Lung Cancer: Targets and Therapy

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REVIEW

New PD-L1 inhibitors in non-small cell lung cancer – impact of atezolizumab

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Abstract: The era of immunotherapy has changed the face of how we approach treatment for many oncologic and hematologic malignancies. Lung cancer has been in the forefront of checkpoint inhibition for the past 2 years and has paved the path for other subspecialties. While PD-1 inhibitors nivolumab and pembrolizumab have been approved for non-small cell lung cancer (NSCLC), this review focuses on atezolizumab, its landmark studies, and ongoing trials. Atezolizumab is the first programmed death ligand 1 (PD-L1) inhibitor to receive US Food and Drug Administration (FDA) approval for metastatic NSCLC patients who have progressed on frontline chemotherapy. This approval was based on two open-label Phase II multicenter trials, POPLAR (NCT01903993) and BIRCH (NCT02031458). Both studies revealed a benefit in overall survival (OS), progression-free survival, and response rate in the atezolizumab arm when compared to single-agent docetaxol. There were also fewest Grade 3–5 treatment-related adverse events (TRAEs) in the atezolizumab cohort. The open-label randomized Phase III OAK trial (NCT02008227) further established the role of atezolizumab in previously treated NSCLC. This study compared atezolizumab with docetaxel in patients with advanced NSCLC (squamous or nonsquamous histologies) who had progressed on one to two prior chemotherapy regimens. OS in the PD-L1-enriched population was superior in the atezolizumab arm (n=241) at 15.7 months compared with docetaxel (n=222) at 10.3 months (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.58–0.93; *p*=0.0102). Patients lacking PD-L1 also had survival benefit with atezolizumab with a median OS (mOS) of 12.6 months versus 8.9 months with chemotherapy (HR 0.75, 95% CI 0.59–0.96). Benefit was noted in both squamous and nonsquamous NSCLC subsets and regardless of PD-L1 expressivity. As seen in the POPLAR and BIRCH studies, the toxicity profile was significantly better with immunotherapy. The future is unfolding rapidly as new checkpoint inhibitors are gaining FDA approval. It is still not known if these agents will be used in combination with chemotherapy, with other immune-modulating agents, radiation therapy, or all of the above. The results of these studies investigating their use in combination with chemotherapy agents, with other immunotherapy agents such as CTLA-4 inhibitors, and with radiation therapy, are eagerly awaited.

Keywords: PD-1, PD-L1, ADCC, CDC,checkpoint inhibition

Lung cancer immunology

Lung cancer had traditionally been considered nonimmunogenic, and multiple attempts to modulate the immune system to treat lung cancer by nonspecific agents such as interleukin-2 (IL-2), interferon, and Bacillus Calmette–Guerin were unsuccessful. Efforts to unleash the immune system using various vaccines were also futile.[1] Recent research has led to an improved understanding of the immune system resulting in

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better therapeutic strategies. The initiation of the immune cascade is a multifaceted, multistep process.[2–4] The major histocompatibility complex (MHC), expressed on the surface of antigen-presenting cells (APCs), assists with internalizing and identifying tumor antigens. This process then stimulates the expression of B7 molecules on dendritic cells. These now activated dendritic cells migrate to lymph nodes, resulting in T-cell activation. When the activated T cell comes in contact with the tumor, it recognizes its surface antigens, resulting in the release of the cytolytic enzymes perforin and granzyme. This then stimulates cytokine activation, recruitment of other members of the immune system, and a downstream proliferative effect. Consequently, the tumor is destroyed and memory T cells are produced. However, there are multiple checkpoints in place to enable modulation of the immune response in order to prevent autoimmune effects and excessive inflammation. These immune checkpoints can be targeted by cancer cells to permit immune tolerance, leading to tumor growth and eventual metastasis. Due to encouraging results observed with immune checkpoint inhibitors across various tumor types, the role of these agents in cancer care is rapidly increasing. Three immune checkpoint antibodies – ipilimumab (Bristol-Myers Squibb, New York, NY, USA), the anti-CTLA-4 inhibitor, and two anti-PD-1 antibodies nivolumab (Bristol-Myers Squibb) and pembrolizumab (Merck, Kenilworth, NJ, USA)– are currently US Food and Drug Administration (FDA) approved for the treatment of metastatic melanoma.[5] Nivolumab is also approved for use in previously treated advanced or metastatic renal cell carcinoma, previously treated advanced bladder cancer, and previously treated classical Hodgkin lymphoma.[6–8] The anti-programmed death ligand 1 (PD-L1) agent atezolizumab (Genentech, San Francisco, CA, USA) was recently granted accelerated approval for previously treated advanced or metastatic urothelial carcinoma.[9] All three agents inhibiting the PD-1/PD-L1 pathway mentioned above have been approved for use as second-line agents in non-small cell lung cancer (NSCLC) and pembrolizumab is approved as frontline treatment in NSCLC patients with high PD-L1 expression.[10–12] The present review focuses on PD-1/PD-L1 inhibitors with particular attention to atezolizumab, a PD-L1 inhibitor, in NSCLC.

