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Combination approaches in NSCLC involving immune checkpoint inhibitors

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Practice points

- NSCLC is a heterogeneous disease.
- Targeted therapies are standard of care in patients with oncogenic driver mutations such as *EGFR* mutations and *ALK* rearrangements.
- Chemotherapy is standard of care in patients without an oncogenic driver mutation.
- Immune checkpoint inhibitors such as anti-PD-1 antibodies are efficacious in patients with NSCLC beyond the first-line setting.
- Combination therapies utilizing immune checkpoint inhibitors with chemotherapy, targeted therapy or other immune checkpoint inhibitors appear safe and have shown promise in early phase studies.
- Larger Phase III studies are currently underway studying various combinations and their results are eagerly anticipated.

Immune checkpoint inhibition has been proven to be highly efficacious in NSCLC and associated with durable responses in a limited number of patients. Chemotherapy and targeted therapies, which have also expanded rapidly in this field lead to high response rates and improved survival although inevitably resistance occurs and hence treatment failure. There is increasing evidence showing that chemotherapy and targeted therapy interplay with the immune system including exerting effects on tumor cells and the host immune cells. Naturally combining both of these treatment modalities to induce cytotoxic effects on tumor cells to release tumor antigens and priming of the immune system should in turn lead to enhanced anticancer activity. This review will explore some of the preclinical rationale and clinical trial data we have to date on combining various systemic therapies with immunotherapies.

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Lung cancer remains the leading cause of cancer deaths worldwide, affecting 1.8 million people in 2012 and leading to approximately 1.6 million deaths [1]. NSCLC is the predominant subtype of lung cancer accounting for 85% of all cases [2]. Adenocarcinoma histology accounts for over 50% of NSCLC, squamous cell histology for 25% and the remaining cases represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma and poorly differentiated histology [3].

NSCLC is a genomically diverse disease with molecular subtyping, demonstrating that both spatial and temporal heterogeneity define molecular clones between primary sites and metastases in

KEYWORDS

• combination therapy
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a branched evolution pattern [4]. These patterns have been reported in both adenocarcinomas and squamous cell tumors, although oncogenic driver mutations appear to be more common in adenocarcinomas than squamous cell tumors to date. Prior to the development of small molecule inhibitors targeting specific oncogenes, platinum-based chemotherapy was shown to improve survival in NSCLC [5].

EGFR mutations and *ALK* rearrangements are the most established targetable oncogenic driver mutations in NSCLC; however, invariably resistance to these agents develops in most patients. Prior to the development of immunotherapies, the only way to potentially eradicate heterogeneous cell types was through chemotherapy, but even this could be completely ineffective or generate mixed responses.

Normal immune checkpoints exist to dampen down immune responses and protect the host from autoimmunity and detrimental chronic inflammation [6]. However, these checkpoints can be manipulated by some tumors, leading to immune tolerance, immunoevasion and subsequent tumorigenesis and progression [6]. Two such checkpoints that are well characterized and robustly investigated in NSCLC are CTLA-4 and the PD-1. Two large Phase III studies have confirmed that nivolumab, an IgG4 monoclonal antibody to PD-1 improves overall survival (OS) compared with second-line docetaxel chemotherapy in both squamous and nonsquamous NSCLC [7,8]. In CheckMate 057 (nonsquamous), the OS was improved with nivolumab versus docetaxel with a hazard ratio (HR) of 0.73; 95% CI: 0.59–0.89; $p = 0.002$ and objective response rate (ORR) of 19 versus 12%; $p = 0.02$ [7]. In CheckMate 017 (squamous), nivolumab was superior to docetaxel in terms of OS with an HR: 0.59; 95% CI: 0.44–0.79; $p < 0.001$ and ORR of 20 versus 9%; $p = 0.008$ [8].

Given the single-agent activity of immune checkpoint inhibitors over chemotherapy, a large number of studies have been launched to investigate combination approaches. This review will summarize currently available evidence and explore the biological rationale of combination therapies in NSCLC.

Combination between chemotherapy & immunotherapy

• Chemotherapy & vaccines

Cancer vaccines operate on the premise that they present tumor antigens to the immune system to

generate tumor-specific T-cell clones. However, to date single-agent activity with cancer vaccines have been disappointing, suggesting that this strategy is insufficient to generate objective tumor regression in both early and advanced settings.

