Abbreviated Clinical Trial Report

Zalutumumab
GEN206

A dose-escalation, randomized phase I/II trial of zalutumumab - a human monoclonal anti-EGF receptor antibody - with or without irinotecan chemotherapy in cetuximab refractory colorectal cancer patients who have failed standard chemotherapy and progressed during or within 6 months of stopping cetuximab-based therapy

Title Page

Title of Trial	A dose-escalation, randomized phase I/II trial of zalutumumab - a human monoclonal anti-EGF receptor antibody - with or without irinotecan chemotherapy in cetuximab refractory colorectal cancer patients who have failed standard chemotherapy and progressed during or within 6 months of stopping cetuximab-based therapy
Trial ID	GEN206
Development Phase	Phase I
EudraCT number	2007-005690-59
Generic Name	Zalutumumab
Indication	Colorectal cancer
Investigators	3 principal investigators at 3 sites, including the international coordinating investigator: [redacted] Belgium
Trial Sites	The trial was conducted at 3 sites in Belgium.
Trial Initiated	24-Apr-2008 (first informed consent signed)
Trial Prematurely Terminated	The trial was terminated 21-Oct-2008 (date of information to regulatory authorities). Data cut-off date (last patient last visit): 12-Feb-2009.
Sponsor	Genmab A/S Bredgade 34 DK 1253 Copenhagen K, Denmark
Responsible Medical Officer	[redacted], MD, PhD, Genmab A/S
International Clinical Trial Manager	[redacted], PhD, Genmab A/S
Statistician	[redacted], PhD, Genmab A/S
Medical Writer	[redacted], PhD, Genmab A/S

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Synopsis

Please refer to the separate synopsis document.

Table of Contents

[redacted]

[redacted]

[redacted]

List of Appendices

[redacted]

List of in-text Tables

List of in-text Figures

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT/ALAT	alanine amino transferase
ALP	alkaline phosphatase
CIOMS	the Council for International Organizations of Medical Sciences
C_{max}	maximum concentration of zalutumumab
CRC	colorectal cancer
CRF	case report form
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CTR	clinical trial report
C_{trough}	pre-infusion concentration
DLT	dose limiting toxicity
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
HAHA	human anti human antibodies
HIV	human immunodeficiency virus
IDMC	independent data monitoring committee
IRC	independent review committee
K_e	elimination rate
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
MPA	master of public administration
MRI	magnetic resonance imaging
PFS	progression free survival
PK	pharmacokinetics
SAE	serious adverse event
SCCHN	squamous cell carcinoma in head and neck
T_{max}	time of C_{max}
WBC	white blood cell

1 Methodology

1.1 Introduction and objectives

This abbreviated clinical trial report (CTR) reports data from the clinical phase I trial GEN206 for the use of zalutumumab in patients with colorectal cancer (CRC).

The trial was designed to evaluate the safety, efficacy, and pharmacokinetic profile of zalutumumab with or without irinotecan chemotherapy in patients with CRC who had failed previous standard chemotherapy and who had progressed during or within 6* months of stopping treatment with cetuximab and irinotecan. Patients who had previously been treated with anti-epidermal growth factor receptor (EGFR) antibodies other than cetuximab were not eligible for the trial. The inclusion and exclusion criteria are presented in detail in the protocol; see Appendix 1.1.

1.2 Overall trial design and assessments

1.2.1 Trial design

The trial design was originally divided in 2 consecutive parts. Part 1 was an open-label dose-escalation design investigating the safety of 8 mg/kg and 16 mg/kg zalutumumab administered intravenously once weekly in combination with irinotecan 180 mg/m^2 every 2 weeks. A total of 3-15 eligible patients were planned to be included in Part 1 (Figure 1.1). The safety of 8 mg/kg and 16 mg/kg zalutumumab administered in combination with irinotecan was evaluated by an independent data monitoring committee (IDMC) (Section 1.2.2).

Figure 1.1: Dose-Escalation of Part 1: Zalutumumab+Irinotecan (CPT-11)

* The time frame for finishing cetuximab based therapy was changed from 3 to 6 months in protocol amendment 2.

Part 2 was an open label, randomized, parallel group design with the aim to investigate the efficacy of zalutumumab with or without irinotecan. If zalutumumab in combination with irinotecan was not safe, Part 2 was to be reduced to a single arm design investigating 16 mg/kg zalutumumab as monotherapy. Patient allocation was terminated (21-Oct-2008) by Genmab A/S before Part 2 was started based on retrospective analyses of several studies with other anti-EGFR therapies (e.g. CRYSTAL and OPUS studies) (1;2) presented at ASCO in June 2008 that changed the standard treatment paradigm. Treatment recommendations were made that only patients with CRC who had wild-type *KRAS* should be treated with anti-EGFR antibodies. It was ultimately decided that trial GEN206 should be terminated after the phase I part of the trial.

This abbreviated CTR includes data from all 9 patients who participated in Part 1 of the trial. The cut-off date for the reported data (last patient last visit) was 12-Feb-2009.

1.2.2 Independent Data Monitoring Committee

The IDMC was established before trial start to ensure an effective and independent safety monitoring during the trial.

The IDMC evaluated all serious adverse events (SAEs) on an ongoing basis and monitored all non-serious adverse events (AEs) prior to the IDMC meetings, or as required, to provide evidence for safety of zalutumumab and to make recommendations for trial continuation, modification or termination temporarily or otherwise. The IDMC decided whether an SAE was a dose limiting toxicity (DLT) and also whether it was safe to proceed to the next dose level. Serious adverse events observed 4 weeks after first infusion of zalutumumab were not considered a DLT. The IDMC supported Corporate Drug Safety, Genmab A/S in performing ongoing surveillance of laboratory data throughout the trial.

Any advice from the IDMC was reported to relevant regulatory authorities.

The IDMC for this trial included:

- [redacted], MD, DMSci, MPA (chairman)
  [redacted], Denmark
- [redacted], MD, DMSci
  [redacted], Denmark
- [redacted], MD, PhD
  [redacted], Denmark

1.2.3 Clinical and laboratory assessments

Schedules of clinical and laboratory assessments during the treatment period (Visits 1-13), the follow-up, and the extended follow-up are outlined in Table 1-1. Procedures that concern administration of zalutumumab and irinotecan and concomitant medication are described in detail in the protocol; see Appendix 1.1.

The patients' eligibility for the trial was evaluated at Visit 1 (screening). From Visit 2 (Week 0) and onwards, eligible patients received weekly doses of zalutumumab in combination with irinotecan 180 mg/m^2 every 2 weeks. Administrations were to continue until disease progression, concurrent disease preventing further administration, unacceptable toxicity, or according to the wish of the patient.

The IDMC performed ongoing safety monitoring during the trial (Section 1.2.2). Safety assessments, including definitions and recording of AEs, are described in detail in the protocol; see Appendix 1.1.

A skin examination was performed every week prior to administration of zalutumumab. Skin rash was graded according to a modification of the common terminology criteria for adverse events (CTCAE) Version 3.0; see Section 4.2 and Appendix 1.1 for details.

On the day of first zalutumumab infusion (Visit 2) blood samples for determination of pharmacokinetics parameters were taken prior to the zalutumumab infusion, at end of infusion, and 30 minutes, 1 hour, 2 hours, 8 hours, and 24 hours after end of infusion. At all subsequent visits, blood samples were taken prior to the zalutumumab infusion.

Response was evaluated locally according to RECIST (3). Further details are included in Section 5.1 and in the protocol; see Appendix 1.1.

The follow-up visit was performed 4 weeks after the administration of the last dose of zalutumumab. Patients withdrawn from treatment had a tumor imaging with computerized tomography (CT) and/or magnetic resonance imaging (MRI) performed if this had not been done within the last 4 weeks.

During the extended follow-up period, the patients were followed-up at 8 week intervals for information on overall survival and SAEs.

At time of termination (21-Oct-2008), the trial status of the 9 allocated patients was as follows:

- [redacted] had died during the treatment period due to colon obstruction and pulmonary embolism, respectively.
- [redacted] were still being treated with zalutumumab and irinotecan and were allowed to continue zalutumumab and irinotecan treatment according to the protocol. At time of last patient last visit (12-Feb-2009), both patients had been withdrawn from treatment, [redacted] due to disease progression, and [redacted] due to an adverse event (bile duct obstruction; Section 4.1.7).
- [redacted] had been withdrawn from treatment [redacted]2008 due to disease progression. This patient received palliative care at home and died on [redacted]-2008.
- [redacted] had been withdrawn from treatment on [redacted]2008 due to disease progression and attended the follow-up visit [redacted]2008 (i.e. approximately [redacted] weeks after trial termination).

- [redacted] were in the extended follow-up at trial termination. [redacted] died on [redacted] 2008 due to disease progression.

Table 1-1: Flow chart of clinical assessments

	Screening	Treatment until Disease Progression												Follow up	
Clinical Assessments															
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13[a]	Follow up[b]	Extended follow up[c]
Day/Week/Month	14 d ≤w0	W0	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	4 weeks after	Every 8 weeks
Visit window			±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
Informed Consent	X[d]														
Eligibility Criteria	X														
Demographics	X														
Medical History[e]	X														
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X													X	
CT scan or MRI[f]	X							X						X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Skin examination[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Zalutumumab		X	X	X	X	X	X	X	X	X	X	X	X		
Irinotecan[j]		X		X		X		X		X		X			
Laboratory Assessments															
Biochemistry / Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test	X													X	
PK serum sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Host immune response (HAHA)	X													X	
KRAS mutation analysis	X														

a) Visits 3-13 could be repeated until disease progression.
b) Follow up visit was to be 4 weeks after last zalutumumab infusion.
c) Extended follow up was every 8 weeks via telephone for collection of overall survival and serious adverse events data.
d) Informed consent could be obtained outside the screening visit window i.e. could be prior to screening date.
e) Signs and symptoms occurring between visit 1 and 2 were recorded as Medical History.
f) Baseline CT scan and / or MRI could be obtained outside the screening window i.e. prior to screening date but within a maximum of 3 weeks prior to randomization.
g) Vital signs including temperature, BP and heart rate were measured according to local routine practice at each visit.
h) Skin examinations for rash should be done at visit 2 and onwards for all patients receiving zalutumumab and graded according to NCI CTCAE version 3.0.
i) Only serious adverse events were collected.
j) Irinotecan administration was according to local guidelines.

1.3 Statistical methods and data presentation

1.3.1 Analysis populations

Data are presented for all patients who have been exposed to zalutumumab or irinotecan, irrespective of their compliance to the planned course of treatment.

1.3.2 Presented data

The following safety data are presented:

- Adverse events
- Skin rash (CTCAE grading, duration)
- Hematology: hemoglobin, leukocytes, lymphocytes, platelets, and white blood cell differential (basophils, eosinophils, neutrophils, and monocytes)
- Biochemistry: alkaline phosphatase, alanine aminotransferase (ALT), lactate dehydrogenase (LDH), albumin, creatinine, magnesium, sodium, and potassium
- Urinalysis: blood, leukocytes, and protein
- Host immune response as assessed by human anti human antibodies (HAHA)
- Clinical safety data: vital signs (temperature, blood pressure and heart rate), physical examination, and electrocardiogram (ECG)

The following pharmacokinetic data are presented:

- Maximum concentration of zalutumumab (C_{max})
- Pre-infusion concentration (C_{trough})
- Time of C_{max} (T_{max})

The following efficacy data are presented:

- Best overall response based on CT scans as evaluated locally according to RECIST criteria
- Progression free survival (PFS) defined as the time from allocation (first dose) until disease progression according to the local evaluation at site, or death

The following additional data are presented:

- Baseline disease characteristics
- Dosing information and exposure
- Medical history
- Concomitant medication

All presented data apply to Part 1 of the trial.

Data have not been subject to any statistical hypothesis test. All data are presented using descriptive statistics in summary tables, figures or individual patient data listings.

1.4 Changes in the conduct of the trial and planned analysis

1.4.1 Protocol amendments

There were 2 protocol amendments to the clinical trial protocol dated 19-Nov-2007, see Appendix 1.1. All patients were screened after approval and implementation of amendment 1.

The following changes were made to the original protocol:

Protocol amendment 1 [redacted]-2008 elaborated on the patient population and the eligibility criteria. This implied that failure and/or intolerance to previous standard chemotherapy and disease progression during or within 3 months after stopping treatment with cetuximab were added to the inclusion criteria. Three exclusion criteria were added: diarrhea CTCAE>1, skin rash CTCAE>1, and intolerance to irinotecan. The amendment also specified that the first irinotecan treatment should be administered on the same day as the first zalutumumab treatment and that the following irinotecan infusions should be done every 2 weeks. It was clarified that the follow-up visit was to be done 4 weeks (and not 2 weeks) after the last zalutumumab infusion. It was decided that response evaluations should be done locally and that the outcome of these evaluations should be entered in the CRF. In addition, an independent review committee (IRC) should evaluate all responses retrospectively*. Clarifications of measurements concerning CT scans or MRI, physical examination, skin examination, and PK samplings were added and it was specified that hospitalization in connection with the first treatment with zalutumumab was not mandatory, but should be done at the discretion of the investigator. Communication procedures between sites and Genmab A/S were clarified.

