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ABSTRACT:

Lung cancer is the leading cause of cancer-related mortality worldwide in both sexes, expected to account, in the near future, for more than 30% of all cancer-related deaths. Recently, improvements in the systemic therapy of non-small-cell lung cancer according to histology and tumor molecular characteristics led to a progressive prolongation of survival, more clinically meaningful in selected groups of patients with tumors harboring specific genomic alterations. As the search for individualized therapeutic approaches could represent one of the potential ways to improve survival expectancy of non-small-cell lung cancer patients with advanced disease stage, the aim of this review is to discuss how currently to select the best front-line therapeutic strategy.

Lung cancer is the leading cause of cancer-related mortality worldwide in both sexes and accounts for 26 and 29% of all female and male cancer deaths, respectively [1]. Incidence rates in women started declining in the late 1990s, more than a decade after observing the same trend in men [2]. Probably, differences in lung cancer incidence patterns between men and women reflect historical differences in tobacco use.

The overall 5-year survival rate for lung cancer is currently approximately 16% and this rate drops down to 4% for those patients diagnosed at advanced stages [1,3].

Owing to relevant epidemiological changes and recent advances regarding systemic therapy of non-small-cell lung cancer (NSCLC) according to histology and molecular characteristics, this review summarizes how to currently choose the best strategy of treatment in front-line setting for patients presenting with advanced disease stage.

Role of cytotoxic chemotherapy

A meta-analysis spanning 25 years of clinical research established that platinum-based chemotherapy doublets are the backbone of treatment for advanced NSCLC. This approach guarantees a modest but statistically significant improvement in survival and quality of life [4,5]. In addition, there is evidence that cisplatin is more effective than carboplatin in terms of objective response rate (ORR; 30 vs 24%, respectively; p < 0.001), despite a less favorable toxicity profile [6].

Commonly used platinum doublets demonstrate comparable activity with differential toxicity profiles (Table 1) [7–9]. In one study, the combination of cisplatin plus docetaxel showed a higher ORR and a better overall survival (OS) in comparison with the other explored regimens [9].

A retrospective review and meta-analysis demonstrated that triplet combinations are associated with an increase in ORR but not in progression-free (PFS) and OS compared with doublets [10]. Overall these findings suggest that chemotherapy for all comers as front-line approach for advanced NSCLC had already reached a therapeutic plateau.

Histology-driven chemotherapy

Evidence generated from a better knowledge of tumor cell biology and the development of drugs targeting specific enzymatic pathways of the tumor cell, such as the folate pathway, have shown

that histology may become one of relevant finding in the therapeutic decision-making process of NSCLC.

In a large Phase III randomized trial, cisplatin plus pemetrexed was not inferior to cisplatin plus gemcitabine for all the tested clinical efficacy outcomes [11]. This study included a preplanned analysis for histology, and patients with nonsquamous NSCLC benefited more from the pemetrexed-based regimen in terms of OS (hazard ratio [HR]: 0.81; 95% CI: 0.7–0.94; p = 0.005), while PFS did not differ between the two groups. On the contrary, patients with squamous cell carcinoma showed a marginally significant superiority in OS (10.8 vs 9.4 months, respectively; HR: 1.23; 95% CI: 1.00–1.51; p = 0.05) and PFS (5.5 vs 4.4 months, respectively; HR: 1.36; 95% CI: 1.12–1.65; p < 0.05) for patients treated with cisplatin plus gemcitabine. Cisplatin plus pemetrexed resulted in a statistically significant inferior incidence of grade 3 and 4 neutropenia, anemia, thrombocytopenia, febrile neutropenia and alopecia (p ≤ 0.001), whereas drug-related grade 3 and 4 nausea was higher (p = 0.004).

The differential activity of pemetrexed in nonsquamous histology has been also supported by a retrospective analysis of a Phase III trial of single-agent pemetrexed versus docetaxel in the second-line treatment of recurrent NSCLC [12] and, prospectively, in a Phase III maintenance study of single-agent pemetrexed [13]. The benefit of continuation maintenance pemetrexed in nonsquamous NSCLC has been further supported by another Phase III study for advanced nonsquamous NSCLC [14,15].

These results have been related to a different expression of thymidylate synthase (TS), one of the main enzymes of the folate pathway targeted by pemetrexed, in different histologic subtypes of NSCLC, which may justify the lower efficacy of pemetrexed in the squamous histology being TS higher in this histotype [16].

Based on these data, patients with adenocarcinoma are more likely to benefit from a pemetrexed-based regimen, and in 2008, pemetrexed in combination with cisplatin was been granted as first-line treatment for patients with advanced NSCLC other than predominantly squamous cell histology.

The predictive role of histology is a peculiar finding in most of the studies investigating pemetrexed in NSCLC, while in previous studies, histology was not associated with any prognostic or predictive value [7,8,17].

