CLINICAL TRIAL SYNOPSIS

(ACCESS)

PHASE II STUDY ON TSR-042 IN ADVANCED CLEAR CELLS SARCOMA

INVESTIGATIONAL MEDICINAL PRODUCT: TSR-042

Protocol Code: ISG-ACCeSs

EudraCT No: 2016-004368-21

Clinicaltrials.gov: NCT04274023

Protocol version: 2.2

Date: 07 May 2021

Phase: II

TITLE	Phase II study on TSR-042 in advanced clear cells sarcoma
PROTOCOL CODE	ISG- ACCeSs EudraCT: 2016-004368-21
NUMBER OF SITES/TRIAL LOCATION	This is a multicenter study A full list of investigators will be available as separate document
STUDY OBJECTIVES	This is a phase II, not randomized, European multicentric study designed to explore the activity of TSR-042, a human monoclonal anti-PD-1 inhibitor, in a population of patients with a diagnosis of advanced/metastatic clear cell sarcoma (CCS). **Primary:** The primary objective of this study is to evaluate the activity of TSR-042 in patients with advanced CCS according to Response Evaluation Criteria In Solid Tumor (RECIST), version 1.1**.** Therefore, with reference to a study population of patients with progressive locally advanced or metastatic CCS, primary end point of the study will be to assess: Overall tumor Response Rate, according to RECIST 1.1 **Secondary:** To assess: • ir-RECIST response rate • CHOI criteria response rate • Overall Survival • Progression Free Survival (PFS) • Clinical Benefit Rate (RECIST CR + PR + SD > 6 months) • Safety • Correlation between response and prior medical treatment • Quality of life reported by patients with Patient-Reported Outcome QoL **Exploratory:** • Correlation between TSR-042 activity and prior antitumor medical therapies. To this end it is foreseen to include at least 5 naïve patients, 5 patients pretreated with DTIC and 5 patients pretreated with an anti-angiogenic agent • Post-treatment TSR-042 targets status assessment by: 1. Immunological monitoring of peripheral blood immune subsets and plasma sample collection. 2. Analysis of pre-post treatment tumor samples (biopsies) to assess the expression level of PD1 and PDL1 on cancer cells and in tumor infiltrating myeloid cells, and the presence of CD20+ B cells, CD56+NK cells and CD3+ T cells together with the assessment of PD1 positivity on tumor infiltrating lymphocytes; whenever available, fresh tumor material from the surgery will be processed for obtaining short-term tumor cells and autologous immune infiltrating cells. The level of PDL1 expression will be evaluated on both tumor cells and immune cells. Co-

<table>
<tr><td></td><td>culture assays of myeloid cells or tumor cells and T cells will be conducted in vitro in the absence or presence of the anti-PDL1 antibody and the functionality of T cells (production of GZMB, IFN-γ, TNFa, CD107a) evaluated both by intracellular cytokine staining and ELISpot assay.</td></tr>
<tr><td>STUDY DESIGN</td><td>This is an European, non-randomized, open-label, multicentric, investigator-initiated, Phase II clinical study to explore the activity of TSR-042, at a dose of 500 mg every 21 days for the first 4 doses, followed by 1,000 mg on day 1 of every 42 day in intravenous (IV) infusion, until progression or unacceptable toxicity, in a population of patients with progressive advanced (i.e. locally advanced or metastatic) CCS. Patients with a documented and centrally reviewed pathologic and radiologic diagnosis of locally advanced or metastatic CCS may enter the study.</td></tr>
<tr><td>STUDY POPULATION</td><td>Patients with progressive advanced (i.e. locally advanced or metastatic Clear Cell Sarcoma (CCS)</td></tr>
<tr><td>INCLUSION CRITERIA</td><td>
1. The patient or legal representative must be able to read and understand the informed consent form (ICF) and must have been willing to give written informed consent for the trial. The subject may also provide an optional consent for the biological/translational sub-study associated. However, the subject may participate in the main trial without participating in biological/translational sub-study
2. Histological centrally and molecularly (ie the presence of translocation t(12;22)(q13;q12) confirmed diagnosis of clear cell sarcoma
3. Confirmed availability of archived FFPE tumor tissue block, or a minimum of 15 slides. If archived FFPE tissue is not available, then a de novo (ie, fresh) tumor sample must be obtained in accordance with local institutional practice for tumor biopsies
4. Locally advanced disease (i.e. surgical resection of local disease unfeasible radically, or unaccepted by the patient, or amenable to become less demolitive, or feasible, or easier, after cytoreduction) and/or metastatic disease
5. Have measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Patient can be naive or previously treated with 1 or 2 systemic regimens given for recurrent and/or metastatic disease
7. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2
8. Adequate bone marrow function, defined as the following:

WBC	>3.0 x 109
ANC	>1.5 x 109
Platelets	>100 x 10
Hb	>9 g/dL

Blood transfusions to reach the baseline requested Hb level are not allowed.

