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Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC)

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Abstract: Treatment for advanced non-small cell lung cancer (NSCLC) has been significantly improved in recent years with the incorporation of drugs targeting antiangiogenesis and more specifically genomic alterations such as the *EGFR* mutations and *ALK* translocations. However, most patients invariably progress and die. The emergence of immune checkpoint inhibitors targeting the pathways involved in tumor-induced immunosuppression have redefined the management of the disease, achieving significant long-lasting responses with manageable safety profiles, regardless of histology. Still, response rates with immunotherapy are deemed suboptimal. Current efforts are focusing on new potential combination strategies with synergistic antitumor activity, using immune checkpoint blockade as a partner for targeted agents. Herein we discuss the available data on the combined use of immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitors, with EGFR and ALK inhibitors and comment on the current status of immunotherapy plus antiangiogenic drugs for molecularly unselected advanced NSCLC.

Keywords: advanced NSCLC, immunotherapy, targeted therapy

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Non-small cell lung cancer (NSCLC), comprising non-squamous carcinoma (adenocarcinoma among other less common histologies) and squamous (epidermoid) carcinoma, accounts for approximately 85% of all new lung cancer cases, and often presents at advanced stages with dismal prognosis.[2]

Before the identification of actionable oncogenic driver alterations in tumor cells and a deeper understanding of tumor microenvironment, platinum-based chemotherapy remained the cornerstone of treatment for fit patients with advanced NSCLC.[3] Since then, tyrosine kinase inhibitors (TKIs) for patients harboring epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) or ROS proto-oncogene 1 (*ROS1*) rearrangements have significantly improved clinical outcomes.[4–14] Many other genetic lesions have been identified in lung cancers, and routine molecular profiling is strongly encouraged.[15–17] However, these genomic alterations occur in a relatively small percentage of NSCLC patients, mainly adenocarcinoma, and when actionable, the efficacy of the available targeted drugs is limited due to the development of acquired resistance through different molecular mechanisms.[18] Even with therapeutic strategies targeting secondary mutations such as the gatekeeper *EGFR* T790M point mutation, patients ultimately progress and require treatment with standard chemotherapy.[19,20]

Antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) have also reshaped the approach to the treatment of advanced NSCLC, although predictive biomarkers to guide therapy for this class of drugs are warranted.[21–24]

The emergence in recent years of immune checkpoint inhibitors that reverse cancer immunosuppression and enhance antitumor immunity, including monoclonal antibodies directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) and its ligand (PD-L1), has redefined management of patients with advanced NSCLC, regardless of histology. Various anti-PD-1/PD-L1 antibodies are already approved for the first- and second-line setting, with manageable toxicity profiles, improved efficacy and longer duration of response compared to standard chemotherapy.[25–29] In untreated metastatic non-squamous NSCLC the front-line combination of pembrolizumab, which is a PD-1 inhibitor, with carboplatin and pemetrexed is also approved for use.[30] Still, a significant number of patients do not respond and a subset progress after initially responding to immunotherapy. Current research is focusing on thorough characterization of crosstalk between tumor and immune cells, and better identification of predictive biomarkers of response, beyond PD-L1 expression, to guide selection of patients most likely to benefit from this approach.[31,32] Mutational load in advanced NSCLC (in both oncogene-addicted and molecularly unselected disease) impacts on tumor immunogenicity.[33] Tumor cell death triggered by chemotherapeutic and targeted agents strengthens the antitumor immune response by release of neoantigens.[33] This offers a unique opportunity for combination strategies with synergistic antitumor activity, using immunotherapy as a partner for chemotherapy, targeted agents and other immune checkpoint inhibitors. Results regarding safety and efficacy of such combinations are still preliminary and immature, mostly based on preclinical models and early phase clinical trials.

Herein we summarize the available data on strategies combining immunotherapy with targeted agents for advanced NSCLC treatment, with a focus on *EGFR*- and *ALK* TKIs and antiangiogenic drugs.

Anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab) and TKIs

Available data on the effects of combining PD-1 inhibitors with TKIs are scarce and obtained from subgroup analysis.

