Second-line combination therapies in nonsmall cell lung cancer without known driver mutations

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ABSTRACT In advanced nonsmall cell lung cancer (NSCLC) patients, platinum-based combination chemotherapy is standard treatment in the first-line setting; however, the large majority of patients ultimately progress. For more than a decade, single-agent therapy with docetaxel, pemetrexed or erlotinib has been the standard of care after failure with platinum salts, showing some benefit over best supportive care. Nonetheless, prognosis remains poor and new second-line strategies are urgently needed. Combinations of cytotoxic agents, including rechallenge with platinum salts, do not offer clear benefit over single-agent therapy for the majority of patients. In patients without a known tumoural oncogenic driver mutation, regimens based on combinations of targeted agents have shown promising results; however, a clear role in therapeutic management is yet to be established. Some success has been reported in recent research combining a cytotoxic agent with targeted therapies.

In this review, we summarise published data for the various strategies evaluated over the past decade in second-line treatment of NSCLC patients without a known driver mutation. We focus on combination treatments and consider future perspectives, including the need to identify predictive markers to support personalised therapeutic strategies.

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Introduction

Lung cancer is the most common cancer worldwide, with its incidence rising dramatically over the past few years. Non-small cell lung cancer (NSCLC) accounts for nearly 80% of all cases and ~70% of these patients are diagnosed with advanced disease, most of whom are eligible for treatment [1, 2]. First-line platinum-based chemotherapy offers a significant improvement over best supportive care (BSC) in terms of disease progression and survival in these patients [3]. Nonetheless, most of these patients will eventually progress and require further treatment. Many factors are taken into account when choosing further therapy, including performance status, previous treatment, histology and the presence of a driver mutation. Driver mutations are generally located in genes coding for signalling proteins in cell proliferation and survival pathways.

Currently three drugs have been approved for the treatment of advanced NSCLC in the second-line setting: docetaxel, pemetrexed and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib. In 2000, Shepherd *et al.* [4] demonstrated a significant survival benefit along with an improvement of disease-related symptoms with single-agent docetaxel (75 mg·m^{-2}) compared to BSC in second-line treatment of advanced NSCLC patients with good performance status who had relapsed after

Received: March 17 2015 | Accepted after revision: March 30 2015

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

first-line platinum-based treatment, reporting a 1-year survival rate of 37% *versus* 11% for BSC. Weekly schedules of docetaxel have been explored, suggesting similar activity with a better toxicity profile; however, these schedules have never been registered [5]. In 2004, Hanna *et al.* [6] demonstrated equivalent efficacy outcomes with fewer side-effects under treatment with pemetrexed compared to docetaxel, leading to its approval in all-comer NSCLC patients. In a secondary analysis, pemetrexed was demonstrated to be more active in nonsquamous cell tumours, leading to its restriction to patients with nonsquamous histology [7]. The EGFR TKIs are the treatment of choice for patients with *EGFR*-mutated tumours in both first and subsequent lines, but their role in *EGFR* wild-type tumours remains controversial and is yet to be clearly established. In 2005, a placebo-controlled trial of erlotinib conducted by Shepherd *et al.* [8] in previously-treated NSCLC patients without *EGFR* status selection, demonstrated a 1-year survival rate of 31% with erlotinib *versus* 22% for the placebo group. This study led to the approval of erlotinib as second- and third-line treatment for advanced NSCLC, independent of the *EGFR* mutational status, which at the time was not routinely tested for. At least 10 randomised trials have compared single-agent EGFR TKIs with single-agent chemotherapy in the second-line setting, showing an improvement in progression-free survival (PFS) but not in overall survival (OS) associated with chemotherapy treatment compared with EGFR TKIs in an *EGFR* wild-type population [9–19]. Regardless of the *EGFR* status of the tumour, treating oncologists have a basic choice between docetaxel, pemetrexed or erlotinib for second-line treatment of NSCLC patients without any known driver mutations. Available evidence suggests that chemotherapy might be the best option for fit patients with performance status 0 or 1, although in all cases it is recommended that the patient's *EGFR* mutational status be determined prior to selecting second-line treatment. Here we review the main second-line options beyond single-agent chemotherapy, including chemotherapy combinations, platinum rechallenging, combinations of chemotherapy with targeted or anti-angiogenic agents and combinations of targeted or anti-angiogenic agents, and also cover promising future approaches currently under development.

Second-line combined chemotherapy treatment

While combinations of cytotoxic drugs have been successful in improving efficacy over single agents in the first-line setting [20, 21] in the second-line setting the role of combination therapy is less clear. Three landmark phase III studies have been performed in NSCLC patients comparing docetaxel-based combination chemotherapy with docetaxel single agent in the second-line setting. Takeda *et al.* [22] evaluated 130 patients randomly assigned to receive docetaxel alone or docetaxel plus gemcitabine. There were no significant differences in response rate ((RR) 6.8% *versus* 7.0%; p=0.71), median survival (10.1 months *versus* 10.3 months; p=0.36) or PFS (2.1 months *versus* 2.8 months; p=0.028) between docetaxel alone and docetaxel plus gemcitabine, respectively, although it should be noted that the study closed prematurely due to a high incidence of interstitial lung disease in the gemcitabine arm [22]. Gebbia *et al.* [5] evaluated weekly docetaxel alone using the same regimen plus gemcitabine, vinorelbine or capecitabine. This randomised phase III trial showed no statistical difference between the arms; however, again the study had no statistical power because of premature closure due to slow accrual (n=84). Finally, a phase III trial conducted by Pallis *et al.* [23] evaluated the efficacy of docetaxel and carboplatin *versus* docetaxel alone in 132 patients and found a significant clinical benefit in PFS (3.33 months *versus* 2.60 months; p=0.012), with no significant difference in OS (10.3 months *versus* 7.70 months; p=0.550).