Programmed death pathway and lung cancer

PD-1, a member of the B7-CD28 superfamily, is a cell-surface coinhibitory receptor expressed on activated lymphocytes (B cells, T cells, and natural killer cells) and monocytes.[2] It has two known ligands, PD-L1 and PD-L2, which are both expressed on APCs. Binding of PD-1 with PD-L1 or PD-L2 results in blunting of T-cell responses through various mechanisms, and this phenomenon is frequently exploited by cancer cells to evade immune-mediated destruction by tumor-infiltrating lymphocytes (TILs). PD-L1 also called cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1) which is considered the most important mediator of PD-1-dependent immunosuppression is also expressed on tumor cells (TCs). In response to cytokines such as interferon-γ released from TILs, malignant cells including those of lung cancer upregulate PD-L1 expression on their surfaces which in turn engage the PD-1 receptors on the T cells and trigger an inhibitory cascade that results in T-cell deactivation and exhaustion. PD-L1 has been correlated with poor prognosis in multiple types of human cancers.[13] While PD-L1 is widely expressed on various immune cells (ICs) and nonimmune cells, the expression of PD-L2 is much more restricted and seems to primarily depend on signals from the microenvironment.[14] To complicate the issue, recent studies have demonstrated that PD-L1 also binds to another receptor, CD80, and that PD-L1/CD80 interaction is also inhibitory to T-cell activation. Inhibiting the programmed death signaling pathway with monoclonal antibodies (mAbs) has been proven to be a very effective anticancer strategy. The complicated interactions between PD-1 and its receptors, PD-L1/PD-L2, as well as the interactions between PD-L1 and CD80 (Figure 1) provide opportunities to inhibit this checkpoint pathway at two points, PD-1 and PD-L1. On the one hand, blocking PD-1 with mAbs inhibits the negative interaction between PD-1 and its ligands, PD-L1 and PD-L2. On the other hand, inhibition of PD-L1 by mAb restrains the negative signaling of T cells via its interactions with PD-1 and CD80.[14]

PD-1 blockade

Two mAbs against PD-1, nivolumab and pembrolizumab, have been approved for use in advanced NSCLC, and many more are in various phases of development.[15]

Nivolumab

Nivolumab, an IgG4 monoclonal antagonist antibody to PD-1, was the first agent in this category to obtain FDA approval.[11] The drug demonstrated improved overall survival (OS) compared to docetaxel in patients with squamous and nonsquamous cell histologies progressing on platinum-doublet chemotherapy in large Phase III trials.[16,17] The first trial, CheckMate 017 trial (NCT01642004), included 272 patients with previously treated advanced squamous

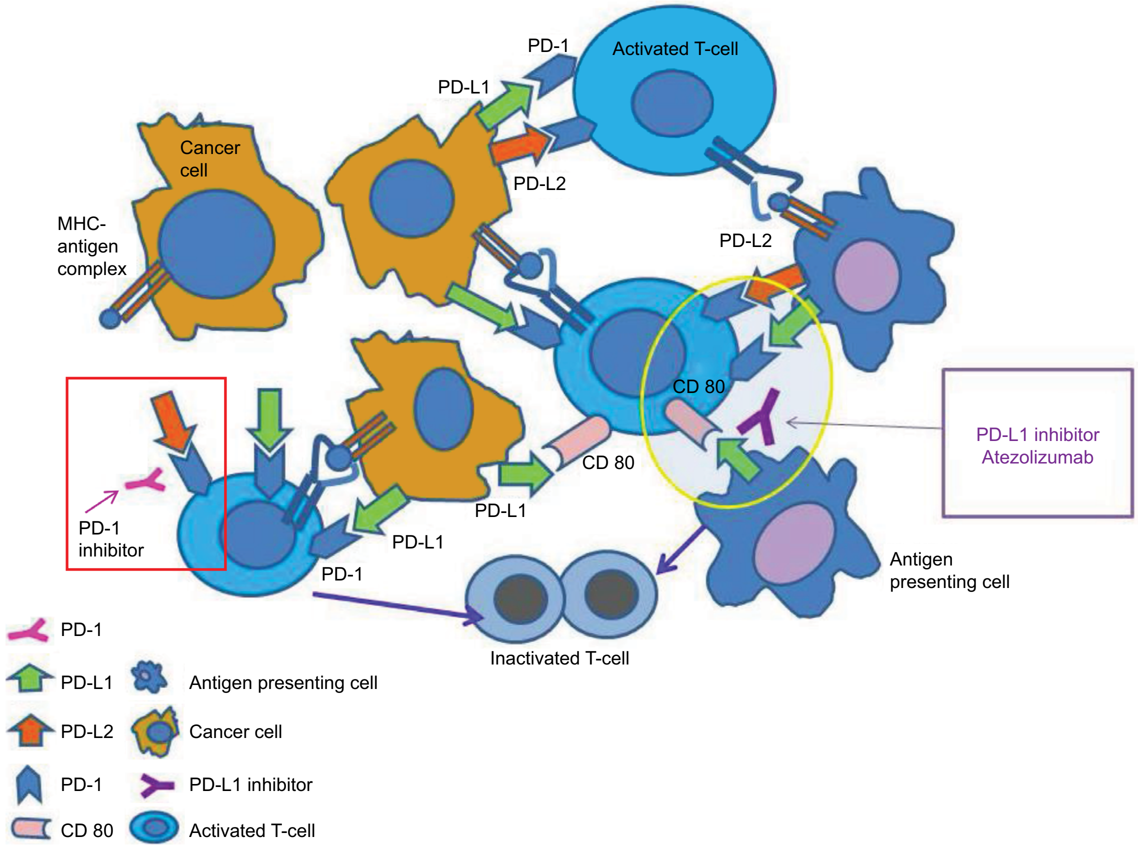

Figure 1 Inhibition of the programmed death pathway–mAbs against PD-1 and PD-L1.

Notes: Antigens released from cancer cells are presented on MHC on cancer cells or APCs to activate T cells. PD-1 receptors expressed on T cells inhibit immune responses by engagement of PD-L1 and PD-L2 on APCs and cancer cells. mAb-mediated blockade of the PD-1 inhibits the tumor suppression resulting from PD-1/PD-L1 as well as PD-1/PD-L2 interactions. In addition to binding to PD-1, PD-L1 binds to CD80 on activated T cells, which serves as an additional immunosuppressive mechanism. mAbs against PD-L1 inhibit PD-L1/PD-1 as well as PD-L1/CD80 immunosuppressive interactions. Red rectangle: monoclonal antibody to PD-1 inhibiting the interactions between PD-1 and its ligands PD-L1 and PD-L2. Yellow oval: monoclonal antibody against PD-L1 inhibiting the interactions between PD-L1 and its receptors, PD-1 and CD80.

