EFFICACY OF ERLOTINIB IN PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) RELATIVE TO CLINICAL CHARACTERISTICS: SUBSET ANALYSES FROM THE TRUST STUDY

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Updated abstract

Background: Erlotinib is proven to prolong survival, delay symptom progression and improve quality of life for pts with advanced NSCLC (Shepherd et al. N Engl J Med 2005;353:123–32). The global, non-randomized, open-label phase IV TRUST study of erlotinib recruited over 7,000 pts across 52 countries.

Methods: Pts with stage IIIB/IV NSCLC who had previously failed on, or were unsuitable for, chemo-/radiotherapy received erlotinib 150mg/d p.o. until disease progression or unacceptable toxicity.

Results: At data cut-off on February 27, 2008, data were available for 6,809 pts in the study; these data were analyzed by gender, histology and smoking status. Disease control rate (DCR) and progression-free survival (PFS) are shown in the table for six subgroups. DCR was consistent across 2nd- and 3rd-line pts in all groups; only group 5 showed any statistically significant difference between 2nd-line and 3rd-line pts in terms of PFS: 13.1 wks vs 8.9 wks, respectively (p=0.0035). Overall survival (OS) data are mature for groups 1 and 5 only; group 1 had median OS of 6.04 mos while group 5 had median OS of 5.58 mos, i.e. no difference between male and female current/former smokers (C/FS) with squamous-cell carcinoma (SqCC). Among pts with non-squamous tumors, never smokers (NS) appear to derive a greater clinical benefit than C/FS. Prognostic and predictive value could not be differentiated in this study as there was no control arm.

Conclusions: These data confirm the results of the phase III BR.21 study, i.e. a wide range of pt subgroups can derive a clinical benefit from erlotinib. No differences were found in DCR between pts treated in 2nd and 3rd line but some subgroups may derive a greater survival benefit when receiving erlotinib 2nd line. These data indicate that pts should not be excluded from receiving erlotinib based on clinical characteristics.

	Group 1 (male C/FS with SqCC)	Group 2 (male NS with SqCC)	Group 3 (male C/FS with non-squamous tumors)	Group 4 (male NS with non-squamous tumors)	Group 5 (female C/FS with SqCC)	Group 6 (female NS with non-squamous tumors)
DCR (CR+ PR+SD), %	69 (<1+46+53) n=973	59 (1+13+44) n=82	64 (<1+8+55) n=1,791	75 (2+18+56) n=426	63 (0+4+59) n=162	80 (2+25+53) n=1,216
PFS, wks	12.4 n=1,205	10.1 n=101	11.9 n=2,292	25.3 n=510	10.3 n=204	30.0 n=1,364

Introduction

- Erlotinib is a potent, orally administered, human epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) that has been proven to prolong survival, delay symptom progression and improve quality of life (QoL) versus placebo in patients with previously treated, advanced NSCLC in a large phase III trial (BR.21).[1,2]
- It has been reported that, among patients with NSCLC, those with adenocarcinoma, women and never smokers are more likely to have tumor responses to EGFR TKIs than other patients.[3-5] Patients with activating mutations in the EGFR TK domain also appear more likely to have tumor responses, such mutations being more common among Asians, non-smokers, women, and patients with adenocarcinoma.[6-8]
- In the BR.21 study, gender and histology were found to be strong prognostic factors, but neither was predictive of a differential survival benefit with erlotinib compared with placebo.[1,9] Smoking history was the only significant predictive factor; never smokers experienced an enhanced benefit from erlotinib compared with placebo, although male current or former smokers with squamous-cell carcinoma nevertheless had a statistically significant survival benefit.[10]
- The global TRUST study provided access to erlotinib for suitable patients in countries prior to licensing, and provided an opportunity to assess the efficacy and safety of erlotinib in a large, global patient population
  - 7,043 patients were enrolled into the open-label, single-arm study at 552 centers in 52 countries worldwide.
- The study also provided an opportunity to evaluate clinical outcomes with erlotinib among certain patient subgroups presumed to be predisposed to beneficial or detrimental outcomes during treatment with EGFR TKIs (albeit in an uncontrolled setting).

