1 TITLE PAGE

Study title:	An open label, multicenter Phase 1-2 study to investigate the effectiveness, safety and immunogenicity of a monotherapy with intradermal IMA910 plus GM-CSF following pre-treatment with low-dose cyclophosphamide in advanced colorectal carcinoma patients who have successfully completed a 12 week first-line treatment with oxaliplatin-based chemotherapy
Test drug:	Peptide-based colorectal cancer vaccine IMA910
Indication:	Advanced colorectal cancer (CRC)
Study dates:	First patient in (date of first HLA-IC): 11-JUN-2008 Last patient out (date of last study visit): 11-JAN-2011
Development phase:	Phase 1-2
Sponsor's name and address:	immatics biotechnologies GmbH Paul-Ehrlich-Strasse 15 D-72076 Tuebingen, Germany Phone: +49-7071-5397-0 Fax: +49-7071-5397-900 Web: www.immatics.com
Study number:	IMA910-101
EUDRACT No.	2007-005666-12
Investigator(s):	Overall co-ordinating investigator (according to German Drug Law) was Prof. Dr. Dr. med. Frank Mayer, University of Tuebingen, Germany. [redacted]
Date:	CSR Full Version – Final (27-SEP-2012)
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2 SYNOPSIS

Title of the study:	An open label, multicenter Phase 1-2 study to investigate the effectiveness, safety and immunogenicity of a monotherapy with intradermal IMA910 plus GM-CSF following pre-treatment with low-dose cyclophosphamide in advanced colorectal carcinoma patients who have successfully completed a 12 week first-line treatment with oxaliplatin-based chemotherapy.
Investigators:	Co-ordinating investigator (according to German Drug Law) was Prof. Dr. Dr. med. Frank Mayer, University of Tuebingen, Germany. [redacted]
Study centers:	A total of 51 study sites in 9 European countries were initiated, 41 sites had screened at least one patient, and 24 centers had actually enrolled one or more patients. [redacted]
Publications (references):	The essential safety results of the first 6 enrolled patients (according to the pre-specified enrollment plan) have been reported in the IMA910-101 Interim Safety Report (final version, released 12-DEC-2008). First clinical and immunological results of the study were presented as posters at the ASCO Gastrointestinal Cancers Symposium 2012 (Abstract ID 555). Clinical (mature OS) and additional immunological results were presented in 2 oral abstract sessions at the ASCO Annual Meeting 2012 (Abstracts ID 2522 and ID 3530).
Period of study:	First patient in (date of first HLA-IC): 11-JUN-2008 Last patient out (date of last study visit): 11-JAN-2011
Clinical phase:	Phase 1-2
Objectives:	<u>Primary objective:</u> The primary objective of the study was to determine whether IMA910 as single agent with GM-CSF as adjuvant following pre-treatment with single-dose cyclophosphamide (CY) is safe and shows sufficient anti-tumor effectiveness in patients with advanced CRC to warrant further development.

	Secondary objectives: Secondary objectives of this study were safety, immunological parameters, and additional effectiveness endpoints. Moreover, it was investigated if and to what extent the additional application of imiquimod at each vaccination time will influence the immune response, clinical effectiveness and safety of IMA910 plus GM-CSF (2^{nd} cohort of patients, defined as per Amendment No. 7).
Methodology (design of study):	This was a multicenter, open-label, 2 cohort, Phase 1-2 study in patients with locally advanced and/or metastatic colorectal cancer (CRC) to investigate the effectiveness, safety and immunogenicity of the tumor multi-peptide vaccine IMA910 plus GM-CSF (1^{st} cohort) given as monotherapy after successful (CR, PR or SD) completion of a 12 week first-line oxaliplatin-based standard chemotherapy (e.g., FOLFOX or XELOX). In addition, safety, immunogenicity and effectiveness of IMA910 plus GM-CSF in combination with topically administered imiquimod were investigated in a 2^{nd} cohort of patients. Prior to vaccination, all study patients in both cohorts received a single dose of cyclophosphamide (CY) as an immune modulator 3 days before the start of vaccination. The planned maximum duration of the regular study (excluding HLA typing at Visit A) in either cohort was approx. 43 weeks (i.e., a maximum of 45 days for Screening [starting with Visit B, Day -45 to Day -4] and CY administration at Visit C [Day -3], 33 weeks of vaccination treatment with 16 vaccinations in total [first vaccination at Visit 1, Day 1], and 4 weeks of follow-up [EOS, Visit 17]). Subsequently, patients were followed for response to subsequent treatments (chemotherapies with or without targeted agents) and survival after the last regular study visit until death. Generally, all patients experiencing disease progression according to RECIST during the course of the study (investigator's assessment) were to be withdrawn from further study treatment. In order to ensure maximum safety for the first 6 patients, a specific enrollment plan was stipulated to protract the initial enrollment (and thus to achieve sufficient exposure periods for proper safety assessment). After successful completion of the screening procedures started at Visit B, all patients received a single infusion of CY (300 mg/m^2) 3 days prior to the first vaccination. Subsequently, all patients were to receive 7 vaccinations in the induction period (Visits 1-7; Day 1 to Day 56) and a further 9 vaccinations at 3-week intervals in the maintenance period (Visits 8-16; Day 57 to Day 225). An end of study (EOS) visit was to be performed 4

	weeks after the last regular vaccination (Visit 17; Day 253). Patients sequentially allocated to the 2nd cohort were treated exactly in the same way as patients of the 1st cohort, but additionally received a dermal application of imiquimod 10-20 minutes after and at the same site of the application of IMA910 at all vaccinations visits and - from Visit 3 onwards - another application of imiquimod 24 hours (up to 48 hours at the latest) after the respective IMA910 administration (applied by the patients at home). All effectiveness and immunological endpoints, overall safety, biomarkers, and analyses of tumor tissue / core needle biopsies were analyzed separately for the 1st and the 2nd cohort and additionally overall for both cohorts. Tumor assessments were performed by either CT or MRI according to RECIST (Version 1.0 for investigators and Version 1.0 including some specific clarifications and more precise criteria taken from RECIST Version 1.1 (e.g. rules on how to handle missing and inevaluable time point assessments, rules for the evaluation of patients with only “non-measurable disease”, clarifications for the term “unequivocal”, definitions for “new lesions”) for the central review). A pre-chemo CT/MRI was to be taken during local standard routine procedures before the start of first-line oxaliplatin-based standard chemotherapy. To assess tumor response at Baseline (Visit B) radiological imaging by CT/MRI of chest and abdomen/pelvis was to be performed at the end of the last first-line oxaliplatin-based chemotherapy cycle (preferably in the second week following start of the last cycle of standard chemotherapy for a regimen with a cycle of 2 weeks (e.g. FOLFOX) or in the third week for a regimen with a cycle of 3 weeks (e.g. XELOX)). Thus, the start of vaccination could be close to the end of chemotherapy. In patients with known or suspected bone metastases of the extremities correlative imaging (X-ray, CT or MRI) of the respective areas was to be performed, as well as in case of suspected brain metastases CT/MRI of the brain was to be undertaken. Tumor imaging was to be performed at intervals of approx. 9 weeks (Visits 8, 11, and 14) until (including) the last scheduled Visit 17 (EOS) or until premature study termination due to disease progression. 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 to be performed at Visits 14 and 17. 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. Blood sampling for cellular immunomonitoring (i.e., T-cell responses to peptides contained in IMA910 and analysis of other immune cell populations potentially influencing T-cell responses such as regulatory T cells) was performed 3 days before the first vaccination, on the day of the first vaccination, and then at Visits 4-9 (including additional Visit 7a) and finally at Visit 14 or EOS (whatever came first). The T-cell response was analyzed by MHC multimer assay and 2 methods of intracellular cytokine staining (ICS). Non-cellular immunomonitoring consisted of serum level analysis of antibodies directed against peptides contained in IMA910 and against MHC/peptide complexes thereof, and analysis of molecules with suspected influence on immune response, such as TGFβ. Non-cellular immunomonitoring was performed at Visit B and Visits 1, 11, and 14. Biomarkers were only sampled at Visit B and EOS visit. Optionally, core needle biopsies of metastases could be sampled at Visit C and Visit 11 in order to investigate gene expression and expression of molecules with suspected influence on immune response. Other tumor samples taken during medically indicated interventions before the start and during the trial including the non-interventional follow-up phase could be collected. Safety assessments in this study included continuous adverse event monitoring as well as scheduled investigations of physical examination, vital signs and lab assessment of hematology, blood chemistry and urinalysis at regular intervals up to the last study visit. In addition, a 12-lead ECG and laboratory assessment of clotting parameters were performed at Visit B and EOS visit. Pregnancy testing was performed according to applicable local legislation (at the very least at Visit B and at EOS). An independent Data Safety Monitoring Board (DSMB), consisting of 3 experts in the field of oncology and immunology, was established to monitor safety. Data were provided to the DSMB about every 6 to 8 weeks in the initial study phase (until 26-MAY-2009) and then at prolonged intervals (about every 2 to 4 months) until the end of the study and the final meeting on 05-DEC-2011. Thus, a total of 13 meetings took place for the review of safety data. 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. [redacted]

