DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Combination checkpoint inhibitors for treatment of non-small-cell lung cancer: an update on dual anti-CTLA-4 and anti-PD-1/PD-L1 therapies

Sonam Puri MD[1], Michael Shafique MD[2]

[1]Division of Medical Oncology, Huntsman Cancer Institute at University of Utah, Salt Lake City, Utah, USA; [2]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

Abstract

Immunotherapy has revolutionized cancer treatment. In non-small-cell lung cancer (NSCLC), monotherapy with immune checkpoint inhibitors has improved survival in metastatic disease. Combinations of immune checkpoint inhibitors have shown synergy in preclinical models and are being studied as part of the treatment armamentarium in NSCLC. This review discusses the rationale, outcomes, and challenges of combination immune checkpoint blockade. Despite the challenges, this paper also presents some solutions and ways to improve our understanding and implementation of such combinations in the future.

Keywords: anti-CTLA-4, anti-PD-1/PDL-1, lung cancer.

Citation

Puri S, Shafique M. Combination checkpoint inhibitors for treatment of non-small-cell lung cancer: an update on dual anti-CTLA-4 and anti-PD-1/PD-L1 therapies. Drugs in Context 2020; 9: 2019-9-2. DOI: 10.7573/dic.2019-9-2

Introduction

Immunotherapy has revolutionized the therapeutic landscape of advanced non-small-cell lung cancer (NSCLC). In the last decade, immune checkpoint antibodies targeting the PD-1 (programmed death protein)/PD-L1 (programmed death protein ligand) and CTLA-4 (cytotoxic T-cell lymphocyte antigen 4) pathways have been evaluated extensively as a treatment strategy for multiple solid tumor malignancies, including lung cancer. Nivolumab is a fully humanized immunoglobulin targeting PD-1 that was first approved by the US Food and Drug Administration (FDA) for the treatment of advanced NSCLC.[1] Additionally, checkpoint inhibitors are now approved for the treatment of advanced NSCLC in the first-line setting (as monotherapy in patients with PD-L1 expression ≥1% or in combination with chemotherapy) and as a monotherapy in previously treated patients.[2–5] In contrast, ipilimumab and tremelimumab are anti-CTLA-4 antibodies that do not have clinically meaningful efficacy as monotherapy in metastatic NSCLC. Although anti-PD-1/PD-L1 therapy has improved outcomes of patients with metastatic NSCLC, many patients, especially with PD-L1 negative tumors, still do not respond to immunotherapy.[6] There remains an unmet need for evaluation of biomarkers for patient selection and identification of combination immunotherapy strategies to improve the clinical efficacy of checkpoint inhibition in advanced NSCLC.

In the last few years, there has been a great interest in evaluating dual checkpoint blockade as a therapeutic strategy for advanced malignancies. Results from the majority of trials evaluating dual checkpoint blockade show that combination therapy is associated with a higher and more durable tumor response, albeit with risk of greater toxicity when compared to single-agent immunotherapy.[7] There is extensive published literature on the clinical activity of dual checkpoint inhibition in advanced NSCLC and there are several clinical studies ongoing. Data from these trials will be crucial in shaping the future of immunotherapy in patients with NSCLC. The purpose of this review is to summarize the clinical development, safety, and efficacy of combination anti-PD-1/PD-L1 and anti-CTLA-4 therapy in metastatic NSCLC.

Methods

A literature search was conducted for clinical trials reporting on the combinations of CTLA-4 inhibitors with PD-1/PD-L1 inhibitors (i.e. ipilimumab with nivolumab or tremelimumab with durvalumab). A search of ongoing studies using these combinations with additional agents was conducted.

Information was obtained from Clinicaltrials.gov (accessed: June 15, 2019, Keywords: anti-PD-1, anti-PD-L1, anti-CTLA-4, lung cancer). Additional publications and presented data were added following peer review to incorporate updates from major conferences. A brief review of the immunobiology and pharmacology of immune checkpoint blockade was performed and summarized for context.

Results

Basic principles of checkpoint inhibitor therapy

The use of checkpoint inhibitors in NSCLC is based upon the paradigm that cancer is an inherently genetic disease. Tumor cells are genetically unstable and acquire numerous non-synonymous mutations.[8] Some of these mutations occur in the expressed genes that are involved in peptide generation in the cell cytosol by proteasomes that are in turn presented by MHC class I molecules on the surface of cancer cells.[9-12] During physiological "immune-surveillance", the T cell receptors (TCRs) bind to these non-synonymous neo-antigen peptides loaded on MHC molecules and can identify cancer cells as 'foreign' leading to cell lysis and death. Tumor cells can evade this fate by exploiting the PD-1/PD-L1 and the CTLA-4/CD-28 axis.[13] PD-1 is a checkpoint protein present on the surface of the T cells. The function of this checkpoint is to downregulate cytotoxic T-cell responses by binding the ligands PD-L1 and PD-L2 on tumor cells or in the tumor microenvironment. CTLA-4 is another checkpoint protein present on the surface of activated T cells in the lymphoid compartment.[14] It competes with CD-28 receptors to bind to B7-1 (CD-80) and B7-2(CD-86) present on antigen-presenting cells. The interaction of CD-28 with B7-1 and B7-2 acts as a costimulatory signal for T cells; however, in competing with CD-28, CTLA-4 inhibits the activation of T cells.[14] Blockade of these inhibitory signals by anti-PD-1/PD-L1 or anti-CTLA-4 antibodies reduces tumor 'immune evasion' and restores 'immune surveillance', leading to tumor reduction and response.

