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A randomized phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolization with intravenous cetuximab (DEBIRITUX) versus systemic treatment with intravenous cetuximab and irinotecan in patients with refractory metastatic colorectal cancer and k-ras wild-type tumours

Short title: DEBIRITUX

Statistical Report

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List of Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BMI	Body mass index
CEA	Carcinoembryonic antigen
CI	Confidence interval
CR	Complete response
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DEB	Drug-eluting beads
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report forms
F	Female
I/E	Inclusion/exclusion
ICF	Informed consent form
INR	International Normalized Ratio
ITT	Intention-to-treat
KKSH	Koordinierungszentrum für Klinische Studien Halle
LLT	Lowest level term
M	Male
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemesis Tool
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical history
Min	Minimum
N	Number
NCI	National Cancer Institute
NMISS	Number of missing values
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PP	Per-protocol
PR	Partial response

PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Stable disease
SOC	System organ class
UICC	Union internationale contre le cancer
ULN	Upper limit of normal

Protocol Synopsis

Title of the study:	A randomized phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolization with intravenous cetuximab (DEBIRITUX) versus systemic treatment with intravenous cetuximab and irinotecan in patients with refractory metastatic colorectal cancer and kras wild-type tumours
Acronym:	DEBIRITUX
Indication:	Metastatic colorectal cancer
Primary objective:	To evaluate the efficacy of Irinotecan Beads in combination with intravenous cetuximab versus intravenous irinotecan in combination with intravenous cetuximab in the treatment of patients with unresectable liver metastases from colorectal cancer
Secondary objectives:	Safety and tolerability of hepatic chemoembolization and the question if the addition of aprepitant to standard antiemetic prophylaxis in patients treated by hepatic chemoembolization is safe and will reduce the rate of acute and delayed nausea and emesis
Study design:	Multicentre, open labeled, prospective, randomised, non comparative phase II study with following stratification criteria for randomization: • Liver only disease vs. other sites included • Bilobar vs. unilobar disease
Study population; I/E criteria:	<u>Inclusion criteria:</u> 1. Patients with confirmed diagnosis of stage IV (UICC) colorectal cancer with unresectable liver metastases (primary tumour may be present) and k-ras wild-type tumours 2. Patients had been treated and shown to be refractory to 5-FU (Capecitabine allowed)/oxaliplatin and/or 5-FU/irinotecan. Prior therapy with VEGF-inhibitors (e.g bevacizumab) is allowed 3. Patients with at least one measurable liver metastasis, with size > 1cm (RECIST criteria) 4. Patients with liver only or liver dominant disease (defined as ≥ 50 % tumour burden confined to the liver)

	5. Patients with a portal vein not interfering with transarterial chemoembolization (e.g. no thrombosis) as judged by the investigator 6. ECOG Performance status ≤ 2 7. Life expectancy > 3 months 8. Age ≥ 18 years 9. At least 4 weeks since last administration of last chemotherapy and/or radiotherapy (bone metastases may be allowed) 10. Patients who received VEGF-inhibition (e.g. with bevacizumab) in prior therapy are eligible if stopped since 4-6 weeks before randomization 11. Haematologic function: ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x 10^9/L 12. INR < 1.5 (patients on therapeutic anticoagulants are not eligible) 13. Adequate liver function as measured by serum transaminases (AST & ALT) ≤ 3 x ULN and total bilirubin ≤ 1.5 x ULN 14. Adequate renal function: Serum creatinine ≤ 1.5 x ULN 15. Normal level of serum magnesium 16. Women of child bearing potential and fertile men are required to use effective contraception (negative serum βHCG for women of child-bearing age 17. Signed, written informed consent <u>Exclusion criteria:</u> 1. Presence of CNS metastases 2. Contraindications to irinotecan therapy (Chronic inflammatory bowel disease and/or bowel obstruction, history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate) 3. Active bacterial, viral or fungal infection within 72 hours of study entry 4. Women who are pregnant or breast feeding 5. Allergy to contrast media 6. Presence of another concurrent malignancy. Prior malignancy in the last 5 years except adequately treated basal or squamous cell skin cancer or carcinoma in situ of the cervix 7. Any contraindication for hepatic embolisation procedures: • Large shunt as determined by the investigator (pretesting with lung perfusion scan not required)

	• Severe atheromatosis • Hepatofugal blood flow 8. Other significant medical or surgical condition, or any medication or treatment, that would place the patient at undue risk, that would preclude the safe use of chemoembolization or would interfere with study participation 9. Known hypersensitivity or contraindication to the drugs used in the trial (eg: cetuximab, 5-HT3 receptor antagonist, dexamethasone, or any component of aprepitant) <u>Additional exclusion criteria (only patients taking part in antiemesis evaluation):</u> 1. Has experienced emesis (i.e., vomiting and/or retching) or clinically significant nausea in the 24 hours preceding the first dose of study medication 2. Has increased intracranial pressure, hypercalcemia, an active systemic infection, or any uncontrolled medical condition (other than malignancy) which in the opinion of the Investigator may confound the results of the study, represent another potential etiology for emesis and nausea (other than CINV) or pose an unwarranted risk to the subject. 3. Has taken/received any medication with known or potential antiemetic activity within the 24-hour period (unless otherwise stated) prior to receiving the first dose of study medication: • 5-HT3 receptor antagonists • benzamide/benzamide derivatives (e.g., metoclopramide, alizapride); • benzodiazepines (except if the subject is receiving such medication for sleep or anxiety) • phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine); • butyrophenones (e.g., haloperidol, droperidol); • corticosteroids (e.g., dexamethasone, methylprednisolone); with the exception that topical steroids for skin disorders including eye and ear drops, and inhaled steroids for respiratory disorders at≤ 10 mg prednisone daily or its equivalent are permitted;

	• first-generation antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine); except for topical use which is permitted; • domperidone; cannabinoids; mirtazapine; olanzapine.
Sample size:	Planned: 80 patients assigned by stratified randomisation to arm A or arm B in a 1:2 ratio (favouring arm B); within arm B randomised (without stratification) in a 1:1 ratio to arm B1 or B2 Actually randomised: 8 patients, of whom 2 in arm A and 6 in arm B (2 in arm B1, 3 in arm B2)
Study therapy:	Arm A (standard) Irinotecan: 180 mg/m² administered every two weeks according to common protocols (Wilke et al. JCO 2008) Cetuximab: Initial dose 400 mg/m², followed by weekly doses of 250 mg/m² Arm B (experimental) Irinotecan DEB: A minimum of two treatments per lobe (four bi-weekly sessions in the event of bilobar disease) at week 0 and 4 with up to 4ml (100-300µm DC Bead loaded with up to 200mg irinotecan) (i.e. for bilobar disease right lobe: week 0, left lobe: week 2, right lobe: week 4 and left lobe: week 6: following toxicity and extending interval if toxicity seen). Cetuximab: Initial dose 400mg/m², followed by weekly doses of 250 mg/m² Patients in experimental Arm B – particularly those with colorectal cancer not confined to liver metastases – could continue on systemic therapy with intravenous irinotecan and cetuximab after having finished chemoembolization procedures accordingly or interruption of intra-arterial treatment due to toxicity. *Arm B 1* Antiemetic regimen: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3 *Arm B 2* Antiemetic regimen: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3, aprepitant 125mg po on day 1 and 80mg po on day 2 and 3
Primary end point:	Progression free survival after 6 months

Secondary end points:	• Safety • Tumour Response (according to RECIST v1.1) • Local tumour response (extent of necrosis in the treated lesions) • Time to progression • Time to liver progression • Change in tumour markers (CEA) • Overall survival • Rate of acute and delayed emesis during chemoembolization with or without aprepitant
Statistical considerations (as laid down in protocol p.19f.):	The required sample size is 80 patients, based on the following assumptions and calculations: The primary efficacy parameter for both arms is the rate of patients without progressive disease in the liver manifestations after 6 months. The analysis will be performed when the last randomized subject has been observed for this period. The proportion of subjects, who do not have disease progression after six months of standard treatment with intravenous irinotecan and cetuximab is expected to be around 40%, based on the BOND study data with 218 patients (Cunningham et al. 2004). Thus, a similar finding in the experimental combination group would be rated as futile. It has to be considered that this trial addressed both, liver only and systemic disease. However, there is no evidence that PFS rates differ markedly between liver only and extrahepatic manifestations. An improvement by 15% points to 55% on irinotecan beads would be considered very promising and of major clinically relevance. The trial should achieve 80% power for declaring the experimental combination as “promising” when the true proportion of subjects with progression-free survival at 6-months is 55% or higher, and at the same time keeping the type I error level of erroneously claiming the new combination to be effective (> 55%), although the true rate is futile (< 40%), below 10%. 49 patients evaluable for progression status at 6 months are required to be observed in the experimental group. According to the

	2:1 randomisation a number of about 25 will be randomised to the reference arm, leading to a total sample size of about n=74. Regarding a drop off rate of 10% 80 patients should be recruited. Populations for analysis: All patients receiving at least one treatment (Irinotecan drug eluted beads, Irinotecan, Cetuximab or Aprepitant) will be evaluable for safety. The Intention-to-treat (ITT) population will include all patients in the study (signed ICF and confirmation of eligibility). All patients will be grouped according to their randomization regardless of treatment received. The Per-protocol (PP) population will include all patients who receive at least two chemoembolization treatment with Irinotecan Bead in combination with intravenous antibody (test group) and who were treated according to their randomization schedule. Patients with major protocol deviations or who did not receive treatment according to their randomization schedule will be excluded from the PP population. Antiemetic regimens The rate of acute nausea and vomitus in patients treated with irinotecan beads-chemoembolization is up to 80% (grade 2). A reduction of the rate to 53% would be considered promising and clinically relevant. In a one sided test the power should be 80% and type I error level below 10%, which leads to a number of subjects of 26 in each arm.
Schedule:	Patient related: Until progression, unacceptable toxicity, investigator's decision, withdrawal of consent. Subsequent follow-up to determine disease status and survival. Study related: First patient in: 17.8.2010; last patient in: 8.12.2011; enrolment period: 16 months (planned 12-16 months, early termination of recruitment: 26.3.2012); study duration incl. follow-up: 30 months (max. 30 months planned); last patient out: 2.2.2012; last follow-up: 8.2.2013

1 General Study Information

1.1 Background and Objectives of the Trial

This document describes the procedures and results of the statistical analysis for the DEBIRITUX study ("A randomized phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolization with intravenous cetuximab (DEBIRITUX) versus systemic treatment with intravenous cetuximab and irinotecan in patients with refractory metastatic colorectal cancer and k-ras wild-type tumours"). The analyses are based on the specifications laid down in the study protocol, chapter 9 "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS", and the final data export file after study database closure on 18th September, 2015.

