Horizon Scanning in Oncology

Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)

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Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)

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Institute for Health Technology Assessment
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1 Drug description

Generic/Brand name/ATC code:

Crizotinib/Xalkori®/L01XE16

Developer/Company:

Pfizer Inc.

Description:

Crizotinib is a selective adenosine triphosphatase (ATP)-competitive small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) and the c-Met/hepatocyte growth factor receptor (HGFR) with antineoplastic activity therefore inhibiting tumour cell growth [1]. The echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene is responsible for the formation of non-small lung cancer (NSCLC) in some cases.

crizotinib inhibits ALK and HGFR

For the identification of patients eligible for treatment with crizotinib ALK-testing is necessary using an accurate and validated assay.

ALK-testing is necessary

The recommended dose schedule of crizotinib is 500 mg daily (250 mg bid) administered orally. The treatment should be continued until disease progression or unacceptable toxicity [2].

tablets for oral administration

2 Indication

Patients with advanced NSCLC harboring a translocation or inversion event involving the ALK gene locus.

patients with ALK-positive NSCLC

3 Current regulatory status

In October 2012, the European Commission (EC) granted a conditional marketing authorisation for crizotinib for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC [2-5]. The authorisation followed the recommendation of the Committee for Medicinal Products for Human Use (CHMP) that considered by consensus the risk-benefit balance of Xalkori® for this indication to be favourable [5]. The conditional marketing authorisation requires the marketing authorisation holder to provide additional data in the future.

EMA: treatment of adults with previously treated ALK-positive advanced NSCLC conditional authorisation

FDA: approval not restricted to previously treated adult patients with ALK-positive NSCLC
FDA-approved ALK test is essential

In August 2011, the U.S. Food and Drug Administration (FDA) approved crizotinib for the orphan indication „treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test" [1, 6, 7]. This authorisation was not restricted to previously treated adult patients. The indication was based on the response rate reported in two clinical trials (phase I and phase II) without data demonstrating improvement in patient reported outcomes or survival. The approval was issued under the provisions of accelerated approval regulations of new drugs for serious or life-threatening illnesses. Its granting is contingent upon completion of postmarketing clinical trials (phase III) to verify and describe the clinical benefit.

orphan drug designations for anaplastic large cell lymphoma and neuroblastoma

Recently, crizotinib also obtained orphan drug designations from the FDA for the treatment of anaplastic large cell lymphoma (28 Nov 2012) and neuroblastoma (31 Oct 2012) [7, 8].

4 Burden of disease

leading cause of cancer-related deaths worldwide

Lung cancer is the leading cause of tumour related mortality worldwide (2.4 %) and even more pronounced in the European region (4.1 %), with 69 % and 75 % of the deaths affecting men, respectively [9]. Worldwide, the age standardized incidence rates (per 100,000 population) were estimated to be 33.8 and 13.5 for men and women respectively, and mortality rates 29.2 and 10.9. Accordingly, for lung cancer in the European Region the incidence rates for men and women were 48.1 and 12.7, and the mortality rates 42.0 and 10.3, respectively [10]. The median age at diagnosis for cancer of the lung and bronchus is 70 years [11].

primary risk factor: tobacco smoking

Various risk factors are associated with lung cancer, tobacco smoking being the most important and accounting for about 90 % of all lung cancers [12]. Both the amount of daily smoked cigarettes and the lifetime duration of smoking increase the risk, while it decreases again when smoking is ceased [13].

Besides exposure to tobacco smoke additional environmental factors like radon, asbestos (particularly among smokers), arsenic or ionising radiation are known to increase the risk to develop lung cancer and also a genetic predisposition, pulmonary fibrosis and HIV infection may affect the risk for this disease [12].

often diagnosed in advanced stages of the disease

Usually lung cancer is asymptomatic particularly during early stage disease. Therefore it is often diagnosed at advanced stages resulting in a poor prognosis [14]. Among the wide range of possible symptoms cough, haemoptysis, dyspnoea, and chest pain are the most common. Other symptoms may occur due to nerve damages (e.g. unilateral paralysis of the diaphragm, Pancoast's syndrome) or metastases that most frequently spread to the liver, bone, brain and adrenal glands [12].

two types of lung cancer: SCLC and NSCLC

Generally, one can differentiate between small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [12]. About 85 % of all lung cancers belong to NSCLC which can be differentiated further into 2 types: non-squamous carcinoma and squamous cell carcinoma [15].

classification according to TNM staging system

Based on the tumour node metastasis (TNM) staging system for NSCLC developed by the International Association for the Study of Lung Cancer (IASLC) four disease stages (stage I, II, III and IV) can be determined [16].

