Systemic therapies in metastatic non-small-cell lung cancer with emphasis on targeted therapies: the rational approach

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ABSTRACT

Historically, first-line treatment of non-small-cell lung cancer (NSCLC) has been based on giving a limited number of cycles of chemotherapy to achieve tumour response or stable disease. Patients are then observed without active therapy until disease progresses, at which point, subsequent lines of therapy are given. In recent years, two new concepts have been introduced to the management of NSCLC: maintenance therapy and therapy with targeted agents. Maintenance therapy—with either a chemotherapeutic or biologic agent—is given immediately after first-line therapy to patients who have achieved tumour response or stable disease. Choice of therapy may include continuation of the agents included in the induction regimen or introduction of different agents (early second-line treatment) with the aim of preventing progression and prolonging progression-free survival. Targeted agents such as bevacizumab and erlotinib target critical molecular signalling pathways and provide several advantages over chemotherapy, including fewer toxicities and the possibility of a longer duration of therapy. This review examines the treatment options in all lines of therapy for metastatic NSCLC, focusing particularly on targeted therapies that have been approved in the United States, Canada, or Europe.

KEY WORDS

Targeted therapies, non-small-cell lung cancer, NSCLC, metastatic, maintenance

1. INTRODUCTION

Historically, treatment of non-small-cell lung cancer (NSCLC) has involved a finite number of cycles of first-line chemotherapy, after which patients with tumour response or stable disease are observed for evidence of disease progression; progression is followed by second-line therapy in suitable patients. However, the therapeutic efficacy of platinum doublets, the most commonly used first-line regimen [1], has reached a plateau, and the introduction of a third chemotherapeutic agent increases toxicity without improving efficacy. Only about 50% of patients in NSCLC clinical trials go on to receive second-line therapy, and only about 50% of those will receive third-line therapy. It is therefore important to ensure that patients receive the best therapeutic option in each line of therapy [2].

In recent years, two new concepts have been introduced to the field of NSCLC: maintenance therapy and targeted biologic agents. Maintenance therapy, with either a chemotherapeutic or biologic agent, is given to patients after first-line therapy. Choice of therapy may include drugs included in the induction regimen or different agents (early second-line treatment) with the aim of preventing progression and prolonging progression-free survival (PFS). Targeted agents modulate events in the cancer cells and provide several advantages over chemotherapeutics, including fewer toxicities and the possibility of a longer duration of therapy [3].

Two main groups of targeted agents for NSCLC are the inhibitors of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Erlotinib and bevacizumab are the respective representatives of these groups, and both are approved for use in the United States, Canada, and Europe based on their safety and efficacy profiles. A wealth of available clinical data supports the use of these agents in the treatment of metastatic NSCLC. Other EGFR inhibitors include cetuximab, which is not currently approved in the United States, Canada, or Europe for the treatment of NSCLC, and gefitinib, which was recently granted marketing authorization by the European Medicines Agency (EMEA) the United States, and Canada for the treatment of *EGFR* mutation–positive NSCLC.

This review examines the treatment options in all lines of therapy for metastatic NSCLC, focusing particularly on targeted therapies that have been approved in the United States, Canada, or Europe.

2. A STEP-BY-STEP APPROACH: CHOOSING THE BEST TREATMENT OPTION FOR EVERY LINE OF THERAPY

2.1 The Beginning: First-Line Treatment

2.1.1 Chemotherapy in First Line

There is currently no universal consensus regarding the accepted standard of care for the first-line treatment of advanced NSCLC. For instance, cisplatin–gemcitabine is the standard regimen in Europe and other parts of the world, but carboplatin–paclitaxel is preferred in the United States [4]. The inclusion of third-generation chemotherapy agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and pemetrexed in platinum-based doublets is more effective in terms of response rates and survival, and also improves tolerability compared with cisplatin alone or older platinum-based combinations [5]. The overall benefit obtained by modifying chemotherapy regimens has been small and has yielded no tangible improvement in overall survival (OS) [6]. Maximum median OS reached with chemotherapy plateaus at 8–10 months, even with third-generation chemotherapy agents such as pemetrexed [4,7].

In a large phase III study comparing platinum doublets, first-line cisplatin–pemetrexed provided efficacy similar to that for cisplatin–gemcitabine, with a median OS of 10.3 months for each treatment arm [7]. In a pre-specified analysis, the median OS was significantly longer for cisplatin–pemetrexed than for cisplatin–gemcitabine in patients with adenocarcinoma histology [$n = 847$; 12.6 months vs. 10.9 months; hazard ratio (HR): 0.84; $p = 0.03$] and large-cell carcinoma histology ($n = 153$; 10.4 months vs. 6.7 months; HR: 0.67; $p = 0.03$). However, the median survival of patients with squamous histology assigned to cisplatin–pemetrexed ($n = 244$) was 9.4 months; it was 10.8 months for patients assigned to cisplatin–gemcitabine ($n = 229$; HR: 1.23; $p = 0.05$). For patients having NSCLC without further subtype classification ($n = 252$), no significant difference was observed between the two arms [7]. These outcomes support the use of cisplatin–pemetrexed in non-squamous tumours only. Carboplatin–pemetrexed demonstrated efficacy similar to that of carboplatin–gemcitabine in the first-line treatment of metastatic NSCLC [8]. Further trials are required to fully elucidate the role of platinum doublets in NSCLC based on histology.

