SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BO21495)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Open-label, multicenter, dose-escalation Phase I/II study to evaluate safety, pharmacokinetics and activity of RO5083945, a glycoengineered antibody against EGFR, in patients with metastatic and/or locally advanced malignant EGFR+ solid tumors. Report No. [redacted], October 2011.		
INVESTIGATORS / CENTERS AND COUNTRIES	5 investigational sites in Spain (3) and France (2).		
PUBLICATION (REFERENCE)	Paz-Ares LG, Gomez-Roca C, Delord J-P, Cervantes A, Markman B, Corral J, et al. Phase I pharmacokinetic and pharmacodynamic dose-escalation study of RG7160 (GA201), the first glycoengineered monoclonal antibody against the epidermal growth factor receptor, in patients with advanced solid tumors. J Clin Oncol 2011;29:3783-3790.		
PERIOD OF TRIAL	June 06, 2008 to June 21, 2011 (first patient screened to last patient last observation)	CLINICAL PHASE	I/II
OBJECTIVES	**Primary Objectives** The primary objective for Part I of the study was: • to describe the pharmacokinetics (PK) and maximum tolerated dose (MTD), if achieved, of RO5083945 in patients with metastatic and/or locally advanced malignant EGFR+ solid tumors The primary objective for Part II of the study was: • to investigate the Tumor Growth Control Rate (TGCR): complete response (CR), partial response (PR) and stable disease (SD) > 2 months and safety profile of RO5083945 in patients with metastatic and/or locally advanced colorectal cancer expressing EGFR and mutant KRAS **Secondary Objectives** The secondary objectives of Part I of the study were as follows: • to describe the tolerability and AE profile of RO5083945		

	• to determine the appropriate dose(s) and regimen(s) of RO5083945 to be used in Part II • to describe the pharmacodynamics (PD) of pEGFR, pAKT, pMAPK status of RO5083945 in skin biopsies (mandatory surrogate tissue) and tumor biopsies (optional) • to describe the PD of immune effector cell (CD16+ cells) status of RO5083945 in blood samples, skin biopsies (mandatory surrogate tissue) and tumor biopsies (optional) • to describe the FcγRIIIa-158 polymorphism • to describe the preliminary anti-tumor activity of RO5083945 The secondary objectives of Part II of the study were as follows: • to describe the anti-tumor activity of RO5083945 using: – Objective Response Rate (ORR): including complete response (CR) and partial responses (PR) – Duration of Response – Progression Free Survival (PFS) • to describe the tolerability and AE profile of RO5083945 • to describe the PD of pEGFR, pAKT, pMAPK status of RO5083945 in skin biopsies (mandatory surrogate tissue) and tumor biopsies (optional) • to describe the PD of immune effector cell (CD16+ cells) status of RO5083945 in blood samples, skin biopsies (mandatory surrogate tissue) and tumor biopsies (optional) • to describe the FcγRIIIa-158 and FcγRIIa-131 (only for Part II) polymorphism.
STUDY DESIGN	Phase I/II, open-label, multicenter study to evaluate the safety, PK and activity of single agent RO5083945 in patients with advanced EGFR+ solid tumors. Part I: dose escalation and schedule evaluation in patients with EGFR+ solid tumors where no standard therapy is available. Part II: Evaluation of recommended dose and schedule from Part I in patients with EGFR+ and mutant KRAS colorectal cancer.
NUMBER OF SUBJECTS	102 patients were recruited in total of whom 100 received study drug RO5083945 (75 patients in Part I, 25 patients in Part II).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The primary inclusion criteria for patients to be eligible for entry into both Parts I and II were : • Age ≥ 18 years • ECOG Performance Status (PS) 0-1 • Centrally confirmed EGFR expression in tumor tissue: ≥ 1% of tumor cells show membrane staining of any intensity • Evidence of radiologically measurable or clinically evaluable disease • Last dose of systemic anti-neoplastic therapy or radiotherapy ≥ 28 days prior to first RO5083945 infusion • All acute toxic effects of any prior radiotherapy, chemotherapy or surgical procedure had resolved to Grade ≤ 1, except alopecia and Grade 2 peripheral neuropathy • Neutrophil count (≥ 1.5 x 10^9 cells/L), platelet count (≥ 75 x 10^9/L, Hb ≥ 8 g/dL), total bilirubin (normal), AST and/or ALT (≤ 2.5× ULN) and serum creatinine (≤ 1.5 ULN). Patients in Part I of the study also had to have: • Histologically or cytologically confirmed advanced stage, primary or metastatic EGFR+ solid tumors for which no standard therapy exists Patients in Part II of the study also had to also have: • Histologically or cytologically confirmed advanced stage, primary or metastatic EGFR+ and mutant KRAS colorectal cancer • Not more than 2 previous cytotoxic regimens for metastatic disease • Evidence of radiologically measurable and documented progressive disease. Further inclusion criteria included provision of informed consent, use of effective contraception and protocol compliance.
TRIAL DRUG / STROKE (BATCH) No.	RO5083945 in 20 mL single-use vial containing 200 mg active drug substance in a buffered histidine solution (pH 6.0) and the excipients trehalose and polysorbate 20 [redacted]
DOSE / ROUTE / REGIMEN / DURATION	**Premedication** The investigator ensured that the following premedication for RO5083945 mandated by the protocol (version D) was suitable for patients according to national prescribing information: • Paracetamol (650-1000 mg orally or IV administered 12 h and approximately 30 min prior to the first