In a Phase II study, belagenpumatucel-L, a vaccine derived from four irradiated NSCLC tumor cell lines demonstrated safety and efficacy in low-volume disease [9]. However, this vaccine failed to demonstrate a survival benefit when used as maintenance versus placebo in patients with advanced NSCLC in the Phase III setting [10]. The MAGRIT Phase III study, which randomized 2272 patients to receiving recombinant MAGE-A3, a tumor-specific antigen expressed in up to 50% NSCLC cells versus placebo in the adjuvant setting, failed to show a progression-free or OS benefit [11].

TG4010 consists of a suspension of recombinant-modified vaccinia Ankara that codes for the MUC1 tumor-associated antigen, which is overexpressed in NSCLC. The combination of TG4010 with first-line chemotherapy for advanced NSCLC was tested in two randomized studies, both of which confirmed their safety and met their respective primary end points of progression-free survival (PFS) at 6 months and ORR [12,13]. The TIME trial was a Phase IIb/III study that randomized patients with high MUC1 expression (at least 50% tumor cells) to TG4010 or placebo with platinum-doublet chemotherapy [14]. The study met its primary end point of PFS (5.9 vs 5.1 months; HR: 0.74; $p = 0.019$) with the addition of TG4010 to chemotherapy.

There was a trend toward improvement in median OS but did not meet statistical significance (12.7 vs 10.6 months; HR: 0.78; $p = 0.055$). In keeping with other immunotherapy studies, there was a longer duration of response observed in the TG4010 arm, 34% ongoing response at 1 year compared with 19% in the placebo arm. There were also no significant grade 3 or 4 adverse events attributed to TG4010 alone. The 4% of grade 3 and 4 adverse events noted in the vaccine arm were neutropenia (2%) and fatigue (1%); however, this was less compared with the placebo arm with 10% grade 3 and 4 adverse events.

The TIME study remains the first Phase III clinical study confirming a survival end point benefit with a cancer vaccine in NSCLC and importantly demonstrated that it is safe and

efficacious when used in combination with cytotoxic chemotherapy.

• Chemotherapy & checkpoint inhibitors

For an effective anti-tumor response, several functional steps are required including availability of tumor antigen via immunogenic cell death, uptake of antigen by antigen-presenting cells, cross-presentation and subsequently activation of T cells, T-cell infiltration into tumor cells and continued T-cell activity without exhaustion by negative regulatory checkpoints [15]. Via their ability to induce immunogenic cell death, chemotherapy, including platinum has been postulated to initiate an immune response [16,17]. These agents have also been shown to sensitize tumor cells to lymphocyte-mediated killing in animal models [18]. Another mechanism of action includes abrogation of T regulatory-mediated immune suppression. Docetaxel and cyclophosphamide have been shown in mouse models to deplete T regulatory cells [19,20].

Targeting immune checkpoints with monoclonal antibodies have proven successful in NSCLC, with both pembrolizumab and nivolumab being US FDA approved in 2015. Ipilimumab, a human monoclonal antibody targeting CTLA-4 has shown benefit in patients with melanoma [21]. A Phase II study randomizing chemotherapy-naïve patients with NSCLC to platinum-doublet chemotherapy and ipilimumab or placebo was published in 2012 [22]. The study met its primary end point of improved immune-related PFS for phased ipilimumab versus control (HR: 0.72; $p = 0.05$) but not for concurrent ipilimumab (HR: 0.81; $p = 0.13$). The median immune-related PFS observed was 5.7 months for phased ipilimumab, 5.5 months for concurrent ipilimumab and 4.6 months for control. There was a trend to improved OS with phased ipilimumab as the median was 12.2 versus 8.3 months for the control group (HR: 0.87; $p = 0.23$). The median OS for concurrent ipilimumab of 9.7 months was similar to control (HR: 0.99; $p = 0.48$). However, the 2-year OS rate was similar at 18% for phased ipilimumab, 16% for concurrent ipilimumab and 18% for control. In the forrest plot, improvement in immune-related PFS in patients who received phased ipilimumab compared with control appeared to be greater for the squamous cell cohort (HR: 0.55; 95% CI: 0.27–1.12) compared with the nonsquamous cohort (HR: 0.82; 95% CI: 0.52–1.28). Nevertheless the numbers

in the subgroups were small and we await results from the Phase III study that has completed recruitment.