	[redacted]
Number of patients:	A total of 70 patients for the 1st cohort (to yield approx. 56 evaluable patients; see Section 9.7.2 for sample size estimation) and about 20 additional patients for the 2nd cohort were planned to be enrolled at approx. 45 experienced medical oncology investigational sites in 8-10 European countries (Western, Central and Eastern Europe). In fact, 66 and 26 patients were enrolled in the 1st and 2nd cohort, respectively, at 24 study sites (Germany: 5, UK: 5, Hungary: 5, Poland: 3, Latvia: 2, Romania: 2, Belgium: 1, and Serbia: 1).
Diagnosis and main criteria for inclusion:	HLA-A*02-positive patients suffering from unresectable, locally advanced and/or metastatic colorectal cancer and having completed 12 week first-line oxaliplatin-based standard chemotherapy (e.g. FOLFOX or XELOX) with either complete or partial response or stable disease as the outcome were eligible for study treatment. Patients improving to a resectable status under first-line chemotherapy were not to be enrolled but to undergo surgical resection of residual tumor mass. The main criteria for inclusion were: • HLA-A*02-positive, • Histologically confirmed CRC with radiological evidence (CT/MRI) of unresectable locally advanced and/or metastatic CRC prior to 12 week first-line oxaliplatin-based standard chemotherapy, • 12 week first-line chemotherapy with an oxaliplatin-based regimen according to an established standard protocol (e.g. FOLFOX or XELOX) administered at the following minimum dosages over this 12 week period: Oxaliplatin 400 mg/m^2, fluorouracil (5FU) 10.000 mg/m^2 or capecitabine 84.000 mg/m^2 (a time window for application of first-line chemotherapy of +4 weeks was allowed), • Response (CR, PR) or stabilization (SD) following a 12 week first-line oxaliplatin-based standard chemotherapy shown by radiological evidence (CT/MRI after last cycle of first-line oxaliplatin-based standard chemotherapy compared to CT/MRI taken before start of first-line oxaliplatin-based standard chemotherapy), • Patients willing to accept a chemotherapy-free interval under close observation (CT or MRI scans performed every 9 weeks), • Maximum period between start of study treatment and start of the last cycle of standard chemotherapy (= first day of last cycle of standard

	chemotherapy) was 42 days; minimum period was 18 days, • Currently no other standard therapy indicated (amendment only applicable for Germany), and • Karnofsky Performance Status ≥80%. All inclusion/exclusion criteria are provided in Section 9.3.1 and Section 9.3.2.
Duration of treatment:	The regular study duration for individual patients in IMA910-101 comprised regularly 18-42 days of screening (excluding HLA-typing), 33 weeks of treatment (16 vaccinations) and 4 weeks follow-up (EOS). Thus, the period between start of screening and end of trial was about 10 months per patient. Patients were withdrawn from study upon progressive disease as assessed by the local investigator. However, all study patients were to be followed for overall survival, and those who signed revised ICF according to Amendment No. 6 were additionally to be followed for response to subsequent treatments (chemotherapies with or without targeted agents and surgeries) after EOS visit until death.
Study therapy, dose and mode of administration, and batch number:	No blinding procedures were performed in this open-label study. <u>1) Pre-treatment with cyclophosphamide (all patients)</u> All patients were administered a single infusion of i.v. CY (300 mg/m^2) 3 days before the first vaccination as an additional immunomodulator (Visit C). [redacted] <u>2) Mode of vaccination (all patients)</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 5.78 mg IMA910, which is composed of 10 HLA Class I-binding TUMAPs, 3 HLA Class II-binding TUMAPs, 1 synthetic HLA Class I-binding peptide [redacted] and 2 non-active ingredients. <u>3) Vaccination schedule (all patients)</u> All study patients were to receive a total of up to 16 vaccinations. The vaccination schedule included an "induction period" (7 vaccinations at Days, 1, 2, 3, 8, 15, 22, and 36 = Visits 1-7) and a "maintenance period" with a further 9 vaccinations given at 3-week intervals (Visits 8-16). Finally, an EOS visit (Visit 17) was performed 4 weeks after the last vaccination. [redacted]

	[redacted] 4) Use of imiquimod in patient Cohort 2 (N=26) As per Amendment No. 7, an additional study treatment adjuvant was introduced for all subsequently enrolled patients. These patients received additional topical treatment with 250 mg imiquimod cream (12.5 mg imiquimod) 10 minutes (up to 20 minutes) after each IMA910 application (Visits 1-16) and from Day 3 (Visit 3) onwards the patients were to additionally apply 250 mg imiquimod cream approx. 24 hours (up to 48 hours at the latest) after the respective IMA910 application at home. [redacted]
Reference therapy:	Not applicable in this non-controlled, 2-cohort study; historical controls were used to further assess the study outcome.
Criteria of evaluation:	Primary safety endpoint (Phase 1 equivalent): Primary safety endpoint was the safety assessment with special emphasis on the inclusion of the first 6 patients enrolled according to a pre-specified enrolment plan. Primary effectiveness endpoint (Phase 2 equivalent): The primary effectiveness endpoint according to the clinical study protocol was defined as the disease control rate (DCR=CR+PR+SD) at Visit 14 (= 27 weeks of vaccination) according to RECIST as described in Section 9.5.3. In addition, any deaths were considered as events for the assessment of DCR. Secondary endpoints: • Time to progression, • Progression-free survival (PFS), • Overall survival (OS), • DCR at Visit 17 (EOS), • Best overall disease control, • Tumor response rates (ORR, CR, PR) and stable disease (SD) rate at Visits 14 (= 27 weeks of vaccination) and Visit 17 (EOS), • Duration of response, • Cellular immunomonitoring (analysis of immune cell populations), • Non-cellular immunomonitoring (antibodies and immune-modulating molecules),

