1 TITLE PAGE

Study title:	Phase II, randomized, open-label, multicenter study of intradermal IMA901 plus GM-CSF with or without low dose cyclophosphamide pre-treatment in advanced renal cell carcinoma patients with measurable disease
Test drug:	Peptide-based renal cell cancer vaccine IMA901
Indication:	Clear-cell renal cell carcinoma (RCC)
Study dates:	First patient in (date of first IC): 29-MAY-2007 Last patient out (date of last visit): 24-AUG-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-901-202
EUDRACT No.	2006-006370-25
Investigator(s):	Overall co-ordinating investigator was Prof. Dr. Arnulf Stenzl (University of Tuebingen, Germany). [redacted]
Date:	CSR Full Version – Final (22. March 2010)
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2 SYNOPSIS

Title of the study:	Phase II, randomized, open-label, multicenter study of intradermal IMA901 plus GM-CSF with or without low dose cyclophosphamide pre-treatment in advanced renal cell carcinoma patients with measurable disease.
Investigators:	Co-ordinating investigator was Prof. Dr. Arnulf Stenzl (University of Tuebingen, Germany). [redacted]
Study centers:	A total of 50 study sites were initiated and 39 sites screened at least 1 patient with 23 centers actually enrolling one or more patients. [redacted]
Publications (references):	Study results or parts of study results were not yet published.
Period of study:	First patient in (date of first IC): 29-MAY-2007 Last patient out (date of last visit): 24-AUG-2009
Clinical phase:	Phase II
Objectives:	Primary objective: The primary objective of this study was to determine whether IMA901 as single agent with GM-CSF as immunomodulator shows sufficient anti-tumor efficacy in patients with advanced renal cell carcinoma (RCC) to warrant further development. Secondary objective: Secondary objectives of this study were safety, immunological parameters, the potential of low-dose cyclophosphamide (CY) to improve immune response to IMA901, and additional efficacy endpoints.
Methodology (design of study):	This was a multi-center, open-label, randomized Phase II study in RCC patients to investigate the effect of a systemic treatment with IMA901 plus GM-CSF on the disease control rate (DCR) after 26 weeks of

	treatment (= primary endpoint). Generally, patients were to remain in the study for a maximum of 42 weeks (i.e., 25 days screening, 35 weeks treatment, and 3 weeks follow-up). After successful screening (period of maximum 25 days) patients were centrally randomized 1:1 to receive a single infusion of low-dose CY (300mg/m2) 3 days prior to the first vaccination vs. no pre-treatment, based on data suggesting that CY might enhance immune responses to therapeutic cancer vaccines and thus improve clinical outcome. Patients were stratified for randomization according to risk groups (i.e., "favorable" or "intermediate" risk based on the MSKCC criteria) and prior therapy (i.e., tyrosine kinase inhibitors(s) or cytokine(s)). Patients of both randomization arms received 7 vaccinations in the first 5 weeks of treatment (induction period). Subsequently, they received a further 10 vaccinations at 3 week intervals for a further 30 weeks (maintenance period). Tumor assessments were performed by either CT or MRI according to RECIST. At Screening, a CT or MRI of the chest, abdomen/pelvis and brain were performed to assess baseline tumor status. In patients with known bone metastases of the extremities or in case of suspected bone metastases of the extremities at Screening correlative imaging (X-ray, CT or MRI) was to be performed of the respective areas. After 8, 14, 20, 26, 32 and 38 weeks repeat CTs or MRIs of the chest, abdomen and pelvis were to be performed. In addition patients were to receive a CT or MRI of the brain after both 26 and 38 weeks. In patients with bone metastases of the extremities detected at Baseline or during the study, repeat assessments of the sites of bone metastases (X-ray, CT or MRI) were performed after 26 weeks and end of study. The same type of imaging as for screening assessments had to be maintained during the study in order to ensure best comparability of measurements throughout the course of the study. Cellular immunomonitoring (i.e., T-cell responses to peptides contained in IMA901 and analysis of other immune cell populations potentially influencing T-cell responses such as regulatory T cells) were performed 3 days before the first vaccination, on the day of the first vaccination, and then 2, 3 and 5 weeks after treatment initiation. In a subgroup of patients who were assessed by the investigator as presumably having benefited

	clinically from IMA901 one additional blood sample was optionally taken during the maintenance period (not before Visit 9) to investigate potential late immune responses. T-cell responses were analyzed by two different assay methods (multimer assay and ELISpot assay) for all patients with sufficient blood cells available and exploratory by a third assay (intracellular cytokine staining). Non-cellular immunomonitoring consisted of serum level analysis of antibodies directed against peptides contained in IMA901 and against MHC/peptide complexes thereof, and analysis of molecules with suspected influence on immune response such as TGF-β. These parameters were assessed 3 days before the first vaccination and then 14 and 26 weeks after treatment initiation (the molecules with suspected influence on immune response additionally on the day of the first vaccination).The following parameters were assessed in tumor tissues in a subgroup of patients with available tumor samples at sufficient amount and quality: Expression of target genes encoding the TUMAPs contained in IMA901 and of genes which might be influenced by IMA901, presentation of TUMAPs contained in IMA901, presence of tumor infiltrating lymphocytes and presence of molecules with suspected influence on immune response such as the immune-inhibitory molecules arginase and indolamine-2,3-dioxygenase. Safety assessments in this study included continuous AE monitoring plus the following scheduled investigations: physical examinations, vital signs and assessment of hematology, blood chemistry and urinalysis at Screening, on the day of CY administration (only in patients randomized to receive CY), at the day of the first vaccination, 3 weeks after the first vaccination and then every 6 weeks during treatment and at the end of study (EOS) after 38 weeks. A 12-lead ECG was performed at Screening and EOS. Pregnancy testing was performed according to applicable local legislation (at the very least during Screening for the study, at Visit 1 before the first dose, and at EOS). An independent Data Safety Monitoring Board (DSMB), consisting of three experts in the field of oncology and immunology was established to monitor safety. Data were provided to the DSMB every 4 to 6 weeks until 2/3 of the patients had been randomized and then at prolonged intervals (about every 2 to 3 months) until the end of the study. A statistician from the lead CRO [redacted] and further staff from the Sponsor and the CRO participated as non-voting members in the DSMB meetings to

