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Atezolizumab for the treatment of non-small cell lung cancer

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Abstract

Introduction—The immune system can restrain or promote cancer development and growth. Antibodies targeting immune checkpoints have revolutionized cancer treatment. Among the best responses have been in non-small cell lung cancer (NSCLC) which is largely caused by chronic exposure to carcinogens; associated with high neoantigen creation and sensitization to immune recognition. Atezolizumab was the first approved antibody that targets the PD-1 ligand (PD-L1).

Areas Covered—This drug profile article covers the basics of the cancer-immunity cycle and reviews some aspects of innate and adaptive immunology. We discuss the discovery of PD-L1 and PD-L2 while highlight the potential differences in targeting PD-L1 versus PD-1. In addition, we briefly summarized the available pre-clinical and clinical data of atezolizumab use in NSCLC. A special section covers the challenges of PD-L1 immunohistochemistry assay.

Expert commentary—PD-1:PD-L1 blockade has taken the lead in the immunotherapeutics field and represents the backbone of developing combination immunotherapies. Atezolizumab represents a step forward in the treatment of advanced NSCLC, nonetheless PD1:PD-L1 blockade in early-stage lung cancer is still a matter of debate.

Keywords

Atezolizumab; Immunotherapy; Lung cancer; PD-L1

1. Brief review of immunology for non-immunologists

Exploration of how the immune system affects cancer progression extends at least back to 1893, when William Coley began treating cancer patients with a mixture of heat-killed bacteria. Shortly thereafter, in the early 1900s, Paul Ehrlich began formulating a theoretical basis for the possible protective effects of immunity against cancer.

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Declaration of Interest

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The last twenty years have seen a dramatic reemergence of interest in this field, with an increasing body of research suggesting that one of the hallmarks of cancer is tumor evasion of immunological destruction [1, 2]. Genomic instability and mutation are characteristics of malignant neoplasms; these can both trigger immunologic response and contribute to tumor escape from immune destruction. The interplay between the cytolytic immune system and ultimate cancer progression, including T cell recognition of cancer cells as “foreign” and conversely immunoediting by cancers to suppress recognition, is complex and dynamic, and has been described in three sequential phases: elimination, equilibrium and escape [3, 4].

1.1. Cancer-immunity cycle

In the first phase of elimination, the innate and adaptive immune system components may eradicate the developing tumor. Antigen presenting cells (APC) can capture and process tumor associated antigens (TAA) for presentation and cross-presentation through MHC (major histocompatibility complex) class II and I respectively, and migrate to draining lymph nodes. Inside secondary lymphoid organs, tumor-antigen-loaded activated dendritic cells can generate a protective cytolytic response, which may include the production of activated CD8⁺ effector T cells and natural killer (NK) cells. Finally, cancer-specific activated CD8⁺ effector T cells and/or NK cells can return to tumor bed and perform cancer cell destruction. Despite the seeming specificity of this response, tumor cells can manage to escape through a myriad of different mechanisms[3].

The process of T cell activation, from a small pool of naive lymphocytes specific for a given tumor associated antigen, leads to replicative expansion generating a large number of effector T cells. Defined TAAs include neoantigens related to somatic mutations and gene rearrangements, and aberrant re-expression of developmentally silenced differentiation factors and so-called cancer testis antigens. The initial activation of naive T lymphocytes occurs mainly in secondary lymphoid organs. Several T cell surface proteins participate in the process of T cell activation, including TCR (T-cell receptor), adhesion molecules, co-receptors and co-stimulators, the latter two of which play critical roles in central tolerance and autoimmunity prevention.

The specific recognition of antigenic peptides presented by the MHC triggers TCR signaling. The co-stimulatory and co-inhibitory receptors on T cells direct T cell function and determine T cell fate. The best characterized central co-stimulatory pathway in T cell activation is represented by the engagement of CD28 with B7-1 (CD80) and B7-2 (CD86) which are expressed on activated APCs. This results in activation of downstream mitogenic signaling pathways including PI3K/AKT and RAS/MAPK, increased expression of anti-apoptotic proteins (e.g. BCL-X_L), production of proliferative cytokines (e.g. IL-2), and differentiation of naive T cells into effector T cells[5].

Several other proteins structurally related to B7-1 and B7-2 or to CD28, have been identified. While some of these are immunostimulatory agonists, other have inhibitory mechanisms, functioning as immune checkpoints. Key inhibitory receptors of the CD28 family include CTLA-4 (cytotoxic T lymphocyte antigen 4) and PD-1 (programmed death 1).

CTLA-4:B7 binding primarily inhibits the initial activation of T lymphocytes in secondary lymphoid organs, while PD-1:PD-L1 interactions are thought to play a larger role in peripheral tissues. As one might predict from the primary localization of the CTLA-4 pathway, blockage of this inhibitory pathway in the central lymphoid organs leaves the inhibitory PD-1:PD-L1 pathway in the tumor microenvironment intact, preventing killing of cancer cells by cytotoxic T lymphocytes (CTL) in the tumor bed.

Furthermore, the immune response to cancer evolves over many years and, in the case of progressive and metastatic cancer, ultimately fails. Myriad factors may contribute to this failure, but one key factor is that after prolonged antigenic exposure, the responses of effector T cells may gradually attenuate. This phenomenon is called T cell exhaustion[6, 7, 8], and is characterized by reduced production of IFN- γ and increased expression of multiple inhibitory receptors, notably PD-1. These observations among others ultimately led to the development of PD-1:PD-L1 pathway blockade as a therapeutic anti-cancer strategy.

1.2. Discovery of PD-L1 and PD-L2

PD-1 is expressed on a large proportion of tumor-infiltrating lymphocytes (TILs). It is transcriptionally induced on activated T cells, on other activated non-T lymphocyte subsets including B cells and NK cells, and on some myeloid cells[9, 10]. The extracellular component of PD-1 consists of a single domain resembling an immunoglobulin variable region (IgV), while the cytoplasmic component contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) followed by an immunoreceptor tyrosine-based switch motif (ITSM), which is required intact for PD-1 function[11, 12]. PD-1 is considered to be a member of the CD28 superfamily and its structural similarity to CTLA-4 and CD28 led to the hypothesis that the ligand for PD-1 might be a member of the B7 family.

