AGMT Arbeitsgemeinschaft Medikamentöse Tumortherapie

CLINICAL STUDY REPORT

Clinical Trial	A two-stage multicenter phase II trial of concurrent induction chemoimmunotherapy with epirubicine, oxaliplatin, capecitabine and panitumumab in KRAS wild-type, resectable type II gastric adenocarcinoma
Clinical Phase	II
Protocol Number	AGMT_GASTRIC-4
EudraCT	2009-011337-27
Coordinating Investigator	Prim. Univ.-Prof. Dr. Richard Greil Universitätsklinik für Innere Medizin III Universitätsklinikum der PMU Salzburger Landeskliniken Müllner Hauptstraße 48, 5020 Salzburg Tel.: 0662/4482-2879 Fax: 0662/4482-3400 e-mail: r.greil@salk.at
Sponsor	AGMT gemeinnützige GmbH Plenergasse 5/31 1180 Wien
Sponsor Contact	Dr. Daniela Wolkersdorfer Tel.: 0664 1422504 e-mail: d.wolkersdorfer@agmt.at
Study initiation date (FPI)	28.12.2010
Study completion date (LPO)	30.05.2012
Date and version of report	Version 1, 05.02.2014

compiled:
Barbara Meininger, AGMT
30.04.2014 .....
date, signature

reviewed:
Dr. Daniela Wolkersdorfer, AGMT
25.2014 .....
date, signature

approved:
Prim. Univ.-Prof. Dr. Richard Greil
08. Mai 2014 .....
date, signature

TABLE OF CONTENTS

1. Ethics 3
2. Investigators and Study Administration Structure 3
3. Rational 3
4. Study Objective 4
   4.1.Primary Objective 4
   4.2.Secondary Objectives 4
5. Investigational Plan 4
6. Overall Study Design 4
7. Early Termination of the Trial 5
8. Study Population 5
9. Cumulative Doses 5
10. Efficacy Evaluation 6
11. Safety Evaluation 6
   11.1.Adverse Events 6
   11.2.Grade 3/4 Adverse Events 8
12. Literature 8

APPENDIX 1: List of investigators 9
APPENDIX 2: List of patients 9
APPENDIX 3: List of serious adverse events (SAE) 10

1. Ethics

The study was conducted in accordance with GCP and all applicable local laws and the Declaration of Helsinki, including archiving of study documents.

The protocol was approved by local ethics committees and informed consent was obtained from all patients.

2. Investigators and Study Administration Structure

Coordinating Investigator: Prim. Univ.- Prof. Dr. Richard Greil.
The list of investigators and participating sites can be found in Appendix 1.

3. Rational

Gastric cancer is the fourth most commonly diagnosed cancer and is the second leading cause of cancer death worldwide (VanCustem, 2007).

Two European phase III trials (MAGIC trial, Cunningham, 2006; FFCD 9703 trial, Boige, 2007) have been designed to provide a definitive demonstration of the efficacy of perioperative treatments (36% vs. 23%, estimated at 5 years for MAGIC; 38% vs 24% estimated at 5 years for FFCD 9703).

EGFR expression increase has been observed in many tumors, including gastric tumors. This EGFR overexpression usually correlates with a more advanced stage of the disease, a poorer prognosis and a worst response to chemotherapy. In preclinical models it was also found that the inhibition of these receptors had anti-tumor activity, and data available suggested synergy with chemotherapy as well as radiotherapy. Drugs directed against EGFR are currently under investigation in gastric cancer. Cetuximab plus FUFOX e.g. is highly active in metastatic gastric cancer, irrespective of the EGFR detection (Lordick, 2007).