	RO5083945 infusion and 30 min prior to the second RO5083945 infusion • Diphenhydramine (25-50 mg orally or IV; or an alternative anti-histamine at an adequate dose) administered 12 h and approximately 30 min prior to the first RO5083945 infusion and 30 min prior to the second RO5083945 infusion • Hydrocortisone 200 mg IV (or equivalent dose of another corticosteroid) administered approximately 30 min prior to the first and second infusion. **Administration of RO5083945** RO5083945 was diluted in 0.9% (w/v) NaCl solution and administered IV (at infusion rates outlined in the study protocol) as follows: Part I 50-1400 mg (flat dose) IV, qW q2W, or q3W Part II 1400 mg, IV on Days 1 & 8, followed by q2W Patients were treated until disease progression, unacceptable toxicities or withdrawal of consent.
REFERENCE DRUG / STROKE (BATCH) No.	N/A
DOSE / ROUTE / REGIMEN / DURATION	N/A
CRITERIA FOR EVALUATION	
EFFICACY:	For Part II, the primary efficacy variable was Tumor Growth Control Rate (TGCR) where a patient was considered to be a responder if their best overall response was either CR, PR or SD and it lasted for at least 16 weeks. Primarily for Part II, secondary efficacy variables were overall response rate (ORR), duration of response (DoR) and progression-free survival (PFS)
PHARMACODYNAMICS:	Secondary variables of Part I and II were the following PD biomarker parameters: *Blood samples* • Multitest: mature human T-cells (CD3+), B cells (CD19+), helper/inducer T-cells (CD3+/CD4+), suppressor/cytotoxic T-cells (CD3+/CD8+), and NK cells (CD3–/CD16+ and CD56+) lymphocytes • NK monocyte/macrophage profile: NK cell markers were (CD3–/CD16+) and for monocyte/macrophage these markers include, but were not limited to