Dong and colleagues[13] in 1999 first described a third member of the B7 family, called B7-H1 (PD-L1 or CD274) which does not bind to CD28, CTLA-4 or ICOS (inducible co-stimulator), however co-stimulation mediated by B7-H1 led to secretion of IL-10. Although PD-L1 shares only about 20% amino-acid identity with B7-1 and B7-2 in its extracellular domain, the secondary structures of these molecules are very similar. They all belong to an emerging family within the immunoglobulin superfamily.

The expression of mRNA encoding PD-L1 is abundant in many tissues. Key oncogenic pathways such as PTEN-PI3K and MAPK pathway have been implicated in the post-transcriptional regulation of its cell surface expression[9]. IFN- γ and type I interferons are also known potent inducers of PD-L1 expression. PD-L1 protein is often found constitutively in immune-privileged sites, including the eyes and placenta. PD-L1 expression in most tissues is dynamic, but has been reported to be constitutively expressed in activated T cells and B cells, dendritic cells, macrophages, NK cells, vascular endothelial cells and mesenchymal stem cells. PD-L1 has been found to be highly expressed in many human cancer types including melanoma, non-small cell lung cancer, nasopharyngeal carcinoma, urothelial carcinoma, gastric carcinoma, and renal cell carcinoma, among others. Levels of PD-L1 expression in cancer cells are also regulated by epigenetic mechanisms through microRNAs. Amplification of 9p24.1, which harbors *PD-L1* and *PD-L2* genes, increases

gene dosage together with *JAK2* in nodular sclerosing Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma[14].

Tumors expressing PD-L1 can render cytotoxic T lymphocytes (CTL) inactive or nonfunctional through engagement of the inhibitory receptor PD-1. The mechanisms by which PD-1 antagonizes T-cell receptor signaling are a subject of intense investigation. Engagement of PD-1 on activated effector T cells causes the recruitment of the phosphatase Shp2 and subsequent inactivation of the PI3K-AKT-mTOR and RAS-MEK-ERK pathways. Hui and colleagues[15] recently showed that the co-receptor CD28 is strongly preferred over the TCR as a target for dephosphorylation by PD-1–recruited Shp2 phosphatase. In addition, metabolic reprogramming has a major role in T-cell differentiation and function, with aerobic glycolysis becoming the dominant metabolic program during activation and expansion. PD-1 may alter T-cell differentiation by restraining T cells from remodeling multiple metabolic pathways. PD-1 suppresses oxygen consumption and impairs the ability of activated T cells to engage in glycolysis and glutaminolysis[16].

In addition to PD-1, PD-L1 may also mediate an immunosuppressive function through interaction with B7-1. Butte et al[17] showed that B7-1 and PD-L1 interact with affinity intermediate to that of B7-1:CD28 and B7-1:CTLA-4. T cell activation and cytokine production were inhibited by the interaction of B7-1 with PD-L1, pointing to a substantial bidirectional inhibitory interaction. In addition to resistance against T-cell destruction, PD-L1 cancer cells also demonstrate increased resistance to Fas-mediated apoptosis [18].

In 2001, Latchman and colleagues[19] first identified and characterized PD-L2, a second ligand for PD-1. PD-L2 has been less extensively studied and its role in modulating tumor immunity is less clear. PD-L2 expression was initially thought to be restricted to antigen-presenting cells such as macrophages and dendritic cells. Relative to PD-L1, basal expression of PD-L2 is low, but its expression can be induced on a wide variety of immune and nonimmune cells by microenvironmental stimuli including Th2 cytokines. The distribution of human *PD-L2* mRNA in normal tissues is more restricted than *PD-L1*. However, some tissues – such as pancreas, lung and liver – express PD-L2 but not PD-L1 and human fetal liver expressed PD-L1 but not PD-L2[19]. PD-1 engagement by PD-L2 or PD-L1 can down-regulate TCR-CD28–stimulation of cytokine production. Consistent with its more restricted tissue distribution, PD-L2 expression across tumor types is less prevalent than PD-L1.

The relative affinity of PD-L2 to PD-1 has been estimated to be 2–6 fold higher than of PD-L1, and its binding appears to involve less complex conformational changes. Nonetheless, the fact that PD-L2 is generally expressed at a lower level may favor PD-L1 as the primary binding ligand of PD-1, except during Th2 responses, when PD-L2 is upregulated. Experimental asthma models, where a high Th2 response is expected, have demonstrated enhanced disease severity in the absence of PD-L2 signaling[20]. The more restricted expression of PD-L2, largely to antigen-presenting cells, is consistent with a role in regulating T-cell priming and T-cell polarization. However, the main physiological function of PD-L2 is still under debate[9].

1.3. PD-1 versus PD-L1 blockade

Because the PD-1/PD-L1 axis has an important role in the maintenance of self-tolerance, therapeutic targeting of this pathway can lead to imbalances in immunologic tolerance, which manifest as immune-related adverse events. A broad range of auto-immune toxicities have been reported in patients treated with inhibitors of this pathway, and nearly all organs can be affected, including skin, GI tract, lung, kidney, heart, thyroid, and pituitary, among others. Even the immune privileged organs such as the eye and the brain can be affected. Mice deficient in PD-1 develop lupus-like proliferative arthritis and late onset glomerulonephritis[21]. In preclinical models, mice deficient in PD-L2 develop less frank autoimmunity, but rather exhibit hypersensitive Th2 responses and attenuated Th1 immunity[22].

Anti-PD-1 antibodies inhibit binding of both PD-L1 and PD-L2 to PD-1 positive activated T cells, inside the tumor bed. This strategy may be particularly appropriate for tumors that express both PD-1 ligands. The possibility that PD-1 can be saturated in the blood with an anti-PD-1 antibody before T cell migration into tumors represents one theoretical advantage of directly targeting PD-1 over PD-L1. However, in organs with high expression of PD-L2, direct PD-1 blockade could raise the potential of increased toxicity relative to targeting PD-L1.

