GFPC 06-2018 TRIAL

A multicentre phase II, open-label, non-randomized study evaluating Platinum-Pemetrexed-Atezolizumab (± Bevacizumab) for patients with stage IIIB/IV non-squamous non-small cell lung cancer with EGFR mutations, ALK rearrangement or ROS1 fusion progressing after Targeted therapies

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This trial is granted by Roche S.A.S that is not involved in the design and conduct of the study, nor in the collection, management, analysis and interpretation of the data.

REGLEMENTARY CLASSIFICATION OF THE TRIAL:
Recherche interventionnelle portant sur la personne humaine de catégorie 1 (RIPH 1)

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Alanine aminotransférase
ALK	Anaplastic Lymphoma Kinase
ASAT	Aspartate aminotransférase
ASCO	American Society of Clinical Oncology
aPTT	Activated Partial Thromboplastin Time
ANC	Absolute Neutrophil Count
AUC	Area Under the concentration-time Curve
BSC	Best Supportive Care
CBC	Complete blood count
CI	Confidence Interval
CNS	Central Nervous System
CPP	Committee for the Protection of Person
CR	Complete Response
CRC	ColoRectal Cancer
CRCL	Creatinine clearance
CRP	C-reactive protein
CT	Computed Tomography
ctDNA	Circulating-tumor DNA
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
DCF	Data Clarification Form
DCR	Disease Control Rate
DLTs	Dose-Limiting Toxicities
DNA	Deoxyribonucleic acid
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFPC	Groupe Français de Pneumo-Cancérologie
GFR	Glomerular Filtration Rate
GI	Gastro-Intestinal
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen

HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HR	Hazard Ratio
IC	Immune Cells
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IM	IntraMuscular
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-treat
IV	Intravenous
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
NSCLC	Non−small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PAD	Pression Artérielle Diastolique
PAS	Pression Artérielle Systolique
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PO	Per os
PQ	Platelets
PR	Partial Response
PS	Performance Status
PUVA	Psoralen plus Ultraviolet A Radiation
Q3W	Every 3 weeks
QLQ C30	Quality-of-Life Questionnaire Core 30
QLQ-LC13	QLQ-LC13 Quality-of-Life Questionnaire Lung Cancer Module
qRT-PCR	Quantitative Reverse Transcriptase-Polymerase Chain Reaction
RCC	Renal Cell Carcinoma
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors

RIPH1	Recherche Interventionnelle portant sur la Personne Humaine de catégorie 1
SAE	Serious Adverse Event
Scr	Serum Creatinine
STAT3	Signal Transducer and Activator of Transcription 3
SmPC	Summary of Product Characteristics
TC	Tumour Cells
TEs	Thromboembolic Events
TKI	Tyrosine Kinase Inhibitor
TMB	Tumor Mutation Burden
TNF	Tumor Necrosis Factor
TTD	Time To Deterioration
TTP	Time To Progression
TTF-1	Thyroid transcription factor−1
UBC	Urothelial Bladder Cancer
ULN	Upper Limit of Normal
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell
WCLC	World Conference on Lung Cancer

2 SYNOPSIS

TITLE	**A multicenter phase II, open-label, non-randomized study evaluating Platinum-Pemetrexed-Atezolizumab (± Bevacizumab) for patients with stage IIIB/IV non-squamous non-small cell lung cancer with EGFR mutations, ALK rearrangement or ROS1 fusion progressing after targeted therapies**
ACRONYM	**GFPC 06-2018**
Coordinators	**Dr Olivier BYLICKI and Dr Radj GERVAIS**
Indication	[**Lung Cancer, NSCLC**]
Design	French open-label, multicentre, non-randomized two parallel cohorts phase II study
Objectives	**Main objective** To assess the efficacy of the combination of Platinum (carboplatin or cisplatin), Pemetrexed, Atezolizumab ± Bevacizumab if eligible, in stage IIIB/IV non-squamous non-small cell lung cancer patients with progression-enhancing mutations following targeted therapies. Efficacy will be defined as the objective response rate (ORR) after 4 cycles of treatment. Two distinct cohorts will be considered as follows since they will allow bringing separate information: ● **Cohort with Bevacizumab** It will provide additional data to the Impower 150 study but with reference chemotherapy in patients with "adenocarcinoma" as a tumor type. The obtained findings could also be used to analyse the data of the erlotinib / bevacizumab combination (Seto T., Lancet Oncol, 2014) and thus better define the place of bevacizumab in patients with EGFR mutation. ● **Cohort without Bevacizumab** It will provide data on the combination Pemetrexed / Atezolizumab in patients with mutation. There are numerous studies (Keynote 021, 189, Impower 132) that evaluate on the efficacy of this combination in NSCLC patients but not in patients with EGFR / ALK mutations. NCCN and that of the regional network "Rhônes-Alpes-Auvergne" recommendations place this association in first place in case of chemotherapy in front of other associations (such as carboplatin / paclitaxel, rather to reserve it to patients with PS> 2 or over 70 years). **Secondary objectives** To assess in each cohort ● The progression-free survival (PFS) ● The duration of response (DOR) ● The time to deterioration (TTD) ● The change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnoea, and cough) scores ● The ORR according to immune RECIST (iRECIST) criteria ● The overall survival (OS) ● The OS rate at 1 and 2 years ● The tolerance profile of the combination in the induction phase and the maintenance phase of treatment

	❖ Creation of a biological collection for ancillary analysis (To look at the correlation between PD-L1 expression levels, Tumor Mutation Burden (TMB) expression and antitumor activity).
Judgement criteria	**Main criterion** Objective response rate (ORR), defined as the proportion of patients who achieved an objective response after 4 cycles of induction (or before progression). Objective response will be considered in case of radiologically confirmed complete (CR) or partial response (PR) according to RECIST v1.1 criteria (Response Evaluation Criteria in Solid Tumors version 1.1) assessed by masked, independent central review. **Secondary criteria** ● Progression-free survival, defined as the time relapsed between inclusion and disease progression (according to RECIST v1.1 criteria as assessed by the investigator) or death from any cause, whichever occurs first ● Duration of response assessed in patients who had an objective response as determined by the investigator using RECIST v1.1 and defined as the time interval from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first ● Time to deterioration in lung-related symptoms, defined as the time from inclusion to the time the patient's score on the EORTC QLQ C30 or QLQ-LC13 shows a ≥10-point increase above baseline in each of the following EORTC-transformed scores for cough, dyspnea (single item), dyspnea (multi-item subscale) and chest pain. ● Objective response rate according to immune (i)RECIST criteria defined similarly as ORR, with the exception that immune RECIST criteria 2017 are used instead of RECIST v 1.1 ● Overall survival, defined as the time between the date of inclusion and death from any cause ● Toxicities occurring during either the induction or maintenance treatment in terms of kind, grade, time of onset, reversibility, according to NCI-CTCAE v5.0 criteria
Inclusion criteria	● Patient older than 18 years ● Subject affiliated to an appropriate social security system ● Signed informed consent before any trial related activities and according to local guidelines ● ECOG performance status of 0 or 1 ● Histologically or cytologically confirmed, stage IIIB/IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition). ● Patient with a sensitizing mutation in the EGFR gene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR TKIs, such as erlotinib, gefitinib, osimertinib or another EGFR TKI appropriate for the treatment of EGFR-mutant NSCLC. Patients with stage IIIB had to be not operable (that means not eligible for radiochemotherapy followed by a maintenance treatment by Durvalumab) ● Patient with an ALK fusion oncogene (confirmed in local laboratory) must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK inhibitors (i.e., crizotinib, alectinib, ceritinib) appropriate for the treatment of NSCLC in patients having an ALK fusion oncogene ● Patient with a ROS1 fusion oncogene (confirmed in local laboratory) must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ROS inhibitors (i.e., crizotinib,) appropriate for the treatment of NSCLC in patients having an ROS1 fusion oncogene

	● No prior chemotherapy treatment for Stage IV non-squamous NSCLC except if less than 3 cycles, with treatment free-interval of at least 1 year from C1 since last chemotherapy ● Patient who has received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from C1since the last chemotherapy, radiotherapy, or chemoradiotherapy ● Patient with an history of asymptomatic CNS metastases is eligible, provided he meets all of the following criteria: ▪ *Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)* ▪ *No ongoing requirement for corticosteroids as therapy for CNS disease* ▪ *No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to C1* ● Measurable disease, as defined by RECIST v1.1 ● Adequate hematologic and end-organ function, defined by the following laboratory ▪ *ANC > 1500* /mm^3 *without granulocyte colony-stimulating factor support* ▪ *Platelet count > 100,000*/mm^3 *without transfusion* ▪ *Hemoglobin ≥ 9.0 g/dL. Patients may be transfused to meet this criterion.* ▪ *INR or aPTT ≤ 1.5 , upper limit of normal (ULN)* *This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be receiving a stable dose.* ▪ *ASAT, ALAT, and alkaline phosphatase ≤ 2.5xULN, with the following exceptions:* *Patients with documented liver metastases: ASAT and/or ALAT ≤ 5 x ULN* *Patients with documented liver or bone metastases: alkaline phosphatase < 5xULN* ▪ *Serum bilirubin ≤1.5xULN* *Patients with known Gilbert disease who have serum bilirubin level ≤ 3xULN may be enrolled.* *Patients with documented liver metastases: Serum bilirubin < 3xULN* ▪ *Calculated creatinine clearance (CRCL) ≥ 45 mL/min or, if using cisplatin, calculated CRCL must be ≥ 60 mL/min using the Cockcroft-Gault Method* ● Adequate method of contraception during the treatment period and at least 5 months after the last dose of atezolizumab or 6 months after the last dose of chemotherapy ▪ *For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year.* ▪ *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 established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.* ▪ *The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.*

	▪ *For men, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:* ▪ *With partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.* ▪ *With pregnant partners, men must remain abstinent or use a condom during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.* ▪ *The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.*
Non-inclusion criteria	❖ **<u>Cancer-specific exclusions</u>** ● Active CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments ● Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to C1 ● Leptomeningeal disease (Presence of cancer cells in cerebral CSF or MRI with leptomeningeal lesion strongly suspected of leptomeningeal disease) ● Uncontrolled tumour-related pain ▪ *Patients requiring pain medication must be receiving a stable regimen at study entry.* ▪ *Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to C1. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.* ▪ *Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to C1.* ● Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently); Patients with indwelling catheters (e.g., PleurX®) are allowed. ● Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium > ULN) ● Malignancies other than NSCLC within 5 years prior to C1, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent) ❖ **<u>General medical exclusions</u>** ● Women who are pregnant, lactating, or intending to become pregnant during the study ● History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins ● Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation

	● 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's 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 regimen are eligible for this study* ▪ *Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:* - Rash must cover less than 10% of body surface area (BSA). - Well controlled disease at baseline only requiring low potency topical steroids. - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids) ● History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan; History of radiation pneumonitis in the radiation field (fibrosis) is permitted. ● Positive test for HIV. All patients will be tested for HIV prior to C1 into the study; patients who test positive for HIV will be excluded from the study. ● Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA. Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA. ● Active tuberculosis ● Severe infections within 4 weeks prior to C1, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia ● Received therapeutic oral or IV antibiotics within 1 week prior to C1; Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible. ● Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to inclusion, unstable arrhythmias, or unstable angina ● Major surgical procedure other than for diagnosis within 28 days prior to C1 or anticipation of need for a major surgical procedure during the course of the study ● Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications ● Symptomatic brain metastases; ● Patients with illnesses or conditions that interfere with their capacity to understand, follow and/or comply with study procedures ● Concurrent participation in any therapeutic clinical trial ● Patient deprived of liberty or placed under the authority of a tutor ● Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

❖ **Exclusion criteria related to medications**

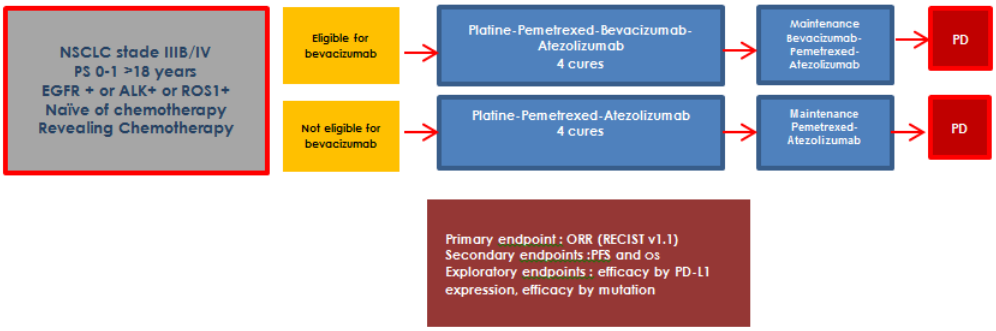
- Any approved anti-cancer therapy, including hormonal therapy within 7 days prior to C1 of study treatment.
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to C1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies
  - *Patients who have had prior anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:*
  - *Last dose of anti-CTLA-4 at least 6 weeks prior to C1*
  - *No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3/4)*
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin 2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to C1; Prior treatment with cancer vaccines is allowed.
- Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to C1Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study. The use of corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

❖ **Exclusion criteria related to chemotherapy**

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v5.0 (cisplatin)
- CRCL < 60 mL/min for cisplatin or < 45 mL/min for carboplatin using the Cockcroft-Gault Method

❖ **Exclusion criteria related to Bevacizumab**

- Medically uncontrolled hypertension (defined as PAS>150 and/or PAD >100 mmHg)
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Clinically significant cardiovascular disease (within 6 months prior to C1) that is uncontrolled by medication or may interfere with administration of trial treatment:
  - Aortic aneurysm requiring surgical repair
  - Recent arterial thrombosis
  - Haemoptysis (>one-half teaspoon of bright red blood per episode (within one months prior to C1) (grade 2 haemoptysis)
- History of documented haemorrhagic diathesis or coagulopathy
- History of abdominal or tracheosphageal fistula or perforation within 6 months prior to C1
- Core biopsy or other minor surgical procedure within 7 days before bevacizumab
- Clinical signs or gastrointestinal obstruction or requirement for routine parenteral hydration, nutrition or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Major surgery within 28 days before C1

	● Serious, non-healing wound, active ulcer or untreated bone fracture ● Proteinuria >1g/24h urine collection ● All patient with >2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤1g of protein in 24 hours. ● Known sensitivity to any component of bevacizumab ● Radiation therapy within 21 days before C1 (except Symptomatic lesions amenable to palliative radiotherapy) ● Adequate hematologic, liver, and renal function required (including creatinine clearance 45 mL/min at baseline and 45 mL/min before the start of any subsequent cycle using the Cockcroft-Gault Method.
Experimental Plan	 **Methodology** Parallel non-randomized two-arm phase II trial on French centres evaluating Platinum-Pemetrexed-Atezolizumab ± Bevacizumab if eligible with progression-enhancing mutations following targeted therapies for stage IIIB/IV non-squamous non-small cell lung cancer. **Target population** ❖ NSCLC stage IIIB/IV ❖ EGFR + ❖ ALK or ROS 1+ ❖ Progressing under first generation TKI (Gefitinib, Erlotinib), 2nd generation (Afatinib), 3rd generation (Osimertinib) ❖ Progression under anti-ALK (Crizotinib, Ceretinib, Alectinib) ❖ Progression under anti-ROS1 (Crizotinib) ❖ Naïve of systemic chemotherapy for metastatic disease or no prior chemotherapy treatment for Stage IV non-squamous NSCLC except if less than 3 cycles, with treatment free-interval of at least 1 year from C1 since last chemotherapy ❖ Revealing Chemotherapy (Patient who progresses on targeted therapy and who can no longer receive another targeted therapy (no resistance mutation or TKI depletion for example) and who must therefore be treated with chemotherapy.

Treatment

Treatment will be initiated within 28 days after completion of baseline assessment prior to C1.

- <u>*Cohort with Bevacizumab*</u>

  4 cycles of induction every 3 weeks with:

❖ Carboplatin area under curve 6 mg/mL per minute per IV route or Cisplatin 75 mg/m² per IV route. It will be possible to start the first treatment cycle with an AUC 5 for patient who met the inclusion criteria but have a poorer blood count or at the discretion of the investigator

❖ Pemetrexed 500 mg/m² per IV route

❖ Atezolizumab 1200 mg per IV route

❖ Bevacizumab 15 mg/kg per IV route

For patients without disease progression, treatment will be followed by maintenance therapy by Atezolizumab + Pemetrexed and Bevacizumab administered at the same dosage on 3-week cycles

- <u>*Cohort without Bevacizumab*</u>

  4 cycles of induction every 3 weeks with:

❖ Carboplatin area under curve 6 mg/mL per minute per IV route or Cisplatin 75 mg/m² per IV route. It will be possible to start the first treatment cycle with an AUC 5 for patient who met the inclusion criteria but have a poorer blood count or at the discretion of the investigator

❖ Pemetrexed 500 mg/m² per IV route

❖ Atezolizumab 1200 mg per IV route

For patients without disease progression, treatment will be followed by maintenance therapy by Atezolizumab + Pemetrexed administered at the same dosage on 3-week cycles

Assessments

Patients will be followed before, during and after treatment up to disease progression or unacceptable toxicities, including.

