Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Chemotherapy of advanced non-small-cell lung cancer: current landscape

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Non-small-cell lung cancer represents the leading cause of cancer-related death in the western world. Unfortunately, the majority of patients are diagnosed with advanced, unresectable disease that remains incurable, while most patients who are treated with curative intent will eventually develop metastatic disease. Improvements in our understanding of the molecular basis of lung cancer have led to the development of targeted agents resulting in a significant clinical benefit. At present, this benefit is confined only to patients with particular molecular tumor characteristics. For all patients, chemotherapy represents the backbone of treatment and is associated with a significant overall survival prolongation and quality of life improvement. The purpose of this paper is to present the current landscape of chemotherapy for advanced non-small-cell lung cancer.

Keywords: chemotherapy • first-line • NSCLC • second-line • treatment

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Lung cancer represents a major public health problem. It is estimated that approximately 1,600,000 new cases and 1,400,000 deaths occur every year worldwide [1]. It is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer diagnoses. Unfortunately, approximately 40% of patients with NSCLC are diagnosed with metastatic disease and most patients who are treated with curative intent will eventually develop metastases [2].

For patients with tumors harboring *EGFR* mutations or *ALK* gene rearrangements, the development of specific tyrosine kinase inhibitors such as erlotinib and gefitinib for EGFR and crizotinib for ALK has led to significant improvement in patient outcomes [3–5]. Unfortunately, this benefit is confined to a subgroup of molecularly selected patients. For patients with adequate performance status (PS), chemotherapy is considered the cornerstone of treatment as it offers a significant overall survival (OS) prolongation and quality of life (QoL) improvement [6–8]. The purpose of this paper is to present the current landscape of chemotherapy for NSCLC. The role of targeted therapies (erlotinib, gefitinib and crizotinib) in the treatment of advanced NSCLC will not be discussed in this review.

Search strategy & selection criteria

A bibliographic search of the Medline database was conducted for papers published from 1 January 2000 to 1 August 2012, with the keywords 'non-small-cell lung cancer', 'chemotherapy', 'cisplatin' 'carboplatin', 'gemcitabine', 'paclitaxel', 'docetaxel' 'pemetrexed' and 'vinorelbine'. The search was limited to articles written in English. When considering chemotherapy, only data from Phase III trials in advanced NSCLC were incorporated. The Medline search was supplemented by a manual search of meeting abstracts (World Conference on Lung Cancer, European Society of

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Medical Oncology Annual Congress, American Society of Clinical Oncology Annual Meeting and European Lung Cancer Conference) as well as reference lists of original and review articles.

Single-agent treatment versus two-drug combinations

Several randomized trials have addressed this question [9–13]. These trials demonstrated that doublets are superior to a single-agent treatment in terms of overall-response rate [ORR], progression-free survival (PFS) [9,10,12,13] and in some studies OS [10,12], no matter which newer agent was used (cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine or vinorelbine). However, a survival benefit was not observed in all studies [9,11,13]. Furthermore, combination treatment was associated with higher toxicity.

A published data-based meta-analysis by Delbaldo *et al.* further clarified this issue [14]. This meta-analysis included 57 trials with 11,160 patients and clearly demonstrated that the addition of a second drug to a single-agent regimen was associated with a statistically significant increase in the objective tumor response rate (Odds Ratio [OR]: 0.42; 95% CI: 0.37–0.47; $p < 0.001$), a significant increase in proportion of patients surviving 1 year (OR: 0.80; 95% CI: 0.70–0.91; $p < 0.001$; 5% absolute benefit with an increase of 1-year survival from 30 to 35%), as well as in median survival (median ratio: 0.83; 95% CI: 0.79–0.89; $p < 0.001$). Toxicity, as expected, was higher with doublet regimens.

Triplets versus doublets

Given that doublets were associated with better clinical outcome compared with single-agent treatment, a logical question was if triplets could result in even better outcome. Numerous Phase III randomized trials studied the role of triplets in first-line treatment of NSCLC (Table 1). Although three-drug combinations led to significantly higher response rates, these therapies in general failed to demonstrate any benefit in terms of PFS and OS, and were associated with significantly higher toxicity. A recently published Phase III study by Boni *et al.* randomly allocated 433 patients to one of four arms: gemcitabine–cisplatin, gemcitabine–vinorelbine, gemcitabine–ifosfamide–cisplatin or gemcitabine–ifosfamide–vinorelbine. Two comparisons were performed: platinum versus non-platinum containing regimens and triplets versus doublets [15]. Although triplet was associated with higher response rate (48 vs 35% for the doublet), median PFS (6.1 vs 5.5 months) and median OS (10.7 vs 10.5 months) were similar.

Two meta-analyses further addressed this issue [14,16]. Both analyses were consistent in demonstrating that although triplets improve response rate, this improvement does not lead to survival prolongation, while it is associated with higher toxicity. On the basis of these data, the American Society of Clinical Oncology (ASCO) recommends against the use of three cytotoxic drug combinations in the treatment of NSCLC [6].

Is there a superior regimen?