At least five randomised phase II trials evaluating the benefit of docetaxel- or pemetrexed-based combination therapy have been conducted over the past few years; however, none have shown a benefit in terms of survival. Smit *et al.* [24] performed a trial (NVALT7) comparing pemetrexed alone with pemetrexed plus carboplatin in 240 patients who had relapsed after platinum-based chemotherapy. The primary end-point was time to progression (TTP) and secondary end-points were overall response rate (ORR) and OS. The results showed a benefit in TTP favouring the combination therapy (4.2 months *versus* 2.8 months, hazard ratio (HR) 0.67, 95% CI 2.5–3.0 months; p=0.005) with no difference in median OS (8.0 months *versus* 7.6 months, HR 0.85; not significant). The 1-year survival rate was 30% for both arms. A subgroup analysis based on histology revealed a longer PFS for nonsquamous histology (3.7 months *versus* 2.8 months), but the addition of carboplatin positively impacted PFS in both nonsquamous and squamous cell patients. Ardizzoni *et al.* [25] performed a phase II trial with same design, also publishing results of a pooled analysis of both trials (n=479; GOIRC 02-2006 and NVALT7 trials). The results showed a higher response rate in the carboplatin-containing arm (15% *versus* 9%; OR 1.72, 95% CI 0.97–3.02; p=0.062) with a non-significantly longer PFS (3.0 months *versus* 3.9 months; HR 0.85, 95% CI 0.70–1.02; p=0.07) and no difference in OS. As expected, in a subgroup analysis, an interaction between the histology and treatment was identified, with the addition of carboplatin doubling survival for squamous histology. The population of this trial was heterogeneous, with a less favourable performance status, a higher proportion of patients with adenocarcinoma histology, shorter platinum-free intervals and fewer responses to prior treatment than in the Italian GOIRC 02-2006 trial. Docetaxel with

or without irinotecan explored in two randomised trials (n=130 and n=108), showed no difference in terms of PFS, survival or response rate [26, 27]. In 2009, Di Maio *et al.* [28] performed a meta-analysis addressing the efficacy of combined therapy. They concluded that there was no difference in OS between the two strategies (37.3 weeks *versus* 34.7 weeks for combination therapy *versus* single agent, respectively), but a statistically significant increase in PFS (14 *versus* 11 weeks, HR 0.79; p=0.0009) and response rate (15.1% *versus* 7.3%; p=0.0004) in favour of the combination therapy, albeit with a much higher incidence of grade 3–4 haematological (41% *versus* 25%; p<0.001) and nonhaematological (28% *versus* 22%; p=0.034) adverse events. Similar findings were reported in a subsequent meta-analysis conducted in 2012 by Qi *et al.* [29]. Table 1 summarises the main combination chemotherapy studies. Taken together, the available evidence does not provide a clear argument supporting the use of combination chemotherapy in the second-line setting in all-comer NSCLC patients, although it could represent a reasonable option for selected fit patients.

Platinum-based chemotherapy rechallenge

In ovarian and small cell lung cancer, rechallenge with platinum-based regimens is a widely used strategy with major benefit reported in patients relapsing after ⩾6 months [31, 32]. To date, no prospective phase III studies directly addressing this approach have been conducted in NSCLC patients. Two major phase II trials evaluating the benefit of carboplatin–pemetrexed *versus* pemetrexed single agent have been performed in patients previously treated with platinum-based regimens with a minimum 3-month interval since the last platinum chemotherapy. The first of them, the above-mentioned NVALT7 Dutch study [24], stratified patients on the basis of performance status, response to prior treatment and treatment-free interval (<6 months *versus* >6 months). The combination therapy resulted in a 33% reduction in the risk of progression. The majority of responding patients had responded to their first-line cisplatin-based chemotherapy, and survival was higher in patients with prior treatment >6 months before randomisation (p=0.001) [24]. The GOIRC trial included patients with ⩾4 weeks since completion of prior chemotherapy, and stratified them for the same factors as the NVALT7 trial but according to a shorter treatment-free interval (3 months *versus* >3 months). In the pooled analysis of both trials, neither prior response to platinum treatment nor longer treatment-free interval were predictive of improved efficacy. The Dutch trial included patients with more responses and longer platinum-free intervals with prior treatments [25].

