2010 Consensus on Lung Cancer, new clinical recommendations and current status of biomarker assessment – First-line therapy

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Introduction

Lung cancer is the most common cancer in the world, and by 2008, there were an estimated 1.6 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.3 million deaths (18.2% of the total) [1]. Every year, in Europe, more than 200,000 new cancer cases are diagnosed, accounting for around 20% of all cancer deaths [2]. Non-small cell lung cancer (NSCLC), including squamous carcinoma, adenocarcinoma and large cell carcinoma, accounts for about 85% of all lung cancer types. The majority of patients diagnosed with NSCLC are unsuitable for surgery since most of them have advanced disease at diagnosis. Unfortunately, in this setting, the prognosis is very poor with a five-year survival <1% and palliative chemotherapy and/or radiotherapy being the standard of care, with the main endpoints represented by the improvement of survival and the relief of disease symptoms. However, chemotherapeutic agents at this stage of the disease seem to have reached a plateau with no doublet combination having a clinically superior result compared with the others [3–5]. These plateaux of effectiveness have led to an increase in the research into understanding cancer biology, with major progress made in recent years towards the mechanisms of oncogenesis, which has allowed the development of novel therapeutic agents that specifically target growth factor pathways dysregulated in tumour cells. Targeting the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways has played a central role in advancing NSCLC research, treatment, and patients' outcome over the last few years. Several targeted agents have been introduced in clinical trials in NSCLC and a series of phase 3 studies have already produced definitive results with some new biological agents already being used in clinical practice. Retrospective analyses and subsequent prospective studies have taught us how to identify patients who can most benefit from this therapy. All these developments have led to a better definition of the first-line approach, addressing the treatment on the basis of clinical (smoker status, sex, age, performance status [PS] and ethnicity), histological (squamous and non-squamous) and biological (*EGFR* mutation status) characteristics of patients.

Here we will discuss the new evidence in the first-line treatment of advanced NSCLC, focussing in particular on the role of patients and tumour characteristics in the current clinical decision-making.

The role of *EGFR* mutation status

NSCLC is characterised by a high expression, about 40–80%, of the EGFR, which is an important mediator in cell growth, differentiation and survival [6]. Two classes of EGFR antagonists have been successfully tested in phase 3 trials: the anti-EGFR monoclonal antibody, cetuximab, and the small-molecule EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib. Both these two small molecules are administered daily orally.

The first evidence of the important role of the *EGFR* mutations was highlighted in 2004 when several groups showed a high percentage of objective response rates (ORR) in patients affected by advanced NSCLC harbouring activating somatic mutations in the *EGFR* gene and treated with EGFR-TKIs [7–10]. The mutations described were small in-frame deletions or amino-acid substitutions clustered around the ATP-binding pocket of the *EGFR* tyrosine kinase domain (in exons 18, 19 and 21). Their frequency was shown to be low in unselected Western patients with advanced NSCLC, but, interestingly, these mutations appeared to be much more frequent in Japanese and East Asian populations. Furthermore, it was also evident that some clinical or pathological characteristics were associated with a higher prevalence of mutation: in detail, the *EGFR* mutation is more frequent in never-smokers, in women, and in patients with adenocarcinoma. Considering these reports, several

Table 1
Phase III randomised trials investigating EGFR-TKIs as the first-line therapy of advanced NSCLC

Author	Selection criteria	Treatment	No. of patients	ORR (%)	PFS (months)	OS (months)
Mok, 2009 [19,24]	Clinical	Gefitinib	609	43	5.7	18.6
		vs				
		CBDCA+PAC	608	32.2	5.8	17.3
Lee, 2009 [20]	Clinical	Gefitinib	159	53.5	6.1	21.3
		vs				
		CDDP+GEM	150	43.5	6.6	23.3
Mitsudomi, 2010 [21]	*EGFR* mutations	Gefitinib	86	62.1	9.2	30.9
		vs				
		CDDP+DOC	86	32.2	6.3	nr
Maemondo, 2010 [22]	*EGFR mutations*	Gefitinib	114	73.7	10.8	30.5
		vs				
		CBDCA+PAC	114	30.7	5.4	23.6
Zhou, 2010 [23]	*EGFR* mutations	Erlotinib	82	83	13.1	nr
		vs				
		CBDCA+GEM	72	36	4.6	

EGFR-TKIs: epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC: non-small cell lung cancer; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; CBDCA: carboplatin; PAC: paclitaxel; CDDP: cisplatin; GEM: gemcitabine; DOC: docetaxel; nr: not reached.

small trials were conducted to test gefitinib or erlotinib as the first-line treatment of patients selected for the presence of *EGFR* mutations [11–15], or selected according to other clinical or molecular putative predictive factors [16,17]. The results coming from these preliminary trials were very promising.