Anti-PD-1/PD-L1 and anti-CTLA-4 agents act at different parts of the cancer immunity cycle.[15] Combining these agents is synergetic and could help overcome resistance to single-agent immunotherapy.[16] Preclinically, this combination has shown promising enhancement in antitumor activity and is associated with the upregulation of the tumor-infiltrating effector and regulatory T cells.[17,18] Multiple clinical studies have been conducted to test the efficacy of dual checkpoint inhibition in solid tumors, and the combination of nivolumab plus ipilimumab is currently approved by the FDA for frontline treatment of metastatic melanoma and renal cell carcinoma.[19–21] A brief pharmacological overview of the checkpoint inhibitors can improve our understanding of the different clinical trial designs and dosing strategies for combined checkpoint inhibition with anti-PD-1/PD-L1 and anti-CTLA-4 agents. Ipilimumab is a human IgG1 monoclonal antibody (mAb) that targets the CTLA-4 antigen, found on activated T cells, and is cleared in a linear manner without time variance.[22] In patients with metastatic melanoma, ipilimumab (0.3–10 mg/kg) dose and minimum steady-state concentration have been associated with overall survival, while other efficacy outcomes are more closely associated with C_{minss}.[15,22] Treatment with higher doses of ipilimumab does appear to be associated with higher incidence of immune-related adverse events (irAEs), and C_{minss} of ipilimumab has also been correlated with higher irAEs.[15] Nivolumab is a fully humanized IgG4 mAb targeting PD-1 that also exhibits linear clearance, but unlike ipilimumab, its clearance varies over time. Additionally, nivolumab exhibits no dose or concentration-dependent relationship with efficacy.[23] However, in patients with NSCLC, nivolumab doses of 3 and 10 mg/kg, as well as C_{minss}, were positively correlated with response rates.[24] When given as combination therapy, the clearance of nivolumab increases in the presence of ipilimumab, but the clearance of ipilimumab remains unchanged.[25]

Tremelimumab is another human IgG2 mAb directed at CTLA-4. Similar to ipilimumab, it displays linear clearance at doses studied in NSCLC.[26] Durvalumab is a human IgG1 mAb targeting PD-L1 that currently is FDA approved for consolidation treatment in stage III NSCLC at the dose of 10 mg/kg every 2 weeks. Durvalumab is frequently combined with tremelimumab for dual checkpoint inhibitor studies in NSCLC, and its clearance is linear for the doses studied. Additionally, there is no reported pharmacokinetic interaction between tremelimumab and durvalumab.[20] In a phase I study evaluating the combination of tremelimumab with durvalumab in metastatic melanoma, tumor responses were more commonly seen at durvalumab doses between 10 and 15 mg/kg[27]; however, there is lack of additional data regarding the relationship between the durvalumab dose with efficacy or toxicity.[22]

Clinical trials with nivolumab and ipilimumab

The safety and efficacy of nivolumab with low-dose ipilimumab for treatment of advanced NSCLC was first demonstrated by the phase I CheckMate 012 trial that evaluated treatment with nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks, or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks randomized in a 1:1:1 ratio for patients with chemotherapy (CT) naïve advanced NSCLC. The combination of nivolumab at 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 (N3I1) or 12 weeks was found to have a favorable tolerability profile without compromising efficacy and was chosen for further clinical development in the phase II setting.[28] The phase II CheckMate 586[29] study accrued 288 CT naïve patients with advanced NSCLC with a primary endpoint of overall response rate (ORR), stratified by PD-L1 expression (Dako PD-L1 IHC expression of ≥1% and <1%). The key secondary endpoints included progression-free survival (PFS), overall survival

(OS), and efficacy stratified by tumor mutation burden (TMB, measured by Foundation One CDx™). The study demonstrated an ORR of 30% with N3I1 for the overall population, and the responses were durable. Tumor PD-L1 expression and TMB emerged as independent biomarkers for predicting the efficacy of N3I1 therapy in this population, though only 29% and 28% of patients were evaluated for PD-L1 and TMB, respectively. The ORR and median PFS was higher for the subgroup of patients with PD-L1 ≥1 *versus* <1% (ORR: 41 *versus* 15% and median PFS: 6.8 *versus* 2.8 months) and TMB ≥10 *versus* <10 mutations per mega base, mut/mb (ORR: 44 *versus* 12%, median PFS 7.1 *versus* 2.6 months). The safety profile of the N3I1 in the study was similar to prior clinical studies with ≥grade 3 treatment-related adverse events (TRAEs) seen in 29% of patients and TRAEs leading to treatment discontinuation in 16% of patients.[29]

The prognostic significance of TMB ≥10 mut/mb identified in the CheckMate 586 study was further validated as a co-primary endpoint of part 1, phase III, CheckMate 227 trial[30] that assessed the efficacy of nivolumab monotherapy, nivolumab-based regimens (nivolumab plus chemotherapy or ipilimumab) and CT alone in CT naïve recurrent or metastatic NSCLC. There were 1739 eligible patients who were initially stratified into two groups based on PD-L1 expression (<1% and ≥1%). In part 1a, patients with PD-L1 expression ≥1% were randomized in a 1:1:1 ratio to treatment with N3I1 or histology-based platinum doublet CT or nivolumab 240 mg alone every 2 weeks. In part 1b, patients with PD-L1 expression <1% were randomized in a similar fashion to treatment with N3I1 or nivolumab plus histology-specific CT or CT alone. The co-primary endpoints of the study included PFS in patients with TMB ≥10 mut/mb and OS in patients with tumor PD-L1 ≥1% treated with N3I1 *versus* CT. The study met its first co-primary endpoint and showed a significantly prolonged PFS with first-line N3I1 in patients with TMB ≥10 mut/mb.[30] CheckMate 227 also met its second co-primary endpoint and demonstrated superior OS with N3I1 compared to CT alone in patients with NSCLC and PD-L1 ≥1%.[31] Patients treated with N3I1 had a median OS of 17.1 months (95% CI: 15.0–20.1), and those treated with chemotherapy alone demonstrated a median OS of 14.9 months (95% CI: 12.7–16.7). The study included several additional secondary and exploratory analyses. In patients with PD-L1 ≤1%, treatment with ipilimumab and nivolumab yielded a median OS of 17.2 months (95% CI: 12.8–22.0), superior to the median OS of 12.2 months (95% CI: 9.2–14.3) with CT alone. Furthermore, the exploratory analyses showed that TMB did not provide any additional predictive information beyond expression of PD-L1 ≥1% and failed to predict survival on treatment with N3I1.