	(CD14+/CD45+) and (CD16+/CD68+) • FcγRIIIa-158 polymorphism (and FCγRIIa-131 in Part II) (clinical genotyping) • CTCs and ctDNA (Part II) *Archival Tumor* EGFR (mandatory for Part I & Part II) KRAS (mandatory for Part II) and PTEN (Part II). *Skin biopsy (mandatory surrogate tissue)* In Parts I and II, skin was evaluated as a surrogate tissue to examine EGFR pathway inhibition and induction of ADCC responses by RO5083945. Paired skin biopsies taken at baseline and from patients with RO5083945-related skin rash were analyzed for: • inhibition of EGFR and downstream signaling EGFR, pEGFR, pAkt and pERK) • immune effector cell infiltration including (NK cells [NKp46], activated NK cells [CD107a and/or NKp44], T cells (CD3+/CD4+/CD8+) and monocyte/macrophage profile (CD68+). *Tumor biopsies (optional)* Paired tumor biopsies taken from consenting patients at baseline and after RO5083945 treatment (around the end of Cycle 1/beginning of Cycle 2) underwent analysis for the determination of the same PD biomarkers as for paired skin biopsies.
PHARMACOKINETICS:	RO5083945 PK parameters C_{max}, t_{max}, C_{last}, t_{last}, C_{min}, t_{min}, AUC_{inf}, AUC_{last}, AUC_{0-T}, $t_{1/2}$, CL, CL_{ss}, V_{ss} and $R_{ac(AUC)}$ in each cycle were derived from RO5083945 serum concentrations according to standard non-compartmental analysis (NCA) methods.
SAFETY:	Safety parameters included adverse events, deaths, laboratory parameters (including HAHA and cytokine detection), vital signs, ECG, and performance status. The intensity of AEs and laboratory parameters were categorized according to NCI-CTC version 3 grading system, All AEs with an onset date on or after study day 1 and less or equal than 28 days after last infusion were reported. Dose limiting toxicities (DLTs) (applicable for Part I) were limited to the RO5083945-related toxicities defined in the study protocol which occurred during the first cycle (the first 2 weeks for q2W regimen or the first 3 weeks for qW and q3W regimens).
STATISTICAL METHODS	There was no statistical hypothesis for this Phase I study. Tumor response data, PD and PK parameters were summarized using descriptive statistics.

METHODOLOGY:

Efficacy:

Tumor assessments were evaluated by physical examination and radiologic imaging (chest X-ray and CT scans of abdomen or pelvis if indicated) according to RECIST v1.0 criteria.

Safety:

In addition to biochemical, hematological and urinalysis analyses, additional laboratory assessments included validated ELISA assays to detect anti-human anti-human antibodies (HAHAs) and cytokine release (TNF-α, IFN-γ, IL-6, IL-8 and IL-10) in serum.

Pharmacokinetics:

Blood samples collected for PK analysis at the time points defined in the schedule of assessments in the study protocol were analyzed for RO5083945 by a validated ELISA method.

PK parameters were derived from RO5083945 serum concentrations according to standard non-compartmental analysis (NCA) methods using WinNonlin version 5.2 (Pharsight, Mountain View, CA, USA):

Pharmacodynamics:

Peripheral blood immunophenotyping of individual immune effector cells was determined by FACs or Multitest IMK and T-reg tests.

Analysis of inflammatory markers (CD markers and NKp46) and EGFR and downstream signaling parameters in skin and tumor biopsies was by IHC.

FcγR clinical genotyping was performed by PCR on DNA was extracted from peripheral blood at baseline and assessed for FcγRIIIa-158 polymorphism (and FCγRIIa-131 in Part II).

For quantification of immune cell infiltration in paired skin or tumor biopsies, the composite immune reactive score (CIRS) was calculated as the sum of infiltrating CD4, CD8, CD16, CD56 and CD68 positive cells/mm^2 of tumor/skin area.

EFFICACY RESULTS:

The main efficacy findings of Parts I and II were as follows:

Part I

- The best overall response in Part I was one patient with CR (1/75 [1.3%]), 2 patients with PR (2/75 [2.7%]) (one patient with a tumor harboring KRAS G12D mutation), 29 patients with SD (29/75 [38.7%]) and 38 patients with PD (38/75 [50.7%]). Five patients had missing post-baseline response assessments.
- The TGCR was 17.3% (13/75: 1 confirmed CR, 2 confirmed PR and 10 confirmed SD).
- The objective responses of CR (disappearance of target lesion) and 2 PRs (tumor shrinkages of 43.0% and 33.5%, respectively after completion of 6 doses of RO5083945) were observed in patients with CRC.

Part II

- In patients with mutant KRAS CRC, the TGCR (confirmed SD at 16 weeks after start of study medication) was 24% (6/25 patients). The best overall response in this study was SD in 10/25 patients (40% at 8 weeks) and PD in 15/25 patients (60%). There were no objective responses (CRs or PRs).

