Abstract No. 188

Efficacy and safety of lapatinib treatment in trastuzumab pretreated patients with HER2 positive metastatic breast cancer: an analysis of IntERB Registry in Czech Republic

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Background

Approximately 15-20% of breast cancers overexpress the HER2 (human epidermal growth factor receptor 2) receptor and the disease is associated with poorer prognosis, greater risk for disease progression, and reductions in both progression-free survival (PFS) and overall survival (OS)

Lapatinib is an oral reversible, small molecule dual tyrosin kinase inhibitor of both EGFR(HER1) and HER2. Lapatinib is registered for treatment of patients with HER2 positive breast cancer:

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (dose 1250 mg once daily continuously)
- In combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy (dose 1500 mg once daily continuously)

In the pivotal registration phase III study EGF100151, the addition of Lapatinib (1250 mg once daily cont.) to Capecitabine (2000 mg/m^2 D1-14) in comparison to Capecitabine (2500 mg/m^2 D1-14) alone prolonged time to progression (TTP) 6.2 vs 4.3 months with the hazard ratio (HR) 0.57 (95% CI, 0.43– 0.77; p < 0.001). In updated analysis median overall survival times were 17.3 vs 14.9 months (HR 0.87; 95% CI 0.71–1.08; p = 0.210). A Cox regression analysis considering crossover as a time-dependent covariate suggested a 20% lower risk of death for patients treated with combination therapy (HR 0.80; 95% CI 0.64 – 0.99; p = 0.043).

We evaluated effectiveness, safety and tolerability of lapatinib treatment using data from IntERB registry. IntERB registry has been initiated and run by the Czech Society for Oncology and Institute of Biostatistics and Analyses at the Masaryk University, Brno, Czech Republic.
The IntERB project has been established as an international clinical registry focused on the collection of records on HER2 positive breast cancer patients who are treated with HER2 targeted therapy. The IntERB project is part of an extensive research program which has been designed to assess the efficacy, safety and other aspects of HER2 targeted therapy in HER2 positive patients within Central and Eastern Europe. The parametric structure of the registry provides an unique opportunity to monitor and describe epidemiological situation within participating countries, to assess the relationships between risk factors and therapy efficacy, long-term survival, and to evaluate economical aspects of the therapy. The projectcurrently includes countries: Czech Republic, Hungary, and Lithuania.

Methods

An analysis included 213 patients from the Czech Republic with HER2 positive metastatic breast cancer treated by lapatinib from January 2007 to September 2011 (53 patients were involved in EAP program until 9/2008). Median age was 56 years (range 23 – 78).
Lapatinib was mostly administered 1250mg/day p.o. with Capecitabine (2000 mg/m^2 D1-14) of a 21-day cycle, 16 patients received lapatinib in monotherapy.
All patients had experienced progression during prior trastuzumab based therapy. No patients were treated with combination of lapatinib and aromatase inhibitor.

References

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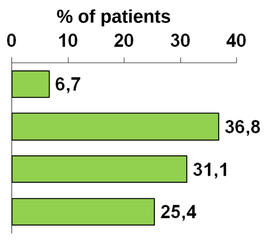
Patients characteristics

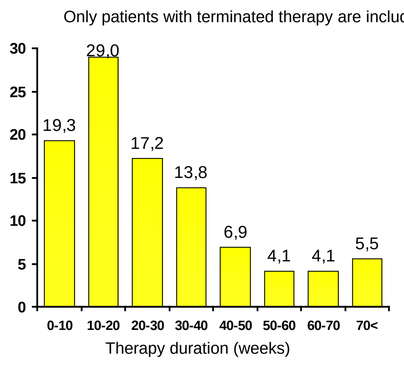
Lapatinib was administered with Capecitabine in 196 patients (92.0%), in 16 patients lapatinib was used in monotherapy, in one patient the treatment combination was not specified.
Lapatinib was used as a 2nd line treatment in 77 patients, as 3rd line in 65 and as 4th or further line in 53, 14 patients received lapatinib after failure of adjuvant trastuzumab therapy.

Line of therapy	N	%
I. line [1)]	14	6.7
II. line	77	36.8
III. line	65	31.1
Further line	53	25.4
Total [2)]	**209**	**100.0**



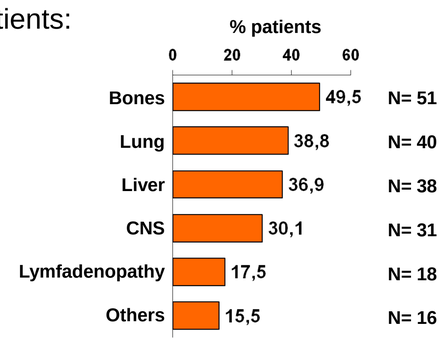
[1)] 14 patients had undergone trastuzumab (neo)adjuvant therapy prior to lapatinib treatment initiated in the I. line
[2)] Line of therapy was not available in 4 patients

Median duration of lapatinib therapy was 20.6 weeks (range 1 – 146 weeks).



