PD-1/PD-L1 Immune Checkpoint Blockade in Non–Small Cell Lung Cancer

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Abstract: The programmed death 1 (PD-1) pathway is an immune checkpoint that has been implicated in tumoral immune escape, and has emerged as a major focus of immunotherapy in non–small cell lung cancer (NSCLC). Multiple agents have progressed through clinical development in recent years, including antibodies targeting both PD-1 and its key ligand, programmed death ligand 1 (PD-L1). This article reviews PD-1/PD-L1 blockade in NSCLC, including completed clinical trials, ongoing studies, future directions, and challenges.

Introduction

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide. Many patients present with metastatic disease,[1] and traditional platinum-based combination chemotherapy fails to provide long-term benefit for most patients, with a median overall survival (OS) of 8 to 10 months.[2] Patients with "actionable" driver mutations enjoy substantially better response rates and progression-free intervals when the appropriate targeted agents are used compared with standard cytotoxic chemotherapy,[3-5] but only approximately 25% to 30% of Western patients with NSCLC have tumors with actionable molecular aberrations, and these abnormalities are largely confined to the nonsquamous cell NSCLC population.[6-10] Because the majority of patients with NSCLC do not have actionable mutations or fusion proteins, novel treatment options are clearly needed for patients with lung cancer.

Immunotherapy attempts to harness the immune system to control and potentially eradicate tumors. This is accomplished by promoting immune recognition of cancer as foreign, stimulating immune responsiveness, and minimizing immune tolerance of tumor growth. Multiple immune checkpoint inhibitors recently have been identified, each of which has resulted in activity in NSCLC as monotherapy or in combination with chemotherapy. Almost all of this progress has been due to the advent of programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. In this review, we explore the data currently available for these agents.

Rationale for Immunotherapy in NSCLC

It is well established that the immune system is capable of recognizing and destroying tumor cells through T-cell activity.[11,12] The presence of tumor-infiltrating T-cells has been correlated with better clinical outcomes,[13-15] and suppression of the immune system is associated with an increased risk of cancer.[16,17] Tumor specimens from patients with resected early-stage lung cancer demonstrate an association between increased tumor infiltration with CD4 and CD8 T-cells and improved overall survival,[18-20] whereas high levels of tumor-infiltrating T-regulatory cells are associated with disease recurrence.[21]

Given the clear importance of immune infiltration to cancer outcomes, it is not surprising that cancer cells have developed the ability to evade immune recognition and elimination. This is achieved by multiple mechanisms, including the modulation of immune checkpoint pathways.[22-24] Immune checkpoints are inhibitory pathways built into the immune system to attenuate immune activation and prevent host tissue damage.[25-27] In the setting of a strong antigenic stimulus, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and PD-1 receptors are upregulated on naive T cells. Once upregulated, CTLA-4 and PD-1 dampen the immune response by binding to key ligands (B7-1/B7-2 for CTLA-4 and PD-L1/PD-L2 for PD-1) and decreasing T-cell proliferation, cytotoxicity, and cytokine production.[28,29] Tumors can utilize immune checkpoint pathways to evade immune system recognition by coopting these inhibitory molecules or their ligands.[30] Expression of PD-1, its ligands PD-L1 and PD-L2, and CTLA-4 have been linked to tumoral immune escape.[24]

Immune checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 recently have demonstrated promising clinical activity in NSCLC across histologic subtypes. In particular, antibodies targeting PD-1 and PD-L1 have demonstrated durable tumor responses in a subset of patients with chemotherapy-refractory metastatic NSCLC. This review will focus on recent advances in PD-1/PD-L1 immune checkpoint inhibition in NSCLC.

Efficacy of PD-1 Inhibition Monotherapy in NSCLC

There are currently 2 US Food and Drug Administration (FDA)–approved antibodies targeting PD-1: nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck). Nivolumab is a fully human monoclonal IgG4 antibody, and pembrolizumab is a humanized monoclonal IgG4 antibody. In a phase 1 trial of single-agent nivolumab (1, 3, or 10 mg/kg every other week) among 129 previously treated patients with advanced NSCLC,[31,32] a 17% overall response rate (ORR) was observed. This response rate is remarkable, given the fact that 54% of patients had received at least 3 prior treatment regimens. Furthermore, the responses were durable, with an estimated median response duration of 17 months. Median OS across all patients was 14.9 months at the 3-mg/kg dose, which was selected for further clinical development. One-year, 2-year, and 3-year survival rates at the 3 mg/kg dose were 56%, 42%, and 27%, respectively.

