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EUROPEAN RESPIRATORY UPDATE

Update on nonsmall cell lung cancer

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Despite recent advances and declining its incidence in males in Western countries, lung cancer remains the main cause of cancer deaths worldwide, mainly because of tobacco smoking epidemics in developing countries and the still moderate efficacy of therapeutic strategies [1–3]. More than 80% of lung cancers are nonsmall cell lung cancer (NSCLC), which can be further sub-divided into squamous cell carcinoma (SCC), adenocarcinoma and large cell carcinoma (LCC). Metastatic stage IV NSCLC remains an incurable disease with a median survival that reached a plateau of 8–10 months at the beginning of the century with available cisplatinum-based regimens [4].

In stage I to III NSCLC, the occurrence of extrathoracic metastasis also leads to a poor 5-yr survival rate of 50% [5]. Indeed, NSCLC has a high metastasis potential, and is often drug resistant, so even after early diagnosis and resection with curative intent, patient prognosis remains poor [6]. Efforts have been made to improve overall survival (OS) of early NSCLC patients, by lowering the distant metastasis rate with adjuvant or neoadjuvant chemotherapy. The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis of adjuvant cisplatinum-based chemotherapy only found a 5-yr absolute benefit of 5.4% (hazard ratio (HR) 0.89; p=0.004) restricted to stage II and III patients, and 5-yr OS remained below 60% [7]. However, in the IALT (International Adjuvant Lung Cancer Trial) study, the benefit was lost at 7 yrs, because of an excess of non-cancer deaths in the chemotherapy arm [8]. Conversely, the long-term follow-up in the ANITA (Adjuvant Navelbine International Trialist Association) trial, using a more recent vinorelbine-cisplatinum doublet strategy, showed that the chemotherapy arm benefit was maintained at 7 yrs [9]. Two meta-analyses [10, 11] of neoadjuvant chemotherapy trials also showed a 5-yr absolute benefit survival of 5.4% [7] and 6% [10, 11], respectively. The results of long-term follow-up of the French Intergroup MIP91 neoadjuvant trial, reported at the American Society of Clinical Oncology (ASCO) meeting in 2010, showed that chemotherapy-induced survival benefit was maintained at 10 yrs [12]. Therefore, no definitive long-term survival difference could be found between neoadjuvant and adjuvant chemotherapy for stage II to III NSCLC.

Concurrent platinum-based chemoradiotherapy has also improved median survival and long-term disease-free survival of stage IIIB NSCLC, with median OS reaching 18 months with current concurrent regimens, leading to 5-yr survivors [13, 14]. This improvement was obtained at the price of a manageable higher haematological and oesophageal toxicity, provided strict rules on irradiated lung volume are respected, limiting radiation acute and chronic pneumonia, the main potentially lethal complication of such treatments. Chemoradiotherapy was also shown, in two phase 3 controlled trials, to compare favourably with surgery, especially when pneumonectomy is needed [15, 16].

Major advances in understanding NSCLC molecular biology have been made in the first decade of the 21st century. Activation of the epidermal growth factor receptor (EGFR) pathway was shown to result in signalling cascades that promote tumour growth and progression. EGFR is actually expressed in a large fraction of NSCLC tumours, with frequently dysregulated downstream signalling pathways [17]. This observation provided the rationale for developing small-molecule tyrosine kinase inhibitors (TKIs) targeting EGFR. In lung adenocarcinoma, *EGFR* mutations are found in ~15% of Caucasian patients, and >40% of Asian patients [18, 19]. Inhibiting EGFR signalling using TKIs (gefitinib or erlotinib) has been shown to be an effective treatment for patients with tumours exhibiting such *EGFR*-sensitising mutations [20].

Anti-angiogenic drugs have been developed for lung cancer, as for other solid tumours, with various and sometimes disappointing results. However, a humanised monoclonal antibody toward vascular endothelial growth factor (VEGF), bevacizumab, added to paclitaxel-carboplatinum, was shown to improve OS in highly selected stage IV nonsquamous NSCLC without cardiovascular comorbidity or brain metastasis; for the first time, an encouraging 1-yr median survival was reached [21].

Finally, new methods for the use of chemotherapy with third-generation drugs have also improved survival results, either by extending length of treatment after induction chemotherapy with the concept of ''maintenance'' therapy [22], or by more aggressively treating elderly patients over the age of 70 yrs [23], who nowadays account for more than one-third of the new cases of lung cancer.

In this update, we will focus on these major recent advances in stage IV NSCLC therapeutics and biology.

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PEMETREXED: THE FIRST HISTO-GUIDED CYTOTOXIC AGENT

ECOG1594, a large phase 3 four-arm trial published in 2002 in the *New England Journal of Medicine* [24], compared four platinum-based doublets (paclitaxel-carboplatinum, paclitaxel-cisplatinum, gemcitabine-cisplatinum and docetaxel-cisplatinum) in stage IV NSCLC patients, and showed that the four regimens were somehow equivalent in terms of OS, reaching a plateau of 8 months of median survival, with 30–35% patients surviving to 1 yr. Since then, no classical cytotoxic agent has emerged to change this pessimistic feature, until pemetrexed. However, two meta-analyses showed modest advantages for gemcitabine-based [25] or docetaxel-based regimens [26] in terms of progression-free survival (PFS) and OS. After the nihilism period following publication of the ECOG1594 results, drug development in NSCLC was essentially centred on new molecular targeted agents that were thought to be the only alternative able to improve on the disappointing results of classical cytotoxic chemotherapy. However, four phase III trials of front-line therapy associating chemotherapy with *EGFR* TKIs in advanced NSCLC (gefitinib or erlotinib: INTACT (IRESSA NSCLC Trial Assessing Combination Treatment) 1 and 2, TALENT (Tarceva Lung Cancer Investigation) and TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin)) [27–30] gave negative results, whereas another series of phase III trials, using the same strategy of front-line association of a targeted new agents (metalloproteinase inhibitors, sorafenib, Toll-receptor 9 agonist, figitunimab, *etc.*) with chemotherapy, failed to reach their survival end-points. In this context, pemetrexed was initially developed in a second-line setting, as mentioned below [31]. The first phase 3 randomised trial comparing pemetrexed-cisplatinum *versus* gemcitabine-cisplatinum in a first-line setting came after pemetrexed second-line registration and was designed as a non-inferiority study [32]. For an 18-month period, 1,725 patients were randomly assigned to either of these regimens, comprising the largest number of patients enrolled onto a single two-arm phase III study. Non-inferiority was actually documented because the median OS time was an identical 10.3 months in each arm, a remarkable 2-month improvement compared with the seminal ECOG1594 trial. However, the most outstanding finding of this trial is the result of a pre-specified subset analysis in the 847 adenocarcinoma patients. In those patients, cisplatinum plus pemetrexed significantly improved survival compared with the cisplatinum plus gemcitabine arm (12.6 *versus* 10.9 months, respectively; HR 0.84, 95% CI 0.71–0.99; interaction p=0.03). Conversely, in the 473 patients with SCC, the cisplatinum plus gemcitabine arm did better in terms of OS compared with the cisplatinum plus pemetrexed arm (10.8 *versus* 9.4 months, respectively; HR 1.23, 95% CI 1.00–1.51; interaction p=0.05).