Abbreviations: PD-L1, programmed death ligand 1; APCs, antigen-presenting cells; mAb, monoclonal antibody; MHC, major histocompatibility complex.

NSCLC randomized to nivolumab (3 mg/kg intravenously every 2 weeks) or docetaxel (75 mg/m^2 intravenously every 3 weeks).[16] The primary endpoint was OS which was achieved with a median OS (mOS) of 9.2 months in the nivolumab arm compared to 6 months in the control arm. One-year survival rate was 42% with nivolumab versus 24% with docetaxel. Other endpoints including objective response rate (ORR) and duration of response (DoR) were higher with nivolumab compared to chemotherapy.

CheckMate 057 trial (NCT01673867) included 582 patients with previously treated advanced nonsquamous NSCLC who had progressed on platinum-based chemotherapy or targeted therapy.[17] Patients were randomized 1:1 to nivolumab or docetaxel. This study also achieved its primary endpoint of OS with a mOS for nivolumab of 12.2 months compared to 9.4 months in the chemotherapy arm. One-year survival rate was 51% with nivolumab compared to 39% with chemotherapy and the 18-month survival rate was 39% and 23%, respectively. ORR was significantly higher with nivolumab (19%) compared to chemotherapy (12%) and median DoR (mDoR) was 17 and 6 months, respectively. Based on these studies, nivolumab was granted approval by the FDA for previously treated NSCLC of both squamous (March 2015) and nonsquamous (October 2015) histologies. Nivolumab was also recently evaluated against standard platinum-doublet chemotherapy in chemotherapy-naïve Stage IV NSCLC patients in a large open-label, randomized Phase III trial, called CheckMate 026 (NCT02041533).[18] A total of 541 treatment-naïve patients with advanced PD-L1-positive NSCLC (at least 1% PD-L1 staining) were randomized 1:1 to receive nivolumab or standard chemotherapy. Patients with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements were excluded from the study. The study did not meet its primary endpoint of progression-free survival (PFS) in patients expressing PD-L1 of 5%. Of the 423 patients with ≥5% PD-L1 expression, PFS was 4.2 months with nivolumab compared to 5.9 months with chemotherapy. One-year PFS rate was also not different between the groups (24% and 23%, respectively). OS was also similar in the two groups (14.4 months for nivolumab versus 13.2 months for chemotherapy) with a 1-year OS rate of 56% and 54%, respectively. ORRs in patients with >5% tumor PD-L1 expression for nivolumab were 26% compared to 34% with platinum-doublet chemotherapy. There was a high crossover rate of 64.2% in the chemotherapy arm compared to 43.6% in the nivolumab arm which may explain lack of OS benefit. Suboptimal patient selection and inclusion of patients with low PD-L1 expression could have also contributed to the negative results. Clinical trials are now evaluating combination of nivolumab with chemotherapy, biologic agents, and other checkpoint inhibitors. One such promising strategy is combining nivolumab with ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor.[19] Based on the encouraging results of a Phase I study that analyzed this combination, a Phase III trial called CheckMate 227 (NCT02477826) was designed.[20,21] This four-arm trial, which is currently recruiting, compares platinum-doublet chemotherapy plus nivolumab versus nivolumab/ipilimumab in PD-L1-expressing NSCLC and platinum-doublet/nivolumab combination versus nivolumab/ipilimumab combination in PD-L1-negative NSCLC.

Pembrolizumab

Pembrolizumab is an IgG4 monoclonal antagonist antibody to PD-1 that is approved for use in previously treated advanced NSCLC-expressing PD-L1 (at least 1% of TCs) as well as in frontline for patients with metastatic NSCLC whose tumors have ≥50% PD-L1 expression.[10] The approval for second-line treatment was obtained in October 2015 based on the efficacy results from multiple KEYNOTE trials. In a Phase I dose expansion KEYNOTE-001 trial (NCT01295827), 495 patients were included of whom 80% had received prior therapy. The trial reported an ORR of 19.4%, a mDoR of 12.5 months, and a mOS of 12 months. Updated results with inclusion criteria enriched with PD-L1 expression (at least 1% of TCs) with 394 previously treated and 101 chemo-naïve patients were subsequently published. ORRs for pretreated and chemo-naïve cohorts were 18% and 25%, respectively, and the mDoR was 10 and 23 months. The mOS was 9.3 and 16 months, respectively. Response rate was not dose, schedule, or histology dependent. However, there was a direct correlation between PD-L1 expression level and outcomes.[22]