❖ <u>At baseline</u>

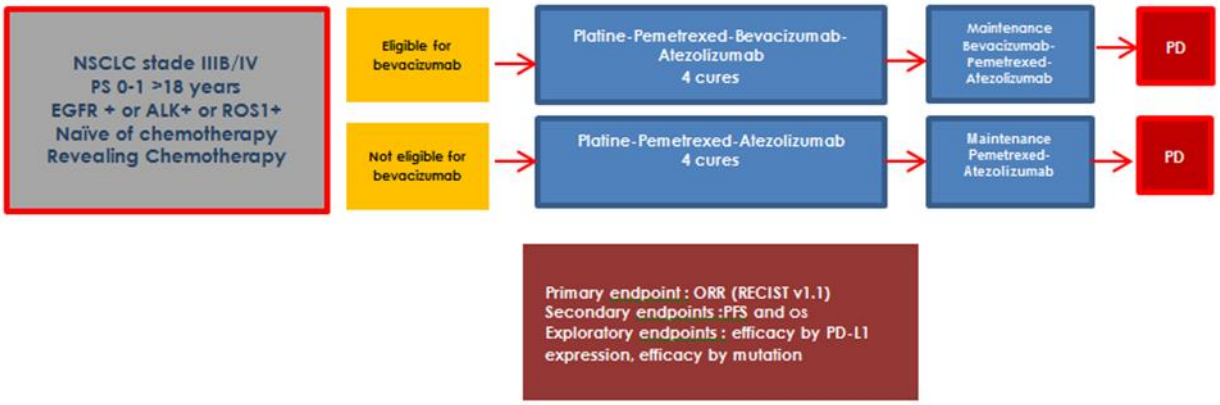
- *Complete clinical and physical examination, including medical and surgical antecedents, previous oncological treatments, concomitant treatments used by the patient within 7 days prior to the screening visit*
- *Complete biological check-up including serology (HIV, HBV, HCV), haematological and biochemical tests, coagulation tests, CRP,*
- *Urinary exam*
- *Oxygen saturation*
- *12-lead ECG*
- *Tumoral evaluation: CT-scan (thoracic and abdomino-pelvis)*
  Pelvic MRI in case of pelvic disease
  Brain CT or MRI to exclude brain metastasis
  Bone scan and neck CT if clinically indicated
- *Quality*-of-life assessment (EORTC QLQ-C30 and QLQ-LC13)
- Blood samples for biological banking (5 tubes EDTA (5x6 mL) collected, centrifuged (4°C) and stored at -80 C before centralization

❖ <u>During treatment up to disease progression or unacceptable toxicities and at the end of treatment (within 30 days after the last dose)</u>

- *Before each cycle*
  - ♦ *Complete clinical and physical examination, concomitant treatments*
  - ♦ *Evaluation of toxicities*

	♦ *Complete haematological and biochemical tests (Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase), LDH, Total Protein, Albumine* ♦ *Creatinin clearance (cycle 1 to 4 of induction)* ♦ *Urinary exam* ♦ *Oxygen saturation* ● *Every* 6 weeks (2 cycles) until 36 weeks, then every 9 weeks until progression, death or lost ♦ Tumoral evaluation: *CT-scan (thoracic and abdomino-pelvis)* *Pelvic MRI in case of pelvic disease* ♦ Quality-of-life assessment (EORTC QLQ-C30 and QLQ-LC13) ♦ Blood samples for biological banking (5 tubes EDTA (5x6 mL) collected, centrifuged (4°C) and stored at -80 C before centralization (at Day 1 of cycle 3 and cycle 5 and at progression) ❖ <u>Follow-up after treatment end for other reason than disease progression</u> ● *Every 3 months for patients who discontinue the treatment for another reason than disease progression will be followed-up every 3 months with:* ♦ *Physical examination similarly as at baseline* ♦ *Adverse events collection* ♦ *Complete haematological and biochemical tests similarly as at baseline* ♦ Tumoral evaluation: *CT-scan (thoracic and abdomino-pelvis)* *Pelvic MRI in case of pelvic disease* ● *For patients withdrawn from treatment due to progression, survival every 6 months.*
Cohorts	149 patients to be enrolled • <u>*Cohort with Bevacizumab*</u> 68 assessable patients are required; to anticipate 10% of non-assessable patients, **75 patients will be enrolled** • <u>*Cohort without Bevacizumab*</u> 67 assessable patients are required; to anticipate 10% of non-assessable patients, **74 patients will be enrolled**
Participating centres	It is planned to open this trial in 25-30 French centers nvolved in GFPC inter-group
Planned calendar	Inclusion period : 24 months Duration of participation for a patient : around 24 months up to disease progression. First patient : June 2019 Last patient : June 2022 End of this study : June 2024 Total length of thy study : 5 years
Ancillary study(ies)	Constitution of a blood collection for further ancillary analyses such as TMB, Follow-up of the circulating tumor DNA and EGFR mutation and others factors

3 STUDY OVERVIEW



4 STUDY FLOW CHART

	Inclusion	All cycles	End of Treatment	Follow-up after progression[5]
Window evaluation (days)	D-28 to D-1	D1 (± 2 days from cycle 2)	≤30 days after the last dose	
Signature of the informed consent form	X			
Verification of all eligibility criteria	X			
Medical and surgical history, including demographic data and histological data	X			
Anteriority of oncological treatments	X			
HIV, HCV, HBV serology	X			
Concomitant treatment	X	X	X	
Evaluation of toxicities (NCI CTCAE v5.0)		X	X	X
Tumour Assessment (RECIST v1.1)	X	Every 6 weeks (2 cycles) ± 3 working days until 36 weeks, then every 9 weeks (+/- 7 days) until progression, death or lost of view		
Self-administered questionnaire for quality of Life evaluation (QLQC30 and QLQ-LC13)	X	Every 6 weeks (2 cycles) ± 3 working days until 36 weeks, then every 9 weeks until progression, death or lost of view		
Physical examination	X	X	X	
Performance Status (ECOG)	X	X	X	
Vital signs[1]	X	X	X	
Oxygen saturation	X	X	X	
12-lead ECG	X	X *(if symptoms)*		
Weight, height	X	X	X	
Thyroid-function testing: thyroid-stimulating hormone [TSH], free T3, free T4); Total T3 will be tested only at sites where free T3 is not performed	X	X	X	
Hematology [2]	X	X	X	
Biochemistry [3]	X	X[3,6]	X[3]	
Coagulation	X			
CRP	X			
Urinalysis	X	X		
B-HCG (if applicable)	X			
Drug accountability		X	X	
Morbidity, survival	X	X	X	X
Ancillary biomarker exploration [4] - **Blood sample** (5 tubes EDTA of 6 mL per sampling)	X	X[4]	X	

[1] Vital signs include pulse rate, respiratory rate, blood pressures, and temperature.
[2] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes,basophils, and other cells), and platelet count.

[3] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin, creatinin clearance.
[4] Blood sample for ancillary exploration: tube EDTA 6 mL at inclusion, Day 1 of C3 and Day 1 of C5 at and progression.
[5] Follow up: every six months
[6] creatinin clearance (cycle 1 to 4 of induction)

5 SCIENTIFIC RATIONALE OF THE STUDY

5.1 DISEASE EPIDEMIOLOGY

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there would be 226,160 new cases of lung cancer and 160,340 lung cancer deaths in the United States alone (Siegel et al. 2012). Similar data from Europe estimate that there were 288,000 new cases of lung cancer and 253,000 deaths in 2008 (Globocan, 2008). In France, the number of incident cases of lung cancer in 2017 was estimated at 49,109, 70% of which had stage IIIB / IV NSCLC and the number of deaths at 30,991 (INVS, 2018).

Non−small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2011). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease is 2%−4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumours commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumours are more commonly located in the lung parenchyma distal to the central airways. Evaluation of NSCLC tumour tissue will reveal cytological differences between the squamous cell type (keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (glandular architecture). In cases where the tumour sample is poorly differentiated or if there is limited tissue available, immunohistochemical markers may support the histologic diagnosis. Thyroid transcription factor−1 (TTF-1) is infrequently expressed in squamous cells and strongly expressed in adenocarcinoma. In contrast, p63, CK5/6, and 34βE12 are strongly expressed in squamous cell carcinoma and less frequently in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the *EGFR*, the rearrangement in the *ALK* genes, and mutations in the *KRAS* gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%−40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). Similarly, the *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is very rare in the squamous histology (Herbst et al. 2008; Langer et al. 2010). In addition, *KRAS* mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011). In the France biomarker study, the mutation rate of EGFR was 11%, that of ALK 5%. This represents potentially 3500 new cancers with EGFR mutation and 1700 patients with ALK rearrangement per year in France (Barlesi et al. 2016). Several mechanisms can lead to resistance to primary anti-EGFR therapies, whether primary or acquired, including (i) the presence of a mutation associated with a natural resistance to TKIs (tyrosine kinase inhibitors) of first generation as insertions in the exon 20, (ii) the emergence of clones carrying resistance mechanisms, the main one being the T790M mutation (Camidge et al. 2014).

5.2 CURRENT TREATMENTS

5.2.1 First-Line Treatment for Advanced NSCLC without an EGFR Mutation or ALK Rearrangement

Patients with previously untreated advanced NSCLC that does not harbour a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (NSCLC Collaborative Group 1995). More recently, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this study, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (Spiro et al. 2004). Patients allocated to chemotherapy had a significantly longer median survival than did those managed with BSC (8 vs. 5.7 months; hazard ratio [HR] = 0.77, 95% CI: 0.66, 0.89).

It globally recognized standard-of-care for patients with inoperable Stage IIIB and Stage IV NSCLC is platinum-based chemotherapy for 4−6 cycles followed by maintenance treatment until progression. This standard-of-care applies to both non-squamous and squamous NSCLC (Pfister et al. 2004; D'Addario et al. 2010; De Marinis et al. 2011; National Comprehensive Cancer Network [NCCN] 2014). Agents that have been partnered with either cisplatin or carboplatin include the taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed. Combinations of these drugs with platinum analogs are superior to single-agent therapy and have been shown to prolong survival (Azzoli et al. 2009).

The Eastern Cooperative Oncology Group (ECOG) conducted a Phase III study (Study E1594) to compare four commonly used platinum-based doublets in patients with Stage IIIB/IV NSCLC who had not previously received chemotherapy (Schiller et al.2002). Gemcitabine plus cisplatin, docetaxel plus cisplatin, and paclitaxel plus carboplatin were compared with paclitaxel plus cisplatin. No significant clinical advantage of any one of the chemotherapy regimens over the others was observed; the median survival rates of the four treatment arms were approximately the same, approximately 8 months. The regimen of paclitaxel plus carboplatin was chosen as the reference regimen for ECOG's future studies because of its more favourable toxicity profile.

Despite modest gains, the benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in ORR (approximately 15%−25%) and median survival (7−11 months). Pemetrexed (Alimta® U.S. Package Insert) has demonstrated activity in the first-line setting where patients with non-squamous carcinoma had improved survival when treated with cisplatin and pemetrexed compared with those treated with cisplatin and gemcitabine (11.8 vs. 10.4 months; p = 0.005) (Scagliotti et al. 2008). In addition, cisplatin and pemetrexed were associated with better tolerability and safety and need less supportive care. The addition of bevacizumab to carboplatin and paclitaxel in patients with non-squamous NSCLC resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (Sandler et al.2006).

Recently, immune checkpoint inhibitors, including PD-L1/PD-1 blocking antibodies, have emerged as a new therapeutic option for first-line treatment of metastatic NSCLC. The KEYNOTE-024 study was a randomized open-label phase III study evaluating pembrolizumab given as monotherapy compared with platinum-based chemotherapy in patients who were previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumour cells. Patients with sensitizing mutation of the EGFR gene or translocation of the ALK gene were excluded from this study. In this study, median PFS was 10.3 months in the pembrolizumab group *versus* 6.0 months in the chemotherapy group (HR = 0.50; 95% CI: 0.37, 0.68; p < 0.001). The estimated rate of OS at 6 months was 80.2% (95% CI: 72.9%, 85.7%) in the pembrolizumab group versus 72.4% (95% CI: 64.5%, 78.9%) in the chemotherapy group; median OS was not reached in either group. OS was significantly longer in the pembrolizumab group than in the chemotherapy group (HR = 0.60; 95% CI: 0.41, 0.89; p = 0.005).On the basis of this study, pembrolizumab was approved for the first-line treatment of metastatic NSCLC in patients whose tumours have high PD-L1 expression (proportion score ≥50%) with no EGFR or ALK gene aberrations (Reck et al. 2016).

The KEYNOTE-042 trial is another phase III study that was planned to include 1,240 patients in order to compare first-line pembrolizumab *versus* chemotherapy for patients with advanced NSCLC with ≥1% PDL1 expression. Patients were randomized at a 1:1 ratio between pembrolizumab 200 mg Q3W for 2

years or until disease progression, or chemotherapy chosen by the physician. The results of this phase III trial were presented in a presidential session at ASCO 2018. The primary objective of the study was OS of patients with PDL1 ≥50%, ≥20%, and ≥1%, with a statistically hierarchical analysis starting with patients with PDL1 ≥50%. A total of 1,274 patients were included (637 in each arm), including 599 PDL1 patients ≥50% (47%) and 818 PDL1 patients ≥20%. The median follow-up at the time of analysis was 12.8 months. OS was significantly increased in the pembrolizumab arm for patients with PDL1 ≥1% (16.7 vs 12.1 months, HR 0.81, 95% CI 0.71–0.93; P=0.0018), PDL1 ≥20% (17.7 vs 13.0 months, HR 0.77, 95% CI 0.64– 0.92; P=0.0020), and PDL1 ≥50% (20.0 vs 12.2 months, HR 0.69, 95% CI 0.56–0.84; P=0.0003) compared to chemotherapy. OS gain was 4.5 months, 4.7 months, and 7.8 months for patients with PDL1 ≥1%, PDL1 ≥20%, and PDL1 ≥50%, respectively. OS benefice was essentially driven by PDL1 ≥50% patients. For patients with PDL1 of 1%–49%, an exploratory analysis found no difference in OS between pembrolizumab and chemotherapy (HR= 0.92, 95% CI 0.77–1.11) (Lopez et al. 2018, abstract ASCO).

The phase III KEYNOTE-189 trial included 616 patients (randomized 2:1) to confirm the results of the KEYNOTE-021 trial on the efficacy of the pembrolizumab – pemetrexed - platinum combination for chemotherapy-naïve NSCLC without EGFR mutation or ALK rearrangement. The main endpoints were PFS and OS. The recently published results supported the use of that combination. PFS was prolonged by 3.9 months for the pembrolizumab arm (median PFS 8.8 months) compared to the placebo arm (median PFS 4.9 months) with HR = 0.52 (95% CI 0.43–0.64, P,0.001), with respective 1-year OS rates of 69.5% and 49.4%. According to subgroup analyses, no PFS benefice was obtained for PDL1 <1% (HR 0.75, 95% CI 0.53–1.05) (Gandhi et al. 2018).

Recently, results from the IMpower 132 trial demonstrate that first-line use of atezolizumab (anti-PD-L1) in combination with carboplatin / cisplatin and pemetrexed chemotherapy followed by pemetrexed and atezolizumab as maintenance therapy improves PFS of stage IV non-squamous NSCLCs. IMpower 132 is an international, open-label, randomized phase III study that enrolled 578 patients. Eligibility criteria included measurable disease according to RECIST v1.1 criteria and an ECOG 0-1 PS. Patients should not have EGFR mutations or ALK rearrangements. Patients were randomized to receive 4 or 6 cycles of carboplatin (AUC 6) or cisplatin 75 mg/m² plus pemetrexed 500 mg/m² every 3 weeks, then pemetrexed as maintenance treatment or the same treatment atezolizumab.

The results of the study show that atezolizumab combined with chemotherapy results in an improvement in PFS (median 7.6 months versus 5.2 months in the control group) associated with a 40% reduction in the risk of progression (HR = 0.60; IC95: 0.49-0.72) in all patients and in the main clinical subgroups, including Asian patients (CI 0.42, 95% CI 0.28-0.63), non-smokers (CI 0.49, 95% CI 0.28-0.87), current and former smokers (CI: 0.61, CI95: 0.50-0.74).

In addition, in an interim analysis of the OS, atezolizumab and chemotherapy resulted in a 4.5-month improvement in OS compared to chemotherapy alone (HR = 0.46, 95% CI 0.22-0.96) (Papadimitrakopoulou et al. 2018, Abstract WCLC).

For patients with advanced squamous-cell NSCLC, the randomized, double-blind, phase III KEYNOTE-407 trial was designed to compare the efficacy and safety of a first-line pembrolizumab - platinum chemotherapy combination, regardless of PDL1 expression. The primary endpoint was PFS, with OS and PFS as secondary-outcome criteria for the population with PDL1 ≥1% expression, as well as ORR (objective response rate), DOR (duration of response), and safety. The study recruited 560 patients, randomized 2:1 between pembrolizumab 200 mg IV QW3 carboplatin plus nab-paclitaxel (Abraxane) and chemotherapy alone. Results of the second interim analysis were presented at ASCO 2018 and are summarized in Table 1. OS increased significantly in the pembrolizumab plus chemotherapy arm (median 15.9 months vs 11.3 months, HR= 0.64, 95% CI 0.49–0.85; P=0.0008). Similarly, median PFS increased from 4.8 months to 6.4 months (HR=0.56, 95% CI 0.45–0.70; P=0.001). ORR increased with pembrolizumab (57.9% vs 38.4%). These positive results were observed regardless of the level of PDL1 expression (Paz-Ares et al. 2018).

Other immunotherapies have shown positive results in combination with chemotherapy in the first line including atezolizumab.

The IMpower 131 trial is a randomized, three-arm phase III trial. Patients with stage IV squamous NSCLC were randomly equally (1:1:1) assigned to one of three treatment groups:

- Atezolizumab plus chemotherapy (carboplatin, AUC = 6 and paclitaxel, 200 mg/m²), 338 patients (Arm A)

Atezolizumab was administered at the dose of 1200 mg every 3 weeks at the same time as chemotherapy, followed by maintenance until progression RECIST 1.1 or loss of clinical benefit.

- Atezolizumab plus chemotherapy (carboplatin and nab-paclitaxel [Abraxane], 100 mg/m² weekly), 343 patients (Arm B)
  Atezolizumab was administered according to the same modalities as in arm A.
- Chemotherapy alone (carboplatin, AUC = 6 and nab-paclitaxel [Abraxane], 100 mg/m² weekly), 340 patients (Arm C, control arm)

After a minimum follow-up of 9.8 months, the median PFS in arm B was 6.3 months versus 5.8 months in the arm C (HR = 0.71, 95% CI 0.60-0.85, p = 0.0001). This benefit was observed in all subgroups and regardless of PD-L1 expression level, with a non-significant difference for negative patients (TC0 and IC0) (HR = 0.81, 95% CI: 0.64 -1.03) (Jotte et al. 2018).

The IMpower 150 study, whose results in PFS have already been presented at the ESMO 2017, is a randomized phase III study addressed to patients with stage IV non-squamous NSCLC not previously treated with chemotherapy for their advanced disease. It aimed to assess the efficacy and safety of atezolizumab in combination with chemotherapy (carboplatin and paclitaxel) with or without bevacizumab. Patients were randomised (1:1:1) to receive:

- Atezolizumab plus chemotherapy (carboplatin, AUC = 6 and paclitaxel, 200 mg/m²), 349 patients (Arm A)
  During the induction phase, atezolizumab was administered at the dose of 1200 mg every 3 weeks at the same time as chemotherapy for 4 or 6 cycles; thereafter, atezolizumab was given in maintenance treatment (1200 mg every 3 weeks) until disease progression or loss of clinical benefit.
- Atezolizumab plus bevacizumab (15 mg/kg) plus chemotherapy (carboplatin and paclitaxel) 359 patients (Arm B)
  Atezolizumab and bevacizumab were given every 3 weeks at the same time as chemotherapy for 4 or 6 cycles and thereafter given in maintenance treatment until disease progression or loss of clinical benefit.
- Bevacizumab plus chemotherapy (carboplatin and paclitaxel), 337 patients (Arm C, control arm)
  Patients received 4-6 cycles followed by maintenance treatment with bevacizumab alone until disease progression.