Overall, the clinical features, such as female gender, adenocarcinoma histology, Asian ethnicity and never-smoking history, which are greatly associated with response to an EGFR-TKI, are more frequently correlated with these mutations. So, among the clinical and molecular predictors of activity, *EGFR* mutations, in exons 18, 19 and 21, to date have constituted the most important prognostic/predictive molecular factor for NSCLC and TKI therapy [18].

Five phase 3 randomised trials investigated the role of EGFR-TKIs *versus* platinum-based chemotherapy in the first-line treatment of advanced NSCLC patients. Two of these trials enrolled patients selected for clinical characteristics known to be associated with a higher prevalence of *EGFR* mutation (never-smokers or former light-smokers, Asian ethnicity, adenocarcinoma histology) [19,20], the other three studies selected patients by *EGFR* mutations (Table 1) [21–23].

Clinical characteristics selection trials

The IPASS (Iressa Pan-ASia Study) trial, comparing gefitinib, 250 mg orally daily, *versus* the carboplatin plus paclitaxel regimen was conducted in 1217 Asian patients [19]. The study was designed to demonstrate that gefitinib was non-inferior to chemotherapy in terms of progression-free survival (PFS). The study results demonstrated the superiority of gefitinib compared with chemotherapy with a hazard ratio (HR) for PFS of 0.74 (95% confidence interval [CI] 0.65–0.85; $P < 0.0001$), while median PFS was similar (5.7 *versus* 5.8 months, for gefitinib and chemotherapy respectively), because of the crossing shape of the curves. ORR was significantly better in the gefitinib group compared with chemotherapy (43% *versus* 32.2%; odds ratio [OR], 1.59; $P < 0.01$). Median overall survival (OS) was 18.8 months in the gefitinib group and 17.4 months in the chemotherapy arm (HR 0.901, 95% CI 0.793–1.023; $P = 0.109$). Subgroup analysis based on molecular characteristics was conducted on the subset of patients with tumour sample available for this analysis (30–36% of the total sample) [24]. In the subgroup of 437 patients analysed for the presence of *EGFR* mutation, gefitinib was significantly better than chemotherapy in terms of PFS in patients with *EGFR*-mutated tumours (HR for PFS 0.48, 95% CI 0.36–0.64; $P < 0.0001$), whereas chemotherapy was significantly better in *EGFR* wild-type patients (HR for PFS 2.85, 95% CI 2.05–3.98; $P < 0.0001$). There was no statistically significant difference between treatments in OS in *EGFR*-mutated tumours (21.6 and 21.9 months for gefitinib and

chemotherapy respectively; HR 1.002; 95% CI 0.756–1.328; $P = 0.990$) or *EGFR* wild-type subgroups (11.2 and 12.7 months respectively; HR 1.181; 95% CI 0.857–1.628; $P = 0.309$). Overall, about 50% of patients from each arm, at progression, received the cross-over influencing, irremediably, the final OS results [23]. Moreover, gefitinib was associated with a lower rate of severe adverse events (28.7% *versus* 61.0% for gefitinib and chemotherapy respectively), and a lower rate of adverse events leading to discontinuation of the drug (6.9% *versus* 13.6%) [19].

The First-SIGNAL (First-line single agent Iressa versus Gemcitabine and cisplatin trial in Never-smokers with Adenocarcinoma of the Lung) phase 3 randomised trial was conducted in Korea, and eligibility criteria were similar to those of the IPASS trial [20]. Overall, 313 patients were randomised to gefitinib or the cisplatin plus gemcitabine regimen. The median OS, the primary endpoint of the study, was similar in both groups (21.3 *versus* 23.3 months for gefitinib and chemotherapy respectively), failing to show the hypothesised superiority of gefitinib compared with chemotherapy (HR = 1.003, 95% CI, 0.749–1.343; $P = 0.428$) with one-year survival of 74.2% and 76.2% respectively. Median PFS was 6.1 *versus* 6.6 months, respectively (HR = 0.813, 95% CI, 0.641–1.031; $P = 0.044$). PFS at one year was 20.3% in the gefitinib arm compared with 5% in the chemotherapy group. ORR was higher in the gefitinib arm, although the difference was not significant (53.5% *versus* 45.3%; OR 1.385; $P = 0.01533$) [20]. In the First-SIGNAL trial, *EGFR* mutational status was known in a minority of patients (n = 96). In *EGFR* mutation-positive cases, median PFS was significantly higher for patients treated with gefitinib (8.4 *versus* 6.7 months), and the proportion of patients without progression at one year was 34.6% with gefitinib *versus* 14.3% with chemotherapy. *EGFR* mutation-positive cases obtained a significantly higher ORR with gefitinib compared with chemotherapy [20].

