A phase II randomized trial of Ablative Radiation Therapy in patients with Oligometastatic castration resistant prostate cancer (ARTO trial)

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Sponsor: Dipartimento di scienze biomediche sperimentali e cliniche "Mario Serio"
Sponsor representative: Prof. Livi Lorenzo

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1. INTRODUCTION

1.1. Background and overall rationale for the study.

Prostate cancer (PCa) is one of the most common malignancies and main causes of cancer death in Western countries [1,2].

Metastatic castration resistant prostate cancer, defined by tumor growth despite a testosterone level of less than 50 ng per deciliter (1.7nmol per liter), causes approximately 258400 deaths annually worldwide[2,3]. Death of patients with this condition, which typically occurs within 24 to 48 months after the onset of castration resistance, is commonly preceded by a sequence of landmark events associated with deterioration of overall health and worsening symptoms.

In the presence of metastatic disease, systemic treatment remains the main clinical option. However, since the introduction of highly sensitive imaging techniques, a new clinical entity of metastatic patients with a limited number of lesions has been defined: oligometastatic patients.

In 1995, Hellman and Weichselbaum [4] first described oligometastatic disease as an intermediate state between local and widespread metastatic dissemination. Although a clear benefit has yet to be demonstrated in this group of patients, the use of stereotactic body radiotherapy (SBRT) or other local therapies directed against all active lesions has been suggested as a possible salvage treatment [5-8].

Irradiation of metastatic foci may delay the emergence of castration resistance because irradiation is effective against both ADT sensitive and ADT resistant prostate cancer cells as shown in re-biopsy studies [9]. Stereotactic body radiation therapy has been used in this setting to defer the initiation of ADT in patients with oligometastatic prostate cancer with notable results [10].

Abiraterone acetate is a first class inhibitor of cytochrome P 450c17, a critical enzyme in extragonadal and testicular androgen synthesis [11-13]. Abiraterone plus low dose

prednisone improves survival in patients with metastatic castration resistant prostate cancer who have already received docetaxel [14] and the combination therapy has received regulatory approval for this indication. Furthermore, Abiraterone acetate is approved also in patients who did not undergo to docetaxel chemotherapy, after the results from the COU-AA 302 study; Results from this phase III trial confirmed the benefit in chemo-naïve patients treated with abiraterone acetate both in terms of overall and radiological progression free survival, if compared to placebo [15-16].

In oligometastatic CRPC, the rationale to use SBRT is that the addition of a local ablative treatment could improve disease control in mCRPC patients treated with a systemic therapy.

Furthermore, macroscopic disease control could affect metastatic behavior by interplay of growth factors or by modulate immune system, leading to an improvement of clinical benefit.

The current phase II randomized trial,"Ablative Radiation Therapy in patients with Oligometastatic castration resistant prostate cancer (ARTO trial)" aims to evaluate the difference in PSA response rate between the experimental arm (AA+SBRT) and control arm (AA) in metastatic castration-resistant prostate cancer patients.

1.2. Zytiga ® (Abiraterone Acetate)

ZYTIGA® (abiraterone acetate) is a prodrug of abiraterone, an irreversible inhibitor of 17α hydroxylase/C17, 20lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone synthesis. This enzyme is found in the testes, adrenal glands and prostate tumors.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ZYTIGA, refer to the latest version of the summary of product characteristics for ZYTIGA.

Hormonal effects have been observed at all doses (200 through 2000 mg) and no dose-limiting toxicities were documented. A daily dose of 1000 mg was selected for Phase 2 and 3 studies in the management of prostate cancer patients and for the routine use of the drug based on its consistent pharmacologic and endocrinologic effects. Abiraterone has been shown to be approximately 21-24 times more potent than ketoconazole in CYP17A1 inhibition [17].

Abiraterone acetate is absorbed after oral administration and rapidly converted in abiraterone. At 1000 mg/die the terminal plasma half life is approximately 17 hours. After oral administration, maximum plasma concentration was reached between 2 to 4 hours. Co administration with food appears to significantly increase both exposure and maximal plasma exposition.
The maximum inhibition of CYP17A1 is achieved within 28 days of continuous dosing.

