

Therapy options for advanced NSCLC

First-line chemotherapy and anti-angiogenic agents

Systemic therapy for advanced non-small-cell lung cancer (NSCLC) depends upon tumor biology or tumor histology, with targeted agents preferentially used in individuals with a specific driver mutation and chemotherapy used for patients whose tumors do not harbor such mutations, or following failure of targeted therapy.

Clinical trials have demonstrated that first-line platinum-based chemotherapy improves survival in patients with advanced NSCLC. Usually, treatment consists of a combination of two chemotherapy agents with different mechanisms of action and safety profiles [1,2]. Several studies demonstrated the superiority of platinum doublets over single agents [3–9]. Cisplatin demonstrated superiority over carboplatin in terms of response rate (RR) in the first-line setting, albeit with an increased risk of side effects [10]. Moreover, cisplatin demonstrated superiority versus carboplatin in terms of survival when used in combination with third-generation agents and in patients with non-squamous histology [10]. At the end of 1990s, several large randomized clinical trials comparing different platinum-based regimens failed to demonstrate any significant differences in RR, progression-free survival (PFS), and overall survival (OS) [11–13]. In addition, a meta-analysis demonstrated that adding a third agent to platinum-based doublets increases RR without any advantage in terms of both PFS and OS [14]. All of the above mentioned studies enrolled NSCLC patients irrespective of tumor biology or histology.

Nevertheless, in 2007 the therapeutic landscape changed following the results of a large phase III randomized trial comparing cisplatin plus pemetrexed (CP) to cisplatin plus gemcitabine (CG). In this study [15], a preplanned analysis for histology showed that patients with non-squamous histology benefited more from CP in terms of OS (hazard ratio [HR] 0.81; $p=0.005$), while CG showed a marginal but significant superiority in OS in the group of patients with squamous cell histology (HR 1.23; $p=0.05$). A potential explanation for the greater efficacy of pemetrexed in non-squamous histology is the differential expression of thymidylate synthase (TS), one of the target enzymes of pemetrexed, among the different histotypes of lung cancer [16].

Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, was the first targeted agent approved for the first-line treatment of NSCLC. Two large phase III trials, the Eastern Cooperative Oncology Group (ECOG) E4599 trial and the AVAiL in Lung Cancer (AVAiL) trial, evaluated the efficacy of bevacizumab in combination with chemotherapy. The ECOG 4599 randomized 855 untreated patients with NSCLC to the combination of carboplatin and paclitaxel with or without bevacizumab. Patients with squamous histology were excluded based on the safety results of a previous phase II trial that showed life-threatening or fatal episodes of hemoptysis in patients receiving chemotherapy plus bevacizumab [17]. The study met its primary endpoint, demonstrating a 20% of reduction in the risk of death for patients in bevacizumab arm [18]. Additional analyses suggested that the magnitude of benefit was greater in patients with adenocarcinoma [19]. Importantly, biomarkers that reliably predict the clinical efficacy of bevacizumab and that allow the selection of patients who will derive the most benefit from this agent have not yet been identified.

The AVAiL trial randomly assigned 1050 patients with non-squamous lung cancer to chemotherapy with cisplatin and gemcitabine alone or in combination with two different bevacizumab doses (7.5 or 15 mg/kg). Although the study met its primary end point of showing improved PFS with the addition of bevacizumab to chemotherapy, no difference in OS was observed [20]. More recently, a meta-analysis of four randomized phase II/III trials confirmed that bevacizumab significantly prolonged

both OS (HR 0.90; $p=0.03$) and PFS (HR 0.72; $p<0.001$) when added to first-line chemotherapy in advanced NSCLC [21]. Bevacizumab also showed a significantly greater effect on OS in patients with adenocarcinoma versus other histologies ($p=0.02$), and in patients with body weight loss $\leq 5\%$ versus $>5\%$ ($p=0.03$) [21].

Both the E4599 and AVAiL trials adopted stringent selection criteria to avoid unexpected toxicities, including the exclusion of individuals with brain metastases. The PASSPORT study, by contrast, was a phase II trial that evaluated the safety of bevacizumab in patients with NSCLC and pretreated brain metastases [22]. The primary objective of the study was the incidence of symptomatic grade ≥ 2 CNS hemorrhage. Bevacizumab was administered at the dose of 15 mg/kg every 21 days as front-line therapy in combination with platinum-based chemotherapy or erlotinib, while second-line bevacizumab was added to the investigators' treatment choice. The study confirmed that adding bevacizumab to standard therapies did not increase the risk of CNS hemorrhage in patients with pretreated brain metastases. In addition, the ARIES (Avastin Registry: Investigation of Effectiveness and Safety) study, a prospective observational study in colorectal cancer and NSCLC, showed no CNS bleeding among 150 patients with NSCLC and CNS metastases [23]. Furthermore, the safety and efficacy of first-line bevacizumab in combination with different chemotherapy regimens was confirmed in the SaiL (Safety of Avastin in Lung) trial, a large phase IV study [24]. In the ATLAS trial (The Avastin Tarceva Lung Adenocarcinoma Study) patients with advanced NSCLC not progressing after four cycles of chemotherapy plus bevacizumab were randomly assigned to continue bevacizumab alone or in combination with erlotinib [25]. The study included individuals with treated brain metastases and only one patient developed a grade 2 cerebral hemorrhage after disease progression.

