1 TITLE PAGE

Study title:	Extension study to evaluate long-term-safety of IMA901 plus GM-CSF in advanced renal cell carcinoma patients who achieved a decrease in tumor load or stabilization of their disease after participation in the open-label, multicenter IMA901-202 Phase 2 study
Test drug:	Peptide-based renal cell cancer vaccine IMA901
Indication:	Clear-cell renal cell carcinoma (RCC)
Study dates:	First patient in (date of first visit): 30-JUN-2008 Last patient out (date of last regular visit): 10-MAR-2009
Development phase:	Phase II
Sponsor's name and address:	immatics biotechnologies GmbH Paul-Ehrlich-Strasse 15 D-72076 Tuebingen, Germany Phone: +49-70 71-56 51 25-0 Fax: +49-70 71-56 51 25-99 Web: www.immatics.com
Study number:	IMA-901-203
EUDRACT No.	2008-000213-30
Investigator(s):	Overall co-ordinating investigator was Prof. Dr. Arnulf Stenzl (University of Tuebingen, Germany). [redacted]
Date:	CSR Full Version – Final (25. May 2010)
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2 SYNOPSIS

Title of the study:	Extension study to evaluate long-term-safety of IMA901 plus GM-CSF in advanced renal cell carcinoma patients who achieved a decrease in tumor load or stabilization of their disease after participation in the open-label, multicenter IMA901-202 Phase 2 study.
Investigators:	Co-ordinating investigator was Prof. Dr. Arnulf Stenzl (University of Tuebingen, Germany). [redacted]
Study centres and number of patients:	Originally, it was expected that approx. 20 patients treated at approx. 20 study sites will be eligible to continue study treatment and be included in the extension study. Later, the decision was taken to conduct the extension study only in Germany. Two out of the 5 centers in Germany, who had enrolled one or more patients in core study IMA901-202, also included patients in this extension study (one patient each). The center numbers were 06 and 08. [redacted]
Publications (references):	Study results or parts of study results were not yet published.
Period of study:	First patient in (date of first visit): 30-JUN-2008 Last patient out (date of last regular visit): 10-MAR-2009
Clinical phase:	Phase II
Objectives:	Primary objective: To investigate the sustained safety of IMA901 plus GM-CSF (immunomodulator) as single agent in advanced RCC patients who achieved a decrease in tumor load or a stabilization of their disease after participation in the core study IMA901-202. Thus, the primary endpoint of this extension study was long-term safety with Visit B (screening visit) of core study IMA901-202 being the reference point. Secondary objective:

	Secondary objectives of this study were efficacy (overall survival, time to progression) and immunological parameters.
Methodology (design of study):	This was a multicenter, open-label, Phase 2 extension study to investigate the sustained safety of IMA901 plus GM-CSF in patients with advanced RCC who previously achieved a decrease in tumor load or a stabilization of their disease after participation in the core study IMA901-202. The end of study (EOS) visit of the core study after 38 weeks (Visit 18) and the first visit of the extension study were identical for those patients who gave informed consent to continue treatment with IMA901+GM-CSF at 3 weeks intervals and to participate in the extension study until evidence of progressive disease (PD) or for a maximum of a further 12 vaccinations (resulting in a maximum extension study period of 36 weeks incl. 3 weeks of follow-up). The numbering of IMA901-203 study visits matched the number of vaccinations (=Visits 18 to 29) with a follow up Visit 30. The overall treatment period was defined as from the first application of the study drug in the core study IMA901-202 (Visit C or Visit 1; depending on the randomization) until the last vaccination in the extension study IMA901-203. Tumor assessments performed at EOS of the core study IMA901-202 were to serve as Baseline for the extension study IMA901-203 imaging. No additional images were required at the beginning of the extension study. In patients terminating the extension study, tumor imaging was to be performed as follows: • In patients terminating the study due to PD, tumor assessments at EOS (Visit 30) had to comprise at least images of the area where the progression occurred. • In patients completing the entire study period of 36 weeks or being withdrawn due to reasons other than PD, images of chest, abdomen, pelvis, and brain were to be performed 3 weeks after the last vaccination (Visit 30). • In patients with known bone metastases of the extremities, assessments (X-ray, CT or MRI) of the sites of bone metastases were also to be performed 3 weeks after the last vaccination (Visit 30) of the extension study. [redacted]

