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Erlotinib (Tarceva®) for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations

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1 Background

1.1 Drug

Generic/Brand name/ATC code: Erlotinib/Tarceva®/L01XE0

Developer/Company: Roche Pharma AG

Description:

Erlotinib, a quinazoline derivative, is a tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR). Since EGFR controls functions such as proliferation and apoptosis [1], enhanced activation of EGFR leads to tumour angiogenesis and tumour growth. Activating EGFR mutations are present in about 15% of patients suffering from non-small cell lung cancer (NSCLC) and several mechanisms can cause an improper activation of the EGFR, including EGFR gene mutation, EGFR protein overexpression or an increased gene copy number [2]. Even though different methods are available to assess EGFR protein expression and EGFR gene copy number such as immunohistochemistry (IHC) or fluorescence in situ hybridisation, EGFR somatic mutation testing is the preferred method to identify eligible patients for erlotinib therapy [3-5]. The most frequent EGFR mutations are the exon 19 deletion and the L858R point mutation in exon 21 [1, 2] which can be detected by several tests [6].

erlotinib is a tyrosine kinase inhibitor of the EGFR

activating mutations of EGFR present in ~ 15% of NSCLC

eligibility for erlotinib treatment determined by detection of EGFR somatic mutations

Administration: 150 mg erlotinib are administered orally once daily until disease progression or unacceptable toxicity.

2 Indication

Erlotinib is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

as first-line therapy for EGFR mutation positive locally advanced or metastatic NSCLC

3 Burden of disease

As NSCLC accounts for about 85% of all lung cancer cases [7] it is one of the leading causes of cancer- deaths worldwide. Its primary risk factors are first- and second-hand smoke exposition [8]. Men are still more often affected by NSCLC than women, with the majority of patients being diagnosed at an age ≥ 65 years [9]. On average, patients are aged 71 years at the time of diagnosis of NSCLC.

lung cancer number one of leading causes of cancer-deaths

Based on the tumour node metastasis (TNM) system which takes characteristics like tumour size, location, invasion of the surrounding tissue, presence of metastasis in the lymph nodes or distant metastasis into account, four stages are distinguished. Locally advanced and metastasised NSCLC corresponds to TNM stage III and IV, respectively [10, 11]. NSCLC can be further distinguished into two groups: non-squamous carcinomas and

most frequent NSCLC = adenocarcinoma

squamous carcinomas (25% of lung cancers), the first one comprising large cell carcinoma (10% of lung cancers), adenocarcinomas (40% of lung cancers) and other, less frequent cell types [8, 12].

first-line therapy depends on several factors such as histo-pathologic subtype, performance status and EGFR mutational status

First-line therapy of advanced NSCLC depends on a number of factors, such as tumour stage, histo-pathologic subtype, co-morbidities and performance status [8, 13]. In addition, due to the development of targeted therapies, EGFR mutational status should also be assessed prior to therapy [3]. However, some guidelines recommend routine testing for EGFR mutations only for non-squamous NSCLC (which comprises adenocarcinomas, the most frequent histo-pathologic subtype), because EGFR mutations in squamous cell carcinomas are present in less than 3.6% of patients [8]. EGFR mutations are also more frequent in women, non-smokers and Asians [13].

an estimated 340 patients potentially eligible for erlotinib

3,600 people died of lung cancer and, about 4,100 new cases of lung cancer were diagnosed in Austria in 2008 [14]. Since 85% of these cancers are NSCLC of which about 65% [9, 15] can be expected to present with advanced disease, an estimated 2,260 persons are diagnosed with advanced NSCLC per year. Applying estimates of an average frequency of activating EGFR mutations (within an Caucasian population about 15%) to these numbers would result in about 340 individuals with activating EGFR mutations and thus potentially eligible for treatment with Tarceva®.

