Clinical Protocol

*A Phase II Trial of atezolizumab plus **CA**rboplatin plus **P**aclitaxel as first-line therapy in metastatic **T**riple-negative PD-L1 positive breast cancer patients – the GIM25-CAPT trial*

Investigational Drug Substance(s):	Atezolizumab
Coordinating Investigator (CI):	Dott.ssa Claudia Bighin
Protocol number/name:	GIM25-CAPT
Protocol version:	1.0
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Sponsor:	Consorzio Oncotech

CONFIDENTIAL

PROTOCOL APPROVALS

SPONSOR

Prof. Sabino De Placido, MD/PhD
President of Consorzio Oncotech

Signature _____ Date 09/12/2019

COORDINATING INVESTIGATOR AND PROTOCOL CO-AUTHOR

Dott.ssa Claudia Bighin, MD/PhD

Signature _____ Date 22/11/19

STATISTICIAN

Dott. Paolo Bruzzi, MD/MPH/PhD

Signature _____ Date 10.12.2019

INVESTIGATOR PROTOCOL APPROVAL

GIM25-CAPT

*"A Phase II trial of atezolizumab plus **CA**rboplatin plus **P**aclitaxel as first-line **T**herapy in metastatic triple-negative PD-L1 positive breast cancer patients"*

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practices and local regulations and requirements.

Investigator:

Name: _____

Signature: _____

Date: _____

STUDY INSTITUTIONS

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SYNOPSIS

Study Title	A Phase II trial of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients
Study Phase	II
Protocol ID	GIM25-CAPT
Target Patients	First-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients
Study objectives	**Primary objective:** To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients as evaluated by % 2years OS. **Secondary objective:** • To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of % OS at 2.5 years • To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of % OS at 2 years in hormonal receptor (HR) between 1% and 10% • To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of post-progression survival • To assess the activity of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of ORR, and time to treatment failure • To assess the safety of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients

	Exploratory Objectives: Exploratory objectives will be focused on the assessment of both tumor-centered characteristics through the NGS analysis of circulating tumor DNA (ctDNA) and immune-centric features through the evaluation of a multiparametric Cancer agnostic circuLating ImmunOsignature (CLIO): • To assess the association between patients' characteristics, treatment activity, efficacy and safety and through a CLIO in metastatic triple-negative breast cancer patients receiving atezolizumab plus carboplatin plus paclitaxel as first-line therapy • To explore the association between the CLIO and treatment activity, efficacy and safety • To explore the dynamics of circulating tumor DNA (ctDNA) levels and detectable aberrations with respect to treatment activity and efficacy Concomitant timepoints will not be used for cross-validations between the two methodologies.
Endpoints	**Primary endpoints** • % Overall survival at 2 years **Secondary endpoints** • % Overall survival at 2.5 years • 2y OS in HR <1% and in HR 1-10% • Post-progression survival • Objective response rate • Time to treatment failure • Incidence and severity of adverse events and serious adverse events **Exploratory end points** • Variation of ctDNA levels from baseline to first evaluation through the multigene FoundationOne® Liquid NGS panel • Variation of ctDNA levels from the first evaluation to progression through the multigene FoundationOne® Liquid NGS panel • Association between archival PD-L1 levels and target genes expression levels through CLIO analysis • Variation of target genes expression levels through CLIO analysis from baseline to first evaluation • Variation of target genes expression levels through CLIO analysis from first evaluation to disease progression

Number of Sites	About 15 centers affiliated with the Gruppo Italiano Mammella (GIM) study group
Number of patients	104 treated patients
Countries	1 – Italy
Background and study rationale	Breast cancer is the most common cancer among women worldwide. Triple-negative breast cancer, defined based on the lack of expression of estrogen and progesterone receptors as well as of HER2 overexpression/amplification, represents 15% of all breast cancers. Patients with metastatic triple-negative breast cancer generally experience rapid progression and shorter overall survival as compared to those with other subtypes of breast cancer. Therefore, there is urgent need to improve the clinical outcomes of this subgroup of patients. Taxane-based chemotherapy represents the preferred standard first-line treatment in triple-negative breast cancer patients. Recent data from the TNT trial confirmed the activity of single agent taxane chemotherapy in this setting, although median progression-free survival was only 4.4 months. The recently presented phase III IMpassion130 study has demonstrated that the combination of atezolizumab plus nab-paclitaxel significantly reduced the risk of disease worsening or death in the intention-to treat and PD-L1 positive population with metastatic triple-negative breast cancer showing also encouraging overall survival results. Therefore, the combination of atezolizumab plus nab-paclitaxel is likely to become soon the new standard of care as first-line treatment of patients with metastatic triple-negative breast cancer. The recent results of randomized phase II TNACITY trial showed that the association of nab-paclitaxel and carboplatin seems the best chemotherapy schedule in terms of median progression free survival as first-line treatment of patients with metastatic triple-negative breast cancer. Recent evidences in metastatic non-small cell lung cancer showed the efficacy of concomitant use of carboplatin, paclitaxel and atezolizumab without any detrimental interaction between atezolizumab and steroid premedication of paclitaxel. Therefore, based on these data, the combination of atezolizumab plus carboplatin and paclitaxel represents a promising combination to be tested as first-line therapy in patients with metastatic triple-negative breast cancer to enhance the clinical activity and efficacy of first-line therapy in this setting.

Inclusion and exclusion criteria	**Inclusion Criteria** 1. Signed Informed Consent Form 2. Women or men aged ≥18 years 3. Histologically or cytologically confirmed adenocarcinoma of the breast with metastatic disease 4. Hormone receptor-negative (ER and PgR < 10%) and HER2-negative (IHC 0,1+ or 2+ ISH not amplified) breast cancer, based on the status of the primary tumor and/or the biopsy of metastatic disease before starting first-line therapy and assessed by local laboratory. 5. PD-L1 positive defined as expression on tumor-infiltrating immune cells ≥1% (SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems), based on the status of the primary tumor and/or the biopsy of metastatic disease before starting first-line therapy and assessed by local laboratory 6. Availability of a representative tumor specimen for translational research 7. Eligible for first-line taxane and carboplatin chemotherapy 8. No prior chemotherapy or targeted systemic therapy (including endocrine therapy) for inoperable locally advanced or metastatic TNBC. Prior radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy; however, patients should have recovered from the effects of radiation before enrollment 9. Previous chemotherapy with taxanes and/or carboplatin for early breast cancer (neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before study entry 10. Previous therapy with immune checkpoint inhibitors for early breast cancer (neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before study entry 11. ECOG performance status of 0 or 1 12. Life expectancy ≥ 12 weeks 13. Measurable or evaluable disease as defined by RECIST v1.1. 14. Adequate hematologic and end-organ function, defined by laboratory results obtained within 2 weeks prior to the first study treatment (Cycle 1, Day 1) 15. Negative human immunodeficiency virus (HIV) test at screening 16. Negative hepatitis B surface antigen (HBsAg) test at screening 17. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive HBcAb test followed by a negative hepatitis B virus

	(HBV) DNA test at screening. The HBV DNA test will be performed only for patients who have a positive HBcAb test 18. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test 19. Women of child bearing potential must agree to either use a contraceptive method with a failure rate of ≤ 1% per year or to remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 5 months after the last dose of atezolizumab, or for at least 6 months after the last dose of paclitaxel. 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 contraceptive methods with a failure rate of ≤ 1% per year include bilateral tubal ligation, male sterilization, 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception 20. Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug 21. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm **Exclusion Criteria** 1. 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 at least 2 weeks prior to enrollment. 2. Known central nervous system (CNS) disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met: a) No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed) b) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to enrollment

	c) No evidence of progression or hemorrhage after completion of CNS directed therapy Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible, if all other criteria above are met. 3. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX® are allowed) 4. Uncontrolled tumor-related pain a) Patients requiring narcotic pain medication must be on a stable regimen at study entry. b) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period. c) Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment. 5. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium >ULN) or clinically significant (symptomatic) hypercalcemia a) Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant (symptomatic) hypercalcemia are eligible. 6. Malignancies other than TNBC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer) 7. Pregnant or lactating women, or intending to become pregnant during the study 8. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome) 9. Significant cardiovascular disease, such as New York Heart

	Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to first dose, unstable arrhythmias, or unstable angina a) Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded b) Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate 10. Presence of an abnormal electrocardiogram (ECG) that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third degree heart block, evidence of prior myocardial infarction, or QT interval corrected using Fridericia's formula (QTcF) >470 ms demonstrated by at least two consecutive ECGs 11. Serious infection requiring antibiotics within 2 weeks prior to enrollment, including but not limited to infections requiring hospitalisation or IV antibiotics, such as bacteremia, or severe pneumonia 12. Major surgical procedure within 4 weeks prior to enrollment or anticipation of the need for a major surgical procedure during the study other than for diagnosis Note: Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted 13. Treatment with investigational therapy within 30 days prior to initiation of study treatment 14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins 15. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells or any component of the atezolizumab formulation 16. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis (MS), vasculitis, or glomerulonephritis (Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with

	controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study) 17. Prior allogeneic stem cell or solid organ transplantation 18. History of idiopathic pulmonary fibrosis (IPF, including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. (Note: History of radiation pneumonitis in the radiation field [fibrosis] is permitted) 19. Positive test for human immunodeficiency virus (HIV) 20. Active hepatitis B (positive hepatitis B surface antigen [HBsAg] test or hepatitis B virus [HBV] DNA polymerase chain reaction [PCR] test at screening) or hepatitis C (positive hepatitis C virus antibody test at screening). Note: • Patients with past HBV infection or resolved HBV infection (defined as having negative HBsAg and HBV DNA test but a positive hepatitis B core antibody [HBcAb] test) are eligible • Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV ribonucleic acid (RNA) 21. Current treatment with anti-viral therapy for HBV 22. Active tuberculosis 23. Receipt of a live, attenuated vaccine within 4 weeks prior to enrollment or anticipation that such a live, attenuated vaccine will be required during the study Note: Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to enrollment, during treatment or within 5 months following the last dose of atezolizumab 24. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to enrollment 25. Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide, and antitumour necrosis factor [TNF] agents) within 2 weeks prior to enrollment, or anticipated requirement for systemic immunosuppressive medications during the trial a) Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study b) Patients with a history of allergic reaction to IV contrast requiring steroid pretreatment should have baseline and

	subsequent tumor assessments performed using MRI c) 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 d) Systemic corticosteroids are allowed as paclitaxel premedication during the trial at a dose ≤10 mg dexamethasone or equivalent in order to avoid severe hypersensitivity reactions 26. Poor peripheral venous access 27. Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment 28. Any other serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study 29. History of hypersensitivity reactions to paclitaxel or other drugs formulated in the same solvent as paclitaxel (polyoxyethylated castor oil) 30. History of hypersensitivity reactions to carboplatin
Study Design:	All eligible patients will receive carboplatin Area Under the Curve (AUC) 2 dd 1,8,15 q 28 dd, paclitaxel 90 mg/m2 dd 1,8,15 q 28 dd and atezolizumab 840 mg dd 1,15 q 28 dd and they will continue this treatment until progression of disease, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. In case of interruption of one of the three drugs for unacceptable toxicity and/or medical decision, the patient may continue to receive one or more of the remaining drugs until progression per RECIST v1.1. If the investigator decides to interrupt carboplatin and paclitaxel (for toxicity and/or medical decision), atezolizumab may be continued as maintenance therapy until disease progression or unacceptable toxicity. All patients who discontinue study treatment (including due to PD) will be followed for survival approximately every 3 months for 2 years from last patient enrolled or until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. Imaging tumor evaluation will be performed every 12 weeks.
Study Treatment	• Atezolizumab at a fixed dose of 840 milligrams via intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle • Carboplatin area under the curve 2 via IV infusion on Days 1, 8, and 15 of each 28-day cycle

	• Paclitaxel at a dose of 90 milligrams per square meter via IV infusion on Days 1, 8, and 15 of each 28-day cycle In the absence of disease progression or unacceptable toxicity, study treatments will continue until the end of the study (2 years from last patient enrolled or study termination by the Sponsor).
Summary Statistical Statements	This phase II, single-arm, study is designed to test the hypothesis that the addition of an anti-PDL1 to 1st line therapy in metastatic triple-negative PD-L1 positive breast cancer is associated with a clinically relevant 2-year increase in OS over what expected based on historical data (54%). **Statistical Considerations:** The statistical design of this phase II trial is influenced by 2-factors: a) The addition of an immunotherapy agent to a polychemotherapy with a considerable activity in TNBC is unlikely to produce a substantial improvement in the Response Rate or in Progression Free Survival. Therefore, the only study endpoint capable of capturing any effect of this addition is Overall Survival. b) Although TNBC is possibly the biological variant of breast cancer which is least susceptible to medical treatments, short term survival of patients with mTNBC is still quite high, with a median OS in excess of 2 years (Tutt et al. 2018; Yardley et al. 2018) As a consequence, the standard design of phase II trials, which is focused on short term markers of response and incorporates stopping rules for futility based on early interim analyses, cannot be used. Instead, this trial is designed as a single stage cohort study in which all patients will be followed til the end of the study, which is set at two years after the enrolement of the last patient, thereby ensuring a minimal potential follow-up of 2 years to all enrolled patients who did not die before 2 years. The primary study endpoint will be the proportion of patient alive at two years (2ys OS%), but, OS% at 2.5 years will represent a important secondary endpoint, since, considering that no less than 1 year will be necessary to enroll all patients into the study, at the time of the final analysis (i.e. 2 years after the enrolment of the last patient), 50% of the enrolled patients will have a follow-up ≥2.5 years. **Expected results and sample size:** In order to reject with power 80% at the 0.05 (1-sided) significance level the null hypothesis that 2yrsOS in mTNBC treated with atezolizumab plus carboplatin and paclitaxel is 54%, under the alternative hypothesis

	that atezolizumab increases this porportion by 12% (i.e. to 66%), it is necessary to enroll into the study 104 patients. With 104 patients, the minimal observed 2yrsOS% allowing rejection of the null hypothesis at the 1-sided 5% significance level is 62.5% (=65 survivors at 2yrs /104 enrolled patients) and the estimated 2yrsOS will have a precision (= width of the exact 90% CI) of approximately +/- 8% (e.g., for 65 successess/104 patients) $0.5401 \leq p \leq 0.7044$)
Planned study timelines	Enrollment period: 2 years approximately First Patient First Visit (FPFV): Feb 2020 Last Patient First Visit (LPFV): Feb 2022 Follow-up: 2 years (from the enrollment of the last patient) Total Study Duration: 4 years approximately

STUDY SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Screening	**Screening**	**All Cycles [a1] (Q28 dd)**			**End of Treatment visit – EoT [b]**	**Follow-up Every 3 months (± 21 days) till 2 years from LP enrolled End of study (EoS): Last FU visit after 2 years from LP enrolled**
	Days -28 to -1	**Days -7 to -1**	**Day 1 (baseline) [a2]**	**Day 8 [a3] [a4]**	**Day 15**	**30 (+/-5) days after last dose**	
Signed Informed Consent [c]	x						
Review of eligibility criteria	x	x					
PD-L1 positivity [d]	x						
Medical, surgical and cancer histories [e]	x						
Head CT or MRI	x						
HIV, HBV, HCV serology [f]	x						
Tumor Assessment [g]	x	Every 12 weeks(± 1 week) starting from day 1, until PD, death, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor regardless of treatment delays, interruptions or discontinuations.					
Physical Examination [h]	x	(x)	x			x	
ECOG PS	x	(x)	x			x	
Vital signs [i]	x		x	x	x	x	
Electrocardiogram [k]	x	Perform as clinically indicated					
Echocardiography	x	Perform as clinically indicated					
Hematology and Serum chemistry [l]	x		x	x	x	x	
Coagulation Panel	x					x	
Urinalysis [m]	x	Perform as clinically indicated					
Pregnancy Test		x[n]	x[o]			x[o]	
TSH, fT3, fT4 [p]	x		x[p]			x	
Adverse events [q]	x	x	x	x	x	x	(x) [q]
Atezolizumab infusion [r]			x		x		
Paclitaxel and Carboplatin administration [a3, a4]			x	x	x		
Survival and anti-cancer therapy follow-up [s]							x
Translational Assessments							
ctDNA blood sample collection (FoundationOne® Liquid)		x	An additional sample will be collected at first evaluation			x	
CLIO blood sample collection		x	Every 12 weeks concomitantly to tumor assessments			x	