Protocol amendment 2 [redacted]-2008 elaborated on the patient population and the eligibility criteria. This implied that the time frame for finishing cetuximab based therapy (inclusion criterion no. 4) was changed from 3 to 6 months (Section 1.4.2) and absence of KRAS mutation in the tumor specimen was added to the inclusion criteria. Furthermore, KRAS analysis was added to the clinical assessments and time windows allowed for CT scans or MRI were clarified. Information on potential risks and side effects of zalutumumab was updated, and the safety of patients who became pregnant during trial participation was elaborated.

1.4.2 Significant protocol deviations

Violation of inclusion or exclusion criteria

[redacted] had documented disease progression at screening, but had completed their cetuximab-based therapy 3-6 months earlier. Thus, they did not fulfill inclusion criterion no. 4 at the time of screening. Inclusion criterion no. 4 was “documented disease progression (verified by CT scan and/or MRI according to RECIST) during or within 6 months of finishing cetuximab-based therapy”. External medical experts advised that it was expected that

* Only local response evaluations were done due to trial termination.

patients eligible for the trial would progress within 3 to 6 months after having terminated cetuximab based therapy. It was therefore decided that these patients should have the opportunity to participate in the trial, as they would otherwise have been left with limited treatment options. The time frame for finishing cetuximab based therapy was therefore changed from 3 to 6 months in protocol amendment 2.

[redacted] had received panitumumab as prior therapy [redacted] years before she started treatment with zalutumumab and therefore met exclusion criterion no. 1. Exclusion criterion no. 1 was "prior treatment with anti-EGFR antibodies other than cetuximab". The discrepancy occurred because the trial site was to obtain information on the patient from another hospital and the site was unaware that it had not received all information on the patient's medical history at time of enrollment. It was decided to allow the patient to continue in the trial and the patient was closely monitored. The patient had been treated with cetuximab 0.1 years before she started treatment with zalutumumab; see EoT Listing 02.04

Violation of visit windows and treatment compliance

[redacted] attended the follow-up visit 1 week after they had received the last zalutumumab dosage. The protocol prescribed that the follow-up visit was to be performed 4 weeks after the last administrated dose. This protocol deviation may result in limited informative data on host immune response for these patients.

Assessment and treatment deviations

[redacted] had a CT scan performed on [redacted]-2008, but the result was not available on [redacted]-2008 where the patient received the planned treatment with zalutumumab ([redacted]). The result from the CT scan was available [redacted]-2008 and showed progressive disease. This was a protocol deviation, because the patient received zalutumumab treatment after disease progression.

Follow-up on adverse events

According to the protocol, a grade ≥ 3 AE should be followed until the AE had been resolved or until the investigator assessed it as chronic or stable. [redacted] had 2 events ('fatigue' (grade 3) and 'increased transaminases' (grade 3) with outcome recorded as 'not recovered' at time of data cut-off ([redacted]2009); see EoT Listing 07.05. On [redacted]2009, Genmab A/S was informed that the event 'fatigue' is yet ongoing with a severity grade between 1 and 2 and that the patient had recovered from the event 'increased transaminases'.

1.4.3 Changes in the planned analysis

According to the statistical analysis plan, the pharmacokinetic endpoints: area under concentration-time curve from start of first infusion to 168 hours ($AUC_{0\text{-}168h}$), half-life ($T_{½}$), clearance (CL), and volume of distribution (V) were to be derived from the terminal phase of the pharmacokinetic profile. However, as the distribution phase of human monoclonal antibodies are expected to be 3-4 days after infusion, the PK sampling scheme in the protocol provided limited information for the estimation. These parameters were therefore not estimated.

2 Patient disposition

The patient disposition is presented in Table 2-1. A total of 11 patients were screened for this trial and 9 patients were exposed (8 mg/kg: 3 patients; 16 mg/kg: 6 patients). The number of infusions ranged from 8 to 13 in the 8 mg/kg group and from 6 to 19 in the 16 mg/kg group; see EoT Table 03.01.

[redacted] died during the treatment period due to colon obstruction and pulmonary embolism, respectively. Six patients were withdrawn from treatment due to disease progression after having received 7, 19, 6, 12, 12, and 13 doses of zalutumumab (see EoT Listing 02.10). One patient was withdrawn from treatment due to a serious adverse event (bile duct obstruction) after having received 18 doses of zalutumumab (Section 4.1.7).
Six of these patients attended the scheduled follow-up visit; see EoT Listing 02.12. [redacted] was withdrawn from treatment due to disease progression and subsequently received palliative care at home. The patient died at home before the follow-up visit; see Section 4.1.7. The trial status of the 9 allocated patients at time of trial termination is described in Section 1.1.

Narratives for the deaths are included in Section 4.1.7.

All 9 exposed patients are included in the safety population.

Table 2-1: Patient disposition, exposed patients

	8 mg/kg + Irinotecan	16 mg/kg + Irinotecan	Total
	N	N	N (%)
Exposed	3	6	9
Withdrawn from Treatment	3	6	9 (100%)
Disease Progression	2	4	6 (67%)
Adverse event	0	1	1 (11%)
Death	1	1	2 (22%)
Entered follow-up	2	4	6 (67%)
End of trial	3	6	9 (100%)
Disease Progression	0	1	1 (11%)
Death	2	2	4 (44%)
Other	1	3	4 (44%)

N : Number of patients
% : Percentages of patients
GEN206 07JAN2010 Program: tab01.01.sas
"Other" is 4 patients with end of trial due to trial termination.

Cross-reference: EoT Table 01.01

GEN206 / Figure 1.1.sas 20OCT2009

Figure 2.1: Flow of visits by patient

Note: [redacted] was withdrawn from treatment [redacted]-2008 due to disease progression and subsequently received palliative care at home. The patient died on [redacted]-2008. Information on the death was obtained on [redacted] 2008 (date of the completed observational contact form).
Cross-reference: EoT Figure 1.01.

Demographic and other baseline characteristics

The median age was 61 years (range: 33-76 years), 6 patients were females, 6 patients were white, and 3 patients were hispanic or latino; see EoT Table 02.01 for a summary table of baseline demographics.

The overall disease characteristics of patients in this trial population are consistent with the eligibility criteria requirements; see protocol in Appendix 1.1. Baseline disease characteristics are presented in Table 2-2. [redacted] had rectum cancer, while the remaining 8 patients had colon cancer. Overall, the disease characteristics reflected the advanced disease status of the patients. The median duration of CRC was 4.1 years (range: 1-8 years) and the majority of the patients (n=8) had CRC staging IV at baseline and 1 patient had CRC staging IIIC. All patients had documented

disease progression at baseline, had previously received cetuximab and irinotecan treatment, and had a WHO performance status ≤ 2, as required by the inclusion criteria.

For summary displays of baseline hematology and biochemistry parameters, see EoT Tables 02.03 and 02.04.

Table 2-2: Diagnosis of Colorectal Cancer (CRC) and Prior Treatments, exposed patients

	8 mg/kg + Irinotecan	16 mg/kg + Irinotecan	Total
	N	N	N (%)
Exposed	3	6	9
Duration of CRC (years)			
N	3	6	9
Min	4	1	1
Median	5.6	3.4	4.1
Max	6	8	8
TNM classification, N(%)			
T3/N0/M1	0	1	1 (11%)
T3/N1/M1	2	1	3 (33%)
T3/N2/M1	0	1	1 (11%)
T3/N2/MX	0	1	1 (11%)
TX/NX/M1	1	2	3 (33%)
PD according to RECIST at baseline			
Yes	3	6	9 (100%)
Stage, N(%)			
IIIC	0	1	1 (11%)
IV	3	5	8 (89%)
Number of prior radiotherapy regimes			
0	3	4	7 (78%)
1	0	2	2 (22%)
Number of surgeries			
1	2	1	3 (33%)
2 or more	1	5	6 (67%)
Prior comb. treatment with cetuximab and irinotecan			
Yes	3	6	9 (100%)
Time since last treatment with cetuximab and irinotecan (months)			
N	3	6	9
Min	3	1	1
Median	5.1	1.5	3.3
Max	5	11	11
WHO Performance status, N(%)			
PS 0	3	4	7 (78%)
PS 1	0	2	2 (22%)

N : Number of patients
% : Percentages of patients
GEN206 20OCT2009 Program: tab02.07.sas

Cross-reference: EoT Tables 02.02,02.05, 02.06 and 2.07

Medical history
No medical histories violated inclusion or exclusion requirements.

Current medical histories affecting 2 or more patients are summarized in Table 2-3. At screening, the patients were most often affected by hypertension (5 patients), anxiety (5 patients), and insomnia (3 patients). The rashes in 2 patients were abdominal rash in [redacted] and skin rash in [redacted]. The skin rash in [redacted] did not meet exclusion criterion no. 4 (skin rash CTCAE > 1). [redacted] also had skin rash grade 1 at Visit 2 (Section 4.2).

Table 2-3: Current medical history in ≥ 2 patients

	8 mg/kg + Irinotecan N	16 mg/kg + Irinotecan N	Total N (%)
Exposed	3	6	9
Hypertension	3	2	5 (56 %)
Anxiety	2	3	5 (56 %)
Insomnia	1	2	3 (33 %)
Rash		2	2 (22 %)
Hypothyroidism	1	1	2 (22 %)
Hypercholesterolaemia	1	1	2 (22 %)
Cancer Pain	1	1	2 (22 %)
Hydronephrosis	1	1	2 (22 %)
Iodine Allergy	2		2 (22 %)
Cataract		2	2 (22 %)

N : Number of patients
% : Percentages of patients
SOC : System Organ Class
GEN206 20OCT2009 Program: tab02.08-10.sas

Cross-reference: EoT Table 02.09.

Past medical histories were single occurrences except cataract which was reported in 2 patients; see EoT Table 02.10.

For summary displays of medical histories, see EoT Tables 02.08 (all), 02.09 (current), and 02.10 (past).

Concomitant medications
All patients reported concomitant medications at screening or during the trial.

Concomitant medications used by 4 or more of the patients are summarized in Table 2-4. For a complete summary table of concomitant medications, see EoT Table 02.11.

Dexamethasone was mainly administered as prophylactic treatment prior to irinotecan infusions. Methylprednisolone was administered as prophylactic treatment (patient [redacted]), to treat back pain [redacted]), and to treat pulmonary embolism ([redacted]).

Disallowed concomitant therapies and procedures were not used; see EoT Listing 02.09.

Table 2-4: Concomitant medication (used by ≥ 3 patients) by ATC code and Generic Name

	8 mg/kg + Irinotecan		16 mg/kg + Irinotecan		Total	
	N (%)	E	N (%)	E	N (%)	E
Exposed	3		6		9	
Any concomitant medication	3 (100%)	72	6 (100%)	85	9 (100%)	157
Dexamethasone	3 (100%)	7	4 (67%)	6	7 (78%)	13
Loperamide	3 (100%)	4	2 (33%)	2	5 (56%)	6
Methylprednisolone	3 (100%)	3	2 (33%)	2	5 (56%)	5
Ondansetron	3 (100%)	5	1 (17%)	1	4 (44%)	6
Paracetamol	2 (67%)	2	2 (33%)	3	4 (44%)	5
Atropine Sulfate	3 (100%)	3	1 (17%)	1	4 (44%)	4
Fentanyl			3 (50%)	4	3 (33%)	4
Ciprofloxacin Hydrochloride	1 (33%)	2	2 (33%)	2	3 (33%)	4
Alizapride	1 (33%)	1	2 (33%)	2	3 (33%)	3
Atropine (ATC codes belladonna alkaloids, tertiary amines)			3 (50%)	3	3 (33%)	3
Omeprazole	2 (67%)	2	1 (17%)	1	3 (33%)	3
Atropine (ATC code anticholinergics)			1 (17%)	1	1 (11%)	1

N : Number of patients
% : Percentages of patients
E : Number of drugs
ATC : Anatomical Therapeutic Chemical
GEN206 20OCT09 Program: tab02.11.sas

Cross-reference: EoT Table 02.11.

3 Extent of exposure

The extent of exposure with zalutumumab is summarized in Table 3-1.

In total, zalutumumab was administered to 9 patients in this trial (8 mg/kg: 3 patients; 16 mg/kg: 6 patients). The median number of doses administered was 12 (range: 6-19).

