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Extending Survival of Stage IV Non-Small Cell Lung Cancer

Carnio S, Novello S, Mele T, Levra MG, Scagliotti GV.

Most of patients with newly diagnosed non-small cell lung cancer (NSCLC) present with locally advanced or metastatic disease. In this setting the goal of treatment is to prolong survival and to control disease- and treatment-related symptoms. Currently systemic cytotoxic chemotherapy remains the first-line treatment for most patients with stage IV NSCLC, but preferred treatments are now defined by histology and based on the presence of specific molecular abnormalities. In first-line the combination of platinum plus pemetrexed with or without bevacizumab is a reasonable choice in patients with non-squamous NSCLC. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as first-line therapy are the recommended for patients with EGFR-sensitizing mutations. A small-molecule TKI of anaplastic lymphoma kinase (ALK), crizotinib, showed pronounced clinical activity in the treatment of patients with NSCLC positive for EML4-ALK and it has rapidly entered into daily clinical practice. Currently no agents are specifically approved for the treatment of squamous cell carcinoma of the lung. Second-line treatments include docetaxel, pemetrexed, or erlotinib as single agents. There is a growing evidence that cytotoxics are better than EGFR-TKIs in EGFR wild-type patients. In the setting of the third line, the only approved agent is erlotinib. In elderly patients with good performance status (PS), doublet chemotherapy including platinum should not be excluded, especially for those patients 70–75 years of age without comorbidities. The better selection of patients, the identification of specific predictive biomarkers, a reasonable sequencing of all active and available treatments, including targeted therapies and cytotoxic, may significantly contribute to extend the natural history of stage IV NSCLC.

Lung cancer remains a relevant health care problem and in the near future will account for almost 30% of all cancer-related deaths. Non-small cell lung cancer (NSCLC) represents more than 80% of all lung cancer cases. The majority of patients with lung cancer are diagnosed at baseline with locally advanced or metastatic disease. The increase in life expectancy with the associated cumulative increase in the risk of cancer has led to an increased incidence of this disease in the elderly population. Overall the incidence and death rates for lung cancer are decreasing for both men and women¹; however, the 5-year survival in stage IV NSCLC remains as low as 1%.² According to the current World Health Organization (WHO) classification for lung tumors, NSCLC includes many histological subtypes, but for therapeutic purposes it can be broadly categorized as squamous and non-squamous. This non-canonical categorization is related to the lack of efficacy of some cytotoxic agents (eg, pemetrexed) or to an excess of toxicity for some targeted agents (eg, bevacizumab and other multiple vascular endothelial growth factor [EGFR] inhibitors) in squamous histology. As consequence over the last few years the histological definition became progressively more important in tuning the therapeutic choices and now is definitively recognized the role of immunohistochemistry in minimizing the amount of NSCLC not otherwise specified (NOS).

Here, we summarize the available data about the best treatment strategy in front line for stage IV NSCLC on the basis of the predictive role of histology and new molecular findings and reviews new data about the treatment customization in elderly patients, as well as treatment choices in second line and beyond.

Treatment Choices In First Line

The Role of Cytotoxic Chemotherapy

First-line chemotherapy improves survival in patients with advanced NSCLC and good performance status (PS). It generally includes two chemotherapy agents with different mechanisms of action and safety profiles.^{3 and 4} Several studies^{5, 6, 7 and 8} and multiple meta-analyses^{9, 10 and 11}

established the superior efficacy of doublet regimens over single agents and the superior activity of cisplatin over carboplatin in terms of objective response rate (ORR)¹² despite a less favorable toxicity profile. Improvements in survival were observed in subgroups of cisplatin-treated patients who had been treated with third-generation platinum-based regimens (hazard ratio [HR] for mortality with carboplatin relative to cisplatin = 1.11; 95% confidence interval [CI], 1.01–1.21) and in patients with non-squamous histology (HR = 1.12; 95% CI, 1.01–1.23).

A decade ago several large randomized clinical trials compared different platinum-based doublets (including third-generation agents such as taxanes, gemcitabine, or vinorelbine) without showing significant differences in ORR, progression-free survival (PFS), and overall survival (OS).^{13, 14 and 15} A meta-analysis investigated the role of adding a third agent to platinum-based doublets and showed that triplets are associated with an increase in ORR, which does not translate into a better PFS or OS rate.¹⁶ Traditionally, the histologic subtype did not matter for the choice of chemotherapy but the therapeutic landscape changed following the results of a large phase III randomized non-inferiority study conducted in 1,725 patients with stage IIIB or IV NSCLC that compared cisplatin plus pemetrexed (CP) to cisplatin plus gemcitabine (CG). A preplanned analysis for histology showed that patients with non-squamous histology benefited more from CP in terms of OS (HR 0.81; $P = .005$), while PFS did not differ between the two groups. On the contrary, patients with squamous cell histology showed a marginally significant superiority in OS when treated with CG (10.8 v 9.4 months, respectively; HR 1.23; $P = .05$) and PFS was also significantly longer (5.5 v 4.4 months, respectively; HR 1.36; $P < .05$). CP resulted in a statistically significant inferior incidence of grade 3–4 neutropenia, anemia, thrombocytopenia, febrile neutropenia, and alopecia ($P \leq .001$), whereas drug-related grade 3–4 nausea was higher ($P = .004$).^{17 and 18} Hypothesis-generating findings support the superior activity of pemetrexed in non-squamous NSCLC on the basis of the differential expression of thymidylate synthase (TS), one of the target enzymes of pemetrexed, among the different histotypes of lung cancer being TS lower in adenocarcinoma than in squamous cell carcinoma.¹⁹ Supportive data indicate extremely high levels of TS in small cell lung cancer where pemetrexed did not show activity.²⁰

Nab-paclitaxel is a biologically interactive albumin-bound paclitaxel and in a phase II trial showed improvement of clinical outcomes with weekly rather than every-3-week administration.²¹ Subsequently, a phase III randomized trial evaluated nab-paclitaxel plus carboplatin (nab-PC) versus standard-paclitaxel plus carboplatin (sb-PC). Nab-PC demonstrated a significantly higher ORR than sb-PC (33% v 25%; $P = .005$). Although ORR by histology was not a prespecified endpoint of the study, nab-PC was significantly more active than sb-PC in patients with squamous histology. nab-PC was as effective as sb-PC in patients with non-squamous histology. In general, nab-PC was better tolerated, with lower rates of grade 3 and 4 neuropathy, neutropenia, arthralgia, and myalgia.²²

Molecular Agents Inhibiting Tumor Angiogenesis

Angiogenesis involves multiple cellular events and many interactions among a variety of cell types. While the primary stimulus for angiogenesis in the tumor microenvironment is the hypoxia-driven activation of hypoxia-inducible factor-1 α (HIF-1 α), and the subsequent activation of vascular endothelial growth factor (VEGF), numerous other growth factors and protein products of oncogenes and tumor-suppressor genes are also involved.²³ Tumor-associated vasculature fails to mature completely, typically due to the development of hypoxic regions in the tumor that stimulate a perpetual cycle of VEGF production, angiogenesis, and further tumor growth.²⁴

Vascular Endothelial Growth Factor and Receptor Inhibitors

Bevacizumab, an anti-VEGF humanized monoclonal antibody which inhibits the interaction between the ligand and VEGF receptors (VEGFRs), has been the first targeted agent approved for the treatment of first-line of metastatic non-squamous NSCLC. The activity of bevacizumab in

combination with chemotherapy has been evaluated in two large phase III clinical trials (Eastern Cooperative Oncology Group [ECOG] trial E4599 and AVAiL in Lung Cancer [AVAiL]). ECOG 4599 randomly assigned 855 PS 0–1 patients with advanced non-squamous NSCLC to receive carboplatin-paclitaxel with or without bevacizumab. The primary endpoint of the study was OS. Patients with squamous histology, those with a history of hemoptysis, brain metastases, bleeding or thrombotic disorders, or the need for anticoagulation were also excluded from the study. The exclusion of patients with squamous histology was mandated from life-threatening or fatal episodes of hemoptysis observed in a phase randomized II trial of bevacizumab plus chemotherapy.²⁵ All the efficacy endpoints were significantly improved with bevacizumab (median OS 12.3 months *v* 10.3 months [HR 0.80; *P* = .003] and median PFS 6.2 *v* 4.5 months, respectively [HR 0.66; *P* < .001]).²⁶ Subgroup analyses suggested that the magnitude of benefit was greater in patients with adenocarcinoma (OS was 14.2 *v* 10.3 months; HR 0.69).²⁷ To date, no biomarkers, including hypertension, have been identified to reliably predict patients with improved survival from the addition of bevacizumab.²⁸

Bevacizumab was also evaluated in combination with cisplatin plus gemcitabine in the another (AVAiL) study in 1,050 patients testing two different dose levels, 7.5 and 15 mg/kg, and having as the primary endpoint PFS. The addition of bevacizumab significantly increased PFS from 6.1 to 6.5 or 6.7 months (in the high- and low-dose groups, respectively; HRs for PFS were 0.75; *P* = .0003 and .85; *P* = .04). No difference in OS was observed. ORR was also significantly higher in both bevacizumab arms (37.8%, *P* < .0001, and 30.6%, *P* = .0002, respectively) versus 21.6% for the chemotherapy arm.²⁹ Treatment with bevacizumab was generally well tolerated, even if more severe bleeding episodes were observed in the bevacizumab arm (4.4% *v* 0.7%, respectively; *P* < .001).

