisplatin, and doxorubicin. Bintrafusp alfa also potentiated the abscopal effect of radiation therapy. These findings suggest that bintrafusp alfa can be combined with standard of care therapies to improve antitumor responses. For all repeat-dose toxicity studies, a no observed adverse effect level (NOAEL) of 140 mg/kg (maximum feasible dose) was established. The only notable clinical effect observed in all studies was a decrease in red blood cell (RBC) counts and related parameters (hemoglobin [Hgb] and hematocrit) from all treated groups; evaluation of peripheral blood smears did not demonstrate evidence of an immune-mediated hemolytic process.

Bintrafusp alfa is being developed as an immuno-oncology agent for treatment in a number of tumor types, including non-small cell lung cancer (NSCLC), biliary tract cancer (BTC), cervical cancer, and triple-negative breast cancer (TNBC).

A total of 689 participants participated in two phase I clinical trials (EMR200647-001 and MS200647-0008, as of 24 August 2018). Maximum tolerated dose (MTD) was not reached in either of the two studies at doses tested up to 30 mg/kg every 2 weeks (q2w). Each study had 1 dose-limiting toxicity (DLT) in 1 participant at the 20 mg/kg dose level. With no DLTs at other dose levels up to 30 mg/kg, bintrafusp alfa at 30 mg/kg is considered tolerable. The emerging safety profile of bintrafusp alfa (from EMR200647-001, MS200647-0008, MS200647-0005, MS200647-0024, MS200647-0037, MS200647-0047, and MS200647-0055) across tumor types investigated is manageable and consistent with other therapies targeting either PD-L1 or TGF-β pathways.

Treatment-emergent AEs of special interest (AESI) for bintrafusp alfa are infusion-related reactions (IRRs), immune-related adverse events (irAEs), skin lesions possibly due to TGF-β inhibition and treatment-related anemia. Since 23 July 2017, IRRs (including hypersensitivity), irAEs / autoimmune disorders, and skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGF-β inhibition are considered to be important identified risks with bintrafusp alfa. Anemia, alterations in wound healing or

repair of tissue damage and embryofetal toxicity remained important potential risks. In addition, mucosal bleeding events are a potential risk for bintrafusp alfa.

Durable clinical activity of bintrafusp alfa was observed in a number of tumor types in the 2 Phase I studies (EMR200647-001 and MS200647-0008), specifically:

- In the 2L NSCLC cohort, durable clinical activity of bintrafusp alfa (1200 mg q2w) was observed in 40 participants regardless of PD-L1 expression status (overall response rate [ORR] by the Independent Endpoint Review Committee [IRC] according to RECIST v1.1; 25.0%), with a higher ORR of 37.0% in the PD-L1 positive group, and 85.7% in the PD-L1 high subgroup. After close to 2 years of follow-up, bintrafusp alfa continues to show manageable safety with encouraging long-term survival (17.1 months), especially in participants with positive to high PD-L1 expression (21.7 months for PD-L1 positive, not estimable for the PD-L1 high subgroup) with 24-month overall survival (OS) rate at 39.7% (data cutoff 15 October 2019).

- In the biliary tract cancer 2L cohort (N = 30), durable responses were observed; the ORR as adjudicated by the IRC according to RECIST 1.1 was 20%. The median duration of response was 9.7 months as assessed by the Investigator. Clinical activity was observed regardless of PD-L1 expression level and was also independent of microsatellite instability-high (MSI-H) status; after close to 2 years of follow-up, bintrafusp alfa continues to show manageable safety with encouraging long-term survival (12.7 months), with 24-month OS rate of 27.7% (data cutoff 24 October 2019).

- In participants with heavily pretreated cervical cancer (N = 25), durable responses were observed. The confirmed ORR as assessed by Investigator according to RECIST 1.1 was 24.0%, with duration of response ranging from 4.2 to 30.4 months. The median OS was 11.6 months, and the 18-month OS rate was 40%.

- In a pooled analysis of participants with heavily pretreated human papillomavirus (HPV)-associated cancers including anal, cervical and squamous cell carcinoma of the head and neck (SCCHN; N = 43), the confirmed ORR as assessed by Investigator according to RECIST 1.1 was 27.9%. Duration of response ranged from 2 to 25 months, with ongoing responses at data cutoff (09 January 2019). The median OS was 16.2 months and 12- and 24-month OS rates were 56.2% and 46.9%, respectively.

- In the TNBC second-line or greater cohort (N = 30), the ORR as assessed by Investigator according to RECIST 1.1 was 12.1%, the median duration of response was 5.4 months (ranging from 4.7 to 5.5 months) for participants with confirmed responses. Median OS was 7.8 months with 12-month OS rate of 33.3%. During integrated biomarker analyses of the TNBC cohort, high expression of high-mobility group AT-hook 2 (HMGA2) was identified as a potential predictive biomarker of clinical response for patients treated with bintrafusp alfa. In tumor samples from participants who experienced disease control, HMGA2 expression was 32-fold higher than in samples from participants who had progressive disease; the ORR for HMGA2-high tumors was 50.0%.

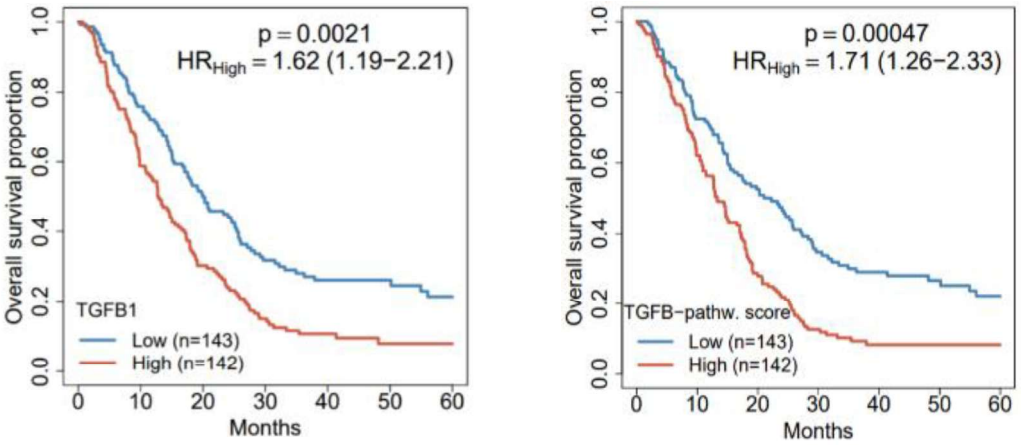
3.4. Rationale for trial design

During the last decade, limited advances have been done since the pemetrexed approval in combination with cisplatin back in 2004[20]. Not surprisingly, life expectancy of MPM remains suboptimal with a median overall survival (OS) of 10-13 months and with 5-year OS of approximately of 5%.[21]

Immune checkpoint inhibitors in MPM demonstrated modest efficacy, partly due to the lack of predictive biomarkers of clinical benefit from immunotherapy and to the immunosuppressive tumor microenvironment and low mutational burden. In MPM, TGF-β signaling pathway is frequently deregulated leading to an epithelial-to-mesenchymal transition (EMT) phenotype that confers more aggressive biological behavior and shorter OS[22-23]. TGF-β promotes cell proliferation and anchorage-independent cell growth of human non transformed mesothelial cells (MeT-5A), while TGFR1 inhibitors can block this effect[24]. Accordingly, asbestos promotes TGF-β secretion and EMT in human mesothelial cells (MeT-5A)[25].

By using publicly available gene-expression data from two large studies in MPM[22,26], we observed that TGF-β overexpression and TGF-β signaling pathway activation were independently associated with worse prognosis (**Figure 1**). These results suggest that deregulation of TGF-β signaling pathway plays a relevant role in mesothelioma and confers an aggressive phenotype.

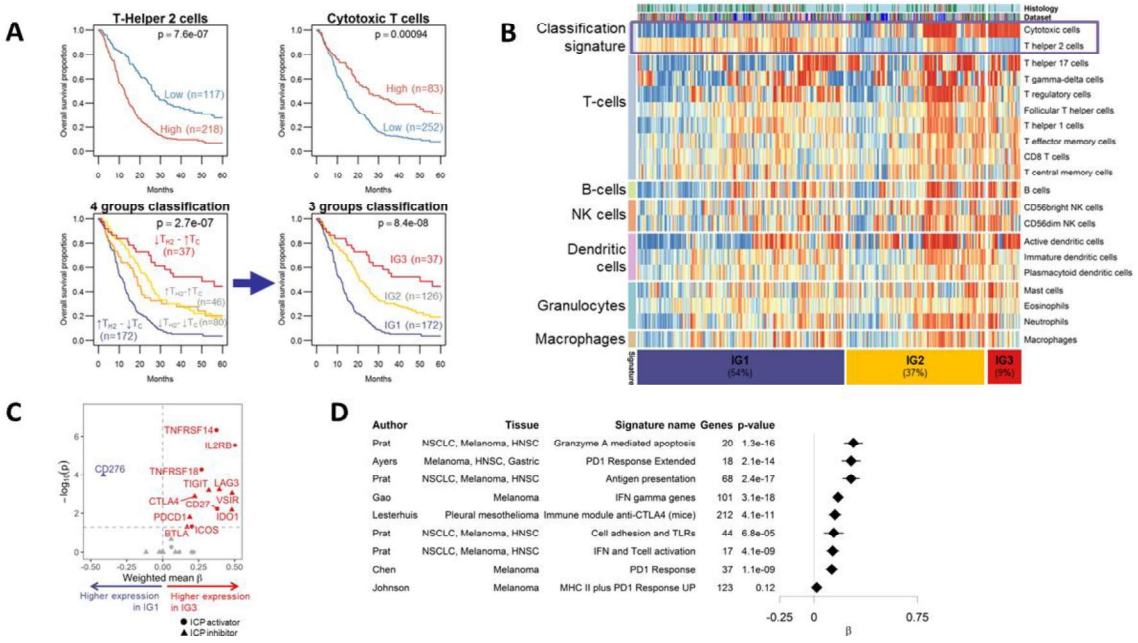
Figure 1. *Kaplan-Meier plots of overall survival according to the expression of TGF-β and TGF-β signaling pathway activation score using publicly available transcriptomic data on MPM.*



We characterized the immune contexture of MPM using gene-expression data from a large cohort of MPM (N=516) to improve patient stratification and enhance a better definition of therapeutic strategies in MPM[27-28]. We found that tumors with upregulation of cytotoxic T cells and low T-helper 2 signatures were associated with better clinical outcome (**Figure 2A**). By combining groups derived from those two signatures, we identified three distinct immune groups based on the relative abundance of T-helper 2 and cytotoxic T cells

(**Figure 2B**). Immune-group 3 (Low T_{H2} – High T_C) was enriched for the expression of members of the TNF receptor superfamily and checkpoint inhibitors (PD1, TIGIT, LAG3) and are more likely to respond to anti-PD1 therapy (**Figure 2C & 2D**).