No single regimen has clearly demonstrated superiority in unselected patients with advanced NSCLC. Three different cooperative groups have conducted multiple-arm randomized trials comparing different platinum-based doublets [17–19]. The largest of these, from Eastern Cooperative Oncology Group (ECOG), randomized a total of 1155 patients to four arms: cisplatin–paclitaxel (control arm), cisplatin–gemcitabine, cisplatin–docetaxel and carboplatin–paclitaxel [17]. The trial failed to demonstrate any difference between the four arms in terms of response rate or OS. There were differences in the observed toxicities and the authors concluded that none of the doublets studied could be considered as the best treatment option.

An important Phase III trial was published by Scagliotti *et al.*, demonstrating a significant interaction between treatment efficacy and tumor histology [20]. This non-inferiority, Phase III study randomized 1725 chemotherapy-naive patients with stage IIIB/IV NSCLC to cisplatin–gemcitabine or cisplatin–pemetrexed. The intention-to-treat analysis trial failed to demonstrate any difference in terms of OS between the two arms (median survival: 10.3 vs 10.3 months, respectively; HR: 0.94; 95% CI: 0.84–1.05). However, a preplanned histology-specific subgroup analysis demonstrated that OS was superior for cisplatin–pemetrexed versus cisplatin–gemcitabine in patients with adenocarcinoma (n = 847; 12.6 vs 10.9 months, respectively; HR: 0.84; 95% CI: 0.71–0.99; $p = 0.03$) and large-cell carcinoma histology (n = 153; 10.4 vs 6.7 months, respectively; HR: 0.67; 95% CI: 0.48– 0.96; $p = 0.03$), while in patients with squamous cell histology, there was a significant improvement in survival in favor of cisplatin–gemcitabine versus cisplatin–pemetrexed (n = 473; cisplatin–pemetrexed vs cisplatin–gemcitabine: 9.4 vs 10.8 months, respectively; HR: 1.23; 95% CI: 1.00–1.51; $p = 0.05$). The differential efficacy of pemetrexed according to NSCLC histology was further confirmed by a review of Phase III trials [21]. This analysis confirmed a differential effect according to histology and demonstrated a survival benefit in patients with non-squamous histology [21]. A superior efficacy of pemetrexed in patients with non-squamous compared with other standard treatment options and a strong treatment by histology interaction was reported in a combined analysis of three Phase III trials [22]. On the basis of these results pemetrexed is now registered only for patients

with non-squamous histology [201]. This fact underlines the need for full definition of histology in pathology reports. NSCLC should not be considered as an acceptable pathology diagnosis any more.

The role of each third-generation (3G) agent (gemcitabine, paclitaxel, docetaxel, vinorelbine) in the treatment of advanced NSCLC was assessed in a meta-analysis by Grossi *et al.* (45 trials/11867 patients) [23]. This meta-analysis had both response and progressive disease rates as outcome measures and compared 3G containing doublets versus 3G free doublets. Although response rate was similar across different regimens, gemcitabine-containing regimens were associated with a significantly lower risk for progression (14% lower risk for PD; OR: 0.86; 95% CI: 0.77–0.95; p = 0.005). Docetaxel was associated with 9% lower risk for progressive disease, but this difference failed to reach statistical significance (OR: 0.91; 95% CI: 0.80–1.04; p = 0.16). On the contrary, paclitaxel containing regimens were connected to a 22% higher risk of PD (OR: 1.22; 95% CI: 1.09–1.37; p = 0.0008). There was no difference between vinorelbine-containing and vinorelbine-free regimens concerning the risk of progression.

Table 1. Randomized trials comparing triplets versus doublets for the treatment of advanced non-small-cell lung cancer.

Author	Regimen	Patients (n)	ORR (%)	Median survival	p value	Ref.
Boni *et al.*	G/P G/V G/P/If G/V/If	433	48 vs 35† months	10.7 vs 10.5† months	NS	[15]
Alberola *et al.*	P/G P/G/V	370	42 months 41 months	9.3 months 8.2 months	NS	[28]
Laack *et al.*	G/V G/V/P	287	13 months 28 months	8.3 months 7.5 months	NS	[29]
Comella *et al.*	P/V P/G P/G/V	180	25 months 30 months 47 months	8.1 months 9.7 months 11.8 months	0.04†, NS†	[115]
Danson *et al.*	C/G M/If/P M/Vin/P	372	30 months 33 months	8.5 months 8.7 months	NS	[116]
Comella *et al.*	G/V G/Pa P/G/V P/G/Pa	433	35 months 48 months	10.5 months 10.8 months	NS	[34]
Paccagnella *et al.*	P/Pa P/Pa/G	324	20.2 months 43.6 months	8.3 months 10.8 months	0.032	[117]
Comella	P/G P/G/Pa P/G/V	343	28 months 48 months 44 months	38 weeks 51 weeks 51 weeks	<0.05 for both	[118]

†2 × 2 design; results for triplets vs doublets.

C: Carboplatin; G: Gemcitabine; If: Ifosfamide; M: Mitomycin; NS: Non-significant; ORR: Overall-response rate; P: Cisplatin; Pa: Paclitaxel; V: Vinorelbine; Vin: Vinblastine.

Platinum-based versus platinum-free doublets

Numerous Phase III trials have evaluated platinum-free doublets (Table 2) as a less toxic alternative compared with platinum-based regimens [24–37]. Although these trials demonstrated similar results for platinum-based and platinum-free regimens, platinum-based treatment showed higher response rates and a trend towards better survival [26,27,30]. This observation was not confirmed in all studies [16,31].

