OUR EXPERIENCES WITH ERLOTINIB IN SECOND AND THIRD LINE TREATMENT PATIENTS WITH ADVANCED STAGE IIIB/ IV NON-SMALL CELL LUNG CANCER

Interim Data Report of TRUST study on patients from Bosnia and Herzegovina

Bakir Mehić[1*], Mirko Stanetić[2],
Ljuljeta Tinjić[3], Vlatka Smoljanović[3]

[1] Clinic for Lung Diseases and Tuberculosis, University of Sarajevo Clinics Centre, Bardakčije 90, 71 000 Sarajevo, Bosnia and Herzegovina
[2] Clinical Centre Banja Luka, Clinic for Lung Diseases, Zdrave Korde 1, 78000 Banja Luka, Bosnia and Herzegovina
[3] Hoffmann-La Roche Ltd., Representative Office Bosnia and Herzegovina, Fra Anđela Zvizdovića 1, 71000 Sarajevo, Bosnia and Herzegovina
[*] Corresponding author

Abstract

HeadHER1/EGFR is known to play a pivotal role in tumorigenesis and is overexpressed in up to 80% of NSCLCs. The study of an Expanded Access Clinical Program of Erlotinib in NSCLC is a phase IV open-label, non-randomized, multicenter trial in patients with advanced (inoperable stage IIIb/IV) NSCLC who were eligible for treatment with erlotinib but had no access to trial participation. Patients for the study from Bosnia and Herzegovina (B&H) were selected from two Clinical centres (Sarajevo and Banja Luka). The aim of study was to evaluated efficacy and tolerability of erlotinib monotherapy in this setting. All patients who received at least one dose of erlotinib and data were entered in the database as of the CRF cut-off date of 14th May 2008 were included in analysis of data (n = 19). This population is defined as the Intent to Treat (ITT) population and includes all patients who had at least one dose of erlotinib regardless of whether major protocol violations were incurred. The findings are consistent with the results of the randomized, placebo-controlled BR.21 study. Indicating that erlotinib is an effective option for patients with advanced NSCLC who are unsuitable for, or who have previously failed standard chemotherapy. In B&H group of patients DCR was almost 84%, and PFS was approximately 24,7 weeks (compared with 44% and 9,7 weeks for erlotinib reported in phase III). Almost three quarter of the patients received erlotinib as their second line of therapy. Overall, erlotinib was well tolerated; there were no patients who withdrew due to a treatment-related AE (mainly rash) and there were few dose reductions. 24% of patients experienced an SAE (most commonly gastrointestinal (GI) disorders).

KEY WORDS: epidermal growth factor receptor, erlotinib, non small-cell lung cancer, Interim Data Report, TRUST study, Bosnia and Herzegovina

Introduction

The treatment of advanced non-small cell lung cancer (NSCLC) has evolved substantially over the past decade. Chemotherapy with a platinum based doublet prolongs survival and improves quality of life in patients with good performance status (PS). A number of malignancies are associated with aberrant- or over-expression of the EGFR. EGFR serves as a target for therapeutic intervention in NSCLC and may be a target in several other tumour types, including breast carcinoma, and a variety of squamous cell carcinomas. Erlotinib is an orally active, potent, and highly selective inhibitor of human epidermal growth factor receptor tyrosine-kinase (TK) activity. A large, phase III trial (BR.21), first presented at ASCO in 2004, showed that as a single agent, second- or third-line erlotinib (150 mg/day) significantly prolonged survival and delayed symptom deterioration in patients with advanced NSCLC (1). These results confirm the therapeutic value of HER1/EGFR inhibition; HER1/EGFR is known to play a pivotal role in tumorigenesis (2–4) and is overexpressed in up to 80% of NSCLCs (5,6). The objective of our work is to evaluate the impact of clinical characteristics on efficacy with erlotinib, among patients with advanced stage IIIB/ IV NSCLC who were eligible for treatment with erlotinib but had no access to trial participation.

Patients and Methods

Phase IV, open-label, single-arm, multi-centre trial in patients with advanced, inoperable, stage IIIB/ IV NSCLC who were eligible for treatment with erlotinib but had no access to trial participation.

