Horizon Scanning in Oncology

Gefitinib (Iressa®) for the 1st-line treatment of non-small cell lung cancer

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1 Background

1.1 Drug

Generic/Brand name/ATC code: Gefitinib/Iressa®/ L01XE02

Developer/Company: Astra Zeneca

Description: Gefitinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. To predict response to this tyrosine kinase inhibitor (TKI), several biomarkers such as EGFR gene copy number or EGFR protein expression were discussed, but DNA mutational analysis is now the preferred method which allows identifying patients with activating mutations in EGFR (i.e. exon 19 deletions or exon 21 L858R point mutations) [1, 2].

gefitinib is a tyrosine kinase inhibitor

Administration: 250 mg gefitinib are administered orally once daily.

1.2 Indication

Gefitinib is indicated as 1st-line mono-therapy for patients with EGFR mutations and advanced or metastatic non-small cell lung cancer (NSCLC).

as 1st-line therapy for EGFR mutation positive locally advanced or metastatic NSCLC

1.3 Burden of disease

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-deaths worldwide. Its primary risk factors are first- and second-hand smoke exposition [1]. Men are still more often affected by NSCLC than women, with the majority of patients being diagnosed at an age ≥ 65 years [3]. 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 and 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 IIIB and IV, respectively [4].

1st-line therapy of advanced NSCLC depends on a number of factors, such as tumour stage, histo-pathologic subtype and performance status [1, 2]. In addition, due to the development of targeted therapies such as gefitinib, EGFR mutational status should also be assessed prior to therapy. Guidelines differ, whether routine testing for EGFR mutations is indicated regardless of the histo-pathologic subtype. For example, the "National Comprehensive Cancer Guidelines" [1] do not recommend EGFR testing for squamous cell carcinoma (one type of NSCLC) due to the low incidence of mutations (i.e. in less than 3.6% of patients) whereas UpToDate online [5] does not differentiate between squamous cell carcinomas and adenocarcinomas.

1st-line therapy depends on several factors such as histo-pathologic subtype, performance status and EGFR mutational status

an estimated 440 patients potentially eligible for gefitinib

3,600 people died of lung cancer and, about 4,100 new cases of lung cancer were diagnosed in Austria in 2008 [6]. As NSCLC accounts for about 85% of all lung cancer cases [7] of which 85% [1, 8] can be expected to present with advanced disease, an estimated 2,960 persons are diagnosed with advanced NSCLC per year. Applying estimates of an average frequency of activating EGFR mutations (within an unselected population about 15%) to these numbers would result in about 440 individuals with activating EGFR mutations and thus potentially eligible for treatment with Iressa®.

1.4 Current treatment options

standard of care for 1st-line therapy…

Treatment options for 1st-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) but for none of these combinations superiority has been established unequivocally. These doublets can be combined with monoclonal antibodies, foremost bevacizumab, in patients with non-squamous NSCLC.
- 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 1st-line treatment is generally used for elderly patients or for those with poor performance status.
- radiation therapy
- targeted therapies:
  - TKIs as mono-therapy (erlotinib (EMA's Committee for Medicinal Products for Human Use adopted a positive opinion for 1st line therapy of NSCLC in July 2011 [9]), gefitinib)
  - monoclonal antibodies (bevacizumab) in combination with chemotherapy [2].

…for patient with EGFR mutations: TKIs

However, if patients are EGFR mutational status positive, EGFR-TK inhibitors such as gefitinib are increasingly used as standard 1st-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) [5].

1.5 Current regulatory status

The EMA granted market authorization for gefitinib for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR TK in June 2009 [10].

EMA: market authorization in June 2009

In the US, the FDA had approved gefitinib in 2003 but limited the indication in 2005 to mono-therapy for the continued treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from gefitinib [11].