Reference documents are

- the Investigational Plan & Clinical Study Protocol, Version: Final 02/12-09 [1],
- the eCRF Layoutvorlage, Version: Final 01 (06.05.2010) [2].

This trial was designed as multicentre, open labeled, prospective, randomised, non comparative phase II study for patients with refractory metastatic colorectal cancer and kras wild-type tumours. Inclusion and exclusion criteria can be found in the study protocol, section 5.2. A sample size of 80 patients was planned to allocate by stratified randomisation to standard treatment arm A or experimental treatment arm B in a 1:2 ratio (favouring arm B). Within arm B, a second non-stratified randomisation for two antiemetic regimens in a 1:1 ratio was conducted. In total, 8 patients were randomised. As a consequence of this poor recruitment, it was terminated before reaching the target number.

The primary objective of the study was to evaluate the efficacy of Irinotecan Beads in combination with intravenous cetuximab versus intravenous irinotecan in combination with intravenous cetuximab, as indicated by 6-month progression free survival, in the treatment of patients with unresectable liver metastases from colorectal cancer.

Secondary objectives were safety and tolerability of hepatic chemoembolization, and safety and efficacy of additional aprepitant to standard antiemetic prophylaxis in patients treated by hepatic chemoembolization.

1.2 Trial Sites

A number of 13 trial sites took part in the DEBIRITUX study. 5 of them enroled patients. These are shown in the following Table 1.1.

Table 1.1 Recruiting trial sites

ID	Trial Site
01	Universitätsklinikum Halle, Klinik für Innere Medizin IV; Halle (Saale)
02	Universitätsklinikum Magdeburg, Klinik für Radiologie und Nuklearmedizin; Magdeburg
04	SLK-Kliniken Heilbronn; Heilbronn
05	Kliniken Essen-Mitte, Klinik für Innere Medizin IV, Internistische Onkologie und Hämatologie, Zentrum für Palliativmedizin; Essen
12	Klinikum der Universität Regensburg, Institut für Röntgendiagnostik; Regensburg

1.3 Application Scheme, Dosage and Duration of Study Treatment

Application scheme and dosage of study medication are described in detail in the study protocol [1], section 6.1.2. Study treatment was scheduled until progression, unacceptable toxicity, investigator's decision or withdrawal of consent, see study protocol [1], section 6.2.

Arm A (standard)

Irinotecan: 180 mg/m² administered every two weeks according to common protocols (Wilke et al. JCO 2008) [3]

Cetuximab: Initial dose 400 mg/m², followed by weekly doses of 250 mg/m²

Arm B (experimental)

Irinotecan DEB: A minimum of two treatments per lobe (four bi-weekly sessions in the event of bilobar disease) at week 0 and 4 with up to 4ml (100-300µm DC Bead loaded with up to 200mg irinotecan) (i.e. for bilobar disease right lobe: week 0, left lobe: week 2, right lobe: week 4 and left lobe: week 6: following toxicity and extending interval if toxicity seen).

Cetuximab: Initial dose 400mg/m², followed by weekly doses of 250 mg/m²

Patients in experimental Arm B – particularly those with colorectal cancer not confined to liver metastases – could continue on systemic therapy with intravenous irinotecan and cetuximab after having finished chemoembolization procedures accordingly or interruption of intra-arterial treatment due to toxicity.

Arm B 1

Antiemetic regimen: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3

Arm B 2

Antiemetic regimen: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3, aprepitant 125mg po on day 1 and 80mg po on day 2 and 3

2 Methods

2.1 Randomisation Method

In this randomised, non-comparative study, a total of 80 patients were planned to be stratified randomised in a 1:2 ratio to standard treatment arm A or experimental treatment arm B (favouring arm B). Furthermore, a second non-stratified randomisation for two antiemetic regimens had to be done in a 1:1 ratio within arm B.

Randomisation lists were generated with SAS software version 9.1.3. Stratification criteria were “liver only disease vs. other sites included” and “bilobar vs. unilobar disease”. For each of the 4 strata, i.e. combination of categories, a separate block randomisation list was produced with block lengths of 3 and 6 in random order. A block length of 4 was used for the additional randomisation list in 1:1 ratio. Central randomisation was carried out via fax.

2.2 Software

Statistical analysis was performed using SAS software version 9.4.

2.3 Definitions of Variables

2.3.1 Primary endpoint

The primary endpoint was progression-free survival (PFS) 6 months after randomisation. PFS was defined as time from randomisation to date of first observed progression or death.

2.3.2 Secondary endpoints

Secondary endpoints were

- safety (adverse events, serious adverse events)
- tumour response (according to RECIST V1.1): best response from start of treatment over all follow up visits or until disease progression/recurrence whichever comes first
- local tumour response (extent of necrosis in the treated lesions): best response in the target liver lesions (CR/PR/SD/PD)
- time to progression: time from randomisation to date of first observed progression
- time to liver progression: time from randomisation to date of first observed progression of liver metastases (progression of target liver lesions, non-target lesions within the treated lobe and/or new lesions within the treated lobe)
- change in tumour marker CEA (measured at baseline and every 3 months): change from baseline value
- overall survival (OS): time from randomisation to date of death

- acute and delayed nausea (no/yes) and emesis (no/yes) during chemoembolization assessed using the MASCC Antiemesis Tool (MAT): one and 4 days after chemotherapy defined as acute and delayed, respectively

2.4 Statistical Methods

Statistical analysis was undertaken in a descriptive way due to small patient number.

Corresponding to sample size calculation based on a one-sample one-sided test in arm B, a one sample test on a significance level of 10% and a one-sided 90% confidence interval should have been calculated to analyse the primary endpoint PFS after 6 months in arm B. Instead, PFS status after 6 months was summarised in frequency tables.

Median event times were estimated, if possible, and given with their 95% confidence intervals. Best tumour response was likewise summarised in frequency tables. Change in tumour marker, nausea and emesis during chemoembolization were listed by patient.

Adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1, English. AEs were summarised by System Organ Class (SOC) and Preferred Term (PT), CTC grade (according to NCI-CTCAE) and relationship to study treatment. Absolute frequencies of AEs and the number of patients experiencing an AE were given. In the summary by CTC grade, only the worst case per PT for each patient was counted, if a patient experienced more than one AE within a PT. All AEs were included in the summary by relationship to study treatment. AEs assessed as possibly, probably or definitely related were grouped as related, the other (unlikely, not related or not assessable causality) as not related.

2.5 Protocol Deviations

Owing to the small number of included patients, the following in the study protocol mentioned statistical methods were not applied: Fisher's exact test, logistic regression, log-rank test, Cox's proportional hazard model, Student's t tests, linear mixed model. See study protocol [1], section 9.6, for details.

3 Patient Flow

See Figure 3.1 for patient flow.

3.1 Patient Recruitment and Trial Duration

Between August 2010 and December 2011, 8 patients were recruited at 5 trial sites (Table 3.1). Before reaching the target sample size of 80 patients, recruitment was terminated early on 26th March, 2012 after recruiting these 8 patients because of inadequate recruitment. In the individual patient, study treatment was scheduled until progression, unacceptable toxicity,

investigator's decision or withdrawal of consent. The last patient completed study treatment in February 2012 and study follow-up in February 2013.