A number of smaller phase II single-arm studies, retrospective trials and prospective series evaluating the benefit of platinum re-challenge were reviewed in a pooled analysis conducted by Petrelli *et al.* [32]. 607 patients with relapsed NSCLC after platinum-based chemotherapy who were rechallenged with platinum and taxanes or pemetrexed combined therapies were included in this analysis. The response rate of patients with second-line therapy was 27.5%, with a median PFS of 3.9 months and median OS of

TABLE 1 Combination *versus* single-agent chemotherapy trials in second-line nonsmall cell lung cancer

First author, year [ref.]	Phase	Patients	Arms	PFS months	p-value	OS months	p-value	Response rate %	p-value
Pallis, 2010 [23]	III	132	Docetaxel + carboplatin	3.33	0.012	10.3	0.55	10.4	0.764
			Docetaxel	2.60		7.70		7.7	
Takeda, 2009 [22]	III	130	Docetaxel + gemcitabine	2.8	0.028	10.3	0.36	7.0	0.71
			Docetaxel	2.1		10.1		6.8	
Gebbia, 2009 [5]	III	84	Docetaxel	12.4 weeks	0.44	40 weeks	0.18	6.4	NR
			Docetaxel + vinorelbine or gemcitabine	13.1 weeks	0.60	32.6 weeks	0.90	16.7	
			Docetaxel + capecitabine	11.9 weeks		39.7 weeks		5.3	
Ardizzoni, 2012 [25]	II	479	Pemetrexed + carboplatin	3.9	0.70	8.7	0.316	15	0.062
			Pemetrexed	3.0		8.2		9	
Smit, 2009 [24]	II	240	Pemetrexed + carboplatin	4.2	0.005	8.0	NS	9	NS
			Pemetrexed	2.8		7.6		4	
Pectasides, 2005 [26]	II	130	Docetaxel + irinotecan	5.6	0.065	6.5	0.49	20	0.36
			Docetaxel	4.8		6.4		14	
Wachters, 2005 [27]	II	108	Docetaxel + irinotecan	15 weeks	0.42	27 weeks	0.69	10	NR
			Docetaxel	18 weeks		32 weeks		16	
Georgoulias, 2005 [30]	II	147	Cisplatin + irinotecan	NR	NR	7.8	0.934	22.5	0.012
			Cisplatin			8.8		7	

Data are presented as n, unless otherwise stated. PFS: progression-free survival; OS: overall survival; NR: not reported; NS: nonsignificant.

DOI: 10.1183/16000617.00002115

8.7 months. Response rate was independent of response to first-line treatment (p=0.24). Analysis of the platinum-free interval period could not be performed due to insufficient data. However, they found that in trials where the majority of patients had a TTP >6 months, the response rate was >40%. Response rate was also better in studies including patients with at least two prior lines of treatment, suggesting that time since the last platinum-based therapy may influence response [33].

The available evidence suggests that platinum rechallenge could represent a valid option for relapsed fit patients with a platinum-free interval treatment of >6 months. Nonetheless, in the absence of a proven role for this strategy, prospective phase III trials should be conducted to definitively address this issue.

Second-line combined treatment with chemotherapy and targeted/anti-angiogenic therapy

Identification of patients who are likely to respond better to therapy is the underlying basis of personalised treatment, and to this end many predictive biomarkers have been identified over the past decade. In NSCLC, the main oncogenic driver mutations that can serve as therapeutic targets are the growth factor receptors EGFR, human epidermal growth factor receptor (HER)2 and BRAF, along with anaplastic lymphoma kinase (*ALK*) rearrangements. An increasing number of trials have evaluated the benefit of a combination of chemotherapy with targeted therapy in advanced NSCLC patients with either wild-type *EGFR* or who are unselected for mutational status. Positive outcomes have only been seen when the targeted agent is combined with docetaxel.

EGFR pathway inhibitors

EGFR is a member of the Erb family of transmembrane tyrosine kinase receptors which, after ligand binding, activates an intracellular cascade of events resulting in cell proliferation and survival. Targeting of the EGFR pathway with erlotinib, a first-generation oral inhibitor of this tyrosine kinase, first demonstrated a survival benefit in second-line therapy in unselected patients in 2005 [8]. Almost 10 years later, Lee *et al.* [34] conducted a three-arm randomised phase II trial comparing the efficacy of combination standard second-line therapies with pemetrexed and erlotinib to either pemetrexed or erlotinib alone (n=240). Combination therapy significantly prolonged PFS over either single agent (7.4 months *versus* 3.8 months with erlotinib, HR 0.57; p=0.002 *versus* 4 months with pemetrexed, HR 0.58; p=0.005). *EGFR* status was analysed in only 22% of the patients, so few patients could be confirmed as wild type. Patients had a high probability of having *EGFR*-mutated NSCLC since the proportions of never-smokers and of Asian ethnicity were both high. In the *EFGR* wild-type subgroup (n=19), the benefit of the combination was superior, in terms of PFS, to either agent alone.

A similar trial conducted by Dittrich *et al.* [35] evaluating combination therapy with pemetrexed and erlotinib *versus* pemetrexed alone in 165 nonsquamous cell patients with unknown *EGFR* mutational status, showed a small but significant benefit in PFS (2.89 months for pemetrexed *versus* 3.19 months for pemetrexed/erlotinib, HR 0.63; p=0.005) and in OS (7.75 months for pemetrexed *versus* 11.8 months for pemetrexed/erlotinib, HR 0.68; p=0.019). While the pemetrexed-alone arm performed as expected, it should be kept in mind that survival may be influenced by subsequent lines of treatment, which were for the most part unknown.