A subsequent single-arm phase 2 study of nivolumab focused on 117 patients with squamous cell NSCLC and confirmed the phase 1 efficacy, finding a 14.5% ORR.[33] Median OS was 8.2 months, with 41% of patients alive at 1 year. Again, these results must be interpreted through the lens of this heavily pretreated population. Among participants, 65% of patients had received 3 or more prior therapies for their cancer. Furthermore, 73% of the population was male and 92% were current or former smokers, both of which are negative prognostic markers for lung cancer in general.[34]

In a phase 1 trial of single-agent pembrolizumab (2 mg or 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks) given to 495 patients with locally advanced/metastatic NSCLC, a response rate of 19.4% was seen across all histologies.[35] Again, this study enrolled a heavily pretreated population; roughly 66% had received 2 or more prior regimens. The drug was similarly well tolerated regardless of dose or schedule, with grade 3 or higher adverse events reported in only 9.5% of patients, and only 1 treatment-related death (pneumonitis). The median duration of response was 12.5 months, and the progression-free survival (PFS) and OS were 3.7 months and 12.5 months, respectively.

Building upon the success of early-stage studies, multiple randomized studies have been undertaken to compare antibodies targeting PD-1 vs standard second-line therapy with docetaxel. The results of 2 phase 3 trials of nivolumab vs docetaxel in advanced NSCLC have been reported. In CheckMate 017 (Study of BMS-936558 [Nivolumab] Compared to Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer [NSCLC]), 272 patients with stage IIIB/IV squamous cell NSCLC were randomly assigned to receive nivolumab at 3 mg/kg every 2 weeks or docetaxel at 75 mg/m^2 every 3 weeks.[36] At the first interim analysis, the study was halted owing to a significant improvement in median OS in the nivolumab arm (9.2 months vs 6.0 months; hazard ratio [HR], 0.59; CI, 0.44-0.79; P<.001). One-year survival was nearly doubled in the nivolumab arm vs the control arm (42% vs 24%), and PFS also was increased (3.5 months vs 2.8 months, respectively; HR, 0.62; CI, 0.47-0.81; P<.001). The response rate was 20% with nivolumab vs 9% with docetaxel (*P*=.008), and patients in the nivolumab arm had a significant improvement in cancer-related symptoms. The results of this trial, which were initially reported in late January 2015, led to the approval of nivolumab as

Table 1. Reported Efficacy of PD-1 and PD-L1 Inhibition Monotherapy in NSCLC

Agent	Trial (Phase)	Treatment Setting[a]	Number of Patients, n	Overall Response Rate, %	Median Response Duration, months	Median PFS, months	Median OS, months
PD-1							
Nivolumab[36]	CheckMate 017 (3)	Advanced/metastatic, previously treated, squamous	272	20	NR	3.5	9.2
Nivolumab[36]	CheckMate 057 (3)[b]	Advanced/metastatic, previously treated, nonsquamous	582	19.2	17.1	2.3	12.2
Pembrolizumab[35,37]	KEYNOTE-001 (1)	Advanced/metastatic, previously treated	495	19.4	12.5	3.7	12.5
PD-L1							
Atezolizumab[40]	POPLAR (2)[b]	Advanced/metastatic, previously treated	287	15	ND	2.8	11.4
MEDI4736[65]	NCT01693562 (1/2)[b]	Advanced/metastatic, previously treated	198	14	ND	ND	ND
Avelumab (MSB0010718C)[66]	NCT01772004 (1)[b]	Advanced/metastatic, previously treated	184	12	ND	2.9	ND
BMS-936559[42]	NCT00729664 (1)	Advanced/metastatic, previously treated	49	10		ND	ND

[a] All histologies included unless otherwise specified.

b Presented in abstract form only.

