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Official Title: "Phase II non-randomized study of atezolizumab (MPDL3280A) in combination with carboplatin plus pemetrexed in patients who are chemotherapy-naïve and have stage iv non-squamous non-small cell lung cancer with untreated brain metastases **(ATEZO-BRAIN)"**

NCT Number: NCT03526900

Document Dates: Summary of Protocol Amendment Version 3.1:

10 December 2020

"PHASE II NON-RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A) IN COMBINATION WITH CARBOPLATIN PLUS PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAÏVE AND HAVE STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER WITH UNTREATED BRAIN METASTASES (ATEZO-BRAIN)"

Study Sponsor: Fundación GECP
EudraCT Number: 2017-005154-11
Sponsor code: GECP 17/05
Roche code: ML40238
Version 3.1

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Protocol Signature Page
(Chairs)

"PHASE II NON-RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A) IN COMBINATION WITH CARBOPLATIN PLUS PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAÏVE AND HAVE STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER WITH UNTREATED BRAIN METASTASES (ATEZO-BRAIN)"

Sponsor code: GECP 17/05

Approved by:

Signature

_____
Dr. Ernest Nadal, Trial Chair

Signature

_____
[redacted]
Fundación GECP President

Principal Investigator Protocol Signature Page

Study Title: “Phase II non-randomized study of atezolizumab (mpdl3280a) in combination with carboplatin plus pemetrexed in patients who are chemotherapy-naïve and have stage IV non-squamous non-small cell lung cancer with untreated brain metastasis”
Sponsor protocol code: GECP 17/05
EudraCT Number: 2017-005154-11
Protocol version: v 3.1, 10/December/2020

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 GCP and will apply due diligence to avoid protocol deviations.

I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by 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 new Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator: _____

Institution’s name and place: _____

Signature Date

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PROTOCOL SYNOPSIS

TITLE:	**PHASE II NON-RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A) IN COMBINATION WITH CARBOPLATIN PLUS PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAÏVE AND HAVE STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER WITH UNTREATED BRAIN METASTASIS**
PROTOCOL NUMBER:	GECP 17/05 (ML40238)
VERSION NUMBER:	3.1
EUDRACT NUMBER:	**2017-005154-11**
TEST PRODUCT:	ATEZOLIZUMAB
PHASE:	II
INDICATION:	Advanced non-squamous non-small cell lung cancer (NSCLC)
SPONSOR:	Fundación GECP

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with carboplatin and pemetrexed in patients with untreated brain metastasis with advanced non-squamous non-small cell lung cancer (NSCLC).

Specific objectives and corresponding endpoints for the study are outlined below:

Primary Efficacy Objective
• To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM based on PFS according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively • To evaluate the safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM based on the NCI CTCAE v4.0
Secondary Efficacy Objective
• To evaluate the efficacy of atezolizumab combined with carboplatin and pemetrexed in patients with NSCLC and untreated BM by measuring objective response and duration of response (RANO in CNS and RECIST v1.1 out of CNS)
Exploratory Objectives
• To assess the neurocognitive function using validated neuropsychological tests at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression.. • To determine the time to neurological deterioration using the NANO scale at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression..

• To record the number of patients requiring an increase steroid dose for ≥96h to control neurologic symptoms • To determine the time to need for salvage therapy during the study (WBRT or SRS) • To determine the quality of life (QoL) measured using EORTC C30 and submodules LC13 and BN20, at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study (30 and 90 days) and/or at disease progression.
Exploratory Biomarker Objective
• To identify tumor biomarkers (e.g. PD-L1 expression) predictive of response to treatment • To identify neuroimaging markers (MRI) in that are predictive of intracranial response to systemic treatment by measuring changes in volumetric brain morphometry (voxel-based morphometry) and blood brain barrier disruption from baseline to week 12 and at progression or end of study • To identify radiomic neuroimaging markers (MRI) that are predictive of intracranial response to systemic treatment by radiomic analysis of baseline and early magnetic resonance images (MRIs)

Study Design

Description of Study

This is a multicenter, national, nonrandomized, phase II trial in subjects with nonsquamous NSCLC patients that have untreated BM. A pre-screening period using brain MRI for patients diagnosed with advanced non-squamous NSCLC EGFR/ALK wild type and ECOG PS 0-1 will be crucial to identify patients with untreated BM. Forty patients will be recruited. Atezolizumab will be administered intravenously (iv) at a dose of 1200 mg over 60 minutes on day 1 of each cycle. The subsequent cycles of atezolizumab can be administered over 30 minutes, if there were no infusion-related toxicities. Pemetrexed will be administered at a dose of 500 mg/m2 iv over 15 minutes on day 1 of each cycle. In addition, folic acid, vitamin B12, and dexamethasone 4mg bid will be administered one day before and after pemetrexed treatment. Carboplatin will be administered at a dose with an area under the curve of 5 over 30 minutes on day 1 of each cycle approximately 30 minutes after the end of the pemetrexed infusion. After completing 4 to 6 cycles of carboplatin plus pemetrexed and atezolizumab, patients will continue with pemetrexed in combination with atezolizumab until unacceptable toxicity, disease progression, patient/physician decision or completion of 2 years of therapy.