The CheckMate 057 and KEYNOTE-010 trials, which demonstrated a statistically significant improvement in overall survival (OS) for nivolumab and pembrolizumab respectively over standard second-line docetaxel chemotherapy in patients with advanced NSCLC, did not show any differences between study arms among *EGFR*-mutant patients.

The CheckMate 057 trial enrolled 582 patients with non-squamous advanced NSCLC regardless of PD-L1 expression level, among which 82 (14%) were positive for *EGFR* mutation and 21 (4%) had *ALK* translocated. Subgroup analyses of OS revealed that patients with *EGFR* mutation, having received or receiving an additional line of TKI, did not benefit from nivolumab compared with docetaxel [hazard ratio (HR) 1.18, 95% confidence interval (CI) 0.69–2.00]. A similar lack of benefit was observed for the subgroup of patients that never smoked, suggesting that low levels of mutational load in these populations might confer less sensitivity to immune checkpoint inhibitors. No data on OS were reported for the patients harboring *ALK* translocations.[26]

In the KEYNOTE-010 trial, which led to the approval of pembrolizumab for previously treated advanced NSCLC with PD-L1 expression on at least 1% of tumor cells, 86 patients (8.3%) were *EGFR*-mutant and 6 (0.6%) were *ALK*-positive. Patients with *EGFR* mutation did not have prolonged OS in response to pembrolizumab compared to docetaxel (HR 0.88, 95% CI 0.45–1.70). Patients with *ALK* translocations were not specifically examined.[28]

Clinical trials testing the combination of nivolumab or pembrolizumab with *EGFR* and *ALK* TKIs in advanced NSCLC are ongoing (Table 1).

The interim analyses from the phase I CheckMate 012 [ClinicalTrials.gov identifier: NCT01454102] trial have already been reported for the cohort of patients with *EGFR*-mutated advanced NSCLC treated with nivolumab and erlotinib. This cohort enrolled 21 patients (20 with acquired erlotinib resistance and one TKI-naïve). Objective response rate (ORR) was 19% with 3 out of the 20 *EGFR* TKI-pretreated patients and the one *EGFR* TKI-naïve patient achieving partial response. Two patients discontinued treatment due to treatment-related adverse events (AEs) (grade 3 AST increase and grade 2 nephritis) but safety profile was generally acceptable.[34]

Table 1. Clinical trials of immune checkpoint inhibitors in combination with *EGFR*/*ALK* TKIs in advanced NSCLC.

Clinical trial	Phase	Setting	Intervention	Status
NCT02574078/ CheckMate 370	I/II	Newly diagnosed/maintenance LA/ stage IV NSCLC	Nivolumab + erlotinib (group D)/ crizotinib (group E)	Ongoing, not recruiting for group E
NCT01998126	I	Stages II–IV TKI-naïve or TKI-treated for less than 6 months *EGFR*- or *ALK*-mutated NSCLC	Nivolumab/ipilimumab + + erlotinib/crizotinib	Ongoing, not recruiting
NCT01454102/ CheckMate 012	I	Newly diagnosed or pretreated stage IIIB/IV NSCLC	Nivolumab + erlotinib (arm E)	Ongoing, not recruiting
NCT02393625	I	Stage IIIB/IV treatment-naïve or pretreated ALK-positive NSCLC	Nivolumab + ceritinib	Recruiting
NCT02039674/ KEYNOTE-021	I/II	Newly diagnosed stage IIIB/IV NSCLC, progression >1 year after adjuvant therapy for stages I–IIIA NSCLC	Pembrolizumab + erlotinib (cohort E)/gefitinib (cohort F)	Ongoing, not recruiting
NCT02364609	I	LA/stage IV/recurrent erlotinib-resistant *EGFR*-mutated NSCLC	Pembrolizumab + afatinib	Recruiting
NCT03157089/ LUX-Lung IO	II	Pretreated stage IIIB/IV squamous NSCLC	Pembrolizumab + afatinib	Not yet open
NCT02511184	I	Newly diagnosed LA/stage IV *ALK*-positive non-squamous NSCLC	Pembrolizumab + crizotinib	Recruiting
NCT02013219	I	LA/stage IV TKI-naïve *EGFR*-mutated and treatment-naïve *ALK*-positive NSCLC	Atezolizumab + erlotinib/ alectinib	Ongoing, not recruiting
NCT02584634/ Javelin Lung 101	Ib/II	LA/stage IV pretreated *ALK*-negative (group A) or *ALK*-positive (group B) NSCLC	Avelumab + crizotinib (group A)/ lorlatinib (group B)	Recruiting
NCT02088112	I	LA/stage IV TKI-naïve *EGFR*-mutated NSCLC	Durvalumab + gefitinib	Ongoing, not recruiting
NCT02898116	I/II	Stage IV *ALK* rearranged NSCLC	Durvalumab + ensartinib	Recruiting
NCT01998126	I	Stages II–IV TKI-naïve or TKI-treated for less than 6 months *EGFR*- or *ALK*-mutated NSCLC	Ipilimumab + erlotinib/ crizotinib	Ongoing, not recruiting
NCT02040064/ GEFTREM	I	LA/stage IV TKI-pretreated *EGFR*-mutated NSCLC	Tremelimumab + gefitinib	Completed