Table 3.1 Recruitment and study duration by trial site

					Duration [d]			
Center	First patient in	Last patient in	Last patient out*	End of Study Follow-Up	Recruit-ment	Therapy	Study incl. Follow-Up	Number of Patients
01	17AUG2010	17AUG2010	08FEB2011	01JUL2011	1	176	319	1
02	01DEC2010	08DEC2011	02FEB2012	08FEB2013	373	429	801	3
04	21FEB2011	29AUG2011	22SEP2011	17JAN2012	190	214	331	2
05	05OCT2010	05OCT2010	16MAR2011	22JUN2011	1	163	261	1
12	10AUG2011	10AUG2011	03NOV2011	01MAR2012	1	86	205	1
Total	17AUG2010	08DEC2011	02FEB2012	08FEB2013	479	535	907	8

* last application of study medication

3.2 Randomisation

Randomisation was conducted centrally at KKSH via fax. Patients were stratified into four strata:

1. Bilobar liver disease and site of metastases: liver only (one patient)
2. Bilobar liver disease and site of metastases: liver plus other site (6 patients)
3. Unilobar liver disease and site of metastases: liver only (no patient)
4. Unilobar liver disease and site of metastases: liver plus other site (one patient)

A total of 8 patients were randomised to one of the following two treatment arms in 1:2 ratio in favour of the experimental therapy according to the above mentioned strata:

Arm A (standard): Irinotecan 180 mg/m² administered every two weeks; cetuximab with initial dose 400mg/m², followed by weekly doses of 250 mg/m²

Arm B (experimental): Irinotecan DEB with a minimum of two treatments (four bi-weekly sessions in the event of bilobar disease) at week 0 and 4 with up to 4ml (100-300µm DC Bead loaded with up to 200mg irinotecan) (i.e. for bilobar disease right lobe week 0, left lobe week 2 right lobe week 4, left lobe week 6: following toxicity and extending interval if toxicity seen); cetuximab with initial dose 400mg/m², followed by weekly doses of 250 mg/m²

So 2 patients were allocated to arm A (2 in stratum 2) and 6 to arm B (4 in stratum 2, in strata 1 and 4 one patient each).

5 of 6 patients in arm B were additionally randomised to one of two antiemetic regimens in a 1:1 ratio without stratification:

Arm B 1: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3

Arm B 2: 5 HT3 serotonin receptor antagonists (iv or po) on day 1, dexamethason 8mg (iv or po) on day 1-3; aprepitant 125mg po on day 1 and 80mg po on day 2 and 3

So 2 and 3 patients of arm B were assigned to arm B1 and arm B2, respectively.

The planned number of 80 patients was not achieved due to poor and subsequently stopped recruitment.

3.3 Blinding / Unblinding

This was a non-blinded (open label) trial.

3.4 Discontinuation / Drop-out / Protocol Violators

One patient did not meet the inclusion criterion “Normal level of serum magnesium” and another patient, both randomised to arm B, gave no consent to the antiemetic treatment concept. All 8 randomised patients received at least one treatment with Irinotecan drug eluted beads, irinotecan, cetuximab or aprepitant. For exposure to trial medication, see Table 11.2 in appendix 11.1. All patients randomised to arm A received at least one intravenous chemotherapy cycle irinotecan and cetuximab. One patient in arm B did not receive at least one chemoembolization treatment with Irinotecan Bead in combination with cetuximab (Table 3.2).

Table 3.2 Number of intravenous chemotherapy cycles, number of chemoembolization treatments with Irinotecan Bead in combination with intravenous antibody and number of antiemetic treatment cycles, randomised n=8

Arm	PATID	Age [yr]	Sex	Number of biweekly cycles irinotecan + cetuximab	Number of chemoembolization treatments with Irinotecan Bead + cetuximab	Number of cycles 5 HT3 + dexamethasone without aprepitant	Number of cycles 5 HT3 + dexamethasone + aprepitant
A	05-002	70	M	12	0	.	.
	12-006	70	M	5	0	.	.
B	02-008	67	M	0	3	.	.
B1	01-001	56	F	0	5	5	0
	04-007	70	F	0	0	1	0
B2	02-003	76	M	0	4	0	4
	02-004	59	M	0	4	0	4
	04-005	76	M	0	2	0	2

Main reasons for end of study therapy were progressive disease (both patients in arm A and 3 in arm B) and withdrawal of informed consent (Table 3.3 and Table 11.1).

Table 3.3 Reasons for end of study therapy, randomised n=8

Reason for end of study therapy	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	N	N
Progressive Disease	2	3	5
Withdrawal of informed consent	0	2	2
Patient's wish	0	1	1

3.5 Data Sets Analysed

All 8 patients receiving at least one treatment (Irinotecan drug eluted beads, irinotecan cetuximab or aprepitant) were evaluable for safety, 2 in arm A and 6 in arm B. The Intention-to-treat (ITT) analysis set included all patients in the study without major deviation of selection criteria, hence safety and ITT analysis set were identical. Per-protocol patients were those 6 patients, 2/4 in arm A/B, without inclusion/ exclusion exceptions who received at least one intravenous chemotherapy cycle (arm A) or at least one chemoembolization treatment with Irinotecan Bead in combination with intravenous antibody (arm B) and who were treated according to their randomisation schedule. For analysis sets by trial site, see Table 3.4.

Table 3.4 Patients randomised and analysis sets by trial site, randomised n=8

	Number of Patients											
	Arm A Standard				Arm B Experimental				Total			
Center	randomised	Safety	ITT	PP	randomised	Safety	ITT	PP	randomised	Safety	ITT	PP
01	0	0	0	0	1	1	1	1	1	1	1	1
02	0	0	0	0	3	3	3	3	3	3	3	3
04	0	0	0	0	2	2	2	0	2	2	2	0
05	1	1	1	1	0	0	0	0	1	1	1	1
12	1	1	1	1	0	0	0	0	1	1	1	1
Total	2	2	2	2	6	6	6	4	8	8	8	6

Concerning the two antiemetic regimens, the safety/ITT analysis set contained 2 patients in arm B1 and 3 in arm B2 (Table 3.5).

Table 3.5 Patients randomised to antiemetic regimen and analysis sets by trial site, randomised B1/B2 n=5

	Number of Patients							
	Arm B1				Arm B2			
Center	randomised	Safety	ITT	PP	randomised	Safety	ITT	PP
01	1	1	1	1	0	0	0	0
02	0	0	0	0	2	2	2	2
04	1	1	1	0	1	1	1	0
Total	2	2	2	1	3	3	3	2

Analyses were performed in the safety/ITT analysis set, primary efficacy analyses additionally in the per-protocol (PP) analysis set.

3.6 Flow Chart

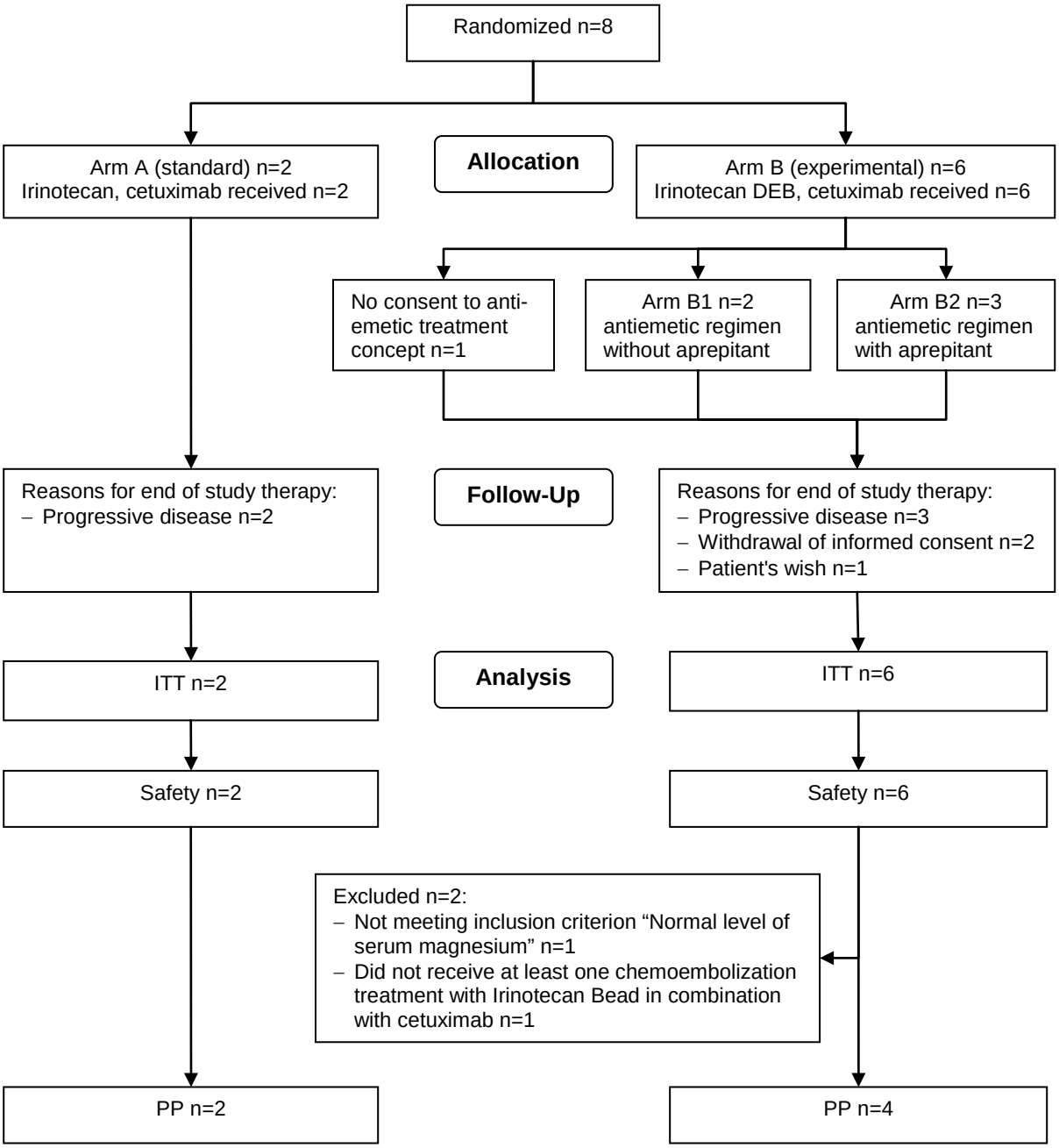

Figure 3.1 Flow diagram

4 Demographic and Other Baseline Characteristics

The ITT analysis set consisted of two 70-year old men in arm A and 4 men and 2 women aged 56-76 years in arm B (Table 4.1and Table 4.2). Body weight was 66 and 85 kg in arm A and between 76 and 85 kg in arm B (Table 4.3). Body height is described in Table 4.4. Body mass index (BMI) was 21.8 and 31.0 in arm A and ranged from 23.2 to 30.9 in arm B (Table 4.5). ECOG performance status was 0 and 1 in 1:1 ratio in arm A and B alike (Table 4.6). For tumour anamnesis, see Table 4.7, Table 4.8 and Table 4.9. Both patients in arm A had bilobar liver disease and metastases not only in liver; in arm B one patient had bilobar liver metastases only, another patient unilobar liver disease and metastases in other site and the remaining 4 patients bilobar liver disease and metastases in other site (see Table 4.10, Table 4.11 and section 3.2). Medical history, coded using MedDRA, can be found summarised by SOC and PT in Table 10.1 in appendix 10.1.