Three meta-analyses addressed this issue. All three meta-analyses (Table 3) demonstrated a slightly higher 1-year survival for patients treated with the platinum-based doublets [38–40]. However, the meta-analysis by D'Addario *et al.* found a non-statistically significant increase in 1-year survival when platinum therapies were compared with platinum-free third-generation-based combination regimens [39]. All three meta-analyses demonstrated higher response rate and higher toxicity for the platinum-based arm [38–40].

On the basis of these meta-analyses, current ASCO guidelines for NSCLC supports that platinum-based doublets should be preferred over non-platinum ones because of their higher response rate and their marginal OS superiority [6].

Cisplatin versus carboplatin

In an attempt to circumvent cisplatin-induced toxicities, carboplatin, another platinum analog, was developed for clinical use [41]. Several randomized Phase III trials have compared cisplatin with carboplatin-based regimens [42–44]. The evidence suggests that cisplatin is associated with higher response rate with a trend towards longer PFS and OS, an observation that raised concerns about whether carboplatin has equivalent efficacy to cisplatin or not [45]. On the other hand, it should be noted that differences in PFS and OS were moderate with debatable clinical relevance.

An individual patient data meta-analysis by Ardizzoni *et al.* (nine trials with 2968 patients) reported a median survival of 9.1 months and a 1-year survival probability of 37% for cisplatin-treated patients while

Table 2. Platinum-based versus platinum-free regimens in first-line treatment of non-small-cell lung cancer.

Author	Regimen	Patients (n)	Median PFS	Median OS	p value	1-year survival (%)	Ref.
Boni *et al.*	G/P G/V G/P/If G/V/If	433	4.9 vs 6.4† months	9.7 vs 11.3† months	0.044	NR	[15]
Georgoulias *et al.*	D/P D/G	441	9.5 months 8 months	10 months 9.5 months	NS	NR	[24]
Kosmidis *et al.*	Pa/C Pa/G	502	6.3 months 6.1 months	10.4 months 9.8 months	0.32	41.7 41.4	[25]
Gridelli *et al.*	G/V G/P P/V	501	17 weeks 22 weeks 22 weeks	32 weeks 38 weeks 38 weeks	0.08	NR	[26]
Smit *et al.*	G/P Pa/P Pa/G	490	5.6 months 4.4 months 3.9 months	8.9 months 8.1 months 6.7 months	NS	32.6 35.5 26.5	[27]
Alberola *et al.*	G/P G/P/V G/V–V/If	557	6.3 months 5.7 months	9.3 months 8.1 months	NS	38 34	[28]
Laack *et al.*	GVP GV	287	19.3 months 22.3 months	32.4 weeks 35.9 weeks	NS	27.5 33.6	[29]
Georgoulias *et al.*	V/P D/G	251	8.5 months 8 months	9.7 months 9 months	0.965	34.3 40.8	[30]
Tan *et al.*	V/P V/G	316	3.9 months 4.4 months	8.6 months 11.5 months	0.001	34.4 48.9	[31]
Kubota *et al.*	C/Pa VG→D	401	5.8 months 5.5 months	14.1 months 13.6 months	NS	55.5 55.6	[32]
Treat *et al.*	G/C G/Pa Pa/C	1135	NR	7.9 months 8.5 months 8.7 months	NS	NR	[33]
Comella *et al.*	P/G (V) G/Pa	433	6.1 months 5.5 months	10.7 months 10.5 months	NS	NR	[34]
Greco *et al.*	C/Pa/G G/V	337	6 months 3.9 months	10.3 months 10.7 months	NS	38 45	[35]
Pujol *et al.*	P/V G/D	311	4.0 months 4.2 months	9.6 months 11.1 months	NS	46 42	[36]
Stathopoulos *et al.*	C/Pa Pa/V	360	NR	11.0 months 10.0 months	NS	42.7 37.8	[37]

†2 × 2 design; results for platinum-based vs platinum-free.

C: Carboplatin; D: Docetaxel; G: Gemcitabine; If: Ifosfamide; NS: Non-significant; NR: Not reported; OS: Overall survival; P: Cisplatin; Pa: Paclitaxel; PFS: Progression-free survival; V: Vinorelbine.

the corresponding median OS and 1-year survival probability were 8.4 months and 34% for carboplatin-treated patients [46]. Carboplatin was associated with a higher risk of death, although the difference was not statistically significant (HR: 1.07; 95% CI: 0.99–1.15; p = 0.100). In a subset analysis, this difference was significant in favor of cisplatin in patients treated with third-generation regimens (HR: 1.11; 95% CI: 1.01–1.21). Cisplatin-based treatment was associated with more renal toxicity and nausea/vomiting; carboplatin-based regimens were associated with more thrombocytopenia. Two other meta-analyses demonstrated a higher response rate in favor of cisplatin but failed to demonstrate a statistically significant difference in terms of survival [47,48]. Patients treated with cisplatin had higher incidence of nausea and vomiting while thrombocytopenia was more frequent in

carboplatin-treated patients. No significant difference in treatment-related mortality was observed [47].

Finally, a meta-analysis by Matsuda *et al.* focused on QoL and demonstrated that carboplatin use was associated with better QoL than cisplatin [49].

