



Immutep

Immutep Announces Final Results In Phase I/II Chemoimmunotherapy Trial In Breast Cancer

ImmuFact IMP321 doubles clinical response rate in first-line metastatic breast cancer

Orsay, France, January 4, 2010, Immutep S.A. announced today the final results from its Phase I/II chemoimmunotherapy clinical trial in metastatic breast carcinoma. The final results confirm the clinical response rate of 50 % using Immutep's IMP321 associated with paclitaxel. This compares to 25 % using paclitaxel alone.

ImmuFact[®] IMP321 is a T cell immunostimulatory agent. Repeated IMP321 injections lead to strong anti-tumour T cell responses. In synergistic combination with chemotherapy, IMP321 doubles the clinical response rate. This therapeutic strategy is called 'chemo-immunotherapy'.

Chemo-immunotherapy 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. However, this initial immune response needs to be sustained and amplified by a CD8 T-cell booster that is non-toxic and can be given repeatedly, such as ImmuFact IMP321.

The study was a multi-centre open-label fixed-dose-escalation trial. Patients received 6 cycles of weekly paclitaxel, 3 weeks out of 4, 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 were studied. The results are based on tumour regression under RECIST criteria in 30 patients 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 highly statistically significant with a p-value of 0.004.

In addition, immuno-monitoring confirmed that IMP321 is a potent agonist of the anti-cancer cellular immune response. Major components of the immune response (monocytes, dendritic cells and the vital CD8 memory T cells) were found to be expanded/activated for several months.

Further evidence of the mechanism of action came from the analysis of tumour regression during the second 3 months compared to the first 3 months. Under chemo alone, most tumour regression takes place during the early period and less during the later period. Using IMP321, however, investigators observed enhanced tumour regression in the later period as well; late responses are characteristic of a cancer immunotherapy effect.

"With such chemo- and non-toxic immunotherapeutic combinations, we have been able to improve the response rate and/or consolidate or stabilize the partial tumour responses obtained with chemotherapy alone," said Dr Maya Gutierrez, Principal Investigator, René Huguenin Cancer Centre.

"These final results based on 30 patients treated and a p-value of 0.004 mean that we have the results required to go forward to a pivotal trial," said Frédéric Triebel, Scientific & Medical Director of Immutep. "This form of chemo-immunotherapy should be applicable to many chemotherapies. For example, it is now being tested in the USA in association with gemcitabine in pancreatic cancer."

"The next steps are a Phase IIb pivotal trial leading to Conditional Marketing Authorisation in Europe and further trials in other cancers and with other chemotherapies. Partnering discussions are in progress," added John Hawken, CEO.

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

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

ImmuFact[®] IMP321 is a first-in-class antigen-presenting cell (APC) agonist. It is a soluble form of the LAG-3 ("lymphocyte activation gene-3") T cell surface receptor that binds, with high affinity, to MHC ("major histocompatibility complex") class II molecules on APC such as monocytes and dendritic cells. Repeated IMP321 injections lead to strong anti-tumour CD8 T cell responses in cancer patients especially in combination with chemotherapy.

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 *chemoimmunotherapy* 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. 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.

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[®] - Clinical Development

More than 600 s.c. injections of IMP321 have been administered to date in Europe and the USA at doses up to 30 mg with no clinically significant drug-related adverse events. A Phase I trial in metastatic renal cell carcinoma with IMP321 alone has been completed. A Phase I/II trial in metastatic breast cancer combining IMP321 with weekly paclitaxel in a chemo-immunotherapy protocol has been completed (<http://clinicaltrials.gov/ct/gui/show/NCT00349934?order=1>). Three Phase I/II clinical trials are in progress: in pancreatic cancer combining IMP321 with gemcitabine in chemoimmunotherapy (<http://www.clinicaltrials.gov/ct2/show/NCT00732082?term=07-0265&rank=1>), a disease-free melanoma study with IMP321 as a therapeutic vaccine adjuvant to peptide antigens and a lympho-depletive/adoptive transfer metastatic melanoma study.