



Cytheris, Centre Léon Bérard and ImmunID Announce Initiation of Clinical Trial to Evaluate Combination Regimen of IL-7 (CYT107) and XELODA® (capecitabine) in Treatment of Metastatic Breast Cancer

Phase IIa study will investigate the optimal schedule for delivery of CYT107 and its ability to prevent or reverse the effects of chemotherapy-induced lymphopenia characterized by a low CD4 T cell count, identified as an independent prognostic factor for overall survival in patients with advanced cancers

First ever study to apply therapeutic approach of global immune reconstitution to treatment of cancer patients

Paris, Lyon, and Grenoble (France) – May 11, 2011 – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, the Centre Léon Bérard (Lyon), the major cancer research and treatment center for the Rhône-Alpes region of France, and ImmunID Technologies SAS (Grenoble), a diagnostic company specialized in innovative immunomonitoring tests and services, today announced initiation of a Phase IIa clinical trial that will evaluate multiple combinations of recombinant human interleukin-7 (CYT107), the investigational multifunctional cytokine under development by Cytheris, and a chemotherapeutic agent, XELODA® (capecitabine, Roche/Genentech), in the treatment of metastatic breast cancer.

The trial is designed to explore the optimal schedule for delivery of CYT107 during standard capecitabine chemotherapy, with the aim of immune reconstitution and collection of preliminary data on the impact of CYT107 on severe hematological toxicity and tumor progression in second line metastatic breast cancer patients. The immunorestorative properties of IL-7, which include its ability to provide T cells to attack any residual disease, are expected to have a significant impact on survival in this patient population, where a low CD4 T cell count associated with poor receptor diversity detected before initiation of chemotherapy is a known predictive factor indicating overall survival of less than 6 months compared to almost two years for non-lymphopenic patients.

Conducted as a collaborative effort of the Centre Léon Bérard (the study sponsor), ImmunID Technologies, and Cytheris, the study, known as ELYPSE-7, is designed to evaluate whether CYT107 treatment is able to correct lymphopenia post-chemotherapy in advanced cancer patients and whether the correction of this lymphopenia by restoration of the immune system will result in a broadening of the repertoire of T cells and a reduction in the risk of severe haematological toxicity, tumor progression and early death.

The study is based on many years of research conducted by the team of Jean-Yves Blay, MD, PhD, Professor of Medicine at the Université Claude Bernard, Lyon, and the current President of the European Organization for Research and Treatment of Cancer (EORTC).

"Lymphopenia (<1000 Lymphocytes/ μ l) or CD4+ T cell lymphopenia (<450/ μ l) detected prior to initiation of chemotherapy as well as Divpenia[®] (low diversity of the T cell repertoire) are known to be predictive factors for toxicity and death in patients with metastatic solid tumors. Correction of this condition through an immunotherapeutic approach would therefore represent a potential paradigm shift in the treatment of patients with various types of cancer," commented Dr. Blay. "In the SEMTOF trial, which included a total of 70 metastatic breast cancer patients in first line treatment, a low T cell receptor (TCR) repertoire diversity (Divpenia[®], as defined and measured by ImmunID Technologies) was associated with a short overall survival of \leq 6 months. Median survival of severely divpenic patients was less than 6 months, compared to >22 months for the remaining patients who were not in this severely lymphopenic state. The outcome of the ELYPSE-7 study is thus expected to have significant implications for overall survival and tumor progression in patients with advanced cancers, including ovarian cancer, metastatic breast cancer, non-Hodgkin lymphoma, and sarcoma."

Qualitative and quantitative alterations of local and circulating immune cells have been identified as playing an important role in breast cancer progression. In a series of studies including more than 3000 patients, Dr. Blay's team has shown that lymphopenia is found in 20-25% of patients with advanced cancers, including 20% of untreated patients with metastatic breast cancer. In a large series of patients it was observed that lymphopenia is associated with a 20% and 50% risk of early death at 1 and 3 months and that T cell CD4 lymphopenia is also an independent risk factor for early death and toxicity in these patients.

