Final Study Report

Intensified chemotherapy in advanced colorectal cancer FOLFOX/bevacizumab with or without irinotecan in first-line treatment for metastatic colorectal cancer.

A randomized phase II study (AIO 0209)

(Multicenter, randomized, two-arm, Phase II-Study)

Investigational Medicinal Products:

Bevacizumab (Avastin®) + Irinotecan + Oxaliplatin + Leucovorin +

5-Fluorouracil + Capecitabin (Xeloda®)

Indication:
Metastatic or recurrent colorectal cancer

Phase of the clinical trial:

Phase II

EudraCT-Number: 2010-022162-27

Register-Number: INCT01321957

Version date: 29.08.2019

Version: V01 Final

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Sponsor

Martin-Luther-Universität Halle-Wittenberg,
represented by the chancellor, represented by the
Dean of the Faculty of Medicine,
Magdeburger Str. 8, 06112 Halle /Saale

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Study start (FPI): 28.07.2011

End of study (LPO): 31.08.2018

Signatures

I agree with the content of the final study report in its final version. The reported clinical trial was conducted in accordance with the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and applicable national laws and regulatory requirements.

Coordinating Investigator, representative of the sponsor	Prof. Dr. med. Hans-Joachim Schmoll	29.08.2019 Date
Statistician	Dr. rer. nat. Stefan Ibach	30.08.2019 Date

Table of content

1. Name of the Sponsor/Company

Martin-Luther-University Halle-Wittenberg, represented by the chancellor, represented by the Dean of the Faculty of Medicine

2. Name of Finished Product	3. Name of Active Substances
Avastin®	Bevacizumab
Irinotecan (site dependent product)	Irinotecan
Oxaliplatin (site dependent product)	Oxaliplatin
Leucovorin (site dependent product)	Leucovorin
5-Fluorouracil (site dependent product)	5-Fluorouracil
Xeloda®	Capecitabine

4. Individual Study Table

Not applicable

5. Title of Study

Intensified chemotherapy in advanced colorectal cancer - FOLFOX/bevacizumab with or without irinotecan in first-line treatment for metastatic colorectal cancer. A randomized phase II study (AIO 0209)

- Protocol-Version: Final 1.2/ 05.05.2011: approved by the EC on 07.06.2011, approved by CA on 07.07.2011.
- Protocol-Version Final 1.1/ 19.02.2011 was approved by the CA on 24.03.2011 but did not apply in the trial. This version was replaced by version Final 1.2 due to requirements by the EC before the first study participant has been enrolled.

6. Investigators	7. Study centers
Study participants has been enrolled in the following trial sites:	
--	25: Universitätsklinikum Halle (Saale), Klinik und Poliklinik für Strahlentherapie, Ernst-Grube-Str. 40 , 06097 Halle/Saale
--	01: Katholisches Krankenhaus St. Johann Nepomuk Erfurt, Klinik für Innere Medizin I / Gastroenterologie, Haarbergstr. 72, 33097 Erfurt
--	04: Klinikum Mutterhaus der Borromäerinnen gGmbH, Hämatologie/ Internistische Onkologie, Feldstr. 16, 54290 Trier
--	05: Praxis für Innere Medizin, Hämatologie und internistische Onkologie, Strahlentherapie und

	Radioonkologie, Neustr. 17a, 46235 Bottrop
--	06: Universitätsklinikum Magdeburg, Klinik für Chirurgie, Arbeitsbereich Onkochirurgie/Chemotherapie, Leipziger Str. 44, 39120 Magdeburg
--	10: Praxis für Innere Medizin und Gastroenterologie, Schalaunische Str. 6/7, 06366 Köthen
--	12: Onkozenrum Dresden, Gemeinschaftspraxis, Leipziger Str. 118-120, 01127 Dresden
--	13: Praxisnetzwerk Hämatologie/Internistische Onkologie, Schloßstr. 18, 53840 Troisdorf
--	16: Gemeinschaftspraxis Hämatologie-Onkologie, Arnoldstr. 18, 01307 Dresden
--	18: Hämato-Onkologische Schwerpunktpraxis, Mercatorstr. 58, 47051 Duisburg
--	19: MVZ Osthessen GmbH, Pacelliallee 4, 36043 Fulda
--	20: FEK Friedrich-Ebert-Krankenhaus Neumünster GmbH, Institution department Klinik für Hämatologie, Onkologie und Nephrologie, Friesenstr. 11, 24534 Neumünster
--	22: Sana Klinikum Hof GmbH, Medizinische Klinik, Eppenreuther-Str. 9, 95032 Hof
--	23: IDGGQ, Institut für med. Dokumentation, Gutachtenerst., Gesundheitsförderung u. Qualitätssicherung, Schneiderstr. 12, 67655 Kaiserslautern
--	26: Marien Hospital Düsseldorf GmbH, Klinik für Onkologie, Hämatologie und Palliativmedizin, Rochusstr. 2, 40479 Düsseldorf
--	28: Gemeinschaftspraxis, Ländgasse 132-136, 84028 Landshut
--	31: Marienkrankenhaus Hamburg, Zentrum Innere Medizin, Alfredstraße 9, 22087Hamburg
--	32: St. Bernward Krankenhaus, Medizinische Klinik II,, Onkologie/Hämatologie/Immunologie, Treibestr. 9, 31134 Hildesheim
--	34: Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Carl-Neuberg-Str. 1, 30625 Hannover
--	35: Universitätsklinikum Hamburg-Eppendorf, Onkologisches Zentrum, Martinistr. 52, 20246 Hamburg
--	36: Ammerland-Klinik GmbH, Klinik für Innere Medizin, Lange Straße 38, 26655 Westerstede
--	38: Universitätsklinikum Rostock, Klinik für Innere Medizin III, Hämatologie, Onkologie, Palliativmedizin, Ernst-Heydemann-Str. 6, 18057 Rostock
--	39: Praxis für Innere Medizin, Hämatologie und

	Onkologie,Theodor-Heuss-Str.2, 04435 Schkeuditz
--	41: Evangelisches Krankenhaus Dinslaken, Medizinische Klinik V Klinik für Innere Medizin, Gastroenterologie, Kardiologie und Onkologie, Kreuzstraße 28, 46535 Dinslaken
--	42: Charité Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie, Campus Virchow Klinikum (CVK), Augustenburger Platz 1, 13353 Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin
--	43: PIUS-Hospital Oldenburg, Klinik für Strahlentherapie und internistische Onkologie, Georgstraße 12, 26121 Oldenburg
--	45: Praxisgemeinschaft für Onkologie und Urologie Wilhelmshaven, Friedrich-Paffrath-Straße 98, 26389 Wilhelmshaven
--	50: St. Vincentius-Kliniken gAG, Medizinische Klinik, Südenstraße 32, 76137 Karlsruhe
--	51: Klinikum Herford, Medizinische Klinik II, Schwarzenmoorstraße 70, 32049 Herford
--	52: Klinikum Magdeburg gGmbH, Klinik für Hämatologie und Onkologie, Birkenalle 34, 39130 Magdeburg
--	53: Ortenau Klinikum - Lahr Ettenheim, Sektion Hämatologie und Onkologie, Klosterstraße 19, 79933 Lahr
--	54: Überörtliche Gemeinschaftspraxis für Innere Medizin, Hohe Weide 17b, 20295 Hamburg
--	55: Universitätsklinikum Schleswig-Holstein, II. Medizinische Universitätsklinik, Campus Kiel, Arnold-Heller-Straße 3, 24105 Kiel
--	56: Praxis Hämatologie und Onkologie, Niederbronner Str. 2, 96317 Kronach
--	57: Partnerschaft FÄ für Innere Medizin, Außenstelle Freiberg, Elisabethstraße 5, 09599 Freiberg
--	58: Gemeinschaftspraxis, Hämatologie und Onkologie, Steinfurter Str. 56, 48149 Münster
--	59: Ev. Diakonie-Krankenhaus gGmbH, Medizinische Klinik Hämatologie und Onkologie, Gröpeliger Heerstr. 406/408, 28239 Bremen
--	60: Medizinisches Versorgungszentrum Mitte Leipzig, Johannisplatz 1, 04103 Leipzig
--	61: Gemeinschaftspraxis Hämatologie und Onkologie, Sachsenring 69, 50677 Köln
--	64: Onco Studies Lörrach-OSL, Senser Platz 2, 79539 Lörrach
--	65: Leopoldina Krankenhaus der Stadt Schweinfurt GmbH, Medizinische Klinik II, Gustav-Adolf-Str. 8,

	97422 Schweinfurt
--	68: Mühlenkreiskliniken AöR, Johannes Wesling Klinikum Minden, Hämatologie/Onkologie und Palliativmedizin, Hans-Nolte-Str. 1,32429 Minden
--	69: Kliniken Nordoberpfalz AG Klinikum Weiden, Medizinische Klinik I, Söllnerstr. 16, 92637 Weiden
--	71: Praxis Innere Medizin/ Gastroenterologie, Kleine Marktstr. 3, 06108 Halle/Saale
--	72: Klinikum Bremen-Mitte gGmbH, Medizinische Klinik I - Hämatologie/ Onkologie, St.-Jürgen-Str. 1, 28177 Bremen
--	73: Schwerpunktpraxis Hämatologie und Onkologie, Hasselbachplatz 2, 39104 Magdeburg
--	75: Diakonie Klinikum GmbH, Jung-Stiling-Krankenhaus, Wichernstr. 40, 57074 Siegen
--	77: Wissenschaftskontor Nord GmbH & Co. KG, Trelleborger Str. 10a, 18107 Rostock Lütten-Klein
--	78: Klinikum Bogenhausen, Interdisziplinäre Onkologische Tagesklinik, Englschalkinger Str. 77, 81925 München
--	79: OnkoNet Marburg GmbH, Erlenring 9, 35037 Marburg

8. Publications

Treatment with bevacizumab and FOLFOXIRI in patients with advanced colorectal cancer: presentation of two novel trials (CHARTA and PERIMAX) and review of the literature. (2012). Stein, A; Glockzin, G; Wienke, A; Arnold, D; Edelmann, T; Hildebrandt, B; Hollernach, S; Illerhaus, G; Königsrainer, A; Richter, M; Schlitt, HJ; Schmoll, HJ. BMC Cancer 12:356. doi: 10.1186/1471-2407-12-356.

FOLFOX / Bevacizumab (Beva) +/- Irinotecan in advanced colorectal cancer (CRC): A randomized phase II trial (AIO KRK 0209, CHARTA). (2016). Schmoll, HJ et al. Annals of Oncology (2016) 27 (6): 1-36. 10.1093/annonc/mdw435

CHARTA: FOLFOX+bevacizumab +/- Irinotecan in advanxed colorectal cancer (CRC) – final results of the randomized phase II trial of the AIO (KRK 0209). (2017). Schmoll HJ et al. J Clin Oncol 35, 2017 (suppl. Abstract 658)

Impact of FOLFOXIRI and bevacizumab (bev) compared to FOLFOX bev on health related quality of life (HRQOL) in patients with metastatic colorectal cancer (MCRC): Analysis of the CHARTA AIO 0209 trial. (2017). Quidde, J et al. J Clin Oncol 35, 2017 (suppl. Abstract 3544)

“CHARTA”: FOLFOX/bevacizumab vs. FOLFOXIRI/bevacizumab in advanced colorectal cancer - Final results, prognostic, and potentially predictive factors from the randomized phase II trial of the AIO. (2017). Schmoll HJ et al. J Clin Oncol 35, 2017 (suppl. Abstract 3533)

FOLFOX/Bevacizumab +/− Irinotecan in advanced colorectal cancer (AIO) “CHARTA”: Final results and multivariate prognostic factor analysis. 2017) Schmoll HJ et al. Annals of Oncology (2017) 28 (suppl_3): iii150-iii153. 10.1093/annonc/mdx302

9. Studied period (years)

Date of first enrolment: 28.07.2011

Date of last completed: 31.08.2019

Between July 28 2011 and September 23, 2014, 250 patients were enrolled. The last patient finished the maintenance treatment in August 2017. Follow-up (LPV) was finished in August 2019.

10. Phase of development

Phase II. The Investigational Medicinal Products used in the trial have a marketing authorization in the member state concerned.

11. Objectives

The primary objective of the CHARTA study was to evaluate the efficacy of FOLFOXIRI and bevacizumab compared to FOLFOX and bevacizumab in patients with initially unresectable metastatic colorectal cancer. Secondary objectives are safety and tolerability of the treatment, efficacy in terms of secondary resectability, prognostic value of stratification into clinical groups, and validity of allocation to these groups and the exploratory question whether the addition of irinotecan might be more effective in terms of response and survival in patient groups to be determined by angiogenic marker profiles, potentially indicating different sensitivity to bevacizumab.

Primary endpoint is PFS rate at 9 months; secondary endpoints include PFS, OS, ORR (according to RECIST v1.1), secondary resection rate, toxicity (according to NCI-CTCAE v4.0) and quality of life (according to EORTC QLQ-C30 and modules CR29 and CIPN20). PFS is defined as time from randomization to date of first observed progression or death (without reintroduction).

12. Methodology

The trial was conducted as a multicentre, open labelled, prospective, randomized phase II study.