The influence of histology was further confirmed by the retrospective reassessment of a second-line phase 3 trial with pemetrexed in which, again, pemetrexed was found to be superior in adenocarcinomas and LCCs compared with SCCs [33]. These analyses led the European Medicines Agency (EMEA) and the US Food and Drug Administration to restrict the pemetrexed license to nonsquamous carcinomas, a decision leading to the first histology-based authorisation in NSCLC.

Some nonexclusive explanations could be proposed to account for these results. First, is the pejorative influence of smoking on survival. The median survival time for never-smokers was a spectacular 15.6 months, compared with 10.2 months for current or former smokers. Such a finding showed consistency, since it was also reported in bevacizumab trials, and one should underline the higher frequency of nonsmokers or former smokers in adenocarcinoma patients than in patients with alternative histologies.

The authors also claimed that a molecular rationale could account for pemetrexed efficacy in adenocarcinoma, since the baseline expression of the *thymidylate synthase (TS)* gene was shown, using immunohistochemistry or mRNA content in a retrospective independent series of patients, to be significantly higher in SCC compared with adenocarcinoma [34]. Pemetrexed is actually known to inhibit TS, and preclinical data suggest that there is reduced activity of pemetrexed in tumours showing a high *TS* expression. However, data on *TS* expression within different histological subtypes are controversial, and largely depend on the technique used, *i.e.* immunohistochemistry (with a versatile commercially available antibody), silver fluorescent *in situ* hybridisation (SISH) or real-time amplification of *TS* gene, since an increase of TS gene copy number has been recently shown in NSCLC.

Most troubling is the inconsistency of histological subtyping analysis, as shown by the number of specimens (n=252) classified in the pemetrexed trial with histology ''not otherwise specified'' (NOS), since it was impossible for them to be classified into the adenocarcinoma, squamous cell or large cell categories. This inconsistency was further emphasised by a US prospective study by the VOILA group (Validation Of Inter-observer agreement in Lung cancer Assessment), reported at the ASCO meeting 2009 [35]. This cooperative pathologist group showed that pathologic agreement for squamous *versus* non-squamous histology determination, only on the basis of haemotoxylin and eosin stains without immunohistochemistry markers, in a series of 96 NSCLC specimens was disappointing. Kappa concordance test for all 24 pathologists was only 0.55 (95% CI 0.53–0.58), ranging from 0.41 for community pathologists to 0.64 for expert lung cancer pathologists (mean kappa 0.52), which is below the widely accepted 0.70 threshold for good clinical agreement. One argued that immunohistochemistery markers could improve pathological diagnosis with a combination of adenocarcinoma markers (TTF-1, CK-7, CK-20, PAS after diastase for mucin stain) and so-called squamous cell markers (p63, CK-5/6, desmocollin 3 and desmoglein 3), increasing the cost of pathological examination [36–38]. However, the specificity of each marker for one particular histological subtype remains low and, for instance, as much as 30% of adenocarcinoma, 37% of LCC and 50% of large cell neuroendocrine carcinoma were shown to express p63 a squamous cell marker, whereas desmoglein 3 expression was shown to have a 98% specificity for SCC histology but only 88% sensitivity [39]. In addition, desmocollin 3, an adhesion marker thought to be specific for the squamous cell lineage, was actually shown to be exclusive from TTF-1 staining, but also positive in as much as 50% of authentic LCC [40]. A combination staining score, with positive and negative markers, could define NSCLC subsets, but would need prospective evaluation before replacing classical histological subtype description in stratifying patients for pemetrexed treatment. Finally, microRNA amplified from paraffin-embedded specimens could also be an alternative for

ascertaining squamous cell histology, with hsa-miR-205 showing a high sensitivity of 96% at 90% specificity for the identification of SCC, either in a training set of 27 NSCLC formalin-fixed, paraffin-embedded samples, or in an independent blinded validation set of 79 NSCLC samples [41]. Besides, this test does not involve subjective human judgment of morphological characteristics, but rather a strict qRT-PCR methodology. Similarly, the easiest way to select patients for pemetrexed could be *TS* content determination; that should also be evaluated prospectively, before being largely accepted as a better surrogate marker for pemetrexed efficacy than histological subtyping.

SECOND- AND THIRD-LINE TREATMENTS TO IMPROVE NSCLC OVERALL SURVIVAL

In the late 1990s, no available second-line therapy could improve survival in stage IV NSCLC patients progressing after cisplatinum-based first-line therapy. Two phase 3 trials compared, in a second- or third-line setting, either docetaxel monotherapy 75 or 100 mg·m^{-2} plus best supportive care, to best supportive care alone, in Shepherd's TAX317 trial, or to a rather inactive monotherapy, ifosfamide or vinorelbin (V/I), in Fosella's TAX320 trial [42, 43]. Both trials showed a 6–10.8% intent-to-treat overall response rate (ORR) in patients treated with docetaxel, with a median OS, as measured from initiation of the second line, ranging from 5.6 to 7.0 months in the docetaxel 75 mg·m^{-2} arms, which represented only a marginal increase in Sheperd's trial ($p=0.047$), and was identical to control arm intent-to-treat survival in Fosella's trial. In this latter trial, only censored survival at the time of administration of the additional post-study chemotherapy was shown to favour docetaxel arms (75 and 100 mg·m^{-2}; $p<0.001$), since crossover treatment impacted survival in one-third of the patients. The most outstanding finding of these trials was the 1-yr survival, which reached 29% and 32%, respectively, after initiation of docetaxel therapy, *versus* 19% in the best supportive care and V/I arms. This led, for the first time, to long-term survivors at 24 months in both trials. Furthermore, in TAX316, all quality of life (QoL) parameters favoured docetaxel-treated patients, and the use of all tumour-related medications was significantly less common in docetaxel-treated patients, compared with patients receiving best supportive care, and significantly fewer docetaxel patients required morphine or non-morphine analgesics for pain [44].

Following those two seminal trials, a third non-inferiority trial demonstrated the non-inferiority of the new cytotoxic agent pemetrexed (500 mg·m^{-2}) compared with docetaxel (75 mg·m^{-2}), with a 2.9 month median PFS in both arms. Pemetrexed also had a much favourable toxcity profile, since median toxicity-free survival was 7.5 months in the pemetrexed arm *versus* 2.3 months in the docetaxel arm (HR 0.57, 95% CI 0.47–0.69; $p<0.0001$) [31].

GRIDELLI *et al.* [45] showed, in a phase III trial, that weekly docetaxel could significantly reduce grade 3/4 neutropenia in comparison to docetaxel administered every 3 weeks, and with the same efficacy but probably higher pharmaceutical costs. Finally, the campthotecin analogue and topoisomerase-I inhibitor, oral topotecan, was compared with *i.v.* docetaxel in a phase III trial in patients who progressed after first-line cisplatinum-based chemotherapy [46], showing a similar time to progression of 2.75 months, with a nonsignificantly inferior 1-yr survival (25% *versus* 29%) for topotecan. However, a higher percentage of anaemia and the lack of QoL score improvement precluded the wide use of topotecan in such indication.