FDA: approved since 2003, limited indication in 2005

1.6 Treatment costs

One package of Iressa® containing 30 tablets à 250 mg costs € 2,463 per month [12]. In a pivotal phase III trial [13], median duration of treatment was 6.4 months. Assuming that treatment is administered for 6 months on average, total treatment costs of € 14,616.- will incur. Savings might arise by sparing patients considerable side-effects associated with platinum-based chemotherapies, leading to a reduction of in-patient treatments.

monthly treatment costs € 2,463

2 Evidence

A literature search was conducted in addition to a hand search on the 25th and 26th of July 2011 in the following databases: Cochrane Library, Ovid Medline, CRD Database and EMBASE. Search terms included were "Carcinoma, Non-Small-Cell Lung", "non small cell lung cancer", "gefitinib", "iressa", "NSCLC", "first line", "1st line", "untreated", "chemotherapy naïve".

7 references reporting results of 4 RCTs and 1 meta-analysis included

After removing duplicates, 553 references were identified. Of those, only randomised controlled trials (RCTs) and meta-analyses presenting results for EGFR mutational positive patients treated with 1st-line gefitinib were included. Overall, 7 references reporting results of 4 RCTs and 1 meta-analysis were included [13-19].

In comparison to the initial HSS report [20], final overall survival (OS) results of the IPASS trial have become available [14], two additional studies were found [17, 21] and the results of the NEJ002 trial have been fully published [19].

2.1 Efficacy and safety - RCTs

Table 1: efficacy and safety of studies enrolling patients regardless of EGFR mutational status

Reference	Mok et al.; Fukuoka et al., IPASS trial [13, 14]	Lee et al., first-SIGNAL study, unpublished, conference presentation available [15, 16]
Sponsor	Astra Zeneca	Astra Zeneca
Country	China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand	Korea
Design	phase III, open-label, multicentre, randomized controlled, non-inferiority trial	Randomized, phase III
Hypothesis	non-inferiority	NA
Number of patients	I 609 vs C 608	I 159 vs C 150
Treatment		
Intervention	gefitinib 250mg/d, orally	gefitinib 250mg/d, orally
Control	200mg/m² paclitaxel (d1), iv + carboplatin (AUC 5-6 mg per millilitre per minute, administered iv over a period of 15-60 minutes) once per cycle (= 3 weeks) for up to 6 cycles	1250mg/m² gemcitabine on day 1 & 8 + 80mg/m² cisplatin on day 1 every 3 weeks up to 9 cycles
Inclusion criteria	untreated patients, NSCLC stage IIIB or IV, non-smokers (<100 cigarettes in their lifetime) or light smokers (≤10 pack-years, or quit smoking ≥ 15 yrs before), ECOG PS 0 to 2	untreated, never-smokers, adenocarcinoma, ECOG PS 0-2, stage IIIB or IV
Participants characteristics		
Median age years (range)	I 57 (24-84) vs C 57 (25-84)	
Females (%)	I 78 vs C 79	I 88 vs C 89
Non-smokers (%)	I 94 vs C 94	I 100 vs C 100
Adenocarcinoma (%)	I 95 vs C 97	I 100 vs C 100
Stage IIIB (%)	I 25 vs C 24	I 10 vs C 10
Stage IV (%)	I 75 vs C 76	I 90 vs C 90
EGFR mutations (%)	I 22 vs C 21	I 49 vs C 37
Performance Status ≤1 (%)	WHO: I 90 vs C 89	ECOG: I 91 vs C 91
Follow-up	median: 5.6 months	NA
OS		(primary outcome)
median (months)	Interim analysis: I 18.6 vs C 17.3 Final analysis: I 18.8 vs 17.4	I 21.3 vs C 23.3

