Pharmacotherapeutic report erlotinib (Tarceva®)

1. Summary

The Medicinal Products Reimbursement Committee (CFH) has approved a pharmacotherapeutic report for the drug erlotinib (Tarceva®). In order to determine its therapeutic value, erlotinib was compared with docetaxel (Taxotere®) and pemetrexed (Alimta®). The committee came to the conclusion that erlotinib is effective in the treatment of patients with locally advanced (stage IIIB) or metastised (stage IV) non-small-cell lung carcinoma (NSCLC) after one or two prior courses of chemotherapy treatment (at least one of which on the basis of a platinum complex). Due to the extremely poor prognosis of this disease, therapeutic value can be attached to a small increased survival of two months. Epidemiological data indicate that the use of erlotinib is particularly beneficial for women with (far) advanced NSCLC, in patients with a bronchioalveolar or adenocarcinoma, in patients who have never smoked and in patients of eastern Asian origin. Biological properties of the tumour that increase the chance of a therapeutic effect are not only sufficient expression of epidermal growth factor receptors (EGFR), but also the presence of activating mutations in the EGFR-gene. On the contrary, K-*ras* mutation in the tumour cells leads to resistance to erlotinib.

Other drugs that can be used for the chemotherapeutic treatment of very advanced NSCLC stage IIIB/IV are docetaxel and pemetrexed. On the basis of published research data, the efficacy of these drugs in second-line treatment is comparative with that of erlotinib. As third-line treatment, however, docetaxel seems to be less effective than erlotinib. Up till now pemetrexed has not yet been researched as third-line treatment.

Due to its poor haematological toxicity the side effects profile of erlotinib is more favourable than that of docetaxel. Characteristic side effects of erlotinib are a rash that can be severe and diarrhoea. Unlike pemetrexed, treatment with erlotinib does not lead to haematological side effects. Although pemetrexed does not cause a rash, on the basis of the literature, it is not possible to draw any further comparison between erlotinib and pemetrexed. Treatment with erlotinib leads to a delay in the occurrence of a number of symptoms characteristic of NSCLC and there is an improvement in physical functions and general quality of life. Unlike docetaxel and pemetrexed, erlotinib can be taken orally.

Final conclusion re therapeutic value

For the treatment of far-advanced stage IIB/IV NSCLC, erlotinib is considered to have a therapeutic added value above docetaxel and pemetrexed. In particular, it would seem useful to use erlotinib for women with very advanced NSCLC, patients with a bronchioalveolar or adenocarcinoma, patients who have never smoked and patients of eastern Asian origin. Where possible sufficient EGRF should have been demonstrated. The chance of a response to erlotinib is greater among patients with an activating mutation in the EGFR-gene. K-*ras* mutation in the tumour cells leads to resistance against erlotinib.

2. Introduction

Drug	Erlotinib
Composition	Erlotinib, 25, 100 or 150 mg (as erlotinib hydrochloride), with additives, in the form of a film-coated tablet.
Registered indication	The treatment of patients with locally advanced or metastised stage IIB/IV non-small cell lung cancer, after the failure of at least one prior chemotherapy regime.
Dose	150 mg per day. When making dose adjustments, the daily dose should be reduced in 50-mg steps.
Mode of action	Erlotinib inhibits the intracellular phosphorylisation of the epidermal growth factor receptor (EGFR/HER1) due to tyrosine kinase. EGFR are expressed particularly in the cell surface of cancer cells. EGF is involved in the development of tumours and the growth of cancer cells. The inhibition of signal transduction of EGFR due to erlotinib is associated with stasis and/or cell death.
Specific details	Docetaxel and pemetrexed (only for the indication mesothelioma) have been allowed on the basis of the CTG-ZAIO [National Health Tariffs Authority] policy regulation 'expensive intramural drugs'.

For extensive information about the drug, see the product text as published in the next edition of the *Farmacotherapeutisch Kompas* [Pharmacotherapeutic Compass].

