European Journal of Cancer (2015) **51**, 569–576

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: A randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie

Sylvie Lorenzen [a], Jorge Riera Knorrenschild [b], Georg-Martin Haag [c], Michael Pohl [d], Peter Thuss-Patience [e], Florian Bassermann [a], Ulrike Helbig [f], Florian Weißinger [g], Elisabeth Schnoy [h], Klaus Becker [i], Gertraud Stocker [j], Josef Rüschoff [k], Andreas Eisenmenger [l], Irini Karapanagiotou-Schenkel [l], Florian Lordick [j,l,*]

[a] *3rd Department of Internal Medicine (Hematology/Medical Oncology), Klinikum rechts der Isar, Technische Universität München, Munich, Germany*
[b] *Department of Hematology and Oncology, University Hospital Marburg, Germany*
[c] *Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany*
[d] *Department of Medicine, Knappschaftskrankenhaus, Ruhr University Bochum, Bochum, Germany*
[e] *Department of Hematology, Oncology and Tumor Immunology, Virchow-Klinikum, Charité, Berlin, Germany*
[f] *3rd Medical Department, Hematology and Oncology, Klinikum Braunschweig, Braunschweig, Germany*
[g] *Department of Medicine, Hematology, Oncology and Palliative Care, Evangelisches Krankenhaus, Bielefeld, Germany*
[h] *Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany*
[i] *Onkologische Praxis Hamburg-Lerchenfeld, Hamburg, Germany*
[j] *University Cancer Center Leipzig (UCCL), University Medicine Leipzig, Leipzig, Germany*
[k] *Targos Molecular Pathology, Kassel, Germany*
[l] *NCT Trial Center, National Center for Tumor Diseases, Heidelberg, Germany*

Received 1 December 2014; received in revised form 17 January 2015; accepted 25 January 2015
Available online 16 February 2015

KEYWORDS
Gastric cancer
HER2
EGFR
Lapatinib

Abstract ***Introduction:*** Human epidermal growth factor receptor 2 (HER2) amplification is present in a subgroup of gastroo-esophageal cancers (GCs). HER2 inhibition with trastuzumab has shown to improve outcomes in advanced disease. Lapatinib ditosylate (LAP), a dual anti-epidermal growth factor receptor (EGFR) and anti-HER2 tyrosine kinase inhibitor with preclinical activity against GC, has been approved in HER2-positive breast cancer. We aimed to study the activity of LAP in HER2-amplified GC.

* *Corresponding author at:* Universitäres Krebszentrum (UCCL), Universitätsklinikum Leipzig, Liebigstraße 20, 04103 Leipzig, Germany. Tel.: +49 0341 97 12560; fax: +49 0341 97 12569.
E-mail address: florian.lordick@medizin.uni-leipzig.de (F. Lordick).

http://dx.doi.org/10.1016/j.ejca.2015.01.059

Materials and methods: Patients (pts) with HER2-positive (gene amplification or increased copy numbers based on predefined criteria) advanced GC were randomly allocated 1:1 to receive LAP 1250 mg per day 1–21 plus capecitabine (CAP) 2000 mg/m^2 on days 1–14 of a 21-day cycle or LAP 1500 mg monotherapy day 1–21 after having failed on a platinum-based first-line therapy. HER2 status was assessed centrally. The primary end-point was the objective response rate (ORR) as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). We aimed to include 38 pts per arm to show an interesting response rate of $\geqslant$20% in either of the two arms.

Results: 37 pts were enrolled (18 to LAP + CAP, 19 to LAP). Pts had received a median of three prior treatment lines. 12 pts in the LAP + CAP group (67%) and 12 pts in the LAP group (63%) had received prior trastuzumab. Only two pts (11.1%; 95% confidence interval (CI): 1.37–34.7), both in the LAP + CAP arm, achieved an objective response. The study was closed prematurely for futility. Median time to progression was 42 (95% CI: 38–61) days in the LAP group and 83 (95% CI: 42–86) days in the LAP + CAP group. Other secondary efficacy end-points (progression-free and overall survival) were comparable in the two treatment groups. Rates of diarrhoea were higher with LAP + CAP (61%; 95% CI: 35–83) compared to 26% (95% CI 9–51) with LAP mono, whereas other adverse events were mostly similar between the groups (18 [100%] versus 17 [90%]).