	address questions raised by the DSMB members. In Germany, an extension protocol (study code IMA901-203) was established in order to maintain the vaccination schedule for a further 36 weeks for patients successfully completing the IMA901-202 study protocol (i.e. stable disease or objective response or a clinical benefit at EOS) (the results arising from the extension protocol are not part of this report but will be provided elsewhere). A visualization of the treatment schedule can be found in Section 9.1. A detailed flow chart including all efficacy and safety measurements is provided in Section 9.5.1.
Number of patients:	A total of 72 patients were planned to be enrolled at 50 experienced medical oncology/urology investigational sites in Europe in order to achieve a number of 57 valid and evaluable patients (based on a sample size estimation, cf. Section 9.7.2). In fact, 68 patients were enrolled at 23 sites. Due to the low drop-out rate this number was considered sufficient to achieve 57 evaluable patients.
Diagnosis and main criteria for inclusion:	Generally, HLA-A*02-positive men or women with advanced clear-cell RCC following a prior systemic therapy for advanced disease and classified as having a "favorable" or "intermediate" risk according to the MSKCC criteria [Motzer *et al.* 2004] were to be enrolled. Patients must be aged 18 years or older, have at least one measurable tumor lesion according to RECIST and must have received first-line tyrosine kinase inhibitor (TKI) or cytokine systemic therapy for advanced disease, during or after which the patient experienced documented disease progression. Patients who were progressive after treatment with two sequential tyrosine kinase inhibitors were also accepted (this was the case for 1 patient). (In Germany and Austria first-line therapy had to contain a tyrosine kinase inhibitor). The main criteria for inclusion were: • HLA-A*02-positive; • Histologically documented advanced clear-cell RCC; • Previous first-line TKI or cytokine systemic therapy for advanced disease and being suitable for second-line therapy (in Germany and Austria first-line therapy had to contain a TKI) **or** previous treatment with two sequential TKIs • Documented tumor progression during or after previous systemic

	therapy; • At least one uni-dimensionally measurable target lesion documented by adequate imaging and assessable according to RECIST; • Karnofsky Performance Status of ≥80%; • "Favorable" or "intermediate" risk according to 3-score MSKCC criteria [Motzer *et al.* 2004]. All inclusion/exclusion criteria are provided in Section 9.3.1 and Section 9.3.2.
Duration of treatment:	The individual study course in protocol IMA901-202 consisted of 25 days screening at maximum, 35 weeks treatment, and 3 weeks follow-up. Thus, patients remained in the study for a maximum of 42 weeks.
Study therapy, dose and mode of administration, and batch number:	1) Randomized pre-treatment with cyclophosphamide After central 1:1 randomization, patients allocated to the CY arm were administered low-dose CY (300 mg/m^2) i.v. as a single infusion 3 days before the first vaccination as an additional immunomodulator. No blinding procedures were performed. [redacted] 2) Mode of vaccination 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. 3) Vaccination schedule All study patients (irrespective of randomization) were to receive a total of up to 17 vaccinations. The vaccination schedule included an "induction period" of 5 weeks (7 vaccinations at Days, 1, 2, 3, 8, 15, 22, and 36 = Visits 1-7) and a "maintenance period" of 30 weeks with a further 10 vaccinations given at 3-week intervals (Visits 8-17). Finally, an EOS visit (Visit 18) was performed 3 weeks after the last vaccination. [redacted]

Reference therapy	Not applicable
Criteria of evaluation:	Primary endpoint: The primary endpoint of this study was defined as the disease control rate (DCR) at Visit 14 (i.e., after 26 weeks of treatment). This endpoint represented a composite of the objective response rate (ORR) and stable disease (SD) rate, where ORR is defined as the complete response (CR) rate plus partial response (PR) rate. All deaths regardless of cause were considered as events for the assessment of DCR. The assessment of the primary endpoint was based on modified RECIST including PD history (i.e., including post-PD assessments) as described in Section 9.5.3 and the Independent Review Committee Charter for central review (cf. Appendix 16.1.10). Secondary endpoints: • Time to progression (TTP); • Progression-free survival (PFS); • Overall survival (OS); • Tumor response rates (ORR, CR, PR) and SD rate at Visits 14 and 18 (after 26 weeks and 38 weeks on study); • Duration of response; • Time to response; • DCR after 38 weeks on study; • Cellular immunomonitoring: o T-cell responses to peptides contained in IMA901 - Percentage of multi-peptide responders (patients responding to ≥2 TUMAPs) - Number of TUMAPs to which a response can be detected o Other immune cell populations that may influence T-cell responses such as regulatory T cells; • Non-cellular immunomonitoring: o Serum levels of antibodies to peptides contained in IMA901 and to 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; • Effect of CY pre-treatment on immune response; • Safety.
Statistical methods:	<u>Efficacy analysis:</u> All primary and secondary endpoints were analyzed in the PP and ITT population. The per-protocol (PP) population was used for the primary analysis of efficacy data. This population consisted of all enrolled patients who had measurable disease according to RECIST at Screening (based on the investigator's assessment), had received at least 6 vaccinations, had at least one post-baseline tumor assessment and did not exhibit major protocol violations (for definitions cf. Statistical Analysis Plan). The safety population consisted of all enrolled patients who have received at least one treatment, i.e. at least one vaccination (administration of GM-CSF only was sufficient) and/or pre-treatment with cyclophosphamide. Analysis of safety parameters were based on the safety population. All efficacy analyses were tabulated stratified by CY treatment and for the total patient population. In a subgroup analysis the subgroups defined by the two randomization strata risk group (favorable or intermediate risk based on MSKCC criteria) and prior therapy (tyrosine kinase inhibitor(s) or cytokine(s)) were analyzed. All overall tumor analyses were reported separately for assessment of the investigator, independent radiologist, and oncologist, respectively. Moreover the overall tumor assessments of the radiologist and oncologist were assessed up to 1st PD (conventional RECIST assessment) and including PD history (i.e. including post-PD assessments). As this study was designed as a non-controlled Phase II study, the aim of this study was to obtain valuable information that can be used to make decisions regarding the further development of IMA901. Therefore, the study was designed to show a clinically relevant effect on the progression of disease with a statistical margin to exclude a non-effect. Based on