In contrast to inhibiting PD-1, targeting PD-L1 leaves PD-L2 uninhibited, which can also represent a double-edged sword. On the one hand, PD-L1 targeting will not inhibit PD-L2-dependent immunosuppressive pathways in tumors. On the other hand, leaving the PD-L2:PD-1 interaction intact may preserve a component of peripheral immune homeostasis. For organs like the lung, this was hypothesized to reduce the likelihood of developing severe inflammatory toxicity. The defined role of PD-L2 in the modulation of Th2 responses, while antitumor immunity may be most dependent on Th1 responses, represents an argument for leaving PD-L2 intact.

The engagement of PD-L1, on T cells or tumor cells, with B7-1 on APCs appears to function uniquely to inhibit T-cell responses and abrogate the anti-apoptotic signaling of PD-L1 pathway respectively. Targeting PD-L1 versus PD-1 provides the additional theoretical advantage of inhibiting the binding of PD-L1 with B7-1, unleashing these anti-tumor response pathways.

2. Generation and preclinical analyses of atezolizumab (MPDL3280A)

The anti-PD-L1 antibody MPDL3280A (subsequently named atezolizumab) was isolated by screening a human phage display library against a recombinant extracellular domain-Fc fusion of human PD-L1[23]. A high-affinity antibody was selected from a single phage clone on a human IgG1 backbone (K_d (dissociation constant) = 0.4 nM). Binding of atezolizumab was strictly dependent on the expression of human PD-L1. Atezolizumab was engineered for reduced Fc effector function via a single amino acid substitution at position 298 (Asn to Ala); this substitution impairs the binding of atezolizumab to Fc γ receptors, and so minimizes in vivo depletion of tumor specific T cells expressing high levels of PD-L1 (and PD-1), antibody-dependent cellular cytotoxicity (ADCC). In an *in vitro* assay for

ADCC, the engineered antibody was unable to mediate killing of two cell lines transfected with human PD-L1. Atezolizumab blocks the interaction of PD-L1 with both PD-1 and B7.1.

Atezolizumab binding residues were moved onto a mouse Fc, and mouse IgG2a against murine PD-L1, PRO304397, was developed in parallel to facilitate analysis in preclinical murine studies without induction of cross-species immunogenicity [24]. Analogous to atezolizumab, PRO304397 was produced in Chinese hamster ovary cells and contains 2 mutations (D266A, N298A) in the Fc domain to prevent efficient binding to murine Fc γ receptors. PRO304397 and atezolizumab have similar PDL1 binding affinity and blocking properties toward both mouse and human PD-L1, and atezolizumab binds to PD-L1 in monkey and human with comparable affinity between species.

Deng and colleagues[24] characterized the pharmacokinetics (PK) of atezolizumab in cynomolgus monkeys, the PK/pharmacodynamics (PD) of PRO304397 in mice, and the tissue distribution and tumor penetration of PRO304397 in two isograft tumor-bearing mouse models (MC38 - murine colorectal cancer cells; and Cloudman - murine melanoma cells which are less sensitive model to PRO304397 treatment).

The PK of atezolizumab and PRO304397 was non-linear in monkeys (from 0.5 to 5 mg.kg⁻¹) and mice (between 1 and 10 mg.kg⁻¹), respectively. They are within the expected range for a typical human/humanized IgG1 in the linear range. Complete saturation of PD-L1 in blood in mice was achieved at serum concentrations of PRO304397 above 0.5 μ g.mL⁻¹. Tissue distribution and tumor penetration studies of PRO304397 in tumor-bearing mice indicated that saturation of target-mediated uptake in non-tumor tissues, and desirable exposure in tumors were achieved at higher serum concentrations. A higher dose of PRO304397 resulted in a greater penetration into tumors and a relatively longer duration of PD-L1 saturation in tumors. The bio distribution data indicated that the efficacious dose is mostly likely higher than that estimated based on simple PK/PD in blood. These data also allowed for estimation of the target clinical dose and facilitated further development of atezolizumab.

3. Clinical efficacy

3.1. Early phase studies

A Phase I, multicenter, first in human, open-label, dose escalation study[23] evaluated the safety, tolerability, and pharmacokinetics of atezolizumab administered as single agent by intravenous (IV) infusion every three weeks (q3w) to participants with locally advanced or metastatic solid malignancies or hematologic malignancies. The study (NCT01375842) was conducted in dose-escalation cohorts, followed by an expansion cohort. This phase I study was also modified in progress to allow for tumor-specific cohorts and biomarker enriched cohorts. Single-patient dose escalation was used for 0.01, 0.03 and 0.1 mg.kg⁻¹ cohorts, and a traditional 3+3 dose-escalation scheme was used for 0.3, 1, 3, 10, and 20 mg.kg⁻¹ cohorts. Five expansion cohorts were opened, including for NSCLC, renal cell carcinoma, melanoma, for other tumor types, and for patients who had mandatory serial biopsies. Formalin-fixed, paraffin-embedded (FFPE) tissue sections were stained for PD-L1 with an

anti-human PD-L1 rabbit monoclonal antibody (clone SP142; Ventana) on an automated staining platform. In contrast to PD-L1 staining protocols pursued in conjunction with other PD-1/PD-L1 directed antibodies, analysis of PD-L1 was performed both on tumor cells and in the tumor microenvironment (see below section on the complementary diagnostic assays).

A total of 277 patients with incurable cancers were enrolled. Mean single-dose PKs were consistent with a typical IgG1 at doses 1 mg.kg^{-1} , with a mean terminal serum half-life of 3 weeks. Treatment-related grade 3–4 adverse events (AE) were observed in 13% of the patients and immune-related grade 3–4 AEs were observed in 1%. The most common AE was fatigue, which often occurred with low-grade fever during the first cycle. No cases of grades 3–5 pneumonitis were seen.

A two-fold increase in activated proliferating CD8⁺ T cells and a trend of increasing circulating IFN- γ were observed by the end of the first cycle. The association of response to atezolizumab treatment and tumor-infiltrating immune cell PD-L1 expression reached statistical significance ($p=0.007$), while the association with tumor cell PD-L1 expression did not. RNA isolated from a regressive lesion displayed expression patterns indicative of a generalized activation of CD8 and Th1 T-cell responses. High PD-L2 expression did not appear to be associated with atezolizumab resistance. In contrast, most progressive tumors showed a lack of PD-L1 upregulation by either tumor cells or tumor-infiltrating immune cells in on-treatment biopsies.

The maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities were observed. Because $15 \text{ mg.kg}^{-1} \text{ q3w}$ was sufficient to maintain predefined target drug levels, the equivalent fixed dose of 1200 mg q3w was moved forward in clinical development.

Horn and colleagues[25] presented at 2015 ASCO annual meeting the updated results of the NSCLC cohort. The dose-expansion phase of this study originally enrolled patients independent of PD-L1 status, and subsequently, patients with NSCLC were selected on the basis of PD-L1 status. 88 patients with advanced NSCLC were evaluated for efficacy. Grades 3–4 AEs were observed in 11% of the patients, and fatigue was the common. No pneumonitis cases were observed. One death was reported. High overall response rates (ORR) were observed in patients with higher PD-L1 expression (TC3 or IC3), which was an independent predictor of response.

3.1.1. Atezolizumab + chemotherapy as first-line treatment of NSCLC—While cytotoxic chemotherapy is transiently immunosuppressive, chemotherapy-induced tumor cytotoxicity can also result in the release of tumor antigens and danger-associated cytokine secretion, which can trigger anti-tumor T-cell immunity[26]. Chemotherapeutic agents can modulate the activity of distinct immune cell subsets or the immune phenotype of tumor and stromal cells. These effects can include enhancing antigen presentation, enhancing expression of costimulatory molecules or downregulating checkpoint molecules. Strategically combining checkpoint inhibitors with chemotherapy can in theory potentiate the anti-tumor response. Defining the optimal choice of chemotherapy agent and timing of

these combinations in different disease contexts will be very important as chemotherapy drugs that deplete proliferating lymphocytes may be detrimental.

Liu and colleagues[27] reported the results of the phase 1b study (NCT01633970) designed to evaluate the safety, pharmacology and preliminary efficacy of atezolizumab administered with carboplatin/paclitaxel (Arm C), carboplatin/pemetrexed (Arm D) or carboplatin/nab-paclitaxel (Arm E) as first-line treatment in patients with locally advanced or metastatic NSCLC. 30 patients receiving atezolizumab plus chemotherapy were evaluated for response. The combination demonstrated robust response rates, with ORR of 67% (95% CI, 47%–83%) while complete responses seen in 10% of the patients. Median duration of response was 24 weeks in Arm C, and had not been reached at the time of reporting for other arms. Responses were seen independent of PD-L1 expression. Overall, treatment was well tolerated without apparent exacerbation of chemotherapy-associated adverse events and no pneumonitis was observed. Potential additive or synergistic effects with the combination of atezolizumab and chemotherapy are being further explored in randomized phase 3 trials. (Table 7)

3.2. Phase 2 studies

The first phase 2 trial was a single-arm study[28] (“FIR”) of atezolizumab, in PD-L1 selected positive patients with stage IIIB/IV NSCLC (NCT01846146), designed to evaluate the efficacy, safety and the relationship between PD-L1 status and efficacy. The primary endpoint was ORR. Eligible participants were categorized into three groups as follows: participants with no prior chemotherapy for advanced disease (cohort 1); participants who progressed during or following a prior-platinum based chemotherapy regimen for advanced disease (cohort 2); and participants who were previously treated for brain metastases and progressed during or following a prior-platinum based chemotherapy regimen for advanced disease (cohort 3). The majority of the patients were enrolled into cohort 2, as two other competing studies were ongoing – “BIRCH” and “OAK” trials. A comparison of outcomes based on modified RECIST (mRECIST) and RECIST v1.1 was also performed. The mRECIST criteria accommodate the possible appearance of new lesions and potential immune-related increases in tumor burden that can appear as progression when RECIST v1.1 is used.

Different PD-L1 selection criteria ([TC2/3 or IC2/3] and IC2/3; Table 1) were employed during the enrollment period for FIR. Overall, the observed prevalence of TC2/3 or IC2/3 tumors was 39%. There was close agreement between mRECIST and RECIST 1.1. In cohort 2, of 93 patients, the ORR was 17% by mRECIST and 16% by RECIST 1.1. In cohort 1, of 31 patients, the ORR was 29% by mRECIST and 26% by RECIST 1.1. Clinical benefit was observed in all cohorts. TC3 and IC3 were independent predictors of response in cohort 2. 95 patients had paired metachronous tumor samples for IHC comparison, which was generally consistent, suggesting that either fresh or archival tissues can be reliably used to assess PD-L1 expression. Atezolizumab showed clinical benefit and an acceptable safety profile in both chemotherapy-naïve and previously treated NSCLC, including patients with known brain metastasis.

The subsequent “POPLAR” study[29] was designed to investigate the efficacy and safety of atezolizumab versus docetaxel in second-line and third-line NSCLC, and to further assess the predictive value of PD-L1 expression levels on tumor cell and tumor-infiltrating immune cells. This was a multicenter, international, randomized, open-label, all-comer phase 2 trial. Patients were stratified by tumor-infiltrating immune-cell PD-L1 expression, previous lines of chemotherapy, and histology. Patients received intravenous atezolizumab (1200 mg fixed dose) or docetaxel (75 mg/m²) q3w on day 1 of each 3-week cycle. The primary endpoint was overall survival in the intention-to-treat population and PD-L1 subgroups. 144 patients were randomly allocated to receive atezolizumab and 143 to receive docetaxel.

At a minimum follow-up of 13 months, atezolizumab significantly improved overall survival compared with docetaxel (12.6 vs 9.7 months; HR 0.73, 95% CI 0.53–0.99; p=0.04).

Progression-free survival was similar between groups (2.7 months with atezolizumab vs 3.0 months with docetaxel; HR 0.94, 95% CI 0.72–1.23). 21 (15%) patients in the atezolizumab group and 21 (15%) patients in the docetaxel group achieved an objective response.

Overall survival in patients with TC0 and IC0 PD-L1 status in the atezolizumab group was similar to that in docetaxel group. Overall survival benefit from atezolizumab increased with increasing PD-L1 expression on tumor cells, tumor infiltrating immune cells, or both (Table 2).