Discussion: Lapatinib showed insufficient activity in HER2-amplified pretreated advanced GC. The safety profile of LAP or LAP + CAP was as expected with some more toxicity in the combination arm. (ClinicalTrials.gov Identifier, NCT01145404).

1. Introduction

Gastro-oesophageal cancer (GC) is one of the leading causes of cancer-related death worldwide [10]. For patients with advanced disease, outcomes are poor with a median survival of 8–12 months with first-line chemotherapy [14]. Despite recent advances in the molecular characterisation of GC, there is still a lack of effective targeted therapies. The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of GC patients. In HER2-positive advanced GC, the international phase III 'Trastuzumab for Gastric Cancer' (ToGA) study showed a significant improvement in overall survival with the addition of trastuzumab to cisplatin and a fluoropyrimidine [1]. Consequently, recent practice guidelines recommend trastuzumab in combination with chemotherapy represents as the standard of care for first-line treatment of HER2-positive advanced GC [15,21]. Unfortunately, when primary or secondary resistance occurs survival is short with a median of only 3–4 months [11]. Post-progression chemotherapy with single agents is effective in advanced GC and has now become a proven treatment option, although the benefit compared to active symptom control is moderate with an improvement in median survival of only 1.5 months [4,5,11]. Recently, the results of the RAINBOW trial have demonstrated that the combination of the vascular endothelial growth factor (VEGF) receptor-2 antibody ramucirumab in combination with paclitaxel can prolong survival by 2.2 months compared with paclitaxel alone and represents a new effective treatment option in second-line therapy of advanced gastric cancer [23].

Lapatinib (LAP) is an orally available small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor (EGFR). In preclinical studies, lapatinib has shown to selectively inhibit HER2-amplified human GC cells and was synergistic with trastuzumab *in vitro* and *in vivo* [22]. Lapatinib was not cross-resistant with trastuzumab in breast cancer cells [12]. The rationale for combining lapatinib and capecitabine in patients with fluoropyrimidine-refractory tumours was the assumption that lapatinib may restall sensitivity to fluoropyrimidines. However, results of the randomised Phase III TRIO-013/Logic trial could not demonstrate a significant improvement in overall survival with the addition of LAP to capecitabine (CAP) plus oxaliplatin (CapeOx) as first-line treatment of advanced HER2-positive GE cancer [8]. Subsequently, the recently published Asian TyTAN trial also failed to show a significant survival benefit for the combination of LAP and paclitaxel to weekly paclitaxel alone in the second line treatment of HER2-amplified GC [17]. Recent evidence has shown that inhibition of EGFR with monoclonal antibodies has not improved outcomes in advanced GC [13,20].

This phase II randomised study was designed to explore the activity and safety of LAP either given alone or in combination with CAP in advanced HER2-positive GC previously treated with a platinum-based first-line therapy.

2. Methods

This multicentre, open-label, randomised, controlled phase II study was conducted at 11 active institutions

within the Arbeitsgemeinschaft Internistische Onkologie (AIO). The protocol was approved by the leading ethics committee (EC) for human research at the University of Heidelberg as well as by the EC of each participating centre. All aspects of the study were done in accordance with the Declaration of Helsinki, including all of its relevant amendments and the guidelines for Good Clinical Practice of the International Conference on Harmonization. An independent data safety and monitoring board (DSMB) monitored recruitment, safety and outcome.

2.1. Patients

Patients $\geqslant$18 years with histologically confirmed HER2-positive metastatic gastrooesophageal adenocarcinoma (GC) were eligible for inclusion if they had documented disease progression during or within 6 months after treatment with at least one cytotoxic regimen for metastatic disease including a platinum compound. The HER2 status was considered positive when HER2 gene amplification (HER2/CEP17 ratio $\geqslant$2.0) was confirmed by central lab using fluorescent *in situ* hybridisation (FISH) (HER2 FISH pharmDx™ Kit (Dako). The HER2/CEP17 ratio was deemed preferable to the heterogeneous HER2 immunohistochemistry (IHC) staining pattern and the subjective categorisation according to different IHC scores used in routine practice. Further inclusion criteria were an Eastern Cooperative Oncology Group performance status $\leqslant$2; a left ventricular ejection fraction (LVEF) of $\geqslant$50%, a measurable cancer lesion, life expectancy of at least 12 weeks and an adequate haematological, renal and hepatic function. All patients gave their written informed consent.