2.1.2 Targeted Therapies in First Line

The anti-VEGF monoclonal antibody bevacizumab was the first targeted agent to increase efficacy in first-line NSCLC when added to a platinum doublet. The key angiogenic factor VEGF plays multiple roles in tumour angiogenesis and has become a target for anticancer drug development. Specifically, VEGF has been shown to promote survival [9] and to increase permeability of existing tumour vasculature [10] while stimulating the growth of new tumour vessels [9]. In addition to its effects on tumour vasculature, VEGF is known to have a direct effect on tumour cells, including survival, migration, and invasion [11].

Anti-VEGF therapy such as bevacizumab has been proposed to exert a "dynamic" anti-angiogenic effect on tumour vasculature throughout the course of its use, with important effects observed early and continued later in treatment. Two early effects of anti-VEGF therapy include regression of existing tumour microvasculature and normalization of remaining tumour vasculature [10]. A third effect is the continued inhibition of new tumour vasculature [12] that may contribute to additional benefits observed over longer periods of time.

Bevacizumab in First Line: Figure 1 shows data from key first-line bevacizumab trials. In a phase II trial, addition of bevacizumab to first-line carboplatin–paclitaxel significantly improved response rates and PFS in patients with advanced NSCLC [13]. The pivotal phase III trial, E4599, demonstrated significant improvements in median OS (12.3 months vs. 10.3 months; HR: 0.79; $p = 0.003$), median PFS (6.2 months vs. 4.5 months; HR: 0.66; $p < 0.001$), and response rates (35% vs. 15%, $p < 0.001$) for bevacizumab in combination with carboplatin–paclitaxel as compared with chemotherapy alone [14]. Bevacizumab is the first novel agent combined with chemotherapy to improve survival beyond the historical benchmark of 1 year for non-squamous patients with advanced NSCLC. Furthermore, exceptional OS benefit (14.2 months vs. 10.3 months for control) has been reported in patients with adenocarcinoma histology treated with bevacizumab in E4599 [17].

The phase III BO17704 (AVAiL) trial is the second large randomized study to confirm the consistent positive efficacy and safety of bevacizumab with platinum doublet chemotherapy (cisplatin–gemcitabine) [15,18]. Because the optimal dose of bevacizumab in lung cancer had not been fully explored at the time, AVAiL adopted a three-arm study design. The aim was to determine the efficacy and safety of two doses of bevacizumab in combination with cisplatin–gemcitabine as compared with placebo combined with cisplatin–gemcitabine, although the study was not powered to allow a direct comparison of the two bevacizumab-containing arms. To avoid the risk that the OS endpoint might be confounded by the increasing use of the second-line therapies that had become available in the four years since the E4599 trial was initiated, and also by any non-protocol crossover of patients from the placebo arm to bevacizumab, PFS was selected as the primary endpoint of AVAiL. Progression-free survival was significantly prolonged with bevacizumab 7.5 mg/kg plus chemotherapy compared with chemotherapy alone (6.7 months vs. 6.1 months; HR: 0.75; $p = 0.003$), and an objective response rate of 34.1% was achieved compared with 20.1% for chemotherapy alone ($p < 0.0001$). Progression-free