ND, not determined; NR, not reached; PD-1, programmed death receptor 1; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival.

second-line treatment in advanced squamous NSCLC. In CheckMate 057 (Study of BMS-936558 [Nivolumab] Compared to Docetaxel in Previously Treated Metastatic Non-squamous NSCLC), 582 patients with stage IIIB/IV nonsquamous cell NSCLC were randomly assigned to receive nivolumab at 3 mg/kg every 2 weeks or docetaxel at 75 mg/m^2 every 3 weeks.[37] This study also was halted early owing to improved median OS with nivolumab vs docetaxel (12.2 vs 9.4 months) and 1-year survival time (51% vs 39%; HR, 0.73; CI, 0.59-0.89; *P*=.001). The response rate was 19.2% with nivolumab compared with 12.4% for docetaxel. In both studies, nivolumab was associated with a longer median response duration than docetaxel (not reached vs 8.4 months in CheckMate 017 and 17.1 vs 5.6 months in CheckMate 057, respectively). Nivolumab also was better tolerated than docetaxel, with 7% to 10.5% of patients in the nivolumab arm experiencing grade 3 or 4 treatment-related adverse effects compared with 53.7% to 55% of patients in the docetaxel group. As of September 2015, nivolumab does not have a formal approval in nonsquamous cell NSCLC, but is listed in compendia and is now included in the National Comprehensive Cancer Network (NCCN) Guidelines. The results of CheckMate 017 and 057 are practice-changing; for now, the standard therapy for the second-line treatment of advanced NSCLC has shifted to PD-1 blockade, regardless of histology.

Efficacy of PD-L1 Inhibition Monotherapy in NSCLC

Atezolizumab (MPDL3280A) is a humanized monoclonal antibody with a modified Fc receptor designed to limit antibody-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDCC).[38] Atezolizumab has been evaluated in a dose-ranging phase 1 study that included an expansion cohort of previously treated patients with advanced NSCLC.[38-40] Among 88 patients treated, an objective response rate of 21% was observed. Median duration of response was 67 weeks, and 1-year OS was 82%. A randomized phase 2 study recently was presented, comparing atezolizumab at 1200 mg/m^2 every 3 weeks vs docetaxel at 75 mg/m^2 every 3 weeks in patients with previously treated NSCLC. Among 287 patients, there was a trend towards improvement in median OS favoring atezolizumab (11.4 months vs 9.5 months; HR, 0.77; CI, 0.59-1.03; *P*=.11).

Multiple other antibodies targeting PD-L1 are currently in early-stage clinical development. In Table 1, we describe the response rates seen for the just-described agents as well as agents earlier in development. The remainder of this review will focus on several clinical considerations pertinent to immune checkpoint blockade in NSCLC, including radiographic response assessment, the role of predictive biomarkers, the use of these drugs in combination with cytotoxic chemotherapy and tyrosine kinase inhibitors, and adverse effects of PD-1 and PD-L1 inhibitors.

Radiographic Response Assessment

Patients treated with immune checkpoint inhibitors can experience alternative patterns and kinetics of response**.** The recognition of "pseudo-progression" in early immunotherapy studies, whereby target lesions grow on an initial scan only to regress on a subsequent scan, has prompted researchers to design a separate set of response criteria, termed the immune-related response criteria.[41] A principal distinction between these response criteria and the more traditional Response Evaluation Criteria in Solid Tumors (RECIST) measurements is that when a patient has increased tumor burden, the clinician has the option to repeat a scan 4 weeks later to confirm progression. However, whether to use immune-related response criteria in lieu of standard RECIST criteria remains controversial. A pseudo-progression rate of 5% to 7% in trials implies that the majority of patients with radiologic evidence of progression on a scan go on to develop bona fide progression at the next scan.[32,36,42] As such, it is possible that many patients will be kept on an ineffective therapy longer than would otherwise be appropriate. Further research is needed to help better identify patients with pseudo-progression. For now, most ongoing trials continue to use RECIST as their primary means of determining response status.

