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Article

Dual targeting of the EGFR/HER2 pathway in combination with systemic chemotherapy in refractory pancreatic cancer – The CONKO-008 Phase I Investigation.

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Received: date; Accepted: date; Published: date

Abstract

BACKGROUND: Targeting therapies alone are still with rare efficacy in pancreatic adenocarcinoma (PC). Lapatinib is an oral dual erbB-1 and erbB-2 inhibitor, which may add efficacy. ErbB-1 inhibition has shown efficacy combined with chemotherapy, but PC cells not only expresses erbB-1 but also erbB-2. We investigate the combination of lapatinib and chemotherapy in patients (pts) refractory to 1st-line treatment.

METHODS: Daily oral given lapatinib was dosed from 1000 mg to 1500 mg by 250 mg. Backbone chemotherapy consisted of ambulatory treatment with the proven 2nd-line OFF-regimen (folinic acid 200 mg/m² day + 5-FU 2000 mg/m² 24h days 1,8,15,22, oxaliplatin 85 mg/m² days 8,22 of a 42 day cycle). All patients had informed consent (EudraCT Number: 2009-009928-37).

RESULTS: 18 pts were treated, dose level 1 (7pts), dose level 2 (5pts), dose level 3 (6 pts). Dose limiting toxicities were observed in 2 of 6 pts (one pt diarrhea grade 3, one pt diarrhea grade 4 and neutropenic enterocolitis). Maximum tolerable dose of lapatinib was set on 1250 mg.

Median time to progression was 3.5 [0.5-15.6] months and median survival in second-line treatment was 7.6 [1.2-24.3] months.

CONCLUSIONS: The combination of daily 1250 mg lapatinib with platinum containing chemotherapy was safe, feasible and seems to have efficacy. This combination may be chosen for confirming trials in refractory cancer patients.

Keywords: refractory pancreatic cancer, lapatinib, tyrosine kinase, targeted therapy

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive disease types and a leading cause of cancer death worldwide. It is expected to become the second leading cause of cancer-related death within this decade [1,2]. The small successes that have taken place in the last few years were achieved through therapy optimizing trials of classically chemotherapy and improved supportive measures. More specific, targeted or immune therapies - as developed in other solid tumors - could not gain acceptance [3-5].

Nowadays in patients with inoperable disease, three main strategies for systemic chemotherapy are exist. Gemcitabine in combination with Nab-paclitaxel has been the main evidence-based first line strategy. By agreement, the more intensive FOLFIRINOX regimen is reserved for patients with a fitter, better general condition while gemcitabine monotherapy is reserved for patients with lower performance status, substantial comorbidities or other contraindications. However, in each of these studies, the median overall survival of patients remained less than one year, supporting the ongoing need to develop more beneficial therapies for this disease [6-8]. Patients who showed progression while receiving Gemcitabine/ Nab-paclitaxel or Gemcitabine alone had a phase III-proven chance of further therapy with a platinium- or irinotecan-based strategy combined with flouropyrimidine, if the performance status was sufficiently maintained [9-11]. After first line treatment with FOLFIRINOX, a strategy change to Gemcitabine/Nab-paclitaxel is possible, but is rarely feasible and lacks any phase III-proven overall survival benefit. Most of pts receiving Gemcitabine. The lack of effective targeted agents, as well as missing validated predictive biomarkers that can probably facilitate therapeutic decision-making, are major barriers in the treatment of pancreatic cancer.

The addition of the EGFR-targeting agent erlotinib to gemcitabine has been demonstrated to modestly improve outcome as compared to gemcitabine alone [6]. The tyrosine kinase inhibitor Lapatinib targets not only the EGF Receptor but also erbB-2. ErbB-2/EGFR heterodimers have a higher tyrosine kinase activity than EGFR homodimers [13], it may thus be more efficient to target both of the receptors. EGFR receptor expression has been reported in about 30-90% of pancreatic cancers, while erbB-2 is expressed in about 10-80% of pancreatic cancer tissue samples [14–19].