	• Biomarkers, • Analysis of tumor tissue (optional), • Overall safety, • Response to subsequent treatments, • Effect of imiquimod on immune response. All effectiveness and immunological endpoints, overall safety, biomarkers and analyses of tumor tissue / core needle biopsies were analyzed separately for the 1st and the 2nd cohort and additionally overall for both cohorts.
Statistical methods:	Generally, effectiveness and immunological endpoints, overall safety, biomarkers and analyses of tumor tissue / core needle biopsies were analyzed separately for the 1st and the 2nd cohort and additionally overall for both cohorts. Effectiveness and immunological data were analyzed in the PP and ITT population, safety data in the safety population. <u>Primary safety endpoint:</u> The primary safety endpoint (Phase 1 equivalent) was the safety of the first 6 patients (1st cohort) who were enrolled according to a specific enrollment plan, closely monitored by the Sponsor and an independent DSMB. The results of this successfully finished study phase have been reported elsewhere [redacted] <u>Primary effectiveness endpoint:</u> The analysis of the primary effectiveness endpoint (Phase 2 equivalent) was performed on all patients enrolled into the PP (including those 6 patients who were initially enrolled according to the enrolment plan). The PP population consisted of all enrolled patients who had received at least 6 vaccinations, had at least one post-baseline tumor assessment and did not exhibit major protocol violations (for more detailed definitions see Statistical Analysis Plans). In addition, the analyses were repeated in the ITT population. No formal sample size calculation was performed for this study. As reference, a "no effect level" (NOEL) was set derived from the PFS curve of the chemotherapy-free interval cohort (Arm 2) of the OPTIMOX2 study (initial estimate of 21% at Week 41 based on early OPTIMOX2 data; this was later updated to 17% at Week 42 based on the final OPTIMOX2 publication). With an expected DCR of 35% at Visit 14 (27 weeks of vaccination), 56 evaluable patients were needed to allow for the calculation

	of a 2-sided 95%-CI with a precision of ±12.5%. In order to allow for a drop-out rate of 20%, 70 patients were planned to be enrolled. Analyses of DCRs (as well as other tumor response assessments) were performed separately by investigator's assessment (based on RECIST 1.0), radiologist's assessment, and oncologist's assessment (considering some modifications provided in RECIST Version 1.1). For DCRs, exact 95%-confidence intervals were generated. <u>Secondary clinical effectiveness endpoints:</u> During the past years accumulating evidence has suggested that cancer vaccines, in contrast to classical anti-neoplastic treatments, are likely to benefit long-term outcome such as overall survival rather than to exert direct tumor shrinkage and related outcomes. It was therefore decided to complement the originally planned overall survival analysis as defined in the clinical study protocol with an OS comparison of IMA910-101 patients with an appropriate historical control. An agreement could be made with the MRC group to use data from patients enrolled in Arm C of the COIN study, which thereby served as appropriate, best available historical control (see Section 9.7.1.3). This analysis was pre-planned in a statistical analysis plan before unblinding OS and response data of the Arm C COIN patients. For this comparison, a propensity score and Mahalanobis distance based matching was performed in order to ensure maximum homogeneity of patient groups. All clinical secondary endpoints were analyzed in the PP and ITT population. The overall tumor assessment was summarized in tables for Cohort 1, Cohort 2 and overall by treatment and total including ORR, CR, PR, and SD rate at visit 14 and 17 and DCR at visit 17. Additionally, DCR at Visit 8 and 11 were tabulated. Absolute and relative frequencies and 95%-CIs were presented. The analyses of the overall tumor assessment were conducted separately for the investigator, independent radiologist and oncologist. The best overall response was summarized in a frequency table containing absolute and relative frequencies and their 95%-CIs for all visits, thus including CR, PR, and SD rates. Best overall disease control was summarized in a frequency table containing absolute and relative frequencies and their 95%-CIs. The number and percentage of patients who were best/not best overall disease controlled was tabulated. Time-dependent endpoints (duration of response, time to progression, progression-free survival) were calculated based on the assessment of the

	independent oncologist (primary analysis) and the independent radiologist and the local investigator (sensitivity analyses), where applicable. These endpoints were graphically presented using Kaplan-Meier plots. In addition, the median time/duration as well as 25% and 75% quantiles and the corresponding 95%-CIs were calculated by cohort and total using Kaplan-Meier estimates. Generally, 3 different time points were used as start for the calculation of the duration of periods: 1=Visit C, 2=Date of baseline imaging, and 3=start of first-line chemotherapy. Further exploratory analyses included the relationship between disease control, OS and PFS and different explanatory variables (using a logistic regression model). <u>Cellular Immunomonitoring:</u> Cellular immunomonitoring included the analysis of T-cell responses to peptides contained in IMA910 (description of T-cell responses, percentage of multi-peptide responders, number of TUMAPs to which a response can be detected) and analysis of other immune cell populations that may influence T-cell responses such as Tregs. In addition, the potential effects of imiquimod on immune responses were analyzed. The immunomonitoring analyses were performed stratified for Cohort 1, Cohort 2, and overall (Cohort 1 and 2) and were done for each specific assay (i.e., MHC multimer Class I assay, ICS Class I assay, and ICS Class II assay), for the combination of the Class I assays, and for the combination of Class I and Class II assays. Analyses were performed in the ITT and PP populations according to SAP. <u>Safety analysis:</u> Safety was analyzed in the safety population. The duration of exposure relative to different start points and number of vaccinations/imiquimod administrations per patient were summarized. AEs were coded using MedDRA Version 11.1. Frequency tables were generated by system organ class (SOC) and preferred terms (Cohort 1, Cohort 2, total population) for all AEs and for treatment-emergent AEs; tables were further separated by drug-related AEs, serious AEs (SAEs), AEs leading to delay or permanent discontinuation of vaccinations, and AEs by NCI-CTC grade (using CTCAE Version 3.0). Laboratory values were flagged to show whether it is a value within, below or above the normal range. In addition, all laboratory values outside the normal range were marked by investigators as "clinically relevant" or "not clinically relevant". NCI-CTC grades were derived for those

	parameters where NCI-CTC grading was available using the NCI-CTC Lab criteria (CTCAE Version 3.0). Summary statistics of the laboratory values by treatment group and for the total population were produced together with absolute and relative changes from Baseline (last available measurement before CY), as well as shift tables for NCI-CTC grades from Baseline to EOS / worst values. In addition, vital signs and ECG data were tabulated descriptively. Pregnancies were to be reported on an individual basis, however, such events did not occur.

Summary and conclusions:

[redacted]

- Patient population

A total of 92 patients were enrolled in the study at 24 study sites (66 in Cohort 1 and 26 in Cohort 2) and included in the safety/ITT population; 82 patients (62 in Cohort 1 and 20 in Cohort 2) were valid for the PP analyses. The most frequently detected major protocol deviation, which led to exclusion from the PP population, was "progressive disease at Baseline" as determined by the independent radiological and oncological review.

- Demographic characteristics

The study patients (all of them of Caucasian origin) were on average 64.5 $\pm$ 9.2 years old; 66.3% were males. The majority of patients in either cohort presented at Baseline with a KPS of 100% (60.6% and 61.5% in Cohort 1 and Cohort 2, respectively). The mean age in Cohort 1 was slightly higher compared to Cohort 2 (65.0 $\pm$ 9.5 years vs. 63.2 $\pm$ 8.3 years); no other relevant imbalances were recorded in the demographic characteristics. Patterns of prior and concomitant diseases and medications were as expected and were also similar between the 2 cohorts.

- Tumor disease characteristics

The colon was the most common location of the primary tumor (53.3% of all study patients), with 29.3% and 23.9% of tumors located on the left and right side of the colon, respectively. Approximately one-third of primary tumors (34.8%) were located in rectum and 12.0% had other (e.g. caecum, rectosigmoid junction, ano-rectal) locations. The histological type was "mucinous" in 35.2% of study patients.

The majority of study patients (72.8%) underwent primary tumor resections. A total of 16 patients (17.1%) underwent (adjuvant) chemotherapy prior to the study-related oxaliplatin-based first-line chemotherapy. FOLFOX 4 (67.4%) was the most frequently applied oxaliplatin-based first-line regimen

in either cohort. The median duration of first-line chemotherapy was 88.5 days [min.–max.: 70-126]. The mean time from the first day of last chemotherapy cycle until the first administration of study medication (CY) at Visit C was 29.2 ± 7.6 days in the total population.