EGFR mutations selection trials

Three randomised phase 3 trials, comparing EGFR-TKIs with chemotherapy, selected the patients by the presence of *EGFR* mutations [21–23].

In the trial conducted by the WJTOG (West Japan Thoracic Oncology Group) 3405 [21], 172 *EGFR*-mutated patients were randomised to receive gefitinib or cisplatin plus docetaxel chemotherapy. The study reached its primary endpoint, with a median PFS of 9.2 and 6.3 months, in the experimental and standard arms respectively (HR 0.489, 95% CI 0.336–0.710; $P < 0.0001$). A very high proportion of patients assigned to the control arm crossed over to gefitinib after disease progression. A significantly higher ORR was obtained in the gefitinib arm compared with chemotherapy (62.1% *versus* 32.2%; OR 3.445, 95% CI 1.609–7.376; $P < 0.0001$). Median OS was 30.9 months in the experimental arm, and has still not been reached in the control arm [21].

In the trial conducted by the North-East Japan study group (NEJ002), 228 *EGFR*-mutated patients were randomised to receive gefitinib or the carboplatin plus paclitaxel regimen [22]. In this trial, too, PFS was the primary endpoint. The study was prematurely stopped following the results of a planned interim analysis that demonstrated a significant superiority for gefitinib compared with chemotherapy in terms of PFS. Median PFS was 10.8 months in the experimental arm, compared with 5.4 months in the standard arm (HR 0.30, 95% CI 0.22–0.41; $P < 0.001$). ORRs were 73.7% for gefitinib and 30.7% for chemotherapy (OR 6.32, 95% CI 3.55–11.25; $P < 0.001$). Median OS was 30.5 and 23.6 months respectively ($P = 0.31$). However, the study protocol recommended the use of the crossover regimen as a second-line treatment, and 95% of patients assigned to the control arm received second-line gefitinib [22].

In all these trials, gefitinib confirmed its good tolerability profile with respect to traditional chemotherapy.

The very impressive results reported by these trials led to the registration of gefitinib for patients with advanced NSCLC harbouring *EGFR* mutation in any line of treatment.

Also, erlotinib, 150 mg orally daily, was investigated *versus* carboplatin plus gemcitabine chemotherapy, in a first-line setting, in 186 NSCLC *EGFR*-mutated patients (82 erlotinib; 72 chemotherapy). Median PFS, the main endpoint, was significantly prolonged with erlotinib *versus* chemotherapy (13.1 *versus* 4.6 months respectively; HR 0.16, 95% CI 0.10–0.26; $P < 0.0001$). The ORR was 83% *versus* 36% respectively. OS data are not yet mature. Also, erlotinib reported a favourable safety profile with a lower incidence of adverse events than chemotherapy [24].

Overall, patients affected by advanced NSCLC, and above all those with particular clinical characteristics (never-/former light smokers or patients with non-squamous histology), must be investigated for *EGFR* mutation status, and if an activating *EGFR* mutation is detected, a TKI should be used. To date, gefitinib is the only drug that has been approved in Europe in this setting, but further agents should be registered.

The role of histology

Histology of NSCLC has never been essential in the choice of first-line treatment. However, recent evidence arising from the availability of new agents has shown that histology represents an important variable in decision-making. NSCLC should be subdivided in two main histological groups: squamous and non-squamous cell carcinoma.

Squamous cell carcinoma

Unfortunately, until now no drugs specifically addressing the treatment of squamous NSCLC have been individuated. The standard approach in this setting with an Eastern Cooperative Oncology Group (ECOG) PS 0–1 is a platinum-based doublet, including third-generation drugs (vinorelbine, gemcitabine, taxanes). Among these regimens [3–5] no differences in survival were reported so no evidence of a single "standard" doublet for the treatment of advanced NSCLC has been suggested. The observation that docetaxel/cisplatin was superior to vinorelbine/cisplatin in a randomised study [25] has not had other confirmation.