Table 3-1: Extent of exposure with zalutumumab

	8 mg/kg + Irinotecan	16 mg/kg + Irinotecan	Total
	N	N	N
Exposed	3	6	9
Number of infusions of zalutumumab			
N	3	6	9
Min	8	6	6
Median	12	13	12
Max	13	19	19
Total dose of zalutumumab (mg)			
N	3	6	9
Min	5352	5406	5352
Median	6312	11900	9872
Max	10096	25325	25325
Duration of dosing (weeks)			
N	3	6	9
Min	7.1	5.1	5.1
Median	11.3	11.6	11.3
Max	13.1	18.3	18.3

N : Number of patients
GEN206 07JAN2010 Program: tab03.01.sas

Cross-reference: EoT Table 03.01.

Overall, the majority of patients adhered to the scheduled zalutumumab dosing and infusion rate. No zalutumumab infusions were skipped due to skin rashes; see EoT Listing 03.01.

Zalutumumab and irinotecan infusions were skipped at Visit 20 in [redacted] due to an AE (bilateral biliar obstruction grade 3); the event is described in Section 4.1.7.

Irinotecan infusions were skipped at Visit [redacted] in [redacted] due to neutropenia grade 3 and diarrhoea grade 3, and at Visit [redacted] in [redacted] due to pulmonary embolism grade 4; see EoT Listing 03.02. The event of pulmonary embolism is described in Section 4.1.7.

4 Safety evaluation

4.1 Adverse Events

The presented AE data include the AEs that had onset after commencement of zalutumumab treatment.

The investigator used the common terminology criteria for adverse events (CTCAE) version 3 to describe the maximum severity of the AE. Throughout this section "CTCAE grade" will be denoted as "grade".

Narratives for SAEs and other significant AEs are included end-of-text.

4.1.1 Overview of Adverse Events

A total of 101 adverse events were reported in 8 of 9 patients in the trial (Table 4-1). The majority of AEs (84/101; 83%) were of grade 1 or 2 in intensity and 17 AEs were of grade 3 or higher: grade 3: 12 events, grade 4: 1 event; grade 5: 4 events. Six of the AEs were serious. No SAEs were judged by the investigator to be related to zalutumumab or irinotecan.

A maximum tolerated dose was not reached and no patients experienced any dose limiting toxicity.

Table 4-1: Overall summary of Adverse Events, exposed patients

	8 mg/kg + Irinotecan N (%) E	16 mg/kg + Irinotecan N (%) E	Total N (%) E
Exposed	3	6	9
All AEs	3 (100%) 32	5 (83%) 69	8 (89%) 101
Deaths	2 (67%) 2	2 (33%) 2	4 (44%) 4
Serious AEs	2 (67%) 3	3 (50%) 3	5 (56%) 6
AEs with severity grade 3 and 4	2 (67%) 2	4 (67%) 11	6 (67%) 13
AEs leading to withdrawal from treatment	1 (33%) 1	3 (50%) 3	4 (44%) 4 *
AEs related to Zalutumumab/Irinotecan	3 (100%) 6	5 (83%) 29	8 (89%) 35
AEs on any infusion day	3 (100%) 10	5 (83%) 41	8 (89%) 51
Infusion related AEs on any infusion day	3 (100%) 5	5 (83%) 6	8 (89%) 11

N : Number of patients with Adverse Events (AEs)
% : Percentages of patients
E : Number of adverse events
GEN206 07JAN2010 Program: tab06.01.sas
* One AE lead the patient being withdrawn from treatment; the 3 other treatment withdrawals were due to AEs that had a fatal outcome.
Cross-reference: EoT Table 06.01.

4.1.2 Frequent Adverse Events

The majority of the AEs were reported within the system organ classes ‘gastrointestinal disorders’ (32 events), ‘skin and subcutaneous tissue disorders’ (17 events), and ‘general disorders and administration site conditions’(10 events); see EoT Table 06.02.

The most frequently reported terms included nausea, dry skin, fatigue, diarrhea, rash, anorexia, vomiting, dyspnea, and neutropenia, as presented in Table 4-2. The majority of these events are expected side effects of treatment with a monoclonal antibody targeting the EGF receptor.

The remaining AEs presented in Table 4-2 were reported by no more than 2 patients. For a summary tabulation of all AEs by MedDRA system organ class and preferred term, see EoT Table 06.02.

Table 4-2: Frequent Adverse Events (N ≥ 2) by Preferred Term

	8 mg/kg + Irinotecan		16 mg/kg + Irinotecan		Total	
	N	(%) E	N	(%) E	N	(%) E
Exposed	3		6		9	
Total number of AEs	3	(100%) 32	5	(83%) 69	8	(89%) 101
Nausea	3	(100%) 4	4	(67%) 4	7	(78%) 8
Dry Skin	2	(67%) 2	5	(83%) 5	7	(78%) 7
Fatigue	3	(100%) 3	4	(67%) 4	7	(78%) 7
Diarrhea	3	(100%) 5	3	(50%) 6	6	(67%) 11
Rash	2	(67%) 2	4	(67%) 4	6	(67%) 6
Anorexia	2	(67%) 2	2	(33%) 2	4	(44%) 4
Vomiting	2	(67%) 3	1	(17%) 1	3	(33%) 4
Dyspnoea			3	(50%) 3	3	(33%) 3
Neutropenia			2	(33%) 3	2	(22%) 3
Abdominal Pain			2	(33%) 2	2	(22%) 2
Disease Progression	1	(33%) 1	1	(17%) 1	2	(22%) 2
Pulmonary Embolism	2	(67%) 2			2	(22%) 2
Urinary Tract Infection	1	(33%) 1	1	(17%) 1	2	(22%) 2
Headache	1	(33%) 1	1	(17%) 1	2	(22%) 2
Myalgia			2	(33%) 2	2	(22%) 2

N : Number of patients with Adverse Events (AEs)
% : Percentages of patients
E : Number of adverse events
SOC : System Organ Class
GEN206 20OCT09 Program: tab06.02-16.sas

Cross-reference: EoT Table 06.02.

4.1.3 Adverse Events by relationship to trial product

The investigator assessed whether an AE was related or not related to trial product, i.e. zalutumumab and irinotecan.

The AEs assessed by the investigator as related to trial product are summarized in Table 4-3.

Table 4-3: Adverse Events related to zalutumumab or Irinotecan by MedDRA SOC and Preferred Term

	8 mg/kg + Irinotecan		16 mg/kg + Irinotecan		Total	
	N (%)	E	N (%)	E	N (%)	E
Exposed	3		6		9	
Total number of AEs	3 (100%)	6	5 (83%)	29	8 (89%)	35
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (100%)	4	5 (83%)	11	8 (89%)	15
Dry Skin	2 (67%)	2	5 (83%)	5	7 (78%)	7
Rash	2 (67%)	2	4 (67%)	4	6 (67%)	6
Pruritus			1 (17%)	1	1 (11%)	1
Skin Fissures			1 (17%)	1	1 (11%)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (67%)	2	2 (33%)	2	4 (44%)	4
Fatigue	2 (67%)	2	2 (33%)	2	4 (44%)	4
GASTROINTESTINAL DISORDERS			3 (50%)	6	3 (33%)	6
Diarrhoea			2 (33%)	4	2 (22%)	4
Dry Mouth			1 (17%)	1	1 (11%)	1
Nausea			1 (17%)	1	1 (11%)	1
EYE DISORDERS			2 (33%)	3	2 (22%)	3
Conjunctivitis			1 (17%)	1	1 (11%)	1
Dry Eye			1 (17%)	1	1 (11%)	1
Eye Irritation			1 (17%)	1	1 (11%)	1
METABOLISM AND NUTRITION DISORDERS			2 (33%)	2	2 (22%)	2
Anorexia			1 (17%)	1	1 (11%)	1
Hypomagnesaemia			1 (17%)	1	1 (11%)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			2 (33%)	2	2 (22%)	2
Myalgia			2 (33%)	2	2 (22%)	2
NERVOUS SYSTEM DISORDERS			1 (17%)	2	1 (11%)	2
Dizziness			1 (17%)	1	1 (11%)	1
Headache			1 (17%)	1	1 (11%)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS			1 (17%)	1	1 (11%)	1
Neutropenia			1 (17%)	1	1 (11%)	1

N : Number of patients with Adverse Events (AEs)
% : Percentages of patients
E : Number of adverse events
SOC : System Organ Class
GEN206 20OCT09 Program: tab06.02-16.sas

Cross-reference: EoT Table 06.03.

The majority of AEs (31 of 35) with a relation to trial product were of grade 1 or 2 in intensity, see EoT Listing 07.02. The remaining 4 AEs were of grade 3 in intensity and were 2 events of diarrhoea, 1 event of neutropenia, and 1 event of fatigue. These 4 events are considered in more detail in Section 4.1.5. None of the AEs with a relation to trial product were serious and none led to withdrawal from treatment.

4.1.4 Adverse Events leading to withdrawals

One AE (bile duct obstruction grade 3) led to withdrawal from treatment. The AE withdrawal was serious and is described in more detail in Section 4.1.7.

4.1.5 Non-serious Adverse Events – Severity Grade 3

A total of 11 non-serious AEs were grade 3 in intensity. Four non-serious grade 3 AEs (indicated in italics below) were assessed by the investigator as related to trial product:

- [redacted] **(16 mg/kg)**
  This patient experienced *fatigue* (grade 3) on the first infusion day ([redacted]2008). The reported outcome was 'not recovered'* . The patient experienced *diarrhea* (grade 3) on [redacted]2008, [redacted] days after initiation of trial treatment ([redacted] after latest dosage). The patient recovered on [redacted]-2008. The patient experienced one more event of *diarrhea* (grade 3) on [redacted]-2008, [redacted]days after initiation of trial treatment ([redacted] days after latest dosage).The patient recovered on [redacted]2008.
- [redacted] **(16 mg/kg)**
  This patient experienced *neutropenia* (grade 3) on [redacted]2008, [redacted] days after initiation of trial treatment. The event was reported on the [redacted] infusion day. The patient recovered on [redacted]2008.

Narratives of the 4 AEs are included end-of-text.

The remaining 7 non-serious grade 3 AEs were assessed as not related to trial product and were single occurrences of abdominal pain, alopecia, diarrhea, leucopenia, 2 events of neutropenia, and increased transaminases; see EoT Listing 07.05. The event increased transaminases was a clinical laboratory test AE (Section 4.4.1):

- [redacted] **(16 mg/kg)**
  This patient experienced *increased transaminases* (grade 3) on [redacted]2009, [redacted]days after initiation of trial treatment ([redacted] days after latest dosage). The reported outcome was 'not recovered'†.

A narrative of the event is included end-of-text.

4.1.6 Infusion related adverse events

Among the 101 reported AEs, 51 (50%) were reported on an infusion day and were experienced by 8 out of 9 patients; see EoT Table 06.08. The majority of the events were grade 1 and 2.

Infusion related AEs were defined by Genmab A/S using pre-specified terms in accordance with the CTCAE v3.0 definition of "allergic reaction/ hypersensitivity" and "cytokine release". Only events with onset on the day of an infusion were considered.

Eleven of the 51AEs reported on an infusion day were within the pre-specified terms for potential infusion related AE (Table 4-4). Three of the infusion related events (all fatigues) were assessed as related to trial drug by the investigator; see EoT Listing 07.13. The remaining AEs of asthenia,

* On 24-Nov-2009, Genmab A/S was informed that the event 'fatigue' is yet ongoing with a severity grade between 1 and 2.
† On 24-Nov-2009, Genmab A/S was informed that the patient had recovered from the event 'increased transaminases'.

nausea, vomiting, arthralgia, and headache might as well have been related to the patients' underlying disease.

No serious infusion related AEs were reported.

Table 4-4: Infusion-related AEs occurring on any infusion day by MedDRA SOC and Preferred Term

	8 mg/kg + Irinotecan N (%)	E	16 mg/kg + Irinotecan N (%)	E	Total N (%)	E
Exposed	3		6		9	
Total number of AEs	3 (100%)	5	5 (83%)	6	8 (89%)	11
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (67%)	2	4 (67%)	4	6 (67%)	6
Fatigue	2 (67%)	2	3 (50%)	3	5 (56%)	5
Asthenia			1 (17%)	1	1 (11%)	1
GASTROINTESTINAL DISORDERS	1 (33%)	2	1 (17%)	1	2 (22%)	3
Nausea	1 (33%)	1	1 (17%)	1	2 (22%)	2
Vomiting	1 (33%)	1			1 (11%)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			1 (17%)	1	1 (11%)	1
Arthralgia			1 (17%)	1	1 (11%)	1
NERVOUS SYSTEM DISORDERS	1 (33%)	1			1 (11%)	1
Headache	1 (33%)	1			1 (11%)	1

N : Number of patients with Adverse Events (AEs)
% : Percentages of patients
E : Number of adverse events
SOC : System Organ Class
GEN206 20OCT09 Program: tab06.02-16.sas

Cross-reference: EoT Table 06.13.

Among the 11 infusion related AEs, the reported outcome was 'recovered' for 6 events and 'not recovered' for the following 5 events: 2 events of fatigue grade 2 and single events of nausea grade 1, vomiting grade 1, and fatigue grade 3; see EoT Listing 07.12.