On the basis of these results ASCO recommends the use of cisplatin over carboplatin whenever it is possible [6].

Newer cytotoxic agents

The combination of solvent-based paclitaxel plus carboplatin represents one of the most commonly used doublets in the first-line treatment of NSCLC, with an ORR of 15–28% and a median OS of 8.0–10.7 months [50–52]. Nab-paclitaxel is a new, albumin-bound formulation of paclitaxel. Preclinical models suggested that nab-paclitaxel may reach the tumor microenvironment more efficiently than solvent based-paclitaxel [53]. Furthermore, this formulation allows the administration of paclitaxel without the use of lipid-based solvents and the need for corticosteroid and antihistamine premedication. A recent Phase III trial with 1052 NSCLC patients compared the efficacy and safety of nab-paclitaxel plus carboplatin with solvent-based paclitaxel plus carboplatin [54]. ORR (primary end point) was significantly higher in the nab-paclitaxel arm (33 vs 25%; p = 0.005), but no difference was observed in PFS and OS. Elderly patients (≥ 70 years) showed a significantly increased OS with nab-paclitaxel. Patients in the nab-paclitaxel arm experienced significantly less grade ≥3 neuropathy, neutropenia, arthralgia and myalgia, but higher thrombocytopenia and anemia. On the basis of this trial nab-paclitaxel is registered for first-line treatment in NSCLC.

Eribulin mesylate is a halichondrin B analogue that inhibits microtubule dynamics by interacting with a distinct binding site on â-tubulin leading to G(2)/M phase cell-cycle arrest and apoptosis [55]. In NSCLC eribulin has been tested as second/third line treatment in the context of Phase II trials [56,57]. Median OS in eribulin-treated patients has been reported as 9.4 months in an unselected population and varies according to taxane sensitivity: 12.6 months in taxane-sensitive disease versus 8.9 months in taxane-resistant disease. An ongoing Phase III trial is comparing eribulin with a treatment of the physician's choice (pemetrexed, docetaxel, vinorelbine, gemcitabine) [202].

Treatment duration

Administration of the initial chemotherapy doublet for more than four to six cycles is associated with a clinically substantial and statistically significant 25% decrease in the relative risk for progression as compared with a standard duration of chemotherapy (HR: 0.75; 95% CI: 0.69–0.81; p < 0.00001) [58]. This treatment also leads to a statistically significant 8% reduction in the relative risk of death as compared with a standard duration of chemotherapy (HR: 0.92; 95% CI: 0.85–0.99; p = 0.03). The magnitude of survival benefit is modest at the expense of increased toxicity. Therefore, extending treatment beyond four to six cycles with platinum doublets is not recommended [6]. Similar results were observed by a meta-analysis by Lima *et al.* [59]. This meta-analysis concluded that administration of more than four cycles of first-line chemotherapy with third-generation regimen was associated with a PFS benefit but not with improvement of OS, at the cost of higher incidence of adverse events.

It should be noted that continuation of treatment with a contemporary single-agent (pemetrexed, erlotinib) after four to six cycles of induction chemotherapy,

Table 3. Meta-analyses comparing platinum-based versus platinum-free doublets as first-line treatment in non-small-cell lung cancer.

Study	Studies/patients	OR for 1-year survival	95% CI	p value	Toxicity	Ref.
Pujol *et al.*	11/4602	0.88†	0.78–0.99	0.044	Higher incidence of grade III–IV gastrointestinal and hematological toxicity for platinum-based treatment. No difference in the risk of febrile neutropenia and the incidence of treatment-related deaths	[38]
D'Addario *et al.*	37/7633	1.21	1.09–1.35	<0.0003	Higher incidence of anemia; neutropenia; thrombocytopenia; renal toxicity; nausea/vomiting for platinum-based treatment. No statistically significant difference for neurotoxicity, febrile neutropenia, and toxic death rate	[39]
Rajeswaran *et al.*	17/4792	1.08	1.01–1.16	0.03	Platinum-based doublets associated with higher risk for anemia, nausea/vomiting and neurotoxicity	[40]

†OR for the risk of death.
OR: Odds ratio.

which is called maintenance treatment, may be of value for some NSCLC patients [60].

Bevacizumab

Development of new blood vessels, known as angiogenesis, is considered as crucial in the development process of solid tumors and in the growth of secondary metastasis [61]. In this process, VEGF plays a major role in the formation of new blood vessels in both normal and tumor angiogenesis [62]. Bevacizumab is a recombinant, humanized, monoclonal antibody against VEGF [63]. Bevacizumab has been tested in combination with chemotherapy as a first-line treatment in advanced NSCLC, in the context of two Phase III trials ECOG 4599 study [51] and AVAiL study [64]). In both trials bevacizumab was continued after the end of chemotherapy until progression or unacceptable toxicity. Both trials demonstrated a significant PFS prolongation, while an OS benefit was observed only in the ECOG trial [51]. However, it should be noted that the primary end point of the AVAiL study was PFS and the trial was not powered for OS [64]. The ECOG4599 trial used a dose of 15 mg/kg [51], while the AVAiL trial tested two different doses (7.5 mg/kg and 15 mg/kg) and demonstrated positive results for both [64]. Therefore, the issue of the optimal dose of bevacizumab is not yet determined. Bevacizumab trials excluded a number of patients with certain clinical characteristics due to significant risk of hemorrhage (squamous histology, history of hemoptysis [>0.5 teaspoon of bright red blood per event]; brain metastases; positive history of thrombotic or hemorrhagic disorders; treatment with anticoagulants; tumors invading or abutting major blood vessels; clinically significant cardiovascular disease; or medically uncontrolled hypertension). Therefore, discrimination between squamous and non-squamous histology is required for safety reasons in the case of bevacizumab treatment. The feasibility and safety of bevacizumab has been further tested in two Phase IV trials (SAiL [65] and ARIES trials [66]).