"In a recent review article (Mackall C et al. *Nat Rev Immunol.* 2011 May; 11(5):330-42) entitled "Harnessing the Biology of IL-7 for Therapeutic Application", the authors conclude that despite the impressive biological effects of IL-7 on T cell populations, the essential issue regarding clinical development of this cytokine is the need to show that the biological effects of IL-7 translate to improved clinical outcomes such as prolonged survival or cure," said Michel Morre, DVM, President and CEO of Cytheris. "Such proof of concept can only be obtained by carrying out careful clinical trials in targeted populations who are at greatest risk owing to T cell immunodeficiency, precisely the goal of the ELYPSE-7 study."

About the Study

ELYPSE-7 is a randomised, monocentric, double-blind Phase IIa study evaluating the impact of IL-7 immunotherapy on CD4 lymphopenia and TCR repertoire diversity, risks of severe haematological toxicity and tumor progression in metastatic breast cancer patients. Twenty-four patients will be enrolled at a single center (Centre Léon Bérard, Lyon, France) where the study is under the direction of Isabelle Ray-Coquard, MD, PhD, Principal Investigator.

The duration of the investigation for each patient will include a study drug treatment period of at least 12 weeks (including 3 x 3-week cycles of chemotherapy) and a follow-up period for a maximum of one year (or until disease progression). Chemotherapy will be extended until disease progression, unacceptable toxicity, or

willingness to stop. The inclusion period is expected to be six months with the treatment period and follow-up lasting up to one year.

All patients will receive standard anti-cancer therapy prescribed for second line metastatic breast cancer patients: XELODA[®] (capecitabine) at an oral dose of 2500mg/day for 14 days over a 21-day cycle period. In addition, all patients will be randomly allocated in a factorial design to one of the following four study arms:

- Arm 1: (Placebo Group) Patients will receive Placebo before the start of chemotherapy (at D0, D7 and D14) and during the 3rd cycle of chemotherapy (D63, D70 and D77).
- Arm 2: (Pre-IL-7 Treatment Group) Patients will receive CYT107 (one subcutaneous injection at 10 µg/kg/week for three weeks) before the 1st cycle of chemotherapy (at D0, D7 and D14) and will receive the placebo during the 3rd cycle of chemotherapy (D63, D70 and D77).
- Arm 3: (Concomitant IL-7 Treatment Group) Patients will receive Placebo before the 1st cycle of chemotherapy (D0, D7 and D14) and will receive CYT107 (one subcutaneous injection at 10 µg/kg/week for three weeks) during the 3rd cycle of chemotherapy (at D63, D70 and D77).
- Arm 4: (Pre- and Concomitant IL-7 Treatment) Patients will receive CYT107 (one subcutaneous injection at 10 µg/kg/week for three weeks) before the 1st cycle of chemotherapy (D0, D7 and D14) and again (one subcutaneous injection at 10 µg/kg/week for three weeks) during the 3rd cycle of chemotherapy (D63, D70 and D77).

The primary endpoint of the study is the evolution of patient CD4 counts from D0 to W12 with repeated measures at D0, W3, W9, and W12. This will help in defining the optimal schedule of CYT107 administration during chemotherapy, based on the restoration of patient CD4 counts.

Secondary endpoints include the impact of CYT107 treatment on the incidence of severe hematological toxicity as indicated by the number of patients experiencing any type of hematological Adverse Event (including anemia, thrombopenia, lymphopenia, or neutropenia) of Grade \geq 3 from D0 to W12. At this stage, the quality of T cell repertoire diversity reconstitution will also be assessed.

About Metastatic Breast Cancer

Breast cancer is the second most frequent cancer in the world, and is by far the most common malignant disease in women (22% of all new cancer cases). Worldwide, the ratio of mortality to incidence is about 36%. It ranks fifth as a cause of death from cancer overall (although it is the leading cause of cancer mortality in women — the 370,000 annual deaths represent 13.9% of cancer deaths in women). In the United States alone, the American Cancer Society estimates that more than 182,400 women will be diagnosed with breast cancer each year, while 40,480 women will lose their lives to this disease. Breast cancer will affect one of every eight American women in their lifetime and is second only to lung cancer as the leading cause of cancer deaths among women in the United States.

Metastatic or advanced breast cancer (frequently referred to as breast cancer stage 4) is the presence of disease at distant sites in the body such as the bone, liver, or lung. Symptoms may include pain from bone metastases, breathlessness from spread to the lungs, and nausea or abdominal discomfort from liver involvement. It is the most prevalent cancer in the world today and there are an estimated 3.9 million women alive who have had breast cancer diagnosed in the past 5 years (compared, for example, with lung cancer, where there are 1.4 million alive). The true prevalence of metastatic disease is high because some women live with the disease for many years. Since 1990, there has been an overall increase in incidence rates of about 1.5% annually.