For this the primary tumour characteristics, the presence or absence of regional lymph node involvement and distant metastases are taken into account. Advanced NSCLC describes a situation, where only systemic treatment is indicated. It comprises disease stage IIIB and stage IV including M1a (formerly partly also described as stage IIIB) with malignant pleural or pericardial effusion, pleural nodules, metastatic nodules in the contralateral lung and M1b, distant metastases.

advanced disease: performance status to estimate patient's prognosis and to establish treatment plan

In patients with advanced disease, performance status is used to estimate patients' prognosis and to establish a treatment plan. Early-stage disease, good performance status (ECOG PS 0, 1 or 2), absence of significant weight loss (not more than 5 %) and female gender are the most important prognostic factors regarding the prediction of survival of NSCLC patients. Age and histological subtypes do not play a major role in prognosis of tumour development [15] but in choice of treatment modalities and chemotherapeutic agents. Activating mutations of the epidermal growth factor receptor (EGFR) gene have a major impact on the level of response to tyrosine kinase inhibitors [17]. In addition to these EGFR mutations, other genetic alterations have been identified as oncogenic drivers in the pathogenesis of NSCLC, especially adenocarcinoma. In 2007, it was reported that a small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the EML4 gene and ALK in NSCLC cells [18].

early stage disease, good performance status, female gender are associated with a good prognosis

EML4-ALK fusion gene responsible for 1-7 % of NSCLC

The EML4-ALK fusion gene is responsible for only 1-7 % of NSCLC. ALK-positive NSCLC are found in patients of all ages, although on average these patients are relatively younger than those without this abnormality. These types of NSCLC are also more common in light cigarette smokers or non-smokers, but a significant number of patients with this disease are current or former cigarette smokers [19].

ALK FISH is the only validated test

Diagnostic approaches to detect ALK rearrangements include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) [20]. Currently, the only clinically validated test to determine ALK status is the Vysis/Abbott ALK FISH break apart test, which is also approved by the FDA [1].

in Austria: 3,400 to 4,300 patients newly diagnosed with lung cancer each year

In Austria, lung tumours account for more than 11 % of all malignant neoplasms and are the leading cause of cancer deaths in males. Within the last 20 years about 3,400 to 4,300 patients were newly diagnosed with lung cancer each year, while the number of people dying of this disease was about 10 % to 15 % lower [21]. Men are more often affected than women (in 2009: 2,747 men vs. 1,492 women; 42.2 vs. 19.5 per 100,000 habitants, respectively), but in recent years the incidence and mortality rates have decreased in men while they have increased in women. More than 80 % of the tumours histologically classified as carcinomas were NSCLCs [21].

30 to 200 patients with ALK-positive NSCLC per year in Austria

Applying the above mentioned estimates approximately 30 to 200 patients will be newly diagnosed with ALK-positive NSCLC per year in Austria. For that, many more patients (about 2,900 diagnosed with NSCLC [21]) will have to be assessed with the ALK assay.

5 Current treatment

choice of treatment depends on cancer stage, ECOG performance status

Surgery, radiation therapy and chemotherapy, targeted therapy and best supportive care are the modalities commonly used for the treatment of NSCLC. Depending on the disease status, ECOG performance status and prognostic factors these treatments can be used either alone or in combination [22]. Patients with early stage disease are treated with surgery, whereas individuals with locally advanced disease are either treated with radiotherapy alone or in combination with chemotherapy, and neo-adjuvant approaches. Patients with advanced disease and good prognosis (ECOG PS 0 to 1) are treated with double-agent chemotherapy or targeted therapy, whereas patients with poor prognosis (ECOG PS 2 to 4) receive single-agent chemotherapy, targeted therapy or best supportive care [14, 15].

first line therapy

According to the NCCN Guidelines the current standards of treatment as first line therapy in patients with advanced NSCLC [15, 19] are:

- a double agent chemotherapy regimen, consisting of one platinum-based agent (cisplatin, carboplatin) in combination with a second agent (paclitaxel, gemcitabine, vinorelbine or docetaxel and pemetrexed in patients with nonsquamous histology)
- chemotherapy in combination with targeted therapeutic agent (bevacizumab)
- for patients with discovered EGFR mutation, erlotinib (and in Europe also gefitinib) is indicated as first line therapy.

maintenance therapy

- for maintenance therapy, treatment options for patients with stable disease or tumour response include [19]:
- the continuation with a single agent targeted therapy (e.g. bevacizumab)
- the continuation with a single agent chemotherapy (e.g. pemetrexed, gemcitabine)
- a switch to erlotinib or pemetrexed.

second line therapy

As second line therapy the following treatments are recommended:

- single agent chemotherapy (docetaxel or pemetrexed)
- targeted agent therapy (e.g. erlotinib)
- a platinum based combination therapy for patients with EGFR mutation and progressive disease after tyrosine kinase inhibitor treatment (e.g. erlotinib)

for ALK-positive NSCLC: crizotinib recommended

For ALK-positive NSCLC patients the targeted agent crizotinib is the currently recommended treatment option as first or second line therapy [15, 19]. Chemotherapy is an appropriate option for these patients with disease progression on crizotinib. As patients with the ALK fusion oncogene do not appear to respond to EGFR tyrosine kinase inhibitors, erlotinib therapy is not recommended [19].

6 Evidence

To identify relevant primary and secondary literature, a systematic literature search was conducted on the 30th of November 2012 in the medical databases Ovid MEDLINE/Pubmed, EMBASE, the Cochrane Library and the CRD database yielding 379 records after removal of duplicates. Of those, 9 records reporting results of 2 single-arm phase I/II trials, were included [23-31].

Also a hand search was performed which included reference lists of topic-related reviews or articles, a free web-search and the websites of the EMA and the FDA. This search resulted in the inclusion of 3 further publications [32-34], one of them reporting interim results of an ongoing phase III trial. Among the material that the manufacturer had sent on request, 8 additional conference papers on the already identified trials including one oral presentation were retrieved [19, 24, 32, 33, 35-38].

all ongoing:
one phase III trial and two phase I/II trials for ALK-positive NSCLC

In summary 3 full text publications and 17 conference abstracts or presentations reporting on one phase III trial [19, 34] and 2 single arm phase I/II trials [19, 23-28, 31-39] were included.

