# A PROSPECTIVE CLINICAL STUDY ON ADJUVANT GEMCITABINE AND DACARBAZINE IN LOCALIZED UTERINE LEIOMYOSARCOMA (AGENTS)

**Protocol Acronym: AGENTS**

**EudraCT Number:**

**Version:** ~~Draft 07~~1.0 08March2016

**Type of study**: no profit

**Sponsor**
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## SYNOPSIS

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| **Sponsor** | Italian Sarcoma Group |
| **Title** | A prospective clinical study on adjuvant gemcitabine and dacarbazine in localized uterine leiomyosarcoma |
| **Sponsor CODE/Acronym** | AGENTS |
| **EudraCT Number** | 2016-001071-72<br>~~XXXXX~~ |
| **Version** | 1.0 08Mar2016 |
| **Principal Investigator** | Paolo Casali, MD<br>Fondazione IRCCS Istituto Nazionale Tumori<br>Via G. Venezian, 1 - 20133 Milano |
| **Type of study** | Phase II not-randomized clinical trial |
| **Study Design** | Italian, multicenter, Phase II single arm study for the adjuvant treatment with Gemcitabine and Dacarbazine of localized uterine Leiomyosarcoma (LMS).<br><br>After being assessed for eligibility criteria the eligible patients will be treated with gemcitabine administered at a dose of 900 mg/mq day 1 and 8 and dacarbazine at dose of 750 mg/mq day 8 every 21 days for a total of 6 cycles.<br><br>The study will be conducted in Italy in approximately 20 investigational centers, in order to recruit 72 evaluable patients over a 6 year period. The follow-up will last approximately 2 years. The recruitment period is expected to last 6 years, with a minimum time for experiencing event of 3 years for each patients |
| **Scope of the trial** | Scope of the study is to determine the impact of the adjuvant treatment with<br><br>gemcitabine-dacarbazine in the **Relapse Free Survival** (RFS) in patients with localized uterine leiomyosarcoma. |
| **Study Objectives** | **Primary** Three-year relapse-free survival ≥65% in the treated population<br><br>**Secondary**<br><br>Overall survival (OS)<br><br>Safety profile (Adverse events by CTCAE 4.03)<br><br>**Exploratory**<br><br>Explore the impact of potential predictors of recurrence or death such as |

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| | patient age, tumor size, cervix involvement (yes or no), and mitotic rate |
| **Study Population** | Female patients with localized high risk uterine LMS previously treated with surgical resection (hysterectomy) |
| **Total Number of Patients to include in study** | The study will enrol 72 patients evaluable for the primary end point. |
| **Selection Criteria** | **Inclusion Criteria**<br>1.Histologically confirmed diagnosis of localized high-risk uterine leiomyosarcoma (LMS), International Federation of Gynecology and Obstetrics (FIGO) stage I (confined to corpus with or without cervix involvement) who underwent to complete hysterectomy (including removal of the cervix). Bilateral salpingo-oophorectomy is not required.<br>2.Centralized pathology review calls the uterine leiomyosarcoma "high grade." Additionally, if the pathology report indicates a mitotic rate, the mitotic rate should be greater than or equal to 5 mitoses/10 high power field.<br>3.All patients must be no longer than 12 weeks from surgical resection of cancer at the time of enrolment on study. If a patient requires a second operation to complete her surgery, i.e. trachelectomy to remove the cervix and/or BSO, the 12 weeks may be counted from the time of the second operation.<br>4.No evidence of persistent or metastatic disease as documented by a chest/abdomen/pelvis post-resection computed tomography (CT) or by CT chest and abdomen/pelvis magnetic resonance imaging (MRI).The post-resection imaging evaluation must be performed within 4 weeks of trial entry.<br>5.Adequate bone marrow, liver, a renal and neurologic function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment:<br>Absolute neutrophil count (ANC) ≥1500/$mm^3$.<br>Platelet count ≥100000$mm^3$<br>Hemoglobin (Hb) ≥ 8.0 g/dl or 4.9 mmol/L<br>Total Bilirubin within ranges.<br>Alanine Aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x UNL |