Patients were randomly be assigned in a 1:1 ratio stratified for the following clinical groups:

- unresectable liver and/ or lung metastasis potentially resectable after treatment induced downsizing, comorbidities allowing surgery
- multiple metastasis, rapid progression, risk of rapid deterioration, unlikely to become resectable
- never resectable and no symptoms or risk of deterioration

Induction chemotherapy with a modified FOLFOX with oxaliplatin at a dose of 85 mg/m^2 iv over two hours (day 1), Leucovorin at a dose of 200 mg/m^2 iv over two hours (day 1) and 5-FU at a dose of 3200 mg/m^2 iv over 48 hours (day 1–3) and bevacizumab at a dose of 5 mg/kg iv over 30 to 90 min (day 1) with or without irinotecan at a dose of 165 mg/m^2 iv over one hour (day 1) in a biweekly schedule was to be administered followed by maintenance with either 5-FU/LV and bevacizumab (same dosage and schedule as above) or capecitabine at a dose of 1600 mg/m^2 in two doses per day 1 to 14 and bevacizumab at a dose of 7.5 mg/kg iv over 30 to 90 min (day 1) every three weeks (choice of 5-FU or capecitabine was at the discretion of the investigator). Treatment with FOLFOX and bevacizumab +/− irinotecan was to be administered until progression, intolerable toxicity, and secondary resection or for a maximum of 12 cycles (6 months). After 6 months of treatment and/or no progression patients continued with a maintenance regimen with bevacizumab and a fluoropyrimidine for

up to 12 months in the absence of progression or intolerable toxicity. Maximum treatment duration was 18 months (6 months of FOLFOX and bevacizumab +/− irinotecan followed by 12 months of maintenance). In case of secondary resection (at any time point) treatment was to be resumed 4–8 weeks postoperatively for a total of 6 months FOLFOX and bevacizumab +/− irinotecan (pre- and postoperative treatment), followed by maintenance treatment for total treatment duration of up to 12 months in the absence of progression or intolerable toxicity. Reintroduction of oxaliplatin +/− irinotecan or restart of treatment in case of progressive disease during maintenance or complete break after 18 months of treatment was at the investigators discretion.

13. Patients

13.1 Number of patients

Patients planned: 250

Patients screened: n.a.

Patients enrolled: 250

A CONSORT-type overview of the status of study patients as of January 2019 (final data cut-off and transfer of data base to biostatistics) is provided in **Fehler! Verweisquelle konnte nicht gefunden werden.**. 242 out of 250 randomized patients comprise the intent-to-treat population (full analysis set, FAS) of this interim analysis.

Arm A: patients allocated to treatment with FOLFOX+bevacicumab

Arm B: patients allocated to treatment with FOLFOXIRI+bevacicumab

Table 1: Patient disposition and analysis sets

Category	Total	Arm A	Arm B
Patients randomized and included in the study database	250	126	124
Excluded from all analyses due to major violations of in/ exclusion criteria	8	5	3
ITT	242	121	121
Not fulfilling criteria for per protocol analysis	1	1	
Per protocol analysis set	241	120	121
Safety analysis set	242	119	123

According to the pre-analysis meetings and blinded decision by the protocol steering group, eight patients had to be excluded, either due to insufficient data for any inclusion in the analysis, mostly caused by withdrawal of consent, or due to major protocol violations. One additional patient had to be excluded from the per protocol analysis, as he had not received adequate treatment according to protocol. Details for each patient are provided in Table 2.

Table 2: Exclusion from the FAS, PP and safety populations

Pat. no.	ITT / FAS	PP	Safety	Comment
026	excl.	excl.	excl.	withdrawal of consent; no therapy started
071	excl.	excl.	excl.	withdrawal of consent; no therapy started
120	--	excl.	excl.	no therapy started because surgical treatment of tumour was possible after randomisation
131	excl.	excl.	excl.	received study therapy until histologic result revealed diagnosis of neuroendocrinic tumour; post-randomisation failure
137	excl.	excl.	excl.	received study therapy until histologic result revealed diagnosis of neuroendocrinic tumour; post-randomisation failure
145	excl.	excl.	excl.	withdrawal of consent; no therapy started
164	excl.	excl.	excl.	pat received CTx 2 months before randomisation; no therapy started due to violation of exclusion criteria no 3
215	excl.	excl.	--	pat received CTx Xeloda and Avastin before randomisation, revealed by monitor after patient had received 2 cycles of study therapy; off-study due to violation of selection criteria
219	excl.	excl.	excl.	withdrawal of consent; no therapy started

13.2 Demographic dafa

Table 3: Age

	Arm A	Arm B	Total
n	**121**	**121**	**242**
<= 30 years	**2**		**2**

	Arm A	Arm B	Total
31-40 years	8	5	13
41-50 years	14	17	31
51-60 years	32	40	72
61-70 years	44	40	84
71-80 years	21	18	39
>80 years		1	1

Table 4: Gender

	Arm A	Arm B	Total
n	121	121	242
male	79	78	157
female	42	43	85

13.3 Baseline Characteristics

Table 5: Baseline characteristics

	Arm A	Arm B	Total
ESMO groups total	121	121	242
ESMO group 1	35	35	70
ESMO group 2	67	67	134
ESMO group 3	19	19	38
ECOG total	118	117	235
ECOG 0	56	62	118
ECOG 1	56	52	108
ECOG 2	6	3	9
RAS tested	106	114	220
RAS mutation	59	61	120
RAS wiltype	47	53	100

	Arm A	Arm B	Total
BRAF tested	**106**	**114**	**220**
BRAF mutation	**5**	**8**	**13**
BRAF wildtype	**91**	**85**	**176**
Datasets sidedness	**116**	**120**	**236**
Left tumor location	**88**	**84**	**172**
Right tumo location	**28**	**36**	**64**
Köhne score classified	**115**	**111**	**226**
Köhne score low risk	**11**	**9**	**20**
Köhne score intermediate risk	**84**	**84**	**168**
Köhne score high risk	**20**	**18**	**38**

14. Diagnosis and main criteria for inclusion

Diagnosis: Patients with metastatic or recurrent colorectal cancer stage IV (UICC)

Inclusion criteria:

- Histologically confirmed diagnosis of stage IV (UICC) colorectal cancer (primary tumor may be present)
- Patients with at least one measurable lesion, with size > 1 cm (RECIST v1.1)
- ECOG Performance status ≤ 2 (ECOG 2, only if tumor related)
- Patients, who are able to tolerate intensive first line treatment as judged by the investigator
- Life expectancy > 3 months
- Age ≥18 years.
- Haematologic function: ANC □ 1.5 x 109/L, platelets □ 100 x109/L, hemoglobin □ 9 g/dl or 5.59 mmol/l
- Patients not receiving therapeutic anticoagulation must have an INR < 1.5 ULN and aPTT < 1.5 ULN within 7 days prior to registration. The use of full dose anticoagulants is allowed as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for anticoagulants for at least two weeks at the time of registration.
- Adequate liver function as measured by serum transaminases (AST & ALT) £ 2.5 x ULN (in case of liver metastases < 5 x ULN) and total bilirubin £ 1.5 x ULN
- Adequate renal function: Serum creatinine £ 1.5 x ULN

- Signed, written informed consent.

Exclusion criteria:

- Treatment with any other investigational agent, or participation in another clinical trial within 30 days prior to entering this study.
- Prior systemic or local treatment of metastatic disease.
- Prior adjuvant or neo-adjuvant chemotherapy/radiotherapy completed less than 6 months prior to study entry.
- Pre History or evidence upon physical/neurological examination of CNS disease (unrelated to cancer) (unless adequately treated with standard medical therapy) e.g. uncontrolled seizures.
- Fertile women (< 1 year after last menstruation) and men of childbearing potential unwilling or unable to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, or surgically sterile).
- Pregnancy or lactation.
- Positive serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women < 1 year after the onset of menopause.
- Past or current history (within the last 2 years prior to treatment start) of other malignancies except metastatic colorectal cancer (patients with curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible).
- Peripheral neuropathy NCI CTCAE-grade ≥ 1
- Known DPD-insufficiency.
- Active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as > 4 loose stools per day)
- History of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis) haemoptoe or evidence of interstitial lung disease on baseline chest X-ray or CT scan.
- Serious, non-healing wound, ulcer or bone fracture.
- Thrombosis or severe bleeding within 6 months prior to entry into the study (except for bleeding of the tumor before its surgical resection) and no evidence of bleeding diathesis or coagulopathy.
- Urine dipstick for proteinuria ³ 2+. If urine dipstick is ³ 2+, 24-hour urine must demonstrate £ 1 g of protein in 24 hours for patient to be eligible.
- Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to treatment.
- Clinically significant cardiovascular disease, for example CVA, myocardial infarction (£ 12 months before treatment start), unstable angina, NYHA Class II CHF, arrhythmia requiring medication, or uncontrolled hypertension.
- Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
- Known hypersensitivity or contraindication to the drugs used in the trial (eg: 5-FU, folinic acid/ leucovorin, capecitabine, oxaliplatin, bevacizumab, irinotecan)

- Concomitant treatment with ASS > 325 mg or NSAIDs, known to inhibit platelet function, sorivudin or analog compounds or preparations of St. John's wort
- Inability or unwillingness to comply with the protocol

15. Test product, dose and mode of administration, batch number

Avastin® (Bevacizumab), 4 ml vial contains 100 mg of bevacizumab, 16 ml vial contains 400 mg of bevacizumab

Marketing Authorisation number: EU/1/04/300/001

Mode of action:	Humanised monoclonal antibody against VEGFR; inhibition of neovascularisation
Dose:	5 mg/kg iv over 30 to 90 min on day 1 of each cycle
Route of administration:	i.v.
Formulation:	Concentrate for solution for infusion
Batch numbers:	Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

Irinotecan, various vials, containing 20 mg of Irinotecan hydrochloride

Marketing Authorisation number: site dependent brand from hospital stock was used

Mode of action:	Inhibition of topoisomerase I; DNA damages; DNA intercalation not depending on a cell cycle
Dose:	165 mg/m^2 iv over one hour biweekly (day 1 and day 15 of each cycle)
Route of administration:	i.v.
Formulation:	Concentrate for solution for infusion
Batch numbers:	Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

Oxaliplatin, various vials, containing 5 mg of oxaliplatin

Marketing Authorisation number: site dependent brand from hospital stock was used

Mode of action:	Inhibition of RNA synthesis; cross-links; DNA-intercalation; not depending on a cell cycle
Dose:	85 mg/m^2 iv over two hours on day 1 each cycle
Route of administration:	i.v.
Formulation:	Concentrate for solution for infusion
Batch numbers:	Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

Leucovorin, 10 ml vials containing 5 mg/ml of Calcium Folinate

Marketing Authorisation number: site dependent brand from hospital stock was used

Mode of action: Additive effect of 5FU, detoxifying agents for antineoplastic therapy

Dose: 200 mg/m^2 iv over two hours on day 1 each cycle

Route of administration: i.v.

Formulation: Concentrate for solution for infusion

Batch numbers: Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

5-Fluorouracil, various vials, containing 50 mg of Fluorouracil

Marketing Authorisation number: site dependent brand from hospital stock was used

Mode of action: Inhibition of RNA synthesis

Dose: 3200 mg/m^2 iv over 48 hours on days 1–3 of each cycle

Route of administration: i.v.

Formulation: Concentrate for solution for infusion

Batch numbers: Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

Xeloda® (Capecitabine), Film-coated tablets containing 150 mg or 500mg capecitabine

Marketing Authorisation number: EU/1/00/163/001

Mode of action: cytostatic therapy (antimetabolite), precursor of cytotoxic 5-Fluorouracil

Dose: 1600 mg/m^2 oral use in two doses per day on days 1 to 14 of each maintainance cycle

Route of administration: oral use

Formulation: Film-coated tablets

Batch numbers: Commercial products not specifically labeled for the study were used from the hospital stock. Therefore the batch numbers were not recorded separately.

16. Duration of treatment

Treatment with FOLFOX+beva+/-irinotecan was planned to be administered until progression, intolerable toxicity, secondary resection or for a maximum of 12 cycles (6 months). After 6 months of treatment and/or no progression patients should continue with a maintenance regimen with bevacizumab and a fluoropyrimidine (choice of 5-FU or capecitabin was at the discretion of the investigator) for up to 12 months in the absence of progression or intolerable toxicity. Maximal treatment duration was 18 months (6 months of FOLFOX+beva+/-irinotecan followed by 12 months of maintenance).

17. Reference therapy, dose and mode of administration, batch number

Not applicable

18. Criteria for evaluation: Efficacy, Safety

18.1. Efficacy

18.1.1. Progression Free Survival

Time from randomization to date of first observed progression or death. The Progression Free Survival Rate at 9 months was determined by the proportion of patients being alive without progressive disease 9 months after randomization.

18.1.2. Response rate

Response rate was evaluated by using RECIST-Criteria (response evaluation criteria for solid tumors) [Therasse 2000]. Recent version v1.1 of RECIST (Eisenhauer, Therasse et al. 2009) considers the change in tumor size using the sum of unidimensional measurements of the longest diameter in up to two target lesions per organ (or five in total, representing all involved organs) and also accounts for non measurable lesions.

RECIST is currently accepted as the basis for assessing antitumor activity in all solid tumor types and is endorsed by regulatory authorities.

Measurement and identification of target lesions: Patients must have at least one measurable lesion, defined as > 10 mm using spiral CT or MRI. Where disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Baseline measurements must be taken no more than 4 weeks prior to randomization. The same measurement technique (CT/MRI) must be used at baseline and follow up. No more than 2 target lesions per organ and 5 lesions in total, representative of all sites involved will be identified. Those with the largest diameters should be included. All other (non-target) lesions should be reported but not measured, in order that their presence or lack thereof may be tracked at follow up.

Criteria for target lesions: Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30 % decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20 % increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Criteria for non-target lesions: Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Response evaluation and reporting: During treatment tumor response was assessed by the investigator according to RECIST v1.1 (CT and/or MRI) every 4 cycles (8 weeks) for the first 6 months and afterwards every 3 months. CT and/or MRI scans were reviewed e.g. for resectability and allocation to the clinical groups.

At each follow up visit, response in target and non-target lesions and presence of any new lesions were determined. Overall response was assigned by combining the response in target lesions, non-target lesions, and the appearance or lack of new lesions as outlined in Table 6.