Figure 2. *A) Kaplan-Meier plots of overall survival according to the expression of T-helper 2 and cytotoxic cells. B) Heatmap showing differential expression of immune cell signatures classified based on the relative abundance of T-helper 2 and cytotoxic T cells. C) Volcano plot showing immune checkpoint (ICP) enrichment in immune group 3. D) Gene signatures predicting benefit from ICP inhibitors are upregulated in immune group 3.*



Prior clinical trials with immune checkpoint inhibitors with anti-PD1 and anti-PD-L1 in previously treated MPM showed modest efficacy probably due to the predominantly immune suppressive tumor microenvironment, the generally low tumor mutational burden as well as the high aneuploidy which is characteristic of this tumor. In the PROMISE-Meso study, pembrolizumab was not superior to single chemotherapy in the second line setting in a non-selected population of MPM[29].

We hypothesize that dual targeting of PD-L1 and TGF-β by Bintrafusp alfa (M7824) may reduce tumor aggressiveness in MPM, can reverse the suppressive tumor microenvironment and extend progression-free survival (PFS). We propose a single-arm phase II clinical trial to assess the efficacy and the safety of M7824 in a cohort of patients with previously treated advanced MPM. We also hypothesize that selection of patients based on the TGF-β pathway activation in tissue or in the blood and stratification of patients based on immune groups will be helpful to identify MPM patients who are more likely to benefit from immunotherapy.

4. Objectives and endpoints

4.1. Primary objective and endpoint

- To determine the efficacy of M7824 in terms of the Progression Free Survival (PFS) assessed by the investigator according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) Version 1.1.

  PFS is defined as the time from administration of first dose of bintrafusp alfa until objective tumor progression or death.

4.2. Secondary objectives and endpoints

- To determine the ORR of the treatment as measured by investigator-assessed overall response rate (ORR) with M7824 according to modified RECIST v1.1.
- To determine the PFS assessed by an independent review committee by revised modified RECIST criteria v1.1.
- To evaluate secondary measures of clinical efficacy including duration of response, disease control rate and the Overall survival (OS).
- To evaluate the safety and tolerability of the treatment assessed by adverse events graded according CTCAE v5.0.

4.3. Exploratory objectives

- To correlate efficacy endpoints (PFS and ORR) with PD-L1 expression. This will be measured by PD-L1 immunohistochemistry in the central laboratory.
- To correlate efficacy endpoints (PFS and ORR) with activation of TGF-β pathway in tumor biopsies obtained at baseline and at tumor progression. This will be measured by SMAD2/3 and phosphor-SMAD2/3 immunohistochemistry in tumor biopsies obtained at baseline and at tumor progression.
- To correlate efficacy endpoints (PFS and ORR) with TGF-β levels along with additional cytokines measured in serum obtained prior to initiation of immunotherapy and cytokines at tumor progression.
- To correlate efficacy endpoints (PFS and ORR) with TGF-β levels along with additional cytokines in pleural effusion obtained prior to initiation of immunotherapy and at tumor progression. To determine the immune cell subpopulations harvested in the pleural effusion at baseline and at tumor progression using flux cytometry in a subset of patients included in the study.
- To determine the predictive value of the immune groups based on the expression of cytotoxic T cells and Th2 cells signature measured in the tumor sample at baseline by using gene expression panels from NanoString technologies.

5. Trial design, duration and termination

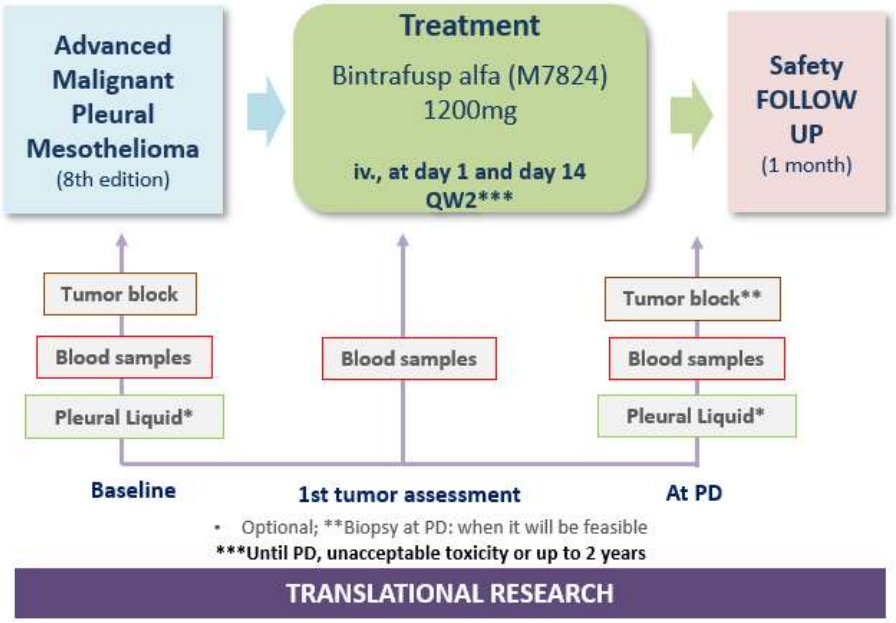
This is an open-label, non-randomized, phase II, single arm, multi-center clinical trial.

Patients enrolled in the study will receive treatment with M7824 that will be administered at day 1 and day 14 o (2 weeks ±3 days) of 28 days cycle. Cycles will be administered until unacceptable toxicity, loss of clinical benefit, disease progression or completion of 2 years of therapy. If the patient has benefit after 2 years, the trial chair and the sponsor must be consulted to evaluate how to continue with the treatment.

Patient accrual is expected to be completed within 1.5 years excluding a run-in-period of 4-6 months. Treatment and follow-up are expected to extend the study duration to a total of 3.5 years. Patients will carry out a safety follow-up 1 month after the end of treatment independently of the cause of end of treatment. The study will end once safety follow-up has concluded.

The trial will end with the preparation of the final report, scheduled for 4.5 years after the inclusion of the first patient approximately.

Study schema:



6. Patient selection

Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention for trial treatment and/or biomaterial submission to the central laboratory.

Patients should only be selected and consented for enrollment if they fulfil the following criteria:

6.1. Inclusion criteria

1. Male or female subjects aged ⩾ 18 years and capable of giving signed informed consent or requirement per local legislation.
2. ECOG performance status of 0-1.
3. Histologically confirmed malignant pleural mesothelioma (all histological subtypes are eligible), unresectable advanced or metastatic.
4. Patients that progressed or be intolerant to ≤ 2 regimens of chemotherapy, including platinum-based chemotherapy with pemetrexed. Prior bevacizumab treatment given during chemotherapy are allowed.
5. Evaluable disease or measurable disease as assessed according to the modified RECIST v1.1 criteria.
6. Availability of tumor tissue for translational research (at least 10 slides); Archival tumor tissue at diagnosis can be sent if it was obtained less than 18 months ago.
7. Life expectancy of at least 3 months.
8. Adequate hematologic and organ function defined by the following laboratory results obtained within 14 days prior to enrollment:

   Hematologic: Absolute neutrophil count (ANC) ⩾ 1.5 × 10^9/L, platelet count ⩾ 100 × 10^9/L, and hemoglobin ⩾ 9 g/dL

   Hepatic: Total bilirubin level ⩽ the upper limit of normal (UNL) range, AST and ALT levels ⩽ 1.5 x ULN and ALP ⩽ 2.5 x ULN. For participants with liver involvement in their tumor, AST ⩽5 x ULN, ALT ⩽ 5 x ULN, and bilirubin ⩽ 3.0 x ULN.

   Renal: Creatinine level ⩽1.5 x ULN or estimated creatinine clearance ⩾ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method) (may be modified to a higher creatinine clearance threshold, e.g. ⩾ 50 ml/min or ⩾ 60 ml/min as appropriate based on the target population or other drugs used in a combination regimen). For participants with Creatinine > 1.5 x ULN, glomerular filtration rate (GFR) can also be used.

   Coagulation: normal international normalized ratio (INR), PT ⩽ 1.5 x ULN and activated partial

thromboplastin time (aPTT) ⩽ 1.5 x ULN.

9. For patients with HIV infection, it needs to be a stable HIV infection on ART for at least 4 weeks, no documented evidence of multi-drug resistance, viral load of < 400 copies/ml and CD4+ T-cells ⩾ 350 cells/µL.
10. For patients with HBV/HCV infection, it needs to be a controlled HBV/HCV infection on a stable dose of antiviral therapy, HBV viral load below the limit of quantification. HCV viral load below the limit of quantification.

11. All patients are notified of the investigational nature of this study and signed a written informed consent in accordance with institutional and national guidelines, including the Declaration of Helsinki prior to any trial-related intervention.
12. For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly throughout the study and for at least 2 months after last bintrafusp alfa treatment administration .
13. For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly.
14. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drugs. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom. For male patients the duration of contraception after the last dose of bintrafusp alfa is 4 months.
15. Women who are not postmenopausal (≥ 12 months of non−therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 8 days prior to initiation of study drug.

6.2. Exclusion criteria

1. Prior immune checkpoint therapy with an anti-PD-1, anti-PD-L1, anti-CD137, or anti-CTLA-4 antibody.
2. Known severe hypersensitivity [Grade ⩾ 3 NCI CTCAE 5.0]) to investigational product or any component in its formulations, any history of anaphylaxis, or recent, within 5 months, history of uncontrollable asthma.
3. Previous malignant disease (other than the target malignancy to be investigated in this study) within the last 3 years. Participants with a history of cervical carcinoma in situ, superficial or noninvasive bladder cancer, localized prostate cancer or basal cell or squamous cell carcinoma in situ previously

treated with curative intent and endoscopically resected GI cancers limited to the mucosal layer without recurrence in > 1 year are NOT excluded.