In contrast, at the same time, another oral drug proved its tolerance and efficacy. The BR21 large phase 3, placebo-controlled trial, reported in 731 patients that had received a maximum of two prior chemotherapy regimens, including a cisplatinum-based doublet, that an *EGFR* TKI, erlotinib, at a dose of 150 mg daily, gave a 8.9% ORR for a median duration of 7.9 months, and an OS of 6.7 *versus* 4.7 months with the placebo ($p<0.001$) [47]. This trial contrasted with the ISEL (IRESSA Survival in Lung Cancer) phase 3 trial, which was conceived essentially with the same design, but used another *EGFR* TKI, gefitinib, and which failed to show any survival improvement in the gefitinib arm compared with the placebo arm [48]. One of the two main differences in these trials was patient selection: in the ISEL trial, a large majority of patients progressed after cisplatinum-based treatment, whereas in BR21 a large fraction of patients had stable disease after first-line cisplatinum-based chemotherapy. Furthermore, in the ISEL trial the gefinib dose was less than half the maximal tolerable dose (MTD) as determined in phase I trials, whereas the 150 mg daily dose of erlotinib was close to the MTD found in phase I trials. In the BR21 trial, all subsets of patients were claimed to benefit from second-line erlotinib treatment, even patients with SCC or those who were current smokers; both these subsets of patients have low or virtually null probability of *EGFR* mutations of the tyrosine kinase domain, a molecular event subsequently shown to be associated with the dramatic efficacy of erlotinib [49]. Indeed, if one excludes from survival analysis objective responder patients, who probably represent the subset of patients with tumour *EGFR* mutation, there is still a significant survival advantage for patients treated with erlotinib compared with patients who received placebo in the BR21 trial. One explanation could rely on the ''stabilisation effect'' observed in patients with tumours exhibiting a high *EGFR* copy number and a high *EGFR* protein expression without any tyrosine kinase mutation. This effect would be sufficient, in a second-line setting, to lower tumour growth and increase progression-free period, thereby significantly affecting survival.

The INTEREST (IRESSA Non-small-cell lung cancer Trial Evaluating Response and Survival against Taxotere) phase 3 trial later showed, by randomising another *EGFR* oral TKI, gefitinib (250 mg daily), *versus* docetaxel (75 mg·m^{-2} every 3 weeks), in a second-line setting after a first cisplatinum-based chemotherapy line for progressing patients, the non-inferiority of gefitinib compared with the more toxic docetaxel [50]. In patients with *EGFR* mutation, PFS was longer with gefitinib than with docetaxel, with a striking 3-month difference in median PFS, (from 4.1 compared with 7.0 months), but OS did not differ since 31% of patients initially treated with gefitinib were ultimately treated with docetaxel when tumour progression occurred and, conversely, 37% of patients treated with docetaxel were crossed over to gefitinib or erlotinib in a third-line setting. Therefore, the sequence of TKI or docetaxel use in the second- or third-line setting appears not to really matter in

patients with *EGFR* mutations, provided that the patients receive both treatments sequentially [51, 52].

BEVACIZUMAB AND NSCLC TREATMENT: FOR FIT HIGHLY SELECTED PATIENTS

There is evidence that angiogenesis accounts for an early event in lung cancer carcinogenesis, since histological features of angiogenesis, called ''angiogenic squamous dysplasia'', are described in epithelial precancerous bronchial lesions, with capillary loops projecting into histologically abnormal epithelium in smoking individuals [53]. Indeed, lung carcinomas are often hypoxic tumours, and hypoxia is known to be the main signal for endothelial cell proliferation and vasculogenesis. Later in the lung carcinogenesis, angiogenic markers, such as hypoxia-inducible factor-α transcription factor, VEGF and *VEGFR, EPO and EPO-R*, were shown to be highly expressed in NSCLC and to associate with worse prognosis [54, 55]. Therefore, it was not particularly surprising that the first open-label phase 3 randomised trial comparing paclitaxel-carboplatin doublet therapy with the same doublet plus bevacizumab, a humanised monoclonal antibody directed to VEGF, the main growth factor for endothelial cells, was reported to be positive in the ECOG1499 trial [21]. The main lesson of this trial was the bevacizumab arm's symbolic 1-yr (12.3 months) median survival, a threshold reached for the first time in lung cancer clinical research history, and one that compared favourably to the 10.3 months OS in the control arm, already better than observed in a previous four-arm ECOG trial. This latter observation immediately raised the question of the selection of a subgroup with better prognosis. Indeed, only patients with non-squamous cell carcinoma were enrolled, because of the risk of fatal pulmonary haemorrhage for SSC proximal tumours treated with bevacizumab in previous phase II trial [56]. Moreover, patients with asymptomatic brain metastasis were also excluded, as were patients with cardiovascular comorbidities, patients with any history of haemoptysis and patients undergoing anticoagulant treatment. Therefore, this trial population was probably enriched in nonsmoking patients, a condition currently known to associate with better prognosis. In an exploratory subgroup analysis, bevacizumab triplet was shown to improve prognosis in all subgroups but females (*i.e.* patients aged >65 yrs, performance status (PS) 1, weight loss $\geqslant$5% and patients with two or more metastatic sites). A subgroup analysis restricted to the 602 patients with adenocarcinoma (excluding large cell and NOS carcinomas), showed an even more favourable effect of bevacizumab, since median OS was 14.2 months in the bevacizumab arm *versus* 10.3 months in the paclitaxel-carboplatin arm (HR 0.69, 95% CI 0.58–0.83). The AVAIL (Avastin in Lung) phase 3 European trial was then designed to exclude the possibility that the prognostic impact of bevacizumab could only have arisen from saving a supposed lower activity of the paclitaxel-carboplatinum regimen popular in the USA, compared to the gemcitabine-cisplatinum doublet more popular in Europe (as cisplatinum *versus* carboplatinum meta-analyses could have suggested) [57]. ORRs in both phase 3 trials were similar (35% and 32% in bevacizumab groups for ECOG and AVAIL trials, respectively), and compared favourably to the control arms (15% and 20% for ECOG and AVAIL trials, respectively), showing a better activity of the anti-angiogenic triplets, at least in terms of tumour shrinkage. However this 3-arm trial comparing gemcitabine-cisplatinum with placebo to gemcitabine-cisplatinum with bevacizumab 7.5 or 15 mg·kg^{-1}, missed its OS statistical end-point, since OS was not improved in bevacizumab arms. It showed that lower dosage of 7.5 mg·kg^{-1} dose was as effective as 15 mg·kg^{-1} with slightly less toxicity, this latter finding relating to dose-dependent cardiovascular toxicity. Many hypotheses have been raised to explain such discrepancies between the US and European bevacizumab trials. SORIA [58] mentioned the particularly high OS of the placebo arm of 13.1 months (*versus* 10.4 months in non-SCC of the pemetrexed trial), showing a strong selection with as many as 24% of nonsmoking patients (*versus* 14% in pemetrexed trial). Another related explanation refers to the higher percentage of patients that received active second-line therapy (65%) compared with previous trials (56% in pemetrexed trial). 44% of this sample enriched in nonsmoking patients, and presumably enriched in EGFR-mutated patients, received *EGFR* TKIs as post-protocol therapy, that could, therefore, have obscured the effect of first-line bevacizumab therapy. Indeed, a *post hoc* exploratory analysis showed that, when only patients without second-line therapy were analysed for OS, a trend toward a better OS was observed in the bevacizumab group (9.1 *versus* 7.6 months; HR 0.82; p=0.11). Finally, a more biological hypothesis was also raised by a paper published in *Cancer Cell*, showing that some cytoxic drugs (paclitaxel and docetaxel) were able to specifically induce a mobilisation of endothelial stem cells [59], but other drugs were not (gemcitabine, cisplatin or vinca-alcaloids), an experimental observation that could account for a synergy between bevacizumab and paclitaxel that is lacking for the bevacizumab-gemcitabine association, and underlining the fact that all combinations are not equivalent regarding angiogenesis. The Gustave Roussy team showed in a pooled analysis of ECOG and AVAIL trials that bevacizumab significantly increased OS at 1 yr, from 50% to 54% (HR 0.89, 95% CI 0.81–0.99; p=0.03) [58]. Based on these data, the European Union approved the use of Avastin at a dose of 7.5 or 15 mg·kg^{-1}, in combination with platinum-based chemotherapy, for the first-line treatment of patients with unresectable advanced, metastatic or recurrent NSCLC with other than predominantly squamous cell histology. As a maintenance bevacizumab monotherapy followed the six cycles of triplet therapy in both trials, until progression, the bevacizumab approval included such a maintenance treatment, the impact of which remains unclear.