Patients ≥18 years with histologically or cytologically confirmed, advanced, unresectable, stage IIIb/IV NSCLC, measurable or non-measurable disease, ECOG PS of 0–3, life expectancy of at least 12 weeks, received at least one course of standard treatment (chemotherapy or radiotherapy) or are unsuitable for standard treatment (chemotherapy or radiotherapy), had no more than two prior chemotherapy regimens; patients must have recovered from toxicities of any prior therapy ≥3–4 weeks since last dose, patients fully recovered from surgery in <4 weeks may be considered, having adequate hematologic, renal, and hepatic function, present negative pregnancy test for women of childbearing potential. Any unstable systemic disease, prior therapy with HER1/EGFR inhibitor (small molecule or monoclonal antibody), any other malignancies within 5 years (except for adequately treated cervical carcinoma or skin cancer), newly diagnosed and/or untreated brain metastases or spinal cord compression, any significant ophthalmologic abnormality.

Patients received oral erlotinib (150 mg/day) until unacceptable toxicity or disease progression. Dose interruption or dose reduction (to 100 mg/day, then 50 mg/day) was permitted for drug related AEs.

Tumour response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST), as per institutional standards (no less than every 2 months). For responding patients, confirmatory evaluation was to be performed 4 weeks after response determined. Clinical and laboratory assessments were conducted at baseline and every 4 weeks during the study. AEs were assessed and graded according to v 3.0 (NCI-CTC). SAS v.8.2 was used for (statistical) analysis and reporting of the data collected for this study.

Results

All patients who received at least one dose of erlotinib and for whom monitored CRF data were available in

		Bosnia and Herzegovina	
		n	**(%)**
Characteristic	**Total number of patients**	**19**	
Age (years)	Median	57	
	Minimum	50	
	Maximum	77	
Gender	Male	16	(84)
	Female	3	(16)
Ethnic origin	Caucasian/white	19	(100)
ECOG Performance Status	0	5	(26)
	1	11	(58)
	2	3	(16)
	3	0	(0)
Stage	Stage III B	13	(68)
	Stage IV	6	(32)
Histology	Adenocarcinoma	5	(26)
	Bronchoalveolar ca.	0	(0)
	Large cell carcinoma	0	(0)
	Squamous cell ca.	14	(74)
Prior Chemotherapy	Erlotinib first line	2	(11)
	Erlotinib second line	15	(79)
	Erlotinib third line	2	(11)
Smoking status	Non-smoker	1	(5)
	Former or Current smoker	18	(95)

TABLE 1. The baseline patients characteristics

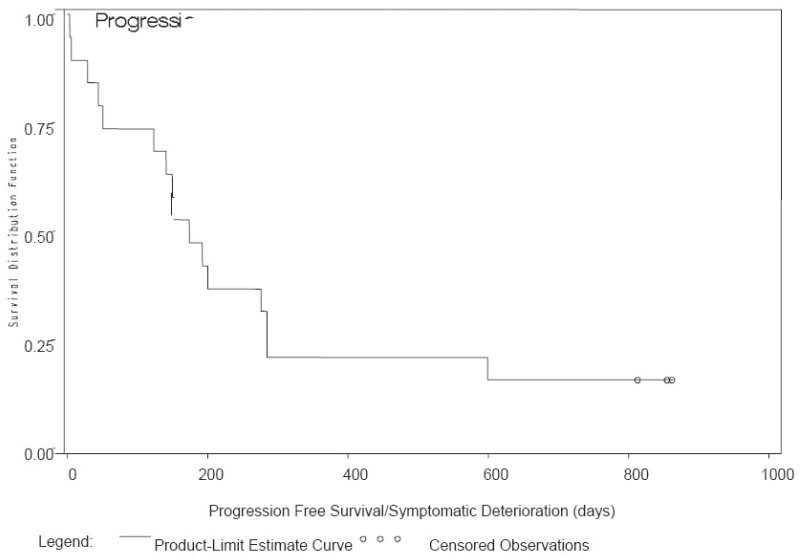

FIGURE 1. Kaplan-Meier Curve for Progression Free Survival/Symptomatic Deterioration (Days)