4. Active central nervous system (CNS) metastases and/or carcinomatous meningitis that require therapeutic intervention or are causing clinical symptoms. Patients with previously treated brain metastases may participate provided they are stable and are not using steroids for at least 7 days prior to randomization.
5. Prior major surgery within 4 weeks prior to the first dose of study intervention.
6. Unstable or unresolved surgical or chemotherapy-related toxicity that would compromise the patient's capacity to participate in the trial. Persisting Grade > 1 NCI CTCAE 5.0 toxicity (except alopecia and vitiligo) related to prior therapy; however, sensory neuropathy Grade $\leqslant$ 2 is acceptable.
7. Prior organ transplantation including allogenic stem-cell transplantation, except transplants that do not require immunosuppression.
8. Live vaccines given 30 days prior to first dose of protocol treatment (M7824). Seasonal flu vaccines that do not contain a live virus are permitted. Also, COVID-19 vaccines approved by the authorities that do not contain live virus are permitted.
9. Drug-induced interstitial lung disease (ILD) or participant has had a history of drug-induced pneumonitis that has required oral or IV steroids, and/or other diseases, which in the opinion of the Investigator might impair the participant's tolerance for the study or ability to consistently participate in study procedures.
10. Active and serious autoimmune disease that might deteriorate upon treatment with immunotherapy. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. 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.
11. Ongoing clinically serious infections requiring systemic antibiotic or antiviral, antimicrobial, or antifungal therapy.
12. Known history of active tuberculosis or any active infection requiring systemic therapy.
13. Patients with diagnosed immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses $\leqslant$ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
14. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure ($\geqslant$ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

15. History of bleeding diathesis or recent major bleeding events within 12 months prior to enrollment (i.e. Grade ⩾ 2 bleeding events in the month prior treatment)
16. History of abdominal or tracheoesophageal fistula, active gastrointestinal ulcer or gastrointestinal perforation within 12 months prior to enrollment
17. Patients with any serious underlying medical condition that might impair patient's capacity to participate in the trial.
18. Substance or alcohol abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial results.
19. Women who are pregnant or in the period of lactation.

7. Patient enrollment

The patients will be eligible for the study after reviewing by the site's staff all the inclusion an exclusion criterion. This trial will use a web-based enrollment system (eCRF-Electronic Case Report Form). Each participating centre will access the system directly to enroll the patients.

Patient eligibility needs to be checked before enrollment of the patient in the Fundación GECP web-based system (eCRF). The dates of the patient signature of the Informed Consent of the study and the specific informed consent to tumor tissue and blood samples are required to be filled in the eligibility checklist of the eCRF.

The treatment should start preferably the date of enrollment or within 1-5 days from the date of enrollment.

8. Trial procedures

8.1. Overview of treatment sequence

8.1.1. **Baseline visit**:

The following procedures must be performed 28 days before enrollment:

1. Sign the informed consent form

2. Demographic data including age and gender and medical relevant history, including comorbidities and allergies, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status and smoking history.

3. To register whether patients experienced weight loss ≥ 5% in the previous 3 months or since mesothelioma diagnosis.

4. Complete physical examination **including skin inspection** and collection of: Height, weight, ECOG performance status, Temperature and blood pressure and oxygen saturation.

5. Laboratory testing must be performed within 14 days before the enrollment and includes:
    - **Hematology and coagulation**: White blood cells (WBC) count, neutrophils, haemoglobin, platelet count, PT, INR and APTT.
    - **Biochemistry**: Ca, Mg, Na, K, Glucose, ALT, AST, LDH, total bilirubin, alkaline phosphatase, creatinine and clearance of creatinine calculated by Cockcroft-Gault formula, total protein, albumin, amylase, lipase.
    - **Thyroid function**: thyroid-stimulating hormone (TSH). Total or free T3 and total or free T4 must be analyzed if TSH result is out of ULN or LLN.
    - **HIV / Hepatitis B/C test**: The following local laboratory assessments should be done within 28 days prior to first dose: Hepatitis B and C testing (HBVsAg, HBV Ab and HCV Ab) and HIV test. In patients with positive hepatitis B/C results, HBV DNA/HCV RNA must be performed (Hepatitis B vaccinated patients are excluded).
    - **Pregnancy Tests**: A serum or urine pregnancy testing is required within 8 days prior to study enrollment.
    - **Urine test**: A urine testing (dipstick is allowed) is required within 3 days prior to study enrollment.

6. Electrocardiograms: A 12-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

7. Baseline symptoms within the sign of study's Informed Consent will be recorded.

8. Medications (e.g. prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) from 7 days prior to initiation of study treatment (day 1 cycle 1) will be recorded.

9. Tumor assessment must be done within 28 days before enrollment (+ 10 days):

- **Chest and abdomen CT SCAN** with oral/IV contrast (unless contraindicated) to determine measurable disease according to modified RECIST v1.1.

10. Correlative studies (exploratory analysis):

    - Blood samples will be drawn before day 1 of week 1 of treatment

    - Pleural effusion liquid (when feasible) before day 1 of weeks 1 of treatment

8.1.2. Patient registration and enrolment

After baseline visit, the enrollment of the patient will be done in the Fundación GECP web-based system (eCRF). The dates of the patient signature of the Informed Consent of the study and the specific informed consent to tumor tissue and blood samples are required to be filled in the eligibility checklist of the eCRF.

8.1.3. Bintrafusp alfa (M7824) treatment

Day 1 of week 1 of treatment will start within 1-5 days from enrollment. Treatment will be administered every 2 weeks (±3 days) until progression or other reason to discontinue. If a pseudoprogression is suspected patient is allowed to continue treatment until loss of clinical benefit as judged by principal investigator and after the permission from the trial chair is granted.

On Day 1 and Day 14 of each cycle (QW2), all eligible patients will receive*:*

Bintrafusp alfa (M7824): 1200mg, IV infusion over 60 minutes

Current experience revealed that IRRs to bintrafusp alfa occur seldomly and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required. If an Investigator deems necessary to administer a premedication to a particular participant, an antihistamine (e.g. 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) is recommended. Premedication should be administered for subsequent bintrafusp alfa doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Management of symptoms should follow the guidelines shown in section 11.2.

The following procedures must be performed on day 1 of every 2/4 weeks (±3 days):

1. Every 2 weeks: Physical examination, including skin inspection and collection of: weight, ECOG, Temperature, blood pressure and oxygen saturation.
2. Every 2 weeks: Blood pressure must be taken always before the drug administration. Blood pressure should be routinely measured before every infusion after a resting period of 10 min. If baseline record is performed more than 3 days before first study dose, they must be repeated on day 1 week 1.
3. Laboratory testing prior to each dose administration within 3 days prior to day 1 administration of each 4 weeks (note that for the first 3 months of treatment, haematology and biochemistry must be done every 2 weeks). If baseline testing is performed more than 3 days before first study dose, they must be repeated on day 1 week 1:
    - **Hematology and coagulation**: WBC count, neutrophils, haemoglobin, platelet count, PT, INR and APTT.
      Note that coagulation must be done only if clinically indicated.
    - **Biochemistry**: Ca, Mg, Na, K, Glucose, ALT, AST, LDH, total bilirubin, alkaline phosphatase, creatinine and clearance of creatinine calculated by Cockcroft-Gault formula, total protein, albumin, amylase, lipase.
    - **Thyroid function**: thyroid-stimulating hormone (TSH). Total or free T3 and total or free T4 must be analyzed if TSH result is out of ULN or LLN.
    - **Pregnancy Tests**: A serum or urine pregnancy testing is required every 4 weeks during treatment.
    - **Urine test**: A urine testing (dipstick is allowed) must be done during treatment only if clinically indicated.
4. Adverse events: Changes from baseline symptoms (new or worsened clinically significant ones) should be recorded as adverse events on the Adverse Event form of the eCRF. For laboratory parameters, only grade 2 events will be reported as an AE. All the other events not related to laboratory values will be reported from grade 1.
5. Concomitant medications: Changes from baseline should be recorded on the eCRF.
6. Tumor assessment will be done every 8 weeks (± 7 days) from cycle 1 week 1. CT SCAN must be performed until progression disease or until last dose of bintrafusp alfa in case of continuing beyond pseudoprogression. The CT SCAN schedule will be maintained even if a delay in administration occurs.
    - **Chest and abdomen CT SCAN** with oral/IV contrast (unless contraindicated) to determine measurable disease according to mRECIST v1.1.

7. Correlative studies (exploratory analysis):

   - Blood samples will be drawn at first tumor assessment

8.1.4. Progression Disease

When the progression disease will be confirmed by mRECIST criteria and/or by principal investigator judgement these samples are strongly recommended to be collected:

- Tumor tissue from a rebiopsy, if clinically feasible and patient accepts this procedure
- Blood samples
- Pleural effusion liquid (when feasible)

8.1.5. End of treatment and first follow up visit

End of treatment is defined as the day of discontinuation of the treatment. The reason for end of treatment should be registered in the medical chart.

A safety follow-up visit must be done within 30 days (±3 days) after the last dose of treatment or immediately before the initiation of any other anticancer therapy. If the **reason for the end of treatment is progression** the following procedures can be performed during the end of treatment visit and should be always conducted between the end of treatment and the initiation of the next treatment. The following procedures must be performed in the safety follow-up visit (or at the end of treatment when the cause is tumor progression):

1. Physical examination, including skin inspection and collection of weight, ECOG, temperature, blood pressure and oxygen saturation.
2. Laboratory testing:
   - **Hematology and coagulation**: WBC count, neutrophils, hemoglobin, platelet count, PT, INR and APTT.
   - **Biochemistry**: Ca, Mg, Na, K, Glucose, ALT, AST, LDH, total bilirubin, alkaline phosphatase, creatinine and clearance of creatinine calculated by Cockcroft-Gault formula, total protein, albumin, amylase, lipase.
   - **Thyroid function**: thyroid-stimulating hormone (TSH). Total or free T3 and total or free T4 must be analyzed if TSH result is out of ULN or LLN.
   - **Pregnancy Tests**: A serum or urine pregnancy testing is required.
   - **Urine test**: A urine testing (dipstick is allowed) is required for proteinuria.

3. Electrocardiograms: A 12-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4. Adverse events: Changes from baseline abnormalities (new or worsened clinically significant ones) should be recorded as adverse events on the Adverse Event eCRF until this visit. For laboratory parameters, only grade 2 events will be reported as an AE. All the other events not related to laboratory values will be reported from grade 1. SAEs and AESIs must be recorded and followed from the subject written informed consent signature to 30 days from last dose of treatment.

5. Concomitant medications: Changes from baseline should be recorded on the eCRF until this visit (30 days from last dose of treatment).

6. Tumor assessment: if the end of treatment reason is other than disease progression the CT SCAN schedule will be performed every 8 weeks:

   a. **Chest and abdomen CT SCAN** with oral/IV contrast (unless contraindicated) to determine measurable disease according to mRECIST v1.1.

   It is not mandatory to perform the tumor assessment in first follow up visit if the end of treatment reason is other than progression disease and a tumor assessment has been performed in the previous 8 weeks.

After the safety follow up visit, all the patients will be followed by a telephone call every 3 months until the end of study participation or last patient last visit.

End of study participation of the patients included in the study will be the date of the last study assessment.

9. Investigational Medicinal Product

Bintrafusp alfa (M7824) is the Investigational Medicinal Products (IMP) used in this trial. Merck will provide the IMPs at no cost for this trial.