3. Starting points for assessment

Non-small-cell lung cancer (NSCLC) is one of the most frequently occurring malign diseases in the Netherlands. Lung cancer is diagnosed in about 9,000 patients every year. In circa 80% of the cases, it involves NSCLC which occurs only in men (man-woman ratio: 4:1). There are four forms of NSCLC: squamous cell carcinoma, adenocarcinoma, large cell and mixed small cell carcinomas. In most of the patients (ca. 75%) the disease is not diagnosed until it has already become advanced or has metastised. The median survival upon diagnosis is eight months. After five years 13% of all patients are still alive. For patients with advanced NSCLC this percentage is lower than 5%. These statistics have only improved slightly over the years (CBO Guideline NSCLC 2004[1]; web-site VIKC, data 1989-2004[2]).

In the early stages (I and II, sometime even IIIA) NSCLC is treated mainly via surgery and radiotherapy. Chemotherapy is only usually added to treatment in a more advanced stage (III). Nowadays, this comprises a platinum compound (carboplatin or cisplatin) in combination with gemcitabine, a taxan (docetaxel or paclitaxel), or vinorelbine. In a locally advanced stage (IIIB) or where there are metastases (IV), treatment is no longer curative but palliative. Apart from providing supportive care, life-extending chemotherapy on the basis of a platinum compound (if possible 3 or 4 cycles)[1] is also used. In this stage of NSCLC, chemotherapy has only a moderate effect and is highly dependent on the (general) condition of the patient with respect to results[1]. Parameters with a predictive value include the ECOG performance score (ECOG-PS; score of 0 [=unimpeded by the disease] to 4 [=extremely poor]), age (results <65 years better than >65 years), type of NSCLC, the results of previous treatment and loss of weight in the period prior to treatment[1].

The EGFR (or the human epidermal growth factor receptor type I [HER1]) is expressed in particular via cancer cells. EGF plays an important role in the development of, among other things, breast cancer and NSCLC[1] (Giaccone 2005[3]; Baselga & Arteaga[4]). One of the ways in which EGFR-tyrosine kinase inhibitors such as erlotinib and gefitinib act is on the signal transduction of the EGFR by occupying the binding of ATP in the kinase domain. As a result the receptor is no longer phosphorylated and the signal transduction ceases. Inhibition is associated with stasis and cell death which results in a reduction in the growth of the tumour[3,4]. Due to fact that the working mechanism of EGFR-tyrosine kinase inhibitors differs from that of the classical cytostatics, these drugs have a different point of action for the treatment of NSCLC[1,3,4].

3.a. Applicability

Erlotinib is registered for the treatment of patients with locally advanced (stage IIIB) or metastised (stage IV) NSCLC after the failure of at least one prior chemotherapeutic course of treatment (1B text[5]).

On the basis of the CBO treatment guideline, this applies to patients who, subsequent to first-line palliative treatment on the basis of a platinum compound, are eligible for second-line treatment without a platinum compound (docetaxel or pemetrexed) or who, after second-line treatment, are only eligible for supportive care[1].

3.b. Choice of comparative treatment

Apart from erlotinib, docetaxel and pemetrexed are also registered for the treatment of patients with locally advanced or metastised NSCLC who are no longer eligible for further palliative treatment with chemotherapy on the basis of a platinum compound[6,7].

On the basis of the registered indication, erlotinib can be used on patients whose condition is at all reasonable (ECOG-PS $\leq$ 2) as an alternative to second-line treatment with docetaxel or pemetrexed or third-line when treatment with docetaxel or pemetrexed has failed. The expected results of treatment seem to be related to certain characteristics on a group level (see 4, 5, and 6) and the density of EGFR, the presence of activating mutations in the EGFR-gene and K-*ras* mutation in the tumour (6).