Table 6: Response evaluation according to RECIST

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

The best overall response is defined as the best response from start of treatment over all follow up visits or until disease progression/recurrence whichever comes first.

18.1.3. Secondary resection rate

Rate of secondary R0-resections in case of resectable disease as curative approach after randomization.

18.1.4. Overall Survival

Overall survival was determined as time from randomization to date of death.

18.1.5. Quality of life (QoL)

Quality of life was assessed using the EORTC QLQ C30 questionnaire and the modules CR29 and CIPN20 at baseline, during treatment every 8 weeks during the first 6 months, afterwards every 12 weeks and at the end of treatment.

18.1.6. Further evaluations

Efficacy of the treatment according to KRAS and BRAF status and the clinical grouping (stratification criteria) was retrospectively analyzed. Further analysis of the allocation to the three clinical groups and achievability of resectability was performed by a blinded board.

Efficacy of adding irinotecan in patients with biomarkers with potential negative predictive value for treatment with bevacizumab (high pre-treatment and/or rising Ang-2, VEGF-A, G-CSF, osteopontin, sVEGFR2, neuropilin, Dll4 levels as well as high pre-treatment tissue hypoxia) compared to patients with potential positive predictive value for treatment with bevacizumab. Further analysis was performed on the prognostic and/or predictive value of these markers and the kinetics during treatment.

18.2. Safety

Safety assessments include physical examinations including vital signs (blood pressure, heart rate, respiratory rate), ECOG, clinical laboratory profile and adverse events.

All observed toxicities and side adverse events were graded according to NCI Common Terminology Criteria for Adverse Events: NCI CTCAE v4.0 (NCI 2009) for all patients and the degree of association of each with the procedure assessed and summarized.

Treatment related Serious Adverse Events rate (SAE), defined as SAEs considered possibly, probably or definitely related to treatment, were determined.

19. Statistical methods

General remarks: With exception of the primary objective of the study, the analysis is generally descriptive using standard calculations and graphical methods to represent the data and their distribution. If not specified otherwise, two-sided tests have been used throughout. In cases of additional missing items in single parameters, the sample sizes for specific analyses may deviate from the numbers given in the specified section.The respective sample size will be provided in these cases. If not stated otherwise, all percentages are calculated with exclusion of missing values. Throughout this report, the comparative arm with the three agent combination FOLFOX and bevacizumab is labelled "Arm A", and the experimental arm consisting of the combination FOLFOXIRI and bevacizumab is named "Arm B".

Populations for Analysis: Patient with major deviation of selection criteria were excluded from statistical analysis. These cases were reported anecdotical. All patients receiving at least one treatment were evaluated for safety. The Intention-to-treat (ITT) population includes all patients in the study (signed ICF and confirmation of eligibility). All patients were grouped according to their randomization regardless of treatment received. The Per-protocol (PP) population include all patients who receive at least one treatment cycle 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 were excluded from the PP population.

The primary efficacy endpoint was the progression free survival rate after 9 month (after randomization). Rates in both groups were compared by logistic regression adjusting for the strata of the stratified randomization procedure.

The secondary efficacy endpoints will be the following variables:

- Response Rate according to RECIST v1.1
- Secondary resection rate
- Progression free survival (PFS)
- Overall survival (OS)
- Toxicity (Safety assessments will include physical examinations (blood pressure, heart rate, respiratory rate), vital signs, clinical laboratory profile and monitoring of adverse events, according to NCI CTCAE v4.0)
- Quality of life using the EORTC QLQ-C30 and the modules CR29 and CIPN20
- Response Rate/PFS/OS stratified by KRAS and BRAF status
- Response Rate/PFS/OS stratified by the three clinical groups
- allocation to the three clinical groups
- achievability of respectability
- Response Rate/PFS/OS in the four marker x treatment groups (defined by pre-treatment and/or kinetics of angiogenic markers as well as pre-treatment tissue hypoxia)

Response rates and secondary resection rate were summarized using frequency tables and be compared by logistic regression to adjust for the strata. In an additional logistic regression analysis the treatment effect of irinotecan was investigated additionally stratified for marker status.

For the time-to-event variables PFS and OS, the Kaplan-Meier method was used to estimate the event free survival, and the log-rank test will be conducted to compare the two treatment groups. Cox‟s proportional hazard model was used to adjust for the influences of the three strata. In an additional Cox analysis the treatment effect of irinotecan was investigated additionally stratified for marker status.

Toxicity and Quality of life were documented in a descriptive way.

All secondary efficacy analyses were based on the ITT population and the corresponding statistical testing results will be interpreted in an exploratory sense.

20. Results

20.1. Efficacy Results

20.1.1. Primary Objective – PFS rate @ 9 months

Primary objective of the study was the rate of patients alive without progression at 9 months after randomization. The difference in the PFS rates should be compared at a significance level of 0.1 according to the statistical analysis plan.

Table 7 provides the absolute progression rates for the ITT population, evaluated according to protocol. Eight patients were not assessable because they were censored before reaching a follow-up of at least 9 months.

Table 7: PFS rate @ 9 months (absolute)

	Arm A	**Arm B**
n	121	121
Progression-free @ 9 months	68 (56.2%)	81 (66.9%)
Progression @ 9 months	48 (39.7%)	37 (30.6%)
Not assessable	5 /4.1%)	3 (2.5%)

The absolute progression rate was compared by different statistical tests, first by applying a logistic regression method, stratified by the clinical stage of patients at baseline, which was the test method prospectively defined in the protocol. Additional test results (Chi-square-test and Fisher’s exact test) are also given in Table 8 for comparison.

Table 8: PFS rate @ 9 months (absolute), statistical tests

	Stratified logistic regression (prospectively defined test method)	**Fisher´s exact test**	**Chi-square-test**
p	0.11	0.135	0.145

Both p-values revealed by Chi^2-Test and Fisher's exact test are higher compared to the p-value evaluated by stratified logistic regression, as to be expected for an approximative method. However, all test methods applied to the primary objective result in a p-value which is higher, compared to the formal significance level of 0.1 according to the statistical planning of the protocol.

However, PFS rate at 9 months was also revealed by the Kaplan-Meier-Method (Table 9). This method takes also the available information for censored patients into account. The comparison of the PFS rate at 9 months by an exact test provides a p-value of 0.082. In summary, the primary objective of the trial (progression-free rate at 9 months in experimental arm B is superior to arm A) could be confirmed, using the Kaplan-Meier method, which is the most appropriate method for this patient population.

Table 9: PFS rate at 9 months (Kaplan-Meier)

	Arm A	Arm B
PFS rate @ 9 months	58%	69%
PFS rate @ 9 months, 95%-C.I.	49%-67%	61%-78%

p = 0.082 (Fisher´s exact test)

20.1.2. Secondary Objectives

20.1.2.1. Progression-free survival (PFS)

Table 10: Total progression event

	Arm A	Arm B	Total
n	121	121	242
Progression events	108 (89.3%)	112 (92.6%)	220 (90.9%)
censored	13 (10.7%)	9 (7.4%)	22 (9.1%)

After a median follow-up of 57 months, 220 progression events have been observed for the whole study population (Table 10). I.e. no additional progression events were reported. The Kaplan-Meier-Plot for PFS (whole ITT population) is provided as Figure 1. The hazard ratio, including 95% confidence interval and p-value of the logrank test is provided in the figure, as well as in Table 11 below. The PFS is improved by 1.7 months.

Table 11: Median PFS A vs. B, logrank 2-sided

Comparison	n (events)	median (months)	HR	95%-c.i.	p
PFS					
Arm A	108	10.32	0.83	0.64-1.08	0.17
Arm B	112	12.02			

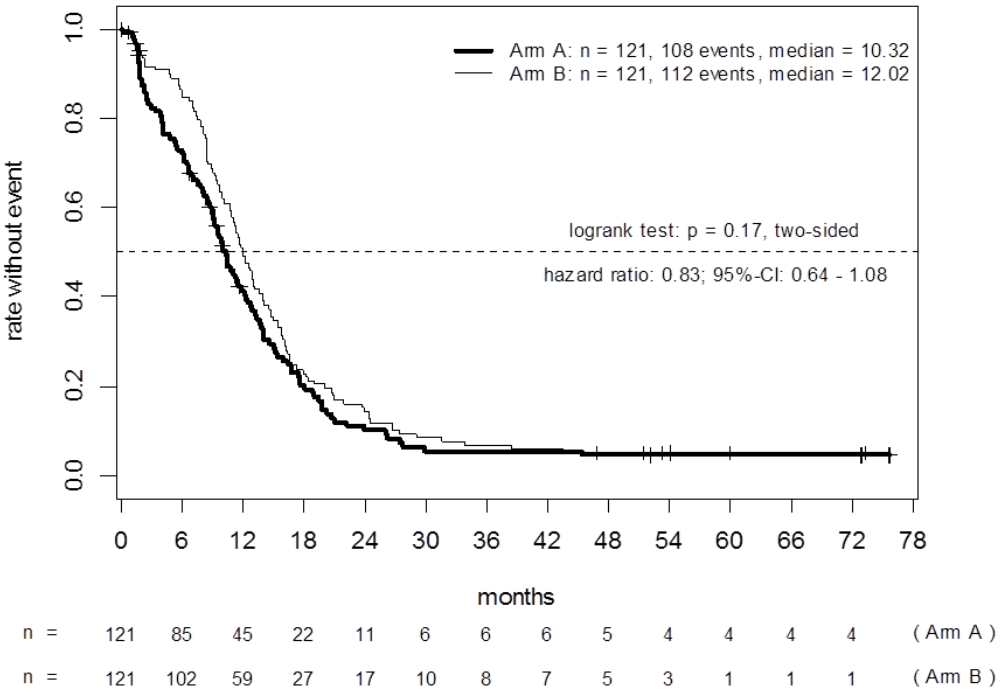

Figure 1: Progression-free Survival

20.1.2.2. Overall survival (OS)

In the final dataset, 194 patient deaths are recorded, 80.2% of all study patients have died there is no difference between both arms (see also Table 12, Table 13, and Figure 1). This means, that the trial is mature and the results are currently near final.

The median OS is 23.95 in arm A vs. 27.96 in arm B, with an improvement of 4 months, very likely due to the limited number of patients.

Table 12: Death events

	Arm A	Arm B	Total
n	121	121	242
Death events	98 (81%)	96 (79.3%)	194 (80.2%)
censored	23 (19%)	25 /20.7%)	48 (19.8%)

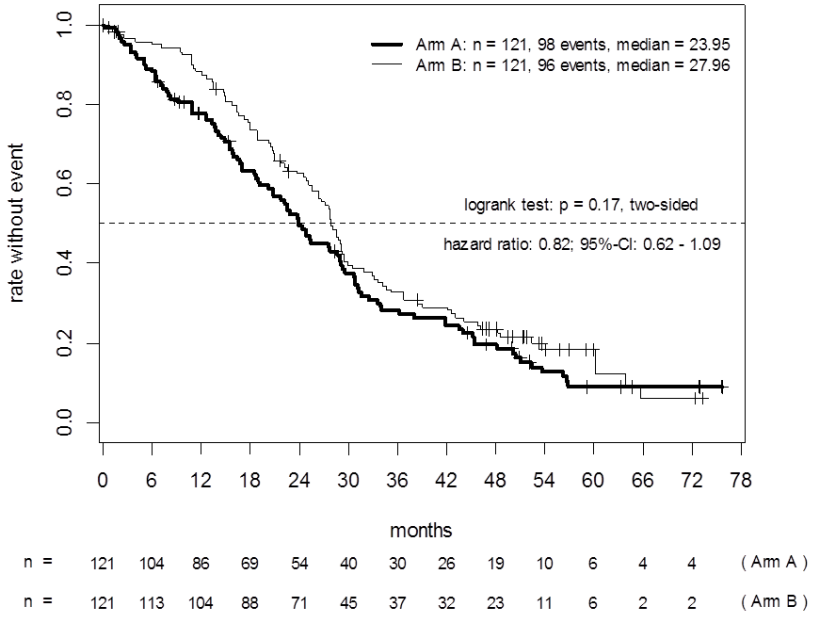

Figure 2: Overall Survival

Table 13: Hazard ratio, confidence intervals and p-value (logrank-test, 2-sided) for OS

Comparison	n (events)	median (months)	HR	95%-c.i.	p
OS					
Arm A	98	23.95	0.82	0.62-1.09	0.17
Arm B	96	27.96			

20.1.2.3. Response rate

The objective response rate was about 10% (60.5% vs. 69.3%) higher in the experimental arm B. There was no difference in CR rate (5.3% in both arms); 2x2-contingency table, p = 0.21, Fisher's exact test, 2-sided.

Table 14: Response rate by arms

	Arm A	Arm B	Total
n	114	114	228
Response (CR + PR)	69 (60.5%)	79 (69.3%)	148 (64.9%)
Failure (SD + PD)	45 (39.5%)	35 (30.7%)	80 (35.1%)
CR	6 (5.3%)	6 (5.3%)	12 (5.3%)
PR	63 (55.3%)	73 (64%)	136 (59.6%)

20.1.3. Local treatment of primary tumor

Table 15: Resection of primary tumor - before randomization

	Arm A	Arm B	Total
No of patients	121	121	242
no resection	65 (53.7%)	72 (59.5%)	137 (56.6%)
primary resected	56 (46.3%)	49 (40.5%)	105 (43.4%)

56.6% had the primary tumor left at randomization (very likely all of them with synchronous disease); 43.4% hab primary resected very likely representing metachronous disease. There is no relevant difference between both arms.

Table 16: Secondary resection of primary tumor– after randomization

	Arm A	Arm B	Total
No of patients	121	121	242
Secondary resection	13 (10.7%)	9 (7.4%)	22 (9.1%)

Those patients who had synchronous disease (20% arm A; 12.5% arm B) received secondary resection while or after treatment, which is not different between both arms (Table 16). Those patients might represent a situation, where the positive effect of the treatment justified the resection of the primary, however this might be driven by other conditions as well.