Complete details of the trial drug logistics, distribution, packaging, labelling, storage and handling as well as accountability are described in the ***BIMES drug supply manual*** that will be provided in the Pharmacy site file to all the participant sites.

Description of the Investigational Medicinal Products

Bintrafusp alfa (M7824) is a bifunctional fusion protein composed of the extracellular domain of the transforming growth factor β (TGF-β) receptor II (a TGF-β "trap") fused to a human immunoglobulin G1 antibody blocking programmed death-ligand 1 (PD-L1).

9.1. Packaging and labelling

Merck will provide the IMP Bintrafusp alfa (M7824) at no cost for this study. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

The Bintrafusp alfa (M7824) drug product is provided as a sterile concentrate solution for infusion 10m/ml in single-use glass vials. The vial is designed to allow an extractable volume of 60 mL (600 mg/60 mL). For further details on the formulation and handling of Bintrafusp alfa (M7824), see the ***BIMES drug supply manual*** and Investigator's Brochure of the IMP.

9.2. Receipt and storage of the IMP

Accurate records of the IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Accountability Log. In the event that the IMPs are destroyed a certification of destruction form should be generated and retained in the Pharmacy Site File.

The IMPs must be stored in a secure area according to local regulations. The investigator must ensure that the IMPs are stored refrigerated at 2-8^{o}C, protected from light and freezing, see the ***BIMES drug supply manual*** for details.

9.3. Unused trial drug supplies

If the IMPs are to be destroyed, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained. Provide a certificate of destruction to Fundación GECP upon disposal. See the ***BIMES drug supply manual*** for details.

10. Trial treatments description

10.1. BINTRAFUSP alfa (M7824)

Patients will receive 1200 mg of M7824 administered once every 14 days (+/- 3 days) over 60 minutes (+/- 10-20 minutes) intravenous infusion in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Refer to ***BIMES drug supply manual*** for detailed instructions on drug preparation, storage, and administration.

11. Dose modifications criteria

Doses cannot be delayed beyond the treatment window. Participants must skip dose if the treatment window is missed. Doses can be omitted until a maximum time of 8 weeks, for longer periods of time, the Trial Chair must be consulted. Reasons for dose delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

11.1. General Notes Regarding Dose Modification

When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

The investigator may use discretion in modifying or accelerating the dose modification guidelines depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

11.2. BINTRAFUSP (M7824). Toxicity Management

Treatment modification guidance for symptoms of infusion-related reactions including immediate hypersensitivity:

NCI-CTCAE Grade	Treatment Modification
Grade 1 - mild Mild transient reaction; in general, infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • Hold infusion if deemed necessary by the investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• Stop the infusion of the study intervention. • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening signs and symptoms, otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. • If not improving, consider administration of glucocorticoids and stop the infusion for that day. • If the participant has a second IRR Grade ⩾ 2 on the slower infusion rate despite premedication, the infusion should be stopped, and the investigator may consider withdrawal of this participant from the study.
Grade 3 or Grade 4 – severe or life-threatening ○ Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. ○ Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • For Grade 3 or 4 IRRs, permanent discontinuation of study intervention is mandated.

Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.
IRR=infusion-related reactions, IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Management of immune-mediated adverse events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for bintrafusp alfa.
Recommended guidance and management for specific irAEs are provided in the current NCCN guideline available at http://www.nccn.org.

Requirements in addition to NCCN guidelines:

- Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura inflammatory arthritis, myositis and polymyalgia-like syndrome.

- For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade $\leqslant$ 1, restarting treatment may be considered.

- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry. If symptoms appear and/or changes in the physical exam are noted, treat as Grade 2.

- For myositis: in case of management with rituximab, treatment should be discontinued.

Management of TGF-β mediated Skin Adverse Events

Skin assessment must be performed at baseline and at least every 6 weeks during treatment and at the end of treatment or 28 (±5 days) days post-treatment safety follow-up (if not performed in the previous 6 weeks).
• Hyperkeratosis • Keratoacanthoma • Cutaneous squamous cell carcinoma (cSCC) • Basal cell carcinoma • Actinic keratosis
Management

• Baseline skin assessment with detailed medical history
• Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
• Emollients may be used
• Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
• Treatment follow-up will depend on number and localization of lesions.
  ○ Single lesion: full excision may be recommended
  ○ Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Topical retinoids may be used after discussion with Investigator.
• Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
• In general, treatment of TGF-β mediated skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing bintrafusp alfa. Consult with Medical Monitor as needed for management of TGF-β mediated skin lesions.

Management of Anemia

• Anemia is considered an important identified risk for bintrafusp alfa. • Hematology assessment must be performed at baseline, prior to each bintrafusp alfa dose, at the end of treatment visit and at 28 (±5 days) days post-treatment safety follow-up. • Participants must enter the study with Hgb values at least 9g/dl • All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible
Basic Anemia Evaluation

• CBC with emphasis on red cell indices
• If indicated and at clinical discretion, the following should be considered:
  ○ Iron studies
  ○ Serum Folate and Vit B12 values
  ○ Coagulation factors
  ○ Fecal occult blood
  ○ Urinalysis
  ○ Hormone panel: TSH, Erythropoietin
  ○ Peripheral blood smear

Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)

• Suspected Hemolysis
  ○ bilirubin, LDH, Coombs test, haptoglobin
• Suspected bleeding:
  ○ Consider imaging/interventional radiology consultation as indicated
  ○ Consider imaging and/or endoscopy as clinically indicated
• Suspected aplastic anemia:
  ○ Hematology consultation
  ○ Consider bone marrow aspiration/morphologic evaluation

Additional consideration: In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Abbreviation: CBC: complete blood count, TSH: thyroid stimulating hormone, LDH: lactate dehydrogenase

Management of Mucosal/Non-tumor and Tumor Bleeding

Mucosal Bleeding	

• Events of mild to moderate severity are a potential risk for bintrafusp alfa.
• In general, these reactions resolve without discontinuation of treatment.
• Events may include, but are not limited to the following:
  ○ Epistaxis
  ○ Hemoptysis
  ○ Gingival bleeding
  ○ Hematuria	

Mucosal/Non-tumor Bleeding	
Grading	Management
Grade 2	• If resolves to Grade $\leqslant$ 1 by the day before the next infusion, study intervention may be continued • If not resolved to Grade $\leqslant$ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.
Grade $\geqslant$3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • In case of alternative explanations, hold study treatment until the event recovers to Grade $\leqslant$ 1 • If Grade $\geqslant$3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention bintrafusp alfa dose should be reduced by 50% (600 mg Q2W. Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with sponsor on potential dose re-escalation after careful benefit-risk assessment
Grade 4	• Treatment must be permanently discontinued if no alternative explanation is identified.

• In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 2.0 g/dL across a 2 weeks period, withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced by 50%. Once Hgb decrease is recovered to ⩽ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of bintrafusp alfa may be re-escalated to full dose once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re escalation may need a case-by-case decision. See Section Table on Management of anemia

Tumor Bleeding	
Grade ⩾ 2	• Study treatment must be held till the event recovers to Grade ⩽ 1 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.
Grade ≥ 3	• If Grade ⩾ 3 bleeding event had been observed, regardless of causality with the study intervention, upon resumption of the study intervention bintrafusp alfa dose should be reduced by 50%. Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with the sponsor potential dose re-escalation after careful benefit-risk assessment. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding. • In case of rapid decrease of hemoglobin (Hgb), see Section Mucosal/Non-Tumor bleeding.

Impaired Wound Healing

• • Impaired wound healing is considered important potential risk for bintrafusp alfa • Management should be discussed with Medical Monitor for participants requiring surgery on study. • It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. • Post-operative wound healing should be closely monitored

12. Prohibited and permitted concomitant treatments

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications form in the eCRF.

Prohibited Concomitant Therapy

The following medications are prohibited while on study, unless otherwise noted:

- Cytoreductive therapy
- Radiotherapy delivered for non-palliative indications
- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs is allowed).
- Live vaccine administration within 30 days before M7824. Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines)

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients on study is allowed at the discretion of the investigator provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

Permitted Concomitant Therapy

Premedication with antihistamines may be administered for any M7824 infusions before day 1 week 1 and week 3. The following therapies should continue while patients are on study:

- Oral contraceptives.
- Hormone-replacement therapy.
- Prophylactic or therapeutic anticoagulation therapy, such as low molecular weight heparin (preferred) or warfarin at a stable dose level.
- Inactive influenza vaccinations.
- COVID-19 vaccination with an approved vaccine is allowed for patients included in the study
- Megestrol administered as an appetite stimulant.

- Inhaled corticosteroids for chronic obstructive pulmonary disease.
- Mineralocorticoids (e.g., fludrocortisone).
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency (e.g oral hidroaltesona 20 mg per day).
- G-CSF is allowed as per local standard.
- Any medications (other than those excluded by the exclusion criteria or the prohibited medicines) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.
- Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2-receptor antagonist per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).

Cautionary Concomitant Therapy

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with bintrafusp alfa. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with bintrafusp alfa therapy. Guidelines for the management of immune-mediated adverse events are described in Appendix 7.

13. Adverse events and reporting

13.1. Definition of an Adverse Event (AE) and AE's reporting

The main criterion for tolerability is the occurrence of toxicities and Adverse Events (AEs). [redacted]

An adverse event can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding) (see **NOTE 1** below), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except events that are clearly consistent with the expected pattern of the disease progression. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study (e.g., "more frequent headaches").

NOTE 1: Abnormal laboratory and vital signs values:

A laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

Is accompanied by clinical symptoms,

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation),

Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy,

Is clinically significant in the investigator's judgment.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium").

A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

Is accompanied by clinical symptoms,

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation),

Results in a medical intervention or a change in concomitant therapy,

Is clinically significant in the investigator's judgment.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin),

Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice.

This abnormal laboratory values related to the liver function should be recorded on the Adverse Event eCRF and reported immediately as a SAE (AESI).

The severity will be classified according to the NCI CTCAE Version 5.0. The CTCAE is available for downloading on the internet (see appendix 1).

The AE severity grade provides a qualitative assessment of the extent or intensity of an AE, as determined by the investigator or as reported by the patients. 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 study drug.

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

1 = Grade 1	Mild
2 = Grade 2	Moderate
3 = Grade 3	Severe
4 = Grade 4	Life-threatening
5 = Grade 5	Fatal

However, depending on the SAE term used, there is some AE that do not have all the grades (e.g., the SAE term Alopecia only has the Grade 1 and 2).