2. OVERVIEW OF STUDY DESIGN

2.1. Hypothesis:

This phase II randomized trial was designed to evaluate the difference in PSA response rate between the experimental arm (AA+SBRT) and control arm (AA). PSA response will be defined as a post-treatment decrease $\geq$ 50% from baseline measured within 6 months.

2.2 Study design

This is a phase II randomized multicenter study in patients affected by oligo mCRPC, treated with standard of care (GnRH agonist or antagonist plus abiraterone acetate and prednisone) and randomized to receive SBRT to all sites of disease. Patients will be randomly assigned in a 1:1 ratio to both treatment, stratified by Centre, Performance Status, and number of metastases.
Randomization will be performed the same day of the baseline evaluation (+/-3 days).
Planned size of the overall study population is 174 patients, 87 for each arm.
The study will include a screening phase and a treatment phase.
The screening phase allows for assessment of subject eligibility, demographics, PSA, testosterone, comorbidities and current drug therapies up to 45 days prior to randomization.
The treatment phase consists of systemic treatment with abiraterone acetate 1000 mg daily and prednisone 10 mg daily, plus GnRH agonist or antagonist (control arm). Furthermore, the patients in the experimental arm will receive SBRT to all metastatic lesions.

SBRT will be delivered in 1 to 5 fractions, and the dose and fractionation schedule will depend on the size and location of the lesion and the surrounding normal tissue constraints in accordance with AAPM Task Group 101 recommendations [19]. Considering an Alfa/beta of 3, a $BED_3 \geq 100$ Gy is recommended.

The total planned duration of the study is 40 months, consisting in 28 months enrollment period, during which patients will perform the screening and will begin standard of care treatment with or without SBRT and later phase of 12 months in which patients will continue the treatment with standard of care and will be submitted to periodic checks every 3 months.

2.3. Study design rationale

Abiraterone acetate is a treatment option in mCRPC patients [15]. Data in literature demonstrated the emerging role of metastasis directed therapy (surgery or radiotherapy) in the management of oligometastatic prostate cancer [20-21]. In particular, stereotactic body radiotherapy (SBRT) seems to be a safe and effective treatment, and has a positive impact on progression free survival. Thus, the association of SBRT to systemic treatment with ADT and abiraterone acetate may have a role in the management of oligometastatic castration resistant prostate cancer patients.

A Phase II study is suitable to investigate the interaction of systemic therapy (ADT and abiraterone) with locoregional therapy (SBRT). The duration of the study equal to 40 months was defined taking into account both the expected time of occurrence of investigated endpoints and feasibility considerations related to patient availability.

3. STUDY OBJECTIVES

3.1. Primary objectives

Primary objective of the study will be to compare the rate of PSA response in nodal and/or bone oligometastatic ($\leqslant$3 lesions), castration resistant prostate cancer patients undergoing SBRT in combination with AA (experimental arm), compared to patients treated with AA (control arm). PSA response will be defined as a post-treatment decrease $\geq$ 50% from baseline measured within 6 months.

3.2.Secondary objectives

-To describe SBRT+AA safety.

-To compare PSA trend in the two treatment arms during the observation period.
-To compare the overall survival (OS) in the two treatment arms.
-To describe quality of life (QoL) data, as measured by EORTC QLQ-C30 during the observation period.
-To describe the use of analgesic drugs and pain experience by means presence/absence of symptoms assessed by the Brief Pain Inventory Short Form (BPI SF)
-To compare the radiographic progression free survival (rPFS) and/or biochemical PFSin experimental vs control arm
rPFS is defined as the time from random assignment to the first occurrence of either progression by bone scan, progression by computed tomography/ (PET/CT) or death resulting from any cause.
Definition of bone scan progression was adapted from PCWG2 consensus [18], with the following criteria:

● If the first bone scan with new lesions compared with baseline is observed within 12 weeks from treatment beginning, a confirmatory bone scan is required, taken 6 weeks or more later, showing additional new lesions if compared to first follow-up scan

● If the first bone scan with new lesions compared with baseline was observed after 12 weeks from treatment beginning (ie, outside of flare window), or at following bone scans, a confirmatory second bone scan is not required

CT or magnetic resonance imaging progression are defined as a 20% increase from nadir in target lesion sum of long diameters, appearance of new soft tissue or visceral lesions, and/or unequivocal progression of baseline target lesions.
According to PCWCG2 consensus, a sequence of rising values at a minimum of 1-week intervals is requested to define biochemical progression, establishing a minimum starting value of 2.0 ng/ml for PSA progression.