However, recent findings have brought attention to new agents in the treatment of squamous histology. Among these, cetuximab, an anti-EGFR monoclonal antibody, has been studied, within two phase 3 randomised trials [26,27], in combination with different chemotherapy regimens in patients with advanced NSCLC. In the FLEX (First-Line ErbituX in lung cancer) trial, 1125 advanced NSCLC patients with EGFR detectable by immunohistochemistry (IHC) were randomised to cisplatin plus vinorelbine, every three weeks with or without cetuximab (400 mg/m^2 initial dose, then 250 mg/m^2/week) [26]. The median OS, the main endpoint, showed a statistically significant improvement in the cetuximab arm (11.3 *versus* 10.1 months; HR = 0.871, 95% CI 0.762–0.996; $P = 0.044$). The main cetuximab-related adverse event was a grade 3 acne-like rash in 57 patients (10%). A survival benefit was seen in all histological subgroups of NSCLC, with median OS of 12.0 (9.6–14.8) *versus* 10.3 months (8.3–12.1) respectively for patients with adenocarcinomas (n = 413), 10.2 (8.2–12.0) *versus* 8.9 months (7.8–9.8) respectively for those with squamous cell carcinomas (n = 347), and 9.0 (6.5–11.5) *versus* 8.2 months (6.9–10.2) respectively for patients with other histological subtypes (n = 185; large-cell, adenosquamous carcinoma and NSCLC non-otherwise specified [NOS]) in the chemotherapy plus cetuximab group *versus* chemotherapy alone group [26]. The FLEX study is the first to demonstrate a survival benefit of a targeted agent in combination with platinum-based chemotherapy across all histological subtypes in the first-line treatment of advanced NSCLC.

In the second phase 3 study (BMS099), 676 patients, without restrictions based on histology or EGFR expression were randomly assigned to cetuximab plus carboplatin plus paclitaxel or docetaxel *versus* chemotherapy alone. The primary endpoint was PFS, assessed by an independent radiological review committee (IRRC), which was 4.4 months with cetuximab plus chemotherapy *versus* 4.24 months with chemotherapy alone (HR = 0.902, 95% CI, 0.761–1.069; $P = 0.236$). This trial did not reach the main endpoint of PFS-IRCC improvement by cetuximab addition to chemotherapy. Median OS was 9.69 *versus* 8.38 months respectively (HR = 0.890, 95% CI, 0.754–1.051; $P = 0.169$). ORR-IRRC was 25.7% *versus* 17.2% respectively ($P = 0.007$). The safety profile of this combination was manageable and consistent with its individual components [27].

The benefit of cetuximab was seen irrespective of either histological subtype or type of platinum-based chemotherapy. Despite cetuximab, in both trials, showing an absolute OS benefit of about 1.2 months, to date, it has not yet been licensed for treatment of advanced NSCLC patients (Table 2).

Non-squamous cell carcinoma

In recent years, research has led to two emerging new drugs being identified, pemetrexed and bevacizumab, which specifically showed efficacy in non-squamous histology.

A phase 3, randomised, non-inferiority trial enrolled 1725 patients to receive cisplatin plus pemetrexed *versus* cisplatin plus gemcitabine. All patients received oral folic acid, vitamin B12 and dexamethasone prophylaxis. The primary objective was the OS, which was 10.3 months in both arms (HR = 0.94, 95% CI 0.84–1.05). Also, median PFS was non-inferior in the two arms (4.8 *versus* 5.1 months respectively; HR = 1.04, 95% CI 0.94–1.15). ORR was 30.6% *versus* 28.2% respectively. For cisplatin plus pemetrexed, the rates of grade 3 or 4 neutropenia, anaemia and thrombocytopenia ($P \leqslant 0.001$); febrile neutropenia ($P = 0.002$); and alopecia ($P < 0.001$) were significantly lower, whereas grade 3 or 4 nausea ($P = 0.004$) was more common for the cisplatin plus gemcitabine arm [28]. The pre-specified analysis for the NSCLC histology subtype reported that non-squamous patients had a longer median OS on cisplatin plus pemetrexed (11 months) than on cisplatin plus gemcitabine (10.1 months; HR = 0.84, 95% CI

Table 2
Main phase III randomised trials of first-line therapy in fit patients affected by advanced NSCLC