As far as grade 3 and 4 immune-related adverse events were concerned, the rates were 15% for phased ipilimumab, 20% for concurrent ipilimumab and 6% for control. These events were made up of rash, diarrhea, colitis, liver-function enzyme rise and hypophysitis. One death occurred in the concurrent ipilimumab group due to septic shock from toxic epidermal necrolysis. Overall this demonstrates modest benefit and safety when ipilimumab is administered as a phased regimen with chemotherapy in NSCLC.

Nivolumab, a human monoclonal anti-PD-1 antibody has well-documented clinical activity in NSCLC. CheckMate 012 is a multiarm Phase I study of nivolumab in combination with chemotherapy and tyrosine kinase inhibitors. In the chemotherapy arm (chemotherapy-naïve), 56 patients were assigned a platinum doublet (gemcitabine/cisplatin, pemetrexed/cisplatin and paclitaxel/carboplatin) in combination with nivolumab [23]. The ORR was 33–47%, 24-week PFS was 38–71% and 2-year OS was 25–62%. No dose-limiting toxicities were observed but 45% patients had grade 3 or 4 toxicities and 7% ($n = 4$) had pneumonitis.

Atezolizumab or MPDL3280A is a human monoclonal antibody that blocks PD-L1 from binding to its receptors PD-1 and B7.1. GP 28328, is a multiarm Phase Ib study, with three arms dedicated to chemotherapy naïve NSCLC patients receiving paclitaxel/carboplatin, pemetrexed/carboplatin or nab-paclitaxel/carboplatin with atezolizumab [24]. Among the 30 patients reported, ORR was 67%. Eleven out of eighteen patients were continuing to respond by the April 2014 data cutoff with a median duration of 24 weeks in one arm and not reached in the other two arms. All patients had at least one adverse event but there were no grade 3 or 4 adverse events reported. The common adverse events include nausea, rash, fatigue and diarrhea.

Pembrolizumab was studied in combination with chemotherapy in chemotherapy-naïve patients (paclitaxel/carboplatin and pemetrexed/carboplatin) in KEYNOTE-021 [25]. A total of 28% patients who received paclitaxel/carboplatin and 58% patients who received pemetrexed/carboplatin had an ORR. 16 out of 24 and 16 out of 25 patients, respectively, remained on study at data cutoff. Two grade 3 and 4 adverse events

were noted including one immune-related rash in the carboplatin/pemetrexed group requiring discontinuation and one liver enzyme rise.

Based on the preliminary results from these three studies, the safety and anti-tumor activity of first-line combination platinum-doublet chemotherapy with anti-PD-1 and anti-PD-L1 antibodies are promising. **Table 1** highlights all currently recruiting studies utilizing this approach and **Table 2** summarizes the data. These studies have resulted in the launch of Phase III chemoimmunotherapy combination studies, where survival is the primary end point. Of considerable interest are studies exploring not just chemoimmunotherapy, but also chemotherapy with bevacizumab and immunotherapy combinations.

Combination between targeted therapy & immunotherapy

• Targeted therapy & checkpoint inhibitors

Both *EGFR* mutations and *ALK* rearrangements have been shown in preclinical models to increase PD-L1 expression, and play an important role in facilitating the immune escape of these tumors. *EGFR* pathway activation, through oncogenic mutations, *EGFR* overexpression or increased ligand expression, lead to increased PD-L1 expression compared with wild-type *EGFR* NSCLC [31,32]. In preclinical cell line and mouse models, *EGFR* signaling directly induces upregulation of PD-L1 expression, at least in part through the ERK1/2/c-Jun pathway [33]. Confirming the importance of *EGFR* signaling, *EGFR* activation increases PD-L1 expression in a dose-dependent manner,

and inhibition of *EGFR* signaling leads to PD-L1 downregulation [32,33].

In addition, *EGFR* activation leads to an immunosuppressive tumor microenvironment in a mouse model of *EGFR*-mutated NSCLC. PD-L1 expression leads to T-cell anergy, increased Tregs and an ineffective immune response [31]. Anti-PD-1 antibodies were able to reverse this immune suppression, leading to increased numbers of CD8⁺ cells and IFN- γ production [31]. Interestingly, blockade of *EGFR* with tyrosine kinase inhibitors (TKIs) *in vitro* has also been shown to reverse this T-cell anergy and increase the production of effector cytokines [31]. Thus, *EGFR* inhibitors are likely to have both a direct lethal effect on tumor cells, and restore the immunological response to them.