3.c. Method of assessment

When making the assessment, study results were used that were included in the EPAR[8], the 1B text[5] and/or were published in renowned (peer-reviewed) journals. For the benefit of the assessment, a literature search took place on 15th November 2005 (Medline via PUB-Med and the Cochrane Library). The search item was erlotinib, whether or not in combination with non-small cell lung cancer or NSCLC, tyrosine kinase inhibitors, docetaxel, gefitinib, cisplatin and carboplatin and pemetrexed. The search supplied a number of additional references[11,12,19-26,27-33].

4. Therapeutic value

The therapeutic value of erlotinib (Tarceva®) was assessed according to the criteria efficacy, effectiveness, side effects, quality of life, experience, applicability and user-friendliness. For the benefit of registration the effect of erlotinib in a single daily 150-mg dose in patients with advanced NSCLC was studied by means of a small (N=52) non-randomised phase-II study (Perez-Soler et al. 2004[9]) and a large (N=731) randomised and placebo-controlled phase III study (erlotinib: placebo = 2:1), the BR.21 trial (Shepherd et al. 2005[10]). At the same time placebo-treated patients received the best possible supportive care (OZ).

The results of a second phase III study in which erlotinib was added to first-line treatment of locally advanced or metastised NSCLC – the combination carboplatin/paclitaxel (TRIBUTE; Herbst et al. 2005[11]) and the combination cisplatin/gemcitabine (TALENT; Gatzemeier et al. 2004[12]) – did not lead to registration of erlotinib for this indication because the addition of erlotinib to the combination chemotherapy did not provide any therapeutic advantage. However, the results of this and other previous studies with erlotinib are important because of the side effects observed due to erlotinib and for determining the therapeutic value of the registered indication[5,8,9,11,12].

The results of four (registration) studies are important for a comparison of erlotinib with docetaxel and pemetrexed: (Shepherd et al. 2000[13] [phase III: docetaxel 100/75 mg/m^2 vs OZ]; Fossella et al. 2000[14] [phase III; docetaxel 100/75 mg/m^2 vs vinorelbine or ifosfamide]; Quoix et al. 2004[15] [phase II; docetaxel 100/75 mg/m^2] and Hanna et al. 2004[16] [phase III; pemetrexed 500 mg/m^2 vs. docetaxel 75 mg/m^2]).

4.a. Efficacy

The efficacy of antineoplastic drugs in the treatment of solid tumours was assessed according to four outcomes (RECIST criteria): complete response (CR), partial response (PR), stabilisation (SD) and progression (PD) of the disease (Therasse et al. 2000[17]).

In the phase II study all patients (average age: 62 years) had undergone at least one prior course of treatment with platinum-containing chemotherapy and had an ECOG-PS of 0-2. Expression of EGFR was demonstrated in all patients. The treatment lasted for a minimum of 8 and a maximum of 52 weeks till progression of the disease or the development of unacceptable toxicity. In 12% of the patients an objective response (OR: CR+PR) was observed with a median duration of 20 weeks. In 39% of the patients treatment led to stabilisation (SD)[9].

In the BR.21 study, half of the patients (60% < 65 years; median age: E: 62 years; P: 59 years) had undergone one prior treatment, mainly (> 90%) with a platinum-containing chemotherapy. The other half had been treated previously with second-line or third-line chemotherapy. An adenocarcinoma was involved in half of the patients. Most of the patients had an ECOG-PS of one (E: 52%; P: 54%) or two (E: 26; P: 23%). In both groups 9% had an ECOG-PS of three. Expression of EGFR was studied in 31(E) and 35% (P) respectively of the patients (E: 16% EGFR+; P: 20% EGFR+)[10]. The results are reflected in table 1. Erlotinib was significantly more effective than placebo (CR+PR+SD: 44.0 vs 27.5%; P =0.004)[8,10]. The trend was that the result of treatment with erlotinib was better in EGFR-positive than in EGFR-negative patients (OR: 11.6 vs 3.2%; P = 0.1). A significantly favourable response relationship was found for Asian patients, woman, patients with an adenocarcinoma and people who had never smoked[8,10].
Discussion: in a limited number of patients (though a large number in comparison with placebo), treatment with erlotinib led to an improvement in the state of the disease. The progression of the disease was temporarily halted in slightly more than one-third of the patients. However, erlotinib has no convincingly favourable effect on about half of the patients.