Author	Histology	Treatment	No. of patients	ORR (%)	PFS (months)	OS (months)
Pirker, 2009 [26]	All histotypes	CDDP+VNR+CET	557	36	4.8	11.3
		vs				
		CDDP+VNR	568	29	4.8	10.1
Lynch, 2010 [27]	All histotypes	CBDCA+TAX+CET	338	25.7	4.4	9.69
		vs				
		CBDCA+TAX	338	17.2	4.24	8.38
Scagliotti, 2008 [28]	All histotypes	CDDP+PEM	862	30.6	4.8	10.3
		vs				
		CDDP+GEM	863	28.2	5.1	10.3
Scagliotti, 2009 [29][a]	Non-squamous	CDDP+PEM	618	28.6	5.26	11
		vs				
		CDDP+GEM	634	22.2	4.96	10.1
Scagliotti, 2009 [29][a]	Squamous	CDDP+PEM	244	23.4	4.4	9.4
		vs				
		CDDP+GEM	229	31.4	5.5	10.8
Sandler, 2006 [30]	Non-squamous	CBDCA+PAC+BEV	434	35	6.2	12.3
		vs				
		CBDCA+PAC	444	15	4.5	10.3
Reck, 2010 [31]	Non-squamous	CDDP+GEM+BEV[b]	345	34	6.7	13.6
		or				
		CDDP+GEM+BEV[c]	351	30	6.5	1.4
		vs				
		CDDP+GEM	347	20	6.1	13.1

NSCLC: non-small-cell lung cancer; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; CDDP: cisplatin; VNR: vinorelbine; CET: cetuximab; CBDCA: carboplatin; TAX: taxanes; PEM: pemetrexed; GEM: gemcitabine; PAC: paclitaxel; BEV: bevacizumab

[a] Pre-planned subgroup analyses.

[b]Bevacizumab at 7.5 mg/kg; [c] Bevacizumab at 15 mg/kg.

0.74–0.96; $P = 0.011$), whereas squamous NSCLC patients had a shorter median OS on cisplatin plus pemetrexed (9.4 months) than on cisplatin plus gemcitabine (10.8 months; HR = 1.23, 95% CI 1.00–1.51; $P = 0.05$). Similarly, non-squamous patients showed a trend that was not significant for a longer PFS on cisplatin plus pemetrexed (5.26 months) than on cisplatin plus gemcitabine (4.96 months; HR = 0.95, 95% CI 0.84–1.06; $P = 0.349$). Squamous patients had a shorter PFS on cisplatin plus pemetrexed (4.4 months) than on cisplatin plus gemcitabine (5.5 months; HR = 1.36, 95% CI 1.12–1.65; $P = 0.002$). ORR was higher in the cisplatin plus pemetrexed arm than in the cisplatin plus gemcitabine arm in patients with adenocarcinoma (28.9% *versus* 21.7%) or other NSCLC tumours (28.3% *versus* 21.2%); higher ORR occurred in patients with squamous cell carcinoma (23.4% *versus* 31.4%) on the cisplatin plus gemcitabine arm [28]. Based on these results and those reported by other trials [29,32], pemetrexed in combination with cisplatin has been granted to be the first-line treatment of patients with advanced NSCLC other than predominantly squamous cell histology.

The humanised monoclonal antibody bevacizumab, directed against VEGF, based on the promising data of a phase 2 randomised trial [33], was investigated in two randomised phase 3 trials [30,31,34]. Squamous histology was excluded because of the risk of grade 5 haemoptysis reported in the previous phase 2 randomised study [33]. In the ECOG (E4599) trial, 878 patients were randomised to receive paclitaxel and carboplatin plus bevacizumab 15 mg/kg, or the same chemotherapy regimen plus placebo. Patients receiving bevacizumab reported a statistically significant advantage in OS (12.3 *versus* 10.3 months; $P = 0.003$), PFS (6.2 *versus* 4.5 months; $P < 0.001$) and ORR (35% *versus* 15%; $P < 0.001$). Rates of clinically significant bleeding were 4.4% and 0.7%

($P < 0.001$) respectively. There were 15 treatment-related deaths in the bevacizumab group, including five from pulmonary haemorrhage [30]. A retrospective analysis showed that the adenocarcinoma patients (n = 602) reported a median OS of 14.2 months for the bevacizumab arm *versus* 10.3 months for the control arm (HR = 0.69, 95% CI 0.58–0.83) [35].