The reasons why these two studies ended up in partially different results is not known, but it could be partially related to differences in the patient cohorts, the inferior activity of paclitaxel and carboplatin versus cisplatin and gemcitabine, and the *in vitro* evidence of synergy between taxanes and bevacizumab.³⁰

Despite the modest OS benefit and the conflicting data bevacizumab added chemotherapy was recommended and progressively implemented in several therapeutic guidelines in patients with stage IV non-squamous NSCLC with good PS and without brain metastases and haemoptysis.^{31, 32, 33, 34 and 35}

Recently a systematic review and meta-analysis of four randomised phase II/III trials confirmed that bevacizumab significantly prolonged OS (HR 0.90; *P* = .03), and PFS (0.72; *P* < .001). Bevacizumab also showed a significantly greater effect on OS in patients with adenocarcinoma versus other histologies (*P* = .02), and in patients with body weight loss $\leq 5\%$ versus $> 5\%$ (*P* = .03).³⁶

Patients with CNS metastases were initially excluded because of the risk of cerebral hemorrhage. Nevertheless, the available data suggest an equal risk of intracranial bleeding in patients with CNS metastases treated with or without bevacizumab. In a phase II study (PASSPORT) the safety of bevacizumab in patients with advanced NSCLC and PS 0–1 previously treated for brain metastases (including whole-brain radiation therapy, radiosurgery, and/or neurosurgery) was prospectively evaluated. Patients received bevacizumab in combination with platinum-based doublet chemotherapy or erlotinib as front-line treatment, while second-line bevacizumab was added to the investigators' treatment choice (erlotinib, pemetrexed, docetaxel). Bevacizumab was administered at the dose of 15 mg/kg every 21 days until disease progression or unacceptable toxicity for a maximum of 1 year. The primary objective of the study was the incidence of symptomatic grade ≥ 2 CNS hemorrhage. One hundred fifteen patients were enrolled and full-dose anticoagulation was allowed. Brain imaging was performed at screening and then every 6–8 weeks. No episode (grade 15) of CNS hemorrhage was reported. Other toxicities were consistent with those previously

reported.³⁷ Additional safety data came from ARIES (Avastin Registry: Investigation of Effectiveness and Safety), a prospective observational cohort study in colorectal cancer and NSCLC that included patients underrepresented in randomized clinical trials, ie, elderly patients, with poor PS, or with CNS metastasis. Among 150 patients with NSCLC and CNS metastases no episodes of CNS bleeding were documented.³⁸ A retrospective exploratory analysis of 13 randomized trials evaluated the safety of bevacizumab in patients with pre-existing brain metastases or with brain metastases detected when patients were already receiving bevacizumab.³⁹ Three of these studies included patients with NSCLC for a total of 8,443 patients of whom 4,760 received bevacizumab. Occult brain metastases were identified in 187 of 8,443 patients (91 in bevacizumab arms and 96 in non-bevacizumab arms). Three patients (3.3%) in the bevacizumab group developed a grade 4 cerebral hemorrhage, compared with one of 96 control patients (1%) who experienced a grade 5 cerebral hemorrhage. Mortality rate was not different between the two groups.^{25, 26 and 29}

SaiL (Safety of Avastin in Lung) is another large phase IV study undertaken to assess the safety and efficacy of first-line bevacizumab combined with several standard chemotherapy regimens in patients with advanced or recurrent non-squamous NSCLC⁴⁰ and another open-label trial (ATHENA)⁴¹ evaluated the safety of bevacizumab in patients with CNS metastases and breast cancer. One hundred eighty-one of the 2,166 patients in SAiL (8.4%) and 140 of the 2,216 patients in ATHENA (6.3%) developed brain metastases. Six of these patients were treated with bevacizumab after diagnosis of CNS metastases, none of whom developed cerebral hemorrhage. Three patients in the SAiL study (0.9% of the patients in the two studies who developed brain metastases) had cerebral hemorrhage, only one grade 3. In the ATLAS study (The Avastin Tarceva Lung Adenocarcinoma Study)⁴² patients with advanced NSCLC who had already treated with an induction treatment including bevacizumab, in the absence of disease progression, were randomly assigned in the maintenance portion of the study either to continue bevacizumab alone or in combination with erlotinib. Patients with treated brain metastases were allowed; only one patient developed a grade 2 cerebral hemorrhage after disease progression. A further review of 57 trials that included 10,598 patients evaluated the safety and efficacy of different anti-VEGF therapies (bevacizumab in 22 trials, sorafenib in 12, sunitinib in 5, and a variety of other agents in 18). Brain metastases were an exclusion criterion in 76% of the trials.⁴³ In the studies that excluded patients with brain metastases (1,755 patients) only two episodes of CNS bleeding were reported (<1%). In the four studies that included patients with brain metastases (2688 patients) there were no episodes of intracranial hemorrhage. In conclusion, several retrospective studies and at least one prospective study confirmed that bevacizumab may be safely used in patients with brain metastases.

In AVAiL, patients remained on study if anticoagulation for venous thrombosis was started while the patient was already treated. Nine percent of patients received therapeutic anticoagulation with either warfarin or low-molecular-weight heparin, and no pulmonary hemorrhages were observed. A retrospective analysis was performed to assess the effect of anticoagulation in AVAiL and in other two randomized trials in metastatic colon cancer.⁴⁴ There were no severe (grade 3) pulmonary hemorrhages in any of the patients receiving anticoagulation and treated with bevacizumab. In SAiL, 15% of patients received concomitant anticoagulation at some point during treatment, and the overall risk of grade ≥ 3 bleeding was low (4%), as well as the risk of grade ≥ 3 pulmonary hemorrhage (1%). Among 1065 patients who completed one or more cycles of bevacizumab, a total of 227 bleeding events occurred in 181 patients (17%) versus 19 bleeding events in 15 of 87 patients (17.2%) receiving anticoagulants.⁴⁵ Therefore, anticoagulation does not increase the risk of bleeding during treatment with bevacizumab.

Data about the safety of bevacizumab in patients with a poor PS are limited. A preliminary report from ARIES included 182 patients with a PS of ≥ 2 . These patients had a worse clinical outcome in terms of PFS and OS compared to the general population.

Several retrospective analyses were performed to identify the potential risk factors associated with pulmonary hemorrhage (PH) in patients treated with bevacizumab,⁴⁶ including central tumor

location, cavitation, and vessel invasion especially in patients on anticoagulant therapy. None of the clinical or radiological features proved to be reliable predictive factors for severe PH. Major blood vessel and bronchial vessel infiltration, encasement, and abutting may predict PH. However, standardized radiological criteria for defining vessel infiltration have not been established. Hypothetically, dilation of the bronchial artery could be a risk factor for PH, but no conclusive data exist to support this hypothesis. A high-resolution computed tomography scan should be used to assess PH occurring in non-squamous NSCLC patients treated with bevacizumab.⁴⁷

Recently, two small studies investigating bevacizumab in combination with chemo-radiotherapy reported an alarmingly high rate of tracheal-esophageal fistula formation.⁴⁸ However, another study has reported acceptable toxicity⁴⁹ and additional studies are ongoing.

Because of the higher efficacy of pemetrexed and bevacizumab in non-squamous NSCLC these two agents have been recently tested with carboplatin in a series of clinical studies. In a multicenter phase II study bevacizumab and pemetrexed maintenance after an initial therapy with pemetrexed and carboplatin plus bevacizumab was assessed.⁵⁰ The study showed an ORR of 55% with a favorable toxicity profile. Median PFS and OS were 7.8 and 14.1 months, respectively. These promising results led to the subsequent phase III (PointBreak) randomized study 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.⁵¹ The primary endpoint of superior OS for the pemetrexed arm was not met (12.6 v 13.4 months, HR 1.00, $P = .949$); however, the study showed a modest improvement in PFS for the pemetrexed arm (6.0 v 5.6 months, HR 0.83, $P = .012$) and a good safety profile.⁵²

A post hoc analysis of patients ≥ 70 years of age in ECOG 4599 previously detected increased adverse events and numerically decreased survival benefit associated with bevacizumab compared to patients < 70 years of age. A pooled analysis of ECOG 4599 and PointBreak data based on age was recently presented.⁵³ The statistically significant benefit associated with the addition of bevacizumab to chemotherapy was consistently reported across all age groups < 75 years. Patients ≥ 75 years receiving bevacizumab had a higher incidence of grade ≥ 3 adverse events relative to chemotherapy alone with no statistically significant survival benefit, although increased grade ≥ 3 adverse events were observed in all age groups.

Another phase III study (PRONOUNCE) evaluated pemetrexed/carboplatin followed by maintenance therapy with pemetrexed compared with bevacizumab plus paclitaxel/carboplatin followed by maintenance therapy with bevacizumab. The primary endpoint was PFS without grade 4 toxicity (G4PFS) according to a superiority study design.⁵⁴ Top line data indicate that pemetrexed/carboplatin was not superior to carboplatin/paclitaxel/bevacizumab in terms of G4PFS and no difference in PFS or OS between the two regimens were observed.