Table 1. Efficacy of erlotinib on patients with advanced NSCLC (Shepherd et al. 2005[10]).

	Erlotinib	Placebo	P-value
Number of evaluated patients with at least 1 (radiologically) demonstrable lesion	427 (88%)	211 (87%)	

(measurable disease)			
Complete Response	4 (0.9%)	1 (< 0.5%)	NB
Partial Response	34 (8.0%)	1 (< 0.5%)	< 0.001
Stable Disease	150 (35.1%)	56 (26.5%)	< 0.001
Progressive Disease	239 (56.0%)	153 (72.5%)	NB
Median duration of response (weeks)	34.3	15.9	NB

NB: unknown.

Conclusion: treatment with erlotinib reduced the progression of the disease, or improvement in the state of the disease occurred, in slightly more than half of the patients.

4.b. Efficacy

The (median) time to progression (TTP) and the (median) progression-free survival (PFS) are regarded as intermediate parameters for efficacy. The (median) total survival (OS) is the definitive measure here. In some cases, where the duration of the study is sufficiently long, progression-free survival can be used as a surrogate parameter (Note for Guidance 2005)[18].

In the BR.21 study, total survival was the primary endpoint. Secondary endpoints included progression-free survival, the degree and duration of the response (4.a.) and quality of life (4.d.)[10]. In the patients treated with erlotinib, both progression-free survival and total survival measured over a period of two years were significantly longer than in the patients treated with placebo (table 2). In comparison with placebo, the stratification factors and the EGFR status-corrected risk (HR) on respectively progression and death were significantly reduced: HR_{prog}: 0.61 (95% BI: 0.51-0.73) and HR_{death}: 0.73 (95% BI: 0.60-0.87)[8,10]. The actuarially calculated yearly survival percentages for patients treated with erlotinib and placebo were respectively 31.2 and 21.5%[8,10]. For total survival a good correlation was found for Asian patients, patients with an adenocarcinoma and persons who had never smoked[8,10].

Table 2. Efficacy of erlotinib in patients with advanced NSCLC (Shepherd et al.[10]).

	Erlotinib	**Placebo**	**P-value**
Number of patients	488	243	
Median progression-free survival:			
In weeks[x]	9.7 (8.4–12.4)[1]	8.0 (7.9–8.1)[1]	< 0.001
In months[x]	2.2 (NB)[1]	1.8 (NB)[1]	< 0.001
Median total survival (months)	6.7 (5.5–7.8)[1]	4.7 (4.1–6.3)[1]	0.001

[1] 95% reliability interval.

Discussion: in comparison with supportive care, treatment with erlotinib lengthened survival with two months. The disease also remained stable for significantly longer.

In more or less comparable patients with advanced NSCLC, median survival increases significantly after treatment with docetaxel (75 mg/m^2, IV, 1x per 3 weeks)[1] in comparison with supportive care over a period of 1.5 years (7.0 vs 4.6 months; P=0.01; N=55 vs N=49), as also does the yearly survival percentage (37 vs 11%; P=0.003)[13]. Fossella et al. reported for treatment with docetaxel a median survival period of 5.7 months (95% BI: 5.1-7.1; N=125) (yearly survival percentage: 32%)[14]. In the phase II study of Quoix et al., the median total survival for this second-line treatment with docetaxel was 4.7 months (95% BI: 3.8-5.9; N=93)[15]. The relatively short duration here would seem to be related to the relatively poor

state of the patients (ECOG-PS 2: 53%; score 3: 24%)[15]. In the phase III study in which docetaxel (NITT=288) was compared with pemetrexed (500 mg/m^2, IV, 1x per 3 weeks; NITT=283), the median total survival was respectively 8.3 (95% BI: 7.0-9.4) and 7.9 months (95% BI: 6.3-9.4). the difference between the treatments is not significant (P=0.226)[17]. For both treatments administered in the second line a yearly survival percentage of 29.7% was calculated. In the above-mentioned studies the response percentages and the period in which the diseased state improved or stabilised were comparable with the results of the BR.21 study with erlotinib[10,13-16].