EGFR MUTATIONS AND OTHER TARGETING STRATEGIES: A NEW PARADIGM FOR TODAY AND TOMORROW

Systematic molecular analysis of tumour DNA from major responders to *EGFR* oral TKIs in phase II trials of *EGFR* TKIs in a second-line setting led to a major discovery, in 2004, by three independent groups [60–62]. The subset of patients in these trials experiencing major clinical and radiological responses with prolonged survival actually had tumours with somatic heterozygous *EGFR* mutations. Those mutations are located in the DNA regions encoding the so-called ATP-pocket of the tyrosine kinase domain, either in exon 21, with point mutations (L858R or L861R being the most frequent events), or in exon 19 (small in-frame deletions). *EGFR* mutations led to a constitutively active receptor, with increased TKI affinity for the tyrosine kinase domain, favouring TKI binding instead of ATP binding. Spontaneously, cell lines harbouring such *EGFR*

mutations show constitutive activation of AKT survival pathway and those molecular events are, therefore, viewed as gain-of-function mutations [63]. The privileged AKT activation is thought to derive from the heterodimerisation of mutated *EGFR* with erbB3 receptor, which once autophosphoryaled, is able to bind phosphatidylinositol 3-kinase (PI3K), which activates AKT signalling [64]. Conversely, when treated with TKIs, lung cancer cell lines with mutated *EGFR* are prone to apoptosis, accounting for the exquisite efficacy of *EGFR* TKIs in patients whose tumours harbour those mutations. Retrospective data from series of patients treated by TKIs, or data from clinical trials, showed rapidly that EGFR mutations were indeed predictive of response and survival in patients receiving erlotinib or gefitinib. Over a dozen studies, the weighted average response rate (RR) to *EGFR* TKI treatment in mutation-positive cases was 78%, the average RR being in contrast 10% in mutation-negative cases [65]. This feature is more controversial for patients receiving chemotherapy, but the concept emerged that *EGFR*-mutated tumours could have better prognosis, with better response to chemotherapy as well. In adenocarcinoma, *EGFR* mutations are described in around 10–15% of Caucasian patients and >40% of Asian patients [66]. The two *EGFR* mutation types, exon 19 deletions and L858R substitution, account for ~90% of all known *EGFR* kinase domain activating mutations [66]. Several studies suggested that patients with the L858R mutation have significantly lower time to progression and survival rate compared with those with exon 19 deletions, but this feature remained controversial [67]. As soon as 2006, it was reported that some patients treated with TKIs, and who were major responders because of an activating *EGFR* mutation, could experience slow disease progression, months or years later [68]. It was documented in up to 50% of those patients that a second molecular event had emerged in cis- of the activating mutation, namely a point T790M mutation in exon 20, and sometimes more complex events, such as in-frame base insertions in exon 20 [69]. This second mutation favours binding of ATP and lowers *EGFR* TKI affinity, giving a survival advantage to cell clones with such a mutational event [69]. However, such clones remain addicted to the *EGFR* pathway and abrupt cessation of TKI treatments led to explosive clinical progression, in the days or weeks following TKI cessation, whereas previously those patients only progressed slowly when still receiving TKIs. So-called ''irreversible'' TKIs that bind covalently with the catalytic pocket of *EGFR* are believed to provide a sustained blockade of *EGFR* signalling and may also retain activity against tumours harbouring T790M resistance mutations [70]. Some are, therefore, under clinical development and phase 3 trials are still ongoing with these new drugs [71].

In <15% of cases with disease progression after initial TKI response, a c-*MET* gene amplification is found instead of the T790M *EGFR* mutation [72], which leads to a signalling heterodimer receptor ErbB3/c-Met able to activate the PI3K/AKT survival pathway independently of *EGFR*. This observation suggested that combination of erlotinib with c-Met inhibitors could prevent the emergence of c-*MET* amplification as a resistance mechanism to *EGFR* TKIs. Clinical development of such approaches is currently ongoing [73].

The most compelling findings in *EGFR* TKI development came in late 2009, with the publication of prospective studies assessing their efficacy in a first-line setting in NSCLC stage IV patients harbouring *EGFR* mutations. The Spanish Lung Cancer group prospectively evaluated the feasibility of large-scale screening for *EGFR* mutations, on a country-wide scale, succeeding in screening lung cancers from 2,105 patients in 129 institutions in Spain for such mutations [19]. *EGFR* exon 19 and exon 21 L868R mutations were found in 350 of 2,105 patients (16.6%). As previously reported by multiple groups, they were more frequent in females (69.7%), in never-smoker patients (66.6%) and in patients with adenocarcinomas (80.9%). 217 patients with *EGFR* mutation were given erlotinib. The ORR was 70.6%; median PFS and OS for those patients were 14 months and 27 months, respectively. Such long median survivals had never been reported previously for stage IV NSCLC patients. Half of the patients received erlotinib as first-line (n=113) therapy, and half as second-line therapy (n=104). Strikingly, both groups had the same PFS and OS. This prospective study emphasised the fact that large-sale systematic screening for EGFR mutations is routinely feasible, and that *EGFR*-mutant lung cancer is actually a distinct class of NSCLC spectacularly benefiting from *EGFR*-TKI therapy. Those results compared favourably with the usual 30% response rate, the 4- to 5-month PFS, and the 10- to 12-month median survival observed in adenocarcinoma patients without EGFR mutations, receiving cisplatinum-based chemotherapy with or without bevacizumab, with or without maintenance therapy (see below).