	thorough discussion with key experts in the field of RCC, a 30% DCR at 6 months was considered to be clinically relevant and set as a target rate in the study protocol; a no-effect level (NOEL) of 18% DCR was set based on the placebo group of a large, randomized phase III study (sorafenib pivotal trial, [Escudier *et al.* 2007]; *EPAR nexavar*] which included patients predominantly after first-line cytokine failure. Consequently, the sample size was calculated to exclude the 18% NOEL with 95% confidence when the observed DCR after 6 months (primary endpoint, based on overall tumor assessment of the Independent Oncologist including PD history) would in fact exceed 30%. Only later, during the conduct of the study, data became available from a study comparing everolimus versus placebo in patients who had progressed on previous TKI (sunitinib, sorafenib or both; [Kay *et al.* 2009, Motzer *et al.* 2008] and the percentage of patients being non-progressive after 6 months (derived from the Kaplan Meier curve for PFS) could then serve as a reference for the NOEL in this patient population after prior kinase inhibitors (DCR was conservatively set at 10%). The primary confidence interval for the DCR after 26 weeks (ca. 6 months of treatment) was additionally compared to a NOEL of 15% DCR which is the weighted average of both levels 10% and 18%. The first level was weighted with the percentage of patients with previous TKI therapy in the present study and the second level with the percentage of patients with previous cytokine therapy. Tumor response rates at all visits were calculated separately for OR (CR or PR), and DCR and ORR were presented with the corresponding exact 95%-CIs. PFS, OS, TTP, and duration of response were analyzed using Kaplan-Meier estimates and Kaplan-Meier plots as applicable. All other efficacy data were summarized descriptively in the total patient population for each visit by frequency counts and percentages for categorical data or mean, standard deviation, median, minimum and maximum for continuous data, and - if applicable - by pre-treatment with CY (with vs. without) and/or prior therapy (TKIs vs. cytokines) and/or risk group (intermediate vs. favorable). <u>Cellular Immunomonitoring:</u> SAP pre-defined analysis of T-cell response data was conducted in the T-cell response evaluable population. To be included into this population, a patient had to belong to the PP population and for each visit where immunomonitoring was scheduled, at least one of the two routine assays [redacted] had to be evaluable for determination of

	vaccine-induced immune responses for every HLA class I peptide included in IMA901. Additional post-hoc analyses of T-cell responses were performed in the ITT population. Pre-treatment characteristics (e.g. pre-existing T-cell responses, baseline Treg levels) were evaluated in the ITT population and for Tregs also in the PP population (SAP pre-defined analysis). Kinetic data for cellular biomarkers were analyzed in the PP population and for selected cases also in the ITT population. Biomarker Analysis: Pre-treatment values from cellular and non-cellular immunomonitoring were analyzed to identify potiential biomarker signatures predictive for immune responses and prognostic / predictive for clinical responses in IMA901-202 patients. Univariate and multi-variate analyses were performed in the PP population and for selected markers additionally in the ITT population. Safety analysis: Safety was analyzed in the safety population. The duration of exposure and number of vaccinations per patient were summarized. AEs were coded using MedDRA. Only treatment-emergent AEs (TEAEs, i.e. AEs occurring or worsening after the first treatment and before EOS visit) were tabulated; a listing of all non-emergent AEs was additionally provided. Frequency tables by system organ class (SOC) and preferred term (PT) were generated for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of vaccinations, AEs leading to delay of further vaccinations, and TEAEs by NCI-CTC grade (CTCAE Version 3.0). Changes in laboratory values and vital signs from Baseline (last available assessment before the first vaccination) to EOS were analyzed descriptively. Each laboratory value was flagged to show whether it was a value within, below, or above the normal range. The proportions of patients with values in each of these categories (either NCI-CTC or categories based on normal range) at each assessment were summarized. If NCI-CTC grades (Lab criteria in CTC Version 2.0) were available, these were used for frequency tables instead. In addition, changes between Baseline and EOS were summarized with respect to the normal range or NCI-CTC grades. Changes in ECG from Baseline to EOS were analyzed descriptively. Pregnancies were to be reported on an individual basis, but such events did not occur. Moreover, for each laboratory parameter shift tables from Baseline to EOS were provided.

	These tables referred to the shift in NCI-CTC grading (if applicable), otherwise the shifts with respect to the categories based on the normal range were presented. The time course of all laboratory parameters (hematology and biochemistry) was shown graphically using box plots.

Summary and conclusions:

Efficacy results - clinical

Summary of the most important clinical efficacy results:

- OS results of cytokine pre-treated patients in the IMA901-202 study compare favorably to historical data for sorafenib and sunitinib in similar patient populations (cf. synopsis pape 19).
- A strong trend for improved overall survival was observed in patients treated with a single dose of cyclophosphamide (CY) given as immunomodulator before peptide vaccination (cf. synopsis page 18).
- IMA901 has moderate effects on disease control of established tumor lesions and other outcomes influenced by those such as PFS in patients with progressive renal cell carcinoma (cf. synopsis page 16).

The results of the IMA901 study, i.e. favorable effect on overall survival while modest effect on DCR and PFS based on RECIST criteria, are in accordance with other immunotherapy studies suggesting that overall survival is a more appropriate endpoint for immunotherapies in advanced cancer patients, allowing more time for the therapy to take effect.

Altogether, 68 patients were enrolled and randomized in study IMA901-202 with 33 patients (48.5%) having received pre-treatment with CY (referred to as CY group) and 35 patients (51.5%) not having received such a pre-treatment (referred to as non-CY group). In terms of the other planned (stratification-based) subgroups, 26 patients (38.2%) had a "favorable" risk vs. 42 patients (61.8%) with "intermediate" risk, and 28 patients (41.2%) had previously received TKIs vs. 40 patients (58.8%) who were previously treated with cytokines. All randomized patients received study treatment and thus were included in the safety and the ITT population (n=68). Four patients needed to be excluded from the PP population (n=64) according to criteria for major protocol violations specified in the statistical analysis plan.

There were no major demographic differences between patients in the CY group compared to those in the non-CY group and patients in the TKI group compared to those in the cytokine group. In terms of baseline characteristics, patients in the CY-pretreated group tended to have a slightly less favorable prognosis than those in the non-CY group (more advanced tumor stage and less patients with nephrectomy in the CY group). As expected, patients in the post-cytokine group had a more favorable prognosis compared to the patients in the post-TKI group (less advanced tumor stage, less patients with liver metastases, more patients with favorable risk in the cytokine group).

There were some numerical differences between the groups in terms of time since initial tumor diagnosis (longer in the TKI and non-CY group) and time from previous antitumor treatment to Visit C (longer in the cytokine group). However, as these parameters seem to be unrelated to DCR, PFS and OS, an impact on disease outcome is unlikely. Apart from these differences, baseline characteristics were well balanced between the CY and the non-CY group and the TKI and cytokine group.

