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

Abstract

Purpose: To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IMP321, a recombinant soluble LAG-3Ig fusion protein which agonizes MHC class II–driven dendritic cell activation.

Experimental Design: Patients with advanced renal cell carcinoma were treated with escalating doses of IMP321 s.c. Blood samples were assayed to determine plasma pharmacokinetic parameters, detect human anti-IMP321 antibody formation, and determine long-lived CD8 T cell responses.

Results: Twenty-one advanced renal cell carcinoma 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. Tumor growth was reduced and progression-free survival was better in those patients receiving higher doses (>6 mg) of IMP321: 7 of 8 evaluable patients treated at the higher doses experienced stable disease at 3 months compared with only 3 of 11 in the lower dose group (P = 0.015).

Conclusion: The absence of toxicity and the demonstration of activity at doses above 6 mg warrant further disease-directed studies of IMP321 in combined regimens (e.g., chemoimmunotherapy). (Clin Cancer Res 2009;15(19):6225–31)

Materials and Methods

Patients. Eligible patients were at least ages 18 y; had histologic documented metastatic renal clear cell adenocarcinoma; an Eastern Cooperative Oncology Group performance status of 0 or 1; measurable IMP321 is the only protein that is presently available for this therapeutic approach (5–8).

The LAG-3Ig protein is efficacious as a vaccine adjuvant to inhibit tumor growth in mice grafted s.c. with different tumor cell lines (9, 10) and spontaneous carcinogenesis in Her2/neu transgenic mice (11). In particular, the mere s.c. presence of LAG-3 leads to RCC tumor (RENCA) rejection in mice, due to boosted tumor-specific cytotoxic CD8 T-cell responses (9). Interestingly, the expression of LAG-3 on a tumor efficiently promotes intratumoral recruitment, activation, and type-1 commitment of APCs, and leads to a wide intratumoral influx of nonspecific and specific reactive cells, and the release of immunoregulatory and cytotoxic mediators (12).

In this report, data are presented demonstrating that in previously treated advanced RCC patients who are immunosuppressed (13–16), IMP321 induced an increase in the percentage of circulating activated CD8 T cells and of long-lived effector-memory (EM) CD8 T cells in all patients treated by repeated injections of doses above 6 mg. Importantly, this immunostimulatory effect was obtained without any detectable toxicity of this first-in-class immunopotentiator targeting MHC class II+ APCs.
In this article, we describe a first-in-man dose-escalation phase I trial of IMP321 (LAG-3 Ig) given to patients with advanced cancers. The data reported here strongly support the future development of this agent for clinical use. IMP321 was safe, well-tolerated, and induced long-lived effector-memory CD8 T-cell responses in all patients treated at doses above 6 mg. The recommended phase II dose for further study was 6 mg s.c. biweekly for 6 months. Phase I/II studies of this first-in-class immunopotentiator plus cytotoxic chemotherapy are currently open to recruitment.

**Study design and treatments.** In this single-center, open-label, non-randomized, fixed dose-escalation trial done in an ambulatory and day-hospital setting, patients received IMP321 s.c. biweekly for six injections.

Three to six patients were enrolled in successive cohorts with the following IMP321 dosing: 0.05, 0.25, 1.25, 6.25, and 30 mg per injection. To be evaluable for the dose escalation decision-making process, a patient must have received at least 6 wk of treatment with IMP321. Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 3.0. Dose-limiting toxicity was defined as any grade 3 to 4 toxicity. If one patient had developed a dose-limiting toxicity, dose escalation would have been stopped and the prior dose level would be considered the maximum tolerated dose. No intrapatient dose escalation was permitted. Also, because of the fixed dose study design, no dose reduction for a patient was allowed.