Cetuximab

EGFR is a member of the HER family of transmembrane receptors [67]. Binding of ligands to the extracellular domain of EGFR results in the initiation of an intracellular signaling downstream pathway that affects cell proliferation, motility and survival [67]. Cetuximab is a monoclonal antibody that competes with the ligands for the extracellular binding domain of EGFR. Cetuximab has been tested in combination with chemotherapy as first-line treatment in advanced NSCLC. A Phase III trial with 1125 NSCLC patients with EGFR immunohistochemistry-positive tumors compared chemotherapy (cisplatin/vinorelbine) versus the same regimen plus cetuximab (FLEX trial) [68]. The trial yielded an identical PFS between the two arms (4.8 vs 4.8 months), and a modest, although statistically significant OS prolongation (11.3 vs 10.1 months; $p = 0.044$) [68]. The same group recently developed an EGFR immunohistochemistry expression score in order to define patients benefiting most from cetuximab [69]. According to this score, patients with high expression (h-score >200) had an OS benefit (median OS cetuximab vs chemotherapy: 12.0 vs 9.6 months; HR: 0.73; 95% CI: 0.58–0.93; $p = 0.011$), while no difference was observed in patients with low EGFR expression (median OS: 9.8 vs 10.3 months; HR: 0.99; 95% CI: 0.84–1.16; $p = 0.88$). A second Phase III trial (BMS099 study) compared carboplatin based doublets (either paclitaxel or docetaxel) with or without cetuximab as first-line treatment but failed to show any benefit in terms of PFS or OS [70]. On the basis of these results cetuximab was not registered by EMEA for first-line treatment.

Patient populations with special considerations: elderly patients

Due to the aging of the Western world population, there is a significant increase in the number of older patients diagnosed with NSCLC. Almost 50% of new NSCLC diagnoses occur in patients older than 65 years and 30–40% of diagnoses in patients older than 70 years [71]. Despite this high incidence in older patients, these patients are generally under-represented in clinical trials due to considerations for increased toxicity [72]. Chemotherapy efficacy in the elderly is similar to that in younger patients and age has not been established as a negative prognostic factor for survival [73].

Prospective, randomized Phase III trials (Table 4) [74–78] have clearly demonstrated that single agent chemotherapy offers a survival benefit versus best supportive care in older NSCLC patients [74]; however, the role of combination regimens remains a subject of debate [75,77]. The South Italian Cooperative Oncology Group (SICOG) reported a significant OS prolongation in favor of the vinorelbine–gemcitabine doublet compared with single-agent vinorelbine [75], while a similarly designed much larger Phase III trial, the Multicenter Italian Lung Cancer in the Elderly Phase III trial, failed to yield any benefit in favor of vinorelbine–gemcitabine doublet compared with either single agent [77]. The conflicting results between the SICOG [75] and the Multicenter Italian Lung Cancer in the Elderly Phase III [77] trials could be due to differences regarding number of patients enrolled in these trials. The SICOG trial reported a very poor median survival of 18 weeks for patients treated with single-agent vinorelbine, unusually

lower than the 28 weeks median survival reported for vinorelbine monotherapy in Phase III trials for elderly populations [74,77] and similar to that reported for best-supportive-care arm of the ELVIS trial [74].

Conflicting results also exist regarding the role of platinum-based doublets in the treatment of elderly NSCLC patients. A recently published Phase III trial reported by Quoix *et al.* with 451 elderly patients demonstrated that a combination regimen of monthly carboplatin with weekly paclitaxel offers a significant PFS and OS prolongation compared with single-agent treatment with either vinorelbine or gemcitabine [78]. On the contrary, a Phase III trial reported by a Japanese group at the ASCO Annual 2011 Meeting, comparing a combination regimen of weekly docetaxel plus weekly cisplatin versus single-agent docetaxel, failed to demonstrate any benefit for the combination regimen [79]. Although single-agent treatment is recommended for elderly patients [80], a carboplatin-based doublet should be considered for fit patients based on the results of the IFCT trial [78].

Table 4. Prospective, elderly-specific, randomized Phase III trials.