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

STUDY TITLE Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with non-small lung cancer harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus (Profile 1007) [19, 34].		
Study identifier	NCT 00932893 EudraCT 2009-012595-27	
Design	Randomized controlled, parallel, open-label, international, multi-centre trial; N = 347 (173 vs. 174); allocation randomly to crizotinib or chemotherapy (pemetrexed or docetaxel); Investigator selection of either pemetrexed or docetaxel as the active comparator;	
	Duration	Enrolment: February 2010 to February 2012 Median follow-up: Crizotinib: 12.2 months (11.0 – 13.4) Chemotherapy: 12.1 months (10.6 – 13.6) Cut-off date for final analysis: March 2012
Hypothesis	Superiority	
Funding	Pfizer Inc.	
Treatment groups	Intervention	Crizotinib 250 mg bid PO, 21-day cycle
	Control	Pemetrexed, 500 mg/m^2, iv infusion over 10 minutes on Day 1 of each 21-day cycle *or* Docetaxel, 75 mg/m^2, iv infusion over 1 hour on Day 1 of each 21-day cycle

Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from random assignment to first progressive disease or death. PFS was detected per independent radiology review (according to RECIST version 1.1).
	Objective response rate (secondary outcome)	ORR	NR
	Duration of response (secondary outcome)	DR	NR
	Disease control rate (secondary outcome)	DCR	NR
	Overall survival (secondary outcome)	OS	NR
	Safety (secondary outcome)	S	NR
	Symptoms of lung cancer (secondary outcome)	Sym	Patient self-reported (cough, dyspnea, fatigue, alopecia, insomnia and pain);
	Time to Deterioration in Lung Cancer Symptoms	TDSym	Patient self-reported; Composite endpoint of pain, cough, dyspnea;
	Health-related quality of life (secondary outcome)	HrQoL	Patient self-reported; EORTC QLQ-C30 and QLQ-LC-13 were used for evaluation;
RESULTS AND ANALYSIS			
Analysis description	ITT-analysis *Primary endpoint:* PFS per independent radiology review – sample size: 217 events (progressive disease or death) are needed to detect a hazard ratio of 0.64 (or increase in median PFS from 4.5 to 7 months) at one-sided 2.5 % significance level with 90 % power *Secondary endpoint:* OS – pre-specified interim OS analysis at time of final PFS analysis; 80 % power to detect 44 % increase in OS when 241 deaths occur		
Analysis population	Inclusion	histologically or cytologically proven diagnosis of NSCLC (Stage IIIB/IV); positive for the ALK fusion gene (test provided by a central laboratory); disease progression after only one prior chemotherapy (regimen must have included one platinum drug); measurable tumours; ECOG performance status 0-2;	
	Exclusion	prior treatment with crizotinib (PF-02341066); current treatment in another clinical trial;	
	Characteristics	347 patients with ALK-positive Stage IIIB/IV NSCLC who had received one prior chemotherapy (platinum-based). Control (n = 174) vs. Intervention (n = 173): *Median age* (years): 49 (24-85) vs. 51 (22-81) *Female* (%): 55 vs. 57 *Ethnicity* Caucasian/Asian/Others (%): 52/45/3 vs. 52/46/2 *Never smoker* (%): 64 vs. 62 *Ex-Smoker* (%): 31 vs. 34 *Current smoker* (%): 5 vs. 3 *Adenocarcinoma* (%): 94 vs. 95 *ECOG performance status 0/1/2* (%): 37/55/8 vs. 42/49/9 *Brain metastases* (%): 35 vs. 35	

Results (interim analysis 12 mo f/up)	Treatment group	*Chemotherapy (pemetrexed or docetaxel)*	*Crizotinib*
	Number of subjects	174	173
	PFS (months) median 95 % CI	 3.0 NR	 7.7 NR
	ORR (%) median 95 % CI	 19.5 NR	 65.3 NR
	OS (months) median 95 % CI	 22.8 NR	 20.3 NR
	Sym	NR	NR
	HrQoL	NR	NR
	Number of subjects	151	162
	TDSym (months) median 95 % CI	 1.4 NR	 5.6 NR
Effect estimate per comparison (interim analysis 12 mo f/up)	*Comparison groups*		*Intervention vs. Control*
	PFS	HR	0.49
		95 % CI	0.37 – 0.64
		P value	< 0.0001
	ORR	HR	3.4
		95 % CI	2.5 – 4.7
		P value	< 0.0001
	OS	HR	1.02
		95 % CI	0.68 – 1.54
		P value	0.5394
	Sym	Point estimate	NR
		95 % CI	NR
		P value	< 0.0001
	TDSym	HR	0.54
		95 % CI	0.40 – 0.71
		P value	< 0.0001
	HrQoL (Global QoL)	Estimated difference	9.84
		95 % CI	5.39 – 14.28
		P value	< 0.0001

ALK … Anaplastic lymphoma kinase; bid … twice daily; CI … Confidence interval; DCR … Disease control rate; DR … Duration of response; ECOG … Eastern Cooperative Oncology Group; EORTC … European Organisation for Research and Treatment of Cancer; ER … Estrogen-receptor; HR … hazard ratio; HrQoL … Health related quality of life; ITT … Intent-to-treat; iv … intravenous; NR … Not re-ported; ORR … Overall response rate; OS … Overall survival; PFS … Progression-free survival; PO … Per os; RECIST … Response Evaluation Criteria in Solid Tumors; S … Safety; Sym … Symptoms of lung cancer; TDSym … Time to Deterioation in lung cancer symptoms.