**Study assessments.** Before initiating treatment, each patient was evaluated for medical history, physical examination, tumor measurement using computer-assisted tomography, Eastern Cooperative Oncology Group performance status, complete differential blood count, serum chemistries, urinalysis, and electrocardiogram. These assessments were also done before each subsequent injection. All observations were recorded, including results of physical examinations, vital signs, adverse events, concomitant medications, and laboratory tests. Patients were monitored every 2 wk and as needed for adverse events. Tumor response and progression were assessed using Response Evaluation Criteria in Solid Tumors with imaging studies done 2 wk after the third and the sixth injections. Blood samples were collected in EDTA-containing tubes for analysis of plasma concentrations of IMP321 after the first s.c. injection, in dry tubes on baseline and 2 wk after the third (day 57) and the sixth (day 85) injection for detection of serum anti-IMP321 antibodies, and in lithium heparin-containing tubes for monitoring the CD8 T-cell immune response.

**IMP321 potency assay.** THP-1, a human acute monocytic leukemia cell line that expresses MHC class II molecules, was used to measure IMP321 potency in inducing the secretion of CCL-4 (MIP-1β). The cells were incubated for 4 h at 37°C with IMP321 in complete RPMI, 10% FCS (Invitrogen). The concentration of CCL4 in supernatants was determined with BD Cytometric Beads Array following manufacturer’s instructions using a FACS Canto cytometer and FCAP Array Software (BD Biosciences). The difference between the blank values and the read-out observed with low concentrations of IMP321 was considered statistically relevant for a P value below 0.001 (parametric two-tailed Student’s t test; XLSTAT software).

**Pharmacokinetics analysis.** Preclinical pharmacokinetics studies had been done on two groups of four cynomolgus monkeys treated with a single LAG-3 Ig dose of 5 mg/kg injected by either the s.c. or i.v. route of administration. Clinical pharmacokinetics studies were done for a total of 14 patients treated at dose levels 2, 3, 4, and 5. Venous blood samples were collected before treatment and at 0.5, 1, 2, 4, and 24 h posttreatment on day 1 in tubes containing EDTA, and plasma was obtained by centrifugation and stored at −80°C until further analysis. The measurement of LAG-3 in the plasma was done by ELISA plates coated with an anti-LAG-3 monoclonal antibody (mAb; clone 11E3). The diluted plasma (1:20 and 1:40) and IMP321 standard (ranged from 500–7.8 pg/mL) were incubated overnight. Soluble LAG-3 was revealed using a biotinylated anti-LAG-3 mAb (clone 17B4, labeled using Pierce Biotechnology’s kit) followed by an incubation with peroxidase-conjugated streptavidin (GE Healthcare) and by the addition of 3,3′,5,5′-tetramethylbenzidine (BD Biosciences). The reaction was stopped by acidification, and absorbance were determined at the 450 and 600 nm wavelengths. OD450 nm minus OD600 nm values were plotted as a function of standard concentration and the standard curve was generated with a quadratic polynomial-2 model.

The levels of cytokines/chemokines in undiluted plasma samples were assessed using the human ProInflammatory 4-plex ultrasensitive kit (allowing the quantitation of IFN-γ, IL-1β, IL-6, and tumor necrosis factor-α) and the human Chemokine 9-plex ultrasensitive kit (allowing the quantitation of Eotaxine, Eotaxine-3, IL-8, IP-10, MCP-1, MCP-4, MDC, MIP-1τ, and TARC) developed by Meso Scale Discovery (MSD). The MSD platform is a solid phase immunoassay methodology that uses electrochemiluminescence to detect protein bound to micro-titer plates with electrodes. The plates were read using the MSD SECTOR Imager Model 1250.

**Detection of anti-IMP321 antibodies.** Serum samples obtained at baseline and 8 and 12 wk after the initial dosing were tested for anti-drug antibodies using ELISA. The serum was diluted 1:100 to avoid any matrix effect, loaded (at least two determinations/sample) on microtiter plates (Maxisorb, NUNC) precoated with IMP321 (1 μg/well) and revealed by a mix of horseradish peroxidase-conjugated goat anti-human κ and goat anti-human λ (Serotec). As controls, various concentrations of a recombinant human mAb fragment Fab-dHXL-HMH directed to IMP321 produced from human Ig library in Escherichia coli (MorphoSys) were added to each plate and the assay sensitivity was 3 ng/mL Fab equivalent. Absorbance were determined at the wavelengths of 450 and 600 nm.