In the same issue of the *New England Journal of Medicine* the results of a seminal Asian phase 3 trial, IPASS (IRESSA Pan-Asia Study), were published, re-enforcing the specificity concept of *EGFR*-mutant lung cancer [18]. In this large open-label study, East Asian chemo-naïve patients who had advanced pulmonary adenocarcinoma and were nonsmokers or former light smokers, were randomly assigned to receive gefitinib (250 $mg \cdot day^{-1}$) (609 patients) or carboplatin plus paclitaxel (608 patients) in 87 centres in Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan and Thailand. The study met its PFS primary objective of showing the non-inferiority of gefitinib in such adenocarcinoma and nonsmoking selected Asian patients. Indeed, median PFS wase 5.7 and 5.8 months in the gefitinib and chemotherapy groups, respectively, the 12-month rates of PFS being 24.9% with gefitinib but only 6.7% with carboplatinum-paclitaxel. As suggested by the non-different median survivals, but diverging 1-yr survivals, survival curves crossed leading to the superiority of gefitinib, as compared with carboplatinum-paclitaxel, for PFS (HR for progression or death 0.74, 95% CI 0.65–0.85; p<0.001). Survival curves crossing suggested that two different subsets of patients had different evolutions with gefitinib. Indeed, in the subgroup of 261 patients who were positive for the *EGFR* mutation, PFS was significantly longer among those who received gefitinib than among those who received carboplatinum-paclitaxel (HR for progression or death, 0.48; 95% CI, 0.36–0.64; p<0.001). Conversely, in the subgroup of 176 patients who were negative for the mutation, PFS was significantly longer among those who received carboplatinum-paclitaxel (HR for progression or death with gefitinib 2.85, 95% CI 2.05–3.98; p<0.001). OS at time of analysis (only 37.0% patients died) was similar between the two arms in the overall population (HR for death in the gefitinib

group 0.91, 95% CI 0.76–1.10), median survival being 18.6 months among patients receiving gefitinib and 17.3 months among patients receiving carboplatinum-paclitaxel, taking into account a substantial fraction of patients that crossed over and received the alternate treatment at progression. Finally, significantly more patients in the gefitinib group than in the carboplatinum-paclitaxel group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L questionnaire.

Two Japanese studies further re-enforced the use of first-line *EGFR* TKIs in NSCLC patients with *EGFR* activating mutations. The North East Japan Gefitinib Study Group reported, at the 2009 ASCO meeting, the results of a randomised study comparing gefitinib *versus* paclitaxel-carboplatinum chemotherapy in PS 0–1 NSCLC patients with a EGFR mutated tumour [74]. Interim analysis resulted in stopping the inclusions after 198 patients were randomised, since the statistical end-point was reached, with ORR being 75% in the gefitinib group *versus* 25% in the chemotherapy group, median PFS being 10.6 *versus* 5.5 months ($p<0.001$), respectively, showing a clear statistically significant superiority for gefitinib.

The West Japan Oncology Group also reported the results of an open label phase 3 study, in which they randomised 177 chemotherapy-naive patients aged 75 yrs or younger, diagnosed with stage IIIB/IV NSCLC or post-operative recurrence, and harbouring *EGFR* mutations (either the exon 19 deletion or L858R point mutation), to receive either gefitinib (n=88) or cisplatinum (80 mg·m^{-2} *i.v.*) plus docetaxel (60 mg·m^{-2} *i.v.*; n=89), administered every 21 days for three to six cycles [20]. The primary end-point was PFS. Not surprisingly, the gefitinib group had significantly longer PFS compared with the cisplatinum plus docetaxel group, with a median PFS time of 9.2 months *versus* 6.3 months (HR 0.489, 95% CI 0.336–0.710; log-rank $p<0.0001$), median OS exceeding an amazing 30 months, without differing in both arms, since 59% of chemotherapy arm patients ultimately received gefitinib in a second-line setting.

All these convergent studies led to a new paradigm in EGFR mutated NSCLC patients, and the EMEA registration of gefitinib for patients whose tumours harbour an activating EGFR mutation, whatever the setting, be it first, second or third line.

The EGFR story represents a proof of concept for a personalised medicine, relying on our ability to translate basic research findings into innovative biologic therapies coming to routine clinical practice. However, the success of such approaches depends on having accurate diagnostic tests that can identify the subsets of patients most benefiting from those targeted therapies. Currently, NSCLC cancers (especially of the adenocarcinoma subtype) that were previously thought of as a commune disease (220,000 new cases each year in the USA, and 27,000 in France) are now viewed as a mosaic of rare diseases, each defined by a specific mutational founder and addictive event, often involving a kinase-driven proliferating pathway. A non-exhaustive list of such mutations, beyond EGFR mutations, can be detailed, involving K-Ras (20–30% of adenocarcinoma patients), c-MET (5%), erB2 (4%), FGFR4 (4%), B-Raf (3%), PI3K (4%), MEK-1 (2%), and so on [75].

Thus, drug development is ongoing for the targeting of some of these kinases. A non-ATP competitive inhibitor, ARQ-197, that binds c-MET receptor tyrosine kinase and stabilises its inactive conformation, was recently used in combination with erlotinib, and compared with erlotinib plus placebo in a randomised controlled phase 2 trial in a second-line setting [76]. This combination showed efficacy in clinical subgroups of patients in whom EGFR TKIs are thought to be less efficient, such as patients with K-Ras mutations (PFS 9.7 *versus* 4.3 months for erlotinib plus placebo arm; HR 0.18), in wild-type EGFR patients (PFS 13.7 *versus* 8.1 months for control arm) or SCC patients (PFS 13.7 *versus* 8.4 months).

In 5% of nonsmoking, EGFR and K-Ras wild-type patients, another oncogenic event has been described, with a gene fusion on chromosome 2, involving ALK1 (anaplastic lymphoma kinase) and N-terminal domain of EML-4 (echinoderm microtubule-associated protein like 4), leading to constitutive activation of ALK1 kinase [77–79]. Such an alteration could be targeted by crizotinib (PF-02341066, a dual ATP competitive inhibitor of c-MET and ALK1). In a phase I trial, some impressive results were reported at the 2010 ASCO meeting, reminiscent of those obtained with EGFR TKI in EGFR mutant patients [80]. 82 patients were treated with crizotinib, most of them in a second-, third- or fourth-line setting, with escalating doses up to 300 mg *b.i.d.*, and then with 250 mg *b.i.d.* dose, in an expanding cohort of patients showing an ALK-EML4 fusion gene in their tumour (by FISH technique). In this molecularly selected subgroup, disease control rate was 87%, response rate was 57% and PFS at 6 months was 72%, leading directly to a future phase 3 prospective trial. Hence, again, the concept of a personalised targeted therapy in NSCLC would be verified with this agent, opening routes for ulterior developments of other drugs targeting molecularly defined NSCLC, and a new era in lung cancer pharmacological therapy.

