The emerging treatment landscape of advanced non-small cell lung cancer

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Abstract: Lung cancer remains the leading cause of cancer related death worldwide. Despite broad advances in diagnostics and therapy, the five-year overall survival for patients with advanced non-small cell lung cancer (NSCLC) has not significantly changed over the past few years. Following the decoding of human cancer genome and the advent of therapies targeting driver mutations, the selection of systemic therapy changed from "one size fits all" approach to a more precise selection of biologic therapies targeting distinct genetic profiles. Molecular alterations can be targeted by specific drugs that are administered orally, have higher response rates and a better toxicity profile compared to standard chemotherapy. More recently, better understanding of the interactions between tumor cells and the immune system has led to the development of new therapeutic strategies that enhance the body's own immune response towards antitumor immunity. Robust data on these new drugs have been generated not only in the second-line setting, but also as first line therapy and in combination with standard therapies. In this review, we aim to illustrate a comprehensive up-to-date within the newest advances in the field of NSCLC, with the view to educate new practitioners and stimulate new thoughts for clinical trials.

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Introduction

Lung cancer is the leading cause of cancer related death worldwide, with approximately 1.6 million deaths anticipated in 2015. Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of cases (1). Despite broad advances in diagnostics and therapy, the five-year overall survival for patients with advanced NSCLC has not significantly changed over the past few years. Following the decoding of human cancer genome and the advent of therapies targeting driver mutations, the selection of systemic therapy changed from "one size fits all" approach to a more precise selection of biologic therapies targeting distinct genetic profiles. Molecular alterations can be targeted by specific drugs that are administered orally, have higher response rates and a better toxicity profile compared to standard chemotherapy. Eventually, clinical and molecular resistance develops, but novel drugs active in this setting have been currently incorporated in clinical practice. Indeed, NSCLC is no longer considered a single entity, but a heterogeneous disease, comprised of molecularly defined subgroups of tumors, susceptible to target inhibition.

Even more recently, better understanding of the interactions between tumor cells and the immune system has led to the development of new therapeutic strategies that enhance the body's own immune response in

order to shift the balance towards antitumor immunity. Genomic instability in cancer favors the generation of immunogenic clones, which can be eliminated by an immunocompetent host (2). However, it is believed that the immune system might lose the ability to eradicate cancer cells or new mutations might render tumor cells poorly immunogenic, so that they can disrupt, suppress or evade immune control. Among mechanisms of immune evasion, the development of a cancer-permissive tumor microenvironment by exploiting immune checkpoints, such as the programmed death ligand 1 (PD-L1)/programmed cell death 1 (PD-1) axis is the most studied. Cancer cells often express the PD-L1 protein on their surface, and binding of PD-L1 to co-inhibitory receptor PD-1 on cytotoxic T cells blocks T cell activation (3). Blockade of the PD-1/PD-L1 pathway by novel drugs unleashes T cells and enhances anti-tumor response. Robust data on these new drugs have been generated not only in the second-line setting of patients with NSCLC, but also as first line therapy and in combination with standard therapies.

Remarkably, there have been a series of rapid and dramatic transformations in the therapeutic landscape of NSCLC over a short period of time. In this review, we aim to illustrate a comprehensive up-to-date within the newest advances in the field of NSCLC, with the view to educate new practitioners and stimulate new thoughts for clinical trials.

New advances in the treatment of NSCLC

Based on tumor mutation testing, patients are divided into three subgroups: patients with EGFR-positive mutations (10–30%), patients with ALK rearrangements (4–7%) and patients who do not harbor EGFR/ALK abnormalities or have unknown mutation status. However, the evolution of molecular profiling and the implementation of next generation sequencing in the evaluation of a patient with advanced NSCLC has currently led to the discovery of targetable alterations in patients who previously had not known actionable targets. As effective treatments are found for novel targets such as HER2, ROS1, RET, BRAF, MET and others, treatment algorithms are becoming more complex (4).

