AGMT Arbeitsgemeinschaft Medikamentöse Tumortherapie

CLINICAL STUDY REPORT

Clinical Trial:	Lapatinib plus Caelyx in patients with advanced or metastatic breast cancer following failure of Trastuzumab therapy – a Phase II study
Clinical Phase:	II
Protocol Number:	AGMT_MBC 5
EudraCT:	2008-004530-25
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Study initiation date (FPI)	July 2009
Study completion date (LPO)	May 2012

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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 ADMINISTRATIVE STRUCTURE

Coordinating Investigator: Prim. Univ.-Prof. Dr. Richard Greil

Site#	Site	Department	Principal Investigator
01	Universitätsklinikum der PMU Salzburg	Univ. Klinik für Innere Medizin III	Prof. Dr. Richard Greil
02	LKH Feldkirch	Interne E	OA Dr. Alois Lang
03	KH Elisabethinen Linz	1. Interne Abteilung	Dr. Rainhard Ziebermayr
04	LKH-Univ. Klinikum Graz	Klinische Abteilung für Onkologie	Prof. Dr. Hellmut Samonigg
05	AKh Linz	Department für Innere Medizin 3	Doz. Dr. Michael Fridrik
06	LKH-Univ. Klinikum Graz	Universitätsklinik für Frauen-heilkunde und Geburtshilfe	Prof. Dr. Edgar Petru
07	Kaiser Franz Josef-Spital	3. Medizinische Abteilung	Prof. Dr. Christian Dittrich
08	Hanusch Krankenhaus	Abteilung für Gynäkologie und Geburtshilfe	Doz. Dr. Michael Medl
09	Klinikum Wels-Grieskirchen GmbH	Abteilung für Innere Medizin IV	Prof. Dr. Josef Thaler

Figure 1: List of sites and investigators

3. INTRODUCTION

Breast cancer is the second most common type of cancer after lung cancer and the fifth most common cause of death, accounting for 502,000 deaths worldwide in the year 2005. Overexpression of the ErbB2 (Her2/neu) oncogene in approximately 25-30% of breast cancer patients, is linked to a particularly virulent disease and greater risk of disease progression and death. Because of this prognostic role for ErbB2 and its ability to predict response to treatment with trastuzumab, a targeted monoclonal antibody, breast tumors are now routinely screened for ErbB2 overexpression.

Trastuzumab is associated with a marked cardiotoxicity. Thus, there is a need for cardiosparing treatment options as well as for agents that can overcome trastuzumab-resistance for patients with progressive disease. Compared to trastuzumab Lapatinib appears to be less cardiotoxic and therefore could be safely given to patients with previous anthracycline exposure and/or cardiovascular risk factors. There is evidence from clinical studies that the combination of Caelyx with trastuzumab is a very effective therapy in patients with advanced breast cancer. Therefore the combination of Caelyx

with Lapatinib will harbor a further reduced risk for cardiac side effects especially after previous cardiostressing agents such as conventional anthracyclines and/or trastuzumab.

In addition to the potential cardiotoxic benefits of both agents, Caelyx as well as Lapatinib can potentially cross the blood-brain barrier and they have been found to induce remissions in brain metastases. One third of patients with HER2 positive metastatic breast cancer develop CNS metastases during treatment with trastuzumab.

The aim of this study is therefore to further evaluate the potential of a Lapatinib plus Caelyx combination therapy as an effective and safe therapeutic regimen with a favorable cardiotoxicity profile in the treatment of metastatic breast cancer following failure of prior trastuzumab.

4. STUDY OBJECTIVES

The primary objective of this study is to determine the efficacy of a Lapatinib plus Caelyx combination regimen in the treatment of advanced metastatic breast cancer in terms of overall response rates (complete or partial response, determined by radiologic evaluation according to Response Evaluation Criteria in Solid Tumors (RECIST)).

Secondary objective are

- To determine the safety profile of a Lapatinib/ Caelyx combination regimen in terms of qualitative and quantitative toxicities from first study treatment dose until completion of study treatment due to progression or for any other reason.
- To evaluate the occurrence of clinically apparent brain metastases.
- To evaluate the study population with respect to the following: overall survival (from treatment start until death from any cause), progression free survival (from treatment start until progression or death from any cause), clinical benefit (CR, PR or stable disease for at least 24 weeks).
- To evaluate Quality of Life (QoL) status within the study population as captured using the EORTC QLQ-C30 standard questionnaire.

5. INVESTIGATIONAL PLAN

This is a non-randomized, multicenter, open-label, single-arm Phase II study.

Patients with advanced or metastatic breast cancer, histologically confirmed, and HER2 overexpression (IHC 3+ and/or FISH positive) and at least one measurable lesion according to RECIST criteria, who are progredient after trastuzumab therapy (palliative or adjuvant) were eligible for inclusion.

Patients received Lapatinib until progression plus Caelyx for a maximum of six cycles. Safety assessments were conducted in 4-weekly intervals, efficacy assessments were conducted at 8-weekly intervals.