Although it is clear that inhibition of *EGFR* signaling can lead to tumor cell death and reversal of an immunoinhibitory environment, it is unclear as to whether the combination of *EGFR*-directed and immunotherapy could have a synergistic effect. This was tested in a co-culture of *EGFR* mutation-positive NSCLC cell line and peripheral blood mononuclear cells [32]. The results showed that both *EGFR* TKIs (in this case, gefitinib in a sensitive cell line, and rocletinib in a cell line harboring the T790M resistance mutation) and anti-PD-1 therapy could independently reduce tumor cell viability, but that the combination was no more effective than an *EGFR* TKI alone [32].

ALK rearrangements have been shown to have a similar effect on PD-L1 upregulation to their *EGFR*-mutated counterparts [34–36]. Marzec *et al.*

Table 1. Chemotherapy and immunotherapy combination clinical trials recruiting.

Study drug	Phase	Population	Clinical trial ID
Ipi + pac/carbo vs pac/carbo	III	Sq NSCLC	NCT01285609
Nivo + gem/cis, pem/cis or pac/carbo	I	Chemo-naive, NSCLC	NCT01454102
Nivo + beva	I	Maintenance NSCLC	NCT01454102
Pembro + gem	I/II	Second-line NSCLC	NCT02422381
Pembro + nab-pac/carbo	I/II	Chemo-naive NSCLC	NCT02382406
Pembro + cis/pem or pem/carbo or pac/carbo $\pm$ beva	I/II	Chemo-naive NSCLC	NCT02039674
Pembro + pem/cis vs pem/cis	III	Chemo-naive, non-Sq NSCLC	NCT02578680
Atezo + pem/carbo or pem/cis vs pem/carbo or pem/cis	III	PD-L1 ⁺ , chemo-naive, non-Sq NSCLC	NCT02409342
Atezo + pac/carbo vs atezo + beva + pac/carbo vs beva + pac/carbo	III	Chemo-naive non-Sq NSCLC	NCT02366143
Atezo + gem/cis or gem/carbo vs gem/cis or gem/carbo	III	PD-L1 ⁺ , chemo-naive, Sq NSCLC	NCT02409355
Atezo + pac/carbo vs atezo + nab-pac/carbo vs nab-pac/carbo	III	Chemo-naive, Sq NSCLC	NCT02367794
Atezo + carbo/pem vs carbo/pem	III	Chemo-naive, nonSq NSCLC	NCT02657434
Atezo + nab-pac/carbo vs nab-pac/carbo	III	Chemo-naive, nonSq NSCLC	NCT02367781
DCVAC + pac/carbo or DCVAC + IFN- α + pac/carbo	I/II	NSCLC	NCT02470468

Atezo: Atezolizumab; Beva: Bevacizumab; Carbo: Carboplatin; Cis: Cisplatin; DCVAC: Dendritic cell vaccination; Gem: Gemcitabine; Ipi: Ipilimumab; Nab-pac: Nab-paclitaxel; Nivo: Nivolumab; Pac: Paclitaxel; Pem: Pemetrexed; Pembro: Pembrolizumab; Sq: Squamous.

Table 2. Summary of studies and data.

Study (year)	NSCLC population	Phase	Treatment	Treatment line	Efficacy	Ref.
Quoix <i>et al.</i> (2016)	Non-Sq and Sq	III	Gem/cis or pem/cis or pac/carbo ± TG 4010 or placebo	First line	PFS: HR: 0.74 (95% CI: 0.55–0.98); p = 0.019	[14]
Lynch <i>et al.</i> (2012)	Non-Sq and Sq	II	Pac/carbo + ipi or placebo	First line	irPFS: HR: 0.72 (95% CI: 0.50–1.06); p = 0.05	[22]
Rizvi <i>et al.</i> (2016)	Non-Sq and Sq	I	Gem/cis, pem/cis or pac/carbo + nivo	First line	ORR: 33%, 47% and 43% OS at 2 years: 25%, 33% and 62%	[23]
Liu <i>et al.</i> (2015)	Non-Sq and Sq	I	Pac/carbo, Pem/carbo or nab-pac/carbo + atezo	First line	ORR: 60%, 75% and 62%	[24]
Papadimitrakopoulou <i>et al.</i> (2015)	Non-Sq and Sq	I	Pac/carbo or pem/carbo + pembro	First line	ORR: 28% and 58%	[25]
Rizvi <i>et al.</i> (2014)	EGFR+ non-Sq	I	Nivo + erlotinib	First line	ORR: 19%	[26]
Antonia <i>et al.</i> (2016)	Non-Sq and Sq	I	Durva + treme	Any line	ORR: 23%	[27]
Patnaik <i>et al.</i> (2015)	Non-Sq and Sq	I	Pembro + ipi	Any line	ORR: 55%	[28]
Antonia <i>et al.</i> (2014)	Non-Sq and Sq	I	Nivo + ipi	First line	ORR: 22%	[29]
Hellmann <i>et al.</i> (2016)	Non-Sq and Sq	I	Nivo + ipi	First line	ORR: 39% and 47%	[30]