Table 2: adverse events

Profile 1007 (NCT 00932893) [19, 34]			
Grade (CTC version not reported)	**Outcome (%)**	**Crizotinib** (n= 172)	**Chemotherapy** (n=171)
Any grade	Vision disorder	103 (60 %)	16 (9 %)
	Diarrhea	103 (60 %)	33 (19 %)
	Nausea	94 (55 %)	64 (37 %)
	Vomiting	80 (47 %)	30 (18 %)
	Constipation	73 (42 %)	39 (23 %)
	Elevated transaminases	66 (38 %)	25 (15 %)
	Oedema	54 (31 %)	27 (16 %)
	Upper respiratory infection	44 (26 %)	22 (13 %)
	Dysgeusia	44 (26 %)	16 (9 %)
	Dizziness	37 (22 %)	14 (8 %)
	Fatigue	46 (27 %)	57 (33 %)
	Alopecia	14 (8 %)	35 (21 %)
	Dyspnea	23 (13 %)	32 (19 %)
	Rash	15 (9 %)	29 (17 %)
Grade 3/4	Elevated transaminases	27 (16 %)	4 (2 %)
	Neutropenia	23 (13 %)	33 (19 %)
	Pulmonary embolism	9 (5 %)	3 (2 %)
	Dyspnea	7 (4 %)	5 (3 %)
	Pneumonia	6 (4 %)	3 (2 %)
	Hypokalaemia	6 (4 %)	0 (0 %)
	ECG QTc prolonged	6 (4 %)	0 (0 %)[a]
	Fatigue	4 (2 %)	7 (4 %)
	Anaemia	4 (2 %)	9 (5 %)
	Constipation	4 (2 %)	0 (0 %)
	WBC decreased	2 (1 %)	8 (5)
	Nausea	2 (1 %)	1 (1 %)
	Vomiting	2 (1 %)	0 (0 %)
	Dizziness	1 (1 %)	0 (0 %)
	Upper respiratory infection	0 (0 %)	1 (1 %)
Grade 5 (Deaths attributed to SAE)	Total	25 (15 %)	7 (4 %)
	Disease progression	14 (8 %)	3 (2 %)
	Treatment-related	3 (2 %)	1 (1 %)
	Arrythmia	1 (1 %)	0 (0 %)
	ILD or pneumonia	2 (1 %)	0 (0 %)
	Sepsis	0 (0 %)	1 (1 %)
	Other causes	8 (5 %)	3 (2 %)

	Unkown cause	1 (1 %)	0 (0 %)
Permanent discontinuations	Total	30 (17 %)	23 (13 %)
	Treatment-related	11 (6 %)	17 (10 %)

a … No on-treatment assessment

AE … Adverse event; CTC … Common Terminology Criteria; ECG … Electrocardiography; ILD … Interstitial lung disease; SAE … Serious adverse event; WBC … White blood cells

estimated study completion date: February 2013, but still ongoing

treatment group: crizotinib

control group: standard chemotherapy (pemetrexed or docetaxel)

The Profile 1007 is an ongoing international, multi-centre, open-label randomised trial (RCT) with 237 recruiting study centres in Europe, North and South America, Asia and Australia [19, 34]. Its objective is to investigate the efficacy and safety of crizotinib versus standard chemotherapy (pemetrexed or docetaxel) in patients with advanced NSCLC with a specific gene profile involving the ALK gene. The estimated study completion date was February 2013, but accordimg to the database ClinicalTrials.gov the trial is still ongoing. This study includes patients with a histologically or cytologically proven diagnosis of stage IIIB or stage IV NSCLC, who are tested positive for the ALK fusion gene. Furthermore patients have to have disease progression after only one prior platinum drug based chemotherapy.
The included patients were about 50 years of age, and more than 90 % had a good ECOG status of 0 or 1. The majority of the study population were never smokers. A proportion of 52 % were Caucasians and 45 % were Asians.
173 patients were randomly assigned to the intervention group consisting of 250 mg crizotinib orally twice daily, and 174 patients were allocated to the control arm receiving chemotherapy with either pemetrexed, 500 mg/m^2 iv or docetaxel, 75 mg/m^2 iv. The chemotherapy regimen was given at investigator's choice. At baseline there were no statistically significant differences between the groups in terms of patient characteristics, smoking status and tumour status.

significantly longer PFS

significantly improved ORR

For the primary endpoint progression free survival (PFS), the interim analysis after a median follow-up of about 12 months showed a statistically significant improvement for the intervention group as determined per independent radiology review (crizotinib group 7.7 months vs. chemotherapy group 3.0 months; HR 0.49 (95 % CI 0.37-0.64; p<0.0001)). In addition, the secondary endpoint objective response rate (ORR) was significantly better in the crizotinib group (65.3 % vs. 19.5 %; HR 3.4 (95 % CI 2.5-4.7; p<0.0001)), but it was not reported whether these were complete responses (CR) or partial responses (PR).

Subgroup analyses for PFS showed also a significant benefit of crizotinib for most of the investigated subgroups (e.g. Non-Asians, Asians, male, female, ECOG 0/1, ECOG 2). No statistically significant improvement in PFS was reported for the small subgroups of patients with non-adenocarcinoma and patients aged 65 or older.