A subsequent Phase II/III study compared two dosing levels of pembrolizumab (2 mg/kg and 10 mg/kg) with docetaxel in 1034 patients with previously treated NSCLC.[23] The results for patients with PD-L1 expression on at least 50% of TCs were first published, with pembrolizumab arms showing significantly longer PFS (5 and 5.2 months compared to 4.1 months) and OS (14.9 and 17.3 months vs 8.2 months) and with fewer adverse events than chemotherapy.[24] Objective response was noted in 30% and 29% of patients on pembrolizumab arms compared to 8% on the chemotherapy arm. Outcomes in the total population were subsequently reported and demonstrated an improved OS with pembrolizumab at both doses (10.4 and 12.7 months) compared 8.5 months with docetaxel. OS at 1 year was 43.2% and 52.3% versus 34.6%. Median PFS (mPFS) in the total population was similar in all the three groups (3.9, 4, and 4 months). Higher ORRs (RECIST v 1.1) were also observed in the overall population (18% and 18% versus 9% for the control group; $p=0.0005$ and $p=0.0002$, respectively).[23] This led to the expansion of the indication in second-line treatment of NSCLC to include all patients with PD-L1-expressing NSCLC in October 2016. A recently completed Phase III trial compared pembrolizumab monotherapy (200 mg intravenously every 3 weeks) with platinum-doublet chemotherapy in the first-line setting.[24] The study included 305 patients with chemo-naïve advanced NSCLC without EGFR mutations or ALK translocations having at least 50% TC PD-L1 staining. The study met its primary endpoint, PFS, which was significantly more prolonged with pembrolizumab (10.3 vs 6 months; hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.37–0.68). A prespecified interim analysis also demonstrated a statistically significant improvement in OS for patients on pembrolizumab arm (HR 0.60, 95% CI 0.41–0.89). Other endpoints including ORRs (45% and 28%, respectively) and mDoR (12.1 and 5.7 months, respectively) were superior in patients on pembrolizumab compared to standard chemotherapy. Several clinical trials are currently underway, exploring the combination of pembrolizumab with chemotherapy, biologic agents, and other immune-modulating agents.[25–27] Of interest is the combination of pembrolizumab with platinum-doublet chemotherapy in frontline setting. A recent Phase II trial compared platinum/pemetrexed-doublet therapy with platinum/pemetrexed/pembrolizumab triplet therapy in 123 patients with PD-L1-unselected, advanced, chemotherapy-naïve nonsquamous NSCLC. The ORR, which was the primary endpoint, was significantly better with the triplet therapy compared to the doublet (55% and 29%, respectively).[25] PFS was also significantly higher in the study arm (13 vs 6 months, respectively; HR 0.53, 95% CI 0.31–0.91).

PD-L1 blockade

PD-L1 is a transmembrane protein that negatively regulates immune responses through its interactions with PD-1 and B7-1 (CD80) receptors. Blocking PD-L1 releases inhibition of the immune response, resulting in enhanced immune surveillance and responses, including immune-mediated antitumor activity.[3] Several mAbs against PD-L1 are currently in development with atezolizumab at the head of the group.

A review of atezolizumab pharmacology

Mechanism of action

Atezolizumab (MPDL3280A) is a selective humanized monoclonal IgG1 antibody against PD-L1 that binds PD-L1 on TCs.[28] Inherently, antibodies of the IgG1 isotype can trigger antibody-dependent cell-mediated cytotoxicity (ADCC) activity and complement-dependent cytotoxicity (CDC). In ADCC,[29] which is mediated by natural killer cells, Fc gamma receptors (FcγR) on the surface of immune effector cells engage with the Fc portion of the mAb, which in turn is bound to the target cell. This then triggers the activation of the effector cell and the secretion of cytolytic enzymes such as perforin and granzyme which destroy the target cell. In CDC,[30] C1q, which is a subcomponent of the C1 complex of the classical complement pathway, binds the Fc portion of the mAb and triggers the complement cascade, which ultimately leads to death of the target cell bound to the antibody. While these could potentially enhance tumor death by inducing apoptosis, they could also result in depletion of PD-L1-expressing T cells, thereby blunting the immune response. In order to eliminate ADCC and CDC at clinically relevant doses, the Fc (the fragment crystallizable) domain of atezolizumab is engineered to reduce its interaction with the complement component C1q and the FcyR.[31] The lack of ADCC and CDC activities has been confirmed with cell-based functional assays.[32]

Metabolism

The metabolism of checkpoint inhibitors is not well understood; however, many theorize that given atezolizumab is a mAb, the expected metabolism is similar to proteins via proteolytic degradation to small peptides and individual amino acids and receptor-mediated clearance.[32]

Pharmacokinetics

The pharmacokinetics of atezolizumab have been characterized in adult patients in multiple clinical trials at doses 0.01–20 mg/kg administered every 3 weeks including the fixed prescribing dose of 1200 mg. Exposure to atezolizumab increased the dose proportionally over the dose range of 1–20 mg/kg, with an estimated terminal half-life of 27 days.[33]

Early-phase trials

Efficacy of this drug in NSCLC was first reported in an adaptive design Phase I study in which a total of 277 patients with advanced incurable cancer received the experimental drug intravenously every 3 weeks. Of the 175 efficacy-evaluable patients, confirmed responses (complete and partial responses) were observed in 18% of the patients with all tumor types and in 21% (11 out of 53) of patients with NSCLC.[34] The ORR and 24-week PFS rate in the NSCLC cohort were 23% and 45%, respectively. Updated results on 88 patients presented at American Society of Clinical Oncology (ASCO) 2015 showed that the efficacy was maintained with an ORR of 23%, a mDoR of 17 months, a mOS of 16 months, and a 1-year survival rate of 63%. Superior outcomes were noted in patients with higher PD-L1 expression, and a trend toward improved responses in former and current smokers was also observed.[35] Toxicity profile was similar to programmed death pathway inhibitors as detailed below with no additional safety concerns.

Phase II trials

The results of the above Phase I trial led to the Phase II FIR trial (NCT01846416), which assessed the safety and efficacy of atezolizumab at a dose of 1200 mg every 3 weeks in three cohorts of advanced NSCLC patients: chemotherapy-naïve patients (Cohort 1); pretreated patients without brain metastases (Cohort 2); and those with treated brain metastases (Cohort 3). The study population was enriched with PD-L1 expression in tumor or ICs as determined by a central laboratory. Results of this study were presented at ASCO Annual Meeting in 2015.[36] As in the Phase I study, PD-L1 expression correlated with response. ORR in the entire population was 26% for Cohort 1, 16% for Cohort 2, and 23% for Cohort 3. In those with highest PD-L1 expression, ORR was 29%, 24%, and 25% in the three cohorts, respectively. mPFS was 4.5 months in Cohort 1, 2.7 months in Cohort 2, and 2.3 months in Cohort 3. Among those with the highest PD-L1 expression, the mPFS was 5.4, 4.1, and 2.3 months, respectively, for the three cohorts. Immune-related AEs were as expected for the class of drug, but one treatment-related death due to constrictive pericarditis was seen.