HR	Interim analysis: 0.91 (95%CI 0.76 to 1.10) Final analysis: 0.90 (95%CI 0.79 to 1.02; p=0.109)			1.00 (95%CI 0.75 to 1.34, p= 0.43)
subgroups according to EGFR status	EGFR mutation positive: HR= 0.78 (95% CI 0.50 to 1.20) EGFR mutation negative: HR= 1.38 (95% CI 0.92 to 2.09)			positive: I 30.6 months vs C 26.5 months HR= 0.82 (95%CI 0.35 to 1.92, p= 0.65) negative: I 18.4 months vs 23.3 months HR=1.2 (95%CI 0.57 to 2.52, p= 0.63)
PFS	(primary outcome)			
median (months)	I 5.7 vs C 5.8			I 6.1 vs C 6.6
HR	0.74 (95% CI 0.65 to 0.85, p<0.001)			0.813 (95%CI 0.641 to 1.031, p=0.044)
subgroups according to EGFR mutational status	positive: HR = 0.48 (95% CI 0.36 to 0.64, p<0.001) negative: HR = 2.85 (95% CI 2.05 to 3.98, p<0.001)			positive: I 8.4 months vs C 6.7 months HR= 0.61 (95%CI 0.31 to 1.22, p= 0.08) negative : I 2.1 months vs 6.4 months HR=1.5 (95%CI 0.88 to 2.62, p= 0.07)
ORR (%)	I 43 vs C 32.2 OR=1.59 (95% CI 1.25 to 2.01, p<0.001)			-
subgroups according to EGFR mutational status	positive: I 71.2 vs C 47.3 (p<0.001) negative: I 1.1 vs C 23.5 (p=0.001)			positive: I 84.6 vs C 37.5, OR= 9.17 (95%CI 2.11 to 39.85, p= 0.002) negative: I 25.9 vs C 51.9, OR= 0.33 (95%CI 0.10 to 1.02, p=0.05)
QoL	FACT-L: OR=1.34 (95% CI 1.06 to 1.69, p=0.01) TOI: OR= 1.78 (95%CI 1.4 to 2.26, p<0.001)			EORTC QLQ-C30 and QLQ-LC13: more favourable outcomes for I group for global health status (p=0.0007), role functioning (p=0.007), social functioning (p=0.002)
subgroups according to EGFR mutational status	positive: FACT-L QoL improvement rate: 70.2% vs 44.5%, p<0.0001 negative FACT-L QoL improvement rate: 14.6% vs 36.3%, p=0.0021			
Any grade AEs		I	C	
Hematologic	Febrile Neutropenia	0.2	0.2	-
Non-hematologic	Rash	66.2	22.4	-
	Dry skin	23.9	2.9	
	Diarrhoea	46.6	21.7	
	Paronychia	13.5	0	
	Anorexia	21.9	42.6	
	Pruritus	19.4	12.6	
	Asthenia	16.8	44.0	
	Stomatitis	17.0	8.7	
	Nausea	16.6	44.3	
	Constipation	12.0	29.4	
	Vomiting	12.9	33.3	
	ILD	2.6	1.4	

Grade ≥3 AEs		I	C	
Hematologic	Leukopenia	1.5	35	-
	Anaemia	2.2	10.6	
	Neutropenia	3.7	67.1	
Non-hematologic	Rash	3.1	0.8	-
	Dry skin	0	0	
	Diarrhoea	3.8	1.4	
	Paronychia	0.3	0	
	Anorexia	1.5	2.7	
	Pruritus	0.7	0.2	
	Asthenia	0.3	1.9	
	Stomatitis	0.2	0.2	
	Nausea	0.3	1.5	
	Constipation	0	0.2	
	Vomiting	0.2	2.7	
Deaths associated with AEs		3.8	2.7	-
Notes	52% of the chemotherapy group received TKIs and 65% of the gefitinib group were treated with chemotherapy after study treatment discontinuation			post-study use of EGFR TKIs in 81% of patients in chemotherapy group

Table 2: efficacy and safety of studies enrolling only patients with EGFR mutations