Tumor measurements by CT scan (systemic response) and brain MRI (intracranial response) will be performed every 6 weeks until the 12th week and thereafter every 9 weeks until disease progression. In case of brain progression, rescue with brain radiotherapy should be considered. In case of exclusive brain progression, patients are allowed to receive brain radiotherapy (WBRT or SRS) and then continue with study therapy if the patients maintain clinical benefit and appropriate performance status (ECOG PS≤2).Immunotherapy should be started no later than 4 weeks after completing radiation therapy (brain radiotherapy 2 weeks + 4 weeks of recovery from potential acute toxicity). In case of systemic progression without brain progression, a novel line of systemic treatment should be considered. Patients experiencing systemic progression and/or

brain progression will be followed and two post-progression visits will be performed at 30 and 90 days.

Response will be assessed independently in the brain and systemically: systemic response will be evaluated according to RECIST v1.1 and brain response according to the RANO response assessment criteria for BM (RANO-BM). Adverse events will be assessed throughout and assessed using the CTCAE version 4.03. EORTC quality of life questionnaire EORTC C30 and the submodules QLQ-LC13 and BN20 will be assessed in the ITT population at baseline, cycle 5 (week 12),cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. Periodic evaluations of the trial data will be conducted by an independent DMC to ensure subject safety and to evaluate the efficacy at the interim analyses.
Neurocognitive assessment including the standardized neuropsychological tests: Hopkins Verbal Learning Test (HVLT), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA) will be assessed at baseline cycle 5 (week 12),cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression.

Number of Patients

40 patients

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status (PS) of 0 to 1
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC; patients with mixed non-small cell histology (i.e. squamous and non-squamous) are eligible whether the major component appears to be non-squamous
- No prior treatment or Stage IV non-squamous NSCLC
    - Patients with a sensitizing mutation in EGFR gene are excluded given that EGFR TKIs are the appropriate front-line treatment for those patients
    - Patients with an ALK fusion are excluded given that ALK TKIs are the appropriate front-line treatment for those patients
    - Patients with unknown EGFR and ALK status require test results at screening, they can be assessed at a local or central laboratory
- Patients who received prior neo-adjuvant, adjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months since the last dose of chemotherapy and/or radiotherapy
- Asymptomatic or oligosymptomatic* (considered to have alterations in the neurological examination, whether or not they are noted in the anamnesis, that do not prevent

appropriate functioning according to the patients' basal state, or that disappear with medical treatment (corticosteroids, analgesics, anticonvulsants) untreated brain metastases.

*olygosymptomatic cases must be consulted with Trial Chair prior to patient enrollment

- Steroids treatment (dexamethasone) is allowed and patients that remained oligosymptomatic or asymptomatic for 2 weeks on steroids will be eligible when they were receiving ≤ 4mg dexamethasone once a day.
- Systemic measurable disease by computed tomography (CT) per response evaluation criteria in solid tumors version (RECIST) 1.1 criteria AND brain measurable disease by magnetic resonance imaging (MRI) per RANO-BM criteria (See Appendix 3: at least one measurable lesion and/or presence of non-measurable lesions)
- Availability of a formalin-fixed paraffin-embedded block (cell blocks will be accepted if tumor biopsy is not available) containing tumor tissue or 10 unstained slides.
- Adequate hematopoietic, hepatic and renal function:
    - ANC ≥ 1,500 cells/µL
    - Lymphocyte count ≥ 500 cells/µL
    - Platelet count ≥ 100,000 cells µL
    - Hemoglobin ≥ 9.0 g/dL (transfusion is allowed)
    - INR or aPTT ≤ 1.5 x upper limit of normal (ULN); patients receiving therapeutic anticoagulation should be on a stable dose
    - ALT, AST and/or alkaline phosphatase ≤ 2.5 x ULN, with the following exceptions:

      -patients with known liver metastasis: ALT and/or AST ≤ 5 x ULN

      -patients with known bone metastasis: alkaline phosphatase ≤ 5 x ULN
    - Serum bilirubin ≤ 1.5 x ULN; patients with known Gilbert disease who have serum bilirubin ≤ 3 x ULN may be recruited)
    - Calculated creatinine clearance (CRCL) ≥ 45 mL/min (based on the standard Cockcroft and Gault formula)
- For women of childbearing potential: agreement to remain abstinent or use contraceptive non-hormonal methods with a failure rate of < 1% per year during the treatment period and for 3 months after the last dose of study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization and copper intrauterine devices.
- For men: agreement to remain abstinent or use a condom, and agreement to refrain from donating sperm. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of other malignancy within 3 years* prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

  *less than 3 years cases can be consulted with trial chair

- Patients harboring an EGFR mutation or an ALK fusion will be excluded
- Leptomeningeal carcinomatosis or metastases in the brain stem, mid-brain, pons, medulla or lesions causing obstructive hydrocephalus
- Patients with neurological symptoms, including those receiving > 4mg of dexamethasone will not be eligible for this study
- Spinal or hemorrhagic metastases will be excluded
- Prior surgical resection of brain or spinal lesions in the prior 14 days
- Previous systemic treatment or neo-adjuvant or adjuvant chemotherapy less than 6 months before enrollment
- Clinically significant comorbidities that impaired administration of platinum-based chemotherapy
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone are eligible for this study
    - Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin are eligible for this study
    - Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g. patients with psoriasic arthritis would be excluded) are permitted provided that they meet the following conditions: rash covers less than 10% of body surface area, disease is well controlled at baseline and only requires low-potency topical steroids, no acute exacerbations during the last 12 months
- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis or active radiation pneumonitis out of the radiation field
- Previous treatment with immune checkpoint inhibitors or CD137 and OX-40 agonists
- Treatment with investigational therapy within 28 days prior to initiation of study drug
- Positive for hepatitis C virus (HCV) antibody or for hepatitis B surface antigen (HBsAg) at screening. Patients with past or resolved hepatitis B virus (HBV) infection (HBcAb positive with absence of HBsAg) would be eligible whether they are negative for HBV DNA. Patients positive for HCV antibody would be eligible whether they are negative for HCV RNA
- Active tuberculosis or HIV infection

- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.

Statistical Methods

The efficacy will be evaluated as PFS at 12 weeks and toxicity will be monitored simultaneously in a cohort of 40 patients using the Bayesian approach of Thall, Simon, Estey (Statistics in Medicine 1995; Journal of Clinical Oncology 1996) and further developed by Thall and Sung (Statistics in Medicine 1998). Toxicity is defined as appearance of a severe toxicity consisting of grade 3-4 treatment-related toxicity that impedes to pursue with the treatment or intracranial complications such a tumor bleeding or significant increase of oedema during the first 9 weeks of treatment. Historical data on similar patients showed a 12-weeks PFS rate of 40% (Barlesi et al. Ann Oncol 2011) and toxicity rate of 35% (phase Ib GP28328 study). This information was given an Effective Sample Size of 40 patients. Independence was assumed between efficacy and toxicity. It is expected for the current trial that Atezolizumab in combination with Pemetrexed and Carboplatin will improve the PFS at 12 weeks to 50% while the toxicity rate is maintained at 35% or below. A sample size of 40 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.257 at most, under the assumption of 50 % of PFS at 12 weeks. The probabilities of efficacy and toxicity for the historical data are modeled by beta distributions (Beta(14,26) and Beta(9,16), respectively). The prior probabilities of PFS rate at 12 weeks and toxicity for the experimental regimen are also modeled by beta distributions (Beta(0.4,0.6) and Beta(0.35,0.65), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1. Denoting the historical probabilities of overall response rate and toxicity rate by {p(PFS12W,H) , p(TOX,H)}, the following decision criteria will be applied:

Let E correspond to the experimental treatment, stop if
Prob{p(PFS12W,H) + δ_{PFS}12W > p(PFS12W,E) | data} > 0.95, where δPFS12W =0.15*
Stop if Prob{p(TOX,H) + δ_{TOX} < p(TOX,E)| data}>0.95, where δTOX =0

It is expected that approximately the 10% of the patients initially enrolled should be discarded because they do not meet the inclusion criteria; so that in order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, it will be replaced by a new subject that fulfil them, this replacement will ensure that the sample size will be the one calculated initially.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
BM	Brain metastases
CBDCA	Carboplatin
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LPLV	Last patient, last visit
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PRO	Patient-reported outcome
PFS	Progression-free survival
PS	Performance status
ULN	Upper limit of normal