The sera from most of the patients were also assessed in the bridging immunogenicity assay on the MSD platform. Streptavidin-coated plates were used to capture IMP321 that had been biotinylated using a kit purchased from Pierce Biotechnology. IMP321 binds to any drug-specific antibody present in serum samples. The drug-specific antibody then binds to another drug molecule, this time labeled by the MSD SULF0-Tag. Only this specific bridge combination leads to a signal, which reduces free drug interference allowing the loading of undiluted serum. The assay is independent of the species that produced the anti-IMP321 antibodies so that the murine anti-LAG-3 mAb (17B4) could be used as reference standard. Equal volumes (25 μL) of biotin-IMP321 at 0.5 μg/mL, SULFO-Tag-IMP321 at 0.5 μg/mL, and 17B4-standard...
diluted (from 1,000-0.1 ng/mL) in neat human AB (Jacques Boy) or patients’ sera were mixed and incubated with shaking at 420 rpm at room temperature for 1 h. Fifty microliters of each mix were transferred to the streptavidin plate previously blocked with 10% FCS in PBS. The plate was then sealed and shaken at room temperature for 1 h. After washing the plate with PBS 0.1% Tween, 150 μL of Read Buffer were added and the plate read using the MDS Imager. The detection limit of this assay was 1 ng/mL. As a control, unlabeled IMP321 was added to 17B4-standard at each level to evaluate the interfering effect of any soluble LAG-3 molecules present in the serum. The addition of free IMP321 had no effect on the signal till up to 50 ng/mL. Some serum samples were added to 100 ng/mL of 17B4 mAb to evaluate the reliability of the assay.

Pharmacodynamics. Following completion of the protocol, a series of peripheral blood mononuclear cells samples grouping the whole kinetics for each individual was thawed and phenotyped to monitor the immune response. Briefly 0.3 to 1 x 10^6 cells were washed in PBS 0.5% bovine serum albumin, 0.1% sodium azide, and incubated with mixtures of fluorochrome-conjugated antibodies (all from BD Biosciences). To monitor the activation of CD8+ T cells, a panel with Multitest CD8-FITC (clone SK1), CD3-PerCP (clone HBT7)/CD3-PerCP (clone SK7)/HLA-DR-APC (clone L343) supplemented with CD69-APC-Cy7 (clone FN50) and CD56-PE-Cy7 (clone B159) was used. For analysis of the differentiation phenotype, the first panel contained CD3-PerCP-Cy5.5 (clone SK7), CD8-APC-Cy7 (clone SK1), CD27-PE (clone L128), CD45RA-PE-Cy7 (clone L48), CD45RO-APC (clone UCHL1), and CD62L-FTTC (clone SK11) antibodies. The phenotype of EM cells was then studied using a second panel with CD3-PerCP-Cy5.5 (clone SK7), CD8-APC-Cy7 (clone SK1), CD27-PE (clone L128), CD45RA-PE-Cy7 (clone L48), and anti-CCR7-Alexa Fluor 647 (clone L48), CD62L-FTTC (clone SK11), and anti-CCR7-Alexa Fluor 647 (clone 3D12) antibodies and a third panel containing CD3-PerCP-Cy5.5 (clone SK7), CD8-APC-Cy7 (clone SK1), CD27-PE (clone L128), CD28-APC (clone CD28.2), CD45RA-PE-Cy7 (clone L48), and CD62L-FTTC (clone SK11) antibodies. Antibodies were incubated with cells for 30 min at 4°C. After washing, cells were analyzed by six-color flow cytometry using a FACS Canto cytometer.

Statistical analysis. Statistical tests were used to determine whether a given response obtained on day 85 (D85) can be discriminated from a given background at baseline, using the formula power calculation as follows (17):

\[ N = \frac{[2 \times P_a \times (1 - P_a) \times (Z_{\alpha} + Z_{\beta})^2]}{\Delta^2} \]

where N is the number of relevant events recorded in each sample for significance, \( P_a \) is the average proportion, and \( \Delta \) is the difference between these two proportions. The term \( (Z_{\alpha} + Z_{\beta})^2 \) is a power index, which varies depending upon the desired power and \( P \) value; \( (Z_{\alpha} + Z_{\beta})^2 = 23.9 \) for 99% power and \( P \) value of 0.005 and \( (Z_{\alpha} + Z_{\beta})^2 = 8.6 \) for 90% power and \( P < 0.05 \) (17).