LA: locally advanced.

Anti-PD-L1 monoclonal antibodies (atezolizumab/MPDL3280A, avelumab/ MSB0010718C, durvalumab/MEDI4736) and TKIs

Targeting PD-L1 has also shown promising results for the treatment of advanced NSCLC. However, very few data are available on the combination of anti-PD-L1 with targeted agents in the subgroup of patients harboring *EGFR* mutations or *ALK* translocations.

The phase III OAK trial comparing atezolizumab *versus* docetaxel in patients with previously treated NSCLC, regardless of PD-L1 expression or histology, demonstrated a statistically significant improvement of OS in favor of the anti-PD-L1 antibody.[29] This trial confirmed the results of the previous phase II POPLAR study of atezolizumab against docetaxel in pretreated NSCLC patients.[35] In view of these data, atezolizumab was recently approved by

regulatory agencies as another second-line therapeutic option for patients with advanced NSCLC progressing after platinum-based chemotherapy. The OAK trial randomized a total of 850 patients, among which 85 (10%) and 2 (0.2%) had received previous TKI therapy for *EGFR*-mutant and *ALK*-positive disease, respectively. When analyzing OS across clinical subgroups, *EGFR*-mutant patients had similar benefit with atezolizumab and docetaxel (HR 1.24, 95% CI 0.71–2.18). This finding mirrors the results reported with anti-PD-1 treatment in this particular setting, suggesting once again decreased immunogenicity in this subgroup of patients. In contrast to the CheckMate 057 trial, however, there was a survival benefit of atezolizumab over docetaxel in the never-smoker population (HR 0.71, 95% CI 0.47–1.08) (which has been associated with lower mutational load and immunogenicity). No information on efficacy was given in the OAK trial for *ALK*-positive patients, probably because of their small number.[29]

Phase III trials are ongoing to evaluate the safety and clinical activity of other anti-PD-L1 antibodies in pretreated advanced NSCLC.

The JAVELIN Lung 200 [ClinicalTrials.gov identifier: NCT02395172] trial is comparing avelumab *versus* docetaxel in subjects with NSCLC progressing after a platinum-containing doublet.

The ARCTIC [ClinicalTrials.gov identifier: NCT02352948] trial is another phase III study for advanced NSCLC investigating durvalumab monotherapy in PD-L1-positive tumors and durvalumab combined with tremelimumab (an anti-CTLA-4 antibody) in PD-L1-negative tumors *versus* standard of care in third-line setting or beyond.[36]

Nevertheless, none of these trials allow patients harboring *EGFR* activating mutations or *ALK* rearrangements for participation.