When the results of studies carried out with docetaxel and pemetrexed are compared with those of the BR.21 study, it appears that the result of using erlotinib to treat patients with advanced stage IIIB/IV NSCLC is comparable with that of treatment with docetaxel or pemetrexed. However, together with this conclusion it should be stated that in the light of the number of patients treated in the third line (erlotinib ± 365[10] vs docetaxel ± 45[13,14]), the result achieved with erlotinib also applies to patients who have already undergone two previous chemotherapeutic cycles of treatment. Pemetrexed has only been investigated in patients who had undergone one previous treatment cycle, largely (> 95%) on the basis of a platinum compound[16].

Conclusion: in comparison with placebo, treatment with erlotinib has a favourable effect on survival and the period during which the disease is stable. The effectiveness of erlotinib seems comparable with that of docetaxel and pemetrexed with respect to patients with advanced stage IIIB/IV NSCLC who have undergone prior treatment with platinum-containing chemotherapy. Erlotinib on the other hand, unlike docetaxel, can be used even in the third line.

4.c. Side effects

In approximately 80% of the patients from the BR.21 study, the dose intensity was 90% or more. For almost all other patients, this was lower than 0%. Approximately 5% withdrew from the study due to the occurrence of side effects[8,10].
The most frequently occurring side effects of erlotinib are an acne-like skin rash and diarrhoea (table 3)[5,8-10] (Robert et al. 2005[19]). These side effects were severe or extremely severe in a number of patients. The dose was reduced in respectively 5 and 1% of the patients as a result of these side effects. Apparently, the occurrence of a skin rash did appear to be correlated to a favourable response to treatment[10]. Other side effects that occurred relatively frequently were anorexia, stomatitis, eye infection (keratitis) and the development of infections (table 3). Temporary increases in the liver enzyme values also occur relatively often[5,8,9].

Table 3. Most frequently occurring (> 10%) severe side effects of erlotinib in patients with advanced NSCLC (Shepherd et al. 2005[10]).

	Erlotinib (N=485)		Placebo (N=242)		Significance (P-value)	
Side effect	**All[1]**	**grade 3/4[1]**	**All[1]**	**Grade 3/4[1]**	**All**	**Grade 3/4**
Rash	76	9	17	0	< 0.001	< 0.001
Anorexia	69	9	56	5	< 0.001	0.06
Nausea	40	3	34	< 1	0.12	0.07
Retching	25	3	23	2	0.52	0.45
Stomatitis	19	< 1	3	0	< 0.001	0.31
Diahorrea	55	6	19	<1	< 0.001	< 0.001
Dehydration	7	4	6	3	0.64	0.67
Eye irritations	28	1	9	< 1	< 0.001	0.67

Tiredness	79	19	74	23	0.22	0.33
Infection	34	2	21	5	< 0.001	0.33
Pulmonary fibrosis	3	< 1	3	0	1.0	1.0
Pneumonitis or pulmonary infiltrates	3	< 1	3	< 1	0.64	1.0

[1] percentage of the number of patients

In the patients treated with EGFR-tyrosine kinase inhibitors, interstitial lung disorders with a fatal outcome have occasionally been reported[9,11,12] (Kris et al., 2003[20]; Fukuoka et al., 2003[21]; Giaccone et al., 2004[22]; Herbst et al., 2004[23]; Thatcher et al., 2005[24]). In the BR.21 study, however, the frequency of these side effects (0.8%) did not differ in the two treatment groups[8,10](Cohen et al., 2005[25]).