One non-serious grade 3 event of fatigue was reported and is considered in Section 4.1.5. The event was reported on the first infusion day; see EoT Listing 07.12. A narrative of this event is included end-of-text. Two infusion related AEs (fatigue grade 1 with outcome 'recovered' and fatigue grade 2 with outcome 'not recovered') were reported on the second infusion day.

Previous clinical experience has indicated that the following infusion related AEs may also be expected with zalutumumab: chills, flushing, pyrexia, hypotension, and hypertension. These AEs were not reported in this trial.

4.1.7 Serious Adverse Events

In total, 5 patients reported 6 SAEs during the trial (Table 4-5) and 4 had a fatal outcome. None of the SAEs were assessed as related to the trial product, see EoT Listing 07.04. SAE narratives in the

form of Council for International Organizations of Medical Sciences (CIOMS) reports are provided end-of-text.

Table 4-5: Serious Adverse Events by MedDRA SOC and Preferred Term

	8 mg/kg + Irinotecan		16 mg/kg + Irinotecan		Total	
	N (%)	E	N (%)	E	N (%)	E
Exposed	3		6		9	
Total number of AEs	2 (67%)	3	3 (50%)	3	5 (56%)	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (33%)	1	1 (17%)	1	2 (22%)	2
Disease Progression	1 (33%)	1	1 (17%)	1	2 (22%)	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (67%)	2			2 (22%)	2
Pulmonary Embolism	2 (67%)	2			2 (22%)	2
GASTROINTESTINAL DISORDERS			1 (17%)	1	1 (11%)	1
Colonic Obstruction			1 (17%)	1	1 (11%)	1
HEPATOBILIARY DISORDERS			1 (17%)	1	1 (11%)	1
Bile Duct Obstruction			1 (17%)	1	1 (11%)	1

N : Number of patients with Adverse Events (AEs)
% : Percentages of patients
E : Number of adverse events
SOC : System Organ Class
GEN206 20OCT09 Program: tab06.02-16.sas

Cross-reference: EoT Table 06.04.

The SAEs (indicated in italics) are briefly described below:

- **[redacted] (8 mg/kg; [redacted])**
  The patient was hospitalized with *pulmonary embolism* (grade 4) on [redacted]2008, [redacted] days after initiation of trial treatment ([redacted] days after latest dosage). The event was not considered related to trial product by investigator. Ongoing treatment with tinzaparine 10000 units/day was initiated on [redacted]2008. On [redacted]2008 the patient was discharged from hospital but had not yet recovered. The patient was withdrawn from zalutumumab treatment on [redacted]g 2008 due to *disease progression*. On [redacted]2008 the patient died [redacted] days after initiation of trial treatment ([redacted] days after latest dosage). The event was not considered related to trial product by investigator.
- **[redacted] (8 mg/kg; [redacted]457)**
  The patient was hospitalized with acute dyspnea on [redacted]2008, [redacted]days after initiation of trial treatment ([redacted] days after latest dosage) and died a few minutes later. The probable cause of death was *pulmonary embolism*. The event was not considered related to trial product by investigator.
- **[redacted] (16 mg/kg; [redacted])**
  The patient was withdrawn from zalutumumab treatment on [redacted]2008 due to disease progression [redacted] days after initiation of trial treatment ([redacted]days after latest dosage). The patient was subsequently treated with palliative care at home. On [redacted]2008, the patient died at

home due to *disease progression*. The event was not considered related to trial product by investigator.

- **[redacted] (16 mg/kg; [redacted])**
  The patient was hospitalized with *colon obstruction* on [redacted]2008, [redacted] days after initiation of trial treatment ([redacted] days after latest dosage). The event was not considered related to trial product by investigator. The patient died on [redacted]2008.

- **[redacted] (16 mg/kg; [redacted])**
  The patient experienced *bile duct obstruction* (grade 3) on [redacted]2009, [redacted]days after initiation of trial treatment ([redacted] days after latest dosage). The patient was withdrawn from treatment due to the event. The patient was hospitalized on [redacted]2009 and was treated by insertion of a biliar prosthesis. The patient recovered on [redacted]2009. The event was not considered related to trial product by investigator.

Overall, the risk of thromboembolic events is increased in patients with solid tumors and infra-diaphragmatic disease in particular, especially in patients with metastatic disease and treated with chemotherapy (4).The 2 events of pulmonary embolism in the GEN206 trial were reported in the low dose group (8 mg/kg) and both the investigator and sponsor assessed the events as related to the patients' underlying disease rather than zalutumumab.

4.2 Skin rash

Skin rash is a frequently occurring side effect of treatment with EGFR antibodies. The presence of skin rash may be a surrogate marker for EGFR inhibition and therefore indicates that the drug is being administered at a therapeutic level (5;6). The expected time frame for development of skin rash after an infusion of an EGFR antibody is 2-3 weeks (trial Hx-EGFr-001; data on file).

A skin examination was performed at Visit 2 and onwards prior to administration of zalutumumab. The skin examination was performed by two persons (e.g. investigator and study nurse). Skin rash was graded according to a modified CTCAE Version 3. As desquamation is not a common side effect of treatment with EGFR inhibition therapy, the patient's skin rash was scored based on rash only. In cases where the grading differed between the two examiners the highest grade was used and recorded in the CRF. A skin rash manual was supplied to all sites and is enclosed in Appendix 1.1.

Any new skin rash or worsening of previously reported skin rash compared to Visit 2 was reported as AEs.

In total, 7 out of 9 patients had skin rashes during the treatment period (Table 4-6). The maximal skin rash was grade 2 and was reported in 2 patients in the 8 mg/kg dose group.

Table 4-6: Maximal skin rash

	8 mg/kg + Irinotecan N	16 mg/kg + Irinotecan N	Total N (%)
Exposed	3	6	9
Skin Rash (any grade)	2	5	7 (78%)
- CTCAE GRADE 1	0	5	5 (56%)
- CTCAE GRADE 2	2	0	2 (22%)

N : Number of patients
% : Percentages of patients
GEN206 20OCT2009 Program: tab05.01.sas

Cross-reference: EoT Table 05.01.

Individual patient data of the skin examinations performed at Visit 2, the first occurrence of skin rash, and data from evaluations performed at the follow-up visit are presented in Table 4-7. [redacted] died during the treatment period and did therefore not attend the follow-up visit (Sections 1.2 and 4.1.7). For patient displays of results from all skin examinations; see EoT Listing 06.01.

Table 4-7: Skin examinations

Treatment arm	Patient number	Visit	Skin Rash?	Intensity
8 mg/kg + Irinotecan	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 1
		[redacted]	Yes	Grade 1
	[redacted]	[redacted]	No	
		[redacted]	No	
	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 2
16 mg/kg + Irinotecan	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 1
	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 1
		[redacted]	Yes	Grade 1
16 mg/kg + Irinotecan	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 1
	[redacted]	[redacted]	Yes	Grade 1
		[redacted]	Yes	Grade 1
16 mg/kg + Irinotecan	[redacted]	[redacted]	No	
		[redacted]	Yes	Grade 1
		[redacted]	No	
	[redacted]	[redacted]	No	
		[redacted]	No	

GEN206 20OCT09 Program: list06.01.sas

Cross-reference: Modified EoT Listing 06.01.

[redacted] had skin rash grade 1 at Visit [redacted]) and Visit [redacted] and this was therefore reported as medical history. The patient had stopped cetuximab treatment on [redacted]2008 and was administered the first zalutumumab dose on [redacted]2008. The patient had received panitumumab as prior therapy[redacted] years before trial enrolment (latest dose [redacted]2007) (Section 1.4.2).

The remaining 6 patients who had skin rash ([redacted]) developed skin rash during the trial. The skin rashes sustained during the treatment period and at the follow-up visit, except for [redacted] who did not have skin rash at the follow-up visit. [redacted] (8 mg/kg) and [redacted] (16 mg/kg) received respectively [redacted] doses and [redacted] doses of zalutumumab during the trial without developing skin rashes. Response evaluations are presented in Section 5.1.

4.3 Host immune response

The presence of human anti-human antibodies (HAHA) was tested at screening and at the follow-up visit 4 weeks after the last infusion. The analysis of HAHA was based on a bridging assay format and included a screening assay and a confirmatory assay performed by [redacted] Belgium. If HAHA was observed by the initial assays, a titer was assessed by [redacted] and a neutralization assay was performed by Genmab B.V., The Netherlands. An 8-fold titer increase or more was considered positive for HAHA development.

All analyses performed for HAHA after treatment with zalutumumab were inconclusive due to high observed levels of zalutumumab concentrations; see EoT Listing 8.1.

4.4 Clinical laboratory evaluation

4.4.1 Clinical laboratory test Adverse Events

Laboratory parameters were graded by the central laboratory according to CTCAE. As stated in the protocol, only laboratory abnormalities that required clinical intervention or further investigation (unless they were associated with an already reported clinical event) were reported as AEs.

Localization of metastases was not entered in the database.

[redacted] experienced concurrent neutropenia (grade 3) and leukopenia (grade 2) [redacted] days after initiation of zalutumumab and irinotean treatment and [redacted] days after initiation of zalutumumab and irinotecan treatment. The 4 events were not serious, were not considered related to zalutumumab and/or irinotecan, and the outcome was ‘recovered’. Two additional clinical laboratory test AEs (hypomagnesemia [grade 2] and hypokalemia [grade 1]) were reported in this patient. The hypomagnesemia was considered related to zalutumumab and/or irinotecan by the investigator. The outcomes of both events were ‘not recovered’.

[redacted] experienced concurrent hyperbilirubinemia (grade 2; outcome: ‘recovered’), increased blood alkaline phosphatase (grade 2; outcome: ‘recovered’), and increased transaminases (grade 3; outcome: ‘not recovered’), [redacted] days after initiation of zalutumumab treatment. The 3 events were not serious and were not considered related to zalutumumab and/or irinotecan. This

patient was concomitantly diagnosed with bile duct obstruction and the patient was withdrawn from treatment due to this event. The event is described in more detail in Section 4.1.7. Additional details on the hematology and biochemistry profiles in this patient are provided in the following sections.

4.4.2 Hematology

Hemoglobin

The majority of patients had hemoglobin levels below normal (Figure 4.1). This was particularly observed in patients who also had hemoglobin values below normal at baseline, see EoT Listing 04.05.

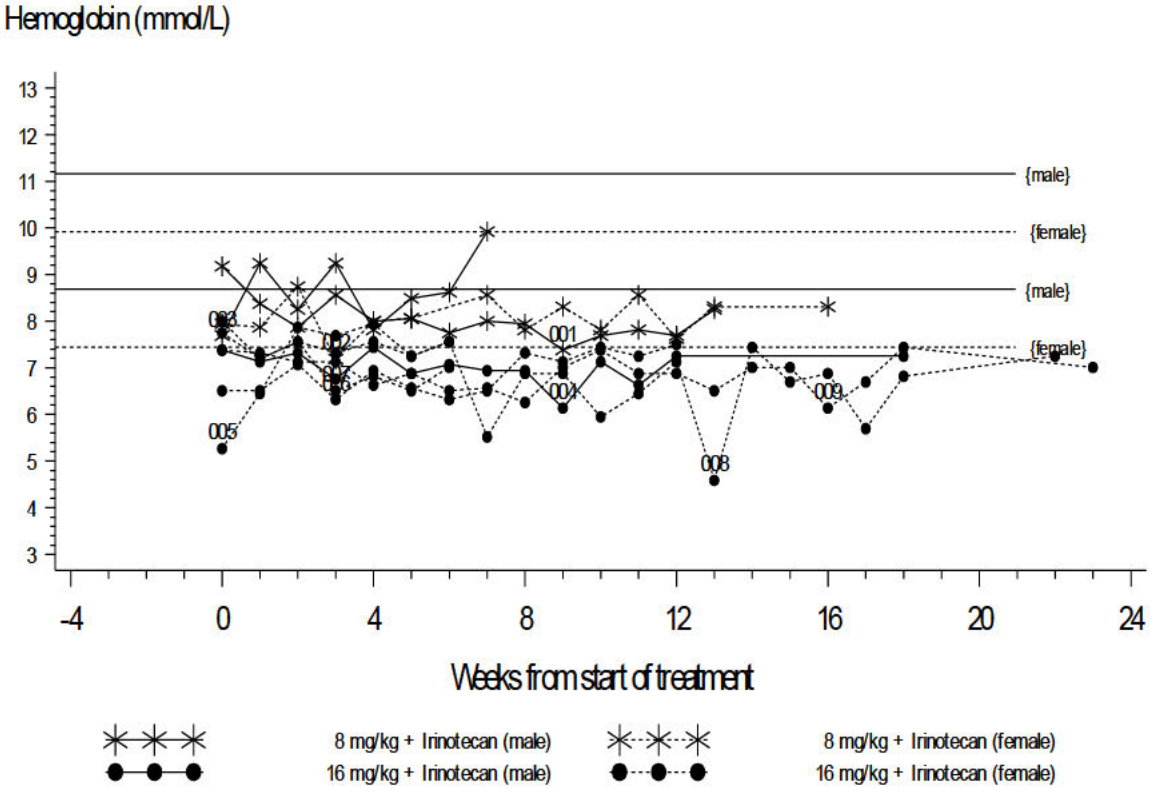

Figure 4.1: Hemoglobin

Cross-reference: EoT Figure 2.11.