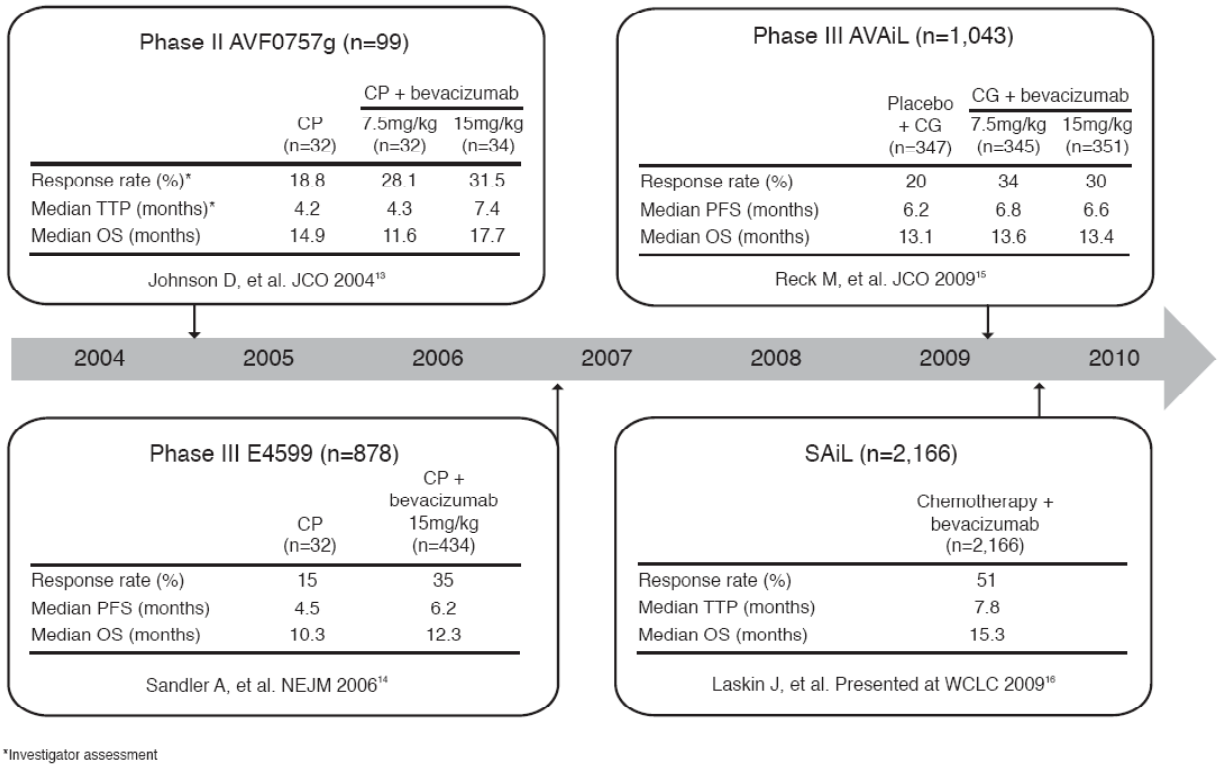

FIGURE 1 First-line bevacizumab data in non-small-cell lung cancer. CP = carboplatin–paclitaxel; TTP = time to progression; OS = overall survival; JCO = J Clin Oncol; CG = cisplatin–gemcitabine; PFS = progression-free survival; NEJM = N Engl J Med; WCLC = World Conference on Lung Cancer

survival was also significantly improved in patients receiving bevacizumab 15 mg/kg plus chemotherapy as compared with placebo (6.5 months vs. 6.1 months; HR: 0.82; $p = 0.03$).

A large phase IV study, MO19390 (SAiL), examined the safety of bevacizumab in the day-to-day clinical setting and confirmed the well-established and favourable safety profile of bevacizumab in a broad patient population [16,19]. That trial involved more than 2000 patients, demonstrated a clinical benefit for bevacizumab not only with cisplatin doublet, but also with carboplatin doublet, regimens (approximately half of all patients). Preliminary efficacy data confirmed the clinical benefit of bevacizumab-based therapy, with a median PFS of 7.8 months and OS of 15.3 months [16].

A large registry trial (ARIES) in the United States further confirmed the safety of bevacizumab in patients underrepresented in randomized controlled trials [20]. Data suggest that most patients with metastatic NSCLC—including elderly patients; those with hypertension, central tumour location, central nervous system (CNS) metastases; and those receiving concurrent anticoagulation therapy at baseline—can receive bevacizumab. Preliminary median PFS is reported to be 6.7 months.

All bevacizumab clinical trials to date have demonstrated benefit when this agent is given first line and until disease progression. Other targeted therapies have shown minimal benefit in the first-line setting. Phase III trials of cetuximab plus taxane–carboplatin (BMS-099) and cetuximab plus cisplatin–vinorelbine (FLEX) failed to demonstrate a PFS benefit in patients with NSCLC (4.4 months vs. 4.2 months and 4.8 months respectively) [21,22]. A marginal OS benefit was observed in FLEX (11.3 months vs. 10.0 months); however, the lack of a PFS benefit raises the question of the influence of subsequent therapies or other still unknown factors (possibly biologic differences) on OS.

A large phase III trial (ESCAPE) of sorafenib, a multikinase inhibitor, in combination with carboplatin–paclitaxel, showed no benefit in patients with NSCLC; moreover, the addition of sorafenib appeared to have a detrimental effect in patients with squamous cell histology. As a result, the trial was stopped prematurely, and the study failed to meet its primary OS endpoint [23]. The BR.24 phase II/III study of cediranib (Recentin: AstraZeneca Pharmaceuticals, Wilmington, DE, U.S.A.) in first-line NSCLC is another trial that was discontinued because of unacceptable toxicity. Although an improvement in objective response and a trend toward better PFS were observed, the disproportional increase in the death rate in the cediranib arm, even at the reduced dose of 30 mg, was considered enough for the study not to have met the predefined criteria for automatic continuation into phase III [24]. A follow-up randomized

phase II/III trial (BR.29) is currently ongoing, testing cediranib at the lower dose of 20 mg in patients with stage IIIB or IV NSCLC. Many other randomized trials of targeted therapies combined with chemotherapy have failed to demonstrate clinical benefit.