OS similar, but data yet not mature

At time of the interim analysis about 30 % of all patients had died in either group. The median overall survival (OS) was with 20.3 months (crizotinib group) vs. 22.8 months (chemotherapy group) similar in both treatment arms, but results were still immature and may have been confounded by crossover (111 patients of the chemotherapy group crossed over to crizotinib outside the Profile 1007 trial).

QoL and symptoms of lung cancer significantly better with crizotinib

Patient reported outcomes were quality of life (QoL), measured by the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 and QLQ-LC13 and symptoms of lung cancer. In terms

of the symptoms, there was a greater improvement from baseline for the crizotinib group in comparison to the chemotherapy group in cough, dyspnea, fatigue, alopecia, insomnia, and pain ($p<0.0001$ for all). Also in global quality of life and in all of the subdomains except cognitive functioning there was a statistically significant benefit for patients treated with crizotinib.

more permanent study discontinuations and more death from SAE

Permanent study discontinuations and deaths attributed to serious adverse events (SAE) occurred more often in the crizotinib group, although the study-treatment-related discontinuations were more frequent in the chemotherapy group (see table 2).

vision disorders: most common AEs

Vision disorders occurred in 60 % of all patients in the crizotinib group compared to only 9 % in the chemotherapy group. Therefore vision disorders were the most common adverse events with crizotinib, none of them being grade 3 or 4.

grade 3/4 AEs comparable

The number of adverse events of grade 3 or 4 affecting more than 3 % of the patients in at least one treatment arm was comparable in both groups. These were elevated transaminases, pulmonary embolism, dyspnea, pneumonia, hypokalaemia, prolonged ECG QTc, neutropenia, anaemia, decreased white blood cell count, and fatigue.
The elevated transaminases, pulmonary embolism, dyspnea, pneumonia, hypokalaemia, and prolonged ECG QTc occurred more often in the intervention group, while neutropenia, anaemia, decreased white blood cell count, and fatigue were more frequent in the control group.

The investigators of the study concluded that crizotinib has a distinct side effect profile when compared with single-agent chemotherapy and is generally tolerable and manageable.

6.2 Efficacy and safety – further studies

To date the interim results of 2 single-arm open label phase I/II trials investigating crizotinib for the treatment of patients with ALK-positive advanced NSCLC have been published.

single arm open label phase I/II trial

In the first trial (Profile 1001) [23-28, 31] patients with ALK-positive stage III or IV NSCLC with only 1 prior chemotherapy treatment (platinum-based) receive oral crizotinib 250 mg twice daily in ensuing 28-day cycles. The data cut-off for the latest interim analysis of this study was January 2012 [2]. At this time 149 patients had been enrolled and 143 were included in the response-evaluable population.

ORR: 61 %
median PFS about 10 months
OS 30 months but not mature
24 % grade 3/4 AEs
one death from drug toxicity

Within this population, 88 achieved an objective response (ORR 61.5 % (95 % CI 53.0-69.5)), with three patients having a CR and 85 having a PR. During follow up (median 16.6 months) the median PFS was 9.9 months (95 % CI 7.7-13.4). At this time the median OS was 29.6 months although OS data were not mature.
Overall, 97 % of the patients experienced treatment-related AEs and 24 % of them had grade 3-4 AEs [26]. The most common grade 3-4 AEs were neutropenia (6 %), raised alanine aminotransferase (4 %), hypophosphataemia (4 %), and lymphopenia (4 %). 12.8 % of the patients had AEs that were associated with permanent discontinuation from treatment, which was treatment-related in 3 patients. One death during the study was attributed to study drug toxicity.

second single arm open label phase I/II trial

The second Phase I/II trial (Profile 1005) investigates crizotinib in patients with ALK-positive advanced NSCLC previously treated with at least 1 chemotherapy regimen [32, 33, 35-39]. All patients receive oral crizotinib 250 mg twice daily in continuous 3-week cycles.
The latest interim analysis (cut-off on January 2012) included the safety results of 901 patients and efficacy results of the population with a centrally confirmed ALK FISH test (first 261 patients enrolled and treated in the study) [37].

ORR: 60 %
median PFS about 8 months

The ORR within the mature population was 59.8 % (95 % CI 53.6-65.9) with CR in 4 patients and PR in 151 patients. At the time of analysis there were 167 PFS events, showing a median PFS of 8.1 months (95 % CI 6.8-9.7).

26 % grade 3/4 AEs
4 treatment-related deaths

Safety results were reported for the overall patient population (n=901) with treatment-related AEs in 91.8 %. Treatment-related grade ≥3 AEs were reported in 25.6 % of patients. The most frequently grade 3/4 were neutropenia (5.5 %), increased alanine aminotransferase (4.0 %), and fatigue (2.0 %). 198 deaths occurred during the study period and 4 of them were considered treatment-related by the investigators.

7 Estimated costs

monthly costs: € 6,100

In Austria the pharmacy retail price for one package of crizotinib containing 60 250mg tablets is € 8,340 [40]. However, the reimbursement price paid by the statutory health insurance funds is with € 6,089 considerably lower [41]. Administered as second line therapy for advanced NSCLC, the recommended daily dose is 500 mg continuously. This results in costs of about € 200 per day equalling € 6,100 per month.

additional costs:
€ 100 per patient for ALK test

As crizotinib is only approved for patients with ALK-positive NSCLC, additional costs of about € 100 per patient for the ALK-testing will be incurred [42]. These costs do not account for the high percentage (above 90 %) of NSCLC patients with ALK-negative test results. For patients (around 2,900) tested in Austria diagnostic costs of 290,000.- would need to be added.