Reference	Mitsudomi et al., WJTOG3405 [17]	Maemondo et al. NEJ002 [18, 19]
Sponsor	West Japan Oncology Group (WJOG)	Japan Society for Promotion of Science , Japanese Foundation for the Multidisciplinary Treatment of Cancer, Tokyo Oncology Group
Country	Japan	Japan
Design	multicentre, randomised, open-label, phase III	multicentre, randomised, phase III
Hypothesis	superiority	superiority
Number of patients	I 86 vs C 86	I 114 vs C 114
Treatment		
Intervention	gefitinib 250mg/d, orally	gefitinib 250mg/d, orally
Control	60mg/m² docetaxel, iv + 80mg/m² cisplatin, iv; administered every 21 days for three to six cycles	200mg/m² paclitaxel, iv + carboplatin (AUC 6), iv; both administered at the first day of a 3-week cycle for at least 3 cycles
Inclusion criteria	NSCLC stage IIIB or IV, WHO PS 0 or 1, activating EGFR mutations, postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, when the interval between the end of adjuvant chemotherapy and registration > 6 months for platinum-doublet therapy and > 1 month for oral tegafur plus uracil therapy, ≤75 years	untreated, advanced non–small-cell lung cancer harbouring sensitive EGFR mutations, ≤75 years

Participants characteristics						
Median age years (range)	I 64 (34–74) vs C 64 (41–75)			I 64 (43-75) vs C 63 (35-75)		
Females (%)	I 69 vs C 70			I 63 vs C 64		
Non-smokers (%)	I 71 vs C 66			I 66 vs C 58		
Adenocarcinoma (%)	I 97 vs C 98			I 90 vs C 97		
Stage IIIB (%)	I 10 pts vs C 9 pts			I 13 vs C 18		
Stage IV (%)	I 41 pts vs C 41 pts			I 77 vs C 74		
EGFRmutations (%)	I 100 vs C 100			I 100 vs C 100		
Performance Status ≤1 (%)	WHO: I 86 vs C 86			ECOG: I 99 vs C 98		
Follow-up	median: 81 days			median: 527 days		
OS						
Median (months)	I 30.9 (95%CI 24.1+) vs C not reached (95% CI 15.0+)			I 30.5 vs C 23.6 (p=0.31)		
HR	1.638 (95% CI 0.75 – 3.58), p=0.21			-		
PFS	(primary outcome)			(primary outcome)		
Median (months)	I 9.2 vs C 6.3			Interim analysis: I 10.4 vs C 5.5 Final analysis: I 10.8 vs C 5.4		
HR	0.489 (95% CI 0.336–0.710; p<0.0001)			Interim analysis: 0.36 (95% CI 0.25 - 0.51; p<0.001) Final analysis: 0.30;(95% CI 0.22 - 0.41; p<0.001)		
ORR (%)	I 62·1 (36 of 58 patients) vs C 32·2 (19 of 59 patients), p<0·0001			I 73.7 vs C 30.7; p<0.001		
QoL	NA			Care notebook questionnaire: time to deterioration of Physical Well-Being: HR = 0.28 (p<0.001) Time to deterioration of Life Well-Being: HR=0.88 (p=0.55)		
Any grade AEs		I	C		I	C
Hematologic	Leucopenia	15	93	Anaemia	18.4	64.6
	Anaemia	38	89	Neutropenia	6.1	77
	Neutropenia	8	92	Thrombocytopenia	7	28.3
	Thrombocytopenia	14	33			
Non-hematologic	Rash	85	8	ILD	5.3	0
	Liver enzymes	70	40	Rash	71.7	22.1
	Dry skin	54	3	Liver enzymes	55.3	32.7
	Diarrhoea	54	40	Dry skin	-	-
	Fatigue	39	83	Diarrhoea	34.2	6.2
	Paronychia	32	1	Fatigue	10.5	27.4
	Stomatitis	22	15	Appetite loss	14.9	56.6
	Nausea	21	94	Neuropathy	0.9	54.9
	Constipation	16	44	Arthralgia	3.5	47.8
	Alopecia	9	76	Pneumonitis	5.3	0
	ILD	2	0			