Results of the CheckMate 227 study have established N3I1 as a potential dual checkpoint inhibitor, non-CT containing first-line treatment strategy for patients with advanced NSCLC. CheckMate 817 is a multicohort phase IIIb/IV trial that is assessing the combination of ipilimumab at 1 mg/kg/6 weeks with a flat dose of 240 mg of nivolumab in a population of patients similar to CheckMate 227. Although the OS data from this study have not been reported yet, the initial results from the study were presented at the World Conference of Lung Cancer at Toronto in September 2018[32] and demonstrate similar efficacy and toxicity with the combination of low-dose ipilimumab and flat-dose nivolumab compared to weight-based nivolumab in CheckMate 227.

Although the majority of studies investigating combinations of checkpoint inhibitors have compared treatment with dual checkpoint inhibitors to CT alone, the S1400I trial (a sub-study of the LUNG-MAP trial) is one of the only studies that directly compared treatment with single-agent immunotherapy and dual checkpoint inhibition. In this multicenter phase III trial, patients with immunotherapy naive stage IV squamous cell lung cancer were randomized in a 1:1 fashion to receive N3I1 or nivolumab 3 mg/m^2 every 2 weeks. The primary endpoint of the study was OS. TMB (Foundation one CDx™) and tumor PD-L1 status (Dako 22C3) analyses were performed in selected patients as an exploratory endpoint. The study was closed early for futility at the time of its first interim analysis and did not show any statistically significant survival benefit of dual checkpoint inhibitions over single-agent nivolumab in the study population. However, in contrast to the CheckMate 227 study, TMB emerged as a strong biomarker in the S1400I study.[33] The exploratory analysis demonstrated that TMB ≥10 mut/mb was a predictor of improved survival (hazard ratio [HR]=0.39; 0.16–0.93, *p*-value=0.004) and that TMB <10 was a predictor of inferior survival (HR: 2.52; 1.03–6.13, *p*=0.042) on treatment with dual checkpoint inhibitor therapy (N3I1) in patients with PD-L1 negative tumors.[34] Other ongoing trials (Table 1) are evaluating the combination of nivolumab and ipilimumab with other novel agents like the triple kinase inhibitor (anti-VEGF, PDGFR, and FGF) nintedanib (NCT 03377023),[35] or an investigational CD122 agonist immunotherapy agent NKTR-214 (NCT02983045). Additionally, the checkpoint doublet is also being assessed in combination with hypofractionated radiation therapy (XRT) in a certain subset of advanced NSCLC patients eligible for localized XRT, and in combination with cytotoxic CT (NCT03573947) or histology-specific platinum doublet CT (NCT03215706).

Clinical trials with durvalumab and tremelimumab

The combination of durvalumab and tremelimumab for the treatment of advanced NSCLC was initially assessed in an early phase, multicenter, dose-escalation study. Durvalumab at a dose of 20 mg/kg with tremelimumab 1 mg/kg (up to four doses) every 4 weeks (D20T1) was found to have an acceptable toxicity profile (17% Grade 3 or 4 AEs) with promising antitumor activity in patients with immunotherapy naïve metastatic NSCLC (ORR 38%) irrespective of tumor PD-L1 status,[36] and this regimen was further developed for dose expansion. To date, at least three phase III trials (MYSTIC, NEPTUNE, ARTIC) are either ongoing or have reported data on the clinical activity of this combination in the first-line or later setting in patients with advanced

Table 1. Ongoing trials with anti-PD-1/PD-L1 plus anti-CTLA-4 agents in advanced and metastatic NSCLC.

NCT number	Study population	Treatment regimen	Phase	Important primary outcome	Status	Sponsor
Ongoing clinical trials with nivolumab and ipilimumab						
NCT03377023	Treatment naïve or pretreated advanced or metastatic NSCLC	Nivolumab plus ipilimumab plus nintedanib	Phase I/II nonrandomized, parallel assignment	Phase I: MTD Phase II: ORR	Recruiting	H.Lee Moffitt Cancer Center
NCT02983045	NSCLC cohort consists of treatment naïve, IO naïve, and post anti-PD-1/PD-L1 relapsed or refractory patients	Two experimental arms (1) NKTR-214 plus nivolumab and ipilimumab (2) NKTR-214 plus nivolumab	Phase I/II, nonrandomized, parallel assignment	Safety, tolerability, ORR	Recruiting	Nektar Therapeutics
NCT03509584	Advanced NSCLC patients that have received at least one prior line of therapy and eligible for localized palliative XRT	Four experimental arms (1) Part #1 NSCLC patients with bone metastasis eligible for localized hypofractionated radiotherapy will receive either nivolumab alone or nivolumab plus ipilimumab with hypofractionated XRT (2) NSCLC patients eligible for localized radiotherapy of one target lesion (outside the brain) will receive either nivolumab alone or nivolumab plus ipilimumab with hypofractionated XRT	Phase I, randomized, parallel assignment	Incidence of immune-related adverse events	Not yet recruiting	Assistance Publique Hopitaux De Marseille
NCT03001882 (Checkmate 592)	Stage IV or recurrent NSCLC with no prior systemic therapy	Nivolumab plus ipilimumab	Phase II, single group assignment	ORR	Recruiting	Bristol-Myers-Squibb
NCT03425331	Stage IV NSCLC with no prior systemic anticancer therapy	Nivolumab plus ipilimumab	Phase II, single group assignment	Best overall ORR	Recruiting	Dana-Farber Cancer Center
NCT03573947 (TOP1705)	Stage IV NSCLC with no prior systemic anticancer therapy	Nivolumab, ipilimumab, and paclitaxel	Phase II, single group assignment	PFS	Recruiting	Jeffery Clarke, Duke University
NCT03215706 (Checkmate 9LA)	Stage IV NSCLC with no prior systemic anticancer therapy	(1) Experimental arm: nivolumab plus ipilimumab with carboplatin/cisplatin and pemetrexed or paclitaxel (2) Active comparator arm: carboplatin/cisplatin and pemetrexed or paclitaxel	Phase III, randomized, parallel assignment	OS	Recruiting	Bristol-Myers-Squibb