Role of biological agents
• Monoclonal antibodies anti-VEGF: bevacizumab

Clinical research efforts with targeted agents have endeavored to improve survival beyond that provided by cytotoxic chemotherapy. The randomized trial ECOG E4599 assessed the addition of bevacizumab, a monoclonal antibody targeting the VEGF and inhibiting its interaction with the VEGF receptors, to carboplatin plus paclitaxel in patients with metastatic nonsquamous NSCLC. The study showed a statistically significant improvement in median OS for the group of bevacizumab-treated patients [18]. Median PFS and ORR were also improved. Adenocarcinoma histology was associated with a greater OS benefit (14.2 vs 10.3 months, respectively). The administration of bevacizumab was well tolerated, even if an excess of severe bleeding episodes was reported in the bevacizumab arm (4.4 vs 0.7%, respectively; p < 0.001).

Based on the outcome of this trial, in 2006, the US FDA rapidly granted approval for bevacizumab administered in combination with carboplatin plus paclitaxel for the initial treatment of patients with unresectable, locally advanced, recurrent or metastatic, nonsquamous NSCLC [19].

In another front line Phase III study, bevacizumab was assessed in combination with cisplatin plus gemcitabine [20]. The study explored bevacizumab at two different dose levels, 7.5 and 15 mg/kg,

showing a statistically significant improvement in PFS, the primary end point of the study, in both bevacizumab arms when compared with chemotherapy alone. The ORR was also significantly greater in both bevacizumab arms (37.8 and 30.6%, respectively, vs 21.6%). All treatment groups achieved a median OS greater than 13 months, but no difference in median OS was observed among treatment groups [21].

A systematic review and meta-analysis of four trials assessing the efficacy of chemotherapy plus bevacizumab versus chemotherapy alone in NSCLC included 2200 patients and confirmed a significantly higher ORR and a better PFS for bevacizumab treated patients with both 7.5 and 15 mg/kg, while there was no statistically significant increase in OS [22]. The discrepancy between a clear benefit in PFS and a not consistent benefit in OS in the above mentioned studies may be the consequence of a different impact of postprogression therapies.

In the USA, bevacizumab is currently licensed at dose of 15 mg/kg in combination with carboplatin plus paclitaxel as first-line therapy in patients with advanced nonsquamous NSCLC, while in Europe its use is in combination with platinum-based chemotherapy at the dose of both 7.5 or 15 mg/kg.

SaiL was a large Phase IV trial undertaken in a real-world population in order to assess the safety and efficacy of first-line bevacizumab combined with several standard chemotherapy regimens [23]. The study confirmed the manageable and consistent safety profile of bevacizumab, as well as its efficacy on treatment outcomes. Safety data coming from different studies excluded an excess of the risk of bleeding following bevacizumab use in NSCLC patients with CNS metastases [24,25] and led to the approval by EMA of bevacizumab in combination with a platinum-based chemotherapy even in patients with untreated CNS metastases [26].

A multicenter Phase II study evaluated the safety and efficacy of bevacizumab and pemetrexed maintenance after initial therapy with pemetrexed and carboplatin plus bevacizumab [27]. The study showed an ORR of 55% (95% CI: 41–69%) with a favorable toxicity profile. The median PFS and OS were 7.8 and 14.1 months, respectively. These promising results led to a subsequent Phase III comparison against the standard regimen containing bevacizumab. The PointBreak study was a multicenter, randomized Phase III study of pemetrexed/carboplatin plus bevacizumab as induction treatment followed by maintenance pemetrexed and bevacizumab compared with paclitaxel/carboplatin plus bevacizumab followed by bevacizumab maintenance in patients with advanced nonsquamous NSCLC [28]. The primary end point of superior OS for the pemetrexed containing arm was not met (12.6 vs 13.4 months; HR: 1.00; p = 0.949); however, the study showed a modest improvement in PFS for the pemetrexed arm (6.0 vs 5.6 months; HR: 0.83; p = 0.012) and a good safety profile [29].

Another study (AVAPERL1) investigated the efficacy of bevacizumab versus bevacizumab plus pemetrexed as maintenance treatment in nonsquamous patients who achieved disease control following induction with cisplatin and pemetrexed plus bevacizumab. The median PFS was significantly improved with the doublet (10.2 vs 6.6 months; HR: 0.50; p < 0.001) but this benefit was associated with significant increase of grade 3 and 4 toxicities in the combination maintenance arm [30].

• Reversible & irreversible EGF receptor–tyrosine kinase inhibitors

Activation of the EGF receptor (EGFR) pathway promotes tumor growth and progression, stimulates cancer cell proliferation, invasion and metastasis, and inhibits apoptosis [31]. Although the therapeutic inhibition of this pathway have been pursued for more than 20 years only recently, following the detection of EGFR-sensitizing mutation in the EGFR gene tyrosine kinase domain, this pathway re-emerged as an attractive target for novel targeted strategies for NSCLC.

Table 2 summarizes the initial series of Phase III trials evaluating the efficacy of oral EGFR–tyrosine kinase inhibitors (TKIs; gefitinib and erlotinib) in combination with platinum-based chemotherapy in the first-line setting [32–35]. None of these studies demonstrated any statistically significant difference in OS between arms. Despite negative results, all these trials detected efficacy of the EGFR–TKIs associated with clinical characteristics as never smoking status, Asian ethnicity, female sex and adenocarcinoma histology [36,37].

The clinical development of gefitinib faced several hurdles. Although in 2003, single-agent gefitinib received accelerated approval by the FDA on the basis of encouraging Phase II data, the conditional approval was subsequently restricted in 2004 because of the negative results of the Phase III ISEL trial [38].