The paired two-tailed nonparametric Wilcoxon test was used to compare the immunomonitoring values obtained at D85 versus D1 within the "low dose" group (grouping patients receiving 0.05, 0.25, and 1.25 mg of IMP321) or within the "high dose" group (grouping patients receiving 6.25 mg and 30 mg of IMP321). The a priori level of significance was a \( P \) value of 0.05. Data were computed using Statistica software.

Differences in percentages of patients experiencing progression-free survival at 3 mo were analyzed with Fisher’s exact test (IMP software).

Results

IMP321 bioactivity in vitro. IMP321 potency was assessed on the MHC class II+ monocyctic cell line THP-1 (Fig. 1). The bioactivity of IMP321 was measurable with a significant degree of precision at a dose as low as 2 ng/mL. A concentration of 10 ng/mL IMP321 induced a significant production of 350 pg/mL CCL4 by THP-1 cells, showing the great potency of IMP321 as an agonist of the immune system.

Safety. All 21 patients enrolled in this fixed dose-escalation trial received at least three doses of IMP321 and were included in the safety analysis. No clinically significant local or systemic treatment-related adverse events were recorded. Of the total 195 adverse events, 20 (10%) were evaluated to be related to IMP321 and were grade 1 local reactions (see Supplementary Table S1). They were mainly observed in the three patients injected with 30 mg who received a large volume (6.8 mL) of IMP321 split at four different s.c. sites of the anterior face of the thigh.

Pharmacokinetics analysis. After i.v. administration in monkeys, (Fig. 2A), the clearance was 100 mL/h/kg and the steady-state distribution volume was 70 mL/kg. After s.c. administration, the peak serum concentration was observed at 6 hours with a secondary half-life of 10 hours. The area under the curve after s.c. administration was ~30% of that after i.v. administration.

In our patients, plasma concentrations of IMP321 were barely detectable in the 1.25 mg dose group (or below). The results of the pharmacokinetics analysis for the 6.25 and 30 mg dose groups are shown in Fig. 2B and C. The mean [C]max at 2 hours were 1.3 (range, 0.2-2.5 h) and 8.0 ng/mL (range, 6.0-12.1 ng/mL), and the area under the curve 14 ± 9 and 118 ± 41 ng h/mL for the 6.25 and 30 mg dose, respectively. The mean concentration of IMP321 at 24 hours was still ~40% of the mean [C]max, showing good systemic exposure to this immune system agonist during for at least 24 hours. The terminal elimination half-life, the apparent volume of distribution at steady-state, and the total body clearance could not be calculated due to the lack of samples at late time points.

Detection of cytokines/chemokines and anti-IMP321 antibodies. To assess the possibility of any cytokine toxicity resulting from this systemic exposure, we used a very sensitive electroluminescence technology able to detect an early surge in physiologic pg/mL chemokine/cytokine concentrations in undiluted plasma. There was no evidence for any significant change in the concentration levels of 12 cytokines and chemokines in the first 24 hours following the first s.c. injection (Supplementary Fig. S1).
Sera collected at baseline and 2 weeks after the third (day 57) and the sixth injection (day 85) were assessed for anti-IMP321 antibodies by direct ELISA (Supplementary Fig. S2). Among 18 tested patients, 1 patient receiving 1.25 mg (patient 11) and 1 patient receiving 6.25 mg (patient 13) showed an increase compared with baseline level by >15%. The sera from these (and other) patients were then assessed without any dilution in the very sensitive bridging immunogenicity assay on the MSD platform. The tested sera gave a signal below the detection range (1 ng/mL). To exclude any false negative results, these two sera were added to 100 ng/mL of anti-LAG-3 mAb. The recovery levels were within the range of the assay: 109 and 115 ng/mL. Together, these results show that there was no induction of anti-IMP321 antibodies after six s.c. injections of up to 30 mg IMP321.