Ramucirumab is an investigational monoclonal antibody that binds to VEGFR-2 and blocks ligand binding and activation.⁵⁵ A phase II open-label study is currently evaluating ramucirumab as first-line therapy in combination with carboplatin/paclitaxel, with preliminary results from the first 15 patients reporting an overall RR of 67%.⁵⁶ Another phase II trial is recruiting patients with previously untreated NSCLC to examine ramucirumab in combination with four different chemotherapeutic regimens as first-line therapy, and a phase III trial is recruiting patients with NSCLC to test ramucirumab in combination with docetaxel as second-line therapy after failure of platinum-based therapy.

Multi-targeted Anti-angiogenetic Agents

Efforts to identify drugs that inhibit key pathways involved in the pathogenesis of cancer have led to the development of multi-targeted agents. Small-molecule TKIs that inhibit receptors such as

VEGFR, platelet-derived growth factor receptor (PDGFR), Raf, and KIT simultaneously may offer advantages over agents with single targets, and therefore a higher likelihood of single-agent activity. In addition, as multi-targeted TKIs are often available orally they may be more convenient for patients. Conversely, a potential disadvantage is the potential for toxicity resulting from off-target kinase inhibition, and additive toxicity, which may be particularly relevant when the agents are combined with chemotherapy.

Sorafenib is a Raf and VEGFR inhibitor (VEGFR-2 and VEGFR-3) with activity against PDGFR and KIT. In xenograft models, sorafenib plus vinorelbine, cisplatin or gefitinib resulted in tumor growth delay at least comparable to that observed with each agent alone. The phase III ESCAPE trial tested carboplatin plus paclitaxel with or without sorafenib as first-line treatment in advanced NSCLC. The primary endpoint of OS was not met and the study was terminated early due to the detrimental effect of sorafenib in patients with squamous cell carcinoma and the lack of effect in non-squamous cell carcinoma.⁵⁷ Similarly, another phase III study (NExUS) evaluated sorafenib with gemcitabine plus cisplatin did not meet the primary endpoint of OS. Patients with squamous histology were excluded from this study based on the results of ESCAPE.⁵⁸

Motesanib, a VEGFR-1, -2, and -3, PDGFR, KIT, and RET inhibitor was investigated in multiple tumor types including NSCLC. In a phase II trial (n = 186) motesanib was combined with carboplatin and paclitaxel and showed comparable efficacy to bevacizumab plus carboplatin and paclitaxel.⁵⁹ In a phase III trial (MONET1), 1,090 patients with advanced non-squamous NSCLC received carboplatin and paclitaxel with or without motesanib; preliminary results reported that neither PFS (5.6 v 5.4 months; HR 0.785; *P* = .006) nor OS (13.0 v. 11.0 months; HR 0.897; *P* = .137) were significantly improved and grade ≥ 3 adverse events were more frequent with motesanib.⁶⁰

Vascular-Disrupting Agents

Vascular-disrupting agents (VDA) are compounds that directly target blood vessels and create central tumor necrosis. VDAs have demonstrated signs of clinical activity in different tumor types,⁶¹ including NSCLC.^{62 and 63} A phase III study in front-line investigated paclitaxel/carboplatin with or without ASA404 was terminated early because an interim analyses showed no increase in OS.⁶⁴

As a class of agents, the clinical development is hampered by cardiovascular and neurological toxicities as single agents, and by hematologic toxicity in combination with chemotherapy and currently there is no predictive marker to identify patients with a high probability of response.

Epidermal Growth Factor Receptor Pathway

Tyrosine Kinase Inhibitors

EGFR is a transmembrane protein with cytoplasmic kinase activity that transduces growth factor signaling from the extracellular milieu to the cell. More than 60% of NSCLCs express EGFR and this receptor is now a relevant therapeutic target for the treatment of these tumors. TKIs of EGFR are especially effective in patients whose tumors harbor activating mutations in the *EGFR* gene and several trials have concluded that initial therapy with a EGFR-TKI instead of chemotherapy is the best treatment choice in patients with tumors harboring a sensitizing mutation ([Table 1](#)). Therefore, mutation testing is mandatory to identify these patients, given that selection based only on clinical-pathologic characteristics is inadequate. They include never-smoking status, female gender, the histologic diagnosis of adenocarcinoma, and the Asiatic ethnicity.

Table 1.

Phase III Randomized Studies Comparing TKIs to Platinum-Based Chemotherapy as First-Line Treatment in “Selected” NSCLC

Study	Treatment	EGFR Mutational Status		ORR (%)	PFS (mo)	OS (mo)
		Test Performed (%)	Test Positive (%)			
IPASS ⁷⁴	Gefitinib v Carbo/Placl	35.9%	59.7%	43.0 v 32.3	5.7 v 5.8	18.6 v 17.3
				<i>P</i> = .0001	HR: 0.74	HR: 0.91
					95% CI: 0.65–0.85	95% CI: 0.76-1.10
					<i>P</i> < .0001	<i>P</i> = .11
First-SIGNAL ⁷⁶	Gefitinib v Cis/Gem	31.6%	43.7%	53.5 v 45.3	6.1 v 6.6	21.3 v 23.3
				<i>P</i> = .153	HR: 0.81	HR: 1.00
					95% CI: 0.64–1.03	95% CI: 0.75-1.34
					<i>P</i> = .044	<i>P</i> = .428
WJTOG ⁷⁸	Gefitinib v Cis/Doce	100%	100%	62.1 v 32.2	9.2 v 6.3	30.9 v nr
				<i>P</i> < .0001	HR: 0.49	HR: 1.64
					95% CI: 0.34–0.71	95% CI: 0.75-3.58
					<i>P</i> < .00001	<i>P</i> = .211
NEJ002 ⁷⁹	Gefitinib v Carbo/Placl	100%	100%	73.7 v 30.7	10.8 v 5.4	30.5 v 23.6
				<i>P</i> < .001	HR: 0.30	<i>P</i> = .31
					95% CI: 0.22–0.41	
					<i>P</i> < .001	
OPTIMAL ⁸⁰	Erlotinib v Carbo/Gem	100%	100%	83.0 v 36.0	13.1 v 4.6	ns
				<i>P</i> < .0001	HR: 0.16	
					95% CI: 0.10–0.26	
					<i>P</i> < .0001	
EURTAC ⁸¹	Erlotinib v platinum	100%	100%	63.6 v 17.8	9.7 v 5.2	19.3 v 19.5
	based chemotherapy [□]			<i>P</i> < .0001	HR: 0.37	HR: 1.04
					95% CI: 0.25–0.54	95% CI: 0.65-1.68
					<i>P</i> < .0001	<i>P</i> = .87

Study	Treatment	EGFR Mutational Status		ORR (%)	PFS (mo)	OS (mo)
		Test Performed (%)	Test Positive (%)			
LUX-Lung 3 ⁸⁸	Afatinib v Cisplatin/ Pemetrexed	100%	100%	56.0 v 23.0	11.1 v 6.9	NR
				<i>P</i> <.0001	HR: 0.58	
					95% CI: 0.43–0.78	
					<i>P</i> = .0004	
LUX-Lung 6 ⁸⁹	Afatinib v Cisplatin/Gemcitabine	100%	100%	66.9 v 23	11.0 v 5.6	OS based on 43% of events shows
				<i>P</i> <.0001	<i>P</i> <.0001	HR=.95
						<i>P</i> =.7593

Abbreviations: Cis, cisplatin; Gem, gemcitabine; Carbo, carboplatin; Pacli, paclitaxel; Doce, docetaxel; ns, not specified; nr, not reached

ORR, objective response rate; PFS, median progression-free survival; OS, median overall survival; HR, hazard ratio; CI, confidence interval; NR, not reported.

Platinum-based chemotherapy options: Cis/Gem or Cis/Doce or Carbo/Doce or Carbo/Gem.