9. Adequate organ function, defined as the following:

total bilirubin	<1.5 times the upper limit of normal (UNL) (≤2.0 in patients with known
</td></tr>
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	Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
AST (SGOT)	<2.5 x UNL unless liver metastases are present, in which case they must be ≤ 5 x ULN
ALT (SGPT)	<2.5 x UNL unless liver metastases are present, in which case they must be ≤ 5 x ULN
Lipase≤ 1.5 x the ULN	≤ 1.5 x the ULN
Creatinine	≤ 1.5 x the ULN within normal institutional limits or creatinine clearance >60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal limits
Alkaline phosphatase	<2.5 x ULN (<5 x upper limit of normal for patients with liver involvement of their cancer and/or have bone metastases)
PT-INR/PTT	<1.5 x upper limit of normal (Patients who are being therapeutically anti-coagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists).

10. Cardiac ejection fraction ≥50% as measured by echocardiogram
11. ≥ 18 years of age on day of signing informed consent.
12. Female participant has a negative serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees use an adequate method of contraception from screening through 150 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
    - ≥45 years of age and has not had menses for >1 year
    - Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
    - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use an adequate birth control method throughout the study, starting with the screening visit through 150 days after the last dose of study treatment. See Section 4.4 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

	Note: Abstinence is acceptable if this is the established and preferred contraception for the patient. 13. Participant must agree to not breastfeed during the study for 150 days after the last dose of study treatment. 14. Male participant agrees to use an adequate method of contraception (see Section 4.4 for a list of acceptable birth control methods) starting with the first dose of study treatment through 150 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient. 15. No history of arterial and/or venous thromboembolic event within the previous 12 months. 16. Participant receiving corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy. 17. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
EXCLUSION CRITERIA	1. Participant must not be simultaneously enrolled in any interventional clinical trial 2. Previous treatment with any non-investigational agents within 14 days of first day of study drug dosing. 3. Must not have received investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior initiating protocol therapy 4. Other primary malignancy with <5 years clinically assessed disease-free interval, except basal cell skin cancer, cervical carcinoma in situ, or other neoplasms judged to entail a low risk of relapse 5. Previous treatment with radiation therapy within 14 days of first day of study drug dosing, or patients who have not recovered from adverse events due to agents administered more than 4 weeks earlier 6. Has known active central nervous system (CNS) metastases, leptomeningeal metastases, and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability 7. Has active, non-infectious pneumonitis 8. Has an active infection requiring systemic therapy 9. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agents 10. Has received a live vaccine within 30 days of planned start of study therapy 11. Major surgery within 3 weeks prior to study entry. Participant must have recovered from any surgical effects.

	12. Any one of the following currently or in the previous 6 months: a. Myocardial infarction, b. congenital long QT syndrome, c. Torsades de Pointes, d. arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation, bradycardia defined as <50 bpm), e. right bundle branch block and left anterior hemiblock (bifascicular block), f. unstable angina g. coronary/peripheral artery bypass graft, h. symptomatic congestive heart failure CHF New York Heart Association Class III or IV), cerebrovascular accident, or transient ischemic attack i. symptomatic pulmonary embolism. 13. Ongoing cardiac dysrhythmias of NCI CTCAE Grade >=3, atrial fibrillation of any grade,or QTcF interval >470 msec at screening (average of triplicate ECG). 14. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, chronic renal disease, chronic obstructive pulmonary disease, uncontrolled major seizure disorder, unstable spinal cord compression, psychiatric disorder that prohibits obtaining informed consent or active uncontrolled infection). 15. Patient experienced ≥ Grade 3 immune-related AE with prior immunotherapy, with the exception of non-clinically significant lab abnormalities. 16. Participant has a diagnosis of immunodeficiency or has receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to initiating protocol therapy 17. Any known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [qualitative] is detected) 18. Any known history of human immunodeficiency virus (type 1 or 2 antibodies) 19. Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment) 20. Expected non-compliance to medical regimens 21. Known history of interstitial lung disease 22. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs); patients with a past history of autoimmune disease will be discussed case by case with the sponsor of the study: i. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible ii. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses less than or equal to (<=)10 milligram (mg) or equivalent prednisone per day