[a1] If a scheduled treatment visit cannot be completed due to a holiday, dosing may be postponed to the earliest next date; subsequent dosing should continue according to the original schedule. However, paclitaxel and carboplatin should not be administered more frequently than every 7 days. After five cycles, one of three cycles may be delayed by one week to allow for vacations.
[a2] Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

[a3] Paclitaxel will be administered at the 90 mg/m2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. Paclitaxel should not be administered more frequently than every 7 days. The Day 8 visits are not required for patients who have discontinued paclitaxel and are continuing treatment with atezolizumab only.
[a4] Carboplatin will be administered at the AUC dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. Carboplatin should not be administered more frequently than every 7 days. The Day 8 visits are not required for patients who have discontinued carboplatin and are continuing treatment with atezolizumab only.
[b] Patients will be asked to return to the clinic within 30 days after their last study drug dose for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., due to PD) may be used as the treatment discontinuation visit.
[c] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to first dosing (except where otherwise specified) may be used for screening assessments rather than repeating such tests. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
[d] PD-L1 positive defined as expression on tumor-infiltrating immune cells ≥1% (SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems), based on the status of the primary tumor and/or the biopsy of metastatic disease before starting first-line therapy and assessed by local laboratory. The PD-L1 positivity may be evaluated in archival or fresh tumor tissue. An archived biopsy prior to therapy is acceptable if the fresh biopsy cannot be obtained and if the archived tissue meets the defined criteria as stated below:

- Obtained from primary or metastatic site
- An archived biopsy (block or slides) contains tumor tissue.
- If an archived block is not available, 10 or more slides containing tumor will be acceptable

[e] Demographic information includes age, gender, and self-reported race/ethnicity. Reproductive status and smoking history should also be captured. Cancer history includes stage, date of diagnosis, and prior anti-tumour treatment.
[f] All patients will be tested for HIV antibody, HBsAg, HBcAb, and HBsAb, and hepatitis C virus antibody (HCVAb) locally, prior to the inclusion into the study. HIV-positive patients will be excluded from the clinical trial. In patients with a negative HBsAg and positive HBcAb serology, HBV DNA must also be collected prior to enrollment. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.
[g] Tumour assessments will be performed every 12 weeks starting from day 1, until PD, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening/baseline. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan, and 3) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. For each patient, the same radiographic procedures and technique must be used throughout the study, and results must be reviewed by the investigator before dosing at the next cycle. Tumour response will be evaluated using RECIST v1.1. During the post-treatment Follow-up period, only patients with no PD will undergo tumour assessments. For patients who discontinue study treatment before EOS for reasons other than PD, tumour assessments will continue until PD, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor.
[h] Complete physical examination at Screening, and EOT, and symptom-driven physical examinations within 96 hours before Day 1 of each cycle, and as clinically indicated. Physical examinations will include a review of the main body organs and systems, with special attention to cardiovascular (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g. shortness of breath, crackling), gastrointestinal (e.g. abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis.
[i] Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated.
[k] Standard 12-lead ECG, taken after resting in a supine position for at least 10 minutes. Additional cardiovascular monitoring (such as ECG and/or echocardiography) may be considered during the patient's study participation, if clinically indicated by the appearance of symptoms or findings at regular vital sign checks or medical examinations suggestive of cardiovascular disease (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs, shortness of breath, crackling) especially if these cannot be explained by thyroid or electrolyte abnormalities.
[l] Haematology consists of RBC count, haemoglobin, haematocrit, WBC count with differential (if clinically indicated), and platelet count. Serum chemistry includes BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, glucose, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Bicarbonates should only be tested at sites where this test is part of the standard safety laboratory panel. Magnesium and phosphorus should be collected at screening, and thereafter only if clinically indicated. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms suggestive of pancreatitis.
[m] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) will be performed at screening, and thereafter only if clinically indicated
[n] Serum pregnancy test within 7 days before Cycle 1, Day 1.
[o] Urine pregnancy test; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on within 96 hours before Day 1 of Cycle 1, and within 96 hours before Day 1 of every second cycle thereafter, and at treatment discontinuation.
[q] After informed consent has been obtained, throughout the treatment period and including the follow-up period, adverse events and serious adverse events will be recorded. After initiation of study drug, all AEs will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report any deaths, SAEs, or other AEs of concern that are considered related to prior treatment with the study drug. The investigator should follow each SAE and Grade ≥3 AE until the event has resolved to baseline grade, assessed as stable by the investigator, or until the patient withdraws consent or is lost to follow-up.
[r] Patients should receive their first dose of study drug on the day 1of each cycle. The first dose of atezolizumab will be delivered over 60 ± 15 minutes; if well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes.
[s] All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information until death, withdrawal of consent, loss to follow-up, or until study termination by the Sponsor. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months ± 21 days. Public information sources (e.g., county records) may also be used to obtain information about survival status only in case the patient withdrew from the study

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
Cmax	Peak concentration
Cmax,ss	Peak concentration at steady state
Cmin	Trough concentration
Cmin,ss	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
Fc	Fragment crystallizable
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
HIV	Human immunodeficiency virus
HR	Hormonal Receptor

HUS	Hemolytic-Uremic Syndrome
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	Interleukin
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
MAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
Q2W	Every 2 weeks
Q3M	Every 3 months
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
QoL	Quality of life
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate

QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SID	Subject identification
sPD-L1	Soluble programmed cell death ligand 1
SOCS3	Suppressor of cytokine signaling 3
SUSAR	Suspected unexpected serious adverse reaction
t½	Half life
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
Tmax	Time to peak concentration
Tmax,ss	Time to peak concentration at steady state
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WFI	Water for injection
WHO	World Health Organization
BICR	Blinded Independent Central Review
PS	Performance status

1 BACKGROUND

1.1 Background on Breast Cancer

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women both in more and less developed regions. There were an estimated 1.67 million new cancer cases diagnosed worldwide in 2012 (25% of all cancers) (Ferlay et al. 2013; Ferlay et al. 2015; Torre et al. 2015). Age-adjusted incidence rates (per 100,000 population) are highest in North America (91.6), followed by Europe (69.9), Latin America (47.2), and Eastern Asia (27.0) (Ferlay et al. 2013).

It is estimated that in 2018 about 52,800 new cases of female breast carcinomas have been diagnosed in Italy. If cutaneous carcinomas are not considered, breast cancer is the most diagnosed neoplasia in women, in which about one malignant tumour out of three (29%) is a breast cancer. (I numeri del cancro in Italia, 2018)

The majority of patients are diagnosed with localized breast cancer, however, approximately 6% of patients present with de novo metastatic disease and between 10% and 40% of patients with localized breast cancer will relapse systemically (Zeichner et al. 2015a; Zeichner et al. 2015b).

Breast cancer ranks as the fifth cause of death from cancer overall in the world (522,000 deaths; 6.4% of all cancer-related deaths), the leading cause of cancer-related deaths in women (14.7% of all cases), and the second cause of cancer death in women in more developed regions (198,000 deaths, 15.4% of total) after lung cancer (Ferlay et al. 2013; Ferlay et al. 2015; Torre et al. 2015). Age-adjusted mortality rates (per 100,000 population) are highest in Europe (16.1), followed by North America (14.8), Latin America (13.0), and Eastern Asia (6.1) (Ferlay et al. 2013). In the USA, it is projected that there will be 40,450 deaths due to BC in 2016 (Siegel et al. 2016; Miller et al. 2016). Also in Italy, breast cancer is the first cause of death for cancer in women, with 12,274 deaths in 2015 (AIOM. 2018).

The above statistics include all subtypes of BC (Ferlay et al. 2013; Collignon et al. 2016). However, BC is a heterogeneous disease encompassing about 15 different types of carcinomas, which are for therapeutic reasons, further classified according to their estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (Brouckaert et al. 2012). These subgroups have important implications for the choice of therapy, treatment outcomes, recurrence rate, and mortality risk. The lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is referred to as triple-negative BC (TNBC) (Trivers et al. 2009; Zeichner et al. 2016).

The prognosis of patients with metastatic breast cancer (mBC) varies from several months to many years depending upon multiple factors, including, but not limited to, ER/PR status and HER2 status (Zeichner et al. 2015a; Zeichner et al. 2015b). Most new treatment options for mBC are only effective for ER/PR-positive or HER2-positive metastatic tumors (Zeichner et al. 2016). The 5-year survival rate following metastatic diagnosis is around 15% (Jemal et al. 2011; Ferlay et al. 2013).

1.1.1 Triple-Negative Breast Cancer (TNBC)

The triple-negative subtype is a heterogeneous group of BCs, characterized by the lack of expression of hormonal receptors and the absence of HER2 overexpression (Collignon et al. 2016). According to the St. Gallen International Expert Consensus (Goldhirsch et al. 2009), and the recommendations of the American Society of Clinical Oncology and the American College of Pathology (Hammond et al. 2010), tumor specimens are ER or PR negative if less than 1% of tumor cells express the estrogen and progesterone receptors via immunohistochemistry (IHC), and HER2-negative if showing IHC 0 or 1+ or in situ hybridization (ISH) negative using single-probe ISH or dual-probe ISH (Wolff et al. 2013).

Although 1% has been used as cut-off for ER positivity, several studies have reported that tumors with ER < 1% have characteristics similar to those with 1% ≤ ER < 10%. Recently an observational study showed that stage II or III HER2-negative primary breast cancer with ER < 10% behaves clinically like triple-negative breast cancer in terms of pCR and survival outcomes and patients with such tumors may have a limited benefit from adjuvant hormonal therapy. It may be more clinically relevant to define triple-negative breast cancer as HER2-negative breast cancer with <10%, rather than <1%, of ER and/or progesterone receptor expression (Fujii T et al. 2017). However, all recent studies that evaluated first-line treatments in TNBC used cut-off of <1% to define ER negativity but it could be extremely interesting and clinically useful to test new combinations also in the ER < 10% breast cancer patients.

Approximately 15%-20% of all BCs belong to the triple-negative phenotype that has distinct risk factors, distinct molecular features, and a particular clinical presentation and outcome (Brouckaert et al. 2012; Lin et al. 2012; Penault-Llorca and Viale, 2012). The TNBC phenotype has been associated with younger age, and more advanced tumor stage at presentation (Millikan et al. 2008; Lund et al. 2009; Trivers et al. 2009; Lin et al. 2012; Danforth et al. 2013). TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBCs exhibit rapid progression and a poor clinical outcome (Mersin et al. 2008; Trivers et al. 2009; Wahba and El-Hadaad, 2015). TNBC is associated with a higher risk of brain or lung metastases, and worse breast cancer specific and overall survival (OS) (Lin et al. 2012); median OS is generally between 12 months (Tutt et al. 2018) and 17 months in patients treated with various chemotherapy agents (Yardley et al. 2018).

Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBCs and their diverse gene-expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies (Hirshfield and Ganesan, 2014). Chemotherapy is the mainstay of treatment of TNBC, and current treatment strategies for triple-negative disease include anthracyclines, taxanes, platinum agents, and bevacizumab (Hudis and Gianni, 2011). However, although TNBC may respond to chemotherapy, including taxanes, relatively few new agents have been approved for the subset of patients with metastatic TNBC (mTNBC) (Carey et al. 2012; O'Shaughnessy et al. 2014; Hirshfield and Ganesan, 2014; Zeichner et al. 2016) and there are no targeted therapies with widespread global approval available for patients with this specific subtype of breast cancer.

Taxane-based chemotherapy represents the preferred standard first-line treatment in triple-negative breast cancer patients (Cardoso et al. 2018). Recent data from the TNT trial confirmed the activity of single agent taxane chemotherapy in this setting, although median progression-free survival (PFS) was only 4.4 months

(Tutt et al. 2018).

The recent results of randomized phase II TNACITY trial showed that the association of nab-paclitaxel and carboplatin seems the best chemotherapy schedule as first-line treatment of patients with metastatic triple-negative breast cancer with a median PFS of about 8 months (Yardley et al. 2018).

Considering the improvement of PFS obtained with the combination compared to the monotherapy, the combination may represent a starting point for exploring new effective treatment regimens for mTNBC.

1.1.2 Taxanes and Paclitaxel in Metastatic Breast Cancer

Taxane-based regimens are considered a standard of care option in first-line therapy for patients with mBC, including TNBC (Cardoso et al. 2018). No standard approach exists for second- or further-line treatment, and options for cytotoxic chemotherapy are the same as those for other subtypes. Single-agent cytotoxic chemotherapeutic agents are generally regarded as the primary option for patients with metastatic TNBC, although combination chemotherapy may be used when there is aggressive disease and visceral involvement. The role of paclitaxel in the treatment of BC is well established. The response rates for paclitaxel administered as a single agent to patients with mBC are approximately 25% in first-line treatment (Wilson et al. 1994; Seidman et al. 1995; Nabholtz et al. 1996; Gradishar et al. 2005). Weekly paclitaxel (80–90mg/m2) is currently considered the most effective schedule for delivering paclitaxel (Swanton et al. 2011), and was found to be associated with higher overall survival (OS) and lower incidence of serious adverse events, neutropenia, neutropenic fever, and peripheral neuropathy compared with the three-weekly taxane schedules in advanced breast cancer (Seidman et al. 2008; Mauri et al. 2010). In addition, a regimen consisting of weekly paclitaxel administrations for three weeks, followed by one-week break was reported to be associated with less neurotoxicity compared to continuous weekly administrations (Swanton 2011).

1.1.3 Platinum-based Regimens in Metastatic Breast Cancer

As predicted by their deoxyribonucleic acid (DNA)-damaging mechanism of action, platinum compounds are expected to be particularly active in tumors characterized by a defect in DNA double-strand break repair, such as those without active breast cancer susceptibility gene (BRCA1/2) proteins (Turner and Tutt 2012; Cardoso et al. 2018; Isakoff et al. 2015). In recent years, substantial evidence has accumulated confirming the link between TNBC and BRCA1/2 mutations (Gerratana et al. 2016; González-Rivera et al. 2016). Approximately 80% of breast cancers with BRCA1 mutation are TNBCs, and up to 20% of patients affected by TNBC are carriers of a BRCA germline mutation. Therefore, TNBCs had been postulated to be particularly sensitive to interstrand cross-linking agents, including platinum analogues (Turner and Tutt 2012; Isakoff et al. 2015; Gerratana et al. 2016).

The clinical activity of first- or second-line platinum monotherapy in mTNBC was demonstrated in a multicentre Phase II clinical trial (TBCRC009; N=86). In this study, objective response rate (ORR) was 25.6% overall (cisplatin and carboplatin groups combined), and 54.5% in patients with germline BRCA1/2 mutations (p=0.022) (Isakoff et al. 2015). In the recent phase III randomized TNT trial (N=376), treatment with carboplatin resulted in a significantly higher ORR versus docetaxel in patients with BRCA1/2 mutations (68% versus 33.3%; P = 0.03) but no difference in terms of ORR and PFS were observed in the

wild-type population (Tutt et al. 2018).

Platinum-containing chemotherapy combinations have demonstrated activity in patients with TNBC both in the neoadjuvant (Alba et al. 2012; von Minckwitz et al. 2014; Sikov et al. 2015; Loibl et al, 2018; Poggio et al. 2018) and metastatic settings (O'Shaughnessy et al. 2011; O'Shaughnessy et al. 2014; Yardley et al. 2018), particularly in TNBC patients with BRCA1/2 mutations (Tutt et al. 2018; Telli et al. 2015).