The causal relationship to study drug is determined by the physician and should be used to assess all AE. The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

About the AEs that must be recorded in the eCRF note that:

- Baseline symptoms will be recorded on the eCRF and changes and updates in grade as well as resolution of an AE during treatment must be reported,
- An AE should be reported for each SAE notified,
- AEs should not be reported in a narrative description.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject (to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

Any AE must be reported by an entry in the eCRF within 5 days of awareness, even if they do not meet the whole information. The diagnosis of the event should be recorded as AE term. If there is a secondary AE separated in time from the initiating event, it should be recorded as an independent event (e.g., if vomiting results in severe dehydration, both events should be reported separately).

13.2. Definition of Serious Adverse Event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Serious Adverse Event (SAE) is defined in general as any undesirable medical occurrence/adverse drug experience that occurs [redacted], regardless of whether it is considered related or not to the study drug and that, at any dose, results in any of the following:

- results in death (fatal)
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE 2** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event. Defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical, laboratory abnormal parameters…) to prevent one of the other serious outcomes listed in the definition above (see **NOTE 3** below)

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

Seriousness is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations

NOTE 2: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission, except if it is considered as an important medical event or life- threatening
- elective surgery which has been planned prior to signing consent

- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- admissions as per protocol for a planned medical/surgical procedure
- admission for administration of anticancer therapy in the absence of any other SAEs
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- progression of disease. 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.

NOTE 3: Any laboratory abnormalities should be documented as a SAE if:

- Intensive treatment in an emergency room or at home for allergic bronchospasm is needed,
- Blood dyscrasias or convulsions that do not result in hospitalization,
- Any untoward event related, and unexpected, to the protocol procedures,
- The laboratory test result is clinically significant or meets the definition of a SAE,
- The laboratory abnormality required the participant to have study drug discontinued or interrupted,
- The laboratory abnormality required the subject to receive specific corrective therapy.

A SAE report should be completed for any event where doubt exists regarding its seriousness. Although overdose, pregnancy, AESI (e.g., potential drug-induced liver injury (DILI)), important medical event, and cancer (secondary malignancy) are not always serious by regulatory definition, these events must be handled as SAEs. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

If the investigator believes that a SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form and an important medical event would be the seriousness.

All deaths that occur during the reporting period that are clearly the result of disease progression should not be reported as a SAE, but they should be collected as an AE. All deaths where it is not due to disease progression and deaths with an unknown cause should always be reported as a SAE.

Death should be considered as an outcome and not the event, the AE causing the death must be reported as the SAE term. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "Death due to Unknown Cause" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), the event should be replaced by the established cause of death.

If the SAE is considered as related to the study drug by the Principal Investigator, it is a Serious Adverse Reaction. The SAR is assessed by the Fundación GECP (SLCG/GECP) to know if it is expected. A SAR that is not listed as a known toxicity of the investigational drug in the summary of product characteristics (Investigator Brochure or Data Sheet) will be considered as a Suspected Unexpected Serious Adverse Reaction (SUSAR). The sponsor will inform to the Principal Investigator that this SAE has been considered as a SUSAR. In Spain, Health authority (AEMPS: Agencia Española del Medicamento y Productos Sanitarios) will also be informed about all SUSARs via EudraVigilance. Also, the autonomous regions will be informed about all SUSARs according to the current Spanish clinical trial regulation.

13.3. Adverse events of Special Interest for M7824 (Immediately reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Fundación GECP (SLCG/GECP) immediately) (no more than 24 hours after learning of the event; see Section 13.5 for reporting instructions), despite not being serious. Adverse events of special interest for this study include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Overdose and secondary malignancies

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as a SAE, indicating “life-threatening” as the seriousness.

Secondary malignancies are not always serious by regulatory definition, these events must be handled as SAEs.

13.5. SAEs and SUSARs reporting

All SAEs that occur within **30** days of the last administered study medication must be collected. Any SAE must be reported by submitting the completed Initial SAE Form in the online eCRF within 24 hours of awareness, even if they do not meet any of the seriousness criteria.

In case of the eCRF is unavailability, the submission could be done by sending the SAE form preferably by email to pharmacovigilance.slcg@gecp.org or by fax to the Fundación GECP (SLCG/GECP) Pharmacovigilance Office: +34 93 419 17 68. An appropriate SAE form (see appendix 3) should be used to report SAEs to Fundación GECP (SLCG/GECP). The paper SAE form has to be sent within the timeline period for reporting of 24 hours of awareness. **Once the eCRF system is available again, the SAE has to be completed and submitted by the site into the eCRF**.

If only limited information is initially available, a follow-up report is required to complete the information as soon as possible. (Note: Follow-up SAE reports should include the same SAE term(s) initially reported.)

The SAE outcome must be reported within 14 days after initial reporting by submitting the Follow up SAE Form in the online eCRF. In case the SAE is reported as ongoing after 14 days, a follow-up report has to be submitted again with the final outcome.

If an ongoing SAE changes in its grade, relationship to study drug, seriousness, SAE term or if new information becomes available, a new follow-up SAE report should be sent within 24 hours to the Fundación GECP (SLCG/GECP) using the same procedure after described.

Any SUSAR occurred during the trial will be notified under Spanish clinical regulation to the principal investigators, to the Health Authority (AEMPS) via Eudravigilance within the timelines specified in the Royal Decree 1090/2015 on clinical trials regarding the recording, evaluation and reporting of adverse events. Also, the autonomous regions will be informed about all SUSARs according to the current Spanish clinical trial regulation.

For any doubt please contact Fundación GECP (SLCG/GECP) pharmacovigilance office by this email: pharmacovigilance.slcg@gecp.org or by the telephone: +(34) 93 430 20 06.

Also, Fundación GECP (SLCG/GECP) will ensure that all SAEs, SUSARs, AESIs and pregnancy reports in the clinical database (eCRF) are reported to the authorization holder y during the conduct of the study including periodic reconciliation.

13.6. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, within 5 months after the last dose of M7824, the investigational product will be permanently discontinued.

Any pregnancy that occurs in a female partner of a male study participant should also be reported to the Fundación GECP (SLCG/GECP). Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if his partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. To allow Fundación GECP (SLCG/GECP) or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

In both cases, the investigator must immediately notify to the Fundación GECP (SLCG/GECP) Pharmacovigilance Office by sending the Pregnancy form (see appendix 4) preferably by email to pharmacovigilance.slcg@gecp.org or by fax to the Fundación GECP (SLCG/GECP) Pharmacovigilance Office: +34 93 419 17 68.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, study discontinuation must be reported following the before procedure described during at least 1 year after child-bearing.

Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) or abortion should be reported as a SAE.

13.7. Other safety considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

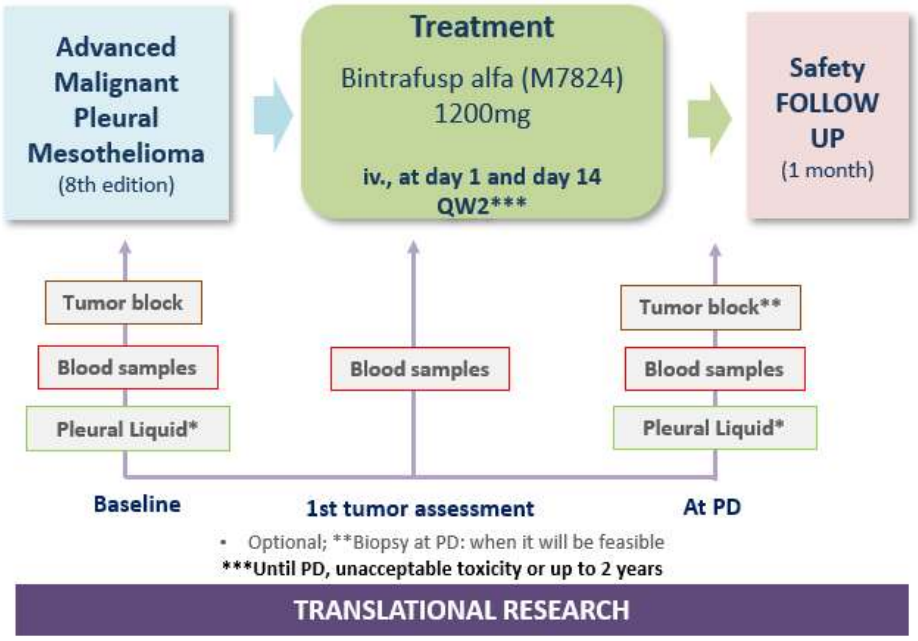
14. Biological material and translational research

Several samples will be collected during the study. All the samples will be stored at:

[redacted]

The following samples will be collected:

- [redacted]
- [redacted]
- [redacted]



Please, refer to the **BIMES Samples Manual** for more information.

15. Case report forms and documentation

eCRFs will only be available on-line at the Remote Data Entry (RDE) facility of Fundación GECP for patient enrollment.

Only the patient pre-screening form will be used in a paper form and will be send scanned by email or by fax (+34 93 419 17 68) to obtain the pre-screening number.

Also, another exception will be a paper SAE form and pregnancy form that will be used only in case of eCRF system unavailability.

16. Statistical considerations

Three populations will be considered for different analyses:

- Per protocol population (PP): Per protocol population will consider patients that will receive a minimum of 3 cycles of treatment or that have at least the first tumor response evaluation carried out. Patients without any radiological evaluation who may die during the first 9 weeks will also be considered PP population. Patients without the first tumor response evaluation carried out but with a progression disease (also clinical progression) at 8 weeks will also be considered into PP population.
- Intention to treat analysis (ITT): Intention to treat analysis will include all patients that fulfill inclusion and exclusion criteria and will be registered into the clinical trial.
- Safety population (SFP): Safety population will include all patients that will be exposed to study treatment (bintrafusp alfa), whatever will be the quantity received

This study is designed to show that experimental treatment will achieve a median PFS of 4.5 months (expected median for standard scheme is 3 months which is equivalent to consider an improvement of 0.66 in terms of hazard ratio), with a statistical power of 90% and a one-sided type I error of 10%. On these bases and considering Lachin design, 45 pts are needed (44 or more events for null hypothesis and 43 or less events for alternative hypothesis) over a period of 18 months with a minimum median follow-up of 12 months to perform an exponential test. Considering a 5 % of drop-out patients and a hazard of 0.04 for dropouts a total sample size of 47 patients will be needed. In case of having 43 or less events during follow-up alternative hypothesis will be concluded and experimental treatment will be declared as promising.

The expected accrual rate is 2 patients per month for the first 6 months, increasing to 4-5 patients per month thereafter. Primary analysis is expected to be available 18 months after the inclusion of the first patient.

In order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, they will be replaced by a new one subject that fulfil them, this replacement will ensure that the sample size will be the one calculated initially.

Reference: Lachin, John M (2000). Biostatistical Methods: The assessment of Relative Risks. John Wiley & Sons, New York, NY.

