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PRODUCT REVIEW

Product review on the Anti-PD-L1 antibody atezolizumab

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ABSTRACT

Immunotherapy as a therapeutic strategy has seized the narrative throughout clinical oncology over the past few years. Once considered a niche treatment for rare cancers, immunotherapy has quickly emerged as the standard of care for many common cancer types. The remarkable rise is largely due to the development of novel checkpoint inhibitors, specifically, antibodies targeting PD-1 and PD-L1. Offering promising efficacy with a favorable toxicity profile, these agents have been approved for use in several malignancies and are under investigation for many more. One of the more appealing features is the chance for meaningful, durable response – uncharacteristic for most cancer therapies. Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1. Atezolizumab has been approved for use in the treatment of advanced non-small cell lung cancer (NSCLC) and bladder cancer and has shown promising activity in several other types of cancer. Here, we provide a product review for atezolizumab.

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Introduction

The role of the immune system in the development and treatment of malignancy has been studied for decades. Early attempts to enhance an anti-cancer immune response using cytokines were met with significant toxicity, balanced with the potential for long-term disease control.[1] Use of this high-risk, high-reward treatment was initially limited to experienced centers and a subset of patients. With the development of checkpoint inhibitors, immunotherapy could be extended to a larger physician and patient base. Monoclonal antibodies targeting CTLA-4 showed impressive activity that led to the approval of ipilimumab in advanced melanoma.[2,3] However, it was the introduction of monoclonal antibodies targeting Programmed Cell Death Protein-1 (PD-1) or its ligand PD-L1, that brought immunotherapy to a wider patient base. With a much more favorable toxicity profile and activity in multiple cancer types, PD-1 and PD-L1 inhibitors quickly evolved from novel, investigational agents used in relatively uncommon cancers to the first-line standard of care for some of the most common cancers in the world. Atezolizumab is a monoclonal antibody that targets PD-L1, the first PD-L1 inhibitor to receive FDA approval and one whose use is rapidly expanding. While data is still maturing, much is already known about this agent and its evolving role in oncology.

Background

PD-1 is a member of the CD28 immunoglobulin family expressed by CD4+ and CD8+ T cells[4] that interacts with ligands in the B7 family, PD-L1 and PD-L2. PD-L1 (B7-H1, CD274) is a type 1 transmembrane protein expressed on tumor cells, antigen presenting cells (APCs) including dendritic cells, macrophages and B cells, and activated T cells. PD-L2 (B7-DC, CD273) expression, however, is limited to APCs. The interaction of PD-1 with PD-L1 suppresses T cell proliferation and cytokine secretion,[5] inhibiting late phase immune responses.[4,6] Monoclonal antibodies targeting PD-1 can facilitate an anti-tumor immune response and have demonstrated durable responses in a variety of cancer types.[7–14] Antibodies that target PD-L1 would preserve the interaction between PD-1 and its other ligand, PD-L2. PD-L2 may play a role in immune tolerance and effector T cell response.[6] Differences between targeting PD-1 and PD-L1 are of unclear significance, as PD-1 inhibitors have not been directly compared to PD-L1 inhibitors.

Atezolizumab (Genentech/Roche), formerly MPDL3280A and now marketed under the trade name Tecentriq, is a genetically engineered, humanized IgG1 monoclonal antibody to PD-L1 produced in Chinese Hamster Ovary (CHO) cells. Atezolizumab binds to PD-L1 and prevents the interaction between PD-L1 and its receptors PD-1 and B7–1 (or CD80). The Fc region of atezolizumab has been engineered to reduce Fc effector function and minimize antibody-dependent cell-mediated cytotoxicity (ADCC).[15] This prevents antibody mediated hypothetical loss of PD L1 expressing T-effectors cells and hence antitumor activity. In conclusion, atezolizumab immunologically interrupts PD L1 –PD1 axis, hence prevents T cell exhaustion, downstream inhibition of cytokines and late phase immune response. Biologically it avers antibody mediated PD L1 expressing T effector cells annihilation and hence antitumor activity.

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Preclinical studies

PRO304397 is a reverse chimera and mouse IgG2a variant antibody to murine PD-L1. Preclinical studies of PRO304397 in mice and atezolizumab in cynomolgus monkeys[15] revealed a dose-dependent pharmacokinetic profile at doses of 0.5 to 5 mg/kg and an approximately linear profile at doses of 5–20 mg/kg. At doses of 0.5 μg/kg, there is approximately 96% saturation of PD-L1 based on PD-L1 occupancy in peripheral blood lymphocytes. Distribution into tumors increased in a dose-dependent manner

Administration

The recommended dose for atezolizumab is a fixed dose of 1200 mg (approximately 15 mg/kg) given over a 1 hour intravenous infusion with no premedication every 21 days. The optimal duration of treatment is unclear and most clinical trials continued treatment until disease progression or unacceptable toxicity or loss of clinical benefit. Additional data is needed to determine optimal duration of treatment.