Gefitinib and erlotinib are first-generation TKIs that selectively target EGFR. Looking back to early single-agent studies with gefitinib (IDEAL-1 and IDEAL-2), initially performed in unselected and previously treated patients, some anti-tumor activity was shown with response rates ranging from 12%–18%, a disease control rate of 42%–54%, with most of the responses achieved within 4–5 weeks, and when patients responded a considerable tumour shrinkage was observed. Activity was superior in adenocarcinoma, females, and never-smokers.^{65 and 66}

These results and the preclinical evidence in preclinical models of a synergism with chemotherapy led to two large randomized phase III trials that explored the efficacy of gefitinib in combination with platinum-based chemotherapy. Both studies did not demonstrate any statistically significant difference in OS between arms and similar results were reported with erlotinib.^{67, 68, 69, 70, 71 and 72} A confirmation of the limited efficacy of EGFR-TKIs in unselected patient population came from the Iressa Survival Evaluation in Lung Cancer (ISEL) trial, a large multicenter phase III trial that compared single-agent gefitinib versus placebo in 1,692 patients with advanced NSCLC after failure of one or two prior chemotherapies and OS was comparable in the two arms.⁷³

The Iressa Pan-Asia Study (IPASS) trial was performed in a clinically selected population of Asian adenocarcinoma patients, who were never-smokers or with limited smoking history (≤ 10 pack-years and ≥ 15 years since quitting) and involved nine countries across Asia. One thousand two hundred seventeen patients were randomized to first-line gefitinib or carboplatin-paclitaxel and the primary end point of the study was the non-inferiority of gefitinib.⁷⁴ The results showed the superiority of PFS for gefitinib compared with chemotherapy in the entire study population (HR 0.74). EGFR mutation analysis was performed on 437 patients (35.9%) and, of these, 60% were positive for one

of the panel of 29 mutations detected by the EGFR kit (DxS, Rotor-Gene Q 5plex, QIAGEN, GER). Among the 261 known EGFR mutants, the benefit of first-line gefitinib was even stronger with a further improvement in PFS (HR 0.48), an increased RR (71% on gefitinib v 47% on chemotherapy). Final OS data based on 78% of the events, showed no differences between gefitinib and chemotherapy in the entire population (18.6 v 17.3 months, respectively; HR 0.91, $P = .11$) and in the mutation-positive subgroup (HR 1.00). In addition, patients with EGFR-mutated tumors in the gefitinib group had a clinically relevant improvement in quality of life and a lower incidence of grade 3–4 adverse events compared to chemotherapy.

A second study randomized 313 Korean never-smokers with adenocarcinoma to gefitinib or cisplatin–gemcitabine. Overall, there was no significant difference between the arms in terms of PFS or OS. Similarly to IPASS, gefitinib improved PFS versus chemotherapy in mutation-positive patients (without reaching the statistical significance) but worsened PFS in mutation-negative patients. OS did not differ between the groups regardless of EGFR status.⁷⁶

The results of the IPASS trial were really practice-changing because of both the impressive results in the EGFR mutation-positive group and the fact that the EGFR mutation-negative patients treated with gefitinib did fairly poor (PFS HR 2.85). These results showed that it is harmful to treat patients who do not harbor *EGFR* mutations with first-line EGFR-TKIs, even if they are never-smokers with adenocarcinoma, and that patients are best screened by genotype testing to determine the most appropriate first-line treatment.

The efficacy of EGFR-TKIs in *EGFR* mutation-positive patients has been further confirmed in three prospective randomised studies performed in Asiatic patients,^{77 and 78} as well as in one study in Caucasian patients.⁷⁹ In all of these studies EGFR-TKIs were associated with a more favorable toxicity profile and improved quality of life. OS ranged from 21.6–30.5 months and was highly influenced by high cross-over rates, with up to 95% of patients receiving EGFR-TKIs after failure of chemotherapy, suggesting that these agents are effective independently from the line of therapy.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines in 2009 recommended gefitinib as first-line treatment for patients with activating *EGFR* mutations. If *EGFR* mutation is negative or unknown, the recommendation favors cytotoxic chemotherapy.³²

A retrospective study investigated the initial impact of erlotinib or gefitinib versus chemotherapy on the risk of CNS progression in patients with *EGFR* mutations. One hundred fifty-five patients were considered (EGFR-TKI n = 101, chemotherapy n = 54). The HR of CNS progression for EGFR-TKIs versus chemotherapy was 0.56 (95% CI, 0.34–0.94). If prospectively validated these data indicate that the treatment with EGFR-TKIs prevent CNS metastases in NSCLC with *EGFR* mutations.⁸⁰

In all studies with EGFR-TKI, it was observed that inevitably, despite the significant improvement in PFS and OS, all patients develop resistance. Mutations in the tyrosine kinase domain that render tumors resistant to erlotinib and gefitinib are the most common mechanism of resistance. The threonine-790–methionine (T790M) point mutation was identified in about half of the patients whose disease progressed during EGFR-TKI therapy and is rarely detected in untreated patients. Other mechanisms of resistance include c-MET overexpression (15%–20% of cases), in-frame duplications and/or insertion in exon 20 (5% of the cases), and unknown mechanisms, which account for about 25%–30%.^{81 and 82}

Irreversible inhibitors of EGFR are a class of agents with the potential to overcome EGFR-TKI resistance. Afatinib (BIBW2992) is an irreversible ErbB-family blocker with potent activity against NSCLC harboring activating *EGFR* mutations and/or the gatekeeper mutation T790M, albeit at lower potency. It has been recently evaluated in several clinical trials with promising results.^{83, 84 and 85} The LUX-Lung 3 was a phase III trial of afatinib versus CP as first-line treatment for

patients with advanced adenocarcinoma harboring EGFR-activating mutations. Patients treated with afatinib had a median PFS, the primary endpoint of the study, of 11.1 versus 6.9 months for chemotherapy (HR 0.58; $P = .0004$). ORR was also significantly higher with afatinib (56% v 23%, $P < .001$), reporting a consistent delay in time to deterioration of cancer-related symptoms.

Recently the results of LUX-Lung 6 have been presented. This study compared the safety and efficacy of first-line afatinib versus gemcitabine plus cisplatin (GC) in Asiatic patients with *EGFR* mutation-positive tumors. Following central testing for *EGFR* mutations, 364 patients were randomized 2:1 to daily afatinib 40 mg or GC (1,000 mg/m² day 1, 8 + 75 mg/m² every 21 days intravenously up to six cycles). PFS, the primary endpoint of the study, was significantly prolonged with afatinib compared with GC (median PFS 11.0 v 5.6 months, HR .28, $P < .0001$). Objective response (66.9% v 23.0%, $P < .0001$) and disease control (92.6% v 76.2%, $P < .0001$) rates were significantly higher with afatinib. Patient reported-outcomes (PROs) showed significantly better control of cancer-related dyspnea, cough, and pain with afatinib. Adverse events in both arms were as expected, with a more favorable safety profile with afatinib ([Table 1](#)).⁸⁶

A phase II trial of afatinib versus gefitinib as first-line treatment (LUX-lung 7) in advanced NSCLC is currently recruiting patients with *EGFR* activating mutations.⁸⁷

Another oral pan-HER inhibitor, dacomitinib (PF-00299804) with affinity for EGFR, HER2, and HER4, also has shown activity in NSCLC. A multinational, multicenter, randomized, open-label, phase 3 study comparing the efficacy and safety of dacomitinib to gefitinib is currently enrolling patients with locally advanced or metastatic NSCLC with EGFR-activating mutations having as primary of the study PFS (NCT01774721).⁸⁸

The different generations TKI and new agents in development, including EGFR-TKI agents against T790 mutation are summarized in [Table 2](#).

Table 2.

Different Generations of EGFR Kinase Inhibitors

First Generation	Second Generation	Third Generation (mutant-selective)
Gefitinib	XL647	WZ4002
Erlotinib	Afatinib	CO-1686
Lapatinib	Icotinib	AP26113
Canertinib	Neratinib	TAS-2913
	Dacomitinib	AZD9291
		Z650

Monoclonal Antibodies Anti-EGFR

Cetuximab is a chimeric monoclonal antibody that selectively binds the extracellular domain of the EGFR on the tumor cells and inhibits the receptor-associated tyrosine kinase activation.^{89 and 90} A handful of randomized trials have evaluated the addition of cetuximab to chemotherapy, with two completed phase III trials.^{91, 92, 93 and 94} The First-Line Erbitux in Lung Cancer (FLEX)⁷⁷ trial enrolled 1,125 patients with EGFR-expressing tumors randomized to receive cisplatin 80 mg/m² day 1 and vinorelbine 25 mg/m² days 1 and 8 (each cycle repeated every 3 weeks for up to six cycles) or the same chemotherapy plus cetuximab. OS was modestly improved with cetuximab (11.2 v 10.1 months; HR 0.871; $P < .044$). The response rate was also improved (36% v 29%; $P < .01$). PFS was 4.8 months in both arms. The marginal OS benefit was observed in all histologic subgroups and there was no difference in quality of life between the study arms, although

compliance with serial quality-of-life questionnaires was low. The main cetuximab-related toxicity was acne-like rash, which occurred in 10% of patients enrolled in the trial. Comparable results were observed in another trial, evaluating the addition of cetuximab to carboplatin plus paclitaxel or docetaxel. Three separate meta-analyses evaluated data from these two phase III trials and from other two randomized phase II trials comparing chemotherapy ± cetuximab^{95, 96 and 97} (Table 3). Among the 2,018 considered patients (1,003 in the cetuximab arm and 1,015 in the control arm), those treated with cetuximab had a 9% reduction in the risk of disease progression (HR 0.91; $P < .06$), a 13% reduction in the risk of death (HR 0.87; $P < .004$), and an approximately 50% increase in ORR ($P < .0001$).⁷⁵ The combination of cetuximab plus chemotherapy induced more grade 3/4 rash (5.2% v 1%, $P < .000$), diarrhea (2.3% v 1.1%, $P < .003$), neutropenia (19.5% v 16.1%, $P < .029$), and infusion reactions (3.9% v 0.9%, $P < .000$).

Table 3.