Grade ≥3 AEs		I	C		I	C
Hematologic	Leukopenia	0	49	Anaemia	0	5.3
	Anaemia	0	17	Neutropenia	0.9	65.5
	Neutropenia	0	84	Thrombocytopenia	0	3.5
	Thrombocytopenia	0	0			
Non-hematologic	Rash	2	0	Overall grade ≥3	41.2	71.7
	Liver enzymes	28	2	Rash	5.3	2.7
	Dry skin	0	0	Liver enzymes	26.3	0.9
	Diarrhoea	1	0	Dry skin	-	-
	Fatigue	2	2	Diarrhoea	0.9	0
	Paronychia	1	0	Fatigue	2.6	0.9
	Stomatitis	0	0	Appetite loss	5.3	6.2
	Nausea	1	3	Neuropathy	0	6.2
	Constipation	0	0	Arthralgia	0.9	7.1
	Alopecia	0	0	Pneumonitis	2.3	0
Deaths associated with AEs		1.1	0		NR	
Notes	interim analysis was originally planned to analyse progression-free survival, but this analysis was not done. Instead, the steering committee held on June 13, 2009, proposed the amendment of the sample size and the final analyses be done using available data. immature data for OS but follow-up on-going			The pre-planned interim analysis was performed 4 months after the 200th patient was enrolled (May 2009); and the independent data and safety monitoring committee recommended termination of the study. Therefore, the study was stopped at the end of May 2009; after study treatment discontinuation, 95% of the chemotherapy group consequently received 2nd-line gefitinib and 68% of the gefitinib group received platinum-based doublets		

Abbreviations: AE= adverse event, EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, TOI= trial outcome index, FACT-L = Functional Assessment of Cancer Therapy – Lung, ILD – Interstitial-lung-disease, 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

Overall four trials report results for 1st-line mono-therapy with gefitinib for patients with EGFR mutations. Of those, one is only available as abstract [15, 16], two trials included only patients with EGFR mutations [17, 19], whereas the other two present results for EGFR mutational positive subgroups [13, 15]. Nonetheless, all trials enrolled patients which are likely to have EGFR mutations (i.e. women, never-smokers, adenocarcinomas).

4 trials included

Results of the IPASS trial, a non-inferiority trial, were published twice: at first, PFS and interim results for OS were reported [13] and, more recently, final results of OS [14]. Another phase III trial by *Maemondo et al.* [19] was stopped after a pre-planned interim analysis had demonstrated superiority of gefitinib. In a 3rd trial, the WJTOG3405 trial [17], a sample size of 200 patients was initially calculated to demonstrate a HR of 0.56. Due to the fact that results of the IPASS as well as NEJ002 trial had been published while the study was on-going, further patient accrual was "considered to be futile and potentially unethical" [17]. The sample size was thus amended and the final analysis was performed based on the data available. However, follow-up data for safety and OS will be collected for an additional 1.5 years.

2 included only patients with EGFR mutations,

2 reported results for EGFR mutational status positive subgroups

PFS was the primary outcome in three trials [13, 17, 19] and showed consistent results for patients with EGFR mutations, favouring the gefitinib groups. Only the first-SIGNAL study deviated, because PFS was not improved in the subgroup with EGFR mutations, but this group was, with only 42 patients, very small. More favourable results were also found for ORR, even though it should be mentioned that assessment of PFS and tumour response was blinded in only one of the trials [19], a fact which might have impacted on these results.

results for PFS consistent , favouring the gefitinib group

For QoL, which was assessed in three trials [13, 15, 18], better results for patients treated with the TKI, again more pronounced in EGFR+ patients, were found.

also better QoL outcomes

In contrast, OS was not prolonged for patients treated with gefitinib in any of the trials, either for the overall populations or for patients with EGFR mutations. Especially the final OS results of the IPASS trial, the largest study, had been awaited with great interest but failed to demonstrate improved outcomes for patients treated with gefitinib. But these findings are likely to be influenced by subsequent lines of therapies, as, for example, 52% of the chemotherapy group received TKIs and 65% of the gefitinib group were treated with chemotherapy in the IPASS trial.