4 Current treatment options

standard of care for first-line therapy…

Systemic treatment options for the first-line therapy for patients with advanced/metastatic disease (TNM IIIB, IV) are

…for patients without EGFR mutations: platinum-based doublets ± monoclonal antibody

- platinum-based chemotherapy: modern regimens are mostly based on a platinum compound (cisplatin, carboplatin) in addition to one out of numerous other substances (e.g. vinorelbine, paclitaxel, docetaxel, gemcitabine, pemetrexed). For neither of these combinations superiority has been established unequivocally, but for patients with non-squamous histology cisplatin + pemetrexed might be the best treatment option [16].
- other chemotherapeutic regimens: due to the toxicity of platinum based regimens, other drug combinations can be used (gemcitabine + docetaxel/paclitaxel/vinorelbine/pemetrexed, paclitaxel + vinorelbine).
- single agent chemotherapy as first-line treatment is generally used for elderly patients or for those with poor performance status.
- targeted therapies:
  - TKIs (i.e. gefitinib) as mono-therapy.
  - monoclonal antibodies: bevacizumab (licensed) in combination with paclitaxel + carboplatin or gemcitabine + cisplatin for patients with non-squamous NSCLC and cetuximab (not licensed for this indication) preferably in combination with cisplatin + vinorelbine for patients with EGFR IHC positive metastatic NSCLC [3, 16].

However, if patients are EGFR mutational status positive, EGFR-TK inhibitors are increasingly used as standard first-line therapy, whereas patients with either unknown EGFR status or without EGFR mutation, should receive chemotherapy doublets, either alone, or in combination with a monoclonal antibody (e.g. bevacizumab) [3, 17]. Different administration schedules apply for these regimens, because chemotherapy is generally administered for 4-6 cycles and EGFR-TKIs are delivered until disease progression or unacceptable toxicity.

…for patient with EGFR mutations: TKIs

5 Current regulatory status

In Europe, the European Medicines Agency (EMA) licensed erlotinib for:

- NSCLC:
  - as mono-therapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy in April 2010.
  - for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.
- Metastatic pancreatic cancer in combination with gemcitabine as first-line therapy in January 2007.

EMA: CHMP recommendation extension of indication for first-line therapy in July 2011

In July 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending an extension of indication for erlotinib as first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations [18].

In the U.S., the Food and Drug Administration (FDA) has not yet approved erlotinib for the first-line therapy of NSCLC. However, market authorisation was granted for:

FDA: not licensed for first-line therapy

- NSCLC:
  - as maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
  - for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.
- For the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine [19].

6 Evidence

two phase III trials, only one fully published

A literature search was conducted on the 7th of November 2011 in four databases (The Cochrane Library, EMBASE, Ovid, CRD Database) yielding 493 references overall. In addition a hand search was performed including the websites of the EMA and the FDA.

Considered were only those studies which had enrolled patients with activating EGFR mutations and advanced/metastatic NSCLC, resulting in two phase III studies [20-22] of which only one [20] is fully published.

In addition, one screening study and one pooled analysis are presented within this report [23, 24]. Several other studies investigating first-line therapy with erlotinib in patients with NSCLC were identified, but their results are not displayed since presence of activating EGFR mutations was not a prerequisite for study entry [25-35].

6.1 Efficacy and safety - RCTs

Table 6.1.-1: efficacy of the OPTIMAL trial

Study title Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase III study [20]			
Study identifier	NCT00874419, OPTIMAL study, CTONG-0802, ML20981		
Design	open-label, randomised, phase III trial, China		
	Duration	Enrolment: 12 months Median follow-up: 15.6 months Primary cut-off date: planned July 2010 but after 10 additional events had occurred an updated analysis was performed in August 2010	
Hypothesis	Superiority		
Funding	Hoffmann-La Roche		
Treatment groups	Intervention (I)	150 mg erlotinib/day orally until disease progression or unacceptable toxic effects	
	Control (C)	1000mg/m² gemcitabine i.v. (days 1 and 8) + carboplatin (AUC =5] i.v. (day 1 of a 3-week cycle) up to four cycles	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	time from the date of randomization to the date of first documentation of progressive disease or date of death from any cause, whichever comes first. Disease progression is defined according to RECIST criteria (version 1.0 [36]).
	Overall Survival	OS	time from the date of randomization to the date of death, regardless of the cause of death.
	Objective response rate	ORR	CR or PR as determined by the RECIST criteria
	Time-to-Progression	TTP	duration from the date of first confirmed partial response or complete response to disease progression or death of any reason (if death occurred earlier than documentation of disease progression).