In the single-arm phase II PrECOG 0105 study, 80 patients with stage I to IIIA (T ≥ 1 cm) TNBC or BRCA1/2 mutation-associated breast cancer received neoadjuvant gemcitabine (1,000 mg/m2 intravenously [IV] on days 1 and 8), carboplatin (area under curve [AUC] of 2 IV on days 1 and 8), and iniparib (5.6 mg/kg IV on days 1, 4, 8, and 11) every 21 days for initially four, and following a protocol amendment, every 6 cycles. In the intent to treat (ITT) population, pathological complete response (pCR) rates were higher in patients with BRCA1/2 mutation (47%), and even higher in patients with TNBC and BRCA1/2 mutations (56%) compared to those who were not carriers of these mutations (Telli et al. 2015).

In a phase II randomized study (n = 123) evaluating the clinical benefits of gemcitabine and carboplatin with or without iniparib in patients with metastatic TNBC, gemcitabine 1000 mg/m2 IV plus carboplatin IV dosed at AUC2 on days 1 and 8 every 3 weeks (n = 62) resulted in a median progression-free survival (PFS) of 3.6 months, a median OS of 7.7 months, and ORR of 32% (O'Shaughnessy et al. 2011). In a subsequent confirmatory randomized phase III study comparing these two regimens in 519 women with metastatic TNBC, gemcitabine plus carboplatin demonstrated median PFS and OS of 4.1 and 11.1 months, respectively in the ITT population and 4.6 and 12.4 months based on an exploratory analysis in patients receiving first-line treatment (O'Shaughnessy et al. 2014).

Other gemcitabine and carboplatin-containing regimens have also been evaluated in patients with advanced TNBC. The combination of carboplatin with eribulin (a mitotic inhibitor) as first-line therapy for locally recurrent or metastatic TNBC resulted in ORR of 57.9%, clinical benefit rate (CBR) of 68.1%, and a median PFS of 8.4 months (95% confidence interval [CI]: 4.6, 10.4) in a recently reported Phase 2 study (Michalaki et al. 2016). The results of phase II tnAcity study comparing weekly nab-paclitaxel 125 mg/m2 plus gemcitabine IV 1000 mg/m2 or carboplatin IV AUC2 versus gemcitabine/carboplatin as first-line treatment of patients with metastatic TNBC have recently been published. Weekly nab-paclitaxel plus carboplatin was associated with significantly longer PFS (7.4 months) compared to weekly regimens of either nab-paclitaxel plus gemcitabine (5.4 months; P=0.02; HR 0.60, 95% CI, 0.39-0.93) or of carboplatin plus gemcitabine (6.0 months; P= 0.03; HR 0.61, 95% CI, 0.39-0.94). Nab-paclitaxel plus carboplatin also prolonged OS (16.4 months) compared to either nab-paclitaxel plus gemcitabine (12.1 months; P=0.07; HR 0.66, 95% CI, 0.42-1.04) or of carboplatin plus gemcitabine (12.6 months; P= 0.18; HR 0.74, 95% CI, 0.48-1.16), however the between-group differences were not statistically significant (Yardley et al. 2018).

A recent systematic review and meta-analysis of 23 randomized trials involving 4625 patients assessed the efficacy and safety of platinum therapy (11 with cisplatin, 11 with carboplatin, and 1 with either agents respectively) in patients with locally advanced or metastatic breast cancer. Although at the expense of significantly increased fatigue, haematological and gastrointestinal toxicity, compared with non-platinum regimens, cisplatin, and carboplatin prolonged OS (HR 0.91; 95% CI 0.83-1.00, p = 0.04), PFS (HR 0.84; 95% CI 0.73-0.97, p = 0.01), and RR (HR 1.27; 95% CI 1.03-1.57, p = 0.03) (Petrelli et al. 2016).

According to the latest (3rd) revision of the European School of Oncology (ESO)- European Society of Medical Oncology (ESMO) international consensus guidelines for advanced breast cancer, in triple-negative ABC patients (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option. (Cardoso et al. 2018).

1.1.4 PD-L1 Inhibitors in the Treatment of TNBC

Recent investigations of targeted therapy for advanced TNBC includes immune checkpoint inhibitors targeting the programmed death receptor 1 (PD-1)/ programmed death ligand 1 (PD-L1; also called B7-H1 or cluster of differentiation [CD]274). PD-L1 is expressed on many cancer and immune cells (e.g., macrophages), and plays an important part in blocking the 'cancer immunity cycle' by binding and stimulating PD-1 and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation. 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; Herbst et al. 2014). B7.1 is a molecule expressed on presenting cells and activated T cells. Binding of PD-L1 to its receptors suppresses T cells migration, proliferation and secretion of cytotoxic mediators, and restricts tumor cell killing, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011; Herbst et al. 2014). The PD-1/PD-L1 pathway has been implicated in tumors evading immune surveillance. Blockage of the PD-1/PD-L1 interaction enables the rapid restoration of the effector function of preexisting anticancer T cells (Chen and Mellman, 2013; Saha and Nanda, 2016). Blocking PD-L1 should therefore enhance anticancer immunity (Herbst et al. 2014).

Based on results of early clinical studies, blockade of the PD-1/PD-L1 axis with atezolizumab (Emens et al. 2015; Adams et al. 2015; Schmid et al. 2017), pembrolizumab (Nanda et al. 2016; Adams et al. 2017a; Adams et al. 2017b), or avelumab (Dirix et al. 2016) has demonstrated promising efficacy and durable responses in patients with advanced TNBC.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary (CHO) cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) 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 human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and haematologic malignancies in humans. Atezolizumab has been approved in the USA for the treatment of locally advanced or metastatic urothelial carcinoma and metastatic non-small cell lung cancer (NSCLC).

1.2.1 Summary of Clinical Studies in Patients with TNBC

Atezolizumab is being investigated in multiple Phase I, II, and III clinical studies, both as monotherapy and in combination with several anti-cancer therapies against solid tumors and hematologic malignancies (see the atezolizumab Investigator's Brochure for study descriptions).

Anti-tumor activity, as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 responses, has been observed across multiple advanced tumor types for both atezolizumab monotherapy (Phase 1a study PCD4989g) as well as in combination with bevacizumab and/or chemotherapy (Phase 1b study GP28328). In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2015; Schmid et al. 2017), and in combination with nab-paclitaxel (Adams et al. 2016).

Combining atezolizumab with chemotherapy is hypothesized to enhance tumor-specific T-cell immunity by exposing the immune system to high levels of chemotherapy-induced tumor antigens and modulating T-cell and NK cell functions (Adams et al. 2016).

1.2.1.1 Efficacy of Atezolizumab Monotherapy in Patients with TNBC

Atezolizumab monotherapy has been evaluated in a mTNBC expansion cohort as part of a multicentre Phase Ia study PCD4989g (clinicaltrials.gov identifier: NCT01375842).

PCD4989g is a first-in-human, ongoing open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, PK, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

Atezolizumab is administered at 15 mg/kg, 20 mg/kg or 1200 mg flat dose IV every three weeks (Q3W). Preliminary results based on the first 21 efficacy-evaluable patients (13 PD-L1 IHC2, and eight PDL-1 IHC3) indicated an unconfirmed RECIST objective response rate (ORR) of 24% (95% confidence interval [CI], 8% to 47%); the confirmed ORR was 19% (95% CI 5.5% to 42%). Of the four patients with confirmed objective response, there were two partial responses (PRs) and two complete responses (CRs) (Emens et al. 2015; Atezolizumab Investigator's Brochure, 2016). Response duration ranged from 0.1 to 41.6 weeks, with the median not reached at the time of reporting.

Overall, the 24-week progression-free survival (PFS) rate was 33% (95% CI, 12% to 53%). Biomarker analysis revealed transient elevation of plasma cytokines and proliferating CD8+ T-cells following atezolizumab treatment (Emens et al. 2015). Among 115 ORR-evaluable patients, investigator-assessed confirmed ORR was 10% (95% CI, 5-16) with 3 complete responses (CRs) and 8 partial responses (PRs). Median duration of objective response (DoR) was 21 months (range 3 to >38 weeks) and all-patient median OS was 8.9 months (95% CI, 7.0-12.6), with a median follow-up duration of 25.3 months. Median PFS was 1.4 months (95% CI, 1.3–1.6). These data suggest a similarity to or advantage over standard of care (SOC) treatment. Higher PD-L1 expression (IC2/3) compared to lower PD-L1 expression (IC0/1) was associated with better clinical outcomes, as evidenced by higher ORR (12% vs. 5% in the two subgroups, respectively), and longer median OS (10.5 months [95% CI, 7.1–14.7] vs 7.0 [95% CI, 5.1–12.6], respectively). Greater treatment benefit was also observed in patients receiving first-line (1L) compared to

subsequent lines (2L+) atezolizumab, as evidenced by higher ORR (24% among 1L patients vs. 6% among 2L+ patients), and longer median OS (17.6 months [95% CI, 10.2–NE], vs. 7.3 months [95% CI, 6.1–10.8], respectively). Median PFS was consistent (approximately 1.4 months) regardless of PDL1 expression or line of therapy (Atezolizumab Investigator's Brochure, 2017). Atezolizumab increased intratumoural tumor infiltrating lymphocytes (TILs), CD8, macrophages and IC PD-L1 expression, but no response association was observed (Schmid et al. 2017).

1.2.1.2 Efficacy of Atezolizumab Combined with Chemotherapy in Patients with TNBC

Building on the promising results of atezolizumab as a single agent, an open-label Phase 1b trial (GP28328; clinicaltrials.gov identifier: NCT01633970) was initiated to evaluate atezolizumab in combination with chemotherapy and/or bevacizumab in locally advanced or metastatic solid tumors. One of the arms (Arm F) is evaluating 4-week cycles consisting of atezolizumab 800 mg Q2W (days 1 and 15) in combination with nab-paclitaxel 125 mg/m2 Q1W (days 1, 8, and 15) in patients with mTNBC, treated with ≤2 prior lines of therapy for metastatic disease. After nab-paclitaxel discontinuation, maintenance atezolizumab is allowed until loss of clinical benefit. Primary endpoints are safety and tolerability; secondary endpoints include clinical activity. Preliminary results are available for the 32 enrolled female patients aged 32 to 84 years (median 56 years). The majority of patients (87%) received prior taxane therapy (Adams et al. 2015; Adams et al. 2016). As of the data cut-off of 14 January 2016, the investigator-assessed ORR per RECIST v1.1 was 37.5% (95% CI, 21.1, 56.3; confirmed responses only); these included one complete CR and 11 PRs. Clinical benefit was observed across all lines of therapy, with ORRs being comparable between patients with one vs three or more previous lines of treatment (46.2% and 40.0%, respectively); refer to the atezolizumab Investigator's Brochure for further details.

1.2.1.3 Efficacy and Safety of Atezolizumab Combined with Nab-paclitaxel in Patients with TNBC

In phase III randomized trial Impassion 130, patients with untreated mTNBC cancer were randomized to receive atezolizumab 840 mg day 1 and 15 every 28 days plus nab-paclitaxel 100 mg/m2 day 1, 8 and 15 every 28 days or placebo plus nab-paclitaxel; patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Stratification factors were the receipt or non-receipt of neoadjuvant or adjuvant taxane therapy, the presence or absence of liver metastases at baseline, and PD-L1 expression at baseline (positive vs. negative). The two primary end points were PFS (in the intention-to-treat population and PD-L1–positive subgroup) and OS (tested in the intention-to-treat population; if the finding was significant, then it would be tested in the PD-L1–positive subgroup).

Each group included 451 patients (median follow-up, 12.9 months). In the intention to-treat analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P = 0.002); among patients with PD-L1–positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P = 0.08); among patients with PD-L1–positive tumors, the median OS was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI, 0.45 to 0.86). Combination therapy with atezolizumab plus nab-paclitaxel had a safety profile that was

consistent with the known toxic effects of each agent. Consistent with observations from other atezolizumab–chemotherapy combination trials, no new adverse-event signals were.

Among patients in the safety population, adverse events, regardless of attribution, occurred in 99.3% of 452 patients in the atezolizumab–nab-paclitaxel group and in 97.9% of 438 patients in the placebo–nab-paclitaxel group. The most common adverse events were similar in the two groups, with no new adverse events identified. Alopecia was the most common event in each group. The frequencies of nausea, cough, neutropenia, pyrexia, and hypothyroidism were at least 5 percentage points greater in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group. The rate of adverse events of grade 3 or 4 was 48.7% in the atezolizumab–nab-paclitaxel group and 42.2% in the placebo–nab-paclitaxel group, and the most common events in these groups (as assessed by the investigator) were neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia. The frequency of peripheral neuropathy of grade 3 or 4 was higher in the atezolizumab–nab-paclitaxel group (25 patients [5.5%]) than in the placebo–nab-paclitaxel group (12 patients [2.7%]). Serious adverse events occurred in 103 patients (22.8%) in the atezolizumab–nab-paclitaxel group and in 80 (18.3%) in the placebo–nab-paclitaxel group.

A total of 259 patients (57.3%) in the atezolizumab–nab-paclitaxel group and 183 (41.8%) in the placebo–nab-paclitaxel group had an adverse event of special interest, which was suggestive of a potential immune-related cause. Grade 3 or 4 adverse events of special interest occurred in 34 patients (7.5%) in the atezolizumab–nabpaclitaxel group and in 19 (4.3%) in the placebo–nab-paclitaxel group. Two grade 5 adverse events of special interest occurred (autoimmune hepatitis in 1 patient in the atezolizumab–nab-paclitaxel group and hepatic failure in 1 patient in the placebo–nab-paclitaxel group). Immune-related hypothyroidism occurred at a higher frequency in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (17.3% vs. 4.3%); all the events were of grade 1 or 2, and none led to the discontinuation of the trial regimen. Pneumonitis was infrequent, occurring in 3.1% of the patients in the atezolizumab–nab-paclitaxel group and in 0.2% of those in the placebo–nab-paclitaxel group; only 1 patient (in the atezolizumab–nab-paclitaxel group) had an event of grade 3 or 4. Fatal adverse events occurred in 6 patients (1.3%) in the atezolizumab–nab-paclitaxel group and in 3 (0.7%) in the placebo–nab-paclitaxel group; three deaths in the atezolizumab–nab-paclitaxel group (from autoimmune hepatitis, mucosal inflammation, and septic shock, in 1 patient each) and one death in the placebo–nab-paclitaxel group (from hepatic failure) were considered by the investigators to be related to the trial regimen). Adverse events that led to withdrawal of any agent occurred in 15.9% of the patients who received atezolizumab–nab-paclitaxel group and in 8.2% of those who received placebo–nab-paclitaxel group. A total of 29 patients (6.4%) had adverse events that led to the discontinuation of atezolizumab, and 6 (1.4%) had adverse events that led to the discontinuation of placebo.

This phase III study showed that Atezolizumab plus nab-paclitaxel prolonged PFS among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. In the PD-L1-positive patients, despite the limits of the statistical design, the median OS observed was very interesting and it has never been reached before (Schmid et al. 2018).

1.2.1.4 Safety of Atezolizumab Combined with Carboplatin and Paclitaxel in Patients with NSCLC

In phase III randomized trial IMPower150 patients with metastatic NSCLC were randomized to receive atezolizumab 1200 mg every three weeks plus 21-day carboplatin plus paclitaxel (ACP), bevacizumab plus

carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both.

In terms of efficacy this trial showed that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic nonsquamous NSCLC without any detrimental interaction between atezolizumab and steroid premedication of paclitaxel.

The safety profile of atezolizumab in combination with other agents was consistent with safety profiles of the individual medicines, including the rate of hemorrhagic events caused by bevacizumab; no new safety signals were identified with the combination. The frequency of treatment-related serious adverse events was similar to that in previously reported studies of chemotherapy combined with checkpoint inhibitors. The incidence and nature of immune-related adverse events in the ABCP group were similar to those with atezolizumab monotherapy (Socinski et al. 2018).

1.2.2 Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

Based on available PK data exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered Q3W. Based on a population PK analysis that included 472 patients in the dose range of 1 mg/kg to 20 mg/kg, the typical population clearance (CL) was 0.20 L/day, the volume of distribution at steady state (Vss) was 6.9 L, and the terminal half-life (t1/2) was 27 days. The population PK analysis suggested that steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the concentration-time curve (AUC), maximum concentration (Cmax), and trough concentration (Cmin) was 1.91, 1.46, and 2.75-fold, respectively. Based on an analysis of exposure-safety, and exposure-efficacy data, the following factors had no clinically relevant effect: age (21 to 89 years), body weight, gender, positive ATA status, albumin levels, tumour burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status. The effect of moderate or severe hepatic impairment (bilirubin > upper limit of normal [ULN] and AST > ULN or bilirubin ≥ 1.0 to 1.5 x ULN and any AST elevation) on the PK of atezolizumab is unknown.