The analysis of the primary efficacy variable in this study (DCR at week 26 in the PP population; oncologist's central review) showed a disease control rate of 24.6% with an associated 95%-CI ranging from 14.5% to 37.3%. Altogether 15 patients had contributed to that DCR: One patient with confirmed PR, 12 patients with SD (no previous PD), and 2 with SD after previously having experienced PD. The analysis of the primary efficacy variable by subgroups revealed that patients with a "favorable" risk assessment had a slightly better disease control than patients with "intermediate" risk assessment (26.9% vs. 22.9%) and patients with cytokine pre-treatment had a DCR more than twice as high than in that observed in the TKI group (30.8% vs. 13.6%); this difference in disease control was maintained over the complete observation period, ie. from visit 8 onwards to visit 18. Patients randomized to receive CY had a lower disease control rate at week 26 than patients without pre-treatment (20.0% vs. 29.0%), however, no consistent pattern was observed for this comparison when DCR was analyzed over time (Visit 8 onwards to Visit 18).

Logistic regression models were established in order to identify explanatory variables for the primary endpoint (disease control rate at 6 months). However, all dichotomous or continuous input variables failed to show a statistically significant influence of any of these variables on the DCR.

The comparison of this primary analysis results with the stipulated NOELs (18% for patients with previous cytokine therapy, 10% for patients previously treated with a TKI and 15% weighted) showed that all study DCRs were numerically higher than their corresponding NOELs (cytokine group 30.8% vs. 18%; TKI group 13.6% vs. 10%; all patients 24.6% vs. 15% weighted average NOEL). The lower limits of the 95%-CIs for the DCRs in the group of all patients (lower limit: 14.5%) and in the group of patients with previous cytokine therapy (lower limit: 17.0%) were very close to the respective NOELs of 15% (weighted average NOEL) and 18% (cytokine NOEL). These findings based on the lower 95%-CI limit (i.e., results close to exploratory statistical significance) were supported by the supplementary calculation of the exploratory p-values for the difference between the overall DCR (24.6%) and the weighted average NOEL of 15% (p=0.067) and the difference between the DCR in the cytokine group (30.8%) and the corresponding NOEL of 18% (p=0.074). In summary, these results suggest that IMA901 positively influenced disease stabilization at 6 months. However, the magnitude of this effect may be regarded as modest, specifically if compared to DCR rates observed with TKI [Motzer *et al.* 2006] or mTOR inhibitors [Kay *et al.* 2009].

Table A: Comparison of DCR at 6 months (PP) with literature data		
	Comparator value	**Study DCR, % [95%-CI]**
All patients *Weighted average NOEL*	15.0% (p=0.067)†	24.6 [14.5; 37.3]
Prior therapy with TKIs *NOEL*	10%	13.6 [2.9; 34.9]
Prior therapy with cytokines *NOEL*	18%* (p=0.074)†	30.8 [17.0; 47.6]

*: This value served as general NOEL in the original study protocol, before the decision was made in the SAP to additionally calculate a weighted average NOEL (cf. next note) based on new published data from patients having failed TKI therapy which became available during the conduct of the IMA901-202 trial.

†: Exploratory p-value for the difference between study DCR and comparator value

Note: The NOEL for patients pre-treated with cytokines was set at 18% (based on the placebo group of the pivotal sorafenib Phase III study [Escudier *et al.* 2007, Escudier *et al.* 2005]), the NOEL for patients pre-treated with TKIs was set at 10% (based on the placebo group of everolimus study; 2nd line after TKI [Kay *et al.* 2009, Motzer *et al.* 2008]), and the *ad hoc* calculated, patient-weighted NOEL average for this study was 14.7% in the safety/ITT population [((28x10%)+(40x18%))/(28+40)] and 15.0% in the PP population [((24x10%)+(40x18%))/(24+40)].

The formal objective response rate based on the central review in the total population was 1.6% according to RECIST (one patient with confirmed PR); According to the investigators' assessment 3 patients had shown an objective response at any time during the observation period (one patient with confirmed CR and two patients with unconfirmed PR; best overall unconfirmed response rate: 4.8%).

TTP and PFS were identical in this study since no patient had died from causes not related to tumor progression. The median PFSs according to central oncologist's assessment were as follows: PP: 101.0 days with a 95%-CI of 59.0-109.0 days; ITT: 97.0 days with a 95%-CI of 59.0-104.0 days). Generally, all reported confidence intervals were rather broad and overlapping for subgroup comparisons which also results from a relatively small sample size and short follow-up at the timepoint of analysis for this CSR. Numerically, median PFSs were better in the CY group compared with the non-CY-group (101.0 days [62.0; 144.0] vs. 62.5 days [59.0; 124.0], however, the Kaplan-Meier curves were rather similar beyond Day 100. Median PFSs were also better in the cytokine group compared with the TKI group (104.0 days [62.0; 146.0] vs. 61.0 days [59.0; 101.0]), and better in patients with favorable risk compared with those with intermediate risk (134.0 days [62.0; 184.0] vs. 61.0 days [59.0; 104.0]; PP population, 95%-CIs given in square brackets).

The proportional hazards models did not point to statistically significant differences in PFS between CY pre-treatment strata or risk group strata, whereas the explanatory variable "prior

therapy" was at least close to significance in the ITT population (HR=1.721, 95%-CI: [0.999; 2.965], p=0.0505).

The median OS in both the ITT and PP total population was not reached until end of treatment of the last patient (mortality rate of 21/64=32.8% in the PP population and 24/68=35.3% in the ITT population); the 25%-quantile estimate was 291 days in the PP population and 217 days in the ITT population. Median OS will be determined in further follow-up of patients and will be reported separately.

The most remarkable observation in the present study was that patients who have been pre-treated with CY showed a strong trend for prolonged OS compared to patients not pre-treated with CY (HR: 0.568, 95%-CI: [0.238; 1.356]; p=0.2027). No clear difference between these groups was observed for PFS and DCR suggesting a long-term immunomodulatory effect when co-administered with the IMA901 therapeutic vaccine. This potential OS benefit in the CY group compared to the non-CY group cannot be explained by imbalances in baseline characteristics in favor of CY pre-treated patients. On the contrary, patients in the CY group tended to have a slightly less favorable prognosis as they had a lower nephrectomy rate and a more advanced tumor stage at the time of the first tumor diagnosis (more patients with distant metastases and N2 nodal state) compared to the non-CY group.

Overall, OS was better in the CY group, in the cytokine group, and in the favorable risk group; specifically, in these groups (when compared with their respective complementary groups):

i) the absolute mortality rates were lower (PP; CY group 9 patients versus non-CY group 12 patients; cytokine group 8 patients versus TKI group 13 patients; favorable risk group 4 patients versus intermediate risk group 17 patients), and

ii) OS estimates for the first quartile were longer (PP; CY group 399 days versus non-CY group 173 days; cytokine group 481 days versus TKI group 164 days; favorable risk group first quartile not reached versus intermediate risk group 168.5 days).

These effects were apparent in both the PP and ITT population.