Treatment	Patients (n)	PFS	p value	OS	p value	1-year OS (%)	Ref.
ELVIS							
VNB	78	–	–	28 weeks	–	32	[74]
BSC	76	–	–	21 weeks	0.03	14	
SICOG							
VNB	60	–	–	18 weeks	–	13	[75]
VNB/GMB	60	–	–	29 weeks	–	30	
WJTOG 99004							
VNB	92	3.1 months	–	9.9 months	–	36.7	[76]
D	90	5.5 months	<0.001	14.3 months	0.138	58.6	
MILES							
VNB	233	18 weeks	–	36 weeks	0.93†	38	[77]
GMB	233	17 weeks	–	28 weeks	0.65†	28	
VNB/GMB	232	19 weeks	–	30 weeks	–	30	
IFCT-0501							
Single agent (VNB or GMB)	226	3.0 months	$<10^{-6}$	6.2 months	0.00004	–	[78]
wPa/mC	225	6.1 months		10.3 months	–	–	
JCOG0803/WJOG4307							
D	137	4.4 months	0.37	14.8 months	0.824	58.2	[79]
D/C	139	4.7 months		13.3 months	–	54.5	

†Versus combination treatment.

BSC: Best supportive care; C: Cisplatin; D: Docetaxel; GMB: Gemcitabine; mC: Monthly carboplatin; OS: Overall survival; PFS: Progression-free survival; VNB: Vinorelbine; wPa: Weekly paclitaxel.

Important differences also exist with regard to recommended first-line chemotherapy in NSCLC patients with performance status of two (PS2) [81]. These patients were typically included as a small fraction of participants in large Phase III chemotherapy trials, therefore, recommendations specific for this subset are not based on well-powered comparisons. At ASCO 2012, Lilenbaum and colleagues presented the results of a Phase III trial comparing first-line pemetrexed versus carboplatin-pemetrexed exclusively in PS2 patients [81]. A significant survival advantage was found in favor of combination therapy (response rates of 24 vs 10.5%, respectively; median OS: 9.1 vs 5.6 months, respectively; HR: 0.57; 95% CI: 0.41–0.79; p = 0.001). Therefore, combination of platinum-based chemotherapy might be considered as first-line treatment of advanced NSCLC with PS2.

Second-line treatment

All NSCLC patients who respond to first-line treatment will inevitably experience tumor progression and at that time many patients will be fit and suitable for second-line treatment.

The potential benefits of second-line chemotherapy with docetaxel were evaluated in a randomized Phase III trial that demonstrated a time-to-progression and an OS prolongation over placebo [82]. This study established single-agent docetaxel as the standard second-line treatment and as standard comparator arm for subsequent randomized trials.

Pemetrexed is another active agent tested in second-line treatment. A noninferiority Phase III study that compared docetaxel with pemetrexed yielded a non-significant difference in OS and 1-year survival, while pemetrexed was associated with a more favorable toxicity profile [83]. This trial led to the approval of pemetrexed in the second-line treatment of NSCLC. It should be underlined that the use of pemetrexed should be limited to patients with non-squamous histology.

Finally, erlotinib has received approval by health authorities as second-line line treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen on the basis of the results of the BR.21 trial, a Phase III trial by the National Cancer Institute of Canada [84]. Patients treated with erlotinib experienced significantly longer PFS and OS over placebo. Thus, docetaxel, erlotinib or pemetrexed are the only approved agents

and could be considered as 'standard' choices for second-line therapy.

The results of second-line treatment with the above agents are generally poor, with response rate of less than 10% and OS of 6–8 months [82–84]. One logical approach to improve these results is to evaluate combination regimens. Several randomized trials have assessed the role of combination regimens in second-line treatment but failed to demonstrate an OS benefit in favor of doublets [85–87]. This observation was further confirmed by a meta-analysis by Di Maio *et al.* [88]. This meta-analysis was based on individual data of 847 patients and compared the efficacy of a doublet chemotherapy regimen with single agent treatment as second-line treatment. The conclusion was that although combination treatment was associated with significantly higher response rate and significant prolongation of PFS, this difference was not translated into a significant survival benefit. Additionally, patients receiving combination treatment experienced significantly more toxicity. On the basis of these results, single agent treatment is considered the standard of care for second-line treatment.

The impact of second-line treatment on QoL was studied in a systematic review by Canguli *et al.* [89]. According to this report, significant improvements in overall QoL with second-line treatment were infrequent.

Maintenance treatment

Despite the 'standard' first-line treatment with four to six cycles of platinum-based doublet, prognosis for these patients remains poor, with 5-year survival rate <5% [90] and a median OS of approximately 1 year [20,51,64,68]. An approach tested in order to optimize treatment in NSCLC was maintenance treatment; that is, the continuation of treatment at the end of a definite number of chemotherapy cycles [91]. Two different approaches have been tested: either continuing an agent that was part of the initial treatment regimen (continuation maintenance) or initiating another agent before disease progression, after a defined number of cycles of the initial treatment regimen (switch maintenance) [91].