Each tumor cell or tumor-infiltrating immune cell level independently contributed to the improvements in overall survival in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 combined groups. Additionally, patients in the atezolizumab group with PD-L1 expression on tumor cells only (TC1/2/3 and IC0 subgroup) and tumor infiltrating immune cells only (IC1/2/3 and TC0 subgroup) had improved overall survival compared with patients receiving docetaxel. Of note, atezolizumab improved overall survival in both responding and non-responding patients compared with docetaxel, implying that some patients may benefit after RECIST-defined progression.

Overall survival was improved in the atezolizumab group with high *PD-L1*, *PD-1*, *B7.1* and *PD-L2* gene expression. The T-effector-associated and IFN- γ -associated gene signature was associated with PD-L1 expression in tumor-infiltrating immune cells as opposed to tumor cells. Unlike overall survival, improved PFS and ORR with atezolizumab was limited to those patients with the highest level of PD-L1 expression (TC3 or IC3 subgroup). In the atezolizumab group, median overall survival for patients with squamous carcinoma was 10.1 months and for patients with adenocarcinoma was 15.5 months.

Treatment-related grades 3-4 adverse events were observed in 11% in the atezolizumab group versus 39% in the docetaxel group. The most common atezolizumab related grade 3 adverse events were pneumonia (three patients) and increased aspartate aminotransferase (three patients). Potential immune-mediated adverse events, such as pneumonitis, colitis, and hepatitis occurred at low frequencies (<5%) in the atezolizumab group and were generally manageable and reversible. Grade 5 adverse events in the atezolizumab group were cardiac failure (related to study treatment), pneumonia, ulcer hemorrhage, pneumothorax, pulmonary embolism, and embolism (one patient each).

3.2.1. First line therapy in advanced NSCLC—Peters and colleagues[30, 31] have recently reported the results of the “BIRCH” study, a phase II single-arm trial of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected NSCLC. Patients with PD-L1 positive tumors (TC2/3 and/or IC2/3) and without brain metastasis were eligible. They were divided in three cohorts: first-line, second-line, and third-line or more. Here we focus on the results of the cohort 1. The primary endpoint of the study was response rate based on central radiologic review, with secondary endpoints including progression-free and overall survival. A total of 139 first-line patients was included in cohort 1. Treatment-related adverse events were generally similar to those reported in the atezolizumab studies discussed above, with most common adverse events being fatigue (18%) and nausea (10%). Key outcome measures are indicated in Table 3. The median duration of response for patients in cohort 1 of this study was 9.8 months (95% CI, 5.6-NR).

3.3. Phase 3 studies

The “OAK” protocol [32] was the first phase 3 study of an anti-PD-L1 immunotherapy in NSCLC. This was a randomized, open-label, international study in patients who had received one or two previous lines of chemotherapy for stage IIIB/IV NSCLC. Patients with EGFR mutations or an ALK fusion oncogene were additionally required to have received previous FDA-approved tyrosine kinase inhibitor therapy. Patients with treated asymptomatic supra-tentorial CNS metastases were eligible. Patients were stratified by PD-L1 expression (IC0 vs IC1 vs IC2 vs IC3 level), number of previous chemotherapy regimens, and histology. Treatment arms were similar to the aforementioned POPLAR trial. The primary endpoint was overall survival within the intention-to-treat (ITT) population and the PD-L1 TC1/2/3 or IC1/2/3 populations.

Of the final 1225 patients randomly assigned in the total patient population, 609 patients received atezolizumab and 578 patients received docetaxel. Of note, 40% of patients receiving atezolizumab were treated beyond progression, with median treatment duration beyond progression of three cycles. Overall survival was better with atezolizumab relative to docetaxel in both the ITT and TC1/2/3 or IC1/2/3 populations (Table 4). Overall survival was improved in the ITT population with atezolizumab (median 13.8 months) versus docetaxel (median 9.6 months), HR 0.73 (95% CI 0.62-0.87; $p=0.0003$). PFS was similar between atezolizumab and docetaxel in the ITT population (2.8 months [95% CI 2.6-3.0] versus 4.0 months [95% CI 3.3-4.2]). Overall response was also similar between arms, 14% with atezolizumab and 13% with docetaxel, with the exception of the TC3 or IC3 group, which showed a greater benefit with atezolizumab. Median duration of response in the ITT population was notably longer in the atezolizumab group at 16.3 months (95% CI 10.0–not evaluable) compared with 6.2 months (4.9–7.6) in the docetaxel group.

Patients with high PD-L1 expression derived the greatest benefit from atezolizumab, although overall survival was improved regardless of PD-L1 expression levels, even in patients with *PD-L1* gene expression lower than the median.

Grade 3 or 4 adverse events were reported in 37% of patients treated with atezolizumab and 54% of patients treated with docetaxel. Fatigue, nausea, decreased appetite, and asthenia

were the most common atezolizumab-related adverse events of any grade. Immune-related adverse events included pneumonitis (2%), hepatitis, and colitis (<1%). There were no deaths related to atezolizumab.

4. Complementary diagnostic assay

PD-L1 analysis has been a source of substantial research attention and controversy in clinical development of checkpoint immunotherapies. Roche/Ventana[33] have developed a complementary diagnostic for atezolizumab using an immunohistochemistry (IHC) assay and an anti-human PD-L1 rabbit monoclonal antibody (SP142) optimized to detect PD-L1 expression in both tumor cells (TC) and tumor-infiltrating immune cells (IC). The Ventana PD-L1 (SP142) assay was validated for use in FFPE samples of NSCLC in a series of studies addressing sensitivity, specificity, robustness, and precision. In a cohort of > 200 NSCLC samples, concordance between two pathologists was > 90%.

Tumor cells typically show membranous staining with a variably component of cytoplasmic staining. PD-L1-positive tumor-infiltrating ICs were typically seen within some patterns including aggregates towards the periphery of the tumor mass, in stromal bands dissecting the tumor mass, or as single cells scattered in the stroma. PD-L1 scores in patients with multiple specimens were based on the highest score. Specimens were scored as in Tables 1 and 5.

