



Immutep Announces Final Results In Advanced Renal Cell Carcinoma

Clinical research paper describes IMP321's potency in inducing progression-free survival improvement and effector memory T cells

Orsay, France, September 29, 2009 - Immutep S.A. announced today the publication of a clinical research paper showing that its lead product, IMP321, improved progression-free survival in advanced renal cell carcinoma patients.

The single-centre open-label dose-escalation Phase I study was carried out at the Institut Gustave Roussy (IGR, Villejuif, France), the largest cancer clinic in Europe, under the supervision of Dr Bernard Escudier, a leading specialist in renal cell carcinoma. The immuno-monitoring was done by Immutep at its laboratories near Paris.

Twenty-one advanced RCC patients received 119 injections of IMP321 at doses ranging from 0.050 to 30 mg/injection s.c. biweekly for 6 injections. No clinically significant adverse events were observed. Good systemic exposure to the product was obtained following s.c. injections of doses above 6 mg. IMP321 induced both sustained CD8 T cell activation and an increase in the percentage of long-lived effector-memory CD8 T cells in all patients at doses above 6 mg. Tumour growth was reduced and progression-free survival was better in those patients receiving higher doses (>6 mg) of IMP321: 7 out of 8 evaluable patients treated at the higher doses experienced stable disease at three months compared to only 3 out of 11 in the lower dose group ($p=0.015$).

The absence of toxicity and the demonstration of activity warranted further studies of IMP321 in combined regimens (e.g. chemo-immunotherapy). Further improving the CD8 memory T cell response seen in the present study by extending the treatment schedule of biweekly injections from 3 months to 6 months may also improve the clinical outcome. To this end, two such chemo-immunotherapy trials are in progress in metastatic breast cancer and advanced pancreatic cancer in which IMP321 is given the day after first-line paclitaxel and gemcitabine, respectively.

"We are very pleased to publish these first data on repeated injections of IMP321 in cancer patients" said Bernard Escudier, the Principal Investigator. "This first-in-class immunopotentiator is well tolerated and effective at dose above 6 mg"

"Assessing the pool of long-lived effector-memory CD8 T cells in the blood 14 days after injection of the antigen-presenting cell activator IMP321 is a very meaningful bioassay because this pool does reflect the long-term capacity of the body cytotoxic CD8 T cells to kill tumour cells. It is remarkable that all patients tested respond to 6 mg IMP321." said Chrystelle Brignone, *ImmuFact* Project Manager and first author of the paper.

Immutep's lead product, *ImmuFact*[®] IMP321, is a potent natural human immunostimulatory factor designed to amplify the T cell immune response. IMP321 can be used either as an immunopotentiator in therapeutic vaccines or alone at higher doses as a monotherapy or in combination with chemotherapy. Seven clinical trials have been initiated with *ImmuFact* IMP321 in the last four years.

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

The published paper

"A Phase I Pharmacokinetic and Biological Correlative Study of IMP321, a Novel MHC Class II Agonist, in Patients with Advanced Renal Cell Carcinoma" Chrystelle Brignone, Bernard Escudier, Caroline Grygar, Manon Marcu and Frédéric Triebel, *Clinical Cancer Research*, October 1 2009.

The importance of effector-memory T cells

The activation of potent CD8 T-cells with high effector activity is one of the goals of immunotherapy. An essential step in achieving this is the induction of a pool of **long-lived effector-memory (EM) CD8 T cells**. These long-lived EM cells traffic to the tumour and display immediate effector function. It has now become clear that EM CD8 T cells are superior to terminally differentiated effector cells in mediating successful tumour clearance. The latter display impaired proliferation and survival *in vivo*, and only mediate short-term anti-tumour effects. In contrast, EM T cells have enhanced proliferative potential and survival, and the potential to provide more robust and enduring protection against tumours.

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 autoimmune disease or cancer. The Company's technologies are based on the LAG-3 immune control mechanism that mediates T cell immune responses.

The LAG-3 immune control mechanism

The lymphocyte activation gene-3 (LAG-3 or CD223) protein binds to the MHC class II molecule which is at the centre of immune response induction. LAG-3 is a two-way signalling molecule that plays a role in:

- the upregulation of the immune system through the activation of MHC class II⁺ antigen presenting cells like dendritic cells and monocytes leading to the expansion of activated CD8 T cells, and
- the downregulation of the T cell response through signalling in T cells, both effector T cells and regulatory T cells.

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.

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. Four Phase I/II clinical trials are in progress: in metastatic breast cancer combining IMP321 with weekly paclitaxel in a chemo-immunotherapy protocol (<http://clinicaltrials.gov/ct/gui/show/NCT00349934?order=1>), in pancreatic cancer combining IMP321 with gemcitabine in chemo-immunotherapy (<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.

ImmuTune[®] - Therapeutic antibodies

Immutep's second product candidate is ImmuTune IMP731, a cytotoxic antibody for depleting activated T cells in autoimmune disease. A clinical candidate has been developed and the Company is planning a Phase I study in psoriasis. Immutep is also developing IMP701, an antagonist antibody designed to increase T cell proliferation against cancer and infectious disease.