Table 1. (*Continued*)

NCT number	Study population	Treatment regimen	Phase	Important primary outcome	Status	Sponsor
NCT03469960 (DICIPLE)	Stage IV NSCLC with no prior systemic anticancer therapy	(1) Experimental arm: 6 months of induction treatment with nivolumab and ipilimumab followed by observation and nivolumab and ipilimumab in case of progression (2) Active comparator arm: 6 months of induction treatment with nivolumab and ipilimumab followed by nivolumab and ipilimumab	Phase III, randomized, parallel assignment	PFS	Recruiting	Intergroupe Francophone de Cancerologie Thoracique
Ongoing trials with durvalumab and tremelimumab						
NCT03275597	Chemotherapy naïve or pretreated patients with stage IV NSCLC with six or less extracranial sites for SBRT	Single experimental arm SBRT followed by durvalumab 1500 mg every 4 weeks plus tremelimumab 75 mg every 4 weeks for up to 4 doses.	Phase Ib, single group assignment	Safety and tolerability	Recruiting	University of Wisconsin
NCT03057106	Treatment naïve stage IV NSCLC	Two arms (1) Durvalumab plus tremelimumab (2) Four cycles of platinum plus gemcitabine or pemetrexed with durvalumab plus tremelimumab (every 3 weeks for four cycles) followed by maintenance durvalumab alone in squamous histology and pemetrexed plus durvalumab in nonsquamous histology.	Phase II, randomized, parallel assignment	OS	Active, not recruiting	Canadian Cancer Trials Group
NCT03164616 (POSEIDON)	Treatment naïve stage IV NSCLC	Two experimental arms and one comparator arm (1) Experimental arm: durvalumab and tremelimumab plus standard of care (SoC) chemotherapy (CT) (2) Experimental arm: durvalumab plus SoC CT (3) Comparator arm: SoC CT alone	Phase III, randomized, parallel assignment	PFS and OS	Recruiting	AstraZeneca

(*Continued*)

Puri S, Shafique M. Drugs in Context 2020; 9: 2019-9-2. DOI: 10.7573/dic.2019-9-2
ISSN: 1740-4398

Table 1. (*Continued*)

NCT number	Study population	Treatment regimen	Phase	Important primary outcome	Status	Sponsor
Ongoing clinical trials with other anti-PD-1/PD-L1 and anti-CTLA-4 agents						
NCT03527251	Locally advanced or metastatic NSCLC	Ipilimumab 1 mg/kg every 34 weeks for two doses followed by anti PD-1 antibody SHR-1210	Phase 1	Safety	Recruiting	Sun Yat-sen University
NCT03580694	Nonsquamous NSCLC with unresectable stage IIIB or stage IV	Two experimental arms (1) Single dose. escalation cohort: cemiplimab (anti-PD-1 mAb) (2) Combination therapy, dose escalation, and dose expansion REGN4659 (anti-CTLA-1 mAb) and cemiplimab	Phase 1	DLTs, TRAEs, irAEs, SAEs, ORR, PK for cemiplimab and REGN4656	Recruiting	Regeneron pharmaceuticals
NCT03430063 (EMPOWER-Lung 4)	Stage IIIB/IIIC not candidates for concurrent chemoradiation and stage IV NSCLC	Three experimental arms (1) Standard dose cemiplimab (REGN2810) (2) High dose cemiplimab (REGN2810) (3) Combination cemiplimab (REGN2810) and ipilimumab	Phase II, randomized, open label	ORR	Active, not recruiting	Regeneron pharmaceuticals and Sanofi
NCT03302234 (Keynote 589)	Treatment naïve stage IV NSCLC with PD-L1>/=50%	Two experimental arms (1) Pembrolizumab 200 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks (2) Pembrolizumab 200 mg every 3 weeks plus placebo	Phase III, randomized, double blinded	OS and PFS	Active, not recruiting	Merck Sharp and Dohme
NCT03515629 (EMPOWER-Lung 2)	Treatment naïve recurrent or metastatic NSCLC with tumor PD-L1 expression>/=50%	Two experimental arms with one active comparator Experimental arm (1) Cemiplmab (REGN2810) plus ipilimumab (2) Cemplimab (REGN280) plus chemotherapy plus ipilimumab Comparator arm Pembrolizumab	Phase III, randomized, open label, parallel assignment	PFS	Active, not recruiting	Regeneron pharmaceuticals

Obtained from clinicaltrials.gov, accessed: June 15, 2019.

DLT, dose-limiting toxicity; irAE, immune-related adverse events; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RR, response rate; SAEs, serious adverse events; TRAEs, treatment-related adverse events.