All but one patient (1.1%) had distant metastases prior to start of oxaliplatin-based first-line chemotherapy. 31.5%, 31.5% and 35.9% of patients had one, two and three or more organs affected with metastasis, respectively. Metastases were most frequently localized in the liver (80.4%), lymph nodes (51.5%) and lungs (44.6%). The mean number of organs affected with metastasis were 2.1 ± 1.0 before start of first-line chemotherapy. Following 12 weeks of first-line chemotherapy 1.1%, 37.0% and 62.0% of patients had CR, PR and SD, respectively according to the local site investigator. Based on the central review, 5.6%, 35.6%, 27.8% and 31.1% of patients had none, one, two and three or more organs affected with any lesions (target or non target), respectively, at baseline (after 12 weeks of first-line chemotherapy). The mean number of organs affected with any lesions was 2.0 ± 1.2 at baseline.

The analysis of tumor disease characteristics suggested that patients enrolled in Cohort 2 had more advanced disease (more organs affected with lesions; 2 organs with lesions: 32.0% in cohort 2 vs. 26.2% in cohort 1; 3 or more organs with lesions: 32.0% in cohort 2 vs. 30.8% in cohort 1; mean number of affected organs: 2.40 ± 1.53 in cohort 2 and 1.85 ± 1.05 in cohort 1) at the beginning of the study than patients in Cohort 1. However, patients in Cohort 1 had more right-side colon cancers and more mucinous tumors (which might indicate more aggressive tumors) than patients in Cohort 2. However, the impact of these factors on prognosis is very difficult to estimate, since some imbalances were in favor of Cohort 1 and some in favor of Cohort 2.

- Disease control rate at Visit 14

The DCR at Visit 14 (i.e., after approximately 26 weeks of study treatment) in the per-protocol population is summarized in Synopsis Table A. Results in the ITT population were similar.

Synopsis Table A: DCR at Visit 14 (26 weeks) in the PP population

	Investigator n/N (%) [95%-CI]	**Oncologist n/N (%) [95%-CI]**
Cohort 1	9/61 (14.8) [7.0; 26.2]	5/55 (9.1) [3.0; 20.0]
Cohort 2	1/18 (5.6) [0.1; 27.3]	2/19 (10.5) [1.3; 33.1]
All patients	10/79 (12.7) [6.2; 22.0]	7/74 (9.5) [3.9; 18.5]

These data showed that the overall DCR was numerically higher based on the investigator's assessment than based on the central review, and that investigators tended to assess a numerically higher DCR in Cohort 1 and a lower DCR in Cohort 2, whereas no differences between cohorts were seen in the central review (oncologist's assessment based on the independent radiology assessment and additional relevant clinical data). However, the comparability of cohorts was limited due to the low

number of cases enrolled in Cohort 2 and the presence of some imbalances in terms of some baseline disease characteristics. The main predefined goal of the implementation of the Cohort 2 was the investigation of immune response. The external reference value for comparison of DCR at visit 14 was the PFS rate at the same time point in Arm 2 of the OPTIMOX2 study (17%; assessed locally by OPTIMOX2 investigators). Thus, the investigator's assessments of DCR in IMA910-101 (13% in the total population) appeared to be fairly comparable to the DCR observed in OPTIMOX2 Arm 2. However, the OPTIMOX2 Arm 2 patients seemed to have better prognosis due to more patients with only one organ affected with metastasis (52% vs. 35%), better responses to initial chemotherapy (60% vs. 42%), and more curative resections after initial chemotherapy (20% vs. 0%).

- DCR at other timepoints and PFS

Expectedly, the DCR decreased over time in the total population from 39.0% at Visit 8 (after approximately 9 weeks of study treatment) to 5.4% at Visit 17 (after approximately 37 weeks of study treatment oncologist's assessment). Based on the oncologist's assessments median PFS using first day of first-line chemotherapy as start point for calculation was 175.0 (95% CI: [168.0; 188.0]. These findings based on the investigator's assessment were similar to the oncologist's assessment.No relevant differences between cohorts were observed in these variables, so no effect of imiquimod on the clinical tumor responses could be established in this study.

- Overall survival

During the course of the study it became increasingly evident based on data from other cancer vaccine trials that OS is a more appropriate measure to evaluate the clinical effects of cancer vaccines. By contrast short-term endpoints relying on tumor response are not well suited to capture the delayed clinical effects of cancer vaccines, especially in fast advancing diseases like colorectal cancer.

These issues have been recognized by experts and were also addressed in the current FDA Guidance for Industry "Clinical Considerations for Therapeutic Cancer Vaccines" (released October 2011)[1] where it is stated: "…..*As a consequence of their immunological mechanisms of action, cancer vaccines may require considerable time after administration to induce immunity. … Due to delayed effect of the vaccine, the endpoint curves may show no effect for the initial portion of the study. If the vaccine is effective, evidence of the effect may occur later in the study...".* Therefore, special emphasis was put on the OS observed in IMA910-101. Generally, all time-dependent variables in IMA910-101 were calculated using 3 different start points: date of Visit C (OS-1), date of baseline tumor CT (OS-2), or start date of first-line chemotherapy (OS-3). OS-2 and OS-3 were related to the preferred start points, since these allowed an appropriate comparison with the COIN study data. At the time of the finalization of this CSR, 2 OS analyses with 2 different stop dates were available; the more immature data based on data base lock in July 2011 (used for the first analysis of study data) and the more mature data after

[1]Link: http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm278673.pdf (last accessed 03-JUL-2012)

the end of the follow-up 1 period (cut-off in November 2011; used for the COIN comparisons and the analysis of associations with the immune responses). Median OS and survival probabilities based on OS-2 and OS-3 are summarized in Synopsis Table B. All data are shown combined as the follow-up in cohort 2 at this point was too short to allow a meaningful analysis for the two cohorts separately.

Synopsis Table B: Overall survival (days) in IMA910-101 (PP population)

	OS-2	OS-3
Data base lock (July 2011)		
Median OS	501.0 [396.0; 588.0]	594.0 [487.0; 715.0]
Survival probability		
Month 6	0.780 [0.674; 0.856]	0.988 [0.917; 0.998]
Month 12	0.690 [0.577; 0.779]	0.756 [0.648; 0.835]
Month 18	0.447 [0.328; 0.559]	0.562 [0.443; 0.665]
Month 24	0.367 [0.249; 0.484]	0.357 [0.237; 0.479]
Month 30	0.367 [0.249; 0.484]	0.357 [0.237; 0.479]
Month 36	nc	nc
Follow-up 1 (November 2011)		
Median OS	507.0 [405.0; 832.0]	598.0 [501.0; 909.0]
Survival probability		
Month 6	0.780 [0.674; 0.856]	0.988 [0.917; 0.998]
Month 12	0.693 [0.580; 0.781]	0.756 [0.648; 0.835]
Month 18	0.459 [0.343; 0.567]	0.564 [0.448; 0.664]
Month 24	0.395 [0.282; 0.506]	0.392 [0.279; 0.504]
Month 30	0.339 [0.204; 0.479]	0.343 [0.214; 0.477]
Month 36	0.339 [nc]	0.343 [nc]

Note: Results by cohort are not provided, since Cohort 2 data were too immature (patients were enrolled after completion of Cohort 1). Square brackets show 95%-CIs, nc=not calculable.