EGFR mutant NSCLC

EGFR mutations have been described in approximately 10–15% of Caucasians with lung adenocarcinoma, most commonly in never smokers (5). In Asians, the frequency of EGFR mutations is three times higher. The most common EGFR mutations are exon 19 deletions (del19) and exon 21 L858R substitutions (45–82% and 30%, respectively), that are commonly referred to as 'sensitizing mutations' as they confer sensitivity to tyrosine kinase inhibitors (TKIs) (6). The current recommended standard of care for EGFR-mutant NSCLC in the advanced stage is EGFR TKI monotherapy, such as gefitinib, erlotinib and afatinib. Gefitinib and erlotinib are both first generation TKIs, whereas afatinib is a second generation TKI. Afatinib covalently binds and irreversibly blocks EGFR, HER2 and HER4, therefore enhancing the effect on important and relevant signaling pathways and delaying resistance (7). Landmark clinical trials have demonstrated superior overall response rate (ORR), progression free survival (PFS) and quality of life compared to the former standard treatment of platinum-based doublet chemotherapy for all TKIs mentioned (8-11). The pooled analysis of the LUX Lung 3 and 6 studies also suggested an overall survival (OS) advantage of afatinib compared to chemotherapy in the first-line setting for the subgroup of patients with exon 19 deletions (12).

Gefitinib and erlotinib have not been compared in the first line setting in EGFR mutant patients, but no difference in efficacy has been found in Asian populations in the second line setting (13). LUX-LUNG 7, a randomized phase IIb trial is the first report of a direct comparison between EGFR TKIs in the first line setting (14). In this landmark trial, afatinib and gefitinib were compared as first line treatment in patients with advanced NSCLC and common EGFR mutations. Afatinib has been shown to improve PFS (HR =0.73) and ORR (70% *vs.* 56%) independently of mutation subtype. Furthermore, OS was numerically higher favoring afatinib, albeit not statistically significant (HR =0.86, P=0.25) (14). In another recent report, dacomitinib, a second-generation TKI, was compared to gefitinib in patients with advanced EGFR mutant NSCLC in the first line setting. Dacomitinib was superior to gefitinib in terms of PFS (14.7 *vs.* 9.2 months, HR =0.59); OS results are awaited (15). The superiority of second (afatinib, dacomitinib) *vs.* first generation TKIs (gefitinib) can be partially explained by their different mechanism of action; second-generation TKIs irreversibly bind to and block signaling from all relevant HER family receptor homo- and heterodimers (EGFR,HER2, HER3 and HER4), whereas gefitinib only inhibits EGFR signaling (7). In the randomized phase III FLAURA trial, gefitinib or erlotinib

are being compared to osimertinib in previously untreated EGFR mutant patients. Osimertinib is a third generation TKI that targets the T790M mutation; the development of this mutation is the most common mechanism of acquired EGFR resistance, but it can also pre-exist on the same allele with the primary EGFR activation in a small population of patients (1–8%), which implies a poorer prognosis (16). In July 2017 it was announced that FLAURA showed a statistically significant and clinically meaningful PFS benefit with osimertinib; final results are eagerly awaited.

Antiangiogenic agents have been also evaluated in EGFR mutant patients. In the phase II single arm BELIEF trial, the combination of erlotinib and bevacizumab was tested in treatment naïve T790M positive and negative patients. The primary endpoint of the study, which was PFS, was met in the T790M positive subgroup (16 months, 12-month PFS 68%) (17). On the other hand, a randomized phase II trial from Japan demonstrated a benefit for the combination of bevacizumab and erlotinib compared to erlotinib monotherapy as first line treatment in patients with NSCLC and common EGFR mutations (18); the combination has been currently approved by the European Medicine's Agency (EMA).

Despite initial benefit, all patients with EGFR mutations ultimately progress due to the development of acquired resistance. Intratumor heterogeneity has been suggested as a possible interpretation of incomplete disease response and acquired resistance, based on preferential response of cell subclones on drug therapy (19). A secondary point EGFR mutation that substitutes methionine for threonine at amino acid position 790 (T790M) is a molecular mechanism that produces a drug-resistant variant of the targeted kinase. The T790M mutation is present in approximately 60% of patients with acquired resistance and acts by increasing the affinity of the receptor to adenosine triphosphatase (20). Retesting for EGFR mutations is now the standard of care, and testing plasma cell free DNA is considered an alternative to tissue biopsy. Many platforms have been developed, such as Cobas EGFR mutation test, therascreen EGFR amplification refractory system mutation (both non-digital) and Droplet Digital PCR, BEAMing digital PCR (both digital). Digital platforms have a higher sensitivity in detecting T790M mutation (81% *vs.* 73%) but concordance between the platforms is above 90% (21). Nevertheless, tissue biopsy is still considered the gold standard, as it displays higher sensitivity and can detect additional mechanisms of acquired resistance, such as HER2 and c-MET amplification and transformation to small cell lung cancer (SCLC) (22).