Recent clinical trials have evaluated the efficacy of combining platinum and pemetrexed chemotherapy with bevacizumab. The PointBreak study was a randomized phase III trial of pemetrexed/carboplatin plus bevacizumab as induction followed by pemetrexed and bevacizumab maintenance, compared with paclitaxel/carboplatin plus bevacizumab as induction followed by bevacizumab maintenance in chemotherapy-naïve

patients with advanced non-squamous NSCLC [26]. The study did not meet the primary objective of superior OS for the pemetrexed arm (Table 2.1). The PRONOUNCE study [27] was a large phase III trial evaluating pemetrexed/carboplatin followed by maintenance therapy with pemetrexed versus bevacizumab plus paclitaxel/carboplatin followed by maintenance therapy with bevacizumab. The primary endpoint was PFS without grade 4 toxicities (G4PFS). The study showed no difference between the two arms for the primary end point of G4PFS as well as for the secondary end-points of RR, PFS and OS. Overall, available data indicate that the combination of platinum and pemetrexed chemotherapy and bevacizumab has similar efficacy to regimens not including both pemetrexed and bevacizumab, with increased costs. Therefore, based on available data, the combination of platinum and pemetrexed chemotherapy or the combination of platinum-based chemotherapy plus bevacizumab is considered the best option for metastatic non-squamous lung cancer patients without activating *EGFR* mutations or *ALK* translocations. In patients with squamous histology, platinum-based doublets remain the standard first-line treatment.

First-line EGFR tyrosine kinase inhibitors

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib (ZD 1839, Iressa®, AstraZeneca, UK), erlotinib (OSI 774, Tarceva®, Genentech, US), and afatinib (Giotrif®[EU], Gilotrif® [US], Boehringer Ingelheim, Germany) are currently approved in many countries for the treatment of patients with advanced NSCLC. Gefitinib and afatinib are

	PemCBev (n=472)	PacCBev (n=467)
Median overall survival (95% CI), months	12.6 (11.3–14.0)	13.4 (11.9–14.9)
Hazard ratio (95% CI)	1.00 (0.86–1.16); p=0.949	
Survival rate (%)		
1-year	52.7	54.1
2-year	24.4	21.2

Table 2.1 Overall survival analysis from the PointBreak study. PacCBev, paclitaxel (Pac), carboplatin (C), and bevacizumab (Bev) followed by bevacizumab; PemCBev, pemetrexed (Pem), carboplatin, and bevacizumab followed by pemetrexed and bevacizumab. CI, confidence interval.

approved for patients with *EGFR* mutations only (*EGFR*^{mut+}), whereas erlotinib is also approved for chemotherapy pretreated *EGFR* wild-type individuals.

Mechanism of action: gefitinib

Gefitinib is an orally bioavailable synthetic anilinoquinazoline agent that selectively binds to the TK region of the intracellular domain of *EGFR*. This prevents adenosine triphosphate (ATP)-binding and blocks *EGFR* autophosphorylation, resulting in inhibition of the *EGFR* signal transduction pathways [28]. Preclinical data showed highly potent gefitinib inhibition of *EGFR*-mediated cellular proliferation and survival; in preclinical models, gefitinib activity, consisting of G1 phase cell cycle arrest/apoptosis, has been showed in a variety of solid tumors known to express *EGFR*, including NSCLC [29]. Pharmacokinetic studies in healthy volunteers showed a peak plasma drug concentration (C_{\max}) between 3 and 7 hours after administration, with a terminal elimination half-life of 28 h [30]. In vitro studies show that gefitinib is metabolized by hepatic cytochrome P450 (CYP) enzymes, predominantly CYP3A4, with minor roles for CYP3A5 and CYP2D6, and this is the main route for clearance in the body [31]. Therefore, inducers or inhibitors of this cytochrome can also influence the pharmacokinetics of drugs as rifampicin, itraconazole and metoprolol [32]. Gefitinib bioavailability, plasma concentrations, and efficacy may be reduced by drugs used to raise gastric pH, such as proton pump inhibitors and histamine- H_2 antagonists. Preclinical data indicated that gefitinib could penetrate into the central nervous system and accumulate in brain tumors [33] and small clinical studies have demonstrated the activity of the drug on brain metastases in patients with NSCLC [34–37].

Mechanism of action: erlotinib

Erlotinib hydrochloride (OSI-774, CP-358774) is an orally administered synthetic anilinoquinazoline compound that selectively binds to the ATP-binding site of *EGFR* TK intracellular domain. After oral administration, erlotinib is widely distributed throughout the body with a bioavailability of 60% [38]. It is metabolized in the liver by cytochrome P450s, primarily by CYP3A4 and CYP1A1 and, in a minor proportion

of people, by CYP3A5 [38]. A population pharmacokinetic study in 591 patients who received single-agent erlotinib showed a median half-life of 36.2 hours with a time to reach steady-state plasma concentration of 7–8 days. Patient age, body weight, or sex seemed not to affect clearance, whereas smokers had a 24% higher rate of erlotinib clearance. After a 100 mg oral dose, 91% of the dose was recovered: 83% in feces and 8% in urine [38]. OSI-420 (desmethyl erlotinib, CP-473420) is the active metabolite. OSI-420 exposure (area under the curve [AUC]) in plasma is 30% (range 12–59%) of erlotinib, and OSI-420 clearance is more than fivefold higher than that of erlotinib [39].

In an in vitro enzyme analysis [40], erlotinib showed comparable binding affinities against wild-type and mutant *EGFR* and no significant differences in activity were found across an enzyme panel of more than 200 isolated targets (predominantly kinases). In addition, erlotinib showed a high growth inhibitory activity across a panel of 34 NSCLC cell lines, including three cell lines harboring activating *EGFR* mutations [41].