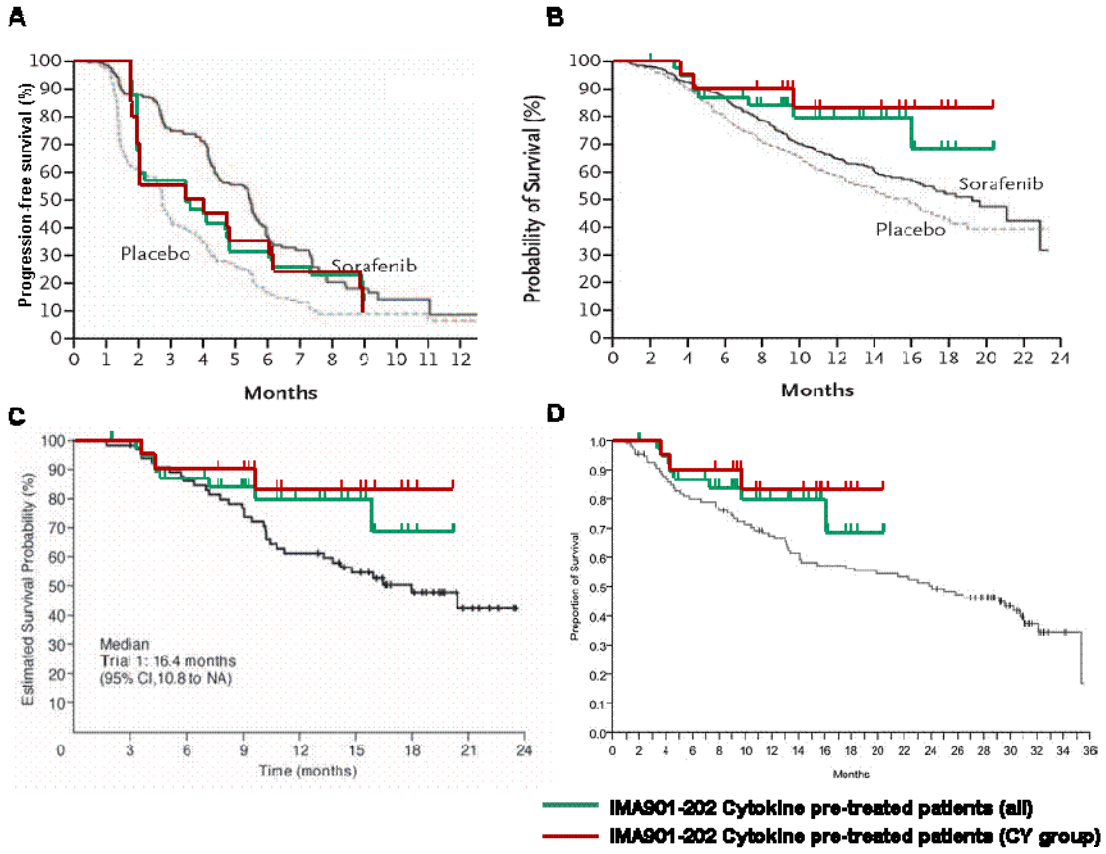
To clarify the outcomes of the survival analysis more precisely, proportional Hazards models were calculated to evaluate the influence of several explanatory variables on survival outcome. In these models, prior therapy (TKI vs. cytokines), risk group (intermediate vs. favorable), total sum of longest diameters of target lesions assessed by the radiologist (continuous), and total number of lesions assessed by the radiologist showed to have a statistically significant influence on the overall survival. Patients with previous nephrectomy showed a trend towards longer OS in the PP population (HR: 0.360, 95%-CI: [0.120; 1.079]; p=0.0682). The DCR at Visit 14 was obviously not associated with the OS.

Being aware of the limitations of a comparison to historical controls, the Kaplan-Meier curves of cytokine pre-treated patients for PFS and OS in study IMA901-202 were compared to the

published survival curves from the Phase III sorafenib study [Escudier *et al.* 2007] and two smaller phase II studies of sunitinib [Motzer *et al.* 2006, Motzer *et al.* 2007]. The patients' baseline characteristics in these studies were in fact highly comparable to those of patients previously treated with a cytokine in the IMA901-202 study in terms of time since initial tumor diagnosis, percentage of patients with nephrectomy, Karnofsky performance status, MSKCC risk score, histological type (clear cell) and location or number of metastatic sites. Of note, in the sorafenib study only 82% of patients have received prior cytokine therapy compared to 100% in the IMA901-202 study. The median PFS was 3.5 months (104 days) in the post-cytokine group of the IMA901-202 and 2.8 months in the placebo group of the sorafenib study. After 6 months 31% of patients in the IMA901-202 cytokine group and about 18% of the patients in the placebo group of the sorafenib Phase III study were progression-free. As can be seen in Figure A/A, the PFS curves of the IMA901-202 cytokine group and the placebo group of the sorafenib Phase III study seem to separate after about 2.5 months indicating that IMA901 may have a positive albeit delayed effect on PFS. Within the IMA901-202 patients no major difference in PFS was observed between the CY pre-treated group and patients in the non-CY group.

Comparison of OS curves showed consistently better OS rates in the IMA901 cytokine group compared to placebo and sorafenib (cf. Figure A/B). Median OS for sorafenib was 19.3 months, whereas the median in IMA901 cytokine patients was not reached at that time (68% of patients were still alive). OS in the IMA901 patients with prior cyclophosphamide treatment appears to be even more favorable (85% of patients still alive when median OS for sorafenib was reached). Similarly, OS in the IMA901-202 study compared also favorably to OS of cytokine refractory patients treated with sunitinib who, again, had very comparable baseline characteristics [Motzer *et al.* 2006, Motzer *et al.* 2007] (cf. Figures A/C and D).

Figure A: Comparison of IMA901-202 cytokine group to historical controls



Note: Comparison of PFS and OS of cytokine pre-treated IMA901-202 patients to historical controls.
(A) PFS of IMA901 treated patients superimposed to PFS of sorafenib 11213 study [Escudier et al. 2007].
(B) OS of IMA901 treated patients superimposed to OS of sorafenib 11213 study [Escudier et al. 2007].
(C) OS of IMA901 treated patients superimposed to OS of RTKC-0511-014 sunitinib study [Motzer et al. 2006].
(D) OS of IMA901 treated patients superimposed to OS of A6181006 sunitinib study [Motzer et al. 2007].

For the TKI subgroup of IMA901 patients a comparison of PFS or OS to historical controls was not performed due to the lack of adequate comparator trials.