"MAKING NEW WITH OLD STUFF": CISPLATINUM-BASED DOUBLET CHEMOTHERAPY, THE MAINTENANCE CONCEPT

The multi-target agent pemetrexed, which essentially targets thymidylate synthase and, thus, thymine nucleotides and DNA metabolism, was the only cytotoxic agent with successful clinical development, initially in second-line setting, and then in front-line therapy of chemo-naïve NSCLC, during the past decade. As with other single-agent monotherapy (vinorelbine, gemcitabine, bevacizumab), *i.v.* pemetrexed monotherapy is well-supported, with limited toxic side-effects, and could be administered in an outpatient setting for a long time in non-progressive patients. As in all phase 2 and 3 trials using targeted monoclonal antibodies against either *EGFR* or VEGF non-progressive patients continued to receive the monoclonal antibody after completion of the initial chemotherapy/antibody combination for four to six cycles, a growing interest emerged for a maintenance concept, initially designed for what were viewed as purely cytostatic agents. Indeed, the ASCO 2004 guidelines stated that front-line systemic platinum-based doublet therapy for stage IV NSCLC should not exceed four to six cycles, before entering a clinical or radiological observation phase until disease progression [13]. This was called the ''stop and go'' strategy. Second-line therapy was initiated at the time of disease progression and three agents were registered in this indication, pemetrexed, docetaxel and erlotinib, as described in a previous paragraph [31, 42, 47]. Initial attempts to

demonstrate the superiority of an alternative strategy, a short course of induction, aggressive, cisplatinum-based therapy with four cycles, immediately followed by a monotherapy until disease progression, were unsuccessful, with some trials showing negative OS [81], some being positive for PFS, but all being underpowered [82, 83].

The definitions of maintenance therapy that uncover different concepts have been recently clarified. Maintenance is now widely defined as any treatment that helps to control cancer after disappearance or shrinkage induced by front-line therapy. To reach that goal, a maintenance drug has to be well tolerated, without cumulative toxicity. Recent clinical trials of maintenance could be stratified into: 1) ''true'' maintenance continuation therapy, in which one of the drugs administered within the front-line regimen that led to response or stabilisation is continued alone until progression; and 2) ''switch'' maintenance therapy, in which one drug of different mechanism of action is initiated immediately after completion of the first-line chemotherapy. Such a sub-strategy could also be called ''early second line'' therapy.

Some authors have argued that only switch maintenance could have an impact on survival, by preventing the emergence of resistant clones.

Evidence for ''true'' maintenance continuation therapy was raised by two targeted agents phase 3 trials, the SATURN (Sequential Tarceva in Unresectable NSCLC) and ATLAS trials. In the SATURN study, 1,949 patients received four cycles of first-line platinum-based chemotherapy. 889 non-progressive patients were then allocated to receive either erlotinib (n=438) or placebo (n=451) [84]. Median PFS was significantly longer with erlotinib than with placebo (HR 0.71, 95% CI 0.62–0.82; p<0.0001). Even though the absolute median PFS survival did not appear to be clinically relevant (1.2 weeks), it translated into a 6-month disease control rate of 25% in the erlotinib arm *versus* 15% in the placebo arm. Analysis for *EGFR* mutation status showed that erlotinib was strikingly more active than placebo in patients with *EGFR*-activating mutations (HR 0.10, 95% CI 0.04–0.25; p<0.0001), but wild-type EGFR patients also benefited from erlotinib maintenance therapy (HR 0.78; p=0.0185), and a survival advantage was also observed in patients with EGFR immunostained tumours (HR 0.69, 95% CI 0.58–0.82; p<0.0001). OS was significantly prolonged with erlotinib *versus* placebo in the intention-to-treat population (median 12.0 *versus* 11.0 months; HR 0.81, 95% CI 0.70–0.95; p=0.0088).

The ATLAS trial was conceived with the same design, except that induction therapy included bevacizumab, and that randomisation aimed to compare bevacizumab plus placebo *versus* bevacizumab plus erlotinib maintenance therapy [85]. Again, the erlotinib arm was shown to significantly increase PFS compared with placebo (HR 0.72, 95% CI 0.592–0.881; p=0.0012), 6-month PFS rate being 40% in the bevacizumab-erlotinib arm *versus* 28.4% in the bevacimab-placebo arm. A 40% rate of crossover (placebo arm patients ultimately receiving erlotinib once progression was observed), and an underpowered design for OS precluded this trial reaching significance for the OS analysis. However, after occurrence of 57% of events, a 2-month benefit (15.9 *versus* 13.9 months, HR 0.90, 95% CI 0.74–1.09; p=0.2686) was reported in the doublet maintenance arm, a finding of clinical relevance that deserves confirmation.

Finally, the main data favouring maintenance concept came from classical cytotoxic trials. A Central European Cooperative Oncology Group randomised phase 3 trial first showed, in 2006, that gemcitabine maintenance in non-progressive patients after four cycles of gemcitabine-cisplatin doublet could increase time to progression compared with best supportive care (3.6 *versus* 2 months; p=0.01) [83]. However, this trial was underpowered to show any improvement of OS in the whole population trial (13 *versus* 11 months; p=0.195), although survival was better in PS 0–1 patients receiving maintenance. Thereafter, FIDIAS *et al*. [82] aimed to determine, after induction treatment with four cycles of carboplatin-gemzar, whether immediate switch maintenance with docetaxel in non-progressive patients could do better than delayed docetaxel treatment at time of progression. Indeed, median PFS was 3 months longer in the immediate arm than in the delayed arm (5.7 *versus* 2.7 months; p=0.0001). However, this trial failed to detect a significant OS advantage, despite a clear trend being shown (12.3 *versus* 9.7 months; p=0.085). When patients that effectively received docetaxel were compared, the OS was strictly identical (12.5 months), since only 62% of patients allocated to the delayed arm effectively received docetaxel, mainly because of disease progression and PS rapid alteration that precluded chemotherapy treatment. Conversely, 91% of patients randomised in the immediate docetaxel arm did receive the allocated treatment, suggesting that maintenance therapy could play a role in increasing drug exposure.

The JMEN phase 3 double-blinded trial tested another switch maintenance therapy by randomising pemetrexed *versus* placebo in non-progressive, PS 0–1 NSCLC patients, who had received any platin-based doublet but not pemetrexed-platinum combination [86]. PFS was, as usual, statistically longer in patients receiving maintenance than in patients receiving placebo (4.0 *versus* 2.0 months; HR 0.60, 95% CI 0.49–0.73; p<0.00001), in every subset of patients, except in patients with SCC. However, this trial also demonstrated a significant advantage in terms of OS for the maintenance pemetrexed arm, with a clinically meaningful 2.8-month difference (13.4 *versus* 10.6 months; HR 0.70, 95% CI 0.65–0.95; p=0.012). Again, this difference was higher in non-SCC patients (15.5 *versus* 10.3 months; HR 0.70, 95% CI 0.56–0.88; p=0.002) than in SCC patients. SCC patients did not benefit from this therapeutic strategy since, in those patients, pemetrexed did even worse than placebo (9.9 *versus* 10.8 months; p=0.678). However, only 62% of placebo arm patients, and 52% of patients in the pemetrexed arm, received a second-line therapy; only 21.5% of patients received erlotinib in this trial with a large representation of East European countries. This issue could explain part of the extremely high survival difference in non-SCC patients, with patients only receiving placebo followed by second-line chemotherapy being probably under-treated with regard to EGFR TKI. In fact, only 33% of patients in the placebo arm received more than one line of therapy, whereas 52% of patients received three lines or more in the pemetrexed arm.