Another support of a potential benefit of our investigation is the synergism of lapatinib with 5-FU derivatives like capecitabine which has been demonstrated in a large trial in breast cancer [20,21].

This phase I investigation was set up to find the maximum tolerated dose of lapatinib in combination with platinum containing chemotherapy in patients pretreated with a gemcitabine-based therapy.

2. Results

18 patients distributed on three different dose cohorts were needed to determine the maximum tolerable dose (MTD) of the combination regimen. Baseline characteristics and patient assignment are given in Table 1 and Figure 1 respectively.

2.1. Dose Level 1: 1000mg Lapatinib

Seven patients were included in the lowest dose level. In the course of the first three patients we had some complications to handle. One patient suffered from transitory ischemic neurologic deficit due to carotid arteriosclerosis and interrupted therapy within cycle 1. One patient did not complete first cycle according to protocol since he was hospitalized due to hypostatic syncope, diarrhea grade 1 and hypokalemia grade 3 after vomiting (gastric outlet stenosis) and another one patient developed fatal liver failure within the first cycle. Since it was initial not clear that the liver failure was a result of severe septicaemia (cholangitis and central vein catheter infection) and not a probably drug induced liver toxicity, we increased the number of patients in the

first dose level to have sufficient safety data. After receiving all the safety data on the fatal case, it was considered not drug related but due to sepsis, and further recruitment on this level was stopped, which is why 4 and not 3 patients were to complete this dose level without a DLT.

2.2 Dose Level 2: 1250mg Lapatinib

We enrolled five patients in dose level 2. In one of the patients, we stopped treatment within the first cycle as the patient withdrew his consent by individual reason, another patient developed progressive disease with hepatic failure within the first cycle. Both patients were considered not to be evaluable for DLTs since they did not finish the first cycle and so two more patients had been recruited. We observed no DLT in this dose level.

2.3 Dose Level 3: 1500mg Lapatinib

We recruited six patients in dose level 3 since we expanded the cohort after the first documented DLT. Overall, two patients experienced a DLT (diarrhea grade 3 in one patient, diarrhea grade 4 and neutropenic enterocolitis in another pt). We provide a detailed survey on toxicities during the first cycle in Table 2.

2.4 Toxicity summary

Toxicities may be cumulative, that is why for the three different dose levels they are given separately for the subsequent cycles. It has to be considered, that for interpretation the number of the given cycles and patients receiving further cycles are necessary. Overall in dose level 1, 14 subsequent cycles were given (1-8/pt, median 2) to 6 remaining patients. For dose level 2, six subsequent cycles (1-3/pt, median 2) were given to three remaining patients, and for dose level 3, 12 subsequent cycles (2-4/pt, median 2) were given to for remaining patients. Figure 1 gives an overview of given cycles; Table 3 gives a survey of the encountered toxicities over the course. Most toxicities were acceptable to the patients, for details comment on the more severe toxicities see comment on encountered SAE during the trial.

2.5 Severe Adverse Events

13 Severe Adverse Events (SAE) were reported within the trial in nine different patients. Most of the events were ranked as SAE through patient's hospitalisation.

One patient experienced a syncope during cycle 1 resulting in hospital admission due to vomiting, dehydration, hypokalaemia and concomitant QT prolongation that improved after fluid and electrolyte substitution. In the same cycle, he was later again hospitalized with vomiting, hypokalaemia and mild diarrhea as well as QTc time prolongation, which was shown to be caused by gastric outlet stenosis due to local progression of his carcinoma. The data safety board considered that both events were not study drug nor protocol procedures related.

One patient suffered from cerebral ischemia due to carotid stenosis within cycle 1 and a traumatic femoral neck shaft fracture during cycle 2, which were both not considered to be related to the study drug nor protocol procedures.

One patient developed septicaemia most likely due to cholangitis and simultaneous catheter infection with consecutive thrombocytopenia, leukocytopenia, liver failure and respiratory failure – he died during cycle 1. Blood cultures were positive for lactobacillus and candida glabrata that made an abdominal focus like cholangitis probable. The fatal event was considered not to be related to study drug nor protocol procedures.