Atezo: Atezolizumab; Carbo: Carboplatin; Cis: Cisplatin; Durva: Durvalumab; Gem: Gemcitabine; HR: Hazard ratio; Ipi: Ipilimumab; irPFS: Immune-related progression-free survival; Nab-pac: Nab-paclitaxel; Nivo: Nivolumab; ORR: Objective response rate; OS: Overall survival; Pac: Paclitaxel; Pem: Pemetrexed; Pembro: Pembrolizumab; PFS: Progression-free survival; Sq: Squamous; Treme: Tremelimumab.

showed high PD-L1 expression in ALK-positive tumors, and induction of PD-L1 expression by ALK, through the STAT3 pathway [34]. The importance of ALK activation was confirmed by Voena *et al.* who demonstrated a reduction in PD-L1 expression, when ALK signaling was reduced with either crizotinib (an ALK-targeted TKI) or gene knockdown [35]. ALK also induced a suppressive tumor microenvironment, with increased Tregs, high expression of T-cell inhibitory molecules PD-1, LAG-3 and TIM-3, similar to that seen with EGFR [35]. Interestingly, this study also found that blockade of PD-L1 could restore the efficacy of an ALK vaccine in a mouse model. Thus, it appears that both EGFR and ALK directly mediate expression of PD-L1 and the regulation of the tumor immune microenvironment, but it is unclear whether the combination of targeted and immunotherapy would offer improved clinical outcomes.

Though there appears to be sound rationale for PD-L1 overexpression in molecularly driven tumors, only some cohort analyses of metastatic or resected NSCLC have shown an association between PD-L1 expression and *EGFR* mutations and *ALK* rearrangements [33,37–39]. Nonetheless, clinical trials of PD-1/PD-L1 therapy have included a number of patients with *EGFR/ALK* lung cancer, usually following progression on a TKI [6,40,41].

In CheckMate 057, patients with *EGFR* mutations comprised 15% of the nivolumab cohort and 13% of the docetaxel cohort [7]. Despite

an OS improvement in the entire nivolumab cohort, the subgroup analysis in *EGFR*-mutated patients did not appear to show benefit with an HR of 1.18 (0.69–2.00). In KEYNOTE-010, pembrolizumab also demonstrated an OS benefit compared with docetaxel in the overall population [40]. *EGFR*-mutated patients comprised 8% receiving pembrolizumab 2 mg/kg, 9% receiving pembrolizumab 10 mg/kg and 8% receiving docetaxel. Unlike CheckMate 057, there remained a survival benefit with pembrolizumab over docetaxel in these subgroups but the HR of 0.88 (95% CI: 0.45–1.70) was modest. Of note, this study selected patients for PD-L1 expression whereas the CheckMate 057 study did not, which may explain the more favorable HR. Nonetheless the HR of 0.88 in the *EGFR* mutant cohort was not as effective, or statistically significant as the HR: 0.66 (95% CI: 0.55–0.80) seen in the *EGFR* wild-type population.

In CheckMate 057, nivolumab was superior to docetaxel with PD-L1 expression 1% (p = 0.06) and 10% (p = < 0.001). In KEYNOTE-010, pembrolizumab improved survival compared with docetaxel in PD-L1 expression >1–49% (HR: 0.76; 95% CI: 0.60–0.96) and >50% (HR: 0.53; 95% CI: 0.40–0.70). In the POPLAR study, atezolizumab improved survival compared with docetaxel with an HR: 0.59 (95% CI: 0.45–0.85; p = 0.005) in the PD-L1 >1–5% expressing group and HR: 0.49 (95% CI: 0.22–1.07; p = 0.068), in the PD-L1 >10% group [41]. None of the studies described PD-L1

expression in patients with EGFR mutations and this would be important to determine potential benefit in these patients.