A recent meta-analyses of three studies that compared immune checkpoint inhibitors against chemotherapy in advanced NSCLC and included TKI-pretreated *EGFR*-mutant subpopulation (the CheckMate 057, the KEYNOTE-010 and the POPLAR studies) showed a lack of OS benefit from immunotherapy targeting the PD-1/PD-L1 axis compared to docetaxel in patients with *EGFR* mutations. The authors suggested careful interpretation of the findings due to the small sample sizes of *EGFR*-mutant subgroups and the limitations associated with a posteriori subgroup analyses. They also recommended further investigation of the underlying mechanisms of acquired resistance to first-line *EGFR* TKIs to guide selection of second-line treatment for these patients.[37]

Another study retrospectively evaluated the response patterns among 22 *EGFR*-mutant and 6 *ALK*-positive NSCLC patients treated with PD-1/PD-L1 inhibitors. Most patients (82%) had previously received and progressed on TKI treatment. When starting immune checkpoint blockade, only 11% were maintained on TKI therapy. ORR in patients with *EGFR* mutations and *ALK* rearrangements was 3.6%, similar to that observed in never- or light smokers. In fact, only a small proportion of *EGFR*-mutant and *ALK*-positive patients presented concurrent PD-L1 expression and high levels of CD8+ tumor-infiltrating lymphocytes, suggesting that lack of inflammatory microenvironment might limit the efficacy of PD-1/PD-L1 inhibitors.[38]

The expression of PD-1/PD-L1 in molecularly selected NSCLC patients was assessed in a retrospective study including 56 *EGFR*-mutated and 10 *ALK*-translocated patients. Presence of *EGFR* mutations was significantly associated with PD-L1 positive status. Levels of PD-L1 were also higher in patients with *ALK* translocations, although the association was not statistically significant. In presence of *EGFR* mutations, PD-L1 positive patients treated with gefitinib or erlotinib had better disease outcome.[39]

Despite the available data that seem to show poor efficacy of immune checkpoint inhibitors for advanced NSCLC patients with *EGFR* mutation or *ALK* translocation, trials are ongoing evaluating anti-PD-L1 antibodies in combination with EGFR and ALK inhibitors, some with particular focus on predictive biomarkers of response (Table 1).

Preliminary results from the combination of atezolizumab with erlotinib in the phase I NCT02013219 trial have been presented. The safety stage included patients with locally advanced or metastatic NSCLC regardless of *EGFR* status and the expansion stage included TKI-naïve patients with *EGFR* mutation. Patients were enrolled regardless of PD-L1 status. At data

cut-off, 28 patients (8 in the safety stage and 20 in the expansion stage) were evaluated for safety and clinical activity. Grade 3–4 AEs occurred in up to 39% of patients, mainly pyrexia and increased ALT. No pneumonitis was reported. ORR reached 75% with median duration of response being 9.7 months. Apparently, the combination led to a clinically significant increase in toxicity without improving the ORR or the OS achieved with TKI monotherapy.[40]

Durvalumab in combination with gefitinib has been evaluated in the phase I NCT02088112 trial. At data cut-off, 20 TKI-naïve *EGFR*-mutant NSCLC patients had been included in the expansion phase. Half of the patients received concurrent durvalumab plus gefitinib (arm 1) while the other half was treated with gefitinib alone for 28 days before starting the combination (arm 2). Grade 3–4 AEs led to treatment discontinuation in four patients, all from arm 2, due to increased ALT and/or AST ($n = 3$) and pneumonitis ($n = 1$). ORRs were 77.8% and 80% for arms 1 and 2, respectively.[41] Paired tumor biopsies from the patients participating in this trial were analyzed for phosphorylated EGFR (pEGFR) inhibition, showing pEGFR inhibition at 10 days after initiation of treatment in most of the paired samples from arms 1 and 2. This finding suggests that the addition of durvalumab to gefitinib does not abrogate the effect of gefitinib with regard to pEGFR inhibition.[42]

The TATTON [ClinicalTrials.gov identifier: NCT02143466] trial is a multi-arm phase I study evaluating osimertinib with novel therapeutics for patients with *EGFR*-mutated advanced NSCLC who have progressed after therapy with an *EGFR* TKI. Although preliminary data on clinical activity for the arm combining osimertinib with durvalumab was encouraging, for both TKI-pretreated and TKI-naïve patients, enrollment into this arm has been terminated due to an increase of pulmonary toxicity. Interstitial lung disease occurred in 26% of *EGFR* TKI-pretreated patients and 64% of *EGFR* TKI-naïve patients. Some of these patients developed grade 3–4 severe pneumonitis.[43] In view of the safety of the combination, recruitment was stopped for the CAURAL [ClinicalTrials.gov identifier: NCT02454933] phase III randomized study to assess osimertinib in combination with durvalumab *versus* osimertinib alone for patients with advanced *EGFR* T790M mutation-positive NSCLC previously treated with *EGFR* TKI.