Biomarker

The need for a predictive biomarker to guide use of checkpoint inhibitors is readily apparent. In early studies of PD-1 inhibitors in NSCLC, the median duration of response exceeded the median overall survival,[8] suggesting the durable benefit was limited to a subset of patients. Identification of these patients would permit proper delivery of the available checkpoint inhibitors and facilitate study of novel approaches in patients unlikely to respond. The intuitive biomarker is PD-L1 expression, but studies have been challenging. In patients with previously treated non-squamous NSCLC, expression of PD-L1 did correlate with response to nivolumab[8] whereas no such relationship was seen in squamous NSCLC.[7] Adding to the challenge is the presence of multiple assays and approaches for scoring PD-L1 expression, discussed at length elsewhere.[16]

PThe SP-142 Ventana PD-L1 assay has been approved as a complementary diagnostic for atezolizumab. This assay considers expression of PD-L1 on tumor cells (TC) and on tumor infiltrating immune cells (IC). Specimens are scored based on the number of cells with expression, not on intensity (Table 1). The limit of detection (LOD) is 1% for both IC and TC. The IC status does not necessarily correlate with the TC status. In the POPLAR study of patients with NSCLC, 26% of patients had both TC and IC expression but an additional 30% had some IC expression and no TC expression and 11% had TC expression without IC expression.[17] At the highest levels (TC3 and IC3), there was almost no overlap but benefit in both groups. A few patients with lower or no PDL1 expression also benefited from the treatment. The patients with higher PD-L1 expression trended to derive greater benefit but biomarkers with improved sensitivity and specificity are still needed.

Table 1. SP -142 Ventana PD L -1 assay.

Tumor cells PD-L 1 expression (TC PD- L1)		Immune cells PD-L 1 expression (IC PD- L1)	
Grade	% of PD – L1 expression	Grade	% of PD – L1 expression
TC 3	≥ 50	IC 3	≥ 10
TC 2	5–49	IC 2	5–9
TC 1	1–4	IC 1	1–4
TC 0	<1	IC0	<1

Clinical studies

Phase I – monotherapy

A phase I study of atezolizumab explored weight-based dosing levels from 0.01 mg/kg to 20 mg/kg in 277 patients with advanced cancer.[18] Similar to other agents in this class, no maximum tolerated dose was identified. The pharmacokinetic profile was consistent with the expected profile for an IgG1 antibody. The serum half-life was 3 weeks. Drug levels were maintained at a dose of 15 mg/kg and a fixed dose of 1200 mg every 3 weeks was selected for future study.

Atezolizumab was well tolerated as a single agent. The incidence of grade 3–4 treatment related adverse events (AEs) was 12.6% with a low (1%) incidence of immune related grade 3–4 treatment related AEs. Specifically, there were only 3 cases (1.1%) of grade 3–4 aspartate aminotransferase (AST) increase, 3 cases of grade 3–4 alanine aminotransferase (ALT) increase and no cases of grade 3–5 pneumonitis. The response rate (RR) in 175 evaluable patients was 18% with activity seen in multiple tumor types, including non-small cell lung cancer (NSCLC, RR 21%), melanoma (RR 26%) and renal cell carcinoma (RCC, RR 13%). The overall median progression free survival (PFS) was 18 weeks. Based on promising activity, atezolizumab monotherapy was then explored in several disease specific studies and several combination studies were initiated.

Non-small cell lung cancer – monotherapy

Several phase II/III studies (Table 2) assessed the activity of atezolizumab in NSCLC including BIRCH (NCT02031458), FIR (NCT01846416), POPLAR (NCT01903993) and OAK (NCT2008227). In all of these studies, atezolizumab was given at a fixed dose of 1200 mg intravenously every 21 days.

The phase II BIRCH trial[19] included 659 patients with advanced, stage IIIB or IV NSCLC in one of three separate cohorts: first line (1L), second line (2L) and third line (3L). All enrolled patients had tumors expressing PD-L1 in at least 5% of tumor cells or immune cells (TC2/3 or IC2/3), evaluated centrally. The primary endpoint was RR by independent review. Interim results were presented for the three cohorts (1L, n = 139; 2L, n = 268); 3L, n = 252). The RR was 24%, 19% and 19% for 1L, 2L and 3L, respectively. Among patients with strong PD-L1 expression (TC3/IC3), the response rate was higher, at 32%, 25% and 30%, respectively. Responses were durable with a median duration of response of 13.1 months for 1L and 14.1 months for 2L/3L. Median overall survival (OS) was 20.1 months in the treatment naïve cohort and 14.7 months for previously treated patients.

FIR was another single arm phase II study of atezolizumab that also had three cohorts: first line (1L), second line and beyond with no brain metastases, and second line and beyond

Table 2. Results of Phase II/III trials for NSCLC.