Two other Phase II trials, POPLAR (NCT01903993) and BIRCH (NCT02031458), confirmed the activity of atezolizumab in lung cancer. BIRCH was an open-label, multicenter, single-arm Phase II trial which enrolled 667 chemotherapy-naïve as well as previously treated PD-L1-positive advanced NSCLC patients without brain metastases.[37] Only patients with PD-L1 expression in tumor or ICs as determined by the

Roche investigational immunohistochemistry (IHC) test were included in the study. Patient characteristics were balanced across cohorts. EGFR and KRAS mutations were identified in 327 and 177 patients overall, respectively. Three cohorts of patients were characterized: 142 chemo-naïve patients (Cohort 1), 271 patients who had progressed after one prior platinum therapy (Cohort 2), and 254 patients who had undergone two or more prior chemotherapy regimens (Cohort 3). All patients received atezolizumab 1200 mg intravenously every 3 weeks. The primary endpoint of the study was ORR. Secondary endpoints included DoR, OS, PFS, and safety. ORR for Cohorts 1, 2, and 3 were 19%, 17%, and 17%, respectively. As noted in other trials, outcomes correlated with PD-L1 expression. Among 302 patients with highest PD-L1 expression, ORRs in untreated and previously treated advanced NSCLC were 26% and 25%, respectively. Six-month survival rates were 82%, 76%, and 71% in intention-to-treat (ITT) Cohorts 1, 2, and 3, respectively. In those with the highest PD-L1 expression, the survival rates were 79%, 80%, and 75%, respectively. Six-month PFS rates were 46%, 29%, and 31% for the three cohorts in the ITT population and 48%, 34%, and 39% in patients with the highest PD-L1 expression. The safety data for atezolizumab in BIRCH (NCT02031458) were similar to those observed in other trials.

POPLAR randomized 287 patients with previously treated NSCLC to atezolizumab monotherapy (144 patients) or docetaxel (143 patients) chemotherapy.[38] Intravenous atezolizumab was administered at 1200 mg every 3 weeks and docetaxel was used at 75 mg/m^2 every 3 weeks. Baseline PD-L1 expression was evaluated by immunohistochemistry in TCs and in tumor-infiltrating ICs. In the overall study population, the results significantly favored atezolizumab 12.6 months versus 9.7 months (HR 0.73, 95% CI 0.53–0.99; *p*=0.04). However, benefit corresponded with level of PD-L1 expression. Patients with the highest level of PD-L1 expression in their tumor or ICs enjoyed the best outcomes with atezolizumab with mOS for this cohort being 15.5 months compared to 11.1 months with chemotherapy. On the contrary, OS was identical in the two arms in patients with PD-L1 negative tumors. Other endpoints were also superior with atezolizumab in patients with highest PD-L1 expression compared to docetaxel PFS 9.7 versus 3.9 months and ORR was 38% and 13%, respectively, for immunotherapy and chemotherapy. On long-term follow-up (minimum 20 months), further separation in OS curves between the atezolizumab and docetaxel arms was noted for both the ITT and PD-L1-enriched populations. As expected, fewer grade 3 to 5 adverse events were experienced by patients treated with atezolizumab compared with docetaxel (44% vs 56%).

Phase III trials

The efficacy of atezolizumab in previously treated NSCLC was further confirmed by a Phase III trial, OAK (NCT02008227) which was an open-label, randomized Phase III trial comparing atezolizumab with docetaxel in patients with advanced NSCLC (squamous or nonsquamous histologies) who had progressive disease after one to two previous cytotoxic chemotherapy regimens (one or more platinum based combination therapies).[39] The primary endpoints of the study were OS in the ITT and PD-L1-positive (≥1% PD-L1 on TCs or tumor-infiltrating ICs) populations. Of the total 1225 patients enrolled in this study, 425 patients received atezolizumab and 425 docetaxel. Primary endpoint, OS was significantly longer with atezolizumab in both the ITT and PD-L1-positive populations. In the ITT population, OS was 13.8 months with atezolizumab compared to 9.6 months with chemotherapy (HR 0.73, 95% CI 0.62–0.87; *p*=0.0003). OS in the PD-L1-enriched population was also superior in the atezolizumab arm (n=241) at 15.7 months compared with docetaxel (n=222) at 10.3 months (HR 0.74, 95% CI 0.58–0.93; *p*=0.0102). Patients with a lack of PD-L1 staining in tumor or immune cells (TC0 and IC0) also had survival benefit with atezolizumab – mOS 12.6 months versus 8.9 months with chemotherapy (HR 0.75, 95% CI 0.59–0.96). Benefit was noted in both squamous and nonsquamous NSCLC subsets. The toxicity profile was significantly better with immunotherapy than chemotherapy, and no new safety signals were observed.

FDA approval

Based on the encouraging results from early phase clinical trials, FDA granted atezolizumab a breakthrough therapy designation in February 2015 for the treatment of PD-L1-positive NSCLC that progressed during or after standard treatments. It subsequently became the first PD-L1 inhibitor to be approved for use in patients with NSCLC who have progressed on platinum-doublet chemotherapy or appropriate targeted therapy.[12]

Ongoing clinical trials

Table 1 lists a selection of ongoing clinical trials in NSCLC with atezolizumab.