Puri S, Shafique M. Drugs in Context 2020; 9: 2019-9-2. DOI: 10.7573/dic.2019-9-2
ISSN: 1740-4398

NSCLC. The phase III MYSTIC trial (NCT02453282)[37,38] enrolled 1118 patients with untreated EGFR and ALK wild-type stage IV NSCLC and randomized (1:1:1) them to receive durvalumab 20 mg every 4 weeks (D), durvalumab plus tremelimumab (D20T1), or standard-of-care CT. The primary endpoint of the trial was an improvement in treatment efficacy with durvalumab and tremelimumab (co-primary endpoint of OS and PFS) or durvalumab (OS) alone compared to CT in patients with PD-L1 ≥25% (Ventana PD-L1 SP263 assay). Neither durvalumab-containing regimen conferred a statistically significant survival benefit compared to CT alone in this first-line setting (median OS: 16.3 *versus* 12.9 months; HR: 0.76; 98.7% CI: 0.61, 1.17; p=0.036 for durvalumab *versus* CT; median PFS: 3.9 *versus* 5.4 months; HR: 1.05; 99.5% CI: 0.722, 1.534; p=0.705 and median OS: 11.9 *versus* 12.9 months; HR: 0.85; 98.7% CI: 0.611, 1.171; p=0.202 for D20T1 *versus* CT).[38] However, both blood-based (N=809) and tumor-based (N=460) TMB were measured as part of an exploratory analysis in the trial and the results were similar to CheckMate 227: a higher blood (b) TMB level (≥20 mut/mb) was prognostic and was associated with a prolonged survival in patients treated with D20T1 compared to durvalumab or chemotherapy alone (median OS for bTMB ≥20 21.9 months for D20T1, 12.6 months for durvalumab, and 10 months for CT alone; HR for D20T1 *versus* CT 0.49; 95% CI: 0.34, 0.81).[39]

Blood-based TMB was incorporated as an important endpoint in the design of the phase III NEPTUNE trial (NCT02542293)[40] that compared treatment with durvalumab plus tremelimumab (D20T1) with standard-of-care (SoC) platinum-based CT for patients with treatment-naïve EGFR/ALK wild-type stage IV NSCLC, irrespective of tumor PD-L1 status. The primary endpoint of the study was OS in patients with bTMB level of ≥20 mut/mb. The official results of the study are not available, yet a recent press release from AstraZeneca in August 2019 confirmed that this combination failed to meet its endpoint and did not show an improvement in survival compared to standard platinum-based CT in the prespecified biomarker-driven population.[41] Another phase III trial (ARTIC trial, NCT02352948) explored the clinical activity of durvalumab plus tremelimumab or monotherapy with either durvalumab or tremelimumab *versus* SoC therapy in advanced/stage IV NSCLC with ≥2 prior lines of treatment including platinum-based CT. The patients were stratified into two subgroups before randomization based on PD-L1 status (Ventana PD-L1 SP263 assay). Patients in the PD-L1 negative group (defined as tumors with PD-L1 <25%) were randomized to treatment with durvalumab plus tremelimumab (D20T1), durvalumab, tremelimumab monotherapy or SoC, and patients with PD L-1 positive tumors (defined as tumors with ≥ PD-L1 25%) were randomized to receive durvalumab alone or SoC. Unfortunately, the study had challenges with accrual and failed to meet its co-primary endpoints of improvement in OS and PFS with durvalumab and/or tremelimumab containing regimens.[42]

Most trials that have evaluated the combination of durvalumab and tremelimumab have been unsuccessful in demonstrating an improvement in survival in biomarker selected or unselected patients with advanced NSCLC, and therefore, other combinations of durvalumab plus tremelimumab are being explored with chemotherapy (NCT02537418 and NCT03057106) or radiation therapy (NCT03275597) (Table 1). NCT02537418 is an ongoing phase 1b trial by The Canadian Cancer Trials Group that assessed the safety and efficacy of treatment with CT plus durvalumab with or without tremelimumab (CT+D±T) in PD-L1 unselected patients with advanced solid malignancies including metastatic NSCLC. The results from the subgroup of 21 patients with treatment-naïve advanced nonsquamous NSCLC showed that durvalumab (15 mg/kg every 3 weeks) and tremelimumab (1 mg/kg every 6 weeks for multiple doses or 3 mg/kg every 6 weeks for three doses) could be safely combined with platinum doublet CT.[43] In the 17/21 patients evaluable for response the ORR was 52.9% (95% CI: 28–77). Most TRAEs were ≤grade 2 and were attributable to the chemotherapy part of the regimen. There were two dose-limiting toxicities (febrile neutropenia and pneumonitis/lung infection). Fatigue (46%), nausea/vomiting (25%), and anorexia (21%) were the most common immune-related AEs (≤grade 2).[43] The phase III POSEIDON is further building on the concept of combining dual checkpoint blockade with chemotherapy as is evaluating treatment with durvalumab with or without tremelimumab SoC CT compared to SoC CT alone for treatment-naïve EGFR/ALK wild-type stage IV NSCLC. The primary endpoint of the study is OS and PFS, and the trial is currently recruiting globally.[44]

Clinical trials with other dual checkpoint inhibitor combinations

There are currently numerous ongoing trials evaluating novel combinations for dual checkpoint inhibition in NSCLC (Table 1). The combination of anti-PD-1 inhibitor cemiplimab with ipilimumab with or without CT is being evaluated in both treatment-naïve (EMPOWER lung 2, EMPOWER lung 3)[45,46] and pretreated advanced NSCLC (EMPOWER lung 4)[47] large clinical trials. Cemiplimab is also being assessed in combination with a newer anti-CTLA-4 agent REGN 4659 (NCT03580694) in an early phase trial. In addition, the KEYNOTE-589 (NCT03302234) is a currently ongoing randomized, double-blind, phase III trial evaluating the effect of combining pembrolizumab with ipilimumab for patients with treatment-naïve stage IV NSCLC and TPS ≥50%. The patients are randomly assigned to pembrolizumab 200 mg every 3 weeks for 35 doses with ipilimumab 1 mg/kg every 6 weeks or placebo with the primary endpoint of OS and PFS.

Discussion

Despite theoretical benefits and promising preclinical evidence of efficacy, combination checkpoint blockade approaches have demonstrated mixed results in large, phase III studies. The published experience with tremelimumab and durvalumab as a combination therapy in NSCLC has generally been disappointing. In contrast, recent trial results show that the

combination of ipilimumab and nivolumab may be a promising first-line option in stage IV NSCLC with wild-type ALK and EGFR. CheckMate 227 met its key co-primary endpoint of OS in the PD-L1 positive population. This combination demonstrated a similar OS in the PD-L1 negative population, an expected and intriguing result. It must be noted, however, that this was a secondary endpoint and not the focus of the trial as designed. Additional randomized trials in a PD-L1 negative population need to be performed to confirm this finding.