Table 4.1 Gender, ITT n=8

Gender	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	N	N
Male	2	4	6
Female	0	2	2

Table 4.2 Age, ITT n=8

Age [yr]	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
N	2	6	8
Min	70	56	56
Median	70.0	68.5	70.0
Max	70	76	76

Table 4.3 Weight, ITT n=8

Weight [kg]	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
N	2	6	8
Min	66	76	66
Median	75.3	79.5	79.5
Max	85	85	85

Table 4.4 Height, ITT n=8

Height [cm]	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
N	2	6	8
Min	165	160	160
Median	169.5	174.0	171.5
Max	174	188	188

Table 4.5 BMI, ITT n=8

BMI [kg/m²]	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
N	2	6	8
Min	21.8	23.2	21.8
Median	26.42	27.09	27.09
Max	31.0	30.9	31.0

Table 4.6 ECOG status, ITT n=8

ECOG performance status	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	**N**	**N**
ECOG 0	1	3	4
ECOG 1	1	3	4

Table 4.7 Tumour anamnesis: Clinical stage at initial diagnosis of colon carcinoma, ITT n=8

Clinical stage		Arm A Standard n=2	Arm B Experimental n=6	Total n=8
		N	**N**	**N**
T	**T3**	1	3	4
	T4	1	2	3
	TX	0	1	1
N	**N0**	0	1	1
	N1	1	2	3
	N2	1	2	3
	NX	0	1	1
M	**M1**	2	6	8

Table 4.8 Tumour anamnesis: Surgery of primary tumour and pathological stage, ITT n=8

Surgery primary tumour and pathological stage		Arm A Standard n=2	Arm B Experimental n=6	Total n=8
		N	N	N
Surgery primary tumour	No	0	2	2
	Yes	2	4	6
T	T3	1	2	3
	T4	1	2	3
N	Missing	1	0	1
	N1	0	2	2
	N2	1	2	3
M	M1	2	3	5
	MX	0	1	1
Stage	Missing	1	2	3
	G2	1	1	2
	GX	0	1	1

Table 4.9 Tumour anamnesis: Resection of liver metastases, ITT n=8

Resection of liver metastases	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	N	N
Missing	1	0	1
No	1	6	7
Yes	0	0	0

Table 4.10 Liver disease, ITT n=8

Liver metastases	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	N	N
unilobar	0	1	1
bilobar	2	5	7

Table 4.11 Site of metastases, ITT n=8

Site of metastases	Arm A Standard n=2	Arm B Experimental n=6	Total n=8
	N	N	N
liver only	0	1	1
liver plus other site	2	5	7

5 Efficacy Analysis

The efficacy analysis was done in the ITT analysis set including 8 patients (2/6 in arm A/B), and with respect to primary endpoint additionally in the PP analysis set of 6 patients (2/4 in arm A/B). Response and event time data are listed by patient in appendix 11.2 in Table 11.3.

5.1 Analysis of Primary Endpoint

Primary endpoint was progression-free survival (PFS) 6 months after randomisation. None of the two patients in arm A and one of 6/4 patients in arm B (ITT/PP) were still progression-free alive after 6 months (Table 1.1 a/b for ITT/PP). Median PFS times with 95% CI were 129 [91,167] days in arm A and 127.5 [82,188] in arm B (Table 5.3 c).

Table 5.1 PFS at 6 months

a. ITT n=8

	PFS status after 6 months		
	Alive without PD	PD/dead	Total
	N	N	N
Arm			
Arm B Experimental	1	5	6
Arm A Standard	0	2	2
Total	1	7	8

b. PP n=6

	PFS status after 6 months		
	Alive without PD	PD/dead	Total
	N	N	N
Arm			
Arm B Experimental	1	3	4
Arm A Standard	0	2	2
Total	1	5	6

5.2 Analysis of Secondary Endpoints

Secondary efficacy endpoints were

- best tumour response
- best local tumour response
- time to progression
- time to liver progression
- overall survival (OS)
- change in tumour marker CEA
- acute and delayed nausea and emesis during chemoembolization

Best response was in none of the two patients in arm A CR or PR and in 0/2 of 6 patients in arm B CR/PR (Table 5.2).

Table 5.2 Best response, ITT n=8

Best response		Arm A Standard n=2	Arm B Experimental n=6	Total n=8
		N	N	N
Local tumour response	CR	0	0	0
	PR	0	2	2
	SD	1	3	4
	PD	1	1	2
Tumour response	CR	0	0	0
	PR	0	2	2
	SD	1	1	2
	PD	1	3	4

Median times to progression and to liver progression with 95% CI were estimated as 129 [91,167] days in arm A and 137 [82,188] days in arm B (Table 5.3 a, b). Median OS time was 191 [118,428] days in arm B (Table 5.3 d). In arm A one patient survived 203 days and the other was still alive (and censored) after 260 days (Table 11.3).

Table 5.3 Median event times with two-sided 95% CIs, ITT n=8

a. Time to liver progression

Arm	Median [d]	95% CI	n	n Event	n Censored
Arm A Standard	129.0	[91,167]	2	2	0
Arm B Experimental	137.0	[82,188]	6	5	1

b. Time to progression

Arm	Median [d]	95% CI	n	n Event	n Censored
Arm A Standard	129.0	[91,167]	2	2	0
Arm B Experimental	137.0	[82,188]	6	5	1

c. Progression-free survival

Arm	Median [d]	95% CI	n	n Event	n Censored
Arm A Standard	129.0	[91,167]	2	2	0
Arm B Experimental	127.5	[82,188]	6	6	0

d. Overall survival

Arm	Median [d]	95% CI	n	n Event	n Censored
Arm A Standard	.	.	2	1	1
Arm B Experimental	191.0	[118,428]	6	5	1

The available data of tumour marker CEA are shown in Table 5.4. Change from baseline value in tumour marker could be calculated for none of the patients in arm A and for 4 of 6 patients in arm B at least once.

Table 5.4 Tumour marker CEA, ITT n=8

Arm	PATID	Age [yr]	Sex	Visit	Day	CEA [µg/l]	Change from baseline CEA [µg/l]
A	05-002	70	M	Baseline	1	185.3	.
	12-006	70	M	Baseline	.	.	.
B	02-008	67	M	Baseline	1	625.6	.
				Month 3	103	13.8	-611.8
				Month 6	180	64.9	-560.7
				Month 9	286	462.0	-163.6
B1	01-001	56	F	Baseline	-1	291.9	.
				Week 12	91	22.3	-269.6
				Week 19	132	51.9	-240.0
				Week 27	188	189.4	-102.5
	04-007	70	F	Baseline	5	22.0	.
B2	02-003	76	M	Baseline	-1	272.7	.
				Week 11	85	437.4	164.7
	02-004	59	M	Baseline	-1	33.9	.
				Week 11	83	5.4	-28.5
	04-005	76	M	Baseline	-22	2.0	.

MAT data for acute and delayed nausea and emesis during chemoembolization were missing for all but one of the chemoembolization treatments in arm B1. In arm B2 (and B1) neither nausea nor emesis was reported except delayed nausea once (Table 5.5).

Table 5.5 Acute and delayed nausea and emesis (MAT) and rescue medication, ITT B1/B2 n=5

Arm	PATID	Age [yr]	Sex	Visit	Acute nausea	Acute emesis	Delayed nausea	Delayed emesis	Rescue medication
B1	01-001	56	F	Week 1	No	No	No	No	No
				Week 5	.	.	.	.	No
				Week 8	.	.	.	.	No
				Week 13	.	.	.	.	No
				Week 19	.	.	.	.	No
	04-007	70	F	Week 1	.	.	.	.	No
B2	02-003	76	M	Week 0	No	No	No	No	Yes
				Week 2	No	No	No	No	Yes
				Week 4	No	No	No	No	Yes
				Week 6	No	No	No	No	Yes
	02-004	59	M	Week 0	No	No	No	No	Yes
				Week 2	No	No	No	No	Yes
				Week 4	No	No	No	No	Yes
				Week 6	No	No	No	No	Yes
	04-005	76	M	Week 0	No	No	Yes	No	No
				Week 3	No	No	No	No	No

6 Safety Analysis

The safety analysis was performed in the safety analysis set which was identical to the ITT analysis set including all 8 randomised patients, 2 in arm A (standard) and 6 in arm B (experimental).

6.1 Adverse Events

The adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1, English. Frequencies of AEs were summarised by System Organ Class (SOC) and Preferred Term (PT), CTC grade, and relationship to study treatment. In the summary by CTC grade, only the worst case per PT for each patient was included, if a patient experienced more than one AE within a PT.