Regulatory Approval Status of Bevacizumab: Based on results from the E4599 trial, bevacizumab plus carboplatin–paclitaxel became the Eastern Cooperative Oncology Group (ECOG) reference standard and received approval from the U.S. Food and Drug Administration for first-line treatment of non-squamous advanced NSCLC. Similsarly, based on AVAiL and E4599, bevacizumab in combination with platinum-doublet chemotherapy received EMEA approval. In April 2009, bevacizumab in combination with carboplatin–paclitaxel was approved in Canada. A meta-analysis of more than 13,000 bevacizumab-treated patients provided reassurance that the risk of CNS bleeding in patients with brain metastases is not unduly increased with the use of bevacizumab [25], which led to an update of the EMEA label to allow patients with untreated CNS metastases to receive the drug [26]. The United States has never had any label restriction on bevacizumab for patients with CNS metastases; however, new data regarding the safety of bevacizumab in patients with CNS metastasis is included in the "warnings and precautions" section of that country's monograph.

2.1.3 Evidence-Based Medicine: A Rational Approach in First Line

With the availability of a wide range of agents, first-line therapy often presents a challenge for physicians treating patients with NSCLC. A number of factors affect the choice of first-line therapy, including available clinical data, patient characteristics (age, disease stage, histology, smoking status, tumour mutation status), patient preference, and physician experience with certain agents.

A wealth of data demonstrate clinical benefit with manageable toxicity for bevacizumab in patients with non-squamous pathology (E4599, AVAiL, SAiL, ARIES). Although pemetrexed has demonstrated an OS benefit in patients with non-squamous NSCLC, that benefit is restricted to a subanalysis of a subgroup of patients and to those eligible for cisplatin [7,27]. Patients not eligible for bevacizumab should receive platinum-containing doublet chemotherapy, of which cisplatin–pemetrexed is the most promising for non-squamous histology. Data from phase III trials will help to determine the role of pemetrexed–cisplatin with bevacizumab in the first-line setting.

Biomarkers are increasingly being used to monitor a patient's clinical course and response to therapy. Specific markers may predict the likelihood of benefit from a particular therapy, permitting an optimal selection of treatment for the individual patient. *EGFR* mutations have been implicated as potential biomarkers for NSCLC, and evidence suggests that EGFR tyrosine kinase inhibitors (TKIS) are particularly effective agents in patients with *EGFR* mutation–positive tumours.

A phase III, randomized, open-label study (the Iressa Pan-Asia Study) examined the efficacy of gefitinib in first line as compared with carboplatin–paclitaxel in clinically selected patients with NSCLC. The results revealed significantly longer PFS times, increased objective response rates, and improved quality of life among *EGFR* mutation–positive patients who received gefitinib than among those who received carboplatin–paclitaxel. The difference in the rates of objective response with gefitinib was remarkable at 71.2% and 1.1% for *EGFR* mutation–positive and –negative patients respectively, suggesting that the presence of an *EGFR* mutation can be a robust predictor of improved efficacy with gefitinib in first-line NSCLC [28]. Currently, there are no predictive markers for anti-VEGF therapy. In mutation-positive patients (exon 19 + 21), EGFR TKIS are the treatment of choice in the first line for metastatic NSCLC. Tests for *EGFR* mutations within tumours are not readily available in Canada. In a case of unknown mutation status, patients should receive chemotherapy combination treatment [29].

2.2 Continuing the Efficacy Benefit: Maintenance

The optimal treatment duration for NSCLC patients remains a matter of discussion. A number of studies have evaluated regimens using either sequential or maintenance chemotherapy as post-first-line treatment for NSCLC patients who have not experienced disease progression. A review of those studies suggests that the optimal timing and duration of maintenance therapy (or immediate compared with delayed second-line therapy) remain unclear [2,30].

2.2.1 Chemotherapy in Maintenance

A recent phase III trial [31] compared the efficacy and safety of docetaxel administered to patients either immediately after first-line gemcitabine–carboplatin or at the time of disease progression. The study showed a statistically significant improvement in PFS of 3 months for patients receiving immediate docetaxel therapy and a nonsignificant trend toward an improved OS. A notable observation from the trial was that, although 95% of patients in the immediate-therapy arm received docetaxel, only 63% of patients in the delayed-therapy arm received docetaxel. When OS was compared for patients in the safety population (that is, only patients that received docetaxel), OS was 12.5 months in both arms.