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2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated brain metastases. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1. Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM	• PFS after enrollment defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause whichever occurs first as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively
• To evaluate the safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and untreated BM	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 criteria • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab combined with carboplatin and pemetrexed in patients with NSCLC and untreated BM	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RANO

	and RECIST v1.1. criteria for brain and systemic disease respectively • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively • OS after enrollment defined as the time from enrollment to death from any cause
Exploratory Objectives	**Corresponding Endpoints**
• To assess the neurocognitive function	• Change from baseline in the following standardized neuropsychological tests: Hopkins Verbal Learning Test (HVLT), Trail Making Test (TMT), Rey–Osterrieth complex figure test (ROCF) and Controlled Oral Word Association Test (COWA) at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression.
• To determine the time to neurological deterioration and to record the number of patients requiring an increase steroid dose for ≥96h to control neurologic symptoms.	• Neurological deterioration from baseline will be determined using the NANO scale at baseline, cycle 5 (week 12), cycle 8 (week 21), at end of study treatment (30 and 90 days) and/or at disease progression. Increase in the steroid use for ≥96h will be recorded in the database.
• To determine the time to need for salvage therapy during the study	• Defined by the median time to brain radiotherapy (WBRT or SRS)
• To determine the quality of life (QoL).	• Change from baseline in HRQol, as assessed through use of the EORTC C30 and submodules LC13 BN20 at baseline, at week 12 (cycle 5), week 21 (cycle 8), and at the end of study treatment (30 and 90 days) and/or at progression
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers that are predictive of response to treatment	• Relationship between PD-L1 expression by 22C3 DAKO in tumor tissue (listed in Section 4.5) and efficacy endpoints
• To identify neuroimaging markers (MRI) in that are predictive of intracranial response to systemic treatment	• Changes in volumetric brain morphometry (voxel-based morphometry) and blood brain barrier disruption from baseline to week 12 and at progression or end of study
• To identify radiomic neuroimaging markers (MRI) that are predictive of intracranial response to systemic treatment (ICIs plus chemotherapy).	• Radiomic analysis of baseline and early magnetic resonance images (MRIs) (MRI corresponding to cycle 5 of systemic treatment or if the last one is not available, corresponding to cycle 3)

HRQol=health-related quality of life.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a non-randomized, Phase II, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with carboplatin + pemetrexed in patients who are chemotherapy naïve and have Stage IV non-squamous NSCLC with untreated brain metastases. Figure 1 presents an overview of the study design. A schedule of activities is provided in **Appendix 1**.

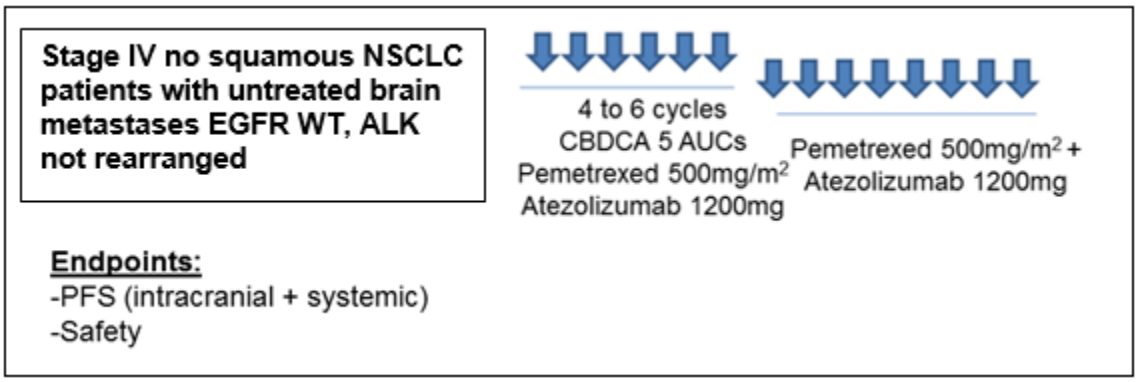

Figure 1. Study Schema

Eligible patients will be registered and will receive the following treatment regimen:

Induction (four or six 21-day cycles)	Maintenance (21-day cycles)
Atezolizumab 1200 mg/iv + carboplatin 5 AUCs + pemetrexed 500mg/m^2	Atezolizumab 1200mg/iv + pemetrexed 500 mg/m^2

The number of cycles of induction treatment (four or six) will be at the discretion of the investigator and will be determined and documented prior to enrollment. Induction treatment will be administered on a 21-day (+/- 3 days) cycles until the following occurs (whichever occurs first): 1) administration of 4 or 6 cycles, 2) unacceptable toxicity, or 3) documented disease progression. Following the induction phase, patients who have not experienced disease progression or unacceptable toxicity will continue treatment with maintenance therapy.