In the AVAiL (AVAstin in Lung) trial, 1043 patients with non-squamous NSCLC were randomised to cisplatin plus gemcitabine alone or in combination with two doses of bevacizumab (7.5 and 15 mg/kg) [31,34]. Median PFS, main endpoint of the trial, was significantly prolonged with the bevacizumab administration, the HRs were 0.75 (6.7 *versus* 6.1 months for placebo; $P = 0.003$) in the low-dose group and 0.82 (6.5 *versus* 6.1 months for placebo; $P = 0.03$) in the high-dose group compared with placebo. ORRs were 20.1%, 34.1% and 30.4% for placebo, low-dose bevacizumab, and high-dose bevacizumab plus chemotherapy. Incidence of grade $\geqslant 3$ adverse events was similar across the three arms with grade $\geqslant 3$ pulmonary haemorrhage rates, which were $\leqslant 1.5\%$ for all arms. Median OS was 13.1 months for chemotherapy alone, 13.6 months for bevacizumab 7.5 mg/kg plus chemotherapy (HR *versus* placebo 0.92, 95% CI 0.77–1.10) and 13.4 months for bevacizumab 15 mg/kg plus chemotherapy (HR *versus* placebo 1.02, 95% CI 0.85–1.22).

Both trials reached the primary endpoint by adding bevacizumab to chemotherapy. To date, bevacizumab is licensed in combination with platinum-based chemotherapy as the first-line therapy of advanced non-squamous NSCLC patients; however, according to the results reported by the studies cited, the carboplatin/paclitaxel combination is the backbone of chemotherapy (Table 2).

Special patient populations

Special patient populations mainly include two groups: the elderly, and ECOG PS 2 patients. These two categories of patients are prognostically different; thus, the therapeutic approach should be adequate for each group.

Elderly patients

More than 50% of NSCLCs are diagnosed in patients aged over 65 and about 30% in patients older than 70. Nowadays, establishing the biological age of a patient is still difficult because of a lack of adequate laboratory tests and tools. Thus, the chronological age is the only indicator we have in defining the elderly, and 70 years may be the most appropriate boundary because the incidence of age-related changes starts to increase after this cut-off age [36]. Important concerns in evaluating the treatment of elderly patients are the presence of comorbidities and the progressive physiological reduction of hepatic, renal and bone-marrow functions, which could have a negative impact on the degree of toxicity. On the basis of these considerations, in order to individualise treatment choice within a group of elderly NSCLC patients of the same chronological age, it would be important to perform a comprehensive geriatric assessment (CGA), which evaluates the patients' global and functional status, in order to improve treatment decisions and outcomes allowing elderly patients to be subdivided into three main categories: fit, pre-frail and frail [37].

Two main randomised phase 3 trials showed single-agent chemotherapy with third-generation agents as the standard of care for first-line therapy of clinically unselected elderly advanced NSCLC patients [38,39]. The Elderly Lung cancer Vinorelbine Italian Study (ELVIS) was the first randomised phase 3 trial ever performed in advanced NSCLC patients aged $\geqslant 70$ years. A total of 191 elderly were randomised to single-agent vinorelbine plus best supportive care (BSC) or BSC alone. Quality of life (QoL) was the primary endpoint of the study. Vinorelbine-treated patients scored better than control patients on QoL functioning scales, and they reported fewer lung cancer-related symptoms, but worse toxicity-related symptoms. Vinorelbine improved median OS, which was 27 *versus* 21 weeks reported by BSC alone ($P = 0.04$). The relative HR for death for vinorelbine-treated patients was 0.65 (95% CI 0.45–0.93) [38]. The MILES (Multicenter Italian Lung Cancer in the Elderly Study) trial accrued 698 patients aged $\geqslant 70$ years to receive the combination of vinorelbine plus gemcitabine *versus* single-agent vinorelbine or gemcitabine. The OS was 36, 28 and 30 weeks, and the probability of being alive at one year 38%, 28% and 30%, for vinorelbine, gemcitabine or their combination respectively. The HR for death was 1.17 (95% CI 0.95–1.44) for the combination treatment *versus* vinorelbine and 1.06 (95% CI 0.86–1.29) for the combined regimen *versus* gemcitabine. Although QoL was similar across the three arms, the combination treatment was slightly more toxic than the two drugs given singly. In fact, combination chemotherapy resulted in higher thrombocytopenia and hepatic toxicity compared with single-agent vinorelbine, and higher neutropenia, vomiting, fatigue, cardiac toxicity and constipation compared with single-agent gemcitabine [39].