	[redacted]
Diagnosis and main criteria for inclusion:	This extension study was to be conducted in men and women with advanced RCC who had regularly completed the core study IMA901-202 and had achieved a decrease in tumor load or a stabilization of their disease at the end of that core study. The main criteria for inclusion were: • Patients who had participated in the core study IMA901-202 over the entire scheduled period and were compliant with the protocol, • Patients who had achieved a decrease in tumor load or a stabilization of their disease after participation in the core study IMA901-202, • Ability to understand the nature of the study and to give written informed consent. All inclusion/exclusion criteria are provided in Section 9.3.1 and Section 9.3.2.
Duration of treatment:	The extension study period covered a further 12 vaccinations at intervals of 3 weeks (=33 weeks) with an additional follow-up visit 3 weeks after the last vaccination, resulting in a total extension study duration of 36 weeks. Patients with PD were to be withdrawn from the study.
Study therapy, dose and mode of administration, and batch number:	<u>Mode of vaccination</u> A single vaccination consisted of i.d. application of GM-CSF (75 µg) followed after 10 to 30 minutes by i.d. injection of 4.13 mg IMA901, which is composed of 9 HLA Class I-binding TUMAPs, 1 HLA Class II-binding TUMAP, and 2 non-active ingredients. <u>Vaccination schedule</u> All patients included in the extension study were to receive a total of 12 additional maintenance vaccinations at intervals of 3 weeks (=Visits 18-29). Finally, an EOS visit (Visit 30) was to be performed 3 weeks after the last vaccination. [redacted]

Reference therapy	Not applicable
Criteria of evaluation:	Primary endpoint: The primary endpoint of this extension study was long-term safety with Visit B of the core study IMA901-202 being the reference point. Secondary endpoints: • Time to Progression (TTP) with Visit 18 assessments being the reference point, • Overall survival (OS). • Cellular immunomonitoring: o Maintenance of T-cell responses to peptides contained in IMA901, o Description of long-term properties of T-cell responses to peptides contained in IMA901, o Description of long-term properties of other immune cell populations that may influence T-cell responses such as regulatory T-cells. • Non-cellular immunomonitoring: o Serum levels of antibodies directed against peptides contained in IMA901 and against MHC/peptide complexes thereof, o Presence of molecules with suspected influence on immune response such as serum TGFβ. • Analysis of tumor tissue (optional in a subgroup of patients with sufficient sample amount and quality): o Analysis of expression of the target genes encoding the TUMAPs contained in IMA901 and of genes which might be influenced by IMA901, o Presentation of TUMAPs contained in IMA901, o Assessment of tumor infiltrating lymphocytes, o Presence of molecules with suspected influence on immune response such as arginase and indolamine-2,3-dioxygenase.
Statistical methods:	The originally planned statistical methods were not applied, since only 2 patients were enrolled in the extension study. Therefore, no sample statistics or tests were performed, and the data provided in this study report are presented as individual case reports and are primarily based on the original paper CRFs of the 2 enrolled patients and the

	corresponding line listings of the core study IMA901-202 analysis. For the clinical study report of the extension trial, OS follow-up stopped when the last patient had completed the extension study. Survival information given in the CRF beyond the official follow-up period (up to 14-JUL-2009 for patient 06-001, 31-AUG-2009 for patient 08-002) was also considered. Further survival follow-up is ongoing. Actually, the demographic and other baseline characteristics were individually described for both the core study baseline and the extension study baseline (Visit 18). The clinical tumor evaluations in study IMA901-203 were solely investigator-based (i.e. no central review). The related outcome assessments (including the assessments in core study IMA901-202) were described individually, as well as the occurrence of adverse events in both the core study period and the extension study period. Laboratory data, vital signs, and other safety variables (ECG, physical examination) were described individually for the extension study period.