Objective

- To evaluate the impact of specific clinical characteristics on efficacy outcomes with erlotinib, among patients with advanced stage IIIB/IV NSCLC who had previously failed on (or were considered unsuitable to receive) standard chemotherapy or radiotherapy.

Methods

Trial design

- Phase IV, open-label, single-arm, multi-center trial in patients with advanced, inoperable, stage IIIB/IV NSCLC who are unsuitable for (or have previously failed on) standard chemotherapy or radiotherapy.

Main inclusion and exclusion criteria

- Inclusion criteria
  - age ≥18 years
  - histologically or cytologically confirmed, unresectable stage IIIB/IV NSCLC
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–3
  - adequate hematologic, renal, and hepatic function
  - life expectancy ≥12 weeks
  - previously received at least one course of standard chemotherapy or radiotherapy, but not more than two chemotherapy regimens (or considered unsuitable for such treatment)
  - at least 3–4 weeks since most recent previous treatment, and fully recovered from related toxicities (patients having had surgery less than 4 weeks previously were considered if fully recovered)
  - negative pregnancy test for women of child-bearing potential.
- Exclusion criteria
  - evidence of unstable systemic disease
  - prior treatment with anti-EGFR agents (either small molecules or monoclonal antibodies)
  - other malignancies in the previous 5 years (except successfully treated cervical carcinoma or skin cancer)
  - untreated brain metastases (newly diagnosed or existing) or spinal cord compression
  - significant ophthalmologic abnormalities.

Study treatment

- Erlotinib (150mg/day, orally [p.o.]) was administered once daily (at least 1 hour before or 2 hours after food) to all patients until unacceptable toxicity, disease progression, or death.
- Dose interruption or reduction (to 100mg/day, then 50mg/day) was permitted in the event of treatment-related adverse events (AEs).

Assessments

- Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST), at least every 2 months. For responders, a confirmatory evaluation was carried out 4 weeks after the initial determination of response.
- Clinical and laboratory assessments were conducted at baseline and then at 4-week intervals throughout the study.

Results

- Enrollment ceased on May 31 2007. At the time of data cut-off for this analysis (February 27 2008), 6,425 patients had discontinued erlotinib treatment; 384 (5.6%) had not progressed and were continuing to receive erlotinib.
- Case report forms (CRFs) were available for 6,809 patients in the intent-to-treat (ITT) population.
- This is an interim analysis of a large, ongoing trial. Consequently, there are some differences between the numbers available for each analysis, subject to the patients' treatment status and the information available on the CRFs received as of February 27 2008.
- The baseline characteristics of the patients are shown in Table 1
  - two-thirds of the patients were male, and almost three quarters were Caucasian/white. Most (~70%) were former or current smokers, and a large majority had non-squamous tumors.
  - almost 80% of patients had stage IV disease, and more than 70% were PS 0–1. Approximately half (49%) received erlotinib as the second line of therapy.

Efficacy (all patients)

- Best response to erlotinib therapy is shown in Table 3. The overall response rate was approximately 13%, while the disease control rate (DCR) at the time of this analysis was 69%.
- By the time of data cut-off, 843 patients (12%) had neither died nor progressed during treatment. Progression-free survival (PFS) data for these patients was censored at the date of last contact. Median PFS (based on RECIST) was 14.3 weeks (95% CI: 13.6–15.0); see Figure 1. Overall survival data was not mature (>25% censored observations).

Efficacy in the second-line setting

- The baseline characteristics of patients who received erlotinib as second-line therapy (n=3,338; 49%) were comparable to those of the overall group (data not shown).
- Outcomes among these patients were very similar to those achieved in the whole group. Thus, the response rate in this setting was approximately 14%, and the DCR was 68%. Median PFS was 14.0 weeks (95% CI: 13.0–15.1).