Frontline

IMpower110 (GO29431, NCT02409342), a randomized open-label Phase III study compares the efficacy and safety of standard platinum-doublet chemotherapy to atezolizumab monotherapy in chemotherapy-naïve patients with PD-L1 positive advanced nonsquamous or squamous NSCLC.[40]

Table 1 Selected ongoing trials of atezolizumab in NSCLC

Name of the study/Phase	Disease/setting	Treatment arms	Details	NCT number
A Phase II, open-label, multicenter, single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant and adjuvant therapy in patients with Stage IB, II, or IIIA resectable and untreated NSCLC	Stage IB, II, or IIIA resectable and untreated NSCLC	Atezolizumab	Primary outcome measures: Major pathologic response (MPR) after surgery – time frame ~10 weeks	NCT02927301
A single-arm, Phase II study of neoadjuvant atezolizumab, nab–paclitaxel, and carboplatin (MAC) in resectable NSCLC	NSCLC	Neoadjuvant MPDL3280A, nab-paclitaxel. and carboplatin (MAC) in NSCLC	Primary outcome measures: MPR time frame: 84 days defined as >90% decrease in viable tumor	NCT02716038
Phase II B-F1RST	Locally advanced or metastatic NSCLC	Atezolizumab (MPDL3280A)	Single-arm study of atezolizumab monotherapy in locally advanced or metastatic NSCLC: clinical evaluation of novel blood-based diagnostics Primary outcome measures: ORR and PFS up to ~28 months	NCT02848651
DARZALEX/Phase Ib/2	Previously treated advanced or metastatic NSCLC	Daratumumab in combination with atezolizumab compared with atezolizumab alone	Open-label, randomized Primary outcome measures: ORR from randomization to end of study (an expected average of 3 years)	NCT03023423
Phase III IMpower110	Chemotherapy-naïve patients with Stage IV nonsquamous or squamous NSCLC	A study of atezolizumab (MPDL3280A) compared with a platinum agent (cisplatin or carboplatin) + (pemetrexed or gemcitabine)	A Phase III, open-label, randomized study of atezolizumab compared with a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1-selected, chemotherapy-naïve patients with Stage IV nonsquamous or squamous NSCLC Primary outcome measures: PFS and OS (up to ~33 months)	NCT02409342
Phase III IM power111	Squamous NSCLC	Atezolizumab (MPDL3280A) Compared with gemcitabine plus (+) cisplatin or carboplatin	Open-label, randomized study of atezolizumab compared with gemcitabine + cisplatin or carboplatin for PD-L1-selected, chemotherapy naïve patients with Stage IV squamous NSCLC Primary outcome measures: PFS	NCT02409355
Phase III IMpower131	Chemotherapy-naïve patients with Stage IV squamous NSCLC	Atezolizumab in combination with carboplatin + paclitaxel or carboplatin + nab–paclitaxel compared with carboplatin + nab–paclitaxel	A Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of atezolizumab (MPDL3280A, anti-PD-L1 antibody) in combination with carboplatin + paclitaxel or atezolizumab in combination With carboplatin + nab–paclitaxel versus carboplatin + nab–paclitaxel in chemotherapy-naïve patients with Stage IV squamous NSCLC Primary outcome measures: PFS: Time frame: Up to ~28 months after the first participant enrolled OS: Time frame: Up to ~44 months after the first participant enrolled	NCT02367794

(*Continued*)

Table 1 (*Continued*)

Name of the study/Phase	Disease/setting	Treatment arms	Details	NCT number
A Phase III IMpower132	Are chemotherapy-naïve and have Stage IV nonsquamous NSCLC	Atezolizumab in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed	Open-label, randomized study of atezolizumab (anti-Pd-L1 antibody) in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed in patients who are chemotherapy-naïve and have Stage IV nonsquamous NSCLC Primary outcome measures: PFS and OS up to ~44 months	NCT02657434
Phase III IMpower210	Locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen	Atezolizumab compared with docetaxel	A multicenter, open-label, randomized, controlled study designed to evaluate the efficacy and safety of the anti-PD-L1 antibody atezolizumab compared with docetaxel in participants with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen Primary outcome measures: OS: From screening until death, loss to follow-up, or study end. Up to ~3 years overall	NCT02813785
A Phase Ib study of the safety and pharmacology of atezolizumab (MPDL3280A) administered with erlotinib or alectinib in patients with advanced NSCLC	Advanced NSCLC	Atezolizumab in combination with erlotinib or alectinib	Primary outcome measures: Percentage of participants with dose-limiting toxicities time frame: Day 8, Cycle 1 until Day 1, Cycle 2 (21 days from start of atezolizumab treatment)	NCT02013219

Abbreviations: NSCLC, non-small cell lung cancer; NCT, National Clinical Trial; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; PD-L1, programmed death ligand 1.

IMpower131 (GO29437, NCT02367794) is another large three-arm Phase III trial that evaluates the combination of atezolizumab with carboplatin and paclitaxel or nabpaclitaxel against standard regimen of carboplatin and nabpaclitaxel in patients with Stage IV squamous cell NSCLC. IMpower132 (GO29438, NCT02657434) is yet another Phase III frontline trial that looks at atezolizumab in combination with carboplatin or cisplatin and pemetrexed in comparison with carboplatin or cisplatin + pemetrexed in Stage IV nonsquamous NSCLC patients. A Phase Ib open-label, multicenter study assesses the safety, tolerability, and pharmacokinetics of atezolizumab in combination with oral erlotinib or alectinib in treatment-naïve EGFR mutation-positive NSCLC patients (NCT02013219).