OS was not prolonged in any of the trials, not even in patients with EGFR mutations

but difficult to interpret this finding, because of subsequent lines of therapy

The most common AEs of any grade in patients treated with gefitinib were rash (I 85% vs C 8%) and diarrhoea (I 54% vs C 40%), whereas administration of chemotherapeutic regimens was more often associated with haematological AEs (e.g. leucopenia I 15% vs C 93%). Similar outcomes were also observed for AEs ≥3. Even though overall frequencies were reported in only one of the trials [19] (I 41% vs C 72%), individual AEs of higher grades also occurred more often in patients treated with chemotherapeutics than in those treated with gefitinib. Nonetheless, a maximum of 5% of patients treated with gefitinib developed interstitial lung disease, a sometimes fatal AE associated with gefitinib and more treatment-related deaths were seen in the TKI group overall (I 3.8% vs C 2.7%).

most common AEs of gefitinib were rash and diarrhoea, whereas haematological AEs were more frequent in chemotherapeutics group

2.2 Efficacy and safety - further studies

Ku et al. [21] conducted a meta-analysis of all trials mentioned above, thus comprising nearly 2,000 patients out of which 650 patients had EGFR mutations. In those patients, the combined HR for PFS was 0.45 (95%CI 0.38 – 0.55; $p<10^{-16}$), but like the individual studies, no significant difference was found for OS. Amongst patients with EGFR mutations the overall estimated odds ratio of ORR was 4.04 (95%CI 2.90-5.61, $p<10^{-15}$).

3 Commentary

all trials conducted in Asia, no results for Caucasian population

Since the EMA granted market authorization for gefitinib in June 2009, several studies focusing on patients with EGFR mutations have been published besides the IPASS trial. In addition, mature data for OS of the IPASS trial have also become available. All trials were conducted in an Asian population, a fact that prompted the EMA already at licensing to require a post-marketing prospective trial within a Caucasian population with confirmed EGFR mutations [22] (estimated study completion date is August 2012 [23]).

gefitinib increasingly standard 1st-line therapy

prolongation of PFS, less toxic than platinum based chemotherapy

Since its licensing, gefitinib has been increasingly used as standard of care for 1st-line therapy of patients who have tested positive for EGFR mutations, not only because of prolongation of PFS but also because of a more favourable toxicity profile than standard platinum-based chemotherapy. The ease of oral application also offers an advantage to patients in comparison to chemotherapy. In addition, even though the median duration of gefitinib therapy was about 6 months in the pivotal phase III study, Iressa® is potentially a long-term therapy, because it can be administered as long as disease does not progress and toxicity remains tolerable, whereas chemotherapies are administered for a maximum of 6 cycles. Consequently, gefitinib therapy after EGFR testing has been incorporated into several treatment guidelines [1, 2, 24].

unclear impact on OS

In contrast to consistent results for improved PFS and QoL in EGFR mutational status positive patients across all trials, no differences were found for OS; a finding which was confirmed in a meta-analysis [21]. However, this result is difficult to interpret, because subsequent lines of therapies might have influenced these outcomes as, for example, up to 81% of patients initially treated with chemotherapy, received TKI therapy after study treatment was discontinued and vice-versa. Also, only one trial explicitly mentioned that assessment of PFS was verified by central reviewers blinded to study treatment. As PFS is prone to assessment bias, especially in open-label trials, results for PFS might have been biased [25].

PFS might be biased due to missing verification by central reviewers

provision of EGFR routine testing and quality assurance programme of testing important

Even though clinical factors (adenocarcinoma, women, non-smokers, Asian ethnicity) are also useful for predicting response to EGFR TKIs [26, 27], the provision of routine EGFR mutation testing supported by a quality assurance programme in Austria is challenging. This is important, because of the consequences associated with either false-positive test results (i.e. denial of access to chemotherapy) or false-negative test results (i.e. denial of access to gefitinib) [28]. Moreover, mutational status might differ depending on where the tissue has been derived from (i.e. primary tumour vs metastatic lesions) [26] and to retrieve enough tumour material from biopsies is also often difficult. Related to that are issues concerning the identification and detection of further biomarkers (e.g. K-ras mutations, EML4-ALK mutations) which allow a more precise definition of patient groups which are either most likely to benefit or which are, or have become resistant to TKIs [1, 26]. Disease progression due to acquired resistance to TKI occurs eventually in all patients treated with gefitinib, leading to the development of new therapeutic approaches using agents which simultaneously inhibit EGFR and HER2 receptors [29].