Early in 2009, REAL3, a multicentre phase III, open labelled, randomized controlled trial, was initiated with the EOX dosing from REAL2, which was 50 mg/m2 epirubicin, 130 mg/m2 oxaliplatin, 1250 mg/m2 capecitabine (EOX50-130-1250) in combination with Pmab. Among the first patients enrolled, a markedly higher rate of grade severe diarrhea was registered than previously observed in REAL2, i.e. 4 of 5 patients in REAL3 as compared to 12% among 227 patients (Cunningham et al. 2008, and personal communication with Prof. Cunningham's trial office, July 30, 2009). This experience required REAL3 to be halted, and the dose-toxicity relation was examined in a stepwise approach among the subsequent patients, resulting in a new recommended dose, which is EOX50-100-1000, for which no grade 3 diarrhea has been observed up to date.

The proportion of patients with grade 4 diarrhea after perioperative EOX-Pmab (Panitumumab) was chosen to both obtain clinically valuable information of potentially life-threatening conditions induced by the selected regimen, and to avoid the development of a regime with inacceptable toxicity. The experience of increased grade 3 or 4 diarrhea from REAL3 represents important information; of note, the investigators described their patients as overall especially advanced cases. Integrating this information in the current trial planning, we felt that strict limits for grade 4 diarrhea be the most relevant measure of inacceptable toxicity, since diarrhea is common in this patient

population, and both EOX and panitumumab add to this toxicity. However, in patients with less advanced stages, though a severe toxicity, we felt that the likelihood of resolution of grade 3 diarrhea is very likely and should not be categorized under "inacceptable toxicity" as it is for grade 4 diarrhea.

4. Study Objective

4.1. Primary Objective

Primary efficacy objective: To assess activity of concurrent EOC and Pmab in study patients, measured by proportion of patients with stage T0 and T1 after neoadjuvant study treatment, according to oesophago-gastroscopic endosonography.

Primary safety objective (endpoint): To assess the tolerability / feasibility of concurrent EOC and Pmab in study patients, measured by proportion of patients with grade 4 diarrhea.

4.2. Secondary Objectives

- ⇨ To assess activity of study treatment, measured by proportion of patients with com-plete (R0) tumour resection
- ⇨ To assess the activity of study treatment, measured by proportion of patients with downstaging of their disease (posttreatment T stage lower than pretreatment T stage) during study treatment, according to oesophago-gastroscopic endosonogra-phy.
- ⇨ To assess the rate of pathologic complete responses in referred to surgery after completion of study treatment, measured by proportion of patients with no viable tumour in the entire surgical specimens, i.e. stomach and regional lymph nodes, ac-cording to local histopathological report
- ⇨ To assess the activity of study treatment in study patients, measured by progression-free survival and overall survival 12 months after surgery / end of study treatment
- ⇨ To assess the rate of both treatment-related and –unrelated (severe) adverse events in study patients, measured by CTCAE grades both during study treatment and surgery, including an intervall of at least 30 days after last administration of study treatment
- ⇨ To assess the tolerability / feasibility of concurrent EOC and Pmab in study patients, measured by proportion of patients completing 3 cycles of concurrent EOC and Pmab.

5. Investigational Plan

This was a non-randomized, multicenter, open-label, single-arm Phase II study in patients with previously untreated resectable type II gastric adenocarcinoma.
It was planned to enroll a total number of 43 patients.

6. Overall Study Design

Eligible patients received 3 cycles of concurrent Epirubicine (50mg/m² i.v. d1, q21d), Oxaliplatin (100mg/m2 i.v. d1, q21d), Capecitabine (500mg/m2 bid d1-21, q21d) and Pmab (9mg/kg d1, q21d). Surgery was performed 3 to 9 weeks after last dose of preoperative treatment.

Follow up was planned to be documented for one year.

7. Early Termination of the Trial

Because of first results of the REAL3 trial the recruitment was set "on hold" in December 2011. As the REAL3 trial investigated the same medication regime as the GASTRIC4 and the data showed a significant deviation of overall survival for patients treated with the reduced EOX scheme from patients treated with the standard EOX scheme it was discussed and decided to stop the study in June 2012.

Last Patient Last Visit (including safety evaluation) was 2012/05/30.

At the time of trial termination, all patients were in follow-up or had already completed their study participation.