Clinical Trials of Cetuximab and Chemotherapy Combination Versus Chemotherapy Alone

Study	Phase	Trial Size (n)	Treatment	Median PFS (mo)	Median OS (mo)
Butts et al (2007) ⁹⁴	II	65	Cis or Carbo/Gem/Cet v Cis or Carbo/Gem	5.09 v 4.21	12.0 v 9.3
Rosell et al (2008) ⁹⁵	II	86	Cis/Vino/Cet v Cis/Vino	5.0 v 4.6	8.3 v 7.3
Pirker et al (2009) FLEX ⁹⁶	III	1125	Cis/Vino/Cet v Cis/Vino	4.8 v 4.8 HR = 0.943 (0.825–1.77) $P = .39$ ns	11.3 v 10.1 HR = 0.87 (0.76–0.996) $P = .044$
		557 Cet arm			
		568 Control arm			
Lynch et al (2010) BMS099 ⁹⁷	III	676	Carbo/pacli or Doce/Cet v Carbo/pacli or Doce/Cet	4.40 v 4.24 HR = 0.9 (0.76–1.07) $P = .236$ ns	9.69 v 8.38 HR = 0.89 (0.75–1.05) $P = .169$ ns
		338 Cet arm			
		338 Control arm			

Abbreviations: Cis, cisplatin; Gem, gemcitabine; Carbo, carboplatin; Pacli, paclitaxel; Doce, docetaxel; Vino, vinorelbine; Cet, cetuximab; HR, hazard ratio; ns, not significant; OS, overall survival; PFS, progression-free survival.

In vitro data indicate that high levels of EGFR expression correlate with sensitivity to cetuximab,^{98 and 99} but a retrospective analysis of the FLEX study suggested that EGFR protein expression by immunohistochemistry is an inadequate predictor of the efficacy of EGFR-targeted therapy. Immunohistochemistry (IHC) measurement of EGFR intensity and frequency on tumor cells was used to generate, on a continuous scale of 0–300, an EGFR IHC score for each assessable patient study in order to investigate whether tumor EGFR expression levels were associated with a predictive role. Treatment outcomes were analysed in patients with low (<200) and high (≥ 200) EGFR IHC scores, representing 69% and 31% of evaluable patients, respectively.¹⁰⁰ For patients with a high EGFR IHC score, median OS was longer in the chemotherapy plus cetuximab arm than in the control arm (12.0 v 9.6 months, respectively; HR 0.73, $P = .011$), without significant increase in cetuximab-related side effects. No corresponding survival benefit was observed in the group of patients with low EGFR IHC score (median OS of 9.8 v 10.3 months, respectively; HR 0.99, $P =$

.88). EGFR expression level was not predictive at all of cetuximab benefit in first-line treatment of recurrent/metastatic squamous cell carcinoma of the head and neck (EXTREME) and K-ras wild-type metastatic colorectal cancer (CRYSTAL).¹⁰¹

Based on existing inconsistent evidence cetuximab is currently not licensed for the treatment of advanced NSCLC even if cetuximab is recommended in combination with chemotherapy based on a lower level of evidence by the National Comprehensive Cancer Network practice guidelines for advanced/metastatic NSCLC.¹⁰²

Nevertheless, EGFR remains an important target for molecularly based therapies and currently another fully humanized monoclonal antibody targeting the EGFR extracellular domain III, necitumumab, is under investigation in two large phase III studies having the potential benefit of lower hypersensitivity reaction risk compared with cetuximab and also equivalent antibody-dependent cell-mediated cytotoxicity.¹⁰³ Recently the phase III study evaluating the addition of necitumumab to pemetrexed and cisplatin in non-squamous NSCLC was prematurely closed due to concerns about the risk of thromboembolic events in the experimental arm.¹⁰⁴ Accrual in the phase III trial of necitumumab in combination with gemcitabine and cisplatin in squamous NSCLC is completed.¹⁰⁵

Anaplastic Lymphoma Kinase Inhibitors

In NSCLC the role of targeted therapies has been further reinforced with the identification of the EML4-ALK (anaplastic lymphoma kinase) fusion gene, a genetic abnormality detected in the 4%–6% of the adenocarcinomas of the lung,¹⁰⁶ and the concomitant identification of a targeted agent, crizotinib, which is highly active in ALK-translocated tumors. 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.^{107, 108 and 109}

Crizotinib is a MET inhibitor that also has activity on ALK and c-ROS1 oncogene (ROS1) pathways. It was first studied in humans in a phase I/II study (PROFILE 1001), with a standard dose-escalation pharmacokinetic schema followed in a second stage by clinical efficacy assessment. Preliminary results from the phase I study clearly demonstrated clinically relevant tumor shrinkage in the majority of enrolled patients.¹¹⁰ On this basis, an expansion cohort of 82 NSCLC patients harboring the ALK rearrangement were enrolled to receive the recommended dose of crizotinib 250 mg twice daily. The ORR was 57% (46 partial responses and one complete response). An additional 33% of patients had stable disease at the 8-week assessment.¹¹¹ An update of this study confirmed a ORR of 61% and the median PFS was 10 months.¹¹² Based on the encouraging response rate of the phase I study, a large multicenter second-line study and beyond in ALK-positive NSCLC patients was performed. Patients characteristics largely corresponded to those of the previous study and the ORR was of 51%.¹¹³ In both the phase I and phase II trials, the majority of responses was achieved during the first 8 weeks of treatment and duration of response was 48.1 and 41.9 weeks, respectively. Patients included in the phase I trial had a survival probabilities at 6 and 12 months of 90% and 81%, respectively. Crizotinib gained approval by the US Food and Drug Administration (FDA) in August 2011 for any line of treatment in locally advanced or metastatic NSCLC, ALK-positive based on the outcome in terms of response rate of the abovementioned studies.

The high level of activity of crizotinib in ALK-positive NSCLC patients has been recently confirmed in a phase III study evaluating crizotinib versus pemetrexed or docetaxel as second-line treatment. The study met its primary endpoint demonstrating the superiority of crizotinib over the standard chemotherapy in prolonging PFS (7.7 v 3.0 months, respectively; HR 0.49, $P < .0001$). ORR was significantly higher in patients treated with crizotinib (65% v 20%, $P < .0001$) and the safety profile was acceptable. An interim analysis of OS showed no significant improvement with

crizotinib as compared with chemotherapy (HR 1.02; $P = .54$). Better control of disease-related symptoms and improvement in quality of life have been reported with crizotinib.¹¹⁴

As already described, thymidylate synthase (TS) level may predict the sensitivity to pemetrexed-based chemotherapy in different histological subtypes of NSCLC, being inversely correlated with pemetrexed efficacy. A recent study evaluating the role of pemetrexed-based chemotherapy in ALK-positive NSCLC patients, showed lower TS levels than the median values in unselected NSCLC. A low TS level has been observed in almost 83% of the evaluated cases ($P = .039$) and the few ALK-positive NSCLC patients with high TS levels had poorest survival outcome.¹¹⁵ These findings suggest that differences in TS expression levels in ALK-positive NSCLC patients may predict the differential responses to pemetrexed but also justify the major efficacy of pemetrexed compared to docetaxel in this subset of patients, as observed in the PROFILE 1007 trial.

The phase III trial PROFILE 1014 (NCT01154140) is currently the only study actively recruiting patients for the evaluation of crizotinib versus cisplatin or carboplatin plus pemetrexed as first-line treatment for previously untreated ALK-positive non-squamous NSCLC patients. The primary endpoint of the study is PFS, while ORR and OS are secondary endpoints. A superiority phase III trial with the same schedule of treatment has been designed for the East-Asian population, but the study is not yet open for accrual.¹¹⁶

Although there are clinical-pathological features associated with ALK rearrangement they do not properly select patients for ALK inhibitors and, consequently, molecular testing is mandatory. There are three methods of detecting ALK rearrangement: the fluorescence in situ hybridization (FISH) break-apart assay, 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.^{117, 118 and 119}

Several second-generation ALK inhibitors are under development and some are more potent and selective than crizotinib in terms of higher response rates or activity in patients who have acquired resistance to crizotinib. LDK378 is being developed as an alternative to crizotinib, based on increased potency and specificity.

In a phase I study, LDK378 was investigated in 123 ALK-positive patients with NSCLC¹²⁰ and the ORR in the 114 evaluable patients treated at 400 mg/d or more was 58%. Activity was essentially the same in crizotinib-resistant and crizotinib-naïve patients, 57% and 60%, respectively. The median PFS and median duration of response (DOR) were 8.6 and 8.2 months, respectively. Treatment with LDK378 was reasonably tolerated.¹²¹ Two phase III trials are planned in ALK-positive NSCLC: in the first study LDK378 will be compared with single-agent chemotherapy after progression on a platinum based doublet and on crizotinib,¹²² while the second study in first-line treatment will compare LDK378 with a platinum-based doublet.¹²³

CH5424802 is another potent selective orally available ALK inhibitor. In a multicenter, phase I/II study, 46 patients with ALK-positive NSCLC were treated with CH5424802 in the phase II portion of the study at the dose level of 300 mg twice daily; none had received prior treatment with an ALK inhibitor. An objective response was observed in 93% of the patients, including two complete and 41 partial responses.¹²⁴

AP26113 is a TKI that potently inhibits mutant activated forms of ALK-positive and EGFR-mutated tumors, and TKI-resistant forms including L1196M (ALK) and T790M (EGFR). AP26113 does not inhibit native EGFR. Currently a phase I/II open-label multicenter study is ongoing in patients with advanced malignancies (except leukemia) refractory to available therapies or for whom no standard treatment exists. AP26113 has promising anti-tumor activity in ALK-positive patients, with initial evidence of activity in EGFR-mutated patients, and is generally well tolerated. Phase II will be initiated after the recommended phase II dose will be defined in four different

cohorts: crizotinib-naïve NSCLC; crizotinib-resistant NSCLC; EGFR TKI-resistant NSCLC; and other tumors¹²⁵ (Table 4).