CheckMate 227 compared ipilimumab and nivolumab to combination chemotherapy and not to current immunotherapy standard-of-care approaches (i.e. pembrolizumab monotherapy or chemotherapy-immunotherapy combinations). This study design will limit definitive recommendations as to the role of dual checkpoint blockade compared to the current standard of care. This implication becomes important when considering the rate of TRAEs in the combination ipilimumab and nivolumab arms. It will be left to clinicians to consider the relative risks of checkpoint inhibitor monotherapy compared to the increased rates of TRAEs in combination regimens.[3,31]

Of particular interest in the development of combination immunotherapies is the role of biomarkers for identifying patients that are most likely to benefit from such treatments. In the reviewed trials, PD-L1 and TMB emerged as potential biomarkers for stratifying patients into subgroups that are more likely to respond to the combination approaches. PD-L1 expression is likely to remain the most useful tool for identifying NSCLC patients with a higher likelihood of benefit from immunotherapy. It is an established predictive biomarker for anti-PD-1/PD-L1 monotherapy, and the accumulation of evidence presented suggests a role for PD-L1 as a biomarker for combination therapy with ipilimumab and nivolumab.[3,48] The results of CheckMate 227 raise the question whether combination checkpoint blockade can be used in a biomarker agnostic setting.

The predictive potential of PD-L1, rather than TMB, may help explain why combination tremelimumab and durvalumab failed to demonstrate a survival advantage compared to SoC platinum-based CT. In the MYSTIC and NEPTUNE trials, the intention-to-treat population included patients unselected for PD-L1 expression. In the ARCTIC trial, PD-L1 expression was included as a factor for stratification before randomization; however, only PD-L1 negative patients (defined as PD-L1 <25%) were randomized to the combination regimen. This population was not enriched for patients with very high PD-L1 expression, who appear to derive the most benefit from dual checkpoint inhibition. Therefore, while CheckMate 227 suggests that combination checkpoint blockade could be used in an unselected population, the results of tremelimumab and durvalumab combinations seem to suggest otherwise.

Despite initial promise, TMB does not appear to be as robust a biomarker as it was originally anticipated to be. There is a lack of consistency regarding its role as a predictor of survival and response to dual checkpoint inhibition across different trials. The S1400I study showed that a TMB cut of 10 mut/mb was a predictor of survival on dual checkpoint inhibitors, but this finding was restricted to patients with PD-L1 negative tumors.[34] Data from the CheckMate 227 study show that high TMB (≥10 mut/mb) was associated with a superior PFS in patients treated with the combination of ipilimumab and nivolumab compared to chemotherapy. However, the OS data for this combination among TMB high patients were not significantly different, and superior OS was seen among patients with PD-L1 expression ≥1%. Therefore, in this study, TMB provided little additional information above the predictive power of PD-L1 expression alone.[31,49] Among patients treated with tremelimumab and durvalumab, TMB was initially promising in an exploratory analysis but failed as a predictive biomarker in the NEPTUNE trial. There are several issues with the use of TMB as a biomarker. First, it may be an imperfect surrogate for what really matters in responses to checkpoint inhibition – that is, neoantigens conferring tumor immunogenicity. Current TMB assays factor in the nonsynonymous mutations that drive tumor-specific immune response with other mutations.[50,51] Additionally, utilizing cutoffs to stratify such a heterogeneous marker into high and low groups may not take into account the proportion of mutations that actually create neoantigens.[51] Finally, additional complexity is introduced in the interpretation of TMB analysis by use of blood *versus* tissue as the source of genomic information in the MYSTIC and NEPTUNE studies. In CheckMate 227, only 57.7% of patients who were enrolled and randomized had valid TMB scores for use in efficacy analysis, highlighting the technical challenges that still need to be addressed in the development of TMB as a clinically useful assay.

Conclusion

Combination treatment with ipilimumab and nivolumab has shown promise in NSCLC among PD-L1 positive patients, and based on the CheckMate 227 trial, it is an emerging treatment option in the first-line setting. In contrast, dual checkpoint therapy with tremelimumab and durvalumab has not demonstrated clear efficacy in NSCLC when compared to platinum-based chemotherapy. Presently, combination checkpoint blockade is not FDA approved for use in NSCLC, and issues with trial design make it difficult to assess the role these combinations would play if approved. PD-L1 expression rather than TMB may remain the most important predictive factor in selecting patients for combination checkpoint blockade. Despite the promise of combination strategies in PD-L1 positive patients, more can be done to improve responses in PD-L1 negative patients. Combination strategies may offer such benefits, based on the OS findings in PD-L1 negative patients in CheckMate 227. However, subsequent randomized trials will need to be conducted to confirm these findings. Additional factors to consider when designing and analyzing subsequent combination trials are the selection of appropriate comparator arms and the effect that treatment-related adverse events have on the duration of therapy.

Contributions: Drs. Puri and Shafique contributed equally to this manuscript. Both authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2019/12/dic.2019-9-2-COI.pdf

Acknowledgments: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/combination-checkpoint-inhibitors-for-treatment-of-non-small-cell-lung-cancer:-an-update-on-dual-anti-ctla-4-and-anti-pd-1-pd-l1-therapies/

Correspondence: Michael Shafique, Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA. Michael.Shafique@moffitt.org

Provenance: invited; externally peer reviewed.