Anti-CTLA-4 monoclonal antibodies (ipilimumab, tremelimumab) and TKIs

Ipilimumab specifically blocks binding of CTLA-4 to its ligands (CD80/CD86), augmenting T-cell activation. Activity in patients with lung cancer was addressed in a phase II trial where chemotherapy-naïve advanced or recurrent NSCLC patients were assigned to receive ipilimumab combined with carboplatin and paclitaxel in a phased schedule (after chemotherapy) or in a concurrent schedule and compared with chemotherapy and placebo. Phased ipilimumab resulted in better immune-related progression-free survival (PFS) compared to the control arm (HR 0.72, $p = 0.05$) and safety profile was consistent with data from published ipilimumab studies. Patients with squamous histology appeared to benefit most.[44] To confirm these results, the phase III NCT01285609 trial of ipilimumab plus carboplatin and paclitaxel in squamous stage IV or recurrent NSCLC was developed. However, this trial has failed to demonstrate an OS benefit for the combination (HR 0.9, 95% CI 0.76–1.07). Neither the phase II nor the phase III trial provide information with regard to *EGFR* mutations or *ALK* rearrangements. The combination of ipilimumab with nivolumab in chemotherapy-naïve advanced NSCLC patients was evaluated in the multicohort phase I CheckMate 012 [ClinicalTrials.gov identifier: NCT01454102] trial and showed encouraging results by means of high response rate and tolerable safety profile. Clinical activity was particularly enhanced in patients with tumor PD-L1 expression of 1% or higher. In patients with *EGFR*-mutated NSCLC, four (50%) of eight had an objective response. Of these eight patients with *EGFR* mutation, PD-L1 expression levels were 1% or more in seven and 50% or more in three.[45] Phase III trials are ongoing to evaluate this dual checkpoint inhibitor blockade as first-line strategy for patients with advanced NSCLC.

Another antibody directed against CTLA-4, tremelimumab, was evaluated in a phase II trial for advanced NSCLC patients as maintenance therapy after achieving stable disease or partial response with first-line platinum-based chemotherapy. Although the study did not meet the primary endpoint demonstrating superior PFS of tremelimumab *versus* placebo, the 4.8% ORR seen in the investigational arm, together with acceptable safety, led to the development of the anti-CTLA-4 antibody in combination with other immune checkpoint inhibitors.[46] The phase I NCT02000947 trial

of tremelimumab plus durvalumab in immunotherapy-naïve locally advanced or metastatic NSCLC demonstrated manageable toxicity, with ORR between 22% and 29% regardless of PD-L1 expression. From the total of patients included in this trial (n = 102), 12.7% harbored an *EGFR* mutation and 0.9% were *ALK*-positive. However, data on antitumor activity in these subgroups of patients are lacking.[47]

Besides the ARCTIC trial in the pretreated setting,[36] other phase III clinical trials are currently ongoing to evaluate the efficacy and safety of the combination of tremelimumab with durvalumab as first-line treatment strategy *versus* standard of care in stage IV NSCLC patients [MYSTIC (ClinicalTrials.gov identifier: NCT02453282), NEPTUNE (ClinicalTrials.gov identifier: NCT02542293), POSEIDON (ClinicalTrials.gov identifier: NCT03164616)]. None of these studies, however, include patients with activating *EGFR* mutations or *ALK* fusions.