All of the 8 patients, 2 in arm A and 6 in arm B, experienced adverse events. In total, 44 AEs were documented, 15 in arm A and 29 in arm B, see Table 6.1 for details.

Table 6.1 AEs by SOC, Safety n=8

N: Number of Patients, N AE: Number of AEs

Adverse Events by System Organ Class (SOC)	Arm A Standard n=2			Arm B Experimental n=6			Total n=8		
	N	N AE	N AE*	N	N AE	N AE*	N	N AE	N AE*
Any AE	2	15	11	6	29	27	8	44	38
Infections and infestations	1	1	1	1	1	1	2	2	2
Blood and lymphatic system disorders	1	1	1	0	0	0	1	1	1
Immune system disorders	0	0	0	1	1	1	1	1	1
Metabolism and nutrition disorders	0	0	0	3	4	4	3	4	4
Psychiatric disorders	0	0	0	1	1	1	1	1	1
Nervous system disorders	1	1	1	0	0	0	1	1	1
Respiratory, thoracic and mediastinal disorders	0	0	0	1	1	1	1	1	1
Gastrointestinal disorders	2	3	3	4	7	6	6	10	9
Hepatobiliary disorders	0	0	0	1	2	1	1	2	1
Skin and subcutaneous tissue disorders	1	7	3	4	4	4	5	11	7
General disorders and administration site conditions	1	1	1	3	6	6	4	7	7
Investigations	1	1	1	1	2	2	2	3	3

***worst case on PT level per patient counted only**

The AEs by CTC grade are given in Table 6.2. In this table, no multiply occurring AE on PT level was counted more than once per patient. None of the patients suffered a CTC grade 5 AE; 2 patients in arm B had CTC grade 4 AEs which were mechanical ileus and infusion related reaction. One patient in arm A had 3 CTC grade 3 AEs (decreased haemoglobin, pyrexia and diarrhoea). In arm B, CTC grade 3 AEs were respiratory depression, abdominal

pain, upper abdominal pain, hepatic pain and pain in one and the same patient, increased blood bilirubin and increased C-reactive protein in another patient and rash in one patient.

Table 6.2 AEs by SOC, PT and CTC grade, Safety n=8

N: Number of Patients

Adverse Events by SOC, PT and Grade			Arm A Standard n=2	Arm B Experimental n=6	Total n=8
			N	N	N
Any AE		Grade 1	1	4	5
		Grade 2	2	4	6
		Grade 3	1	3	4
		Grade 4	0	2	2
		Grade 5	0	0	0
		NMISS	0	2	2
		All AEs	2	6	8
Infections and infestations		Grade 1	1	0	1
		Grade 2	0	1	1
		All AEs	1	1	2
	Abscess limb	Grade 1	1	0	1
		All AEs	1	0	1
	Bronchitis	Grade 2	0	1	1
		All AEs	0	1	1
Blood and lymphatic system disorders		Grade 1	1	0	1
		All AEs	1	0	1
	Neutropenia	Grade 1	1	0	1
		All AEs	1	0	1
Immune system disorders		Grade 2	0	1	1
		All AEs	0	1	1
	Drug hypersensitivity	Grade 2	0	1	1
		All AEs	0	1	1
Metabolism and nutrition disorders		Grade 1	0	2	2
		Grade 2	0	1	1
		All AEs	0	3	3
	Decreased appetite	Grade 1	0	1	1
		All AEs	0	1	1
	Hypokalaemia	Grade 1	0	1	1
		Grade 2	0	1	1
		All AEs	0	2	2
	Hypomagnesaemia	Grade 1	0	1	1
		All AEs	0	1	1
Psychiatric disorders		NMISS	0	1	1
		All AEs	0	1	1
	Sleep disorder	NMISS	0	1	1
		All AEs	0	1	1

Adverse Events by SOC, PT and Grade			Arm A Standard n=2	Arm B Experimental n=6	Total n=8
			N	N	N
Nervous system disorders		Grade 1	1	0	1
		All AEs	1	0	1
	Polyneuropathy	Grade 1	1	0	1
		All AEs	1	0	1
Respiratory, thoracic and mediastinal disorders		Grade 3	0	1	1
		All AEs	0	1	1
	Respiratory depression	Grade 3	0	1	1
		All AEs	0	1	1
Gastrointestinal disorders		Grade 1	1	1	2
		Grade 2	1	1	2
		Grade 3	1	1	2
		Grade 4	0	1	1
		NMISS	0	1	1
		All AEs	2	4	6
	Abdominal pain	Grade 2	0	1	1
		Grade 3	0	1	1
		All AEs	0	2	2
	Abdominal pain upper	Grade 3	0	1	1
		All AEs	0	1	1
	Abdominal tenderness	Grade 1	0	1	1
		All AEs	0	1	1
	Diarrhoea	Grade 3	1	0	1
		NMISS	0	1	1
		All AEs	1	1	2
	Haematochezia	Grade 1	1	0	1
		All AEs	1	0	1
	Ileus paralytic	Grade 2	1	0	1
		All AEs	1	0	1
	Mechanical ileus	Grade 4	0	1	1
		All AEs	0	1	1
Hepatobiliary disorders		Grade 3	0	1	1
		All AEs	0	1	1
	Hepatic pain	Grade 3	0	1	1
		All AEs	0	1	1

Adverse Events by SOC, PT and Grade			Arm A Standard n=2	Arm B Experimental n=6	Total n=8
			N	N	N
Skin and subcutaneous tissue disorders		Grade 1	1	2	3
		Grade 2	1	0	1
		Grade 3	0	1	1
		NMISS	0	1	1
		All AEs	1	4	5
	Dermatitis acneiform	Grade 1	0	1	1
		All AEs	0	1	1
	Onychoclasis	Grade 1	1	0	1
		All AEs	1	0	1
	Palmar-plantar erythrodysaesthesia syndrome	Grade 2	1	0	1
		All AEs	1	0	1
	Rash	Grade 1	0	1	1
		Grade 2	1	0	1
		Grade 3	0	1	1
		All AEs	1	2	3
	Rash generalised	NMISS	0	1	1
		All AEs	0	1	1
General disorders and administration site conditions		Grade 2	0	2	2
		Grade 3	1	1	2
		Grade 4	0	1	1
		NMISS	0	1	1
		All AEs	1	3	4
	Fatigue	NMISS	0	1	1
		All AEs	0	1	1
	General physical health deterioration	NMISS	0	1	1
		All AEs	0	1	1
	Infusion related reaction	Grade 4	0	1	1
		All AEs	0	1	1
	Pain	Grade 2	0	1	1
		Grade 3	0	1	1
		All AEs	0	2	2
	Pyrexia	Grade 2	0	1	1
		Grade 3	1	0	1
		All AEs	1	1	2
Investigations		Grade 3	1	1	2
		All AEs	1	1	2
	Blood bilirubin increased	Grade 3	0	1	1
		All AEs	0	1	1
	C-reactive protein increased	Grade 3	0	1	1
		All AEs	0	1	1
	Haemoglobin decreased	Grade 3	1	0	1
		All AEs	1	0	1

Besides CTC grade, Table 10.2 shows relationship of AEs to study treatment. In this table, all AEs were included. In arm A, 8/10 of 15 AEs were related, i.e. possibly, probably or definitely related, to irinotecan (a)/ cetuximab (b); 8/10/17 of 29 AEs were related to irinotecan (a)/ cetuximab (b)/ chemoembolization (c) in arm B. Of these AEs evaluated as related to study treatment were 3/0 and 8/2 with CTC grade 3/4 in arm A and arm B, respectively. Regarding arm A, these were decreased haemoglobin, pyrexia and diarrhea, all CTC grade 3 AEs mentioned above, related to irinotecan and cetuximab. In arm B, the CTC grade 4 AEs mechanical ileus and infusion related reaction were related to chemoembolization and the latter to irinotecan too. One of the CTC grade 3 AEs in arm B was related to cetuximab (rash), the other 7 were related to chemoembolization: hepatic pain (twice), abdominal pain, upper abdominal pain, pain, increased blood bilirubin and increased C-reactive protein. The most frequent chemoembolization related AE was pain (pain, abdominal pain, upper abdominal pain, hepatic pain). Because of pain, chemoembolization was carried out under general anaesthesia in trial site 02 [4]. No aprepitant related AE (d) was documented. For further details, see Table 10.2 in appendix 10.2.

6.2 Serious Adverse Events

The number of patients experiencing a serious adverse event (SAE) and the number of SAEs are displayed in Table 6.3. All SAEs are listed by patient in Table 11.4 in appendix 11.3.

In total, 5 SAEs were reported in 3 of 8 patients. In arm A, one patient had 3 SAEs: diarrhoea and decreased haemoglobin, both possibly related to irinotecan and cetuximab, and paralytic ileus. In arm B, both SAEs were possibly chemoembolization related: increased C-reactive protein and mechanical ileus (one patient each).

Table 6.3 SAEs by SOC and PT, Safety n=8

N: Number of Patients, N SAE: Number of SAEs

SAEs nach SOC und PT		Arm A Standard n=2		Arm B Experimental n=6		Total n=8	
		N	N SAE	N	N SAE	N	N SAE
Any SAE		1	3	2	2	3	5
Gastrointestinal disorders		1	2	1	1	2	3
	Diarrhoea	1	1	0	0	1	1
	Ileus paralytic	1	1	0	0	1	1
	Mechanical ileus	0	0	1	1	1	1
Investigations		1	1	1	1	2	2
	C-reactive protein increased	0	0	1	1	1	1
	Haemoglobin decreased	1	1	0	0	1	1

6.3 Deaths

None of the AEs resulted in death. 6 of 8 patients, one in arm A and 5 in arm B, died during study follow-up most of them due to tumour/progression (Table 6.4 and Table 11.1).