Mechanism of action: afatinib

Afatinib is an orally administered, irreversible *EGFR*, *HER2* and *HER4* inhibitor, which shows preclinical activity against cancer cells harboring common activating *EGFR* mutations and the *T790M* mutation, albeit with a lower potency [42]. As with other *EGFR*-TKIs, the pharmacokinetic profile of afatinib supports a once-daily dosage regimen. A retrospective analysis including 221 patients with advanced solid tumors evaluated the pharmacokinetic profile of afatinib by using non-compartmental methods [43]. Maximum plasma concentration was achieved 2–5 hours after dosing and thereafter declined at least bi-exponentially. Steady-state plasma concentrations were achieved within 8 days after the start of dosing, whereas median half-life was about 37 hours. There was moderate intra-individual variability in afatinib trough concentration values (the geometric coefficient of variation [gCV] ranged from 22.2–67.5 %). The inter-patient variability in plasma concentrations was moderate to high (eg, at the 40 mg dose, the gCVs ranged from 35.6–221 %). Interestingly, the exposure to afatinib (as measured by AUC and C_{max}) correlated with the severity of diarrhoea and rash [43]. Phase I studies established the

maximum tolerated oral dose at 50 mg daily, with diarrhea and rash being the most common adverse events [44].

Clinical data

Several phase II and III studies evaluated the efficacy of gefitinib, erlotinib or afatinib in patients harboring classical (exon 19 deletion or L858 substitutions in exon 21) *EGFR* mutations. Table 2.2 illustrates results from phase III trials comparing an *EGFR*-TKI versus platinum-based chemotherapy in untreated patients harboring *EGFR* mutations. Nine large randomized phase III clinical trials (First-SIGNAL, IPASS, WITOG 3405, NEJ002, OPTIMAL, EURTAC, ENSURE, LUX-3, LUX-6) demonstrated that an *EGFR*-TKI is the best front-line therapy for *EGFR*^{mut+} patients [45–53]. All trials demonstrated that an *EGFR*-TKI was superior to standard-platinum-based chemotherapy in terms of RR, PFS, toxicity profile and quality of life; the lack of difference in terms of OS was probably due to the confounding effect of crossover.

Four phase III studies (IPASS, First-SIGNAL, WJTOG3405 and NEJ002) compared gefitinib versus chemotherapy as first-line therapy in *EGFR*^{mut+} patients or with clinical characteristics predictive for the presence of *EGFR* mutations [45–48]. The IPASS trial was a randomized phase III study where previously untreated patients in East Asia who had advanced lung adenocarcinoma and who were non-smokers or former

Study	EGFR TKI	n	Median PFS in TKI arm (months)	P value	HR
OPTIMAL	Erlotinib	154	13.7	<0.0001	0.16
First Signal	Gefitinib	42	8.4	0.084	0.48
IPASS	Gefitinib	261	9.5	<0.0001	0.36
WJTOG 3405	Gefitinib	177	9.2	<0.001	0.42
NEJSG 002	Gefitinib	200	10.8	<0.001	0.36
EURTAC (Caucasians)	Erlotinib	174	10.4	<0.0001	0.42
ENSURE	Erlotinib	217	11.0	0.0001	0.34
LUX-3	Afatinib	308	11.1	0.001	0.58
LUX-6	Afatinib	364	11.0	<0.0001	0.28

Table 2.2 Studies of *EGFR*-TKIs versus chemotherapy as first-line therapy in patients with *EGFR*^{mut+} NSCLC. *EGFR*-TKI, epidermal growth factor-tyrosine kinase inhibitor; HR, hazard ratio; PFS, progression-free survival.

light smokers were randomized to receive gefitinib or carboplatin/paclitaxel [45]. The primary objective of the study was to assess the non-inferiority of gefitinib versus carboplatin/paclitaxel for PFS. The study demonstrated the superiority of gefitinib over chemotherapy in terms of PFS in the intent-to-treat (ITT) population. Another trial compared gefitinib with cisplatin/gemcitabine as first-line treatment in Asian never-smokers with advanced adenocarcinoma [46]. Three hundred and nine patients, mostly women (89%), were randomly allocated 1:1 to gefitinib 250 mg/day or cisplatin/gemcitabine. The primary endpoint was OS. In the whole population, no difference in response, PFS or OS was detected. Nevertheless, similar to the IPASS study, when the analysis was restricted to patients who harbored *EGFR* mutations, RR and PFS were significantly improved in the gefitinib arm compared with the chemotherapy arm, with no difference in terms of survival, most likely due to the post-study use of EGFR-TKIs in 80.7% of subjects enrolled in the chemotherapy arm. Two phase III Japanese studies have been performed specifically in *EGFR*^{mut+} patients to compare the efficacy of gefitinib versus chemotherapy in the first-line treatment of NSCLC [46,47]. In the WJTOG3405 trial, 172 patients with *EGFR*^{mut+} NSCLC were randomly assigned to receive gefitinib or chemotherapy with cisplatin/docetaxel [47]. The study met its primary objective, showing a significant improvement in PFS in the gefitinib arm. The NEJ002 trial randomly assigned patients with *EGFR*^{mut+} NSCLC to gefitinib or chemotherapy with carboplatin/paclitaxel [48]. The study confirmed that gefitinib was superior to chemotherapy in terms of PFS (10.4 versus 5.5 months), reinforcing the evidence that EGFR-TKIs should be preferred to chemotherapy in the presence of *EGFR* mutations.

Three trials, OPTIMAL, EURTAC and ENSURE, compared erlotinib to chemotherapy [49–51] in patients with NSCLC. In 2011, Zhou and colleagues published the results of the OPTIMAL trial, a phase III study that compared erlotinib to carboplatin/gemcitabine in Chinese *EGFR*^{mut+} patients [49]. A significant improvement in PFS was observed for patients assigned to the erlotinib arm, with an impressive HR of 0.16 (95% CI 0.10–0.26). The Spanish Lung Cancer Group coordinated a large phase III study (EURTAC) comparing for the first time erlotinib versus standard platinum-based chemotherapy in Caucasian chemo-naïve

EGFR^{mut+} patients [50]. Median PFS was 9.7 months in the erlotinib group, compared with 5.2 months in the standard chemotherapy group and patients receiving erlotinib had a 63% relative reduction in risk of progression compared with those receiving standard chemotherapy (HR 0.37, $p < 0.0001$). More recently, investigators reported the results of the ENSURE study, an open-label phase III trial comparing erlotinib versus cisplatin plus gemcitabine as first-line therapy in Asian patients with *EGFR*^{mut+} NSCLC [51]. The study, conducted in a total of 217 patients, confirmed the superiority of erlotinib versus chemotherapy for the primary end-point of PFS (HR 0.42; $p = 0.0001$).