	iii. Administration of steroids through a route known to result in a minimal systemic exposure are acceptable 23. Known severe hypersensitivity reactions to monoclonal antibodies (including TSR-042 components or excipients), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of partially controlled asthma Global Initiative for Asthma 2011)
TRANSLATIONAL STUDY	An optional biological study will be conducted in the subject who will give their additional informed consent for the translational research. The following analysis will be performed comparing the pre-treatment status and correlated with radiologic evaluation in the patients treated according to the protocol • Immunological monitoring of peripheral blood immune subsets and plasma sample collection • Analysis of pre-post tumor lesions (biopsies)
EXPECTED NUMBER OF PATIENTS	A maximum of 16 patients evaluable for the primary end-point will be enrolled in about 2 years. To reach the target of 16 evaluable patients, a total number of 21 patients will be included in the study.
STUDY DRUG	The Investigational Medicinal Product (IMP) is TSR-042. TSR-042 is an IgG4 humanized monoclonal antibody that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This anti-PD-1 therapeutic antibody concept is being developed in oncological settings by TESARO.
STARTING DOSES AND SCHEDULE	Subjects will receive an IV infusion of TSR-042 at a dose of 500 mg (over the duration of 30-minutes) every 21 days for the first 4 doses, followed by 1,000 mg on day 1 of every 42 day.
STATISTI-CAL METHODS	To estimate the sample size, it has been taken into account the published response rate based on RECIST 1.1 in CCS patients treated with anthracycline-based chemotherapy which correspond to <20%. In addition, for first line, ≥30% RR is considered as a reference value to suggest drug activity in advanced STS. A total of 16 patients is required to detect a response rate of 30% or greater and to exclude a response rate of 5% or less, type-I (alfa) and type-II (beta) error levels being fixed at 10%. RR<5% was excluded since this is what expected with the standard chemotherapy; for first line, ≥30% RR is considered as a reference value to suggest drug activity in advanced STS. For time-to-event variables (e.g. PFS or OS) Kaplan-Meier estimations will be used. In case of positive result (i.e 5 RECIST responses of 16 evaluable patients), an expansion of this study will be considered.

Flow chart

Protocol Activities	Screening[1] (≤28Days)	1 cycle = 21 days[2]					1 cycle = 42 days[2]		End of Treatment/ Withdrawal Visit[3]	Safety Follow-up after 30 days[4]	Safety Follow-up after 90 days Phone call visit[5]	Follow-up Phone call visit[6]
		Cy1		Cy2	Cy3	Cy4	Cy5	Cyn		30 days after last dose	90 days after last dose	Every 12 weeks
		Day1	Day 7 and 14	Day1	Day1	Day1	Day1	Day1				
Visit Time Window		±1	±1	−3/+1	−3/+1	−3/+1	−3/+1	−3/+1		+5		
Study Informed Consent[7]	X											
Translational Study Informed Consent (optional)	X											
Demography (birth date, sex)	X											
Medical History	X											
Tumor History[8]	X											
Height	X											
Vital Signs, weight[9]	X	X	X	X	X	X	X	X	X	X		
Physical Examination[10]	X	X	X	X	X	X	X	X	X	X		X
Baseline Signs and Symptoms[11]	X									X		
ECOG Performance Status[12]	X	X		X	X	X	X	X	X	X		X
Concomitant Treatment	X	X	X	X		X	X	X	X	X		
Single 12-lead ECG[13]	X	After 6 months from treatment start							X			
Echocardiogram[14]	X	After 6 months from treatment start							X			
Hematology[15]	X	X	X	X	X	X	X	X	X			
Blood Chemistry[16]	X	X	X	X	X	X	X	X	X	X		
Coagulation[17]	X	X	X	X	X	X	X	X	X	X		
TSH, FT3, FT4[18]	X	X	X	X	X	X	X	X	X	X		
HBV, HCV[19]	X											
Urinalysis[20]	X	X		X	X	X	X	X	X	X		
Pregnancy Test[21]	X	X		X	X	X	X	X	X	X		
Mandatory Archival FFPE Tumor Tissue Block[22]	X											
Tumor Assesment												
Whole CT[23]	X	Every 6 weeks					Every 12 weeks		X			
MRI and/or CT of the tumor site[23]	X	Every 6 weeks					Every 12 weeks		X			
Bone scan[24]	X											
Study treatment												
TSR-042[25]		X		X	X	X	X	X				
Adverse event assesment												
Adverse Events[26]		X	X	X	X	X	X	X	X	X	X	
Quality of Life Evaluation												
QoL questionnaire[27]		X		X	X			X	X	X		