In summary, OS results of cytokine pre-treated patients in the IMA901-202 study compare favorably to historical data for sorafenib and sunitinib in very similar patient populations. Furthermore, OS seems to be prolonged by a single administration of cyclophosphamide (believed to exert immunomodulatory effects; see also immunomonitoring section) prior to the first vaccination with IMA901/GM-CSF. Importantly, the survival benefit in patients treated with IMA901 does not seem to be explained by the use of other anti-cancer therapies after study treatment as the majority of patients in the IMA901-202 trial (almost 80% of patients in the post-cytokine group) did not receive any further anti-tumor therapy for RCC (data derived from post-study questionnaire; [redacted]

Taken together, it is concluded that IMA901 has only a moderate effect on disease control of established tumor lesions and other outcomes influenced by those such as PFS while showing

promising effects on overall survival. With a median PFS of 3.5 months in cytokine pre-treated patients, many patients have progressed by the time of the first scan, scheduled at 2 months, such that patients may have reached the progression endpoint before an immune response to IMA901 could turn into effective anti-tumor response. Progression as defined in this protocol may therefore have reflected in part what was in progress at the time of enrollment, and not necessarily progression on therapy. For this reason, PFS may not be an appropriate endpoint when testing the effect of immunotherapy in this patient population. Similar observations, i.e. a moderate, delayed effect of immunotherapy on PFS and positive results for OS, have also been observed in other vaccination trials [e.g. [Small *et al.* 2006] and Phase III IMPACT trial with sipuleucel-T presented at AUA 2009]. Overall survival is therefore regarded to be a more appropriate endpoint for immunotherapies in advanced renal cell cancer patients, because time to death is much later than time to progression events, thus allowing more time for agents such as IMA901 to take effect.

Efficacy results – Routine immunomonitoring

Analysis of vaccine-induced T-cell responses by cellular immunomonitoring was the major non-clinical endpoint in this study. 64 out of 68 (94%) patients in the ITT population in this multi-center trial were evaluable for their immune responses to IMA901 according to pre-defined criteria. An immune responder rate of 64% and a multi-TUMAP response rate of 26% in the PP population were observed (66% and 27% in the ITT, respectively). This observed immunogenicity was comparable to the results obtained from the phase I study IMA901-101 (immune responder 74%; multi-TUMAP responder 30%). A slightly lower rate of immune responses (compared to the phase I trial) was expected due to the lower number of post-vaccination time points analyzed (6 in IMA901-101, 3 in IMA901-202).

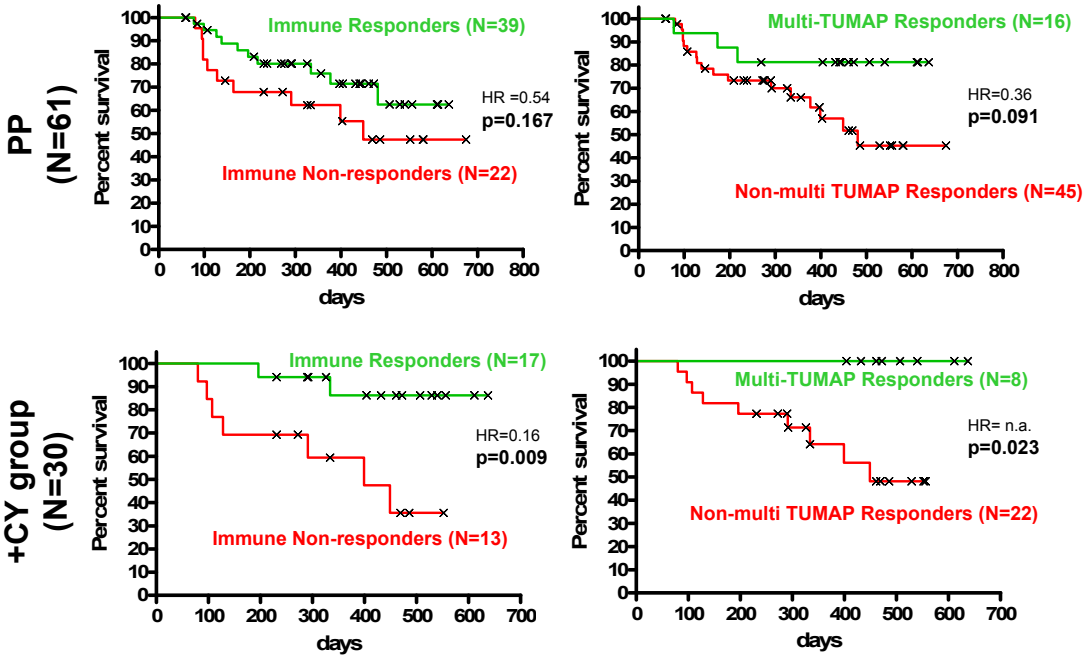
Patients in the CY pre-treated and non-CY study arm and in subpopulations according to 1st line therapy (TKI vs. cytokines) did not differ significantly in their immune response rates. Most relevantly, multi-TUMAP responses were homogeneously distributed. Major prognostic baseline characteristics (MSKCC risk factor, tumor burden) were also not significantly different between immune responders and non-immune responders and between multi-TUMAP responders and patients responding to 0 or 1 TUMAP, arguing against a role of IMA901 induced T-cell responses as a prognostic biomarker.

A major observation from the current phase II study was the observation of a correlation between multi-TUMAP responses and clinical outcome as observed in the phase I study. However, for disease control at 6 months (primary endpoint of the study), the association was only moderate and non-significant compared to the IMA901-101 results (33% disease control for multi-TUMAP responders vs. 21% in responders to 0 or 1 TUMAP) and, correspondingly, PFS did not correlate with immune responses. This discrepancy might be explained by the different patient population, and immunomodulation by CY. Indeed, a trend to better disease control in multi-TUMAP responders was more prominent in patients after 1st line cytokine therapy (44% DCR for multi-TUMAP responders vs. 25% for responders to 0 or 1 TUMAP). Interestingly, the correlation of

disease control with multi-TUMAP responses increases at later timepoints of analysis (20% DCR for multi-TUMAP responders vs. 10% for responders to 0 or 1 TUMAP at V18, after 9 months of treatment, 33% vs. 11% after cytokine 1st line therapy). This observation is in line with recent reports that immunotherapy requires several months to establish an effective anti-tumor activity resulting in a delayed clinical anti-tumor effect [Finke *et al.* 2007, Hamid *et al.* 2007, Weber *et al.* 2008].