20.1.4. Secondary resection of metastases

Table 17: Secondary resection of metastases

	Arm A	Arm B	Total
No of patients	121	121	242
No of datasets	120	121	241
no secondary resection	95 (78.5%)	91 (75.2%)	186 (76.9%)
secondary resection of metastases	25 (20.7%)	30 (24.8%)	55 (22.7%)

22.7% of patients received secondary resection of metastases, with no difference between both arms (20.7% arm A; 24.8% arm B), with a p-value of 0.54.

Table 18: Number of secondary metastases resections by patient

No of secondary metastases resections	Arm A	Arm B	Total
n	25	30	55
1 met resection	22 (88%)	20 (66.7%)	42 (76.4%)
2 met resection	3 (12%)	8 (26.7%)	11 (20%)
>2 met resections		2 (6.7%)	2 (3.6%)

Of those resected patients, 76.4% (88% vs. 66.7%) had only one resection; 20% of the patients (12% arm A; 26.7% arm B) had two metastatic resections, and 2 patients (6.7% in arm B vs 0 in arm A) had more than two resections; this indicates a numerical advantage for the 4-drug-combination.

Table 19: Location of secondary metastases resections

No of secondary metastases resections	Arm A	Arm B	Total
n	25	30	55
liver	23 (92%)	29 (96.7%)	52 (94.5%)
lung	2 (8%)	1 (3.3%)	3 (5.5%)
peritoneum		2 (6.7%)	2 (3.6%)
other	3 (12%)	4 (13.3%)	7 (12.7%)

Liver metastases resection was as expected with 21.5%, 19% vs 24%). The most frequent surgical intervention, lung 1.2% (1.6 vs, 0.8%), peritoneum 0.8% (0% vs. 17%) and other sites 2.9% (2.5% vs. 3.3%).

The distribution between both arms is comparable. However it is much more relevant to compare the resection rates in those patients where at least in principle secondary metastases resection is a treatment aim, which is related with a better outcome. This is in

particular ESMO group 1 and 3 – which was the reason for stratification in ESMO groups before randomization. These data are currently evaluated and not part of this report. Since those data are not available in other trials, this trial is unique for this question.

In summary, in the 4-drugarm is a clear trend for a higher rate of secondary metastases resection, including a rate of two or more resections, and also resection of peritoneum metastases (2 vs 0) in arm B. There is a strong trend favoring arm B which indicates the higher anti-tumor activity for the 4-drug-combination.

20.1.5. Second and further line treatment

Table 20: Number of further therapy lines by arms

No of treatment line	Arm A	Arm B	Total
No of patients	121	121	242
No of dataset	214	240	454
2	82 (67.8%)	89 (73.6%)	171 (70.7%)
3	49 (40.5%)	53 (43.8%)	102 (42.1%)
4	27 (22.3%)	32 (26.4%)	59 (24.4%)
5	13 (10.7%)	13 (10.7%)	26 (10.7%)
6	7 (5.8%)	7 (5.8%)	14 (5.8%)
7	3 (2.5%)	3 (2.5%)	6 (2.5%)
8		2 (1.7%)	2 (0.8%)
9		1 (0.8%)	1 (0.4%)
Maintenance	20 (16.5%)	25 (20.7%)	45 (18.6%)
Reinduction	13 (10.7%)	15 (12.4%)	28 (11.6%)

70.7% of patients received at least second line therapy (67.8% vs. 73.6%), 42.1% received at least third line treatment (40.5% vs. 43.8%).

Also the rate of further lines is the same for both arms.

Reinduction as part of the strategy in case of progression under maintenance treatment was not prescribed by the protocol, although a standard option. 11.6% of the patients received reinduction, with no differences in both arms.

Table 21: Regimens in second line – all patients

	Arm A	Arm B	Total
n	82	89	171
Folfiri + Bevacizumab	16 (19.5%)	23 (25.8%)	39 (22.8%)
Folfiri/ Iri + Cetuximab/ Panitumumab	19 (23.2%)	16 (18%)	35 (20.%)

	Arm A	Arm B	Total
Foflfox/ Folfiri/ Folfoxiri/ Iri + Aflibercept	15 (18.3%)	17 (19.1%)	32 (18.7%)
Capecitabine/ 5FU	19 (12.2%)	4 (4.5%)	14 (8.2%)
Folfiri	8 (9.8%)	6 (6.7%)	14 (8.2%)
Bevacizumab	1 (1.2%)	4 (4.5%)	5 (2.9%)
Cetuximab/ Panitumumab	2 (2.4%)	3 (3.2%)	5 (2.9%)
Folfox + Bevacizumab	3 (3.7%)	2 (2.2%)	5 (2.9%)
Folfox	3 (3.7%)	1 (1.1%)	4 (2.3%)
Folfox + Cetuximab/ Panitumumab	1 (1.2%)	2 (2.2%)	3 (1.8%)
Folfoxiri/ Iri		3 (3.4%)	3 (1.8%)
Regorafenib	1 (1.2%)	2 (2.2%)	3 (1.8%)
Capecitabine/ 5FU +Cetuximab/ Panitumumab	1 (1.2%)	1 (1.1%)	2 (1.2%)
Experimental therapy	1 (1.2%)	1 (1.1%)	2 (1.2%)
Folfox/ Folfiri + Ramucirrumab		1 (1.1%)	1 (0.6%)
Folfoxiri + Bevacizumab		1 (1.1%)	1 (0.6%)
Local therapy (metastases)		1 (1.1%)	1 (0.6%)
Mitomycin + 5FU/ Folfox etc.		1 (1.1%)	1 (0.6%)
Tas 102	1 (1.2%)		1 (0.6%)

70.8% of patients in arm B received Irinotecan as part of a second line therapy; however the rest of the patients are very likely have received Irinotecan as part of a further line.

Table 22: Regimen in second line – RAS wt

	Arm A	Arm B	Total
n	32	38	70
Folfiri/ Iri + Cetuximab/ Panitumumab	16 (50%)	14 (36.8%)	30 (42.9%)
Cetuximab/Panitumumab	1 (3.1%)	2 (5.3%)	3 (4.3%)
Folfox + Cetuximab/ Panitumumab		2 (5.3%)	2 (2.9%)

	Arm A	Arm B	Total
Capecitabine/ 5FU + Cetuximab/ Panitumumab		1 (2.6%)	1 (1.4%)

Regarding the use of salvage treatment with an EGFR-Antibody, the information is only availiable of 70 patients, also 51.5% of RAS wildtype patients received Cetuximab or Panitumumab as part of the second line therapy (53.1% vs. 50%); however this treatment was also applied in third and further lines (data currently being evaluated).

20.1.6. Subgroups

Table 23: Subgroup efficacy (log rank, two sided test, Fisher´s exact test)

	PFS in months				OS in months				RR		
	A	B	HR	p	A	B	HR	p	A	B	P
ECOG 0	11	12.3	0.88	0.52	28.7	29.4	0.91	0.64	73.2%	67.8%	0.55
ECOG 1-2	9.2	12	0.78	0.2	20.3	25.1	0.77	0.2	50%	68.6%	0.08
ESMO grp1	11.4	13	0.8	0.4	29.3	29.9	0.69	0.19	56.2%	67.6%	0.45
ESMO grp2	9.6	11.5	0.93	0.67	20.3	26.4	0.9	0.96	62.5%	67.7%	0.58
ESMO grp3	11	16	0.55	0.097	30.8	29.4	0.79	0.33	61.1%	77.8%	0.47
Köhne Score low	17.6	12.7	1.25	0.67	31.7	27.7	1.18	0.76	72.7%	66.7%	1
Köhne Score intermediate	11.2	12	0.83	0.24	24.9	29	0.76	0.1	65.1%	70%	0.51
Köhne Score high	7	11.9	0.66	0.22	14.8	15.4	0.92	0.82	35.3%	64.7%	0.17
Dose intensity < 70%	3.4	11.8	0.48	0.28	7	40.6	0.08	0.01	25%	50%	0.57
Dose intensity 70-90%	10.6	12.3	0.84	0.46	22.5	28	0.74	0.22	57.1%	66.7%	0.46
Dose intensity >90%	10.4	12	0.85	0.36	25	28.5	0.85	0.4	63.4%	73.3%	0.28
Left Ras wt	9.8	13.1	0.71	0.15	29	30.5	0.76	0.29	54,1%	73.5%	0.14
Left Ras mut	11.3	12.3	0.79	0.32	24.4	29.2	0.81	0.42	62.2%	66.7%	0.81
Right Ras wt	8.5	9.5	0.81	0.6	19.1	18.9	0.87	0.78	85.7%	66.7%	0.62
Right Ras mut	9.6	14	0.97	0.94	22.5	27.8	1.02	0.95	57.9%	83.3%	0.15

ECOG/ ESMO groups/ Köhne-score:

The difference in patient characteristics is relevant for the interpretation of the results represented by ECOG-status, ESMO group 1,2,3 and Köhne- score low/ intermediate/ high. In total, there is no statistically significant different in outcome for all parameters (PFS/OS RR). For these different categories (15.2.6), however there is a clear trend for improved PFS in all ESMO and ECOG groups; for the Köhne-score groups this is only in the high risk group (HR 0.66) the case. However this does not translate into improved survival, except ECOG 1-2 vs. 0, ESMO group 3 and Köhne intermediate score. The best improvement in response rate for the 4-drug-combination was seen in ECOG 1-2, ESMO group 1, 3 and Köhne-score high.

Dose intensity:

Dose intensity analysis showed improvement in all categories, however a particular benefit was seen for patients with - different to the expectation – dose intensity <70% (HR 0.08 p 0.1). This shows that the dose modification have mainly be done due to toxicity, since even with strong dose reduction the outcome is improved.

RAS mutation:

The subgroup of RAS mut and location of primary right vs. left is even more complex due to the low number of patients. However, despite these limitations, most benefit in terms of PFS by the 4-drug-regimen was achieved in left tumor location and both RAS subtypes (wt, mut). For the relatively poor prognosis of patients with right tumor and RAS mutation the median PFS and OS was numericaly increased (9.6 vs. 14 months; 22.5 vs. 27.8 months; RR 57.9% vs. 83.3%) – but the hazard ratios are not improved due to cross-over which is very likely due to the low number of patients.

20.2. Quality of Life and Safety

The quality of life was evaluated in almost all patients using the QLQ C30 colon modul and CIPN20. The overall score did not change significantly, with no relevant difference for the 4-drug-combination. In contrast there was an improvement of the quality of life over time which might reflect the regression the disease and thereby symptoms and general health status – despite treatment associated toxicity which is however present in both arms.

This is in accordance with the toxicity data which are in general not very different, despite the addition of the 4-drug; this might be due to adequate dose reductions.

The treatment effect was evaluated for those patients who received a planned dose reduction of 25% of Irinotecan in the Arm B in the first cycle; the outcome parameter have been identical.

20.2.1. EORTCF-QLQ C30

Table 24: Global health status - Arm A

	Baseline	Cycle 5	Cycle 9	MT Cycle 1	End of therapy
n	109	82	61	39	56
Mittelwert ± SD	58 ± 22	61.2 ± 21.6	57 ± 22.5	62.2 ± 15.3	56 ± 20.5
Median	58.3	66.7	58.3	66.7	50
Quartile	41.7 - 66.7	50 - 75	41.7 - 66.7	50 - 66.7	50 - 68.8
Range	0 - 100	8.3 - 100	0 - 100	33.3 - 91.7	16.7 - 100

Table 25: Global health status - Arm B

	Baseline	Cycle 5	Cycle 9	MT Cycle 1	End of therapy
n	109	79	67	45	52
Mittelwert ± SD	54.8 ± 21.5	57 ± 22.2	62.4 ± 18.9	60.9 ± 19.8	56.9 ± 25.5
Median	50	58.3	66.7	66.7	66.7
Quartile	41.7 - 66.7	41.7 - 75	50 - 75	50 - 83.3	33.3 - 83.3
Range	0 - 100	0 - 100	0 - 100	0 - 100	0 - 100

20.2.2. EORTCF-QLQ CIPN20

When presenting score level data, the scoring instructions for the CIPN-20 module highly recommends calculation of Cronbach's alpha coefficient as indicator for reliability of the multi-item score levels. That coefficient should preferably be above 0.70 for any given multi-item scale. The values of Cronbach's alpha for each scale for the CHARTA data are presented in Table 26.

Table 26: Cronbach's alpha coefficient values for CHARTA CIPN-20 data

Multi item scale of CIPN-20 module	Cronbach's alpha
Sensory scale	0.86
Motor scale	0.83
Autonomic scale	0.59

Since Cronbach's alpha for the autonomic scale is less than 0.7 in this study, only the score values for both sensory scale and motor scale are presented in the following tables (Table 27-30).