		Number of patients (N = 100%)		ORR %		Median PFS, months		OS, months		Median DOR, months	
BIRCH[19]	1L	139		24		7.3		20.1		13.1	
	2L	268		19		2.8		15.5		14.1	
	3L+	252		19		3.0		13.2		14.1	
FIR[20]	1L	31		29		39		NR		NR	
	2L+	71		17		35		NR		12	
	2Lb+	12		12		NE		NR		NR	
OAK[22]		Atz	Dox	Atz	Dox	Atz	Dox	Atz	Dox	Atz	Dox
	ALL	425	425	14	13	2.8	4.0	13.8	9.6	16.3	6.2
	IC-TC 0	180	199	7.8	10.6	2.6	4.0	12.6	8.9	NE	6.2
	IC-TC 1/2/3	241	222	17.8	16.2	2.8	4.1	15.7	10.3	16.0	6.2
	IC-TC 2/3	129	136	22.5	12.5	3.6	4.1	16.3	10.8	14.7	9.2
	IC-TC 3	72	65	30.6	10.8	3.3	4.2	20.5	8.9	12.5	6.3
POPLAR[17]		Atz (144)	Dox (143)	Atz	Dox	Atz	Dox	Atz	Dox	Atz	Dox
	ALL	287		14.6	14.7	2.7	3.0	12.6	9.7	14.3	7.2
	IC-TC 0	92		7.8	9.8	1.7	4.1	9.7	9.7	NR	NR
	IC-TC 1/2/3	195		18.3	16.7	2.8	3.0	15.5	9.2	NR	NR
	IC-TC 2/3	105		22.0	14.5	3.4	2.8	15.1	7.4	NR	NR
	IC-TC 3	47		37.5	13.0	7.8	3.9	15.5	11.1	NR	NR

NR- Not reported; NE- Not evaluable; Atz- Atezolizumab; Dox- Docetaxel; ORR –Overall response rate; PFS- Progression free survival; OS- Overall survival; DOR- Duration of response; L- Line of treatment; b- treated asymptomatic brain metastases; IC –Immune cell; TC- Tumor cell.

with treated brain metastases. Eligible patients were PD-L1 positive by central review using the SP142 antibody (TC2/3, IC2/3). An interim report[20] noted a RR of 29% in the first line cohort, 17% in the pretreated patients with no brain metastases, and 17% in the pretreated patients with treated brain metastases, though the sample size was small (n = 31, n = 71, n = 12, respectively). Responses were higher in the TC3/IC3 patients.

With promising results from single arm studies, the phase II randomized POPLAR trial was launched comparing atezolizumab to docetaxel (75 mg/m^2 every 3 weeks) in patients with NSCLC previously treated with platinum-based chemotherapy.[17] Atezolizumab continued until loss of clinical benefit in the absence of unacceptable toxicity and docetaxel continued until disease progression or unacceptable toxicity. The study randomized 287 patients with 1–2 prior lines of therapy. PD-L1 expression was not required but patients were stratified by PD-L1 status as well as histology and number of prior lines of therapy. The primary endpoints were OS in the intention-to-treat (ITT) population and the PD-L1 subgroups; no crossover from docetaxel to atezolizumab was permitted though 7 patients received subsequent PD-1 or PD-L1 inhibitors. The study met its primary endpoint, as atezolizumab improved OS compared with docetaxel (HR 0.73, 95% CI 0.53–0.99, p = 0.04) in the ITT analysis. The median OS with atezolizumab was 12.6 months compared to 9.7 months with docetaxel. The improvement was more pronounced with greater PD-L1 expression. In the TC2/3 and IC2/3 subgroup (HR 0.54, 05% CI 0.33–0.89) and the TC1/2/3 and IC1/2/3 subgroup (HR 0.59, 95% CI 0.40–0.85), survival was superior with atezolizumab compared to docetaxel while in the TC0 and IC0 subgroup, survival was similar in both arms. PD-L1 expression did not predict docetaxel efficacy. The PFS with atezolizumab was 2.7 months, similar to the PFS of 3.0 months with docetaxel. The response rate in both arms was 15%, though responses were much more durable with atezolizumab (14.3 months vs. 7.2 months) and atezolizumab improved survival in patients who achieved a response and those who did not. Outcomes for 57 patients who continued atezolizumab beyond RECIST progression were presented.[21] Among these patients, 14% had achieved a subsequent response and 33% achieved stable disease after their initial progression. The OS from progression was 11.1 months in patients who continued atezolizumab after progression (n = 57) and 8.3 months in the patients who received an alternate therapy (n = 30), though there are many confounders in this type of analysis. Patients in the docetaxel arm who received subsequent therapy after progression (n = 46) had an OS of 9.6 months from the time of progression.

In POPLAR, atezolizumab had a favorable toxicity profile. Grade 3–4 AEs were less common with atezolizumab (40% vs. 53%) as were treatment-related grade 3–4 AEs (11% vs. 39%). Treatment related AEs that led to dose modification or interruption were also less common with atezolizumab (11% vs. 24%) and discontinuation due to AEs was seen in only 1% of patients receiving atezolizumab, compared to 18% with docetaxel. There was 1 grade 5 treatment related AE in the atezolizumab arm (cardiac failure) and 3 in the docetaxel arm.

Table 3. Results of IMvigor 210; Phase II study of atezolizumab as a single agent in locally advance or metastatic bladder cancer patients.