4. STUDY POPULATION

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Metastatic disease and only ≤3 metastatic sites recorded (irrespective if nodal or bone).
2. Patients should have received abiraterone acetate for 30 days before eventual start of radiotherapy in the experimental arm (+/– 3 days)
3. Asymptomatic or mildly symptomatic patients according to clinical judgement.
4. Age ≥ 18 years.
5. Subject must have signed an informed consent document indicating that they understand the purpose of procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

1. More than 3 metastatic lesions.
2. Visceral involvement.
3. Known or suspected contraindications or hypersensitivity to Abiraterone, GnRH agonist/antagonist or Radiotherapy.
4. Comorbidities that contraindicate Abiraterone, GnRH agonist/antagonist or Radiotherapy.
5. Any condition for which, in the option of the investigator, participation would not be in the best interest of subject.
6. Patients who received previous therapies for mCRPC (excluded hormonal therapy)

5. STUDY EVALUATIONS

5.1. PreTreatment Evaluation

Baseline evaluations include:

- demographics data;
- staging, PSA value and Gleason Score at the time of prostate cancer diagnosis;
- previous treatments for prostate cancer;
- active comorbidities and current medical treatments;
- assessment of Performance Status with the Eastern Cooperative Oncology Group (ECOG) Score;
- presence/absence of symptoms assessed by the Brief Pain Inventory Short Form (BPI SF) and the quality of life assessment by EORTC QLQ-C30 (baseline evaluation should be performed before radiotherapy beginning);
- complete haematological and biochemical exams [including Lactate Dehydrogenase (LDH)], PSA value and testosterone before randomization (baseline assessment should be performed within 15 days(+/-3)
- Imaging procedures (baseline assessment should be performed within 45 days before randomization):
    - Tomography/Computed Tomography (PET/CT), or
    - Bone Scan and Computed Tomography thorax-abdomen pelvis (CT) with contrast.

5.2. Evaluation During Treatment

Patients will be evaluated as follows:

- every 3 months from start of Abiraterone therapy with ECOG Score; PSA value and testosterone; Blood count and LDH.
- every 3 months from start of Abiraterone the feedback of BPISF and EORTC QLQ-C30 questionnaire will also be carried out.
- every 6 months from randomization or in case of suspected clinical or biochemical progression, with the same radiological exams used at the beginning

(PET/CT or Bone Scan and CT Computed Tomography thorax-abdomen pelvis (CT) with contrast).

Furthermore, in baseline evaluation as well as in case of disease progression, the use of additional diagnostic exams (such as magnetic resonance imaging, MRI) is allowed according to clinical judgement.

5.3. Statistical Analysis

Continuous variables will be presented as mean values ± standard deviation (SD) and categorical variables as numbers and percentages. Comparisons between groups will be performed using a two-sided Student's t-test, after checking data are normally distributed (based on the Shapiro-Wilk statistic) for continuous variables and a two-sided Wilcoxon's rank-sum test otherwise. Categorical data will be analysed using the contingency table analysis with the Chi-square or Fisher's test, as appropriate.
Time-to-event data will be analyzed using Kaplan-Meier product-limit survival curve estimates and log-rank tests for comparison between groups.
Data-analysis will be performed on intention to treat population (ITT) and safety data-analysis will be performed on all patients receiving at least one dose of study treatment (the full analysis set). p-values of 0.05 or less will be considered statistically significant and all tests will be two-sided.
Assuming that the proportion of patients achieving a ≥50% PSA level decline in control arm is equal to 62% [15,16], with a 5% type 1 error rate and a power of 80%, a total of 156 patients are required to show an absolute improvement in proportion of patients in the experimental arm of +21%. Considering a 10% rate of drop out during follow-up, the final sample size needed is 174 patients (87 for each arm).