Submitted: 15 September 2019; **Peer review comments to author:** 8 October 2019; **Revised manuscript received:** 27 November 2019; **Accepted:** 3 December 2019; **Publication date:** 13 January 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editor-in-Chief gordon.mallarkey@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. U.S. Food and Drug Administration. FDA expands approved use of opdivo in advanced lung cancer. 2015. https://www.curetoday.com/articles/fda-expands-opdivo-approval-in-lung-cancer. Accessed December 29, 2019.
2. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078–2092. https://doi.org/10.1056/NEJMoa1801005
3. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823–1833. https://doi.org/10.1056/NEJMoa1606774
4. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017;389(10066):255–265. https://doi.org/10.1016/S0140-6736(16)32517-X
5. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (poplar): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387(10030):1837–1846. https://doi.org/10.1016/S0140-6736(16)00587-0
6. Reslan L, Dalle S, Dumontet C. Understanding and circumventing resistance to anticancer monoclonal antibodies. *MAbs.* 2009;1(3):222–229. https://doi.org/10.4161/mabs.1.3.8292
7. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline summary. *J Oncol Pract.* 2018;14(4):247–249. https://doi.org/10.1200/JOP.18.00005
8. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature.* 2013;499(7457):214–218. https://doi.org/10.1038/nature12213
9. Praest P, Liaci AM, Forster F, Wiertz E. New insights into the structure of the MHC class I peptide-loading complex and mechanisms of TAP inhibition by viral immune evasion proteins. *Mol Immunol.* 2018. https://doi.org/10.1016/j.molimm.2018.03.020
10. Spiliotis ET, Manley H, Osorio M, et al. Selective export of MHC class I molecules from the ER after their dissociation from TAP. *Immunity.* 2000;13(6):841–851. https://doi.org/10.1016/s1074-7613(00)00081-9
11. Brown SD, Warren RL, Gibb EA, et al. Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival. *Genome Res.* 2014;24(5):743–750. https://doi.org/10.1101/gr.165985.113

12. Gubin MM, Zhang X, Schuster H, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature.* 2014;515(7528):577–581. https://doi.org/10.1038/nature13988
13. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(4):252–264. https://doi.org/10.1038/nrc3239
14. Keir ME, Butte MJ, Freeman GJ, et al. Pd-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677–704. https://doi.org/10.1146/annurev.immunol.26.021607.090331
15. Feng Y, Roy A, Masson E, et al. Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clin Cancer Res.* 2013;19(14):3977–3986. https://doi.org/10.1158/1078-0432.CCR-12-3243
16. Kvistborg P, Philips D, Kelderman S, et al. Anti–CTLA-4 therapy broadens the melanoma-reactive $CD8^+$ T cell response. *Sci Transl Med.* 2014;6(254):254ra128. https://doi.org/10.1126/scitranslmed.3008918
17. Reck M, Borghaei H, O'Byrne KJ. Nivolumab plus ipilimumab in non-small-cell lung cancer. *Future Oncol.* 2019;15(19):2287–2302. https://doi.org/10.2217/fon-2019-0031
18. Chae YK, Arya A, Iams W, et al. Current landscape and future of dual anti-CTLA4 and PD-1/PD-L1 blockade immunotherapy in cancer; lessons learned from clinical trials with melanoma and non-small-cell lung cancer (NSCLC). *J Immunother Cancer.* 2018;6(1):39. https://doi.org/10.1186/s40425-018-0349-3
19. Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A.* 2010;107(9):4275–4280. https://doi.org/10.1073/pnas.0915174107
20. Tatipalli M, Song X, Pak M, et al. Pharmacokinetics and pharmacodynamics of MEDI4736, a fully human anti-programmed death ligand 1 (PD-L1) monoclonal antibody, in combination with tremelimumab in patients with advanced non-small-cell lung cancer (NSCLC). *Journal of Clinical Oncology.* 2017;33(Suppl. 15). https://doi.org/10.1200/jco.2015.33.15_suppl.e14010
21. ASCO. FDA approves nivolumab in combination with ipilimumab for metastatic melanoma. 2015. https://melanoma.org/sites/default/files/press-release/IpiNivoApproval_1.pdf. Accessed December 29, 2019.
22. Centanni M, Moes D, Troconiz IF, et al. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. *Clin Pharmacokinet.* 2019;58(7):835–857. https://doi.org/10.1007/s40262-019-00748-2
23. Bajaj G, Gupta M, Feng Y, et al. Exposure-response analysis of nivolumab in patients with previously treated or untreated advanced melanoma. *J Clin Pharmacol.* 2017;57(12):1527–1533. https://doi.org/10.1002/jcph.962
24. Agrawal S, Feng Y, Roy A, et al. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *J Immunother Cancer.* 2016;4:72. https://doi.org/10.1186/s40425-016-0177-2
25. Spain L, Larkin J. Combination immune checkpoint blockade with ipilimumab and nivolumab in the management of advanced melanoma. *Expert Opin Biol Ther.* 2016;16(3):389–396. https://doi.org/10.1517/14712598.2016.1141195
26. Wang E, Kang D, Bae KS, et al. Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma. *J Clin Pharmacol.* 2014;54(10):1108–1116. https://doi.org/10.1002/jcph.309
27. Eroglu Z, Kim DW, Wang X, et al. Long term survival with cytotoxic T lymphocyte-associated antigen 4 blockade using tremelimumab. *Eur J Cancer.* 2015;51(17):2689–2697. https://doi.org/10.1016/j.ejca.2015.08.012
28. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol.* 2017;18(1):31–41. https://doi.org/10.1016/s1470-2045(16)30624-6
29. Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. *J Clin Oncol.* 2019;37(12):992–1000. https://doi.org/10.1200/jco.18.01042
30. Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med.* 2018;378(22):2093–2104. https://doi.org/10.1056/NEJMoa1801946
31. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med.* 2019. https://doi.org/10.1056/NEJMoa1910231
32. Paz-Ares L, Urban L, Audigier-Valette C, et al. P1.01-79 CheckMate 817: safety of flat-dose nivolumab plus weight-based ipilimumab for the first-line (1L) treatment of advanced NSCLC. *J Thorac Oncol.* 2018;13(10):S493. https://doi.org/10.1016/j.jtho.2018.08.635
33. Bazhenova L, Redman MW, Gettinger SN. A phase III randomized study of nivolumab plus ipilimumab versus nivolumab for previously treated patients with stage IV squamous cell lung cancer and no matching biomarker (Lung-MAP SUB-STUDY S1400I, NCT02785952). *J Clin Oncol.* 2019;37(Suppl. 15):9014–9014. https://doi.org/10.1200/JCO.2019.37.15_suppl.9014
34. Bazhenova L, Redman M, Gettinger S, et al. OA04.01 A phase III randomized study of nivolumab/ipilimumab vs nivolumab for previously treated stage iv squamous cell lung cancer. *J Thorac Oncol.* 2019;14(10):S214. https://doi.org/10.1016/j.jtho.2019.08.423