8. Study Population

In total 10 patients were enrolled. Median age was 46,5 years at study entry. 6 patients were female, 4 were male. The list of enrolled patients can be found in appendix 2.

9. Cumulative Doses

All patients received 3 cycles of induction therapy before surgery. By mistake one patient got less Oxaliplatin than required by protocol for two cycles. One patient had to stop Panitumumab because of an adverse event (paresthesia hand and feet). Cumulative doses are shown in table 1.

Patient	Number of Cycles	Cumulative doses Epirubicin [mg] (days of exposition)		Cumulative doses Oxaliplatin [mg] (days of exposition)		Cumulative doses Capecitabine [mg] (days of exposition)		Cumulative doses Panitumumab [mg] (days of exposition)	
01/01	3	300	(42)	600	(42)	126000	(63)	2835	(42)
01/02	3	300	(42)	600	(42)	126000	(63)	2174	(42)
01/03	3	300	(42)	520	(42)	126000	(63)	2220	(42)
01/04	3	270	(42)	750	(42)	119070	(63)	2132	(42)
01/05	3	240	(41)	475	(41)	100800	(62)	1530	(41)
02/01	3	262,5	(42)	525	(42)	113400	(63)	1755	(42)
03/01	3	310,5	(42)	621	(42)	126000	(63)	2538	(42)
03/02	3	214,5	(43)	431	(43)	91350	(64)	1231,2	(43)
05/01	3	240	(42)	510	(42)	103950	(63)	1620	(42)
05/02	3	270	(42)	540	(42)	126000	(63)	1252	(42)

Table 1 Cumulative doses of Epirubicin, Oxaliplatin, Capecitabine and Panitumumab per patient

10. Efficacy Evaluation

Staging of the tumor was done according the TNM system. At baseline and after 3 months of therapy staging was performed by oesophago-gastroscopic endosonography. After surgery the size and spread of the stomach tumour was evaluated again.

At baseline four patients presented with T 2, three patients with T 3 and three patients with T 4.

All patients underwent surgery.

Table 2 summarizes the T stadium of all patients at screening, after 3 cycles and after surgery.

	T stage at Screening	T stage after 3 cycles	Outcome surgery
01/01	2	NA	2
01/02	4	NA	3
01/03	2	3	0
01/04	4	NA	4
01/05	4	NA	4
02/01	3	3	3
03/01	3	3	2
03/02	3	3	4
05/01	2	3	3
05/02	2	3	4

Table 2 T-stage all patients

According to the poor enrolment there can be no statement about efficacy of the neo-adjuvant treatment.

11. Safety Evaluation

11.1. Adverse Events

All reported adverse events are listed in Table 3. Grading was done using the CTCAE version 3.0.

52 adverse events were documented. 10 of them were in the opinion of the investigator at least possibly related to Panitumumab. 7 serious adverse events (SAE) were reported, 1 of them was considered possibly related to Panitumumab, none was classified as SUSAR. The list of SAEs including a detailed description is attached (appendix 3).

Patient-number	Event Nr.	Event	Grade	Start	Stop	Relation to Panitumumab	SAE
01/01	1	Suspected bloody vomitus	3	04.01.2011	07.01.2011	0	yes
01/01	2	Dermatitis	2	05.01.2011	01.03.2011	3	no
01/01	3	Stomatitis	2	07.01.2011	08.02.2011	1	no
01/01	4	Elevated CRP	2	18.01.2011	08.02.2011	0	no
01/01	5	Pulmonary embolism	3	02.03.2011	04.03.2011	0	yes