INTEREST was a large Phase III study that compared second-line gefitinib to docetaxel in unselected patients with adenocarcinoma of the lung and it demonstrated the noninferiority of gefitinib in comparison with docetaxel (HR: 1.02; 95% CI: 0.90–1.15). Patients treated with gefitinib had a lower rate of treatment-related toxicity (8.5 vs 40.7%) and a better improvement in quality of life and, once more, this study confirmed the superior activity of gefitinib in specific subgroups of patients with NSCLC [39].

In 2004, somatic gene mutations of the *EGFR* gene were discovered and their presence related to the higher response to EGFR–TKIs [40–42]. The most common mutations are in frame deletion in exon 19 around codons 746–750 (45–50% of all somatic *EGFR* mutations) and a missense mutation at codon 858 (L858R) in exon 21 (35–45% of all *EGFR* mutations). The frequency of mutations is ethnicity-related and more frequent in never smokers, women and patients with adenocarcinoma [43]. This discovery led to a new wave of studies that explored the role of gefitinib and other EGFR–TKIs in clinically enriched or molecularly defined patient populations (Table 3).

First, IPASS provided evidence of efficacy of an EGFR–TKI inhibitor as front-line treatment in a clinically enriched population [44]. The study, designed to demonstrate the noninferiority of gefitinib versus chemotherapy in terms of PFS, met its primary end point and also showed the superiority of gefitinib versus chemotherapy in terms of PFS in the intention-to-treat analysis (HR: 0.74; 95% CI: 0.65–0.85; $p < 0.0001$). Patients with tumor samples available for molecular analysis were considered in a subgroup analysis, which showed the superiority of gefitinib in terms of PFS in patients with *EGFR*-mutated tumors (HR: 0.48; 95% CI: 0.36–0.64; $p < 0.0001$). On the contrary, chemotherapy was significantly better in *EGFR* wild-type patients (HR: 2.85; 95% CI: 2.05–3.98; $p < 0.0001$) [44]. Final OS data, based on 78% of events, showed no differences between gefitinib and chemotherapy in the whole population (18.6 vs 17.3 months, respectively, HR: 0.91; 95% CI: 0.76–1.10; $p = 0.11$) and in the mutation positive subgroup (HR: 1.00: 95% CI: 0.76–1.33). The improvement in PFS in gefitinib treated patients was coupled with a significant improvement in quality of life and a lower incidence of grade 3–4 adverse events compared with chemotherapy [50].

A similar study, the First-SIGNAL trial, compared gefitinib versus cisplatin plus gemcitabine in Korean patients [45]. While OS and PFS were similar in both groups (Table 3), the shape of the PFS curves resembled that seen in IPASS. Again in the *EGFR* mutation-positive patients, median PFS was significantly improved in the gefitinib arm (8.4 vs 6.7 months) as well as ORR (84.6 vs 37.5%; $p = 0.002$).

A series of other Phase III studies were conducted in genotype-defined *EGFR* mutant population which compared single-agent EGFR–TKI with cytotoxic chemotherapy and all invariably showed the superiority in terms of ORR and PFS of single-agent EGFR–TKI (Table 3) [46–49].

In July 2009, gefitinib received from EMA the approval for the treatment of locally advanced or metastatic NSCLC with activating mutations of the *EGFR* gene across all lines of therapy and, currently, is the treatment of choice for patients with advanced NSCLC harboring *EGFR* mutations.

Among the above mentioned studies, mostly conducted among Asiatic patients, the EURTAC trial was the first performed in a Caucasian population and it proved the superiority of erlotinib versus chemotherapy as front-line treatment [49]. Median PFS was 9.7 months (95% CI: 8.4–12.3) for patients treated with erlotinib compared with 5.2 months (95% CI: 4.5–5.8) for those treated with standard chemotherapy.

Sequential use of chemotherapy and EGFR TKIs has been tested as an alternative strategy in the first-line setting. FAST-ACT was a Phase II study that investigated whether the sequential administration of erlotinib and chemotherapy versus chemotherapy alone improves clinical outcomes in unselected, previously untreated patients with advanced NSCLC [51]. Patients were randomly assigned to receive erlotinib or placebo on days 15–28 of a 4-week cycle that included cisplatin or carboplatin plus gemcitabine. The primary end point of the study was non-progression rate (NPR) at 8 weeks. No significant difference in NPR was observed between the two treatment arms (80.3 vs 76.9%, in the erlotinib and placebo arm respectively; p = 0.51). ORR was higher in the chemotherapy-erlotinib arm (35.5 vs 24.4%, respectively) and median PFS was also significantly longer in the erlotinib arm (29.4 vs 23.4 weeks, in the erlotinib and placebo arm respectively; HR: 0.47; 95% CI: 0.33–0.68; p = 0.0002) No significant difference in OS was observed [51]. These encouraging results led to a large confirmatory randomized Phase III trial, the FAST-ACT II trial, which showed a significantly prolonged PFS with erlotinib versus placebo (7.6 vs 6.0 months, respectively; HR: 0.57; 95% CI: 0.46–0.70; p < 0.0001). ORR was significantly improved in the erlotinib arm (42.9 vs 17.8%, respectively; p < 0.0001) and a nonsignificant trend toward longer OS was seen with erlotinib versus placebo (18.3 vs 14.9 months, respectively; HR: 0.78; 95% CI: 0.60–1.02; p = 0.069) [52].