	Health related quality-of-life	HR-QoL	assessment of HR-QoL and lung cancer symptoms is based on the answer of patient to FACT-L and LCSS questionnaire. FACT-L and LCS questionnaire should be completed at the baseline and every 6 weeks during the treatment and every time of follow-up during post-treatment period.

Results and analysis			
Analysis description	Intention-to–treat (ITT) analysis, which is defined as all the randomized patients that received study drug treatment for at least one time. Two side log-rank test is the main method for comparison of the progression free survival (PFS) in erlotinib and chemotherapy arms, and the significance level will be 0.05.		
Analysis population	Characteristics	Age: I 57 yrs (31 – 74) vs C 59 (36 – 78), <65 yrs: I 77% vs C 71% Sex: Males: I 41% vs C 40%, Females: I 59% vs C 60% Histology: Adenocarcinoma: I 88% vs C 86%, Non-adenocarcinoma: I 12% vs C 14% Smoking Status: Present or former smoker: I 28% vs C 31%, Non-smoker: I 72% vs C 69% EGFR mutation type: Exon 19del: I 52% vs C 54%, L858R mutation: I 48% vs C 46% ECOG-PS: 0-1: I 91% vs C 96%, ECOG-PS 2: I 9% vs C 4% Disease stage: IIIB: I 13% vs C 7%, IV: I 87% vs C 93%	
	Inclusion	> 18 years, confirmed advanced or recurrent stage IIIB or IV NSCLC (Union for International Cancer Control classification version 6) with a confirmed activating mutation of EGFR—i.e., an exon 19 deletion or an exon 21 L858R point mutation. They also had measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST version 1.0), an Eastern Cooperative Oncology Group performance status of 0–2, and adequate haematological, biochemical, and organ function.	
	Exclusion	if patients had uncontrolled brain metastases or had received previous systemic anticancer therapy for advanced disease (although adjuvant or neoadjuvant therapy was allowed for non-metastatic disease in which relapse had occurred ≥6 months after final treatment).	
Descriptive statistics and estimated variability	Treatment group	*Intervention*	*Control*
	Number of subjects	82	72
	PFS (months) Median 95%CI	 13.1 10.58 – 16.53	 4.6 4.21 – 5.42
	OS	NR	NR
	ORR, n (%) CR PR	68 (83) 2 (2) 66 (80)	26 (36) 0 (0) 26 (36)
	HR-QoL	-	-
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS	HR	0.16
		95%CI	0.10 – 0.26
		P value	0.0001

	HR-QoL	FACT-L (logistic regression analyses based on several covariates) P- Value	<0.0001
		LCS score (logistic regression analyses based on several covariates) p-Value	<0.0001

Abbreviations: AE= adverse event, WHO PS – World Health Organisation performance status, ECOG PS – Eastern Cooperative Oncology Group performance status, iv – intravenously; NCI-CTC – National Cancer Institute Common Terminology Criteria, version 3.0 (http://www.eortc.be/services/doc/ctc/ctcaev3.pdf), OS = overall survival, PFS = progression-free survival, ORR = overall response rate, QoL =quality-of-life, CI = confidence interval, HR = hazard ratio, NR = not reached, AUC = area under the curve

Table 6.1.-2: Adverse events of the OPTIMAL trial

Grade (according to NCI CTC AE version 3.0)	**Outcome, n (%)**	**Intervention** (n=83)	**Control** (n= 72)
Any Grade*	Neutropenia	5 (6)	50 (69)
	Thrombocytopenia	3 (4)	46 (64)
	Anaemia	4 (5)	52 (72)
	Skin rash	61 (73)	14 (19)
	Diarrhoea	21 (25)	4 (6)
	Vomiting or nausea	1 (1)	33 (46)
	Increased ALT	31 (37)	24 (33)
	Fatigue	4 (5)	17 (24)
Grade 3 or 4	Neutropenia	0 (0)	30 (42)
	Thrombocytopenia	0 (0)	29 (40)
	Anaemia	0 (0)	9 (13)
	Infection	1 (1)	0 (0)
	Skin rash	2 (2)	0 (0)
	Diarrhoea	1 (1)	0 (0)
	Stomatitis	1 (1)	0 (0)
	Vomiting or nausea	0 (0)	1 (1)
	Increased ALT	3 (4)	1 (1)
	Fatigue	0 (0)	1 (1)
Other outcomes	Treatment-related AEs (all grades)	72 (87)	68 (94)
	Dose reduction due to a drug-related AE	5 (6)	38 (53)
	Discontinuation due to a drug-related AE	0 (0)	4 (6)
	Treatment-related SAE	2 (2)	10 (14)
	Treatment-related death	0	0
	ILD-like events	0	0