	Number of patients (N −100%)	Any Grade TrAEs(%)	Grade ≥3 TrAEs(%)	OS, months	Median PFS, months	ORR(%)
Treatment naïve and cisplatin ineligible[24]	119	66	16	15.9	2.7	23
Progressed on or following platinum-based chemotherapy[25]	310	69	16	7.9	2.1	45

ORR –Overall response rate; PFS- Progression free survival; OS- Overall survival; TrAES- Treatment related adverse events.

Immune related AEs with atezolizumab were noted but were uncommon: increased AST in 4%, increased ALT in 4%, pneumonitis in 3%, and colitis in 1%.

The randomized phase III OAK study randomized 850 patients to atezolizumab or docetaxel 75 mg/m^2 every 3 weeks.[22] Similar to POPLAR, eligible patients had stage IIIB or IV NSCLC with 1–2 prior lines of therapy (including platinum-based chemotherapy). PD-L1 expression was not required; patients were stratified by PD-L1 expression, histology and number of prior lines of therapy (1 vs. 2). The co-primary endpoints were OS in the ITT population and the PD-L1 positive cohort (TC1/2/3 or IC1/2/3). The study also met its primary endpoint. In the ITT population, OS was better with atezolizumab compared to docetaxel (13.8 months vs. 9.6 months; HR 0.73, 95% CI 0.62–0.87, p = 0.0003). Atezolizumab was also superior to docetaxel in the PD-L1 positive population (15.7 months vs. 10.3 months; HR 0.74, 95% CI 0.58–0.93, p = 0.0102). The greatest benefit was noted in patients with the highest PD-L1 expression (TC3 or IC3), with a median OS of 20.5 months with atezolizumab vs. 8.9 months with docetaxel. However, in the TC0 and IC0 subgroup, atezolizumab was still superior with a median OS of 12.6 months vs. 8.9 months. Of note, 17% of patients in the docetaxel arm received subsequent immunotherapy. Subsequent chemotherapy was given to 41% of the patients in the atezolizumab arm and 31% in the docetaxel arm. While OS was superior with atezolizumab, PFS was similar in both arms (2.8 months with atezolizumab vs. 4.0 months with docetaxel; HR 0.95, 95% CI 0.82–1.10) supporting the challenges of PFS as a useful endpoint with immunotherapy. The RR was similar in the two arms (14% with atezolizumab vs. 13% with docetaxel) but the duration of response was much greater with atezolizumab (16.3 months vs. 6.2 months). Predefined subgroup showed atezolizumab was superior to docetaxel regardless of histology, presence of treated CNS metastases and smoking status but no significant difference was seen in the subgroup of patients with a sensitizing mutation in *EGFR* (HR 1.24, 05% CI 0.71–2.18).

Consistent with prior experience, atezolizumab offered a superior safety profile to docetaxel. The most common atezolizumab-related AEs of any grade were fatigue (14%), nausea (9%), decreased appetite (9%) and asthenia (8%). Grade 3–4 treatment related AEs were seen in 15% of patients treated with atezolizumab and 43% of patients with docetaxel. The incidence of immune-mediated AEs was low including pneumonitis (1% any grade, <1% grade 3), hepatitis (<1%), and colitis (<1%). AEs leading to discontinuation were noted in 8% of patients with atezolizumab and 19% of patients with docetaxel. Based on efficacy and safety in the OAK and POPLAR studies, atezolizumab was approved for use in patients with NSCLC after progression on platinum-based chemotherapy regardless of PD-L1 status.

Bladder cancer – monotherapy

The phase I study of atezolizumab also demonstrated promising efficacy in a cohort of patients with previously treated urothelial bladder cancer.[23] Entry into the cohort was initially limited to patients with PD-L1 expression on tumor infiltrating immune cells but this requirement was later removed. Ultimately, 68 patients were treated in this cohort. The median duration of treatment was 65 days and atezolizumab was well tolerated. While 57% of patients reported a treatment related AE, only 4% were grade 3 in severity (one case each of asthenia, thrombocytopenia and hypophosphatemia). The most common immune-mediated AEs reported were decreased appetite (only grade 1–2) and fatigue (only grade 1–2). The overall response rate was 26% with a higher response rate in patients with higher PD-L1 expression (IC2/3 RR 43%) than those with low or no expression (IC/1 RR 11%). Among patients with IC2/3 tumors and a minimum of 12 weeks of follow up, the RR was 52%. PD-L1 expression on tumor cells did not correlate with response in this study. The efficacy seen in this study prompted a larger phase II study, IMvigor 210, which explored the efficacy of atezolizumab in treatment naïve patients ineligible for cisplatin therapy (cohort 1) and patients previously treated with platinum-based chemotherapy (cohort 2), irrespective of PD-L1 expression (Table 3).