8 Ongoing research

3 further phase III/IV trials for NSCLC

A search in the databases ClinicalTrials.gov and cinicaltrialsregister.eu yielded 3 further on-going phase III/IV trials investigating crizotinib, besides the Profile 1007 trial (NCT00932893), of which interim results are presented in this report. All of them are conducted in patients with NSCLC:

NCT01154140: (EudraCT 2010-021336-33): PROFILE 1014 – A parallel open-label randomized controlled phase III trial, testing the efficacy of crizotinib versus standard chemotherapy (pemetrexed/cisplatin or carboplatin) in patients with ALK positive non squamous cancer of the lung. The estimated study completion date is December 2013.

NCT01639001: A cross-over open-label randomized controlled phase III trial of crizotinib versus chemotherapy (pemetrexed/cisplatin or pemetrexed/ car-

boplatin) in previously untreated ALK positive East Asian NSCLC patients. The estimated study completion date is September 2015.

NCT01597258: An observational single-arm phase IV trial evaluating the safety and efficacy of crizotinib in patients with NSCLC. The study is part of the regulatory post marketing commitment plan. The estimated study completion date is May 2017.

6 phase I/II trials for NSCLC
9 phase I/II trials for other types of cancer

In addition there are 6 on-going phase I/II trials for crizotinib alone or in combination with chemotherapy for patients with NSCLC and 9 on-going phase I/II trials investigating crizotinib in advanced cancer patients (various types of cancer), patients with anaplastic large cell lymphoma or children with diffuse pontine glioma (DIPG) or high-grade glioma (HGG).

9 Commentary

contingent approval in Europe and USA

To date crizotinib is approved by the FDA for treatment of patients with ALK-positive NSCLC [6]. The approval was based on data of 2 phase I/II single arm trials demonstrating a favourable benefit-risk profile for crizotinib when compared to chemotherapeutic agents approved for NSCLC. In Europe this approval is restricted only to second line therapy for ALK-positive NSCLC patients with disease progression after chemotherapy [2]. Both grantings are contingent upon the completion of postmarketing clinical phase III trials to verify and describe the clinical benefit of crizotinib [2, 6].

one randomized phase III trial for NSCLC

For ALK-positive NSCLC, results of 2 single arm phase I/II trials and 1 randomized phase III trial were found. Compared to an unselected NSCLC population, study participants are relatively young and more likely to be never or light smokers, which seems to be representative for an ALK positive NSCLC population.

significantly better than chemotherapy in PFS, ORR and QoL

no differences in OS and higher grade AEs

In the phase III trial (Profile 1007) crizotinib was investigated as second line therapy in comparison to standard chemotherapy. Interim results after a median follow-up of about 12 months showed statistically significant better PFS (7.7 months vs. 3.0 months) and ORR (65.3 % vs. 19.5 %) for the crizotinib group. The OS rates were comparable in both groups, but the authors mentioned that these data were immature at the time of analysis. Furthermore, due to a possible confounding by a high cross over rate, it could be generally difficult to determine mature overall survival data in this study.
Improved QoL in favour of crizotinib was found in all domains of the EORTC QLQ-C30 and QLQ-LC-13 questionnaires and this improvement was statistically significant for all but one (cognitive functioning) domain. Furthermore, there was a significant benefit in terms of lung cancer symptoms in the crizotinib group. Concerning AEs of higher grade both groups showed quite similar rates of about 50 %, with the most common AEs being elevated transaminases (16 %) for crizotinib and neutropenia (19 %) for chemotherapy. Although the number of overall deaths was comparable in both groups, there was an increased number of deaths related to SAEs within the crizotinib group, mostly due to disease progression. In addition, different types of vision disorders occurred in a higher proportion of patients treated with crizotinib, but all of them seemed to be of lower grades.

more deaths related to SAE

It has to be mentioned that none of the trials investigating crizotinib in NSCLC patients has been completed yet and results are only based on interim analyses. Furthermore most of them are available as conference posters or oral presentation slides only, provided by the manufacturer. Especially for the phase III trial no publication in a peer review journal is at hand, hence the possibility of bias cannot be excluded.

no completed trial for NSCLC, only interim results

FISH-assay is only validated test, but it is complex and results are not always clear

As the effectiveness of crizotinib is based on the inhibition of ALK, it only affects ALK-positive NSCLC patients. Therefore, reliable ALK-testing prior to treatment initiation is crucial for patient selection. At the moment the FISH assay used in the phase I/II and phase III trials is the only validated assay for ALK. But according to Thunnissen et al. interpretation of the ALK FISH analysis is more complex than for other FISH assays (e.g. the fusion inversion occurs in the same chromosome arm and the red and green signals may be slightly separated and the fusion to yellow flourescence is not apparent) [20]. Because of this, a specific training and experience with ALK FISH is needed. Moreover FISH is not feasible in all laboratories and the results are not always clear. McLeer-Florin et al. [43] reported that 19 % of all specimen analyzed by FISH were not interpretable. Based on calculations using data of the Profile 1001 trial Chihara et al. suggested that a substantial number of patients identified as having ALK rearrangements by means of FISH analysis had false positive results [44]. The authors therefore concluded that diagnosis using FISH is of limited value. However, the question of how best to select patients that may benefit from crizotinib treatment needs to be answered. There is evidence that immunohistochemistry IHC could be useful and less expensive than FISH and some of the difficulties in interpreting FISH results may be alleviated by automated procedures. Anyway, rigorous quality assessment is of maximum importance to ensure reliable results and appropriate patient selection [20]. Otherwise there is a potential risk for NSCLC patients to be treated with a single agent therapy, that is crizotinib, which is not effective at all, thus foregoing other, effective treatment options.