01/02	1	Ferritin deficiency	2	21.06.2011	22.08.2011	0	no
01/02	2	Exanthema	1	28.06.2011	22.08.2011	3	no
01/02	3	Mucositis	2	30.06.2011	05.07.2011	2	no
01/02	4	Mucositis	1	06.07.2011	02.08.2011	2	no
01/02	5	Polyneuropathy	1	12.07.2011	14.07.2011	0	no
01/02	6	Hand Foot Syndrome	1	02.08.2011	22.08.2011	0	no
01/02	7	Constipation	1	13.07.2011	23.08.2011	0	no
01/02	8	Loss of appetite	1	21.06.2011	22.08.2011	0	no
01/03	1	Exanthema (Face, upper body, upper extremities)	1	09.08.2011	20.09.2011	3	no
01/04	1	Fatigue	2	09.08.2011	11.08.2011	0	no
01/04	2	Lassitude	2	09.08.2011	11.08.2011	0	no
01/04	3	Increased emesis	3	06.09.2011	12.09.2011	0	yes
01/04	4	Intermittent emesis	1	19.09.2011	ongoing	0	no
01/05	1	Exanthema	1	21.09.2011	ongoing	3	no
01/05	2	Diarrhoea (intermittent)	1	21.09.2011	29.09.2011	0	no
01/05	3	Hand Foot Syndrome	1	20.10.2011	ongoing	0	no
01/05	4	Thrombophlebitis right lower arm	2	09.11.2011	17.11.2011	0	no
02/01	1	Acne like rash	1	30.08.2011	11.09.2011	4	no
02/01	2	Hand Foot Syndrome	1	12.10.2011	14.11.2011	0	no
03/01	1	Rash	2	25.02.2011	28.04.2011	1	no
03/01	2	Diarrhea	1	07.03.2011	28.04.2011	1	no
03/01	3	Fatigue	1	23.04.2011	28.04.2011	1	no
03/01	4	Suspicion of Anastomoser dehiscence post Surgery	4	25.05.2011	07.07.2011	1	yes
03/01	5	Pulmonary embolism	3	23.05.2011	n.k.2011	1	no
03/02	1	Mucositis	1	30.03.2011	10.05.2011	1	no
03/02	2	Diarrhea	3	02.04.2011	11.04.2011	1	yes
03/02	3	Nausea	3	02.04.2011	11.04.2011	1	yes
03/02	4	Thrombophlebitis v. basilica rechts	2	13.04.2011	ongoing	1	no
03/02	5	Thrombose v. Brachiales rechts	3	13.04.2011	ongoing	1	no
03/02	6	Thrombotischer Verschluss der (rechts) v. axillaris + v. subclavia	3	13.04.2011	ongoing	1	no
03/02	7	Schwindel	1	28.04.2011	10.05.2011	1	no
03/02	8	Schwere Beine	1	28.04.2011	10.05.2011	1	no
03/02	9	Gefühlsstörung Schlund, Finger, Gesicht	1	21.04.2011	10.05.2011	1	no
03/02	10	Müdigkeit	1	28.04.2011	10.05.2011	1	no
03/02	11	Konjunktivitis beidseitig	1	10.05.2011	20.06.2011	1	no
03/02	12	Akneiformer Hautausschlag	1	10.05.2011	20.06.2011	1	no
03/02	13	Cephalia	2	31.03.2011	31.03.2011	1	no
03/02	14	Abdominal pain	2	31.03.2011	31.03.2011	1	no
05/01	1	Acne exanthema	2	18.01.2011	n.k.03.2011	4	no
05/01	2	Obstipation	mild	04.02.2011	29.02.2011	0	no
05/01	4	Bacteriemia	2	31.03.2011	05.04.2011	0	no

05/01	5	Nausea	2	29.04.2011	17.05.2011	0	no
05/02	1	Nausea	2	30.05.2011	03.06.2011	0	no
05/02	2	Paresthesia hand and feet	3	15.06.2011	15.06.2011	2	yes
05/02	3	Acne exanthema	2	15.06.2011	nk.08.2011	3	no
05/02	4	Diarrhea	2	11.07.2011	nk.08.2011	0	no
05/02	5	Soor mukositis	2	01.06.2011	10.08.2011	0	no

Table 3: List of all reported adverse events; Relation: 0=Unrelated; 1=Unlikely; 2=Possible; 3=Probable; 4= Definite; 5= Unknown

11.2. Grade 3/4 Adverse Events

Grade 3 and grade 4 AEs are summarized in Table 3. 10 adverse events grade 3 or 4 were documented. No grade 4 diarrhea was observed.