Table 1. Baseline patient characteristics: all patients (n=6,809)

Characteristic	Subgroup	Age (median [range]; years) 63 (19–96) n	%
Gender	Male	4,121	61
	Female	2,687	39
	No data	1	<1
Ethnic origin	Caucasian	4,976	73
	Black	29	<1
	Oriental	1,340	20
	Other	454	7
	No data	10	<1
Histology	Adenocarcinoma	3,276	55
	Bronchioloalveolar carcinoma	374	5
	Large-cell carcinoma	387	6
	Squamous cell carcinoma	1,618	24
	Other	694	10
	No data	10	<1
Smoking status	Never-smoker	2,083	31
	Former/current smoker	4,708	69
	No data	18	<1
ECOG PS	0	1,515	22
	1	3,573	52
	2	1,302	19
	3	411	6
	No data	8	<1
Disease stage	Stage IIIB	1,477	22
	Stage IV	5,290	78
	No data	17	<1
Previous lines of chemotherapy	0	926	14
	1	3,338	49
	2	2,488	37
	Other	54	<1
	No data	3	<1

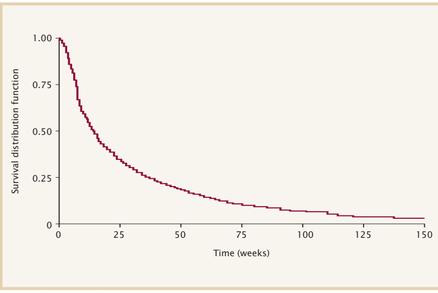


Figure 1. PFS: all patients.

Efficacy outcomes according to gender, histology and smoking status

- The baseline characteristics of specific patient subgroups (selected on the basis of gender, histology and smoking status) are summarized in Table 2. There were some notable differences between the baseline characteristics of the different subgroups. For example, the proportion of patients of Oriental ethnicity in group 6 was 40%, compared with 5% in group 5. This and other differences may have had an influence on the differences between the clinical outcomes for the various subgroups investigated.
- The best response data for erlotinib in the subgroups is shown in Table 3. Tumor response rate varied considerably between the different subgroups, from 4% in female current/former smokers with squamous-cell carcinoma, to 27% in never-smoking women with non-squamous tumors. There was also notable variability in DCR, which ranged from 59% in male never smokers with squamous tumors to 80% in female never smokers with non-squamous tumors.

Table 2. Baseline patient characteristics: analysis subgroups

n	Total study population*	1 Male C/F smoker SqCC 1,205		2 Male never smoker SqCC 101		3 Male C/F smoker non-squamous 2,292		4 Male never smoker non-squamous 511		5 Female C/F smoker SqCC 204		6 Female never smoker non-squamous 1,365	
Age (median [range]; years)		65 (29–92)		65 (29–83)		63 (22–96)		62 (19–90)		64 (35–86)		62 (22–91)	
	%	n	%	n	%	n	%	n	%	n	%	n	%
Ethnic origin													
Caucasian	73	965	80	76	75	1,748	76	306	60	180	88	710	52
Black	<1	3	<1	2	2	12	<1	3	<1	0	–	4	<1
Oriental	20	177	15	17	17	375	16	155	30	10	5	530	39
Other	7	59	5	6	6	156	7	43	8	13	6	120	9
No data	<1	1	<1	0	–	1	<1	4	<1	1	<1	1	<1
ECOG PS													
0	22	223	19	14	14	513	22	135	26	45	22	324	24
1	52	624	52	68	67	1,186	52	274	54	98(48)	48	719	53
2	19	282	23	17	17	456	20	72	14	44	22	239	18
3	6	75	6	2	2	133	6	29	6	17	8	83	6
No data	<1	1	<1	0	–	4	<1	1	<1	0	–	0	–
Disease stage													
Stage IIIB	22	410	34	29	29	412	18	87	17	68	33	261	19
Stage IV	78	790	66	72	71	1,866	81	419	82	133	65	1,095	80
Other	–	3	<1	0	–	5	<1	2	<1	3	1	2	<1
No data	<1	2	<1	0	–	9	<1	3	<1	0	–	7	<1
Previous lines of chemotherapy													
0	14	124	10	12	12	294	13	64	13	30	15	234	17
1	49	560	46	58	57	1,108	48	263	51	93	46	682	50
2	37	513	43	30	30	871	38	180	35	77	38	440	32
Other	<1	8	<1	1	<1	19	<1	4	<1	4	2	7	<1
No data	<1	0	0	0	–	0	–	0	–	0	–	2	<1