The main reason patients with breast cancer fail treatment is relapse. Relapse of breast cancer occurs because the high-dose chemotherapy used in its treatment is unable to kill all the cancer cells in the patient, leaving residual disease which results in relapse.

Following treatment failure with first line chemotherapy agents, the standard reference treatment for second line metastatic breast cancer is a chemotherapeutic regimen with XELODA[®] (capecitabine). Monotherapy with XELODA[®] is indicated for the treatment of patients with metastatic breast cancer resistant to paclitaxel or to paclitaxel plus an anthracycline-containing chemotherapy regimen and for whom further anthracycline therapy is not indicated, e.g., patients who have received cumulative doses of 400 mg/m² of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen. XELODA[®] in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

About Recombinant Human Interleukin-7 (CYT107)

Recombinant human interleukin-7 (CYT107) is a critical immune-modulator for immune T-cell recovery and enhancement. As a growth factor and cytokine physiologically produced by marrow or thymic stromal cells and other epithelia, IL-7 has a critical and, at some steps, a non-redundant stimulating effect on T lymphocyte development, notably on thymopoiesis and, downstream from the thymus, on homeostatic expansion of peripheral T-cells.

Clinical trials including more than 180 patients in Europe, North America, South Africa and Taiwan have demonstrated the potential of IL-7 to expand and protect CD4 and CD8 T-cells. Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HCV, HBV, post-BMT and cancer. Additional studies include a NIAID/NIH-sponsored trial (ICICLE) in idiopathic CD4 lymphocytopenia (ICL); a cancer vaccine study in children with Ewing's sarcoma family of tumors or similar genetic tumors sponsored by US National Cancer Institute; and, a multi-company/institutional study (EraMune 01) sponsored by ORVACS (the international HIV organization funded by the French Bettencourt Schueller Foundation) aimed at attacking the HIV viral reservoir.

About Cytheris – www.cytheris.com

Cytheris SA is a privately held clinical-stage biopharmaceutical company focused on research and development of new therapies for immune modulation. These drugs aim at reconstituting and enhancing the immune system of patients suffering from cancer, chronic viral or bacterial infections such as HCV, HBV and HIV, or lympho-depleting treatments such as chemotherapy, radiotherapy, bone marrow transplantation (BMT) and hematopoietic cell transplantation (HCT). The company operates from its headquarters and laboratories in Issy-les-Moulineaux, a suburb of Paris, and its U.S. subsidiary in Rockville, Maryland.

About Centre Léon Bérard - www.centreleonberard.fr

Located in Lyon, France, the Centre Léon Bérard is a multidisciplinary, private, non-profit hospital dedicated to cancer treatment and research. It serves as the referral center for the Rhône-Alpes region of France and provides patient care, aftercare, screening and prevention, with particular strengths in the areas of hematology with autologous bone marrow transplant, lung cancer, immunology, head and neck surgery gastrointestinal surgery, breast and plastic surgery, and high technology radiotherapy. With a staff of 1300 professionals, the Centre Léon-Bérard today serves more than 22,000 patients a year while continuing research and innovation as well as education and training in the field of oncology

About ImmunID Technologies - www.immunid.com

Located in Grenoble, France, ImmunID Technologies is a molecular diagnostics company focused on the discovery, development and commercialization of innovative diagnostic and immunomonitoring tests and services. With its biomarkers contributing to the development of personalized medicine, the company is focused on monitoring cancer therapy (e.g. breast, lung, leukemia, and lymphoma) as well as infectious disease (e.g. HIV, HVC, and sepsis). ImmunID has developed a proprietary method of analysis of the immune repertoire diversity aimed at characterizing dysfunctions of the immune system and analyzing the impact of immunotherapies on the immune repertoire, including monoclonal antibodies (e.g. anti-CD19, anti-CD20), interleukins (e.g. IL-7), and chemotherapies. Importantly, ImmunID is responsible for introducing the concept of Divpenia® (www.divpenia.com), defined as a clinical state of reduced T and B lymphocyte immune diversity which is correlated with a higher risk of infection and mortality.

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