Flow chart

Protocol Activities	Screening[1] (≤28Days)	1 cycle = 21 days[2]					1 cycle = 42 days[2]		End of Treatment/ Withdrawal Visit[3]	Safety Follow-up after 30 days[4]	Safety Follow-up after 90 days Phone call visit [5]	Follow-up Phone call visit 6
		Cy1		Cy2	Cy3	Cy4	Cy5	Cyn		30 days after last dose	90 days after last dose	Every 12 weeks
		Day1	Day 7 and 14	Day1	Day1	Day1	Day1	Day1				
Visit Time Window		±1	±1	−3/+1	−3/+1	−3/+1	−3/+1	−3/+1		+5		
Biological samples for traslational study												
Blood Biospecimen for translational study [28]		X		X	X		X At the time of radiological assessment		X			
De Novo Tumor Biopsy [29]	X								X Whenever is possible after the EOT			

Footnotes

1. **Screening**: All assessment need to be performed within 28 days prior to Day1Cycle1
2. **Study Cycle:** Cycle length is 21 days for the first 4 cycles, then will be 42 days.
   Participants may continue protocol therapy for a max of 2 years or until one of the following criteria applies: disease progression (RECIST 1.1), serious or life-threatening adverse event,, severe noncompliance with protocol as judged by the Investigator and/or Sponsor, participant decision, participant becomes pregnant, investigator, Sponsor, and/or TESARO becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues
3. **End of Treatment/Withdrawal**: Obtain these assessments if not completed within the prior week, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks
4. **Safety Follow-up:** First patient safety follow up must occur 30 days after the last dose of study treatment but before any new therapy is started. For patients who initiate another anticancer therapy after the initial 30-day follow-up visit, subsequent safety follow-up visits are no longer mandatory
5. **Safety follow-up after 90 days** could be performed as phone call visit
6. **Survival Follow-up:** Patients without evidence of disease progression at the time of treatment discontinuation should remain on the study and continue to have tumor assessment radiological scans every 8 weeks until documented progressive disease. Patients who have discontinued study treatment due to progressive disease should be followed for survival every 4 months for the first 24 months from Day1Cycle1, then from 25-60 months, every 6 months
7. **Informed consent:** must be obtained prior to the performance of any study-related procedure. Results of screening tests or examinations performed prior to obtaining informed consent may be used rather than repeating required tests if they met the specified time schedule
8. **Tumor History**: Includes collection of tumor history, prior antitumor regimen(s), including treatment and best response observed
9. **Vital Signs, and weight**: Blood Pressure, Pulse and Temperature. Blood pressure (BP) and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
10. **Physical Examination** Includes an examination of major body system

Physical examination, vital signs, concomitant medications and laboratory evaluations will be performed on day 1, day 7 (+/- 1 day), day 14 (+/- 1 days) during the first cycle

11. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the14 days prior to study enrollment
12. **ECOG Performance status:** Use Eastern Cooperative Oncology Group (ECOG) **(Appendix 8)**
13. **Single 12-Lead ECGs:** ECG will be performed and recorded for every subject within 7 days prior to Day1 Cycle1 to provide a baseline in case of unexpected future AEs, then after 6 months from treatment start, and again at the end of treatment visit. ECG must be performed at any visit during which a subject exhibits a heart rate ≤ 50 bpm or other clinical indication for ECG, ECG will be repeated
14. **ECHO:** ECHO will be performed and recorded for every subject within 7 days prior to Day 1, Cycle 1 to provide a baseline in case of unexpected future AEs, then after 6 months from treatment start, and again at the end of treatment visit.
15. **Hematology**: WBC, ANC, Hemoglobin, platelet count, Absolute Lymphocytes, Absolute Monocyte, Absolute Eosinophils, Absolute Basophils (**Appendix 1A)**
    Tests will be performed at the screening, at Cycle1Day1, Cycle1Day7, Cycle1Day14 and on day 1 of each cycle. The results should be available for review prior to infusion of treatment.
16. **Blood Chemistry:** Glucose (non-fasted), Creatinine, AST, ALT, Alkaline Phosphatase, Sodium, Potassium, Calcium, Phosphorus or Phosphate, Total Bilirubin, Urea, Lipase, Albumin, Total protein,. Tests will be performed at the screening, at Cycle1Day1, Cycle1Day7, Cycle1Day14 and on day 1 of each cycle. The results should be available for review prior to infusion of treatment. **(Appendix 1A)**
17. **Coagulation:** No need to repeat on Cycle1Day1 if baseline assessment performed within 7 days prior to that date.
    Tests will be performed at the screening, at Cycle1Day1, Cycle1Day7, Cycle1Day14 and on day 1 of each cycle. The results should be available for review prior to infusion of treatment **(Appendix 1A)**
18. **Thyroid Function Tests**: TSH, Free T3 and Free T4. Tests will be performed at the screening, at Cycle1Day1, Cycle1Day7, Cycle1Day14 and on day 1 of each cycle. The results should be available for review prior to infusion of treatment **(Appendix 1A)**
19. **HBV serology, and HCV serology:** measured at screening and then as clinically indicated **(Appendix 1A)**
20. **Urinalysis:** Dipstick is acceptable. Microscopic analyses must be performed if dipstick is abnormal **(Appendix 1A)**
21. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential a serum pregnancy test will be performed at the start of screening and pre-Day1Cy1 immediately before the investigational product administration. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. **(Appendix 1A)**
22. **Mandatory FFPE Tumor Tissue:** A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided. If tissue from multiple surgeries is available, the most recent specimen should be submitted
23. **Tumor Assessments***:* Tumor assessments will include all known or suspected disease sites
    Whole-body computed tomography (CT) included brain CT-, bone scan and MRI and/or CT of the tumor site will be evaluated at baseline
    During treatment evaluation the whole-body CT and MRI and/or CT of the tumor site will be repeated after 6 weeks (2 cycles), then after the 4th cycle, and every 12 weeks (every 2 cycles). In case partial response (PR), complete response (CR) or Progressive Disease (PD) is observed according to RECIST v.1.1 and immune-related Response Criteria (irRC) confirmation CT or MRI should be performed no sooner than 4 weeks after the first documentation of response. Tumor assessment should be repeated at the End of Study visit if more than 4 weeks have passed since the last evaluation. (RECIST and irRECIST criteria: Appendix 2 and 3)
24. **Bone Scan:** Bone scan will be performed at screening only
25. **Study Treatment:** TSR-042 will be administered via a 30-minute (-5-minute/+15-minute infusion window allowed) IV infusion on Day 1 of every 21day cycle (i.e., Q3W) at 500 mg for the first 4 doses, followed by 1,000 mg on Day 1 of every 42 day cycle
26. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded every two weeks. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 will be used (**Appendix 5**)
27. **Quality of Life Questionnaires**: EORTC QLQ-C30 and EUROQol5 dimension (EQ-5D) are to be administered on Day1Cycle 1, and on Day1Cycle 2 and then every 3 cycles (Day1Cy6, Day1Cy9,…) of each subsequent cycle prior to study treatment administration, at the End of Treatment/Withdrawal visit and at the first Follow-up visit at least 28 days and not more than 35 days after discontinuation of treatment (**Appendix 6 and 7**)
28. **Blood Biospecimen for translational study:** Blood samples for each patient will be collected at the following timepoints 1) At baseline (within 72 hours prior to starting TSR-042), 2) pre-treatment at Cycle2 day1, 3) pre-treatment Cycle3 day1, 4) pre-treatment at time of each radiological assessment from Cycle 3 on, including at time of disease

progression, 5) at the end of treatment visit

29. **De Novo Tumor Biopsy:** surgical specimens/biopsies collected before and whenever possible after the TSR-042 treatment (optional not-mandatory)

Appendix 1A. Required Laboratory Tests

Hematology	Chemistry panel	Urinalysis*	Coagulation	Pregnacy Test
Hemoglobin	Creatinine	Protein,	PT INR	For female patients
Platelets	ALT	Glucose	PT	of childbearing potential,
WBC	AST	Blood,	aPTT	serum or urine
Absolute Neutrophils	Alkaline Phosphatase	Albumine		
Absolute	Sodium			
Lymphocytes	Lipase			
Absolute Monocytes	Potassium			
Absolute Eosinophils	Calcium			
Absolute Basophils	Phosphorus or Phosphate			
	Glucose (non-fasted)			
	Total Bilirubin			
	Urea			
	Albumin			
	Total Protein			

Sierology Panel
HBV, HCV serology

Thyroid Function Tests
Free T3, Free T4, TSH

***** Dipstick is acceptable Microscopic analyses must be performed if dipstick is abnormal

ALT=alanine aminotransferase, ANA=antinuclear antibody, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, HBV= hepatitis B virus, HCV= hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cell

Appendix 2. RECIST CRITERIA 1.1

The determination of antitumor efficacy during this study will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation.