The LUX-LUNG 3, a multicenter, randomized, open-label phase III study compared afatinib with cisplatin plus pemetrexed in patients with locally advanced or metastatic lung adenocarcinoma harboring *EGFR* mutations [52]. Among the 1,269 screened patients, 345 were randomized in a 2:1 fashion to afatinib 40 mg daily or chemotherapy up to a maximum of six cycles and without any maintenance therapy. As expected, patients were mainly East Asian, never-smokers and women. *EGFR* mutations were predominantly exon 19 deletions and L858R point mutations. The PFS assessed by independent review, the primary endpoint of this trial, was significantly prolonged in the afatinib arm compared to chemotherapy arm, with a median PFS of 11.1 and 6.9 months, respectively. Median PFS among patients with classical (exon 19 deletion or exon 21) *EGFR* mutations was 13.6 for afatinib versus 6.9 months for chemotherapy. Afatinib achieved a higher RR compared with chemotherapy according to both independent (56% versus 23%) and investigator (69% versus 44%) assessment and a higher disease control rate (90% versus 81% by independent review). The most frequent ($\geq 20\%$ incidence) adverse events observed with afatinib were diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite and pruritus. Although grade ≥ 3 treatment-related adverse events occurred in nearly 50% of patients receiving afatinib, the treatment was discontinued in just 8% of patients. In another study, the LUX LUNG 6, Asian patients with *EGFR*^{mut+} NSCLC were randomized in a 2:1 fashion to afatinib 40 mg daily or cisplatin plus gemcitabine [53]. The study showed that patients treated with afatinib had a significantly longer PFS than individuals who received

chemotherapy (median PFS 11.0 versus 5.6 months, $p<0.0001$), as well as higher RR (66.9% versus 23.0%, $p<0.0001$) and higher disease control rate (92.6% versus 60.2%, $p<0.0001$). More recently, a pooled analysis of LUX-3 and LUX-6 trials was presented (Figure 2.1). Although in both trials, separately, no difference in survival emerged between afatinib and the chemotherapy arm, combined data demonstrated that the EGFR-TKI was superior to chemotherapy in terms of OS, with an HR of 0.81 [54]. Interestingly, the survival benefit was confined to individuals harboring an exon 19 *EGFR* mutation, whereas no difference was observed in patients with an exon 21 *EGFR* mutation. These findings reinforce the evidence that the exon 19 *EGFR* deletion is the mutation most sensitive

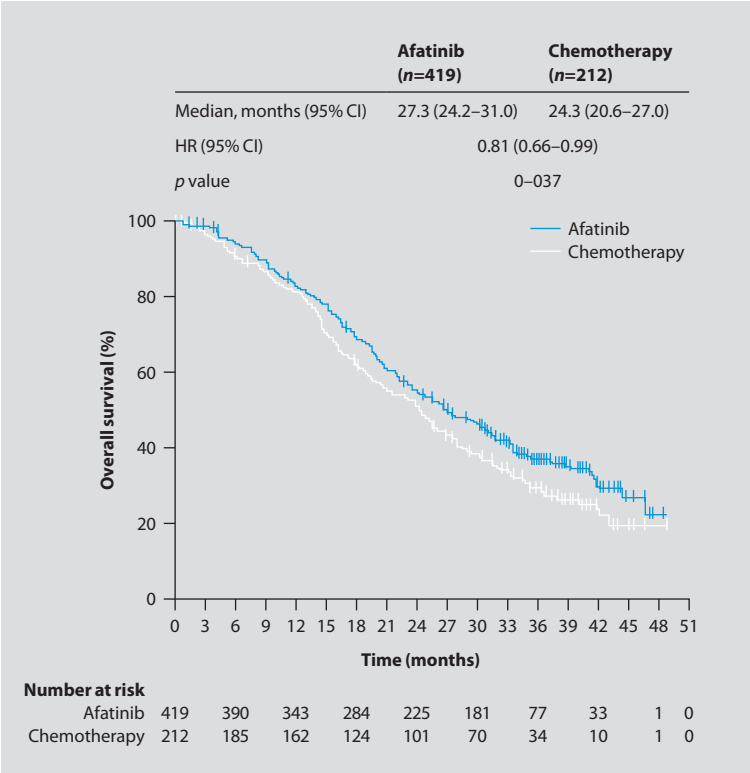


Figure 2.1 Overall survival (combined analysis of LUX-Lung 3 and LUX-Lung 6) in patients with common *EGFR* mutations. CI, confidence interval; HR, hazard ratio. Reproduced with permission from Yang et al [54]. ©2015 Elsevier Ltd.

to TKI inhibition and that all EGFR-TKIs are more effective in patients harboring this genetic alteration.

Overall, data with afatinib demonstrated that the drug is effective in patients with *EGFR*^{mut+} NSCLC, supporting its use in front-line setting.