The development of anti-therapeutic antibodies (ADAsATAs) has been observed in patients at all dose levels. ADAATA positivity had no major effect on atezolizumab concentrations and PK although there was a trend for lower Cmin values in the ADAATA positive subgroup. The presence of ADAsATAs did not appear to have a clinically significant impact on PK, safety, or efficacy of atezolizumab.

1.3 Study Rationale and Benefit-Risk Assessment

1.3.1 Atezolizumab

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

As detailed in Section 1.2, 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-L1 is expressed on many cancer and immune cells, and overexpression of PD-L1 on tumor cells has been reported to impede

anti-tumor immunity (Blank and Mackensen 2007; Herbst et al. 2014). Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators, and restricts tumor cell killing (Herbst et al. 2014). The PD-1/PD-L1 pathway has been implicated in tumors evading immune surveillance. Therefore, interruption of the PDL1/ PD-1 and the PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity (Blank and Mackensen 2007; Chen and Mellman, 2013; Herbst et al. 2014; Saha and Nanda, 2016).

The rationale for investigating PD-L1 inhibitors in TNBC stems from a number of key clinical observations. ER-negative breast cancers have a higher density of tumor infiltrating lymphocytes (TILs) than their ER-positive counterparts (Loi et al. 2014), and greater numbers of TILs have been associated with better clinical outcomes in patients with TNBC (Cancer Discov. 2015). PD-L1 expression is also more prevalent in TNBC than in other breast cancer subtypes (Emens et al. 2014). TNBCs have a higher mutational burden compared with their ER-positive counterparts, and have been linked with increased immunogenicity (Wang et al. 2014). Gene expression profiling of TNBCs has identified an immunomodulatory subtype that is characterized by increased expression of genes involved in T-cell function (Lehmann et al. 2011; Saha and Nanda, 2016). Due to the higher mutation rate and a higher number of TILs relative to other breast cancer subtypes, TNBC may be particularly susceptible to immunotherapy (Cancer Discov. 2015).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies, including patients with TNBC, who have failed standard-of care therapies. The observation that high CD8+ T-cell density in primary breast tumors is correlated with improved OS, and that mTNBC tumors have fewer TILs than their matched primary tumors, suggests that the immune system is able to partially restrain human breast cancer but that immune suppression becomes more prevalent with increasing growth and metastasis (Cimino-Mathews et al. 2013; Adams et al. 2014; Loi 2014). The identification of immune-enriched subtypes of TNBC underscores the potential to harness pre-existing host anti-tumor immunity in this disease (Lehmann et al. 2011). In this setting, re-invigorating T-cell activity with atezolizumab may be an effective treatment strategy.

Atezolizumab has been generally well tolerated in clinical trials (see Section 1.2.1); adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/elevated transaminases, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, the majority of these events have been manageable without requiring treatment discontinuation.

1.3.2 Rationale for the Atezolizumab Dose and Schedule

Atezolizumab will be administered IV at a flat dose of 840 mg every two weeks (Q2W) to align with the chemotherapy schedule.

The fixed dose of 840 mg administered Q2W was selected with the intent of selecting a dose that is the exposure equivalent of the fixed dose of 1200 mg Q3W (weight-based equivalent of 15 mg/kg), which has been approved for treating patients with urothelial carcinoma and NSCLC (refer to the TECENTRIQTM prescribing information). Of note, the exact equivalent dose is 800 mg; however, because atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL, and in the

interest of simplifying administration, the exact dose used in this study will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single syringe. The 840 mg dose is not expected to result in meaningfully different exposure compared with the 800 mg dose.

In the Phase Ia Study PCD4989g, patients were treated with doses ranging from 0.1 to 20 mg/kg. Anti-therapeutic antibodies (ADAsATAs) to atezolizumab were associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but not for patients treated at 10, 15, and 20 mg/kg, including the approved dose of 1200 mg. To date, no relationship has been observed between the development of measurable ADAsATAs and safety or efficacy.

1.3.3 Rationale for Patient Population and Analysis Groups

The target population will include patients with previously untreated inoperable locally advanced or metastatic PD-L1 positive TNBC. Patients will be either newly diagnosed or have disease progression after completing treatment for early breast cancer at least 12 months prior to enrollment.

As detailed in Section 1.1.1, TNBC is more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBC are characterized by a more aggressive course compared to other subtypes (Wahba and El-Hadaad, 2015) and a poor clinical outcome (Mersin et al. 2008; Trivers et al. 2009), including worse breast cancer-specific survival and OS (Lin et al. 2012), generally with rapid progression and a median OS generally between 13 months (Kassam et al. 2009) and 17.5 months in patients treated with various chemotherapy agents (Yardley 2018). Although TNBC may respond to chemotherapy, including taxanes, there are no targeted therapies with widespread global approval available for patients with this subtype of breast cancer, and relatively few new agents have been approved for mTNBC (Carey et al. 2012; O'Shaughnessy et al. 2014; Hirshfield and Ganesan, 2014; Zeichner et al. 2016). Therefore, there is a pressing need for clinically active targeted therapy for mTNBC.

Regarding its immunologic properties, TNBC is characterized by high DNA mutational rates (TCGAN, 2012) which have been postulated as a source of immunogenic tumour specific neoantigens. Consistent with this, a significant proportion of TNBC patients display CD8+ tumour infiltrating lymphocytes at diagnosis, which has been correlated with a better prognosis (Ali et al. 2014) and suggests that activation of the immune system in TNBC patients could be utilized to modify the course of the disease.

Atezolizumab showed promising anti-tumor activity, as determined by RECIST v1.1 response, across multiple advanced tumor types (including TNBC) both as monotherapy (Phase 1a study PCD4989g) as well as in combination with bevacizumab and/or chemotherapy (Phase 1b study GP28328). In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2015), and most notably in combination with nab-paclitaxel (Adams et al. 2016).

1.3.4 Rationale for Concomitant Carboplatin and Paclitaxel Treatment

The taxane class of cytotoxic agents (paclitaxel, docetaxel, nab-paclitaxel) have significant antitumor activity in breast cancer. Despite the expansion of the therapeutic landscape for mBC over the last three decades, including the increasing availability of targeted therapies for various BC subtypes, cytotoxic taxane-based regimens remain standard of care in first-line therapy for patients with mBC, including

TNBC (Cardoso et al. 2018; Greene and Hennessy 2015; Hernandez-Aya and Ma 2016; Fukada et al. 2016).

Several studies and meta-analyses support the benefit of taxanes on clinical outcomes in mBC (Piccart-Gebhart et al. 2008; Qi et al. 2013; Ghersi et al. 2015), and these benefits were generally comparable to those of anthracyclines in randomized controlled clinical studies. However, in a recent meta-analysis of 28 studies (N= 6871 randomized women), the combined hazard ratio (HR) for OS and time to progression (TTP) favored the taxane-containing compared to the anthracycline regimens (HR 0.93, 95% CI 0.88 to 0.99, P = 0.002, deaths = 4477; and HR 0.92, 95% CI 0.87 to 0.97, P = 0.002, estimated 5122 events, respectively). When the analyses were restricted to first-line treatments, this effect persisted for OS (HR 0.93, 95% CI 0.87 to 0.99, P = 0.03) but not for TTP.

Tumor response rates were higher with taxane-containing chemotherapy in assessable women (RR 1.20, 95% CI 1.14 to 1.27, P < 0.00001). Taxanes were also associated with an increased risk of neurotoxicity but less nausea and vomiting compared to non-taxane containing regimens (Ghersi et al. 2015).

Paclitaxel, docetaxel, and nab-paclitaxel are approved drugs for the treatment of recurrent and metastatic BC in many countries. Paclitaxel is administered weekly (80-90 mg/m2) (Swanton 2011) or every three weeks (175 mg/m2 dose recommended by the current Prescribing Information for Taxol® IV injection), with weekly paclitaxel (80–90mg/m2) currently considered the most effective schedule for delivering paclitaxel (Swanton 2011). A meta-analysis of 11 randomized clinical trials (n=2,540 patients) comparing weekly- and three-weekly taxanes in patients with advanced BC found that weekly administration of paclitaxel resulted in higher OS compared to the three-weekly schedule (HR 0.78; 95% CI, 0.67–0.89 P=0.001); PFS was similar between the two schedules. The incidence of serious adverse events, neutropenia, neutropenic fever, and peripheral neuropathy were also significantly lower with the weekly compared to the three-weekly taxane schedules (Mauri et al. 2010). In addition, a regimen consisting of weekly paclitaxel administrations for three weeks, followed by one-week break was reported to be associated with less neurotoxicity compared to continuous weekly administrations (Swanton 2011). This finding is consistent with the lower neurotoxicity rate observed in the HER2-negative mBC population of the studies E2100 (Miller et al. 2007) and MERIDIAN (Miles et al. 2017), both using a 90 mg/m2 3-week on/1-week off weekly paclitaxel schedule, compared to study CALGB9840 (Seidman et al. 2008) using continuous 80 mg/m2 weekly paclitaxel dosing without interruption. Taken together, these findings support the selected regimen for paclitaxel (90 mg/m2 on days 1, 8, and 15 of every 28-day cycle) in the current study.

The solvents used to enhance the solubility of taxanes have been associated with allergic reactions and peripheral neuropathy (ten Tije et al. 2003). Therefore, to reduce the risk of severe hypersensitivity reactions, study patients should be premedicated as described in Section 4.3.1.1.

In most circumstances, single agents are currently preferred over chemotherapy combinations for the treatment of recurrent/metastatic breast cancer; however, this recommendation is based on a lack of compelling evidence demonstrating superiority of combination chemotherapy over treatment with sequential single agents in terms of survival [12, 14]. However, features that often accompany TNBC relapses such as short disease-free intervals (DFIs), high tumor burdens, significant visceral disease, and/or symptomatic disease warrant the consideration of combination chemotherapy in these settings. Treatment

guidelines specifically addressing patients with mTNBC are limited, and no specific standard of care exists for this patient population [12, 13].

The recent results of randomized phase II TNACITY trial showed a median PFS significantly longer with nab-paclitaxel 125 mg/m2 plus carboplatin AUC 2 on days 1 and 8 every 3 weeks versus nab-paclitaxel plus gemcitabine [8.3 versus 5.5 months; hazard ratio (HR), 0.59 [95% CI, 0.38-0.92]; P = 0.02] or carboplatin plus gemcitabine (median, 8.3 versus 6.0 months; HR, 0.58 [95% CI, 0.37-0.90]; P = 0.02). OS was numerically longer with nab-paclitaxel/carboplatin versus nab-paclitaxel/gemcitabine (median, 16.8 versus 12.1 months; HR, 0.73 [95% CI, 0.47-1.13]; P = 0.16) or carboplatin/gemcitabine (median, 16.8 versus 12.6 months; HR, 0.80 [95% CI, 0.52-1.22]; P = 0.29). ORR was 73%, 39%, and 44%, respectively. Grade ≥3 adverse events were mainly hematologic (Yardley et al. 2018).

On hese bases, a taxane in combination with carboplatin seem to be the best first-line treatment for mTNBC.

1.3.5 Rationale for Atezolizumab in Combination with Carboplatin and Paclitaxel

The recently published phase III IMpassion130 study has demonstrated that the combination of atezolizumab plus nab-paclitaxel significantly reduced the risk of disease worsening or death in the intention-to treat and PD-L1 positive population with metastatic triple-negative breast cancer showing also encouraging overall survival results (Schmid et al. 2018). Therefore, the combination of atezolizumab plus nab-paclitaxel is likely to become soon the new standard of care as first-line treatment of patients with metastatic triple-negative PD-L1 positive breast cancer.

Recent evidences in metastatic non-small cell lung cancer showed the efficacy and the safety of concomitant use of carboplatin, paclitaxel and atezolizumab without any detrimental interaction between atezolizumab and steroid premedication of paclitaxel (Socinski et al. 2018).

Therefore, based on these data, the combination of atezolizumab plus carboplatin and paclitaxel represents a promising combination to be tested as first-line therapy in patients with metastatic triple-negative breast cancer to enhance the clinical activity and efficacy of first-line therapy in this setting.

The selection of PD-L1 positive patients could lead to further evidence of increased efficacy of this first-line treatment as evidenced by the results of Impassion130 study.

1.3.6 PD-L1-positive patients' selection

Administered as first-line treatment, the combination of atezolizumab with nab-paclitaxel as part of the IMpassion130 study led to significantly longer progression-free survival than was seen with placebo plus nab-paclitaxel in both the intention-to-treat population and the subgroup of patients with PD-L1–positive tumors.

Although the boundary for declaring a statistical advantage for atezolizumab–nab-paclitaxel in the intention-to-treat population at the first interim analysis of overall survival was not crossed, and formal testing was not performed in the PD-L1–positive subgroup, numerical increases in median overall survival were observed in both the intention-to-treat population and the PD-L1–positive subgroup. A clinical benefit

with atezolizumab–nab-paclitaxel was particularly notable in the PD-L1–positive subgroup, as shown by a median progression-free survival that was significantly longer by 2.5 months, by a median overall survival that was 10 months longer and a numerically higher objective response rate. (Schmid P. et al., NEJM 2018)

These data confirm phase I observations of improved outcomes in patients with high PD-L1 expression who were receiving treatment with atezolizumab, pembrolizumab or avelumab. As has been found regarding existing chemoimmunotherapy data from patients with other solid tumors who received atezolizumab plus chemotherapy or pembrolizumab plus chemotherapy, IMpassion130 trial established the benefit of adding a checkpoint inhibitor to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer, with most of the benefit realized in the PD-L1–positive subgroup. It is important for patients' PD-L1 expression status on tumor-infiltrating immune cells to be taken into consideration to inform treatment choices for patients with metastatic triple-negative breast cancer.

According to the data of exploratory analyses subsequently presented at the 2018 San Antonio Breast Cancer Symposium in Texas, it was confirmed that PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel (Emens LA et al., SABCS 2018 abstract #GS1-04).

For the moment PD-L1 IC is the most robust predictive biomarker for selecting untreated metastatic TNBC patients who benefit from atezolizumab and nab-paclitaxel, and for this reason we would like to test the promising combination of atezolizumab plus carboplatin and paclitaxel as first-line therapy in metastatic triple-negative breast cancer really in the subgroup of patients with PD-L1–positive tumors (defined as expression on tumor-infiltrating immune cells ≥1% by VENTANA SP142 IHC assay).

1.3.7 Rationale for the multiparametric cancer agnostic circulating immunosignature (CLIO)

It has been observed that the tumor-associated immune microenvironment can affect the efficacy of both chemotherapy and target therapies and therefore impact on the clinical outcome of cancer patients (Mittal D et al, Voron T, et al). Notably, a key role in this context is played by tumor associated macrophages (TAM), that are recruited by specific chemokines and polarized in populations with immune stimulating (M1) or tumor supportive properties (M2) (Heusinkveld M, et al). M2 macrophages are capable to negatively affect immune activation by expressing immunomodulatory cytokines and by suppressing T cells and the presence of M2 cells is a predictor of metastasis and poor outcome.

Although it is well established that PD-1/PD-L1 blockade activates T cell, PD-1 expression impacts on numerous immune cell subsets, including tumor-associated macrophages, in which it has been shown to influence the polarization towards M1 or M2 phenotype.

EMILIN2 is an extracellular matrix molecule that plays multifaceted functions in the tumor microenvironment, mainly in a tumor suppressive manner. Preliminary data indicate, however, that EMILIN2 may play a role in the modulation of tumor associated inflammation also through PD-1 and PD-L1, that are found to be increased in Emilin2 knock-out mice (Emilin2-/-). Interestingly, ex vivo analysis confirmed that macrophages isolated from Emilin2-/- mice expressed higher levels of PD-L1 but were also more prone to acquire an M2 phenotype (i.e. immunosuppressive) compared to their wt counterpart.