2.2. Study design

Patients were randomly assigned in a 1:1 ratio to receive LAP + CAP or LAP alone. Randomisation was done via a centralised internet-based system. The combination regimen consisted of LAP at a dose of 1250 mg daily, 1 h before or after meal on a continuous basis, and CAP at a dose of 2000 mg per square metre of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle. LAP monotherapy was administered at a dose of 1500 mg daily d1–21, with one cycle defined as 21 days.

Dose adjustments were made for grade 3 toxicity or higher. Standard recommendations for CAP dosage modifications were followed for the management of adverse events (2006). LAP was withheld for up to 14 days for $\geqslant$grade 4 haematological toxicity or any other $\geqslant$grade 3 toxicity. After recovery from $\geqslant$grade 4 haematologic toxicity or grade 3 toxicity, LAP was to be resumed at a one-time decrease of dose by 250 mg. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

Patients continued on protocol until disease progression, symptomatic deterioration, unacceptable toxicity, treatment delay for any reason >2 weeks or withdrawal of consent.

2.3. Tumour assessments

Patients were assessed every 6 weeks during study treatment until progression of disease or death. Survival status was assessed until six months following study treatment. The determination of response was based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Safety and laboratory assessments were performed at screening, on day 1 and once every 3 weeks and at the end of study. 12-lead electrocardiograms (ECGs) and echocardiography were performed at screening, at cycle 3 and at cycle 7.

2.4. Study end-points

The primary end-point was the objective response rate (ORR) defined as complete or partial response (CR or PR) according to RECIST – all to be confirmed by at least two consecutive response assessments within no shorter than 4 weeks. Response was assessed by the local investigator team. Secondary end-points were time to progression (TTP), defined as the time from first dose of study medication to first observed progression, progression-free survival (PFS), defined as the time from the date of first dose of treatment to the date of the first progression of disease (PD) or death due to any cause, overall survival (OS), defined as the time from first treatment administration to death from any cause, and safety.

2.5. Statistical analysis

The sample size estimation was based on the primary end-point, ORR and was calculated by Simon two-stage minimax design [18] for each study arm. No formal statistical comparison between the two arms was planned. The stipulated working null hypothesis for the ORR was 5% versus an alternative hypothesis of an ORR of 20%. The type I error for each of the two arms in this two-stage design was 5%, and the power was 90%. Under these assumptions, the required sample sizes of the first and second stages were 29 and nine patients in each arm, i.e. a maximum total patient number of 38 per arm.

Considering the premature closure of this trial after the inclusion of 37 patients, any confirmatory statistical analyses were deemed inappropriate. The statistical analysis actually performed was therefore done in a strictly exploratory and mainly descriptive manner. All

data collected which have value towards assessing the safety, efficacy or other properties of the drug are reported in either the summary presentations or listings or in both.

Exploratory analysis of the efficacy end-points: Estimates of the ORR and exact 95% confidence intervals (CIs) were calculated for the percentage of patients with response according to Clopper–Pearson [2]. Standard methods for survival analysis were used in the analysis of time-to-event end-points TTP, PFS and OS. The Kaplan–Meier estimate was used to compute the proportion surviving with the 95% CI, calculated using Greenwood's formula. The treatment group effect is estimated using the log-rank test. The hazard ratio and the corresponding 95% CI are estimated by proportional Hazards regression [3].

2.6. Analysis of the safety data

AEs were coded according to MedDRA (Medical Dictionary for Regulatory Activities) 15.0 and grouped by body system. Patient disposition was presented using the CONSORT flow diagram [16]. Summary descriptive statistics were performed for all other data collected i.e. patient characteristics, prior and concomitant medications, vital signs, ECG, study drug administration, extent of exposure and laboratory data.