In cohort 1 of IMvigor 210, treatment naïve patients with advanced urothelial cancer who were ineligible for cisplatin were given atezolizumab at a dose of 1200 mg every 3 weeks until progression.[24] Cisplatin ineligibility was defined as a glomerular filtration rate between 30–60 mL/min, grade 2 or higher hearing loss, grade 2 or higher neuropathy or an ECOG performance status of 2. In this cohort, 119 patients were treated with atezolizumab with a median treatment duration of 15 weeks. The safety profile was comparable to other studies. Treatment related AEs seen in at least 10% of patients included fatigue, diarrhea and pruritis. Grade 3–4 treatment related AEs were seen in 16% of patients including fatigue (3%), increased ALT (3%), increased AST (3%) and there was one treatment related grade 5 event (sepsis). The primary endpoint was RR which was 23% overall with a 9% complete response (CR) rate. The median time to response was 2.1 months though late responses were noted and the duration of response had not yet been reached. Responses were seen in both PD-L1 positive and negative tumors. The median OS was 15.9 months though the median PFS was only 2.7 months. These data led to the approval of atezolizumab for cisplatin-ineligible patients with advanced urothelial bladder cancer.

Cohort 2 of IMvigor 210 included patients with advanced urothelial bladder cancer who had progressed after platinum-based chemotherapy.[25] In this cohort, 310 patients were treated with atezolizumab 1200 mg every 3 weeks until progression. Median duration of treatment in this cohort was 12 weeks. Treatment related AEs were seen in 69% of patients, though only 16% were grade 3–4 and there were no treatment related deaths. Fatigue was the most common grade 3–4 treatment related AE (2%). Immune mediated AEs (any grade) were seen in 7% of patients including 2 cases each (1%) of pneumonitis, increased ALT, increased AST, rash and dyspnea. The overall RR was 15% but RR was higher in patients with PD-L1 expression. In the IC2/3 group, RR was 26% and in the IC1/2/3 group, the RR was 18%. There was also a 5% rate of CR which was higher in the IC1/2/3 group (6%) and the IC2/3 group (11%). These data supported the approval of atezolizumab for advanced urothelial cancer following progression on platinum-based chemotherapy.

Triple-negative breast cancer – monotherapy

Triple-negative breast cancer (lacking expression of estrogen receptor and progesterone receptor and with no overexpression or amplification of HER2) continues to be an area of unmet need and while there are no approved immunotherapy agents for this disease, the prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer provides rationale for their study.[26] An expansion cohort of the phase I study of atezolizumab included patients with triple-negative breast cancer. Patients received atezolizumab 15 mg/kg or 20 mg/kg (later changed to 1200 mg) every 3 weeks for 1 year. Initially, enrollment was limited to TC2/3 or IC2/3 patients but the study was modified to include patients with any PD-L1 status. Preliminary results on 115 safety-evaluable (112 efficacy-evaluable) patients were recently presented.[27] Patients were heavily pretreated with a median of 7 prior lines of therapy (range 0–21), though 17% were treatment naïve. The safety profile was similar to that seen in other diseases, with grade 3–5 treatment related AEs seen in 13% of patients but only 3% of patients withdrawing from treatment due to an AE. The RR by RECIST version 1.1 criteria was 10% overall, 13% in the IC2/3 subgroup (n = 71) and 5% in the IC0/1 subgroup (n = 37). The RR was 26% in treatment naïve patients (n = 19). As expected, responses were durable with a median duration of response of 21.1 months. With a median follow-up of 15.2 months, median OS was 9.3 months and 1-year OS was 41%.

RCC

RCC has historically been considered an immunogenic tumor and responses to atezolizumab were noted in the phase I study. A randomized phase II study (NCG01984242) explored its activity in treatment naïve RCC. Patients were randomized to receive atezolizumab 1200 mg with the anti-VEGF-A monoclonal antibody bevacizumab 15 mg/kg every 3 weeks, atezolizumab alone, or sunitinib 50mg daily for 4 out of 6 weeks. Crossover to atezolizumab plus bevacizumab was permitted. Interim results reported a RR of 32% with atezolizumab and bevacizumab, 25% with atezolizumab alone and 29% with sunitinib.[28] In PD-L1 positive patients (IC1/2/3), the response rates were 46%, 28% and 27%, respectively. A phase III study is ongoing (NCT02420821).

Phase I – chemotherapy/biologic combinations

While atezolizumab and other checkpoint inhibitors offer the potential for durable disease control and are often better tolerated and more effective than cytotoxic chemotherapy, only a minority of patients achieve a response. In an effort to expand this benefit to a larger patient population, combination strategies are in development. Combining atezolizumab with cytotoxic chemotherapy is one approach. Despite many preconceptions, the relationship between cytotoxic chemotherapy and the immune system is complex and not necessarily antagonistic.[29] Cytotoxic chemotherapy can promote an antitumor immune response through several mechanisms including depletion of myeloid derived suppressor cells,[30] promoting a shift from protumorigenic M2 macrophages to antitumorigenic M1 macrophages,[31] increasing intratumoral CD8 T cells,[32] enhancing T cell proliferation,[33] upregulating MHC class I,[34] and increasing sensitivity of tumor cells to immune mediated apoptosis.[35,36]

A phase Ib study exploring the safety and preliminary efficacy of atezolizumab combinations included a cohort of patients with treatment naïve NSCLC who received atezolizumab with one of three platinum doublet regimens: carboplatin plus paclitaxel, carboplatin plus pemetrexed or carboplatin plus nab-paclitaxel.[37] Patients received 4–6 cycles of chemotherapy followed by maintenance atezolizumab (1200 mg fixed dose) until unacceptable toxicity or loss of clinical benefit. Patients receiving carboplatin plus pemetrexed could continue pemetrexed maintenance therapy. Preliminary results on the first 37 patients were presented and there was no apparent exacerbation of expected chemotherapy associated AEs though there was no control arm in this non-randomized study. The overall RR was 67% including 60% with carboplatin plus paclitaxel, 75% with carboplatin plus pemetrexed and 62% with carboplatin plus nab-paclitaxel including a 23% CR rate.