In order to put the overall survival data into perspective, an effort was made during the ongoing trial to identify a suitable (historical) control group. The MRC study group agreed to provide all relevant clinical data from their recently conducted, large randomized phase 3 study called “MRC COIN trial”. To allow for an unbiased comparison, a separate analysis plan was set up which allowed for a blinded matching procedure of IMA910-treated patients vs. COIN patients and to compare survival between the resulting data sets. Arm C of the COIN trial can be considered an appropriate external control for the IMA910-101 population, since the same mode of first-line oxaliplatin-based chemotherapy was applied (12-weeks first-line chemotherapy), the same patient population was studied (unresectable first-line CRC patients; patients with stable or responding disease after 12-week of initial chemotherapy entered the anti-tumor treatment-free interval in COIN Arm C, while IMA910 was applied in the treatment-free interval in IMA910-101), and a large number of patients were enrolled in COIN, thereby facilitating the choice of best matching patients, and single patient data were available for the targeted procedures. I

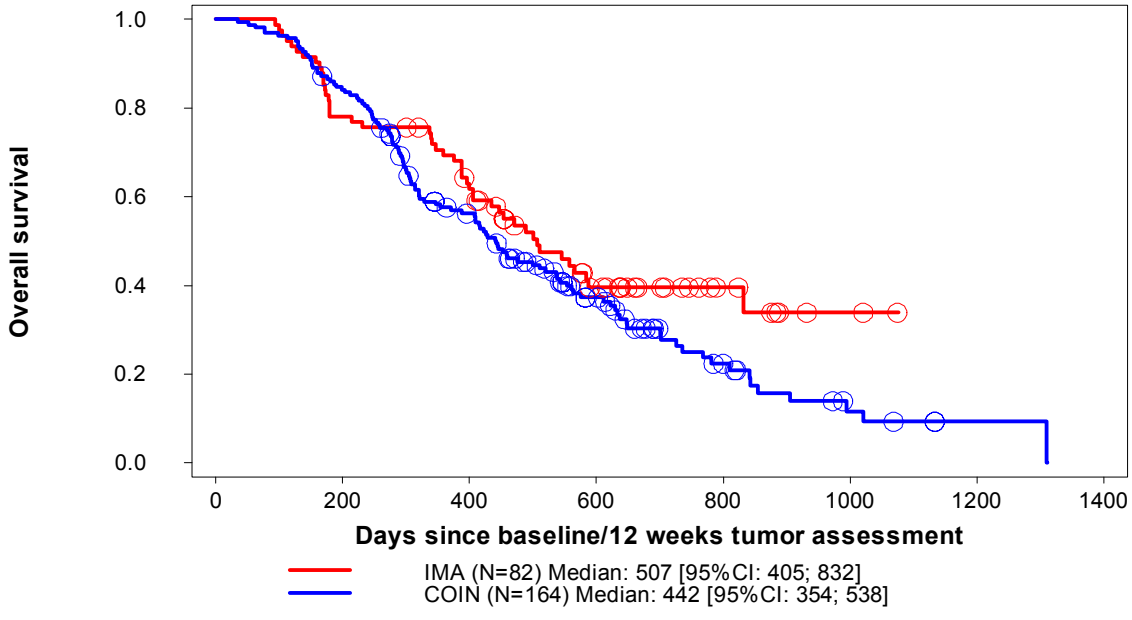
ndeed, the MRC COIN trial is the only trial which fulfilled all the requirements outlined above and was thus regarded as the best and most reliable external control for comparison of the IMA910-101 data. Other trials investigating a discontinuous chemotherapy regimen either enrolled a relatively favorable patient population with respect to organs affected with metastasis resulting in a high rate of metastasectomies (R0 resections), had different treatment schedules, small sample size or combinations of those and were therefore regarded as less suited for this comparison.

- Overall survival compared to COIN Arm C study population

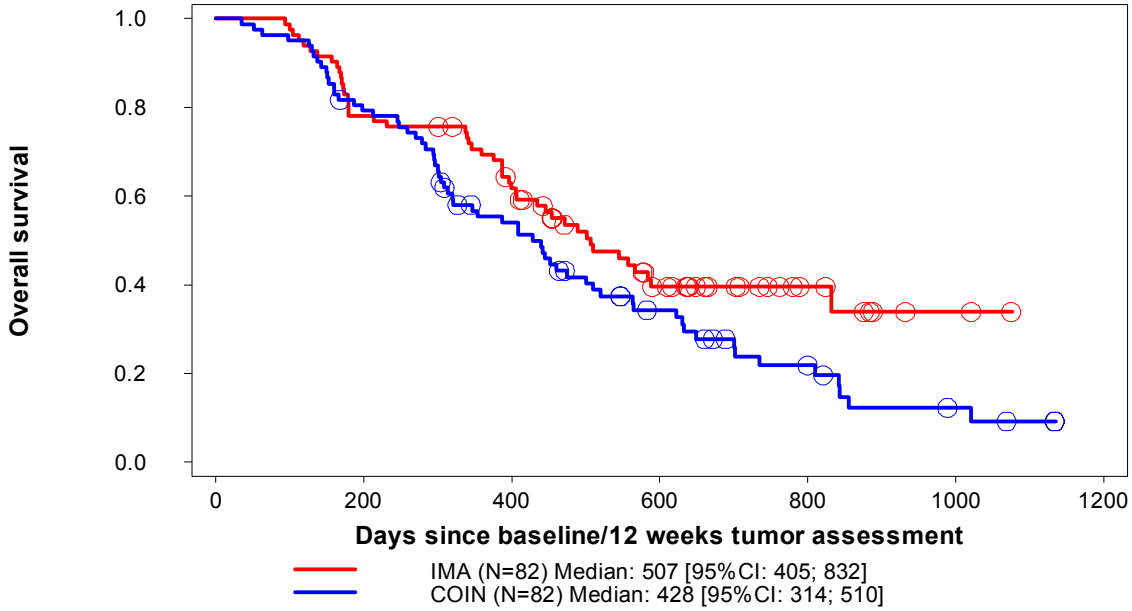
The data provided in Synopsis Table B were compared with an external control taken from Arm C of the COIN study. Generally, this study had similar essential features in terms of enrolled patients and treatments, and comprehensive matching procedures (such as propensity scoring and calculation of Mahalanobis distance) were applied in order to create a best matching population (see 11.4.1.11 for details).

The matching procedures were successful and resulted in well balanced patient populations. All potentially influencing variables could be balanced between studies groups (an imbalance was still observed for "prior adjuvant chemotherapy", but in an exploratory analysis this factor did not significantly affect OS in COIN Arm C PP patients). The OS comparisons between IMA910-101 and COIN patients was performed twice, once involving all suitable COIN patients independent of their HLA-type (1:2 match) and second involving primarily HLA-A*02 positive COIN patients (1:1 match). The analogue to OS-2 in IMA910-101 (start with baseline tumor assessment) was the time of the 12-week tumor assessment in COIN. The main results arising from that comparison (1:2 match and 1:1 match) are displayed in Synopsis Figure A and B.

Synopsis Figure A: OS-2 in IMA910-101 vs. COIN (1:2 match; PP population)



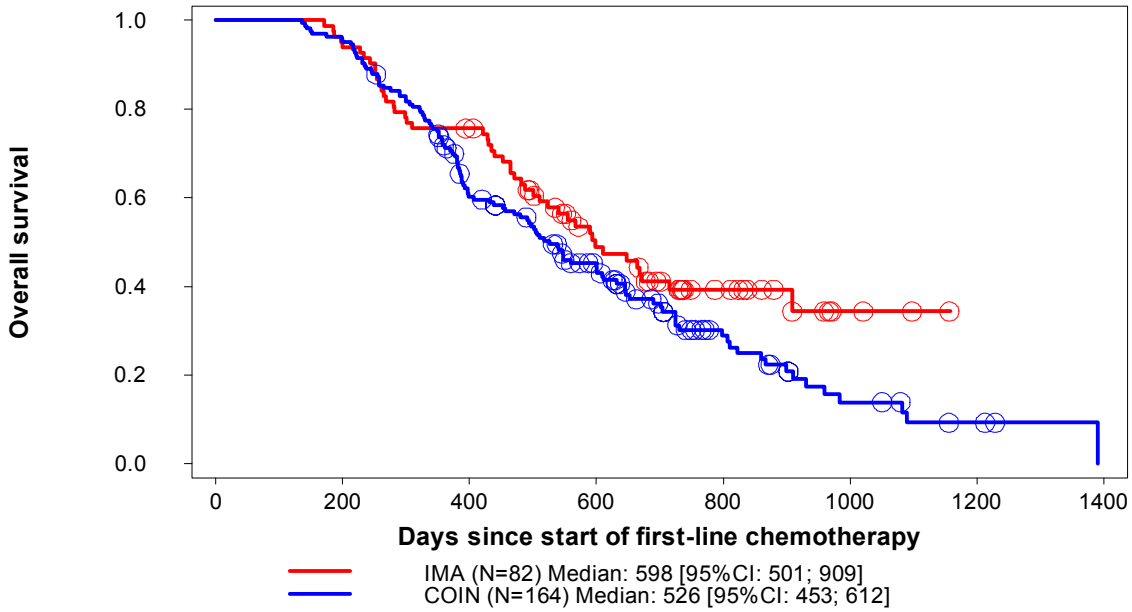
Synopsis Figure B: OS-2 in IMA910-101 vs. COIN (1:1 match; PP population)