Second and subsequent lines

Several studies involving atezolizumab alone or in combination with other agents are currently recruiting patients. For example, a Phase I/II trial evaluates the combination of daratumumab, a CD38 inhibitor with atezolizumab in previously treated NSCLC patients (NCT03023423). Another Phase II study evaluates the combination of atezolizumab and CDX-1401 which is a fusion protein consisting of a mAb specific to dendritic cell receptor DEC-205 linked to the NY-ESO-1 tumor antigen in NY-ESO-1-positive advanced NSCLC (NCT02495636).

Other settings

Ongoing trials also examine the efficacy and safety of atezolizumab in neoadjuvant and adjuvant settings. Studies also evaluate the combination of atezolizumab with external beam radiation in patients with locally advanced lung cancer.

Other PD-L1 inhibitors

Durvalumab

Durvalumab (AstraZeneca, Wilmington, DE, USA) is an engineered, high-affinity IgG1 human mAb that blocks PD-L1 binding to PD-1 and B7-1. It does not affect the interaction between PD-1 and PD-L2, which may avoid immune toxicities associated with that interference. In addition, the Fc domain of durvalumab has a triple mutation engineered to reduce ADCC and CDC. Durvalumab was investigated as a first-line or subsequent treatment in patients with Stage IIIB/IV in a Phase I/II study presented at European Society for

Medical Oncology (ESMO) 2016 (NCT02572843). PD-L1 expression was assessed on archived or fresh tissue with high expression defined as at least 25% of TC staining for PD-L1 (regardless of intensity) and low expression as <25%. Of the 304 patients enrolled, 53% had squamous histology and 47% were nonsquamous. Fifty patients had a confirmed response. Out of the 154 patients with high PD-L1 expression, 25% achieved a response, including 14 patients in the first-line setting, 12 as second-line setting, and 13 as third-line setting or beyond. Among the 115 patients with low PD-L1 expression, only 6% achieved a response. Of the responders, 48% had ongoing responses at the time of data cutoff, which ranged from 1.4 to 22 months or longer. The 1-year OS rates for patients receiving durvalumab as second-line treatment were 56% for patients with high PD-L1 expression and 39% in those with low expression; similar 1-year OS rates were seen in those patients receiving third-line or higher therapy in the high and low expressors of 51% and 37%, respectively. The mOS for patients treated in the second line according to high and low expression was 17.8 months compared with 8.2 months; for patients in the third line or higher, the mOS was 13 months compared with 7.6 months for the high and low expressors, respectively. Results from the Phase II ATLANTIC Study (NCT02087423) investigating durvalumab in third-line or higher NSCLC were presented at International Association for the Study of Lung Cancer (IASLC) 2016. Cohort 2 included 146 patients with high and 93 patients with low PD-L1 expression as above, and Cohort 3 included 68 patients with >90% of TC staining for PD-L1 expression. In Cohort 2, the median ORR for the high versus low PD-L1 staining was 16.4% versus 7.5%, respectively, with a disease control rate (DCR) of 28.8% versus 20.4% and mDoR of 12.3 months for the high expressors and was not reached in the low expressors. The mPFS was 3.3 months versus 1.9 months, mOS was 10.9 months versus 9.3 months, with 1-year OS of 47.7% and 34.5%, respectively. The Cohort 3 patients achieved an ORR of 30.9%, DCR of 38.2%, mPFS of 2.4 months, and 1-year OS 50.8% with mDoR and mOS not reached.[41] Durvalumab is currently being investigated in combination with other agents such as tremelimumab and mocetinostat, a histone deacetylase inhibitor.[42,43]

Avelumab

Avelumab (MSB0010718C; Pfizer, New York, NY, USA) is an anti-PD-L1 fully human IgG1 mAB which retains a native Fc region enabling ADCC via engagement of the innate immune system. Results of a Phase Ib trial investigating avelumab as first-line therapy in patients with NSCLC regardless of PD-L1 expression were reported at IASLC 2016. Of the 145 patients treated, 63% had adenocarcinoma and 27% had squamous cell carcinoma. Among the 75 patients with >3 months of follow-up, there was an ORR of 19% including 1 complete response with 12 responses ongoing. An additional 45% had stable disease for a DCR of 64%.[44] Avelumab is currently being investigated in a first-line randomized Phase III trial compared with platinum-based doublet chemotherapy (JAVELIN Lung 100; NCT02576574) and a Phase III multicenter (JAVELIN Lung 200; NCT02395172) clinical trial randomizing patients to avelumab versus docetaxel in patients with advanced NSCLC in the second-line setting following platinum-based doublet chemotherapy.

Toxicity of PD-L1 inhibitors

Immune-related adverse events are the most common toxicities associated with immune checkpoint inhibitors; however, fortunately, most of these toxicities are Grade 1 or Grade 2.[45] These immune-related toxicities usually present in the first 3 months of therapy, but there can also be some delayed presentations even as late as 1 year or longer into treatment. In the Phase II POPLAR study (NCT01903993), 40% of patients in the atezolizumab group experienced Grade 3–4 treatment-related adverse events (TRAEs), including elevated aspartate aminotransferase (4%), elevated alanine aminotransferase (4%), pneumonitis (3%), colitis (1%), and hepatitis (1%).[38] One patient sustained grade 5 cardiac failure that was attributed to atezolizumab. In the Phase III OAK trial (NCT02008227), there were no deaths related to atezolizumab.[39] Grade 3 or 4 adverse events occurred in 37% of patients treated with atezolizumab, including fatigue (14%), nausea (9%), decreased appetite (9%), and asthenia (8%) which were the most common adverse events. Immune-mediated adverse events occurred in ≤1% patients included: pneumonitis, hepatitis, and colitis; overall, 8% of patients discontinued atezolizumab due to adverse events.