Numerous randomized Phase III trials using modern cytotoxic and targeted agents have evaluated both the continuation and the switch-maintenance approach (Table 5). All these trials have clearly demonstrated that maintenance treatment (either continuation or switch) significantly prolongs PFS [92–102], while some of these studies also demonstrated a survival benefit in favor of the maintenance treatment [96,97,103]. Based on these trials, pemetrexed and erlotinib have recently been registered as maintenance treatment by both the US FDA and European Medicines Agency. It should be noted that the use of pemetrexed should be limited to patients with non-squamous histology. However, despite the extensive research in the field of maintenance treatment, a number of significant questions remain to be answered. It is not clear from the recent switch-maintenance studies whether the benefit seen could be considered as a result of the early institution of non-cross-resistant therapy (maintenance arm) over the control arm (treatment at document progression) [60]. The docetaxel (early vs delayed) maintenance study by Fidias *et al.* that specifically reported the outcomes of control patients who actually received docetaxel, showed no survival difference. Although this might be a biased analysis (because it selects patients with a less aggressive and more indolent course of disease in the control arm), it may imply that timing is less important than the ability to really administer second-line therapy at time of progression [104]. Furthermore, the above switch maintenance studies [95–99,102] are criticized because only a relatively small percentage of patients in the placebo arm (ranging between 18 [96] and 62% [95]) crossed over to active, while a substantial percentage of patients did not receive any kind of second-line therapy. Unlike studies of new truly experimental drugs, where the efficacy of the experimental agent is unknown, these studies used as maintenance treatment agents with known and proved efficacy in patients who have progressed after treatment with platinum-based chemotherapy [105]. The IFCT-0502 study is very important in that respect, with more than 90% of patients in the control group actually receiving second-line treatment and this trial failed to demonstrate any survival benefit (it should be noted that the trial had PFS as primary end point and, therefore, was not powered for OS differences) [99]. On the other hand, it should be noted that in clinical practice only 50–60% of patients are expected to receive second-line treatment. In the vast majority of cases the reason for not administering second-line treatment is rapid disease progression. This suggests that some patients can safely receive a treatment break, while others will experience a rapid disease progression and will not be able to receive second-line treatment, and perhaps maintenance treatment is the most effective way to deliver second-line therapy [60]. Unfortunately, we lack a reliable tool to identify patients who will rapidly progress and might potentially benefit from maintenance therapy.

Continuation maintenance trials have all showed a PFS benefit but only the PARAMOUNT trial demonstrated a survival benefit [103]. A meta-analysis by Behera *et al.* (12 studies/4286 patients) demonstrated that single-agent maintenance treatment was associated with an OS (HR: 0.86; 95% CI: 0.80–0.92; $p = 0.0003$) and PFS benefit (HR: 0.80; 95% CI: 0.77–0.84; $p < 0.0001$) [106]. Switch maintenance resulted in

Table 5. Randomized Phase III trials of maintenance treatment in non-small-cell lung cancer.

Study	Induction chemotherapy	Maintenance chemotherapy	Patients (n)	PFS	p value	OS (months)	p value	Ref.
Brodowicz *et al.*	CDDP/GMB	GMB Placebo	138 68	3.6 months 2.0 months	<0.001	10.2 8.1	0.172	[92]
Belani *et al.*	Carboplatin/ GMB	GMB Placebo	128 127	7.4 months 7.7 months	NR	8.0 9.3	0.84	[93]
PARAMOUNT	CDDP/PEM	PEM Placebo	359 180	4.1 months 2.8 months	0.00025	13.9 11.0	0.019	[94,103]
Fidias *et al.*	Carboplatin/ GMB	Docetaxel Placebo	153 156	5.7 months 2.7 months	0.0001	12.3 9.7	0.0853	[95]
JMEN	Platinum-based doublet	PEM Placebo	441 222	4.0 months 2.0 months	<0.0001	13.4 10.6	0.012	[96]
SATURN	Platinum-based doublet	Erlotinib Placebo	438 451	12.3 weeks 11.3 weeks	<0.0001	12.0 11.0	0.0088	[97]
ATLAS	Platinum-based doublet	Bev/erlotinib Bev/placebo	370 373	4.76 months 3.71 months	0.0006	14.39 13.31	0.5604	[98]
IFCT-GFPC 0502	CDDP/GMB	Erlotinib Placebo GMB	155 155 154	2.8 months 2.1 months 3.8 months	0.002 <0.0001	11.4 10.8 12.1	0.30 0.34	[99]
EORTC 08021-ILCP 01/03	Platinum-based doublet	Gefitinib Placebo	86 87	4.1 months 2.9 months	0.002	10.9 9.4	0.204	[100]
WJTOG0203	Platinum-based doublet	Gefitinib Platinum-based doublet	300 298	4.6 months 4.3 months	<0.001	13.7 12.9	0.11	[101]
INFORM	Platinum-based doublet	Gefitinib Placebo	148 148	4.8 months 2.6 months	<0.0001	18.7 16.9	0.2608	[102]
AVAPERL	CDDP/PEM/Bev	Bev PEM/Bev	125 128	6.6 months 10.2 months	<0.001	No mature data yet		[119]

Bev: Bevacizumab; CDDP: Cisplatin; GMB: Gemcitabine; NR: Not reported; OS: Overall survival; PEM: Pemetrexed; PFS: Progression-free survival.

both OS (HR: 0.84; 95% CI: 0.77–0.91; p = 0.00026) and PFS significant prolongation (HR: 0.62; 95% CI: 0.57–0.67; p < 0.0001), while continuation maintenance did not result in OS benefit (HR: 0.927; 95% CI: 0.78–1.09; p = 0.33).

Another important question is should all patients receive maintenance treatment? The major disadvantage of the maintenance approach is that it constrains patient to continuous treatment without treatment breaks in a disease in which the primary goal of treatment is palliation, and although the incidence of grade III/IV toxicities in maintenance treatment was low, a prolonged exposure of patients to grade I/II toxicities may have a negative impact on patients QoL [107]. Can we select patients for maintenance treatment on the basis of unequivocal response to first-line treatment? Unfortunately, results are conflicting with switch maintenance trials demonstrating greater benefit for patients with stable disease [96,97] while in the PARAMOUNT study greater benefit was observed in responders [94].