The characteristic side effects and diarrhoea seen in the BR.21 study were also observed as such in the phase II[9] study and the phase III studies in which the effect of erlotinib was studied in combination with first-line palliative chemotherapy on the basis of a platinum complex[11,12]. The side effects profile of erlotinib demonstrates a great deal of similarity with that of gefitinib[19-25].

Discussion: characteristic side effects for treatment with erlotinib are the rash and diarrhoea, which can be severe. These side effects are usually temporary in nature, treatable (diarrhoea) or are reduced by lowering the dose[6,9-11].

The treatment of advanced NSCLC with docetaxel is characterised by the occurrence of severe haematological side effects, in particular (febrile) neutropenia. This often leads to hospital admission and requires supportive treatment with growth factors and/or blood transfusions[1,6,13-16]. Severe diarrhoea and loss of hair also occur relatively frequently[1,6,13-16]. The side effects profile of pemetrexed is more favourable than that of docetaxel, in particular, due to the very much lower frequency of severe haematological side effects[6-10,16].

On the basis of the research data published, the side effects profile of docetaxel is clearly less favourable than that of erlotinib and pemetrexed. Apart from the fact that haematological side effects hardly occur with erlotinib, the available research data do not clearly indicate whether the difference in the composition of the side effects profile of erlotinib is favourable or less favourable is than the profile of pemetrexed.

Conclusion: the main side effects of erlotinib are rashes and diarrhoea. Anorexia, stomatitis, eye irritations and infections also occur relatively often. The side effects profile of erlotinib is more favourable than that of docetaxel, in particular because there are hardly any (severe) haematological side effects. With the exception of the rash and the haematological side effects, there is a lack of clarity about the degree to which the nature and severity of the side effects caused by erlotinib and pemetrexed differ.

4.d. Quality of life

During the phase II and III studies, secondary outcome parameters were collected over the quality of life by using the EORTC QLQ-C30 and LCSS/LC13 questionnaires. When treated with erlotinib in the BR.21 study, the participating patients (87% upon initiation [and > 70% during treatment]) experienced a delay in the exacerbation in disease-related symptoms such as coughing (4.9 vs 3.7 months; P=0.04), tightness of the chest (4.7 vs 2.9 months; P=0.04) and pain (2.8 vs 1.9 months; P=0.03)[5,8,10](Bezjak et al. 2006[25]). The improvement in these primary outcomes related to the response (CR+PR vs SD and PD; P<0.01) occurred in respectively 44% (vs placebo: 27%), 34% (vs 23%) and 42% (vs 28%) of the patients treated

with erlotinib[25]. The delay in the occurrence of the disease phenomena went hand-in-hand with an improvement in physical functioning (erlotinib: 31% vs placebo: 19%; P=0.01) and the general quality of life (31 vs 26%; P<0.0001). With respect to the occurrence of tiredness, the improvement was a trend (45 vs 36%; P=0.06)[25].

Conclusion: The occurrence of a number of disease phenomena characteristic of NSCLC was delayed in patients who responded to treatment with erlotinib and there was an improvement in physical functioning and general quality of life.

4.e. Experience

In November 2004 erlotinib was granted marketing-permission in the United States for use in the same indication as in Europe[26]. Approximately 20,000 patients have been treated with erlotinib throughout the world (manufacturer's claim). The experience obtained with erlotinib is limited.

4.f. Applicability

Erlotinib is mainly metabolised in the liver via the enzyme CYP3A4 and, to a lesser degree, CYP1A2. After conversion, most of the dose is eliminated in the faeces via the gal (> 90%). A small proportion of the dose is cleared renally (< 10%). In the light of this, interactions are to be expected: when used simultaneously with ketoconazole the amount of erlotinib in the blood is considerably increased whilst the CYP3A4-inductor rifampicin increases the clearance by a factor of three[9,21]. For this reason dose adjustment seems to be necessary when inductors and inhibitors of CYP3A4 are used simultaneously[5,8].