** only AEs of any grade ≥20% are reported*

One open-label randomised controlled trial, conducted in China, compared first-line therapy with erlotinib to gemcitabine + carboplatin in patients with stage IIIB or stage IV NSCLC. 549 patients were screened for activating mutations of EGFR (exon 19 deletion or exon 21 L858R point mutation), leading to the inclusion of 165 individuals overall. In the erlotinib group, one patient was excluded and in the chemotherapy group 9 patients withdrew consent and 1 did not start treatment after randomisation, resulting in 82 patients treated with erlotinib and in 72 patients treated with gemcitabine + carboplatin. More patients were females, younger than 65 years and non-smokers and the majority (i.e. >85%) of patients had stage IV adenocarcinomas and a good performance status.

one trial in China comparing erlotinib to platinum-based chemotherapy

The primary outcome, progression-free survival (PFS), showed a gain of 8.5 months for patients treated with erlotinib in comparison to those who had received gemcitabine + carboplatin, corresponding to a HR of 0.16 (95%CI 0.10 – 0.26; $p<0.0001$). Of note, this trial was an open-label study and thus investigators were not blinded to the intervention the patients had been allocated to. Since assessment of PFS was not subject to review by an independent committee, results might have been influenced. Moreover, 9 patients in the chemotherapy group withdrew consent before they had received at least one cycle of the assigned therapy and were therefore not considered in the intention-to-treat analysis. The primary cut-off date for PFS was also changed from July to August because 10 more events had occurred, but it is unclear how these events were distributed between the groups. These factors might have also contributed to the impressive gain in PFS.

+8.5 months in PFS for erlotinib group

but no independent review, 9 patients withdrew consent in the chemotherapy group, cut-off date was changed

Pre-planned and exploratory subgroup analyses including characteristics such as sex, smoking status or EGFR mutation type, favoured, in terms of prolongation of PFS, with two exceptions always the erlotinib group. Not significant results were only found for the subgroup of patients with IIIB stage disease and for those with ECOG-PS 2, but both of these groups comprised only a very small number of patients.

The overall response rates were 83% for erlotinib and 36% for chemotherapy. The majority of these responses were partial, because only 2 patients (i.e. 2%) treated with erlotinib experienced complete responses, but no complete response was observed in the comparison group. Overall survival was not yet mature, but 88 patients will be followed-up.

ORR: erlotinib 83% vs chemotherapy 36%

mainly partial responses

Quality-of-life, assessed by the FACT-L and the LCS scores were also evaluated. Significantly improved results were found for both of these scores, when several characteristics (e.g. performance status, smoking history and sex) were considered in covariate analyses. Again, since this trial was open-label - which was justified since blinding to two different ways of administrations would have proven difficult - these results might have been distorted.

some data for improvements in QoL

Adverse events of all grades were very frequent in both groups. However, the side-effect profiles differed, since skin rash, a common side effect associated with TKI therapy, diarrhoea, increased ALT-levels and infections were more often observed in the erlotinib group and haematological AEs were higher in the chemotherapy group. AEs grade 3 or 4 occurred overall in 65% of patients in the chemotherapy and in 17% of patients treated with the TKI. Foremost haematological AEs of higher grades were much more common in the chemotherapy group, but only minor differences occurred for other AEs. The frequency of any serious AE (SAE) were comparable (I 12% vs C 14%), but those thought to be treatment-related showed also more favourable re-

haematological AEs more common in chemotherapy group, erlotinib associated with higher frequency of skin rash and diarrhoea

erlotinib showed favourable toxicity profile

sults for erlotinib (I 2% vs C 14%). Dose modifications and treatment interruptions were also more frequent in the chemotherapy group. No deaths and no cases of interstitial lung disease were observed.