Lymphocytes

Overall, the patients had lymphocyte values within or below normal range during the treatment period; see Figure 4.2. Two patients had consistent low lymphocyte values at almost all visits, [redacted], range: 10-30%; [redacted], range: 7-27%); see EoT Listing 04.05.

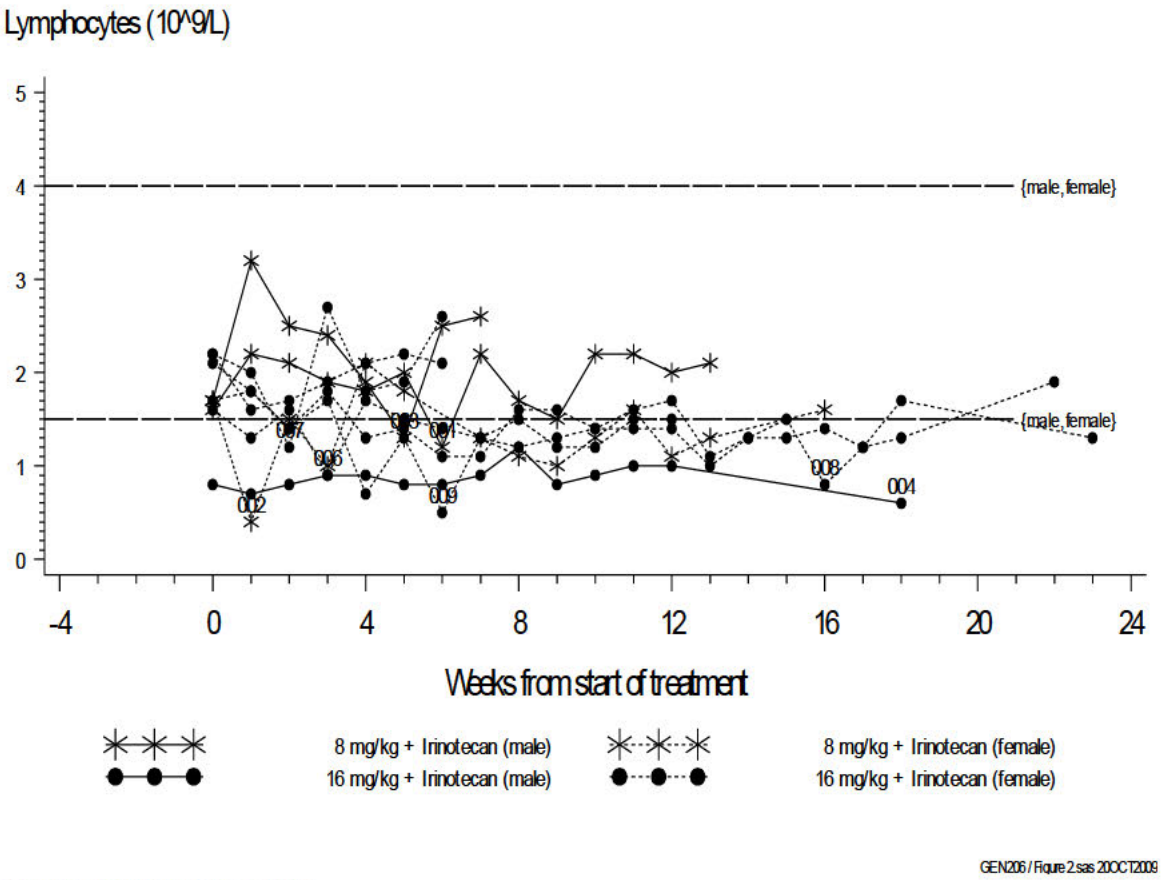

Figure 4.2: Lymphocytes

Cross-reference: EoT Figure 2.13.

Basophils, Eosinophils, Neutrophils, Monocytes, Leukocytes, and Platelets

The majority of white blood cell differential values (basophils, eosinophils, neutrophils, and monocytes) and platelets were within normal range; see EoT Figures 2.09, 2.10, 2.15, 2.14, 2.12, and 2.16. The values that were outside normal range were scattered among patients and visits, with no pattern being obvious. Myelosuppression is an expected side effect after treatment with irinotecan with typical nadir occurring at days 7-10 after infusion. Irinotecan was administered every second week in this trial and caused decreased neutrophil and leukocyte levels 1 week after infusion in the majority of the patients, as exemplified for leukocyte levels in Figure 4.3.

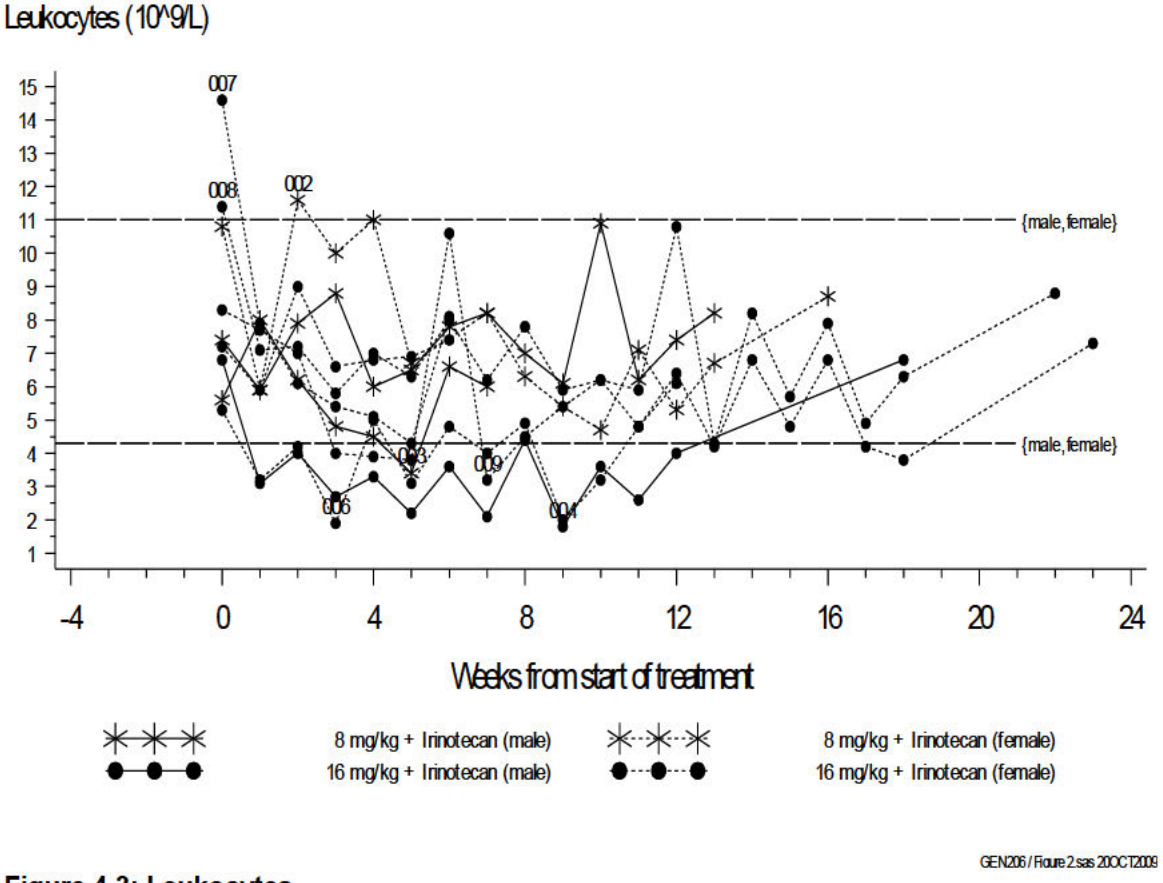

Figure 4.3: Leukocytes

Cross-reference: EoT Figure 2.12

For laboratory hematology values outside normal range, see EoT Listing 04.05 and for individual plots, see EoT Figures 2.09 to 2.16. For summary displays of changes in hematology laboratory parameters compared to baseline, see EoT Tables 07.09 to 07.16. For normal ranges of hematology parameters, see EoT Listing 04.03.

4.4.3 Biochemistry

Alkaline phosphatase

Alkaline phophatase (ALP) values were within normal range in the majority of patients during the treatment period (Figure 4.4). [redacted] had ALP values above normal range at all visits. The patient also had elevated LDH levels during the treatment period. The patient had hepatomegaly recorded as current medical history at screening.

[redacted] had ALP values above normal between baseline and Visit [redacted], but the values appeared to decrease during the treatment period. This patient had [redacted] at screening. [redacted] had normal ALP between screening and Week [redacted] but ALP levels were above normal at the 5 subsequent visits (Week [redacted]: 143 U/L; Week [redacted]: 229 U/L; Week [redacted]: 466 U/L; Week [redacted]: 597 U/L; Week [redacted]: 174 U/L). The patient had concurrent ALT levels above normal. The abnormal laboratory findings in this patient are likely due to the bile duct obstruction reported in this patient at Visit 20 (Section 4.1.7). [redacted] had ALP values above normal at all visits.

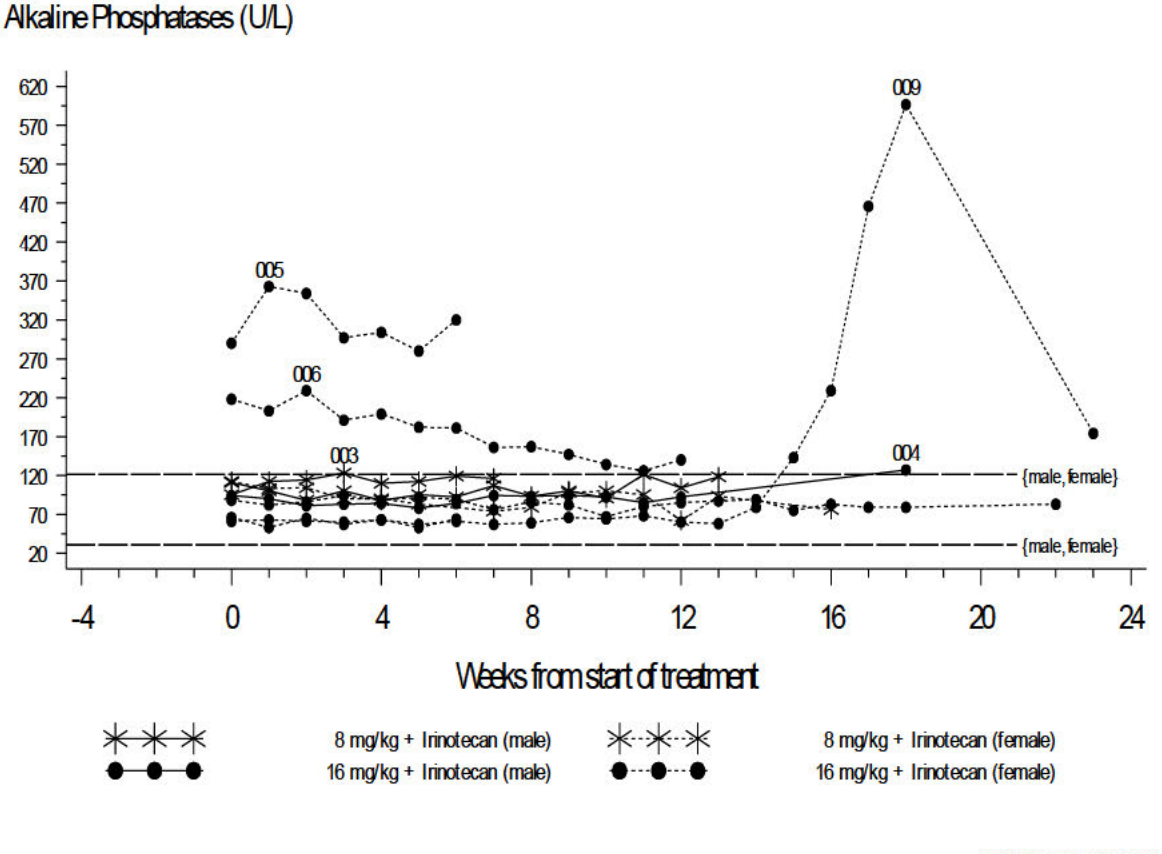

Figure 4.4: Alkaline Phosphatase (ALP)

Cross-reference: EoT Figure 2.02.