4.1. Challenges in detecting PD-L1 by immunohistochemistry

In an ongoing effort initiated by the American Association for Cancer Research (AACR) and the International Association for the Study of Lung Cancer (IASLC) together with four pharmaceutical companies (Bristol-Meyers Squibb, Merck, Genentech/Roche, and AstraZeneca) and two diagnostic companies (Dako and Ventana), four PD-L1 assays were compared on the same set of tumors - the Blueprint Project[34] - to better understand the similarities and differences between antibodies and platforms. Each IHC assay was developed with a unique primary antibody (clone) against PD-L1, namely, 28-8 (Dako) with nivolumab, 22C3 (Dako) with pembrolizumab, SP263 (Ventana) with durvalumab, and SP142 (Ventana) with atezolizumab.

One concern in comparing PD-L1 antibodies that have been used for IHC analysis is that different antibodies bind to different extracellular and cytoplasmic domains on the PD-L1 protein. The antibodies SP142 and E1L3N bind to the cytoplasmic domain of PD-L1, while other antibodies, including 28-8, 22C3, SP263, and E1J2J all bind to the extracellular domain of the PD-L1. There is a wide difference in the PD-L1 expression measured by the different antibodies. Only the SP142 assay includes a measure of infiltrating PD-L1 positive ICs. Three pathologists, all of whom were experts in interpreting their respective clinical cutoffs of the assays used in this study, independently evaluated all 156 immuno-stained slides from the 39 cases. This analysis revealed that three PD-L1 IHC assays (28-8, 22C3, and SP263) are closely aligned with regard to PD-L1 expression on TCs, whereas SP142 consistently reported fewer TCs expressing PD-L1. All the assays demonstrated PD-L1 expression on ICs, with greater variance than expression on TCs.

Rimm and colleagues[35] further conducted a United-States based study to again compare the performance of available antibodies, assays, and test platforms for the ability to accurately and reliably measure PD-L1 (SP142, 22C3, 28-8, and E1L3N [laboratory-based test]). This study corroborated the results from the aforementioned Blueprint pilot project, demonstrating that the SP142 assay is an outlier and that pathologists are much more consistent at scoring TCs than ICs.

5. Overview of the market and regulatory affairs

Based on the safety and efficacy data of the OAK and POPLAR trials, in October 2016, the FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with *EGFR*-mutant or *ALK*-rearranged tumors should have disease progression on FDA-approved tyrosine kinase inhibitors prior to receiving atezolizumab. The SP142 assay had been previously approved in May 2016, as a complementary diagnostic test for patients with metastatic urothelial carcinoma.

Multiple other agents have been approved or are in active clinical development in this space. Pembrolizumab was the first anti-PD1 therapy to be approved for patients with recurrent metastatic NSCLC, in patients with TCs expression of PD-L1 greater than or equal 1% as determined by an FDA-approved test. Very shortly thereafter, nivolumab was approved for the same indication, without a limitation based on PD-L1 staining. Nivolumab was developed using a slightly more frequent schedule of infusion, every two weeks, versus the three week intervals for atezolizumab and pembrolizumab. In October 2016, the FDA also approved pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors have PD-L1 expression greater than 50%, with no *EGFR* or *ALK* alterations, and no prior systemic treatment. Phase III trials that supported these approvals are summarized in Table 6.

6. Expert commentary and 5-year review

Cancer immunotherapies targeting PD-1 and PD-L1 have revolutionized the treatment of advanced non-small cell lung cancer. The ultimate goal of immunotherapy is to establish a renewable population of highly active tumor-specific T cells that can lyse tumor cells and durably eradicate cancers. Many efforts have been made to define biomarkers to predict the groups of patients that will respond to immunotherapy. Efficacy has been correlated with several factors including the molecular smoking signature, total mutational burden, high neoantigen load, and DNA repair pathway mutations[36, 37, 38, 39]. Pre-existing anti-tumor CD8⁺ T-cells is of utmost importance for therapeutic PD-1/PD-L1 blockade and several groups are studying the value of immune genetic signatures[40, 41].

PD-L1 expression is heterogeneous, dynamic, and can be assessed using a multitude of assays with different characteristics[42]. The lack of consistent homogeneity between assays represents a major limitation for routine clinical use. Nevertheless, PD-L1 expression in tumor remains a key biomarker, correlating with the efficacy of anti-PD-1 and anti-PD-L1 therapies across multiple disease types.

Atezolizumab has improved survival irrespective of PD-L1 status and histology in the treatment of patients with advanced and recurrent NSCLC. An initial concern for possibly reduced anti-tumor efficacy due to lack of PD-L2 blockade was not confirmed. Atezolizumab has demonstrated similar benefit, and a similar toxicity spectrum, to the FDA-approved anti-PD-1 therapies. With the limitations, inherent in PD-L1 assessment methodologies, phase II and III trials of atezolizumab have suggested that expression of PD-L1 on tumor cell and immune cells have non-redundant roles in regulation of anti-tumor immunity and in predicting response to therapy.

One unexpected and somewhat intriguing difference that has been observed between PD-1 and PD-L1 blockade is that female patients demonstrated better outcome than male patients in the subgroup analysis of the phase III atezolizumab trial. This observation is opposite to that of the three previously published anti-PD1 phase 3 trials for recurrent advanced NSCLC, which consistently favored male patients in their subgroup analysis. We acknowledge that these trials had insufficient statistical power to make this comparison, that sex differences were not anticipated or prespecified, and as a result, future studies would need to be conducted to further address this apparent difference. A large body of data has suggested that sex is an important variable in tumor immunopathogenesis and immunotherapy response[43, 44, 45].

For NSCLC patients, whose tumors harbors specific alterations in oncogenic drivers, such as *EGFR* mutation, *ALK* and *ROS1* rearrangement, targeted therapies have offered impressive anti-tumor activity. Unfortunately, resistance almost inevitably develops. In NSCLC mouse models and cell lines harboring *EML4-ALK* rearrangements and *EGFR* mutations, induction of PD-L1 expression due to constitutive oncogenic signaling has been reported[46, 47, 48]. Furthermore, treatment with ALK and EGFR TKIs has been shown to attenuate PD-L1 expression in these models.