Table 6.1.-3: efficacy of the EURTAC trial

Study title European Erlotinib Versus Chemotherapy (EURTAC) phase III randomised trial [21, 22]			
Study identifier	ML20650 (EURTAC), NCT00446225, EURTAC-SLCG, GECP06/01, EudraCT:2006-003568-73		
Design	Phase III, multicentre, open-label, randomised in Spain, Italy and France, stratification according to ECOG status and deletion in exon 19 and mutation in exon 21 L858R		
	Duration	Enrolment: February 2007 – January 2011 Median follow-up: I 14.3 months vs C 10.7 months Interim analysis: August 2010 Updated results: post-hoc analysis in January 2011	
Hypothesis	Superiority		
Funding	NA		
Treatment groups	Intervention	erlotinib arm received 150 mg/day orally until disease progression, unacceptable toxicity or death occurred.	
	Control	The following combinations of chemotherapy were allowed to be used per protocol for a maximum of 4 cycles: • Cisplatin plus docetaxel: cisplatin 75 mg/m2 intravenous (i.v.) day 1 and docetaxel 75 mg/m2 i.v. on day 1, cycle repeated every 3 weeks • Cisplatin plus gemcitabine: Cisplatin 75 mg/m2 i.v. on day 1 and gemcitabine 1250 mg/m2 on days 1 and 8. Repeat cycles every 3 weeks. In the case of patients not eligible for treatment with cisplatin, cisplatin could be replaced by carboplatin. The schedules were the following: • Docetaxel 75 mg/m2 day 1 and carboplatin AUC = 6 day 1, every 21 days. • Gemcitabine 1000 mg/m2 days 1 and 8 and carboplatin AUC = 5 day 1, every 21 days	
Endpoints and definitions	Progression-free survival (investigator assessed) (primary outcome)	PFS	NA
	Overall survival	OS	NA
	Quality of life	QoL	lung cancer symptom scale (LCSS)
	Objective response rate (investigator assessed)	ORR	NA
Results and analysis			
Analysis description	interim analysis was pre-specified after 88 out of 135 planned events had occurred. A Lan-DeMets alpha-spending function was used to maintain the significance level at 5%.		
Analysis population	Characteristics	Median age (range): I 63.5 years (24 – 82 years) vs C 64.1 years (29 - 82 years), <65 years: I 49% vs C 51%	

		Sex: Females I 68% vs C 79%, Males: I 32% vs C 21% Smoking Status: Current-smoker: I 4% vs C 13%, Past-smoker: I 26% vs C 13%, Never-smoker: I 70% vs C 74% Histology: Adenocarcinoma: I 95% vs C 88% Disease stage: IIIb: I 8% vs C 7%, IV: 91% vs C 93%	
	Inclusion	histologic diagnosis of NSCLC, stage IV or stage IIIB with malignant pleural effusion or N3 tumours not candidates for thoracic irradiation who present exon 19 deletions or an exon 21 L858R mutation in the TK domain of EGFR (histology was performed locally), ECOG Performance status ≤2; age >18 years; measurable and evaluable disease; ECOG PS 0-2; adequate bone marrow reserve, kidney and liver function.	
	Exclusion	previous treatment with chemotherapy for metastatic disease. The administration of neo-adjuvant or adjuvant chemotherapy was allowed as long as it was completed ≥ 6 months before entering the study. Previous treatment with therapeutic agents targeting EGFR. Patients could have received radiotherapy as long as the irradiated lesion was not the only target lesion for evaluating response and as long as radiotherapy had been completed before initiating the study treatment (a 2-week period was recommended).	
Descriptive statistics and estimated variability	Treatment group	*Intervention*	*Control*
	Number of subjects	77	76
	PFS (months), interim analysis Median 95%CI	 9.7 7.9 – 12.3	 5.2 4.4 – 5.8
	PFS (months), updated analysis Median 95%CI	 9.7 8.4 – 12.6	 5.2 4.5 – 6.0
	OS (months) median 95%CI	 22.9 NA	 18.8 NA
	ORR (%) 95%CI CR (n (%)) PR SD PD	54.5 42.8 – 65.9 2 (2.6) 40 (51.9) 18 (23.4) 6 (7.8)	10.5 4.7 – 19.7 0 (0) 8 (10.5) 42 (55.3) 10 (13.2)
	QoL	NA	NA
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS	HR (by investigator) interim analysis	0.42
		95%CI	0.27-0.64
		P value	<0.0001