3. Results

From December 2010 to February 2013, 65 Patients were screened in 11 centres and 37 patients were randomised into the two treatment groups (Fig. 1). In March 2013 the study was stopped prematurely after discussion within the DSMB due to scientific reasons. The decision was based on the high probability that the study endpoints would not be met. It was not based on the formally planned interim analysis or an accumulation of SAE or death. Of the 37 randomised patients, 19 patients were randomly assigned to LAP alone, and 18 were assigned to LAP + CAP. The main reasons for discontinuation of study treatment were death in five and investigators decision in two patients in the LAP + CAP arm, and withdrawal of informed consent in three, investigators decision in three and death in three patients in the LAP arm. For the other patients, progression of disease

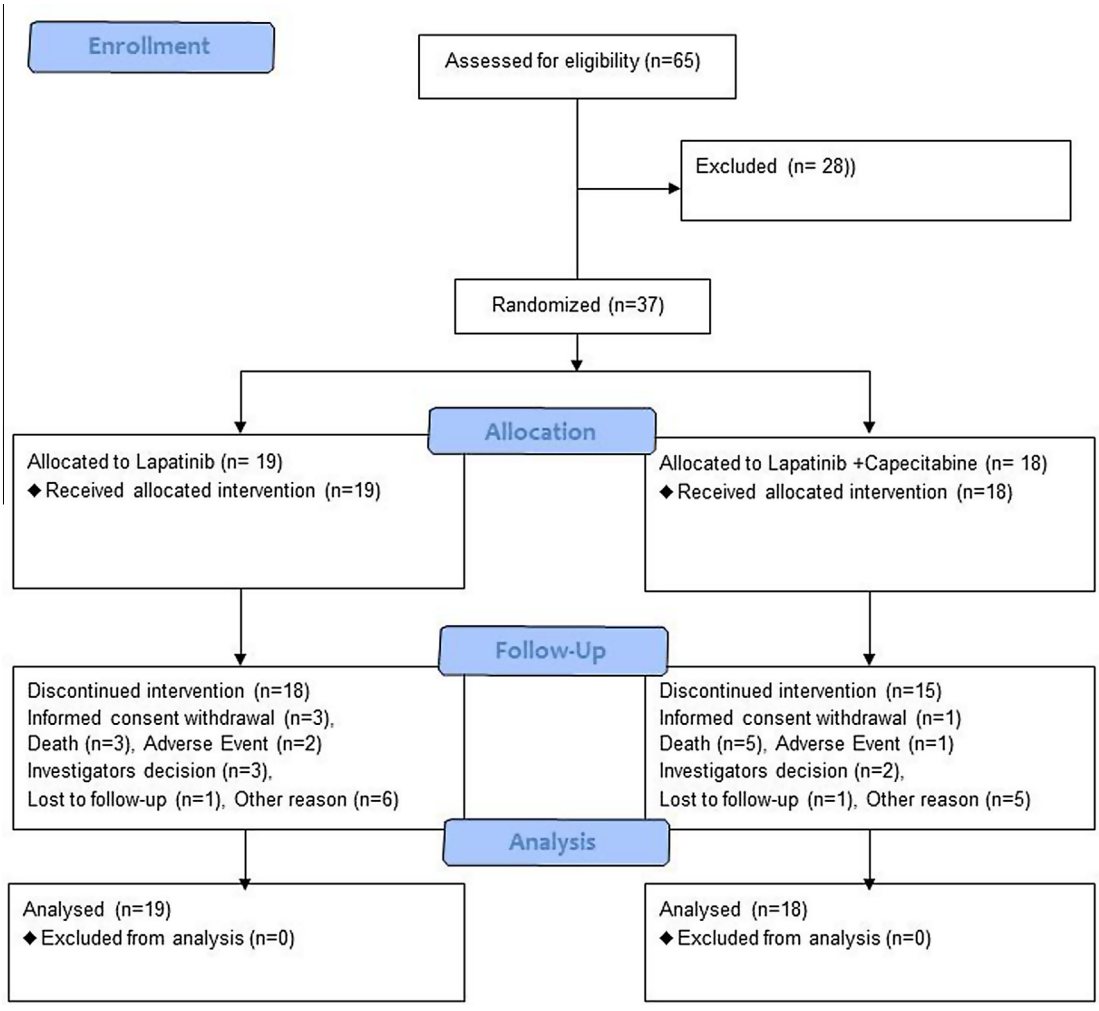

Fig. 1. Patient disposition CONSORF flow diagram.

led to termination of study treatment. Here we report the results of the analysis of all 37 patients.