Ipilimumab is currently being tested in association with erlotinib or crizotinib in a phase I trial including patients with *EGFR*-mutant or *ALK*-rearranged NSCLC. In TKI-pretreated *EGFR*-mutant stage IV NSCLC patients, the combination of tremelimumab with gefitinib was tested in the phase I GEFTREM [ClinicalTrials.gov identifier: NCT02040064] trial. Disease stabilization was obtained in 67% of the evaluable patients and the safety profile was consistent with the previously defined AE profile (Table 1).[48]

Immune checkpoint inhibitors and antiangiogenics

Different agents targeting the VEGF/VEGFR pathway, a crucial mediator of tumor survival and growth, have been developed for advanced NSCLC. Bevacizumab is an anti-VEGF monoclonal antibody approved for use in combination with carboplatin and paclitaxel as first-line treatment for patients with advanced non-squamous NSCLC.[21] In treatment-naïve *EGFR*-mutated NSCLC the addition of bevacizumab to erlotinib improves PFS, particularly in the presence of coexisting pretreatment T790M mutation.[22,49]

In the second-line setting, two drugs in combination with docetaxel have demonstrated clinical benefit over docetaxel alone in NSCLC: ramucirumab, which is a monoclonal antibody targeting VEGFR, and nintedanib, a triple angiokinase inhibitor which targets VEGFR, platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR).[23,24]

Angiogenic factors are immunosuppressive, and with the emergence of immune checkpoint blockade for advanced NSCLC the combination of antiangiogenic drugs with immune therapies may exhibit potential synergistic antitumor activity.

Several trials exploring the combined use of immune checkpoint inhibitors with antiangiogenic agents are ongoing (Table 2).

The CheckMate 012 [ClinicalTrials.gov identifier: NCT01454102] phase I trial evaluated the efficacy and safety of switching to nivolumab as maintenance treatment, alone or combined with bevacizumab, in a cohort of advanced NSCLC patients with response to first-line platinum-based chemotherapy. Preliminary results of the trial reported an acceptable toxicity profile for the combination. Median PFS reached 37.1 weeks in the arm of non-squamous patients treated with nivolumab plus bevacizumab (n = 12). In the nivolumab monotherapy arms, the median PFS for non-squamous (n = 13) and squamous (n = 8) patients was 21.4 and 16 weeks, respectively.[50]

The combination of ramucirumab with pembrolizumab has been explored in the NCT02443324 phase I trial in patients with advanced solid tumors including NSCLC. Data from the preliminary toxicity results did not reveal unexpected safety concerns.[51] Disease control rate with the combination has recently been reported as achieving 85%.

Data from trials evaluating safety and efficacy of combined treatment with immunotherapy and antiangiogenic TKIs have not yet been reported. However, the phase I PEMBIB [ClinicalTrials.gov identifier: NCT02856425] study of pembrolizumab with nintedanib in advanced NSCLC is currently ongoing and results are highly anticipated.

Discussion

Immunotherapy has expanded the range of treatment options for patients with advanced NSCLC. Currently three drugs (nivolumab, pembrolizumab and atezolizumab) are approved for the second-line setting after platinum-based chemotherapy. Pembrolizumab is also indicated as both upfront monotherapy and combination therapy

Table 2. Clinical trials of immune checkpoint inhibitors and antiangiogenic agents in advanced NSCLC.

Clinical trial	Phase	Setting	Intervention	Status
NCT02574078/ CheckMate 370	I/II	Newly diagnosed/maintenance LA/stage IV NSCLC	Nivolumab + bevacizumab (group A)	Ongoing, not recruiting for group A
NCT01454102/ CheckMate 012	I	Newly diagnosed or pretreated stage IIIB/IV NSCLC	Nivolumab + bevacizumab maintenance (arm D)	Ongoing, not recruiting
NCT02039674/ KEYNOTE-021	I/II	Newly diagnosed stage IIIB/IV NSCLC, progression >1 year after adjuvant therapy for stages I–IIIA NSCLC	Pembrolizumab + bevacizumab + carboplatin + paclitaxel (cohort B)	Ongoing, not recruiting
NCT02681549	II	Anti-PD-1/PD-L1-naïve metastatic melanoma or non-squamous NSCLC with untreated brain metastases	Pembrolizumab + bevacizumab	Recruiting
NCT02443324	I	Treatment-naïve or pretreated LA unresectable/metastatic solid tumors including NSCLC	Pembrolizumab + ramucirumab	Recruiting
NCT02856425/ PEMBIB	I	Pretreated advanced solid tumors including LA/stage IV/locally recurrent adenocarcinoma and squamous NSCLC	Pembrolizumab + nintedanib	Recruiting
NCT02366143/ IMpower 150	III	Treatment-naïve stage IV non-squamous NSCLC	Atezolizumab + bevacizumab + carboplatin + paclitaxel (arm B)	Ongoing, not recruiting
NCT01633970	I	Pretreated advanced solid tumors	Atezolizumab + bevacizumab (arm A)	Ongoing, not recruiting
NCT02174172	I	LA/metastatic solid tumors including LA/ stage IV TKI-pretreated *EGFR*-mutated or *ALK* rearranged NSCLC	Atezolizumab + bevacizumab + PEG-interferon alfa-2a (arm D)	Recruiting
NCT02572687	I	LA unresectable/metastatic solid tumors including pretreated NSCLC	Durvalumab + ramucirumab	Recruiting