One patient experienced severe hypoglycaemia while on insuline therapy in cycle 2 and 4 which were both not considered to be related to study drug nor protocol procedures.

One patient developed gastrointestinal bleeding grade 3 without concomitant thrombocytopenia but concomitant transaminase elevation grade 4 that was considered to be caused by hypoxic liver damage during cycle 1. The event was due to cancer infiltration of the stomach and thus was not judged to be drug related nor protocol procedures.

One patient was hospitalized during cycle 1 for positive stool test for occult blood; gastroscopy showed no signs of bleeding and further stool tests were negative. The patient showed also hypokalaemia probably due to pre-existing mild diarrhea; both events were not considered drug related nor protocol procedures. The same patient was later hospitalized again in the same cycle for cholangitis grade 1, antibiotics were given and biliary drainage was performed. There was also no relation to study drug nor protocol procedures.

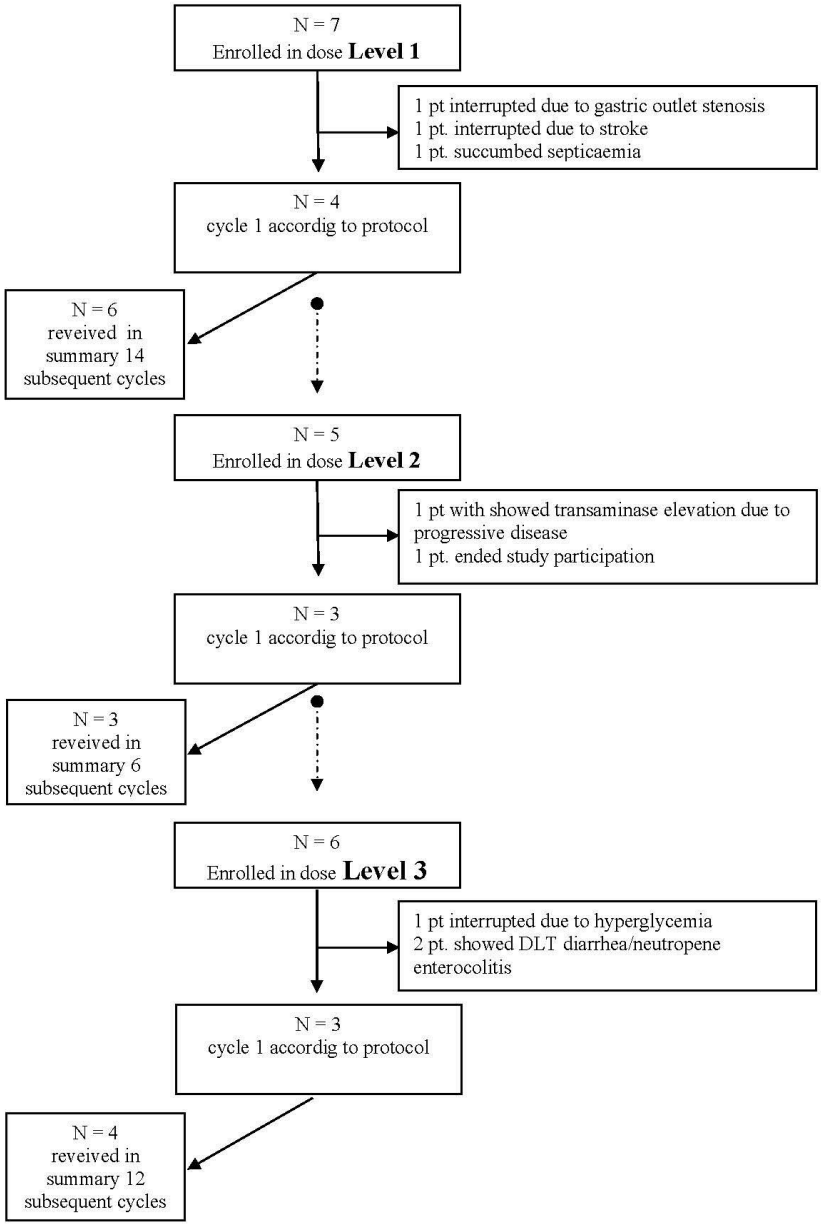
One patient developed diarrhea grade 4 and neutropenic enterocolitis within cycle 1 that was considered related to lapatinib and possibly 5-FU and oxaliplatin and thus considered to be a DLT.