3.1. Treatment delivery

The median duration of treatment with LAP was 44 days (range 7–133 days) and 56 days (range 2–286 days) with LAP + CAP. The median number of treatment cycles was 3 in both groups. The median daily dose of CAP was 3.400 mg in the LAP + CAP group. The median daily dose of LAP in the LAP + CAP group was 1250 mg and 1500 mg in the LAP group. Of the 37 randomised patients one patient (3%) treated in the LAP arm had a dose reduction, while no dose reductions of lapatinib were necessary in the LAP plus CAP arm.

Reasons for treatment discontinuation included progressive disease, 10 (55.6%) with LAP + CAP versus 16 (84.2%) with LAP; death 3 (16.7%) with LAP + CAP; toxicity 1 (5.6%) with LAP + CAP and 1 (5.3%) with LAP, and patient refusal 1 (5.6%) with LAP + CAP and 2 (10.5%) with LAP.

3.2. Patient population

Baseline characteristics for the 37 eligible and assessable patients are presented in Table 1. All 37 patients had received previous chemotherapy for advanced disease. There was an imbalance between the two treatment groups with regard to previous surgery (72.2% with LAP + CAP versus 36.8% with LAP). A similar number of patients in both arms had been pre-treated with trastuzumab (12 pts in each arm). Of note, patients in the LAP + CAP arm had a longer median time from end of previous chemotherapy to first documentation of disease progression compared to patients treated in the LAP arm (135 days versus 76 days).

3.3. Her-2 overexpression

In 35 of the 37 patients HER2 was tested positive (HER2/CEP17 ratio $\geqslant 2$) with FISH. The mean HER2/CEP17 ratio was 5.33 in the LAP plus CAP arm and 6.99 with LAP alone (Table 1). IHC was not requested in 24 patients. The majority of the patients with available IHC ($n = 13$) were reported to have an IHC score 3+($n = 11$) or 2+($n = 2$) staining intensity.

3.4. Safety

All patients in the LAP + CAP group had adverse events of any grade compared with 17 (89.5%) patients in the LAP group (Table 2). Most AEs were grade 1

Table 1
Patient, tumour and treatment characteristics.

	LAP + CAP		LAP	
	No.	%[a]	No.	%[a]
No. of patients	18		19	
Median age, years; (range)	56 (44–75)	62 (46–76)		
Gender				
Male/female	17/1	94/6	14/5	74/26
ECOG Performance status, median				
0	8	44	10	53
1	8	44	8	42
2	2	11	1	5
Site of tumour				
Lower oesophagus	4	22	3	16
Esophagogastric junction	9	50	6	32
Stomach	5	28	10	53
Histological subtype (Laurén classification)				
Intestinal	9	75	10	83
Non-intestinal (mixed or diffuse)	3	25	2	17
Missing	6		7	
Mean HER2/CEP17 ratio (range)[b]	18	5.33 (2.28–17.83)	17	6.99 (2.21–22.50)
Number of metastatic sites				
0–2	7	39	4	21
$\geqslant 3$	11	61	15	79
Previous anti-cancer treatment				
Chemotherapy for advanced disease	18	100	19	100
Platinum plus fluoropyrimidine	18	100	19	100
Prior trastuzumab	12	67	12	63
Primary tumour present	5	28	12	63
Prior GC surgery	13	72	7	37

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; LAP, lapatinib; CAP, capecitabine.

[a] Percentage was calculated on non-missing values only.

[b] HER2/CEP17 ratio $\geqslant 2$; central laboratory test. Two cases had not enough tumour sections to complete biomarker analysis and results from peripheral pathology institutes were accepted for inclusion.