Table 27: Sensory scale - Arm A

	Baseline	Cycle5	Cycle9	MT Cycle1	End of therapy
n	105	78	58	35	53
Mittelwert + SD	4.7 + 8.4	19.1 + 18.1	20.6 + 16.5	33.5 + 21.1	29 + 23.1
Median	0	14.8	18.5	33.3	18.5
Quartile	0 - 7.4	7.4 - 25.9	11.1 - 25	25.9 - 44.4	11.1 - 51.9
Range	0 - 44.4	0 - 85.2	0 - 77.8	0 - 88.9	0 - 85.2

Table 28: Sensory scale - Arm B

	Baseline	Cycle5	Cycle9	MT Cycle1	End of therapy
n	101	73	64	45	45
Mittelwert + SD	5.5 + 10.5	15.8 + 16	20.4 + 17.3	33.8 + 21.3	25.3 + 20.8
Median	0	11.1	14.8	29.6	22.2
Quartile	0 - 7.4	7.4 - 18.5	7.4 - 26.9	18.5 - 48.1	7.4 - 33.3
Range	0 - 44.4	0 - 77.8	0 - 74.1	0 - 77.8	0 - 74.1

Table 29: Motor scale - Arm A

	Baseline	Cycle5	Cycle9	MT Cycle1	End of therapy
n	76	56	41	24	34
Mittelwert + SD	4.1 + 7.5	7.4 + 12.4	9.5 + 14.9	11.6 + 12.3	12.9 + 13.7
Median	0	0	4.2	8.3	8.3
Quartile	0 - 4.2	0 - 8.3	0 - 12.5	4.2 - 16.7	0 - 19.8
Range	0 - 29.2	0 - 58.3	0 - 75	0 - 45.8	0 - 45.8

Table 30: Motor scale - Arm B

	Baseline	Cycle5	Cycle9	MT Cycle1	End of therapy
n	79	54	45	30	32
Mittelwert + SD	3.4 + 6.3	8.3 + 12.9	9.3 + 10.5	14.3 + 13	11.5 + 16.8
Median	0	4.2	8.3	12.5	8.3
Quartile	0 - 4.2	0 - 11.5	0 - 12.5	4.2 - 24	3.1 - 12.5
Range	0 - 25	0 - 62.5	0 - 45.8	0 - 37.5	0 - 83.3

20.3. Multivariate Analysis

Table 31: Univariate and multivariate analysis of prognostic factors for PFS

Prognostic factor (first item in each category is reference)	Univariate HR (95% CI) p	Multivariate complete model HR (95% CI) p	Multivariate reduced model HR (95% CI) p
Therapy arm A vs. B	0.83 (0.68-1,08) p = 0.17		
ESMO groups groups 1&3 vs. 2	1.36 (1.04-1.78) p = 0.024	1.18 (0.88-1.58) p = 0.2814	
Age <60 vs. >=60	0.77 (0.59-1) p = 0.05		
Age continuous	0.99 (0.97-1) p < 0.0001	0.99 (0.98-1.01) p = 0.3239	0.99 (0.97-1) p = 0.0691
Gender male vs. female	0.81 (0.62-1.08) p = 0.15		
ECOG 0 vs. 1&2	1.06 (0.81-1.39) p = 0.67		
Number of metastatic sites 1 vs. >=2	1.81 (1.07-3.07) p = 0.025	1.08 (0.56-2.07) p = 0.8198	
Leucocytes <10 vs. >= 10 nl	1.22 (0.9-1.64) p = 0.19		
Thrombocytes < 400 vs. >= 400 nl	0.91 (0.67-1.24) p = 0.57		
AP <300 vs. >= 300 U/l	1.4 (0.97-2.02) p = 0.071	1.38 (0.93-2.06) p = 0.1083	
CEA <20 vs. >= 20 µg/ml	1.41 (1.05-1.88) p = 0.02	1.2 (0.86-1.66) p = 0.2848	
KRAS wt vs. mut	0.88 (0.67-1.17) p = 0.39		
Tumor localization left vs. right	1.01 (0.74-1.37) p = 0.97		
Adj pretreatment no vs. yes	1.13 (0.71-1.79) p = 0.61		
Synchronous vs. metachronous	0.56 (0.37-0.86) p = 0.0076	0.67 (0.39-1.14) p = 0.1374	0.59 (0.38-0.9) p = 0.0149

Table 32: multivariate analysis of prognostic factors (reduced model including treatment arm for PFS

Prognostic factor (first item in each category is reference)	Univariate HR (95% CI) p	Multivariate complete model HR (95% CI) p	Multivariate reduced model with therapy arm HR (95% CI) p
Therapy arm A vs. B	0.83 (0.64-1.08) p = 0.17		0.75 (0.57-0.98) p = 0.0344
Age continuous	0.99 (0.97-1) p < 0.0001	0.99 (0.97-1) p = 0.0691	0.99 (0.97-1) p = 0.0427
Synchronous vs. metachronous	0.56 (0.37-0.86) p = 0.0076	0.59 (0.38-0.9) p = 0.0149	0.55 (0.35-0.84) p = 0.0065

Table 33: Univariate and multivariate analysis of prognostic factors for OS

Prognostic factor (first item in each category is reference)	Univariate HR (95% CI) p	Multivariate complete model HR (95% CI) p	Multivariate reduced model HR (95% CI) p
Therapy arm A vs. B	0.82 (0.62-1,09) p = 0.17		
ESMO groups groups 1&3 vs. 2	1.57 (1.18-2.08) p = 0.0021	1.42 (1.02-1.97) p = 0.0352	1.58 (1.18-2.13) p = 0.0023
Age <60 vs. >=60	0.84 (0.64-1.12) p = 0.23		
Age continuous	0.99 (0.98-1.01) p < 0.0001	0.99 (0.98-1.01) p = 0.4214	
Gender male vs. female	0.7 (0.51-0.94) p = 0.018	0.61 (0.44-0.87) p = 0.0053	0.65 (0.48-0.89) p = 0.0073
ECOG 0 vs. 1&2	1.63 (1.22-2.17) p < 0.001	1.47 (1.07-2.02) p = 0.0172	1.49 (1.11-2) p = 0.0078
Number of metastatic sites 1 vs. >=2	1.23 (0.71-2.12) p = 0.46		
Leucocytes <10 vs. >= 10 nl	1.51 (1.1-2.06) p < 0.001	1.23 (0.86-1.76) p = 0.2477	
AP <300 vs. >= 300 U/l	1.89 (1.29-2.78) p < 0.001	1.71 (1.1-2.65) p = 0.0174	1.86 (1.26-2.73) p = 0.0017
CEA <20 vs. >= 20 µg/ml	1.49 (1.09-2.04)	1.16 (0.81-1.67)	

Prognostic factor (first item in each category is reference)	Univariate HR (95% CI) p	Multivariate complete model HR (95% CI) p	Multivariate reduced model HR (95% CI) p
	p = 0.013	p = 0.4201	
KRAS wt vs. mut	0.95 (0.71-1.28) p = 0.72		
Tumor localization left vs. right	1.31 (0.95-1.81) p = 0.095	1.41 (1-2) p = 0.0514	
Adj pretreatment no vs. yes	1.19 (0.74-1.92) p = 0.47		
Synchronous vs. metachronous	0.56 (0.35-0.89) p = 0.013	0.76 (0.46-1.27) p = 0.2973	0.59 (0.38-0.9) p = 0.0149

Table 34: Multivariate analysis of prognostic factors (reduced model including treatment arm for OS

Prognostic factor (first item in each category is reference)	Univariate HR (95% CI) p	Multivariate complete model HR (95% CI) p	Multivariate reduced model with therapy arm HR (95% CI) p
Therapy arm A vs. B	0.82 (0.62-1.09) p = 0.17		0.83 (0.62-1.11) p = 0.21
ESMO groups groups 1&2 vs. 2	1.57 (1.18-2.08) p = 0.0021	1.58 (1.18-2.13) p = 0.0023	1.58 (1.18-2.13) p = 0.0024
Gender male vs. female	0.7 (0.51-0.94) p = 0.018	0.65 (0.48-0.89) p = 0.0073	0.65 (0.48-0.89) p = 0.0078
ECOG 0 vs. 1&2	1.63 (1.22-2.17) p < 0.001	1.49 (1.11-2) p = 0.0078	1.49 (1.11-2) p = 0.0081
AP <300 vs. >=300 U/l	1.89 (1.29-2.78) p < 0.001	1.86 (1.26-2.73) p = 0.0017	1.87 (1.27-2.75) p = 0.0015

The number of patients is by far too low for getting solid and potentially significant results for known prognostic or predictive factors, when we want to elucidate a specific strong effect of the experimental treatment. However, the advantage of the study is that at least one of the major “prognostic-factor-grouping”, the ESMO groups 1,2,3, – which might also be predictive – was used for stratification; such an approach all previous trials are lacking. In particular the potential value of the ESMO group has never been investigated before, neither in 4-drug nor in 3-drug-combinations.

Beyond the known factors age </> 60 years, gender, N metastatic sites 1 vs. >1, leucocytes </> 10, platelets </> 400, AP </> 300, CEA </> 20, synchronous vs. metachronous mets, the following factors have been prognostic for survival also in the multivariate model: ESMO

groups, age as continuum, gender, ECOG status, leucocytes, AP, CEA, localization left vs right, synchrounos vs. metachronous. Further reduction of the model revealed the following factors for PFS: age continuos, synchronous vs. metachronous and treatment arm (HR 0.75 p = 0.3). For overall survival, in the reduced model treatment as a factor was not significant anymore (HR 0.83 p = 0.21), however ESMO groups remained (p = 0.0023), gender (p = 0.007), ECOG status (p = 0.0078) and AP (p = 0.0017)

In conclusion these data are highly interesting and illustrate that at least for PFS the 4-drug-regimen is predictive for an improvement, as well as the ESMO groups 1+3 vs. 2. As expected, due to the different biology, the more intensive regimen seems to be in particular attractive for ESMO group 1, less for ESMO group 2. The characterization of the patients into these comprehensive clinical subgroups seems to be an interesting and potentially important characterization of the patient should used in clinical trials.

20.2. Safety Results

Adverse events were counted for induction treatment if their start and/or stop date occurred during induction treatment plus 30 days, or between end of induction and start of maintenance. Events which stopped before start of study treatment were excluded. Events which occurred more than 30 days after end of induction were counted for follow –up, if no maintenance treatment was started. Any events after start of maintenance were counted for this part of therapy, also with a wash-out-period of 30 days.

Adverse events are listed with their preferred term (MedDRA) in alphabetical order (Appendix). Events with a total frequency equal or above 10% are highlighted. Population: according to the guidelines described in, Table 1 and 3, as well as in the protocol, the safety population differs from other parts of the analysis, and amounts to 119 subjects for arm A, and 123 subjects for arm B, respectively.

13 Summary and Conclusion

13.1 Rationale

The question of this trial was, if the addition of Irinotecan to the standard triplet induction chemotherapy in untreated metastatic colorectal cancer patients with FOLFOX+Bevazicumab would increase the efficacy, measured by PFS/OS and response rate. The primary endpoint for this randomized phase II trial with limited number of patients (n=250) was the progression free survival rate at 9 months, with a significant level of p=<0.1. It would have been useful to include more patients in that trial to have the definitive PFS as a significant difference, however the sponsor did not allow a higher number of patients due to financial reasons, therefore this PFS at 9 months is taken as a surrogate for efficacy.

The treatment was given for induction period of 6 months (in comparison to the comparative trials who gave the induction treatment for 4 months only), followed by maintenance until progression or other event with 5-FU (intravenous or oral), and salvage/second-line-treatment at progression. The treatment with reinduction chemotherapy was allowed. The aim of this trial is, to give complementary information regarding the 3 vs. 4 drug-combination for first-line-induction chemotherapy, however using FOLFOX+Bevazicumab (OLIVIA; STEAM) as in contrast to the most of the other trials who gave FOLFIRI+Bevazicumab as a standard arm (TRIBE I, TRIBE II).

13.2 Course of trial

After randomization of 250 patients, the possibility of enlarge the trial to achieve more statistical power and in particular in comparison to the other ongoing trials, this option was

evaluated with the sponsor. However, this discussion took more or less one year, which put the trial on hold for further patients until decision was done. Finally, the decision was negative and the trial was finished with this number of patients.

The medium follow up is 57 months which indicates a mature data situation, regarding PFS and OS data.

13.3 Patient disposition

Table 1 gives the overview of the patient number, exclusion etc. and the number of patients for per protocol (pts 241) analysis and safety analysis (242). This is a basis for the ongoing evaluation data.

13.4 Results

13.4.1 Primary endpoint – progression free survival at 9 month

56.2 % vs. 66.9 % have been free of progression at 9 months, with a p-value of 0,082 (Fisher´s exact test), and shows a significant difference. Therefore the primary endpoint was met according to Kaplan Meyer method. By using the Chi-square and Fisher´s exact test, as well as logistic regression method, the p-value is above 0,1.

13.4.2 Secondary endpoints

13.4.2.1 Progression free survival

The progression free survival showed a median of 10.3 months (Arm A) vs. 12 months (Arm B), with a HR 0.83 (p = 0.17). This is the difference which has been seen in all comparative trials and which have been significant in TRIBE I and II; however, in CHARTA this is not very likely due to the low number of patients. However, in principle, CHARTA shows the same type of benefit for the 4-drug-combination, which has been shown in the other trials comparing FOLFIRI, Bevacizumab with the 4-drug-combination.

13.4.2.2 Overall survival

The overall survival is 23.95 (Arm A) vs. 27.96 (Arm B), showing a 4 months difference, with HR 0.82 (p = 0.17). This is the same magnitude of difference which has been shown in the other comparative trials with 3 vs. 4 drug comparison.

13.4.2.3 Response rate

The response rate is again numeric different with 60.5% vs. 69.3%, HR 0.82, again not significant (p = 0.21). This shows that the response rate is in the same range as indicated by all other comparable trials.

13.4.3 Further efficacies

Of major importance for efficacy is the number of secondary metastases resection. The secondary resection was done in 20.7% (Arm A) vs. 24.4 % (Arm B), which is more or less comparable; however the rate of resection of 2 and more than 2 metastases is numerical higher in Arm B, indicating some better efficacy of this combination (Table 17 und Table 18). Resection sites have been mainly liver and lung, but in the 4-drug-combination also in the

peritoneum. The patients, who received secondary resection, had a response rate of 76% vs. 78.6 % (no difference) in comparison to 56.2% vs. 66.3% for those patients, who had no secondary resection. However it is more relevant to compare the right patients groups, based on the Köhne-score (not stratified) and in particular the ESMO-groups (stratification criteria). In ESMO-group 1 (limited metastases, potentially resectable) the response rate is higher in Arm B (56.2% vs. 67.6 %), in comparison to group 2 no difference was seen; this was also the case in group 3 with smoldering disease (61.1% vs. 77.8%).