One patient was shortly hospitalized in cycle 3 with hyperglycaemia and lethargy most likely due to new start of parenteral nutrition; both not considered to be related to study drug nor protocol procedures.

One additional patient developed hyperglycaemia during cycle 1 after start of parenteral nutritional support.

2.2. Figures, Tables and Schemes

171 *Figure 1: Patients assignment/ flow chart*



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178 Table 1: Patients baseline characteristics

Baseline Characteristics	**N=18**
Gender	
Female: n (%)	6 (33)
Male: n (%)	12 (67)
Race:	
Caucasian: n (%)	12 (100)
Median age: years [range]	62 [50-75]
Median KPS: Percent [range]	80 [60-90]
90%: n (%)	1 (6)
80%: n (%)	14 (77)
70%: n (%)	2 (11)
60%: n (%)	1 (6)
Median BMI: kg/m² [range]	18.3 [16.1-27.9]
UICC: Disease Stage	
IV: n (%)	18 (100)
Primary inoperable cancer	9 (50)
Curative intended surgery with recurrence	9 (50)
Histopathology	
Ductal Adenocarcinoma: n (%)	17 (94)
Papillary Adenocarcinoma: n (%)	1 (6)
Grading	
G2: n (%)	12 (67)
G3: n (%)	6 (33)
Previous chemotherapy	
Gemcitabine: n (%)	7 (38)
Gemcitabine/Erlotinib: n (%)	6 (33)
Gemcitabine/Aflibercept: n (%)	1 (6)
Gemcitabine/Sorafenib: n (%)	3 (17)
Gemcitabine/Capecitabine: n (%)	1 (6)

179 KPS = Karnofsky Performance Status, UICC = Union for International Cancer Control
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187 Table 2: Heat-map of toxicities in cycle 1

Toxicities in cycle 1, number of maximum toxicities per cycle and patient.												
	Dose Level 1 (Lapatinib 1000 mg)				Dose Level 2 (Lapatinib 1250 mg)				Dose Level 3 (Lapatinib 1500 mg)			
CTC AE 4.0 Grade	**I**	**II**	**III**	**IV**	**I**	**II**	**III**	**IV**	**I**	**II**	**III**	**IV**
Anemia	6	1	0	0	3	1	1	0	4	1	0	0
Leukopenia	2	0	0	0	1	0	0	0	0	0	0	0
Neutropenia	1	0	1	0	1	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	1*	0
Plattelets	2	0	0	1	1	0	0	0	0	0	0	0
Potassium	2	1	1	0	0	0	2	0	1	0	1	0
Sodium	2	0	0	0	2	0	1	0	1	0	1	0
Albumin	3	0	0	0	1	3	0	0	1	3	0	0
ALT	1	0	1	0	2	0	1	0	1	0	0	0
AST	1	0	0	1	3	0	0	1	1	0	0	0
GGT	2	2	2	0	2	1	2	0	0	1	2	1
Alkaline phophatase	0	2	0	0	4	0	0	0	0	0	1	0
Creatinine	1	0	0	0	1	0	0	0	0	0	0	0
Bilirubin	2	0	0	1	1	0	0	0	0	0	1	0
QTc - time	1	0	0	0	0	0	0	0	0	0	0	0
Hypertension	0	3	0	0	1	2	0	0	3	2	1	0
Nausea	3	2	0	0	2	1	0	0	3	1	0	0
Vomiting	2	1	0	0	1	0	0	0	1	0	0	0
Diarrhea	4	1	0	0	2	2	0	0	1	2	1*	1*
Infection	0	0	0	1	1	0	0	0	0	0	0	0
Fatigue	3	2	0	0	3	2	0	0	1	2	0	0
Hand-Foot Syndrome	1	0	0	0	1	0	0	0	3	0	0	0
Synkopae	0	0	1	0	0	0	0	0	0	0	0	0
Gasteric outlet stenosis	0	0	1	0	0	0	0	0	0	0	0	0
Stroke	0	0	1	0	0	0	0	0	0	0	0	0
GI Bleeding	0	0	1	0	0	0	0	0	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	0	0	0	0	0	1
Pain	1	2	1	0	3	0	2	0	1	0	0	0