PHARMACODYNAMIC RESULTS:

The main pharmacodynamic biomarker findings of Parts I and II were as follows:

Peripheral blood immunophenotyping

Treatment with RO5083945 caused:

- a notable reduction of detectable NK lymphocytes (CD3–/CD16+ and/or CD56+, as well as CD8NK [CD3–/CD8+]) circulating in the peripheral blood by Cycles 2 and 3 (Day 1)

compared to those seen pre-infusion Cycle 1 (Day 1).

- reduced expression of CD16 (the FcγRIII, which engages with IgG bound to a target cell and activates NK cells) in those circulating NK lymphocytes, as evidenced by:
  - Reduced CD16 MFI (mean fluorescent intensity of the CD16+ population within the NK population [CD3–/CD56+]); here, reduced CD16 expression may be an indirect measure of CD16 down-regulation following receptor engagement
  - Reduced CD16%; the percentage of NK cells (CD3–/CD56+) also expressing CD16.

Paired skin biopsies

Compared to matched normal skin biopsies collected at baseline, biopsies of RO5083945-dependent rash skin (at Day 8 of Cycle1 and Cycle 3) were characterized by:

- an increase in composite immune reactive score (CIRS) in immune infiltrates in the dermis (in 13/14 paired skin biopsies) of skin rash biopsies (median change from baseline of 8.5 [–1, 13] in scoring class). On-treatment normal skin biopsies, by comparison, showed a modest increase in CIRS (1.5 [–7, 6] scoring class).
- infiltration of immune effector cells particularly around dermal skin structures such as hair follicles, sebaceous glands and blood vessels as indicated by an increase in CIRS in adnexal and perivascular (ADPV) structures
- a notable increase in nuclear pERK (median increase of 2 [–3, 3] in scoring class in 12/14 paired biopsies for pERK nuclear intensity 3). This increase in nuclear pERK staining mirrored the increase in CIRS for rash infiltrates in the epidermis and reflected the presence of infiltrating immune cells rather than modulation of pERK expression in pre-existing skin cells or structures.

Paired tumor biopsies

From the patients in Part II who provided paired tumor biopsy samples before and after treatment with study drug, RO5083945 caused:

- Immune effector cell tumor infiltration, as demonstrating by an increase in CIRS (in 7/9 evaluable tumor pairs), and notably including CD68+ macrophages (8/10 pairs) and CD16+ (FCγR-III) cells (comprising both macrophages and NK cells, in 6/9 evaluable tumor pairs)
- Marginal reduction of nuclear pERK expression in 5/7 evaluable tumor pairs (–13.0 [–38, 7]% change from baseline).

PHARMACOKINETIC RESULTS:

Part I

RO5083945 exhibited the following i.v. PK profile:

- peak serum concentrations (T_{max}) ~8 h around the time of the end of infusion, following which concentrations declined in a biphasic manner.
- dose-dependent increase in serum concentrations with total exposure (AUC) increasing in a dose-proportional manner at doses > 400mg up to the highest dose of 1400 mg, and consistent across schedules.
- minimal difference in clearance (CL) between dose groups at doses of ≥ 400 mg.
- $t_{1/2}$ estimates increased with increasing dose (~ 12-120 h over 50-1400 mg dose range at Cycle 3 for qW dosing).
- apparent Vss ~2-5 L consistent with the drug residing mainly within the confines of the central compartment (total plasma volume ~ 3 L per 70 kg adult male)
- apparent accumulation at doses ≥ 400 mg for qW ($R_{ac(AUC\ at\ Cycle\ 3/Cycle\ 1)}$~2.0-fold) and ≥ 1000 mg for q2W ($R_{ac(AUC)}$ ~1.8-fold) schedules.
- target trough concentration of 50 µg/mL attained in all subjects administered a dose of ≥ 700 mg RO5083945 qW and for the q2W dosing schedule, serum concentrations remained above 50 µg/mL for the entire dosing interval in the majority of patients administered RO5083945 at 1400 mg.