Several monoclonal antibodies targeting EGFR have been evaluated in NSCLC. A phase III study conducted by Kim *et al.* [36] found no benefit of adding cetuximab (which binds to the extracellular domain of EGFR) to standard second-line chemotherapy with pemetrexed or docetaxel, in terms of OS, PFS or response rate, regardless of *EGFR* status and histology, and was associated with more adverse events (n=939). Matuzumab, an IgG1 monoclonal antibody against the EGFR-binding domain with a longer half-life than cetuximab, has demonstrated activity in preclinical studies [37, 38], resulting in further evaluation in the clinic. Combination second-line therapy of matuzumab with pemetrexed was evaluated in a phase II study (n=148) in 2010 by Schiller *et al.* [39]. The results showed a trend for improved survival and a rate response benefit with an acceptable toxicity profile in patients with EGFR-expressing tumours. A novel EGFR recombinant monoclonal fully human antibody, necitumumab, has been evaluated in squamous NSCLC patients in combination with standard chemotherapy in the phase III SQUIRE trial [40]. The primary end-point of improved survival in the first-line setting was met, so that necitumumab efficacy could be investigated in the second-line setting. However, there was no improvement in OS with the addition of necitumumab to first-line pemetrexed–cisplatin in metastatic nonsquamous cell NSCLC patients [41].

Blocking the RAS/RAF/MEK/extracellular signal-regulated kinase pathway

K-Ras and BRAF are downstream of EGFR in this signalling pathway. *K-Ras* mutations are present in ~15–30% of all NSCLC tumours. It has been postulated that constitutive activation of K-Ras leads to cell proliferation irrespective of EGFR inhibition, predicting a lack of benefit with EGFR inhibitors and poorer

survival [42, 43]. A phase II trial in the second-line setting evaluating docetaxel combined with selumetinib, an inhibitor of MEK1-MEK2 downstream of K-Ras, showed a significant benefit for PFS and response rate in *K-Ras*-mutated NSCLC patients [44]. However, the docetaxel arm did not perform as expected (PFS 5.3 months *versus* 2.1 months; HR 0.58, p=0.014; rate response 37.2% *versus* 0%) and the treatment groups were not well balanced. Although to date there are no approved drugs for *K-Ras*-mutated NSCLC patients, selumetinib seems to be a promising option meriting further research.

Antibodies against the vascular endothelial growth factor pathway

Angiogenesis is essential for tumour growth and proliferation. Targeting anti-angiogenic pathways with bevacizumab, a human monoclonal antibody binding vascular endothelial growth factor (VEGF), in combination with carboplatin–taxane chemotherapy as first-line treatment, demonstrated a survival benefit in nonsquamous cell NSCLC patients [45]. Bevacizumab was then evaluated in the second-line setting and beyond in nonsquamous cell patients. The single-arm phase II NCCTG/SWOG study N0426 gave a PFS of 4 months with combined pemetrexed and bevacizumab, although the primary end-point was not reached because of a low number of events referring to the primary end-point [46]. In a phase II trial conducted by Herbst *et al.* [47] bevacizumab was evaluated in combination with second-line chemotherapy (pemetrexed or docetaxel) or with erlotinib *versus* chemotherapy alone in nonsquamous cell patients unselected for *EGFR* status. The results showed superior survival with both bevacizumab combination therapies (1-year survival rate of 53.8% for bevacizumab plus pemetrexed/docetaxel *versus* 57.4% with bevacizumab plus erlotinib *versus* 33.1% with chemotherapy alone). A retrospective analysis of the efficacy of the combination therapy of bevacizumab and weekly paclitaxel in metastatic nonsquamous NSCLC patients as fourth-line therapy and beyond (n=20) showed clinical benefit in 75% of the patients with an acceptable toxicity profile [48]. Based on these promising results a large phase III trial (IFCT-1103 ULTIMATE) evaluating the efficacy of paclitaxel and bevacizumab combination therapy compared with standard docetaxel as second- or third-line therapy in 251 nonsquamous cell NSCLC patients is ongoing (NCT01763671). Aflibercept is a recombinant human fusion protein targeting the extracellular domains of the VEGF receptors (VEGFR) 1 and 2, which is approved for treatment of pre-treated colorectal cancer patients. It was recently evaluated in combination with docetaxel *versus* docetaxel alone in 913 platinum pre-treated advanced NCSLC patients in a phase III trial conducted by Ramlau *et al.* with OS as the primary end-point [49]. Combination therapy did not improve survival, but did prolong PFS (5.2 months *versus* 4.1 months, p=0.0035) and ORR (23.3% *versus* 8.9%, p<0.001) compared to standard second-line chemotherapy alone, and had a similar toxicity profile to other VEGFR-targeted therapies.

Additional studies have been conducted with novel anti-angiogenic drugs including ramucirumab, a fully humanised IgG1 antibody that targets the extracellular domain of VEGFR2. The REVEIL trial conducted by Garon *et al.* [50] evaluated the addition of ramucirumab to conventional docetaxel therapy *versus* docetaxel plus placebo (n=1253). Overall, 14% of patients had been pre-treated with bevacizumab in the experimental arm. Of note, 17% of the patients were never-smokers and 25% were squamous NSCLC patients. The results showed prolonged OS (10.5 months *versus* 9.1 months; HR 0.86, p=0.023), the primary end-point, and PFS (4.5 months *versus* 3.0 months; HR 0.76, p<0.0001) in the ramucirumab group. The control group performed as expected, although patients with performance status 2 and those at high risk for anti-angiogenic therapy were excluded. No differences in benefit were seen for females or squamous cell patients, although the study was not powered for subgroup analysis.