Another cohort of the same study combined atezolizumab with nab-paclitaxel in patients with metastatic triple negative breast cancer.[38] Preliminary results from 32 patients showed a favorable safety profile with no dose limiting toxicities. The overall confirmed RR was 42% but varied by line of therapy. In the front-line setting (n = 9), the RR was 67%, higher than in second line (25%, n = 8) and in third line and beyond (29%, n = 7). Correlative biomarker studies included analysis of circulating activated CD8+ T cells and nab-paclitaxel was not found to impact the proliferation of these cells. An ongoing phase III trial in treatment naïve small cell lung cancer is comparing carboplatin plus etoposide with or without atezolizumab.[39] Randomized trials comparing chemotherapy with atezolizumab versus chemotherapy alone are underway and will further inform any potential benefit with this strategy.

Bevacizumab has been shown to enhance T cell infiltration in preclinical studies. A combination of atezolizumab with bevacizumab was explored in a separate cohort of the above study and preliminary outcomes were reported for a subset of patients with metastatic colorectal cancer with microsatellite instability (MSI-high).[40] Patients received atezolizumab 1200 mg with bevacizumab 15 mg/kg every 3 weeks. In this subset, the RR was 30% and 40% of patients experienced a treatment related AE though only one led to discontinuation of atezolizumab. A combination of FOLFOX, bevacizumab and atezolizumab has also been explored in patients with treatment naïve, metastatic colorectal cancer.[41] The unconfirmed RR was 44% (8/18) in a preliminary report though more mature data are needed.

While combinations of atezolizumab with chemotherapy and/or biologics show promise, it is difficult to make significant conclusions without comparator arms and until data are more mature.

Phase I – immunotherapy combinations

Another appealing combination strategy is to pair atezolizumab with other immune modulators. These data are also maturing but have shown some promise. Cobimetinib is a potent, orally bioavailable MEK inhibitor and preliminary studies have

shown that MEK inhibition can increase intratumoral T cell accumulation and upregulate MHC class I.[42] The combination of atezolizumab and cobimetinib was explored with preliminary results reported for the cohort with advanced colorectal cancer.[43] No dose limiting toxicities were noted in the first 23 patients; grade 3 treatment related AEs included diarrhea (9%), fatigue (4%), rash (4%), nausea (4%), AST increase (4%), and vomiting (4%). There were no treatment related grade 4 or 5 AEs. The confirmed RR was 17%, higher in patients with a KRAS mutation (20%). MOXR0916 is an OX40 agonist that can stimulate effector T cells and reduce regulatory T cells. A combination of MOXR0916 with atezolizumab is being explored and a report of safety data reported no dose limiting toxicities, no grade 4/5 treatment related AEs and no AEs leading to study discontinuation.[44] Atezolizumab has also been combined with the adenosine 2A receptor antagonist, CPI-444.[45] The combination of CPI-444 with atezolizumab was well tolerated and a disease control rate of 39% (n = 14) was reported which included 2 patients with a partial response and regression in patients refractory to prior PD-1 or PD-L1 therapy.

Regulatory summary

Atezolizumab is approved by the US FDA for two disease types, NSCLC and urothelial bladder cancer. Atezolizumab was granted accelerated approval for locally advanced or metastatic urothelial carcinoma following progression on platinum chemotherapy. The approval was granted on May 18th, 2016, based on IMvigor 210, cohort 2. On April 17, 2017, its approval was then extended to cisplatin-ineligible patients based on IMvigor, cohort 1. Atezolizumab was also approved for the treatment of metastatic NSCLC who progressed on platinum chemotherapy. This approval, given on May 18th, 2016, was based on the OAK and POPLAR studies.

Conclusion

Atezolizumab was the first monoclonal antibody targeting PD-L1 to be approved for clinical use. Its favorable safety profile and promising efficacy have led to approval for the treatment of advanced NSCLC and urothelial bladder cancers. Ongoing studies will help define its role in the treatment of other malignancies and in various clinical setting, both as monotherapy and in combination with other therapeutic interventions.

Commercial Issues

Practically, atezolizumab competes with nivolumab (BMS) and pembrolizumab (Merck) in the NSCLC space, as well as other agents likely to gain regulatory approval soon. While both atezolizumab and nivolumab are approved in the second line setting for all comers, regardless of PDL1 status, pembrolizumab is currently approved for first line with chemotherapy, regardless of PD-L1 status, as well as first line and second as single agent for PDL >50% based on the Dako 22C3 PDL assay. Furthermore, studies are ongoing with other combination immunotherapy agents as well (e.g. nivolumab/ipilumimab, and durvalumab/tremelumimab. Because of the differences across studies and with each study enrolling different patient populations, it will make cross trial comparisons difficult, and practically result in different drugs approved for different situations, as well as a very complicated, competitive commercial landscape.