Alanine Aminotransferase (ALT)

No pattern of change was observed for alanine aminotransferase (ALT) levels during the treatment period, but relatively high values were seen sporadically for some patients (Figure 4.5). [redacted] had ALT levels within normal range between screening and Week 14, but had ALT levels above normal at the 4 subsequent visits (Week 15: 52 U/L; Week 16: 48 U/L; Week 17: 150 U/L; Week 18: 210 U/L). The patient had concurrent ALP levels above normal (see above). At the last visit (Week 23) the ALT level was 15 U/L.

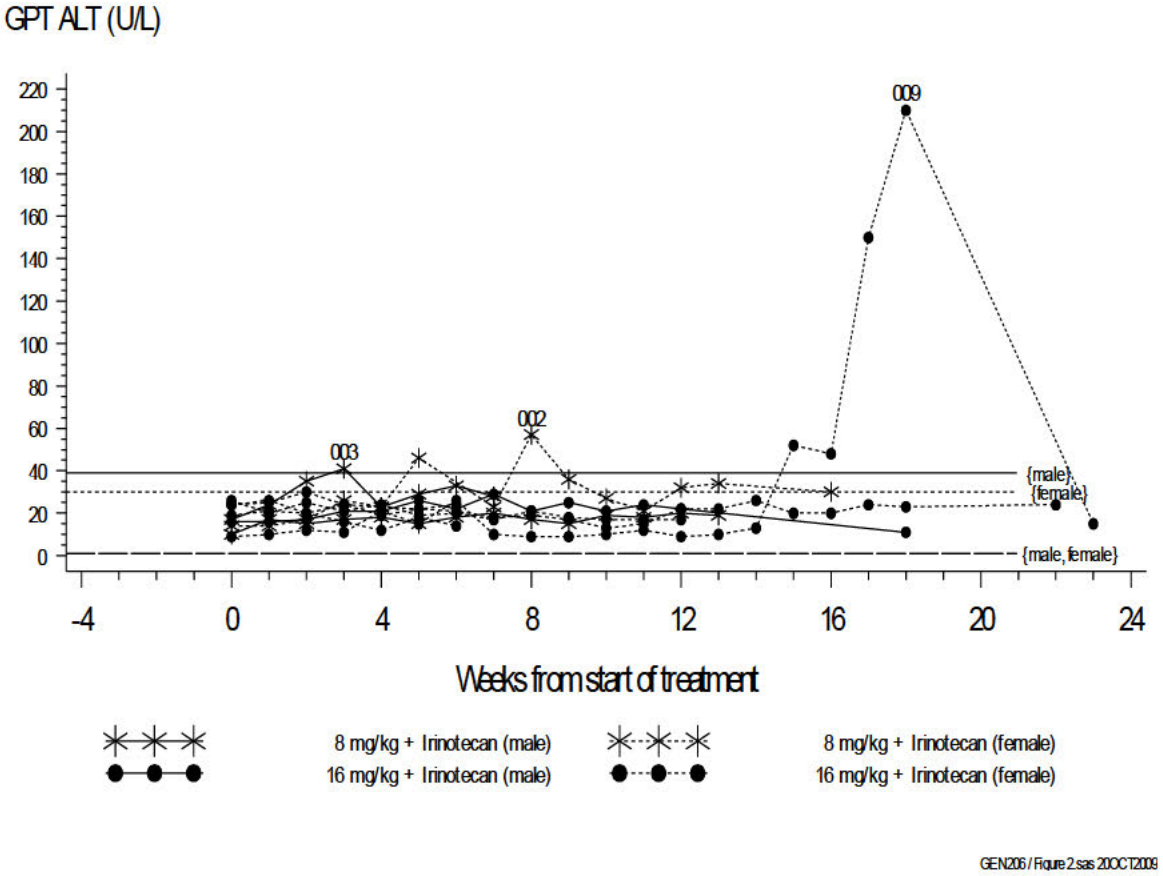

Figure 4.5: Alanine Aminotransferase (ALT)

Cross-reference: EoT Figure 2.04.

Lactate Dehydrogenase (LDH)

Overall, the patients had LDH values within or above normal range during the treatment period (Figure 4.6). [redacted] had LDH values above normal at all visits; concurrent elevated ALP values were observed in this patient (see above).

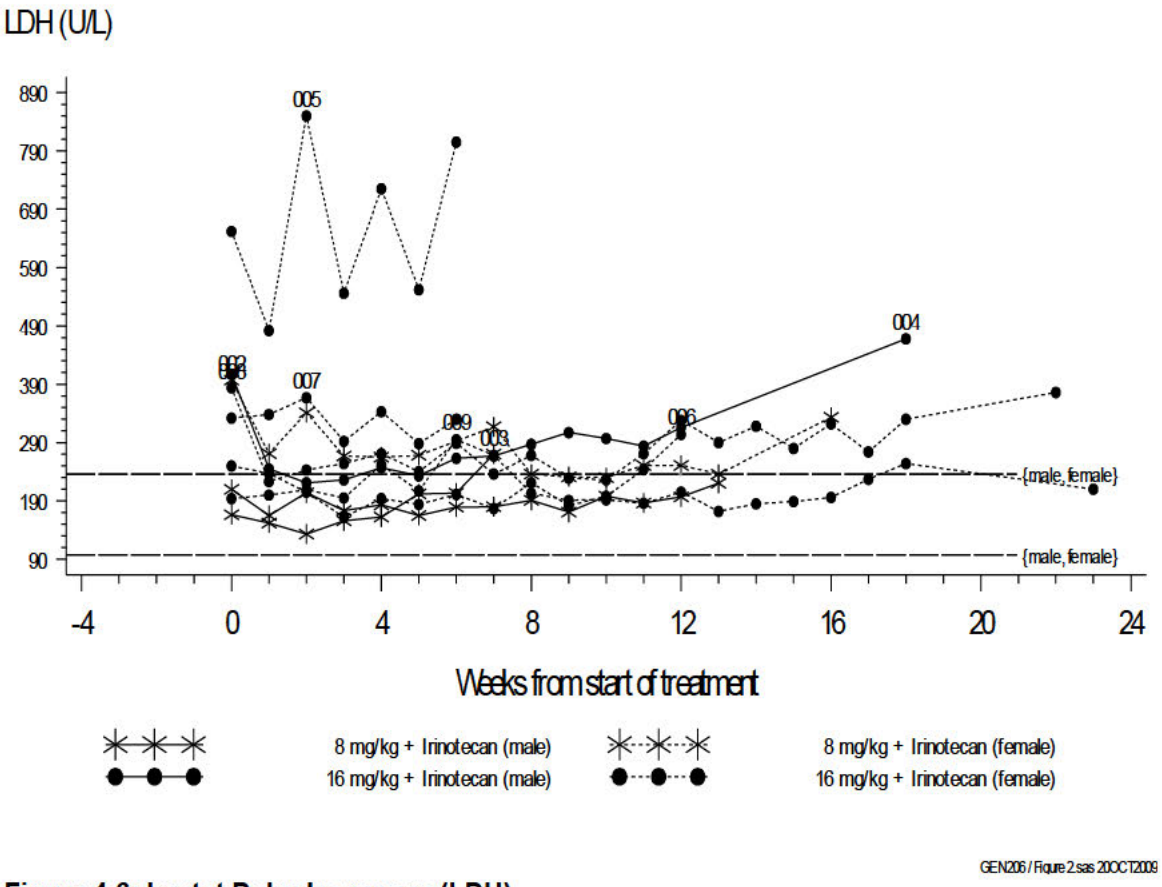

Figure 4.6: Lactat Dehydrogenase (LDH)

Cross-reference: EoT Figure 2.05.

Creatinine

Creatinine levels were within normal range in the majority of patients (Figure 4.7). [redacted] had creatinine levels above normal at all visits, including the screening visit (range: 130-146 µmol/L). These observations are likely due to the presence of hydronephrosis at screening.

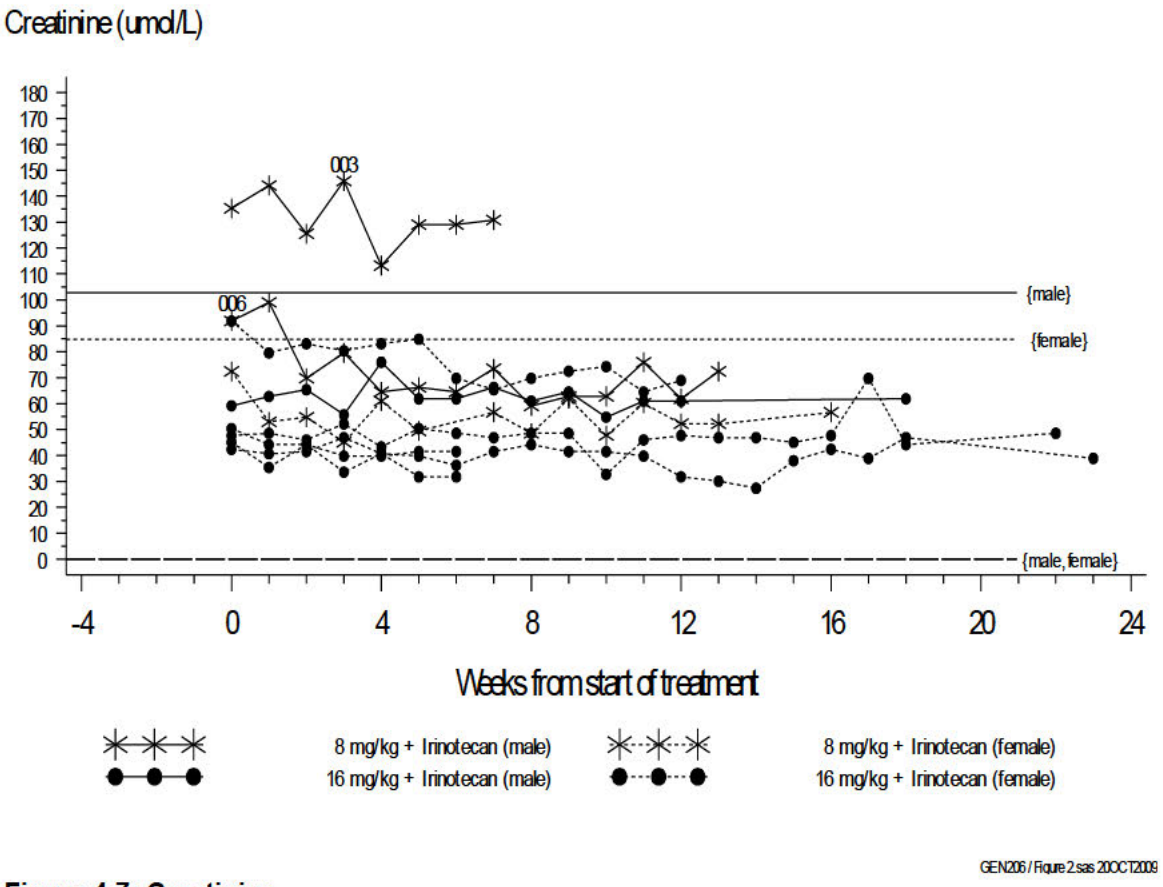

Figure 4.7: Creatinine

Cross-reference: EoT Figure 2.03.

Magnesium

Magnesium levels appeared to decrease in [redacted] during the treatment period with onset after 5-6 treatments (Figure 4.8). [redacted] had hypomagnesemia reported as a clinical laboratory test AE (Section 4.4.1). The patient was treated with magnesium gluconate and the magnesium levels subsequently appeared to stabilize to a level of 0.4 mmol/L during the rest of the treatment period. No other patients received magnesium supplementation; see EoT Listing 02.08.