There is one reported study using the combination of erlotinib and nivolumab in *EGFR*-mutant NSCLC [26]. This Phase I trial included 21 chemotherapy-naïve patients, with 20 having developed acquired resistance to erlotinib prior to study entry and one patient being treatment naïve. The ORR was 19% (4 of 21 patients), with 3 of 20 previously treated patients achieving a partial response. The median PFS was 29.4 weeks, and 1-year OS was 73%. The combination appeared tolerable, although 24% suffered grade 3/4 AEs (two with diarrhea and three with elevated liver transaminases). No pneumonitis was seen. Thus, the combination appears to be relatively safe in this small cohort, but further studies are needed to explore whether a combination approach would offer additional benefits over a sequential use of these therapies.

These responses are somewhat higher than expected given the nature of resistance patterns seen with first-generation TKIs including the gatekeeper T790 gene-resistance mutation in approximately half of patients rendering inability of further tumor response to these drugs. Recent studies have shown a modest response rate of 0–22% in patients who had progressed on gefitinib, received at least one line of systemic chemotherapy and then were rechallenged with gefitinib [42,43]. T790 mutation stratification was not described in these patients. Osimertinib, a third-generation TKI has an ORR of 77% and median PFS of 19.3 months in patients with T790 mutation-positive disease and has been approved by the FDA for this indication [44].

Perhaps more intriguing was a study of 24 patients who became resistant to first-generation TKIs and were treated with a combination of a first-generation TKI and bevacizumab [45]. The overall response rate observed was 13% but when stratified this was 0% (0/7) in T790 mutation-positive disease and 18% (3/17) in T790 mutation-negative disease. The rationale for responses in this subgroup could be due to VEGF as a resistance mechanism in T790 mutation-negative disease. An alternate mechanism is immune modulation with the combination, although this is hypothetical. In the report by Rizvi *et al.*, the T790 mutation status was not presented and this would be an important observation in order to investigate options in patients with T790 mutation-negative disease.

Currently we await the results of ongoing trials of combination targeted and immunotherapy to guide us as to whether this strategy will be more efficacious than either treatment alone. Table 3 summarizes the currently recruiting studies in this area and Table 2 summarizes the data.

• Combination immune checkpoint inhibitors

The ORR of PD-1/PD-L1 pathway inhibition is in the order of 10–30% in PD-L1 unselected patients with NSCLC [46]. To improve on the number of patients who benefit from immune checkpoint blockade, combination approaches utilizing anti-CTLA-4 and anti-PD-1/PD-L1 agents are of interest. Antonia *et al.* presented their findings on combination between an anti-PD-L1 agent durvalumab and anti-CTLA-4 agent tremelimumab in both chemotherapy-naïve and chemotherapy-pretreated patients with

Table 3. Targeted therapy and immunotherapy combination trials recruiting.			
Study drug	Phase	Population	Clinical trial ID
Ipi + erlotinib or crizotinib	I	EGFR ⁺ and ALK ⁺ NSCLC	NCT01998126
Pembro + erlotinib or gefitinib	I/II	EGFR ⁺ NSCLC	NCT02039674
Pembro + afatinib	I	EGFR ⁺ NSCLC	NCT02364609
Nivo + erlotinib	I	EGFR ⁺ NSCLC	NCT01454102
Nivo + EGF816	II	EGFR ⁺ NSCLC	NCT02323126
Durva + gefitinib	I	EGFR ⁺ TKI-naïve NSCLC	NCT02088112
Atezo + cobimetinib	I	Solid tumors including NSCLC	NCT01988896
Atezo + erlotinib or alectinib	I	EGFR ⁺ NSCLC	NCT02013219
Atezo + rociletinib	I	EGFR ⁺ NSCLC	NCT02630186
Pembro + crizotinib	I	ALK + NSCLC	NCT02511184
Nivo + ceritinib	I	ALK + NSCLC	NCT02393625
Avelu + crizotinib or lorlatinib	I	ALK + NSCLC	NCT02584634
ALK: Anaplastic lymphoma kinase; Atezo: Atezolizumab; Avelu: Avelumab; Durva: Durvalumab; Ipi: Ipilimumab; Nivo: Nivolumab; Pembro: Pembrolizumab; TKI: Tyrosine kinase inhibitor.			

Table 4. Combination immunotherapy trials recruiting.