Third generation TKIs, such as osimertinib, rociletinib, olmutinib and ASP8273 have preferential activity against both T790M and EGFR sensitizing mutations. Among them, rociletinib is no longer being developed due to insufficient data supporting its approval. Osimertinib is now currently approved in several countries. AURA II was a single arm, open label phase II trial that evaluated osimetinib in T790M positive patients after failure of first line TKI. Osimertinib achieved a 70% RR and a 92% disease control rate (DCR). In the phase III AURA III trial, osimetinib was compared to platinum-based chemotherapy as second line therapy after initial TKI failure in 419 patients with T790M positive disease. Osimertinib was superior in terms of PFS (10.1 *vs.* 4.4 months, HR =0.30) and RR (71% *vs.* 31%) with a better toxicity profile. On the other hand, T790M negative patients are usually treated with chemotherapy. In patients with c-Met amplification, clinical trials assessing MET inhibitors have demonstrated disappointing results (6). Of note, continuation of EGFR TKI therapy and administration of local therapy is strongly recommended in patients with asymptomatic progression or oligoprogression (23).

Uncommon EGFR mutations represent a heterogeneous group and account for approximately 10–15% of EGFR mutations. These most frequently include exon 20 insertions and point mutations G719X, L861Q, and S768I (24). Exon 20 insertions are typically resistant to EGFR TKIs, although preclinical studies suggest response to osimertinib (25). The largest dataset for uncommon mutations comes from post hoc analyses of pooled afatinib outcomes from clinical trials LUX-Lung 2, 3 and 6, where 11% of patients recruited harbored uncommon EGFR mutations. ORR with afatinib was 71.1% in patients with point mutations or duplications in exons 18–21, 14.3% in patients with *de novo* T790M mutations and 8% in patients with exon 20 insertions (26).

ALK positive patients

In 2007, Soda and colleagues identified in a patient with adenocarcinoma of the lung, a small inversion in the small arm of chromosome 2 resulting in an oncogenic fusion gene comprising of *EML4* (echinoderm microtubule-associated protein-like 4) and *ALK* gene (27). ALK rearrangements occur in approximately 4–7% of lung cancers, most commonly in light and non-smokers.

Advances in the management of ALK positive NSCLC

commenced with the development of ALK inhibitor crizotinib, which showed clinical benefit in early phase I trials. The phase III PROFILE 1014 trial compared crizotinib to standard platinum-based chemotherapy in 343 treatment-naïve patients with advanced ALK positive NSCLC (28). The primary endpoint of PFS was significantly increased in patients treated with crizotinib (10.9 *vs.* 7.0 months in patients treated with chemotherapy, HR =0.45; P<0.001). ORR was also substantially higher (74% for crizotinib *vs.* 45% for chemotherapy (P<0.001). Furthermore, crizotinib had a better toxicity profile. However, all patients treated with crizotinib eventually develop tumor progression. Mechanisms of resistance include the development of secondary mutations, ALK amplification, activation of bypass pathways such as EGFR and IGFR, phenotypic change such as development of epithelial mesenchymal transition (EMT), and limited penetration to central nervous system (CNS) (29). It has been postulated that approximately 70% of patients treated with crizotinib experience progression in the CNS (30).

Second generation TKIs ceritinib and alectinib have demonstrated impressive RRs in crizotinib-pretreated patients. In 2014, FDA approved ceritinib for patients with advanced ALK positive NSCLC following treatment with crizotinib, based on the results of phase I ASCEND I trial, which demonstrated an ORR of 56.4% in pretreated patients (31). The efficacy of ceritinib was confirmed in single arm phase II ASCEND II trial, which demonstrated an ORR of 38.6% and PFS of 5.7 months in both chemotherapy and crizotinib pretreated patients (32). Alectinib, another second generation ALK inhibitor has also demonstrated tremendous efficacy in crizotinib pretreated patients. Two large phase II trials evaluated the efficacy and safety of alectinib in patients with ALK positive NSCLC who had progressed on crizotinib. The first study demonstrated an ORR of 50.8% with an intracranial RR of 58.8% (33). In the second trial, a similar ORR was shown, and intracranial RR was as high as 75% (34).