Table 2
Haematological and non-haematological AEs (National Cancer Institute Common Toxicity Criteria, Version 3.0).

Adverse event	LAP–CAP ($n = 18$)				LAP alone ($n = 19$)			
	Any grade		Grade 3/4/5		Any grade		Grade 3/4/5	
	No.	%	No.	%	No.	%	No.	%
Anaemia	4	22	2	11	2	11	2	11
Leucopenia	1	6	1	6	0	0	0	0
Abdominal Pain	4	22	1	6	2	11	0	0
Diarrhoea	11	61	1	6	5	26	0	0
Nausea	5	28	0	0	5	26	0	0
Emesis	3	17	1	6	4	21	1	5
Stomatitis	2	11	0	0	0	0	0	0
Fatigue	8	44	2	11	6	32	1	5
Asthenia	5	28	1	6	3	16	2	11
Hypokalaemia	4	22	1	6	1	5	1	5
Peripheral neuropathy	1	6	0	0	1	5	0	0
Rash	1	6	0	0	3	16	0	0
Pruritus	2	11	0	0	1	5	0	0
Hand-foot syndrome	4	22	0	0	0	0	0	0
Dysponea	0	0	0	0	4	21	3	16

Abbreviations: LAP, lapatinib; CAP, capecitabine.

or 2. Diarrhoea, fatigue and nausea were the most common adverse events in both treatment arms, however diarrhoea was more common in the combination than in the monotherapy group (61 versus 26%) but was generally mild. Severe adverse events (CTCAE grade 3–5) were comparable in both arms (10 patients in each group). Cardiac events were identified in three patients (17%) in the combination-therapy group ($n = 2$ sinus tachycardia, $n = 1$ palpitations) and in two patients (11%) in the monotherapy group ($n = 2$ tachyarrhythmia). All of these events were considered to be unrelated to treatment, and all patients had a left ventricular ejection fraction (LVEF) value that was at or above the lower limit of the normal range on subsequent assessment.

The number of patients who discontinued treatment due to an AE was higher with LAP + CAP compared with CAP (33.3% versus 26.3%). No toxic death with suspected relation to study treatment was observed with either treatment regimen. On total, nine patients, three in the LAP (15.8%) and six with LAP + CAP (33.3%) stopped study treatment due to disease progression.

3.5. Efficacy results

After the DSMB recommended premature study discontinuation, all efficacy parameters were analysed for the intent-to-treat (ITT) analysis set.

With respect to the primary end-point, objective response rate was 11% ($n = 2$) with LAP + CAP and 0% with LAP (95% CI 1.37–34.7). The corresponding disease control rates were 17% for LAP + CAP and 11% for LAP (Table 3). Response data were unavailable in five patients in LAP + CAP (28%) and in two patients in the LAP group (11%). Median time to progression was 83 days (95% CI 42–86) in the LAP + CAP group and 42 days (95% CI 38–61) in the LAP group (Fig. 2A). The results of the other efficacy end-points (PFS and OS) were comparable in the two treatment groups. Median OS was not reached in the

Table 3
Antitumour activity ($n = 37$).

End-point	LAP–CAP ($n = 18$)		LAP ($n = 19$)	
	n (%)	95%-CI	*n* (%)	95%-CI
Overall response (RECIST)				
Complete response (CR)	–	–	–	–
Partial response (PR)	2 (11)	1.7–34.7	0 (0)	.–17.6
Stable disease (SD)	1 (6)	1.4–27.3	2 (10)	1.3–33.1
Progressive disease (PD)	10 (56)	30.8–78.5	15 (79)	54.4–93.9
Disease control rate (PR + SD)	3 (17)	3.6–41.4	2 (10)	1.3–33.1
TTP (days) median (95% CI)		83 (42–86)		42 (38–61)
PFS (days) median (95% CI)		47 (40–83)		41 (37–50)
OS (days) median (95% CI)		–		142 (53–.)

Abbreviations: LAP, lapatinib; CAP, capecitabine; CI, confidence interval; CR, complete remission, PR, partial remission, RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TTP, time to progression; OS, overall survival.