Adverse Event	Grade 3/4	Frequency
Thrombosis	3	2
Nausea	3	1
Diarrhea	3	1
Parathesia	3	1
Pulmonary embolism	3	2
Suspicion of Anastomoser dehiscence post Surgery	4	1
Increased emesis	3	1
Suspected bloody vomitus	3	1

Table 4: Grade 3 and grade 4 adverse events

12. Literature

Cunningham et al. (2008). Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. *N Engl J Med 2008, 358 (1)*, S. 36-46.

Lordick. (2007). ASCO Annual Meeting Proceedings Part I. 2007, Vol 25, No. 18S. *Journal of Clinical Oncology*, S. 4256.

VanCustem, E. (2007). Open-label phase III trial of Pmab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol2007 25 (13)*, S. 1658-64.

APPENDIX 1: List of investigators

Study site	Department	Principal Investigator	Site Initiation
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	Universitätsklinik für Innere Medizin III	Prim. Univ.- Prof. Dr. Richard Greil	13.10.2010
Krankenhaus St. Vinzenz in Zams	Innere Medizin	Prim. Univ. Doz. Dr. Ewald Wöll	15.12.2010
Landeskrankenhaus-Universitätskliniken Innsbruck	Universitätsklinik für Innere Medizin: Klinische Abteilung für Allgemeine Innere Medizin	Univ.- Prof. Dr. Wolfgang Eisterer	14.12.2010
Klinikum Wels-Grieskirchen GmbH	Abteilung für Innere Medizin IV	Prim. Univ.- Prof. Dr. Josef Thaler	25.11.2010
AKh Linz	Interne 3 - Zentrum für Hämatologie und Med. Onkologie	Prim. Univ.- Doz. Dr. Michael Fridrik	15.12.2010
A.ö. Krankenhaus der Elisabethinen Linz	1. Interne Abteilung: Hämatologie mit Stammzellentransplantation, Hämostaseologie und medizinischer Onkologie	OA Dr. Reinhard Ziebermayr	20.12.2010
Landeskrankenhaus Feldkirch	Interne E (Hämatologie und Onkologie)	OA Dr. Alois Lang	-

APPENDIX 2: List of patients

Study Site	Pat #	YoB	Sex	Inclusion Date	Status
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	01/01	1952	Male	28.12.2010	Completed
A.ö. Krankenhaus der Elisabethinen Linz	05/01	1965	Female	13.01.2011	Completed
Landeskrankenhaus-Universitätskliniken Innsbruck	03/01	1964	Female	15.02.2011	Completed
Landeskrankenhaus-Universitätskliniken Innsbruck	03/02	1964	Female	08.03.2011	Completed
A.ö. Krankenhaus der Elisabethinen Linz	05/02	1947	Female	24.05.2011	Completed
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	01/02	1964	Male	21.06.2011	Completed
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	01/03	1970	Male	19.07.2011	Completed
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	01/04	1946	Male	08.08.2011	Withdrawal
Krankenhaus St. Vinzenz in Zams	02/01	1960	Female	17.08.2011	Completed
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	01/05	1969	Female	09.09.2011	Completed

APPENDIX 3: List of serious adverse events (SAE)