In the meta-analysis by SOON and co-workers [87, 88] that included the JMEN study plus 13 other randomised trials (but

not SATURN or the ATLAS trials), and collected data on 1,684 patients with maintenance and 1,395 without, maintenance therapy was shown to slightly, but significantly, improve OS (HR 0.92, 95% CI 0.86–0.99; p=0.03), pleading for a new paradigm in NSCLC treatment.

Finally, the design of a phase 3 trial from the French Intergroup, presented at the 2010 ASCO meeting, resolved the latest issues raised by JMEN trial [89]. Patients received four cycles of gemcitabine-cisplatin induction therapy and non-progressive patients were randomised into three arms: observation, erlotinib switch maintenance or gemcitabine continuation maintenance; all were given a fixed second-line at progression, of pemetrexed. The primary end-point was PFS, the trial was statistically designed to test the erlotinib arm *versus* observation, and the gemcitabine arm *versus* observation. 464 patients were randomised. The trial met its main end-points, since gemcitabine resulted in a 3.8-month median PFS, *versus* 1.9 months in the observation arm (HR 0.55, 95% CI 0.43–0.70; p<0.0001), whereas erlotinib gave a 2.9-month PFS (HR 0.82, 95% CI 0.73–0.93; p=0.002), an advantage limited to patients with EGFR immunopositive tumours. Preliminary OS results favoured, although not significantly, the gemcitabine (HR 0.86, 95% CI 0.66–1.12) or erlotinib (HR 0.91, 95% CI 0.80–1.04) arms compared with the observation arm. Pemetrexed second-line was effectively given to 76% of observation arm patients, 60.4% of gemcitabine arm patients and 64.3% of erlotinib-treated patients. Morevover, half of the observation arm patients also received erlotinib third-line treatment, and 41% of gemcitabine-treated patients ultimately received erlotinib in a third-line setting. Thus, the authors raised the hypothesis that OS impact of maintenance strategy might not be solely due to the increased proportion of patients exposed to multiple treatment lines, since a substantial fraction of patients in all groups received multiple lines, but rather to a specific effect. Taking into account all these cumulated data, one could therefore consider maintenance therapy as a new standard for NSCLC stage IV patients that actually impacts OS [22].

ELDERLY PATIENTS DESERVE ACTIVE TREATMENT

The recent and rapid increase of lung cancer incidence in elderly patients is the consequence of two phenomena: increased life expectancy and increased incidence of cancer with age, probably secondary to the age-related decrease of efficient DNA repair mechanisms. Therefore, at least one-third of lung cancer patients are 70 yrs of age or older [90, 91]. Those patients want to live to the following year as strong as younger patients and call for efficacious treatments. More and more patients aged over 70 yrs stay physically and intellectually fit, although cardiovascular comorbidities also increase in this fast-growing segment of population.

Historical phase 3 trials were conducted by Italian investigators who showed that vinorelbine or gemcitabine monotherapy could improve OS compared with best supportive care (1-yr survival 32% with vinorelbine *versus* 14% with best supportive care; p=0.03) [92], but that vinorelbine-gemcitabine doublet therapy was more toxic without any gain of efficacy [93]. Oral vinorelbin recently demonstrated similar efficacy and similar toxicity profile in a phase 2 trial [94].

LILENBAUM *et al*. [95] reported in 2007 a small randomised phase 2 trial using weekly docetaxel or docetaxel every 3 weeks, in patients 70 yrs of age and older with PS 0–1, or in patients of any age and with PS 2. Haematological toxicity was shown to be significantly lower in the weekly schedule group, with a trend toward better survival (6.7 *versus* 3.5 months). A subset exploratory analysis of 30 octogenarian patients revealed similar outcomes as in 70- to 79-yr-old patients.

Monthly docetaxel (60 $mg \cdot m^{-2}$) was compared to vinorelbin monotherapy in a Japanese phase 3 trial dedicated to PS 0–1 patients over the age of 70 yrs, which showed a better, although not statistically different, median OS of 14.3 months for docetaxel as compared with 9.9 months for vinorelbin, with a rather good 58.6% 1-yr survival when compared to 36.7% for patients receiving vinorelbin [96]. However, those good results were obscured by a 14% increase in grade 3/4 neutropenia involving as many as 83% of the docetaxel-treated patients, a proportion that could be judged as unacceptable for such a fragile population, even if the authors claimed that such toxicity did not impair QoL scores.

In the randomised phase 2 INVITE (IRESSA in NSCLC *versus* Vinorelbine Investigation in the Elderly) trial, treatment with the EGFR TKI gefitinib was shown to lead to a 33.9% 12-month OS, similar to the 33.2% for vinorelbin, in chemotherapy-naive elderly patients with unknown EGFR mutational status. Tolerability was shown better for gefitinib, but higher EGFR gene copy number, as detected by FISH, surprisingly predicted better response and survival in patients treated with vinorelbin [97].

Front-line pemetrexed or sequential pemetrexed-gemcitabine monotherapies were also evaluated in a randomised phase 2 design and showed similar 1-yr survivals of 28% that did not represent any advance when compared with the Italian seminal trials ELVIS and MILES [98].

Second-line chemotherapy in elderly patients is still poorly studied. A subgroup analysis of the large phase III second-line pemetrexed trial focused on 86 patients aged $\geqslant$70 yrs, and showed that all efficacy parameters, ORR, PFS and OS were similar in both elderly and younger patients [99]. Older patients randomly assigned to pemetrexed had longer time to progression (4.6 *versus* 2.9 months) and longer median OS (9.5 *versus* 7.7 months) than patients treated by docetaxel. Overall, elderly patients tolerated second-line chemotherapy as well as their younger counterparts, with more haematological toxicity in the docetaxel arm than in the docetaxel arm. A modified docetaxel schedule of 37.5 $mg \cdot m^{-2}$ on days 1 and 8 every 3 weeks was then shown to be better tolerated in a second-line setting for patients older than 70 yrs, with a promising 56% disease control rate, pleading for confirmation studies [100]. Finally, exploratory subgroup analysis of BR21 phase 3 trial showed that erlotinib second-line therapy in unselected patients was as efficacious in the 112 patients aged over 70 yrs as in the 376 younger patients, when compared with placebo in both groups, and that erlotinib could represent a valuable option for second-line therapy in elderly patients [101].

Despite accumulating evidence supporting chemotherapy in stage IV elderly NSCLC patients, a recent analysis of the SEER (Surveillance, Epidemiology and End Results) database showed

that only 25.8% of patients older than 66 yrs (25,285 patients with advanced NSCLC incident from 1997 to 2002) received first-line therapy [102]. Conversely, multivariate analysis showed that receipt of any chemotherapy and platinum-based doublet regimens was associated with reduction in the adjusted hazard of death (0.558, 95% CI 0.547–0.569) and an increase in adjusted 1-yr survival from 11.6% (95% CI 11.1–12.0) to 27.0% (95% CI 26.4–27.6) [91]. In that retrospective large-scale analysis, platinum-doublet receipt increased adjusted 1-yr survival in comparison to treatment with single agents, from 19.4% (95% CI 18.3–20.4) to 30.1% (95% CI 28.9–31.4).