17. Criteria for termination of the trial

17.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the product leads to doubt as to the benefit/risk ratio, by decision of Fundación GECP or Trial Steering Committee, or at the suggestion of the IDMC.

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

17.2. Discontinuation of protocol treatment and from the study for individual patients

Patients may be withdrawn from the protocol treatment and from the study in the following situations:

- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Disease progression per investigator assessment according to mRECIST v1.1 and loss of clinical benefit
- Symptomatic deterioration attributed to clinical disease progression
- Intercurrent 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
- 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.
- If a patient refuses to have follow-up examinations and tests needed to determine whether the treatment is safe and effective
- Protocol non-compliance or study termination by sponsor or site closure by the sponsor (poor protocol adherence, inaccurate or incomplete data recording…)

- Pregnancy
- Patient non-compliance, defined as a failure to comply with the protocol requirements as determined by the protocol

The decision for discontinuation of protocol treatment and the study of individual patients is taken by the treating physician based on his medical evaluation and taking into consideration the patient's individual situation. Specific reasons for trial discontinuation in which further collection of data is not allowed are: withdrawal of consent, patient lost to follow up, death.

All possible measures will be undertaken to maintain the investigation program and to continue the follow-up even if the treatment was prematurely concluded and/or if the patient did not attend the follow-up visits at the participating institution.

The primary reason for the treatment and study discontinuation should be documented on the appropriate eCRF.

18. Ethics aspects, regulatory approval, and Patient Informed Consent

The Investigator will ensure that this study 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 study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH6 Tripartite Guideline (January 1997) or local Spanish 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).

18.1. Ethical Review Board/Ethics Committee/Health Authority

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 Ethic Committee decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The Ethic Committee 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.

Any modifications made to the protocol must be submitted to the appropriate Ethic Committee 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.

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other 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.

18.2. 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". Once 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 site file. The informed consent form must be available in the case of data audits.

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 tumor 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. It is preferable that the patient who gives the consent signs the form but if it is not possible or 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 Good Clinical Practice and the "Declaration of Helsinki".

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”.

19. Governance and administrative issues

19.1. Study documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval.

19.2. Protocol non-compliances/deviations

The investigator should document and explain any protocol non-compliances/deviations. The investigator should promptly report any non-compliances/deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol non-compliances/deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. All protocol non-compliances/deviations will be recorded by the monitoring team.

19.3. Protocol amendment

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

19.4. Final report

A final clinical trial report will be written and distributed to the Ethic committees and Health Authorities as required by applicable regulatory requirements.

19.5. Independent Data Monitoring Committee (IDMC)

The trial will be presented periodically for review to the Fundación GECP BICR (blinded independent central review). This IDMC will held expedite meeting/s if any safety issue or other concerns come up during the study. The management staff of the Fundación GECP, will be in charge of informing the IDMC of any issue related with the study.

19.6. Publication

Authorship on the final manuscript or publications or provisional extracts will be decided in accordance with the Fundación GECP publication and authorship guidelines (SOP GECP: Política de publicaciones y autorías). None of the participants will present data to his center in isolation from the rest of the results of the study and will need to seek approval from the sponsor.

19.7. Financial disclosure

Investigators will provide the sponsor with enough, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

19.8. Clinical trial insurance

Spanish legislation demands cover with a civil responsibility policy for subjects participating in a clinical trial. Fundación GECP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician.

19.9. Quality assurance

Fundación GECP conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial Data Manager reviews each eCRF as per monitoring plan schedule.

Fundación GECP will conduct periodic triggered visits to the participating sites 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 Fundación GECP, or to ethics committee and health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the center will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study 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.

19.10. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a pre-screening number at the pre-screening phase to identify the biological material and a unique identifier assigned by the eCRF of the study once enrolled. Sites are responsible to keep a patient log locally to be able to link the pre-screening number and the unique identifier to the record of the patient.

No identifiable / personal data will be stored in the trial database or the tissue repositories in the central laboratories.

Regulatory authorities and pertinent Ethics Committees (IRB/ERB) may have access to patient data on-site. Fundación GECP audit or monitoring personnel will also have access to such data on-site.

In Spain to ensure the patient confidentiality of data applies from the 25th of May 2018 the Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD) and the Organic Law 3/2018, 5th of December, on Personal data protection and digital rights guarantee.

19.11. Study monitoring team

The Fundación GECP will be responsible for monitoring the trial at Spanish sites.

The clinical monitor is obliged to rigorously follow the study. For this, the clinical monitor will regularly visit the study centers and the investigators as well as maintain necessary written and telephone communications.

The clinical monitor will assess the data collected in the acquisition forms and compare them with the original data of the clinical history and other original documents in conjunction with the study investigator.

The contact persons will be:

[redacted]
Fundación GECP CRA
Meridiana 358, 6ª planta
08027 Barcelona
Tel. 93 430 20 06
Fax. 93 419 17 68
[redacted]

[redacted]
Fundación GECP Lead CRA
Meridiana 358, 6ª planta
08027 Barcelona
Tel. 93 430 20 06
Fax. 93 419 17 68
[redacted]

19.12. Record retention

The center 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 25 years after the termination of the trial.

In the event of 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 must be given to the Fundación GECP and the local Ethics Committee at least 1 month in advance.

20. References

1. [redacted]

[redacted]

[redacted]

Appendices:

1. Common Terminology criteria for Adverse Events (CTCAE)
2. Modified RECIST (mRECIST) criteria version 1.1 for malignant pleural mesothelioma
3. SAE Form
4. Pregnancy Form
5. Mesothelioma TNM definitions according to the 8th edition

APPENDIX 1. Common Terminology criteria for Adverse Events (CTCAE)

Version 5.0: November 27, 2017 is available from the internet at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX 2. Modified RECIST (mRECIST) criteria version 1.1 for malignant pleural mesothelioma

1. Supplementary Data: Proposed Radiology Guidelines for Inclusion in Clinical Trial Protocols

Guidelines for measuring pleural mesothelioma as per modified RECIST 1.1
Measurement of pleural tumor and other sites at baseline:

1.1. *Definition of measurability*

- Pleural tumor is measurable if there exists at least one pleural site for which tumor thickness is ≥7 mm.
- Non-pleural sites of disease can determine measurability, and will have a unidimensional greatest diameter of ≥10 mm at baseline.
- Measurable involved lymph nodes have a short-axis measurement ≥15 mm at baseline.
- Pleural effusion is not considered a measurable lesion.

1.2. *Measurement sites at baseline*

- Unidimensional pleural tumor measurements should be determined by constructing a line segment perpendicular to a tangent to the curve of the pleura at the outer measurement point (Figure 1). The outer measurement point is best placed on the chest wall or mediastinum, avoiding the anterior pleural reflexion.
- Image sections chosen for measurement should be readily identified at subsequent time points and ideally related to clear fixed anatomical mediastinal or chest wall landmarks (Figure 2).
- Areas of pulmonary atelectasis, pleural effusion, and indistinct tumor boundaries should be avoided if possible.
- Where a measurement site is related to the pulmonary fissures, unidimensional measurements should be made perpendicular to a tangent to the pleura at that point (Figure 3).

- Pleural thickness is recorded at up to two measurement sites, if possible, at each of up to three separate axial sections (levels) of the thoracic CT scan at baseline (Figures 2 and 4). Axial sections should be at least 1 cm apart. The sum of these (up to) 6 measurements gives the baseline sum of pleural measurements.

- Each selected measurement must individually satisfy the criterion for minimally measurable disease.

- In the event of bilateral disease, the pleura is considered a single organ and pleural measurement sites may be distributed across both hemithoraces, up to three independent CT sections per hemithorax, no more than two measurement sites per section, to a total of 6 sites.

- Additional unidimensional non-pleural target lesion measurements meeting the definition of measurable disease may be made of involved lymph node sites, chest wall masses, or metastatic disease and added to the sum of pleural tumor thickness measurements to give a baseline sum of target lesion measurements. Measurements of non-pleural disease may be included from a maximum of five lesions total, and a maximum of two lesions per organ. Measurements acquired from pleural sites are to be considered a contribution from one organ.

- Other disease present at baseline should be recorded as "non-target lesions." In the case of diffuse pleural disease, examples of descriptive notations include: "extensive pleural thickening," "circumferential pleural thickening," "tumor indistinguishable from diaphragm in base," "extensive pleural nodularity," or similar. This may include non-measureable disease as well as measurable but non-measured pleural disease. It is not practical to separately identify individual pleural lesions that are contiguous or exceed a reasonable number.

- Images of the baseline scan measurement segments should be stored for visual reference when measuring subsequent images.

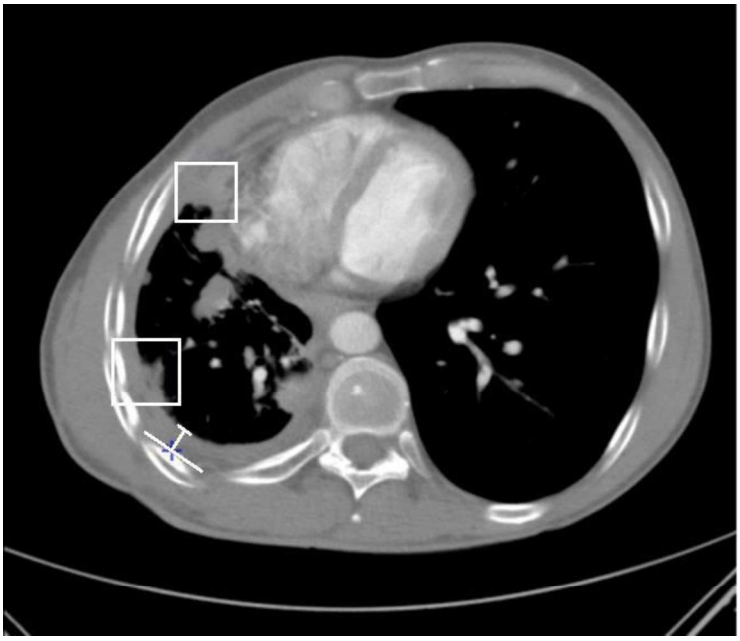
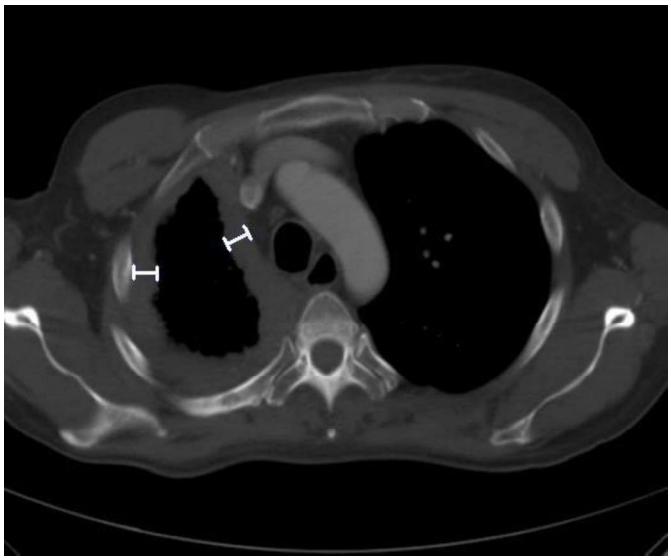
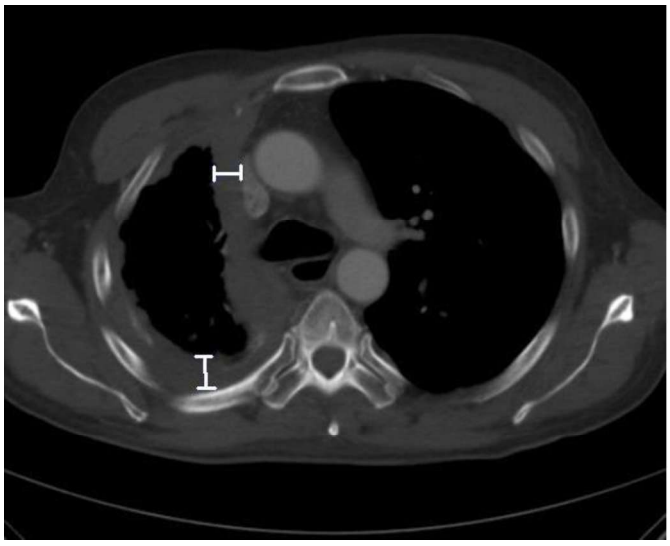