However, retrospective analyses from large phase 3 randomised trials showed similar efficacy and tolerability when elderly and adult patients were compared [40]. This issue has recently been addressed in two prospective randomised phase 3 trials [41,42].

Single-agent gemcitabine or vinorelbine was compared *versus* carboplatin plus weekly paclitaxel regimen in 451 patients aged 70–89 years. Primary endpoint was OS, which was significantly longer for patients treated with combination chemotherapy (10.4 *versus* 6.2 months; HR 0.639, 95% CI 0.515–0.792; $P < 0.0001$). The one-year survival was 45.1% for the double- and 26.9% for the single-agent with a median PFS of 6.1 *versus* 3.0 months respectively. ORR was 29% *versus* 10.9% respectively. However, grade 3–4 haematological toxicities and treatment-related deaths were significantly more frequent in patients treated with carboplatin and paclitaxel compared with single-agent gemcitabine or vinorelbine [41]. A total of 181 patients, aged $\geqslant$70 years, were randomised to receive carboplatin plus gemcitabine or carboplatin plus paclitaxel. The doses employed were similar to those generally administered in younger patients. The main endpoint was QoL. Overall, grade 3–4 toxicity occurred in 75% and 60% of patients treated with carboplatin plus gemcitabine or paclitaxel respectively. The ORR were 27% and 19% with a median PFS of 4.7 and 4.5 months and an OS of 8.6 and 6.9 months respectively. Mean global QoL score at baseline did not differ between the two arms with no statistically significant difference at the 18-week analysis [42].

In these two trials, carboplatin-based doublets were administered with doses typically used for adult patients, reporting an high incidence of severe side effects. It means that there is a need for studies investigating platinum-based regimens with doses specifically for the elderly. In this respect, several published phase 2 studies of combination chemotherapy based on modified schedules of carboplatin (low-dose or weekly administration) have shown interesting activity and good tolerability [40]. A phase 1/2 randomised trial, MILES-2P, evaluated the feasibility of cisplatin at attenuated doses combined with gemcitabine or vinorelbine in elderly patients with advanced NSCLC. Cisplatin was feasible and active at 60 mg/m^2 on day 1, with gemcitabine and at 40 mg/m^2 on day 1, with vinorelbine. With the former combination, 83.3% of patients were treated without unacceptable toxicity, ORR was 43.5% (95% CI 30.6–56.8), and the median PFS and OS were 25.3 and 43.6 weeks respectively. With the latter combination, 82% of patients were treated without unacceptable toxicity, ORR was 36.1% (95% CI 24.2–49.4), and the median PFS and OS were 21.1 and 33.1 weeks respectively. The combination of cisplatin plus gemcitabine, which provided a higher dose of cisplatin, deserved further investigation *versus* single-agent chemotherapy in this setting of patients (Table 3) [43].

Platinum-based chemotherapy, with attenuated doses or a weekly schedule, may therefore be the preferred option for elderly patients having PS 0–1 and adequate organ function, while single-agent therapy is recommended for unfit elderly patients.

ECOG PS 2 patients

Patients with PS 2, according to the ECOG classification, have symptoms and are confined to bed, although they have less than 50% waking hours [46]. Patients with advanced NSCLC and PS 2 have a significantly worse prognosis compared with fit patients, with median OS not longer than 3–5 months [47]. Single-agent chemotherapy (gemcitabine, vinorelbine, taxanes) represents an historical option for palliative treatment of patients with PS 2. Although there is a lack of specific prospective comparative trial data of platinum-based combination regimens *versus* single-agent chemotherapy in PS 2 patients, the combinations with cisplatin are possible treatment options [47].

A subgroup analysis of PS 2 patients randomised into two phase 3 trials was performed. Patients randomised to combination chemotherapy (carboplatin and paclitaxel) in one trial and single-agent therapy (gemcitabine or vinorelbine) in the second were included in this analysis. A total of 201 patients were treated with combination and 190 with single-agent therapy. ORR was 37% and 15% respectively. Median time to progression (TTP) was 4.6 and 3.5 months respectively ($P < 0.001$) with a median OS of 8.0 and 6.6 months, and a one-year survival rate of 31% and 26% respectively [48]. Two prospective phase 3 randomised trials investigated paclitaxel poliglumex (PPX), a macromolecule drug conjugate of paclitaxel and polyglutamic acid, which reduces systemic exposure to peak concentrations of free paclitaxel and may lead to increased concentrations in tumours because of the enhanced vascular permeability. A total of 381 PS 2 patients randomly received single-agent PPX *versus* single-agent vinorelbine or gemcitabine. Median OS, the primary endpoint of this phase 3 randomised study, was 7.3 months for PPX *versus* 6.6 months for the control arm (HR = 0.95; $P = 0.686$). The one-year survival rates were 26% in both arms. Grade $\geqslant$3 dyspnoea was 13% *versus* 17%, fatigue 10% *versus* 9%, neutropenia 2% *versus* 8% and anaemia 3% *versus* 9% respectively [44]. In another