Table 4.

Second-Generation ALK Inhibitors

ALK Inhibitors	Phase	n	ORR (n)	ORR (%)	PFS
LDK378	I	88	62	79	8.6 mo (95% CI. 4.3–19.3)
CH5424802	I/II	46	43	93.5	—
AP26113	I/II	18	10	56	—

Abbreviations: ORR, objective response rate; PFS, median progression-free survival.

Early Palliative Care

The symptom burden of patients with lung cancer is extensive and includes loss of appetite, dyspnea, and other symptoms that lead to decreased quality of life. A landmark study examined the benefit of early palliative care integrated with standard oncologic care versus standard oncologic care and palliative care only “as needed” on patient-reported outcomes, the use of health services, and the quality of end-of-life care among patients with metastatic NSCLC. The study was a prospective, nonblinded, randomized, controlled trial of outpatients conducted at a single center. Quality-of-life scores improved significantly in patients assigned to intervention compared with standard care. A 2.7-month difference in median survival ($P = .02$) in favor of the group assigned to early palliative care was also observed, although survival was not a primary end point of the trial. This outcome needs to be validated in future studies.¹²⁶

Second-Line Treatment

Single Agents

Although cytotoxic chemotherapy and/or molecularly targeted agents as first-line treatments may delay disease progression and prolong survival, almost all of patients develop progressive disease and require additional therapies. The choice of treatment at relapse or progression depends on PS, comorbidity, histology, molecular characteristics, and, obviously, patient preference. Second-line therapy should be considered in patients with a good PS with clinical or radiological progression because this approach is associated with symptom palliation and increased survival in selected patients.^{127 and 128} The benefit of second-line treatment also affects the outcome with first-line therapy. In a systematic review it was shown that post-progression survival is highly associated with OS for first-line chemotherapy, whereas PFS is only moderately associated with OS.¹²⁹

Single-agent docetaxel or pemetrexed and erlotinib are currently registered options. Other cytotoxic agents that are active as initial therapy also may have activity, but they have not been compared in randomized trials in previously treated patients with either best supportive care (BSC) or approved agents.¹³⁰

Supportive evidence for the approval of docetaxel as second-line therapy came from a couple of small phase III studies.^{131 and 132} Although the every-3-week schedule of docetaxel is considered a standard of care recent data indicate the weekly schedule (33.3 mg/m² to 40 mg/m² for 6 weeks followed by a 2-week rest) as an equally effective treatment but less toxic as clearly concluded by a meta-analysis.¹³³ In a pivotal phase III study pemetrexed demonstrated to be non-inferior to docetaxel in terms of efficacy with a toxicity profile favoring pemetrexed.¹³⁴ Retrospective data

showed a differential activity of pemetrexed by histology with better survival with pemetrexed in patients with non-squamous histology (9.3 months v 8 months; $P \leq .048$), whereas patients with squamous cell histology did better with docetaxel (7.4 months v 6.2 months; $P < .018$).^{135 and 136}

Few studies have evaluated the combination of two cytotoxic agents in second-line and all these trials have failed to demonstrate superiority of the two-drug combination over docetaxel.^{137, 138, 139, 140, 141 and 142}

In the second-/third-line setting erlotinib in a phase III study in chemotherapy-refractory patients, without limitation for EGFR status and histology, was demonstrated to be modestly superior to placebo. The ORR to erlotinib was 8.9%, with an additional 36% of patients achieving stable disease. There was a significant improvement in PFS (2.2 v 1.8 months; HR 0.61; $P = .001$) and median survival time (6.7 v 4.7 months; HR 0.70; $P = .001$) favoring erlotinib. The effect of erlotinib on survival was similar across most of the considered subsets. Never-smokers and patients with EGFR-positive tumors had the larger survival benefit.¹⁴³

In a similar study, gefitinib versus placebo failed to demonstrate improved survival in truly chemotherapy-refractory patients (ISEL trial).⁷¹ However, the subset of Asian origin showed significant improvement in survival.

In a phase IIb/III trial in stage IIIB/IV patients with adenocarcinoma who had received one or two previous chemotherapy regimens and with disease progression after at least 12 weeks of treatment with reversible EGFR-TKIs, afatinib was tested against placebo. Although there was no benefit in terms of OS (10.8 v 12.0 months; HR 1.08) median PFS was longer in the afatinib arm (3.3 v 1.1 months; HR 0.38; 95% CI, 0.31–0.48), as well as more patients reached an objective response (29 v 1 patient).⁸³

Only one small randomized phase II study compared gefitinib with erlotinib in the this setting in 96 patients who failed to respond to first-line chemotherapy and had either EGFR mutation or at least two out of three clinical factors associated with a higher incidence of EGFR mutations. Both gefitinib and erlotinib showed activity and tolerable toxicity profiles.¹⁴⁴

Several randomized studies that compared an EGFR-TKI versus chemotherapy in unselected or EGFR wild-type patients are summarized in [Table 5](#) and [Table 6](#). All of these studies indicate a marginal or detrimental effect of EGFR TKIs on PFS, especially in EGFR wild-type patients, without registering any difference in terms of OS.^{75, 76, 77, 78, 79, 80, 81, 82 and 83} This information is fully consistent with the concept of the superior efficacy of EGFR-TKIs in EGFR-mutant tumors even in the context of additional lines of therapy.

Table 5.

Randomized Trials Comparing EGFR-TKI Versus Chemotherapy in Advanced NSCLC in EGFR Unselected Patients

Trial	Regimen	n	Median PFS (mo)	HR (95% CI)	Median OS (mo)	HR (95% CI)
INTEREST	Gefitinib	733	2.2	1.04 (0.93–1.18)	7.6	1.02 (0.91–1.15)
	Docetaxel	733	2.7		8.0	
V15-32	Gefitinib	245	2.0	0.90 (0.72–1.12)	11.5	1.12 (0.89–1.40)
	Docetaxel	244	2.0		14.0	

Trial	Regimen	n	Median PFS (mo)	HR (95% CI)	Median OS (mo)	HR (95% CI)
ISTANA	Gefitinib	82	3.3	0.73 (0.53–1.00)	14.1	0.87 (0.61–1.24)
	Docetaxel	79	2.4		12.2	
HORG	Erlotinib	166	3.6	NR	7.9	NR
	Pemetrexed	166	2.7		8.9	
TITAN	Erlotinib	203	1.4	1.19 (0.97–1.46)	5.3	0.96 (0.78–1.19)
	Docetaxel/pemetrexed	221	2.0		5.5	
DELTA	Erlotinib	151	2.0	1.22 (0.97–1.55)	14.8	0.91 (0.68–1.22)
	Docetaxel	150	3.2		12.2	

Abbreviations: PFS, progression-free survival; HR, hazard ratio; OS, overall survival; CI, confidence interval; NR, not reached.

Table 6.

Randomized Trials Comparing EGFR-TKI Versus Chemotherapy in Advanced NSCLC in EGFR Wild-Type Patients

Trial	Regimen	n	Median PFS (mo)	HR (95% CI)	Median OS (mo)	HR (95% CI)
INTEREST	Gefitinib	106	1.7	1.24 (0.94–1.64)	6.4	1.02 (0.78–1.33)
	Docetaxel	123	2.6		6.0	
TITAN	Erlotinib	75	1.4	1.25 (0.88–1.78)	6.4	0.85 (0.59–1.22)
	Docetaxel/Pemetrexed	74	2.0		4.5	
TAILOR	Erlotinib	107	2.4	1.45 (1.08–1.92)		N.A.
	Docetaxel	104	3.4			
DELTA	Erlotinib	109	1.3	1.45 (1.09–1.94)	9.0	0.98 (0.69–1.39)
	Docetaxel	90	2.9		10.1	

Abbreviations: PFS, progression-free survival; HR, hazard ratio; OS, overall survival; CI, confidence interval; NA, not available.

Heat shock protein 90 (Hsp90) is a molecular chaperone required for the stability of a number of conditionally activated and/or expressed signalling proteins, as well as multiple mutated, chimeric, and overexpressed signalling proteins, that promote cancer cell growth and/or survival. Ganetespib is a novel, second-generation Hsp90 inhibitor with a favorable safety profile, active as single agent especially in ALK-positive NSCLC.¹⁴⁵ Based on synergistic preclinical interactions between docetaxel and ganetespib, a phase II study enrolled 255 adenocarcinoma patients previously treated with one line of therapy. Co-primary endpoints were PFS in patients with elevated lactate dehydrogenase (LDH) or in tumors harboring KRAS mutations. The study demonstrated that ganetespib in combination with docetaxel had an acceptable safety profile with an improvement in OS and PFS compared to docetaxel alone. The improvements in OS and PFS were substantially enhanced in patients with a diagnosis of advanced disease >6 months and the observed improvement

in survival does not appear to be associated with EGFR or KRAS mutational status.¹⁴⁶ A phase III study in second line in patients with advanced adenocarcinoma progressing >6 months from diagnosis is currently ongoing.