However, subsequent clinical reports have found that the frequency of PD-L1 expression among EGFR-mutant patients was low relative to other lung cancer patients, both prior to TKI exposure and at the time of acquired resistance. Also, few EGFR mutant and ALK-positive specimens exhibited both CD8⁺ tumor infiltrating lymphocytes and concomitant PD-L1 expression. Gainor and colleagues[49] observed a low objective response rate in a cohort of 58 patients treated with PD-1/PD-L1 inhibitor (3.6% in *EGFR*-mutant or *ALK*-positive patients versus 23.3% in *EGFR* wild-type and *ALK*-negative/unknown patients; p=0.053). Recent meta-analyses[50] to assess the role of immune checkpoint inhibitors as second-line therapy in *EGFR*-mutant advanced NSCLC showed that immunotherapy does not improve OS over docetaxel in this population.

Prior to introduction of immunotherapeutics, the 5-year survival of metastatic NSCLC was approximately 1%. Reports of long-term efficacy and safety with immune checkpoint inhibitors are limited. Brahmer and colleagues[51] at the 2017 AACR Conference presented updated data on the longest survival follow-up for an immune checkpoint inhibitor in advanced NSCLC, from the original phase I nivolumab dose-escalation and cohort expansion trial (CA209-009; NCT00730639). The 5-year OS in all NSCLC patients (n=129) was 16%. OS rates were similar between histologies and, of the 16 patients who survived, 3

had PD-L1 expression <1% and 2 patients had stable disease and progressive disease as the best overall response. These limited but intriguing results support the potential durability of the immune response, while also underscoring the heterogeneous features of the long-term survivors.

Ongoing research efforts are focused on both better identifying the subset of long-term responders, and attempting to stimulate non-responders to achieve optimal therapeutic benefit. Understanding of the mechanisms of primary and acquired resistance to immune checkpoint inhibitors will help define the future of combination therapies[52, 53, 54]. The evasion of immune attack by cancers is clearly multifactorial, with contributing factors including a lack of strong cancer antigens or epitopes recognized by T cells, minimal activation of tumor-specific T cells, immunosuppressive tumor microenvironment, and other factors[55].

A personalized immunotherapy program may prove to be a keystone of cancer therapy. Components of such a strategy that have been and are actively being explored include pretreatment assessment of several factors including the presence of immune-related biomarkers, PD-L1 expression, quantitative and qualitative assessments of mutation burden, and location and signature of the immune infiltrate. The individual cancer-immune biology may ultimately help tailor the best strategy for each patient.

There are hundreds of ongoing immunotherapy trials, and a subset of those involving atezolizumab is presented in Table 7. Combination of checkpoint inhibitors with chemotherapy and radiation is been tried in order to augment the response rate, and ultimately lead to an improve in overall survival. Numerous additional immunomodulatory pathways as well as inhibitory factors expressed or secreted by myeloid and stromal cells in the tumor microenvironment are potential targets for synergizing with immune checkpoint blockade.

Dual anti-CTLA-4 and anti-PD-1/PD-L1 blockade is the combination that has perhaps been most extensively studied. The rationale for combining these drugs is strong, because these pathways have different mechanisms for inhibiting the function of T cells. Besides removing the competition for the second signal which is required for T cell priming and activation, CTLA-4 blockade reduces the interaction of CD8⁺T cells with T regulatory cells. This approach has demonstrated some unprecedented high response rates, but with a concomitant increase in the frequency and severity of adverse events. As one example, Hellmann and colleagues reported the first results of the “CheckMate 012”[56], an open-label phase 1 study for nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) as first-line treatment of advanced NSCLC. In the cohort of nivolumab 3 mg.kg⁻¹ q2w and ipilimumab 1mg.kg⁻¹ q6w the confirmed ORR was 39% for all-comers and 86% for patients with PD-L1 expression greater than 50%. Grades 3-4 treatment-related adverse events were observed in 33% of the patients.

Given the breath of the emerging immunotherapy field, clinicians should be aware of the unique set of drug-related adverse effects, now known as immune-related adverse events (irAE). Fortunately, most cases can be controlled with drug discontinuation and a stepwise

immunosuppressive approach. Rapid identification of irAEs and prompt initiation of immunosuppression may optimize outcomes[57, 58, 59, 60]. Whereas most irAEs are reversible, endocrinopathies require chronic hormone replacement. Furthermore, the safety of immune checkpoint blockade in patients with underlying autoimmune disorders and interstitial chronic lung disease is unknown, since these patients have been excluded from the clinical trials.

7. Conclusion

The landscape of second-line treatment of patients with NSCLC has three checkpoint inhibitor drugs approved, with similar activities and safety profiles. Only atezolizumab and nivolumab are approved for patients whose tumors have PD-L1 expression <1%, which comprises 30-40% of all NSCLC patients. A head-to-head prospectively comparison between them is unlikely. Immune-related adverse events management requires a close collaboration between oncologists and other specialists, including rheumatologists and endocrinologists. Use of atezolizumab for treatment of chemotherapy naïve Stage IV NSCLC and early-stage NSCLC is being studied. This agent represents a substantial step forward in the treatment of lung cancer patients.

8. Key issues

- Currently approved immunotherapy agents for second line treatment for recurrent metastatic NSCLC without known actionable mutation, irrespective of PD-L1 status, include atezolizumab and nivolumab. Pembrolizumab requires tumor-cells PD-L1 expression ≥ 1%.
- Atezolizumab is a humanized IgG1 antibody anti-PD-L1, modified to limit ADCC, that blocks the interaction of PD-L1 with PD-1 and B7-1.
- Atezolizumab's lack of activity against PD-L2 does not appear to have a major impact on either its activity or safety, relative to those of the PD-1 inhibitors.
- Atezolizumab has improved overall survival over docetaxel, in patients with metastatic NSCLC whose tumor progressed after platinum-based therapy.
- Checkpoint inhibitor therapy in the adjuvant or neo-adjuvant setting is still a focus of ongoing research.
- More investigations are needed to define optimal predictive biomarkers.
- Personalized immunotherapy is a promising tool for cancer therapy.

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* of interest

** of considerable interest

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Figure 1.
Atezolizumab phase 2 and phase 3 studies outline

Table 1

PD-L1 scoring criteria according to SP142 assay.