Another interesting therapeutic challenge for physicians is how best to manage at the best patients who benefited from EGFR-TKIs, but then experienced disease progression after a durable response. Several cases report and retrospective analyses indicated that responsive patients to EGFR–TKIs were successfully under therapeutic control after subsequent re-administration of the same EGFR–TKIs or another agent with a similar mechanism of action, supporting the hypothesis that these *EGFR*-mutated tumors continue to be 'oncogene-addicted' to EGFR [53–55]. Prospective trials have recently showed that the re-administration of EFGR–TKIs in those patients who initially responded to these agents and then were treated at progression with systemic chemotherapy could be a valid therapeutic option at the time of second progression albeit with a lower ORR and PFS [56,57].

Acquired resistance to EGFR–TKIs is most commonly characterized by the presence of the gatekeeper mutation T790M [58,59]. Among second-generation TKIs afatinib (BIBW2992) is an irreversible ErbB-family blocker with potent activity against NSCLCs harboring activating *EGFR* mutations and/or the gatekeeper mutation T790M, albeit at lower potency. It has been recently evaluated in several clinical trials for advanced NSCLC with promising results (Table 4) [60–63]. The LUX-Lung 3 was a front-line Phase III trial of afatinib versus cisplatin/pemetrexed for patients with advanced lung adenocarcinoma harboring EGFR-activating mutations. Patients treated with afatinib had a median PFS, the primary end point of the study, of 11.1 versus 6.9 months for the chemotherapy group (HR: 0.58; 95% CI: 0.43–0.78; p = 0.0004). ORR was also significantly higher with afatinib (56 vs 23%; p < 0.001), reporting a consistent delay in time to deterioration of cancer-related symptoms [62]. Most common afatinib-related adverse events were diarrhea (95%), skin rash (62%) and paronychia (57%). On the basis of results coming from the LUX-Lung 3 trial, afatinib has been recently approved by the FDA and by EMA for the first-line treatment of *EGFR* mutation-positive metastatic NSCLC.

Another study, LUX-Lung 6 compared afatinib with cisplatin plus gemcitabine in Asiatic patients with *EGFR* mutation-positive advanced adenocarcinoma of the lung (Table 4). The study showed a clear benefit in terms of median PFS (11.0 vs 5.6 months; HR: 0.28; 95% CI: 0.20–0.39; p < 0.0001) and ORR (66.9 vs 23.0%; p < 0.0001) in favor of afatinib, which showed a favorable tolerability profile, with few cases of grade 3 and 4 toxicities [63]. Currently, afatinib is currently

under evaluation in a Phase II trial against gefitinib as first-line treatment in advanced NSCLC patients with EGFR-activating mutations [64].

Another second-generation TKI, dacomitinib (PF-00299804) – an irreversible inhibitor of EGFR/HER1, HER2 and HER4, has been evaluated in a Phase II trial versus erlotinib in previously treated (one/two prior chemotherapy regimens were allowed) advanced NSCLC patients. The median PFS was 2.86 months for patients treated with dacomitinib and 1.91 months for those treated with erlotinib (HR: 0.66; 95% CI: 0.47–0.91; p = 0.012), while median OS was 9.53 and 7.44 months, respectively (HR: 0.80; 95% CI: 0.56–1.13; p = 0.205). The most common treatment-related adverse events were dermatologic and gastrointestinal disorders, mostly of grade 1 and 2, and more frequently associated with dacomitinib [65]. These results represented the backbone information for an ongoing Phase III study in which 800 patients will be enrolled having as primary end point PFS [66].

• Monoclonal antibodies anti-EGFR: cetuximab

Cetuximab is a chimeric monoclonal antibody that selectively binds the extracellular domain of the EGFR on the tumor cell and inhibits the receptor-associated tyrosine kinase activation [67,68]. A large Phase III trial (FLEX) compared cisplatin plus vinorelbine with the same combination plus cetuximab in chemotherapy-naive advanced NSCLC patients with EGFR-positive tumors (≥1% positive cells) as assessed by immunohistochemistry [69]. The addition of cetuximab demonstrated a small but statistically significant benefit in terms of median OS over chemotherapy alone (11.3 vs 10.1 months, respectively, HR 0.87; p = 0.0441), while PFS was similar in both arms. The main cetuximab-associated toxicity was acne-like rush, which occurred in 10% of patients. Similar results were observed in another trial with a different chemotherapy backbone [70]. This second study did not show improvement of PFS, but showed a trend to improved OS, the secondary end point of the study, for patients treated with cetuximab plus chemotherapy (9.7 vs 8.4 months, respectively, HR: 0.890; 95% CI: 0.75–1.05; p = 0.17).