**Pharmacodynamics.** We monitored the CD3+CD4+ and CD3+CD8+ T-cell immune responses in peripheral blood mononuclear cells collected at baseline and 14 days after the third (day 57) and the sixth (day 85) IMP321 injections. At the first three dose levels (0.05, 0.25, and 1.25 mg), there was a trend toward a decrease in the percentage of CD8+ T cells expressing the activation marker CD69 (mean of percentage of change, -22%; Fig. 3A, right), which may be explained by the progressive immunosuppression observed in the course of this disease. Conversely, the percentage of CD8+CD69+ T cells at the two higher dose levels (6.25 and 30 mg) was generally higher after the last administration of IMP321 compared with baseline (mean of percentage of change, 78%; Fig. 3A, left). To restrict the analysis to long-lived activated CD8 T cells that may reside in the blood as a consequence of IMP321 injection 14 days before, we analyzed the percentage of CD3+CD8+CD69+CD38+HLA-DR+ cells. We found a significant increase in the frequency of circulating activated CD8+ T cells expressing the three activation markers, CD69, CD38, and HLA-DR, in seven of eight patients in the 6.25/30 mg pooled dose group (P = 0.008; mean of percentage of change, 219% versus -36% for the low dose group; Fig. 3B). No sustained T-cell activation 14 days after the last IMP321 injection was ever observed in the CD4 T-cell subset (data not shown).

To further characterize the effect of a systemic exposure to IMP321 on CD8 T cells, we analyzed whether the percentage of CD45ROhi CD45RA-CD62L- EM cells was increased in the 6.25/30 mg pooled dose group (Fig. 4, right). We found an increase in eight of eight patients (P = 0.008; mean of percentage of change, 22%), whereas the analysis of this subpopulation in patients in the three first dose groups revealed a heterogeneous response (mean of percentage of change, 4%; Fig. 4, left). Further phenotyping using a different panel of antibodies and six-color cytometry analysis revealed that these EM CD8 T cells did not express CCR7 (a marker for central memory cells) as expected but expressed the costimulation molecule CD28, with

![Fig. 2. Pharmacokinetics (PK) profiles in monkeys and RCC patients. Preclinical PK study was done on monkey after i.v. (▴, dashed line) or s.c. (・, solid line) injection of 5 mg/kg LAG-3 Ig (A). PK profiles from the six RCC patients who received 6.25-mg dose (B) and the three patients who received 30-mg dose (C). Soluble LAG-3 was measured by ELISA in the plasma at different time points following the first s.c. injection.](https://www.aacrjournals.org/doi/10.1158/1078-0432.CCR-09-0068)

![Fig. 3. IMP321 increases the percentages of activated CD8+ T cells. The percentage of CD3+CD8+ T expressing CD69 (A) and expressing three activation markers (namely CD69, CD38, HLA-DR+) cells; B) are shown. The data from dropped-out patients (patient 8, 12, and 17) are not presented. The poststudy time point sample for patient 5 was not available. Fold increase values between D85 and D1 are indicated in brackets only for patient displaying significant increase (*, P < 0.05; **, P < 0.005). Differences in the percentage of CD8+ T cells expressing activator markers from baseline to poststudy time points were compared using Wilcoxon rank sum tests within each pooled group. When the difference is significant, the P value is indicated.](https://www.aacrjournals.org/doi/10.1158/1078-0432.CCR-09-0068)
an increase in seven of eight patients ($P = 0.008$; mean of percentage of change, 29%; Fig. 5A). Based on CD28 and CD27 expression, the EM subsets can further be distinguished into four subpopulations: CD28+ either CD27+ (EM1) or CD27- (EM4), and CD28- either CD27+ (EM2) or CD27- (EM3; ref. 18). Among these four subsets, only the EM1 and EM4, which are long-lived memory cells, were increased in seven and eight of eight patients ($P = 0.016$ and $P = 0.014$; mean of percentage of change, 32% and 40%), respectively (Fig. 5B).