		HR (by independent review committee), interim analysis	0.47
		95%CI	0.28 - 0.78
		P value	0.0030
		HR, updated analysis	0.37
		95%CI	0.25 – 0.54
		P value	<0.0001
	OS	HR	0.80
		95%CI	0.47 – 1.37
		P value	0.42
	ORR	OR	10.20
		95%CI	4.32 – 24.08
		P value	NA

Abbreviations: NA = not available, HR = Hazard ratio, OR = Odds ratio, CI = confidence interval, AUC = area under the curve, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

EURTAC: for the first time phase III trial assessing EGFR TKI in European population

erlotinib versus standard-chemotherapies

Result of the EURTAC trial, on which the CHMP recommendation for the extension of indication for erlotinib was based, have not been published yet [21, 22]. This trial was conducted in Europe and comprised 155 patients with untreated stage IIIB/IV NSCLC. Only patients with EGFR activating mutations were enrolled and received either erlotinib or standard first-line platinum-based doublet chemotherapy at the discretion of the treating physician. PFS, the primary outcome, showed improved results for the erlotinib group, because PFS was 9.7 months in the intervention group and 5.2 months in the control group (HR=0.42, p<0.0001). These numbers were determined by the investigators and a review by an independent data monitoring committee was performed only retrospectively and not for all scans. PFS by analysis of the independent committee was nevertheless consistent with that of the investigators. Due to these favourable results, the independent data monitory committee recommended to stop the trial. A post-hoc analysis (cut-off date January 2011) showed even more improved results since the risk of progression or death was reduced by 63%; the absolute gain in median PFS was with +4.5 months for patients in the erlotinib group unchanged.

PFS significantly improved for erlotinib at interim analysis: HR = 0.42

OS was not mature, but cross-over to EGFR TKI therapy will confound results

The data for OS were not mature at the time of the interim analysis and did not show any significant differences. In addition, patients in both groups had already received further lines of therapy, including TKIs, at that time (I 36% vs C 67%), thus confounding results. For the updated analysis, no detailed numbers are available for OS. It is only mentioned that the number of patients who had either received further lines of therapy or who had crossed-over to erlotinib had risen to 77%.

no data for QoL

Due to too low response rates no conclusions can be drawn for QoL.

AEs were very common in both groups, because nearly every patient experienced at least one AE. The most frequent ones in the erlotinib group were skin rash and diarrhoea and asthenia and anaemia in the chemotherapy group. AEs of grade ≥3 were observed in 66% in the chemotherapy group and in 41% in the TKI group, but no difference in terms of SAEs existed between the two groups. However, 6% of SAE in the erlotinib group were considered as treatment-related and one treatment-related death was observed in that group, comparable numbers are missing for the chemotherapy group. Of note, treatment duration in the erlotinib group was considerably longer than in the chemotherapy group, which might explain, for example, higher numbers of SAE in the erlotinib group [21].

higher grade AEs more frequent in chemotherapy group, but no differences in severe AEs…

..due to longer treatment duration in erlotinib group?

Table 6.1-4: Adverse events of the EURTAC trial [21]

Grade	Outcome (%)	Intervention (n=75)	Control (n= 74)
Any Grade	Overall	72 (96)	73 (99)
	Neutropenia	0 (0)	27 (37)
	Anaemia	8 (11)	34 (46)
	Skin rash	37 (49)	1 (1)
	Diarrhoea	43 (57)	14 (19)
	Nausea	17 (23)	30 (41)
	Asthenia	40 (53)	51 (69)
	Vomiting	10 (13)	16 (22)
	Constipation	6 (8)	16 (22)
	Cough	34 (45)	26 (35)
	Dyspnoea	31 (41)	19 (26)
	Decreased appetite	21 (28)	25 (34)
Grade ≥3	Overall	31 (41)	49 (66)
Grade 5	Overall	7 (9)	4 (5)
Others	SAE	NA (27)	NA (26)
	AEs leading to dose modification/interruption	20 (27)	39 (53)
	AEs leading to discontinuation	NA (12)	NA (15)
	Treatment-related SAE	5 (6)	NA
	Treatment-related death	1 (1)	NA