The JMEN trial evaluated maintenance pemetrexed plus best supportive care (BSC) against placebo plus BSC. With maintenance pemetrexed, the PFS in the overall patient population was 4.0 months as compared with 2.0 months for placebo [32]; however, patients with squamous histology did not benefit from pemetrexed therapy. The trial excluded patients who had previously received pemetrexed with cisplatin, and it was therefore similar to the immediate-docetaxel arm of the trial by Fidias and colleagues: the lack of a delayed

pemetrexed arm means that it is difficult to ascertain the true benefit of immediate compared with second-line pemetrexed. It should also be noted that only patients who responded to initial chemotherapy (stable disease or better) were randomized to pemetrexed or placebo, and therefore the trial assessed pemetrexed only in patients who were known to have chemosensitive tumours. Furthermore, only 19% of patients in the placebo arm received pemetrexed in the second line, raising a question concerning whether the observed survival benefit would have been maintained if more patients had received second-line pemetrexed.

Myelosuppression is a known dose-limiting toxicity of pemetrexed therapy. Patients are required to continuously take prophylactic folic acid and vitamin B_{12} to reduce treatment-related toxicities, especially hematologic toxicities. The most common adverse events related to pemetrexed therapy include neutropenia and fatigue.

2.2.2 Targeted Therapies in Maintenance

All bevacizumab clinical trials to date have demonstrated efficacy when bevacizumab is administered in combination with first-line chemotherapy, followed by bevacizumab monotherapy as maintenance. In the maintenance phase of AVAiL, there was a significant increase in PFS for patients in the bevacizumab arm as compared with the placebo arm [33] (4.6 months vs. 3.2 months; Table I). Furthermore, the ATLAS trial confirmed the efficacy of maintenance bevacizumab and demonstrated that the benefit is further improved with the addition of erlotinib (4.76 months vs. 3.75 months; HR: 0.722) [35]. A large proportion of patients (66%) received maintenance therapy in AVAiL, suggesting that more patients can benefit from maintenance therapy after having received first-line bevacizumab-based therapy. In patients who receive first-line chemotherapy without bevacizumab, erlotinib maintenance therapy can still deliver a significant efficacy benefit: in the SATURN trial, a 41% improvement in PFS was observed for erlotinib as compared with placebo [34]. In addition, SATURN demonstrated a significant survival benefit for maintenance erlotinib over placebo—a benefit that extended to all patient subgroups, including squamous tumour pathology, which is especially important because this benefit was independent of *EGFR* mutation status [36].

2.2.3 Combining Agents to Maximize Benefit: Future Directions in Maintenance Therapy

In a phase II trial, Patel *et al.* [37] evaluated the efficacy and safety of first-line pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab in non-squamous NSCLC patients. An overall response rate of 55% was achieved, with a median PFS of 7.8 months and an OS of 14.1 months. Another phase II trial demonstrated that bevacizumab plus pemetrexed and oxaliplatin followed by bevacizumab maintenance delivered a median PFS of 7.8 months and a median OS of 16.7 months [38]. These data suggest that consistent clinical benefit is achieved when bevacizumab is combined with different agents and continued in the maintenance setting. Phase III trials of bevacizumab with pemetrexed maintenance therapy in NSCLC are pending.

2.2.4 Evidence-Based Medicine: A Rational Approach in Maintenance

Clinical trial data in colorectal cancer suggest that patients eligible for bevacizumab therapy should continue bevacizumab to keep VEGF levels down and to deliver continued clinical benefits [39]. Patients who are not eligible for bevacizumab may receive pemetrexed or erlotinib. Erlotinib treatment is well tolerated and is associated with manageable adverse events such as rash or diarrhea. Furthermore, oral administration of erlotinib means fewer hospital visits for the patient; erlotinib therefore remains the agent of choice in patients with advanced NSCLC who are not eligible for bevacizumab and who prefer more convenient treatment. Unlike pemetrexed, erlotinib therapy is also effective in patients with squamous histology [34].

TABLE I Efficacy outcome of trials in the maintenance setting in patients with non-small-cell lung cancer

Reference	*Trial short name*	*Treatment*	*Patients (n)*	*Median PFS (months)*	*HR*
Belani *et al.* 2009 [32]	JMEN	Pemetrexed	441	4.0	0.5
		Placebo	222	2.0	(p<0.0001)
Cappuzzo *et al.* 2009 [34]	SATURN	Erlotinib	437	NR	0.71
		Placebo	447	NR	(p<0.0001)
Mezger *et al.* 2009 [33]	AVAiL	Placebo	41	3.2	NR
		Bevacizumab 7.5 mg/kg	174	4.6	
		Bevacizumab 15 mg/kg	162	4.6	
Miller *et al.* 2009 [35]	ATLAS	Bevacizumab + erlotinib	370	4.76	0.722
		Bevacizumab + placebo	373	3.75	(p=0.0012)

PFS = progression-free survival; HR = hazard ratio; NR = not reported.