Response will be assessed independently in the brain and systemically: systemic response will be evaluated according to RECIST v1.1 and brain response according to the RANO response assessment criteria for BM (RANO-BM). PFS event will be possible based on three potential clinical scenarios due to the dual component of the PFS endpoint:

CNS (RANO-BM)	Non-CNS (RECIST 1.1.)	PFS event	Note
CR, PR or SD	Progressive disease	Yes	Log as non-CNS progressive disease
Progressive disease	CR, PR or SD		Log as CNS progressive disease
Progressive disease	Progressive disease		Log as both non-CNS and CNS progressive disease

CR: complete response; PR: partial response; SD: stable disease.

Patients will undergo tumor assessments (body CT scan and brain MRI) at baseline every 6 weeks for the first 12 weeks following Cycle 1, Day 1, regardless of dose delays and thereafter tumor assessments will be performed every 9 weeks until disease progression or loss of clinical benefit (for atezolizumab-treated only patients who continue treatment beyond radiographic disease progression), withdrawal of consent, study termination by Sponsor or death, whichever occurs first.

During induction or maintenance treatment, treatment with chemotherapy should be discontinued in all patients who exhibit evidence of progressive disease. Atezolizumab administration may continue beyond progressive disease in case they have clinical benefit as assessed by the investigator as described below:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

In case of brain progression according to RANO-BM criteria (Appendix 3), rescue with brain radiotherapy should be considered. In case of exclusive brain progression, patients are allowed to receive brain radiotherapy (WBRT or SRS) and then continue with atezolizumab if the patients maintain clinical benefit and appropriate performance status (ECOG PS≤1) and can start immunotherapy not later than 4 weeks after completing radiation therapy (brain radiotherapy 2 weeks + 4 weeks of recovery from potential acute toxicity). In case of systemic progression by RECIST v1.1 without brain progression, a novel line of systemic treatment should be considered but patients should follow brain radiographic assessments to document the CNS disease progression.

Patients who discontinue study treatment for reasons other than radiographic disease progression (e.g. toxicity) will continue scheduled tumor assessments until disease progression of loss of clinical benefit (for atezolizumab-treated only patients who continue treatment beyond radiographic disease progression), withdrawal of consent, study termination by Sponsor or death, whichever occurs first.

Secondary endpoints are investigator-assessed CNS and non-CNS or systemic response rate (RR) based on RANO-BM criteria and RECIST v1.1 criteria respectively, time to need for salvage therapy defined as the time from enrollment to the time of brain radiotherapy and landmark OS analysis at 6, 12 and 18 months. Exploratory endpoints are duration of response of brain metastases, the assessment of neurocognitive function, progression-free to neurological deterioration and quality of life. Additionally, several neuroimaging markers will be assessed in the baseline MRI to predict response to systemic therapy.

This study will initially enroll 40 patients across all sites.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient whichever occurs later. The end of the study is expected to occur 18 months after the last patient is enrolled. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years. In addition, the Sponsor may decide to terminate the study at any time.

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4.3.2.1 Atezolizumab

Patients will receive 1200 mg of atezolizumab administered by IV infusion every 21 days (+/- 3 days) in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.1.5.2. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