LA: locally advanced.

for selected patients with advanced NSCLC. However, response rates with immune checkpoint blockade are deemed suboptimal, with more than half of the patients ultimately progressing.

Research efforts in advanced NSCLC are now moving toward combination strategies using immunotherapy as a partner for existing therapies (antiangiogenic drugs and chemotherapy in molecularly unselected disease, targeted drugs for oncogene-addicted tumors) that are already regarded immunogenic due to their induction of tumor cell death and release of neoantigens.[33,52]

Pro-angiogenic factors can modulate the immune response by reducing tumor T-cell infiltration and through systemic effects on immune-regulatory cell function such as inhibition of T-regulatory cell proliferation, myeloid-derived suppressor cell function and dendritic cell maturation.[53] NSCLC related to smoking history also appears to predict clinical benefit from immunotherapy approaches, probably due to a high mutational burden that generates immunogenic neoantigens.[54] In *EGFR*-mutated cell lines, a correlation between *EGFR* pathway activation and a signature of immunosuppression by upregulation of PD-1, PD-L1, CTLA-4 and proinflammatory cytokines has been identified.[55] Similarly, overexpression of ALK fusion protein has shown to increase PD-L1 expression.[56]

Although PD-L1 expression has consistently shown to be enriched for patients most likely to benefit from immune checkpoint blockade, responses to PD-1/PD-L1 inhibitors have also been described in patients with PD-L1 negative tumors, and label indications for nivolumab and

atezolizumab for second-line treatment of patients with advanced NSCLC do not actually rely on the basis of PD-L1 status. This suggests that other factors related to tumor microenvironment beyond PD-L1 are determinants of the response to immunotherapy. In advanced NSCLC, as for other types of cancers, clinical studies are beginning to define these factors as concrete immune phenotypes that can predict outcome of immune checkpoint blockade.[57] PD-L1 may be induced by oncogenic signals or can be upregulated *via* interferon gamma (INFG) in a STAT-1 and NF-κB-dependent manner. A recent study evaluating pretreatment levels of INFG in tumor samples from patients with advanced NSCLC and melanoma demonstrated that intermediate and high levels of INFG microRNA expression correlated with longer PFS and OS and higher disease control rates with anti-PD-1 therapies, even when PD-L1 expression was low. In contrast, low levels of INFG correlated with lack of response.[32] In *EGFR*-mutated NSCLC, where anti-PD-1/PD-L1 therapies appear to benefit less, a recent study reported low expression of INFG in tumor samples. This correlated with increased expression of the immunosuppressive molecule CD73, suggesting that overexpression of CD73 in *EGFR*-mutated NSCLC might partly explain the reduced benefit from PD-1/PD-L1 inhibition.[58] Tumor mutational burden (TMB), epithelial mesenchymal transition and transforming growth factor-beta, among other factors, also impact on tumor immunogenicity.[59–61] TMB is reduced in lung cancer harboring *EGFR* mutations and *ALK* or *ROS1* fusions as known drivers.[62] In the phase III CheckMate 026 trial, nivolumab did not yield longer PFS than platinum-based chemotherapy when used as a first-line therapy for patients with untreated advanced NSCLC and a PD-L1 tumor-expression level of 5% or more. Interestingly however, patients with both a high TMB and a PD-L1 expression level of 50% or more treated with nivolumab had a higher response rate (75%) than those with only one of these factors (32% among patients with a high TMB only and 34% among those with a PD-L1 expression level of 50% or more only) or neither factor (16%).[63] Deeper understanding of cross-talk between tumor cells and immune system and careful identification of predictive biomarkers of response therefore remain a priority, especially with therapeutic combination strategies in development.