Multitarget agents encompassing the VEGF pathway

A number of anti-angiogenic agents targeting multiple cell receptors have been evaluated in the second-line NSCLC setting in combination with chemotherapy. de Boer *et al.* [51] assessed vandetanib, an oral inhibitor of EGFR/VEGFR/RET, combined with pemetrexed compared to pemetrexed plus placebo in 534 pre-treated patients, reporting a nonsignificant benefit in PFS and OS, although with a modest, albeit significant, benefit in ORR (19.1% *versus* 7.9%, p<0.001) in the combination arm. This trial did not meet its primary end-point. More encouraging results were reported when vandetanib was combined with docetaxel in the large-scale ZODIAC trial (n=1391) conducted by Herbst *et al.* [52]. Significant improvements in PFS, the primary end-point (4.0 months *versus* 3.2 months; HR=0.79, p<0.0001), response rate (17% *versus* 10%, p=0.0001) and time to deterioration of symptoms were seen with the addition of vandetanib to conventional treatment, although no differences in any of the subgroup analyses, including females, were found, in contrast to previously reported phase II findings [53]. A retrospective analysis of potential biomarkers predictive of benefit with vandetanib showed that greater clinical benefit was seen in patients with *EGFR*-mutated tumours (PFS: HR 0.51, 95% CI 0.25–1.06 and OS: HR 0.46, 95% CI 0.14–1.57) and EGFR fluorescence *in situ* hybridisation (FISH)-positive tumours (PFS: HR 0.61, 95% CI 0.39–0.94 and OS: HR 0.48, 95% CI 0.28–0.84); *K-Ras*-mutated tumour patients did not benefit from combined therapy [54].

DOI: 10.1183/16000617.00002115

The combination of pemetrexed with nintedanib, an oral inhibitor of VEGFR1–3, fibroblast growth factor receptor 1–3, platelet-derived growth factor receptor (PDGFR), RET, FLT3 and Src, compared to single-agent chemotherapy, was evaluated by Hanna *et al.* [55]. The LUME-Lung 2 trial (n=713) has been terminated prematurely following a preplanned futility analysis of PFS which showed an absence of any benefit, although a posterior analysis revealed a small benefit in PFS with the combination arm (4.4 months *versus* 3.6 months; p=0.0435). The LUME-Lung 1 trial, conducted by Reck *et al.* [56] evaluated the addition of nintedanib to conventional docetaxel therapy in 1314 patients. Patients were stratified by performance status, previous bevacizumab (n=27, 4.1%), brain metastases and histology. Results demonstrated a significant improvement in the primary end-point of PFS (3.5 months *versus* 2.7 months, HR 0.85; p=0.007) in all predefined subgroups. OS was significantly longer among patients progressing within 9 months (10.9 months *versus* 7.9 months, HR 0.75; p=0.0073) and in the adenocarcinoma group (12.6 months *versus* 10.3 months, HR 0.83; p=0.0359) treated with docetaxel plus nintedanib, although no difference was seen in the overall patient population or in patients with squamous cell carcinoma. Subsequent treatment was balanced between the two groups and the control group performed as reported in other phase III trials [4, 6]. Table 2 summarises the major studies reporting chemotherapy combined with targeted agents. Taking into account the aforementioned data, integrating anti-angiogenic agents into the therapeutic strategy for adenocarcinoma, a known effective approved option in the first-line setting, also represents a potentially valid option in the second-line setting.

Second-line treatment with combined targeted and anti-angiogenic therapy

Combining therapies targeting different molecular markers in a given signalling pathway is a logical strategy for overcoming resistance mechanisms to obtain survival benefits with fewer adverse events. Several trials have been conducted to evaluate the potential benefit of combining targeted agents, notably with agents targeting the EGFR and VEGF pathways. Herbst *et al.* [47] in 2007, in the previously cited phase II trial,

TABLE 2 Combination chemotherapy with targeted therapy *versus* chemotherapy alone in second-line nonsmall cell lung cancer