reliable results and appropriate patient selection are of maximum importance

acquired drug resistance is major limitation

One of the major limitations of crizotinib is the primary or acquired drug resistance, which has also been observed with other targeted therapies [45]. This may be a reason why an increased number of patients died due to disease progression in the Profile 1007 trial. The mechanisms of drug resistance are under investigation in several recent studies. Understanding these specific mechanisms may help in the development of effective subsequent clinical treatments. How to best treat patients who develop acquired resistance to crizotinib has not been defined yet [45]. Moreover, several clinical trials are planned or under way to evaluate the efficacy of new ALK inhibitors and combination strategies to overcome resistance [46].

studies investigating strategies to overcome resistance are under way

When compared to standard chemotherapy, the costs for crizotinib are rather high (about 2 to 4 times higher). For the budget impact, one has to consider, that the number of patients suitable for this therapy is small (1 %-7 % of NSCLC), but also costs for the ALK testing of all NSCLC patients have to be taken into account.

seemingly positive results, but confirmation is needed suitable for small patient group

In summary the interim results of one RCT have shown a statistically significant benefit of crizotinib over standard chemotherapy in terms of PFS, ORR and QoL, with comparable results for OS and AEs of higher grade. Nevertheless these seemingly positive results have to be confirmed by the final results of this study and further RCTs, as demanded by the European and US regulatory authorities. However this therapy option is only suitable for the relatively small group of ALK-positive patients, but at least a tenfold of persons have to be tested for the ALK gene mutation.

References

1. U.S. Food and Drug Administration (FDA). *202570Orig1s000 - Medical Review*. 2011 15 Sept 2011 [cited 20 Nov 2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000MedR.pdf.
2. European Medicines Agency (EMA). *Xalkori: Public assessment report*. 19 Jul 2012 [cited 20 Nov 2012]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002489/WC500134761.pdf.
3. European Commission (EC) (2012) *Notice No 2012/C 371/03: Summary of European Union decisions on marketing authorisations in respect of medicinal products from 1 October 2012 to 31 October 2012*. Official Journal of the European Union **Volume**, 8
4. European Commission (EC). *Product information - XALKORI*. Community register of medicinal products for human use 2012 [cited 5 Dec 2012]; Available from: http://ec.europa.eu/health/documents/community-register/html/h793.htm.
5. European Medicines Agency (EMA). *Xalkori: EPAR - Annexes I-IV*. [cited 20 Nov 2012]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002489/WC500134759.pdf.
6. U.S. Food and Drug Administration (FDA). *Xalkori - Approval Letter*. 2011 24 Aug 2011 [cited 20 Nov 2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000Approv.pdf.
7. U.S. Food and Drug Administration (FDA). *Orphan Drug Product Designations - Index number 310610*. 2012 [cited 3 Dec 2012]; Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=310610.
8. U.S. Food and Drug Administration (FDA). *Orphan Drug Product Designations - Index number 379712*. 2012 [cited 3 Dec 2012]; Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=379712.
9. World Health Organization (WHO). *Cause-specific mortality, 2008. Summary Tables: Estimates of deaths by cause for the year 2008 - WHO region*. Global Health Observatory Data Repository May 2011 [cited 7 Dec 2012]; Available from: http://www.who.int/gho/mortality_burden_disease/global_burden_disease_DTH6_2008.xls.
10. Ferlay J, et al. *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10*. GLOBOCAN 2008 v2.0 2010 [cited 10 Dec 2012]; Available from: http://globocan.iarc.fr.
11. National Cancer Institute (NCI). *SEER Stat Fact Sheets: Lung and Bronchus*. 2012 [cited 08 Jan 2013]; Available from: http://seer.cancer.gov/statfacts/html/lungb.html.
12. Midthun, D. *Overview of the risk factors, pathology, and clinical manifestations of lung cancer*. 2012 [cited 10 Dec 2012]; Available from: http://www.uptodate.com/contents/overview-of-the-risk-factors-pathology-and-clinical-manifestations-of-lung-cancer.
13. Mannino, D. *Cigarette smoking and other risk factors for lung cancer*. 2012 [cited 10 Dec 2012]; Available from: http://www.uptodate.com/contents/cigarette-smoking-and-other-risk-factors-for-lung-cancer.
14. 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.
15. National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology - Non-Small Cell Lung Cancer, Version 1.2013*. 2013 [cited 08 Jan 2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
16. Thomas, K. and M. Gould. *Tumor node metastasis (TNM) staging system for non-small cell lung cancer*. 2012 [cited 7 Dec 2012]; Available from: http://www.uptodate.com/contents/tumor-node-metastasis-tnm-staging-system-for-non-small-cell-lung-cancer.
17. Horn, L. and W. Pao, *EML4-ALK: honing in on a new target in non-small-cell lung cancer.* J Clin Oncol, 2009. **27**(26): p. 4232-5.