A meta-analysis considered four cetuximab studies and included 1003 and 1015 patients treated with chemotherapy plus cetuximab or chemotherapy alone, respectively [71]; it showed a 9% reduction in the risk of disease progression (HR: 0.91; 95% CI: 0.83–1.00; p = 0.06), a 13% reduction in the risk of death (HR: 0.87; 95% CI: 0.78–0.96; p = 0.005) and an approximately 50% increase in ORR (odds ratio: 1.48; 95% CI: 1.22–1.80; p < 0.0001) for cetuximab-treated patients [71].

High levels of EGFR expression correlate with *in vitro* sensitivity to cetuximab [72,73]. Recently, FLEX data were reanalyzed and the immunohistochemistry assessment of EGFR intensity and frequency in tumor cells was used to generate, on a continuous scale of 0–300, an EGFR immunohistochemistry (EGFR IHC) score for each assessable patient, in order to investigate whether tumor EGFR expression levels were associated with a predictive role. Treatment outcomes were analyzed in patients with a low (<200) and high (≥200) EGFR IHC score, representing 69 and 31% of evaluable patients, respectively [74]. For patients with a high EGFR IHC score, median OS was longer in the chemotherapy plus cetuximab arm than in the control arm (12.0 vs 9.6 months, respectively; HR: 0.73, 95% CI: 0.58–0.93; p = 0.011), without significant increase in cetuximab related side effects. No corresponding survival benefit was observed in the group of patients with low EGFR IHC score (median OS of 9.8 vs 10.3 months, respectively; HR: 0.99; 95% CI: 0.84–1.16; p = 0.88) [74].

A fully humanized monoclonal antibody targeting the EGFR extracellular domain III, necitumumab, is currently under investigation having the potential benefit of lower hypersensitivity reaction risk as compared with cetuximab and also equivalent antibody-dependent cell-mediated cytotoxicity [75]. The Phase III trial INSPIRE (NCT00982111) that evaluated the addition of necitumumab to cisplatin/pemetrexed as first-line treatment for advanced nonsquamous NSCLC

was prematurely closed owing to the increased risk of thromboembolic events in the experimental arm [76]. The SQUIRE trial (NCT00981058) is another Phase III study of first-line cisplatin/gemcitabine plus necitumumab versus chemotherapy alone for advanced squamous NSCLC [77]. The study fully accrued the requested number of patients and a recent press release indicated that it met its primary end point.

• ALK inhibitors

ALK is one of the newest and attractive biological targets in NSCLC. ALK is aberrantly activated because of a chromosomal rearrangement in approximately 4% of NSCLC tumors, leading to the expression of an oncogenic fusion protein, such as EML4–ALK [78,79]. In NSCLC, the *ALK* gene rearrangement is associated with specific clinical–pathological features, including male sex, young age, absent or minimal smoking history, adenocarcinoma histology and usually mutual exclusivity between EML4–ALK and *EGFR* and *KRAS* mutations [80–82]. Preclinical and clinical studies have shown that cancer cells harboring EML4–ALK and other ALK abnormalities are exquisitely sensitive to ALK inhibition [79,83].

The identification of EML4–ALK as an oncogenic driver in NSCLC occurred relatively early in the clinical development of crizotinib, an ALK inhibitor originally under investigation as a c-MET inhibitor, and led to the rapid clinical development of this drug [84]. Initial results from the Phase I study clearly indicated significant and clinically relevant tumor shrinkage in the majority of enrolled patients [85]. Subsequently, an expansion cohort of 82 NSCLC patients harboring the ALK rearrangement was enrolled at the recommended dose of 250 mg twice daily. The ORR for the expanded cohort was 57% (46 partial responses and one complete response). An additional 33% of patients had stable disease at the 8-week assessment [86]. An update of this study with 119 enrolled patients was subsequently presented showing a consistent ORR of 61% with two complete responses and 69 partial responses and the median PFS for was 10 months (95% CI: 8.00–15.00) [87]. Based upon the encouraging ORR of the Phase I study, a large multicenter second- and subsequent-line study in ALK-positive NSCLC patients was initiated. Patient characteristics largely corresponded to those of the previous study and the ORR was 51% [88]. In both the Phase I and II trials, the majority of responses was achieved during the first 8 weeks of treatment and duration of response was 48.1 and 41.9 weeks, respectively [87,88].

In August 2011, based on the Phase I and II trial data, the FDA granted in USA accelerated approval of crizotinib for the first or subsequent lines of treatment of locally advanced or metastatic ALK-positive NSCLC [89]. Final FDA approval will be contingent on analysis of outcome measures in the ongoing Phase III studies [90,91].

PROFILE 1007, a Phase III study evaluating the use of crizotinib versus pemetrexed or docetaxel as second line of treatment for ALK-positive NSCLC patients met its primary end point by demonstrating the superiority of crizotinib over chemotherapy in prolonging PFS (7.7 vs 3.0 months, respectively; HR: 0.49) and ORR (65 vs 20%; p < 0.0001), while the safety profile was acceptable [92]. These findings led to the EMA authorization for the use of crizotinib as the standard of care for previously treated ALK-positive NSCLC patients in Europe.