First author, year [ref.]	Phase	Patients	Arms	PFS months	p-value	OS months	p-value	Response rate %	p-value
Lee, 2013 [34]	II	240	Pemetrexed + erlotinib	7.4		20.5		44.7	
			Erlotinib	3.8	0.002	22.8	0.747	29.3	0.031
			Pemetrexed	4.4	0.005	17.7	0.168	10.0	<0.001
Dittrich, 2014 [35]	II	165	Pemetrexed + erlotinib	3.19	0.0047	11.8	0.019	17.1	0.180
			Pemetrexed	2.89		7.75		10.8	
Hanna, 2013 [55]	III	713	Pemetrexed + nintedanib	4.4	0.0435	12.2		9.1	
			Pemetrexed + placebo	3.6		12.8		8.3	
de Boer, 2011 [51]	III	534	Pemetrexed + vandetanib	4.4	0.108	9.2	0.219	19.1	<0.001
			Pemetrexed + placebo	2.9		10.5		7.9	
Kim, 2013 [36]	III	938	Pemetrexed + cetuximab	2.9	0.76	6.9	0.86	7	0.20
			Pemetrexed	2.8		7.8		4	
			Docetaxel + cetuximab	2.4	0.39	5.8	0.31	8	0.68
			Docetaxel	1.5		8.2		7	
Schiller, 2010 [39]	II	148	Pemetrexed + matuzumab LD	2.3		12.4		16	
			Pemetrexed + matuzumab HD	2.5		5.9		2	
			Pemetrexed	2.7		7.9		4	
Chiappori, 2010 [57]	II	160	Pemetrexed + enzastaurin	3.0	0.544	9.6	0.171	3.9	
			Pemetrexed + placebo	3.0		7.4		2.6	
Jänne, 2013 [44]	II	87	Docetaxel + selumetinib	5.3	0.014	9.4	0.21	37.2	<0.001
			Docetaxel + placebo	2.1		5.2		0	
Ramlau, 2012 [49]	III	913	Docetaxel + aflibercept	5.2	0.0035	10.1	0.90	23.3	<0.001
			Docetaxel + placebo	4.1		10.4		8.9	
Herbst, 2010 [52]	III	1391	Docetaxel + vandetanib	4.0	<0.0001	10.3	0.371	17	0.0001
			Docetaxel + placebo	3.2		9.9		10	
Reck, 2014 [56]	III	1314	Docetaxel + nintedanib	3.4	0.0019	10.1	0.2720	4.4	0.3067
			Docetaxel + placebo	2.7		9.1		3.3	
Garon, 2014 [50]	III	1253	Docetaxel + ramucirumab	4.5	<0.0001	10.5	0.023	23	<0.0001
			Docetaxel + placebo	3.0		9.1		14	
Herbst, 2007 [47]	II	120	Docetaxel/pemetrexed + bevacizumab	4.8		12.6		12.5	
			Erlotinib + bevacizumab	4.4		13.7		17.9	
			Docetaxel/pemetrexed	3.0		8.6		12.2	

Data are presented as n, unless otherwise stated. PFS: progression-free survival; OS: overall survival; LD: low dose; HD: high dose.

evaluated the combination of erlotinib and bevacizumab, along with standard chemotherapy. Median OS was better with combined erlotinib and bevacizumab compared to chemotherapy alone (13.7 months *versus* 8.6 months, respectively), along with a better safety profile. However, a phase III trial conducted by the same group comparing combined erlotinib and bevacizumab *versus* erlotinib plus placebo in 636 nonsquamous cell NSCLC refractory patients, where >90% of the patients were *EGFR* wild-type and >75% were *K-Ras* wild-type, gave conflicting results. No significant difference was seen for the primary end-point (HR 0.97, p=0.7583), although a nonsignificant trend for benefit in PFS and response rate was apparent. Subgroup analysis did not identify statistical significance nor any predictive biomarkers [58].

Sunitinib, an oral tyrosine kinase inhibitor of VEGFR-PDGFR-KIT-FTL3-RET, has demonstrated some activity in phase II studies in NSCLC refractory patients [59]. This agent was evaluated in combination with erlotinib *versus* erlotinib plus placebo, targeting dual signalling by the EGFR and angiogenic pathways. *EGFR* status was unknown in >90% of the patients in both groups, but the majority of patients included were neither Asian nor never-smokers. The results show similar OS for both groups (9.0 months *versus* 8.5 months; HR 0.92, p=0.0471), PFS was 3.6 months *versus* 2.0 months (HR 0.80, p=0.0023) and response rate was 10.6% *versus* 6.9% (p=0.471) for combination therapy and erlotinib plus placebo treatment, respectively. The incidence of grade 3 toxicity was higher in the combination group [60]. Sorafenib, another multikinase inhibitor of VEGFR 2,3-PDGFR-RAF1-FLT3-cKIT that has demonstrated clinical benefit in NSCLC [61] and may represent, when combined with erlotinib, a means of dual inhibition of major lung cancer targets. Spigel *et al.* [62] conducted a phase II trial evaluating erlotinib in combination with sorafenib *versus* erlotinib plus placebo. In *EGFR* wild-type tumours, median PFS was 3.38 months for combination therapy *versus* 1.77 months for erlotinib plus placebo (p=0.018), median OS was 8.0 months *versus* 4.5 months (p=0.019) and response rate was 14% *versus* 0%, respectively, with similar results in EGFR FISH-negative patients. K-RAS was not found to be a good predictive biomarker in any subgroup. Although some benefits in *EFGR* wild-type and EGFR FISH-negative patients may merit further studies, it is important to note that combination treatment increased haematological, gastrointestinal, skin toxicity and general disorders. Furthermore, patient characteristics were not well balanced and the small number of patients in the control group makes it difficult to draw definitive conclusions.