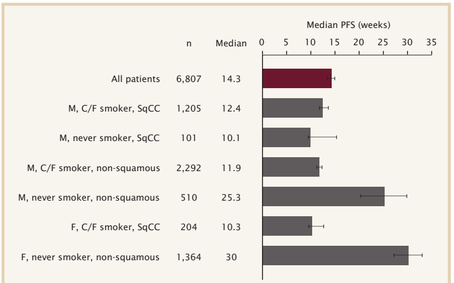
*Included for comparison
C/F = current/former; SqCC = squamous cell carcinoma; PS = performance status

Table 3. Best response to erlotinib for all patients and specific subgroups

n°	All patients 5,567		Male C/F smoker SqCC 973		Male never smoker SqCC 82		Male C/F smoker non-squamous 1,791		Male never smoker non-squamous 426		Female C/F smoker SqCC 162		Female never smoker non-squamous 1,216	
Best response	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Complete response	47	<1	1	<1	1	1	6	<1	8	2	0	0	25	2
Partial response	672	12	43	4	11	13	148	8	76	18	7	4	299	25
Stable disease	3,110	56	632	65	36	44	991	55	237	56	95	59	645	53
Progressive disease	1,495	27	246	25	29	35	565	32	84	20	57	35	209	17
Not evaluable	243	4	51	5	5	6	81	5	21	5	3	2	38	3
Response rate	–	13	–	5	–	14	–	9	–	20	–	4	–	27
Disease control rate	–	69	–	69	–	59	–	64	–	75	–	63	–	80

*Excluding patients with no response data available

- Median PFS for the various subgroups is shown in Figure 2. While some subgroups showed particularly long PFS (e.g. 30 weeks in never-smoking women with non-squamous tumors), in none of the subgroups was PFS less than 10 weeks.
- Overall survival data were mature (<25% censored observations) for only two subgroups
  - male current/former smokers with squamous-cell carcinoma; median 6.04 months (95% CI: 5.49–6.50)
  - female current/former smokers with squamous-cell carcinoma; median 5.58 months (95% CI: 4.40–6.57).



C/F = current/former; SqCC = squamous-cell carcinoma; F = female; M = male

Figure 2. PFS according to patient characteristics.

Summary and conclusion

- The results of this global phase IV trial reflect clinical experience with erlotinib in more than 6,000 unselected patients with advanced NSCLC. The findings are consistent with the positive results of the randomized, placebo-controlled BR.21 study,[1] indicating that erlotinib is an effective option for patients with advanced NSCLC who are unsuitable for, or who have previously failed on, standard chemotherapy
  - DCR was almost 70%, and PFS was approximately 14.3 weeks (compared with 45% and 9.7 weeks for erlotinib reported in the phase III setting[11])
  - almost one half of the patients received erlotinib as their second line of therapy; outcomes on erlotinib among these patients were very similar to those for the overall patient population.
- The results also suggest that clinical benefits can be achieved with erlotinib in a wide range of patients, including groups with characteristics that have previously been assumed to predispose against beneficial outcomes during treatment with TKIs
  - although response rates were particularly high for some groups (never smokers with non-squamous tumors), and low for others (current/former smokers with squamous-cell carcinoma) the DCR was at least 59% in all subgroups
  - median PFS was not less than 10 weeks in any of the subgroups investigated. This compares favorably with the 8.0 weeks reported for the placebo arm of the BR.21 trial[11] suggesting that all subgroups were likely to have achieved some benefit from treatment with erlotinib
    - however, the uncontrolled nature of the study meant that possible prognostic and predictive effects of particular patient characteristics could not be identified or distinguished
  - there was no evidence to suggest that any particular patient characteristic predisposes against achieving a clinical benefit with erlotinib, or to support exclusion of particular patient groups from treatment on the basis of such characteristics. In none of the subgroups was PFS substantially shorter than that for the overall study population.

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