For the Köhne-classification, which is not prognostic, we see an improvement in response rate only in patients with high risk according to the Köhne-score, with 35.3% vs. 64.7% response rate.

Dose intensitiy was defined as <70%, 70%-90% and <90%. There is no clear different outcome for dose intensities; however, those patients with low dose intensity below 70%, have with respect to response rate PFS/OR a benefit from the 4-drug-combination, which is statistically not significant (difference for OS 0.08). For the other groups there are no clear differences between the dose intensities.

The mutations for RAS and BRAF are revealing a typical pattern; the data combined with the location of the primary tumor (left vs. right); however, the best benefit of the 4-drug-combination is seen in left sided RAS-wildtype tumors, and right sided RAS-mutated tumors. In contrast, there is no improvement by the 4-drug-combination for right wild type RAS-tumors.

The multivariate analysis for PFS indicated the following factors as prognostic: ESMO-group I + III (vs. II), younger vs. older age (continuous variable), number of metastastic sites 1 vs. >1, alkaline phosphatase < vs. > 300, CEA < vs. >20 and synchronous vs. metachronous metastases. In a reduced model, age and synchronous vs. metachronous metastases were significant factors, as well as treatment with Arm B (HR 0.75, p 0.034).

For overall survival, the following factors have been predictive: ESMO groups, age, gender, ECOG 0 vs. 1-2, leucocytes > vs. < 10, alk. phosphatase > vs. < 300, CEA < vs. > 20, left vs. right location of the primary and synchronous vs. metachronous metastases.

In the reduced model, ESMO groups, gender, ECOG and alkaline phosphatase remain, but the treatment effect disappeared (HR 0.83, p = 0.21). This shows that the 4-drug-combination had impact on PFS, but very limited effect on OS; this might be due to salvage treatments and low patient number. However, in conclusion this Cox-model revealed for the first time important factors, which are relevant for the future trials; in particular for the first time, the relevance of the predefined ESMO groups for stratification was definitely demonstrated.

13.5 Conclusion

This study demonstrates, although with statistically very limited power due to the number of patients, that the 4-drug-combination has a clinical relevant and statistically significant “PFS at 9 months”-benefit. Furthermore, it has been shown for the first time that the disease category defined according to the ESMO-subgroups is an important prognostic factor and therefore stratification using this classification for future trials is strongly recommended.

This data also demonstrates that the benefit of the 4-drug-combination is also shown for FOLFOX/ Bevacizumab as a comparator - in accordance to STEAM and OLIVIA and shows, that the benefit by initial starting with 4 drugs results in a general improvement in comparison to either standard regimen.

Recently, early trials have shown the same trend for 4-drug-combination including Cetuxi-/Panitumumab. All together, CHARTA adds to the definition of the new treatment standard for the majority of patients who are candidates for more intensive treatment in the first-line-chemotherapy; therefore, despite the low number of patients in the most subgroups,

CHARTA adds an important piece of information for defining the best treatment approach for advanced colorectal cancer. FOLFOXIRI + Bevazicumab is a standard option for a majority of these patients.

14 Appendix

Table 35: Adverse Events - max. CTC grade (categorized) by MedDRA PT and patient, Arm A

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
No. of patients	119	119	119	119
No. of datasets	10	742	106	858
Abdominal discomfort	-	1 (0.8%)	-	1 (0.8%)
Abdominal distension	-	3 (2.5%)	-	3 (2.5%)
Abdominal pain	-	11 (9.2%)	1 (0.8%)	12 (10.1%)
Abdominal pain upper	-	3 (2.5%)	-	3 (2.5%)
Abnormal sensation in eye	-	1 (0.8%)	-	1 (0.8%)
Acidosis hyperchloraemic	-	1 (0.8%)	-	1 (0.8%)
Acute myocardial infarction	-	-	1 (0.8%)	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Ageusia	-	3 (2.5%)	-	3 (2.5%)
Alanine aminotransferase increased	-	1 (0.8%)	-	1 (0.8%)
Allergy to metals	-	1 (0.8%)	-	1 (0.8%)
Alopecia	-	12 (10.1%)	-	12 (10.1%)
Anaemia	-	7 (5.9%)	2 (1.7%)	9 (7.6%)
Anal abscess	-	-	1 (0.8%)	1 (0.8%)
Anal haemorrhage	-	1 (0.8%)	-	1 (0.8%)
Anaphylactic reaction	-	1 (0.8%)	-	1 (0.8%)
Anastomotic complication	-	-	1 (0.8%)	1 (0.8%)
Aphthous stomatitis	-	1 (0.8%)	-	1 (0.8%)
Appetite disorder	-	1 (0.8%)	-	1 (0.8%)
Arthralgia	-	6 (5%)	1 (0.8%)	7 (5.9%)
Arthropathy	-	1 (0.8%)	-	1 (0.8%)
Ascites	-	-	1 (0.8%)	1 (0.8%)
Aspartate aminotransferase increased	-	1 (0.8%)	-	1 (0.8%)
Asthenia	-	7 (5.9%)	-	7 (5.9%)
Back pain	-	4 (3.4%)	1 (0.8%)	5 (4.2%)
Biliary colic	-	1 (0.8%)	-	1 (0.8%)
Blood albumin decreased	-	1 (0.8%)	-	1 (0.8%)
Blood alkaline phosphatase increased	-	1 (0.8%)	-	1 (0.8%)
Blood creatinine increased	-	2 (1.7%)	-	2 (1.7%)
Blood pressure increased	-	1 (0.8%)	-	1 (0.8%)
Blood urea decreased	-	1 (0.8%)	-	1 (0.8%)
Body temperature increased	-	1 (0.8%)	-	1 (0.8%)
Bone pain	-	2 (1.7%)	-	2 (1.7%)
Buccal mucosal roughening	-	1 (0.8%)	-	1 (0.8%)
C-reactive protein increased	-	5 (4.2%)	1 (0.8%)	6 (5%)
Campbell de Morgan spots	-	1 (0.8%)	-	1 (0.8%)
Cardiovascular disorder	-	1 (0.8%)	-	1 (0.8%)
Cervical vertebral fracture	-	-	1 (0.8%)	1 (0.8%)
Cheilitis	-	1 (0.8%)	-	1 (0.8%)
Chills	-	5 (4.2%)	-	5 (4.2%)
Chronic obstructive pulmonary disease	-	1 (0.8%)	-	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Circulatory collapse	-	-	1 (0.8%)	1 (0.8%)
Clostridium colitis	-	1 (0.8%)	-	1 (0.8%)
Confusional state	-	1 (0.8%)	-	1 (0.8%)
Constipation	1 (0.8%)	18 (15.1%)	-	19 (16%)
Cough	-	4 (3.4%)	-	4 (3.4%)
Cushing's syndrome	-	1 (0.8%)	-	1 (0.8%)
Cystitis	-	1 (0.8%)	-	1 (0.8%)
Decreased appetite	-	15 (12.6%)	-	15 (12.6%)
Deep vein thrombosis	-	1 (0.8%)	1 (0.8%)	2 (1.7%)
Dehydration	-	1 (0.8%)	-	1 (0.8%)
Depression	-	5 (4.2%)	-	5 (4.2%)
Dermatitis	-	1 (0.8%)	-	1 (0.8%)
Device related infection	-	2 (1.7%)	-	2 (1.7%)
Diabetes mellitus inadequate control	-	-	1 (0.8%)	1 (0.8%)
Diarrhoea	-	34 (28.6%)	9 (7.6%)	43 (36.1%)
Disease progression	-	-	1 (0.8%)	1 (0.8%)
Disturbance in attention	-	1 (0.8%)	-	1 (0.8%)
Diverticulitis	-	1 (0.8%)	-	1 (0.8%)
Dizziness	-	11 (9.2%)	-	11 (9.2%)
Drug hypersensitivity	-	2 (1.7%)	-	2 (1.7%)
Drug intolerance	-	-	1 (0.8%)	1 (0.8%)
Dry mouth	-	5 (4.2%)	-	5 (4.2%)
Dry skin	-	2 (1.7%)	-	2 (1.7%)
Dysgeusia	-	13 (10.9%)	-	13 (10.9%)
Dyspepsia	-	3 (2.5%)	-	3 (2.5%)
Dysphagia	-	4 (3.4%)	-	4 (3.4%)
Dysphonia	-	4 (3.4%)	-	4 (3.4%)
Dyspnoea	-	4 (3.4%)	1 (0.8%)	5 (4.2%)
Dyspnoea exertional	-	2 (1.7%)	-	2 (1.7%)
Ear discomfort	-	1 (0.8%)	-	1 (0.8%)
Ear pain	-	1 (0.8%)	-	1 (0.8%)
Eczema	-	1 (0.8%)	-	1 (0.8%)
Epistaxis	-	22 (18.5%)	-	22 (18.5%)