2.3 A Step Further: Second Line

2.3.1 Chemotherapy in Second Line

Patients with advanced NSCLC eventually relapse or become refractory to first-line treatment. Acceptable toxicity and improved quality of life are especially important for those patients (although efficacy remains the main goal of therapy). Several chemotherapy agents, including docetaxel and pemetrexed, have demonstrated efficacy and have been approved by the U.S. Food and Drug Administration for second-line treatment of patients with locally advanced or metastatic NSCLC [40–43]. In Canada, approved second-line chemotherapy agents are intravenous docetaxel and intravenous pemetrexed, the latter for non-squamous histology only. Docetaxel has been reported to achieve response rates of 15%–20% [44,45], an OS of 8.3 months [42], and 1-year survival rates of up to 37% [40]. However, docetaxel is associated with serious toxicities. Pemetrexed offers a similar median OS of 7.9 months, but with a milder toxicity profile than is seen with docetaxel [42].

2.3.2 Targeted Therapies in Second Line

Erlotinib is an EGFR TKI that suppresses intracellular signalling pathways, which normally promote cell growth and proliferation [46,47]. Erlotinib is the only approved targeted biologic agent for NSCLC in the second-line setting in Canada. Unlike chemotherapy, erlotinib has no cumulative hematologic toxicities, allowing for a longer treatment duration. In contrast, the toxicities associated with chemotherapy allow for only a limited number of cycles (approximately 4 cycles median). Table II compares clinical data for erlotinib, docetaxel, and pemetrexed.

In a randomized, placebo-controlled study (BR.21), erlotinib demonstrated improvement in median OS (6.7 months vs. 4.7 months) and quality of life across all subgroups [43,49]. The safety and efficacy of erlotinib was confirmed in a phase IV trial (TRUST) in a broad patient population [50], where median OS was 8.1 months, with a 1-year survival rate of 38.6%. Another EGFR TKI, gefitinib, failed to demonstrate a survival advantage in the overall population of a phase III trial (ISEL). A phase II study of single-agent sorafenib in second line suggests that this agent has modest benefits and specific toxicity [51], but that finding has yet to be demonstrated in a phase III trial.

Vandetanib (Zactima: AstraZeneca) is a monotherapy agent that combines targeting of VEGF receptor–dependent tumour angiogenesis and EGFR-dependent tumour cell proliferation and survival. Phase III trials of second-line single-agent vandetanib have demonstrated only modest benefit to date [52–54]. In ZEST, vandetanib monotherapy showed efficacy equivalent to that with erlotinib, but with additional toxicity in second-line treatment of NSCLC. The ZEAL trial showed no statistical benefit for pemetrexed plus vandetanib compared with pemetrexed alone in previously-treated NSCLC patients. The ZODIAC trial assessed the efficacy of docetaxel in combination with vandetanib compared with docetaxel and placebo in NSCLC patients who progressed after treatment with standard chemotherapy. Combination therapy demonstrated improved PFS and quality of life as compared with docetaxel alone.

2.3.3 Evidence-Based Medicine: A Rational Approach in Second Line

The selection of second-line therapy often depends on the first-line therapy used to treat the patient. A good response to first-line chemotherapy may warrant further chemotherapy in second line. The benefit of single-agent versus doublet chemotherapy was evaluated in a meta-analysis, and the improvements in response rate achieved with doublet chemotherapy were not found to translate into a PFS or OS benefit; moreover, they were associated with additional toxicity [55].

For patients who did not respond to first-line chemotherapy or who tolerated it poorly, an EGFR inhibitor may be the preferred choice in second line. Non-inferiority in terms of OS for gefitinib, an EGFR TKI, compared with docetaxel was demonstrated in a phase III trial (INTEREST). Non-inferiority was shown regardless of a patient's EGFR protein expression, *EGFR* gene mutation, or k-*ras* gene mutation status.

TABLE II Efficacy data in the second-line setting

Outcome	*Erlotinib* [43] *(150 mg daily)*	*Docetaxel* [40–42,48] *(75 mg/m^2 every 3 weeks)*	*Pemetrexed* [42] *(500 mg/m^2 every 3 weeks)*
Risk ratio (%)	8.9	6.7–8.8	9.1
Median duration of response (months)	7.9	5.3–9.1	4.6
Median PFS (months)	2.2	2.7–6	2.9
Median OS (months)	6.7	5.7–7.9	8.3
1-Year survival (%)	31	30–37	30
2-Year survival (%)	13	0	0
Median OS (months)[a]	9.4	9.1	9.4

[a] In patients with a performance status of 0 or 1 with 1 prior regimen.
PFS = progression-free survival; OS = overall survival.

Survival results were significantly different only for patients who received third-line treatment, with a longer survival observed for those receiving docetaxel compared with those receiving gefitinib. Given the lack of difference in clinical benefit relating to the sequence of chemotherapy versus EGFR TKI in the second and third lines (INTEREST), as well as lesser toxicity and easy oral administration, EGFR TKI agents are preferred second-line agents for NSCLC. Obtaining mutation status (*EGFR* exon 19 + 21) of the tumour for second-line NSCLC treatment is not a necessity. When available in future, k-*ras* mutations could also facilitate the decision on choice of treatment.