In breast cancer, M2 TAMs promote angiogenesis and extracellular matrix breakdown and remodeling, thus enabling breast tumor cells to intravasate into the peripheral blood. Furthermore, by communicating

and cooperating with breast tumor cells, M2 cells also migrate into peripheral circulation by intravasating across intratumor capillary barriers. Thus, circulating M2-like monocytes might be a subset of disseminated TAMs that derived from breast cancer tissue.

Taking into consideration just PD-L1 could be, therefore, misleading and should be integrated with additional parameters and, since the immune system is highly dynamic, there is the need to optimize a liquid biopsy technique capable to capture its adaptations in real-time.

Notably, tumor cells may escape immune surveillance by acquiring different genetic alterations. A higher expression of mesenchymal transition genes (e.g. AXL, ROR2, WNT5A, LOXL2, TWIST2), immunosuppressive genes (e.g. IL10, VEGFA, VEGFC) and chemokines that recruit immunosuppressive cells (e.g. CCL2, CCL7, CCL8, CCL13) may be associated with innate anti-PD-1 resistance. It has been observed that the evaluation of mesenchymal transition, angiogenesis, hypoxia and wound healing-related genes (IPRES) was able stratify metastatic melanoma patients according to anti-PD-1 resistance (OR = 4.6; p = 0.013 for IPRES-enriched tumors). Conversely, the IPRES signature showed no similar association with respect to anti-CTLA-4 treatment (Hugo W et al). By contrast, a subset of patients quickly develop resistance, even after an initial benefit, suggesting the rapid proliferation of a resistant clone.

A pivotal role in decreased antigen presentation and immune escape has been observed for mutations in IFN receptor pathway genes (e.g. JAK1, JAK2) and for MHC-I structure genes (e.g B2M) (Ribas et al).

2 STUDY DESIGN

2.1 Description of the Study

2.2 Overview of the Study Design

This is a Phase II single-arm multicenter study designed to evaluate the efficacy and safety of atezolizumab administered in combination with paclitaxel and carboplatin in patients with previously untreated, inoperable locally advanced or metastatic, PD-L1 positive TNBC.

A biomarker discovery translational analysis was moreover built-in to better dissect tumor and immune-related characteristics that could be further evaluated for treatment response stratification.

A total of approximately 104 patients will be enrolled and treated in approximately 15 centers affiliated with the Gruppo Italiano Mammella (GIM) study group.

All eligible patients will receive carboplatin, paclitaxel and atezolizumab and they will continue this treatment until progression of disease. In case of interruption of one of the three drugs for unacceptable toxicity and/or medical decision, the patient may continue to receive one or more of the remaining drugs until progression.

Tumor assessments will be performed at screening/baseline and approximately every 12 weeks (± 1 week) until disease progression (PD), withdrawal of consent, death, unacceptable toxicity or study termination by the Sponsor, whichever occurs first.

Tumor assessments performed as part of standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used as baseline assessments rather than repeating the tests. Tumor assessments will be performed on the specified schedule regardless of treatment delays, interruptions or discontinuations. Radiologic imaging performed during the screening period should consist of 1) computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis, 2) bone scan or PET scan, and 3) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. For each patient, the same radiographic procedures and technique must be used for disease evaluation throughout the study (e.g., the same contrast protocol for CT scans and/or MRI). Evaluation of tumor response (e.g., for estimation of PFS, PFS rate, ORR, DoR and CBR) will be completed per RECIST v1.1.

Patients enrolled must discontinue all study treatment upon determination of PD per RECIST v1.1. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

All patients who discontinued study treatment before End Of Study (including due to PD) will be followed for survival approximately every 3 months for 2 years from last patient enrolled or until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. Information regarding PFS2 and the use

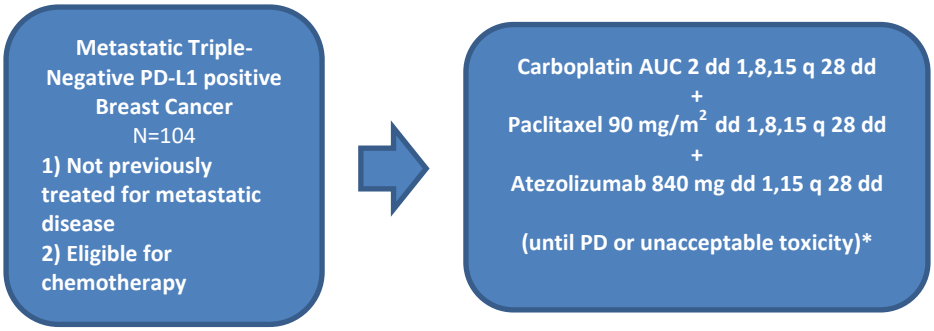
of subsequent anti-cancer agents for metastatic TNBC will also be collected during the survival follow-up period. In addition, for patients who discontinue study treatment before EOS for reasons other than PD, tumor assessments will continue until PD, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor.

The study Steering Committee (SC) will provide scientific oversight for the trial.

A schedule of assessments is provided in section Study schedule of Assessments and Procedures.

A study design schema is presented in Figure 1.

Figure 1. Study design



* In case of interruption of one of the three drugs for unacceptable toxicity and/or medical decision, the patient may continue to receive one or more of the remaining drugs until disease progression.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective:

To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of % Overall Survival at 2 years.

3.1.2 Secondary objectives:

- To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of % Overall Survival at 2.5 years.

- To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of % OS at 2 years in hormonal receptor (HR) between 1% and 10%.
- To provide preliminary evidence on the efficacy of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of post-progression survival

- To assess the activity of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients in terms of ORR and time to treatment failure.
- To assess the safety of atezolizumab plus carboplatin plus paclitaxel as first-line therapy in metastatic triple-negative PD-L1 positive breast cancer patients.

3.1.3 Exploratory objectives:

Exploratory objectives will be focused on the assessment of both tumor-centered characteristics through the NGS analysis of ctDNA and immune-centric features through the evaluation of a multiparametric Cancer agnostic circuLating ImmunOsignature (CLIO):

- To assess the association between patients' characteristics, treatment activity, efficacy and safety and through a CLIO in metastatic triple-negative breast cancer patients receiving atezolizumab plus carboplatin plus paclitaxel as first-line therapy

- To explore the association between the CLIO and treatment activity, efficacy and safety

- To explore the dynamics of ctDNA levels and detectable aberrations with respect to treatment activity and efficacy

Concomitant timepoints will not be used for cross-validations between the two methodologies.

3.2 Endpoints

3.2.1 Primary endpoint:

- % Overall Survival at 2 years

3.2.2 Secondary endpoints:

- % Overall survival at 2.5 years
- Overall Survival at 2 years in HR <1% and in HR 1-10%
- Post-progression survival
- Objective response rate
- Time to treatment failure
- Incidence and severity of adverse events and seious adverse events

3.2.3 Exploratory endpoints:

- Variation of ctDNA levels from baseline to first evaluation through the multigene FoundationOne® Liquid NGS panel
- Variation of ctDNA levels from the first evaluation to progression through the multigene FoundationOne® Liquid NGS panel
- Association of CLIO and ctDNA with Objective response rate and survivalAssociation between archival PD-L1 levels and target genes expression levels through CLIO analysis
- Variation of target genes expression levels through CLIO analysis from baseline to first evaluation

  Variation of target genes expression levels through CLIO analysis from first evaluation to disease progression

4 MATERIALS AND METHODS

4.1 Patients

The target population will include patients with previously untreated inoperable locally advanced or metastatic PD-L1 positive TNBC. Patients will be either newly diagnosed or have disease progression after completing treatment for early breast cancer at least 12 months prior to enrollment,

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Women or men aged ≥18 years
3. Histologically or cytologically confirmed adenocarcinoma of the breast with metastatic disease
4. Hormone receptor-negative (ER and PgR < 10%) and HER2-negative (IHC 0,1+ or 2+ ISH not amplified) breast cancer, based on the status of the primary tumor and/or the biopsy of metastatic disease before starting first-line therapy and assessed by local laboratory
5. PD-L1 positive defined as expression on tumor-infiltrating immune cells ≥1% (SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems), based on the status of the primary tumor and/or the biopsy of metastatic disease before starting first-line therapy and assessed by local laboratory
6. Availability of a representative tumor specimen for translational research
7. Eligible for first-line taxane and carboplatin chemotherapy
8. No prior chemotherapy or targeted systemic therapy (including endocrine therapy) for inoperable locally advanced or metastatic TNBC. Prior radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy; however, patients should have recovered from the effects of radiation before enrollment
9. Previous chemotherapy with taxanes and/or carboplatin for early breast cancer (neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before study entry
10. Previous therapy with immune checkpoint inhibitors for early breast cancer (neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before study entry
11. ECOG performance status of 0 or 1
12. Life expectancy ≥ 12 weeks
13. Measurable or evaluable disease as defined by RECIST v1.1
14. Adequate hematologic and end-organ function, defined by laboratory results obtained within 2 weeks prior to the first study treatment (Cycle 1, Day 1):
    a) Absolute neutrophil count (ANC) ≥ 1500 cells/μL (without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)
    b) Lymphocyte count ≥ 500/μL
    c) Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
    d) Haemoglobin ≥ 9.0 g/dL
       Patients may be transfused or receive erythropoietic treatment to meet this criterion
    e) Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤

2.5× the upper limit of normal (ULN), with the following exceptions:
   i. Patients with documented liver metastases: AST and ALT ≤ 5× ULN
   ii. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5× ULN

f) Serum bilirubin ≤ 1.25× ULN
   Patients with known Gilbert's disease who have serum bilirubin level ≤ 3× ULN may be enrolled.
g) International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5× ULN
   This applies only to patients who are not receiving an anticoagulant medicinal product; patients receiving an anticoagulant medicinal product should be on a stable dose and have an INR which is not above the target therapeutic range.
h) Calculated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault).

15. Negative human immunodeficiency virus (HIV) test at screening
16. Negative hepatitis B surface antigen (HBsAg) test at screening
17. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. The HBV DNA test will be performed only for patients who have a positive HBcAb test
18. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test
19. Women of child bearing potential must agree to either use a contraceptive method with a failure rate of ≤ 1% per year or to remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 5 months after the last dose of atezolizumab, or for at least 6 months after the last dose of paclitaxel. 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 contraceptive methods with a failure rate of ≤ 1% per year include bilateral tubal ligation, male sterilization, 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception
20. Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug
21. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    a. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of paclitaxel. Men must refrain from donating sperm during this same period.
    b. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal

are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

1. 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 at least 2 weeks prior to enrollment
2. Known central nervous system (CNS) disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met:
   a) No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed)
   b) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to enrollment
   c) No evidence of progression or hemorrhage after completion of CNS directed therapy

Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible, if all other criteria above are met.

3. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX® are allowed)
4. Uncontrolled tumor-related pain

   a) Patients requiring narcotic pain medication must be on a stable regimen at study entry.
   b) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
   c) Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
5. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium >ULN) or clinically significant (symptomatic) hypercalcemia

   a) Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant (symptomatic) hypercalcemia are eligible.

6. Malignancies other than TNBC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer)
7. Pregnant or lactating women, or intending to become pregnant during the study
8. Evidence of significant uncontrolled concomitant disease that could affect compliance with the

protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)

9. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to enrollment, unstable arrhythmias, or unstable angina

    a) Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded
    b) Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate

10. Presence of an abnormal electrocardiogram (ECG) that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third degree heart block, evidence of prior myocardial infarction, or QT interval corrected using Fridericia's formula (QTcF) >470 ms demonstrated by at least two consecutive ECGs
11. Serious infection requiring antibiotics within 2 weeks prior to enrollment, including but not limited to infections requiring hospitalisation or IV antibiotics, such as bacteremia, or severe pneumonia
12. Major surgical procedure within 4 weeks prior to enrollment or anticipation of the need for a major surgical procedure during the study other than for diagnosis
    Note: Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted
13. Treatment with investigational therapy within 30 days prior to initiation of study treatment

Exclusion Criteria Related to Atezolizumab

14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
15. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells or any component of the atezolizumab formulation
16. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis (MS), vasculitis, or glomerulonephritis
    (Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study)
17. Prior allogeneic stem cell or solid organ transplantation
18. History of idiopathic pulmonary fibrosis (IPF, including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. (Note: History of radiation pneumonitis in the radiation field [fibrosis] is permitted)
19. Positive test for human immunodeficiency virus (HIV)
20. Active hepatitis B (positive hepatitis B surface antigen [HBsAg] test or hepatitis B virus [HBV] DNA polymerase chain reaction [PCR] test at screening) or hepatitis C (positive hepatitis C virus

antibody test at screening)

Note:

- Patients with past HBV infection or resolved HBV infection (defined as having negative HBsAg and HBV DNA test but a positive hepatitis B core antibody [HBcAb] test) are eligible
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV ribonucleic acid (RNA)

21. Current treatment with anti-viral therapy for HBV
22. Active tuberculosis
23. Receipt of a live, attenuated vaccine within 4 weeks prior to enrollment or anticipation that such a live, attenuated vaccine will be required during the study

Note: Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to enrollment, during treatment or within 5 months following the last dose of atezolizumab

24. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to enrollment
25. Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide, and antitumour necrosis factor [TNF] agents) within 2 weeks prior to enrollment, or anticipated requirement for systemic immunosuppressive medications during the trial

    a) Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study
    b) Patients with a history of allergic reaction to IV contrast requiring steroid pretreatment should have baseline and subsequent tumor assessments performed using MRI
    c) 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
    d) Systemic corticosteroids are allowed as paclitaxel premedication during the trial at a dose ≤10 mg dexamethasone or equivalent in order to avoid severe hypersensitivity reactions

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

Exclusion Criteria Related to Paclitaxel and Carboplatin

29. History of hypersensitivity reactions to paclitaxel or other drugs formulated in the same solvent as paclitaxel (polyoxyethylated castor oil)
30. History of hypersensitivity reactions to carboplatin

4.2 Study Treatment

Atezolizumab, paclitaxel and carboplatin are considered investigational medicinal products (IMPs) in this study. Non-investigational medicinal products (NIMPs) used in the study include premedication (see Section 4.3.1.1), medications that may be administered to manage adverse events (see Section 4.3.1.2), and other permitted concomitant medications (see Section 4.3.1.3).

The term "study drug" is used throughout this protocol to refer to all protocol-mandated treatment (atezolizumab, paclitaxel and carboplatin).

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Atezolizumab

Atezolizumab will be supplied by Roche already relabeled for the study and released.

The atezolizumab drug product is provided in a single-use, glass vial as a colourless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration.

Atezolizumab could be supplied in 2 different formulations, detailed in the following table:

	Formulation A – 840 mg	**Formulation B – 1200 mg**
Nominal atezolizumab amount per vial	840 mg	1200 mg
Concentration of atezolizumab	60 mg/mL	60 mg/mL
Primary packaging	15 mL glass vial	20 mL glass vial
Extractable volume	14 mL	20 mL

Important note: Regardless of the formulation provided, 14 mL of atezolizumab concentrate should be withdrawn from the vial in order to have the right dose of atezolizumab.

Both of the formulations contain histidine acetate, buffered at pH 5.8, sucroseand polysorbate 20.Atezolizumab (both of the formulations, A and B) will be administered in 250 mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 or 0.22 µm in-line filters. The IV bag may be constructed of polyvinylchloride (PVC), polyethylene or polyolefin; the IV infusion line may be constructed of PVC or polyethylene, polybutadiene, or polyurethane; and the 0.2 or 0.22 µm in-line filter may be constructed of polyethersulfone or polysulfone. No incompatibilities have been observed between atezolizumab and these infusion materials (bags and infusion lines).

Atezolizumab vials must be refrigerated at 2°C-8°C (36°F-46°F) upon receipt until use.

Vials should not be used beyond the expiration date provided by the manufacturer.

Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. Any unused portion of drug left in a vial should be discarded.

Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Further details on the storage and preparation of atezolizumab are provided in the most updated Investigator's Brochure of atezolizumab .