Caution is required with patients with a liver disorder. It is possible to treat patients with this disorder with a lower dose of erlotinib[5,8].
Erlotinib has not been studied in children and adolescents.

Conclusion: erlotinib is mainly metabolised in the liver. Patients with liver function disorder should therefore be treated with a lower dose of erlotinib. When inductors and inhibitors of CYP3A4 are being used simultaneously, it may also be necessary to adjust the dose of erlotinib.

4.g. User-friendliness

Erlotinib is taken once daily per os, a minimum of one hour before or two hours after the intake of food. In comparison with the parenteral administration of docetaxel and pemetrexed, the oral administration form of erlotinib is an advantage.

5. Other considerations

5.a. Costs

Table 4. Costs of drugs used to treat advanced local or metastised NSCLC (AIP excl. VAT, source: Z-Index November 2005).

Drug	Price (€)	Dose	Costs (€) per 3 months
Erlotinib (package à 30 tablets)	2,184.00	150 mg/day oral	6,552.00
Docetaxel (120-140 mg/3 wks)[1]	1,230.00-1,430.00	75 mg/m^2, IV, 3 wks => 120-140 mg/3 wks	4,920.00-5,718.00[3]
Pemetrexed (2 flacons à 500 mg/m^2 - 3 wks)[2]	3,234.00	500 mg/m^2, IV/3 wks => 850-900 mg/3 wks	12,936.00[3]

[1] ave. dose male: 1.8m^2 x 75 mg =135 mg; ave. dose female: 1.7m^2 x 75 mg = 127.5 mg.

[2] ave. dose male/female = 900/850 mg.

[3] 4 cycles IV.

5.b. Specific details

Although EGF plays an important role in the development of solid tumours such as the NSCLC, it has now become clear that the use of EGFR tyrosine kinase-inhibiting substances does not always lead to a clear therapeutic effect[11,12,22-24] (Doroshow 2005[27]; Hirsch & Bunn[28]). This suggests that various intracellular signal transduction systems may be involved in EGFR-mediated processes, of that the EGFR sometimes play a less dominant role in the development of the disease than is currently assumed. A number of genetic factors also affect the efficacy of erlotinib with respect to EGFR in patients with NSCLC. EGFR-tyrosine kinase inhibitors have proven to be particularly efficient and effective in patients with bronchioalveolar and adenocarcinoma, female patients, patients who have never smoked and patients of Eastern-Asian (Chinese/Japanese) origin. It has become clear that this is largely related to the genetic make-up of EGFR[3,4,24,26-28] (Tsao et al. 2005[29]; Bell et al. 2005[30]; Eberhard et al. 2005[31]; Pao & Miller 2005[32]). With these types of tumours and groups of patients, EGFR occur relatively often, with a greater sensitivity to erlotinib and gefitinib as a result of somatic mutations in the different protein structure of the ATB binding locations in exons 18-21. Mutations in the signal transduction of KRAS protein involved in EGFR seems in part to be the cause of the limited efficacy of tyrosine kinase inhibitors on (ex)-smokers[3,4,24,31,32]. However, in as far as the molecular analysis has taken place of EGFR of patients involved in phase II and III studies of erlotinib and gefitinib has not demonstrated an unequivocal relationship between receptor density (determined with IHC), the number of gene copies (determined with FISH or quantitative PCR) and the presence of mutated EGFR (PCR) and survival [27-32](Onn & Herbst 2005[33]; Gandara & Gumerlock 2005[34]). For this reason prospective studies are essential for identifying patients who can benefit from treatment with erlotinib or who are resistant to it. Although the group characteristics and the combined results of IHC and FISH/PCR determinations seem to have a certain predictive value, and the occurrence of skin reactions is associated with efficacy, it is still not an easy matter to select the right patients for treatment with erlotinib. As long as no clear 'markers' have been found, the effect of erlotinib and other EGFR-tyrosine kinase inhibitors cannot be estimated at their real value. In view of this situation it is therefore probable that these drugs will eventually turn out to be effective only in a limited group of patients[3,4,10,24,27-32]. In this regard, it is not clear whether treatment with erlotinib makes sense in patients who do not belong to the above-named groups of patients and who have a low receptor density and/or non-mutated EGFR or a K-*ras* mutation, in comparison with a result that could be achieved by treatment with docetaxel or pemetrexed[10,24,28]. The importance of screening for EGFR with respect to receptor status and genetic make-up prior to treatment with an EGFR tyrosine kinase inhibitor is illustrated by the results of the BR.21 study. Due to the heterogeneous character of the treatment groups and the lack of sufficient screening in advance, there was a lack of convincing evidence that erlotinib was more effective in EGFR-positive patients than in EGFR-negative patients[8,10,27].