The results presented at ESMO 2017 were for the arms B and C comparison and showed a significant benefit in PFS in favour of quadruple-therapy [8.3 months vs 6.8 months (HR = 0.617, 95% CI: 0.517-0.737), p <0.0001]. The OS was significantly higher with quadruple therapy (arm B) than in the standard arm with 800 pts in ITT [19.8 months vs 14.9 months (HR = 0.76, 95% CI: 0.63-0.93)]. This benefit was observed irrespective of the level of expression of PD-L1 on tumour cells (TC) and immune cells (IC), even in negative patients (TC0 and IC0) and more clearly in patients with hepatic metastasis (HR = 0.54). An important element was the significant efficacy of this regimen in patients with an advancing EGFR mutation or ALK rearrangement after TKIs. The median OS was not achieved at present [NE vs 17.5 months (HR = 0.54, 95% CI: 0.29-1.03)]. On the other hand, survival with the chemotherapy regimen + atezolizumab (arm A) was not significantly different from that observed in the control arm [19.4 months vs 14.7 months (HR = 0.88, 95% CI: 0, 72-1.08, p = 0.2041) and in particular for the mutated patients EGFR and ALK+ (HR = 0.42, 95% CI: 0.49-1.37) and in those with hepatic metastasis (HR = 0.85, 95% CI 0.53-1.36). This study shows that the carboplatin-paclitaxel-bevacizumab-atezolizumab combination is superior in terms of PFS and survival to the reference regimen without immunotherapy regardless of the expression level of PD-L1 (Socinski and al. 2018).

Table 1. First line study with association immune-checkpoints inhibitors and chemotherapy

ICI	*Type*	*Study*	*Histology*	*Phase*	*Endpoint*	*PD-L1*	*n*	*Treatment Arm*	*OS (months)*	*HR (95%CI)*	*p*	*PFS (months)*	*HR (95%CI)*	*p-value*	*ORR(%)*	*AEs ≥3*
PEMBROLIZUMAB	ICI+ CT	KEYNOTE 021	Non Squamous NSCLC	II	ORR	not selected	123	Pembrolizumab+ Carbo/Pem	NR	0.56 (0.32-0.95)	0.0151	13	0.50 (0.31-0.91)	0.001	55	39
								Carbo/Pem	21.1			8.9			29	26
	ICI+ CT	KEYNOTE 189	Non Squamous NSCLC	III	OS+ PFS	not selected	616	Pembrolizumab+ Carbo/Pem	NR	0.49 (0.38-0.64)	0.001	8.8	0.52 (0.43-0.64)	0.001	47.6	67.2
								Carbo/Pem	11.3			4.9			18.9	65.8
	ICI+ CT	KEYNOTE 407	Squamous NSCLC	III	OS+ PFS	not selected	559	Pembrolizumab+ carbo-paclitaxel or nab-paclitaxel	15.9	0.63 (0.49-0.85)	0.008	6.4	0.56 (0.45-0.70)	0.001	58.4	69.8
								carbo-paclitaxel or nab-paclitaxel	11.3			4.8			35	68
NIVOLUMAB	ICI+ ICI	CHECKMATE 227	NSCLC	III	PFS	high TMB	393	Nivo 3 mg/kg Q2W +Ipi 1mg/kg Q6W				7.2	0.58 (0.41-0.81)	0.001	45.3	31.2
								Platinum-CT				5.5			26.9	36.1
	ICI+ CT	CHECKMATE 227	NSCLC	III	PFS	<1%	550	Nivo 3 mg/kg Q2W +Ipi 1mg/kg Q6W				4.4			Not reported	35
								Nivo + Platinum-CT				4.7	0.74 (0.58-0.94)	0.001	36.7	52
								Platinum-CT				5.6			23.1	25
ATEZOLIZUMAB	ICI+ CT	IMPOWER 150	NSCLC	III	PFS	not selected	692	Atezolizumab + Carbo+Paclitaxel+ Bevacizumab	19.2	0.78 (0.64-0.96)	0.02	8.3	0.62 (0.52-0.74)	0.001	63.5	58.5
								Carbo-paclitaxel + Bevacizumab	14.7			6.8			48	50
	ICI+ CT	IMPOWER 131	Squamous NSCLC	III	PFS and OS	not selected	1021	Atezolizumab+ carbo-paclitaxel								
								Atezolizumab+ carbo-nab-paclitaxel	14	0.09§ (0.78-1.18)	0.6931	6.3	0.71 (0.60-0.85)	0.0001	49	
								carbo-nab-paclitaxel (control arm)	13.9			5.6			41	
	ICI+ CT	IMPOWER 132	Non Squamous NSCLC	III	PFS and OS	Not selected	578	Atezolizumab+ Carbo/CDDP-Pem	NR			7.6	0.60 (0.49-0.72)	0.0001		
								Carbo/CDDP-Pem	NR			5.2				
DURVALUMAB	ICI+ ICI	MYSTIC	NSCLC	III	PFS and OS	>25%	1022	Durvalumab				Negative but not published				
								Durvalumab + Tremelimumab								
								Platinum-CT								

abbreviations : ICI immnuo-checkpoints inhibitors, CT Platinum based chemotherapy, Carbo Carboplatin, Pem Pemetrexed , OS overall survival, PFS progression-free-survival, HR hazard radio, ORR overall response rate, AEs Adverse events, TC/IC Tumors cell/immun cell, Q3W query three weeks, Q2W query two weeks

5.2.2 First-Line Treatment for Advanced Non–Small Cell Lung Cancer with an EGFR Mutation or ALK Rearrangement

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC. In the France biomarker study, the mutation rate of EGFR was 11%, that of ALK 5% (Barlesi et al. 2016).

Several randomized phase III studies of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (LUX-LUNG 3) showed significant improvement of PFS and ORR compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Sequist et al. 2013, respectively). Similarly, the *ALK* inhibitor crizotinib has demonstrated efficacy in patients with NSCLC positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; XALKORI® U.S. Package Insert). Both *EGFR* TKIs and crizotinib have been shown to be generally well tolerated. Recently, other molecules have been approved for treatment in the first line of patients with EGFR mutations: Osimertinib (FLAURA) and for patients with ALK rearrangement, Alectinib (ALEX) (Soria et al. 2018; Peters et al. 2017), Brigatinib (Camidge et al. 2018). Studies have also evaluated the combination Erlotinib - Bevacizumab in mutated EGFR patients. Preclinical evidence suggests that NSCLCs with both activating EGFR and T790M mutations exhibit elevated levels of phosphorylated signal transducer and activator of transcription 3 (STAT3). Experimental results have shown that STAT3 upregulates VEGF expression. A combined treatment with EGFR-TKIs and VEGF-neutralising antibodies might attenuate the development of resistance driven by the interleukin 6–STAT3–VEGF pathway in EGFR-mutant NSCLC (Gao et al. 2007). Two phases II studies evaluated this association (Belief and JO25567) with interesting results (Seto et al.2014, Rosell et al. 2017).

5.3 MECHANISM OF ACTION OF DRUGS

5.3.1 Bevacizumab (Avastin®)

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth. Increased levels of VEGF have been found in most tumours examined to date, including tumours of the lung where, in addition, overexpression is associated with a poorer prognosis (Giatromanolaki et al. 2001; Brattstrom et al. 2004).

Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody to VEGF that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumour environment. Additional anti-tumour activity may be on tumour vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumour cells (Jain et al. 2001).

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck et al. 2009).

❖ **Clinical Studies of bevacizumab and platinum-based treatment in NSCLC**

Two Phase III studies have demonstrated the benefit of bevacizumab in combination with platinum-based chemotherapy as first-line treatment of patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC.

➢ ***Efficacy***

The first study, conducted by the ECOG (Study E4599) was an open-label, randomized, phase III study comparing the regimen of bevacizumab at the dose of 15 mg/kg every 3 weeks (Q3W) in combination with carboplatin and paclitaxel versus carboplatin and paclitaxel alone as first-line treatment of patients with advanced non-squamous NSCLC. This phase III study was based on a randomized phase II study in patients with recurrent or advanced NSCLC that evaluated carboplatin and paclitaxel (up to six cycles) with or without bevacizumab (7.5 or 15 mg/kg) and found that the combination of bevacizumab 15 mg/kg with carboplatin/paclitaxel for up to six cycles followed by maintenance with bevacizumab until disease progression resulted in increased response rates (31.5% vs. 18.8%) and prolonged time to progression (TTP) (7.4 vs. 4.2 months; p = 0.023) compared with chemotherapy alone (Johnson et al. 2004). There was also a non-significant improvement in OS (17.7 vs. 14.9 months) (Johnson et al. 2004). A higher incidence of bleeding was noted in the bevacizumab-treated patients. Severe pulmonary haemorrhage, which was observed in 6 patients (9.1%) and led to 4 fatalities, was more common in patients with squamous cell histology, tumour necrosis, and cavitation, and central tumours (Johnson et al. 2004). On the basis of the results of this phase II study, patients with squamous cell histology were excluded from this and other studies utilizing bevacizumab in NSCLC. In the study E4599, patients who received 6 cycles of bevacizumab plus chemotherapy without disease progression continued on single-agent bevacizumab until progression. A total of 878 patients were enrolled. Median OS was 12.3 months versus 10.3 months (HR = 0.79; p < 0.003); PFS was 6.2 months versus 4.5 months (HR = 0.66; p < 0.001), and the response rate was 35% (133 of 381) versus 15% (59 of 392) (p < 0.001) for patients treated with bevacizumab versus chemotherapy alone (Sandler et al. 2006).

The second study (BO17704 or AVAiL) was a randomized, double-blind, multicenter, two-stage, phase III study of bevacizumab in combination with cisplatin and gemcitabine versus placebo, cisplatin, and gemcitabine as first-line treatment in patients with advanced or recurrent non-squamous NSCLC. A total of 1043 patients were randomized. Bevacizumab-based therapy until disease progression reduced the risk of disease progression. Bevacizumab at a dose level of 7.5 mg/kg resulted in an HR for PFS of 0.75 (median PFS, 6.7 vs. 6.1 months; p = 0.003), and bevacizumab at a dose level of 15 mg/kg resulted in an HR of 0.82 (median 6.5 months vs. 6.1 months, p = 0.03). These results were maintained with a longer follow-up. OS was a secondary endpoint, and the PFS benefit did not translate into a significant OS benefit. Nevertheless, median OS in all treatment arms of the study exceeded 13 months (Reck et al. 2009; Reck et al. 2010).

➢ ***Safety***

In the initial phase II and III clinical studies, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events (TEs), and haemorrhage. Additional completed phase II and III studies of bevacizumab and spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III studies include congestive heart failure (primarily in metastatic breast cancer), gastrointestinal perforations, wound-healing complications, and arterial TEs. Reversible posterior leukoencephalopathy syndrome and fistula have also been reported infrequently.

In summary, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC not harbouring an activating *EGFR* mutation or *ALK* gene rearrangement. In particular, for newly diagnosed advanced-stage non-squamous NSCLC, the current standard-of-care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, these regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by elderly and poor performance status patients. Therefore, novel therapies that deliver an improved therapeutic index are urgently needed for non-squamous NSCLC.

5.3.2 Atezolizumab (Tecentriq®)

Atezolizumab (MPDL3280A) is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). It is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells. Atezolizumab preserves PD1-PDL2 binding compared to anti-PD1 immunotherapies.

Atezolizumab is being investigated as a potential therapy against solid tumours and hematologic malignancies in humans. Atezolizumab is approved in monotherapy for the treatment of patients with metastatic NSCLC after prior chemotherapy (Rittmeyer et al. 2017).

❖ **Summary of Nonclinical Studies**

The nonclinical strategy of the atezolizumab program was to demonstrate *in vitro* and *in vivo* activity, to determine *in vivo* pharmacokinetic (PK) behaviour, to demonstrate an acceptable safety profile, and to identify a phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab (Study PCD4989g).

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

❖ **Clinical experience with atezolizumab**

➢ ***Ongoing* Clinical Studies**

Atezolizumab is currently being tested in multiple phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Summary of Product Characteristics [SmPC] of Atezolizumab for study descriptions). The single-agent safety and efficacy data available to date include data from the following studies:

- Study PCD4989g is a phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion Q3W to patients with locally advanced or metastatic solid malignancies or hematologic malignancies
- Study GO28753 (POPLAR) is a randomized, phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen
- Study GO28915 (OAK) is a randomized, phase III, open-label study assessing the efficacy and safety of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen

- Study GP28328 is a phase Ib study assessing the safety and pharmacology of atezolizumab in combination with bevacizumab and/or chemotherapy in patients with advanced solid tumours.

➢ ***Clinical* Safety of atezolizumab as single-agent in Patients with NSCLC**

Study PCD4989g, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumours or hematologic malignancies, provides the majority of data (with 558 safety-evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urothelial bladder cancer (UBC), melanoma, and renal cell carcinoma (RCC). Safety data for NSCLC are also derived from Studies GO28625 (FIR), GO28915 (OAK), and Study GO28753 (POPLAR).

❖ **Rationale for Testing Atezolizumab in Combination with Bevacizumab**

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumour angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that in the tumour microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune cell recruitment to the tumour site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signalling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumour activity, prolonged survival, and increased trafficking of T cells into tumours (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab: (Hodi et al. 2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients. Therefore, combined treatment with PD-L1 and bevacizumab may increase the anti-tumour immune response, resulting in improved and more durable clinical benefit.

5.3.3 Pemetrexed (Alimta®)

Pemetrexed disodium (Alimta®, pemetrexed) is a novel pyrrolo[2,3 d]pyrimidine based folic acid analogue. In *in vitro* studies, pemetrexed inhibited multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase) crucial in the de novo biosynthesis of thymidine and purine nucleotides (Shih et al. 1997).

❖ **Pemetrexed plus platinum compounds in first-line NSCLC**

Two phase II studies demonstrated that the combination of pemetrexed and carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice (Kelly et al. 2001; Scagliotti et al. 2002; Fossella et al. 2003; Reck et al. 2010). The toxicity profile of the pemetrexed - carboplatin combination appears to be more favourable than that seen with other standard regimens in first-line NSCLC.

A phase III non-inferiority study comparing the efficacy of cisplatin - pemetrexed (n = 862) versus cisplatin - gemcitabine (n = 863) in patients with incurable stage IIIB or IV NSCLC who had received no prior chemotherapy. Median OS, PFS, and TTP were comparable between the two treatment groups. However, among patients who had adenocarcinoma or large-cell carcinoma, patients treated with

cisplatin - pemetrexed had significantly better median OS than patients treated with cisplatin - gemcitabine (12.6 vs. 10.9 months for adenocarcinoma [HR = 0.84; 95% CI: 0.71, 0.99; p = 0.03]); 10.4 vs. 6.7 months for large-cell carcinoma [HR = 0.67; 95% CI: 0.48, 0.96; p = 0.03]). In addition, cisplatin - pemetrexed was associated with better tolerability and safety and necessitated less supportive care (Scagliotti et al. 2008).

In addition, a supportive study named PRONOUNCE was designed to assess the efficacy and safety of pemetrexed + carboplatin (Pem + Cb) followed by pemetrexed maintenance versus paclitaxel + carboplatin + bevacizumab followed by bevacizumab maintenance (Pac + Cb + Bev) in patients with advanced non-squamous NSCLC. The median PFS was 4.44 months for Pem + Cb versus 5.49 months for Pac + Cb + Bev (HR=1.06; 95%CI: 0.84,1.35; p=0.610). The median OS for Pem + Cb was 10.5 months versus 11.7 months for Pac + Cb + Bev (HR = 1.07; 95% CI: 0.83, 1.36; p = 0.615). One- and 2-year survival rates were not significantly different between the arms and were 43.7% and 18.0% for Pem + Cb and 48.8% and 17.6% for Pac + Cb + Bev, respectively. Response rate and disease control rate (DCR) were 23.6% and 59.9% for Pem + Cb and 27.4% and 57.0% for Pac + Cb + Bev (p = 0.414 and 0.575, respectively) (Zinner et al. 2015).

❖ Pemetrexed maintenance therapy in NSCLC

A Phase III, randomized, double-blind, placebo-controlled, study that explored the use of pemetrexed as switch maintenance in first-line patients with NSCLC after four cycles of induction therapy using one of six standard platinum doublets (gemcitabine, paclitaxel, or docetaxel with either carboplatin or cisplatin). Patients who achieved a complete response (CR), partial response (PR), or stable disease were then randomized to maintenance therapy with pemetrexed plus BSC or placebo plus BSC until progression (Ciuleanu et al. 2009). A significant improvement in PFS was reported for patients who received pemetrexed maintenance therapy compared with those who received placebo (4.04 vs. 1.97 months; unadjusted HR, 0.50; 95% CI: 0.42, 0.61; p < 0.00001). In patients with non-squamous histology, the median PFS for patients receiving pemetrexed versus placebo was 4.5 months versus 2.6 months (unadjusted HR, 0.44; 95% CI: 0.36, 0.55; p < 0.00001). The median follow-up for OS was 11.2 months for patients in the pemetrexed group and 10.2 months for those receiving placebo. The median OS following induction chemotherapy in the overall study population was 13.4 months with pemetrexed and 10.6 months with placebo (unadjusted HR, 0.798; 95% CI: 0.65 to 0.95; p = 0.012). In the non-squamous population, the median OS was 15.5 months for pemetrexed-treated patients and 10.3 months for patients on placebo (unadjusted HR, 0.70; 95% CI: 0.56 to 0.88; p = 0.002).

A second study also explored the value of pemetrexed in the continuous maintenance setting. In this study, patients who had not received prior treatment for lung cancer received four cycles of pemetrexed + cisplatin. Maintenance therapy was continued if stable disease, a PR, or a CR was documented. Patients were then randomized in a 2:1 fashion to either pemetrexed + BSC or placebo + BSC. The median PFS in patients who received pemetrexed was 4.1 months (range, 3.2-4.6 months) compared with the median PFS of 2.8 months (range, 2.6-3.1 months) in patients who received placebo. The HR for PFS as assessed by the investigator was 0.62 (95% CI: 0.49, 0.79; p = 0.00006). The PFS benefit was internally consistent, and benefit was seen across all clinically important subgroups. OS data from this study are pending (Paz-Ares et al. 2012).

❖ Rationale for testing Atezolizumab in combination with Pemetrexed

Platinum-based regimens remain the standard first-line option for patients with locally advanced or metastatic NSCLC that is not harbouring EGFR mutations or ALK gene rearrangements. However, the survival benefit conferred by cytotoxic chemotherapy has reached a plateau, with overall response rates of approximately 20% and 1-year survival ranging from 31% to 36% (Schiller et al. 2002), leaving considerable room for improvement in outcomes. TC killing by cytotoxic chemotherapy can reasonably

be expected to expose the immune system to high levels of tumour antigens, and invigorating tumour-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signalling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in NSCLC patients will enable future tests of this hypothesis.

The combination of platinum-based doublet chemotherapy and atezolizumab in NSCLC was evaluated in the Phase Ib study GP28328. On the basis of results observed in GP28328, the study GO29438 is designed to evaluate whether the anti-tumour effect seen in atezolizumab-treated patients would translate into statistically significant and clinically relevant improvement in PFS and OS when used in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed in patients with non-squamous NSCLC. This study will allow for the evaluation of the efficacy of atezolizumab in the ITT population.