PD-L1 scoring criteria	TC3	TC2	TC1	TC0	IC3	IC2	IC1	IC0
Tumor cell scoring (%)	50%	5% and <50%	1% and <5%	<1%	-	-	-	-
Tumor-infiltrating immune cell scoring (%)	-	-	-	-	10%	5% and <10%	1% and <5%	<1%

PD-L1 status is determined by the proportion of tumor area occupied by PD-L1 expressing tumor-cells (% TC) or tumor-infiltrating immune cells (% IC) of any intensity. SP142 assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissue.

Table 2

Hazard Ratios for overall survival in PD-L1 subgroups in the POPLAR trial.

	n (%)	HR	95% CI	P value	Median overall survival (months [95% CI])	Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0.49	0.22–1.07	0.068	15.5 (9.8–NE)	15.5 (9.8–NE)	11.1 (6.7–14.4)
TC2/3 or IC2/3	105 (37%)	0.54	0.33–0.89	0.014	15.1 (8.4–NE)	15.1 (8.4–NE)	7.4 (6.0–12.5)
TC1/2/3 or IC1/2/3	195 (68%)	0.59	0.40–0.85	0.005	15.5 (11.0–NE)	15.5 (11.0–NE)	9.2 (7.3–12.8)
TC0 and IC0	92 (32%)	1.04	0.62–1.75	0.871	9.7 (6.7–12.0)	9.7 (6.7–12.0)	9.7 (8.6–12.0)
Intention to treat	287	0.73	0.53–0.99	0.040	12.6 (9.7–16.4)	12.6 (9.7–16.4)	9.7 (8.6–12.0)

Table 3

“BIRCH” efficacy data according to PD-L1 expression - cohort 1

	TC3 or IC3 (High)	TC 2/3 or IC2/3 (Medium and High)
Median OS, months (95% CI)	NE (12.0–NE)	20.1 (20.1–NE)
Median PFS, months (95% CI)	5.6 (2.7–8.3)	5.4 (3.0–6.9)
ORR (95% CI)	31% (20–43)	30% (15–29)

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Table 4

Hazard Ratios for overall survival in PD-L1 subgroups in the OAK trial

	n (%)	HR (95% CI)	P value	Median overall survival	
				Atezolizumab (n=425)	Docetaxel (n=425)
TC3 or IC3	137 (16)	0.41 (0.27–0.64)	0.0001	20.5	8.9
TC2/3 or IC2/3	265 (31)	0.67 (0.49–0.90)	0.008	16.3	10.8
TC1/2/3 or IC1/2/3	463 (54)	0.74 (0.58–0.93)	0.01	15.7	10.3
TC0 and IC0	379 (45)	0.75 (0.59–0.96)	0.02	12.6	8.9
Intention to treat	850 (100)	0.73 (0.62–0.87)	0.0003	13.8	9.6

Table 5

PD-L1 scoring criteria, prevalence and overlap between PD-L1 expression on TCs and tumor-infiltrating ICs.

Overall prevalence			Prevalence in overlapping subgroups	
Subgroup	POPLAR	OAK	Subgroups	POPLAR
TC3 or IC3	16%	16%	TC3 and IC3	<1%
TC2/3 or IC2/3	37%	31%	TC2/3 and IC2/3	7%
TC1/2/3 or IC1/2/3	68%	54%	TC1/2/3 and IC1/2/3	26%
TC0 and IC0	32%	45%	TC0 and IC0	32%

Table 6

Overall survival data from the Phase III trials for the FDA-approved anti-PD-(L)1 drugs.

Trial	Anti-PD-(L)1	Control	n	HR (95% CI)	OS (95% CI)		P value
					Anti-PD-(L)1	Control	
Second-line therapy							
Checkmate 057 (Adeno)[61]	Nivolumab 3mg.kg ⁻¹ q2w	Docetaxel 75 mg/m ² q3w	582	0.73 (0.59–0.89)	12.2m (9.7–15.9)	9.4m (8.1–10.7)	0.002
Checkmate 017 (Squamous)[62]	Nivolumab 3mg.kg ⁻¹ q2w	Docetaxel 75 mg/m ² q3w	272	0.59 (0.44–0.79)	9.2m (7.3–13.3)	6.0m (5.1–7.3)	<0.001
Keynote 010 (PD- L1>1%)[63]	Pembrolizumab 2mg/kg q3w	Docetaxel 75 mg/m ² q3w	687	0.71 (0.58–0.88)	14.9m (10.4–NR)	8.2m (6.4–10.7)	0.0002
OAK[32]	Atezolizumab 1200mg q3w	Docetaxel 75 mg/m ² q3w	850	0.73 (0.62–0.87)	13.8m (11.8–15.7)	9.6m (8.6–11.2)	0.0003
First-line therapy							
Keynote 024 (PD-L1 50%)[64]	Pembrolizumab 200mg q3w	Platinum-base chemotherapy	305	0.6 (0.41–0.89)	NR	NR	0.001

Table 7

Atezolizumab ongoing clinical trials

Clinical trial	Phase	Treatment arms	Inclusion criteria
NCT02013219	1b	Atezo + Erlotinib or Alectinib	<i>EGFR</i> -mutant or <i>ALK</i> -positive Stage IV NSCLC
NCT02486718	3	Atezolizumab vs BSC	Stage IB-III A NSCLC after surgery and adjuvant chemotherapy
NCT02409342	3	Atezo vs chemotherapy	Stage IV NSCLC PD-L1 positive (1L)
NCT02367794	3	Atezo + chemo vs chemotherapy	Stage IV Squamous cell carcinoma (1L)
NCT02657434	3	Atezo + chemo vs chemotherapy	Stage IV Adenocarcinoma (1L)
NCT02927301 2		Neoadjuvant + Adjuvant Atezolizumab	Stage IB-III A NSCLC
NCT02599454	1	Atezolizumab + SBRT	Inoperable Stage I NSCLC
NCT02655822 1/1b		Atezo + CPI-444 (adenosine-A2A receptor inhibitor)	Selected Incurable Cancers
NCT02495636	2	Atezo + CDX-1401	Stage IIIB/IV recurrent NSCLC

Abbreviations: SBRT: Stereotactic Ablative Radiotherapy; Chemo: chemotherapy; BSC: best supportive care; Atezo: atezolizumab