An important clinical question is which EGFR-TKI should be preferentially used as front-line therapy in *EGFR*^{mut+} patients. Indirect comparisons have indicated that skin rash and diarrhea, the two most typical adverse events of EGFR-TKIs, are more frequently observed with afatinib than with erlotinib or gefitinib, with no difference in terms of efficacy between these three agents. Katakami et al presented the results of a randomized phase III study comparing gefitinib versus erlotinib as second-line therapy in metastatic NSCLC [55]. The study, conducted in 559 patients with or without *EGFR* mutations, showed no difference between the two drugs in terms of RR, PFS or OS in the general population as well as in the group of patients with or without *EGFR* mutations (Table 2.3). The study also showed a greater incidence of skin toxicities with erlotinib compared with gefitinib, whereas liver toxicity in terms of elevation of transaminase was significantly more common in the gefitinib arm [55]. The ARCHER 1009 trial randomly assigned pretreated NSCLC patients to erlotinib or dacomitinib, another irreversible EGFR-TKI. The study, conducted in 80 patients with NSCLC irrespective of *EGFR* status, showed no difference in RR, PFS and OS between the two arms in the whole study population as well as in *KRAS* wild-type patients, as illustrated in Figure 2.2. Diarrhea was significantly more frequently observed in the dacomitinib arm [56]. Therefore, available data indicate that gefitinib, erlotinib and afatinib differ in their toxicity profiles, with no evidence of different efficacy.

Population	Treatment	Median PFS (months)	P value
<i>EGFR</i> ^{mut+}	Erlotinib	10.09	0.532
	Gefitinib	8.90	
<i>EGFR</i> ^{mut-}	Erlotinib	2.10	0.221
	Gefitinib	2.07	
General population	Erlotinib	2.53	0.878
	Gefitinib	2.27	

Table 2.3 PFS results from the WJOG 5180L randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced NSCLC. PFS, progression-free survival.

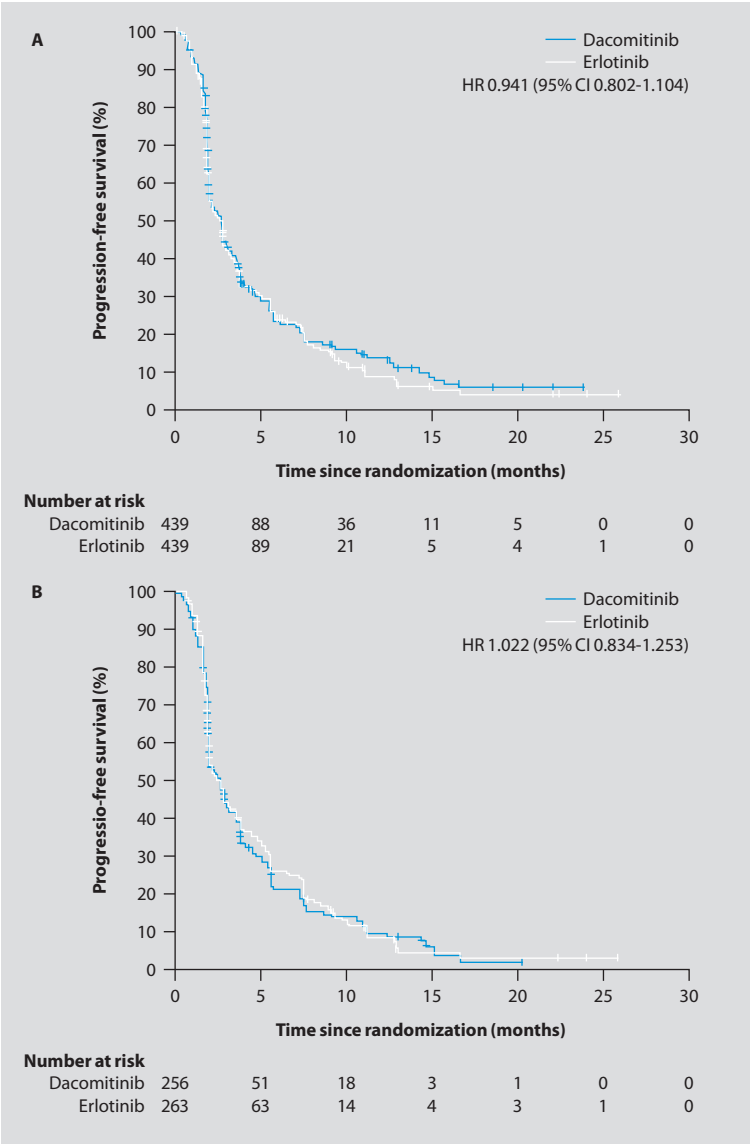


Figure 2.2 Kaplan-Meier curves for progression-free survival per independent review in a phase III study of dacomitinib versus erlotinib in patients with previously treated advanced NSCLC. Progression-free survival for all patients (A) and patients with *KRAS* wild-type (B). HR, hazard ratio. Reproduced with permission from Ramalingham et al [56]. ©2014 Elsevier Ltd

ALK inhibitors

The role of targeted therapies in NSCLC has been further reinforced with the identification of the *EML4* (*echinoderm microtubule-associated protein-like 4*)-*ALK* (*anaplastic lymphoma kinase*) fusion gene, a genetic abnormality detected in 3–7% of patients with adenocarcinomas of the lung [57]. *ALK* gene rearrangement is associated with specific clinical-pathological features, including male sex, young age, absent or minimal smoking history, adenocarcinoma histology, and usually mutual exclusivity between *EML4-ALK* and *EGFR* and *KRAS* mutations [58–60]. Although there are clinical features associated with *ALK* rearrangement, they do not properly select patients for *ALK* inhibitors and, consequently, molecular testing is mandatory. As illustrated in Table 2.4, there are three methods of detecting *ALK* rearrangement: the fluorescence in situ hybridization (FISH) break-apart assay, immunohistochemistry (IHC), and reverse transcriptase polymerase chain reaction (RT-PCR). Currently FISH is the gold standard and is the approved companion diagnostic test (Vysis *ALK* break apart FISH probe kit; Abbott Molecular, USA) by the US FDA [61–63].

At the present time, three agents, crizotinib, ceritinib and alectinib, are clinically available for *ALK*-translocated NSCLC, with crizotinib approved for first-line therapy in the US, ceritinib FDA approved in the second-line setting and alectinib approved in Japan only. Several additional agents are under investigation.