❖ **Rationale for using chemo-immunotherapy combination in asymptomatic CNS metastases**

In a pooled analysis of the KEYNOTE 021, 181 and 407 randomized trials that compared the combination of pembrolizumab-chemotherapy (platinum-based doublet) with this single chemotherapy, S. F. Powell et al. studied the benefit of the chemo-immunotherapy combination, in the particular subpopulation of patients with brain metastases (Powell et al. 2019). It was noted that patients with brain metastases could be included if 1) they received local treatment, were clinically stable for at least 2 weeks and without systemic corticosteroids or 2) for KEYNOTE 189 and 407 only, metastases asymptomatic cerebral palsy : without corticosteroids, and <15mm in size. In this population, the pembrolizumab-chemotherapy combination significantly prolonged overall survival (HR = 0.48, 95% CI = 0.32-0.70), and the benefit appeared to be greater in magnitude than in patients without cerebral metastasis (HR = 0.63, 95% CI = 0.53-0.75). This study seems to confirm the benefit of chemo-immunotherapy in this indication.

The new chemotherapy-immunotherapy combination trials no longer contraindicated untreated asymptomatic brain metastases.

5.4 STUDY RATIONALE AND PURPOSE

Encouraging clinical data emerging in the field of tumour immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD-L1 on TCs has been reported to impede anti-tumour immunity, resulting in immune evasion (Blank et al. 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumour-specific T-cell immunity.

PD-L1 expression is prevalent in many human tumours, and elevated PD-L1 expression is associated with a poor prognosis in patients with NSCLC (Mu et al. 2011).

For patients with NSCLC stage IIIB / IV, immuno-checkpoint inhibitors have emerged as a standard in first-line management of patients without oncogenic addiction (Socinski et al.2018; Gandhi et al. 2018; Reck et al. 2016).

For patients with EGFR mutation, several phase III trials comparing EGFR TKIs with chemotherapy showed a benefit of TKI versus chemotherapy with no proven benefit on overall survival. After a first line of treatment with a TKI, most patients progress and are eligible according to the mechanism of progression to a TKI of third generation in case of resistance T790M or to chemotherapy. For patients with ALK translocation, crizotinib, brigatinib and alectinib showed a first-line benefit compared to a platinum doublet.

Despite these major advances, most patients progress after targeted therapies and chemotherapy and pose the problem of an anti-PD1/PDL1 monotherapy treatment. Three phase III trials on monotherapy anti-PD1/PD-L1 (Fehrenbacher et al. 2016; Herbst et al. 2016; Borghaei et al. 2015) showed benefits for patients with non-epidermoid NSCLC. However, data on patients with EGFR and ALK mutations are inconsistent with other subgroups.

In the CHECKMATE 057 trial, of the 292 patients treated with Nivolumab, only 15% had an EGFR mutation (44/292) and 4% had an ALK translocation (13/292). Subgroup analysis showed no difference in efficacy (OS) in mutated EGFR patients (HR = 1.38) and non-smokers (HR = 1.02). For ALK patients, no analysis is available given the low number of patients (Borghaei et al. 2015).

Lung cancer in never smoker is more frequent among women, and adenocarcinoma. In addition, the mutation profile in never smoker strongly differs from smokers. It is known from the BioCAST study that they are more often mutated with, for example, 43% EGFR mutated patient and 13% ALK rearrangement in the bioCAST cohort (Couraud et al. 2015).

In the KEYNOTE 010 trial, 15.5% (77/495) of patients treated with Pembrolizumab were EGFR mutation and 2% (9/495) had an ALK translocation. The OS benefit of Pembrolizumab was not significant in the mutated EGFR group (HR= 0.89 (95% CI 0.45-1.70) (Herbst et al. 2016).

In the POPLAR trial, 11 patients in the Atezolizumab group had an EGFR mutation and none presented an ALK translocation. The article does not provide information on this subset of patients. In the phase III trial (OAK) evaluating Atezolizumab as a single-line monotherapy, 85 EGFR+ patients were included (including 42 in the immunotherapy arm). There was no OS benefit in the EGFR+ subgroups (HR = 1.24, 95%CI 0.71-2.18) (Fehrenbacher et al. 2016).

In a retrospective analysis (Gainor et al. 2016), objective response to immunotherapy was reported in 1 of 28 (3.6%) EGFR-mutant or ALK-positive patients versus 7 of 30 (23.3%) EGFR wild-type and ALK-negative/unknown patients (P = 0.053). Similarly, Mazièrès et al. presented to ASCO 2018 very low response rate under checkpoint inhibitors monotherapy for ALK+ and EGFR+ patients (0% for ALK, 12% for EGFR) (Mazieres et al. 2018). Nevertheless, several data seem to show a lower efficacy of monotherapy immunotherapy in patients with oncogenic addiction.

In this proposed trial, it is hypothesized that the addition of chemotherapy to immunotherapy could increase the ORR in these subgroups of patients with oncogenic dependence.

However, recent data were presented to ESMO immuno-oncology and ASCO 2018. The IMpower 150 trial evaluated the efficacy of the combination Atezolizumab (Atezo), Carboplatin-Paclitaxel (CP) and Bevacizumab (Bev) as the first line of NSCLC. The results of the analysis of Arm B (Atezo + CP + Bev) versus C (CP + Bev) have shown a benefit in PFS for arm C with HR at 0.617 p <0.001 with a PFS at 6 months of 72% versus 57% in favour of arm B (Socinski et al. 2018).

In this study, 13% of patients included with an addictive mutation for EGFR (126 patients) or for ALK (43 patients). The subgroup analysis showed a benefit for the arm B with HR=0.59 and a 9.7 month median PFS in the arm B versus 6.1 months in the chemotherapy arm (Socinski et al. 2018). These data may suggest efficacy of immunotherapy and chemotherapy combinations in subgroups of patients with addictive mutation.

The phase II we propose may strengthen the results of the IMpower 150 trial, which put forward efficacy data in patients with EGFR / ALK mutation. The data obtained by this trial may be supplemented by the IMpower 132 study, which evaluated the combination of pemetrexed and atezolizumab in the first line

in NSCLC patients but did not include patients with EGFR / ALK mutation (criteria for exclusion in IMpower 132). We will have data on the association pemetrexed / atezolizumab and bevacizumab.

The choice of chemotherapy by Pemetrexed / Platinum is justified by the fact that it is the standard of care in the first line of patients with cancer type "adenocarcinoma" in thoracic oncology.

Given their different mechanisms of action and minimally overlapping toxicity profiles, the combination of pemetrexed and an EGFR TKI might be expected to provide synergistic antitumor activity with manageable toxicity. This supposition is supported by preclinical studies, which have shown cytotoxic synergism between pemetrexed and erlotinib in several NSCLC cell lines. (Giovannetti et al. 2008; Li et al. 2007). In addition, gefitinib has been shown to suppress TS expression in NSCLC cell lines (Okabe et al. 2008); a lower level of thymidylate synthase expression appears to be associated with improved outcomes to pemetrexed treatment (Liu et al. 2015).

In addition, the test data KEYNOTE 021 and 189 showed that the combination of pemetrexed and immunotherapy seemed well tolerated and effective. In the KEYNOTE 189 study evaluating the platinum- based drug combined with pemetrexed and pembrolizumab, the estimated rate of OS at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group (HR=0.49; 95% CI, 0.38 to 0.64; P<0.001). Median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR= 0.52; 95% CI, 0.43 to 0.64; P<0.001) (Ghandhi et al. 2018). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group. The addition of pembrolizumab did not appear to increase the frequency of adverse events that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum- based drug. Similarly, the incidence of most immune-mediated adverse events was not higher with pembrolizumab-combination therapy than that previously observed with pembrolizumab monotherapy.

As for tolerance profile of the proposed combination, some particular attention may be paid given the fact there is little data on immunotherapy in combination with chemotherapy in patients with oncogenic mutation. Data from the IMpower 150 study do not report greater toxicity. Nevertheless, immunotherapy association and targeted therapies studies have shown some toxicity.

Thus, a Phase I clinical trial (NCT02013219) reported the preliminary results of erlotinib plus atezolizumab treatment in patients with NSCLC. The safety phase included patients with locally advanced or metastatic NSCLC, and the extension phase included patients with EGFR mutations who did not receive TKIs. Toward the end of the trial, 28 patients (eight in the safety phase and 20 in the extension phase) were evaluated for safety and efficacy. This study found that 39% of the patients had grade 3–4 adverse reactions, mainly fever and elevated alanine aminotransferase levels, although there were no reports of interstitial pneumonia interstitial lung disease (ILD) (Ma et al. 2016).

Another Phase I clinical trial (NCT02088112) evaluated the treatment of patients with NSCLC using gefitinib and durvalumab. By the end of the trial, 20 EGFR-TKI-naïve patients with EGFR-mutant NSCLC were included in the expansion phase; half of these received both durvalumab (10 mg/kg once every 2 weeks) and gefitinib (250 mg/day) (group 1), while the other half received gefitinib monotherapy for 28 days, followed by combined gefitinib and durvalumab treatment (group 2). Due to extensive grade 3–4 adverse reactions, four patients in group 2 discontinued treatment; three patients had elevated activities of alanine aminotransferase/aspartate aminotransferase and one patient developed ILD (Gibbons et al. 2016).

The Phase Ib TATTON study evaluated combination treatments with osimertinib and MEDI4736, AZD6094, or selumetinib in EGFR active mutant lung cancer and also determined the efficacy of axitinib in combination with the anti-PD-L1 antibody durvalumab. A total of 34 patients were assigned to the EGFR-TKI-treated group (23 cases, increasing dose phase, group A) and EGFR-TKI initial treatment

group (11 cases, extended phase, group B). The treatment regimen was osimertinib (80 mg once a day) plus durvalumab (3 mg/kg or 10 mg/kg once every 2 weeks). The combination was associated with a high incidence of ILD, which occurred in 38% (13/34) of patients overall (26% [6/23] in group A and 64% [7/11] in group B). In contrast, the incidence of ILD associated with osimertinib and durvalumab as single agent was only 2%–3% and ,2%, respectively (Antonia et al. 2014).

Similarly, recent data shows a hepatotoxicity risk in patients treated with immunotherapy (ICI) and crizotinib sequentially. A study of 453 patients with NSCLC who harbored an oncogenic alteration in ALK receptor tyrosine kinase gene (ALK), ROS1, or MET proto-oncogene, receptor tyrosine kinase gene (MET) who were treated with crizotinib (11 with and 442 without prior ICI therapy). Among the 11 patients treated with an ICI followed by crizotinib, five (cumulative incidence 45.5% [95% confidence interval (CI): 14.9-72.2]) experienced development of a grade 3 or 4 increase in alanine transaminase level and four (cumulative incidence 36.4% [95% CI: 10.0-64.2]) experienced development of a grade 3 or 4 increase in aspartate transaminase level. In comparison, among the 442 patients who received crizotinib only, a grade 3 or 4 increase in alanine transaminase level occurred in 34 patients (cumulative incidence 8.1% [95% CI: 5.7-11.0, $p < 0.0001$]) and a grade 3 or 4 increase in aspartate transaminase level occurred in 14 (cumulative incidence 3.4% [95% CI: 1.9-5.5, $p < 0.0001$]). All cases of hepatotoxicity after sequential ICI and crizotinib use were reversible and nonfatal, and no case met the Hy's law criteria. (Lin et al. 2018).

These data urge us to be cautious. In this context, we plan to include a safety analysis for the first 20 patients enrolled in each cohort: all the safety events that will have occurred will be collected and discussed with the Independent Data Monitoring Committee to assess that no over toxicity is observed.

5.5 TRANSLATIONAL PERSPECTIVES

5.5.1 Translational research on tumor tissue

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti−PD-1 therapy（Topalian et al. 2012). This correlation was also observed with atezolizumab in Studies PCD4989g (Herbst et al. 2014; Horn et al. 2015), GO28625 (FIR) (Spiegel et al. 2015), GO28754 (BIRCH) (Besse et al. 2015), GO28753 (POPLAR) (Fehrenbacher et al. 2016), and GO28915 (OAK) (Rittmeyer et al. 2017).

In addition, POPLAR data suggest that higher expression of genes related to PD-L1 and T-effector biology in tumor tissue is associated with improved efficacy of atezolizumab compared with docetaxel (Fehrenbacher et al. 2016). Similar observations have been reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015; Higgs et al. 2018).

Other potential biomarkers for the selection of populations sensitive to ICIs have emerged in the literature, eg, the tumor-mutation burden (TMB). Because the most effective ICIs against tumors have elevated levels of somatic mutations, it has been suggested that TMB could play an important role in the response to PD1/PDL1 inhibitors (Rivzi et al. 2018). Sequencing of the entire exome of pembrolizumab-treated NSCLC showed that a high TMB was associated with a PFS benefit and higher ORR (Campesato et al. 2016). A study evaluating the role of comprehensive cancer-gene panels (300 genes) to estimate TMB showed that the association between TMB and ICI clinical benefit was also seen when cancer-gene panels were used to estimate TMB.

In addition to the assessment of PD-L1 status and TMB, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed. DNA and/or RNA extraction and analysis may be performed to enable identification of somatic mutations by use of NGS (Next-Generation Sequencing) and to evaluate expression of genes (including but not limited to PD-L1, PD-1, and others) to assess their association with efficacy and to increase understanding of disease pathobiology.

5.5.2 Translational research on blood samples

“Liquid biopsies” is a large concept integrating circulating tumor cells, constitutional DNA, circulating-tumor DNA (ctDNA), circulating RNA, microRNA…

In routine practice, detection of *EGFR* activating and resistance mutations in ctDNA is used to guide patient’s treatment. Oxnard et al demonstrated the feasibility and the clinical impact of Osimetinib treatment initiation based on T790M mutation detection in plasma (Oxnard et al. 2016). Regarding fusions, ALK-rearrangements are not routinely detected in plasma related to technical issues but several panel are emerging, allowing the identification of the fusion and of the fusion partner.

Although targeted detection technics such as ddPCR and Beaming demonstrated their feasibility with high sensitivity, NGS assay evaluating large panel of genes could also be used on plasma in order to better characterize tumor heterogeneity. In a recent study, Aggarwal et al., demonstrated high disease control rate (85.7%) in patients who received a targeted therapy based on 73-gene NGS assay on plasma in a cohort of advanced NSCLC patients with different oncogenic driver mutations, reinforcing the role of liquid biopsies mainly when tissue is limiting (Aggrawal et al.2018).

Recent works highlighted the fact that mutation detected in plasma could not be related to ctDNA but to cfDNA derived from peripheral blood cells known as clonal hematopoiesis (somatic acquisition of genomic alterations in hematopoietic stem and/or progenitor cells, leading to clonal expansion). Therefore, clonal hematopoiesis might be a recurring source of discordance between tumor genotyping and plasma and should be taken into account in ctDNA studies.

Finally, TMB is an emerging and controversies biomarker and only preliminary data are available regarding blood TMB.

An exploratory objective of this study is to evaluate surrogate biomarkers (that may include circulating-tumor DNA [ctDNA], gene expression, tumor burden biomarkers, and others) in blood samples. Evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab.

In addition, potential correlations of these biomarkers with the safety and activity of atezolizumab will be explored.

To be able to propose some further translational explorations, we plan to collect information on tumor tissue availability and to constitute blood banking for further exploratory objectives.

6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVE

The primary objective is to assess the efficacy of the combination of Platinum (carboplatin or cisplatin), Pemetrexed, Atezolizumab ± Bevacizumab if eligible, in stage IIIB/IV non-squamous non-small cell lung cancer patients with progression-enhancing mutations following targeted therapies. Efficacy will be defined as the objective response rate (ORR) after 4 cycles of treatment (induction treatment).

Two distinct cohorts will be considered as follows since they will allow bringing separate information:

- **Cohort with Bevacizumab**

  It will provide additional data to that of Impower 150 but with reference chemotherapy in patients with "adenocarcinoma" as a tumor type. The obtained findings could also be used to analyse the data of the erlotinib / bevacizumab combination (Seto T et al, 2014) and thus better define the place of bevacizumab in patients with EGFR mutation.

- **Cohort without Bevacizumab**

  It will provide data on the combination Pemetrexed / Atezolizumab in patients with mutation. There are numerous studies (Keynote 021, 189, Impower 132) on the efficacy of this combination in NSCLC

patients but not in patients with EGFR / ALK mutations. The recommendations of the NCCN and that of the regional network “Rhônes-Alpes-Auvergne” place this association in first place in case of chemotherapy in front of other associations (such as carboplatin / taxol, rather to reserve it to patients with PS> 2 or over 70 years) (Référentiel RAA 2018).

6.2 SECONDARY OBJECTIVES

The secondary objectives for this study are to assess in each cohort:

- The progression-free survival (PFS)
- The duration of response (DOR)
- The time to deterioration (TTD)
- The change from baseline in patient-reported lung cancer symptoms (chest pain, dyspnoea, and cough) scores
- The ORR according to iRECIST criteria
- The overall survival (OS)
- The OS rate at 1 and 2 years
- The tolerance profile of the combination in the induction phase and the maintenance phase of treatment

6.3 BIOLOGICAL BANKING

Blood collection will be constituted and information on availability of tumour tissue will be collected in order to be able to consider some further exploratory translational studies.

These translational researches may include the evaluation of the relationship between tumoral and blood biomarkers (including, but not limited to, PD-L1, PD-1,Tumor Mutation Burden, EGFR/ALK mutation in blood, somatic mutations and others), as defined by immunohistochemistry (IHC), quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), NGS, and/or other methods and measures of efficacy.

The assessment of predictive, prognostic, and pharmacodynamic exploratory biomarkers (in tumor tissue and/or blood) and their association with disease status, mechanisms of resistance, and/or response to study treatment would also warrant to be explored.

To compare tumor-based genomics and liquid biopsy genomics by evaluating if circulating free tumor DNA (ctDNA) in the blood stream (liquid biopsy) yields similar genomic results as the tumor analysis, for the genomic characterization at baseline and the dynamic changes on therapy. Sensitivity, specificity, dynamic changes in the allelic fraction, correlation with RECIST 1.1 criteria will be evaluated. If possible, samples will be processed by targeted-NGS assay, optimized for sensitivity and specificity of all classes of molecular alterations, including base substitutions, insertions and deletion, focal amplifications and gene fusions and whole exome sequencing.

To provide data for biomarker discovery, Targeted gene expression profiles using High Throughput Genome (HTG) molecular diagnostics technology (2,560 transcripts).

Blood TMB:

To compare TMB evaluated on blood and tissue.

At disease progression, to correlate blood TMB and associated resistance mutations in driver genes (EGFR and ALK).

To assess treatment efficacy (ORR and mPFS) based on blood TMB.