18.Soda, M., et al., *Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer.* Nature, 2007. **448**(7153): p. 561-6.
19.Shaw, A.T., *Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) PROFILE 1007 [Oral presentation (abstract # 2862/LBA1_PR) at presidential symposium I]*, in *37th European Society of Medical Oncology Congress*. 2012: Vienna.
20.Thunnissen, E., et al., *EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations.* Virchows Arch, 2012. **461**(3): p. 245-57.
21.Zielonke, N. *Krebsinzidenz und Krebsmortalität in Österreich*. 2012 [cited 10 Dec 2012]; Available from: http://www.statistik.at/web_de/static/krebsinzidenz_und_krebsmortalitaet_in_oesterreich_2012_065928.pdf.
22.Lilenbaum, R. *Overview of the treatment of advanced non-small cell lung cancer*. 2012 [cited 10 Dec 2012]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-advanced-non-small-cell-lung-cancer?source=search_result&search=nsclc&selectedTitle=3%7E150.
23.Bang, Y., et al., *Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).* Journal of Clinical Oncology, 2010. **28**(18).
24.Camidge, D.R., et al., *Clinical activity of crizotinib (PF-02341066), in ALK-positive patients with non-small cell lung cancer (NSCLC).* Annals of Oncology, 2010. **21**: p. viii123.
25.Camidge, D.R., et al., *Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC).* Journal of Clinical Oncology, 2011. **29**(15).
26.Camidge, D.R., et al., *Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study.* Lancet Oncology, 2012. **13**(10): p. 1011-9.
27.Kwak, E.L., et al., *Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer.[Erratum appears in N Engl J Med. 2011 Feb 10;364(6):588].* New England Journal of Medicine, 2010. **363**(18): p. 1693-703.
28.Solomon, B., et al., *Timing of responses to crizotinib (PF-02341066) in anaplastic lymphoma kinase (ALK)-positive Patients with advanced non-small cell lung cancer (NSCLC).* European Journal of Cancer, Supplement, 2010. **8**(7): p. 117.
29.Shaw, A.T., et al., *Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis.* Lancet Oncology, 2011. **12**(11): p. 1004-12.
30.Shaw, A.T., et al., *Impact of crizotinib on survival in patients with advanced, ALK-positive NSCLC compared with historical controls.* Journal of Clinical Oncology, 2011. **29**(15).
31.Camidge, D.R., et al., *Clinical Activity of Crizotinib (PF-02341066) in ALK-Positive Patients with Advanced Non-Small Cell Lung Cancer.* 35th European Society of Medical Oncology Congress, 2010. **abstract # 366PD**.
32.Besse, B., et al. *Visual disturbances in patients (pts) with anaplastic lymphoma kinase (alk)-positive advanced non-small cell lung cancer (NSCLC) treated with crizotinib [abstract # 1268P]*. 37th European Society of Medical Oncology Congress 2012 [cited; Available from: http://oncologypro.esmo.org/meeting-resources/meeting-abstracts/european-society-for-medical-oncology-esmo-2012/visual-disturbances-in-patients-pts-w-2567.aspx.
33.Salgia, R., B.J. Solomon, and A.T. Shaw, *Visual effects in anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) patients treated with crizotinib [abstract # 7596].* Journal of Clinical Oncology, 2012. **30**(suppl.).
34.Shaw, A.T., D.W. Kim, and K. Nakagawa. *Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) PROFILE 1007 [abstract # LBA1_PR]*. 37th European Society of Medical Oncology Congress 2012 [cited; Available from: http://abstracts.webges.com/myitinerary/day.html.
35.Crinò, L., D. Kim, and G.J. Riely, *Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005.* Journal of Clinical Oncology, 2011. **29**(suppl.).
36.Crinò, L., D. Kim, and G.J. Riely, *Initial phase 2 results with crizotinib in advanced ALK-positive non-small cell lung cancer PROFILE 1005.* ASCO Annual Meeting, 2011. **abstract # 7514**.
37.Kim, D.W., et al., *Updated Results of a Global Phase II Study with Crizotinib in Advanced ALK-positive Non-small Cell Lung Cancer.* 37th European Society of Medical Oncology Congress, 2012. **abstract # 1230PD**.

38.Kim, D.W., M.J. Ahn, and Y. Shi, *Results of a global Phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer.* ASCO Annual Meeting, 2012. **abstract # 7533**.
39.Kim, D.W., et al., *A global phase 2 study including efficacy, safety and patientreported outcomes (PROS) with crizotinib in patients (pts) with ALK-positive non-small cell lung cancer (NSCLC).* European Journal of Cancer, 2011. **47**: p. S617.
40.Anstaltsapotheke LKI-Universitätskliniken Innsbruck. 2012.
41.Warenverzeichnis des Österreichischen Apothekerverlages, 2013.
42.Abbott Gesellschaft mbH. 2012.
43.McLeer-Florin, A., et al., *Dual IHC and FISH testing for ALK gene rearrangement in lung adenocarcinomas in a routine practice: a French study.* J Thorac Oncol, 2012. **7**(2): p. 348-54.
44.Chihara, D. and R. Suzuki, *More on crizotinib.* New England Journal of Medicine, 2011. **364**(8): p. 776-7; author reply 778.
45.Sasaki, T. and P.A. Janne, *New strategies for treatment of ALK-rearranged non-small cell lung cancers.* Clin Cancer Res, 2011. **17**(23): p. 7213-8.
46.Katayama, R., et al., *Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers.* Sci Transl Med, 2012. **4**(120): p. 120ra17.