	FISH	IHC	RT-PCR
Current standard for <i>ALK</i> detection	Yes	No	No
Sensitivity	Break-apart signal can be subtle	High for some antibodies	High
Detection of unknown variants	Yes	Yes	Possible with some platforms
Labor intensive	Yes	No	No
Highly specialized training required	Yes	No	No
Simultaneous visualization of cell morphology	No	Yes	No

Table 2.4 Comparison of FISH, IHC and RT-PCR as screening modalities for *ALK* rearrangement. FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction.

Mechanism of action and clinical data

Crizotinib is a selective ATP-competitive small-molecule inhibitor of ALK, ROS1 and c-MET tyrosine kinases and their oncogenic variants, including ALK and ROS1 fusion proteins or c-MET mutant variants. Its synthesis was based on the structure of a parental compound, PHA-665752 [64,65]. PHA-665752 was a potent MET inhibitor that targeted the ATP site of the tyrosine kinase domain of MET and demonstrated antitumor activity in preclinical models. However, the high metabolic clearance, low solubility at pH 7.4 and scarce permeability made PHA-665752 unsuitable for its use in the clinic. Crizotinib was specifically designed to be less lipophilic and to have optimized interaction with the tyrosine kinase domain [64].

In enzymatic inhibition assays, as well as in a panel of more than 120 kinases, crizotinib selectively inhibited ALK and MET kinases, resulting in an approximately 20-fold greater potency than against other kinases. Consistent with its mechanism of action, crizotinib dose-dependently inhibits kinase activity of ALK and c-MET and their downstream signaling pathways, thus arresting tumor cell proliferation both in in vitro and in vivo models.

To date, the role of crizotinib in ALK-positive NSCLC has been evaluated in four trials and their results are summarized in Table 2.5 [66–69]. The

Trial	n	Treatment	RR	mDOR (mos)	PFS		OS	
					Median (mos)	HR P value	Median (mos)	HR P value
PROFILE 1001, (Ph.I)	143	CRZ	61	12.2	9.7	–	NR	–
PROFILE 1005, (Ph.II)	255	CRZ	53	10.7	8.5	–	NR	–
PROFILE 1007, (Ph. III)	173	CRZ	65	8.0	7.7	0.49	20.3	0.54
	174	PEM/TXT	20	6.1	3.0	<0.001	22.8	0.54
PROFILE 1014, (Ph.III)	172	CRZ	74	12.2	10.9	0.45	nr	0.82
	171	Platinum/ PEM	45	5.7	7.0	<0.001	nr	0.18

Table 2.5 Efficacy of crizotinib in the PROFILE trials. CRZ, crizotinib; HR, hazard ratio; mDOR, median duration of response; NR, not reported; nr, not reached; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; TXT, docetaxel.

first open-label, multicenter, phase I trial of crizotinib, the A8081001 study, started accrual in 2006 and consisted of two parts. In the dose-escalating phase conducted in 36 patients with different types of advanced cancers, two patients experienced grade 3 fatigue at the higher dose level of 300 mg twice daily and a dose reduction to 250 mg twice daily was determined as the maximum-tolerated dose and as the recommended dose to test in subsequent phase II studies [70]. As crizotinib was initially developed as a MET inhibitor, the second part of this trial aimed to test the activity of crizotinib with a specific focus on tumors harboring MET deregulation, including *MET* amplification or *MET* mutation. Overall, a total of 25 patients harboring a wide range of *MET* alterations received crizotinib, but only in *MET*-amplified tumors – such as NSCLC, gastro-esophageal carcinoma and glioblastoma – was significant tumor shrinkage observed [71–73]. However, during the escalating phase, the occurrence of similar dramatic responses in two NSCLC cases that carried an *ALK* rearrangement shifted investigators towards clinical development of the drug in this molecularly defined setting and the protocol was amended to screen simultaneously patients for both *ALK* translocation and *MET* amplification.

Preliminary results from the first 82 patients with *ALK*-positive NSCLC enrolled in the expansion cohort of the phase I PROFILE 1001 trial showed that treatment with crizotinib produced a response rate of 57% and an estimated 6-month PFS of 72%, with no median reached [66]. Two years later, updated results after an enrollment of approximately 150 patients confirmed activity in terms of RR of more than 60%, with a median PFS exceeding 9 months [67]. Similar findings have been observed in a large, multicenter, single arm phase II study, known as PROFILE 1005 [74]. This trial served as a companion trial to the second-line randomized study (PROFILE 1007) for patients who were randomized to and progressed on the chemotherapy arm of PROFILE 1007. According to the trial design, patients in the standard chemotherapy arm were not permitted to directly crossover to crizotinib at the time of progression. As a consequence, these patients had to be enrolled in the PROFILE 1005 study. Nevertheless, after the completion of US accrual in PROFILE 1007, some major changes in eligibility criteria allowed the inclusion in PROFILE 1005 of all NSCLC patients with *ALK* translocations irrespective of line of treatment and

presence of measurable disease. At the data cut-off in January 2012, a total of 901 patients were included in the study. Two-hundred-and-fifty-five patients were analyzed for efficacy. The RR was 53% at the time of data cut-off. Notably, responses were long lasting (median duration of response 43 weeks) and PFS was approximately 8 months [74]. Based on these results, in August 2011 crizotinib received FDA accelerated approval for the treatment of *ALK*-positive NSCLC.