4.2.1.2 Paclitaxel and Carboplatin

Specific details for the carboplatin and paclitaxel regimen are given below. It is the responsibility of the investigator to ensure that recommendations in the Italian SmPCs for administration of the carboplatin and paclitaxel are followed. The SmPC is updated from time to time, up-to-date SmPCs are posted on the AIFA Website https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci

For information on the formulation, packaging, and handling of paclitaxel and carboplatin, refer to the local prescribing information for paclitaxel and carboplatin.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Atezolizumab

Patients will receive atezolizumab 840 mg (in 250 mL 0.9% sodium chloride [NaCl]) by IV infusion administered on Day 1 and Day 15 (± 3 days) of every 28-day cycle. The first dose (Cycle 1, Day 1) will be administered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

For the first infusion of atezolizumab, no premedication will be administered.

However, should the patient experience infusion-related reaction(s) during any infusion, premedication with antihistamines will be administered for subsequent infusions at the discretion of the treating physician.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1. Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion • Infuse 840 mg of atezolizumab in 250 mL 0.9% NaCl over 60 (±15) minutes. • Record patient's vital signs (heart rate,	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered at subsequent infusions at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before

respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated • Patients will be informed about the possibility of delayed symptoms following infusion and instructed to contact their study physician if they develop such symptoms.	starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (±10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (±10) minutes Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated.

4.2.2.2 Paclitaxel

Paclitaxel will be administered at the 90 mg/m2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. On days of scheduled infusions of atezolizumab and paclitaxel (i.e., Day 1 and Day 15 of every cycle), paclitaxel is to be administered after infusion of atezolizumab. Doses of paclitaxel should not be administered more frequently than every 7 days.

In the absence of unacceptable toxicity, paclitaxel will be administered until PD or until the end of the study, whichever occurs earlier. Paclitaxel, carboplatin and atezolizumab may be discontinued for toxicity independently of each other in the absence of disease progression.

To reduce the risk of severe hypersensitivity reactions, study patients will be premedicated as described in Section 4.3.1.1. Sites should follow their institutional standard of care for determining the paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Guidelines for paclitaxel dosage modification and treatment interruption or discontinuation due to toxicity are provided in Section 5.1.5.3.2.

4.2.2.3 Carboplatin

In this study, carboplatin will be administered after the completion of paclitaxel administration by short-term IV infusion over 15 to 60 minutes, to target AUC 2 mg/ml/min on Days 1, 8, and 15 of every 28-day cycle. For guidance on carboplatin dose modifications and interruptions due to toxicity, refer to Section 5.1.6.3.2.

There is no known antidote for carboplatin overdose. If necessary, the patient may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment. Doses up to 1600mg/m2 have been associated with patients feeling extremely ill with diarrhea and alopecia developing. Use of higher than recommended doses of carboplatin have also been associated with loss of vision (Carboplatin SmPC).

In the absence of unacceptable toxicity, carboplatin will be administered until PD or until the end of the study, whichever occurs earlier. Paclitaxel, carboplatin and atezolizumab may be discontinued for toxicity independently of each other in the absence of disease progression.

For further details, refer to the local prescribing information for carboplatin.

4.2.3 Investigational Medicinal Product accountability

The IMP Atezolizumab required for completion of this study will be provided by Roche. The IMPs Paclitaxel and Carboplatin are considered standard of care in patients with TNBC and they will be supplied by the local Institution. The study site will acknowledge receipt of atezolizumab and confirm the shipment condition and content. Any damaged shipments will be replaced and must be reported immediately to the study monitor.

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

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

The local site pharmacy department and the investigator are both responsible for study drugs accountability, reconciliation, and record maintenance. In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product administered to study patients Product accountability records must be maintained throughout the course of the study.

After completion of the study, a final inventory of accountability records and unused study medications will be performed by the site personnel and study monitor, according to study procedures. Unused study medications will be destroyed and proof of destruction will be forwarded to the Sponsor.

4.3 Concomitant Therapy

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

Between the treatment discontinuation and the End Of Study visit (after 2 years from last patient enrolled),

only new anti-cancer treatment will be recorded.

4.3.1 Permitted Therapy

4.3.1.1 Premedication

For the first infusion of atezolizumab, no premedication will be administered. However, should the patient experience infusion-related reaction(s) during any infusion, premedication with antihistamines may be administered for subsequent infusions at the discretion of the treating physician.

To reduce the risk of severe hypersensitivity reactions, all patients should be premedicated prior to paclitaxel administration. Prior to receiving the first two study infusions of paclitaxel, all patients will receive corticosteroids (8-10 mg dexamethasone or equivalent) as part of either the institutional standard of care or the following premedication:

- Dexamethasone 8-10 mg (or equivalent) administered orally approximately 12 and 6 hours prior to the paclitaxel infusion

  Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.

- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion

- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

Nausea and vomiting, which are generally delayed until 6 to 12 hours after administration of carboplatin, may be prevented or controlled with antiemetics.

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumor immune activity, it is recommended that the dose of dexamethasone (or equivalent) is minimized to the extent that is clinically feasible. For example, if paclitaxel is well tolerated during the first two weekly infusions without apparent hypersensitivity reaction, a reduction in the dose of dexamethasone premedication (or equivalent) should be considered for subsequent cycles if permitted by institutional standard of care. This approach has been reported to be successful in the literature (Berger et al. 2012).

4.3.1.2 Treatment of Infusional Adverse Events

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine (or equivalent substitutes, per local practice), and/or famotidine or another H2 receptor antagonist, per standard practice.

Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive

therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists)

4.3.1.3 Other Permitted Therapy

The following therapies are permitted on study:

- 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 bone metastases) provided it does not interfere with assessment of tumor target lesions. Candidate lesions for radiotherapy must be decided prior to study entry.

  Note: It is not required to hold atezolizumab during palliative radiotherapy; paclitaxel and carboplatin should be interrupted per institutional standard of care.

- Inactivated vaccinations (including for influenza)
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g.,fludrocortisone)
- Low-dose corticosteroids (≤10 mg prednisone equivalent per day) for patients with orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates or denosumab for the prevention of skeletal events
- Anticonvulsants at a stable dose are allowed, e.g., for patients with CNS metastases
- Narcotic pain medication is permitted as long as the patient is on a stable regimen at study entry.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per local standards.

Patients who use contraceptives should continue their use during the treatment period and for at least 5 months after the last dose of study treatment; refer to Section 4.1.1.

4.3.2 Prohibited and Cautionary Therapy related to atezolizumab

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies have been conducted for atezolizumab, and there are no known PK interactions with other medicinal products.

Excessive activation of the immune system is a potential risk associated with atezolizumab and has been observed when atezolizumab is used in combination with other immunomodulating agents. Therefore, the use of these agents is prohibited (i.e., immune checkpoint modulators) or limited (e.g. interferons or IL-2; prohibited within 28 days or five half-lives of the drug prior to enrollment, whichever is longer) prior to enrollment, during study treatment, and for 10 weeks after atezolizumab discontinuation.

Medications that are prohibited while the patient is receiving study treatment, and their respective washout periods prior to enrollment are listed in Table 2.

Table 2. Prohibited Medications and Treatments

Prohibited Medication/Class	**Minimum Washout Period** **Prior to initiation of study drug**
Any other systemic anti-cancer therapy	28 days or five half-lives of the drug (whichever is longer)
Any investigational therapy	30 days
Immunomodulatory agents, e.g., interferons or IL 2 [1]	28 days or five half-lives of the drug (whichever is longer)
Immunosuppressive medications, e.g., cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide [2]	14 days
Corticosteroids as therapy for CNS disease	1 day
Any live, attenuated vaccine (e.g., FluMist®) [3]	28 days
Stereotactic radiation for CNS metastases Whole-brain radiation for CNS metastases	7 days 14 days

[1] These agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.

[2] These agents could potentially alter the activity and the safety of atezolizumab.

[3] Any live, attenuated vaccine is prohibited within 28 days prior to enrollment, during treatment, and within 5 months following the last dose of atezolizumab.

4.3.3 Additional Restrictions Related to Chemotherapy

4.3.3.1 Restrictions for Paclitaxel

The metabolism of paclitaxel is catalysed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. The PK of paclitaxel was shown to be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. Therefore, caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been

evaluated in clinical trials.

Granulocyte-colony stimulating factor (G-CSF) as haematopoietic support is permitted for patients receiving paclitaxel. The primary prophylaxis should be administered per the ASCO, EORTC, and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors, such as age>65 years, previous chemotherapy or radiation therapy, preexisting neutropenia or bone marrow involvement, infection, comorbidities, etc. (Smith et al. 2015; Aapro et al. 2011; Crawford et al. 2009).

Consistent with the latest ASCO recommendations (Smith et al. 2015), and results of meta-analyses of primary G-CSFs in adults undergoing chemotherapy for a solid tumour or lymphoma (Pinto et al. 2007; Cooper et al. 2011; Renner et al. 2012), both conventional (e.g., filgrastim) and long-acting, or pegylated (e.g., pegfilgrastim) G-CSFs may be used for the prevention of treatment-related febrile neutropenia. The choice of agent will be at the discretion of the investigator, depending on the clinical situation and institutional standard of care practice.

Anti-emetics, anti-allergic measures, and other treatments for concomitant paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the local prescribing information for paclitaxel.

Refer to the local prescribing information (label) for paclitaxel for all boxed warnings and contraindications.

4.3.3.2 Restrictions for Carboplatin

- Concomitant use of yellow fever vaccine is prohibited, and vaccination with other live attenuated vaccine should be avoided;
- Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished;
- Concomitant use of phenytoin or fosphenytoin is not recommended due to the risk of exacerbation of convulsions, risk of toxicity enhancement or loss of efficacy of the cytotoxic drug;
- The concomitant use of the following agents should be approached with caution: (i) ciclosporin, tacrolimus, and sirolimus (risk of excessive immunosuppression); (ii) nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, including loop diuretics (risk of increased, exacerbated, or cumulative toxicity)
- Concurrent (given together or ≤7 days apart) radiotherapy should be avoided.

Refer to the local prescribing information (label) for carboplatin for all boxed warnings and contraindications.

4.4 Study Assessments

Please see Schedule of Assessments for the schedule of activities to be performed during the study.

4.4.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures or evaluations. Informed Consent Forms for enrolled patients and for patients who are screening failures will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before initiation of study drug. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.4.2 Medical History and Demographic Data

General medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol, and drugs of abuse. TNBC history will include prior cancer therapies, procedures, and an assessment of tumor mutational status (breast cancer susceptibility gene [BRCA] mutational status, where available). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study drug (Cycle 1, Day 1) will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.4.3 Physical Examinations

A complete physical examination should be performed at screening. Any abnormality identified at baseline should be recorded on the eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the eCRF.

4.4.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated.

4.4.5 Tumor and Response Evaluations

Tumor assessments will be performed at screening/baseline, approximately every 12 weeks (± 1 week) (see Schedule of Assessments) until disease progression (PD), withdrawal of consent, death, unacceptable toxicity or study termination by the Sponsor, whichever occurs first. All sites of measurable and non-measurable disease must be documented at screening/baseline and re-assessed at each subsequent tumor evaluation.

4.4.5.1 Screening/Baseline Tumor Evaluations

Tumor assessments performed as part of standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used as baseline assessments rather than repeating the tests.

Radiologic imaging performed during the screening period should consist of the following:

1) Initial screening assessments must include computerized tomography (CT) scans (with oral/IV contrast unless contraindicated) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If a CT scan for tumor assessment is performed using a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

2) Bone scan or PET scan should be performed to evaluate for bone metastases;

3) A CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis at screening in the event of an equivocal scan.

   Patients with active or untreated CNS metastasis are not eligible for this study (see Section 4.1.2 for CNS-related exclusion criteria);

4) CT scans of the neck should also be performed if clinically indicated during the screening period;

5) At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

4.4.5.2 On-treatment Tumor and Response Evaluations

After enrollment, tumor assessments evaluation of tumor response per RECIST v1.1 (see Appendix 1) will be performed according to the schedule of assessments, regardless of treatment delays, interruptions or discontinuations.

For each patient, the same radiographic procedures and technique used to assess disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans and/or magnetic resonance imaging [MRI]), and results must be reviewed by the investigator before dosing at the next cycle. All known sites of disease documented at screening/baseline should be re-assessed at each subsequent tumor evaluation. To the extent feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if progressive disease is suspected. If the initial screening bone scan or PET scan does not show evidence of bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the

treating physician's discretion.

Evaluation of tumor response will be completed by the investigator based on physical examinations, computed tomography (CT) scans, and other modalities, per RECIST v1.1 (see Appendix 1).

If treatment is discontinued prior to disease progression per RECIST v1.1 (e.g., due to study treatment-related toxicity), tumour response assessment should continue to be performed per the schedule specified in the Schedule of Assessments. During the post-treatment follow-up period, only patients with no PD will undergo tumor assessments.

4.4.6 Laboratory, biomarker, and other biological samples

An overview of the standard safety laboratory, biomarker, and other sampling requirements is provided below. For additional details on laboratory assessments and sample handling, refer to the laboratory manual

4.4.6.1 Local laboratory assessments

Samples for the following laboratory tests will be analysed by the local laboratory:

- Hematology: red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential - neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells (if clinically indicated), and platelet count will be performed at screening, at each treatment visit and at the End of Treatment visit.

- Serum chemistry: blood urea nitrogen (BUN) or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, total protein, and albumin. Bicarbonates should only be tested at sites where this test is part of the standard safety laboratory panel will be performed at screening, at each treatment visit and at the End of Treatment visit.

  The Cockcroft-Gault formula will be used to calculate creatinine clearance. Patients must have a CrCl ≥ 30 mL/min to be eligible for enrolment. Levels of magnesium and phosphorus must be tested during screening. During treatment, levels of magnesium and phosphorus should be tested as clinically indicated.

- Coagulation panel: activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR); performed at screening/baseline and at the End of Treatment visit.

- Serum pregnancy test for women of childbearing potential at screening/baseline (within 7 days prior to initiation of study drug); after initiation of study drug, urine pregnancy tests will be performed at each cycle during treatment and at the End of Treatment visit.. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is 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).

- Thyroid function testing: thyroid-stimulating hormone (TSH), free T3 (or total T3 for sites where free T3 is not performed), free T4; performed at screening, within 96 hours before Day 1 of Cycle 1, and within 96 hours before every second cycle thereafter, and at the End of Treatment visit.

- Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood; performed at screening, and thereafter only if clinically indicated.

- In addition, all patients will be tested for HIV antibody, HBsAg, hepatitis B surface antibody (HBsAb), total hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) locally during screening. HIV-positive patients will be excluded from the clinical trial. In patients with a negative HBsAg and positive HBcAb serology, HBV DNA must also be collected prior to initiation of study drug. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.

- PD-L1 positivity: it's defined as expression on tumor-infiltrating immune cells $\geqslant$1%. The test will be performed by each local laboratory on the primary tumor and/or the biopsy of metastatic lesion before starting first-line therapy through the SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems provided by Roche.

All laboratory tests results must be available for the Investigator's review before treatment administration.

4.4.6.2 Blood-based biomarker assays

4.4.6.2.1 CLIO Samples

Blood samples will be analyzed through a multiparametric Cancer agnostic circuLating ImmunOsignature (CLIO), based on the combination of immune-related mutations detectable in the circulating tumor DNA (ctDNA), buffy coat-based RNA sequencing (bcRNAseq) and plasma-based enzyme-linked immunosorbent assay (ELISA). The ctDNA sequencing part will be based on a customized panel that includes, but is not limited to, PIK3CA, PTEN, TP53, EMILIN2, MMRN2 and TNFα. PTPRC and GAPDH will be used as normalizers for the bcRNAseq analysis.

CLIO blood samples will be collected at screening, progression and concomitantly to each per-protocol imaging based-evaluation (i.e. every 12 weeks).