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase downstream of the phosphoinositide 3-kinase (PI3K)/AKT/PTEN (phosphatase and tensin homologue) pathway, regulating cell growth and proliferation. The PI3K/AKT/PTEN/mTOR pathway is thought to be activated in NSCLC and provides a possible mechanism of resistance to EGFR TKIs [63, 64]. It has consequently been postulated that combination therapy of EGFR TKIs and mTOR inhibitors may be beneficial in this setting. Inhibition of this molecular target with everolimus, an oral mTOR inhibitor, has shown some activity in NSCLC as single agent, and has been studied in combination with EGFR TKIs for chemotherapy refractory NSCLC patients. In 2010, Price *et al.* [65] performed a phase II study evaluating the combination of gefitinib and everolimus in NSCLC in the first- and second-line settings, reporting a response rate of 9.6% and median OS of 11 months in pre-treated patients with a 1-year survival rate of 39%. In a phase II trial published in 2014 by Besse *et al.* [66], combination of erlotinib and everolimus treatment showed no benefit in terms of survival or PFS over erlotinib plus placebo, with an increased incidence of grade 3–4 events (72.7% *versus* 32.3%, and 31.8% grade 3–4 stomatitis with combination therapy). *EGFR* status was not assessed. On the basis of these trials, combination therapy did not add worthwhile benefit to EGFR TKIs in unselected populations.

The binding of ligand to the c-MET tyrosine kinase receptor activates downstream signalling involving the RAS pathway, promoting cell growth and proliferation. *MET* deregulation can be caused by overexpression, amplification or mutation, and has been found in several malignancies, including NSCLC, and predicts both resistance to EGFR TKIs and poorer survival [67]. Tivantinib, an oral MET inhibitor, was evaluated in a phase II study conducted by Sequist *et al.* [68] in combination with erlotinib in pre-treated NSCLC patients showing no survival benefit compared to erlotinib plus placebo. A significant PFS benefit was reported in *K-Ras*-mutated patients (HR 0.18, p<0.01).The phase III trial (n=1048) failed to meet its primary end-point in the total patient population (HR 0.98, p=0.81), but did show benefit in the subset of patients with MET expression (2+ positive MET immunostaining in >50% of tumour cells) with the combination therapy (HR 0.45, c-MET FISH >5) [69]. A humanised monovalent monoclonal antibody against the MET receptor, onartuzumab, has given modest benefit in combination with erlotinib in patients with high MET expression; the ongoing METLung phase III trial is evaluating this combination in patients with high MET expression in the second-line setting, and results should be available soon (NCT01456325). Other studies of combined erlotinib therapy over erlotinib plus placebo have been conducted, but none of them reported a benefit in terms of OS and PFS [70–72]. Table 3 summarises combination therapies with targeted and anti-angiogenic agents in second-line NSCLC.

DOI: 10.1183/16000617.00002115

TABLE 3 Combination therapy with targeted and anti-angiogenic agents in second-line nonsmall cell lung cancer

First author, year [ref.]	Phase	Patients	Arms	PFS months	p-value	OS months	p-value	Response rate %	p-value
Herbst, 2011 [58]	III	636	Erlotinib + bevacizumab	3.4		9.2		13	
			Erlotinib + placebo	1.7		9.3		6	
Scagliotti, 2012 [60]	III	960	Erlotinib + sunitinib	3.6	0.0023	9.0	0.1388	10.6	0.0471
			Erlotinib + placebo	2.0		8.5		6.9	
Spigel, 2011 [62]	II	168	Erlotinib + sorafenib	3.38	0.196	7.62	0.29	8.0	0.56
			Erlotinib + placebo	1.94		7.23		11.0	
Besse, 2013 [66]	II	133	Erlotinib + everolimus	2.9	0.228	9.1		12.1	
			Erlotinib	2.0		9.7		10.4	
Price, 2010 [65]	II	31	Gefitinib + everolimus			11.0		9.6	
Sequist, 2011 [68]	II	167	Erlotinib + tivantinib	3.8	0.24	8.5	0.47	10	NS
			Erlotinib + placebo	2.3		6.9		7	
Ramalingam, 2011 [70]	II	172	Erlotinib + R1507 weekly	1.9		8.1		8.8	
			Erlotinib + R1507 every 3 weeks	2.7	0.67	8.1	0.48	7.0	
			Erlotinib + placebo	1.5	0.73	12.1	0.04	8.8	

Data are presented as n, unless otherwise stated. PFS: progression-free survival; OS: overall survival; NS: non significant.

A recent meta-analysis of published data conducted by Qi *et al.* [73] evaluating combined targeted agents *versus* single-agent erlotinib, found benefits in OS (HR 0.9, p=0.024) and PFS (HR 0.83, p=0.018) favouring combination therapy over erlotinib alone, in *EGFR* wild-type and *K-Ras*-mutated patients. However, given that mutational status was rarely reported along with the limitations of a meta-analysis based on non-individual patient data, results must be interpreted with caution. In summary, combined targeted therapy may be a promising strategy in unselected NSCLC patients. Outcomes appear to be linked to mutational status, making identification of predictive biomarkers for patients more likely to benefit from the various target agents a crucial aspect of the treatment strategy for NSCLC.