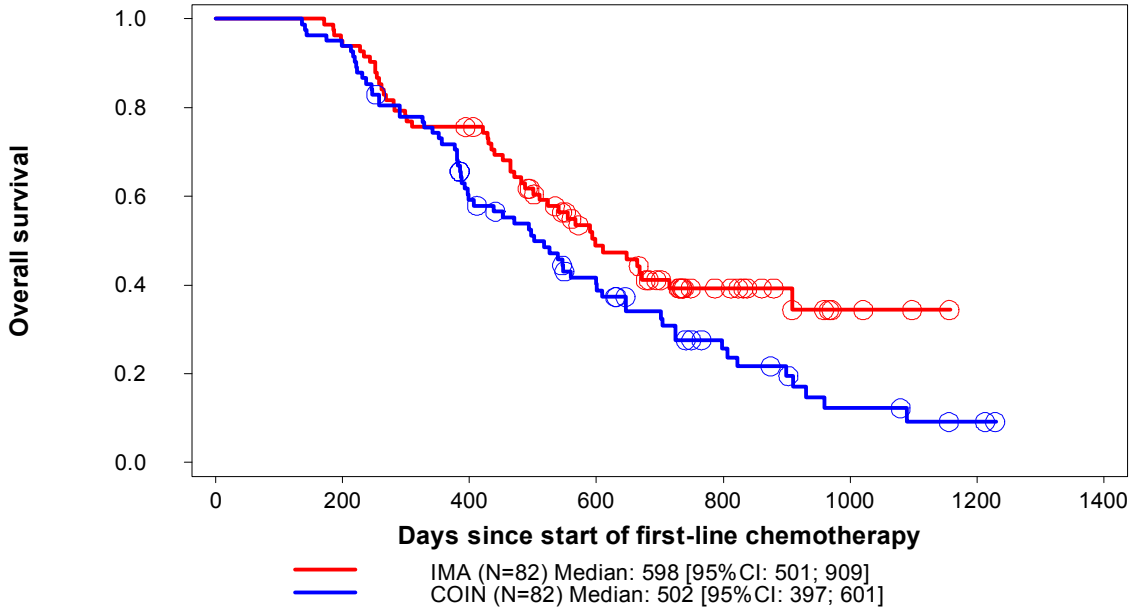
The main survival analysis (OS-2 related to baseline in IMA910-101 and 12-weeks tumor assessment after 12 week first-line chemotherapy in COIN; 1:2 and 1:1 match) showed that IMA910-treated patients seemed to have a longer overall survival compared to matched COIN patients (1:2 match: HR=0.741, p=0.0972; 1:1 match: HR=0.675, p=0.0470). The Kaplan-Meier survival curves of IMA910-treated and COIN patients separated after approximately 9 months for both matchings and thereafter the IMA910 survival curve remained above the COIN curve. This so-called “delayed clinical effect” was not unexpected and is in accordance with the mode of action of effective cancer vaccines (see Section 13.1). Moreover, there seemed to be a trend towards increasing improvement in OS over time among patients treated with IMA910 vs. the matched COIN patients, since the difference in survival rates in favor of IMA910 was more pronounced at Year 2 (OS-2: 39.5% vs. 26.3% (1:2 match) and vs. 23.8% (1:1 match)) than at Year 1 (OS-2: 69.3% vs. 57.6% (1:2 match) and vs. 55.3% (1:1 match)).

Overall survival between IMA910-treated and COIN patients was also compared in relation to start of first-line chemotherapy (starting point for measuring OS-3 in both studies) are displayed in Synopsis Figure C and D.

Synopsis Figure C: OS-3 in IMA910-101 vs. COIN (1:2 match; PP population)



Synopsis Figure D: OS-3 in IMA910-101 vs. COIN (1:1 match; PP population)



The observed difference in OS seemed somewhat more pronounced when comparing OS in relation to first day of chemotherapy (OS-3) between IMA910-treated and matched COIN patients (1:2 match: HR=0.728, p=0.0768; 1:1 match: HR=0.665, p=0.0386). This is likely to resemble the “real” difference and may well be explained by the different study-specific procedures: in the IMA910-101 study the CT after 12 week first-line chemotherapy was conducted later than in the COIN trial due to the informed consent and screening procedures in IMA910-101 which took a certain time before the baseline CT

(after 12 week first-line chemotherapy) could be performed, while the informed consent and screening procedures in the COIN trial had been conducted before start of chemotherapy. Survival rates at Year 1 for OS-3 (IMA910-101 vs. COIN) were 75.6% vs. 71.2% (1:2 match) and vs. 71.8% (1:1 match) and at Year 2 for OS-3 were 39.2% vs. 31.2% (1:2 match) and vs. 27.6% (1:1 match).

One of the caveats when analyzing OS might always be that factors other than the treatment under investigation, specifically any further disease-specific interventions, could have influenced the outcome. Therefore, subsequent systemic treatments and surgical interventions with curative intent applied to patients following their active study participation were analysed in IMA910-treated patients and matched COIN patients and their influence on OS was carefully evaluated. These comparative analyses of subsequent systemic and surgical treatments employed in IMA910-treated and matched COIN patients did not show relevant differences in the proportions of patients with no or at least 1 or 2 subsequent systemic treatments (1:2 match and 1:1 match). No relevant differences in the percentage of applied chemotherapies (IMA910-treated patients received more irinotecan-based whereas matched COIN patients received more oxaliplatin-based follow-on therapies) or the number of patients with tumor resection with curative intent was noted. Not unexpected, a higher rate of targeted therapies in IMA910-treated patients was detected (25.4% vs. 6.7% (1:2 match) or vs. 6.1% (1:1 match)) since biological agents are not readily available in UK. Based on a systematic literature review the mean survival benefit for patients receving additionally targed therapies was calculated to be 1.74 months. However, the impact in this trial would be significantly lower since the imbalance between IMA910-101 and COIN patients in subsequent targeted therapies is only about 20 percent points. Moreover, additional exploratory analyses of OS in relation to subsequent treatments were conducted and longer OS in IMA910-treated patients within all of the analyzed strata (no or at least 1 or 2 subsequent systemic treatments using 1:2 matched and 1:1 matched patiens) could consistently be shown, thereby indicating that the beneficial effects were indeed related to the IMA910 treatment (i.e. IMA910 treatment in IMA910-101 vs. pure observation in the COIN study) and not depending on any differences in subsequent treatments.

<u>- Immunological responses to IMA910</u>

IMA910 contains 10 HLA-A*02 (Class I) restricted and 3 promiscuous HLA-[redacted] (Class II) TUMAPs, which are the active pharmaceutical ingredients of IMA910 and were selected based on their natural presentation on CRC. Class I (i.e., CD8) responses were analyzed with multimer and ICS assays, while Class II (i.e., CD4) responses were determined by ICS assay. Overall, Class I responses were evaluable for 90/92 (98%) ITT patients and for 81/82 (99%) PP patients. Class II responses were evaluable for 80/92 (87%) of ITT patients and for 71/82 (87%) PP patients. Evaluability of Class I plus Class II responses was identical to the Class II evaluability rate.