Based on non-compartmental analysis of PK data for Part I, simulations of target trough concentrations using a population pharmacokinetics (PPK) model, optimal safety and preliminary anti-tumor activity of RO5083945 administered 1400 mg q2W in Part I, the recommended regimen chosen for Part II was 1400 mg RO5083945 administered on Days 1 and 8 followed by 1400 mg q2W for subsequent infusions.

Part II

Following administration RO5083945 1400 mg d1 & d8, followed by 1400 mg q2W:

- RO5083945 exposure and peak concentrations were higher (~25% for $AUC_{0-\tau}$ in Cycle 3) than those reported for the 1400 mg dose administered q2W in Part I. This was likely due to the additional administration of RO5083945 on Day 8 of Cycle 1, as well as optimized sampling in Part II of the study
- At Cycle 3, $t_{1/2}$ was ~150 h, apparent Vss was ~3 L and accumulation ratio ($R_{ac(AUC\ at\ Cycle\ 3/Cycle\ 1)}$) was ~1.6-fold
- target therapeutic concentration of 50 µg/mL was achieved immediately and maintained throughout the study in the majority of patients, validating the predictions from the PPK model.

SAFETY RESULTS:

Table. 1 Overview of Safety in Parts I and II

	Part I	**Part II**
	RO5083945 (50-1400 mg) qW, q2W or q3W	RO5083945 (1400 mg) d1 & d8, q2W
Patients with at least one:	N = 75	N = 25
AE	75 (100%)	25 (100%)
Related AE	75 (100%)	25 (100%)
Grade 3/4 AE	40 (53.3%)	15 (60%)
Related Grade 3/4 AE	31 (41.3%)	12 (48%)
SAE	19 (25.3%)	1 (4%)
Related SAE	6 (8.0%)	–
AE Leading to Death	3 (4%)	–
AE leading to Withdrawal	8 (10.7%)	–
AE leading to dose modification	4 (5.3%)	–

The median number of infusions administered per patient was 7 (range: 1-37) for Part I (across all doses and schedules) and 5 (range: 2-24) for Part II.

The most frequent Investigator-reported AEs of any grade (> 10% patients in both Parts I and II) were rash, infusion-related reactions (IRRs), asthenia, hypomagnesemia, decreased appetite, paronychia, diarrhoea, vomiting, nausea, constipation, dry skin, stomatitis and paronychia.

The large majority of the AEs in Parts I and II (≥ 89.5%) were Grade 1 or 2 (mild to moderate) in intensity. The most frequent Investigator-reported Grade 3/4 AEs (reported in more than one patient) were rash, IRRs, hypomagnesemia, asthenia and paronychia (Table 2), cytolytic hepatitis, hyperbilirubinemia, and anemia. All other Grade 3/4 AEs were experienced by one

patient only.

Table. 2 Most Frequently Reported AEs (≥ 10% Patients Reporting AE of Any Grade in Both Parts I and II), Grade 3/4 and Relationship of AE to Study Drug in Parts I and II