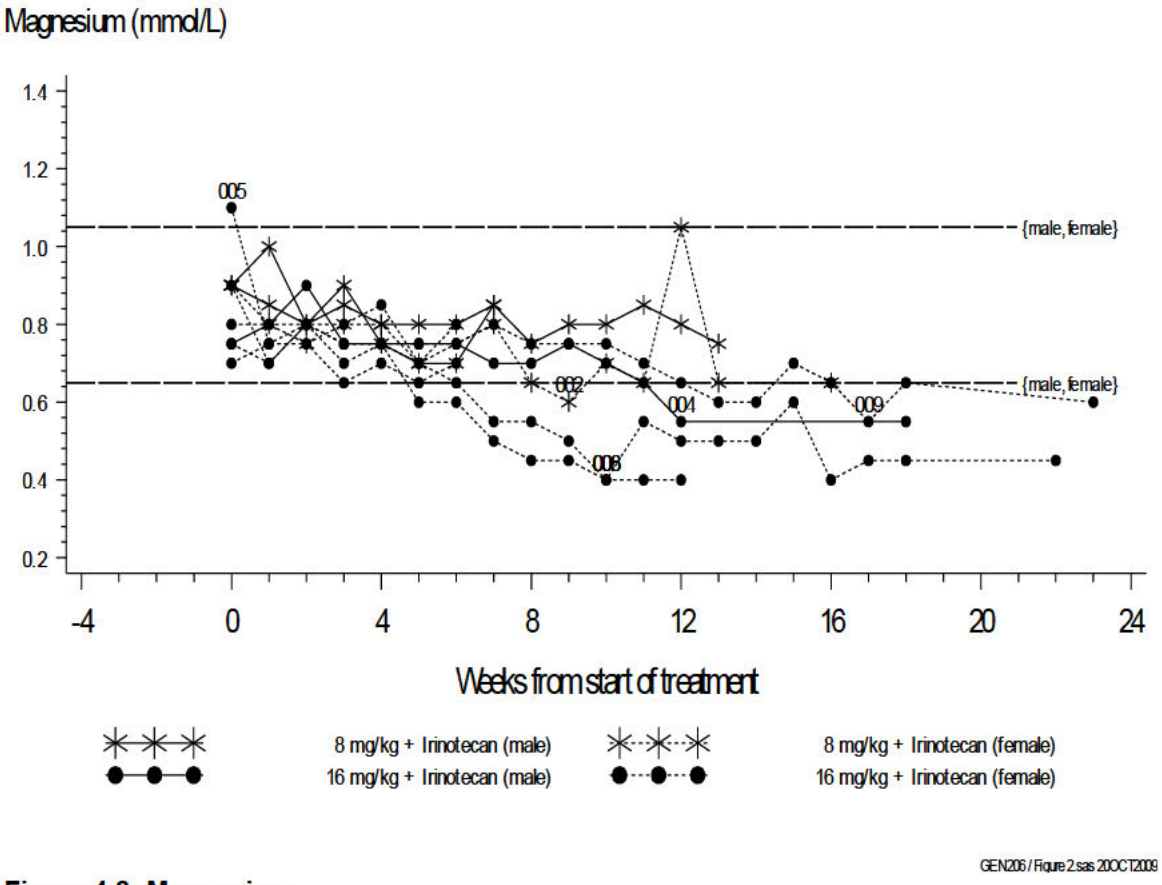

Figure 4.8: Magnesium

Cross-reference: EoT Figure 2.06.

Albumin, Sodium, and Potassium

No pattern of change was observed for albumin, sodium and potassium levels during the treatment period. The majority of values were within normal range, see EoT Figures 2.01, 2.08, and 2.07. However, [redacted] experienced hypokalemia that was reported as a clinical laboratory test AE (Section 4.4.1).

For laboratory biochemistry values outside normal range, see EoT Listing 04.04 and for individual plots, see EoT Figures 2.01 to 2.08. For summary displays of changes in biochemistry parameters compared to baseline, see EoT Tables 07.01 to 07.08. For normal ranges of biochemistry parameters, see EoT Listing 04.03.

4.4.4 Urinalysis

All patients were tested positive for hematuria and leukocyturia at at least one visit during the treatment period with no pattern being obvious. Isolated occurrences of proteinuria were observed in [redacted] (Week [redacted] and [redacted] (Week [redacted] and proteinuria was not observed in [redacted]. The remaining patients had proteinuria at 2 or more visits.

For urinalysis values outside normal range, see EoT Listing 04.06.

4.5 Vital signs, physical examination findings and other safety findings

No changes in physical examination findings or vital signs suggested an increased safety risk with zalutumumab; see EoT Listing 04.01 and EoT Figures 3.01-3.04.

[redacted] had a weight decrease of 4 kg between Visit [redacted] ([redacted]kg) and Visit [redacted] ([redacted] kg) that was reported as an AE (grade 1). During this period, the patient also experienced anorexia, vomiting and diarrhea. The patient recovered, and the body weight stabilized at subsequent visits.

Three patients had abnormal ECG findings at screening. None of these findings were clinically relevant; see EoT listing 04.02.

No other safety findings were raised by this trial. No pregnancies were reported in this trial.

4.6 Summary of safety results

- A maximum tolerated dose was not reached and no patients experienced any dose limiting toxicity
- Of all 9 exposed patients, 8 experienced a total of 101 adverse events. The vast majority of adverse events (84/101; 83%) were of grade 1 or 2 in intensity and 17 adverse events were of grade 3 or higher: grade 3: 12 events, grade 4: 1 event; grade 5: 4 events
- The most frequently reported terms were diarrhea (11 events in 6 patients), nausea (8 events in 7 patients) dry skin (7 events in 7 patients), fatigue (7 events in 7 patients), and rash (6 events in 6 patients)
- 35 of 101 (35%) adverse events were assessed as related to zalutumumab or irinotecan and 31 of these events were of grade 1 or 2 in intensity. None of the adverse events with a relation to trial product were serious and none led to withdrawal from treatment
- 11 non-serious grade 3 AEs were reported and 4 of these events were assessed as related to zalutumumab and/or irinotecan
- Among the 101 reported AEs, 51 (50%) were reported on an infusion day and 11 AEs were judged by Genmab A/S to be an infusion related adverse event. Three of the infusion related events (all fatigues) were assessed as related to zalutumumab and/or irinotecan by the investigator. No serious infusion related adverse events were reported

- 6 SAEs in 5 patients were reported, with 4 having a fatal outcome (1 event of pulmonary embolism, 1 event of colon obstruction and 2 events of disease progression). The 2 other SAEs were 1 event of pulmonary embolism (grade 4) and 1 event of bile duct obstruction (grade 3). None of the SAEs were assessed as related to zalutumumab and/or zalutumumab
- 7 patients reported skin rashes during the treatment period. The maximal skin rash was grade 2 and was reported in 2 patients in the 8 mg/kg dose group
- Analyses performed for HAHA after treatment with zalutumumab were inconclusive
- No unexpected observations in clinical laboratory hematology and biochemistry parameters were made. No pattern of change was observed during the treatment period, except that magnesium levels appeared to decrease during the course of treatment. As expected, irinotecan caused decreased neutrophil and leukocyte levels 1 week after infusion in the majority of the patients
- No changes in physical examination findings or vital signs suggested an increased safety risk with zalutumumab

5 Efficacy

5.1 Best overall response

Treatment responses of measurable target lesions (i.e. presence of at least one measurable lesion where the longest diameter is ≥ 20 mm) were classified according to RECIST as follows:

- Complete response (CR) was defined as the disappearance of all target lesions.
- Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
- Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started, *or* the appearance of one or more new lesions since the prior scan.
- Stable disease (SD) was defined as responses not fulfilling CR, PR or PD.

Treatment responses of non-measurable target lesions (i.e. lesions where the longest diameter is < 20 mm and truly non-measurable lesions such as bone lesions and ascites) were classified according to RECIST as follows:

- CR was defined as the disappearance of all non-target lesions.
- PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
- Non PD was defined as CR or SD.

The best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence. Best overall response evaluations are summarized in Table 5-1.

All response evaluations are presented by patient and visit in Table 5-2.

No patients responded to treatment although [redacted] was evaluated by investigator as having a PR at Visit [redacted] ([redacted]2008). However, the patient died from pulmonary embolism on [redacted]2008, before a confirmatory scan had been performed. The response for this patient is therefore included as SD in Table 5-1.

Table 5-1: Best overall response according to RECIST criteria

	8 mg/kg + Irinotecan	16 mg/kg + Irinotecan	Total
	N	N	N (%)
Exposed	3	6	9
Best Overall Response, N(%)			
Complete Response	0	0	0 (0%)
Partial Response	0	0	0 (0%)
Stable Disease	3	4	7 (78%)
Progressive Disease	0	2	2 (22%)
Not evaluable	0	0	0 (0%)

N : Number of patients
% : Percentages of patients
GEN206 20OCT2009 Program: tab04.01.sas
Note: Response was evaluated locally according to RECIST (3).

Cross-reference: EoT Table 04.01.

Table 5-2: All response evaluations according to RECIST criteria – listed by patient

Treatment arm	Patient Number	Visit	Response according to RECIST
16 mg/kg + Irinotecan	[redacted]	[redacted]	PD
	[redacted]	[redacted]	SD
		[redacted]	SD
		[redacted]	PD
		[redacted]	PD
8 mg/kg + Irinotecan	[redacted]	[redacted]	SD
		[redacted]	PD
		[redacted]	PD
	[redacted]	[redacted]	SD
		[redacted]	PD
		[redacted]	PD
	[redacted]	[redacted]	PR
16 mg/kg + Irinotecan	[redacted]	[redacted]	SD
		[redacted]	SD
	[redacted]	[redacted]	PD
16 mg/kg + Irinotecan	[redacted]	[redacted]	SD
		[redacted]	PD
	[redacted]	[redacted]	SD
		[redacted]	SD
		[redacted]	SD

GEN206 20OCT09 Program: list05.01.sas
Note: Response was evaluated locally according to RECIST (3).
[redacted] was evaluated by investigator as having a PR at Visit [redacted] 2008). However, the patient died from pulmonary embolism on [redacted] 2008, before a confirmatory scan had been performed.

Cross-reference: Modified EoT Listing 05.01.

5.2 Progression Free Survival

Progression Free Survival (PFS) was defined as the time from allocation (first dose) until disease progression according to the local evaluation at site, or death. The Kaplan-Meier estimates of PFS are presented by dose group and for all patients in Figure 5.1.

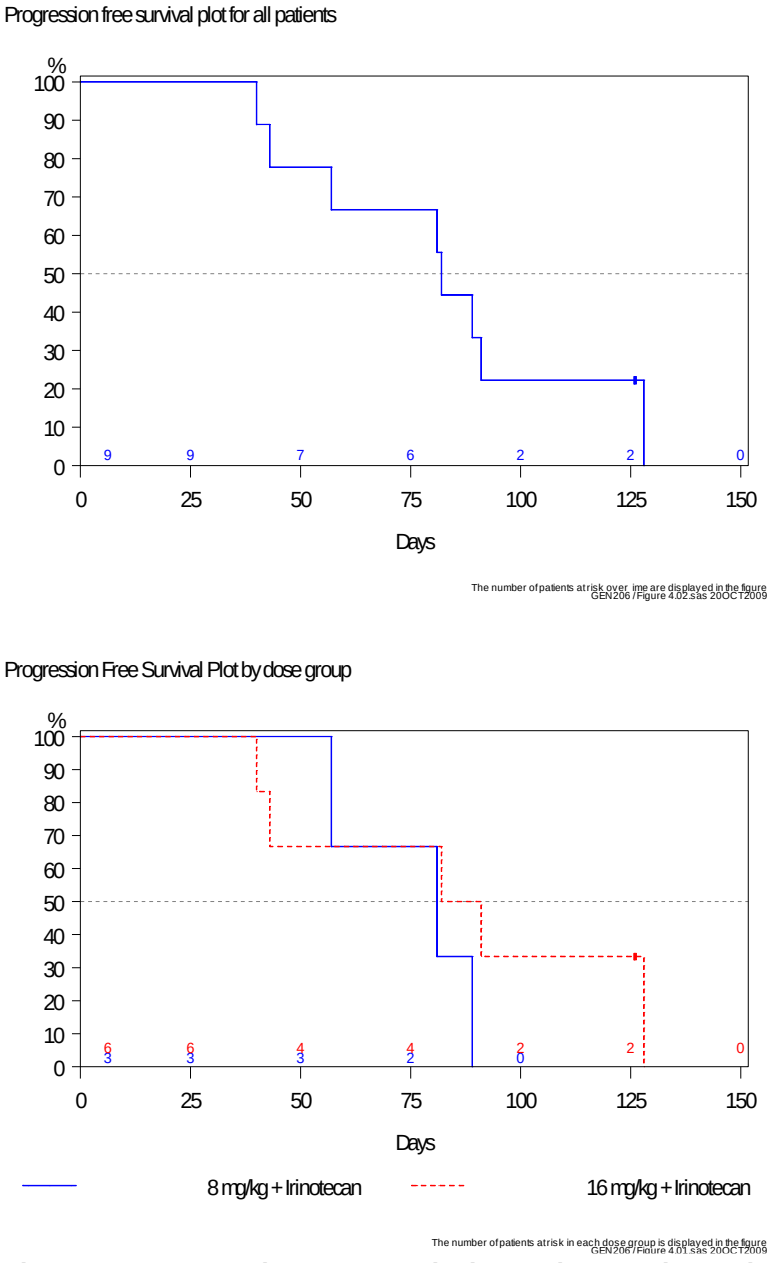

Figure 5.1: Progression Free Survival Based on Kaplan-Meier estimates for all patients (upper panel) and by dose group (lower panel)
Cross-reference: EoT Figure 04.01 and 04.02.

5.3 Summary of efficacy results

- Best overall response, as evaluated locally according to RECIST, was stable disease in 7 patients and progressive disease in 2 patients.

6 Pharmacokinetics

On the day of first zalutumumab infusion (Visit 2) blood samples for determination of pharmacokinetic parameters were taken prior to the zalutumumab infusion, at end of infusion, and 30 minutes, 1 hour, 2 hours, 8 hours, and 24 hours after end of infusion. At all subsequent visits, blood samples were taken prior to the zalutumumab infusion.