Second generation TKIs have been also assessed in the first line setting. Ceritinib has been recently approved for first line treatment, following the results of the ASCEND-4 randomized phase III trial, which compared ceritinib to chemotherapy in treatment naïve ALK positive patients (35). This trial showed a statistically significant improved PFS in favor of ceritinib (16.6 *vs.* 8.1 months, HR =0.55, P<0.001). Ceritinib also achieved an intracranial RR of 72%, albeit with a less striking PFS benefit (HR =0.70). Of note, study drug related adverse events led to drug discontinuation in 5.3% of ceritinib patients.

Alectinib has been evaluated in first line setting in the Japanese phase III J-ALEX trial, where it was directly compared to crizotinib, albeit with a lower dose than the one used in two aforementioned phase II trials (300 mg instead of 600 mg) (36). Alectinib demonstrated significant prolonged PFS (median PFS not reached *vs.* 10.2 months with crizotinib). Although J-ALEX trial was conducted only in Japan and used a different dose of the drug, it led to FDA granting alectinib breakthrough therapy designation for first-line treatment. The results of the international ALEX phase III study comparing alectinib at the standard dose of 600 mg to crizotinib, that was recently reported at the 2017 ASCO Annual Meeting, has shed light to the efficacy of alectinib in crizotinib-naïve patients (37). Alectinib demonstrated statistically significant superiority *vs.* crizotinib, reducing risk of progression/death by 53% (HR 0.47, P<0.0001). Median PFS was also increased in favor of alectinib (not reached *vs.* 11.1 months). Furthermore, specific HR of CNS progression was 0.16 for alectinib (95% CI: 0.10–0.28; P<0.0001). Of note, rates of AEs leading to discontinuation, dose reduction and interruption were lower with alectinib (37).

Finally, brigatinib and the third-generation ALK inhibitor lorlatinib are currently being investigated for their effectiveness and safety in ALK positive NSCLC patients who have progressed after one or two ALK inhibitors. In the phase II ALTA trial, patients with crizotinib refractory disease were randomly assigned to receive 90 or 180 mg of brigatinib daily (38). It was shown that patients who received the higher dose achieved a RR of 54% *vs.* 45% for patients who received the lower dose and a PFS of 12.9 *vs.* 9.2 months. Of note, 69% of patients enrolled had baseline brain metastases and brigatinib at the dose of 180 mg achieved an intracranial ORR of 67%. As a result, FDA granted accelerated approval to brigatinib for patients with ALK positive NSCLC who have progressed on initial therapy. The phase III ALTA-1L trial that carries a head to head comparison of brigatinib versus crizotinib in the first line setting of ALK positive NSCLC is currently underway. On the other hand, lorlatinib demonstrated impressive results in a phase I study in heavily pretreated patients (ORR of 46% and a PFS of 11.4 months) (39).

Other driver mutations

ROS1 is a receptor TK that acts as a driver oncogene in 1–2% of NSCLC via a genetic translocation between

ROS1 and other genes, the most common of which is CD74 (40). ROS1 translocation commonly occurs in adenocarcinoma patients who are young and never smokers. The ROS1 TK is highly sensitive to crizotinib due to a high degree of homology between the ALK and ROS TK domains. Crizotinib is FDA approved for both pretreated and treatment naïve patients; in an open-label, phase I international study of 50 patients with ROS1-translocated NSCLC, ORR was 72% and median PFS was 19.2 months (41). The majority of recruited patients were pretreated. Second generation TKIs ceritinib and alectinib are currently being investigated in this subpopulation of patients.

Activating BRAF mutations have been observed in 1–3% of NSCLC and are usually associated with a history of smoking. They can occur either at the V600 position of exon 15, like in melanoma, or outside this domain (42). For these patients, chemotherapy or immunotherapy is recommended as first line therapy. The combination of dabrafenib plus trametinib has been approved by the FDA for BRAF mutant NSCLC patients who have progressed to chemotherapy. In phase II study of 78 patients with previously treated, advanced NSCLC with the V600E mutation, the combination of dabrafenib plus trametinib was associated with an ORR of 63% in 52 evaluable patients, with a DCR of 79% and PFS of 9.7 months (43).
Other driver mutations include HER2 mutations, MET abnormalities and RET translocations. There is currently no approved targeted therapy for these subgroups of patients. Case series suggest that patients with HER2 insertions respond to trastuzumab in combination with chemotherapy or afatinib (44). Patients with MET exon 14 skipping mutations might respond to crizotinib or cabozantinib (45), whereas tumors with RET translocations might be sensitive to cabozantinib or vandetanib (46,47).