Finally, the issue of using EGFR tyrosine kinase inhibitors as maintenance treatment in unselected NSCLC patients remains questionable [60]. Although both SATURN [97] and INFORM trials [102] reported a statistically significant PFS benefit for the intention-to-treat population (SATURN: HR: 0.71; 95% CI: 0.62–0.82; p < 0.0001; INFORM: HR: 0.42; 95% CI: 0.32–0.54; p < 0.0001), this benefit was primarily driven by EGFR activating mutations positive with striking HR in both trials in favor of EGFR mutation positive patients (SATURN: HR: 0.10; 95% CI: 0.04–0.25; p < 0.0001; INFORM: HR: 0.17; 95% CI: 0.07–0.42; p = not reported). Similarly, the biomarker analysis of the ATLAS trial reported a significant benefit in terms of PFS in patients with tumors bearing *EGFR* mutations in the erlotinib arm (HR: 0.44) [108].

Customized chemotherapy

Basic and translational research results indicated a number of tumor-based biomarkers that could serve as indicators of sensitivity or resistance to chemotherapy.

These markers mainly include expression of a number of genes of DNA repair or nucleotide metabolism, such as *ERCC1*, *RRM1*, *BRCA1* and thymidylate synthase. Detailed description of these markers and preclinical evidence for their potential use in the clinic is beyond the scope of this paper and can be found elsewhere [109,110]. The optimal biomarker selection for clinical testing, platform of testing (mRNA vs protein level) and cut-off points are still under investigation.

The first large Phase III randomized clinical trial assessing the role of customized chemotherapy in advanced NSCLC was conducted by the Spanish Lung Cancer Study Group [111]. In this study, 444 patients from 24 European centers were randomly allocated to control arm of first-line docetaxel and cisplatin versus genotypic arm based on ERCC1 mRNA expression. Patients with low ERCC1 expression received docetaxel and cisplatin whereas those with high expression received docetaxel and gemcitabine. Although response rate was higher in the genotypic arm (51 vs 38%; p = 0.019) PFS and OS was not different (median PFS of 6.1 and 5.2 months in genotypic and control arm, respectively; median OS: 9.9 and 9.8 months, respectively). This trial was able to demonstrate the feasibility of ERCC1 expression evaluation by quantitative RT-PCR on a large scale in a multi-institutional setting.

Several other important Phase II clinical trials have been conducted in advanced NSCLC with ERCC1 and other markers suggesting superior efficacy of cytotoxics in patients allocated to chemotherapy based on their genetic profile [112,113]. Based on preliminary evidence, two important Phase III clinical trials with customized chemotherapy are ongoing [203,204]. Before using these markers in practice, the proof of their utility must be obtained through such Phase III comparative studies.

Conclusion

Cytotoxic chemotherapy still represents the backbone of treatment for the vast majority of NSCLC patients. Although several new cytotoxic agents have been introduced in the treatment of NSCLC during the last decade, only small improvements in the survival of patients with advanced/metastatic lung cancer have been observed. It is clear that chemotherapy has reached a plateau of activity in the treatment of NSCLC and further improvement in treatment is likely to require integration of novel targeted therapies [114].

Future perspective

Although targeted agents are the first option for a subgroup of NSCLC patients, the majority of patients are still treated with cytotoxic chemotherapy. Although several new active cytotoxic agents have been introduced during the last decade, these agents have not led to a substantial prolongation of survival and the prognosis of these patients remains poor, with a median OS of approximately 1 year. Hopefully, advances in our understanding of molecular features associated with sensitivity or resistance to cytotoxic agents and their integration with novel targeted therapies will lead to substantially better outcomes of patients with this devastating disease.

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Executive summary

- For patients with advanced non-small-cell lung cancer with no *EGFR* mutations, first-line chemotherapy doublets are the standard of care.
- Chemotherapy doublets are superior to single-agent treatment in first-line treatment and three-drug combinations do not offer any benefit in terms of overall survival compared with two-drug regimens.
- Platinum-based doublets are preferred over platinum-free doublets because they are associated with a modest 1-year survival benefit. Platinum-free regimens represent an alternative in patients who cannot tolerate platinum-based treatment.
- Cisplatin is associated with a moderately lower risk of death compared with carboplatin at the expense of a different toxicity profile and less convenient administration. Cisplatin should be considered as a preferred option for patients with no contraindications to this cytotoxic agent.
- Treatment with the initial chemotherapy regimen for more than four cycles is associated with a progression-free survival (PFS) benefit but only a moderate overall-survival prolongation; therefore, four cycles represent the standard of care.
- Maintenance therapy provides a PFS benefit; however, survival benefit of this strategy remains debatable due to mixed results of clinical trials and limited data on comparisons with early second-line treatment.
- In second-line treatment, combination regimens offer a PFS prolongation but no overall survival benefit over single-agent therapy; therefore, single-agent treatment is the gold standard. Docetaxel, pemetrexed and erlotinib are the registered agents for second-line therapy.

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