Dynamic changes in blood TMB will be evaluated to predict tumor response according to RECIST1.1 and iRECIST criteria.

7 ENDPOINTS

7.1 PRIMARY ENDPOINT

The objective response rate (ORR) is defined as the proportion of patients who achieved an objective response after 4 cycles of induction treatment (or before progression).

Objective response will be considered in case of radiologically confirmed complete (CR) or partial response (PR) according to RECIST v 1.1 criteria (Response Evaluation Criteria in Solid Tumors version 1.1) by the masked, independent central board. Patients not meeting these criteria, including patients without any post-baseline tumour assessment, will be considered non-responders. The confirmation of response in accordance with RECIST v.1.1 is not required, but ORR with confirmation may be evaluated as an exploratory endpoint.

7.2 SECONDARY ENDPOINTS

7.2.1 Progression-free survival

PFS is defined as the time relapsed between inclusion and disease progression (according to RECIST v1.1 criteria as assessed by the investigator) or death from any cause, whichever occurs first.

Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumour assessment date. If no tumour assessments were performed after the date of the first occurrence of a CR or PR, PFS will be censored at the date of the first occurrence of a CR or PR plus 1 day.

7.2.2 Duration of response

DOR will be assessed in patients who had an objective response (CR or PR) as determined by the investigator using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first.

Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumour assessment date. If no tumour assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

7.2.3 Time to deterioration

TTD in lung-related symptoms is defined as the time from inclusion to the time the patient's score on the EORTC QLQ C30 or QLQ-LC13 shows a ≥10-point increase above baseline in each of the following EORTC-transformed scores for cough, dyspnea (single item), dyspnea (multi-item subscale) and chest pain. A ≥10-point change in score is perceived by patients to be clinically significant (Osoba et al. 1998).

If no baseline or post-baseline assessment is performed, data for patients will be censored at the date of inclusion plus 1 day. TTD in symptoms will be analysed in the Intent-to-treat (ITT) population through use of the same methods described for the PFS and OS analyses.

7.2.4 Objective response rate according to Immune RECIST criteria

It is defined similarly as ORR, with the exception that immune RECIST (Seymour et al. 2017) criteria are used instead of RECIST v 1.1.

7.2.5 Overall survival

OS is defined as the time between the date of inclusion and death from any cause. Patients who are not reported as having died at the date of analysis will be censored at the date when they were last

known to be alive. Patients who do not have post-baseline information will be censored at the date of inclusion plus 1 day.

7.2.6 Toxicities

Safety of the chemotherapy and immunotherapy will be assessed by toxicities that will occur either in the induction treatment or the maintenance treatment. Toxicities will be evaluated according to NCI CTCAE v5.0, in terms of kind, grade, time of onset, reversibility.

8 STUDY DESIGN

8.1 METHODOLOGY

We propose to implement a multicentric open-label, non-randomized, two parallel cohorts, and phase II trial aiming to assess the association of Platinum-Pemetrexed-Atezolizumab ± Bevacizumab for stage IIIB/IV non-squamous non-small cell lung cancer with EGFR mutation, ALK rearrangement or ROS1 fusion following targeted therapies.

8.2 STUDY DURATION

This trial is planned to be conducted with 25-30 participating French centres, involved in the GFPC inter-group.

The duration of the inclusion period is estimated to around 36 months to enrol 149 patients overall. For a patient, the expected duration of follow-up is around 2 years up to disease progression.

The study duration is therefore estimated to around 5 years.

8.3 SUBJECTS SELECTION

Patients must meet all of the following criteria to be eligible for study entry.

8.3.1 Inclusion criteria

- Patient older than 18 years
- Subject affiliated to an appropriate social security system
- Signed informed consent before any trial related activities and according to local guidelines
- ECOG performance status of 0 or 1Histologically or cytologically confirmed, stage IIIB/IV non-squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition).

  Patient with a sensitizing mutation in the EGFR gene must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR TKIs, such as erlotinib, gefitinib, or another EGFR TKI appropriate for the treatment of EGFR-mutant NSCLC. Patients with stage IIIB had to be not operable (that means not eligible for radiochemotherapy followed by a maintenance treatment by Durvalumab).

  Patient with an ALK fusion oncogene (confirmed in local laboratory) must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ALK inhibitors (i.e., crizotinib, alectinib, ceritinib) appropriate for the treatment of NSCLC in patients having an ALK fusion oncogene
- Patient with a ROS1 fusion oncogene (confirmed in local laboratory) must have experienced disease progression (during or after treatment) or intolerance to treatment with one or more ROS inhibitors (i.e., crizotinib,) appropriate for the treatment of NSCLC in patients having an ROS1 fusion oncogene
- No prior chemotherapy treatment for Stage IV non-squamous NSCLC except if less than 3 cycles, with treatment free-interval of at least 1 year from C1 since last chemotherapy
- Patient who has received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-

free interval of at least 6 months from C1 since the last chemotherapy, radiotherapy, or chemoradiotherapy

- Patient with a history of asymptomatic CNS metastases is eligible, provided he meets all of the following criteria:
  - *Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)*
  - *No ongoing requirement for corticosteroids as therapy for CNS disease*
  - *No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to C1*
- Measurable disease, as defined by RECIST v1.1
- Adequate hematologic and end-organ function, defined by the following laboratory
  - *ANC > 1500 cells/uL without granulocyte colony-stimulating factor support*
  - *Platelet count > 100,000/uL without transfusion*
  - *Hemoglobin ≥ 9.0 g/dL. Patients may be transfused to meet this criterion.*
  - *INR or aPTT ≤ 1.5 upper limit of normal (ULN)*

    This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be receiving a stable dose.
  - *ASAT, ALAT, and alkaline phosphatase ≤ 2.5xULN, with the following exceptions:*

    Patients with documented liver metastases: ASAT and/or ALAT ≤ 5 x ULN

    Patients with documented liver or bone metastases: alkaline phosphatase < 5xULN
  - *Serum bilirubin ≤1.5 xULN*

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3xULN may be enrolled.

    Patients with documented liver metastases: Serum bilirubin < 3xULN
  - *Calculated creatinine clearance (CRCL) ≥ 45 mL/min or, if using cisplatin, calculated CRCL must be ≥ 60 mL/min using the Cockcroft-Gault Method*
- Adequate method of contraception during the treatment period and at least 5 months after the last dose of atezolizumab or 6 months after the last dose of chemotherapy
  - For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year.
  - 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, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
  - For men, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    - With partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.
    - With pregnant partners, men must remain abstinent or use a condom during the chemotherapy treatment period and for at least 6 months after the last dose of chemotherapy.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

8.3.2 Non-inclusion criteria

Patients who meet any of the criteria below will be excluded from study entry.

❖ **Cancer-specific exclusions**

- Active CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to C1 Leptomeningeal disease (Presence of cancer cells in cerebral CSF or MRI with leptomeningeal lesion strongly suspected of leptomeningeal disease)
- Uncontrolled tumour-related pain
    - *Patients requiring pain medication must be receiving a stable regimen at study entry.*
    - *Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to inclusion. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.*
    - *Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to C1.*
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently); Patients with indwelling catheters (e.g., PleurX®) are allowed.Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium > ULN)Malignancies other than NSCLC within 5 years prior to C1, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

❖ **<u>General medical exclusions</u>**

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- 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's 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 regimen are eligible for this study*
    - *Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:*
        - Rash must cover less than 10% of body surface area (BSA).
        - Well controlled disease at baseline only requiring low potency topical steroids.
        - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan; History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV. All patients will be tested for HIV prior to C1 into the study; patients who test positive for HIV will be excluded from the study.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV

infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA. Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.

- Active tuberculosis
- Severe infections within 4 weeks prior to C1, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or IV antibiotics within 1 week prior to C1; Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to C1 unstable arrhythmias, or unstable angina
- Major surgical procedure other than for diagnosis within 28 days prior to C1 or anticipation of need for a major surgical procedure during the course of the study
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
- Symptomatic brain metastases;
- Patients with illnesses or conditions that interfere with their capacity to understand, follow and/or comply with study procedures
- Concurrent participation in any therapeutic clinical trial
- Patient deprived of liberty or placed under the authority of a tutor
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

❖ **Exclusion criteria related to medications**

- Any approved anti-cancer therapy, including hormonal therapy within 7 days prior to C1 of study treatment.
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to C1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies
    - *Patients who have had prior anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:*
    - *Last dose of anti-CTLA-4 at least 6 weeks prior to C1*
    - *No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3/4)*
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin 2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to C1 Prior treatment with cancer vaccines is allowed.
    - Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to C1
    - Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.
    - The use of corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

❖ **Exclusion criteria related to chemotherapy**

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v5.0 (cisplatin)
- CRCL < 60 mL/min for cisplatin or < 45 mL/min for carboplatin using the Cockcroft-Gault Method

❖ **Exclusion criteria related to Bevacizumab**

- Medically uncontrolled hypertension (defined as PAS>150 and/or PAD >100 mmHg)
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Clinically significant cardiovascular disease (within 6 months prior to C1 that is uncontrolled by medication or may interfere with administration of trial treatment:
  - Aortic aneurysm requiring surgical repair
  - Recent arterial thrombosis
  - Hemoptysis (>one-half teaspoon of bright red blood per episode (within one months prior to C1) (grade 2 hemoptysis)
- History of documented haemorrhagic diathesis or coagulopathy
- History of abdominal or tracheosphageal fistula or perforation within 6 months prior to C1
- Core biopsy or other minor surgical procedure within 7 days before bevacizumab
- Clinical signs or gastrointestinal obstruction or requirement for routine parenteral hydration, nutrition or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Major surgery within 28 days before C1
- Serious, non-healing wound, active ulcer or untreated bone fracture
- Proteinuria >1g/24h urine collection
- All patient with >2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤1g of protein in 24 hours.
- Known sensitivity to any component of bevacizumab
- Radiation therapy within 21 days before C1 (except Symptomatic lesions amenable to palliative radiotherapy)
- Adequate hematologic, liver, and renal function required (including creatinine clearance 45 mL/min at baseline and 45 mL/min before the start of any subsequent cycle using the Cockcroft-Gault Method)

8.4 STUDY PLAN

8.4.1 Consent sign

The study will be proposed by oncologists to patients meeting the eligibility criteria. Patients will be given study information (explanation on the study, reading and giving of the information notice). Patients will have a reflection period of the duration of their choice. After collection of the signed informed consent, the selection criteria will be verified before inclusion in the trial.
The specific exams/procedures requested in the study before inclusion (baseline visit) will be realized after signed consent and before inclusion.

8.4.2 Inclusion procedure

After collection of the signed informed consent and checking of all eligibility criteria, inclusion will be performed before initiation of treatment.
Inclusion of the patient will be performed on the eCRF system.
An inclusion number will be assigned to the patient and will be used during all the study duration.

In case of problem, please contact the following persons in charge of the study:

Principal investigator: Dr BYLICKI Olivier
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8.4.3 Drug administration

Combined treatment will be initiated within 28 days after completion of screening based on baseline assessment prior to inclusion, as detailed in Table 2. Information on premedication is detailed on next section.

- *Cohort with Bevacizumab*

  4 cycles of induction every 3 weeks with:
  - Carboplatin area under curve 6 mg/mL per minute per IV route or Cisplatin 75 mg/m² per IV route. It will be possible to start the first treatment cycle with an AUC 5 for patient who met the inclusion criteria but have a poorer blood count or at the discretion of the investigator
  - Pemetrexed 500 mg/m² per IV route
  - Atezolizumab 1200 mg per IV route
  - Bevacizumab 15 mg/kg per IV route

  For patients without disease progression, treatment will be followed by maintenance therapy by Atezolizumab + Pemetrexed and Bevacizumab administered at the same dosage on 3-week cycles.

- *Cohort without Bevacizumab*

  4 cycles of induction every 3 weeks with:
  - Carboplatin area under curve 6 mg/mL per minute per IV route or Cisplatin 75 mg/m² per IV route It will be possible to start the first treatment cycle with an AUC 5 for patient who met the inclusion criteria but have a poorer blood count or at the discretion of the investigator
  - Pemetrexed 500 mg/m² per IV route
  - Atezolizumab 1200 mg per IV route

  For patients without disease progression, treatment will be followed by maintenance therapy by Atezolizumab + Pemetrexed administered at the same dosage on 3-week cycles.

Treatment regimen is described in the table below.

Table 2. Treatment Regimen and Order of Administration for All Treatment Arms

Agent	*Atezolizumab*	*Bevacizumab*	*Pemetrexed*	*Cisplatine*	*Carboplatine*
Dose and administration route	1200 mg IV	15 mg/kg IV	500 mg/m² IV	75 mg/m²	AUC 6 IV or AUC5 *
Order of administration	1	2	3	4	4
Infusion rate	Over 60 (± 15) min (for the first infusion); 30 (± 10) min for subsequent infusions if tolerated	Over 90 (± 15) min (for the first infusion); shortening to 60 (± 10) then 30 (± 10) min for subsequent infusions if tolerated	Over approximately 10 min on Day 1	Over 1–2 hours on Day 1	Over approximately 15 – 30 min

Frequency		Day 1 of every cycles of 21 days			
Induction Phase *(4 cycles)*	cohort **with** Bevacizumab	**X**	**X**	**X**	**X**
	cohort **without** Bevacizumab	**X**		**X**	**X**
Maintenance Phase *(up to progression of unacceptable toxicities, max 30 cycles)*	cohort **with** Bevacizumab	**X**	**X**	**X**	
	cohort **without** Bevacizumab	**X**		**X**	

AUC = Area under the concentration time curve; IV = intravenous.

**at the discretion of the investigator*

8.4.4 Premedication

Premedication will be administered before the initiation of treatment and pursued up to 3 weeks after discontinuation of Pemetrexed, as summarized in Table 3 and in line with premedication used in the Impower 132 trial.

Patients should receive IV hydration for platinum-based treatments according to the local standard of care, and manufacturer's instruction.

Table 3. Premedication for platinum-based treatment and pemetrexed treatment

Drug	*Dose and Route*	*Timing*
PLATINUM-based treatment (induction phase only)		
1/ Solumedrol (D1)	60mg IV	D1, 30 min before treatment
2/ Ondansetron	8mg IV	D1 30 min before treatment
3/ Aprepitant	125 mg PO 80 mg PO	D1, 1-2 h before treatment D2-D3
PEMETREXED treatment		
Folic acid	350–1000 µg PO	Once daily beginning at least 5–7 days before Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Vitamin B12	1000 µg IM	q9w beginning Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Prednisone (or equivalent)	30 mg PO	Twice daily the day before, the day of, and the day after pemetrexed administration

IM= intramuscular; PO =oral; q9w =every 9 weeks

8.5 SCHEDULE OF ASSESSMENTS

8.5.1 Assessments at baseline

The following assessments will be completed within one week prior to start of treatment and will include:

- Clinical assessment: medical history including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.
- Demographic data will include age, sex
- Complete physical examination, including
  - Weight, height, ECOG, vital signs
  - An evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems
  - Oxygen saturation
  - Urinalysis
- Laboratory Assessments:
  - Complete blood count (CBC) and platelets
  - Biochemistry: glucose, BUN or urea, creatinin, creatinin clearance, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, total bilirubin, ALAT, ASAT, alkaline phosphatase, LDH, total protein, and albumin
  - Coagulation (aPTT or INR)
  - CRP
  - Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed on Day 1 of each cycle during treatment prior to

administration of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥ 12 months of amenorrhea).

- ♦ Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood; dipstick permitted
- ♦ Thyroid-function testing: thyroid-stimulating hormone [TSH], free T3, free T4); Total T3 will be tested only at sites where free T3 is not performed.
- ♦ HBV serology: hepatitis B surface antigen (HBsAg), antibodies against HBsAg, total hepatitis B core antibody (HBcAb)

  HBV DNA test must be performed prior to inclusion if patient has a negative serology for HBsAg and a positive serology for HBcAb. HBV DNA test must be negative.
- ♦ HCV serology: hepatitis C virus antibody (anti-HCV)

  HCV RNA test must be performed prior to inclusion if the patient tests positive for anti-HCV.
- ♦ HIV testing

  All patients will be tested for HIV prior to inclusion into the study, and HIV-positive patients will be excluded from the clinical study.

The following assessments will be completed within 4 weeks prior to start of treatment and will include:

- An electrocardiogram (ECG)

  12-lead ECG is required at screening and as clinically indicated.
- CT scan (with oral/IV contrast unless contraindicated) or MRIs of the chest abdomen and pelvis.
- A Brain CT (with contrast if not contraindicated) or MRI scan must be done at screening to exclude CNS metastasis.
- Bone scans and CT scans of the neck to be performed if clinically indicated. Tumour assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Patients with history of irradiated brain metastases at screening are not required to undergo imaging brain scans at subsequent tumour evaluations, unless scans are clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.
- Quality of Life assessment: EORTC QLQ-C30 and QLQ-LC13

For patients having given specific consent for translational research:

- Blood samples will be obtained for biological banking. Samples will be processed to obtain 5 tubes EDTA (5x6 mL) will be collected. After centrifugation (4°C), plasma will be aliquoted and stored at -80 C before centralization.

8.5.2 Assessments during treatment (induction)

❖ **Day 1 of cycle 1**

- Complete physical examination similarly as at baseline
- Concomitant treatments
- Oxygen saturation
- Urinalysis

- Laboratory Assessments **(to be realized if the previous was realized more than 7 days before D1) :**
  - ♦ Complete blood count (CBC) and platelets
  - ♦ Biochemistry: glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, total bilirubin, ALAT, ASAT, alkaline phosphatase, creatinin clearance, LDH, total protein, and albumin
  - ♦ Thyroid-function testing: thyroid-stimulating hormone [TSH], free T3, free T4); Total T3 will be tested only at sites where free T3 is not performed.
  - ♦ Coagulation (INR and aPTT or PTT)

- For patients having given specific consent for translational research:

  If not realized at baseline, blood samples will be obtained for biological banking. Samples will be processed to obtain 5 tubes EDTA (5x6 mL) will be collected. After centrifugation (4°C), plasma will be aliquoted and stored at -80 C before centralization.