Regarding other PD-L1 inhibitors, most adverse events related to durvalumab were noted to be low grade and resolved with delaying treatment and/or steroids. In one study of durvalumab, it was noted that 10.2% of patients had a Grade ≥3 TRAE that led to discontinuation of therapy in 2.7% of patients.[46] In the avelumab JAVELIN Lung 200 study (NCT02395172), 56.6% of patients had some type of TRAE, the most common of which were infusion-related reactions and fatigue; 9% had a Grade 3 or higher TRAE.[44] Immune-related adverse events occurred in 2.8% of patients, all of which were Grade 1 or Grade 2, including pneumonitis and hypothyroidism; there were no treatment-related deaths in this study.

Predictive biomarkers

The success of PD-1/PD-L1 inhibition is clearly dependent on optimal patient selection. Availability of a biomarker (or biomarkers), preferably blood based that accurately and reliably predicts response to programmed death pathway inhibitors, would be ideal but that has been elusive to date. Several tissue- and blood-based biomarkers have been studied, and some have been shown to correlate with response.[47] These include baseline tumor characteristics such as mutational load, PD-L1 immunohistochemistry, presence of immune infiltrates, and baseline peripheral blood markers (T-cell subsets, neutrophil–lymphocyte ratio).[48–52] Clinical characteristics such as smoking history and concurrent use of antibiotics have also been shown to correlate with response. However, identifying biomarkers of cancer immunotherapy is challenging, given the dynamic changes within the tumor and its microenvironment, molecular heterogeneity of tumors, adaptive nature of immunity, and presence of multiple immune checkpoints involved in T-cell regulation. Of all these biomarkers, PD-L1 expression on the tumor and peritumoral ICs most closely reflects the mechanism of action of PD-1/PD-L1 inhibitors. PD-L1 is aberrantly expressed in several solid tumors, including NSCLC. PD-L1 overexpression has been demonstrated to correlate with advanced tumor stage, aggressive behavior, and poor survival, suggesting a prognostic role of PD-L1 expression. Even though PD-L1 expression by immunohistochemistry has been shown to be predictive of response to multiple agents inhibiting the programmed death pathway, there is no uniformity in the testing process, with each compound being developed with its own companion test, cutoff value, and grading methodology (Table 2). There are other limitations to using PD-L1 as a predictive biomarker. PD-L1 expression is heterogeneous within the tumor and metastatic sites and can change over time either spontaneously or induced by other cancer-directed therapies. This rationalizes the responses observed in patients with PD-L1-negative tumors and iterates the need for multiple and repeated biopsies.

Future directions

The current broad list of active clinical trials involving atezolizumab and other immune checkpoint inhibitors outline the long list of unanswered questions of the optimal use of these agents in the treatment of patients with lung cancer. Results of these studies investigating their use in combination with chemotherapy agents, with other immunotherapy agents such as CTLA-4 inhibitors, and with radiation therapy, are eagerly awaited. Whether these agents will have a role in the treatment of patients with earlier stage disease in currently under investigation wityh clinical trials evalautaing atezolizumab in combination with chemotherapy and/or radiation therapy in locally advanced inoperable disease as well as in the neoadjuvant and adjuvant settings. Refining our knowledge of predictive biomarkers is essential so that these treatments can be utilized in those patients most likely to benefit, thereby limiting a patient's exposure to potential toxicity, both clinically and financially. On the contrary, it is vitally important to understand the etiology behind nonresponders as well as reasons for disease progression in initial responders. Other areas of interest include a better understanding of patients who experience pseudoprogression, a phenomenon that can occur in ~2%–3% of patients with lung cancer treated with immune checkpoint inhibitors.[55] Other areas of exploration include the potential role of rechallenging patients with these agents after subsequent treatment with another line of chemotherapy or radiation therapy that could theoretically alter PD-1/PD-L1 expression in tumors.

Conclusion

With the three FDA-approved immune checkpoint inhibitor drugs for use in NSCLC – atezolizumab, nivolumab, and pembrolizumab – their place in therapy is becoming better defined. All three have firm second-line (or higher)

Table 2 PD-L1 assays

Drug	Class of drug	IHC antibody	Positive staining specifics	Cutoff
Nivolumab	PD-1 inhibitor	Dako 28-8[11]	Membranous staining of tumor cells	5%
Pembrolizumab	PD-1 inhibitor	Dako 22C3[53]	Membranous staining of tumor cells or immune cells that are intercalating or at the tumor interface	1%; 50%
Atezolizumab	PD-L1 inhibitor	Ventana-SP142[38]	Score based on both tumor and immune cell (TC/IC) staining	TC1-3/IC1-3 (1%–50%)
Durvalumab	PD-L1 inhibitor	Ventana-SP263[54]	Membranous staining of tumor cells	25%

Abbreviation: IHC, investigational immunohistochemistry.

indications, with atezolizumab and nivolumab being more efficacious than chemotherapy regardless of PD-L1 expression; however, pembrolizumab is approved for use in those patients with ≥1% staining. Pembrolizumab holds a first-line indication for single-agent treatment in those patients with ≥50% PD-L1 expression, which included 28% of first-line patients in the KEYNOTE trials. The OAK trial demonstrated a survival benefit over chemotherapy in both squamous and nonsquamous disease, regardless of the PD-L1 expression; however, significant responses and survival benefits were seen in patients with high PD-L1 expression, confirming this as a reliable predictive biomarker for identifying those patients most likely to benefit from atezolizumab. Interestingly, PD-L1 expression was unrelated to nivolumab efficacy in squamous histology. However, which checkpoint inhibitor should be used in the second-line setting is still unresolved. Currently, atezolizumab may be more attractive, given its dosing schedule of every 3 weeks as opposed to every 2 weeks for nivolumab and pembrolizumab. It also does not require a minimum PD-L1 percent expression. Additional study results will help define the further role of these agents, including potential indications for the other PD-L1 inhibitors avelumab and durvalumab.

Disclosure

The authors report no conflicts of interest in this work.

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