mutational status can change and differs between metastases and primary tumour

due to acquired EGFR resistance, further therapies are being developed

In addition, EMA's Committee for Medicinal Products for Human Use has recently adopted a positive opinion to license erlotinib as 1st-line therapy for NSCLC patients with activating mutations of EGFR [30]. Since the costs of erlotinib are similar to those of gefitinib [12], a thorough comparison of efficacy and safety of these two drugs is of great interest. Some initial evidence from a retrospective study which included 154 Asian patients indicates that therapy with gefitinib might be associated with fewer adverse events than erlotinib therapy [31].

erlotinib, another TKI, was recently licensed for 1st line NSCLC therapy

NICE recommended gefitinib under patients access scheme = costs for gefitinib are fixed at £ 12,200

Concerning costs, the English "National Institute for Health and Clinical Excellence" evaluated gefitinib and recommended it for the 1st-line treatment of NSCLC, given that the drug will be provided under the patient access scheme at a fixed price [32]. This scheme determines that the costs per patients are fixed at £12,200 (≈ € 13,600) per patient. If patients are treated less than 3 months with gefitinib, no costs will occur at all. Of note, the costs for one package Iressa® in England are the same like in Austria.

4 References

1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (V.3.2011).* 2011 [cited 2011 21.07]; Available from: www.nccn.org.
2. UpToDate. *Targeted agents in the initial systemic treatment of advanced non-small cell lung cancer.* 2011 [cited 2011 21.07.]; Available from: http://www.uptodate.com/contents/targeted-agents-in-the-initial-systemic-treatment-of-advanced-non-small-cell-lung-cancer?source=search_result&selectedTitle=7~150#H14.
3. National Cancer Institute, *SEER Stat Fact Sheets: Lung and Bronchus.* 2011.
4. UptoDate 19.2. *Diagnosis and staging of non-small cell lung cancer.* 2011 [cited 2011 22. August]; Available from: http://www.uptodate.com/contents/diagnosis-and-staging-of-non-small-cell-lung-cancer?source=search_result&selectedTitle=2~150.
5. UpToDate 19.2. *Initial systemic chemotherapy for advanced non-small cell lung cancer.* 2011 [cited; Available from: http://www.uptodate.com/contents/initial-systemic-chemotherapy-for-advanced-non-small-cell-lung-cancer?source=search_result&selectedTitle=3~150#H14.
6. Statistik Austria. *Statistiken - Gesundheit - Krebserkrankungen - Luftröhre, Bronchien, Lunge.* 2011 [cited 2011 22.August]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/luftroehre_bronchien_lunge/index.html.
7. Stinchcombe, T.E. and M.A. Socinski, *Current treatments for advanced stage non-small cell lung cancer.* Proc Am Thorac Soc, 2009. **6**(2): p. 233-41.
8. National Horizon Scanning Centre, *Cetuximab (Erbitux) for Non-Small Cell Lung Cancer: horizon scanning technology briefing.* 2006, Birmingham: National Horizon Scanning Centre (NHSC). 6.
9. European Medicines Agency. *Pending EC decision - Tarceva.* 2011 [cited 2011 10. October]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000618/smops/Positive/human_smop_000263.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d127.
10. European Medicines Agency. *EPARs for authorised medicinal products for human use.* 2009 [cited 2009 24.11.]; Available from: http://www.emea.europa.eu/humandocs/Humans/EPAR/iressa/iressa.htm.
11. U.S. Drug and Food Administration. *Drugs@FDA - Label and Approval History Iressa.* 2003 [cited 2011 25.August]; Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.
12. ami-info.at. *Arzneispezialitäten und Wirkstoffe.* 2011 [cited 2011 26.07.]; Available from: http://www.ami-info.at/.
13. Mok, T.S., et al., *Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.* New England Journal of Medicine, 2009. **361**(10): p. 947-957.
14. Fukuoka, M., et al., *Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected*

Patients With Advanced Non-Small-Cell Lung Cancer in Asia (IPASS). J Clin Oncol, 2011. **29**(21): p. 2866-74.