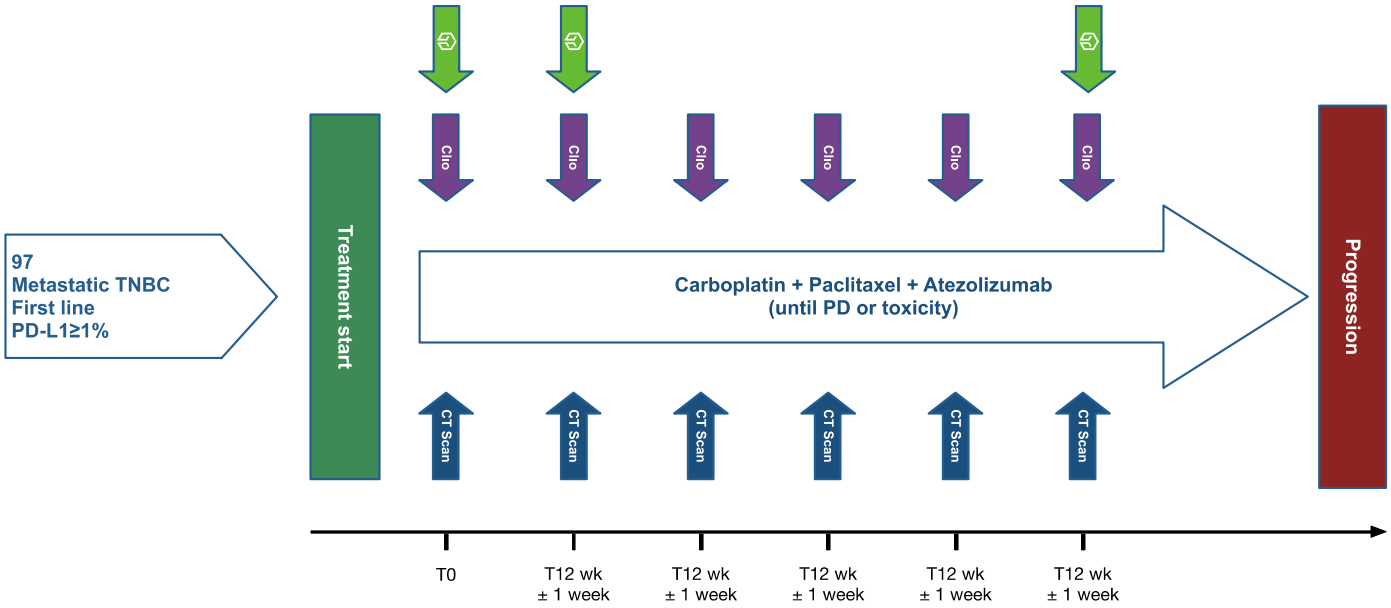
4.4.6.2.2 ctDNA Samples

Tumor-focused ctDNA analyses will be performed through the FoundationOne® Liquid platform according to the vendor's protocols and will be performed at baseline, first evaluation and disease progression.

Since the evaluation is made for research purposes only, FoundationOne® Liquid results will be sent to the Center's investigators only and not to the single enrolled patients.

4.4.6.2.3 Blood sample collection and management

Blood draws timing will follow the schedule reported below:



Timepoint	Sample Type	Volume	Visit
Day -7 to day 1 (any time before of study treatment)	CLIO	10 mL	Screening
	FoundationOne® Liquid	17 mL	
After 12 week (± 1 week)	CLIO	10 mL	Concomitantly to the first per-protocol imaging based-evaluation
	FoundationOne® Liquid	17 mL	
Every 12 week (± 1 week)	CLIO	10 mL	Concomitantly to each per-protocol imaging based-evaluation
Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy.	CLIO	10 mL	EOT due to disease progression
	FoundationOne® Liquid	17 mL	

Table 3. Biological sample collection plan

Plasma preparation from blood collected in ccfDNA stabilizing tubes for CLIO assesment

CLIO plasma sample preparation and management protocols are provided in the laboratory manual.

Buffy-coat preparation from blood collected in ccfDNA stabilizing tubes for CLIO assesment

CLIO buffy-coat sample preparation and management protocols are provided in the laboratory manual.

Sample preparation for FoundationOne® Liquid

FoundationOne® Liquid sample preparation and management protocols are provided in the vendor's data sheet and are included in the laboratory manual.

CLIO sample shipment procedures

CLIO samples will be shipped to the centralized laboratory at the IRCCS CRO Aviano National Cancer Institute. Shipment procedures are provided in the laboratory manual.

4.5 Patient, Treatment, Study, and Site Discontinuation

4.5.1 Patient Withdrawal

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:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.2 Study Drug Discontinuation

Patients must discontinue the study drug if they experience any of the following:

- Intolerable toxicity related to the study drug
- Any medical condition that may jeopardize the patient's safety if he or she continues receiving study drug
- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.5.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates potential health hazard to patients
- Patient enrolment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5 ASSESSMENT OF SAFETY

5.1 Safety Plan

5.1.1 General Plan to Manage Safety Concerns

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined in Section 5.1.2 below. Please refer to the latest atezolizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study.

These include stringent eligibility criteria (see Sections 4.1.1 and 4.1.2), designed to exclude patients at higher risk for toxicities, administration of the study drug in a controlled setting, and close safety monitoring of patients during the study (see Section 4.5), including assessment of the nature, frequency, and severity of adverse events (see Section 5.3.3). Administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

General safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol specified physical examinations, ECGs and safety laboratory assessments (including serum chemistries and blood counts), measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study; see Schedule of Assessment for the list and timing of study assessments.

Laboratory values must be reviewed prior to each infusion. During the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection. After initiation of study drug, all adverse events (regardless of relationship to study drug) will be reported until 30 days after the last dose of atezolizumab or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug; refer to Section 5.3.1 for further details. Adverse events will be defined and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0). All serious adverse events and protocol defined events of special interest will be reported in an expedited fashion (see Sections 5.2.2 and 5.2.3, respectively).The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.2 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related adverse events, specifically the induction or enhancement of autoimmune conditions. To

date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, hypophysitis, myasthenic syndrome/myasthenia gravis, meningoencephalitis, nephritis and myocarditis; refer to Section 5.2.3. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Additional details regarding clinical safety are provided in the latest atezolizumab Investigator's Brochure.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management of procedures for suspected immune-related adverse events are provided in the latest Atezolizumab Investigator's Brochure.

5.1.3 Risks Associated with Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. Therefore, study patients may be premedicated according to local paclitaxel prescribing information and institutional standard of care practice. Such premedication may consist of a corticosteroid (dexamethasone 8 - 10 mg PO administered approximately 12 and 6 hours before paclitaxel), diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and a H2 antagonist (cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before paclitaxel). Patients who experience severe hypersensitivity reactions to paclitaxel despite premedication must not be rechallenged with the drug.

Warnings related to paclitaxel use include bone marrow suppression (primarily neutropenia), which is dose-dependent and is the dose-limiting toxicity during paclitaxel treatment, with neutrophil nadirs occurring at a median of 11 days. Infectious episodes occurred in 30% of all patients exposed to paclitaxel in clinical trials; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. Thrombocytopenia (platelet count below 100,000 cells/mm3 at least once while on treatment) was reported in 20% of the patients, with bleeding episodes in 14% of all patients receiving paclitaxel in clinical trials. Anemia (hemoglobin <11 g/dL) was observed in 78% of all patients and was severe (hemoglobin <8 g/dL) in 16% of the cases, with no consistent relationship between dose or schedule and the frequency of anemia.

Other warnings for paclitaxel use include severe cardiac conduction abnormalities (documented in <1% of patients), which required pacemaker placement in some cases.

In addition, paclitaxel can cause fetal harm when administered to a pregnant woman.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel (in 12%, 3%, and 1% of patients, respectively), but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Other significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients, and included syncope, rhythm abnormalities, and venous thrombosis.

Paclitaxel treatment is frequently associated with peripheral neuropathy; however, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of the drug. Other serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site; more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have also been reported, with onset during or up to 10 days after paclitaxel infusions.

Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors, and inducers of CYP3A4 or CYP2C8; refer to Section 4.3.3.

For more details regarding the safety profile of paclitaxel, refer to the local paclitaxel prescribing information.

Patients will be monitored for paclitaxel-related adverse events throughout the study.

5.1.4 Risks Associated with Carboplatin

Warnings and precautions related to carboplatin use include:

- Myelosuppression (closely related to the renal clearance of the drug), with median day of nadir reported as day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. Peripheral blood counts, renal and hepatic function tests should be monitored closely during carboplatin treatment

- Allergic reactions: as with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusion. Patients should be observed carefully and an appropriate symptomatic treatment (including antihistamines, adrenaline and/or glucocorticoids) must also be initiated in such cases

- Renal toxicity (with higher incidence and severity in patients with pre-existing impairment in renal function or previous nephrotoxicity as a result of cisplatin therapy)

- Hemolytic-uremic syndrome (HUS): Carboplatin should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia (rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required

- Neurologic toxicity: may manifest as peripheral neurologic toxicity (generally common, but mild), or visual disturbance or loss of vision (generally associated with higher than recommended doses or renal impairment, and appears to resolve within weeks of stopping carboplatin)

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior

Reversible Encephalopathy Syndrome (PRES): a rare, reversible (after treatment discontinuation), rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances

- Auditory defects / ototoxicity
- Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents such as carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Very common (frequency ≥ 1 per 10 exposed patients) adverse reactions associated with carboplatin include the following (listed by preferred term): thrombocytopenia, neutropenia, leucopoenia, anemia, vomiting, nausea, abdominal pain, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased.

For further details on the risks, including adverse reactions associated with carboplatin treatment, refer to the current local prescribing information for carboplatin.

5.1.5 Management of Patients who experience specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Diagnostic criteria for hemophagitic lymphohistio-cystosis (HLH) and macrophage activation syndrome (MAS) systemic immune activation are presented in Section 5.1.5.1. For details on the management of infusion-related reactions and all other immune related adverse events, including but not limited to, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, or eye toxicity refer to the current atezolizumab Investigator's Brochure.

5.1.5.1 Hemophagocytic lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100 × 109/L (100,000/μL)
  - ANC < 1.0 × 109/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181 × 109/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 1.

Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

• Event	• Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

5.1.5.2 Pulmonary events/Pneumonitis

5.1.5.2.1 Atezolizumab

Management guidelines for pulmonary events are provided in the latest atezolizumab Investigator's Brochure.

5.1.5.2.2 Paclitaxel

Pneumonia, interstitial pneumonia, pleural effusion, lung fibrosis, pulmonary embolism,and respiratory failure are rare adverse effects, occurring in ≥1/10,000 and <1/1,000 ofpatients, and dyspnoea is a common adverse effect, occurring in ≥1/100 and <1/10 of patients treated with paclitaxel. Paclitaxel, particularly in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of interstitial or radiation pneumonitis. Fatal cases of pneumonia have also been reported.

Paclitaxel should be permanently discontinued upon ruling out infectious etiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. After infectious aetiology is ruled out, IV high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Refer to the local paclitaxel prescribing information for further details.

5.1.5.3 Infusion-Related Reactions

5.1.5.3.1 Atezolizumab

No premedication is indicated for the administration of atezolizumab in Cycle 1. However, patients who experience an infusion-related reaction with atezolizumab in Cycle 1 may receive premedication with

antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Infusion-related reactions should be managed according to institutional guidelines.

5.1.5.3.2 Paclitaxel and Carbopaltin

Paclitaxel and carboplatin infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria; these events should be treated with aggressive symptomatic therapy; refer to Section 5.1.6.2.2.

5.1.6 Dose Modifications and Interruptions due to Adverse Events

5.1.6.1 General Considerations

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

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

If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab or paclitaxel or carboplatin) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

When treatment is temporarily interrupted because of toxicity caused by atezolizumab or paclitaxel or carboplatin , the treatment cycles will be restarted such that the atezolizumab, paclitaxel and carboplatin infusions remain synchronized.

If it is anticipated that paclitaxel will be delayed by >2 weeks, then atezolizumab should be given without the chemotherapy, as long as there is no contraindication.

In general, the start of a cycle may be delayed to allow recovery from toxicities, but there should be no delays within cycles. Cycle length is fixed at 28 days, and dosing on Days 8 and 15 of a cycle may be skipped but should not be delayed outside of the +3 days window.

The treating physician may use discretion in accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient.

5.1.6.2 Events requiring Permanent Treatment Discontinuation

5.1.6.2.1. Atezolizumab

Patients must permanently discontinue Atezolizumab if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event

- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment

- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

- Use of another non-protocol anti-cancer therapy

- Pregnancy

- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

For further details, including complete management guidelines for the immune-related events, refer to the latest atezolizumab Investigator's Brochure.

5.1.6.2.2. Paclitaxel

Paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria; these events should be treated with aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

In addition, paclitaxel should be permanently discontinued upon ruling out infectious etiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. Consideration may be given to performing pulse oximetry and pulmonary function tests to confirm respiratory and ventilation compromise in patients with suspected pneumonitis.

Other events that required discontinuation of paclitaxel in clinical trials include cases of severe neurotoxicity, such as peripheral neuropathies (1% of all patients). Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.

Refer to the local paclitaxel prescribing information for further details.

5.1.6.2.3. Carboplatin

Carboplatin infusions should be discontinued immediately in case of severe hypersensitivity reaction, and at first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopoenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH (risk of HUS).

In addition, carboplatin infusions should be permanently discontinued in case of severe and persistent

myelosuppression, or severe impairment in renal or hepatic function.

Refer to the local carboplatin prescribing information for further details.

5.1.6.3 Dose Modifications and Interruptions

5.1.6.3.1 Atezolizumab

Dose reduction of atezolizumab is not permitted in this study.

Atezolizumab infusions may be temporarily suspended in case of an adverse event that requires a dose to be held. If atezolizumab is held because of adverse events for >12 weeks beyond the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety as specified in Section 5.5. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold of >12 weeks, study drug may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be held for up to 12 weeks until steroids are discontinued or reduced to prednisone dose (or dose equivalent) of ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.6.3.2 Paclitaxel and Carboplatin

Haematologic Toxicities

Absolute neutrophil count (ANC) must be ≥1500/mL (≥1500 cells/mm3) and platelet count must be ≥100,000/µL (≥100,000 cells/mm3) for the patient to receive paclitaxel on any treatment day (Day 1, 8, 15 of any 28-day cycle).

Dose modifications should be made according to the following table:

ANC		**Platelets**	**Paclitaxel dose**
≥1,500/ µL (≥1,500 cells/mm3)	and	≥100,000/µL (≥100,000 cells/mm3)	90 mg/m2
1,000-1,499/µL (1,000-1,499 cells/mm3)	or	75,000-99,999/µL (75,000-99,999 cells/mm3)	65 mg/m2
<1,000/µL (<1,000 cells/mm3)	or	<75,000/µL (<75,000 cells/mm3)	Hold [1]

[1] If treatment is held, the CBC should be repeated until ANC ≥1500/µL (≥1500 cells/mm3) and platelets ≥100,000/µL (≥100,000 cells/mm3). If paclitaxel/carboplatin therapy must be held for > 3 weeks to allow for resolution of haematologic toxicity, the patient will discontinue paclitaxel/carboplatin treatment but may continue receiving atezolizumab.

For any patient experiencing any of the following hematologic toxicities, the paclitaxel dose should be reduced to 65 mg/m² for all subsequent cycles:

- Fever (>38.5°C) associated with ANC <1,000/μL (<1,000 cells/mm3)
- Absolute granulocyte count <500/ μL (<500 cells/mm3) for > 5 days
- Significant bleeding associated with a platelet count <40,000/ μL (<40,000 cells/mm3)
- Any platelet count <20,000/ μL (<20,000 cells/mm3).

If these severe hematologic toxicities recur in subsequent cycles despite dose reduction, paclitaxel should be discontinued, however the patient may continue receiving atezolizumab.

If the start of a cycle is delayed (i.e. both atezolizumab and paclitaxel and carboplatin are held) for low counts, Day 1 will be postponed, and dosing resumed when ANC recovers to ≥1500/ μL (≥1500 cells/mm3) and platelet count returns to ≥100,000/ μL (≥100,000 cells/mm3).