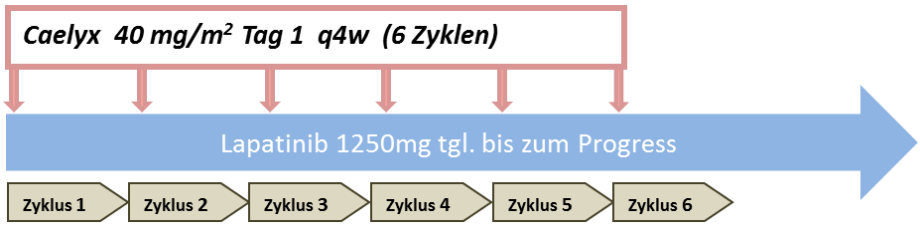

Figure 2: Treatment schedule

Following a two-stage design efficacy and safety of the Lapatinib plus Caelyx combination will be evaluated after the recruitment of the first 20 patients. Upon favorable results a further 10 patients will be recruited to reach the target population of 30 evaluable patients.

6. EFFICACY EVALUATION

Between July 2009 and September 2011 a total of 24 female patients entered the trial. Recruitment was stopped prematurely after 24 patients because Caelyx was not produced by MA holder any more. Mean age was 58 years (minimum age 40 years, maximum age 78 years).

Average time between first cancer diagnosis and study inclusion was 52 months with a minimum of 6 and a maximum of 185 months.

All patients showed overexpression of the ErbB2 (Her2/neu) oncogene. 22 patients were 3+ IHC; the two remaining patients were positive by FISH analysis (1 patient 2+ ICH and 1 patient with no IHC analysis).

9 patients had a single metastatic site, 7 with visceral and 2 with non-visceral metastases as the only manifestation. All patients with metastases at two or more organ sites had a combination of visceral and non-visceral metastases.

All patients were progredient after trastuzumab therapy, 7 patients had trastuzumab as adjuvant treatment, 12 in the metastatic setting, and 4 patients had trastuzumab as adjuvant and palliative treatment.

8 patients completed 6 cycles of therapy. Lapatinib maintenance treatment was started in 5 patients, maximum total cycles were 12 (in 2 patients).

Response

The study was performed as a single-arm two-stage Green-Dahlberg design, testing best overall response rate (CR or PR) of 0.1 versus 0.3 on a significance level of 0.05 with a statistical power of 0.8. It was planned to include a total of 30 patients, however only 24 patients were included. The study reached the second stage since the criteria that at least two responses should be observed was fulfilled (according to the interim analysis there were n=6/17 partial responses).

The regimen was concluded to be effective if seven or more responses out of 30 (23.3%) are observed at the end of the trial. Best overall response was 13 out of 24 patients (54.2%), including one complete response and 12 partial responses. n=6 patients reached stable disease. n=3 patients progressed and n=2 patients had no outcome evaluation. The ITT best response rate of 54.2% was higher than the projected response rate of 23.3%.

Progression

Progression was documented in 19 of 24 patients. Median progression free survival was 5.8 months. Estimated one-year progression free survival was 27%.

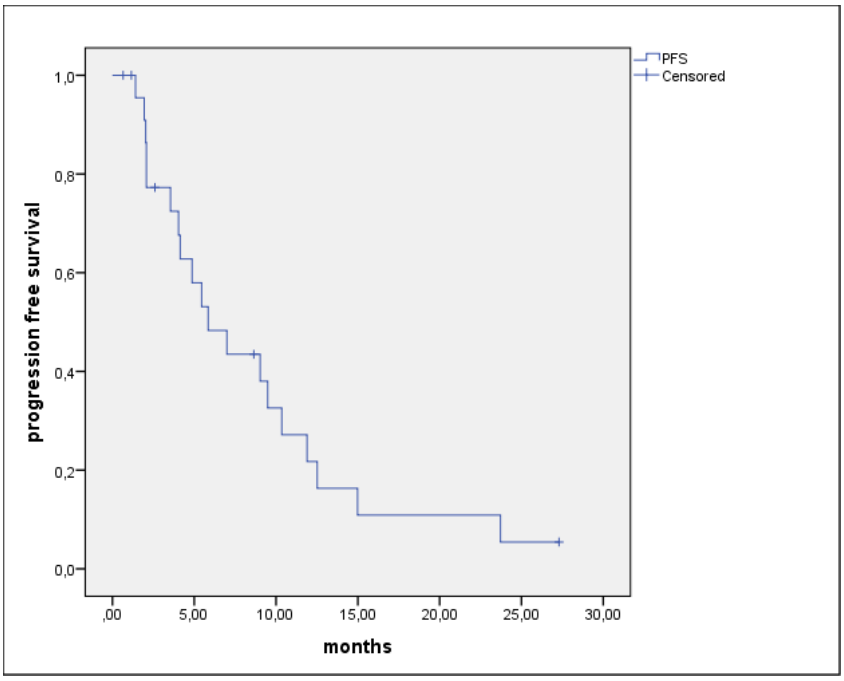

Figure 3: Progression free survival (Kaplan-Meier curve)

Survival

Death was documented in 8 of 24 patients. All deaths were directly related to breast cancer. Median overall survival time was 23.3 months.
Estimated one-year overall survival was 76%.