As already reported above, the TS level may predict the sensitivity to pemetrexed-based chemotherapy in different histologic subtypes of NSCLC, being inversely correlated with pemetrexed efficacy [16]. A recent study evaluating the role of pemetrexed-based chemotherapy in ALK-positive NSCLC patients, showed lower TS levels than the median values established in unselected cases. A low TS level has been observed in almost 83% of the evaluated patients (p = 0.039) and the few ALK-positive NSCLC patients with high TS levels had the poorest survival outcomes observed [93]. These findings suggest that differences in TS expression levels in ALK-positive NSCLC patients may predict the differential responses to pemetrexed, but also justify the

superior efficacy of pemetrexed compared with docetaxel in this subset of patients, as observed in the PROFILE 1007.

Another Phase III trial PROFILE 1014 (NCT01154140) is currently actively recruiting patients to evaluate the efficacy and safety of crizotinib versus cisplatin or carboplatin/pemetrexed as a first-line treatment for previously untreated ALK-positive nons1quamous NSCLC patients [91]. The primary end point of the study is PFS, while ORR and OS are included among the secondary end points. A superiority Phase III trial testing the same crizotinib schedule has been designed for the east Asian population [94].

Crizotinib has recently also demonstrated a marked anti-tumor activity in patients with advanced NSCLC harboring *ROS1* chromosomal rearrangements, which leads to the expression of oncogenic ROS1 fusion kinases and to sensitivity to ROS kinase inhibition, without any overlap with other oncogenic drivers. This rearrangement has been detected in almost 1% of NSCLC cases, usually in younger patients, never or light smokers and with adenocarcinoma histology [95,96].

The expansion cohort of the Phase I study of crizotinib PROFILE 1001 (NCT00585195) recruited patients with advanced NSCLC harboring ROS1 rearrangement, as determined using a break-apart FISH assay [97]. The study showed an ORR of 54% and a disease control rate at 8 weeks of 85%, with a safety profile similar to that observed in ALK-positive NSCLC patients receiving crizotinib [97].

Conclusion & future perspective

Moving toward the next decade and looking to the several landmark changes in the understanding the biology and treatment of NSCLC that we observed in the last few years, it is almost impossible to deny that significant improvements have been made in extending survival of selected groups of patients with tumors harboring specific genomic alterations. Although such genetic changes have been detected in more than 50% of adenocarcinoma and, more recently also, in the vast majority of squamous cell carcinoma and small cell lung cancers, effective and approved targeted therapy approaches are currently available only for a significant minority of our patients. EGFR–TKIs should be the preferred front-line treatment choice for advanced patients with nonsquamous tumors harboring *EGFR*-sensitizing mutations. For patients harboring *ALK* gene rearrangements an attractive and promising strategy of treatment is represented by crizotinib and second-generation ALK-inhibiting agents. Up to date, despite the huge effort of clinical research therapeutic choices based on histology are still the standard of care for the majority of patients with advanced NSCLC. In the setting of nononcogene addicted nonsquamous NSCLC patients, either the combination of a platinum agent with pemetrexed or the addition of bevacizumab to carboplatin and paclitaxel are doable therapeutic solutions and the choice should be guided by clinical, pathologic and cost-efficacy issues. In squamous histology, doublet platinum-based chemotherapy remains the standard approach.

Although the implementation of the systematic sequencing of the lung cancer genome will definitively lead to a progressive increase of the proportion of patients that will be treated by specific targeted therapies, it is quite unlikely that a druggable target or more than one target will be discovered and efficiently blocked in every tumor. More potential crosstalks exist between cancer pathways, allowing new DNA mutations to create new pathways to cancer when pre-existing ones are blocked. Given the seemingly almost intrinsic genetic instability of many late-stage cancers we should question if we will be able to truly cure most victims of widespread metastatic cancer.

In addition, tumors exposed to effective targeted therapies develop, sooner or later, acquired resistance and it can be hypothesized that resistance to gene-targeted agents also comes as a consequence of the radical changes in the underlying patterns of gene expression that accompany

the epithelial–mesenchymal cell transitions in cancer cells when their surrounding environments become hypoxic.

It should additionally be noted that areas of further exploration are focusing on the inhibition of the complex DNA repair machinery and, more specifically, on homologous recombination and end joining mechanisms to repair double strand breaks which arise from ionizing radiation or x-rays, free radicals and chemicals including cytotoxics.

In the near future, we will focus much more on the wide range of metabolic and oxidative vulnerabilities that arise as consequences of the uncontrolled growth and proliferation capacities of cancer cells.

Only the definition of homogeneous subgroups of tumors with the same genetic and metabolic characteristics and the search for individualized approaches could represent the way to improve survival expectancy for these patients.

Table 1. Therapeutic plateau of platinum-based chemotherapy involving third-generation agents as first-line treatment for non-small-cell lung cancer.

Table 1. Therapeutic plateau of platinum-based chemotherapy involving third-generation agents as first-line treatment for non-small-cell lung cancer.