Both dose groups attained measurable concentrations of zalutumumab after first infusion (lower level of quantification (LLoQ): 0.4 mg/L).

Trough values were defined as concentration of zalutumumab prior to dosing. In general, trough concentrations increased during the treatment course and higher zalutumumab concentrations were observed in the 16 mg/kg group than in the 8 mg/kg group. Median trough values after the first infusion were 74 mg/L in the 8 mg/kg group and 98 mg/L in the 16 mg/kg group and increased to 130 mg/L and 173 mg/L respectively after the second infusion; see EoT Table 09.02. Hereafter, the increments of trough concentrations became less pronounced as presented in Figure 6.1 and EoT Table 09.02. For graphic presentations of the individual patients' zalutumumab serum concentrations, see EoT Figures 6.01.01 to 6.09.02. For trough concentrations presented by patient and visit, see EoT Listing 09.01.

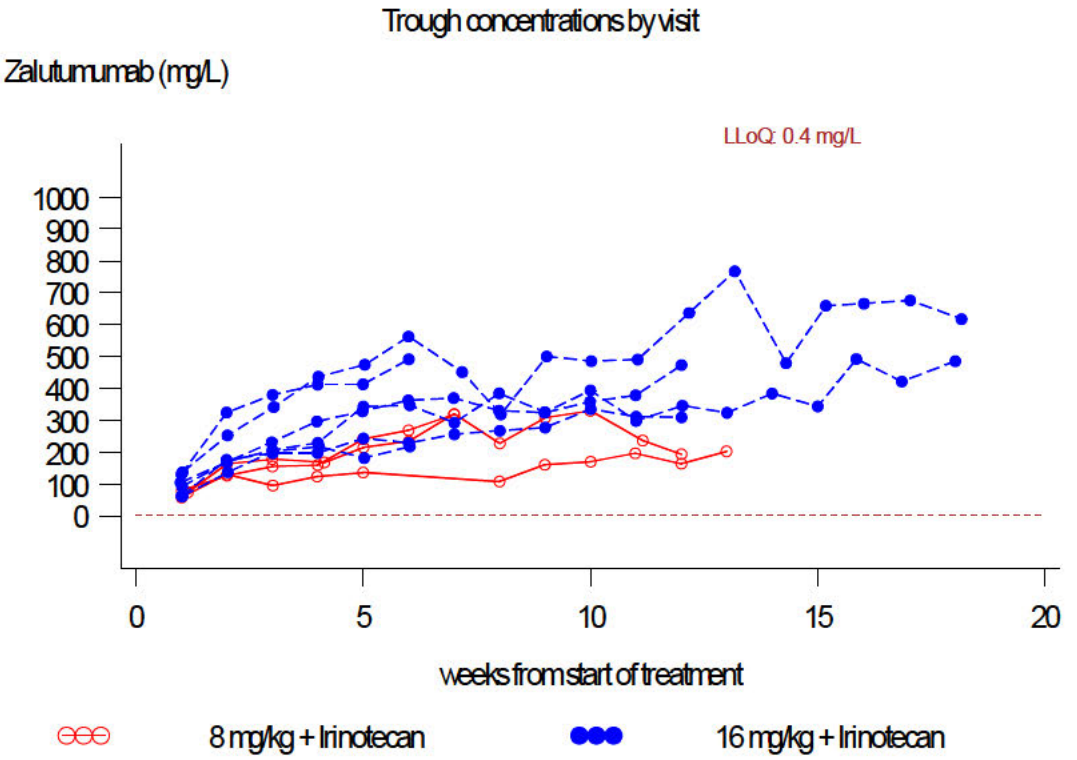

Figure 6.1: Trough concentrations by patient and treatment group

Cross-reference: EoT Figure 6.10.

[redacted] had positive anti-EGFR concentrations at screening. One of the inclusion criteria for trial enrollment was previous treatment with cetuximab and the patients should not have received other anti-EGFR treatment*. The ELISA used for measuring zalutumumab also measures other anti-EGFR IgG1 antibodies. It is assumed that cetuximab is measured with similar efficiency as zalutumumab, and thus, that the anti-EGFR concentrations measured at screening were cetuximab. Hence, the wash-out period after treatment with cetuximab had not been sufficiently long in these patients; see EoT Listings 02.04 and 03.01 for information on prior monoclonal anti-body treatment and zalutumumab administrations. The concentration of zalutumumab was therefore set to below LLoQ at screening in these patients.

[redacted] had a positive anti-EGFR concentration at Visit [redacted] before infusion and this positive anti-EGFR measurement was set to below LLoQ. Correction to concentration values after infusion was made by subtracting the calculated residual of cetuximab over the relevant time points. The cetuximab concentration was estimated assuming constant elimination, with elimination rate K_e=0.027 h^{-1}, calculated as the clearance rate 0.03 L/h/m^2 divided by the volume of distribution 1.11 L/m^2 obtained from Figure 14.6 and Table 14.2 in Nolting A.et al. (7). For information on the calculated cetuximab residuals, see EoT Listing 09.02.

[redacted] had a BMI that was [redacted] kg/m^2, but the zalutumumab dose was not adjusted. This implied higher zalutumumab concentrations in this patient than expected since plasma volume is not proportional to body weight; see EoT Figure 6.01.01.

The median maximum concentration (C_{max}) of zalutumumab after the first infusion was 240 mg/L in patients treated with 8 mg/kg and 343 mg/L in the 16 mg/kg group. Time of C_{max} (T_{max}) was 2 hours in the 8 mg/kg group and 1 hour in the 16 mg/kg group.

6.1 Summary of Pharmacokinetics results

- Both dose groups attained measurable concentrations of zalutumumab after first infusion.
- Trough concentrations, defined as concentration of zalutumumab prior to dosing, increased during the treatment course and higher zalutumumab concentrations were observed in the 16 mg/kg group than in the 8 mg/kg group.
- Median trough values almost doubled between the first and the second infusion. Hereafter, the increments of trough concentrations became less pronounced.

* Note: [redacted] had received panitumumab [redacted] years before trial enrollment (Section 1.4.2). No panitumumab residuals are present after this amount of time.

7 Discussion

This abbreviated CTR reports data from the clinical trial GEN206 for the use of zalutumumab in patients with CRC. Patient allocation was prematurely terminated (21-Oct-2008) by Genmab A/S due to changed standard treatment recommendations implying that only patients with CRC who had wild-type *KRAS* should be treated with anti-EGFR antibodies (Section 1.1). The cut-off date for the reported data was 12-Feb-2009 and the CTR includes data from 9 patients enrolled in Part 1 of the trial. The enrolled trial population had metastatic CRC, had failed previous standard chemotherapy, and had progressed during or within 6 months of stopping treatment with cetuximab and irinotecan.

Due to the low number of patients, data have not been subject to any statistical hypothesis test and the data are therefore presented using descriptive statistics (summary tables, listings and figures).

Zalutumumab 8 mg/kg (3 patients) and 16 mg/kg (6 patients) was administered once weekly in combination with irinotecan 180 mg/m^2 every 2 weeks. Overall, the majority of patients adhered to the scheduled zalutumumab dosing and infusion rate.

The safety profile was in accordance with what could be expected after treatment with a monoclonal antibody targeting the EGF receptor in combination with irinotecan. The infusion schedule was generally well tolerated, supported by the finding that the patients received at least 6 infusions. A maximum tolerated dose was not reached and no patients experienced any dose limiting toxicity. A total of 101 adverse events were reported in 8 of 9 patients and 84 of 101 (83%) of adverse events were of grade 1 or 2 in intensity. The most common terms were expected side effects upon treatment with zalutumumab such as diarrhea, nausea, rash, dry skin, and fatigue. Adverse event frequency was also influenced by severity of underlying CRC. In total, 35 adverse events were assessed as having a relation to trial product (zalutumumab or irinotecan); none of these AEs were serious and none led to withdrawal from treatment. Eleven adverse events were judged to be an infusion related adverse event and and 3 of these events (all fatigues) were assessed as related to trial drug by the investigator. Serious infusion related adverse events were not reported. Six SAEs in 5 patients were reported; none of the SAEs were assessed as having a relation to the trial product. Four of the SAEs (1 event of pulmonary embolism, 1 event of colon obstruction, and 2 events of disease progression) had a fatal outcome. Overall, the risk of thromboembolic events is increased in patients with solid tumors and infra-diaphragmatic disease in particular, especially in patients with metastatic disease and treated with chemotherapy (4).The 2 events of pulmonary embolism in the GEN206 trial were reported in the low dose group (8 mg/kg) and both the investigator and sponsor assessed the events as related to the patients' underlying disease rather than zalutumumab.

Skin rash is a frequently occurring side effect of treatment with EGFR antibodies. The presence of skin rash may be a surrogate marker for EGFR inhibition and therefore indicates that the drug is being administered at a therapeutic level. In total, 7 out of 9 patients reported skin rash during the treatment period. The maximal skin rash was grade 2 in 2 patients in the 8 mg/kg dose group. Six patients developed sustaining skin rash during the treatment period. This may indicate that

zalutumumab was administered at a therapeutic level in these patients. Two patients received respectively [redacted] doses and [redacted] doses of zalutumumab during the trial without developing skin rashes.

No unexpected observations in clinical laboratory hematology and biochemistry parameters were made for the patient population investigated in this trial. No pattern of change was observed during the treatment period, except that magnesium levels appeared to decrease in some patients during the course of treatment. One patient had hypomagnesemia reported as a clinical laboratory test adverse event and was treated with magnesium gluconate. Myelosuppression is an expected side effect after treatment with irinotecan with typical nadir occurring at days 7-10 after infusion. Myelosuppresion was observed in this trial in terms of decreased neutrophil and leukocyte levels 1 week after irinotecan infusion in the majority of the patients.

No changes in physical examination findings or vital signs suggested an increased safety risk with zalutumumab.

Best overall response, as evaluated locally according to RECIST, was stable disease in 7 patients and progressive disease in 2 patients. It should be noted that one patient was evaluated by investigator as having a partial response, but the patient died from pulmonary embolism, evaluated as not related to zalutumumab, before a confirmatory scan had been performed. The patient was therefore considered as having stable disease. It should be noted that the *KRAS* status was not known for any of the 9 patients.

For pharmacokinetics. trough values increased over time during a treatment course with multiple infusions. Higher zalutumumab concentrations were observed in the 16 mg/kg group than in the 8 mg/kg group. Median trough values after first infusion were 74 mg/L in the 8 mg/kg group and 98 mg/L in the 16 mg/kg group and almost doubled after the second infusion. The low trough values after the first infusion can probably be explained by accelerated clearance at low concentrations. Similar observations have been made for cetuximab (9). The increments of trough concentrations became less pronounced after several infusions as they were approaching a steady state level.

In summary, data from this phase I trial indicate that zalutumumab was safely administrated in doses up to 16 mg/kg in combination with irinotecan in patients with colorectal cancer who have failed cetuximab and irinotecan based therapy. A maximum tolerable dose was not reached and no patients experienced any dose limiting toxicity. Best overall response, as evaluated locally according to RECIST, was stable disease in 7 out of 9 patients. It should be noted that the *KRAS* status was not known for any of the 9 patients, and no conclusion can therefore be drawn with respect to evaluation of efficacy.

8 Conclusion

- Zalutumumab was safely administrated in doses up to 16 mg/kg in combination with irinotecan in patients with colorectal cancer who have failed cetuximab and irinotecan based therapy. A maximum tolerable dose was not reached and no patients experienced any dose limiting toxicity.

- Zalutumumab and irinotecan resulted in stable disease in 7 patients. However, the *KRAS* status was not known for the 9 patients.

References

(1) Van Cutsem E, Lang I, D' Haens G, Moiseyenko V, Zaluski J, Folprecht G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. Journal of Clinical Oncology 26[suppl; abstract 2]. 2008.
Ref Type: Abstract

(2) Bokemeyer C, Bondarenko I, Hartmann JT, De Braud FG, Volovat C, Nippgen J, et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience. Journal of Clinical Oncology 26[20 Suppl]. 2008.
Ref Type: Abstract

(3) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000 Feb 2;92(3):205-16.

(4) Khorana AA, Liebman HA, White RH, Wun T, Lyman GH. The Risk of Venous Thromboembolism in Patients with Cancer. American Society of Clinical Oncology 2008;240-8.

(5) Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? J Clin Oncol 2005 Aug 1;23(22):5235-46.

(6) Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005 Aug 20;23(24):5578-87.

(7) Nolting A, Floyd E, Kovar A. Clinical Drug Development of Cetuximab, a Monoclonal Antibody. In: Meibohm B, editor. Pharmacokinetics and Pharmacodynamics of Biotech Drugs - Principles and Case Studies in Drug Development.Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2006. p. 353-71.