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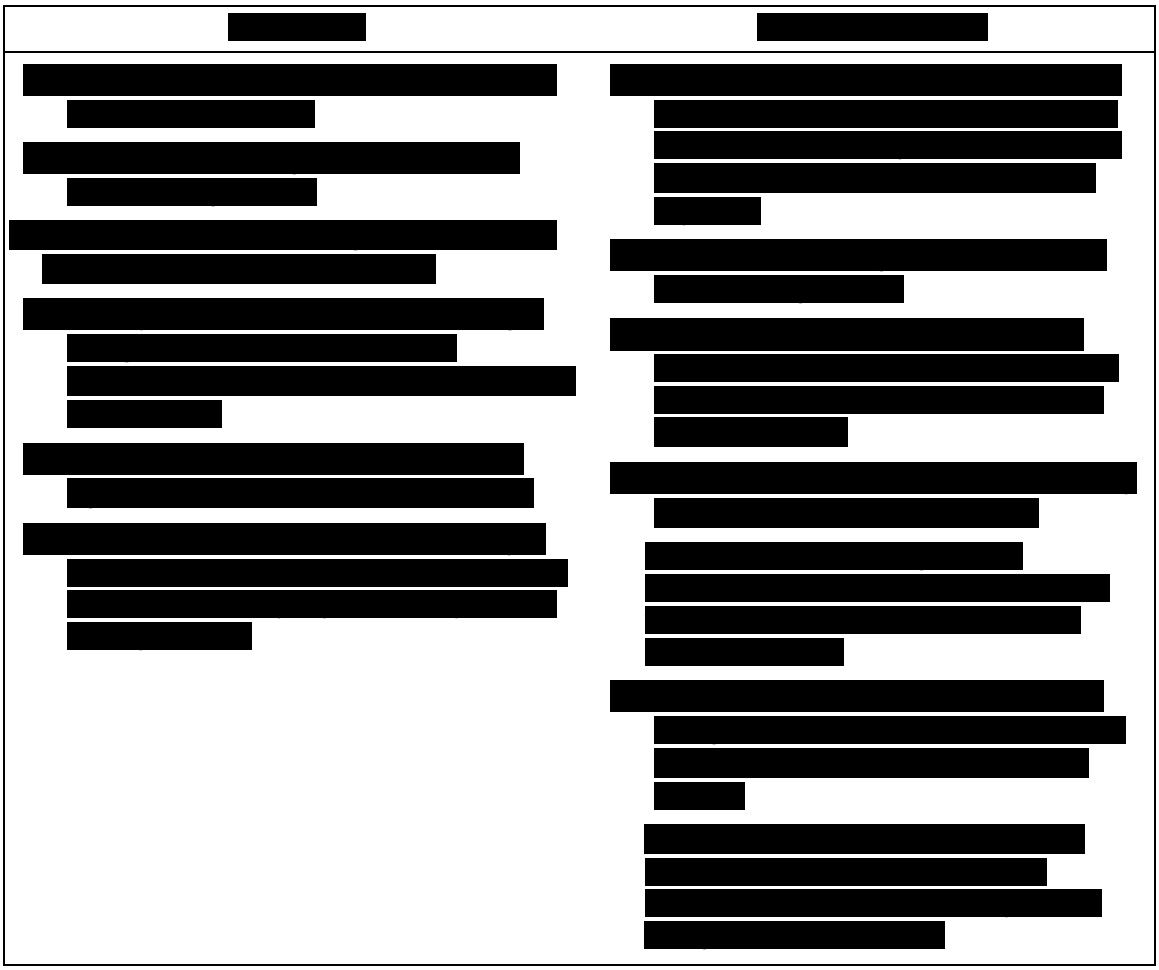

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4.3.2.2 Pemetrexed+Carboplatin

4.3.2.2.1 Pemetrexed

Institutions should follow their standard administration procedures for pemetrexed. The premedication doses administered should be in compliance with the prescribing information. All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-inflammatory drugs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

4.3.2.2.2 Carboplatin

Carboplatin should be administered 30 minutes after completion of pemetrexed administration by IV infusion over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the CRCL.The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CRCL} = \frac{(140 - \text{age})\ (\text{weight})}{72 \times \text{Scr}}\ (\times 0.85 \text{ if female})$$

Where: CRCL = creatinine clearance in mL/min; age = patient's age in years; weight = patient's weight in kg; Scr = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate the GFR through use of a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the U.S. Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg • min/mL) × (GFR + 25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg.
For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg.

4.3.3 Investigational Medicinal Product Accountability

The investigational medicinal product for this study is atezolizumab.. Pemetrexed and Carboplatin are considered non−investigational medicinal product (NIMP). The study site will acknowledge receipt of the IMPs to confirm shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor or designee with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT THERAPY

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 eCRF.

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4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in **Appendix 1**.

Patients will be closely monitored for safety and tolerability throughout the study. All activities must be performed and documented for each patient. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

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5. ASSESSMENT OF SAFETY

Atezolizumab has been approved by the European Medicine Agency (EMA) for the treatment of locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and for the treatment of locally-advanced or metastatic NSCLC after prior chemotherapy. Human experience is still limited, and the entire safety profile is not known at this time. The safety plan for patients in this study is based on clinical experience

with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined below. Please refer to the atezolizumab Investigator's Brochure for a complete summary of safety information.

5.1 SAFETY PLAN

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo close safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All serious adverse events and adverse events of special interest will be recorded during the study and for up to 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events will be recorded during the study and for up to 30 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 *Risks Associated with Atezolizumab*

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events (ir-AE), specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, pneumonitis, myositis, and myasthenia gravis, have been observed in the Phase Ia study PCD4989g. For further details regarding clinical safety, including a detailed description of the anticipated safety risks for atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup and management guidelines procedures for suspected immune-mediated adverse events are provided in the Atezolizumab Investigator's Brochure.

5.1.2 Risks Associated with Pemetrexed Administration

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, edema and rash. For more details regarding the safety profile of pemetrexed, see the prescribing information for pemetrexed.

5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events. For more details regarding the safety profile of carboplatin, refer to the prescribing information for carboplatin.