15. Lee, J.S., et al., *A Randomized Phase III Study of Gefitinib versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung. .* Journal of Thoracic Oncology, 2009. **4** (Suppl 1(9)): p. S283.
16. Lee, S., et al. *A Randomized Phase III Study of Gefitinib (IRESSATM) versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung First-line Single Agent Iressa versus Gemcitabine and cisplatin Trial in Never-smokers with Adenocarcinoma of the Lung First-SIGNAL.* in *13th World Conference on Lung Cancer*. 2009. San Francisco, CA.
17. Mitsudomi, T., et al., *Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.* The Lancet Oncology, 2010. **11**(2): p. 121-128.
18. Yoshizawa, H., et al., *QOL analysis from NEJ 002 study comparing gefitinib to chemotherapy for non-small cell lung cancer with mutated EGFR.* Annals of Oncology, 2010. **21**: p. viii122.
19. Maemondo, M., et al., *Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.* N Engl J Med, 2010. **362**(25): p. 2380-8.
20. Nachtnebel, A., *Gefitinib (Iressa) for the first-line treatment of non-small cell lung cancer*. 2010, Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA).
21. Ku, G.Y., B.A. Haaland, and G. de Lima Lopes Jr, *Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials.* Lung Cancer, 2011.
22. European Medicines Agency. *Iressa*. 2009 [cited 2011 05. September]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001016/human_med_000857.jsp&mid=WC0b01ac058001d124.
23. ClinicalTrials.gov. 2011 [cited 2011 22. August]; Available from: http://clinicaltrials.gov/ct2/show/study/NCT01203917?term=gefitinib&cond=lung&cntry1=EU%3AGB&phase=23&rank=4&show_locs=Y#locn.
24. Goeckenjan, G., et al., *Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. Interdisziplinäre S3-Leitlinie der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin und der Deutschen Krebsgesellschaft.* Pneumologie, 2010. **64**(S: 2): p. e1-e164.
25. U.S. Department of Health and Human Services, F.a.D.A., Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*. 2007.
26. UpToDate 19.2. *Small molecule epidermal growth factor receptor inhibitors for advanced non-small cell lung cancer*. 2011 [cited 2011 05. August]; Available from: http://www.uptodate.com/contents/small-molecule-epidermal-growth-factor-receptor-inhibitors-for-advanced-non-small-cell-lung-cancer?source=search_result&selectedTitle=1~150#H5.

27. Pircher, A., et al., *Basic clinical parameters predict gefitinib efficacy in non-small cell lung cancer.* Anticancer Res, 2011. **31**(9): p. 2949-55.
28. Medical Advisory Secretariat, *Epidermal Growth Factor Receptor Mutation (EGFR) testing for prediction of response to EGFR-targeting Tyrosine Kinase Inhibitor (TKI) drugs in patients with advanced non-small-cell lung cancer: an evidence-based analysis* Ont Health Technol Assess Ser, 2010. **10**: p. 1-48.
29. Doebele, R.C., et al., *New strategies to overcome limitations of reversible EGFR tyrosine kinase inhibitor therapy in non-small cell lung cancer.* Lung Cancer, 2010. **69**(1): p. 1-12.
30. European Medicines Agency. *Summary of opinion: Tarceva - Erlotinib* 2011 [cited 2011 04. August]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000618/WC500109251.pdf.
31. Togashi, Y., et al., *Differences in adverse events between 250mg daily gefitinib and 150mg daily erlotinib in Japanese patients with non-small cell lung cancer.* Lung Cancer, 2011. **74**(1): p. 98-102.
32. National Institute for Health and Clinical Excellence, *Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer.* 2010, London: National Institute for Health and Clinical Excellence (NICE).