A total of 62% of patients in the PP population responded to the [redacted] antigen marker peptide [redacted] thereby indicating that the vaccinations were generally capable of inducing CD8 T-cell responses in CRC patients. Overall, IMA910 induced at least one response to a Class I-restricted

peptide and at least one response to pan HLA-[redacted] binding TUMAPs in 69% (49/71) of patients (PP population). 34% (24/71) of patients showed multiple vaccine-induced CD8 and CD4 T-cell responses (i.e., ≥2 Class I and Class II TUMAP responders). 89% and 65% of patients had at least one or at least two pan HLA-[redacted] binding TUMAP responses, respectively. Whereas 73% and 43% mounted at least one or more than one vaccine induced HLA-A*02 restricted immune response, which was in a similar range compared to immune responder rates with the sister product IMA901 in RCC patients.

The immunogenicity of IMA910 individual TUMAPs was highly heterogeneous ranging from 0% [redacted] to 83% [redacted] of patients in the PP population. In general, HLA[redacted] restricted peptides were more immunogenic than HLA-A*02 binding peptides. The two [redacted] derived peptides [redacted] were the most immunogenic TUMAPs.

Generally, the clinical baseline characteristics were well balanced between patients with multiple TUMAP responses and single or non-responders in the IMA910-101 clinical trial. "Age" was the only factor that was statistically significant different between the responder groups, and was inversely associated with responses to multiple TUMAPs. However, age was not found to be associated with OS. Overall, a similar prognosis of IMA910 multi- and non-multi immune responders (Class I, Class II, Class I+II) could be assumed.

The comparative analyses of the 2 study cohorts indicated increased Class I single and multi-TUMAP responder rates in patients who were additionally treated with imiquimod compared to those without imiquimod. The frequencies of patients with CD8 T-cell responses in Cohort 2 compared to Cohort 1 were higher in the Class I ICS assay, but not in the Class I multimer assay. The response magnitude of CD8 T-cell responses detected by Class I multimer assay was increased in the patients additionally treated with imiquimod compared to Cohort 1. Class II immune responses, however, were comparable between study cohorts. Overall, a similar prognosis of IMA910 multi- and non-multi immune responders (Class I, Class II, Class I+II) could be assumed.

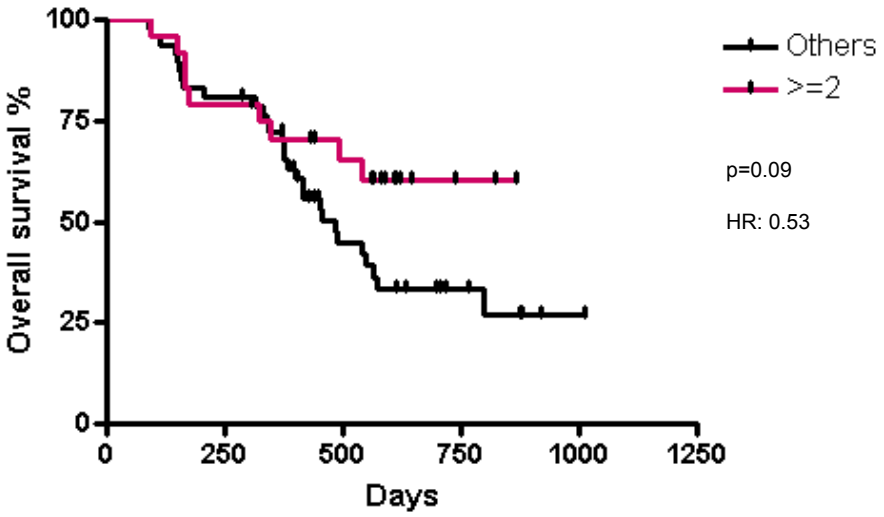
<u>- Association of immunological response with tumor response</u>

A significantly higher number of patients had disease control at 6 months if patients responded to at least 1 (0% vs. 13%; binary logistic regression p=0.02) or at least 2 (2% vs. 19%; binary logistic regression: p=0.01) TUMAPs compared to 0 TUMAP or 0-1 TUMAP responders, respectively. Likewise, a significantly increased number of patients had controlled disease at 6 months, if patients responded to at least 2 (0% vs. 17%; binary logistic regression: p=0.01) Class II binding TUMAPs compared to 0-1 TUMAP responders. Consequently, the DCR in patients responding to ≥2 Class I and ≥2 Class II TUMAPs was significantly increased compared to the complementary group of patients with other responses. Generally, the association between immune responses and disease control increased with observation time, indicating a delayed effect of immunotherapy on clinical response parameters. Generally, these data suggested a positive association between immune responses and disease control. Consistent trends were seen in the association analyses of PFS/TTP and immune response.

- Associations of immunological responses with overall survival (OS-2)

In the IMA910-101 study, patients with multiple T-cell responses to Class I, Class II and class I and II TUMAPs showed consistently longer OS compared to patients without multiple responses. Strong trends for increased OS were observed in Class I multi-TUMAP responder (HR: 0.59; p=0.08; log-rank test) and Class II multi-TUMAP responder (HR: 0.6; p=0.12) compared to the complementary (0-1) T-cell responder groups. The longest OS was found in patients with multiple Class I and Class II TUMAP responses compared to the complementary group of patients (HR: 0.53; p=0.09; see Synopsis Figure E). These data underlined the close relationship between immune response and clinical benefit.

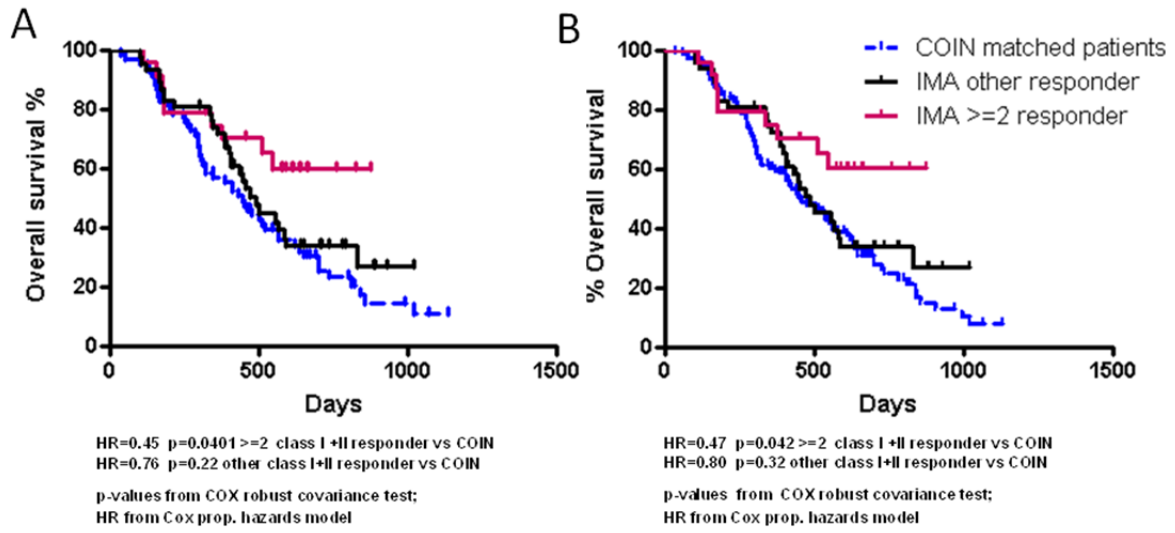
Synopsis Figure E: Association between Class I+II T-cell responses and OS (PP population)



Note: Provided is the OS-1 (relative to Visit C (start of study treatment)) of PP patients responding to ≥2 Class I and Class II TUMAPs [N=24] vs. the complementary groups (n=22 and 47, respectively). The p-values were calculated by log-rank test; Hazard ratios are from Cox proportional Hazards model.