In line with this hypothesis, overall survival as the latest and most relevant clinical endpoint correlated with multi-TUMAP responses (cf. Figure B). Hazard ratio = 0.36 in PP; p=0.091 [log rank test]). This association was most obvious in patients pre-treated with CY with no recorded deaths among multi-TUMAP responders (p=0.023 [log rank test], hazard ratio could not be calculated). In the CY arm, immune responses to ≥1 TUMAP also correlated with survival (Hazard ratio = 0.16, p=0.009 [log rank test]). Thus, while in the phase I study (without CY pre-treatment) only multi-peptide responders were associated with clinical benefit (measured as DCR at 3 months), in the CY arm of the phase II study all immune responders (including single and multi-peptide responders) were associated with clinical benefit (measured as OS).

Figure B: Overall survival stratified by immune response variables for the PP population and CY pre-treated patients within the PP



Note: Kaplan-Meier-Plots are shown for overall survival for the PP population stratified by the immune response variables "immune responders (y/n)"(left side) and "multi-TUMAP responders (y/n)" (right side). Additionally, graphs for the subgroup of patients that received CY pre-treatment are shown. p values indicate the error probability calculated by log-rank test (cf. Tables 14.4.7.12.2 / 14.9.7.12.2). HR indicates the estimated hazard ratio (cf. Tables 14.4.7.12.1 / 14.9.7.12.1).

Immune responses tended to a later onset in the patients pre-treated with CY vs. those in the non-CY arm suggesting a change of immune response kinetics induced by CY (patients with immune responses at V5: 26% in +CY arm vs. 39% in –CY arm; V6: 21% vs. 29%; V7: 39% vs. 33%). This observation is in line with observations that CY pre-treatment may support late onset immune responses and leads to an enhancement of secondary but not primary CTL responses [Mitchell *et al.* 1988, Taieb *et al.* 2006].

Efficacy results – Immunomonitoring: Analysis of Treg kinetics

CY was applied three days before initiation of vaccinations with IMA901 based on the hypothesis that CY might reduce levels of regulatory T cells. Indeed, a significant reduction of absolute Treg frequencies in the blood was found in patients pre-treated with CY within 3 days after application (median reduction of -18.1%, p=0.014 [paired Wilcoxon test V1 vs. VC values]) while a similar reduction was absent in non-CY pre-treated patients. This effect was not due to a drop in overall lymphocytes indicating a specific sensitivity to the DNA alkylating substance CY. As predicted by the mechanism of action of CY, the reduction was most prominent in proliferating ($Ki67^+$) Tregs (median reduction -37% from VC to V1 in absolute levels of Tregs expressing Ki67; p=0.001 [paired Wilcoxon test V1 vs. VC values]) in CY pre-treated patients. Therefore, the initial

hypothesis that a single low dose CY intervention is able to reduce peripheral Treg levels has been confirmed.

Efficacy results – Cellular and non-cellular biomarkers

An important secondary endpoint of this study was the analysis of cellular and non-cellular biomarkers before study treatment that may be indicative of the individual immune status of the patients. The primary objective was to investigate whether a biomarker measured pre-treatment may be of relevance for immune and/or clinical responses in IMA901-202 patients.

The most important cellular biomarker assessed were the levels of baseline regulatory T cells. Further exploratory analyses included the measurement and phenotypic characterization of myeloid-derived suppressor cells (MDSCs), expression of TCRzeta and nitrotyrosine on T cells (as markers for dysfunctional T cells) and levels of IL-17^{+} and other cytokine positive T cells after polyclonal stimulation.

Two major observations were made from the analysis of regulatory T cells: 1. Peripheral Treg levels at baseline did not predict immune responses or multi-TUMAP responses in the overall population in contrast to the observations during the phase I study IMA901-101. For the patients pre-treated with CY this was expected due to the fact that CY intervention had a clear modulatory effect on Tregs. On the other hand (as expected), for patients not pre-treated with CY, there was a trend observed that multi-TUMAP responses were more frequent in patients with lower baseline Treg levels resembling the observation in the phase I study (median Treg levels: 1.25% of CD45^{+} cells for multi-TUMAP responders vs.1.51% for responders to 0 or 1 TUMAP). 2. Interestingly, baseline Treg levels were significantly reduced in patients after 1st line sunitinib therapy (median: 15.1 Tregs per µl blood) compared to all other patients (21.3 per µl blood). These results confirm recent publications from preclinical models and clinical observations in RCC patients [Finke *et al.* 2008, Hipp *et al.* 2008, Lenahan *et al.* 2008, Salas *et al.* 2008].

Data for MDSCs, dysfunctional T cells (TCRzeta and nitrotyrosine), and levels of IL-17^{+} and other cytokine positive T cells and the subsequent analyses of their role as potential biomarkers for IMA901 treated patients are summarized in the result section of this CSR.

Data from all biomarkers analyses, including non-cellular biomarkers and multi-variate analyses will be summarized in a separate report.

Safety results

A total of 59 patients (86.8%) had experienced at least one treatment-emergent adverse event and 12 patients (17.6%) at least one SAE during the course of the study. Both the AE and SAE incidence seemed not to be influenced by pre-treatment with CY, since the event rates were similar between the pre-treatment groups. Based on MedDRA preferred terms (PTs), the most frequently reported AEs (i.e., those occurring in ≥10.0% of study patients) were anemia (16 patients, 23.5%), asthenia (11 patients, 16.2%), pyrexia (10 patients, 14.7%), back pain (8

patients, 11.8%), dyspnea (8 patients, 11.8%), and fatigue (7 patients, 10.3%). Striking differences between pre-treatment groups in the incidence of AEs at preferred term level were not seen.

The administration of CY at Visit C (median dose: 600.0 mg; range: 369.0-760.0 mg) was not associated with relevant adverse events, since all AEs considered drug-related to CY were non-serious, of mild intensity only, and quickly resolved (nausea, fatigue, and vomiting; 3 patients affected).

A total of 25 patients (36.8%) experienced AEs that were considered drug-related (i.e. possible, probable, or certain relationship) to IMA901 and/or GM-CSF. This incidence was comparable between pre-treatment groups (13 patients [39.4%] in the CY group vs. 12 patients [34.3%] in the non-CY group). As expected, the majority of the events occurred within the SOC "general disorders and administration site conditions" (17 patients, 25.0%); other SOCs including more than one patient were "skin and subcutaneous tissue disorders" (5 patients, 7.4%), "blood and lymphatic system disorders" (3 patients, 4.4%), "gastrointestinal disorders" (3 patients, 4.4%), and "immune system disorders" (2 patients, 2.9%). The drug-related AEs occurring in more than 1 patient at preferred term level were "injection site erythema" (5 patients, 7.4%), "Injection site pruritus" (4 patients, 5.9%), "pyrexia" (4 patients, 5.9%), "nausea" (3 patients, 4.4%), "chills" (2 patients, 2.9%), "fatigue"(2 patients, 2.9%), "injection site edema" (2 patients, 2.9%), "injection site irritation" (2 patients, 2.9%), "injection site pain" (2 patients, 2.9%), "injection site reaction" (2 patients, 2.9%), and "rash" (2 patients, 2.9%).