Figure 1: Unidimensional measurements are determined by constructing a line segment perpendicular to a tangent to the curve of the pleura at the outer measurement point. Avoid areas of pleural reflexion or unclear disease boundaries (boxes).

(i)



(ii)



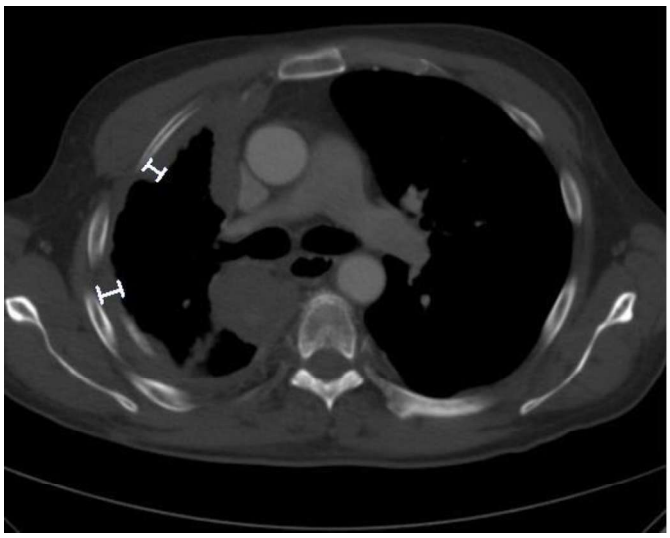
(iii) 

Figure 2: Example of two measurements at each of three anatomically reproducible levels (i, ii, and iii).

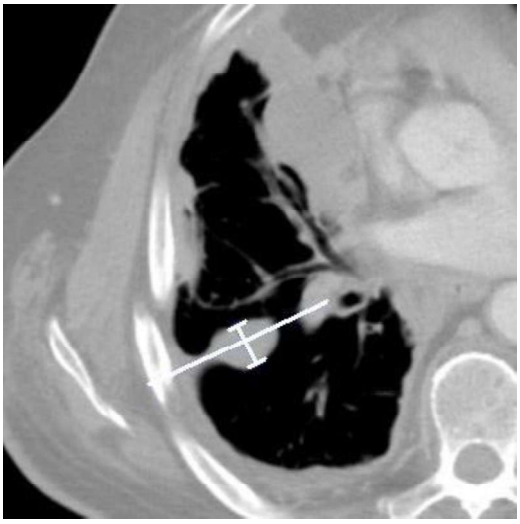


Figure 3: Lesions in the pleural fissure should be measured perpendicular to the fissure at that point.

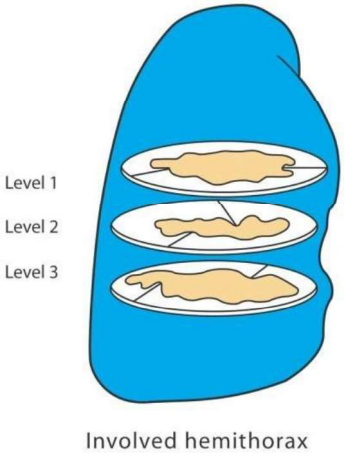
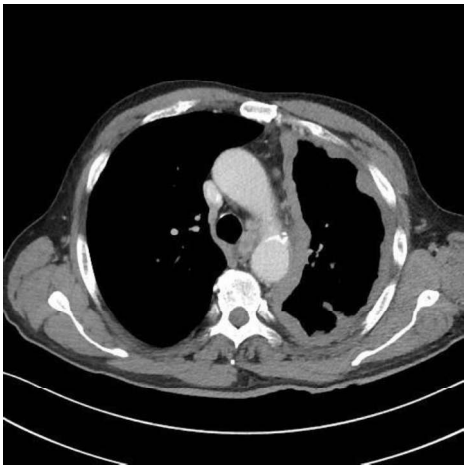


Figure 4: Pleural thickness is recorded at up to two measurement sites at each of up to three separate axial sections (levels) of the thoracic CT scan at baseline. Axial sections should be at least 1 cm apart.

(i)



(ii)

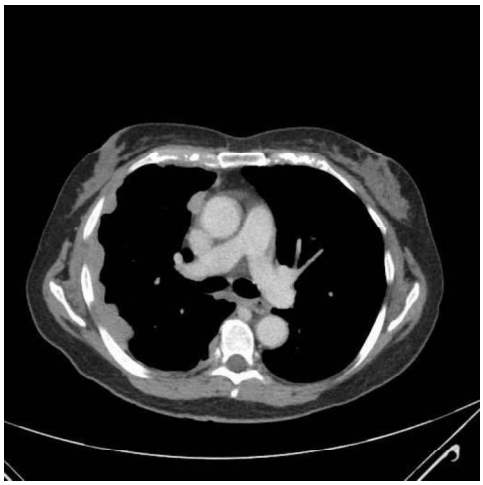


Figure 5: Examples of (i) “circumferential pleural thickening” in non-target lesion descriptor and (ii) “extensive pleural nodularity” in non-target lesion descriptor.

2. Measurement of disease at subsequent time points:

- Pleural tumor measurements should always be performed at the same site, in the same orientation (direction), and with the same image display parameters as the baseline measurement, irrespective of changes in lesion morphology and shape. If tumor is present at a site but is too thin to measure on a magnified window, a default value of 2 mm should be used.
- Lesions that are viewed on the same image slice at baseline but are subsequently best viewed on different images slices due to alterations in thoracic contraction, respiration, or patient positioning may be measured on different slices on subsequent scans.
- Modified RECIST 1.1 recommends that the same observer acquire measurements from all CT scans from a given patient.
- Stored images of the baseline measurement line segments should be visually referenced when acquiring measurements from scans at subsequent time points.

3. Definitions of objective response:

Complete response (CR): Disappearance of all pleural and non-pleural disease (including pleural thickening considered to represent tumor).

Partial response (PR): Summed measurement decrease by at least 30% from the baseline scan summed measurement, which must be confirmed at a subsequent follow-up scan at least 4 weeks later (at which time the summed measurement must not exceed 70% of the baseline scan summed measurement).

Progressive disease (PD): Summed measurement increase by at least 20% from the nadir of the summed measurements from all prior scans (up to and including the baseline scan), even if the summed measurement is $\leq$70% of the baseline scan summed measurement; classification as PD also requires an absolute summed measurement increase of at least 5 mm over the nadir summed measurement. An unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size (and represents either a pleural tumor mass physically distinct from that associated with existing measurement sites or a region of a previously existing pleural tumor mass that would now unequivocally qualify as a measurement site) would be considered progressive disease[#].

Stable disease (SD): A decrease in the summed measurement that does not qualify as PR, or an increase in the summed measurement that does not qualify as PD.

Note: Confirmation of objective response on a subsequent occasion at least 4 weeks later is required to assign a response of Confirmed PR or Confirmed CR.

An unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size (and represents either a pleural tumor mass physically distinct from that associated with existing measurement sites or a region of a previously existing pleural tumor mass that would now unequivocally qualify as a measurement site) would be considered progressive disease; the assessment of "unequivocal," however, requires judgment and careful review to ensure that the lesion was not present previously in an adjacent section.

APPENDIX 3. SAE Form

SERIOUS ADVERSE EVENTS NOTIFICATION FORM (SAE) GECP	PROTOCOL Code: GECP 20/09 (BIMES)	
	Site:	
TYPE OF NOTIFICATION: ☐ INITIAL ☐ FOLLOW UP nº.....	Investigator:	SAE Form Nr:

SERIOUS ADVERSE EVENT INFORMATION

PATIENT CODE	DATE OF BIRTH	AGE	GENDER ☐ Male ☐ Female	WEIGHT (kg)	HEIGHT (cm)
DATE OF SAE AWARENESS: I_____I_____I_____I			SAE NOTIFICATION DATE: I_____I_____I_____I		

SERIOUS ADVERSE EVENT (please, fill in the following field with the information related to the serious adverse events. The first one has to be the more relevant. The SAE term has to be filled in with the verbatim term. The SAE term according to the CTCAE will be coded by the Fundación GECP pharmacovigilance department in the study data base.