6.0 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

6.1 Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death should it have been more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted when the nature or severity is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug (Adverse Drug Reaction)

An adverse event is considered associated with the use of the drug when the attribution is possible, probable, or very likely by the definitions listed below.

6.2 Attribution Definitions

Not Related: An adverse event that is not related to the use of the drug.

Doubtful: An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible: An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely: An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

6.3 Severity Criteria

The NCI-CTCAE v4.0 will be used to grade the severity of adverse events. Any AE not listed in the CTCAE will be graded as follows:

Grade 1, Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2, Moderate: Sufficient discomfort is present to cause interference with normal activity.

Grade 3, Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4, Life-threatening: Urgent intervention indicated.

Grade 5, Death: Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

6.4 Special Reporting Situations

Safety events of interest on an investigational medicinal product that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of an investigational medicinal product
- Suspected abuse/misuse of an investigational medicinal product
- Accidental or occupational exposure to an investigational medicinal product
- Any failure of expected pharmacologic action (ie, lack of effect) of an investigational medicinal product
- Unexpected therapeutic or clinical benefit from use of an investigational medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

6.5 Procedures

6.5.1 All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety.. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

6.5.2 Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event: Prof. Lorenzo Livi, AOU Careggi, SODc Radioterapia.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site , and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, when a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported when they fulfill the serious adverse event definition.

During the follow-up phase of the study, deaths regardless of causality and serious adverse events thought to be related to blinded study drug will be collected and reported within 24 hours of discovery or notification of the event and documented.

6.5.3 Pregnancy

All initial reports of pregnancy in in partners of male subjects included in the study must be reported to the Sponsor-Investigator by investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Unforeseeable risks to the embryo or fetus (for both maternal and paternal exposure):

There may be risks with the use of abiraterone acetate that are not yet known, and these may cause unforeseeable risks to the embryo or fetus and on sperm (i.e. for both maternal and paternal exposure). Because of this, the subjects included should not become father of a baby while participating in this study.

Pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

6.5.4 SUSAR Reporting

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to investigators (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

6.5.5 Annual Safety Reports

An annual report for each trial must be submitted by the sponsor to the competent authorities and the ethics committees, taking into account all new available safety information received during the reporting period.
The aim of the annual safety report is to describe concisely all new safety information relevant to the IMP, providing with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

6.5.6 Adverse Drug Reactions Associated with Abiraterone Acetate (ZYTIGA®)

Infections and infestations

- very common: urinary tract infection

Endocrine disorders

- uncommon: adrenal insufficiency

Metabolism and nutrition disorders

- very common: hypokalaemia
- common: hypertriglyceridaemia

Cardiac disorders

- common: cardiac failure *(a)*, angina pectoris, , atrial fibrillation, tachycardia

- uncommon: arrhythmia

Vascular disorders

- very common: hypertension

Respiratory, thoracic and mediastinal disorders

- Rare: Allergic alveolitis (c)

Gastrointestinal disorders

- common: dyspepsia

Hepatobiliary disorders

- very common: alanine aminotransferase increased, aspartate aminotransferase increased (d)
- Rare: Acute hepatic failure (c), Hepatitis fulminant (c)

- *Musculoskeletal and connective tissue disorders*
  - Uncommon: Myopathy/rhabdomyolysis (c)

Renal and urinary disorders

- common: haematuria

General disorders and administration site conditions

- very common: oedema peripheral

Injury, poisoning and procedural complications

- common: fractures (*b*)

(a) Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

(b) Fractures includes osteoporosis and all fractures with the exception of pathological fracture

(c) ADR is based on spontaneous reports from post-marketing experience

(d) Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

Frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000).

7.0 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the manufacturing company, and are mandated by regulatory agencies worldwide.

7.1 Procedures

All initial PQCs must be reported to the company by the investigational staff as soon as possible after being made aware of the event.
If the defect is combined with a serious adverse event, then the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the company.