Eructation	-	2 (1.7%)	-	2 (1.7%)
Erythema	-	2 (1.7%)	-	2 (1.7%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Eye pain	-	1 (0.8%)	-	1 (0.8%)
Fall	-	1 (0.8%)	-	1 (0.8%)
Fatigue	1 (0.8%)	30 (25.2%)	-	31 (26.1%)
Febrile infection	-	-	1 (0.8%)	1 (0.8%)
Femoral neck fracture	-	-	1 (0.8%)	1 (0.8%)
Flatulence	-	2 (1.7%)	-	2 (1.7%)
Flushing	1 (0.8%)	1 (0.8%)	-	2 (1.7%)
Gait disturbance	-	1 (0.8%)	-	1 (0.8%)
Gamma-glutamyltransferase increased	-	2 (1.7%)	-	2 (1.7%)
Gastroenteritis	-	-	1 (0.8%)	1 (0.8%)
Gastrointestinal stoma complication	-	2 (1.7%)	-	2 (1.7%)
General physical health deterioration	-	3 (2.5%)	4 (3.4%)	7 (5.9%)
Gingival bleeding	-	1 (0.8%)	-	1 (0.8%)
Gingival pain	-	1 (0.8%)	-	1 (0.8%)
Glossodynia	1 (0.8%)	-	-	1 (0.8%)
Haematochezia	-	1 (0.8%)	-	1 (0.8%)
Haemoglobin decreased	-	1 (0.8%)	-	1 (0.8%)
Headache	-	11 (9.2%)	2 (1.7%)	13 (10.9%)
Hiccups	-	2 (1.7%)	-	2 (1.7%)
Hyperglycaemia	-	1 (0.8%)	1 (0.8%)	2 (1.7%)
Hyperkalaemia	-	-	1 (0.8%)	1 (0.8%)
Hypersensitivity	-	2 (1.7%)	-	2 (1.7%)
Hypertension	-	7 (5.9%)	7 (5.9%)	14 (11.8%)
Hypertensive crisis	-	-	1 (0.8%)	1 (0.8%)
Hypoacusis	-	2 (1.7%)	-	2 (1.7%)
Hypoaesthesia	-	1 (0.8%)	-	1 (0.8%)
Hypocalcaemia	-	1 (0.8%)	-	1 (0.8%)
Hypogeusia	-	1 (0.8%)	-	1 (0.8%)
Hypokalaemia	1 (0.8%)	5 (4.2%)	1 (0.8%)	7 (5.9%)
Hyponatraemia	-	-	1 (0.8%)	1 (0.8%)
Hypotension	-	1 (0.8%)	-	1 (0.8%)
Hypothyroidism	-	1 (0.8%)	-	1 (0.8%)
Hypovolaemia	-	1 (0.8%)	-	1 (0.8%)
Ileus	-	-	1 (0.8%)	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Impaired healing	-	4 (3.4%)	-	4 (3.4%)
Implant site extravasation	-	-	1 (0.8%)	1 (0.8%)
Incontinence	-	1 (0.8%)	-	1 (0.8%)
Increased upper airway secretion	-	1 (0.8%)	-	1 (0.8%)
Infection	-	6 (5%)	3 (2.5%)	9 (7.6%)
Infectious peritonitis	-	1 (0.8%)	-	1 (0.8%)
Influenza	-	1 (0.8%)	-	1 (0.8%)
Infusion related reaction	-	1 (0.8%)	-	1 (0.8%)
Initial insomnia	-	1 (0.8%)	-	1 (0.8%)
Insomnia	-	2 (1.7%)	-	2 (1.7%)
Intestinal perforation	-	1 (0.8%)	-	1 (0.8%)
Iron deficiency	-	1 (0.8%)	-	1 (0.8%)
Lacrimation increased	-	2 (1.7%)	-	2 (1.7%)
Large intestine perforation	-	-	1 (0.8%)	1 (0.8%)
Leukopenia	-	8 (6.7%)	1 (0.8%)	9 (7.6%)
Lymphocyte count decreased	-	-	1 (0.8%)	1 (0.8%)
Malaise	1 (0.8%)	2 (1.7%)	-	3 (2.5%)
Malnutrition	-	1 (0.8%)	-	1 (0.8%)
Mental disorder due to a general medical condition	-	-	1 (0.8%)	1 (0.8%)
Metabolic acidosis	-	1 (0.8%)	-	1 (0.8%)
Migraine	-	1 (0.8%)	-	1 (0.8%)
Mouth ulceration	-	1 (0.8%)	-	1 (0.8%)
Mucosal dryness	-	1 (0.8%)	-	1 (0.8%)
Mucosal inflammation	-	16 (13.4%)	2 (1.7%)	18 (15.1%)
Muscle spasms	-	2 (1.7%)	-	2 (1.7%)
Musculoskeletal chest pain	-	1 (0.8%)	-	1 (0.8%)
Musculoskeletal pain	-	3 (2.5%)	-	3 (2.5%)
Myalgia	-	1 (0.8%)	-	1 (0.8%)
Nasal dryness	-	2 (1.7%)	-	2 (1.7%)
Nasopharyngitis	-	14 (11.8%)	-	14 (11.8%)
Nausea	-	51 (42.9%)	3 (2.5%)	54 (45.4%)
Neck pain	-	2 (1.7%)	-	2 (1.7%)
Neuropathy peripheral	-	10 (8.4%)	-	10 (8.4%)
Neurotoxicity	-	3 (2.5%)	-	3 (2.5%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Neutropenia	-	5 (4.2%)	12 (10.1%)	17 (14.3%)
Neutrophil count decreased	-	-	3 (2.5%)	3 (2.5%)
Nocturia	-	1 (0.8%)	-	1 (0.8%)
Oedema peripheral	-	2 (1.7%)	-	2 (1.7%)
Oesophageal candidiasis	-	1 (0.8%)	-	1 (0.8%)
Omphalitis	-	1 (0.8%)	-	1 (0.8%)
Onychoclasis	-	1 (0.8%)	-	1 (0.8%)
Onycholysis	-	1 (0.8%)	-	1 (0.8%)
Oral herpes	-	2 (1.7%)	-	2 (1.7%)
Oral mucosal eruption	-	1 (0.8%)	-	1 (0.8%)
Oral pain	-	1 (0.8%)	-	1 (0.8%)
Oropharyngeal pain	-	7 (5.9%)	-	7 (5.9%)
Osteoporosis	-	1 (0.8%)	-	1 (0.8%)
Pain	-	7 (5.9%)	1 (0.8%)	8 (6.7%)
Pain in extremity	-	2 (1.7%)	1 (0.8%)	3 (2.5%)
Pain in jaw	-	1 (0.8%)	-	1 (0.8%)
Palmar-plantar erythrodysaesthesia syndrome	-	8 (6.7%)	-	8 (6.7%)
Pancytopenia	-	1 (0.8%)	-	1 (0.8%)
Paraesthesia	-	11 (9.2%)	1 (0.8%)	12 (10.1%)
Paraesthesia oral	-	1 (0.8%)	-	1 (0.8%)
Pelvic fracture	-	-	1 (0.8%)	1 (0.8%)
Pelvic venous thrombosis	-	1 (0.8%)	-	1 (0.8%)
Performance status decreased	-	1 (0.8%)	-	1 (0.8%)
Periodontitis	-	1 (0.8%)	-	1 (0.8%)
Peripheral coldness	-	2 (1.7%)	-	2 (1.7%)
Peripheral motor neuropathy	-	1 (0.8%)	-	1 (0.8%)
Peripheral sensory neuropathy	-	6 (5%)	1 (0.8%)	7 (5.9%)
Petechiae	-	1 (0.8%)	-	1 (0.8%)
Phlebitis	-	1 (0.8%)	-	1 (0.8%)
Photosensitivity reaction	-	1 (0.8%)	-	1 (0.8%)
Platelet count decreased	-	1 (0.8%)	1 (0.8%)	2 (1.7%)
Pneumonia	-	1 (0.8%)	1 (0.8%)	2 (1.7%)
Pneumothorax traumatic	-	1 (0.8%)	-	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Polyneuropathy	-	44 (37%)	3 (2.5%)	47 (39.5%)
Portal vein thrombosis	-	1 (0.8%)	-	1 (0.8%)
Postoperative wound complication	-	1 (0.8%)	-	1 (0.8%)
Procalcitonin increased	-	1 (0.8%)	-	1 (0.8%)
Procedural pain	-	4 (3.4%)	-	4 (3.4%)
Procedural site reaction	-	2 (1.7%)	-	2 (1.7%)
Proctalgia	-	1 (0.8%)	-	1 (0.8%)
Productive cough	-	2 (1.7%)	-	2 (1.7%)
Proteinuria	-	2 (1.7%)	1 (0.8%)	3 (2.5%)
Pruritus	1 (0.8%)	2 (1.7%)	-	3 (2.5%)
Pruritus generalised	-	1 (0.8%)	-	1 (0.8%)
Pulmonary embolism	-	2 (1.7%)	3 (2.5%)	5 (4.2%)
Pyelonephritis acute	-	-	1 (0.8%)	1 (0.8%)
Pyrexia	2 (1.7%)	12 (10.1%)	-	14 (11.8%)
Rash	-	5 (4.2%)	-	5 (4.2%)
Rash pustular	-	1 (0.8%)	-	1 (0.8%)
Red blood cell count decreased	-	1 (0.8%)	-	1 (0.8%)
Renal colic	-	1 (0.8%)	-	1 (0.8%)
Renal disorder	-	-	1 (0.8%)	1 (0.8%)
Restlessness	-	2 (1.7%)	-	2 (1.7%)
Rhinitis	-	1 (0.8%)	-	1 (0.8%)
Rhinorrhoea	-	2 (1.7%)	-	2 (1.7%)
Salpingo-oophoritis	-	1 (0.8%)	-	1 (0.8%)
Scar pain	-	2 (1.7%)	-	2 (1.7%)
Sciatica	-	-	1 (0.8%)	1 (0.8%)
Sensory disturbance	-	1 (0.8%)	-	1 (0.8%)
Seroma	-	1 (0.8%)	-	1 (0.8%)
Sinus tachycardia	-	1 (0.8%)	-	1 (0.8%)
Skin discolouration	-	2 (1.7%)	-	2 (1.7%)
Skin disorder	-	1 (0.8%)	-	1 (0.8%)
Skin fissures	-	2 (1.7%)	-	2 (1.7%)
Sleep disorder	-	4 (3.4%)	-	4 (3.4%)
Somnolence	-	1 (0.8%)	-	1 (0.8%)
Stomatitis	-	10 (8.4%)	1 (0.8%)	11 (9.2%)
Subileus	-	-	1 (0.8%)	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Syncope	-	-	2 (1.7%)	2 (1.7%)
Temperature intolerance	-	1 (0.8%)	-	1 (0.8%)
Tendon rupture	-	1 (0.8%)	-	1 (0.8%)
Throat irritation	-	1 (0.8%)	-	1 (0.8%)
Throat tightness	-	1 (0.8%)	-	1 (0.8%)
Thrombocytopenia	-	16 (13.4%)	-	16 (13.4%)
Thrombosis	-	1 (0.8%)	-	1 (0.8%)
Thrombosis in device	-	2 (1.7%)	-	2 (1.7%)
Tinnitus	1 (0.8%)	-	-	1 (0.8%)
Tongue coated	-	1 (0.8%)	-	1 (0.8%)
Transaminases increased	-	-	1 (0.8%)	1 (0.8%)
Traumatic haematoma	-	1 (0.8%)	-	1 (0.8%)
Trismus	-	1 (0.8%)	-	1 (0.8%)
Tumour pain	-	-	1 (0.8%)	1 (0.8%)
Urinary tract infection	-	6 (5%)	1 (0.8%)	7 (5.9%)
Urinary tract obstruction	-	1 (0.8%)	1 (0.8%)	2 (1.7%)
Urosepsis	-	-	1 (0.8%)	1 (0.8%)
Urticaria	-	1 (0.8%)	-	1 (0.8%)
Vaginal discharge	-	1 (0.8%)	-	1 (0.8%)
Venous thrombosis	-	1 (0.8%)	-	1 (0.8%)
Vertigo	-	2 (1.7%)	-	2 (1.7%)
Vision blurred	-	1 (0.8%)	-	1 (0.8%)
Vomiting	-	23 (19.3%)	3 (2.5%)	26 (21.8%)
Weight decreased	-	8 (6.7%)	-	8 (6.7%)
White blood cell count decreased	-	-	1 (0.8%)	1 (0.8%)
White blood cell count increased	-	1 (0.8%)	-	1 (0.8%)
Wound complication	-	1 (0.8%)	-	1 (0.8%)