Pat #	YoB	SAE #	Received	Event Term	Onset Date	Outcome Date	SAE Status	SUSAR
01/01	1952	A100260	05-Jan-11	Suspected Bloody Vomitus	04-Jan-11	07-Jan-11	Resolved	No
Patient was hospitalized on 05-Jan-11 due to "suspected bloody vomitus". Until "suspicion" is clarified, capecitabine administration is stopped temporarly. No abnormalities can be detected in an oesophago-gastro-scopy (done on 05-Jan-11). No decreasing hemoglobin value is given during hospitalization and neither nausea nor vomitus were represent. So capecitabine treatment (1000 md,bid) was restarted on the 07-Jan-11. Patient was discharged on 07-Jan-11 in good condition.								
01/01	1952	A100275	02-Mar-11	Pulmonary Embolism	02-Mar-11	04-Mar-11	Resolved	No
Patient was hospitalized on 02-Mar-11 due to pulmonary embolism both sides, detected in CT from 01-Mar-11. Anticoagluation with Lovenox was started on 02-Mar-11. Therapy with elastic bandage followed and surgical hose was prescribed. An echocardiography was done on 03-Mar-11 "No abnormalities detected". So patient was discharged in good contition on 04-Mar-11.								
03/01	1964	A100301	25-May-11	Suspicion of Anastomoser dehiscence post surgery	25-May-11	15-Jun-11	Resolved	No
Patient had an Abdomino right-thoracic Erophagus. Resection on 17-May-11 in Bezirkskrankenhaus St.Johann. Postoperativ everything was regular. On 23-May-11 patient got pain (at thoracic-side). The CT-scan showed a pulmonary embolism on both sides. On 24-May-11 patient got a Pigtail-Drainage. On 24-May-11 patient was transferred to Univ. Klinik für Chirurgie Innsbruck for clarification. There the patient underwent surgery with Re-Thoracotomy, Re-laparatomy, Anastomosis. The patient was in intensive care until the 31-May-11. The Drainage was removed on 14-Jun-11. On the 15-Jun-11 the patient was in good general condition and was transferred back to the hospital St. Johann.								
03/02	1964	A100284	04-Apr-11	Diarrhea/ Nausea	02-Apr-11	05-Apr-11	Resolved	No
Patient suffered from Nausea and Diarrhea (CTCAE Grade 3) since 02-Apr-11. Her husband and her daughter also had Diarrhea, so a virus infection is suspected. Since hospitalization the event improves. Event resolved and patient was discharged from hospital on 05-Apr-11. Xeloda was stopped for two days (03-Apr-11 to 04-Apr-11) and started again on 05-Apr-2011. No dose modification. A virus infection is still suspected as primary reason for diarrhea and nausea.								
03/02	1964	A100288	07-Apr-11	Diarrhea/ Nausea	05-Apr-11	11-Apr-11	Resolved	No
Patient had Diarrhea and Nausea from 02-Apr-11 till 05-Apr-11 (see previous SAE). Patient was discharged from hospital on 04-Apr-11 and at home the event diarrhea started again. Due to diarrhea and reduced conditions patient was hospitalized on 07-Apr-11. Viral infection was suspected due to familiar situation (husband and daughter also had diarrhea) and was confirmed by laboratory (Noro Viral positive stool sample). Now diarrhea and nausea is resolved and patient was discharged from hospital on 11-Apr-11.								
05/02	1947	A100310	16-Jun-11	Paraesthesia Hand and Feet	15-Jun-11	15-Jun-11	Resolved	No
Relation to Oxaliplatin and Panitumumab. Patient was hospitalized due to Paraesthesia Hand and Feed during treatment. After administration of Fenistil, Soludacortin and Ulsal the Paraesthesia was resolved and the patient could be discharged on 16-Jun-2011.								
01/04	1946	A100344	08-Sep-11	Increased Emesis	06-Sep-11	12-Sep-11	Resolved	No
Patient was hospitalized on 06-Sep-11 due to increased emesis. After diverse staging examinations were done (Gatroscopy 08-Sep-11, Chest/Abdominal X-ray 07-Sep-11, Chest/Abdomens pelvis CT, Gastroscopy 12-Sep-11) a subileus could be excluded and a gastric exit stendosis was confirmed. So a stent implantation was done on 12-Sep-11. Patient was also supported with rich in calories dietary supplement the whole stay. Patient was discharged in good general conditions without increased emesis on 15-Sep-11.								