*dose limiting toxicities

Table 3: Heat-map of toxicities in subsequent cycles

Toxicities in subsequent cycles, based on maximum toxicity per patient and cycle.

Tox	Dose Level 1 (Lapatinib 1000 mg)				Dose Level 2 (Lapatinib 1250 mg)				Dose Level 3 (Lapatinib 1500 mg)			
CTC AE 4.0 Grade	I	II	III	IV	I	II	III	IV	I	II	III	IV
Anemia	8	7	0	0	4	2	0	0	10	0	0	0
Leukopenia	6	0	0	0	2	1	0	0	3	0	0	0
Neutropenia	3	0	0	0	0	0	2	0	1	0	0	0
Febrile Neutro.	0	0	0	0	0	0	0	0	0	0	0	0
Trombocytopenia	5	1	0	0	3	1	0	0	1	0	0	0
Potassium	4	1	2	0	1	0	1	0	2	0	0	0
Sodium	3	0	0	0	1	0	2	0	4	0	0	0
Calcium	5	7	0	0	2	3	1	0	5	1	0	0
Magnesium	9	0	0	0	6	0	0	0	4	0	0	0
Albumin	5	4	1	0	2	4	0	0	5	0	0	0
ALAT	3	1	0	0	1	1	0	0	3	0	0	0
ASAT	7	0	0	0	4	0	0	0	3	0	0	0
GGT	9	2	2	0	3	2	1	0	1	1	2	0
Alkaline Phosphatase	8	0	0	0	4	0	0	0	3	1	1	0
Creatinine	0	0	0	0	0	0	0	0	0	0	0	0
Bilirubin	0	0	0	0	0	0	0	0	0	0	0	0
Ejection fraction	0	1	0	0	0	0	0	0	0	0	0	0
QTc - time	1	0	0	0	0	1	0	0	0	0	0	0
Hypertension	3	4	0	0	3	2	1	0	5	1	0	0
Nausea	4	2	0	0	1	0	0	0	5	2	0	0
Vomiting	4	1	0	0	0	0	0	0	2	0	0	0
Diarrhea	6	3	2	0	3	1	0	0	3	2	1	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	4	7	0	0	3	3	0	0	6	5	0	0
Hand-Foot-Syndrome	7	1	0	0	2	0	0	0	7	0	0	0
Hyperglycemia	0	0	0	0	0	0	0	0	0	0	1	0
Pain	2	1	1	0	2	1	2	0	6	0	0	0
Fracture	0	0	1	0	0	0	0	0	0	0	0	0
Hypoglycemia	0	0	0	0	0	0	2	0	0	0	0	0
Thromboembolism	0	0	0	0	0	0	1	0	0	0	0	0

3. Discussion

In this trial, we found the fix combination of systemic chemotherapy with oxaliplatin, 5-Fluorouracil and folinic acid combined with a dose of 1250 mg lapatinib daily to be a tolerable combination. Diarrhea grade 3 in one patient and diarrhea grade 4, accompanied by febrile enterocolitis in another patient was defined as DLT on the dose level of 1500 mg. We consider the dose of 1250 mg as the maximum tolerated dose (MTD) for this combination.