	Part I		Part II	
	RO5083945 (50-1400 mg) qW, q2W or q3W N = 75		RO5083945 (1400 mg) d1 & d8, q2W N = 25	
Patients with at least one:	All Grade	Grade 3/4	All Grade	Grade 3/4
Rash *	60 (80%)	19 (25%)	25 (100%)	5 (20%)
	60 (80%)	**19 (25%)**	**25 (100%)**	**5 (20%)**
IRR	58 (77%)	6 (8%)	21 (84%)	1 (4%)
	58 (77%)	**6 (8%)**	**21 (84%)**	**1 (4%)**
Asthenia	40 (53%)	3 (4%)	19 (76%)	–
	18 (24%)	**1 (1%)**	5 (20%)	**–**
Hypomagnesemia †	26 (35%)	2 (3%)	20 (80%)	5 (20%)
	21 (28%)	**2 (3%)**	**19 (76%)**	**5 (20%)**
Decreased appetite	16 (21%)	–	12 (48%)	
	6 (8%)	**–**	**1 (1%)**	
Paronychia	16 (21%)	2 (3%)	11 (44%)	1 (4%)
	15 (20%)	**2 (3%)**	**11 (44%)**	**1 (4%)**
Diarrhoea	18 (24%)	–	8 (32%)	–
	9 (12%)	**–**	**4 (16%)**	**–**
Vomiting	17 (23%)	–	3 (12%)	–
	6 (8%)	**–**	**1 (1%)**	**–**
Nausea	14 (19%)	–	5 (20%)	–
	7 (9%)	**–**	**–**	**–**
Constipation	13 (17%)	–	4 (16%)	–
	–	**–**	**–**	**–**
Dry Skin	10 (13%)	–	7 (28%)	–
	10 (13%)	**–**	**7 (28%)**	**–**
Stomatitis	12 (16%)	–	4 (16%)	–
	12 (16%)	**–**	**4 (16%)**	**–**
Pyrexia	10 (13%)	–	5 (20%)	–
	3 (4%)	**–**	**2 (8%)**	**–**

Only AEs (of any grade) reported by ≥ 10% patients in both Parts I and II are shown.

Values in bold are AEs considered to be related to study drug.

* Includes the preferred term dermatitis acneiform.

† The incidence rate of hypomagnesemia based on NCI-CTCAE grades from biochemistry laboratory values following conversion of Investigator Units to SI Units was 56% (42/75 patients) in Part I (2/75 [5%] Grade 3/4) and 92% (23/25 patients) in Part II (6/25 [24%] Grade 3/4).

All AEs of rash and IRRs, and the large majority of other dermatological toxicities (paronychia, pruritis, dry skin and erythema nodosum) and hypomagnesemia, were considered to be related to study drug treatment by the Investigator (Table 2).

In the dose escalation (Part I) the incidence of treatment-related rash and hypomagnesemia appeared to be dose-related, while for IRRs, there was no correlation between RO5083945 dose and the incidence of IRRs in either of the schedules.

There were 24 SAEs affecting 20 patients in Part I and Part II. All of the 6 SAEs related to study treatment were in Part I. Four of these treatment-related SAEs were IRRs. The other treatment-related SAEs were erythema nodosum in a single patient and confusional state which occurred within 24 hours of the first infusion in a patient with brain metastasis diagnosed on the same day. All treatment-related SAEs resolved without sequelae following treatment or withdrawal except for the one patient with erythema nodosum which was ongoing at final contact.

Of the 8 patients who died in Parts I and II, 5 died of progressive disease. The cause of death for the other 3 patients was hematemesis related to underlying disease, pneumonia and cardiac failure and acute pulmonary oedema in a patient who had a history of cardiac disease. None of the deaths was considered by the Investigator to be related to RO5083945 treatment.

For most hematological and biochemical clinical laboratory safety parameters, there were no clinically significant changes of mean values from baseline following initial dosing or on subsequent cycles of RO5083945 administration for any dose or schedule. Mean magnesium levels in both Part I and Part II decreased from a value of ~0.82 mmol/L at baseline to ≤ 0.60 mmol/L after 5 cycles or more of RO5083945 treatment (normal range: 0.8-1.2 mmol/L).

The most commonly reported treatment-emergent Grade 3/4 shifts in biochemical laboratory parameters were elevated GGT (26 patients), elevated ALP (10 patients) and decreased magnesium (10 patients). The majority of patients with elevated liver enzyme parameters had liver metastatic lesions at study entry and elevated liver enzyme parameters at baseline.

No apparent trend for clinically significant changes from pre-infusion baseline values was seen for ECG parameters, supine systolic and diastolic BP, or heart rate during the initial RO5083945 infusion on subsequent cycles following cumulative dosing of RO5083945.