6. The value of erlotinib as claimed by the manufacturer

6.a. Manufacturer's claim

Erlotinib is intended for the treatment of patients with locally advanced or metastised NSCLC stage IIIB/IV after the failure of at least one prior chemotherapy regime. Treatment with erlotinib is life-extending, irrespective of the condition of the patients or the number of prior treatments. Treatment with erlotinib also improves a number of symptoms directly related to the disease. Erlotinib is well-tolerated and its character is mild in comparison with the alternatives available in the form of radiotherapy and chemotherapy.

6.b. CFH's assessment of the manufacturer's claim

Erlotinib has only proven to be effective in the treatment of patients with extremely advanced NSCLC stage IIIB/IV who, after one or two prior treatments with chemotherapy (one of which on the basis of a platinum complex). In light of the very poor prognosis of the disease at this stage, a small survival gain of two months is regarded as valuable. Erlotinib should only be given if sufficient EGFR have been demonstrated in the patient. Due to the lack of suitable 'markers' it is not yet clear whether patients are being treated optimally with erlotinib. Activating mutations in the EGFR-gene lead to a higher chance of a response; K-*ras* mutation in the tumour, on the other hand, causes resistance.
Other drugs that can be used for the treatment of advanced NSCLC stage IIIB/IV are docetaxel and pemetrexed. As second-line treatment the efficacy of docetaxel, erlotinib, and pemetrexed is comparable. As third-line treatment docetaxel seems less effective than erlotinib. Pemetrexed has not been studied as third-line treatment. Due to the limited haematological toxicity, the side effects profile of erlotinib is more favourable than that of docetaxel. Unlike pemetrexed, treatment with erlotinib does not lead to haematological side effects. Although pemetrexed does not cause skin rash, it is not possible to draw further comparisons between erlotinib and pemetrexed on the basis of the literature.
The occurrence of a number of disease symptoms that are characteristic of NSCLC can be delayed by treatment with erlotinib and there is an improvement in physical functioning and general quality of life. Unlike docetaxel and pemetrexed, erlotinib can be taken orally.

7. CFH-advice

After chemotherapy based on a platinum complex fails, erlotinib can be used in the palliative chemotherapeutic treatment of advanced non-small cell lung carcinoma (stage IIIB/IV). In particular the use of erlotinib seems to be beneficial for women with advance NSCLC, patients with a bronchioalveolar carcinoma or adenocarcinoma, patients who have never smoked and patients of Eastern-Asian origin. If possible, a sufficient quantity of epidermal growth factor receptors (EGFR[HER1]) should be demonstrated. Patients with an activating mutation in the EGFR-gene have a better chance of a therapeutic effect of erlotinib. K-*ras* mutation in the tumour leads to resistance to erlotinib. Apart from erlotinib, the parenterally administered docetaxel or pemetrexed can also be used for this indication. In view of the more favourable side effects profile and the oral administration, the preference of the CFH goes out to erlotinib for the above-mentioned groups of patients.

8. Literature

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This text was approved by the Medicinal Products Reimbursement Committee during their meeting on 27th February 2006.

The data from this pharmacotherapeutic report will be incorporated into chapter 17 of the Farmacotherapeutisch Kompas.