2.4 Looking Further Down the Line: Third Line

A retrospective practice review found that second-line erlotinib treatment is efficacious and well-tolerated, and does not diminish the benefit of third-line chemotherapy [56]. Furthermore, erlotinib and docetaxel can be given for third-line treatment of NSCLC. Pemetrexed is approved for use in second line in the United States and Canada, and it remains a strong candidate for patients who experience disease progression after bevacizumab and erlotinib in previous lines of therapy.

A number of trials are investigating the role of anticancer therapies in the third- or fourth-line setting. BIBW 2992, a dual inhibitor of EGFR (Erb1) and HER2, was evaluated in a phase IIB/III trial of BSC versus placebo and BSC in NSCLC patients who had failed 1–2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1). Interim results have been reported, and the trial completed accrual in August 2009 [57]. Two ongoing trials (phase II SUN-1058 and phase III SUN-1087) are exploring the combination of sunitinib with erlotinib as second- and third-line therapy. Results from the phase III ZEPHYR trial will help define the role of vandetanib in the third- and fourth-line settings after EGFR TKI failure. Results are expected in 2010. A phase III trial of sorafenib versus placebo as third- or fourth-line therapy is currently recruiting patients; data are expected in April 2011. Combining an insulin-like growth factor inhibitor with erlotinib after progression of disease in second line to try to reverse resistance to erlotinib is also under investigation. Sufficient tumour biopsies will be essential to guide decisions for treatment with targeted agents.

2.4.1 Evidence-Based Medicine: A Rational Approach in Third Line

Clinical data are suggestive of improved third-line options for NSCLC.

The use of erlotinib as third-line therapy is supported by the BR.21 study, in which approximately half the patients had failed two previous lines of chemotherapy. In addition to an acceptable safety profile, erlotinib demonstrated clinical benefit in terms of response and OS in patients with a good or poor ECOG performance status. Erlotinib should therefore be considered a viable third-line treatment option for patients who have not yet received this agent.

The non-inferiority of the EGFR TKI gefitinib over docetaxel in terms of OS (INTEREST), together with its improved safety profile and preferred oral administration over a longer period of time, makes EGFR TKIS prime candidates for second-line rather than third-line treatment in patients with NSCLC. Educating physicians about the importance of re-biopsying the tumour at the time of progression to help guide treatment decisions in the future (and about optimal biopsy techniques) will be of utmost importance.

3. FUTURE STEPS

The main goal is to provide the best possible treatment in terms of both efficacy and safety in each line of therapy. The striking improvements in outcomes demonstrated in both first- and second-line settings with targeted therapies provide a rationale for their use. The targeting of multiple pathways using a wide range of new drugs and combinations of agents is currently under investigation. The mode of action of bevacizumab suggests that its continued use may prevent recurrence of tumour angiogenesis. The advantage of continuing bevacizumab therapy beyond progression has been demonstrated in an observational study (BRiTE) in patients with colorectal cancer [39]. Compared with alternative or no post-progression treatment, bevacizumab given to patients post progression resulted in superior improvement in OS. However, these data have yet to be confirmed in a prospective phase III trial in patients with NSCLC.

As compared with chemotherapeutic agents, targeted agents may offer reduced toxicity, especially with prolonged use. Combinations of targeted agents may also have potential as novel treatment paradigms, perhaps even representing an alternative to chemotherapy. Bevacizumab and erlotinib combination therapy has shown promise in phase I/II [58] and phase II trials [59] in patients with recurrent NSCLC, with reduced toxicity as compared with chemotherapy. In the phase III trial BETA-Lung, the addition of erlotinib to second-line bevacizumab led to an improvement in PFS, but did not translate into a longer OS [60]. Strict criteria for patient selection resulted in the recruitment of healthier patients in each treatment arm, and these patients went on to receive multiple (up to 5) lines of post-progression treatment, which may have confounded the OS result. However, this combination has demonstrated significant benefit when used as maintenance therapy post first line (ATLAS). Table III summarizes ongoing and future trials of bevacizumab and erlotinib.