Only AEs any grade ≥20% are displayed

6.2 Efficacy and safety - further studies

screening study including first and second-line erlotinib therapy

Rosell et al. [24] conducted a screening study in Spain. Of 2,105 patients, EGFR mutations were detected in 350 (16.6%) individuals. Of these, 217 patients were treated with erlotinib, either as first-line or as second-line therapy. Response was assessed in 197 patients of whom the majority showed partial responses (58.4%). Complete responses were observed in 12.2%. It is unclear though how these numbers can be allotted to the different lines of therapies. Specific results for first-line therapy are available for PFS (14.0 months, 95%CI 9.7 – 18.3 months) and for OS (28.0 months, 95%CI 22.7 – 33 months). Most common AEs were comparable to those reported in the phase III studies (skin rash: 70%, diarrhoea: 44%) but were mainly of grade 1 or 2. Toxic skin effects of grade 3 were observed in 7% and diarrhoea of grade 3 in 4% of patients. One case of interstitial lung disease occurred.

AEs similar to phase III studies

pooled analysis confirmed better results in PFS for first-line EGFR TKI therapy

A pooled analysis evaluated EGFR-TKIs (erlotinib and gefitinib) and chemotherapy in patients with EGFR mutations [23]. Prospective and retrospective studies were included without restrictions to a certain line of therapy. Better PFS results were shown for both EGFR TKIs than for chemotherapy regardless of the line of therapy, but consistent findings were observed if predominantly untreated patients were considered. For this indication median PFS was 12.5 months for erlotinib, 9.9 months for gefitinib and 6.0 months for chemotherapy.

7 Estimated costs

no costs estimates for Austria

in Germany: € 2,900 for one month therapy

savings due to fewer AEs and oral administration possible

No price estimates are available yet for Austria, but in Germany one package of 30 tablets erlotinib 150mg, which equals the monthly dosage, is € 2,900 [37]. Since erlotinib replaces chemotherapy, this would be the only costs for first-line therapy. In addition, due to the oral administration and fewer side-effects, potential savings might incur since hospital admissions might be reduced. On the other hand, costs for EGFR testing prior to erlotinib therapy have to be taken into account, but no information on the associated costs is available.

8 On-going studies

one on-going phase III study for the investigated indication

One on-going phase III study assessing first-line therapy in erlotinib in patients with NSCLC and EGFR activating mutations was found at ClinicalTrials.Gov:

NCT01342965: evaluates erlotinib versus gemcitabine/cisplatin as the first-line treatment for stage IIIB/IV NSCLC patients with mutations in the tyrosine kinase domain of EGFR in their tumour. Estimated study completion date is February 2013.

No further phase III trial was identified for this indication on the EU Clinical Trials Register, but erlotinib is under investigation in phase II trials in combination with other experimental drugs for NSCLC in general (e.g. OSI-906, U3-1287, MetMAb).

erlotinib also under investigation for other cancers and as combination therapy for NSCLC

Other on-going phase III studies evaluate erlotinib for cancers including hepatocellular carcinoma, colorectal cancer and oesophageal cancer.

9 Commentary

extension of indication to first-line setting recommended in July 2011

In July 2011, the CHMP recommended to extend the indication of erlotinib to first-line therapy for locally advanced/metastatic NSCLC with EGFR activating mutations [18]. Two phase III studies investigated this indication [20, 21]. One was conducted in China [20], whereas the EURTAC trial was conducted in European countries and assessed, for the first time, efficacy of an EGFR-TKI for the treatment of lung cancer in Caucasian patients. In both trials, the comparator(s) used were platinum-based doublet chemotherapies, currently the standard-of-care for first-line therapy of NSCLC. PFS was significantly improved for patients treated with erlotinib, yielding a risk reduction of 53% to 84%. More favourable outcomes for tumour response, mainly partial responses, were also found for these patients. However, no reliable statements can be made on the impact of erlotinib on OS, either due to cross-over or immature data. QoL related outcomes were reported in only one of these trials [20], showing significant improvements for patients treated with erlotinib, but these results are potentially compromised due to the study design (open label). However, partial responses of 50%-80% (in comparison to 10% -36% in the chemotherapy group), fewer SAEs and the oral administration of erlotinib give support that improvements in QoL can be expected.