**Efficacy.** There was no objective tumor response in the 21 patients enrolled in this trial but tumor growth at final scan was reduced in the higher dose group. The percentage change in the sum of target lesion tumor diameters (Response Evaluation Criteria In Solid Tumors) is shown in Fig. 6. In the low dose group, two of the patients with little change in tumor diameter were classified as having progressive disease (PD) as new lesions had appeared. Progression-free survival was significantly better in those patients receiving higher doses (>6 mg) of IMP321: 7 of 8 evaluable patients treated at the latter doses experienced stable disease at 3 months compared with only 3 of 11 in the lower dose group ($P = 0.015$).

**Discussion**

The activation of potent CD8 T cells with high effector activity is one of the goals of an effective immunotherapy. The data presented in this article showed that both the circulating activated CD8 T cell subset and the long-lived EM CD8 T-cell pool are increased by IMP321. These long-lived EM cells can traffic to and reside in diverse nonlymphoid sites and display immediate effector function (19, 20). The importance of the development of such memory cells during an effective immune response has been increasingly documented (21, 22). In particular, the development of CD8+ T cells with long-term survival and proliferative potency correlates with a good clinical outcome (23). It has now become clear that CD8 T cells with memory potential are superior to terminally differentiated effector cells in mediating successful tumor clearance (24). The latter display impaired proliferation and survival in vivo, and only mediate short-term antitumor effects. In contrast, memory T cells have enhanced proliferative potential and survival, and the potential to provide more robust and enduring protection against tumors (24). It is therefore essential to assess CD8 T-cell immunologic end points...
at least 10 days after injection of any immunostimulatory product to monitor these vital long-lived memory T cells.

The detection of a greater number of both activated CD8 T cells expressing in particular the HLA-DR late activation antigen and long-lived EM CD8 T cells 14 days after the last IMP321 injection showed that enhanced and sustained numbers of effector CD8 T cells are induced in patients receiving doses above 6 mg. In other patient groups receiving lower doses, the decrease over time of these activated or EM CD8 T cells may be due to the further deterioration of the immune system. In addition, IMP321 increases only the pool of EM cells that express CD28, and are thereby equipped to receive the costimulatory signal given to Ag-experienced T cells and thus be fully activated at the tumor site (25). Finally, the maintained expression of CD27, a costimulatory receptor in the generation of T-cell memory (26), and of CD28, which defines the EM T-cell subset, has been shown to be involved in the long-term immune response causing tumor regression in adoptive transfer clinical trials (27). EM is the main subset of EM CD8 T cells and also that benefits most from IMP321 injections.

Treatment with ipilimumab, a monoclonal IgG1 anti-CTLA-4 neutralizing antibody, has shown objective clinical response rates of around 10% to 15% and some long-lasting disease stabilizations. Clearly, the patterns of response in these patients differ from those seen following cytotoxic chemotherapy. For instance, late responses may be seen and these may occur after an initial period of tumor progression (28). Here, given that we observed a significant increase in the number of patients not progressing at 3 months when treated with high (i.e., >6 mg) versus low doses of IMP321, it is possible that extending the treatment schedule to 6 months in patients with a better immune status may show clinical benefit in terms of increased progression-free survival.

Combination therapies are currently being evaluated clinically with the goal of enhancing overall antitumor activity, to allow treatment of patients with large tumor burdens. Our data indicate that it should be relatively straightforward to combine IMP321 with any first-line chemotherapy for optimal antitumor efficacy in carcinoma patients with a good immune status, as in first-line regimens. It is clear that apoptotic cell death induced by chemotherapy leads to a beneficial immunoadjuvant effect (29–31). More specifically, evidence has been presented recently for chemotherapy-induced enhancement of CD8 memory T-cell response in cancer patients (32). Adding the immunoadjuvant effect of chemotherapy to that of IMP321 without adding further toxicity would seem to make sense.

In addition, further improving the CD8 memory T-cell response seen in the present study by extending the treatment schedule of biweekly injections from 3 to 6 months may also improve the clinical outcome. To this end, two such chemiomunotherapy trials have now been started in metastatic breast cancer (3) and advanced pancreatic cancer (4) in which IMP321 is given s.c. the day after first-line paclitaxel and gemcitabine, respectively.

Disclosure of Potential Conflicts of Interest
Frédéric Triebel is a co-inventor on some patents related to LAG-3.

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