Table 6.4 Deaths and their causes, Safety n=8

Death and cause of death		Arm A Standard n=2	Arm B Experimental n=6	Total n=8
		N	N	N
Death	No	1	1	2
	Yes	1	5	6
Cause of death	Tumour/progression	1	4	5
	unknown	0	1	1

7 Summary and Discussion

Primary objective of this multicentre, open labeled, prospective, randomised, non comparative phase II study was to evaluate the efficacy of Irinotecan Beads in combination with intravenous cetuximab versus intravenous irinotecan in combination with intravenous cetuximab, as indicated by 6-month progression free survival, in the treatment of patients with unresectable liver metastases from colorectal cancer. Secondary objectives were to assess safety and tolerability of hepatic chemoembolization, and safety and efficacy of additional aprepitant to standard antiemetic prophylaxis in patients treated by hepatic chemoembolization.

Standard study treatment (arm A) consisted of irinotecan (according to common protocols) and cetuximab; experimental study treatment (arm B) of Irinotecan DEB in combination with cetuximab. Antiemetic regimen was 5 HT3 serotonin receptor antagonists and dexamethason in arm B1 and B2, plus aprepitant in arm B2. Study treatment was scheduled until progression, unacceptable toxicity, investigator's decision or withdrawal of consent.

Sample size calculation was based on a one-sample one-sided test and a significance level α=10%, and 6 month PFS rates of 0.40 for comparison and 0.55 as considered to be effective in the experimental arm. A number of 49 evaluable patients in the experimental arm B was required. According to the 2:1 randomisation and a drop out rate of 10%, 80 patients should have been recruited. As a consequence of poor recruitment and subsequent early termination, only a total of 8 patients were randomised, 2 to standard arm A, 6 to experimental arm B, and within arm B 2 to arm B1 and 3 to arm B2. All patients received at least one study treatment and thus were evaluable for safety. All patients were included in the ITT analysis set. Reasons for end of study therapy were progressive disease (2/3 patients), withdrawal of informed consent (0/2) and patient's wish (0/1) in standard/ experimental arm.

Two 70-year old men with bilobar liver disease and metastases not only in liver were in standard arm A; 4 men and 2 women aged 56-76 years in experimental arm B. One of the patients in arm B had bilobar liver metastases only, another unilobar liver disease and also metastases in other site and the other 4 patients bilobar liver disease and metastases not only in liver.

Primary endpoint was progression-free survival 6 months after randomisation. None of the two patients in standard arm A and one of 6 patients in experimental arm B were still progression-free alive after 6 months. Secondary efficacy endpoints were best tumour response, best local tumour response, time to progression, time to liver progression, overall survival, change in tumour marker CEA, acute and delayed nausea and emesis during chemoembolization. Frequencies of best tumour response were CR 0/0, PR 0/2, SD 1/1 and PD 1/3, of best local tumour response CR 0/0, PR 0/2, SD 1/3 and PD 1/1 in standard/

experimental arm. Median times to progression and to liver progression with 95% CI were 129 [91,167] days in standard arm A and 137 [82,188] days in experimental arm B, median OS time in arm B 191 [118,428] days. In arm A, one patient survived 203 days and the other at least 260 days. Change in tumour marker could not be determined in standard arm A for lack of data, but was listed by patient in experimental arm B. Data on nausea and emesis during chemoembolization were missing for all but one of the chemoembolization treatments in arm B1. In arm B2 (and B1) neither nausea nor emesis was reported except delayed nausea once.

All patients had adverse events. In total, 15 AEs were documented in standard arm A (2 patients) and 29 AEs in experimental arm B (6 patients). The highest occurring CTC grades were 3 and 4 in arm A and B, respectively. In arm A, the 3 CTC grade 3 AEs were decreased haemoglobin, pyrexia and diarrhoea which were evaluated as related to irinotecan and cetuximab. In arm B, the both CTC grade 4 AEs were mechanical ileus and infusion related reaction which were both related to chemoembolization and the latter also to irinotecan; the CTC grade 3 AEs were hepatic pain (twice), abdominal pain, upper abdominal pain, pain, increased blood bilirubin and increased C-reactive protein which were all 7 related to chemoembolization; rash related to cetuximab; respiratory depression not related to study treatment. In arm A, one patient had 3 SAEs: diarrhea, decreased haemoglobin and paralytic ileus. In arm B, 2 patients had SAEs: increased C-reactive protein and mechanical ileus.

This study was designed to evaluate the efficacy of Irinotecan Beads in combination with intravenous cetuximab and safety and tolerability of hepatic chemoembolization. In one trial site, chemoembolization was carried out under general anaesthesia due to pain. When drawing conclusions from this study the limited number of patients should be considered. Actually, only 8 patients, i.e. one-tenth of the planned number, could be randomised, 6 of them to the experimental arm. However, the analysis of the primary endpoint PFS after 6 months and secondary efficacy analyses of response, time to progression and overall survival did not give results which allow to answer the study questions.

8 Signatures

Prof. Dr. A. Wienke, Biometrician

Date, Signature

Prof. Dr. D. Arnold, LKP, Representative of the Sponsor

Date, Signature

ANHANG

9 References

[1] Investigational Plan & Clinical Study Protocol: A randomized phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolization with intravenous cetuximab (DEBIRITUX) versus systemic treatment with intravenous cetuximab and irinotecan in patients with refractory metastatic colorectal cancer and k-ras wild-type tumours. Version: Final 02/12-09

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[3] Wilke H, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aguilar EA, Aapro MS, Esser R, Loos AH, Siena S. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. J Clin Oncol 2008, 26 (33):5316-9

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10 Tables

10.1 Baseline Characteristics

Table 10.1 Medical history (MedDRA-Version 13.1 EN), ITT n=8

N: Number of Patients, N MH: Number of MHs

Medical History by SOC and PT		Arm A Standard n=2		Arm B Experimental n=6		Total	
		N	N MH	N	N MH	N	N MH
Any MH		2	7	6	29	8	36
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1	1	2	2	3	3
	Mantle cell lymphoma stage III	1	1	0	0	1	1
	Metastases to lung	0	0	1	1	1	1
	Prostatic adenoma	0	0	1	1	1	1
Blood and lymphatic system disorders		1	1	0	0	1	1
	Hypochromic anaemia	1	1	0	0	1	1
Immune system disorders		0	0	1	3	1	3
	Drug hypersensitivity	0	0	1	1	1	1
	Iodine allergy	0	0	1	1	1	1
	Seasonal allergy	0	0	1	1	1	1
Metabolism and nutrition disorders		0	0	2	2	2	2
	Diabetes mellitus	0	0	1	1	1	1
	Obesity	0	0	1	1	1	1
Nervous system disorders		0	0	2	2	2	2
	Cerebrovascular accident	0	0	1	1	1	1
	Parkinson's disease	0	0	1	1	1	1
Eye disorders		0	0	1	1	1	1
	Glaucoma	0	0	1	1	1	1
Ear and labyrinth disorders		0	0	1	1	1	1
	Hypoacusis	0	0	1	1	1	1
Cardiac disorders		1	2	1	1	2	3
	Coronary artery disease	1	1	1	1	2	2
	Myocardial infarction	1	1	0	0	1	1
Vascular disorders		1	1	3	3	4	4
	Hypertension	1	1	3	3	4	4
Respiratory, thoracic and mediastinal disorders		0	0	1	1	1	1
	Dyspnoea	0	0	1	1	1	1
Gastrointestinal disorders		0	0	2	3	2	3
	Anal fissure	0	0	1	1	1	1
	Diarrhoea	0	0	1	1	1	1
	Diverticulum intestinal	0	0	1	1	1	1
Skin and subcutaneous tissue disorders		0	0	1	1	1	1
	Acne	0	0	1	1	1	1
Renal and urinary disorders		1	1	1	1	2	2
	Renal cyst	0	0	1	1	1	1
	Renal failure	1	1	0	0	1	1

Medical History by SOC and PT		Arm A Standard n=2		Arm B Experimental n=6		Total	
		N	N MH	N	N MH	N	N MH
Reproductive system and breast disorders		0	0	1	1	1	1
	Benign prostatic hyperplasia	0	0	1	1	1	1
Investigations		1	1	1	1	2	2
	Anti-HBc antibody positive	1	1	0	0	1	1
	Sensory level abnormal	0	0	1	1	1	1
Surgical and medical procedures		0	0	3	6	3	6
	Appendicectomy	0	0	1	1	1	1
	Cholecystectomy	0	0	2	2	2	2
	Hysterectomy	0	0	1	1	1	1
	Knee arthroplasty	0	0	1	1	1	1
	Varicose vein operation	0	0	1	1	1	1

10.2 Adverse Events

Table 10.2 AEs (MedDRA-Version 13.1 EN) by SOC, PT, CTC grade and relationship to study treatment