NSCLC with no driver mutations

First line therapy

First line platinum-based chemotherapy remains the mainstay of treatment in the majority of patients with NSCLC who do not harbor a driver mutation. On the other hand, the introduction of PD-1/PD-L1 immune checkpoint inhibitors and their incorporation into clinical practice has ultimately changed NSCLC treatment algorithm in the first line setting. PD1 is a co-inhibitory receptor that belongs to the CD28 family and is expressed on the cell surface of activated T cells, as well as B, NK cells, and monocytes after prolonged antigen exposure. Normally and upon binding to its main ligands, PD-L1 and PD-L2, PD-1 inhibits T cell activation and limits effector T cell activity in peripheral organs and tissues during inflammation, thus preventing autoimmunity. PD-L1 expression occurs frequently in a variety of tumors, including NSCLC. It is currently believed that binding of tumor-expressed PD-L1 to PD-1 blocks T cell activation and leads to immune evasion (2). This is the rationale for enhancing tumor response through blockade of PD-1 pathway with anti-PD-1/anti-PD-L1 antibodies pembrolizumab, nivolumab, atezolizumab and durvalumab.

High expression of PD-L1, which is defined as expression on at least 50% of tumor cells) has been reported as a predictive biomarker for response in early phase I pembrolizumab trials. On the basis of this observation, the phase III KEYNOTE 024 trial randomized 305 patients with high PD-L1 expression >50% to pembrolizumab (200 mg fixed dose every 3 weeks for 35 cycles or until disease progression) or platinum doublet (48). Of note, this trial did not include patients with EGFR mutations or ALK translocations, following the adverse outcomes of immunotherapy in these subgroups of patients in phase II trials. The primary endpoint, which of PFS was met favoring pembrolizumab (10.3 *vs.* 6 months in the chemotherapy arm, HR =0.50, P<0.001). Improvement in ORR was also statistically significant (44.8% for pembrolizumab-arm *vs.* 27.8% for chemotherapy-arm, P<0.001). One-year OS was also superior in the pembrolizumab-arm, albeit not statistically significant; this might be attributed to crossover in almost half of the patients in the control arm. In October 2016, pembrolizumab was FDA approved as front-line treatment in patients with NSCLC and strong PD-L1 positivity (>50%) and is now the standard of care for these patients. The results of this trial contrast the outcomes of CHECKMATE-026, which assessed the efficacy of nivolumab *vs.* chemotherapy as front-line treatment in patients with PD-L1 expression >5% (49). The trial was negative, with primary endpoint PFS favoring chemotherapy (5.9 months in the chemotherapy-arm *vs.* 4.2 months in the nivolumab arm).

Low PD-L1 expressers are treated with first line platinum-based doublet chemotherapy typically for 4–6 cycles. Platinum based therapies offer a median OS of 7–10 months and a median time to progression of 3–6 months. All regimens are considered equivalent in an unselected population (50). However, histology has emerged as an important factor for regimen selection. Cisplatin/

Pemetrexed has been shown to be superior in patients with adenocarcinoma *vs.* cisplatin/gemcitabine, whereas cisplatin/gemcitabine improves survival *vs.* cisplatin/pemetrexed in patients with squamous cell carcinoma (51). Carboplatin/Nab-paclitaxel has been more recently introduced as a therapeutic option in the first line setting; in a phase III trial, it was associated with an increased ORR compared to carboplatin/paclitaxel and with a numerically higher albeit not statistically significant improvement in OS in elderly patients >70 years old (19.9 *vs.* 10.9 months, P=0.009) (52). Bevacizumab has been shown to significantly improve OS in patients with non-squamous histology when added to standard-chemotherapy (53). On the other hand, necitumumab is the first monoclonal antibody against EGFR recently approved for squamous cell lung cancer in the first line setting. In the phase III SQUIRE trial, which evaluated the addition of necitumumab to cisplatin/gemcitabine in treatment-naïve patients with squamous cell lung cancer, OS was superior in favor of necitumumab (11.5 *vs.* 9.9 months, HR=0.84, P=0.01) (54). After the completion of chemotherapy and before disease progression, maintenance therapy with pemetrexed and/or bevacizumab is typically administered to patients with non-squamous histology, based on older landmark studies (55,56). Maintenance therapy implies the "down-shifting" to a less challenging but still effective therapy with a view to decrease toxicity.