Diarrhea was already the dose-limiting toxicity in the CONKO 003 study establishing the second-line combination with Oxaliplatin/5-FU/FS. Higher doses of Lapatinib than 1250mg seems to be enhanced this specific side effect. In line with our results, a phase I trial of the combination of Lapatinib and Capecitabine in patients with solid cancers detected also diarrhea to be the DLT at a combination of Lapatinib 1500 mg and Capecitabine 2000 mg/m². The MTD was set on Lapatinib 1250 mg daily and Capecitabine 2000 mg/m² [22].

Another trial evaluating Lapatinib and FOLFOX4 in patients with solid cancers found no dose limiting toxicities up to a Lapatinib dose of 1500 mg daily, which is above the MTD found in our trial. However, in the cited trial, DLT were differently defined. In the 1500 mg dose level of that trial, 7 of 28 patients experienced grade 3 diarrhea, but this was only considered to be a DLT in case of maximum supportive care [23].

Evaluating the combination of oxaliplatin 130 mg/m² every three weeks together with capecitabine 1500 mg/m² day 1-14 and Lapatinib in diverse solid cancers, Dennie et al., too, found diarrhea as the dose limiting toxicity and the dosage of 1000 mg Lapatinib daily to be the maximum tolerated dose [24]. In our trial, the MTD of Lapatinib was higher, but there was also a lower Oxaliplatin dose and a continuous 24h-infusion of 5-FU as the combination partner, which might translate into better gastrointestinal tolerability. A phase 1 trial evaluating Lapatinib in combination with either Gemcitabine/Oxaliplatin or Gemcitabine only demonstrated a daily dose of 1500 mg Lapatinib in combination with Gemcitabine and a daily dose of 1000 mg in combination with Gemcitabine/Oxaliplatin to be the maximum tolerated dose with nausea and anorexia as DLT [25]. Nausea and anorexia were interestingly no major toxicities in our investigation.

In conclusion, diarrhea seems to be the most prominent toxicity of lapatinib in combination with fluoropyridines and with or without oxaliplatin, and, as in accordance with most other trials, a dose of 1250 mg lapatinib daily per os was found to be well tolerated in our trial.

Cardiac toxicity is a side effect of many tyrosine kinases and furthermore a common side effect of the erbB-2 targeting antibody trastuzumab. In this small number of patients, one patient showed a transient worsening of ejection fraction possibly related to lapatinib in cycle 3 of dose level 1, which recovered after stop of study drug. In this patient, study participation was ended due to progressive disease at the same time. Lapatinib is, as trastuzumab, known to provoke mostly transient decreases in ejection fraction [23], although this side effect is not as frequent and pronounced as in trastuzumab [26] and clinical studies have reported occurrence of symptomatic cardiac impairment in about 0,5% of the patients [27].

In the Gemcitabine/Erlotinib trial, one of the major findings was the prediction of response probability based on the rash. The pathophysiology of rash is not detailed understood, but delayed maturing of keratinocytes and thinning of superficial skinlayers, immune response and possibly individual differences in response to EGFR inhibition by PI3 kinase activation are discussed [28]. Interestingly, in this trial, no significant rash was found, and usually, rash seems to be less pronounced in erbB-1/erbB-2 inhibitors than in pure erbB-1 inhibitors like Erlotinib. A study evaluating these differences in skin specimen found less epidermal atrophy and neutrophilic infiltrations in skin specimens of patients treated with dual inhibitors compared to erbB-1 inhibitors alone as well as an increased expression of pAKT and a decreased dermal expression of the proliferation marker K27 and the negative growth regulator p27 [29].

No higher responses than stabilization were documented in this trial. However, a median OS of 7.6 months after progression of first line treatment seems to be at least equivalent to the published survival data of the available Phase III second-line trials [9,11].