The superiority of crizotinib versus standard chemotherapy was demonstrated in two large phase III studies [68,69]. The first trial, PROFILE 1007, compared second-line crizotinib to standard chemotherapy with either pemetrexed or docetaxel in 347 patients with advanced *ALK*-rearranged NSCLC who had failed one prior platinum-based regimen [68]. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group. Patients treated with crizotinib had a 51% relative reduction in risk of progression compared with those receiving standard chemotherapy (HR 0.49; $p < 0.001$). Treatment with crizotinib was also associated with a higher response rate (65% versus 20%, ITT population, $p < 0.001$) and a more favorable toxicity profile. By splitting results according to type of chemotherapy, the worst outcome in terms of RR and PFS was observed in the docetaxel arm when compared with the pemetrexed arm (RR 7% vs 29%; PFS 4.2 versus 2.6 months). Notably, the subset analyses confirmed a significant PFS benefit in favor of the crizotinib arm that was independent of age (>65 versus <65 years), sex, performance status (EGOG PS 0-1 versus 2), histology (adenocarcinoma versus non-adenocarcinoma) and presence of brain metastases. Consistent with what was observed in all phase III trials with front-line EGFR-TKIs [64–71], the improvement in PFS did not translate into a significant advantage in OS in favor of crizotinib therapy. Also in this case, the vast majority of patients assigned to the chemotherapy arm received crizotinib at progression, with an inevitable confounding effect on survival. Despite this, the unusual silhouette of survival curves seems to suggest an inversion in the natural course of *ALK*-positive disease.

The second trial, PROFILE 1014, aimed to demonstrate the improvement in PFS of crizotinib over standard platinum-base chemotherapy in previously untreated advanced non-squamous *ALK*-positive NSCLC [69].

Overall, a total of 343 patients were randomized 1:1 to receive crizotinib or the combination of pemetrexed with either cisplatin or carboplatin, every three weeks for a maximum of six cycles. According to the trial design, at the time of progression patients randomized to the standard arm crossed-over to crizotinib, whereas patients in the experimental arm were allowed to continue crizotinib beyond progression at the investigator's discretion. The study demonstrated the superiority of crizotinib over chemotherapy in prolonging PFS: the median PFS was 10.9 months in the crizotinib arm versus 7.0 months for chemotherapy (HR 0.454; $p < 0.0001$). Moreover, patients receiving crizotinib had a higher probability of response than those receiving chemotherapy (74% vs 45%; $p < 0.0001$). Considering that more than 60% of patients in the standard arm received crizotinib at the time of progression, no difference in OS was observed between the two groups (HR 0.821, $p = 0.1804$). These results clearly established crizotinib as the standard of care in untreated advanced *ALK*-positive non-squamous NSCLC.

References

- 1 Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J*. 1995; 311: 899-909.
- 2 Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol*. 2008; 26: 4617-4625.
- 3 Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol*. 1998;16:2459-2465.
- 4 Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2000;18:122-130.
- 5 Lilenbaum RC, Herndon JE 2nd, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the Cancer and Leukemia Group B (Study 9730). *J Clin Oncol*. 2005; 23:190-196.
- 6 Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group Trial. *J Clin Oncol*. 2001;19: 3210-3218.
- 7 Le Chevalier T, Scagliotti GV, Natale R, et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. *Lung Cancer*. 2005; 47: 69-80.
- 8 Douillard JY, Laporte S, Fossella F, et al. Comparison of docetaxel- and vinca alkaloid-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer: a meta-analysis of seven randomized clinical trials. *J Thorac Oncol*. 2007; 2: 939-946.

- 9 Grossi F, Aita M, Defferrari C, et al. Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach. *Oncologist*. 2009;14:497-510.
- 10 Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2007; 99: 847-857.
- 11 Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med*. 2002; 346: 92-98.
- 12 Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol*. 2002; 20: 4285-4291.
- 13 Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003; 21:3016-3024.
- 14 Delbaldo C, Michiels S, Syz N, et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. *JAMA*. 2004; 292:470-484.
- 15 Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543-3551.
- 16 Ceppi P, Volante M, Saviozzi S, et al. Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer*. 2006;107:1589-1596.
- 17 Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004; 22: 2184-2191.
- 18 Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006; 355: 2542-2550.
- 19 Sandler A, Yi J, Dahlberg S, Kolb MM, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol*. 2010;5:1416-1423.
- 20 Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol*. 2009; 27:1227-1234.
- 21 Soria JC, Mauguen A, Reck M, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2013; 24:20-30.
- 22 Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol*. 2009; 27:5255-5261.
- 23 Wozniak AJ, Garst J, Jahanzeb M, et al. Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): results from ARIES, a bevacizumab (BV) observational cohort study (OCS). *J Clin Oncol*. 2010; 28 (abstr 7618).
- 24 Crinò L, Dansin E, Garrido P, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAIL, MO19390): a phase 4 study. *Lancet Oncol*. 2010;11:733-740.
- 25 Johnson BE, Kabbavar F, Fehrenbacher L, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2013; 31:3926-3934.
- 26 Patel J, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus

- paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013; 31:4349-4357.
- 27 Zinner R, Ross HJ, Weaver R, et al. Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab (PCB) followed by maintenance bevacizumab in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2013; 31 (suppl; abstr LBA8003).
 - 28 Ranson M, Hammond LA, Ferry D, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a Phase I trial. *J Clin Oncol*. 2002;20:2240-2250.
 - 29 Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res*. 2000;6:2053-2063.
 - 30 Swaisland H, Laight A, Stafford L, et al. Pharmacokinetics and tolerability of the orally active selective epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in healthy volunteers. *Clin Pharmacokinet*. 2001;40:297-306.
 - 31 Swaisland HC, Cantarini MV, Fuhr R, et al. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. *Clin Pharmacokinet*. 2006;45:633-644.
 - 32 Swaisland HC, Ranson M, Smith RP, et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet*. 2005;44:1076-1081.
 - 33 Heimberger AB, Learn CA, Archer GE, et al. Brain tumors in mice are susceptible to blockade of Epidermal Growth Factor Receptor (EGFR) with the oral, specific, EGFR-tyrosine kinase inhibitor ZD1839 (Iressa). *Clin Cancer Res*. 2002; 8:3496-3502.
 - 34 Cappuzzo F, Ardzisoni A, Soto-Parra H, et al. Epidermal growth factor receptor targeted therapy by ZD 1839 (Iressa) in patients with brain metastases from non-small cell lung cancer (NSCLC). *Lung Cancer*. 2003;41: 227-231.
 - 35 Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. 2004;15:1042-1047.
 - 36 Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2004;46:255-261.
 - 37 Namba Y, Kijima T, Yokota S, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: review of 15 clinical cases. *Clin Lung Cancer*. 2004; 6:123-128.
 - 38 Johnson JR, Cohen M, Sridhara R, et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic of non-small cell lung cancer after failure of at least one prior chemotherapy regimen. *Clin Cancer Res*. 2005; 11:6414-6421.
 - 39 Meany HJ, Fox E, McCully C, et al. The plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite (OSI-420) after intravenous administration of erlotinib in non-human primates. *Cancer Chemother Pharmacol*. 2008; 62:387-392.
 - 40 Speake G. A pharmacological comparison of gefitinib (IRESSA) and erlotinib. 97th American Association of Cancer Research Annual Meeting, Washington, DC, USA 2006; poster 3784.
 - 41 Yuza Y, Glatt KA, Jiang J, et al. Allele-dependent variation in the relative cellular potency of distinct EGFR inhibitors. *Cancer Biol Ther*. 2007; 6:661-667.
 - 42 Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008; 27:4702-4711.
 - 43 Wind S, Schmid M, Erhardt J, et al. Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clin Pharmacokinet*. 2013;52:1101-1109.
 - 44 Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible ErbB1 (EGFR) and ErbB2 (HER2) kinase inhibitor BIBW 2992 in patients with advanced solid tumours. *J Clin Oncol* 2010; 28: 3965-3972.
 - 45 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009; 361:947-957.
 - 46 Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012; 30:1122-1128.

- 47 Mitsudomi T, Morita S, Yatabe Y, 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. *Lancet Oncol.* 2010; 11:121-128.
- 48 Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* 2010;362: 2380-2388.
- 49 Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011; 12:735-742.
- 50 Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012; 13:239-246.
- 51 Wu YL, Liang CK, Zhou C, et al. First-line erlotinib versus cisplatin/gemcitabine (GP) in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC): interim analyses from the phase 3, open-label, ENSURE study. *J Thorac Oncol.* 2013; 8:s603 (Suppl. 2).
- 52 Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31: 3327-3334.
- 53 Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harboring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15:213-222.
- 54 Yang JC, Wu J C-H, Schuler YL, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.* 2015;16:141-151.
- 55 Katakami N, Morita S, Yoshioka H, et al. Randomized phase III study comparing gefitinib (G) with erlotinib (E) in patients (pts) with previously treated advanced lung adenocarcinoma (LA): WJOG 5108L. *J Clin Oncol.* 2014; 32:5s, (suppl; abstr 8041).
- 56 Ramalingam SS, Jänne PA, Mok T, et al. Dacomitinib versus erlotinib in patients with advanced stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2014;15:1369-1378.
- 57 Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin. Cancer Res.* 2008; 14: 4275-4283.
- 58 Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from non smokers with wild-type EGFR and KRAS. *Cancer.* 2009; 115:1723-1733.
- 59 Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbour EML4-ALK. *J Clin Oncol.* 2009; 27: 4247-4253.
- 60 Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. *Mod Pathol.* 2009;22:508-515.
- 61 Bang YJ, Treatment of ALK-positive non-small cell lung cancer. *Arch Pathol Lab Med.* 2012;136:1201-1204
- 62 Thunnissen E, Bubendorf L, Manfred D, et al. EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations. *Virchows Arch.* 2012; 461:245-257.
- 63 Horn L, and Pao W, EML4-ALK: homing in on a new target in non-small-cell lung cancer. *J Clin Oncol.* 2009; 27: 4232-4235.
- 64 Cui JJ, Tran-Dubé M, Shen H, et al. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). *J Med Chem.* 2011; 54:6342-6363.
- 65 Tanizaki J, Okamoto I, Okamoto K, et al. MET tyrosine kinase inhibitor crizotinib (PF-02341066) shows differential antitumor effects in non-small cell lung cancer according to MET alterations. *J Thorac Oncol.* 2011; 6:1624-1631.
- 66 Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; 363: 1693-1703.

- 67 Camidge DR, Bang YJ, Kwak EL, 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 Oncol.* 2012;13:1011-1019.
- 68 Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*, 2013; 368: 2385–94.
- 69 Mok T, Kim D-W, Wu Y-L, et al. First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014). *J Clin Oncol.* 2014; 32:5s (suppl; abstr 8002).
- 70 Kwak EL, Camidge DR, Clark J, et al. Clinical activity observed in a phase I dose escalation trial of an oral anti-c-met and ALK inhibitor, PF-02341066. *J Clin Oncol.* 2009; 27; 15 (suppl; abstract 3509).
- 71 Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol.* 2011; 6:942-946.
- 72 Lennerz JK, Kwak EL, Ackerman A, et al. MET Amplification Identifies a Small and Aggressive Subgroup of Esophagogastric Adenocarcinoma With Evidence of Responsiveness to Crizotinib. *J Clin Oncol.* 2011;29:4803-4810.
- 73 Chi AS, Batchelor TT, Kwak EL, et al. Radiographic and Clinical Improvement After Treatment of a MET-Amplified Recurrent Glioblastoma With a Mesenchymal-Epithelial Transition Inhibitor. *J Clin Oncol.* 2012;30:e30-e33.
- 74 Kim D-W, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK positive non-small cell lung cancer. *J Clin Oncol.* 2012; 30: abstract 7533.

Guide to Targeted Therapies: Treatment Resistance in
Lung Cancer

Cappuzzo, F.

2015, VII, 67 p. 14 illus. in color., Softcover

ISBN: 978-3-319-20740-7