❖ **<u>Day 1 of each cycle from cycle 2 to end of treatment</u>**

- Complete physical examination similarly as at baseline
- Adverse events collection
- Concomitant treatments
- Oxygen saturation
- Urinalysis
- Laboratory Assessments *(within 3 days prior to the administration of study medication)*
  - ♦ Complete blood count (CBC) and platelets
  - ♦ Biochemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, total bilirubin, ALAT, ASAT, alkaline phosphatase), LDH, total protein, and albumin
  - ♦ Thyroid-function testing: thyroid-stimulating hormone [TSH], free T3, free T4); Total T3 will be tested only at sites where free T3 is not performed.
  - ♦ Creatinin clearance from cycle 1 to 4 of induction

- For patients having given specific consent for translational research, only at Day 1 of cycle 3 and cycle 5, and at progression:

  Blood samples will be obtained for biological banking. Samples will be processed to obtain 5 tubes EDTA (5x6 mL) will be collected. After centrifugation (4°C), plasma will be aliquoted and stored at -80 C before centralization

<u>Every 6 weeks (2 cycles) until 36 weeks, then every 9 weeks</u> until progression, death or lost, tumor assessment before day 1 of cycle including**:**

- CT-scan (thoracic and abdomino-pelvis)
- Brain CT or MRI
- Quality of Life assessment: EORTC QLQ-C30 and QLQ-LC13 (Aaronson et al. 1993, Bergman et al. 1994)

8.5.3 Assessments at the end of treatments

Patients who discontinue the treatment for another reason than disease progression will be followed-up 30 days after the last dose of study treatment. The evaluations will include:

- Physical examination similarly as at baseline
- Adverse events collection

- Concomitant treatments
- Oxygen saturation
- Urinalysis
- Laboratory Assessments
    - Complete blood count (CBC) and platelets
    - Biochemistry: glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, total bilirubin, ALAT, ASAT, alkaline phosphatase, LDH, total protein, and albumin
    - Thyroid-function testing: thyroid-stimulating hormone [TSH], free T3, free T4); Total T3 will be tested only at sites where free T3 is not performed.
- Tumour evaluation
    - CT-scan (thoracic and abdomino-pelvis)
    - Brain CT or MRI
- Quality of Life assessment: EORTC QLQ-C30 and QLQ-LC13

8.5.4 Follow-up assessments

Patients who discontinue the treatment for another reason than disease progression will be followed-up every 12 to 18 weeks up to progression with:

- Physical examination similarly as at baseline
- Adverse events collection
- Tumour evaluation (+/- 7 days)
    - CT-scan (thoracic and abdomino-pelvis)
    - Brain CT or MRI
- Quality of Life assessment: EORTC QLQ-C30 and QLQ-LC13

For patients withdrawn from treatment due to progression, a follow-up for survival will be performed about every 6 months. The following treatment is at the discretion of physician.

8.6 PATIENT AND TREATMENT DISCONTINUATION

Patients have the right to voluntarily withdraw from the study at any time for any reason.
In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for withdrawal from the study may include but are not limited to the following:

- Documented disease progression
- Need to initiate another anti-tumour treatment such as radiotherapy (with the exception of antalgic radiotherapy that does not interfere with tumour evaluation).
- Unacceptable toxicity, not compatible with anticancer treatments, namely:
    - Permanent discontinuation of Atezolizumab for toxicity (whatever treatment phase, induction or maintenance)
    - During induction treatment, permanent discontinuation of Platinum and/or Pemetrexed for toxicity
    - NB: Patients requiring permanent discontinuation of bevacizumab for toxicity will not be considered as withdrawn from the study
- Patient's decision (the data already collected during the search can be kept and exploited unless the patient opposes it through withdrawal of consent)
- Intercurrent illness or other reason that necessitates stopping treatment of the study
- Use of another non protocol-specified anti-cancer therapy
- Pregnancy
- Patient lost to view
- Patient non-compliance

- Investigator's decision

Any patient who prematurely withdraws from the study treatment will only continue to be followed, unless he decides to withdraw from the study or is lost to view.
Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal and/or anticancer treatment discontinuation from the study should be documented on the appropriate electronic Case Report Form (eCRF).

8.7 CONCOMITANT MEDICATION

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator and must be recorded on the appropriate Concomitant Medications eCRF.

8.7.1 Authorized treatments

The following treatments/procedures are permitted:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bony metastases) provided it does not interfere with the assessment of tumour target lesions (e.g., the lesion being irradiated is not the only site of disease, as that would render the patient not evaluable for response by tumour assessments according to RECIST v1.1)
  - It is not a requirement to withhold atezolizumab during palliative radiotherapy.
- Inactive Influenza vaccinations
  - Corticosteroids (≤ 10 mg oral prednisone or equivalent)
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

8.7.2 Non Authorized treatments

The following treatments are not permitted:

- Any concomitant therapy intended for the treatment of cancer (except antalgic radiotherapy)
- The following medications are prohibited while in the study, unless otherwise noted:
  - Phenytoïne
  - Any live, attenuated vaccine within 4 weeks prior to inclusion, during treatment, or within 5 months after the last atezolizumab dose.
  - Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, non-contrast CT of the chest and non-contrast CT or MRI scans of the abdomen and pelvis should be performed.
  - The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

8.7.3 Treatments to be particularly followed

The following treatments are to be particularly followed:

- Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance)
- Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy.
- Antihypertensive drugs like loop diuretics (increased risk of nephrotoxicity)
- Antihypertensive drugs based on furosemide, hydralazine, diazoxide and propranolol for patients receiving cisplatin (increased risk of nephrotoxicity)

9 PHARMACEUTICAL FORM OF ANTICANCER MEDICATIONS

Atezolizumab and Bevacizumab will be considered as experimental drugs: on this basis, they will be provided by Roche SAS in this study.

As for Pemetrexed and Platinum (either cisplatin or carboplatine), a request for exemption will be made according to article R. 1121-3 of the Code of Public Health on the price in derogatory charge by the health insurance (not entitled to reimbursement) of medicines experiments for research purposes noncommercial.

9.1 ATEZOLIZUMAB

9.1.1 Presentation of the product

The chemical name of the study treatment is ATEZOLIZUMAB (MPDL3280A).

9.1.2 Packaging and Labelling

The atezolizumab drug product is provided as a sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

For further details on the formulation and handling of atezolizumab, see the Pharmacy Manual and SmPC.

9.1.3 Storage conditions

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IMP (investigational medicinal product) and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions (2-8 °C), in accordance with applicable regulatory requirements. Screening will be required for staff members authorized to handle controlled substances who are not medical practitioners.

9.1.4 Method of administration

Patients will receive 1200 mg of atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

9.2 BEVACIZUMAB

9.2.1 Presentation of the product

The chemical name of the study treatment is Bevacizumab (AVASTIN®).

9.2.2 Packaging and Labelling

Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be based on the patient's weight at screening and will remain the same throughout the study unless the patient's weight changes by > 10%.

9.2.3 Storage conditions

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions (2-8 °C), in accordance with applicable regulatory requirements. Screening will be required for staff members authorized to handle controlled substances who are not medical practitioners.

9.2.4 Method of administration

Bevacizumab will be diluted in 0.9% sodium chloride injection, USP, to a total volume of 100 mL. The initial dose will be delivered over 90 ± 15 minutes. If the first infusion is tolerated without any infusion-associated adverse events (i.e., fever and/or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes. Bevacizumab infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. If infusion-related symptoms occur, patients should be treated according to best medical practice, and patients will be monitored until adequate resolution of signs and symptoms.

9.3 CISPLATIN / CARBOPLATIN

9.3.1 Packaging

Carboplatin and cisplatin are packaged as infusion solution vials.

9.3.2 Storage conditions

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions (below 25°C), in accordance with applicable regulatory requirements. Screening will be required for staff members authorized to handle controlled substances who are not medical practitioners.

9.3.3 Method of administration

❖ **Cisplatin**

IV infusion should be administered approximately 30 minutes after completion of the pemetrexed infusion at a dose of 75 mg/m² over 1–2 hours or per standard of care at the institution. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and after receiving cisplatin.

Refer to local clinical practice guidelines for further details.

❖ **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 6 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 5/6 will be calculated using the Calvert formula (Calvert et al. 1989) as follows:

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 (Cockcroft et al. 1976) using the following formula:

CRCL = (140 – age) (wt) (*0.85 if female) / (72*Scr)

Where:

CRCL = creatinine clearance in mL/min

age = patient's age in years

wt = 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 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC=6, the maximum dose is 800 mg.

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.

Refer to the FDA's communication regarding carboplatin dosing at the following Web site for more details: http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm

9.4 PEMETREXED

9.4.1 Presentation of the product

The chemical name of the study treatment is Pemetrexed, marketed as Alimta®.

9.4.2 Packaging and Labelling

Pemetrexed is packaged as powder for solution for infusion.

9.4.3 Storage conditions

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions (below 25°C), in accordance with applicable regulatory requirements. Screening will

be required for staff members authorized to handle controlled substances who are not medical practitioners.

9.4.4 Method of administration

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.

Cycle should not be started until both of the following requirements are met:

- The patient has taken folic acid for at least 5 days immediately preceding the first dose of pemetrexed, and
- The patient has received a vitamin B12 injection (which can be given on Cycle 1, Day 1)

Subsequent cycles will be delayed until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the subsequent cycle.

10 DOSE ADJUSTMENTS OF ANTICANCER PRODUCTS

10.1 GENERAL RULES

Dose reduction will be applied only for cisplatin/carboplatin, pemetrexed or bevacizumab.

Adjustment dose for atezolizumab will not be permitted but treatment discontinuation will be applied, according to manufacturer recommendations.

When several toxicities with different grades of severity occur at the same time, the dose modifications should be done 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 combined study treatment (i.e., atezolizumab, carboplatin or cisplatin, pemetrexed and/or bevacizumab 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.

Once dose reduced, no dose increase will be authorized. Any patients requiring more than 2 dose reductions for a same drug will be withdrawn from the study.

For chemotherapy drugs, the maximum delay allowed is 42 successive days for all the medications. Beyond this delay, patient will permanently discontinue at least one chemotherapy drug and will be followed up as specified in section 8.6.

For Atezolizumab, patients may temporarily suspend study treatment for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. Beyond this delay, the patient will definitively discontinue atezolizumab treatment and will be followed up as specified in section 8.6.

10.2 SPECIFIC INFORMATION FOR ATEZOLIZUMAB AND BEVACIZUMAB

For Atezolizumab and/or for Bevacizumab, concerning the temporarily suspend treatment, management is explained in **SmPCs section 4.4 “special warning and precautions” and also in the SmPC table 1 “dose modification advice**”.

For Atezolizumab more specifically, the SmPC indicates that “Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more

than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed.

Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones."

Before any treatment administration, the following laboratory parameters should be checked:

- ANC ε1500/ mm^3
- PQ ε100,000/ mm^3
- CRCL according to MDRD formula must be ε60 mL/min (if cisplatin is administered, > 45 ml/min)

10.2.1 Specific information for Bevacizumab

Bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥ 28 days and until wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment. If possible, a sample for ATA assessment will be collected at the time of discontinuation.

Bevacizumab infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

All patients receiving bevacizumab should have their baseline scans reviewed with a radiologist at the investigational site.

- If the patient is found to have the features of cavitation and/or tumor invasion of thoracic vessels at baseline, the subsequent scans should also be reviewed and the decision to withdraw patients from bevacizumab should be based on the appearances of the scan.
- If the high-risk features are still apparent on the later scans, the investigator should consider withdrawing the patient from bevacizumab
- If the high-risk features are no longer visible on post-baseline scans, the investigator should make a benefit-risk assessment in consultation with a radiologist whether or not to continue treatment with bevacizumab
- If the patient did not have features of cavitation or tumor invasion of thoracic vessels at baseline, but develops cavitation during treatment, the investigator should make a benefit-risk assessment in consultation with a radiologist whether or not to continue treatment with bevacizumab.

10.2.2 Specific information for Atezolizumab

❖ **Anaphylaxis precautions**

♦ **EQUIPMENT NEEDED**

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

♦ **PROCEDURES**

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations

❖ **Systemic Immune Activation**

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

10.3 DOSE ADJUSTMENT ACCORDING TO TOXICITY

10.3.1 Hematological toxicities

Dose adaptation will be done according to NADIR at each cycle, as described in Table 4.

Table 4. Dose adaptation of each study drug in case of haematological toxicities.

Nadir	Cisplatin or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Hematologic Toxicity				
ANC <1000/⌠L plus fever of ε38.5°C	75% of previous dose	75% of previous dose	No dose reduction	No dose reduction
PQ ε50,000/ mm^3 ANC <500/mm^3 and	75% of previous dose	75% of previous dose		
PQ<50,000/ mm^3, regardless of ANC	75% of previous dose	75% of previous dose		
PQ <50,000/ mm^3 with Grade ε2 bleeding, whatever regardless of ANC	50% of previous dose	50**%** of previous dose		

If toxicity remains after 2 reductions of dose, the treatment will be discontinued.

- If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment will then be resumed. For patients in the maintenance phase with a controlled disease, it will be possible to continue atezolizumab in combination or not with bevacizumab after stopping pemetrexed for toxicity.
- **No dose reductions are recommended for anemia.** Patients should be supported per the treating physician's institution's guidelines.

10.3.2 Neurologic toxicity

Table 5. Dose adaptation of each study drug in case of neurological toxicity.

Event	Cisplatin or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Neurological toxicity				
Grade 0–1	100% of previous dose	100% of previous dose	No dose reduction Except for **All grade of immune relative adverse reaction** : *(Guillain-Barré syndrome, noninfective meningitis noninfective encephalitis, myasthenic syndrome/myastehia gravis)* **Permanent discontinuation***	No dose reduction Except for **All grade of *Posterior Reversible Encephalopathy Syndrome (PRES)* Permanent discontinuation** **
Grade 2	50% of previous dose	100% of previous dose		
Grade 3-4	**permanent discontinuation**	**permanent discontinuation**		

*__Atezolizumab__: Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2mg/kg/day of prednisone or equivalent) should be considered.

**__Bevacizumab__: PRES is a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin®.

Immune-mediated Myelitis:

- Patients should be monitored for clinical signs and symptoms that are suggestive of myelitis. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.
- Refer patient to neurologist.
- For Grade 1 or Grade 2 myelitis, continue immunotherapy unless symptoms worsen or do not improve.
- Atezolizumab should be permanently withdrawn for ≥Grade 2 immune-mediated myelitis.

➢ Treatment recommendations in case of immune-mediated Myelitis:
- For Grade 2: Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine.
- For Grade 3: Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. Admit patient for methylprednisolone pulse dosing 1 g/day and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days
- For Grade 4: Start methylprednisolone pulse dosing 1 g/day and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days.

Immune-mediated Facial Paresis:

- Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.
- Refer patient to neurologist.
- Atezolizumab should be withheld for patients with Grade 1 or 2 immune-mediated facial paresis and permanently withdrawn for ≥Grade 3 immune-mediated facial paresis

➢ Treatment recommendations in case of immune-mediated facial paresis:
- Grade 2: Initial observation OR initiate prednisone 0.5-1 mg/kg/day (if progressing from mild). Gabapentin, pregabalin, or duloxetine for pain.
- Grade 3-4: Initiate IV methylprednisolone 2-4 mg/kg/day and proceed as per Guillain-Barré syndromemanagement.

10.3.3 Renal toxicity

Table 6. Dose adaptation of each study drug in case of renal toxicity.

Event	Cisplatin or carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Proteinuria				
Grade 1 Urine dipstick 1 + or urine collection 0.15 to 1.0 g/24 hr	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 2 Urine dipstick 2+ to 3+ or urine collection > 1.0 to 3.5 g/24 hr	100% of previous dose	100% of previous dose	No dose reduction	● For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose ● Withhold bevacizumab for proteinuria > 2 g/24 hr and resume when proteinuria is ≤ 2 g/24 hr.
Grade 3 Urine dipstick 4+ or urine collection > 3.5 g/24 hr	75% of previous dose	75% of previous dose	No dose reduction	● For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. ● For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab. ● Withhold bevacizumab for proteinuria > 2 g/24 hr

				and resume when proteinuria is ≤ 2 g/24 hr.
Grade 4 Nephrotic syndrome	75% of previous dose	75% of previous dose	No dose reduction Except if immune related syndrome: **Permanent discontinuation**	**Permanent discontinuation**
Nephrotoxiciy				
Nephritis grade 2 (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	ClCr has to be calculated, and the dose adjustment should follow the ClCr adaptations	ClCr has to be calculated, and the dose adjustment should follow the ClCr adaptations	Withhold Atezolizumab - Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day	No dose reduction
Nephritis grade 3 or 4 (creatinine level > 3.0 x baseline or > 3.0 x ULN)	ClCr has to be calculated, and the dose adjustment should follow the ClCr adaptations	ClCr has to be calculated, and the dose adjustment should follow the ClCr adaptations	Permanently discontinue Atezolizumab	No dose reduction
CrCl : 45 à 59 mL/min*	Replacement of cisplatin by carboplatin AUC 5	100% of previous dose	No dose reduction	No dose reduction
CrCl < 45 mL/min*	**Permanent discontinuation**	**Permanent discontinuation**	No dose reduction	No dose reduction

* CrCL: For the adjustment of the doses according to the clearance, the calculation is made on the pre-treatment assessment and not on the nadir

10.3.4 Hepatic toxicity

Table 7. Dose adaptation of each study drug in case of hepatic toxicity.

Event	Cisplatin or carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Bilirubinemia				
Grade 0 – 1 <1.5 x ULN	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 2 1.5 -3 x ULN	100% of previous dose	100% of previous dose	**Temporary discontinuation***	

Grade 3-4 >3 x ULN	75% of previous dose	75% of previous dose	**Permanent discontinuation**	
Transaminases elevation				
Grade 0 – 1 < 3x ULN	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 2- 3 -5 x ULN	100% of previous dose	Treatment stop until recovery of grade 0-1, then reduce to 75%of previous dose	**Temporary discontinuation***	
Grade 3 5-20 x ULN	75% of previous dose	75% of previous dose	**Permanent discontinuation**	
Grade 4 > 20x ULN	**Temporary discontinuation for carboplatin**	75% of previous dose	**Permanent discontinuation**	

*__Atezolizumab Temporary discontinuation__: Treatment with atezolizumab should be withheld if Grade 2/3 event persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.

10.3.5 Gastrointestinal toxicity

Table 8. Dose adaptation of each study drug in case of digestive toxicity.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Nausea/vomiting				
Grade 3 or 4 Despite use of antiemetics	75% of previous dose	75% of previous dose	No dose reduction	No dose reduction
Mucositis				
Grade 3 or 4	50% of previous dose	50% of previous dose	No dose reduction	No dose reduction
Diarrhea and colitis				
Diarrhea grade 2	**Any diarrhea requiring hospitalization (irrespective of grade):** 75% of previous dose	**Any diarrhea requiring hospitalization (irrespective of grade):** 75% of previous dose	**Temporary discontinuation***	No dose reduction
Diarrhea grade 3 Or symptomatic colitis	75% of previous dose	75% of previous dose	**Temporary discontinuation***	No dose reduction
Diarrhea grade 4 Or colitis grade 4	75% of previous dose	75% of previous dose	**Permanent discontinuation**	No dose reduction
GI (gastro-intestinal) perforation - Fistula				
Grade 2	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**

invasive intervention not indicated				
Grades 3-4	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Fistula				
Grade 2 invasive intervention not indicated	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**
Grades 3-4	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Pancreatitis				
Amylase, lipase Grades 3-4	75% of previous dose	100% of previous dose	**Temporary discontinuation****	No dose reduction
Pancreatitis Grade 2	100% of previous dose	100% of previous dose	**Temporary discontinuation****	No dose reduction
Pancreatitis Grade 3	75% of previous dose	75% of previous dose	**Temporary discontinuation****	No dose reduction
Pancreatitis Grade 4	75% of previous dose	75% of previous dose	Or **pancreatitis recidive (all grade) Permanent discontinuation**	No dose reduction
Bowel obstruction				
Grade ≥ 2	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**
Wound dehiscence				
Any grade Requiring medical or surgical therapy	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**

***Atezolizumab**: **Temporary discontinuation for Diarrhea and colitis**: (Immune-related colitis) : Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.