Data Management and entered in the database as of the CRF cut-off date of 14th May 2008 were included in analysis of data (n = 19). This population is defined as the ITT population and includes all patients who had at least one dose of erlotinib regardless of whether major protocol violations were incurred. Registered patients who did not start treatment with erlotinib for whatever reason (i.e., screen failures) were removed from this Interim Analysis. At the time of the data cut-off, 16 patients had discontinued study treatment and 3 patients (16%) were still ongoing (non-progressive) in TRUST. At the time of the data entry freeze date of 14th May 2008, a total of 19 patients, out of 19 patients registered in TRUST Bosnia and Herzegovina. The baseline patients and disease characteristics of 19 assessable patients are listed in Table 1. The analysis of tumour response is based on the best overall response, according to RECIST criteria. Best Response as per investigators assessment, is presented in Table 2 and excludes those patients with response as "no data" and/or "not done". The second PFS curve includes all patients with PD plus those patients with clinical progression who discontinued due to 'Symptomatic Deterioration' (Table 3, Figure 1). By the time of data cut-off, 3 patients (15,8%) had neither died nor progressed during treatment. PFS data for

Best Response to Therapy	**n = 17**	**(%)**
CR	0	(0)
PR	2	(10,5)
SD	14	(73,5)
PD	1	(5)
RESPONSE "no data" and/or "not done"	2	(10,5)
DISEASE CONTROL RATE (CR+PR+SD)	16/17	(84)

TABLE 2. Best Response (excluding patients without any response data)

		n = 19	
Patients with event		16	
Patients without event (censored)		3	
Percent censored		15,79	
Progression Free Survival	**Days**	**Weeks**	**Months**
Median Progression Free Survival	173	24,7	5.68
95% CI for Median#	123 - 284	17,6 – 40,6	4,04 – 9,33
25% and 75%-ile	50, 284	7,1, 40,6	1,64, 9,33
Range##	3 - 862*	0,4 – 123,1*	0,10 – 28,32*

 # Kaplan-Meier estimate
including censored observations * censored observations

TABLE 3. Progression Free Survival (PD patients according to RECIST + clinical progression patients)

	n = 19		
Patients with event	14		
Patients without event (censored)	5**		
Percent censored	26,32		
	Days	**Weeks**	**Months**
Median Survival	**283**	**40.4**	**9.30**
95% CI for Median#	199 - 521	28,4 - 74,4	6,54 - 17,12
25% and 75%-ile	98, 521	14.0, 74.4	3,22, 17,12
Range##	3 - 862*	0,4 - 123,1*	0,10 - 28,32*
1 Year Survival Rate (%)		**36,8**	
95% CI 1 Year Survival Rate		13,8 - 59,9	

Kaplan-Meier estimate
including censored observations * censored observations
***** Out of the 5 patients without event two patients were recorded as lost to follow up.***

TABLE 4. Overall Survival

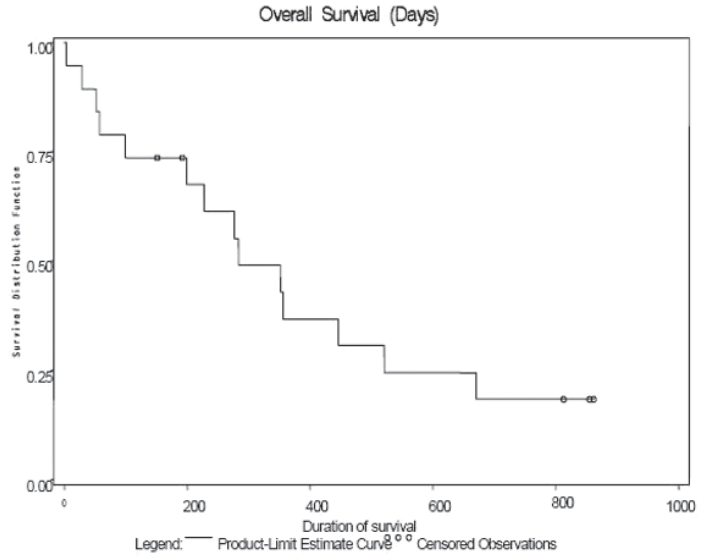

FIGURE 2. Kaplan-Meier Curve for Overall Survival (Days)

these patients was censored at the date of last contact. The survival analysis is based on 19 patients. Those who had not died at the time of the data cut-off were censored at the date of last contact (n = 5). In this study we followed the date of registration as a first date of survival of patients on erlotinib treatment. The data of overall survival are shown in Table 4 and Figure 2. Adverse events (per preferred term) observed during treatment graded using Common Toxicity Criteria (CTCAE v3.0) of US-NCI (Table 5). The following safety data were collected: incidence of erlotinib-related rash, Serious Adverse Events (SAEs), Adverse Events (AEs) and unexpected erlotinib-related AEs are not described in population of B&H patients. Rash: 24% of patients experienced a rash, of which 12% were grade 5 (Table 5). SAEs: 24% of patients experienced an SAE (Table 5), most commonly GI disorders (4 patients). Dose reductions: 12% of patients had dose reductions due to an erlotinib-related event. The unique reasons were rash (12%). Withdrawals: There were no patients withdrawing from treatment due to therapy related AE's (Table 5). Specifications for ending treatment are shown in Table 6.

