Overall survival analyses of first-line erlotinib versus chemotherapy in the EURTAC study population controlling for the use of post-study therapy

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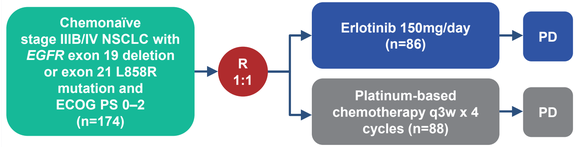
INTRODUCTION

- Overall survival (OS), defined as the time from randomisation to death from any cause, is considered the gold-standard endpoint for randomised trials in lung cancer, as OS is easily measured, unambiguous and clinically relevant[1]
  - however, disadvantages of OS as an endpoint include the need for long-term follow-up, large patient numbers, the potential confounding effects of successive treatment lines and the increase in non-cancer deaths during long follow-up periods.[2]
- OS as an endpoint in trials of first-line therapy is particularly challenging due to the effect of post-study therapy (PST)
  - OS benefit may not be observed despite a clear benefit in progression-free survival
  - this leads to uncertainty regarding an agent's true efficacy.
- This exploratory analysis of the first-line EURTAC study assesses the effect of erlotinib on OS in epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC), using statistical models to control for second-line PST use.

METHODS

- EURTAC recruited patients from 42 hospitals across France, Italy and Spain between February 2007 and January 2011.
- Patients with *EGFR* mutation-positive NSCLC were randomised 1:1 to receive once-daily erlotinib or up to 4 cycles of chemotherapy in the first-line setting (**Figure 1**).[3]

Figure 1. Study design



ECOG PS, Eastern Cooperative Oncology Group performance status; PD, disease progression; q3w, every 3 weeks

- In this analysis, three statistical methods controlled for PST use
  - the first two approaches focus on second-line PST, defined as any anticancer therapy initiated post-PD
  - the third approach accounts for treatment cross-over, PST use initiated either pre-PD or post-PD, where cross-over for the chemotherapy group is defined as initiation of a tyrosine kinase inhibitor (TKI) therapy, and cross-over for the erlotinib group is defined as initiation of a non-TKI therapy.
- Approach 1 was based on censoring patients at the time they initiated second-line therapy (standard Cox models and Kaplan–Meier were applied); by censoring patients in this manner, only the follow-up time during which they were 'unexposed' to second-line therapy was evaluated.
- In approach 2, Cox models were applied where second-line therapy exposure was incorporated as a time-dependent covariate
  - patients who initiated second-line therapy were considered 'unexposed' to second-line therapy at follow-up times prior to their date of second-line initiation and 'exposed' at follow-up times after starting second-line therapy
  - the impact of second-line therapy was adjusted for in the Cox model through this time-dependent covariate, which reflects if and when patients initiate second-line therapy during their follow-up time course
  - unlike the first approach, patients are not censored due to second-line therapy initiation, and their entire follow-up time course is evaluated.
- Approach 3 accounts for pre-PD or post-PD treatment crossover
  - since cross-over can occur either prior to or after PD, a more dynamic modelling approach is necessary to incorporate patients' PD status across their follow-up; here we apply the marginal structural modelling (MSM) methodology.[4]

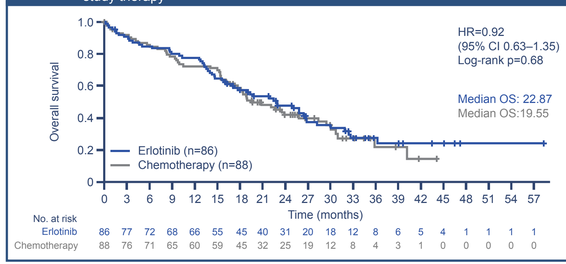
RESULTS

- Baseline characteristics were balanced between the two arms (erlotinib n=86; chemotherapy n=88 comprising 87 randomised patients and 1 patient enrolled then treated with chemotherapy prior to randomisation, **Table 1**).
- In the OS analysis (data cut-off 11 April 2012) in which PST was not controlled for, the hazard ratio (HR; erlotinib vs chemotherapy) for OS was 0.92 (95% confidence interval [CI] 0.63–1.35, p=0.68; median 22.9 months versus 19.6 months for erlotinib versus chemotherapy; **Figure 2**).
- When adjusted for baseline factors (age, gender, ECOG PS, smoking history and *EGFR* mutation type), the HR was 0.86 (95% CI 0.58–1.27).