****Atezolizumab**: **Temporary discontinuation for Pancreatitis:** Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or

symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.

10.3.6 Cardiovascular toxicity

Table 9a. Dose adaptation of each study drug in case of hypertension.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Hypertension				
Grade 1 (asymptomatic, transient [< 24 hr] blood pressure increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	100% of previous dose	100% of previous dose	No dose reduction	No bevacizumab dose modifications
Grade 2 Recurrent or persistent [> 24 hr] or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits	100% of previous dose	100% of previous dose	No dose reduction	**Temporary discontinuation***
Grade 3	75% of previous dose	75% of previous dose	No dose reduction	Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, **Permanent discontinuation**
Grade 4 Including hypertensive encephalopathy	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**

***Bevacizumab**: **Temporary discontinuation for hypertension**: Withhold bevacizumab. Start antihypertensive therapy. Once blood pressure is < 150/100 mmHg, patient may continue bevacizumab therapy

Table 9b. Dose adaptation of each study drug in case of hemorrhage.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Non-pulmonary or non-CNS hemorrhage				
Grade 1 or 2 Non-pulmonary or non-CNS events	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 3 Non-pulmonary or non-brain or non-spinal cord hemorrhage	75% of previous dose	75% of previous dose	No dose reduction	**Temporary discontinuation*** **Permanent discontinuation** Patients who experience a repeat Grade 3 hemorrhagic event will be

				discontinued from bevacizumab.
Grade 4 Non-pulmonary or non-brain or non-spinal cord hemorrhage	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Pulmonary or CNS hemorrhage				
Grade 1 Pulmonary or brain or spinal cord hemorrhage	100% of previous dose	100% of previous dose	No dose reduction	**Temporary discontinuation***
Grade 2 Pulmonary or brain or spinal cord hemorrhage	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**
Grade 3 or 4 Pulmonary or brain or spinal cord hemorrhage	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**

*__Bevacizumab__: **Temporary discontinuation for haemorrhage:** Withhold bevacizumab until all of the following criteria are met:

- The bleeding has resolved and hemoglobin is stable.
- There is no bleeding diathesis that would increase the risk of therapy.
- There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.

Table 9c. Dose adaptation of each study drug in case of other cardiovascular toxicity.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Venous thromboembolic event				
Grade 1 or 2	100% of previous dose	100% of previous dose	No dose reduction	No dose modifications
Grade 3 or asymptomatic Grade 4	75% of previous dose	75% of previous dose	No dose reduction	**Temporary discontinuation***
Symptomatic Grade 4	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Arterial thromboembolic event *(new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)*				
Grade 1 or 2	100% of previous dose	100% of previous dose	No dose reduction	**Permanent discontinuation**
Grade 3 or 4	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Myocarditis				

Grade 1	100% of previous dose	100% of previous dose	**Temporary discontinuation****	**Permanent discontinuation**
Grade 2	100% of previous dose	100% of previous dose	**Permanent discontinuation**	**Permanent discontinuation**
Grade 3 or 4	75% of previous dose	75% of previous dose	**Permanent discontinuation**	**Permanent discontinuation**
Congestive heart failure (left ventricular systolic dysfunction)				
Grade 1 or 2	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 3	75% of previous dose	75% of previous dose	No dose reduction	**Temporary discontinuation** Withhold bevacizumab until resolution to Grade ≤ 1
Grade 4	75% of previous dose	75% of previous dose	No dose reduction	**Permanent discontinuation**
Immuno-mediated pericardial disorders including pericarditis, pericardial effusion and cardiac tamponade				
Grade 1	100% of previous dose	100% of previous dose	**Permanent discontinuation*****	**Permanent discontinuation**
Grade 2	100% of previous dose	100% of previous dose	**Permanent discontinuation*****	**Permanent discontinuation**
Grade 3 or 4	75% of previous dose	75% of previous dose	**Permanent discontinuation*****	**Permanent discontinuation**
The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain. - **The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients with chest pain associated with dyspnea or hemodynamic instability.** - **Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.**				

***Bevacizumab**: **Temporary discontinuation for venous thrombotic event:** If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met:
The patient must have an in-range INR (usually between 2 and 3) if on warfarin; Low molecular weight heparin (LMWH), warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment.
The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.

****Atezolizumab**: **Temporary discontinuation for myocarditis:** Treatment with atezolizumab should be withheld for Grade 2 myocarditis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day

*** Atezolizumab: **Permanent discontinuation for Immuno-mediated pericardial disorders**: Treatment with atezolizumab should be withheld and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg/day of methylprednisolone IV or equivalent should be started and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If the event does not improve within 48 hours after initiation of corticosteroids, consider adding an immunosuppressive agent.

10.3.7 Endocrine toxicity

Table 10. Dose adaptation of each study drug in case of endocrine toxicity.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Hypothyroidism/hyperthyroidism				
Symptomatic	100% of previous dose	100% of previous dose	**Temporary discontinuation** until controlled symptoms by adapted treatments	No dose reduction
Adrenal insufficiency				
Symptomatic	100% of previous dose	100% of previous dose	**Temporary discontinuation***	No dose reduction
Hypophysitis				
Grade 1	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Grade 2	100% of previous dose	100% of previous dose	**Temporary discontinuation****	No dose reduction
Grade 3	75% of previous dose	75% of previous dose	**Temporary discontinuation****	No dose reduction
Grade 4	75% of previous dose	75% of previous dose	**Permanent discontinuation**	**Temporary discontinuation***** **if** related to bevacizumab
Type I Diabetes				
Grade 1 or 2	100% of previous dose	100% of previous dose	No dose reduction	No dose reduction
Hyperglycaemia Grade 3-4 **(Glc jeun >250 mg/d L ou 13.9 mmol/L)**	75% of previous dose	75% of previous dose	**Temporary discontinuation*****	**Temporary discontinuation***** **if** related to bevacizumab

***Atezolizumab**: **Temporary discontinuation for adrenal insufficiency:** atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow.
If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

****Atezolizumab**: **Temporary discontinuation for hypophysitis:** atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

*****Atezolizumab**: **Temporary discontinuation for hyperglycemia**: Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

10.3.8 Pneumonitis

Table 11. Dose adaptation of each study drug in case of pneumonitis

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Pneumonitis				
Grade 2	100% of previous dose	100% of previous dose	**Temporary discontinuation**	No dose reduction
Grade 3-4	75% of previous dose	75% of previous dose	**Permanent discontinuation***	**Temporary discontinuation** if** related to bevacizumab

***Atezolizumab**: **Temporary discontinuation for pneumonitis:** to 2 mg/kg/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.

****Bevacizumab**: **Temporary discontinuation:** if SAE or a Grade 3 or 4 related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If delayed because of toxicity for > 42 days, the patient must be permanently discontinued from bevacizumab.

10.3.9 Cutaneous toxicity

Table 12. Dose adaptation of each study drug in case of cutaneous toxicity

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Rash				
Grade 3	75% of previous dose	75% of previous dose	**Temporary discontinuation***	**Temporary discontinuation** if** related to bevacizumab
Grade 4	75% of previous dose	75% of previous dose	**Permanent discontinuation**	**Temporary discontinuation** if** related to bevacizumab
Cutaneus reaction or Stevens-Johnson syndrome or toxic epidemic necrolysis				
SEVERE CUTANEOUS ADVERSE REACTION (**Atezolizumab and/or Pemetrexed**) **For suspected SCARs, patients should be referred to a specialist for further diagnosis and management.** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, **atezolizumab should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids** at a dose of 1-2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be **permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered**. Atezolizumab should **be withheld for patients with suspected SJS or TEN**. **For confirmed SJS or TEN**, atezolizumab should be **permanently discontinued**.				

Some severe skin reactions have been reported with Pemetrexed including cases of Stevens Johnson syndrome and Toxic epidermal necrolysis (some cases fatal), Pemphigoid, Dermatitis bullous, Acquired epidermolysis bullosa etc. Pemetrexed should **be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, pemetrexed should be permanently discontinued.**

*__Atezolizumab__: **Temporary discontinuation for rash:** Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10mg prednisone or equivalent per day
__Bevacizumab__: **Temporary discontinuation: if SAE or a Grade 3 or 4 related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If delayed because of toxicity for > 42 days, the patient must be permanently discontinued from bevacizumab.

10.3.10 Hypersensitivity reactions and Infusion reactions

Table 13. Dose adaptation of each study drug in case of Hypersensitivity reactions/infusion reactions

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Hypersensitivity reactions/infusion reactions				
Reaction during infusion grade 1-2	**Infusion should be discontinued and appropriate medical therapies should be administered** 100% of previous dose	100% of previous dose	**Rate of infusion should be reduced or Temporary discontinuation***	**Infusion should be discontinued and appropriate medical therapies should be administered**
Reaction during infusion grade 3-4	**Infusion should be discontinued and appropriate medical therapies should be administered** 75% of previous dose	75% of previous dose	**Permanent discontinuation**	**Temporary discontinuation** if** related to bevacizumab

*__Atezolizumab__: **Temporary discontinuation for infusion related reactions**: patients may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

10.3.11 Muscular toxicity

Table 14. Dose adaptation of each study drug in case of Myositis

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Myositis				
Grade 2	100% of previous dose	100% of previous dose	**Temporary discontinuation***	No dose reduction
Grade 3	75% of previous dose	75% of previous dose	**Temporary discontinuation***	**Temporary discontinuation****
Grade 4 or recurrent grade 3	75% of previous dose	75% of previous dose	**Permanent discontinuation**	**Temporary discontinuation****

*__Atezolizumab__: **Temporary discontinuation in case of immunological toxicity:** Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisone or equivalent per day.

__Bevacizumab__: **Temporary discontinuation for other toxicities: if SAE or a Grade 3 or 4 related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If delayed because of toxicity for > 42 days, the patient must be permanently discontinued from bevacizumab

10.3.12 Other toxicities

Table 15. Dose adaptation of each study drug in case of other toxicities.

Event	Cisplatin Or Carboplatin	Pemetrexed	Atezolizumab	Bevacizumab
Other toxicities				
Grade 2	100% of previous dose	100% of previous dose	In case of Immunological toxicity **Temporary discontinuation***	No dose reduction
Grade 3	75% of previous dose	75% of previous dose	In case of Immunological toxicity **Temporary discontinuation***	**Temporary discontinuation****
Grade 4	75% of previous dose	75% of previous dose		

*__Atezolizumab__: **Temporary discontinuation in case of immunological toxicity:** Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisone or equivalent per day.

__Bevacizumab__: **Temporary discontinuation for other toxicities: if SAE or a Grade 3 or 4 related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If delayed because of toxicity for > 42 days, the patient must be permanently discontinued from bevacizumab

11 EFFICACY AND SAFETY CRITERIA

11.1 EFFICACY CRITERIA

Response to the combined treatment will be evaluated according to RECIST v1.1 criteria.

The analysis population for ORR will be done on all enrolled patients.

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A spiral CT scan of the chest may be obtained but is not a requirement.
A CT (with contrast if not contraindicated) or MRI scan of the head must be done at screening to exclude CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for the study.

If a CT scan for tumour assessment is performed in a positron emission tomography (PET) or CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All known sites of disease must be documented at screening and re assessed at each subsequent tumor evaluation. Patients with history of irradiated brain metastases at screening are not required to undergo imaging brain scans at subsequent tumor evaluations, unless scans are clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

Response will be assessed by masked, independent central review using RECIST v1.1 and modified RECIST for patients in Cohort A and Cohort B. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.
Tumor assessments should occur every 6 weeks (± 3 days) for 36 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, after the completion of the Week 36 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1 only), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.
Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.
Patients who are treated with atezolizumab who continue to experience clinical benefit, despite evidence of radiographic progression, will continue tumor assessments as per the schedule listed above.

11.2 SAFETY CRITERIA

The safety assessment will be done by evaluating the general condition (PS, weight) and clinical status of the patients, and by collecting the events occurring during and after the treatment during the visits.

The intensity of the events will be estimated according to the NCI-CTCAE version 5.0 classification (grade 1 to 5 toxicity).

The intensity of adverse events not listed in this classification will be graded as follows:

- Grade 1: mild Discomfort noticed but no disruption of normal daily activity

- Grade 2: moderate Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
- Grade 3: severe Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
- Grade 4: Life-threatening/disabling

  An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
- Grade 5: Death AE resulting in death

12 SAFETY

12.1 GENERAL RULES – INSTRUCTIONS

Safety management will be conducted according to the French regulatory requirements

12.2 DEFINITIONS

12.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to it.

12.2.2 Adverse Reaction

All untoward medical occurrence in a patient or clinical investigation subject which participate to research involving the human person **related to the study procedure or to the experimental product.**

All untoward responses to an investigational medicinal product related to any dose administered.

12.2.3 Serious Adverse event

A serious adverse event (SAE) is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event*.

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Some “hospitalization/prolonged hospitalization” are not considered to be reported as serious adverse event:

- Admission for administrative or social reasons

- Hospitalization predefined by the protocol
- Hospitalization for medical or surgical treatment planned before the beginning of the trial
- Passage to day hospital
- Hospitalizations for pre-existing signs and symptoms that have not been aggravated

12.2.4 Suspected Unexpected Adverse Reaction

Any serious adverse reaction for which the nature, severity, frequency or outcome is not consistent with the applicable product information (e.g summary of product characteristics for an authorised product).

Any serious adverse reaction for which the nature, severity, frequency or outcome is not consistent with the applicable product information, diagnostic or therapeutic study mandated procedure (non-invasive and/or invasive) evaluated in the protocol.

12.3 INVESTIGATOR'S RESPONSIBILITIES

12.3.1 Detection and registration of adverse events

All adverse events have to be searched, reported and recorded, processed and evaluated.

Once the informed consent form has been signed, all adverse events occurring **during treatment and 30 days after the last study drug administration/** must be recorded by the investigator.

The intensity of the events will be estimated according to the NCI-CTCAE classification version 5.0 (grade 1 to 5 toxicity). The intensity of adverse events not listed in this classification will be graded as follows:

- **Grade 1:** **mild** : Discomfort noticed but no disruption of normal daily activity
- **Grade 2:** **moderate** : Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
- **Grade 3:** **severe** : Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
- **Grade 4:** **Life-threatening/disabling :** An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
- **Grade 5:** **Death AE or resulting in death**

The investigator will specify for each event:

- ✔ The seriousness
- ✔ The date of start +/- the date of end of the event
- ✔ The duration
- ✔ The intensity
- ✔ The causality assessment
- ✔ The outcome

Adverse Events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormality as AE should be avoided unless one of the following is met:

- ✔ Any criterion for an SAE is fulfilled

- ✔ Causes study treatment discontinuation
- ✔ Causes study treatment interruption
- ✔ Causes study treatment dose reduction
- ✔ The investigator believes that the abnormality should be reported as an AE

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

If a SAE occurs, the sponsor should be notified of the event awareness by the investigator without any delay. This will be done by mailing sponsor's Serious Adverse Event Report Form.

12.3.2 SAE reporting process

The investigator has to report the Sponsor of all serious adverse events occurring, once the informed consent form has been signed, **during treatment and 30 days after the last study drug administration**

All late Serious Adverse Events and considered as reasonably related to the study treatment(s) or to the study procedure must be reported without delay limitation.

The investigator has to immediately report to the sponsor all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the SmPC.

This will be done by mailing sponsor's Serious Adverse Event Report Form, and it will be following by some report, as needed, containing all available information concerning the SAE.

The investigator will specify for each event:

- ✔ The description as clear as possible according to the medical terminology,
- ✔ The intensity,
- ✔ The date of start and the date of end of the event,
- ✔ Measures taken and the necessity or not for a corrective treatment,
- ✔ If the treatment of the study was discontinued or if dose was modified
- ✔ The outcome: For a non-fatal event, the event should be followed until resolution or return to the initial status or to stabilization of potential sequels,
- ✔ The **causality assessment**: he has to assign a causality of "related to study treatment", if there is a "reasonable possibility" that the study treatment caused the event, or "not related to study treatment" if there is "no reasonable possibility" that the study treatment caused the event. The investigator must also assess whether the serious adverse event is "possibly related" to any study mandated procedure or activity, or others concomitants treatments, or under study or any others disease.

The investigator should also, when possible, attach to the serious adverse event report:

- ✔ A copy of the hospital report/hospitalization prolongation,
- ✔ A copy of the autopsy report,
- ✔ A copy of the results of all additional exams performed, including relevant negative results together with the range of normal laboratory values,
- ✔ Any other document judged useful and pertinent (including imaging)

All these documents should be **anonymised**.
Additional information may be requested by the sponsor.

The investigator should document the event as best as possible, provide medical diagnosis where possible and establish a causal link between the serious adverse event and the research, the study treatment, the associated drugs, an underlying pathology, progression of the disease or other cause.
The investigator shall promptly provide the sponsor with additional information regarding serious adverse events as he becomes aware of them.
The investigator should follow the patient who has had a serious adverse event until resolution, stabilization at a level acceptable to the investigator or return to the previous status, even if the patient withdraws from study and inform the sponsor of the serious adverse event outcome.

12.3.3 Special cases

ADVERSE EVENT OF SPECIAL INTEREST

An adverse event of special interest (AESI) is a serious or non-serious adverse event that requires special attention and will be specifically searched. **AESIs should be notified and followed as serious adverse events.**

As part of this research, the following events are considered as AESI:

- Immune-related diseases:
  - haemolytic anaemia,
  - myocarditis,
  - adrenal insufficiency,
  - Guillain-Barré syndrom,
  - hepatitis including AST or ALT > 10xULN,
  - hyperthyroidism,
  - hypophysitis,
  - hypothyroidism,
  - meningoencephalitis,
  - myasthenic syndrome / myasthenia gravis,
  - myositis,
  - nephritis,
  - pancreatitis,
  - pneumonitis,
  - severe cutaneous reaction,
  - vasculitis,
  - Non infectious cystitis
  - Pericarditis, immunomediated pericardial effusion and cardiac tamponade
- Hypersensitivity
- Infusion-related reactions
- Rhabdomyolysis
- Systemic immune activation / cytokine release syndrome

ONLY for patients who received Bevacizumab:

- Bleeding / haemorrhage
- Congestive heart failure
- Fistula / abscess
- Gastrointestinal perforation
- Hypertension if grade ≥ 3
- Posterior reversible encephalopathy syndrome
- Proteinuria if grade ≥ 2

- Arterial thromboembolic event
- Wound healing complications

PARTICULAR EVENT REGARDING IMPs EXPOSITION

Overdose, misuse or medical errors with ATEZOLIZUMAB or BEVACIZUMAB should be considered as SAE; They have to be notified using the same process as SAE reporting.