Biomarkers to Predict Response to PD-1/PD-L1 Inhibitors

As described earlier, immune checkpoint inhibition has demonstrated remarkable clinical results in a subpopulation of patients with advanced NSCLC, including durable responses in heavily pretreated patients. It remains unclear, however, which patients will benefit from immune checkpoint inhibition. Because the PD-1 pathway is presumed to be a key mechanism of immune escape in a subgroup of patients with NSCLC, PD-L1 expression in the tumor or its surrounding inflammatory cells has emerged as a candidate biomarker of drugs targeting the PD-1 pathway.[31,36,39,43,44] There are, however, a number of important limitations that must be addressed before using PD-L1 as a biomarker. One of the most important is that PD-L1 expression is a continuous variable, and the best cutoff for determining PD-L1 "positivity" has yet to be clearly defined. This is further complicated by technical issues, including the assay type used, the quality of the tissue sample, and whether the cells evaluated are tumor, immune, stromal, or some combination thereof. In addition, tumor PD-L1 expression is dynamic and inducible; it has been shown that PD-L1 expression can be upregulated by interferon.[44-46] Even within a single tumor, the degree of PD-L1 expression can be heterogeneous, and primary vs metastatic lesions may not have the same degree of expression.

In light of these aforementioned limitations, it is perhaps not surprising that data regarding the use of PD-L1 as a biomarker of response to immune checkpoint inhibition have been mixed thus far.[31-33,35-37,40] Furthermore, although higher response rates have been seen for PD-L1–positive tumors in many trials,[31,33,35,37,40] responses also have been seen in PD-L1–negative patients, suggesting that PD-1/PD-L1 inhibition still retains some activity in this subgroup. In the phase 3 trial of nivolumab vs docetaxel in advanced squamous NSCLC, PD-L1 protein expression was evaluated retrospectively in pretreatment tumor biopsy specimens. Samples were categorized as positive when staining of the tumor-cell membrane was observed at prespecified expression levels of 1%, 5%, or 10%. A total of 83% of patients had tumors with quantifiable PD-L1 expression, with rates of expression well balanced across the 2 arms. PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints.[36] In the nearly identically designed phase 3 trial of nivolumab vs docetaxel in advanced nonsquamous cell NSCLC, PD-L1 expression was associated with benefit from nivolumab, with the drug showing improved efficacy across all endpoints at predefined PD-L1 expression cutoff points of 1%, 5%, and 10% (OS HR, 0.59 for the 1% cutoff, 0.43 for the 5% cutoff, and 0.40 for the 10% cutoff).[37] Further muddying the waters, a phase 1 study of pembrolizumab in NSCLC using an expression cutoff of 50% found that response rates approached 50%.[35] The PFS was 6.3 months in this cohort, compared with 3.3 months in those with an expression of 1% to 49%, and 2.3 months in those with no PD-L1 expression. Similarly, median OS was not reached in those with PD-L1 expression of 50% or greater, vs 8.8 months in those with expression ranging from 0% to 49%. Of note, this study required a fresh tumor biopsy for PD-L1 analysis and used a proprietary PD-L1 assay.

Given the questionable utility of PD-L1 expression as a biomarker of response, there has been significant interest in identifying other predictive biomarkers of clinical benefit for immune checkpoint inhibitors. For instance, it has been hypothesized that clinical responses to PD-1 blockade occur in patients with a preexisting interferon-mediated adaptive immune response to their tumors. Retrospective

analyses of tumor specimens from trials of pembrolizumab in melanoma and head and neck cancer recently were used to derive an RNA-based gene signature to measure the tumor level pretreatment immune response.[47,48] Although these gene signatures are strongly associated with response rates, they will require prospective validation in larger data sets. Smoking history also has emerged as an interesting clinical biomarker of response to PD-1 blockade in NSCLC. Smoking-related malignancies are associated with a higher mutational burden,[49] a biomarker of response to other forms of immunotherapy.[50] In published studies of nivolumab and pembrolizumab in NSCLC, patients with heavy prior tobacco exposure had significantly higher response rates.[31,35,51,52] Beyond this, patients with no smoking history or the presence of an epidermal growth factor receptor (EGFR) mutation gained no benefit from the use of PD-1 blockade.[37] It is likely that smoking represents a clinical surrogate for the true biology underlying these findings, similar to what was previously noted with erlotinib (Tarceva, Genentech/Astellas) response in never or light smokers.[53-55] Hence, quantifying smoking history by number of pack-years of consumption may prove to be just as sensitive an indicator of benefit as PD-L1 expression.