Discussion

Several studies have investigated the effect of targeted therapies as monotherapy or in combination with chemotherapy in the second or third line setting. A large phase III study BR.21 (1) has reported the benefit of erlotinib monotherapy in patients with advanced refractory NSCLC who were ineligible for further chemotherapy. There were shown (Table 7) the results of comparison the interim efficacy analysis of global phase IV trial, that reflect the clinical experience with erlotinib in more than 6000 unselected patients with advanced NSCLC, from 552 centres in 52 countries worldwide (7), the results of landmark trial BR.21 (1), and interim efficacy analysis of TRUST patients from Bosnia and Herzegovina.

	n = 17	**%**
Patients with at least one AE	4	(24)
AEs Regardless of Causality by worst severity	2	(10,5)
Grade 3	1	(6)
Grade 4	1	(6)
Grade 5	2	(12)
Patients with at least one Erlotinib-Related AE Other than the 15 Most Frequently Occurring	0	(0)
Erlotinib-Related AE Other than the 15 Most Frequently Occurring by worst severity		
Patients with at least one SAE	4	(24)
Patients with at least one treatment-related SAE	1	(6)
Patients who discontinued study due to treatment-related AEs	0	(0)
Patients who died on treatment or within 30 days after treatment end	4	(24)
Patients who died due to a treatment-related AE	0	(0)

TABLE 5. Overall Summary of Safety

Reason End of Treatment	n	(%)
Total patients with specification for ending treatment	16	(100)
Progressive disease (PD)	10	(63)
Symptomatic deterioration	4	(25)
Lost to follow-up	1	(6)
Study drug related adverse event	0	(0)
Patient refusal	0	(0)
Death	0	(0)
Death due to malignant disease	0	(0)
Death due to toxicity	0	(0)
Death due to other reason (Pulmonary embolism)	1	(6)
Other	0	(0)

TABLE 6. Reason for End of Treatment

Study	MPFS* (weeks)	1-year survival (%)	DCR** (%)	ORR*** (%)
BR.21	9,7	31,2	44	8.9
Interim analysis of TRUST	14,3		69	13
Interim analysis B&H patients from TRUST	24,7	36,8	84	10,5

***Median Progression Free Survival**
****Disease Control Rate**
*****Overall Response Rate**

TABLE 7. Comparison of efficacy

Conclusion

The results of Interim Data Report of TRUST study on patients from Bosnia and Herzegovina reflect clinical experience with erlotinib in 19 unselected patients with advanced NSCLC. The findings are consistent with the positive results of the randomized, placebo-controlled BR.21 study: Indicating that erlotinib is an effective option for patients with advanced NSCLC who are unsuitable for, or who have previously failed on, standard chemotherapy. In B&H group of patients DCR was almost 84%, and PFS was approximately 24,7 weeks (compared with 44% and 9,7 weeks for erlotinib reported in the phase III setting) (1). Almost three quarter of the patients received erlotinib as their second line of therapy; Overall, erlotinib was well tolerated; there were no patients who withdrew due to a treatment-related AE (mainly rash) and there were few dose reductions. 24% of patients experienced an SAE (most commonly gastrointestinal (GI) disorders).

List of Abbreviations

HER1/EGFR	-	Epidermal Growth Factor Receptor
CRF	-	Complete Report Form
DCR	-	Disease Control Rate
PFS	-	Progression Free Survival
AEs	-	Adverse Events
SAEs	-	Serious Adverse Events
ASCO	-	American Society of Clinical Oncology
NCI-CTC	-	National Cancer Institute-Common Toxicity Criteria
US-NCI	-	United States-National Cancer Institute
ECOG	-	Eastern Cooperative Oncology Group
CR	-	Complete Response
PR	-	Partial Response
SD	-	Stable Disease
PD	-	Progressive Disease

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