This review focuses on the available data and ongoing trials evaluating the combined use of immunotherapy with *EGFR* and *ALK* TKIs in the subset of patients with advanced NSCLC harboring *EGFR* mutations and *ALK* rearrangements. We have also commented on the current status of immunotherapy plus antiangiogenic drugs for molecularly unselected advanced NSCLC.

Results regarding the efficacy of combining immune checkpoint inhibitors with *EGFR* TKIs have been obtained from subgroup analyses derived from the phase III CheckMate 057, KEYNOTE-010 and OAK trials in second-line setting NSCLC. These analyses suggest that patients with *EGFR* mutations tend to be less responsive to immune checkpoint blockade compared with *EGFR* wild-type population, but with some limitations. For example, information on type of sensitizing *EGFR* mutation, previous TKI therapy received and presence of known acquired resistance mutations is lacking from these trials. Molecular testing for *EGFR* mutation was not performed for all participants, nor centrally reviewed when detected. Overall, the interpretation of these subgroup analyses is complex, not to mention the limitations of the wide confidence intervals for the calculated HRs in such small subgroups of patients. No data from these phase III trials with immunotherapy for pretreated advanced NSCLC are available for the subset of patients with *ALK* rearrangements.

There are currently several trials ongoing to evaluate a range of next-generation *EGFR* and *ALK* TKIs available in clinical practice for combination with immunotherapeutics in selected TKI-naïve or TKI-pretreated *EGFR*- or *ALK*-mutated NSCLC populations, some with particular focus on predictive biomarkers of response. Early results emerging from these combination trials suggest that such approaches elicit increased antitumor responses through synergism of the drugs involved, although in some cases safety concerns are nontrivial. Additional long-term safety and efficacy data are eagerly awaited.

With respect to combining immunotherapy and antiangiogenic agents for advanced NSCLC patients, preliminary data from the ongoing trials are consistent with an acceptable toxicity profile and potential synergistic antitumor activity.

In this era of immune checkpoint blockade and identification of targetable genetic alterations

beyond *EGFR* mutations and *ALK* translocations, novel rational combinations for the treatment of advanced NSCLC patients are warranted. These include immunotherapy as the backbone for combined use with the emerging targeted agents in the subsets of patients harboring *ROS1* and *RET* fusions, *MET* exon 14 skipping mutations, *MET* and *FGFR* amplifications, and *HER2* and *BRAF* mutations (both V600 and non-V600 *BRAF* mutations).[14,64–70] To the best of our knowledge, no clinical trials evaluating combinations of these new oncogene-directed targeted drugs with immune checkpoint blockade are ongoing at the moment.

Vaccine immunotherapy enhancing T-cell activation against specific tumor-associated antigens on cancer cells, though not addressed in this review, may well serve as partners for combination strategies with targeted therapies.[71] Based on the positive results of a phase III trial evaluating the epidermal growth factor (EGF) vaccine CIMAvax-EGF as switch maintenance therapy *versus* placebo for previously chemo-treated advanced NSCLC patients,[72] our group is planning to conduct a preclinical study evaluating the CIMAvax-EGF vaccine in combination with *EGFR* TKI in *EGFR*-mutated NSCLC tumors (EPICAL trial).

Conclusions

Combination strategies with synergistic antitumor activity using immunotherapy as a partner for targeted agents represents a promising field for the treatment of patients with advanced NSCLC.

Results regarding the safety and efficacy of such combinations are still immature and additional long-term data are warranted. Deeper characterization of the interactions between immune and tumor cells, identification of reliable predictive biomarkers of response, and full understanding of the mechanisms involved in the development of acquired resistance in the subset of oncogene-addicted tumors are active areas of research, with the aim of improving patient selection and overall therapeutic efficacy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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