Therapy duration	
N	145
Mean	26.9 weeks
Median	20.6 weeks
Min – Max	1 weeks – 146 weeks

Characteristics of distant metastases were evaluable in 103 patients:



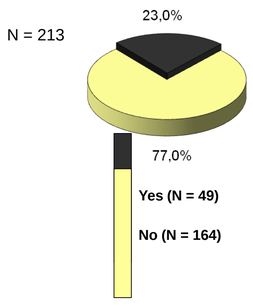
Some patients have more than one metastatic site.

Median was 60% LVEF before lapatinib treatment (range 48 – 90%, evaluated in 172 patients).

Results

Adverse events during therapy:

Occurrence of adverse events



Type of adverse events

Type of adverse events	N[1)]	% of total number of patients (N=213)
Diarrhoea	25	11.7
Skin toxicity	23	10.8
Nausea / vomiting	11	5.2
Hepatotoxicity	5	2.3
Paronychium	2	0.9
Dyspnoe	1	0.5
Other	3	1.4

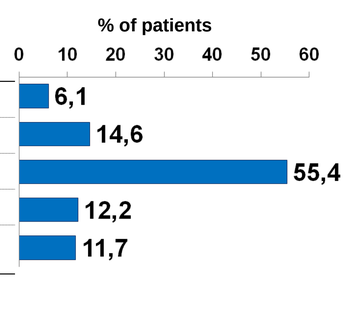
[1)] One patient can experience more adverse events.

No cardiac toxicity was reported. Therapy was terminated in 106 patients (73.1%) due to the disease progression and 10 patients (6.9%) died because of progressing disease. Thirteen patients (9.0%) discontinued therapy due to its toxicity. In for patients therapy ended after achieving complete or partial response.

Response to therapy:

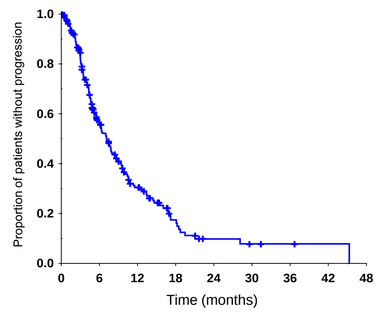
We evaluated the best response to lapatinib therapy. Complete response was achieved in 13 patients (6.1%), partial response in 31 patients (14.6%), producing ORR 20.7%. Stable disease was achieved in 118 patients (55.4%), in 26 patients disease did not respond and progressed (12.2%). In 25 patients the response could not be assessed (11.7%).

Therapy response	N	%
CR	13	6.1
PR	31	14.6
SD	118	55.4
PD	26	12.2
Unknown / Not yet available	25	11.7
Total	213	100.0



Survival results

Progression-free survival:

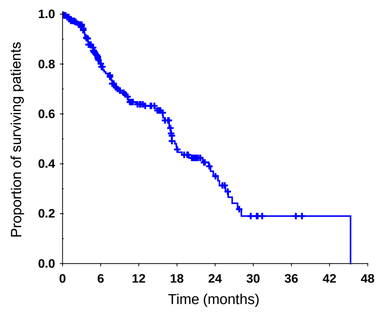


	N*=207
	PFS
Median PFS (95% CI)	**7.1 months** (5.8; 8.5)
	PFS (%, 95% CI)
6-month survival without progression	55.4 (48.1; 62.8)
1-year survival without progression	30.4 (23.1; 37.8)

* Appropriate data for progression free survival calculation was not available in 6 patients.

Patients' progression-free survival was assessed by Kaplan-Meier method.

Overall survival:



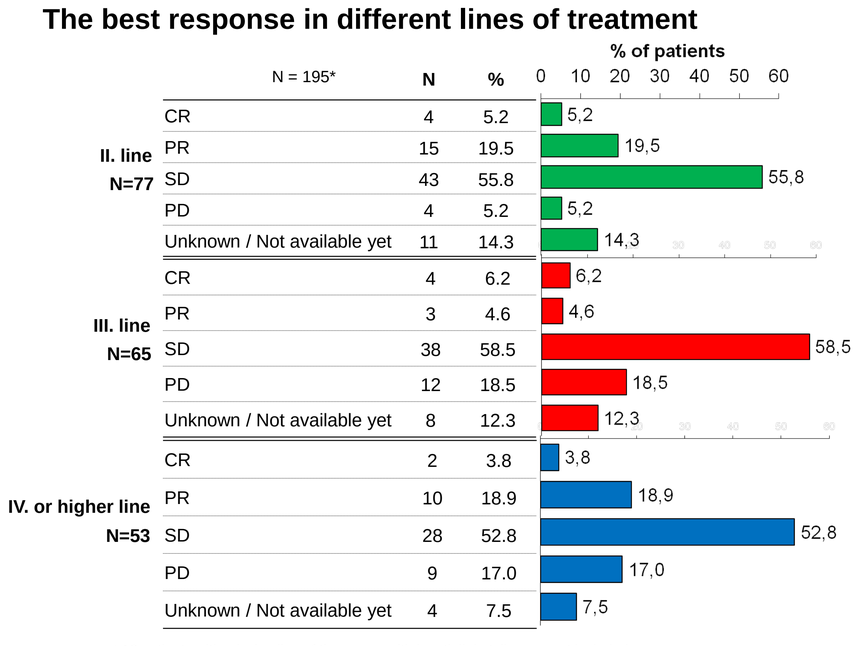
	N*=207
	Overall survival
Median survival (95% CI)	**17.2 months** (15.8; 18.6)
	Overall survival (%, 95% CI)
6-month survival	80.3 (74.3; 86.3)
1-year survival	64.0 (56.4; 71.6)