Moreover, OS of IMA910 immune responder groups (patients with at least 2 Class I and at least 2 Class II TUMAP responses and patients with fewer responses) was compared to OS of COIN patients matched to immune evaluable IMA910 patients. OS of IMA910 patients with at least 2 Class I and at least 2 Class II TUMAP responses was prolonged as compared to other IMA910 responder or matched COIN patients (see Synopsis Figure F). Similar results were obtained with two independent matchings (1:1 and 1:2 match). Importantly, baseline parameters were similar in IMA responder groups and COIN patients, indicating a comparable initial prognosis of all analysed patients groups.

Synopsis Figure F: Association between Class I+II T-cell responses and OS-2 compared to matched COIN patients (PP population, A 1:1 match; B 1:2 match)



Note: P-values for Cox robust covariance test HR are from Cox proportional hazards model.

Overall, these data consistently showed a strong association between the extent of immune response induced by IMA910 and improvements in DCR and subsequently in OS, thereby confirming the clinical activity of IMA910.

- Safety of study treatment

A total of 68 study patients (73.9%) experienced any TEAEs during the course of the study. The overall AE and SAE rates (74.2% vs. 73.1% and 9.1% vs. 11.5%, respectively) were similar in Cohort 1 and Cohort 2, while AEs leading to permanent discontinuation of IMA910 or GM-CSF (6.1% vs. 19.2%) and Grade 3-5 AEs (4.5% vs. 15.4%) seemed to occur more frequently in Cohort 2. Only one case of a treatment-emergent death (unrelated acute MI) not primarily associated with disease progression was reported.

Due to the coincident administration of GM-CSF, IMA910 and in Cohort 2 imiquimod, most of the TEAEs that were considered drug-related by investigators (observed in 38.0% of study patients) were related to both GM-CSF and IMA910 or, in Cohort 2, related to GM-CSF, IMA910 and imiquimod. The most frequently reported related AEs were "injection site reactions" (15 patients, 16.3%), "injection site erythema" (7 patients, 7.6%), "arthralgia" (4 patients, 4.3%), "fatigue" (4 patients, 4.3%), "injection site pruritus" (4 patients, 4.3%), and "vomiting" (4 patients, 4.3%). Local injection site reactions were overall frequent, but usually mild and self-limiting. A low frequency of TEAEs related to the administration of CY was reported (7 patients, 7.6%).

Overall, 19 patients (20.7%) experienced TEAEs with an NCI-CTC Grade 3. The Grade 3 AEs occurring in more than 1 patient at preferred term level were "fatigue" (3 patients, 3.3%), "abdominal pain" (2 patients, 2.2%), "bone pain" (2 patients, 2.2%), "femoral neck fracture" (2 patients, 2.2%), and

"hypersensitivity" (2 patients, 2.2%). Across both cohorts, 9 patients (9.8%) discontinued IMA910 plus GM-CSF permanently due to AEs. Numerically, more patients in Cohort 2 than in Cohort 1 experienced Grade 3 TEAEs (30.8% vs. 16.7%) and AEs leading to permanent discontinuation of study drug treatment (19.2% vs. 6.1%), but these differences might be at least partly explained by some differences in baseline characteristics to the disadvantage of Cohort 2 (i.e., rather more advanced stage of disease). No other obvious relevant differences between cohorts were noted. Adverse events with Grade 4 or Grade 5 intensity were infrequent in either cohort and included each 1 case of "subileus" (non-serious, unrelated), "hypersensitivity" (serious, related), and "myocardial infarction" (serious, unrelated). No drug-related deaths were reported.

In total 9 patients (9.8%) experienced 11 SAEs; preferred terms were "hypersensitivity" (3 patients) "constipation" (1 patient), "vomiting" (1 patient), "catheter site infection" (1 patient), "pneumonia" (1 patient), "femoral neck fracture" (2 patients), "myocardial infarction" (1 patient), and "musculoskeletal pain" (1 patient). Apart from the patient with the fatal myocardial infarction, all other SAEs resolved (with sequelae in 2 cases). Four of the SAEs (3 cases of hypersensitivity and 1 case of pneumonia) were considered drug-related. The 3 serious hypersensitivity reactions (thereof 2 cases only related to GM-CSF and 1 case related to both GM-CSF and [redacted] which is the most immunogenic Class II peptide in IMA910) were well manageable with remedial therapy commonly used in such situations (i.e., intravenous corticosteroids and antihistamines) and disappeared within a few hours after their occurrence. In accordance with previous experience gained in the RCC study IMA901-202 with the sister product IMA901, also these 3 patients treated with IMA910 developed the reaction at a relatively late stage of the vaccination schedule, i.e., with vaccination 10 (i.e., Visit 10) at the earliest. As recommended by the DSMB a routine pre-medication with antihistamines prior to vaccination from vaccination 10 onwards was included. As regards the reported pneumonia, the patient's condition and history provided alternative explanations for the occurrence of that finally resolved infection, but the event was nevertheless reported by the Sponsor as an SUSAR. No obvious associations between immune response data and the occurrence of AEs were found, and also the analyses of laboratory data and vital signs were unsuspicious and did not give rise to any relevant safety concerns.

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, IMA910, GM-CSF and in Cohort 2 imiquimod. Overall, the pattern of "related" adverse events (i.e. those events regarded by site investigators as "certainly", "probably", or "possibly" related to the administration of the study drugs) was in line with the previous experience with IMA901, the sister product of IMA910.

In conclusion, repeated intradermal injection of IMA910-101 plus GM-CSF with or without topically applied imiquimod was shown to be overall safe and well tolerated throughout the study period.

- Overall conclusions

- Repeated vaccination with IMA910 plus GM-CSF with or without imiquimod and pre-treatment with CY is overall safe and well tolerated. Injection site reactions, the most frequent related adverse events, were mostly of mild-moderate intensity and well manageable.
- A low percentage of patients experienced systemic allergic reactions to the vaccination which were all well manageable with standard concomitant medication. A certain observation period following each vaccination is therefore recommended to detect and treat potential systemic reactions.
- The observed data for classical cytotoxic read-out criteria such as objective response rates (ORR) and disease control rates (DCR) did not suggest a major effect of IMA910 on such short-term parameters. DCRs at Visit 14 in IMA910-101 appeared to be similar to the reference results observed in OPTIMOX2.
- In contrast, long-term observation suggested a delayed clinical benefit of IMA910 with encouraging overall survival data for the patient population analyzed. The OS of IMA910-treated patients was longer compared to matched COIN patients (1:2 match: p=0.0972, HR=0.741; 1:1 match: p=0.0470, HR=0.675) with higher survival rates at Year 1 (69% vs. 58% (1:2 match) and vs. 55% (1:1 match)) and Year 2 (40% vs. 26% (1:2 match) and vs. 24% (1:1 match)). The OS benefit seemed to increase over time and was, as expected, delayed, since OS curves dissociated after approximately 9 months.
- A high proportion of patients showed an immune response to Class I (73%) and Class II (89%) TUMAPs. T-cell responses to all but one individual Class I TUMAPs and all Class II TUMAPs were detected. Additional application of the immune modulator imiquimod was associated with a moderate increase in frequency and quality of CD8, but not CD4 T-cell responses.
- A close association between the extent of measureable immune responses and clinical outcomes was observed, since multi-TUMAP responders (≥2 Class I responses or ≥2 Class II responses or ≥2 Class I+II responses) showed consistently improved clinical outcome with respect to DCR, PFS and OS (either significant or by trend). This better clinical outcome in multi-TUMAP responders did not seem to be a reflection of a better prognosis in these patients as the prognostic baseline factors were well balanced between multi-TUMAP responders and others.
- Most important, the observed difference in OS versus matched COIN patients seemed to be exclusively mediated by multi-TUMAP responders who had a significantly longer OS than matched COIN patients for all analyses conducted; in contrast, IMA910-non-multi-TUMAP responders had survival curves almost identical to the matched COIN patients.
- In summary, these encouraging study results clearly warrant further development of IMA910 for treatment of patients with CRC.