A recent meta-analysis¹⁴⁷ of randomized trials evaluated the efficacy and safety of single agent erlotinib versus different combinations of molecular targeted agents in second line. Eight eligible trials were identified, involving 2,417 patients. The intention-to-treatment (ITT) analysis demonstrated that combinations of targeted therapies significantly improved OS (HR 0.90, $P = .024$), PFS (HR 0.83, $P = .018$), and ORR (OR 1.35, $P = .04$). In the subgroup analyses based on type of studies, EGFR status and KRAS status there was a tendency to improve PFS and OS in combining targeted therapies, except that for patients with EGFR mutation or wild-type KRAS, which favored single-agent erlotinib. Additionally, grade 3 or 4 rash, fatigue, and hypertension were more frequently reported with combinations of targeted therapy. Based on the results of each individual studies included in the abovementioned meta-analysis, there is no convincing evidence supporting the use of combinations of targeted agents in second line, mainly because of the lack of OS benefit and for the higher toxicity profile of the combinations that reduce the trade-off between activity and toxicity. The same conclusions may be applied to the combination of cytotoxic agents with a wide array of targeted therapies.

Lung cancer is a progressive and dynamic genetic process that leads to acquisition of several alternative escape mechanisms that overcome the simple drug interference on one or two pathways (eg, EGFR/VEGFR or EGFR/MET). For this reason it is mandatory to continuously search for specific predictive biomarkers with the goal to identify subtypes of NSCLC responsive to the different biological agents. The inclusion of unselected populations of NSCLC patients in clinical trials should be abandoned.

Treatment Opportunities Beyond Second Line

Treatment options for patients whose tumors have failed to respond to two or more conventional chemotherapy regimens are limited, with erlotinib and crizotinib being the only agents currently approved as third-line therapy for patients with advanced/metastatic NSCLC.

The efficacy of gefitinib and erlotinib as third-line therapy was assessed retrospectively through the Taiwan Cancer Registry and the National Insurance claim databases. Among 984 patients recruited, the two agents showed comparable OS (median, 10.2 v 9.9 months; $P = .524$) and TTF (median, 5.5 v 3.4 months; $P = .103$). At multivariate analyses, both treatments had similar risk of overall mortality (adjusted HR 1.04, $P = .629$) and treatment failure (adjusted HR 0.94, $P = .417$). Subgroup analyses based on age, tumor histology, and gender also did not reveal differences in OS and TTF. For patients who received gefitinib or erlotinib for more than 3 or 6 months, there was no difference in TTF, but patients who received erlotinib had longer OS.¹⁴⁸

The paucity of approved agents for third-line therapy and beyond constitutes an important unmet medical need.¹⁴⁹ Several targeted agents, including some with multiple targets, have been or are currently being evaluated as third- and fourth-line therapy.

In a large study (ZEST) vandetanib, an orally administered inhibitor of VEGFR, EGFR, and RET, was compared with erlotinib after failure of one or two prior chemotherapy regimens. The study failed to show improvement in either PFS or OS.¹⁵⁰ Similarly in the ZEPHYR trial, which compared vandetanib with placebo after failure of one to two prior chemotherapy regimens, including a prior EGFR-TKI, vandetanib did not increase OS, although it significantly improved PFS (HR 0.6; $P < .0001$), ORR (2.6% v 0.7%; $P = .028$), and disease control rate at 8 weeks (30% v 16%; $P < .0001$).¹⁵¹

Single-agent sorafenib, a raf kinase and angiogenesis inhibitor, was investigated in a phase II study in heavily pretreated patients (two or more lines of therapy) using a randomized discontinuation design. Patients received 400 mg of sorafenib orally twice daily for two cycles (step 1). Responding patients continued on sorafenib, while progressing patients went off study. Patients with stable disease were randomized to receive placebo or sorafenib with a cross-over from placebo allowed upon progression. Two hundred ninety-nine patients were evaluable for step 1 and 81 eligible patients were randomized on step 2. The 2-month disease control rates after randomization were 54% and 23% for sorafenib and placebo, respectively ($P = .005$). The HR for progression of step 2 significantly favored sorafenib and there was also a trend for an improved survival.¹⁵² These data were the background for the subsequent double-blind, placebo-controlled, multicenter phase III study (MISSION), which assessed whether third-/fourth-line treatment with sorafenib plus best supportive care would improve OS relative to best supportive care plus placebo in patients with relapsed/refractory NSCLC of predominantly non-squamous histology. A total of 703 patients were randomized with baseline demographic data and prior treatments generally well balanced. Median OS was similar in the two groups, whereas PFS, TTF, ORR, and disease control rate were significantly greater in the sorafenib group. Rates of all and serious adverse events were higher in the experimental arm.¹⁵³ Based on these data, no further development of sorafenib in this setting has been planned.

Apatinib (YN968D1) is a multiple kinase inhibitor with in vitro activity against VEGFR-2, PDGFR-beta, c-Kit, and c-src.¹⁵⁴ In addition, it counteracts the effects of multidrug resistance conferred by ABCB1 and ABCG2 proteins at concentrations lower than those associated with kinase inhibition.¹⁵⁵ Results of a phase II randomized, placebo-controlled, study in patients with non-squamous NSCLC after two previous treatment regimens was conducted in China. Among 135 patients randomized to receive apatinib at the dose of 750 mg or placebo orally once daily until disease progression or unacceptable toxicity, median PFS was 4.7 months for apatinib and 1.9 months for placebo (HR 0.28). Response rate and disease control rate were also significantly better in the experimental arm. Adverse events known to be associated with anti-angiogenic multiple TKI agents were generally mild or moderate in severity and manageable.¹⁵⁶

Incorporation of genetic analysis for a better selection of treatments beyond second line is quite likely a future requirement at least in the context of clinical trials, but it yields additional and more complicated challenges and perspectives. This task may be particularly challenging in the second- and third-line settings, where the availability of tissue for molecular analysis is often limited and not routinely collected.¹⁵⁷

Even if at the present time repeat biopsies outside of a specific trial setting are not a requirement given the relative infrequency of clearly actionable targets with readily available treatments, it is equally important to recognize we have made huge progress in our understanding of molecular oncology that led to some of the new treatment options based on a greater emphasis on tissue collection and identifying relevant mutations.

The Emerging Role Of Immunotherapy

Despite the limited efficacy of immunotherapy in the treatment of lung cancer in the past and the various mechanisms that lung cancer can use to thwart the immune system attack, vaccines are currently being evaluated in phase III trials, and checkpoint inhibitors show potential promise in NSCLC.¹⁵⁸

A phase I trial of nivolumab, an anti-PD-1 antibody (BMS-936558) administered once every 2 weeks, included a large dose expansion cohort of patients with NSCLC. Patients with advanced NSCLC who had been previously treated with a prior platinum-containing regimen were eligible but could have received no more than five prior treatment regimens for their advanced disease. Besides being included in the dose-escalation portion of the trial, patients with NSCLC were

randomly assigned to 1, 3, and 10 mg/kg to include equal numbers of squamous and non-squamous cell histology at each dose level. A total of 122 patients with NSCLC were enrolled, of whom 76 were assessable for response at the time of data analysis. The majority of patients with NSCLC were heavily pretreated; 55% of patients received at least three prior lines of therapy. Fourteen patients had objective responses (18%). Responses were seen at all dose levels studied and in squamous as well as non-squamous histology. Interestingly, tumor PD-L1 expression may be associated with tumor response. Patients without tumor expression of PD-L1 had no documented tumor responses, but 36% of patients with tumor PD-L1 expression were objective responders.¹⁵⁹ Long follow-up data of this cohort of patients showed an encouraging sustained OS across histologies with a median survival time exceeding 9 months¹⁶⁰ (Table 7). MPDL328A, a human monoclonal antibody containing an engineered Fc domain designed to optimize efficacy and safety that targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1 has been tested recently in a phase I expansion study in NSCLC. Early efficacy data indicate an ORR of 24% observed in squamous and non-squamous histology, including several responses with rapid tumor shrinkage.¹⁶¹ Preliminary data from a phase II study of nivolumab in combination with chemotherapy have been recently presented.¹⁶²

Table 7.