Table 1. Baseline characteristics of the EURTAC population for analysis of OS with PST controlled for by statistical models

Characteristics	Erlotinib N=86	Chemotherapy N=88
Median age, years (range)	65.0 (24.0–82.0)	64.5 (29.0–82.0)
Race, n (%)		
Caucasian	86 (100)	86 (98)
Other	0 (0)	2 (2)
Gender, n (%)		
Male	28 (33)	20 (23)
Female	58 (67)	68 (77)
Smoking status, n (%)		
Current	7 (8)	12 (14)
Former	22 (26)	13 (15)
Never	57 (66)	63 (72)
ECOG PS, n (%)		
0	27 (31)	31 (35)
1	47 (55)	45 (51)
2	12 (14)	12 (14)
EGFR mutation type, n (%)		
Exon 19 deletion	57 (66)	58 (66)
Exon 21 L858R	29 (34)	30 (34)

Figure 2. Kaplan–Meier curve for OS in the EURTAC population not controlled for post-study therapy



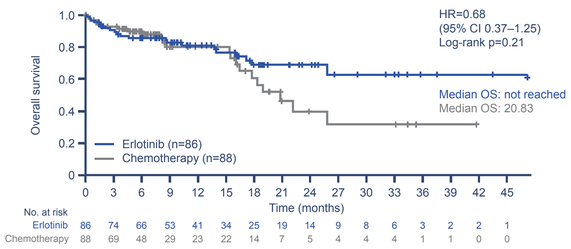
- A total of 58% of patients received any second-line PST (**Table 2**)
  - TKIs were received by 37% of the erlotinib arm and 64% of the chemotherapy arm; platinum-based compounds were used by 48% of the erlotinib arm and 4% of the chemotherapy arm; and antimetabolites were used in 43% of erlotinib patients and 18% of chemotherapy patients.

Table 2. Any second-line post-study treatment received by the EURTAC population

Second-line agent, n (%)	Erlotinib N=86	Chemotherapy N=88
Gemcitabine	10 (12)	1 (1)
Gemcitabine hydrochloride	1 (1)	0 (0)
Pemetrexed	37 (43)	16 (18)
Carboplatin	16 (19)	3 (3)
Cisplatin	25 (29)	1 (1)
Afatinib	8 (10)	3 (3)
Erlotinib	15 (17)	49 (56)
Gefitinib	9 (10)	4 (5)

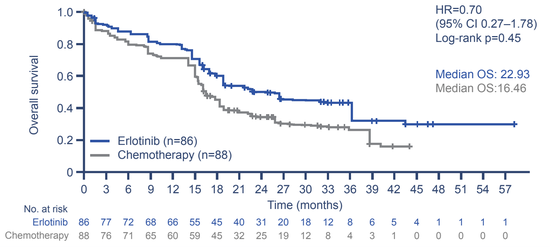
- Median time to earliest initiation of second-line PST from time of disease progression (n=117 experienced progression, n=102 used second-line post-study therapy) was 0.85 months for erlotinib and 0.36 months for chemotherapy.
- Using approach 1, the HR for OS was 0.68 (95% CI 0.37–1.25, p=0.21). Median OS was not reached with erlotinib and was 20.8 months with chemotherapy (**Figure 3**)
  - the adjusted HR for approach 1 was 0.63 (95% CI 0.34–1.19).

Figure 3. Kaplan–Meier curves for OS with second-line post-study therapy controlled by approach 1



- Using approach 2, the unadjusted HR for OS was 0.69 (95% CI 0.38–1.26), with an adjusted HR of 0.65 (95% CI 0.35–1.20).
- MSM modeling methods used in approach 3 were also applied with similar results.
- In approach 3, the earliest treatment cross-over occurred prior to PD for 6% of patients (erlotinib) and 26% of patients (chemotherapy), while the earliest treatment cross-over occurred after PD for 56% in both groups.
- Using approach 3, the HR for OS was 0.70 (95% CI 0.27–1.78; p=0.45); median OS (Cox MSM) estimate was 22.9 months with erlotinib and 16.5 months with chemotherapy (**Figure 4**).

Figure 4. Kaplan–Meier curves for OS with cross-over, pre-PD or post-PD, evaluated by approach 3



CONCLUSIONS

- **While the protocol-specified, intent-to-treat analysis of OS is potentially subject to the confounding effects of PST, it should be noted that these exploratory methods of analysing OS have their own limitations:**
  - **approach 1 may be subject to informative censoring and information loss due to censoring many OS events at the time of second-line PST**
  - **in approaches 2 and 3, the Cox model estimates assume that the first-line treatment effects and PST effects are proportional across time (Cox proportional hazards assumption). This assumption may be debatable for the PST effects, especially for approach 3 where we adjust for pre-PD and post-PD use**
  - **in our applications of MSMs for approach 3, to account for confounding, we utilised information on patients' PD status, history of treatment-related grade 3 adverse events, ECOG PS (longitudinal), weight (longitudinal), and the baseline factors in Table 1. Residual confounding could still be present after adjustment for these factors.**
- **Despite these limitations, these exploratory results suggest a trend towards a survival benefit for first-line erlotinib versus chemotherapy, which was previously unobserved potentially due to the confounding effects of non-randomised PST use.**

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