4. Materials and Methods

We designed this trial as a classical cohort escalation regimen. Systemic chemotherapy was based on established doses for folinic acid 200 mg/m² (30 minutes) and 5-FU 2000 mg/m² (24h continuous infusion); both drugs were delivered on day 1,8,15, 22 of a 43 day cycle whereas oxaliplatin at a dose of 85 mg/m² (2h infusion) was given on day 8 and 22 [1]. Lapatinib was applied daily per os with an initial dose of 1000 mg that was planned to be escalated stepwise by 250 mg to a maximum of

1500 mg. If none of three consecutive patients at the dose level would develop dose limiting toxicity within the first 42-day cycle of chemotherapy, the dose of Lapatinib became escalated. In case of a DLT, another three patients would be included in the same dose level, and in case of DLTs in two or more of six patients, we would consider the level below as maximum tolerated dose.

Inclusion criteria were histologically proven pancreatic adenocarcinoma, CT-confirmed progression of 1st-line treatment within the last 4 weeks, normal cardiac function in cardiac ultrasound, normal liver,- bone marrow and renal function, a Karnofsky-Performance-Status of ≥ 60%, age over 18 and written informed consent. Most important exclusion criteria were any history of cardiac arrhythmia, cardiac insufficiency grade NYHA 2-4, a history of coronary events, thrombembolic events or cerebral bleeding within the last 6 months and previous irradiation.

We evaluated the response to treatment every 6 weeks by CT scan. In order to count as a confirmed response or stable disease, two subsequent routinely performed CT evaluations had to show stable disease or partial/complete response. Furthermore, we monitored the cardiac function every 6 weeks by cardiac ultrasound and electrocardiogram.

Primary objective of the trial was definition of the MTD of Lapatinib in combination with OFF, secondary objectives were toxicity and tolerability. We graded observed toxicities according to the CTCAE 4.0 schedule.

We defined DLTs as follows:

- Every grade 3 or 4 non-hematologic toxicity with the exception of nausea and vomiting
- Grade 4 thrombocytopenia or grade 3 or 4 thrombocytopenia with concomitant bleeding
- Grade 4 neutropenia for more than 7 days or febrile neutropenia
- Every new toxicity grade 2 or higher with the exception of nausea, vomiting, rash, alopecia or anemia persisting for longer than day 35 after the first cycle.

To be counted as DLT, a relationship to the study drug had to be presumed. Responses were to be considered confirmed responses if in the next CT scan after 6 weeks the response proved true.

The study protocol was approved by the local ethical committee and registered by the European authorities (EudraCT-Nr. 2009-009928-37).

5. Conclusions

In conclusion, daily 1250 mg lapatinib combined with oxaliplatin (85 mg/m²), 5-FU (2000 mg/m² 24h CI) and folinic acid (200 mg/m² 30 min) given on an outpatient basis is safe and well feasible. The strategy qualifies for further investigations in pancreatic or other cancers.

Author Contributions:

Conceptualization: HR, UP, JMS, HO; methodology: JMS, UP, HR; software: SB; validation: SB, UP; formal analysis: SB, UP, JMS, HR; investigation: JKS, JMS, CCMN, DM, MS, PG, DPM, MB, SS, HO, HR, UP; resources: HR, HO, UP, SS; data curation: SB, UP, HR, JMS; writing—original draft preparation: JMS, UP, HR, JKS; writing—review and editing: JKS, JMS, CCMN, DM, PG, DPM, MB, SS, HO, HR, UP; visualization: SB,

UP; supervision: HR, SS, UP; project administration: JMS, JKS, UP, HR; HO funding acquisition: HR, HO, JMS, UP. All authors have read and agreed to the published version of the manuscript.

Funding: The trial was sponsored and supported by research funding of the Charité Universitaetsmedizin Berlin and received partial financial support and Lapatinib free of charge by GlaxoSmithKline GmbH & Co. KG. Grant Number: Charite 89771219. The study has not undergone peer-review by the supporting body. The conception of the trial was in accordance with GlaxoSmithKline GmbH & Co. Data collection, analysis, interpretation of data and manuscript writing is independent from GlaxoSmithKline GmbH & Co.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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