Study drug	Phase	Population	Clinical trial ID
Pembro + ipi	I/II	NSCLC	NCT02039674
Durva + treme	I/II	NSCLC	NCT02000947
Durva + MEDI0680	I	Solid tumors	NCT02118337
Nivo + ipi	I	Chemo-naïve NSCLC	NCT01454102
Nivo + IL-21	I	Solid tumors	NCT01629758
Atezo + MOXR0916	I	Solid tumors	NCT02410512
Atezo: Atezolizumab; Durva: Durvalumab; Ipi: Ipilimumab; Nivo: Nivolumab; Pembro: Pembrolizumab; Treme: Tremelimumab.			

NSCLC [27]. One hundred and two patients were enrolled on their Phase I study, and at publication there was only 18.8 weeks of median follow-up. ORR in the evaluable population was 23% (6/26), which included 2/9 that were PD-L1 positive and 4/14 that were PD-L1 negative.

However, grade 3–4 toxicity was high with 11% diarrhea, 9% colitis and 8% increased lipase noted. Twenty-two patients died during the study and three of the deaths were attributable to treatment-related complications including myasthenia gravis, pericardial effusion and neuromuscular disorder. By comparison, studies that led to the approval of pembrolizumab and nivolumab had a 7–11% rate of grade 3–4 adverse events and <1% deaths [7,40].

In KEYNOTE-021, cohort D included chemotherapy-naïve and chemotherapy-pretreated patients with recurrent NSCLC who received pembrolizumab with ipilimumab [28]. Eighteen patients were enrolled at data cutoff. Various dose levels were used in this study and 3 patients received pembrolizumab 10 mg/kg with ipilimumab 1 mg/kg, 3 patients received pembrolizumab 10 mg/kg with ipilimumab 3 mg/kg and 12 patients received pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg. Only three patients had grade 3–4 adverse events of which two were rash and one was adrenal insufficiency. Both patients with rash discontinued, one had received pembrolizumab 10 mg/kg and ipilimumab 3 mg/kg and the other had received pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg. Of the evaluable patients, there was an ORR of 39% (7/18), 50% (6/18) in pembrolizumab 10 mg/kg and ipilimumab 1 and 3 mg/kg while the ORR was 33% (12/18) in pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg.

In a study by Antonia *et al.*, 46 chemotherapy-naïve patients were treated with nivolumab and ipilimumab [29]. Fourteen out of 24 patients who received nivolumab 1 mg/kg and ipilimumab 3 mg/kg had grade 3–4 adverse events, consisting of diarrhea (3/24), increased liver

transaminases (3/24), rash (1/24), adrenal insufficiency (1/24) and pneumonitis (2/24). In comparison, 10/25 patients who received nivolumab 3 mg/kg and ipilimumab 1 mg/kg had grade 3–4 adverse events, of which 2/25 diarrhea, 3/25 colitis, 1/25 raised liver transaminases, 1/25 rash, 1/25 adrenal insufficiency and 1/25 pneumonitis. There was a higher rate of discontinuation in the nivolumab 1 mg/kg and ipilimumab 3 mg/kg arm at six patients.

In an updated American Society of Clinical Oncology (ASCO) 2016 presentation exploring two separate chemotherapy-naïve cohorts, 38 patients with NSCLC were treated with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 12 weeks while 39 patients received nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks [30]. ORR of 47 and 39% were seen, respectively. Impressively the 1-year median OS rates in both groups were not reached and 69% respectively. Grade 3–4 treatment-related AE consisted of 37 and 33% in each group with no treatment-related deaths.

Overall it appears that responses are significantly enhanced with combination checkpoint inhibitors, however, at the cost of higher toxicity, and longer data follow-up is required to evaluate this. **Table 4** summarizes the current recruiting studies and **Table 2** summarizes the data.

Conclusion & future perspective

Systemic treatment modalities in NSCLC have expanded rapidly in a relatively short period of time. With their low toxicity and potential for durable responses, immune checkpoint inhibition is a huge area of interest and active research. Building on the limited success of single-agent immunotherapy, combination approaches may offer better responses to a larger group of patients with the ultimate goal of deep and durable responses and improvement in survival. However, this may come at the cost of increased toxicity, which based on the current data appears to be manageable. With more immunological targets

entering the clinic, combination approaches are likely to be important in the future management of lung cancer. Of critical importance is the need to identify predictive markers so that treatment combinations can be tailored to those most likely to obtain benefit. Thus far, there is emerging and promising data from interim Phase I and II studies and we eagerly await longer term follow-up data and Phase III data of which multiple studies are underway.

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