Future perspectives

Over the past decade, evolving and improving knowledge of lung cancer biology has changed the previous paradigm based on histology-oriented treatment to one based on biomarker-driven therapy. To date, targeted therapy is restricted to only a few biomarkers, notably *EGFR* mutations and *ALK/ROS1* translocations. Additional drivers have been described and are being explored in NSCLC, such as *BRAF* V600E mutations (2%) that can be targeted with vemurafenib or dabrafenib [74], and mutations in *HER2* (3%) [75]. Thus, a proportion of patients who are qualified today as wild-type NSCLC may well be reclassified tomorrow and treated with specific targeted agents. In terms of moving towards a personalised therapy approach, there are several upcoming screening programmes using tumoural molecular profiling to guide patients as to access clinical trials using targeted therapies, such as the European Organisation for Research and Treatment of Cancer SPECTAlung (Screening Patients with thoracic tumors for Efficient Clinical Trial Access) study (NCT02214134).

Immunotherapy is another area of ongoing research that represents an alternative treatment approach for NSCLC patients. Evolving knowledge of the immune environment of lung cancer had led to NSCLC being considered an immunological targetable disease, with the consecutive development of several new drugs targeting immune checkpoint inhibition. Numerous immune checkpoints can be blocked in order to modulate and enhance the patient's natural immune response to cancer. Cytotoxic T-lymphocyte-associated protein (CTLA)-4 and programmed cell death protein (PD)-1 are the main targets which have been studied over the last few years. Both are expressed on activated T cells, and interact with ligands on antigen-presenting cells limiting the immune response.

A phase II study in the first-line setting evaluating platinum-based chemotherapy with ipilimumab, a fully humanised monoclonal antibody blocking CTLA-4, used two regimens, one concurrent and one sequential, reached the primary end-point in the ipilimumab sequential arm [76]. A prolonged immune-related PFS was seen compared with chemotherapy alone. Subgroup analysis found squamous cell patients had a greater improvement in PFS and in OS compared to those with nonsquamous histology. A confirmatory phase III trial in metastatic or recurrent squamous cell NSCLC patients is ongoing (NCT01285609).

Nivolumab (BMS-936558), a fully humanised monoclonal IgG4 antibody blocking PD-1, gave promising responses in a phase I study conducted by Topalian *et al.* [77] in advanced NSCLC patients, with a 32% ORR and an OS rate of 42% at 1 year. Rizvi *et al.* [78] evaluated the efficacy and safety of nivolumab in 117 patients with advanced refractory squamous NSCLC in a phase II single-arm trial, with an objective response confirmed in 14.5% of the patients, a median PFS of 1.9 months and a median OS of 8.2 months, which compare favourably to historical data of single cytotoxic agent efficacy in this population. Two phase III trials evaluating nivolumab *versus* docetaxel in nonsquamous cell (NCT01642004) and squamous cell (NCT01673867) patients in the second-line setting have been performed. The primary objective (OS) of the later trial has been reported as met in a recent press release [79]. Nivolumab has been approved in the USA for the treatment of squamous NSCLC patients refractory to chemotherapy and expended access programmes have been open in various countries. An antibody blocking programmed death-ligand (PD-L) 1 has also shown encouraging results in a phase I trial. Soria *et al.* [80] evaluated the safety and efficacy of MPDL3280A in 53 patients, with an ORR of 24% in all NSCLC patients, 100% in PD-L1-positive patients (n=4) and 15% in PD-L1-negative patients. Higher response rates were also seen in former/current smokers compared with never-smokers, making this the first study to suggest a potential relationship with smoking status and response to inhibitors of the PD-1 pathway. A phase III trial comparing MPDL3280A with docetaxel as second-line treatment is underway (NCT02008227).

Vaccines constitute an active form of immunotherapy which can be used to treat cancer, many of which are under investigation in NSCLC. TG4010, a vaccine based on a poxvirus that codes for MUC1 tumour-associated antigen and interleukin-2, was evaluated in a phase IIb trial in combination with standard first-line chemotherapy *versus* chemotherapy alone, in 148 patients with NSCLC expressing MUC1. This trial showed an improvement in its primary end-point PFS compared with the control group (6 months PFS 43.2% *versus* 35.1%, respectively) so that its activity could be explored in other settings, including combination with antibodies against PD-1 and PD-L1 [81]. A human recombinant EGF-based vaccine showed encouraging results in a phase II trial in the second-line setting with a trend towards increased survival [82]. Racotumomab, a ganglioside vaccine, is also currently being investigated in combination with docetaxel in the second-line setting (NCT01240447). Several other immunotherapies are under investigation with promising results.

Conclusions

Single-agent chemotherapy remains the most validated standard option in the second-line setting for NSCLC patients without any known driver mutations. Although combination chemotherapy treatment does not appear to prolong survival compared to single-agent therapies, it may nonetheless offer benefit in selected fit patients. Platinum rechallenge therapy only appears to be an effective approach in patients with late progression after first-line platinum chemotherapy. Integrating anti-angiogenic therapies into chemotherapeutic approaches in adenocarcinoma patients is a realistic option, although the optimal setting and sequences have yet to be defined. Combining targeted therapies result in promising efficacy but a recommended role is yet to be defined, mostly due to side-effects. A better understanding of which patients will obtain greater benefit from the different therapies and identification of reliable predictive biomarkers are critical. The continuing identification of novel oncogene drivers *via* improved diagnostic techniques and new-generation "liquid biopsies" which can be used to measure cell-free tumour DNA in the blood, offering a means of early detection of the tumoural mutational status, will provide the framework for the development of new targeted agents and selection of more efficient therapeutic approaches for individual patients.

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