In certain situations, (see Section 5.1.5.1) a cycle may begin with the administration of atezolizumab alone (without paclitaxel and carboplatin on Day 1). If paclitaxel or carboplatin cannot be administered on Day 8 of the cycle, they may be administered on Day 15 if counts have recovered to permissible levels. If paclitaxel and carboplatin cannot be administered on Day 15 of the cycle, the next dose of paclitaxel or carboplatin should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels.

Hepatic Toxicities

In case of hepatic toxicities, dose modifications should be made according to the following table:

AST		**Bilirubin**	**Paclitaxel dose**
≤ 5 x ULN	and	≤ 1.5 mg/dL (≤ 25.65 μmol/L)	90 mg/m2
> 5 but ≤ 10 x ULN	or	1.6 - 2.5 mg/dL (27.36 - 42.75 μmol/L)	65 mg/m2
> 10 x ULN	or	≥ 2.6 mg/dL (≥ 44.46 μmol/L)	Hold [1]

AST: aspartate aminotransferase; ULN: upper limit of normal

[1] Hold therapy until AST < 10 x ULN and bilirubin < 2.5 mg/dL. If paclitaxel must be held for > 3 weeks to allow for resolution of hepatic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving atezolizumab.

Patients requiring a delay in paclitaxel therapy due to hepatic toxicity should be evaluated for possible progressive hepatic metastases.

Peripheral Neuropathy

If grade 3 toxicity develops, paclitaxel/carboplatin treatment should be withheld until the neuropathy

recovers to < grade 1 (atezolizumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel/carboplatin dose should be reduced permanently to 65 mg/m². If grade 3 neuropathy persists for > 3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel/carboplatin treatment but may continue receiving atezolizumab.

Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with standard antiemetics and will not result in dose modification.

Anaphylaxis/Hypersensitivity

- Mild symptoms (e.g., mild flushing, rash pruritus): No treatment needed. Supervise at bedside and complete paclitaxel infusion.
- Moderate symptoms (moderate flushing, rash, mild dyspnea, chest discomfort): Stop paclitaxel/carboplatin infusion. Administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). After recovery of symptoms, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, the reaction should be reported as an adverse event and the patient will discontinue paclitaxel/carboplatin treatment but may continue atezolizumab.
- Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilators, generalized urticaria): Stop the infusion and administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). Add epinephrine or bronchodilators if needed. The reaction should be reported as an adverse event and the patient will discontinue paclitaxel/carboplatin treatment but may continue atezolizumab.

Gastrointestinal Toxicity

If the patient develops any other grade 3 or 4 toxicity considered related to paclitaxel/carboplatin, paclitaxel/carboplatin should be held until symptoms resolve to grade 1 or less (atezolizumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel/carboplatin dose should be reduced permanently to 65 mg/m². If grade 3 toxicity persists for >3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel/carboplatin treatment but may continue atezolizumab.

Refer to the local paclitaxel/carboplatin prescribing information for further details.

5.2 Safety Parameters and Definitions

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

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

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- Note: This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug;
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

Adverse events of special interest for this study include the following conditions specific for atezolizumab:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including Rrhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune haemolytic anaemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis).

The following events also require immediate reporting:

- Cases of potential drug-induced liver injury that include elevated ALT or AST level in combination with either elevated bilirubin levels or clinical jaundice, as defined by Hy's law (see Section 5.3.5.5.1);
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Product Complaints

A product complaint is any deficiency related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of the product. Product complaints are required to be reported by

the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

5.3 Methods and timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 (immediate reporting), Section 5.5 (follow-up), and Section 5.6 (events occurring after the reporting period).

For each adverse event, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4) on the eCRF.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events (regardless of relationship to study drug) will be reported until 30 days after the last dose of atezolizumab or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period (defined as 90 days after the last dose of atezolizumab) are provided in Section 5.6.

5.3.2 Eliciting Adverse Event information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. **Table 3** will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 - Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life-threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2.2.

A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered a SAE.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered related to the study drug, and answer "yes" or "no" to the question: “Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?”

Causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or

"anaphylactic reaction") on the eCRF. If possible, ambiguous terms such as "systemic reaction" should be avoided. Associated signs and symptoms should be recorded on the eCRF. If a patient experienced both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the eCRF, with signs and symptoms also recorded separately on the eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events that are secondary to other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, except for severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal haemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4 for reporting instructions). The eCRF should be updated by changing the

event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation);
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy;
- Is clinically significant in the investigator's judgment.

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 xULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5.1 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 x ULN) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report

as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 x ULN in combination with total bilirubin >2 x ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST >3 x ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of mTNBC should be recorded on the eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on eCRF and immediately reported to the Sponsor (see Section 5.4).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death,

within 24 hours after the patient was last seen alive and stable.

If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of mTNBC should be recorded only on the eCRF, while the date of death should be captured on the eCRF. Reporting of deaths that occur after the adverse event reporting period is described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study.

Such conditions should be recorded on the eCRF.

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

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

- The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer (including symptoms).

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

- Hospitalization for outpatient care outside of normal outpatient clinic operating hours that is required per protocol or per local standard of care.

5.3.5.11 Special situations

For this study, the following events are considered "Special Situations":

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug. In some cases, a medication error may be intercepted prior to administration of the drug.

Any study drug overdose or medical error of study drugs should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4), noted on the eCRF and reported as a protocol deviation. Any overdose or incorrect administration of paclitaxel should be noted on the eCRF and reported as a protocol deviation.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

5.4 Immediate reporting requirements

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

- Serious adverse events (see Section 5.2.2 for further details)
- Adverse events of special interest (see Section 5.2.3 for further details)
- Special situations (see Section 5.3.5.11 for further details)
- Pregnancies (see Section 5.4.2 for further details)
- Product complaints (see Section 5.4.3 for further details)

Contact details of Sponsor Safety Desk for reporting are available in the Safety Desk section of this Protocol.

All SAEs and adverse events of special interest will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of study drug or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The sponsor will indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator. A SAE report and accompanying cover page will be sent via email to Sponsor by Investigator..

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

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

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

5.4.1.1 Events That Occur prior to Study Drug Initiation

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

5.4.1.2 Events that Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the eCRF.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study drug. The study Pregnancy Surveillance Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancies should not be recorded on the eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the eCRF. In addition, the investigator will update the Pregnancy Surveillance Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drugs. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, only in case of pregnancy, the Sponsor should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.2.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

5.4.2.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on

the eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

5.4.3 Reporting requirements for Product complaints

The investigator must report all product complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). If the complaint is related to an adverse event to the study patient, the event must be reported on the eCRF. If the event is serious, the SAE report has to be completed and forwarded to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

5.5 Follow-up of patients after adverse events

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome, by following the reporting instructions provided in Section 5.4.2.

5.5.2 Sponsor Follow-Up

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

5.6 Adverse Events that occur after the adverse event reporting period

At the treatment discontinuation visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse events of special interest that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of the study drug), if the event is believed to be related to prior treatment with study drugs. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in

this study.

5.7 Expedited reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

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

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

- Atezolizumab Investigator's Brochure
- Local prescribing information for paclitaxel and carboplatin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This phase II, single-arm, study is designed to test the hypothesis that the addition of an anti-PDL1 to 1st line therapy in metastatic triple-negative breast cancer is associated with a clinically relevant 2-year increase in OS over what expected based on historical data (54%; Schmid et al. 2018)

6.1 Statisitical Considerations

The statistical design of this phase II trial is influenced by 2-factors:

a) The addition of an immunotherapy agent to a polychemotherapy with a considerable activity in TNBC is unlikely to produce a substantial improvement in the Response Rate or in Progression Free Survival. Therefore, the only study endpoint capable of capturing any effect of this addition is Overall Survival.
b) Although TNBC is possibly the biological variant of breast cancer which is least susceptible to medical treatments, short term survival of patients with mTNBC is still quite high, with a median OS in excess of 2 years (Tutt et al. 2018; Yardley et al. 2018)

As a consequence, the standard design of phase II trials, which is focused on short term markers of response and incorporates stopping rules for futility based on early interim analyses, cannot be used. Instead, this trial is designed as a single stage cohort study in which all patients will be followed til the end of the study, which is set at two years after the enrolement of the last patient, thereby ensuring a minimal potential follow-up of 2 years to all enrolled patients who did not die before 2 years. The primary study endpoint will be the proportion of patient alive at two years (2ys OS%), but, OS% at 2.5 years will represent a important secondary endpoint, since, considering that no less than 1 year will be necessary to enroll all patients into the study, at the time of the final analysis (i.e. 2 years after the enrolment of the last patient), 50% of the enrolled patients will have a follow-up ≥2.5 years.

6.2 Expected results and sample size

In order to reject with power 80% at the 0.05 (1-sided) significance level the null hypothesis that 2yrsOS in mTNBC treated with atezolizumab plus carboplatin and paclitaxel is 54%, under the alternative hypothesis that atezolizumab increases this porportion by 12% (i.e. to 66%), it is necessary to enroll into the study 104 patients. With 104 patients, the minimal observed 2yrsOS% allowing rejection of the null hypothesis at the 1-sided 5% significance level is 62.5% (=65 survivors at 2yrs /104 enrolled patients) and the estimated 2yrsOS will have a precision (= width of the exact 90% CI) of approximately +/- 8% (e.g., for 65 successess/104 patients) $0.5401 \leq p \leq 0.7044$)

6.3 Efficacy Analyses

The primary and secondary efficacy analyses will include all enrolled patients, in accordance with the Intention to Treat Principle.

6.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is % Overall survival at 2 years, defined as the proportion of patients alive 2 years after enrollment. Due to the fact that the information of vital status of an individual

(alive/dead) is not covered by privacy and is available to anyone in Italy from the municipality of residence, and that this study will not terminate for at least 2 years after the enrolment of the last patient, no censored survival times are expected in the first 2 years of follow-up, making it possible to compute the crude proportion of patients alive at 2 years, which will be used in the primary analysis. However, should the information be missing for some patients (e.g. due to adiministrative reasons, or to errors in the registration of patient' data) the proportion of survivors at 2 years estimated by the Kaplan Meier will be used instead. The resulting loss in statistical power can be considered negligible, as the number of patients lost to follow-up and for whom the information on the vital status cannot be retrieved is expected to be very small. The proportion of 2-yrs survivors with its 90% exact CI's according to Clopper-Pearson will be presented

The comparison between the observed and the expected (54%) proportion of patients surviving at 2 years will be based on the exact binomial probability distribution under H0 (Proportion = 54%)

6.3.2 Secondary Efficacy Endpoints

- % Overall survival at 2.5 years
- Overall Survival at 2 years in HR <1% and in HR 1-10%
- Post-progression survival
- Objective response rate
- Time to treatment failureIncidence and severity of adverse events and serious adverse events

6.3.2.1 % Overall survival at 2.5 years

% Overall survival at 2.5 years is defined as the proportion of patients alive 2.5 years after enrollment.

6.3.2.2 Overall Survival at 2 years in HR <1% and in HR 1-10%

% Overall survival at 2 years is defined as the proportion of patients alive 2 years after enrollment in patients with Hormonal Receptor (HR) <1% and in patients with HR 1-10%

6.3.2.3 Post-Progression survival

Post-Progression Survival (PPS) is defined as the time from tumor progression until death or is censored on the date of the last follow-up consultation

6.3.2.4 Objective Response Rate (see Appendix 1)

An objective response is defined for patients with measurable disease at baseline as either a partial response (PR) or a complete response (CR) using RECIST v1.1. An estimate of ORR (CR plus PR) will be calculated in all patients evaluable for response and its 95% CI will be calculated using the Clopper-Pearson method.

6.3.2.5 Time to treatment failure

Time to treatment failure (TTF) is defined as the time from enrollment to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death.

6.3.2.6 Incidence and severity of adverse events and serious adverse events

Safety analyses will include all enrolled patients who received at least one dose of study treatment (atezolizumab or paclitaxel or carboplatin).

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, study treatment exposures, and will be presented by treatment arm.

Treatment-emergent events (defined as events occurring on or after the first dose of study treatment and within 30 days prior to the last dose of study treatment) will be summarized by MedDRA term, appropriate MedDRA levels (for example, system organ class [SOC] and preferred term [PT]), and NCI CTCAE v5.0 grade, regardless of relationship to study drug as assessed by the investigator. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will also be summarized:

- Adverse events assessed as related to the study drug
- Adverse events leading to permanent discontinuation of study drug (with or without withdrawal from the study)
- Adverse events leading to dose reduction or interruption
- Grade ≥3 adverse events
- Grade 5 adverse events
- Serious adverse events; and Adverse Events of Special Interest (AESI)

All deaths and causes of deaths will be summarized.

Relevant laboratory values will be summarized by time, with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmnized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The protocol and the proposed informed consent form must be reviewed and approved by Independent Ethics Committee (IEC) of all participating centers before study start.

7.2 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Oncotech-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines.

The investigator/institution should take measures to prevent accidental or premature destruction of these documents. Essential documents (written and electronic) should be retained for a period of not less than twenty-five (25) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

7.3 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the Sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

7.4 Audits and inspections

Source data/documents must be available to inspections by the Sponsor or designee or Health Authorities.

7.5 Financial disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

7.6 Patient protection

The responsible investigator of each site will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

7.7 Subject identification – Personal Data Protection

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, year of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see Section 8.8 below). Such information must (i) identify the roles of the holder ("titolare") and processor ("responsible", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patient information or documentation may be considered "anonymous", and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer

available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

7.8 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before any study procedure starts. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative". The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

7.9 Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

7.10 Data ownership

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.Study insurance

The sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with Section 5.8 of the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the exclusion of those attributable to willful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer's certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.

8 STUDY MANAGEMENT

8.1 Training of study site personnel

Investigational staff involved in the study will be adequately trained by the local PI and representatives of the Contract Research Organization before any activities related to the Study are initiated.

8.2 Study timetable and end of study

Enrollment period: 2 years approximately
First Patient First Visit (FPFV): Feb 2020
Last Patient First Visit (LPFV): Feb 2022
Follow-up: 2 years (from the enrollment of the last patient)
Total Study Duration: 4 years approximately

9 DATA MANAGEMENT

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Sponsor personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms and the results of any other tests or assessments.

All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. The Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs, AESIs, pregnancies and special situations.

9.3 Data collection

This study will use an Electronic Data Capture (EDC) system (eClinical platform provided by Clinical Research Technology). The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using eClinical platform provided by Clinical Research Technology, a fully validated secure web- enabled software that conforms to FDA requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs allow modification or verification of the entered data by the investigator staff. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

The Sponsor personnel (or designated CRO) will review the data entered by investigational staff for

completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data. Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The occurrence of any protocol violations will be determined. After the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Biostatistics and Data Management and the Sponsor.

10 PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the Sponsor, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IEC it cannot be implemented.

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the IEC. Only amendments that are required for patient safety may be implemented prior to IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the IEC at the study site should be informed within 10 working days.

11 PUBLICATION POLICY

After completion of the study, the Principal Investigator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be delivered to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by all the other Investigators and the Steering Committee for coordination and homogeneity purposes: specific advance periods for submission and review may be specified in the protocol.

The timing of publications (in the event several Centers should be participating in the Study) may be coordinated, and publication delayed if patentable inventions should be involved (for the time required in order to file the relevant patent applications); otherwise, according to the Ministry of Health's Decree of May 12, 2006, investigators cannot be precluded from or limited in publishing the results of their studies (IECs must verify that no excessive restriction is contained in the protocols submitted to their review and approval).

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APPENDIX 1: Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer et al. 2009) are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: □

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of

the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrolment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop

contraindications to contrast after baseline contrast CT is done, the decision as to whether noncontrast CT or MRI (enhanced or nonenhanced) will be performed should also be based on the tumour type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of nontarget disease or new lesions since the same lesion may appear To have a different size using a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm X 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.) To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment.

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level) All lymph nodes must be non-pathological in size (< 10 mm short axis).

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease.

In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not. A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs.

Table A provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore nontarget) disease only, Table B is to be used.

Table A Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR

CR	Not evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

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

Table B Timepoint Response: Patients with Nontarget Lesions Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes or no	PD

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.
If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more nontarget lesions are not assessed, the response for nontarget lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the nontarget response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.