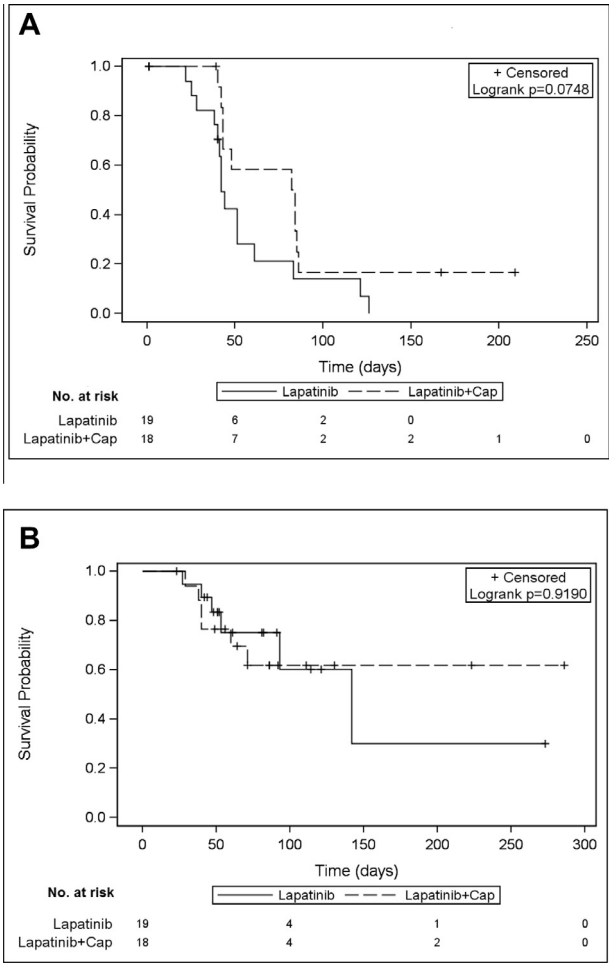

Fig. 2. Kaplan–Meier estimates of time to progression (TTP, A) and overall survival (OS, B).

combination-therapy group and was 142 days with LAP monotherapy (HR 1.06; 95% CI 0.34–3.29) (Fig. 2B).

Of note, the two patients treated with LAP + CAP who achieved a partial response were both tested FISH positive with a HER2/CEP17 ratio of 9.52 and 3.28, respectively. Both patients were also tested IHC3+ (in an after study review). One patient had received trastuzumab during 1st-line and was on study treatment for 8.3 months. He also received further post-progression therapy. The survival time since start of LAP + CAP therapy was 18 months. The other patient was trastuzumab-naïve and was on study treatment for 9.3 months. The survival time of this patient after start of LAP + CAP therapy was also 18 months.

4. Discussion

This trial failed to show a clinically relevant activity of lapatinib in patients with HER2-positive gastric cancer who had progressed to platin-fluoropyrimidine-based chemotherapy in previous treatment lines given for advanced disease. In our trial, only two objective responses (11%) were observed with the combination of LAP plus CAP, and no objective response was reached with LAP alone. In view of the currently available evidence from several studies, including ours, one must conclude that LAP is probably not an effective agent for treating GC [8,9,17]. The responses observed in our study can potentially be attributed to CAP treatment alone and they are comparable to the rate of partial remissions seen with 2nd-line irinotecan or docetaxel, showing a partial response rate between 7% and 10% [4,11,19]. TTP was almost doubled when CAP was added to LAP, while TTP with LAP monotherapy of only 42 days was in the range of what is expected with best supportive care alone [5]. In addition, OS with LAP monotherapy was modest with a median of 142 days which is comparable with 4–5 months of what has been reported with second-line chemotherapy [11,19]. Recently the phase III TYTAN study failed to demonstrate any OS and PFS benefit with the combination of LAP and weekly paclitaxel compared to paclitaxel alone [17], however, there was a significant benefit in ORR with the addition of LAP (27% versus 9%; $p < 0.001$). Of note, better efficacy for the LAP combination was demonstrated in IHC3+ patients; however, the subgroup in TYTAN was small and interpretation has to be done with caution. As the sample size in our trial was even smaller and IHC analysis was not mandatory, further subgroup analysis could not be performed.