Table 36: Adverse Events - max. CTC grade (categorized) by MedDRA PT and patient, Arm B

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
No. of patients	123	123	123	123
No. of datasets	33	719	165	917
Abdominal discomfort	-	1 (0.8%)	-	1 (0.8%)
Abdominal distension	-	1 (0.8%)	-	1 (0.8%)
Abdominal pain	-	11 (8.9%)	2 (1.6%)	13 (10.6%)
Abdominal pain upper	1 (0.8%)	7 (5.7%)	2 (1.6%)	10 (8.1%)
Acute polyneuropathy	-	1 (0.8%)	-	1 (0.8%)
Acute prerenal failure	-	1 (0.8%)	-	1 (0.8%)
Adenovirus test positive	-	-	1 (0.8%)	1 (0.8%)
Ageusia	-	1 (0.8%)	-	1 (0.8%)
Agitation	1 (0.8%)	-	-	1 (0.8%)
Alanine aminotransferase increased	-	1 (0.8%)	-	1 (0.8%)
Alopecia	2 (1.6%)	24 (19.5%)	1 (0.8%)	27 (22%)
Anaemia	-	14 (11.4%)	2 (1.6%)	16 (13%)
Anal fissure	-	1 (0.8%)	-	1 (0.8%)
Anal haemorrhage	-	3 (2.4%)	-	3 (2.4%)
Anorectal discomfort	-	1 (0.8%)	-	1 (0.8%)
Aphthous stomatitis	1 (0.8%)	-	-	1 (0.8%)
Appetite disorder	-	1 (0.8%)	-	1 (0.8%)
Arrhythmia	-	-	1 (0.8%)	1 (0.8%)
Arthralgia	1 (0.8%)	-	-	1 (0.8%)
Ascites	-	-	1 (0.8%)	1 (0.8%)
Aspartate aminotransferase increased	-	1 (0.8%)	-	1 (0.8%)
Asthenia	2 (1.6%)	9 (7.3%)	1 (0.8%)	12 (9.8%)
Back pain	-	6 (4.9%)	-	6 (4.9%)
Benign prostatic hyperplasia	-	-	1 (0.8%)	1 (0.8%)
Biliary tract disorder	-	-	1 (0.8%)	1 (0.8%)
Biloma	-	-	1 (0.8%)	1 (0.8%)
Bladder pain	-	1 (0.8%)	-	1 (0.8%)
Blood alkaline phosphatase increased	-	1 (0.8%)	-	1 (0.8%)
Blood bilirubin increased	-	-	1 (0.8%)	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Blood creatinine increased	-	2 (1.6%)	-	2 (1.6%)
Blood pressure increased	-	-	1 (0.8%)	1 (0.8%)
Body temperature increased	-	2 (1.6%)	-	2 (1.6%)
Bone pain	-	2 (1.6%)	-	2 (1.6%)
Bronchial secretion retention	-	1 (0.8%)	-	1 (0.8%)
Bronchitis	1 (0.8%)	4 (3.3%)	1 (0.8%)	6 (4.9%)
C-reactive protein increased	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Cachexia	-	1 (0.8%)	-	1 (0.8%)
Calcium deficiency	-	1 (0.8%)	-	1 (0.8%)
Candidiasis	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Cardiac failure	-	1 (0.8%)	-	1 (0.8%)
Cardiovascular disorder	-	1 (0.8%)	-	1 (0.8%)
Cataract	-	-	1 (0.8%)	1 (0.8%)
Cerebral artery occlusion	-	-	1 (0.8%)	1 (0.8%)
Chest discomfort	-	1 (0.8%)	-	1 (0.8%)
Chest pain	-	4 (3.3%)	1 (0.8%)	5 (4.1%)
Chills	-	1 (0.8%)	-	1 (0.8%)
Cholecystitis	-	1 (0.8%)	-	1 (0.8%)
Circulatory collapse	-	2 (1.6%)	-	2 (1.6%)
Colitis	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Communication disorder	-	1 (0.8%)	-	1 (0.8%)
Constipation	1 (0.8%)	8 (6.5%)	-	9 (7.3%)
Contrast media allergy	-	1 (0.8%)	-	1 (0.8%)
Coronary artery disease	-	1 (0.8%)	-	1 (0.8%)
Cough	-	3 (2.4%)	-	3 (2.4%)
Cystitis noninfective	1 (0.8%)	1 (0.8%)	-	2 (1.6%)
Death	-	-	1 (0.8%)	1 (0.8%)
Decreased appetite	-	13 (10.6%)	3 (2.4%)	16 (13%)
Dehydration	-	3 (2.4%)	1 (0.8%)	4 (3.3%)
Depressed mood	-	2 (1.6%)	-	2 (1.6%)
Depression	-	2 (1.6%)	-	2 (1.6%)
Dermatitis	-	1 (0.8%)	-	1 (0.8%)
Dermatosis	-	1 (0.8%)	-	1 (0.8%)
Device related infection	-	-	2 (1.6%)	2 (1.6%)
Diarrhoea	2 (1.6%)	51 (41.5%)	18 (14.6%)	71 (57.7%)
Diplopia	-	2 (1.6%)	-	2 (1.6%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Disturbance in attention	-	1 (0.8%)	-	1 (0.8%)
Dizziness	-	9 (7.3%)	-	9 (7.3%)
Drug intolerance	-	1 (0.8%)	-	1 (0.8%)
Dry mouth	-	6 (4.9%)	-	6 (4.9%)
Dry skin	-	2 (1.6%)	-	2 (1.6%)
Duodenal ulcer	-	1 (0.8%)	-	1 (0.8%)
Dysaesthesia	-	1 (0.8%)	-	1 (0.8%)
Dysgeusia	-	13 (10.6%)	-	13 (10.6%)
Dysmenorrhoea	-	1 (0.8%)	-	1 (0.8%)
Dyspepsia	-	5 (4.1%)	-	5 (4.1%)
Dysphagia	-	5 (4.1%)	1 (0.8%)	6 (4.9%)
Dysphonia	-	5 (4.1%)	-	5 (4.1%)
Dyspnoea	1 (0.8%)	4 (3.3%)	-	5 (4.1%)
Dyspnoea exertional	-	1 (0.8%)	-	1 (0.8%)
Dysuria	-	2 (1.6%)	-	2 (1.6%)
Electrolyte imbalance	-	1 (0.8%)	-	1 (0.8%)
Enteritis	-	1 (0.8%)	-	1 (0.8%)
Epistaxis	-	9 (7.3%)	-	9 (7.3%)
Eructation	-	1 (0.8%)	-	1 (0.8%)
Erythema	-	1 (0.8%)	-	1 (0.8%)
Extrasystoles	-	1 (0.8%)	-	1 (0.8%)
Extravasation	-	1 (0.8%)	-	1 (0.8%)
Eye pain	-	2 (1.6%)	-	2 (1.6%)
Facial bones fracture	-	-	1 (0.8%)	1 (0.8%)
Faecaloma	1 (0.8%)	-	-	1 (0.8%)
Fall	-	2 (1.6%)	-	2 (1.6%)
Fatigue	1 (0.8%)	21 (17.1%)	4 (3.3%)	26 (21.1%)
Febrile infection	-	2 (1.6%)	-	2 (1.6%)
Febrile neutropenia	-	-	2 (1.6%)	2 (1.6%)
Feeling cold	-	1 (0.8%)	-	1 (0.8%)
Feeling hot	-	1 (0.8%)	-	1 (0.8%)
Flank pain	-	2 (1.6%)	-	2 (1.6%)
Flatulence	-	2 (1.6%)	-	2 (1.6%)
Fluid retention	-	1 (0.8%)	-	1 (0.8%)
Fungal infection	-	1 (0.8%)	-	1 (0.8%)
Fungal skin infection	-	1 (0.8%)	-	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Gamma-glutamyltransferase increased	-	-	1 (0.8%)	1 (0.8%)
Gastroenteritis	-	3 (2.4%)	1 (0.8%)	4 (3.3%)
Gastroenteritis norovirus	-	1 (0.8%)	-	1 (0.8%)
Gastrointestinal fistula	1 (0.8%)	-	-	1 (0.8%)
Gastrointestinal haemorrhage	-	-	1 (0.8%)	1 (0.8%)
Gastrointestinal infection	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Gastrointestinal toxicity	-	-	1 (0.8%)	1 (0.8%)
Gastrooesophageal reflux disease	-	1 (0.8%)	-	1 (0.8%)
General physical health deterioration	-	2 (1.6%)	3 (2.4%)	5 (4.1%)
Generalised oedema	-	-	1 (0.8%)	1 (0.8%)
Gingivitis	-	1 (0.8%)	-	1 (0.8%)
Glycosuria	-	1 (0.8%)	-	1 (0.8%)
Gout	-	1 (0.8%)	-	1 (0.8%)
Granulocytopenia	1 (0.8%)	1 (0.8%)	-	2 (1.6%)
Haematochezia	-	3 (2.4%)	-	3 (2.4%)
Haematoma	-	1 (0.8%)	-	1 (0.8%)
Haematotoxicity	-	1 (0.8%)	-	1 (0.8%)
Haemoglobin decreased	-	1 (0.8%)	-	1 (0.8%)
Haemorrhoids	-	1 (0.8%)	-	1 (0.8%)
Headache	-	5 (4.1%)	-	5 (4.1%)
Hepatic failure	-	-	2 (1.6%)	2 (1.6%)
Hepatic pain	-	1 (0.8%)	-	1 (0.8%)
Hepatitis toxic	-	-	1 (0.8%)	1 (0.8%)
Herpes zoster	-	1 (0.8%)	-	1 (0.8%)
Hiccups	-	2 (1.6%)	-	2 (1.6%)
Hydronephrosis	-	1 (0.8%)	-	1 (0.8%)
Hyperbilirubinaemia	-	1 (0.8%)	-	1 (0.8%)
Hypercalcaemia	-	3 (2.4%)	-	3 (2.4%)
Hyperglycaemia	-	-	2 (1.6%)	2 (1.6%)
Hyperhidrosis	1 (0.8%)	4 (3.3%)	-	5 (4.1%)
Hyperkalaemia	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Hypersensitivity	-	2 (1.6%)	-	2 (1.6%)
Hypertension	-	9 (7.3%)	8 (6.5%)	17 (13.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Hypertensive crisis	-	-	1 (0.8%)	1 (0.8%)
Hyperthyroidism	-	1 (0.8%)	-	1 (0.8%)
Hypoaesthesia	-	3 (2.4%)	-	3 (2.4%)
Hypoaesthesia oral	-	2 (1.6%)	-	2 (1.6%)
Hypokalaemia	-	10 (8.1%)	3 (2.4%)	13 (10.6%)
Hypotension	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Ileus	-	1 (0.8%)	2 (1.6%)	3 (2.4%)
Impaired healing	-	1 (0.8%)	-	1 (0.8%)
Implant site extravasation	-	2 (1.6%)	-	2 (1.6%)
Implant site pain	-	1 (0.8%)	-	1 (0.8%)
Implant site swelling	-	1 (0.8%)	-	1 (0.8%)
Increased appetite	-	1 (0.8%)	-	1 (0.8%)
Infection	-	5 (4.1%)	-	5 (4.1%)
Inflammatory marker increased	-	1 (0.8%)	-	1 (0.8%)
Ingrowing nail	-	1 (0.8%)	-	1 (0.8%)
Initial insomnia	-	1 (0.8%)	-	1 (0.8%)
Insomnia	-	2 (1.6%)	-	2 (1.6%)
Iron deficiency	-	1 (0.8%)	-	1 (0.8%)
Lacrimation increased	-	2 (1.6%)	-	2 (1.6%)
Leukopenia	-	15 (12.2%)	9 (7.3%)	24 (19.5%)
Loose tooth	-	1 (0.8%)	-	1 (0.8%)
Loss of consciousness	-	-	1 (0.8%)	1 (0.8%)
Malnutrition	-	1 (0.8%)	-	1 (0.8%)
Middle insomnia	-	1 (0.8%)	-	1 (0.8%)
Mucosal inflammation	-	15 (12.2%)	3 (2.4%)	18 (14.6%)
Muscle spasms	-	1 (0.8%)	-	1 (0.8%)
Muscle tightness	-	1 (0.8%)	-	1 (0.8%)
Musculoskeletal chest pain	-	1 (0.8%)	-	1 (0.8%)
Musculoskeletal discomfort	-	1 (0.8%)	-	1 (0.8%)
Musculoskeletal pain	-	1 (0.8%)	-	1 (0.8%)
Nail disorder	-	1 (0.8%)	-	1 (0.8%)
Nasal abscess	-	1 (0.8%)	-	1 (0.8%)
Nasal discomfort	-	2 (1.6%)	-	2 (1.6%)
Nasal dryness	-	2 (1.6%)	-	2 (1.6%)
Nasopharyngitis	1 (0.8%)	6 (4.9%)	-	7 (5.7%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Nausea	2 (1.6%)	44 (35.8%)	9 (7.3%)	55 (44.7%)
Neuropathy peripheral	1 (0.8%)	6 (4.9%)	-	7 (5.7%)
Neurotoxicity	-	3 (2.4%)	3 (2.4%)	6 (4.9%)
Neutropenia	-	12 (9.8%)	26 (21.1%)	38 (30.9%)
Neutrophil count decreased	-	1 (0.8%)	-	1 (0.8%)
Night sweats	-	3 (2.4%)	-	3 (2.4%)
Ocular discomfort	1 (0.8%)	-	-	1 (0.8%)
Oedema	-	1 (0.8%)	-	1 (0.8%)
Oedema peripheral	-	4 (3.3%)	-	4 (3.3%)
Oesophageal candidiasis	-	1 (0.8%)	-	1 (0.8%)
Oesophageal pain	-	2 (1.6%)	-	2 (1.6%)
Onychoclasis	-	1 (0.8%)	-	1 (0.8%)
Oral herpes	-	2 (1.6%)	-	2 (1.6%)
Oral pain	-	1 (0.8%)	-	1 (0.8%)
Orchitis	-	-	1 (0.8%)	1 (0.8%)
Oropharyngeal pain	-	1 (0.8%)	-	1 (0.8%)
Orthostatic intolerance	-	1 (0.8%)	-	1 (0.8%)
Pain	-	5 (4.1%)	-	5 (4.1%)
Pain in extremity	-	1 (0.8%)	-	1 (0.8%)
Pain in jaw	-	1 (0.8%)	-	1 (0.8%)
Painful defaecation	-	2 (1.6%)	-	2 (1.6%)
Palmar-plantar erythrodysaesthesia syndrome	-	3 (2.4%)	1 (0.8%)	4 (3.3%)
Paraesthesia	2 (1.6%)	12 (9.8%)	-	14 (11.4%)
Paraesthesia oral	-	1 (0.8%)	-	1 (0.8%)
Parosmia	-	1 (0.8%)	-	1 (0.8%)
Periodontitis	-	1 (0.8%)	-	1 (0.8%)
Peripheral coldness	-	1 (0.8%)	-	1 (0.8%)
Peripheral sensory neuropathy	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Pleural effusion	-	2 (1.6%)	-	2 (1.6%)
Pneumonia	-	1 (0.8%)	-	1 (0.8%)
Pneumonia primary atypical	-	-	1 (0.8%)	1 (0.8%)
Pneumonitis	-	-	1 (0.8%)	1 (0.8%)
Polyneuropathy	-	37 (30.1%)	2 (1.6%)	39 (31.7%)
Portal vein thrombosis	-	-	1 (0.8%)	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Post procedural fistula	-	1 (0.8%)	-	1 (0.8%)
Posterior reversible encephalopathy syndrome	-	1 (0.8%)	-	1 (0.8%)
Postoperative wound infection	-	-	1 (0.8%)	1 (0.8%)
Procedural pain	-	-	1 (0.8%)	1 (0.8%)
Proctalgia	1 (0.8%)	1 (0.8%)	-	2 (1.6%)
Proctitis	-	3 (2.4%)	1 (0.8%)	4 (3.3%)
Proteinuria	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Pruritus	-	1 (0.8%)	-	1 (0.8%)
Psoriasis	-	1 (0.8%)	-	1 (0.8%)
Pulmonary embolism	-	-	3 (2.4%)	3 (2.4%)
Pyrexia	-	12 (9.8%)	-	12 (9.8%)
Radiation oesophagitis	-	-	1 (0.8%)	1 (0.8%)
Rash	-	2 (1.6%)	-	2 (1.6%)
Rectal discharge	-	-	1 (0.8%)	1 (0.8%)
Red blood cell count decreased	-	1 (0.8%)	-	1 (0.8%)
Renal failure	-	-	1 (0.8%)	1 (0.8%)
Respiratory tract infection	-	2 (1.6%)	-	2 (1.6%)
Rhinitis	-	2 (1.6%)	-	2 (1.6%)
Salivary hypersecretion	1 (0.8%)	-	-	1 (0.8%)
Sciatica	-	1 (0.8%)	-	1 (0.8%)
Sinus tachycardia	-	1 (0.8%)	-	1 (0.8%)
Sinusitis	-	1 (0.8%)	-	1 (0.8%)
Skin exfoliation	-	2 (1.6%)	-	2 (1.6%)
Skin fissures	-	3 (2.4%)	-	3 (2.4%)
Skin irritation	-	1 (0.8%)	-	1 (0.8%)
Sleep disorder	-	2 (1.6%)	-	2 (1.6%)
Somnolence	-	1 (0.8%)	-	1 (0.8%)
Speech disorder	-	1 (0.8%)	-	1 (0.8%)
Spondylolisthesis	-	1 (0.8%)	-	1 (0.8%)
Stomatitis	-	13 (10.6%)	1 (0.8%)	14 (11.4%)
Swelling face	-	1 (0.8%)	-	1 (0.8%)
Syncope	-	1 (0.8%)	-	1 (0.8%)
Tachyarrhythmia	-	-	1 (0.8%)	1 (0.8%)
Tachycardia	-	1 (0.8%)	-	1 (0.8%)

Number (rate) by NCI CTC grade	unknown	grade 1 – 2	grade 3 - 5	Total
Thrombocytopenia	-	17 (13.8%)	-	17 (13.8%)
Thrombocytosis	1 (0.8%)	-	-	1 (0.8%)
Thrombophlebitis	-	1 (0.8%)	-	1 (0.8%)
Tooth infection	1 (0.8%)	1 (0.8%)	-	2 (1.6%)
Toothache	-	1 (0.8%)	-	1 (0.8%)
Transaminases increased	-	1 (0.8%)	1 (0.8%)	2 (1.6%)
Tremor	1 (0.8%)	-	-	1 (0.8%)
Upper respiratory tract infection	-	-	1 (0.8%)	1 (0.8%)
Urinary retention	-	1 (0.8%)	-	1 (0.8%)
Urinary tract infection	-	5 (4.1%)	-	5 (4.1%)
Urinary tract infection bacterial	-	1 (0.8%)	-	1 (0.8%)
Urosepsis	-	-	1 (0.8%)	1 (0.8%)
Ventricular fibrillation	-	-	1 (0.8%)	1 (0.8%)
Vertigo	-	2 (1.6%)	-	2 (1.6%)
Vomiting	1 (0.8%)	25 (20.3%)	4 (3.3%)	30 (24.4%)
Vomiting projectile	-	1 (0.8%)	-	1 (0.8%)
Vulvovaginal candidiasis	-	1 (0.8%)	-	1 (0.8%)
Weight decreased	1 (0.8%)	5 (4.1%)	-	6 (4.9%)