SAE term	Grade (1-5)	Start Date/Stop date	Causality[1]	Key for seriousness[2]	Outcome[3]
		Start D.: I___I___I___I Stop D.: I___I___I___I	*_____		Outcome date: I___I___I___I
		Start D.: I___I___I___I Stop D.: I___I___I___I	*_____		
		Start D.: I___I___I___I Stop D.: I___I___I___I	*_____		
		Start D.: I___I___I___I Stop D.: I___I___I___I	*_____		
		Start D.: I___I___I___I Stop D.: I___I___I___I	*_____		

[1] Causality (relation to study drugs):

0: Not related; 1: Related; 2: Not applicable*

*Specify drug and/or therapy (e.g Radiotherapy)

[2] Key for Seriousness:

1: Death; 2: Life threatening; 3: Initial/Prolonged hospitalization admission; 4:Congenital Anomaly/Birth Defect;5: Persistent or significant Disability ; 6: Medically significant (important medical event) ; 7: Non-serious adverse event of special interest (AESI) as per protocol; 8: Non-serious secondary malignancy as per protocol

[3] Outcome

1: Resolved without sequelae ; 2: Resolved with sequelae; 3: Fatal; 4: Ongoing 5: Unknown

SAE COMMENTS (Please, point out any relevant data related to the SAE, test results, any additional relevant information, in case of death, please add information about date of death, cause and autopsy if applicable)

SAE Form_v.3.0_16Abr2019

1 of 2

PATIENT CODE	PROTOCOL CODE GECP 20/09 (BIMES)	SAE FORM N°

INFORMATION ABOUT INVESTIGATIONAL MEDICAL PRODUCT

Trial Medication (Generic name/Brand name)	Dose and units	Route (IV, PO, SC...)	Date of administration before SAE	Action taken[4]	Stopped the event when the medication was discontinued?[5]	The event returned when the medication is resumed?[5]

¿IS THERE ANY OTHER EXPLANATION OR CAUSE FOR THE ADVERSE EVENT?

☐ CONCOMITANT DISEASE ☐ POSSIBLE RELATION WITH CONCOMITANT DRUGS ☐ STUDY PROCEDURES ☐ NOT APPLICABLE ☐ OTHERS (SPECIFY):

_____

[4] **Action taken with regard to trial medication:** *0: none; 1: Reduced; 2: Delayed; 3:Delayed and Reduced; 4: permanent discontinuation; 5: other (specify):*_____

[5] **Stopped or returned the adverse event when the medication was discontinued or resumed?** *0: YES; 1: NO; 2: Not applicable*

PREVIOUS RELEVANT MEDICAL HISTORY

PREVIOUS RELEVANT MEDICAL HISTORY (PREVIOUS DIAGNOSIS, SURGERIES, ALLERGY, PREGNANCIES, CONCOMITANT DISEASES, ETC):

CONCOMITANT MEDICATION *(Medication took by the patient due to basal diseases or supportive Clinical trial medication)*

CONCOMITANT MEDICATION (Brand name)	Daily Dose	Route (IV, PO, SC...)	Onset Date	Ending date or Ongoing?	Prescription reason[6]

[6] **Prescription reason: 1: Regular medication/baseline conditions; 2: Concomitant Medication/prophylaxis; 3: Adverse event; 4: Other (specify)**

INFORMATION ABOUT THE SPONSOR AND THE PRINCIPAL INVESTIGATOR (PI) OF THE TRIAL

NAME AND CONTACT DETAILS OF THE SPONSOR	DATE RECEIVED AND SIGNATURE OF THE SPONSOR:	NAME AND CONTACT DETAILS OF THE PI:	DATE AND SIGNATURE OF THE PI:
Fundación GECP *Av. Meridiana, 358 6ª pl* *08027 Barcelona* *Tel: (34) 93 430 20 06* *Fax: (34) 93 419 17 68*	|_____|_____|_____|		|_____|_____|_____|

PLEASE FAX THIS FORM TO THE Fundación GECP (SLCG/GECP): + 34 93 419 17 68 or EMAIL IT TO:
pharmacovigilance.slcg@aecp.org

APPENDIX 4. Pregnancy Form

PREGNANCY NOTIFICATION FORM	PROTOCOL Code: GECP 20/09 (BIMES)	
GECP	Site:	
TYPE OF NOTIFICATION: ☐ INITIAL ☐ FOLLOW UP nº.....	Investigator:	PREGNANCY Form Nr:

PATIENT CODE	DATE OF BIRTH	AGE	GENDER ☐ Male ☐ Female	WEIGHT (kg)	HEIGHT (cm)
DATE OF PREGNANCY AWARENESS: I_____I_____I_____I			PREGNANCY NOTIF. DATE: I_____I_____I_____I		

PREGNANCY REPORT INFORMATION

The pregnancy has occurred in: ☐ Clinical trial subject * ☐ Female partner of trial subject
*If in pregnant trial subject. Was she withdrawn consent from study? ☐ YES** ☐ NO
** Date of withdrawal of the study I_____I_____I_____I
State of the pregnancy at the moment of the withdrawal: ☐ Suspected ☐ Positive pregnancy test ☐ Confirmed

PHASE OF THE TREATMENT WHERE PREGNANCY WAS DETECTED AND TYPE OF CLINICAL TRIAL

☐ Screening Phase ☐ Randomized or included patient* ☐ During Follow up Phase ☐ NA (the study not started yet)
Is it a blind Clinical trial? ☐ NO ☐ YES; If yes, Was the blind broken? ☐ NO ☐ YES*
*Specify (treatment arm, treatment...):_____

MATERNAL INFORMATION

Mother date of birth: I_____I_____I_____I	**Contraception information:**
Date of last menstrual period: I_____I_____I_____I	Was the mother/father using a method of contraception? ☐ Yes* ☐ No
Estimated delivery date: I_____I_____I_____I	
Father date of birth: I_____I_____I_____I	*Specify: ☐ Oral contraception ☐ Condom ☐ Diaphragm ☐ Others (specify): _____
First pregnancy awareness date: I_____I_____I_____I	Has the mother any previous pregnancies? ☐ YES (complete next section) ☐ NO
PI awareness date of the pregnancy: I_____I_____I_____I	

PREGNANCY RELEVANT MEDICAL HISTORY

Number of full-term pregnancies: I_____I Number of pre-term pregnancies: I_____I

Previous pregnancies outcome:
Normal births (nº): I_____I; Children born with defects: I_____I; Spontaneous abortion: I_____I;
Induced abortion: I_____I; Ectopic pregnancy: I_____I; Others I_____I (specify): _____

Are any risk factors to the current pregnancy outcome? (e.g: alcohol or substance abuse, chronic diseases, family history of birth defects...), specify: _____

PATIENT CODE	PROTOCOL CODE GECP 20/09 (BIMES)	PREGNANCY Form N°

PREVIOUS RELEVANT MEDICAL HISTORY FROM MOTHER AND/OR FATHER

PREVIOUS RELEVANT MEDICAL HISTORY (PREVIOUS DIAGNOSIS, SURGERIES, ALLERGY, CONCOMITANT DISEASES, ETC):

INFORMATION ABOUT INVESTIGATIONAL MEDICAL PRODUCT

Trial medication (Generic name/Brand name)	Time of exposure[1]	Daily dose	Route (IV, PO, SC...)	Start Date	Stop date or Ongoing?	Action taken with regard to trial medication[2]

[1]Time of exposure: 0: pre-conception; 1: 1st trimester; 2: 2nd trimester; 3: 3rd trimester

[2] Action taken with regard to trial medication: 0: None; 1: Reduced; 2: Delayed; 3: Delayed and reduced; 4: permanent discontinuation; 5: other (specify): _____

CONCOMITANT MEDICATION *(medication took by the patient due to basal diseases or supportive clinical trial medication)*

CONCOMITANT MEDICATION (Brand name)	Daily dose	Route (IV, PO, SC...)	Onset Date	Ending date or Ongoing?	Prescription reason[3]

[3] Prescription reason: 1: Regular medication/baseline conditions; 2: Concomitant medication/prophylaxis; 3: Adverse Event; 4: other (specify)

CURRENT PREGNANCY STATUS AND OUTCOME

ONGOING □ Yes □ No (complete section) □ Unknown □ Lost to follow up: I_____I_____I_____I	Newborn birth date: I_____I_____I_____I (delivery date)
Induced abortion date: I_____I_____I_____I	Delivery mode: □ vaginal □ caesarian □ Unknown/others:
Spontaneous abortion date: I_____I_____I_____I	Gestational weeks at birth: I_____I
Ectopic pregnancy date: I_____I_____I_____I	Duration of delivery: _____ hours _____ minutes
Others date: I_____I_____I_____I	Has any prenatal testing been performed? □ YES (attach anonymized report) □ NO
PI date of awareness: I_____I_____I_____I	

PATIENT CODE	PROTOCOL CODE GECP 20/09 (BIMES)	PREGNANCY Form N°

NEWBORN BABY INFORMATION

(If multiple births complete this section for each enfant)

Number of babies: I_____I	Gender: □ Male □ Female		
Apgar 1 min_____ 5 min_____10 min_____	Weight (Kg):	Height (cm):	Head circumference (cm):
If any abnormality in the newborn appeared, then answer the following question: Are there any hints that these incidences may be related to the drug exposure of the mother/father during pregnancy? □ YES (complete SAE Form) □ NO	General status of the newborn baby (specify):		
Other relevant information about the delivery/ newborn:			

INFORMATION ABOUT THE STAFF WHO ATTENDED THE DELIVERY

GYNECOLOGIST:	PEDIATRICIAN:	OTHERS:

INFORMATION ABOUT THE SPONSOR AND THE PRINCIPAL INVESTIGATOR (PI) OF THE TRIAL

NAME AND CONTACT DETAILS OF THE SPONSOR	DATE RECEIVED AND SIGNATURE OF THE SPONSOR:	NAME AND CONTACT DETAILS OF THE PI:	DATE AND SIGNATURE OF THE PI:
Fundación GECP *Av. Meridiana, 358 6º pl* *08027 Barcelona* *Tel: (34) 93 430 20 06* *Fax: (34) 93 419 17 68*	I_____I_____I_____I		I_____I_____I_____I
PLEASE FAX THIS FORM TO THE Fundación GECP (SLCG/GECP): + 34 93 419 17 68 or EMAIL IT TO: *pharmacovigilance.slcg@gecp.org*			

T – Primary Tumour

T1	Tumour involving the ipsilateral parietal or visceral pleura only
T2	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • diaphragmatic muscle • pulmonary parenchyma
T3[1]	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • endothoracic fascia • mediastinal fat • chest wall, with or without associated rib destruction (solitary, resectable) • pericardium (non-transmural invasion)
T4[2]	Tumour involving ipsilateral pleura (parietal or visceral pleura) with invasion involving at least one of the following: • chest wall, with or without associated rib destruction (diffuse or multifocal, unresectable) • peritoneum (via direct transdiaphragmatic extension) • contralateral pleura • mediastinal organs (oesophagus, trachea, heart, great vessels) • vertebra, neuroforamen, spinal cord or brachial plexus • pericardium (transmural invasion with or without a pericardial effusion)

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, paraoesophageal, peridiaphragmatic, pericardial, intercostal and internal mammary nodes)
N2	Metastases to contralateral intrathoracic lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis present

[1]T3 describes locally advanced, but potentially resectable tumour.

[2]T4 describes locally advanced, technically unresectable tumour.

STAGE	T	N	M
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	N0, N1, N2	M0
IV	Any T	Any N	M1