Study	Regimen	Patients (n)	ORR (%)	Median OS (95% CI); months	1-year survival (95% CI); %	Ref.
ECOG 1594	Cis/pacli 135 mg/m^2	288	21	7.8 (7.0–8.9)	31 (26–36)	[7]
	Cis/gem	288	22	8.1 (7.2–9.4)	36 (31–42)	
	Cis/doce	289	17	7.4 (6.6–8.8)	31 (26–36)	
	Carbo/pacli 225 mg/m^2	290	17	8.1 (7.0–9.5)	34 (29–40)	
ILCP	Cis/vnr	201	30	9.5 (8.3–11.0)	37 (NR)	[8]
	Cis/gem	205	30	9.8 (8.6–11.2)	37 (NR)	
	Carbo/pacli 225 mg/m^2	201	32	10.0 (9.0–12.5)	43 (NR)	
TAX 326	Cis/vnr	404	25	10.1 (9.0–11.3)	41 (35–46)	[9]
	Cis/doce	408	32	11.3 (10.1–12.4)	46 (42–51)	
	Carbo/doce	406	24	9.4 (8.7–10.6)	38 (33–43)	

Carbo: Carboplatin; Cis: Cisplatin; Doce: Docetaxel; Gem: Gemcitabine; NR: Not reported; ORR: Objective response rate; OS: Overall survival; Pacli: Paclitaxel; Vnr: Vinorelbine.

Table 2. Phase III randomized studies comparing tyrosine kinase inhibitors with platinum-based chemotherapy as first-line treatment in 'unselected' non-small-cell lung cancer.

Table 2. Phase III randomized studies comparing tyrosine kinase inhibitors with platinum-based chemotherapy as first-line treatment in 'unselected' non-small-cell lung cancer.

Study	TKI	Treatment	ORR (%)	Median PFS (months)	Median OS (months)	Ref.
INTACT 1	Gefitinib	Cis/gem + gefitinib 500 mg/day vs cis/gem + gefitinib 250 mg/day vs cis/gem + placebo	50.3 vs 51.2 vs 47.2 (p = NS)	5.5 vs 5.8 vs 6.0 (p = 0.7633)	9.9 vs 9.9 vs 10.9 (p = 0.4560)	[32]
INTACT 2	Gefitinib	Carbo/pacli + gefitinib 500 mg/day vs carbo/pacli + gefitinib 250 mg/day vs carbo/pacli + placebo	30.0 vs 30.4 vs 28.7 (p = NS)	4.6 vs 5.3 vs 5.0 (p = 0.0562)	8.7 vs 9.8 v 9.9 (p = 0.64)	[33]
TALENT	Erlotinib	Cis/gem + erlotinib 150 mg/day vs cis/gem + placebo	31.5 vs 29.9 (p = NS)	5.53 vs 5.74 (HR: 0.98; 95% CI: 0.86–81.11; p = 0.74)	10.0 vs 10.2 (HR: 1.06; 95% CI: 0.90–91.23; p = 0.49)	[34]
TRIBUTE	Erlotinib	Carbo/pacli + erlotinib 150 mg/day vs carbo/pacli + placebo	21.5 vs 19.3 (p = 0.36)	5.1 vs 4.9 (HR: 0.93; p = 0.36)	10.6 vs 10.5 (HR: 0.99; 95% CI: 0.86–81.16; p = 0.95)	[35]

Carbo: Carboplatin; Cis: Cisplatin; Gem: Gemcitabine; HR: Hazard ratio; NS: Not significant; ORR: Objective response rate; OS: Overall survival; Pacli: Paclitaxel; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor.

Table 3. Phase III randomized studies comparing tyrosine kinase inhibitors with platinum-based chemotherapy as first-line treatment in 'selected' non-small-cell lung cancer.

Table 3. Phase III randomized studies comparing tyrosine kinase inhibitors with platinum-based chemotherapy as first-line treatment in 'selected' non-small-cell lung cancer.

Study	Treatment	*EGFR* mutational status		ORR (%)	Median PFS (months)	Median OS (months)	Ref.
		Status known (%)	*Positive status known (%)*				
IPASS	Gefitinib vs carbo/pacli	35.9	59.7	43.0 vs 32.3 (p = 0.0001)	5.7 vs 5.8 (HR: 0.74; 95% CI: 0.65–60.85; p < 0.0001)	18.6 vs 17.3 (HR: 0.91; 95% CI: 0.76–71.10; p = 0.11)	[44]
First-SIGNAL	Gefitinib vs cis/gem	31.6	43.7	53.5 vs 45.3 (p = 0.153)	6.1 vs 6.6 (HR: 0.81; 95% CI: 0.64–61.03; p = 0.044)	21.3 vs 23.3 (HR: 1.00; 95% CI: 0.75–71.34; p = 0.428)	[45]
WJTOG	Gefitinib vs cis/doce	100	100	62.1 vs 32.2 (p = 0.0001)	9.2 vs 6.3 (HR: 0.49; 95% CI: 0.34–30.71; p < 00001)	30.9 vs NR (HR: 1.64; 95% CI: 0.75–73.58; p = 0.211)	[46]
NEJ002	Gefitinib vs carbo/pacli	100	100	73.7 vs 30.7 (p < 0.001)	10.8 vs 5.4 (HR: 0.30; 95% CI: 0.22–20.41; p < 0.001)	30.5 vs 23.6 (p = 0.31)	[47]
OPTIMAL	Erlotinib vs carbo/gem	100	100	83.0 vs 36.0 (p < 0.0001)	13.1 vs 4.6 (HR: 0.16; 95% CI: 0.10–10.26; p < 0.0001)	Not specified	[48]
EURTAC	Erlotinib vs platinum-based chemotherapy[†]	100	100	63.6 vs 17.8 (p < 0.0001)	9.7 vs 5.2 (HR: 0.37; 95% CI: 0.25–20.54; p < 0.0001)	19.3 vs 19.5 (HR: 1.04; 95% CI: 065–061.68; p = 0.87)	[49]

[†]Platinum-based chemotherapy options: cis/gem or cis/doce or carbo/doce or carbo/gem.
Carbo: Carboplatin; Cis: Cisplatin; Doce: Docetaxel; Gem: Gemcitabine; HR: Hazard ratio; NR: Not reached; ORR: Objective response rate; OS: Overall Survival; Pacli: Paclitaxel; PFS: Progression-free survival.