PD-1/PD-L1 Combinations With Other Therapies

As the efficacy of immunotherapy in NSCLC becomes apparent, it will be essential to understand how to incorporate PD-1/PD-L1 inhibitors into care alongside cytotoxic chemotherapy, tyrosine kinase inhibitors, and other forms of immunotherapy. Many studies have revealed preliminary evidence of synergy between immunotherapy and other agents.[51,56-58] In this regard, we discuss preliminary data of PD-1–directed therapy in combination with other antineoplastic agents. It should be noted that all of these efforts are preliminary, precluding any definitive conclusions.

In an ongoing randomized phase 3 study, patients with advanced NSCLC are randomly assigned to receive platinum doublet chemotherapy with or without concurrent pembrolizumab.[59] In a separate trial, among 20 patients receiving carboplatin, paclitaxel, and pembrolizumab, an overall response rate of 30% was seen, with a disease control rate of 60% to 80% (depending on the dose of pembrolizumab). On the other hand, 24 patients in this trial who were receiving carboplatin, pemetrexed, and pembrolizumab had an ORR of as much as 50% to 67%, with a disease control rate of 92% to 100%. In another trial of 56 patients with advanced NSCLC who received nivolumab plus concurrent platinum-based chemotherapy, an ORR of 33% to 50% was observed, and 1-year OS rates were 59% to 87%.[51] In a phase 1 study of atezolizumab combined with platinum doublet chemotherapy, 37 patients tolerated the combination without significant toxicity.[40] The ORR ranged from 60% to 75%, depending on the chemotherapy platform.

In a study of 20 patients with *EGFR*-mutated lung cancer resistant to erlotinib, the combination of nivolumab and erlotinib led to a 15% response rate.[56] Combination therapy with nivolumab and erlotinib was well tolerated, with grade 3 toxicities in 5 patients (liver enzyme elevations, weight loss, and diarrhea), but no grade 4 or higher toxicities.

With regard to combination immunotherapy, a phase 1 study of ipilimumab (Yervoy, Bristol-Myers Squibb) with pembrolizumab in advanced NSCLC recently was reported. In this study, 17 patients with disease progression on chemotherapy were given the combination of ipilimumab for 4 cycles, and maintenance pembrolizumab.[60] At the time of analysis, responses were seen in all dose groups among the 11 patients on treatment for at least 6 weeks, including 1 complete response (9%) and 5 partial responses (45%). No patients experienced progressive disease. Seventeen percent of patients had grade 3 or higher toxicity, and 33% had immune-mediated adverse effects, most of which were mild.

Certain combinations of chemotherapy and immunotherapy, or immunotherapy alone, may be of particular benefit in patients with minimal disease burden for whom long-term control may be a realistic goal. However, there are no clinical data as of yet to support a role for this treatment modality in the adjuvant or locally advanced disease setting in NSCLC. Such studies are just being initiated.

Adverse Effects Related to PD-1/PD-L1 Inhibition

Immune checkpoint inhibition targeting the PD-1 pathway is relatively well tolerated and generally better tolerated than prior immunotherapies such as CTLA-4 inhibitors, but is associated with a unique spectrum of side effects. Both immune-related and non–immune-related adverse effects of PD-1/PD-L1 immune checkpoint inhibition are summarized in Table 2. The majority of data regarding immune-related adverse events (irAEs) comes from clinical trials with nivolumab and pembrolizumab in patients with advanced melanoma. However, similar side effects are emerging with the use of other antibodies directed against PD-1 and PD-L1, and in other malignancies such as NSCLC in which these checkpoint inhibitors are being studied. IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events.