* Appropriate data for overall survival calculation was not available in 6 patients.

Patients' survival was assessed by Kaplan-Meier method.

Evaluation according to line of treatment:

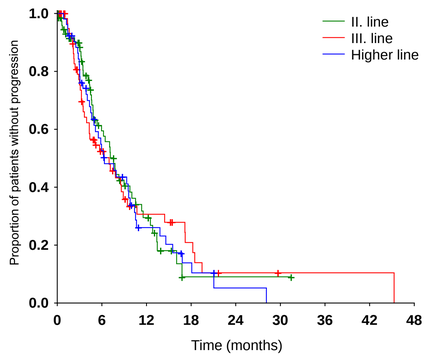
The best response in different lines of treatment



N = 195*	N	%
CR	4	5.2
PR	15	19.5
SD	43	55.8
PD	4	5.2
Unknown / Not available yet	11	14.3
CR	4	6.2
PR	3	4.6
SD	38	58.5
PD	12	18.5
Unknown / Not available yet	8	12.3
CR	2	3.8
PR	10	18.9
SD	28	52.8
PD	9	17.0
Unknown / Not available yet	4	7.5

* 18 patients with missing line of therapy or with lapatinib in I. line are not included.

Progression-free survival in different lines of treatment



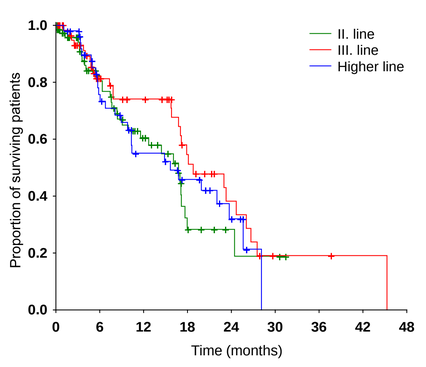
	N=191*
	Median PFS (95% CI)
II. line (N=76)	**7.6 months** (6.0; 9.1)
III. line (N=63)	**7.0 months** (3.5; 10.5)
Higher line (N=52)	**6.3 months** (3.8; 8.9)
	6-month survival without progression (%, 95% IS)
II. line (N=76)	59.5 (47.0; 71.9)
III. line (N=63)	52.5 (39.1; 65.9)
Higher line (N=52)	52.6 (38.5; 66.8)

Patients' progression-free survival was assessed by Kaplan-Meier method.

* 18 patients with missing line of therapy or with lapatinib in I. line are not included. Appropriate data for progression-free survival calculation was not available in 4 patients

The difference among groups of patients was tested by means of Log rank test. On the significance level α=0.05 there was no statistical significant difference, p=0.933

Overall survival in different lines of treatment



	N=191*
	Median survival (95% CI)
II. line (N=76)	**16.8 months** (12.0; 21.6)
III. line (N=63)	**18.8 months** (12.3; 25.3)
Higher line (N=52)	**15.7 months** (4.2; 27.1)
	1-year survival (%, 95% CI)
II. line (N=76)	60.5 (47.4; 73.7)
III. line (N=63)	74.1 (61.8; 86.5)
Higher line (N=52)	55.1 (39.8; 70.4)

Patients' survival was assessed by Kaplan-Meier method.

* 18 patients with missing information about line of therapy or with lapatinib in I. line are not included. Appropriate data for overall survival calculation was not available in 4 patients

The difference among groups of patients was tested by means of Log rank test. On the significance level α=0.05 there was no statistical significant difference, p=0.412

Results

- **Lapatinib with Capecitabine is an effective combination in trastuzumab pretreated metastatic HER2 positive breast cancer patients.**
- **Therapy was overall well tolerated.**
- **There were no significant differences in treatment outcome for different lines of treatment.**
- **Treatment specific registries are useful and feasible method for cancer treatment evaluation in standard clinical practice.**

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