improvements in PFS and ORR

impact on OS unclear

improvements in QoL likely

Overall AEs were very common in the erlotinib and in the chemotherapy group, affecting nearly all patients. Distinct differences in the toxicity profiles of erlotinib and chemotherapeutic regimens exist, because skin rash (in up to 73%) and diarrhoea (in up to 57%) were more frequent in the erlotinib group, whereas more patients treated with chemotherapy experienced haematologic side-effects. A higher proportion of individuals had grade ≥3 AEs in the platinum-based doublet groups and treatment-related SAEs were also more often observed in this group [21]. Similarly, dose modifications or treatment discontinuations were necessary in considerably fewer patients treated with erlotinib than in those receiving chemotherapy.

more favourable toxicity profile than chemotherapies

Erlotinib will be, besides gefitinib, the second EGFR-TKI licensed for the first-line therapy of advanced/metastatic NSCLC with EGFR activating mutations in Europe. Both drugs have been incorporated into European Guidelines [3, 38]. In contrast, neither of these agents has received marketing authorization for the first-line therapy of NSCLC in the U.S., but the American Society of Clinical Oncology adopted nevertheless a provisional opinion, recommending EGFR testing in the first-line setting [5]. Both drugs are EGFR-TKIs and might be used interchangeably [3, 8], but since no head-to-head trials comparing these two drugs have been performed, it is unclear if one drug offers specific advantages over the other.

erlotinib is after gefitinib 2nd EGFR TKI licensed for first-line NSCLC therapy

differences between these drugs?

to date no comparison of different EGFR mutation tests available

for all patients or based on histological cancer type?

For both drugs, issues relating to identification of eligible patients by EGFR testing need to be addressed. Several testing methods are available to date (e.g. Sanger method, Cobas® 4800 EGFR mutation test, High Resolution Melt, TheraScreen EGFR 29 by DxS Ltd) which might have different accuracies. Thus a comparison of these tests might be useful in determining the best method [6]. Even though EGFR mutation testing is a prerequisite for EGFR-TKI therapy, the evidence is a bit patchy if testing is only indicated for patients with adenocarcinomas, non-squamous carcinomas or if it should be performed regardless of histology [3, 5, 8, 39]. In any case, EGFR testing should be performed only within quality-assurance programmes.

tests for resistance?

Another issue is resistance to EGFR TKIs which eventually develops in all patients treated with these drugs. In both phase III studies enrolment was based on the presence of EGFR activating mutations, but testing for mutations which confer resistance, for example mutation T790M in exon 20, an "acquired resistance mutation", where not considered [5, 6]. Despite the fact that presence of T790M mutations are associated with a short PFS [2], the European Society for Medical Oncology state that patients should not be precluded from EGFR-TKI therapy even if T790M mutations are detected [3]. This might be based on the fact that even if patients develop second resistance to erlotinib, this resistance might be lost and TKI therapy might become effective again after TKI treatment was stopped [6]. Thus monitoring of the tumours' genotype during therapy might be indicated. Even though material from cytology cell blocks is usually required for determining EGFR mutations [5], the material retrieved by biopsies is sometimes not sufficient for a complete molecular analysis [40]. Therefore other approaches for the determination of EGFR activating mutations such as cytological smears or circulating tumour cells from blood samples have been investigated [40, 41].

EGFR-TKIs have become standard of care for first-line therapy of NSCLC with activating EGFR mutations

In summary, due to gains in PFS and a more favourable toxicity profile in comparison to platinum-based chemotherapy, EGFR-TKIs have increasingly become standard first-line therapy for patients with activating EGFR mutations and advanced/metastatic NSCLC. Open questions mainly concern EGFR testing and determinants of resistance.

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