Table 4. **Relevant clinical trials of afatinib for advanced non-small-cell lung cancer.**

Study	Phase	Treatment	Selection criteria	ORR (%)	Median PFS (months)	Median OS (months)	Ref.
LUX-Lung 1	IIb/III	Afatinib vs placebo	Stage IIIB/IV adenocarcinoma patients after failure of gefitinib and/or erlotinib and previous one/two chemotherapy	7.0 vs <1.0 (p = 0.0071)	3.3 vs 1.1 (HR: 0.38; 95% CI: 0.31–30.48; p < 0.0001)	10.8 vs 12.0 (HR: 1.08; 95% CI: 0.86–81.35; p = 0.74)	[60]
LUX-Lung 2		Afatinib	Stage IIIB/IV *EGFR* mutation-positive adenocarcinoma patients after failure of one previous chemotherapy or chemotherapy-naive	61	10.1 (95% CI: 8.12–13.80)	24.8 (95% CI: 21.98–38.74)	[61]
LUX-Lung 3	III	Afatinib vs cisplatin/pemetrexed	Stage IIIB/IV *EGFR* mutation-positive/chemotherapy-naive adenocarcinoma patients	56.0 vs 23.0 (p < 0.0001)	11.1 vs 6.9 (HR: 0.58; 95% CI: 0.43–40.78; p = 0.0004)	NR	[62]
LUX-Lung 6	III	Afatinib vs cisplatin/gemcitabine	Stage IIIB/IV *EGFR* mutation-positive/Asian chemotherapy-naive adenocarcinoma patients	66.9 vs 23.0 (p < 0.0001)	11.0 vs 5.6 (HR: 0.28; 95% CI: 0.20–0.39; p < 0.0001)	(HR: 0.95; p = 0.7593)	[63]

HR: Hazard ratio; NR: Not reported; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

EXECUTIVE SUMMARY

Background

Lung cancer is the leading cause of cancer-related mortality worldwide, and the actual challenge is to better personalize the therapeutic approaches to improve survival expectancy.

Role of standard chemotherapy

Platinum-based chemotherapy doublets are the backbone of treatment for non-small-cell lung cancer (NSCLC), giving a modest but significant improvement in survival and quality of life in comparison with best supportive care.

Cisplatin is more effective than carboplatin in terms of objective response rate (ORR) and overall survival (OS).

Triplet combinations are associated with increased ORR but similar survival.

Histology-driven chemotherapy

On the basis of survival benefit, pemetrexed in combination with cisplatin has been granted as first-line treatment for advanced nonsquamous NSCLC.

Role of biological agents

Bevacizumab, a monoclonal antibody anti-VEGFR, has been licensed in the USA in combination with carboplatin/paclitaxel as first-line treatment option for advanced

nonsquamous NSCLC, on the basis of its survival benefit; in Europe it is licensed in combination with any platinum-based chemotherapy.

- In NSCLC patients with *EGFR* mutation-positive tumors, first-line single-agent therapy with either gefitinib or erlotinib, two reversible EGFR–TKIs, when compared with standard platinum-based chemotherapy, are associated with a significantly longer PFS, higher ORR, a more favorable toxicity profile and better quality of life.
- Gefitinib and erlotinib received from EMA, the authorization for the treatment of locally advanced or metastatic *EGFR* mutation-positive NSCLC, across all lines of therapy.
- Afatinib, an irreversible EGFR–TKI, has recently showed a clear survival benefit in terms of PFS in NSCLC patients harboring EGFR-activating mutations, receiving from the US FDA and the EMA the authorization for first-line treatment in this subgroup of patients.
- Cetuximab, a monoclonal antibody anti-EGFR, in association with platinum-based chemotherapy has demonstrated a small but significant survival benefit in terms of OS, despite a more severe toxicity profile.
- Crizotinib, an ALK inhibitor, has showed significant and clinically relevant tumor shrinkage in the majority of ALK-positive NSCLC patients.
- In the USA, it has been licensed for the treatment of locally advanced or metastatic ALK-positive NSCLCs across all lines of therapy, while in Europe its use is allowed in previously treated NSCLC patients harboring *ALK* gene rearrangements.
- Crizotinib has recently demonstrated a marked anti-tumor activity in NSCLC patients harboring ROS1 chromosomal rearrangements.

Conclusion & future perspective

- The definition of homogeneous subgroups of tumors with the same genetic characteristics and the search for individualized approaches could improve survival expectancy for NSCLC patients.

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