Measurability of Tumor Lesions

At baseline, individual tumor lesions will be categorized by the Investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumor lesion: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (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.

Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm 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 and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent.”

Techniques for Assessing Measurable Disease

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

Definitions of Tumor Response

Target Lesions

Complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR) is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (PD) is defined as a □20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (CR) is defined as the disappearance of all non-target lesions.
All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD is defined as a persistence of □1 non-target lesions.

Progressive disease (PD) is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4

weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Determination of Tumor Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in the following table.

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor 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
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

[1]Measurable lesions only.

[2]May include measurable lesions not followed as target lesions or non-measurable lesions.

[3]Measurable or non-measurable lesions.

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment. It should also be noted that a tumor marker increase does not constitute adequate objective evidence of tumor progression. However, such a tumor marker increase should prompt a repeat radiographic evaluation to document whether or not objective tumor progression has occurred.

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

Appendix 3. ir-RECIST CRITERIA

irRECIST 1.1	
Baseline	
Target lesions (TL)	Maximum of 5 TL in total, and maximum of 2 TL per organ
	Extranodal: ≥10 mm (LAD)
	Nodal: ≥15 mm (SAD)
Non-target lesions (Non-TL)	All other measureable and non measureable lesions, may be grouped
Follow-up	
Target lesion (TL)	Re-measurement of extranodal TL in LAD
	Re-measurement of nodal TL in SAD
Non-target lesion (Non-TL)	Absent, present, or unequivocal progression.
New lesion	Add to TL, in total max. 5 additional TL and 2 per organ
	Extranodal: ≥10 mm (LAD) extranodal
	Nodal: ≥15 mm (SAD) nodal
	All other add to Non-TL
Time-point response	
Progressive disease (PD)	≥20 % increase in sum of TL including new lesions
	(Reference: Nadir; requires confirmation after 4 weeks)
Partial response (PR)	≥30 % decrease in sum of TL including new lesions
	(Reference: Baseline)
Complete response (CR)	Dissappearance of all TL and Non-TL
Stable disease (SD)	Neither qualifying for PD, PR, or CR
	(Reference: Nadir)

Appendix 4. – CHOI CRITERIA

Response	Definition
CR (Complete Response)	Disappearance of all lesions No new lesions
PR (Partial Response)	A decrease in size*≥ of 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of non-measurable disease
SD (Stable Disease)	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD (progressive Disease)	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: HU=Hounsfield Unit; CT=computed tomography, RECIST=Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.

Appendix 5. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 5., dated 27 November 207) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm**Appendix 6. EORTC QLC C-30**

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7. EuroQoL EQ-5D

Health Questionnaire

English version

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑

I have slight problems walking ❑

I have moderate problems walking ❑

I have severe problems walking ❑

I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(eg, work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN/DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

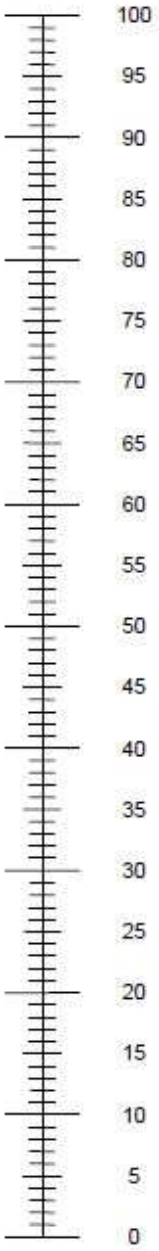
I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

The best health you can imagine



The worst health you can imagine

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

Appendix 8 PRO-CTCAE

The PRO-CTCAE form in all the validated languages may be reviewed online at the following NCI website:

https://healthcaredelivery.cancer.gov/pro-ctcae/instrument.html

Appendix 9 ECOG PERFORMANCE STATUS

ECOG Status	**ECOG Grade**
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	1
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	4
Dead	5