Subgroup analyses dealing with patients aged over 65 or 70 yrs in a large phase III platinum-based chemotherapy trial [103], or in population-based cohort studies [104], showed that leukopenia and neuropsychiatric toxicity were more common in older than in younger patients, whereas efficacy results (response rate, PFS and OS) were similar. In the same manner, for patients with resectable disease included in adjuvant chemotherapy phase III trials, despite elderly patients receiving less chemotherapy, adjuvant vinorelbine and cisplatin improves survival in patients older than 65 yrs with acceptable toxicity [105]. However, prospective trials specifically dedicated to elderly patients and first-line platinum-based chemotherapy are rare.

Some phase II trials dedicated to patients older than 70 yrs prospectively explored platinum-based doublets. A group from Italy first showed, in a phase I–II trial using either cisplatin (60 $mg \cdot m^{-2}$) plus gemcitabine or cisplatin (40 $mg \cdot m^{-2}$) plus vinorelbin, a slight increase in 1-yr survival to 41% and 37%, respectively, at the price of a manageable excess of haematological toxicity (up to 3.4 and 3.2%, respectively, of febrile neutropenia grade 3–4) [106].

Weekly cisplatin (25 $mg \cdot m^{-2}$) plus weekly docetaxel (25 $mg \cdot m^{-2}$) on days 1, 8, and 15 every 4 weeks was explored in 48 elderly patients by Chinese investigators, showing encouraging activity with a 10.9-month median survival and no excessive toxicity [107]. An interesting 43.3% 1-yr survival was also observed by Japanese investigators in patients aged over 70 yrs, with the monthly docetaxel-carboplatin doublet; a finding deserving further prospective studies with docetaxel doublets [108].

Lastly, three phase 2 trials, and a subset analysis restricted to elderly patients from a phase 3 trial, also showed that weekly paclitaxel plus monthly carboplatin chemotherapy could be administered safely to elderly patients with promising OS results [109–112]. Indeed, in all these trials, involving a total of 206 patients over the age of 70 yrs, 1-yr survival ranged from 31% to 62%.

The balance of efficacy and toxicity is of course the main factor that limits platinum-based doublet administration in patients aged over 70 yrs. Some efforts have been made to predict febrile neutropenia risk with prediction models [113]. Strategies to prevent deaths from toxicity in the most exposed elderly fragile population have included either prophylactic use of granulocyte-colony stimulating factors when febrile neutropenia risk is >20%, weekly schedules that have been proved to lower haematological grade 3/4 adverse effects without penalising efficacy in this population [112, 114], or use of non-platinum doublets [115, 116].

Finally, the first phase 3 randomised trial of platinum-based doublet therapy in an elderly population, presented in the plenary session of the 2010 ASCO meeting by the French Intergroup, addressed many issues raised by previous phase 2 trials [117]. This trial included 451 patients >70 yrs, and was closed at the second interim analysis since results greatly favoured weekly paclitaxel-monthly carboplatin doublet over the monotherapy arm (either vinorelbin or gemcitabine, depending on the choice of the centre). Patients received either four cycles of the paclitaxel doublet on a 4-weekly schedule or five cycles of bi-monthly monotherapy and evaluation was done at week 18 in both arms. At progression, or in case of excessive toxicity, both arms were switched to erlotinib 150 $mg \cdot day^{-1}$ as second-line therapy. PFS was doubled in the paclitaxel-carboplatin arm from 3.0 to 6.1 months ($p<10^{-6}$), and 1-yr OS was dramatically increased in the doublet arm from a classical 26.9% to a remarkable 45.1% (HR 0.63, 95% CI 0.51–0.79; $p=0.0004$). PS 0–1, never-smoking history, adenocarcinoma histology, weight loss <5% and activities of daily living (ADL) score 6 were associated with significantly favourable outcome in multivariate analysis, whereas Mini-Mental Score (MMS), Charlson Comorbidity Index and age over 80 yrs did not show any prognostic value. Moreover, subgroup analysis demonstrated that, in all subsets of patients except for lower MMS patients, doublet chemotherapy was statistically superior to single-agent therapy in terms of OS. In lower MMS score patients, doublet chemotherapy did not provide a survival benefit but was not deleterious. Toxicity was statistically higher in the doublet arm with notably 4% death rate due to toxicity in the weekly paclitaxel arm compared with 1.33% in the monotherapy arm ($p=0.035$) but, conversely, the number of early deaths (within 3 months) was significantly higher in the monotherapy arm compared with the doublet arm, correlating with higher rate of early progressive disease for monotherapy patients. It should be analysed whether functional/cognitive capacity impairment, as measured by geriatric score, could predict for haematological toxicity, as previously suggested [118], and deserve specific prophylactic measures in altered patients.

Therefore, weekly paclitaxel-monthly carboplatin doublet provided longer PFS, longer OS and higher response rate than single agent therapy, with a beneficial effect on survival in most of the subgroups tested (PS 2, older age, smokers and lower ADL score). ADL geriatric index showed prognostic value but was not predictive for specific survival with doublet or monotherapy. Despite a higher toxicity profile, this combination might change the treatment paradigm for elderly patients with advanced NSCLC, and thereby clearly change natural history of this incurable disease in patients aged over 70 yrs, allowing prognosis of elderly patient to become closer to younger patients' prognosis.

CONCLUSION

Over the past decade, substantial improvements have been made in the standard of care of advanced NSCLC patients. We have observed a 1-year survival increase from 30% to 55% with third-generation regimens with or without front-line targeted agents, or with available efficient second- and third-line

therapies in selected patients with good PS. The emergence of targeted therapies in first- and second-line settings has spectacularly changed the natural history of disease in some subsets of NSCLC, leading to dramatically prolonged OS in subgroups of molecularly defined patients. Maintenance therapy, either with targeted agents or cytotoxic drugs, also improved survival for larger groups of patients, mainly with non-SCC. Indeed, NSCLC, formerly viewed as a frequent unique disease of uniform presentation, in now viewed as a mosaic of rarer diseases defined either by pathological characteristics (non-squamous, SCC, adenocarcinoma with bronchioalveolar carcinoma features, *etc.*), molecular characteristics (driver oncogenic mutations such as EGFR mutations, Ras mutations, ALK-EMLK4 fusion gene, *etc.*), or by clinical characteristics (never-smoker patients, females, or Asian or elderly patients). Main survival progresses are now coming from improving treatment paradigms in those subcategories of patients, either by targeted agents needing a fine molecular identification of patients that do not represent >5% of all NSCLC, or by specific strategies such as weekly doublet platinum-based therapy in patients older than 70 yrs. Association of targeted agents and hormonal therapies are under evaluation in females, specific strategies are currently being explored in bronchioalveolar carcinomas, and Asian patients are clearly thought to present a distinct disease especially sensitive to EGFR-targeting agents.

However, tobacco smoke epidemics, although declining in Occidental countries, is exploding in developing countries, particularly in Africa and Asia, and will still kill 1 billion patients over the course of the 21st century, a fact that emphasises the need to further eradicate this unique cause of lung cancer death in humankind [119, 120].

STATEMENT OF INTEREST

G. Zalcman has received fees for speaking, for organising education, and reimbursement for attending international meetings from Lilly-France, Roche-France, GSKbio, AstraZeneca-France, MSD-France, Merck Serrono-France, and for participating in advisory boards from Roche-France, Elli Lilly, GSKbio and BMS.

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