Most of the "related" adverse events were mild to moderate in severity. Only 3 patients experienced severe (Grade 3) adverse events considered related to study drug, these were one case each of anemia, neutropenia, and the below mentioned local hypersensitivity reaction respectively. The only life-threatening (Grade 4) event with suspected relationship to IMA901 and/or GM-CSF was the below mentioned anaphylactic reaction in one patient.

Serious adverse events were documented in 12 patients (17.6%). The SAE incidence was comparable between pre-treatment groups: 5 patients (15.2%) in the CY group and 7 patients (20.0%) in the non-CY group. The majority of SAEs were fully resolved by the end of the study. Only 2 SAEs in 2 patients were considered related to IMA901 and GM-CSF, these were an anaphylactic reaction with laryngeal edema, which quickly resolved upon symptomatic treatment (most likely caused by GM-CSF as assessed by a basophil degranulation assay and a leukotriene release assay) and a local hypersensitivity reaction without systemic signs which also resolved after anti-allergic treatment. The latter patient had continued study treatment until the scheduled end of the study without any further signs of intolerance (and with no prophylactic therapy). All other SAEs were comprehensibly not related to study drug treatment.

Altogether 24 patients had died during the course of the study; 15 of them died during the follow-up period (therefore no primary reason for death provided) and 9 died within the treatment period (all due to tumor progression). No treatment-related deaths were reported.

In summary, 12 study patients (17.6%) experienced AEs that resulted in permanent premature treatment discontinuation. Notably, only one of these AEs (anaphylactic reaction most likely caused by GM-CSF, see above) was considered drug-related, indicating that the drug survival in this study was not relevantly influenced by the safety profile of the vaccinations.

The analysis of the other safety variables (safety laboratory data, vital signs, and ECG) did not indicate relevant or unexpected risks of study treatment with CY, IMA901 and GM-CSF.

Overall conclusions:

- **IMA901 positively influenced disease stabilization at 6 months.** Overall, the comparison of observed disease control rates (DCR) with the pre-defined no effect levels (NOELs) derived from historical controls showed that the study DCRs after 6 months were always numerically higher than their corresponding NOELs (cytokine group 31% vs. 18%, p=0.074; TKI group 14% vs. 10%, p=0.760; all patients 25% vs. 15% weighted average NOEL, p=0.067).
- **A strong trend for improved overall survival was observed in patients treated with a single dose of cyclophosphamide (CY) before peptide vaccination.** A relatively low dose of cyclophosphamide (300mg/m2) was applied once 3 days before the first vaccination with the hypothesis that the CY´s immunomodulatory properties may positively impact on the clinical effect of a peptide-based therapeutic cancer vaccine. In fact, an obvious clinical albeit not significant difference was seen between the 2 groups in terms of overall survival (15.8 months median OS in the no-CY group versus median OS not reached (>21 months) in the CY group (p=0.20).
- **OS results of cytokine pre-treated patients in the IMA901-202 study compare favorably to historical data for sorafenib and sunitinib in similar patient populations.** The median OS for sorafenib has been reported at 19.3 months in a patient population almost identical to the post-cytokine group patients studied in the IMA901-202 trial. Median OS in these patients in IMA901-202 was not reached at the time of database lock with about 68% of patients being alive at 19.3 months. OS seems to be further prolonged by a single administration of cyclophosphamide prior to the first vaccination with IMA901/GM-CSF (85% of patients still alive at 19.3 months). Similar results were seen when the IMA901 survival data were compared to studies of sunitinib in a comparable patient population. Importantly, the favorable survival observed after treatment with IMA901 is not explained by the use of other post study anti-cancer therapies as only a minority of patients in the IMA901-202 trial received any further systemic therapy.
- **IMA901 appears to have a moderate albeit delayed effect on PFS as compared to historical control.** Median observed PFS was 3.5 months in the cytokine group (3.8 months in the subgroup pretreated with cyclophosphamide) of the IMA901-202 study compared to 2.8 months in the placebo group and 5.5 months in the sorafenib group of the sorafenib pivotal study. PFS curves of the IMA901-202 cytokine group and the placebo group of the sorafenib

Phase III study seem to separate after about 2-3 months indicating that IMA901 may have a positive albeit delayed effect on PFS. After 6 months, approximately 31% of patients in the IMA901-202 cytokine group were progression-free compared to about 18% of the patients in the placebo group and about 38% of the patients in the sorafenib group of the sorafenib Phase III study.

- **An immune responder rate of 64% and a multi-TUMAP response rate of 26% in the PP population were observed.** The observed immunogenicity and the immunogenicity of the single TUMAPs contained in IMA901 were comparable to the results obtained from the phase I study IMA901-101.
- **Multi-TUMAP responses correlated significantly with overall survival.** In the overall immune-evaluable population, multi-TUMAP responders showed a strong trend to better overall survival. For patients after a single low dose of cyclophosphamide as immunomodulatory agent, this correlation was strongest with no deaths occurring during the observation time among 8 multi-TUMAP responders. In the +CY arm immune responses to 1 TUMAP were also associated with longer survival. The better correlation of multi-TUMAP responses with later evaluation of clinical endpoints (survival and disease control after 9 months) is in line with recent reports of delayed anti-tumor efficacy observed for immunotherapeutic interventions in cancer.
- **A single application of low-dose CY significantly reduced absolute blood Treg levels within 3 days.** The median change from baseline was -18.1% in the +CY arm (p=0.014) and was most prominent among the proliferating ($Ki67^+$) Treg subset (median reduction of -37%, p=0.001), as predicted for a DNA alkylating agent such as cyclophosphamide.
- **IMA901/GM-CSF was overall safe and well tolerated.**
  - The most frequently reported AEs *independent of relationship* were anemia (24%), asthenia (16%), pyrexia (15%), back pain (12%), dyspnea (12%), and fatigue (10%).
  - Most of the adverse events considered *at least possibly related* to IMA901 and/or GM-CSF were injection site reactions with 15 (22%) patients experiencing at least one type of injection site reaction. Except for one patient, local reactions were mild or moderate in severity.
  - Only two serious adverse events related to IMA901/GM-CSF were reported: a life-threatening anaphylactic reaction with laryngeal edema most likely caused by GM-CSF and a pronounced local reaction without systemic signs. Both events quickly resolved without sequelae after symptomatic anti-allergic treatment.