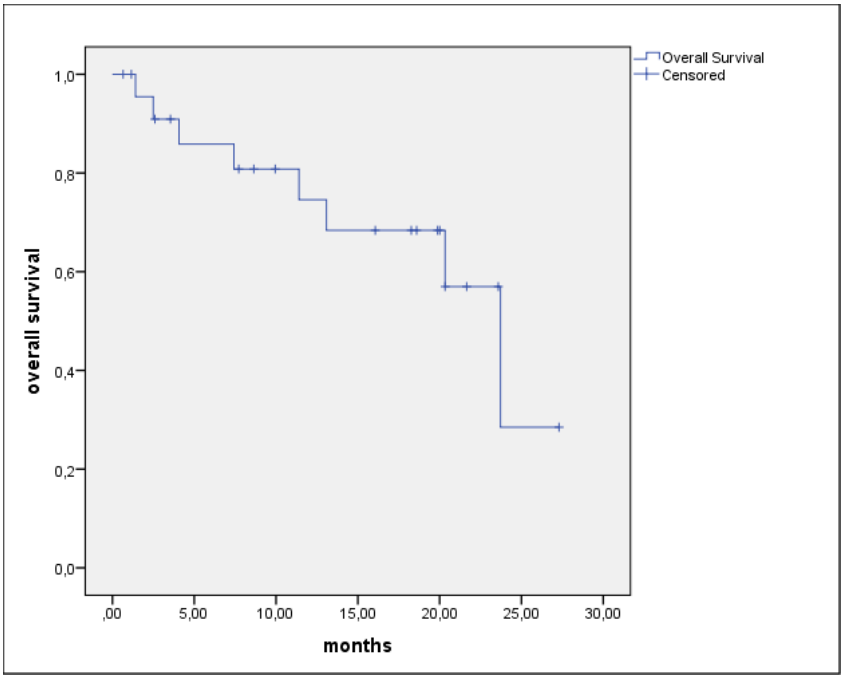

Figure 4: Overall survival (Kaplan-Meier curve)

7. SAFETY EVALUATION

Adverse Events were MedDRA coded. A total of n=192 adverse events were observed. These events belonged to the following SOC categories (see below). Skin and subcutaneous tissue disorders were most frequent, followed by gastrointestinal disorders.

SOC categorie	***Frequency***
Skin and subcutaneous tissue disorders	63
Gastrointestinal disorders	57
General disorders and administration site conditions	20
Infections and infestations	16
Musculoskeletal and connective tissue disorders	7
Nervous system disorders	5
Injury, poisoning and procedural complications	4
Investigations	4
Metabolism and nutrition disorders	4
Ear and labyrinth disorders	3
Eye disorders	3
Psychiatric disorders	2
Reproductive system and breast disorders	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1
Respiratory, thoracic and mediastinal disorders	1
Total	***192***

The following adverse events (using the PT term) were classified as grade 3 or higher. Toxicity grading was done using the CTCAE version 3.0.

PT term	***Frequency***	***CTC grade***
Stomatitis	3	3
Diarrhea	2	3
Alanine aminotransferase increased	1	3
Depressive symptom	1	3
Femur fracture	1	3
General physical health deterioration	1	3
Palmar-plantar erythrodysaesthesia syndrome	1	3
Pharyngitis	1	3
Pneumonia	1	3
Polyneuropathy	1	3
General physical health deterioration	1	5
Pneumonia	1	5
Sepsis	1	5
Total	***16***	

10 patients had at least one SAE, 13 SAEs in total were reported. 8 of these were considered related to study treatment and none was classified as SUSAR.

Event Term	***Onset Date***	***Outcome***	***Outcome Date***	***Relation***	***SUSAR***
Depression grade 3	24.01.2010	Resolved	05.02.2010	Not related	No
Skin breakdown grade 2	21.11.2009	Resolved	04.12.2009	Related	No
Diarrhea Grade 3	14.11.2009	Resolved	18.11.2009	Related	No
Reduced General Condition (previous syncope)	13.01.2011	Resolved	18.01.2011	Not related	No
Pneuminia, Respiratory failure	30.10.2020	Fatal	04.11.2010	Related	No
Erysipel	15.11.2010	Resolved	24.11.2010	Not related	No
Gastroenteritis	08.12.2010	Resolved	16.12.2010	Not related	No
Reduced general condition	26.11.2010	Fatal	13.12.2010	Related	No
Pneumonia, Fever, Epigastric pain	20.02.2011	Resolved	24.02.2011	Related	No
Diarrhea	10.02.2011	Resolved	16.02.2011	Related	No
Elevated ALT > 3 x ULN	14.02.2011	Resolved	27.03.2011	Related	No
Fracture proximal femur, right side	04.11.2011	Resolved	26.11.2011	Not related	No
Sepsis	16.12.2011	Fatal	20.12.2011	Related	No