8. STUDY LIMITATIONS

Study results have to be interpreted considering that participant sites constitute a convenience sample of all centers. In each site, investigators are recommended to enroll patients in a consecutive manner. Characteristics of enrolled patients will be described in order to provide all necessary information.
No formal associations will be assessed, but some patients and treatment characteristics could have an impact on investigated outcomes. Thus, age, relevant concomitant disease and therapies, Gleason score, ECOG PS, previous and subsequent treatment for mCRPC will be collected in order to be considered in the analysis.
Finally, target sample size is considered to be achievable during the enrolment period on the basis of feasibility considerations.

9. STUDY SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Final protocol and, if applicable, amendments/addenda.
- Independent Ethics Committee or Institutional Review Board (IEC/IRB)-approved informed consent form (and any other written materials to be provided to the subjects).
- Independent Ethics Committee or Institutional Review Board (IEC/IRB)-approved subject recruiting materials.
- Applicable recruiting materials.
- Applicable questionnaires.
- Information regarding funding, contact name of the promoter, institutional affiliations, other potential conflicts of interest.
- Any other documents that the IEC/IRB requests to fulfill its obligation.
- Pharmaco vigilance guideline for the interventional study session.
- All material needed for data collection according to this protocol in order to strictly avoid any additional cost for the Investigator Structure and/or patients.

10 .Regulatory Ethics Compliance

10.1. Investigator Responsibilities

The investigator is responsible for ensuring that this phase II study is performed in accordance with the protocol, concurrent ICH guidelines on Good Clinical Practice (GCP) and applicable regulatory and country specific requirements.

In Italy the clinical trials are regulated by regulated by a ,entered into force in January 2004 (Decreto legislativo 24 giugno 2003, n.211).This decree transposes the concerning the implementation of in the conduct of clinical trials on medicinal products for human use.
Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the

principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

10.2. Independent Ethics Committee or institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or promoter where required) will provide the IEC/IRB with concurrent and complete copies of the following documents (as required by local organisation):

- Final protocol and, if applicable, amendments/addenda
- Promoter approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's brochure for Zytyga (or equivalent information) and amendments/addenda
- Promoter approvedsubjectrecruitingmaterials
- Information regarding funding, institutional affiliations, other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the informed consent and privacy form, applicable recruiting materials, and subject compensation programs, and the promoter has received a copy of this approval.
This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved. Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB.
During the study the investigator (or promoter where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)

- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the promoter
- New edition(s) of the Investigator's Brochures and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of theIEC/IRB
- Reports of adverse events that are serious, unlisted/unexpected, and associated with treatments in study
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Any other requirements of the IEC/IRB
- Paper CRF

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).
At the end of the study, the investigator (or promoter where required) will notify the IEC/IRB about the study completion.

10.3. Informed Consent

The process of obtaining informed consent should be documented in the patient source documents. Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The informed consent form [ICF(s)] must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the

promoter and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects (or their legally acceptable representative) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long term follow up if needed and that their records may be accessed by health authorities and authorized sponsor stuff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or legally acceptable representative) is authorizing such access, including permission to obtain information about his survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his survival status.

The subject (or a legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's (or his/her legally acceptable representative's) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Written assent should be obtained from subjects who are able to write.

10.4. Privacy of Personal Data

Confidentiality of patient records will be maintained at all times. The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries. The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Protocol Amendments

Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. When the change(s) involves only logistical or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

11.2. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the promoter studysite contact for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. All reports and communications relating to the study will identify subjects by subject identification and date of birth. The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

11.3 Source Documentation

At a minimum, source documentation must be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures;dates of visits;adherence to protocol procedures;results of safety and efficacy parameters as required by the protocol;record of all AEs and followup of AEs;concomitant medication;drug receipt/dispensing/return records;and date of subject completion or withdrawal from the study, and the reason if appropriate. In addition, the author of an entry in the source documents should be identifiable.
At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).
Data from medical records of each enrolled patient will be collected uscing a paper CRF. CRF's will be sent through e-mail or fax to the promoter of the study at baseline and every 3 months.

11.4 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section. The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the promoter. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the promoter.If it becomes necessary for the promoter or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

11.5 Study Completion

The final data from the study site will be sent to the promoter (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

11.6. Study Termination

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the

intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

11.7. On Site Audits

Representatives of the promoter's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and studysite personnel are responsible for being present and available for consultation during routinely scheduled studysite audit visits conducted by the promoter or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the promoter if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

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