REPORTING EXCEPTIONS

Serious adverse event not to be notified immediately

Any event that is part of the natural history of the disease (progression of the disease or hospitalization for progression of the disease) should not be notified to pharmacovigilance on the SAE form but has to be reported into the e-CRF.

Some "hospitalization/prolongation of hospitalization" are not considered as serious adverse events and do not require notification to pharmacovigilance (see last paragraph "Serious adverse event ").

PREGNANCY

If a woman starts a pregnancy as part of the study or in some cases if her partner participates in the study (drug that can reach the seminal line of the man), the investigator has to report pregnancy to the sponsor.

The investigator informs the sponsor who will send him the "pregnancy notification form". The investigator has to follow the patient until the end of the pregnancy or its interruption and notify the outcome to the sponsor. If the outcome of pregnancy falls within the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, ...) the investigator should follow the SAE reporting process.

If it's a paternal exposure, the investigator has to obtain the parturient consent to report pregnancy data.

13 STATISTICAL CONSIDERATIONS

13.1 NUMBER OF SUBJECTS

This is an open-label multi-centre non-randomized non-comparative phase II study. The primary endpoint of the study is the Objective Response Rate (ORR), as assessed by masked, independent central review by RECIST criteria v1.1. The sample size was calculated independently in the two cohorts with different hypotheses.

- For the chemotherapy plus atezolizumab with bevacizumab cohort (Cohort A)

  The null hypothesis is a rate of 35% or lower. An ORR of 35% will be considered undesirable (p0 = 35%) compared with historical control (Mok T et al 2017, Soria JC et al. 2017). In this patient population, the alternative hypothesis is an ORR higher than 35%.

An ORR of 50% was considered to warrant further investigations (p1 = 50%).
Sample size is based on a one stage design and the exact binomial distribution (A'Hern, 2001). Sixty eight evaluable patients must be included in the trial (n=68) to reject the null hypothesis with a one-sided type-1 error rate α=5% and a power of 80% when the true non progressive disease rate is 50%. The sample size might be higher to anticipate non evaluable patients who will be replaced in order to obtain 68 evaluable patients.

To anticipate 10% of non-assessable patients, we plan to enrol **75 patients** in cohort A.

- For the chemotherapy plus atezolizumab without bevacizumab cohort (Cohort B),

  The null hypothesis is a rate of 30% or lower. An ORR of 30% was considered undesirable (p0 = 30%) compared with historical control (Mok T et al. 2017, Soria JC et al. 2017). In this patient population, the alternative hypothesis is an ORR higher than 30%.

An ORR of 45% was considered to warrant further investigations (p1 = 45%)
Sample size is based on a one stage design and the exact binomial distribution (A'Hern, 2001). Sixty seven evaluable patients must be included in the trial (n=67) to reject the null hypothesis with a one-sided type-1 error rate α=5% and a power of 80% when the true non progressive disease rate is 45%. The sample size might be higher to anticipate non evaluable patients who will be replaced in order to obtain 67 evaluable patients.
To anticipate 10% of non-assessable patients, we plan to enrol **74 patients** in cohort B.

13.2 STATISTICAL ANALYSIS

13.2.1 Decision rules

Confidence intervals of the ORR will be provided at the 90% 2-sided confidence level. The study conducted in the cohort A will be declared positive for the primary endpoint if the lower boundary of the 90% 2-sided confidence interval is higher than 35%. The study conducted in the cohort B will be declared positive for the primary endpoint if the lower boundary of the 90% 2-sided confidence interval is higher than 30%.

13.2.2 Definition of population

❖ **Efficacy analysis population**

The population of eligible subjects who receive at least one full dose of treatment will serve as the primary population for the analysis of efficacy data in this study. Major protocol violations will be defined in the Statistical Analysis Plan (SAP).

❖ **Safety analysis population**

The safety analysis population is defined as all enrolled patients who receive any amount of any component of protocol treatment.
At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

13.2.3 Outcome measures

❖ **Primary outcome measure**

Objective response rate (ORR) is defined as the proportion of patients who have achieved complete response (CR) or partial response (PR) according to RECIST 1.1 after 4 cycles of induction treatment (or before progression).

❖ **Other secondary outcome measures**

♦ Overall survival

Overall survival (OS) is defined as the time from inclusion to death due to any cause. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

- Progression-free survival
  Progression-Free Survival (PFS) is defined as the time from inclusion to progressive disease (PD) or death, whichever occurs earlier, based upon investigator assessment using RECIST 1.1. Patients without documented PD/death will be censored at the last disease assessment date.

- Duration of response
  Duration of response (DOR) is defined as the time interval between the date of first response (CR/PR) and the date of progression as defined according to RECIST 1.1 criteria.

- Response rate according to immune iRECIST criteria
  Response rate (ORR) is defined as the proportion of patients who have achieved complete response (CR) or partial response (PR) according to iRECIST criteria (Seymour et al. 2017)

❖ **Safety endpoints**

The primary safety endpoints are adverse events (AEs) graded using CTCAE (Version 5.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received at least one dose of investigational treatment including AEs, AESIs and SAEs. Safety will be monitored by cumulative data reviews throughout the trial.
Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs, and physical examinations.
***Note**:* Patients discontinuing all of the investigation treatments due to toxicity will still be considered evaluable for response.

13.2.4 Statistical Analyses

Both cohorts A and B will be analysed separately using the same procedure at the end of the study.

❖ **Efficacy analyses**

Unless otherwise stated, all statistical tests will be conducted at the $\alpha = 0.05$ (1-sided) level.

- Primary outcome, Overall response rate

ORR will be estimated as the proportion of patients with complete or partial response according to RECIST 1.1 after 4 cycles of induction treatment (or before progression) among eligible participants who received at least one dose of treatment.

Primary analysis

The primary analysis will be performed on the efficacy population. Non-evaluable patients (missing RECIST 1.1. criteria because of death before or health state too bad for evaluation), will be considered as non-responders.
The ORR will be estimated using binomial distributions. Confidence intervals will be provided at the 90% 2-sided confidence level, the lower limit of the 90% bilateral confidence interval being equivalent to the lower limit of the 95% unilateral confidence interval.

Secondary analyses

Sensitivity analyses will be conducted to assess the robustness of findings to plausible alternative assumptions about the missing data for non-evaluable patients.
If a substantial amount of primary endpoint data are missing (more than 20% of participants), using nonparametric estimation to estimate the ORR requires the missing completely at random (MCAR) assumption and may give misleading results.

Analyses of the primary endpoint at the primary time point will be performed using parametric generalized linear models fit by maximum likelihood. These methods provide unbiased estimation and inferences under the parametric modeling assumptions and the assumption that the missing data are missing at random (MAR). MAR assumes that the probability of an observation being missing may depend upon the observed responses and upon observed covariates, but not upon any unobserved factors. Multiple imputation and weighted estimating equations can exploit these observed data to reduce bias from missing data and improve the precision of estimates (Little et al. 2012). A generalized linear model for the ORR will use a binomial error distribution. The model will include as covariates all available baseline predictors of the missing outcomes.
Another secondary analysis will be performed excluding the non-evaluable patients.

♦ Secondary efficacy outcomes

Survival curves for OS, PFS, and duration of response will be estimated using the Kaplan- Meier method.

For OS, subjects without documented death at the time of analysis will be censored at the date last known to be alive.

For PFS, subjects without documented PD/death will be censored at the last disease assessment date. Any subject who is lost to follow-up will be included in the analysis and their PFS time will be censored on the last date that the subject was known to be progression-free, defined as the date of the last tumor assessment not indicating progression. As a sensitivity analysis, the primary analysis of PFS will be performed reconsidering subjects without documented PD or death who discontinued treatment or received new anticancer therapy to have been progressed at the date of treatment discontinuation or initiation of new anticancer therapy, whichever occurs later.
To assess the consistency of the study results, demographics (e.g., age, sex) and baseline prognostic characteristics (e.g., ECOG performance status, smoking status, and type of chemotherapy, …), will be considered as covariates to analyse the duration of PFS.

For DOR, subjects who have not yet progressed by the last disease assessment will be censored at the last disease assessment; this is intended to describe censoring rules for the analysis where only responders are used.

❖ **Safety analyses**

Safety analyses will be performed on the safety-evaluable population. Patients will be allocated according to whether any full or partial dose of atezolizumab was received, including when atezolizumab was received in error.

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences, laboratory tests, vital signs, and ECG measurements.

Frequency and percentages of patients who had at least one AE will be calculated by category:

- Any adverse event (AE)
- Any AE related to study drug
- Any AE leading to permanent study drug discontinuation
- Any serious AE
- Any serious AE related to study drug

- Any serious AE leading to permanent study drug discontinuation

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v5.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment cohort.
Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment cohort and grade.
Changes in vital signs will be summarized by treatment cohort.
Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment cohort.

13.3 PROTOCOL DEVIATIONS

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: (1) receiving unscheduled study agent infusions/injections; (2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the eligible subjects.

14 QUALITY CONTROL

14.1 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set-up to ensure the protection of patients, to ensure the ethical conduct of the study, to evaluate the benefit/risk ratio of the study and to insure an independent review of the scientific outcomes during and at completion of the study.

The Independent Committee exercises a consultative role for the promoter who takes the final decision for implementing the recommendations proposed by the committee.

The committee will include a statistician, a pharmacologist and clinical physicians.

This committee will be at least consulted:

- **Before the trial initiation**
- **After the inclusion of 20 patients in each cohort with a minimum follow-up of 2 cycles of induction**
  - **to check no over toxicity is observed (review of safety events without statistical analysis)**
  - **to review protocol deviations**

  Safety data and protocol deviations will be sent to IDMC for review, validation and agreement to continue the study (Inclusions will not be suspended during this IDMC consultation).

  The safety data will include disposition, demographic data, adverse event data (e.g. serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data. Efficacy data (excluding data on deaths) will not be included in the IDMC safety data reviews.
- **During the final analysis**

Dealing with safety, the committee will be informed by the Sponsor of all the observed toxicities (AESIs, SAEs) for regular reviewing of safety data and advice. It should propose to stop inclusions in case of unacceptable toxicities (in terms of severity and/or frequency).

For this purpose, regular teleconferences will be planned and will contain two parts: the first one with the Sponsor introducing the teleconference with a safety review, and the second one with only IDMC members who will independently deliberate. The Sponsor will be in charge of reporting all safety concerns to the IDMC, in terms of grade and timing along with treatment protocol adherence.

All the decisions will be documented in writing and communicated to all the investigators.

If needed, ad hoc teleconferences may be organized for any safety alert.

14.2 INDEPENDENT REVIEW BOARD

An independent review board will blindly evaluate the primary endpoint of this study (ORR) on anonymized CT-scanner. This board will meet three times a year.

14.3 QUALITY ASSURANCE

In order to ensure the authenticity and credibility of data in accordance to Good Clinical Practices (GCP), the sponsor will implement a quality assurance system that includes:

- the management of the test according to the procedures of the Clinical Research Unit
- the quality control of the data of the investigator site by the monitor whose role is to check the concordance and the coherence of the data of case report form of observation compared to the documents-source
- the provision if the funding provides for dedicated staff in the service to assist the investigator in the logistics of the study and the collection of data in the case report form.

15 ETHICS AND REGULATORY CONSIDERATIONS

The study will be conduct in accordance with the French Public Health Law, specially relating to research involving the biomedical human person of the Public Health Code, articles L1121-1 and following (Law No. 2012-300 of 05/03/2012 as amended by Ordinance No. 2016-800 of 16 June 2016), the Bioethics Law, the law related to the protection of physical persons for the treatments of personal data and related to information technology, database and liberties, the Helsinki declaration and the Good Clinical Practices

15.1 CLINICAL TRIAL AUTHORISATION

An authorization request will be sent by the sponsor to the French regulatory authorities before the study initiation:

- Ethics Committee (Committee for the Protection of Persons, CPP)
- Competent Health Authority (ANSM)

An Information will be given to the Competent Authority (ANSM), with transmission of the synopsys of the study and the favorable opinion of the CPP.

This study is under of the "Reference Methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the law of 6 January 1978 as amended relating to data processing, files and freedoms. This change was approved by decision of 5 January 2006.

The François Baclesse Center respects the regulations in force, in particular the rights of the persons being treated according to the EU regulation 2016/679 on the protection of data ("RGPD").

Any substantial modification in the protocol about objectives, design, population, evaluation, significant administrative modifications will need the coordinator approval, the sponsor approval, CPP approval and the competent authority authorization.

15.2 INFORMATION OF PATIENTS INVOLVED IN THE RESEARCH

Patients will be completely and faithfully informed with understandable words on the objectives and constraints of the research, potential risks, required measures for monitoring and safety, of their right to decline the participation in the study or the possibility to withdraw from the study at any time.
All these information are included in the informed consents form given to the patient: one for the main study, other for ancillary studies. The investigator, or the physician who represents him, will collect the signed written informed consent(s) before the definitive inclusion in the study. A copy of the information and consent form signed by the two parties will be given to the patient; the investigator will keep the second copy.
For any significant modification of the protocol related to the objectives of the research, its design, the population, the exams or significant administrative aspects, a new consent from each person participating to the research will be collected if needed.

15.3 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator of each participating center is committed to conduct the clinical trial in accordance with the trial protocol and with the regulations in force, notably the decision of 24 November 2006 related to Good Clinical Practices.
The Principal Investigator is responsible for:

- ✔ Giving to Sponsor his/her curriculum vitae and that of co-investigators
- ✔ Identifying persons involved in the research in his/her team and defining their responsibilities
- ✔ Initiating the inclusion of patients after Sponsor authorization
- ✔ Making the maximum effort to include the required number of patients within the established recruitment period.

Each Investigator is responsible for:

- ✔ Obtaining the signed and dated informed consent and personally signing this consent for each participating patient before any procedure specific to the trial
- ✔ Regularly completing the Case Report Form (CRF) for each patient included in the trial and to allow to CRAs mandated by the Sponsor a direct access to source data in order to validate the data entered in the CRF
- ✔ Dating, correcting and signing any correction in the CRFs and data clarification forms (DCF)
- ✔ Accepting the regular monitoring visits of the monitor and eventual auditors mandated by the Sponsor or inspectors of supervisory authorities

Source documents, defined as any document or original item that allow to prove the existence or accuracy of a data or a fact recorded during the study, will be kept during 15 years by the investigator or the hospital if the source is a hospital medical record.

The archiving of the data will be the responsibility of the investigator and according to the legislation. The patient should keep the data and a patient identification list for a minimum of 15 years after the end of the study.

15.4 DATA CONFIDENTIALITY

The investigator will ensure the confidentiality of all information concerning the project for himself and for all persons involved in the conduct of the trial until the publication of the test results. This confidentiality obligation will not apply to information that the investigator will be required to provide to patients in the context of their participation in the trial or to information already published. The investigator will ensure not to publish, disclose or use, in any way, directly or indirectly, scientific or technical information of the trial.

The study may not be the subject of any written or oral commentary without the agreement of the sponsor; all the information communicated or obtained during the realization of the test belonging in full right to the sponsor who can freely dispose of it.

16 DATA AND DOCUMENTS KEEPING

16.1 DATA ENTRY AND HANDLING

Data management will be performed by the Data Processing Center (CTD) of the North West Cancéropôle (Centre de Traitement des Données du Cancéropôle Nord-Ouest). The CTD provides a database management software dedicated to clinical research: Ennov Clinical (version 7.5.10, ENNOV / CLINSIGHT, 33155 Cenon, France).

This software package, which is based on an Oracle database architecture, is designed for the overall management of clinical and epidemiological studies, meets the regulatory requirements related to this type of study. The CTD Ennov Clinical instance is validated in its computing environment. A data validation plan will be developed jointly by the Clinical Research Unit and the Data Processing Center and will describe in detail the controls to be performed for each variable.

A database specific to the study will be created, tested and validated before the start of the study. All information required by the protocol must be recorded on the paper observation books - or on the electronic observation booklet - under the responsibility of the principal investigator and an explanation must be provided for each missing data item. The data will have to be entered in these notebooks as they are obtained, and the sponsor will take over the monitoring.

The data will then be checked by the CTD in accordance with the data validation plan.

The database will be frozen after final quality control and then exported to the adequate format for statistical analysis according to an automated and validated procedure.

16.2 ARCHIVING

The sponsor must ensure the archiving of essential documents on the conduct of the study in conditions ensuring their safety, for the minimum duration provided by BPC, 15 years after the end of the research.

These documents are the protocol and annexes including any amendments, original signed informed forms and consents, questionnaires, case report forms, follow-up documents, statistical analyses, the final report of the study.

16.3 PUBLICATION POLICY

The results of this study, property of the Sponsor (Centre François Baclesse), will be published under scientific articles. Publications relating to or resulting from this research will be communicated and submitted for review by the study coordinators to all investigators.

The authors include investigators that have included most patients, the biostatistician who has performed the data analysis, the clinical researcher monitor and the participants who provided substantial contribution to the development of the study, the analysis and interpretation of results and / or the writing of the manuscript.

Acknowledgement to IDMC members will be indicated in final publication.

No publication or presentation of the results will be allowed without the agreement of all the parties. Each investigator will be author in the order determined by the number of eligible patients included. No publication or communication will be performed without the agreement of the coordinating investigator and the Sponsor with the obligation to mention the name of the Sponsor, the organism which financially supported the conduct of the trial and thanking to Laboratories ROCHE that provided atezolizumab and bevacizumab.

Some dedicated publications for ancillary studies will be also performed.

This work will be the property of all authors and will be at their disposal for transversal communications and publications.

Publications related to the results of potential ancillary studies need prior approval of the coordinating investigator and methodologist and will be done after the publication of the main study, which should be cited as reference.

17 FUNDING AND INSURANCE

17.1 FUNDING

Any additional costs referred to the Code of Public Health are being negotiated between the CFB and the representative of the institution, taking into account the financial resources available to the CFB in the frame of its public promotion activities.

However, the CFB will ensure the study implementation and supply of the following material (protocol, CRF, investigator file) needed to the conduct of the study.

In the case of equipment or treatments are provided by other partners, the conditions must be specified in the study agreement.

17.2 INSURANCE

The sponsor has subscribed for the duration of the study an insurance covering his own liability and that of any physician involved in the realization of the study. It will also ensure full compensation for the harmful consequences to search for the person undergoing it and assigns, unless evidence against him that the damage is not attributable to its fault or that of any intervener, without that can be opposite the act of a third party or the voluntary withdrawal of the person who had originally agreed to participating to research (Article L 1121-10).

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