Table 3
Main phase III randomised trials of first-line therapy in special patient populations (elderly or PS 2) affected by advanced NSCLC

Author	Population	Treatment	No. of patients	ORR (%)	TTP (months)	OS (months)
Gridelli, 2003 [39]	Elderly	VNR	233	18	4.5	8.3
		or				
		GEM	233	16	4.25	6.5
		vs				
		GEM+VNR	232	21	4.75	6.9
Quoix, 2010 [41]	Elderly	GEM or VNR	226	10.9	3.0[a]	6.2
		vs				
		CBDCA+PAC	225	29.5	6.1[a]	10.3
Biesma, 2011 [42]	Elderly	CBDCA+GEM	90	27	4.7[a]	8.6
		vs				
		CBDCA+PAC	91	19	4.5[a]	
O'Brien, 2008 [44]	PS 2	PPX	191	11	3.1	7.3
		vs				
		GEM or VNR	190	15	3.8	6.6
Langer, 2008 [45]	PS 2	CBDCA+PPX	199	20	3.9	7.9
		vs				
		CBDCA+PAC	201	37	4.6	8.0

NSCLC: non-small-cell lung cancer; ORR: objective response rate; TTP: time-to-progression; OS: overall survival; PS 2: performance status 2; VNR: vinorelbine; GEM: gemcitabine; CBDCA: carboplatin; PAC: paclitaxel; PPX: paclitaxel poliglumex.
[a] Progression-free survival.

phase 3 randomised trial, 400 PS 2 patients were randomised to receive carboplatin plus paclitaxel or PPX. Alopecia, arthralgias/myalgias, and cardiac events were significantly less frequent with carboplatin plus PPX, whereas grade $\geqslant$3 neutropenia and neuropathy showed a trend towards worsening. Median OS was 7.9 months for carboplatin plus PPX and 8 months for carboplatin plus paclitaxel (HR = 0.97; $P = 0.769$) with one-year survival rates of 31% for both arms. Disease control rates were 64% and 69% respectively with TTP of 3.9 and 4.6 months respectively ($P = 0.210$; Table 3) [45].

These data underlined that PS 2 NSCLC patients are a heterogeneous group who have significantly different outcomes. Taking into account these results, single-agent therapy is a reasonable approach, but also platinum-based regimens, mainly with attenuated doses of drugs, may be considered an option for these patients.

Conclusion

When approaching a patient affected by advanced NSCLC, the histotype definition, which is the main factor in addressing the treatment, is of importance.

In patients with *EGFR* mutation-positive tumours, a TKI inhibitor is recommended as first-line treatment; to date, gefitinib is the only drug that has been approved in Europe. In the presence of *EGFR* mutation-negative tumours or those of unknown status, fit patients with advanced squamous NSCLC, chemotherapy with a third-generation platinum-based doublet is the standard of care. In non-squamous NSCLC patients, cisplatin plus pemetrexed and platinum-based chemotherapy plus bevacizumab are also reasonable treatment choices. Elderly patients, defined as $\geqslant$70 years old, should receive third-generation single-agent chemotherapy, but in elderly patients with good PS, without major co-morbidities and with adequate organ function, platinum-based doublets with attenuated doses can be a valid option. In PS 2 patients, a single-agent third-generation drug is a reasonable choice, even if combination chemotherapy with carboplatin or low doses of cisplatin is a suitable alternative. Overall, the special patient populations are heterogeneous, and the optimal approach in these patients remains controversial and should be individualised.

In order to improve continuously the survival results of advanced NSCLC patient therapy, well-designed and large randomised phase 3 trials specifically addressing single subsets of patients are welcome.

Conflict of interest statement

C. Gridelli: Honoraria as speaker bureau and advisory board member for Roche and Merck Serono. A. Rossi: Honoraria as speaker bureau member for Lilly and advisory board member for Roche. P. Maione: Honoraria as speaker bureau member and advisory board member for Lilly and Roche.

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