35. Puri S, Niyongere S, Chatwal MS, et al. Phase I/II study of nivolumab and ipilimumab combined with nintedanib in advanced NSCLC. *J Clin Oncol.* 2018;36(Suppl. 15):TPS9112. https://doi.org/10.1200/JCO.2018.36.15_suppl.TPS9112
36. Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small-cell lung cancer: a multicentre, phase 1b study. *Lancet Oncol.* 2016;17(3):299–308. https://doi.org/10.1016/S1470-2045(15)00544-6
37. Peters S, Antonia S, Goldberg SB, et al. 191TiP: MYSTIC: a global, phase 3 study of durvalumab (MEDI4736) plus tremelimumab combination therapy or durvalumab monotherapy versus platinum-based chemotherapy (CT) in the first-line treatment of patients (pts) with advanced stage IV NSCLC. *J Thorac Oncol.* 2016;11(4):S139–S140. https://doi.org/10.1016/S1556-0864(16)30300-8
38. Rizvi NA, Chul Cho B, Reinmuth N, et al. LBA6 - durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: Mystic. *Annals of Oncology.* 2018;29(suppl_10). http://dx.doi.org/10.1093/annonc/mdy511.005
39. Peters S, Cho BC, Reinmuth N, et al. Abstract CT074: tumor mutational burden (TMB) as a biomarker of survival in metastatic non-small-cell lung cancer (MNSCLC): blood and tissue TMB analysis from MYSTIC, a phase III study of first-line durvalumab ± tremelimumab vs chemotherapy. *Cancer Res.* 2019;79(Suppl. 13):CT074. https://doi.org/10.1158/1538-7445.Am2019-ct074
40. Mok T, Schmid P, Arén O, et al. 192TiP: NEPTUNE: a global, phase 3 study of durvalumab (MEDI4736) plus tremelimumab combination therapy versus standard of care (SoC) platinum-based chemotherapy in the first-line treatment of patients (pts) with advanced or metastatic NSCLC. *J Thorac Oncol.* 2016;11(4):S140–S141. https://doi.org/10.1016/S1556-0864(16)30301-X
41. AstraZeneca. Update on the phase III NEPTUNE trial of imfinzi plus tremelimumab in stage IV non-small-cell lung cancer. 2019. https://www.astrazeneca.com/media-centre/press-releases/2019/update-on-the-phase-iii-neptune-trial-of-imfinzi-plus-tremelimumab-in-stage-iv-non-small-cell-lung-cancer-21082019.html. Accessed August 22, 2019.
42. Kowalski DM, Reinmuth N, Orlov SV, et al. 13780 Arctic: Durvalumab + tremelimumab and durvalumab monotherapy vs soc in ≥ 3l advanced nsclc treatment. *Annals of Oncology.* 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy292.001
43. Juergens R, Hao D, Laurie S, et al. MA09.03 cisplatin/pemetrexed + durvalumab +/- tremelimumab in pts with advanced non-squamous NSCLC: a CCTG phase IB study - IND.226. *J Thorac Oncol.* 2017;12(1):S392–S393. https://doi.org/10.1016/j.jtho.2016.11.445
44. Mok T, Johnson M, Garon E, et al. P1.04-008 POSEIDON: a phase 3 study of first-line durvalumab ± tremelimumab + chemotherapy vs chemotherapy alone in metastatic NSCLC. *J Thorac Oncol.* 2017;12(11):S1975. https://doi.org/10.1016/j.jtho.2017.09.867
45. Rizvi N, Lee S, Curtis P, et al. P3.04-24 EMPOWER-Lung 2: cemiplimab and ipilimumab ± chemotherapy vs pembrolizumab in advanced NSCLC with PD-L1 ≥50%, a phase 3 study. *J Thorac Oncol.* 2018;13(10):S931. https://doi.org/10.1016/j.jtho.2018.08.1731
46. Rizvi N, Lee S, Curtis P, et al. P3.04-25 EMPOWER-Lung 3: a phase 3 study of cemiplimab, ipilimumab and chemotherapy in advanced NSCLC with PD-L1 <50%. *J Thorac Oncol.* 2018;13(10):S931. https://doi.org/10.1016/j.jtho.2018.08.1732
47. Rizvi N, Lee S, Curtis P, et al. P3.04-26 EMPOWER-Lung 4: a phase 2 study of cemiplimab plus ipilimumab in the second-line treatment of advanced NSCLC with PD-L1 <50%. *J Thorac Oncol.* 2018;13(10):S931–S932. https://doi.org/10.1016/j.jtho.2018.08.1733
48. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7
49. Bristol-Myers Squibb reports fourth quarter and full year financial results [press release]. https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-reports-fourth-quarter-and-full-year-fina. Accessed January 24, 2019.
50. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to pd-1 blockade in non-small-cell lung cancer. *Science.* 2015;348(6230):124–128. https://doi.org/10.1126/science.aaa1348
51. Goto Y. Tumor mutation burden: is it ready for the clinic? *J Clin Oncol.* 2018;36(30):2978–2979. https://doi.org/10.1200/JCO.2018.79.3398