Phase I Trials of Anti-PD-1 and Anti-PD-L1 Antibodies in NSCLC

Agents	Phase	Treatment	N	ORRs	OS, mo (95% CI)
Anti-PD-1 ¹⁶⁰	I	Nivolumab in previously treated advanced NSCLC	122	16% Non-squamous 15% Squamous 19%	9.6 (7.4-13.7) 9.6 (5.3-13.7) 9.2 (7.6-NR)
Anti-PD-1 ¹⁶²	I	BMS-936558 plus platinum-doublets in chemotherapy-naive NSCLC	43 A arm: 12 (squamous) B arm: 15 (non-squamous) C arm: 16 (3 squamous + 13 non-squamous)	33%, 33%, 31%	—
Anti-PD-L1 ¹⁶¹	I	MPDL3280A	37	24% PD-L1 tumor status-positive 100% (4/4) PD-L1 tumor status-negative 15% (4/26)	—

Abbreviations: PT-doublet, platinum-based doublet chemotherapy with (A) nivolumab/gemcitabine/cisplatin or (B) nivolumab/pemetrexed/cisplatin; or (C) nivolumab/carboplatin/paclitaxel; ORR, objective response rate; OS, overall survival; CI, confidence interval.

Systemic Treatment In The Elderly

Based on the outcome of phase III studies¹⁶³ and ¹⁶⁴ single-agent vinorelbine or gemcitabine has been the recommended treatment for most patients with stage IV NSCLC who are aged 70–79 years.³¹ Older fit patients are often considered unable to tolerate platinum-based systemic therapy.

A retrospective analysis of ECOG 5592, a phase III trial in which chemotherapy-naïve patients with stage IIIB or IV NSCLC were randomized to cisplatin plus either etoposide or paclitaxel, showed in elderly patients more treatment-related toxicity but comparable ORR and OS with the overall treated patients.¹⁶⁵ The combined assessment of six studies of the combination of docetaxel plus gemcitabine revealed no difference in efficacy according to age, but showed an increase in the incidence of mucositis in elderly patients.¹⁶⁶ However, in a phase III trial (Multicenter Italian Lung Cancer in the Elderly Study) conducted in patients ≥ 70 years old the combination of vinorelbine/gemcitabine did not show an advantage over single agent gemcitabine or vinorelbine in terms of quality of life and OS.¹⁶⁸

In a Japanese trial (JCOG 0207) 126 patients ≥ 70 years with stage III/IV advanced NSCLC and a PS of 0–1 were randomized to docetaxel (20 mg/m²) and cisplatin (25 mg/m²) weekly for 3 weeks every a 28-day cycle compared with docetaxel (25 mg/m²) alone with the same schedule. The trial stopped early at the second interim analysis because of a survival benefit favoring the combination in the subgroup of patients who were 70–74 years of age (HR 0.23; $P \leq .077$). The rate of grade 3/4 neutropenia, anemia, and anorexia were higher in the combination arm. In those patients ≥ 75 years of age, toxicity was higher without any OS benefit.¹⁶⁷ Another Japanese study compared the same weekly schedule of cisplatin and docetaxel with docetaxel alone administered every 3 weeks in chemotherapy-naïve patients ≥ 70 years and PS 0–1. This study failed to demonstrate any advantage of the combination over single agent.¹⁶⁸

The French multicenter randomized phase III trial (IFCT 0501) successfully compared a platinum-based combination versus single-agent therapy.¹⁶⁹ Carboplatin (area under the concentration curve [AUC] 6 on day 1) and paclitaxel (90 mg/m² on days 1, 8, and 15 every 28 days) was compared with either vinorelbine (25 mg/m² on day 8 every 21 days) or gemcitabine (1,150 mg/m² on days 1 and 8 every 21 days). ORR (27% v 10%, $P < .0001$), median PFS (6.0 v 2.8 months, $P < .0001$), and median survival time (10.3 v 6.2 months; HR 0.64; $P < .001$) were significantly longer in the combination compared with the single-agent arm. Toxicity was increased in the combination arm with higher rate of grade 3/4 neutropenia, febrile neutropenia, thrombocytopenia, anemia, and sensory neuropathy, as well as treatment-related deaths (4.1%).

A subset analysis of a trial already mentioned demonstrated that in patients age ≥ 70 years nab-paclitaxel plus carboplatin versus standard paclitaxel and carboplatin showed a significant increase in OS (19.9 v 10.4 months; $P = .009$).¹⁷⁰

In 2010, the Elderly Task Force of the European Organization of Research and Treatment of Cancer and Lung Cancer Group and the International Society for Geriatric Oncology published a systematic review on the treatment of NSCLC in elderly patients. It was recommended to consider two-drug combinations in selected elderly patients with a good PS and a lack of significant comorbidities.¹⁷¹

Systemic Treatment In Poor Performance Status Patients

As in other cancers PS has a defined prognostic role in advanced NSCLC and in PS 2 patients median survival is 3–5 months with 1-year survival $< 20\%$.¹⁷² PS 2 patients usually account for a small proportion of patients enrolled in trials and for this reason the strength of existing recommendations for this type of patients is quite weak.¹⁷³ The ECOG 1594 trial randomly assigned patients to one of four different platinum based double-agent chemotherapy regimens. It was observed an excessive rate of adverse events among PS 2 patients, which led to a hold on enrollment of these patients in the early phase of the study. This observation contributed to the exclusion of PS 2 patients from subsequent trials investigating platinum-based therapy.¹⁷⁴ The Cancer and Leukemia Group B (CALGB) 9730 trial was a phase III trial that compared carboplatin and paclitaxel to paclitaxel. PS 2 patients assigned to doublet experienced a significantly higher ORR, better median survival time, and a statistically significant higher 1-year OS rate.⁷ Furthermore

a retrospective review confirmed that the combination of carboplatin and paclitaxel in PS 2 patients had a toxicity rate similar to that observed in PS 0–1 patients.¹⁷⁵ A combined analysis compared single-agent (gemcitabine or vinorelbine) versus carboplatin and paclitaxel and confirmed a higher ORR and median TTP with the combination without significant difference in OS.¹⁷⁶ A prospective phase III trial of carboplatin and gemcitabine compared with gemcitabine alone revealed a significantly higher ORR (21.1% and 6.1%, $P < .01$), which did not translate in any statistically significant improvement in median PFS (3.8 and 2.7 months, $P = .14$) or OS (6.7 and 5.1 months, $P = .24$).¹⁷⁷

More recently another phase III trial assessed carboplatin and pemetrexed with pemetrexed alone. Patients treated with doublet chemotherapy experienced a significantly higher ORR (24% v 10.5%, $P = .029$), longer PFS (HR 0.46; $P < .001$; median PFS 5.9 v 3.0 months, respectively), and OS (HR 0.57; $P < .001$; median OS 9.1 v 5.6 months, respectively).¹⁷⁸

Limited amount of data are available for targeted agents. Erlotinib was compared with carboplatin and paclitaxel in first-line for patients with PS 2. This study showed a lower PFS and OS compared with chemotherapy.¹⁷⁹ A randomized trial comparing gefitinib versus placebo in patients not candidates for chemotherapy with PS 2–3 revealed no advantage in OS and PFS for patients receiving gefitinib. Only in the subgroup with FISH-positive EGFR was there a statistically significant advantage in PFS.¹⁸⁰

To date, no standard of care exists for patients with advanced NSCLC and PS 2; in these patients, clinical assessment and risk-benefit ratio must be taken into account in the choice of treatment.

Conclusions

Most of the newly diagnosed patients with NSCLC have metastatic disease and for these patients there are many new emerging treatment options currently in clinical trials aiming to further improve survival beyond the boundaries reached with cytotoxic chemotherapy. To date, histology as a surrogate marker and in the context of the different lines of therapy, has already influenced efficacy outcomes. Improvements have been made in extending survival in selected groups of patients with tumors harbouring specific genomic alterations without a significant impact on the overall population of patients with advanced NSCLC. Only the discovery through systematic search of homogeneous subgroups of tumours with the same genetic characteristics and the search for individualized approaches could represent the way to improve survival expectancy for these patients. Some progress has been made targeting two of the major biological pathways in lung cancer, the EGFR and VEGFR pathways, and deepening our knowledge about the mechanisms of tumor growth and differentiation mediated by these markers or associated molecules. EGFR-TKIs should be the preferred front line treatment choice for advanced patients with non-squamous tumors with EGFR-sensitizing mutations. For the minority of patients harboring *ALK* gene rearrangements, the preferred treatment is represented by crizotinib. Second generation and more potent *ALK* inhibitors are currently in development and have already demonstrated activity in crizotinib-resistant patients. For all other non-squamous NSCLC patients, the doublet of a platinum agent with pemetrexed or the triplet combination of carboplatin plus paclitaxel and bevacizumab are recommended treatment options. Standard of care for patients with advanced squamous cell carcinoma remains doublet chemotherapy. Second-line therapies include single-agent docetaxel, pemetrexed, and erlotinib. Re-challenge with the same combination doublet used in first line remains an experimental option that needs validation and may be eventually considered in extremely fit patients with a long-lasting tumor response or disease stabilization. Treatment options for patients whose tumors have failed to respond to two or more conventional chemotherapy regimens are limited; erlotinib and crizotinib are the only agents currently approved in many countries as third-line therapy for patients with advanced/metastatic NSCLC. Targeted agents in development may contribute to the unmet need in third line and beyond, and agents with multiple targets may have the potential for greater efficacy with acceptable toxicity profiles. Biomarker

correlates will likely be the key to identifying those patients most likely to benefit from newer targeted agents.

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