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| | Patient with a documented Gilbert' Syndrome is allowed if total bilirubin<br>is ≤1.5 x UNL and AST, ALT and Alkaline phosphatase meet the criteria detailed<br>Serum Creatinine ≤ 1.5 x UNL<br>Neuropathy (sensory and motor) less than or equal to CTCAE 4.03 grade 1.<br><br>6.GOG performance status of 0 or 1; Eastern Cooperative Oncology Group (ECOG) Performance Status ECOG <2 or KPS >= 80%<br><br>7.Female patients with Age > 18 years<br><br>8.Paraffin-embedded tumor block available for centralized review<br><br>9.Patients must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up. Informed Consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient´s routine clinical management (e.g. blood count, imaging tests, etc.) and obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol.<br><br>**Exclusion Criteria**<br><br>1.Patients with recurrent uterine LMS<br><br>2.Uterine Leiomyosarcoma with uterine serosa involvement<br><br>3.Prior systemic treatment at any time in their history with gemcitabine or dacarbazine<br><br>4.Tumor surgery treatment (hysterectomy) occurred over 12 weeks before the study enrolment<br><br>5.Patients with a history of prior whole pelvic radiation.<br><br>6.Patients with a known history of congestive heart failure or LVEF < 50% (or less than institutional normal limits)<br><br>7.Patients who are breast-feeding.<br><br>8. History of other invasive malignancies (except basal cell carcinoma adequately treated), unless in remission from 5 years or more and judged of negligible potential of relapse<br><br>9.Concurrent treatment with hormone replacement therapy is permitted at the discretion of the treating physician. Patients who |

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| | have been taking hormonal/hormone blocking agents for breast cancer or breast cancer prevention or other indication are eligible. Use of anti-hormonal agents (tamoxifen, medroxyprogesterone, aromatase inhibitors) is permitted at the discretion of the treating physician. Documentation of concurrent medications is required.<br>10. Active major infection<br>11. Active viral hepatitis or chronic liver disease<br>12. Any unstable cardiac condition, including congestive heart failure or angina pectoris, myocardial infarction within 12 months before enrolment, uncontrolled arterial hypertension or arrhythmias<br>13. Known history of human immunodeficiency virus (HIV) infection.<br>14. Substance abuse or medical, psychological, or social conditions that may interfere with the subject´s participation in the study or evaluation of the study results.<br>15. Any illness or medical conditions that are unstable or serious or could jeopardize the safety of the subject and his/her compliance in the study |
| **Treatment** | Patients will receive adjuvant 6 cycles of<br>▪ Gemcitabine: 900 mg/m2 on Day 1 and 8 given intravenously over 90 min<br>▪ Dacarbazine: 750 mg/m2 on Day 8 intravenously over 60 min<br><br>Each cycle will be repeated every 21 days (3weeks)<br>Treatment should continue for 6 cycles or until unacceptable toxicity occurs. |
| **Patient assignment** | After giving informed consent and being assessed for eligibility criteria, eligible patients can be registered through a web-based system. |
| **Statistical methods and samples size** | A Bayesian two-stage dual threshold design (DTD) will be adopted. The primary response variable of interest is 3 Years PFS proportion. The trial is expected to yield a minimum interest in response of 65% and a no further interest response rate of 55%. The anticipated response rate is assumed to be equal to the minimum interest response rate and is associated to a vague prior (nprior=3); the overall threshold probability at the start and end of the trial are set at 0.7 and 0.8 respectively, along with a default setting of p=0.05. At stage I, if < 15 responses out of the first 26 patients will be achieved, the trial will be stopped, since the |

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| | probability of a response ≤55% is 70%. Otherwise, the study will include further 46 patients for a total sample of 72 patients.<br><br>If ≥ 51 responses out of 72 patients will be detected, the trial results will be considered worth for further studies, since the probability of a response>65% is 80%.<br><br>Estimates of 3YPFS will be provided with the corresponding Credibility Intervals.<br><br>PFS and Overall survival will be also described by means of Kaplan-Meier approach.<br><br>Safety data will be reported as absolute frequencies and relative percentages |
| **Translational studies** | No translational study is associated with the trial. |