



Immutep Announces Positive Interim Results in Phase I/II Chemoimmunotherapy Trial in Breast Cancer

ImmuFact IMP321 associated with paclitaxel doubles clinical response rate

Orsay, January 5, 2009, Immutep S.A. announced today interim results from its ongoing Phase I/II chemoimmunotherapy clinical trial in metastatic breast carcinoma. *ImmuFact* IMP321 was administered the day after weekly paclitaxel for six months. The interim results show a clinical response rate of 50 % compared to 25 % with paclitaxel alone. In addition, a robust immune response was observed in clinically-responding patients.

IMP321 is a first-in-class immunopotentiator that agonizes MHC class II molecules thereby stimulating antigen-presenting cells, such as dendritic cells and monocytes, leading to markedly improved cytotoxic CD8 T cells responses against tumours.

Chemoimmunotherapy is a new approach to the treatment of cancer. Chemotherapy drugs induce tumour cell apoptosis and cause modulation of the immunological environment combined with a burst of tumour antigen release. The resulting T cell immune response contributes to the regression of the tumour and, importantly, may seek out and destroy metastases. However, this initial immune response needs to be sustained and amplified by a T-cell booster that is non-toxic and can be given repeatedly, such as *ImmuFact* IMP321.

The design of the study is a multi-centre open-label fixed dose-escalation trial. One of the lead centre's main Principal Investigators, Maya Gutierrez, is coordinating the team carrying out the trial at the René Huguenin Cancer Centre, Saint Cloud, near Paris.

Patients receive 6 cycles of low-dose weekly paclitaxel at Day 1, Day 8 and Day 15 of a 4-week cycle as first line chemotherapy plus bi-weekly IMP321 administered the day after the paclitaxel to make a total of 12 injections of IMP321 over 24 weeks. Three dose levels of IMP321 are being studied in three cohorts of 8 patients each. The interim results are based on tumour regression under RECIST criteria in the first two cohorts of 16 patients out of the total of 24 compared to the historical control group which is the weekly paclitaxel arm of a recent randomised phase III study (N. Engl. J. Med. 2007; 357:2666-76). The improvement is statistically significant with a p-value of 0.03.

"Such sequential chemo- and then non-toxic immunotherapeutic combos may be a way to improve the response rate and/or consolidate or stabilize the partial tumour responses obtained with chemotherapy alone," said Dr Maya Gutierrez, Principal Investigator of this Phase I trial. "We are very pleased to be testing this innovative therapeutic approach at our Institute."

"Boosting the dendritic cell network when it is loaded with tumour antigens following chemotherapy with repeated injections of IMP321 is an effective way to amplify the cytotoxic CD8 T cell responses observed in first-line chemotherapy," said Frédéric Triebel, Scientific & Medical Director of Immutep. "A similar approach will shortly be tested in the first trial of IMP321 in the USA in pancreatic cancer patients receiving first-line gemcitabine."

"These positive results have encouraged us to engage in discussions with potential partners over Immutep's plans for the advanced development stages of IMP321 as we continue to collect data from this study at the highest dose," added John Hawken, CEO.

For further information please visit the web-site www.immutep.com.

Metastatic Breast Cancer and Chemoimmunotherapy

Metastatic breast cancer remains incurable. The failure of current approaches is generally attributed to the outgrowth of breast tumour cells that are inherently resistant to standard treatments. Manipulating the immune system to recognize and eradicate breast tumour cells is a highly attractive alternative approach to disease management. Active immunization offers multiple theoretical advantages over all other therapies, including low toxicity. The sustained antitumour effect due to *immunological memory* would obviate the requirement for prolonged, repetitive cycles of therapy.

The objective of chemo-immunotherapy is to amplify *natural pre-existing* T cell responses specific for any known or unknown tumour antigen and to recruit and amplify *new* tumour-specific T cell responses resulting from the use of cytotoxic drugs known to induce tumour cell apoptosis. The direct cytolytic effect of some cytotoxic drugs, such as paclitaxel, can enhance antigen presentation by inducing tumour cell apoptosis. This mechanism of therapeutic synergy has been shown with cyclophosphamide, doxorubicin, or paclitaxel when given with dendritic cell-based vaccines. Until 8 years ago, it was thought that the T cell depletion caused by chemotherapy would make immunotherapy ineffective. However it has now been shown that, on the contrary, the vigorous T cell repopulation following depletion can be directed against the tumour, the so-called "rebound" effect.

Soluble LAG-3 protein is a prognostic factor in breast cancer

ImmuFact IMP321 is closely related to the soluble form of the LAG-3 (Lymphocyte Activation Gene-3) protein which is a prognostic indicator for survival in breast cancers expressing oestrogen or progesterone receptors. This was shown in a study carried out by researchers at the René Huguenin Cancer Centre and Pr. Frédéric Triebel when he was at the Pharmacy Faculty of University Paris 11. These results paved the way for the current clinical trial. (Immutep Press Release No 6, April 2006)

Centre René Huguenin de Lutte contre le Cancer

The René Huguenin Centre for the Fight against Cancer is a comprehensive cancer centre that treats more than 3,000 new cases of cancer each year, with more than 2,000 new cases of breast cancer. It has a medical staff of 66 practitioners. Besides participation in therapeutic trials, the Centre has developed special expertise in the field of tumorigenesis and pharmacogenetics of breast cancers. Professor Jean-Nicolas Munck is the Directeur-Général of the Centre.

Immutep S.A.

Immutep S.A. is a biopharmaceutical company developing immunostimulatory factors for the treatment of cancer and chronic infectious diseases and immunomodulatory therapeutic antibodies for the treatment of cancer or autoimmune disease. The Company's technologies are based on the LAG-3 immune control mechanism that mediates T cell immune responses.

ImmuFact[®] - T cell Immunostimulatory Factors for amplifying the T cell response

The lead product, ImmuFact[®] IMP321, is a highly potent T cell immunostimulatory factor. It is a soluble form of LAG-3 that binds, with high affinity, to MHC class II molecules expressed by dendritic cells (DC) and monocytes. This binding leads to DC maturation, migration to the lymph nodes and enhanced cross-presentation of antigens to T cells. As a result, strong and sustained anti-tumour or anti-viral cytotoxic T cell responses are obtained.

Clinical Development

Immutep has completed two randomised single-blind escalating-dose Phase I studies in 108 healthy individuals with IMP321 alone and combined with two well-defined standard types of antigens to show safety of the product alone and as an adjuvant in therapeutic vaccines. Four Phase I/II clinical trials are in progress: in metastatic renal cell carcinoma with IMP321 injected alone, in metastatic breast cancer combining IMP321 with paclitaxel in a chemo-immunotherapy protocol, a disease-free melanoma study with IMP321 as an adjuvant to peptide antigens and a lympho-depletive/adoptive transfer metastatic melanoma study. A new Phase I/II chemo-immunotherapy study in advanced pancreatic cancer will start shortly in the USA. More than 500 s.c. injections of IMP321 have been administered to date at doses up to 30 mg with no clinically significant drug-related adverse events.