Expert opinion

Atezolizumab has displayed notable clinical activity in patients with advance NSCLC and bladder cancer with relatively low toxicity. Similar to other PD 1 checkpoint inhibitor, response are still low but durable. Further studies are needed to increase response with immunotherapy and identify patient population that going to benefit from the treatment.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

1. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. J Immunol. 2014;192(12):5451–8. doi:10.4049/jimmunol.1490019. PMID:24907378.
2. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, Lebbe C, Baurain JF, Testori A, Grob JJ, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517–26. doi:10.1056/NEJMoa1104621. PMID:21639810.
3. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23. doi:10.1056/NEJMoa1003466. PMID:20525992.
4. Iwai Y, Hamanishi J, Chamoto K, Honjo T. Cancer immunotherapies targeting the PD-1 signaling pathway. J Biomed Sci. 2017;24(1):26. doi:10.1186/s12929-017-0329-9. PMID:28376884.
5. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000;192(7):1027–34. doi:10.1084/jem.192.7.1027. PMID:11015443.
6. Rozali EN, Hato SV, Robinson BW, Lake RA, Lesterhuis WJ. Programmed death ligand 2 in cancer-induced immune suppression. Clin Dev Immunol. 2012;2012:656340. doi:10.1155/2012/656340. PMID:22611421.
7. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35. doi:10.1056/NEJMoa1504627. PMID:26028407.
8. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627–39. doi:10.1056/NEJMoa1507643. PMID:26412456.
9. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–50. doi:10.1016/S0140-6736(15)01281-7. PMID:26712084.
10. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–1833. doi:10.1056/NEJMoa1606774. PMID:27718847.

11. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, Saba NF, Weiss J, Wirth L, Sukari A, et al. Pembrolizumab for Platinum- and Cetuximab-refractory head and neck cancer: Results from a single-arm, Phase II study. J Clin Oncol. 2017;35(14):1542–1549. doi:10.1200/JCO.2016.70.1524. PMID:28328302.
12. Ferris RL, Blumenschein G, Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–1867. doi:10.1056/NEJMoa1602252. PMID:27718784.
13. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J, Snyder ES, Ricart AD, Balakumaran A, Rose S, et al. Programmed Death-1 Blockade with pembrolizumab in patients with classical Hodgkin Lymphoma after Brentuximab Vedotin failure. J Clin Oncol, 2016;34(31):3733–3739. doi:10.1200/JCO.2016.67.3467.
14. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, Armand P, Fanale M, Ratanatharathorn V, Kuruvilla J, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016;17(9):1283–94. doi:10.1016/S1470-2045(16)30167-X. PMID:27451390.
15. Deng R, Bumbaca D, Pastuskovas CV, Boswell CA, West D, Cowan KJ, Chiu H, McBride J, Johnson C, Xin Y, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs. 2016;8(3):593–603. doi:10.1080/19420862.2015.1136043. PMID:26918260.
16. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, Richardson W, Towne P, Hanks D, Vennapusa B, et al. PD-L1 immunohistochemistry assays for lung cancer: Results from Phase 1 of the Blueprint PD-L1 IHC assay comparison project. J Thorac Oncol. 2017;12(2):208–222. doi:10.1016/j.jtho.2016.11.2228. PMID:27913228.
17. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837–46. doi:10.1016/S0140-6736(16)00587-0. PMID:26970723.
18. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563–7. doi:10.1038/nature14011. PMID:25428504.
19. Wakelee H, Patel JD, Heist R, Balmanoukian A, Besse B, Felip E, Carcereny Costa E, Chow LQ, Koczywas M, Garassino MC, et al. ORAL01.04: Phase II Trial of Atezolizumab for patients with PD-L1-selected advanced NSCLC (BIRCH): Updated efficacy and exploratory biomarker results: Topic: Medical oncology. J Thorac Oncol. 2016;11(11S):S251–S252. doi:10.1016/j.jtho.2016.09.009. PMID:27969443.
20. Spigel DR, et al. Clinical activity and safety from a phase II study (FIR) of MPDL3280A (anti-PDL1) in PD-L1–selected patients with non-small cell lung cancer (NSCLC). J Clin Oncol. 2015;33(suppl):8028.
21. Mazieres J, Fehrenbacher L, Rittmeyer A, Spira AI, Park K, Smith DA. Non-classical response measured by immune-modified RECIST and post-progression treatment effects of atezolizumab in 2L/3L NSCLC: results from the randomized phase II study POPLAR. J Clin Oncol. 2016;34(suppl):9032.
22. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–265. doi:10.1016/S0140-6736(16)32517-X. PMID:27979383.
23. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng SL, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558–62. doi:10.1038/nature13904. PMID:25428503.
24. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67–76. doi:10.1016/S0140-6736(16)32455-2. PMID:27939400.
25. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909–20. doi:10.1016/S0140-6736(16)00561-4. PMID:26952546.
26. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, Martino S, Wang M, Jones VE, Saphner TJ, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2014;32(27):2959–66. doi:10.1200/JCO.2013.55.0491. PMID:25071121.
27. Schmid P, Cruz C, Braiteh FS, Eder JP, Tolaney S, et al. Atezolizumab in metastatic TNBC (mTNBC): Long-term clinical outcomes and biomarker analyses. Proceedings of the 107th Annual Meeting of the American Association for Cancer Research. 2017;2017(Washington, DC):2986.
28. McDermott DF, Atkins MB, Motzer RJ, Rini BI, Escudier BJ, Fong L. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). J Clin Oncol. 2017;35(suppl 6S):431. doi:10.1200/JCO.2017.35.6_suppl.431.
29. Antonia SJ, Larkin J, Ascierto PA. Immuno-oncology combinations: a review of clinical experience and future prospects. Clin Cancer Res. 2014;20(24):6258–68. doi:10.1158/1078-0432.CCR-14-1457. PMID:25341541.
30. Ko HJ, Kim YJ, Kim YS, Chang WS, Ko SY, Chang SY, Sakaguchi S, Kang CY. A combination of chemoimmunotherapies can efficiently break self-tolerance and induce antitumor immunity in a tolerogenic murine tumor model. Cancer Res. 2007;67(15):7477–86. doi:10.1158/0008-5472.CAN-06-4639. PMID:17671218.
31. Fridlender ZG, Sun J, Singhal S, Kapoor V, Cheng G, Suzuki E, Albelda SM. Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms. Mol Ther. 2010;18(11):1947–59. doi:10.1038/mt.2010.159. PMID:20683443.
32. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res. 2003;63(15):4490–6. PMID:12907622.
33. Lesterhuis WJ, Punt CJ, Hato SV, Eleveld-Trancikova D, Jansen BJ, Nierkens S, Schreibelt G, de Boer A, Van Herpen CM, Kaanders JH, et al. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. J Clin Invest. 2011;121(8):3100–8. doi:10.1172/JCI43656. PMID:21765211.
34. Wan S, Pestka S, Jubin RG, Lyu YL, Tsai YC, Liu LF. Chemotherapeutics and radiation stimulate MHC class I expression through elevated interferon-beta signaling in breast cancer cells. PLoS One. 2012;7(3):e32542. doi:10.1371/journal.pone.0032542. PMID:22396773.
35. Menard C, Martin F, Apetoh L, Bouyer F, Ghiringhelli F. Cancer chemotherapy: not only a direct cytotoxic effect, but also an adjuvant for antitumor immunity. Cancer Immunol Immunother. 2008;57(11):1579–87. doi:10.1007/s00262-008-0505-6. PMID:18369619.
36. de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res. 2014;20(21):5384–91. doi:10.1158/1078-0432.CCR-14-1298. PMID:25204552.
37. Liu SV, Powderly JD, Ross Camidge D, Ready N, Suk Heist R, Hodi FS, Giaccone G, Liu B, Wallin J, Funke RP, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based

doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2015;33:8030.
38. Adams S, Diamond JR, Hamilton EP, Pohlmann PR, Tolaney SM, Molinero L. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 2016;34(suppl):1009.
39. Horn L, Mansfield AS, Reck M, Mok T, Spira AI, Tang X. Phase I/III trial of atezolizumab with carboplatin and etoposide in ES-SCLC in first-line setting (IMpower133). J Clin Oncol. 2017;35(suppl):TPS8584.
40. Hochster HS, et al. Efficacy and safety of atezolizumab (atezo) and bevacizumab (bev) in a phase Ib study of microsatellite instability (MSI)-high metastatic colorectal cancer (mCRC). J Clin Oncol. 2017;35(suppl 4S):673. doi:10.1200/JCO.2017.35.4_suppl.673..
41. Bendell JC, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) and/or FOLFOX in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol. 2015;33 (suppl 3):704. doi:10.1200/jco.2015.33.3_suppl.704..
42. Ebert PJ, Cheung J, Yang Y, McNamara E, Hong R, Moskalenko M, Gould SE, Maecker H, Irving BA, Kim JM, et al. MAP kinase inhibition promotes T Cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity. 2016;44(3):609–21. doi:10.1016/j.immuni.2016.01.024. PMID:26944201.
43. Bendell J, Kim TW, Goh BC, Wallin J, Oh D-Y, Han SW, et al. Clinical activity and safety of cobimetinib and atezolizumab in colorectal cancer. J Clin Oncol. 2016;34(suppl):3502. PMID:27458302.
44. Infante JR, Hansen AR, Pishvaian MJ, Man Chow LQ, McArthur GA, Bauer TM. A phase Ib dose escalation study of the OX40 agonist MOXR0916 and the PD-L1 inhibitor atezolizumab in patients with advanced solid tumors. J Clin Oncol. 2016;34(suppl):101.
45. Emens LA, Powderly J, Fong L, Brody J, et al. CPI-444, an oral adenosine A2A receptor (A2AR) antagonist, demonstrates clinical activity in patients with advanced solid tumors. Proceedings of the 108th Annual Meeting of the American Association for Cancer Research. 2017;2017(Washington, DC). Oral presentation-CT119.