Not related:=unlikely+not related+not assessable, Related:=definitely+probably+possibly, N: Number of Patients, N AE: Number of AEs

a. Irinotecan, Safety n=8

Adverse Events by SOC, PT and Grade			Causality Irinotecan											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Any AE		Grade 1	1	4	1	4	1	8	3	4	2	2	4	6
		Grade 2	2	3	1	1	2	4	4	5	1	2	4	7
		Grade 3	0	0	1	3	1	3	3	9	0	0	3	9
		Grade 4	0	0	0	0	0	0	1	1	1	1	2	2
		Grade 5	0	0	0	0	0	0	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	2	2	1	3	2	5
		All AEs	2	7	2	8	2	15	5	21	4	8	6	29
Infections and infestations		Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	1	1	1	1	1	1	0	0	1	1
	Abscess limb	Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Bronchitis	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Blood and lymphatic system disorders		Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Neutropenia	Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0

Adverse Events by SOC, PT and Grade			Causality Irinotecan											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Immune system disorders		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Drug hypersensitivity	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Metabolism and nutrition disorders		Grade 1	0	0	0	0	0	0	1	2	1	1	2	3
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	3	1	1	3	4
	Decreased appetite	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Hypokalaemia	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	2	0	0	2	2
	Hypomagnesaemia	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Psychiatric disorders		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Sleep disorder	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Nervous system disorders		Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Polyneuropathy	Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Respiratory depression	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Irinotecan											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Gastrointestinal disorders		Grade 1	1	1	0	0	1	1	0	0	1	1	1	1
		Grade 2	1	1	0	0	1	1	0	0	1	2	1	2
		Grade 3	0	0	1	1	1	1	1	2	0	0	1	2
		Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	2	2	1	1	2	3	2	3	3	4	4	7
	Abdominal pain	Grade 2	0	0	0	0	0	0	0	0	1	2	1	2
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	1	2	2	3
	Abdominal pain upper	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Abdominal tenderness	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Diarrhoea	Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	1	1	1	1	0	0	1	1	1	1
	Haematochezia	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Ileus paralytic	Grade 2	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Mechanical ileus	Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Hepatobiliary disorders		Grade 3	0	0	0	0	0	0	1	2	0	0	1	2
		All AEs	0	0	0	0	0	0	1	2	0	0	1	2
	Hepatic pain	Grade 3	0	0	0	0	0	0	1	2	0	0	1	2
		All AEs	0	0	0	0	0	0	1	2	0	0	1	2

Adverse Events by SOC, PT and Grade			Causality Irinotecan											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Skin and subcutaneous tissue disorders		Grade 1	1	3	1	1	1	4	2	2	0	0	2	2
		Grade 2	1	2	1	1	1	3	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	1	5	1	2	1	7	3	3	1	1	4	4
	Dermatitis acneiform	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Onychoclasis	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Palmar-plantar erythrodysaesthesia syndrome	Grade 2	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Rash	Grade 1	1	2	1	1	1	3	1	1	0	0	1	1
		Grade 2	1	2	0	0	1	2	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	1	4	1	1	1	5	2	2	0	0	2	2
	Rash generalised	NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1

Adverse Events by SOC, PT and Grade			Causality Irinotecan											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
General disorders and administration site conditions		Grade 2	0	0	0	0	0	0	2	2	0	0	2	2
		Grade 3	0	0	1	1	1	1	1	1	0	0	1	1
		Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		NMISS	0	0	0	0	0	0	1	1	1	1	1	2
		All AEs	0	0	1	1	1	1	3	4	2	2	3	6
	Fatigue	NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	General physical health deterioration	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Infusion related reaction	Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Pain	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	2	0	0	2	2
	Pyrexia	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	1	1	0	0	1	1
Investigations		Grade 3	0	0	1	1	1	1	1	2	0	0	1	2
		All AEs	0	0	1	1	1	1	1	2	0	0	1	2
	Blood bilirubin increased	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	C-reactive protein increased	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Haemoglobin decreased	Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0

b. Cetuximab, Safety n=8

Adverse Events by SOC, PT and Grade			Causality Cetuximab											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Any AE		Grade 1	1	4	1	4	1	8	0	0	4	6	4	6
		Grade 2	1	1	1	3	2	4	3	5	2	2	4	7
		Grade 3	0	0	1	3	1	3	2	8	1	1	3	9
		Grade 4	0	0	0	0	0	0	2	2	0	0	2	2
		Grade 5	0	0	0	0	0	0	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	2	4	1	1	2	5
		All AEs	2	5	2	10	2	15	5	19	5	10	6	29
Infections and infestations		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1	1	1	0	0	1	1
	Abscess limb	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Bronchitis	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Blood and lymphatic system disorders		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Neutropenia	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
Immune system disorders		Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Drug hypersensitivity	Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1

Adverse Events by SOC, PT and Grade			Causality Cetuximab											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Metabolism and nutrition disorders		Grade 1	0	0	0	0	0	0	0	0	2	3	2	3
		Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	3	4	3	4
	Decreased appetite	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Hypokalaemia	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	2	2	2	2
	Hypomagnesaemia	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
Psychiatric disorders		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Sleep disorder	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Nervous system disorders		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Polyneuropathy	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Respiratory depression	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Cetuximab											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Gastrointestinal disorders		Grade 1	1	1	0	0	1	1	0	0	1	1	1	1
		Grade 2	1	1	0	0	1	1	1	2	0	0	1	2
		Grade 3	0	0	1	1	1	1	1	2	0	0	1	2
		Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	2	2	1	1	2	3	3	6	1	1	4	7
	Abdominal pain	Grade 2	0	0	0	0	0	0	1	2	0	0	1	2
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	3	0	0	2	3
	Abdominal pain upper	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Abdominal tenderness	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Diarrhoea	Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	1	1	1	1	1	1	0	0	1	1
	Haematochezia	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Ileus paralytic	Grade 2	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Mechanical ileus	Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Hepatobiliary disorders		Grade 3	0	0	0	0	0	0	1	2	0	0	1	2
		All AEs	0	0	0	0	0	0	1	2	0	0	1	2
	Hepatic pain	Grade 3	0	0	0	0	0	0	1	2	0	0	1	2
		All AEs	0	0	0	0	0	0	1	2	0	0	1	2

Adverse Events by SOC, PT and Grade			Causality Cetuximab											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Skin and subcutaneous tissue disorders		Grade 1	0	0	1	4	1	4	0	0	2	2	2	2
		Grade 2	0	0	1	3	1	3	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	1	7	1	7	1	1	3	3	4	4
	Dermatitis acneiform	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Onychoclasis	Grade 1	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Palmar-plantar erythrodysaesthesia syndrome	Grade 2	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0
	Rash	Grade 1	0	0	1	3	1	3	0	0	1	1	1	1
		Grade 2	0	0	1	2	1	2	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	1	5	1	5	0	0	2	2	2	2
	Rash generalised	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Cetuximab											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
General disorders and administration site conditions		Grade 2	0	0	0	0	0	0	2	2	0	0	2	2
		Grade 3	0	0	1	1	1	1	1	1	0	0	1	1
		Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		NMISS	0	0	0	0	0	0	1	1	1	1	1	2
		All AEs	0	0	1	1	1	1	3	5	1	1	3	6
	Fatigue	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	General physical health deterioration	NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Infusion related reaction	Grade 4	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Pain	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	2	0	0	2	2
	Pyrexia	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	1	1	0	0	1	1
Investigations		Grade 3	0	0	1	1	1	1	1	2	0	0	1	2
		All AEs	0	0	1	1	1	1	1	2	0	0	1	2
	Blood bilirubin increased	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	C-reactive protein increased	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Haemoglobin decreased	Grade 3	0	0	1	1	1	1	0	0	0	0	0	0
		All AEs	0	0	1	1	1	1	0	0	0	0	0	0

c. Chemoembolization, Safety n=8

Adverse Events by SOC, PT and Grade			Causality Chemoembolization											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Any AE		Grade 1	1	8	0	0	1	8	3	5	1	1	4	6
		Grade 2	2	4	0	0	2	4	3	3	3	4	4	7
		Grade 3	1	3	0	0	1	3	2	2	2	7	3	9
		Grade 4	0	0	0	0	0	0	0	0	2	2	2	2
		Grade 5	0	0	0	0	0	0	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	2	2	1	3	2	5
		All AEs	2	15	0	0	2	15	4	12	6	17	6	29
Infections and infestations		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1	1	1	0	0	1	1
	Abscess limb	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Bronchitis	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Blood and lymphatic system disorders		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Neutropenia	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
Immune system disorders		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Drug hypersensitivity	Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Chemoembolization											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Metabolism and nutrition disorders		Grade 1	0	0	0	0	0	0	2	3	0	0	2	3
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	3	4	0	0	3	4
	Decreased appetite	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Hypokalaemia	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		Grade 2	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	2	2	0	0	2	2
	Hypomagnesaemia	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Psychiatric disorders		NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Sleep disorder	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
Nervous system disorders		Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Polyneuropathy	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Respiratory depression	Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Chemoembolization											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Gastrointestinal disorders		Grade 1	1	1	0	0	1	1	0	0	1	1	1	1
		Grade 2	1	1	0	0	1	1	0	0	1	2	1	2
		Grade 3	1	1	0	0	1	1	0	0	1	2	1	2
		Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	2	3	0	0	2	3	0	0	4	7	4	7
	Abdominal pain	Grade 2	0	0	0	0	0	0	0	0	1	2	1	2
		Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	2	3	2	3
	Abdominal pain upper	Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Abdominal tenderness	Grade 1	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Diarrhoea	Grade 3	1	1	0	0	1	1	0	0	0	0	0	0
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	1	1	0	0	1	1	0	0	1	1	1	1
	Haematochezia	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Ileus paralytic	Grade 2	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Mechanical ileus	Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
Hepatobiliary disorders		Grade 3	0	0	0	0	0	0	0	0	1	2	1	2
		All AEs	0	0	0	0	0	0	0	0	1	2	1	2
	Hepatic pain	Grade 3	0	0	0	0	0	0	0	0	1	2	1	2
		All AEs	0	0	0	0	0	0	0	0	1	2	1	2