Summary and conclusions:

The extension study IMA-901-203 was planned and initiated to assess the long-term safety and sustained effectiveness of a continued vaccination regimen in patients who had previously benefitted from a series of 17 vaccinations in the core study IMA901-202.

As only 2 patients have been enrolled in the extension study, the data provided in this study report are presented as individual case reports.

Patient 06-001, who had presented with 2 target lesions (right lung, kidney) and 1 non-target lesion in the left lung at core study baseline entered the extension study period on Visit 18 while being on "complete remission" based on the investigator's assessment ("partial remission" based on the central review) and maintained this assessment until the regular completion of the extension study at Visit 30. This patient had received all 29 scheduled vaccinations, was 523 days on regular study (Visit C to Visit 30), and still was alive 649 days after beginning of the core study when the last follow-up for survival was documented in the CRF of the extension study. This patient had experienced 3 mild and non-serious AEs during the core study period (resolved injection site pruritus, resolved balanitis, unresolved worsening of hyperthyreosis) and 2 AEs during the extension study period (mild resolved non-serious hyperuricemia and moderate resolved lymph edema on the left leg. The latter event (no local injection site reaction, since the site of vaccination was the right thigh) was considered "serious" because the patient was hospitalized due to worsening of local symptoms at the left leg and was considered "unrelated", since the patient had experienced deep vein thrombosis prior to core study entry. Overall, the only drug-related AE was the injection site pruritus. In this patient, a vaccine-induced immune response

(not detected during the core study) against 1 TUMAP [redacted] was detected during the extension study at Visit 18 and Visit 30, while no vaccine-induced immune responses were observed at the early immunomonitoring time points (Visit 5, 6, and 7).

Patient 08-002 entered the core study with 4 target lesions in lung, liver, and peritoneum, and with 2 non-target lesions (lung and distant lymph nodes). This patient had experienced early PD in the core study at Visit 8 but remained stable afterwards until Visit 18, so that it was decided to continue treatment. Since the patient developed a brain metastasis during the extension study period, the vaccinations were stopped after the 21st vaccination, and the patient was rated as progressive (328 days from Visit C to diagnosis of new brain metastasis). Overall, patient 08-002 was 354 days on regular study (Visit C to Visit 30/EOS), and was still alive 683 days after the beginning of the core study when the last follow-up for survival was documented in the CRF of the extension study. He suffered 11 AEs during the core study period and one AE (mild fever, resolved, unrelated) during the extension study period. The drug-related AEs (all mild and resolved) were associated with reactions on the injection site, apart from one short fever episode and hip rash. The AEs ongoing at the time of when the patient had entered the extension study period were hepatomegaly and exertional dyspnea (fluctuating [mild-moderate-mild] during the extension period), but these events as well as their persistence were considered unrelated to study drug treatment and likely to explain by the pattern of metastases (several metastases in lungs and liver). No SAEs were noted during the entire treatment period. In this patient, no additional vaccine-induced immune responses were detected during the extension study. [redacted]

In conclusion, the study IMA901-203 does not provide statistical, but rather anecdotal evidence. Therefore, robust statements concerning the effectiveness and safety of long-term-treatment with IMA901 plus GM-CSF cannot be derived from this study. Based on the local site investigators' assessment, one patient with no measurable immune response remained on sustained complete remission (from core study Visit 12 onwards), whereas the other patient (a multi-TUMAP responder, who had a higher tumor burden from the beginning of the core study) had to discontinue the extension study period because of disease progression after the 21st vaccination. Compared to the initial treatment period in the core study, the continuation of vaccinations beyond 17 vaccinations up to a total of 29 vaccinations was not associated with an increased risk of experiencing more or more intense/problematic adverse events in these 2 patients.