One could argue that selection of patients with HER2 positive GC by in-situ-hybridisation was not the best choice. On the other hand, a recent study published by Gomez et al. has demonstrated that the level of HER2 amplification or increased copy numbers has a predictive value for the efficacy that can be reached with trastuzumab treatment in GC [6]. In contrast, ToGA and TYTAN showed a good correlation between HER2 IHC scores and response to trastuzumab and LAP.

The safety profile for lapatinib was consistent with data from advanced breast cancer [7] and gastric cancer [17]. Lapatinib did not appear to significantly augment toxicities from concomitant fluoropyrimidine therapy. The most frequent adverse events were diarrhoea, fatigue and nausea. The excess in adverse events in the combination therapy group appeared specific to the toxicity profile of capecitabine, with patients more likely to suffer from mild diarrhoea, stomatitis and hand-foot-syndrome. Of note, the unexpected high number of patients who terminated treatment due to early disease progression (three with LAP and six with LAP + CAP), can be explained by the very poor prognosis of this disease, specifically after previous treatment lines. In addition, it is also an expression of an ineffective therapy.

In summary, although there was a trend towards a survival advantage with LAP plus CAP in the exploratory analysis, LAP failed to show sufficient activity,

both as monotherapy and in combination with capecitabine in HER2-amplified pretreated advanced GC. However, due to the premature enrolment termination, any far-reaching conclusions with regard to study objectives would not be appropriate. The presence of drug resistance mechanisms or alternative pathways of escape from HER2- targeted therapy requires further investigation.

Role of the funding source

We thank for the support of this trial by a research grant by GlaxoSmithKline – Germany.

Conflict of interest statement

None declared.

References

[1] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376(9742):687–97.

[2] Clopper CP, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

[3] Colette D. Modelling survival data in medical research. London: Chapman & Hall; 1994.

[4] Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15(1):78–86.

[5] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383(9911):31–9.

[6] Gomez-Martin C, Plaza JC, Pazo-Cid R, Salud A, Pons F, Fonseca P, et al. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab. J Clin Oncol 2013;31(35):4445–52.

[7] Guan Z, Xu B, DeSilvio ML, Shen Z, Arpornwirat W, Tong Z, et al. Randomized trial of lapatinib versus placebo added to paclitaxel in the treatment of human epidermal growth factor receptor 2-overexpressing metastatic breast cancer. J Clin Oncol 2013;31(16):1947–53.

[8] Hecht JR, Bang YJ, Qin S. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial. J Clin Oncol 2013;31(Suppl.) [abstr. LBA4001].

[9] Iqbal S, Goldman B, Fenoglio-Preiser CM, Lenz HJ, Zhang W, Danenberg KD, et al. Southwest Oncology Group study S0413: a phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer. Ann Oncol 2011;22(12):2610–5.

[10] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24(14):2137–50.

[11] Kang JH, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30(13):1513–8.

[12] Konecny GE, Pegram MD, Venkatesan N, Finn R, Yang G, Rahmeh M, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. Cancer Res 2006;66(3):1630–9.

[13] Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14(6):490–9.

[14] Lordick F, Lorenzen S, Yamada Y, Ilson D. Optimal chemotherapy for advanced gastric cancer: is there a global consensus? Gastric Cancer 2014;17(2):213–25.

[15] Lorenzen S, Lordick F. How will human epidermal growth factor receptor 2-neu data impact clinical management of gastric cancer? Curr Opin Oncol 2011;23(4):396–402.

[16] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Method 2001;1:2.

[17] Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in asian populations: TyTAN-A randomized, Phase III study. J Clin Oncol 2014;32(19):2039–49.

[18] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10(1):1–10.

[19] Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47(15):2306–14.

[20] Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14(6):481–9.

[21] Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl. 6):vi57–63.

[22] Wainberg ZA, Anghel A, Desai AJ, Ayala R, Luo T, Safran B, et al. Lapatinib, a dual EGFR and HER2 kinase inhibitor, selectively inhibits HER2-amplified human gastric cancer cells and is synergistic with trastuzumab in vitro and in vivo. Clin Cancer Res 2010;16(5):1509–19.

[23] Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15(11):1224–35.