Adverse Events by SOC, PT and Grade			Causality Chemoembolization											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
Skin and subcutaneous tissue disorders		Grade 1	1	4	0	0	1	4	2	2	0	0	2	2
		Grade 2	1	3	0	0	1	3	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	1	7	0	0	1	7	3	3	1	1	4	4
	Dermatitis acneiform	Grade 1	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Onychoclasis	Grade 1	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Palmar-plantar erythrodysaesthesia syndrome	Grade 2	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0
	Rash	Grade 1	1	3	0	0	1	3	1	1	0	0	1	1
		Grade 2	1	2	0	0	1	2	0	0	0	0	0	0
		Grade 3	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	1	5	0	0	1	5	2	2	0	0	2	2
	Rash generalised	NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1

Adverse Events by SOC, PT and Grade			Causality Chemoembolization											
			Arm A Standard n=2						Arm B Experimental n=6					
			Not related		Related		All AEs		Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE	N	N AE	N	N AE	N	N AE
General disorders and administration site conditions		Grade 2	0	0	0	0	0	0	0	0	2	2	2	2
		Grade 3	1	1	0	0	1	1	0	0	1	1	1	1
		Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		NMISS	0	0	0	0	0	0	1	1	1	1	1	2
		All AEs	1	1	0	0	1	1	1	1	3	5	3	6
	Fatigue	NMISS	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	General physical health deterioration	NMISS	0	0	0	0	0	0	1	1	0	0	1	1
		All AEs	0	0	0	0	0	0	1	1	0	0	1	1
	Infusion related reaction	Grade 4	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Pain	Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	2	2	2	2
	Pyrexia	Grade 2	0	0	0	0	0	0	0	0	1	1	1	1
		Grade 3	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	1	1	1	1
Investigations		Grade 3	1	1	0	0	1	1	0	0	1	2	1	2
		All AEs	1	1	0	0	1	1	0	0	1	2	1	2
	Blood bilirubin increased	Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	C-reactive protein increased	Grade 3	0	0	0	0	0	0	0	0	1	1	1	1
		All AEs	0	0	0	0	0	0	0	0	1	1	1	1
	Haemoglobin decreased	Grade 3	1	1	0	0	1	1	0	0	0	0	0	0
		All AEs	1	1	0	0	1	1	0	0	0	0	0	0

d. Aprepitant, Safety B2 n=3

Adverse Events by SOC, PT and Grade			Causality Aprepitant Arm B2 n=3					
			Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE
Any AE		Grade 1	3	5	0	0	3	5
		Grade 2	2	4	0	0	2	4
		Grade 3	1	1	0	0	1	1
		Grade 4	2	2	0	0	2	2
		Grade 5	0	0	0	0	0	0
		All AEs	3	12	0	0	3	12
Infections and infestations		Grade 2	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
	Bronchitis	Grade 2	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
Metabolism and nutrition disorders		Grade 1	2	3	0	0	2	3
		All AEs	2	3	0	0	2	3
	Decreased appetite	Grade 1	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
	Hypokalaemia	Grade 1	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
	Hypomagnesaemia	Grade 1	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1

Adverse Events by SOC, PT and Grade			Causality Aprepitant Arm B2 n=3					
			Not related		Related		All AEs	
			N	N AE	N	N AE	N	N AE
Gastrointestinal disorders		Grade 1	1	1	0	0	1	1
		Grade 2	1	2	0	0	1	2
		Grade 4	1	1	0	0	1	1
		All AEs	2	4	0	0	2	4
	Abdominal pain	Grade 2	1	2	0	0	1	2
		All AEs	1	2	0	0	1	2
	Abdominal tenderness	Grade 1	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
	Mechanical ileus	Grade 4	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
Skin and subcutaneous tissue disorders		Grade 1	1	1	0	0	1	1
		Grade 3	1	1	0	0	1	1
		All AEs	2	2	0	0	2	2
	Rash	Grade 1	1	1	0	0	1	1
		Grade 3	1	1	0	0	1	1
		All AEs	2	2	0	0	2	2
General disorders and administration site conditions		Grade 2	1	1	0	0	1	1
		Grade 4	1	1	0	0	1	1
		All AEs	1	2	0	0	1	2
	Infusion related reaction	Grade 4	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1
	Pain	Grade 2	1	1	0	0	1	1
		All AEs	1	1	0	0	1	1

11 Listings

11.1 Patient Flow

Table 11.1 Analysis sets, study duration, reason for end of therapy and status at end of study/follow-up, randomised n=8

				Analysis set			End of therapy		End of study/follow-up		
Arm	PATID	Age [yr]	Sex	Safety	ITT	PP	Day*	Reason for end of study therapy	Day	Status	Cause of death
A	05-002	70	M	Y	Y	Y	163	progressive disease	261	Alive	
	12-006	70	M	Y	Y	Y	85	progressive disease	204	Dead	Tumour/progression
B	02-008	67	M	Y	Y	Y	57	Therapiepause vom Patient erwünscht	429	Dead	Tumour/progression
B1	01-001	56	F	Y	Y	Y	175	progressive disease	318	Dead	Tumour/progression
	04-007	70	F	Y	Y	N	21	withdrawal of informed consent: Einverständnis bzgl. Therapie wg. Diarrhoe, Fatigue, generalisierter Ausschlag	138	Alive	
B2	02-003	76	M	Y	Y	Y	84	progressive disease	160	Dead	Tumour/progression
	02-004	59	M	Y	Y	Y	70	progressive disease	192	Dead	Tumour/progression
	04-005	76	M	Y	Y	N	48	withdrawal of informed consent: kein kurativer Ansatz, sei unter Therapie schwächer geworden.	119	Dead	unknown

* last application of study medication

Table 11.2 Exposure to trial medication, randomised n=8

Arm	PATID	Age [yr]	Sex	Number of weeks cetuximab	Mean weekly dose cetuximab [mg]	Number of biweekly cycles irinotecan	Mean biweekly dose irinotecan [mg]	Number of chemo-embolization treatments with Irinotecan Bead	Mean dose irinotecan per chemo-embolization treatment [mg]	Mean dose irinotecan DEB per chemo-embolization treatment [ml]
A	05-002	70	M	24	502.9	12	360.0	.	.	.
	12-006	70	M	10	462.4	5	304.0	.	.	.
B	02-008	67	M	5	280.0	.	.	4	200.0	7.0
B1	01-001	56	F	25	470.8	.	.	5	200.0	4.0
	04-007	70	F	1	752.0	.	.	1	200.0	4.0
B2	02-003	76	M	11	493.4	.	.	4	167.5	11.8
	02-004	59	M	10	516.1	.	.	4	200.0	12.3
	04-005	76	M	6	524.5	.	.	2	200.0	4.0

11.2 Results

Table 11.3 Response, time to liver progression, time to progression, PFS and OS, ITT n=8

				Best response		Liver progression		Progression		Progression-free survival			Overall survival	
Arm	PATID	Age [yr]	Sex	Liver target lesions	Tumour	Time [d]	Status	Time [d]	Status	Time [d]	Status	Status at 6 months	Time [d]	Status
A	05-002	70	M	SD	SD	167	PD in liver	167	PD	167	PD/dead	PD/dead	260	Alive
	12-006	70	M	PD	PD	91	PD in liver	91	PD	91	PD/dead	PD/dead	203	Dead
B	02-008	67	M	PR	PR	179	PD in liver	179	PD	179	PD/dead	PD/dead	428	Dead
B1	01-001	56	F	PR	PR	188	PD in liver	188	PD	188	PD/dead	Alive without PD	317	Dead
	04-007	70	F	PD	PD	137	PD in liver	137	PD	137	PD/dead	PD/dead	137	Alive
B2	02-003	76	M	SD	PD	84	PD in liver	84	PD	84	PD/dead	PD/dead	159	Dead
	02-004	59	M	SD	PD	82	PD in liver	82	PD	82	PD/dead	PD/dead	191	Dead
	04-005	76	M	SD	SD	48	No PD in liver	48	No PD	118	PD/dead	PD/dead	118	Dead

11.3 Adverse Events

Table 11.4 SAEs (MedDRA-Version 13.1 EN), Safety n=8

Arm	PATID	Age [yr]	Sex	SAE as reported	Preferred Term (PT)	CTC Grade	Start Day	End Day	Causality*	Outcome	Action taken
A	12-006	70	M	Hemoglobin level decreased to 6,8 g/dl Transfusion of packed red blood cells	Haemoglobin decreased	3	43	45	I: possibly C: possibly E: NA A: NA	recovered /resolved	therapy interrupted
				Paralytic Ileus	Ileus paralytic	2	92	100	I: unlikely C: unlikely E: NA A: NA	recovered /resolved	therapy discontinued
				Diarrhoe	Diarrhoea	3	65	85	I: possibly C: possibly E: NA A: NA	recovered /resolved	therapy interrupted
B	02-008	67	M	increase CRP	C-reactive protein increased	3	12	31	I: unlikely C: NA E: possibly A: NA	recovered /resolved	none
B2	04-005	76	M	Ileus Mechanischer Ileus, Bridenileus	Mechanical ileus	4	47	62	I: NA C: unlikely E: possibly A: unlikely	recovered /resolved	none

* I: Irinotecan, C: Cetuximab, E: Chemoembolization, A: Aprepitant, NA: not assessable