General guidelines for the management of irAEs caused by checkpoint inhibitors are incorporated in the FDA Risk Evaluation and Management Strategies (REMS) for ipilimumab.[29] Most irAEs in patients treated with checkpoint inhibitors are effectively managed by prompt

Table 2. Most Common and Severe Adverse Events in PD-1/PD-L1 Trials in NSCLC

	CheckMate 017 Phase 3, nivolumab in squamous-cell NSCLC, n=131	**KEYNOTE-001** Phase 1, pembrolizumab in NSCLC, n=495	**NCT00729664** Phase 1, BMS936559 in advanced solid tumors, n=207 (75 NSCLC)	**POPLAR** Phase 2, atezolizumab in NSCLC, n=142	**NCT01693562** Phase 1, MEDI4736 in NSCLC, n=228
	Percentage of patients evaluable for safety with an event				
Fatigue	16	19.4	16	NR	NR
Grade 3-5	1	0.8	1	NR	2
Arthralgia	5	9.1	7	16	NR
Grade 3-5	0	0.4	0	2	<1
Asthenia	10	4.8	NR	10	NR
Grade 3-5	0	1	NR	1	NR
Myalgia	2	2.6	1	6	NR
Grade 3-5	0	0	0	1	<1
Pyrexia	5	4.2	3	NR	NR
Grade 3-5	0	0.6	0	NR	NR
Rash	4	9.7	7	NR	8
Grade 3-5	0	0.2	0	NR	0
Pruritus	2	10.7	6	NR	NR
Grade 3-5	0	0	0	NR	NR
Nausea	9	7.5	6	22	12
Grade 3-5	0	0.8	0	1	0
Diarrhea	8	8.1	9	17	7
Grade 3-5	0	0.6	0	1	<1
Decreased appetite	11	10.5	3	33	NR
Grade 3-5	1	1	0	1	<1
Pneumonitis	5	3.6	NR	2	1
Grade 3-5	1	1.8	0	NR	0
Hypothyroidism	4	6.9	3	6	4
Grade 3-5	0	0.2	0	1	0
Anemia	2	4.2	1	15	NR
Grade 3-5	0	0	0	3	NR
AST elevation	2	3	NR	4	2
ALT elevation	2	2.2	1	4	3
Grade 3-5 AST	0	0.6	NR	NR	<1
Grade 3-5 ALT	0	0.4	0	NR	1
Infusion or hypersensitivity reaction	1	3	10	NR	NR
Grade 3-5	0	0.2	<1	NR	NR

ALT, alanine transaminase; AST, aspartate aminotransferase; NR, not reported; NSCLC, non–small cell lung cancer.

interruption of the checkpoint inhibitor and/or administration of systemic corticosteroids.[61,62] For patients with grade 2 (moderate) immune-mediated toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity resolve to grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) should be started if symptoms do not resolve within a week. For patients experiencing grade 3 or 4 (severe or life-threatening) immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) should be given. When

symptoms subside to grade 0 or 1, corticosteroids can be gradually tapered over the course of 1 month.

The safety of checkpoint inhibitors in patients with an underlying autoimmune condition is uncertain. Given the biology underlying immune checkpoints, there is at least a theoretical concern that therapeutic blockade of these receptors could lead to exacerbations of underlying autoimmune conditions. Preclinical models suggest that CTLA-4 blockade can exacerbate autoimmune diseases.[63,64] Because patients with underlying autoimmune conditions typically have been excluded from immunotherapy trials, a paucity of clinical data address this issue. By the same token, the safety and efficacy of these agents in transplant patients who remain on antirejection drugs are unknown.

Conclusions

Immune checkpoint inhibition has revolutionized the care of NSCLC. Heavily pretreated patients can experience unprecedented rates and durations of response. There are many PD-1 and PD-L1 inhibitors emerging for clinical use, a number of different settings in which to test them, and multiple possible combinations that must be evaluated. As of September 2015, based on survival benefit compared with conventional chemotherapy, nivolumab is the only PD-1 inhibitor approved for use in advanced NSCLC in the second-line setting, but other similar agents are expected to follow suit. One of the major challenges moving forward is determining appropriate biomarkers to predict response. In addition, understanding unconventional response patterns and managing immune-related adverse effects will be critical for oncologists as the use of immune checkpoint inhibitors continues to grow.

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