CONCLUSIONS:

In conclusion, RO5083945 demonstrated an acceptable safety profile and promising anti-tumor activity in a heavily pre-treated patient population, including third-line treatment for CRC patients with KRAS mutations. The major findings addressing the primary and secondary objectives of Study BO21495 were as follows:

Part I

In patients with metastatic and/or locally advanced malignant solid tumors overexpressing EGFR:

- RO5083945 exposure (AUC and C_{max}) increased approximately dose-proportionally for doses between 400-1400 mg. Target therapeutic concentrations of 50 µg/mL were reached in all subjects at ≥ 700 mg qW and for the entire dosing interval in the majority of patients administered RO5083945 at 1400 mg, q2W. The MTD was not reached up to the maximum 1400 mg dose in either qW, q2W or q3W regimens.
- The overall safety profile of RO5083945 was acceptable. The large majority of AEs (89.5%) were Grade 1 or 2 in intensity. The most frequently reported drug-related AEs were rash (80% including the preferred term acneiform dermatitis) followed by IRRs (58/75 [77%] patients, 19/75 [25%] Grade 3/4), asthenia (40/75 [53%], 3/75 [4%] Grade

3/4) and hypomagnesemia (26/75 [35%], 2/75 Grade 3/4 [3%]). There was a trend for a dose-related increase in the incidence and severity of rash and hypomagnesemia, while IRRs occurred independently of RO5083945 dose. RO5083945 was generally well tolerated. Eight patients withdrew from study treatment due to an AE. Of the AEs leading to the deaths of three patients, none was considered by the Investigator to be related to study drug treatment.

- Preliminary anti-tumor activity was inferred by best overall responses of 1 CR and 2 PRs all in patients with CRC, of which one PR was for a patient with a tumor harboring a KRAS G12D mutation, and SD in 29 patients.
- Objective tumor responses and confirmed stable disease were observed in patients of all FcγRIIIa (CD16) polymorphisms known to affect macrophage/NK CD16-antibody binding affinity.
- Based on the PK, safety profile and preliminary efficacy data, and PK simulations using a population PK model, the chosen dose for Part II was 1400 mg on Day 1 and 8 followed by 1400 mg q2W for subsequent infusions/

Part II

- In patients with metastatic and/or locally advanced CRC expressing EGFR and mutant KRAS:
- The TGCR (defined as CR, PR and SD > 2 months after start of study medication (SD confirmed at 16 week tumor assessment) was 24% (6/25 patients). The best overall response in this study was stable disease in 10/25 patients (40% at 8 weeks) and progressive disease in 15/25 patients (60%). There were no objective responses (CRs or PRs). Confirmed SDs were observed in patients with each of the FcγRIIIa (CD16) polymorphisms known to affect macrophage/NK CD16-antibody binding and independently of KRAS mutational status of the tumor.
- The safety profile was generally consistent with that described during the dose escalation in Part I. Rash (in all 25 [100%] patients, 5/25 [20%] Grade 3/4), IRRs (21/25 [84%], 1/25 [4%] Grade 3/4), and hypomagnesemia (20/25 [80%] patients, 5/25 [20%] Grade 3/4), were again the most frequently reported treatment-related AEs. The dose and regimen chosen for Part II was well tolerated. There were no AEs leading to death, RO5083945 withdrawal or dose modification.
- Of the PD biomarkers reflecting immune effector cell modulation, RO5083945 treatment caused:
  - enhanced tumor infiltration of CD68+ macrophages (in 8/10 evaluable tumor pairs), and CD16+ cells (macrophages and NK lymphocytes – in 6/9 evaluable tumor pairs), accompanied by significant reductions in detectable NK lymphocytes (CD3–/16+ and/or CD56+, as well as CD8NK) circulating in the peripheral blood (with both fewer numbers of CD16 -expressing cells and reduced CD16 expression on the surface of the remaining NK cells)
  - an infiltration of immune cells involved in ADCC in skin rash biopsies, and to a lesser extent in on-treatment normal skin, compared to normal skin biopsies taken in the same patient at baseline.
- Of the PD biomarkers reflecting inhibition of EGFR and downstream signaling, treatment with RO5083945 caused a marginal reduction of nuclear pERK expression in 5 out of 7 evaluable paired tumor biopsy samples (–13.0 [–38, 7]% change from baseline.