Preclinical data have shown that chemotherapy modulates immune response and might increase PD-L1 expression on tumor cells (57,58). The synergism of chemotherapy and immunotherapy has been evaluated in the front line setting in the multicohort phase I/II KEYNOTE 021 trial. In cohort G of the phase II part of the study, the combination of chemotherapy and pembrolizumab was compared to chemotherapy alone in treatment-naïve patients with advanced non-squamous NSCLC (59). The addition of pembrolizumab to chemotherapy dramatically improved ORR (55% *vs.* 29%, P=0.0016); PFS was also superior in the combination arm (13 *vs.* 8.9 months, P=0.0102), although at the expense of greater grade 3–4 toxicity (39% in the concomitant arm *vs.* 26% in the chemotherapy only arm). The predictive value of PD-L1 was difficult to assess, since RR was 80% among high PD-L1 expressers (80%), but also up to 57% in patients with PD-L1 expression <1%. In May 2017, the FDA granted accelerated approval to pembrolizumab in combination with carboplatin/pemetrexed in the front line setting in patients with advanced non-squamous NSCLC. A phase III trial is currently underway.

Second line therapy

Immunotherapy is now recommended as second line therapy in all patients with NSCLC and no driver mutations. Three immune checkpoint inhibitors that target the PD-1/PD-L1 pathway are currently approved. Nivolumab was the first immune checkpoint inhibitor to show impressive efficacy with a better toxicity profile in the second line setting in patients with advanced NSCLC irrespectively of PD-L1 expression. Two phase III trials, CHECKMATE-057 and CHECKMATE-017 have tested nivolumab *vs.* docetaxel in squamous and non-squamous NSCLC respectively (60,61). Median OS was superior with nivolumab in both trials (9 *vs.* 6 months in the control arm in CHECKMATE-057 (60) and 12.2 *vs.* 9.4 months in the control arm in CHECMATE-017 (61). On the other hand, pembrolizumab was compared to standard docetaxel chemotherapy in patients with previously treated NSCLC and PD-L1 expression >1% in the phase III KEYNOTE-010 trial (62). Pembrolizumab was associated with improved OS compared to docetaxel (10.4 *vs.* 8.4 months, HR =0.71, P<0.001) and can be used as a therapeutic option in patients with PD-L1 >1%.

Atezolizumab is a fully humanized monoclonal antibody that targets PD-L1. The randomized phase II POPLAR trial evaluated the efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC (63). Patients were stratified by PD-L1 tumor-infiltrating immune cell status, histology, and previous lines of therapy, and were randomly assigned to receive intravenous atezolizumab or docetaxel. The primary endpoint of OS was 12.6 months for atezolizumab *vs.* 9.7 months for docetaxel (HR 0.73, P=0.04). Increasing improvement in OS was associated with increasing PD-L1 expression. Based on these results, FDA granted approval to atezolizumab for patients with advanced NSCLC whose disease progressed on platinum-based chemotherapy in 2016. In the phase III OAK trial, atezolizumab was compared to docetaxel as second line treatment in patients with advanced NSCLC. PD-L1 was measured in tumor cells (TCs) and tumor infiltrating immune cells (ICs) and primary endpoint was OS in the intention to treat (ITT) population and in the group of patients with >1% PD-L1 expression on TCs (TC1/2/3) or ICs (IC 1/2/3). Co-primary endpoints were met; median OS in the ITT population was 13.8 *vs.* 9.6 months (P=0.003), whereas in the TC1/2/3 or IC1/2/3 groups it reached 15.7 *vs.* 10.3 months (P=0.01) in favor of atezolizumab (64). Of

note, a favorable HR was also observed in never-smokers.

PD-L1 monoclonal antibodies durvalumab and avelumab have also been investigated in NSCLC. In a dose-expansion cohort of the phase Ib Javelin trial, avelumab achieved a 12% RR and a 36% DCR in previously treated patients, with 13% of patients experiencing grade 3 events (65). Durvalumab is currently being tested in combination with tremelimumab in phase II/III trials following clinical activity in a phase Ib study (66).