3.1 Tailoring Therapy

Predictors of response may help to guide individual treatment decisions; however, for most drugs, clinically validated markers have yet to be identified. Until

TABLE III Selected ongoing and future trials of erlotinib and bevacizumab

Study short name	*Phase*	*Pts (n)*	*Eligibility*	*Regimen*	*Line of therapy*	*Primary endpoint*
PASSPORT (AVF3752g)	II	110	Previously treated or untreated non-squamous NSCLC with treated CNS metastases	Chemotherapy or erlotinib followed by bevacizumab	First/second	Grade 2 or greater symptomatic CNS hemorrhage
BRAIN (AVF21823)	II	115	Stage IV non-squamous NSCLC with asymptomatic brain metastases in first and second line	First line: bevacizumab + carboplatin/paclitaxel Second line: bevacizumab + erlotinib	First/second	PFS
EAGLES (ML21896)	II	78	Patients older than 70 years without important comorbidities	Bevacizumab + gemcitabine OR bevacizumab + gemcitabine/cisplatin	First	PFS at 6 months
	II	~250	Patients 65 years or age or older with advanced metastatic or recurrent non-squamous NSCLC	Bevacizumab + pemetrexed OR bevacizumab + pemetrexed/carboplatin	First	Proof of non-inferiority of bevacizumab + pemetrexed
BRIDGE (AVF2744g)	I/II	40	Previously untreated squamous NSCLC	Bevacizumab + carboplatin/paclitaxel	First	Grade 3 or greater pulmonary haemorrhage
ABIGAIL (BO21015)	II	~300	Locally advanced, metastatic or recurrent non-squamous NSCLC	Bevacizumab + carboplatin/gemcitabine OR carboplatin/paclitaxel	First	Correlation of biomarkers with response
MIMEB (ML21803)	II	40	Histologically confirmed advanced non-squamous NSCLC stage IIIB/IV	Bevacizumab + erlotinib	First	Accuracy of FDG- or FLT-PET and DCE-MRI for early prediction of non-progression
EURTAC	III	146	*EGFR* mutation-positive NSCLC	Erlotinib	First	PFS in patients with mutation
SATURN (BO18192)	III	1949	Previously untreated advanced NSCLC	Erlotinib	First	PFS in all patients and in patients with *EGFR* IHC-positive tumours
RADIANT		945	Advanced NSCLC	Erlotinib vs. placebo	Adjuvant	DFS
FASTACT-2	III	450	Asian patients with previously untreated advanced NSCLC	Erlotinib + chemotherapy vs. placebo + chemotherapy	First line	PFS
ATLAS (AVF3671f)	III	1150	Previously untreated advanced NSCLC	Bevacizumab + carboplatin/paclitaxel OR + gemcitabine/cisplatin OR + carboplatin/docetaxel Non-progressing pts randomized (1:1) to bevacizumab + erlotinib OR bevacizumab + placebo	First line maintenance	PFS
TARGET	II	428	*EGFR* mutation–positive NSCLC	Erlotinib	First	PFS
TORCH	III	900	Previously untreated advanced NSCLC	First-line erlotinib, second-line gemcitabine/cisplatin vs. first-line gemcitabine/cisplatin, second-line erlotinib	First/second	OS

Pts = patients; NSCLC = non-small-cell lung cancer; CNS = central nervous system; PFS = progression-free survival; FDG = ^{18}F-2-fluorodeoxy-D-glucose; FLT = ^{18}F-fluorodeoxythymidine; PET = positron-emission tomography; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; *EGFR* = gene for the epidermal growth factor receptor; IHC = immunohistochemistry; DFS = disease-free survival; OS = overall survival.

reliable biomarkers for response and resistance (old or newly developed) are identified, differences in toxicity between chemotherapeutic and targeted agents may provide the best guide for individual treatment decisions, in view of similar efficacy.

Gefitinib recently received EMEA and Canadian approval for treatment of patients with *EGFR* mutation–positive disease. *EGFR* mutations can be viewed as predictive markers of high clinical benefit with EGFR TKI therapy, especially for first-line treatment in eligible patients.

Histology appears to be an important consideration for optimal outcomes with both pemetrexed and bevacizumab. A trial (BRIDGE) in patients with predominantly squamous-cell histology (who are currently excluded from bevacizumab clinical trials) is ongoing to determine ways in which to safely integrate bevacizumab into the treatment of these patients. A personalized targeted approach is the future of treatment in all lines, but tumour re-biopsy will be required for analysis of biomarkers, including not only newly developed markers of resistance to EGFR TKI, but also sensitivity to agents such as BIBW 2992 (T790M mutation and c-Met amplification). Analysis of circulating tumour cells and blood biomarkers to define predictors of tumour response and treatment benefit is a great need for the future.

4. SUMMARY

Given the plateau reached with chemotherapy, and the toxicity associated with prolonged chemotherapy, there is a need to improve outcomes in every line of therapy of advanced NSCLC. Targeted biologic agents are effective and well tolerated in NSCLC, either combined with chemotherapy or as monotherapy, with bevacizumab (first line) and erlotinib (second and third line) having gained approval in Europe, the United States, and Canada. Novel targeted therapies and their combinations with chemotherapeutic agents are also being explored. Future challenges involve identifying predictors of response and efficacy for targeted NSCLC therapies and selecting the optimal therapy for maximum survival benefit in each line of treatment from among currently approved agents.

5. CONFLICT OF INTEREST DISCLOSURE

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