5.1.4 General Plan to Manage Safety Concerns

5.1.4.1 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1.. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest will be reported in an expedited fashion (see Section 5.4.2). Patients will be followed for serious adverse events and adverse events of special interest for 90 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. For all other adverse events, patients will be followed for 30 days after their last dose of study drug or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

5.1.5 Dose Modification

5.1.5.1 General Notes Regarding Dose Modification

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v4.0 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment i.e., atezolizumab, carboplatin and/or pemetrexed (if applicable) and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab, carboplatin and/or pemetrexed (if applicable), the treatment cycles will be restarted such that the atezolizumab (if applicable) infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a specific toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.
- The investigator may use discretion in modifying or accelerating the dose modification guidelines described below 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.

Refer to the Atezolizumab Investigator's Brochure for more detailed information regarding dose modification.

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5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious and non-serious adverse events, and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.2.2.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), 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 as described in Section 5.3.4.9
- 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)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is *fatal* (i.e., the adverse event actually causes or leads to death)
- Is *life threatening* (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.4.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.2; the event itself may be of relatively minor medical significance (such as severe

headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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5.2.4 Infusion-Related Reactions

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 possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction 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, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.2.2 and 5.2.3..

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity and causality (see Section 5.3.2 and 5.3.3)

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. 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 (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug will be reported until 90 days after the last dose of study drug or initiation of non-protocol systemic anti-cancer therapy, after the last dose of study treatment whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered to be related to study treatment regardless of time after study (see Section 5.2.3).

5.3.2 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 10 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 10 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b, c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.1. [d] Grade 4 *and 5* events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.1.

5.3.3 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.4 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.4.1 Diagnosis versus Signs and Symptoms

For *all* adverse events, a diagnosis (if known) *rather than individual signs and symptoms* should be recorded on the Adverse Event eCRF (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.4.2 Adverse Events that are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example: If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF. If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.4.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.4.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. 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

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.4.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. 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

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

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.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.4.6 Abnormal Liver Function Tests

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.4.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. 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.

During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.3.4.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.4.9 Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the NSCLC should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.4.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2 except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.4.11 Adverse Events Associated with an Overdose or Error in Drug Administration

Study overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded in the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.4.12 Clinical-Reported Outcome Data

Adverse event reports will not be derived from clinPRO data, and safety analyses will not be performed using clinPRO data. However, if any clinPRO responses suggestive of a possible adverse event are identified during site review of the clinPRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Please, see contact information page 2.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study treatment or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurs first.

Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.5.3.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study, within 5 months after the last dose of atezolizumab, or within 6 months after the last dose of cisplatin. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to the Sponsor. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. 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) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to the sponsor that will send immediately to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Atezolizumab is not expected to be genotoxic. In addition, the anticipated concentrations of atezolizumab in seminal fluid as well as the potential risk to the developing conceptus is low following seminal transfer of atezolizumab to a female partner.

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.5.3 Post-Study Adverse Events

Investigators are instructed to report all serious adverse events or adverse events of special interest that occur after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug for adverse events and 90 days after the last dose of study drug for serious adverse events and adverse events of special interest or initiation of new systemic anti-cancer therapy after the last dose of study treatment , whichever occurs first), if the event is believed to be related to prior study drug treatment, regardless of time after study.

The investigator should report these events directly to the Sponsor, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Prescribing information for each chemotherapy agent (cisplatin, carboplatin and pemetrexed)

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document. Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Three populations will be considered for different analyses:

- **Per protocol population (PP):** Per protocol population will consider patients that will receive a minimum of two cycles of atezolizumab, pemetrexed and carboplatin (whichever dose will be received) that have a 12-weeks tumor response evaluation. Patients without any radiological evaluation who may die during the first 12 weeks will also be considered PP population. Patients without 12 weeks tumor evaluation but with a progression disease at 6 weeks will also be considered into PP population. A patient without radiological evaluations at 6 weeks and at 12 weeks but alive at 12 weeks will be replaced by another patient with these evaluations available.
- **Intention to treat analysis (ITT):** Intention to treat analysis will include all patients that will be registered into the clinical trial.
- **Safety population (SFP):** Safety population will include all patients that will be exposed to study treatment (atezolizumab), whatever will be the quantity received.

Efficacy endpoints will be evaluated mainly per protocol population (PP) since this is an early phase II clinical trial. Decisions about continuing to phase III clinical trial will be made based upon PP population. Efficacy analysis will be also conducted with ITT population but only as a measure of sensitivity. Safety endpoints will be assessed using SF population. A patient with missing information about efficacy will be replaced for PP population, but never for SF if fulfills SFP population definition.

This is sequential clinical trial with two stopping rules for efficacy and toxicity and with a maximum sample size of 40 patients. These rules will be calculated in each interim analysis and recruitment will be stopped if any of these were achieved.