Most recently, antiangiogenic agents have shown promising results in the second line treatment of NSCLC. The phase III LUME LUNG 1 trial has shown superiority of docetaxel in combination of VEGFR TKI nintetanib *vs.* docetaxel alone in terms of OS in patients with adenocarcinoma histology. Furthermore, the study has demonstrated a non-statistically significant PFS benefit in first line treatment refractory patients (67). On the other hand, the REVEL randomized phase III trial demonstrated a modest OS benefit of the addition of the VEGFR2 inhibitor ramucirumab to docetaxel in both squamous and non-squamous NSCLC (10.5 *vs.* 9.1 months in the docetaxel arm, P=0.023) (68).

Of note, the pan-HER-targeted EGFR inhibitor afatinib was shown to result in superior PFS and OS in comparison with erlotinib in squamous cancers in the 2nd–3rd line setting and has been recently approved in that setting (69).

Expert commentary

Periodically, new data emerge from clinical trials and modify the standards of care, moving the decision-making process within a tumor type to a different level. Several years ago, such advances changed the treatment algorithm of advanced NSCLC to a more histology- and molecular biology-oriented approach, reflecting the development of drugs specifically effective in patients with certain histologies and the introduction of TKIs targeting distinct genetic profiles. However, at that point and for the vast majority of patients, platinum-based doublet chemotherapy remained the cornerstone of treatment, as it had been for more than a decade.

Since that time, there have been a series of rapid and dramatic transformations in this therapeutic landscape. All these advances in the field of oncology emphasize that NSCLC is no longer a single disease entity, but represents a heterogeneous group of different tumors defined by histologic subtype, genomic profile and more recently, tumor immunophenotype, increasingly pushing treatment selection towards personalizing therapy.

Intrapatient and intratumor heterogeneity add another level of complexity, in some cases predicting acquired resistance mechanisms. For patients with oncogene-driven lung cancer, new generation agents, such as osimertinib in EGFR mutant NCLC and ceritinib/alectinib in ALK positive NSCLC, represent new therapeutic options in patients who develop resistance in front line EGFR TKIs or ALK inhibitors respectively. However, the specific sequence of these agents is still unclear; osimertinib and alectinib have also shown promising results in the front line setting and ceritinib is already approved in treatment-naïve patients. In addition, it is unknown if a specific sequence of therapeutic agents influences the biology of cancer or clinical course of the patient. On the other hand, combination therapy that targets multiple pathways may provide greater clinical benefit.

But it is the new class of checkpoint inhibitors where the most profound advances were made. The results of KEYNOTE-024 that led to the incorporation of immunotherapy in the first line setting in high PD-L1 expressers (48), have displaced the role of chemotherapy in treatment-naïve NSCLC patients without driver mutations for the first time in the history of oncology. However, the fact that a similar trial in design, CHECKMATE-026 (49), did not meet its primary endpoint, creates a confusion about when and how to evaluate PDL-1 status. In addition, nivolumab and atezolizumab are approved in the second line setting irrespectively of PD-L1 status, whereas pembrolizumab can be administered only in patients with PD-L1 expression ≥1%. Despite the fact that the PD-L1 IHC assay seems to be a good predictive assay, it is becoming increasingly clear that PD-L1 expression is not yet a perfect test. Many questions are still unresolved regarding the best antibody, the right cutoff for positivity, the relevance of PD-L1 expression on immune cells versus tumor cells, and the heterogeneity of PD-L1 expression (1). Other potential molecular biomarkers under investigation, such as mutation burden, could also be used to help select the best candidates for therapy. On the other hand, immunotherapy is likely ineffective in patients with EGFR mutations and ALK rearrangements, possibly reflecting the low mutational burden in tumors developed in never-smokers.

Finally, the combination of immunotherapy with chemotherapy is still an area of active investigation. The results of KEYNOTE-021 have prompted accelerated approval of the combination of chemotherapy and

pembrolizumab, but the clinical or molecular setting in which concomitant therapy could be the appropriate selection of treatment is not clear and there has been no direct comparison between the combination and pembrolizumab monotherapy.

Conclusions

It is becoming increasingly clear that NSCLC is a diverse disease comprising of clinically and genetically distinct subgroups and each individual patient is truly unique. Researchers continue to elucidate many molecular pathways involved in thoracic malignancy. Following the introduction of targeted therapies and immunotherapy into clinical practice, treatment algorithms for NSCLC have dramatically changed over the past few years. Indeed, it is likely that this current state of treatment in advanced NSCLC will continue to evolve, as new studies are completed and new preclinical data help to explain the underlying biology beneath the clinical outcomes observed.

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Footnote

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