The efficacy will be evaluated as PFS at 12 weeks and toxicity will be monitored simultaneously in a cohort of 40 patients using the Bayesian approach of Thall, Simon and Estey and further developed by Thall and Sung (43–45). Toxicity is defined as appearance of a severe toxicity consisting of grade 3-4 treatment-related toxicity that impedes to continue with the treatment or intracranial complications such a tumor bleeding or significant increase of oedema during the first 9 weeks of treatment. Historical data on similar patients showed a 12-weeks PFS rate of 40% with platinum and pemetrexed (10) and toxicity rate of 35% (phase Ib GP28328 study). This information was given an Effective Sample Size of 40 patients. Independence was assumed between efficacy and toxicity. It is expected for the current trial that atezolizumab in combination with Pemetrexed and Carboplatin will improve the PFS at 12 weeks to 50% while the treatment-related grade 3-4 toxicity will remain at 35% or below. The probabilities of efficacy and toxicity for the historical data are modeled by beta distributions (Beta(14,26) and Beta(9,16), respectively). The prior probabilities of PFS rate at 12 weeks and toxicity for the experimental regimen were also modeled by beta distributions (Beta(0.4,0.6) and Beta(0.35,0.65), respectively), which have the same means as the corresponding beta distributions for the historical data, and an Effective Sample Size of 1.

6.1 DETERMINATION OF SAMPLE SIZE

A maximum sample size of 40 patients [redacted]

[redacted]

It is expected that approximately the 10% of the patients initially enrolled should be discarded be-cause they do not meet the inclusion criteria; so that in order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, it will be replaced by a new subject that fulfil them, this replacement will ensure that the sample size will be the one calculated initially.

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6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who will be enrolled, discontinued, or completed the study will be summarized. A frequency table with patients with inclusion-exclusion criteria not met, patients with tumor evaluations at 12 weeks available, number of cycles with full dose and dose modifications will be performed. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY AND PATIENTS' CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, primary tumor status (controlled or not), histology, tumor affected sites (other than NCS), Performance status, EGFR status, ALK status, Steroid levels) will be summarized using means, standard deviations, medians and ranges for continuous variables and proportion for categorical variables, as appropriate.

6.4 EFFICACY ANALYSES

To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and asymptomatic BM three endpoints will be used: PFS rate at 12 weeks, PFS estimation, objective response, duration of overall response and overall survival estimation.

6.4.1 Primary Efficacy Endpoint

Rate of PFS at 12 weeks after enrollment defined as the rate of patients free of disease progression (intracranial or systemic) or death from any cause whichever occurs first at 12 weeks as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

[redacted]

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-free survival (PFS)

PFS after enrollment defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause whichever occurs first as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

[redacted]

6.4.2.2 Objective response rate (ORR)

Objective response defined as a complete response or partial response on two consecutive evaluations 6 weeks apart, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

[redacted]

6.4.2.3 Duration of overall response (DoR)

Duration of response defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

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6.5 SAFETY ANALYSES

The safety analysis population will include all patient patients who received at least one dose of study drug. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to **NCI CTCAE v4.0.**

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7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. The Sponsor of the study will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the data management and monitoring team of the sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. Patient and clinical reported outcomes (PROs and ClinROs) will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. . All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee. .

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data. Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinrRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 25 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with

each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures as the translational research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The sponsor is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. The sponsor is also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

Investigators must comply with requirements for reporting serious adverse events to the Sponsor, and the sponsor must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, 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 (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 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.

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by the Fundación GECP and funded by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 10 sites globally will participate to enroll 40 patients. Enrollment will occur through the eCRF of the study.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected as tumor response and progression will be evaluated by and Independent Review Committee (IRC), a copy of brain MRIs and body CTs will be requested.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

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).

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EQ-5D questionnaire references:

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Appendix 1-Schedule of Activities (cont.)

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EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. **Table 1** provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, **Table 2** is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

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[3] *Lin N, Lee EQ, Aoyama H et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 2015; 16 (6): e270-e278.*

[redacted]

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Response
Complete response, partial response, or stable disease	Complete response, partial response, or stable disease	Log as CNS and non-CNS complete response, partial response, or stable diseases
Complete response, partial response, or stable disease	Progressive disease	Log as CNS complete response, partial response, or stable disease; log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as CNS progressive disease; log as non-CNS complete response, partial response, or stable disease
Progressive disease	Progressive disease	Log as both CNS and non-CNS progressive disease

Table 3: CNS and non-CNS response assessment

CNS (RANO-BM)	Non-CNS (RECIST 1·1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a progression-free survival event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a progression-free survival event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a progression-free survival event	Log as both CNS and non-CNS progressive disease

Table 4: Bi-compartmental progression-free survival

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 2: Summary of the response criteria for CNS metastases proposed by RANO-BM

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Table 4.

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