Urothelial carcinoma (also known as transitional-cell carcinoma) is the most common subtype of bladder cancer, accounting for more than 90% of bladder cancer diagnoses in the United States. In 2016, nearly 77,000 cases of bladder cancer were expected to be diagnosed in the United States, and >16,000 people were estimated to die from this disease. The incidence of bladder cancer increases with age, with a median age of 73 years at diagnosis.

Bladder cancer is more common in men than in women and is the fourth most common cancer in men, after prostate, lung, and colorectal cancer. Although not common in women, those diagnosed with bladder cancer have a worse prognosis than men. The 5-year relative survival rate for localized disease is 70%, which decreases to 5% for distant disease.

High recurrence rates, intensive surveillance strategies, and expensive treatments for bladder cancer significantly contribute to its medical costs. In 2010, bladder cancer was the ninth most costly cancer in the United States, with cumulative costs of $4 billion.

Treatment of locally advanced and metastatic bladder cancer has remained unchanged for the past several decades. Platinum-based and gemcitabine-containing chemotherapy regimens are used for the initial treatment of advanced-stage disease, and no specific agent or regimen is considered standard therapy in the relapsed setting.

For patients with relapsed bladder cancer, the current National Comprehensive Cancer Network guidelines prioritize participation in clinical trials.

Data show that several types of solid tumors are vulnerable to checkpoint inhibition, including bladder cancer. The immune system recognizes foreign proteins (antigens) as abnormal and destroys them, while protecting “self”-tissue. Immune checkpoints, including programmed-cell death (PD)-1 and PD ligand 1 (PD-L1), are pathways that are hardwired into the immune system to allow self-tolerance. By blocking these immune checkpoint pathways, novel immuno-oncology agents can strengthen the ability of tumor-infiltrating T-lymphocytes (T-cells) to recognize the danger associated with cancer cells and subsequently remove them.

**Lung Cancer**

Lung cancer is the second most common cancer in the United States, with an estimated 222,500 new cases projected for 2017. Non–small-cell lung cancer (NSCLC) accounts for approximately 80% to 85% of all cases of lung cancer, and claims more lives than any other type of cancer; NSCLC is responsible for approximately 25% of all cancer deaths in the United States.

Although the 5-year survival rate for localized lung cancer is 55%, only 16% of patients with lung cancers are diagnosed at this early stage. Among lung cancer cases (all stages) that were diagnosed between 2005 and 2011, the 1-year and 5-year relative survival rates were 44% and 17%, respectively. Lung cancer is the fifth costliest cancer in the United States—the total estimated national expenditure for lung cancer in 2016 exceeded $13 billion.

**Atezolizumab Approved for Bladder and Lung Cancers**

On May 18, 2016, the US Food and Drug Administration (FDA) approved atezolizumab (Tecentriq; Genentech), a PD-L1 inhibitor administered via intravenous (IV) infusion, for the treatment of patients with locally advanced or metastatic urothelial carcinoma that progressed during or after platinum-containing chemotherapy, and for patients whose disease progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Concurrently, the FDA approved the Ventana PD-L1 (SP142) assay, a companion diagnostic test that detects the expression of PD-L1 levels on the tumor, which can help clinicians identify patients who would benefit most from atezolizumab therapy.

This approval was done using the FDA’s accelerated approval program.

On October 18, 2016, atezolizumab received an FDA
Table 1  Atezolizumab Efficacy in Patients with Advanced Bladder Cancer

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>All patients (N = 310)</th>
<th>Patients with PD-L1 expression&lt;5% (N = 210)</th>
<th>Patients with PD-L1 expression≥5% (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF-assessed confirmed responses, N</td>
<td>46</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Objective response rate, %</td>
<td>14.8 (95% CI, 11.1-19.3)</td>
<td>9.5 (95% CI, 5.9-14.3)</td>
<td>26 (95% CI, 17.7-35.7)</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>5.5</td>
<td>2.4</td>
<td>12</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>9.4</td>
<td>7.1</td>
<td>14</td>
</tr>
<tr>
<td>Median duration of response, mo (range)</td>
<td>NR (2.1+ to 13.8+)^a</td>
<td>12.7 (2.1+ to 12.7)^a</td>
<td>NR (4.2 to 13.8+)^a</td>
</tr>
</tbody>
</table>

^aPD-L1 expression in tumor-infiltrating immune cells.
^bThe plus sign (+) indicates censored value.
CI indicates confidence interval; IRF, independent review facility; NR, not reached; PD-L1, programmed cell death ligand 1.
Source: Tecentriq (atezolizumab) injection prescribing information; October 2016.

approval for patients with metastatic NSCLC that progressed during or after platinum-containing chemotherapy.\textsuperscript{14,15} Patients with EGFR or ALK mutations should have disease progression with FDA-approved therapy for these aberrations before receiving atezolizumab.\textsuperscript{14,15}

“Tecentriq provides these patients with a new therapy targeting the PD-L1 pathway. Products that block PD-1/PD-L1 interactions are part of an evolving story about the relationship between the body’s immune system and its interaction with cancer cells,” stated Richard Pazdur, MD, FDA’s Director of the Office of Hematology and Oncology Products.\textsuperscript{13}

Mechanism of Action

PD-L1 on tumor cells and tumor-infiltrating immune cells contribute to the inhibition of the body’s antitumor immune response in the tumor microenvironment.\textsuperscript{14} When PD-L1 binds to PD-1 and B7.1 receptors on T-cells and antigen-presenting cells, cytotoxic T-cell activity, T-cell proliferation, and cytokine production are suppressed.\textsuperscript{14}

Atezolizumab is a monoclonal antibody that, when bound to PD-L1, blocks its interactions with PD-1 and B7.1 receptors and releases PD-L1– and PD-1–mediated inhibition of the body’s immune response.\textsuperscript{14}

Dosing and Administration

Atezolizumab is available as a 60-mg/mL solution in a single-dose vial. For patients with urothelial carcinoma or NSCLC, atezolizumab is administered via IV infusion, 1200 mg every 3 weeks, until disease progression or until unacceptable toxicity.\textsuperscript{14}

The first infusion of atezolizumab should be administered for 60 minutes. If this infusion is well-tolerated, subsequent infusions can be delivered for 30 minutes. Atezolizumab should not be administered as an IV push or bolus.\textsuperscript{14}

Atezolizumab Distribution

Atezolizumab is distributed through specific specialty pharmacies and healthcare networks, including ASD Healthcare, Besse Medical, BioSolutions Direct, Cardinal Health Specialty Distribution, Curascript Specialty Distribution, Dakota Drug, DMS Pharmaceutical, M&D Specialty Distribution, McKesson Specialty Health, McKesson Plasma and Biologics, Oncology Supply, and Smith Medical Partners.\textsuperscript{16}

Clinical Trials

IMvigor 210: Urothelial Cancer

The efficacy of atezolizumab in urothelial cancer was established in the open-label, multicenter, phase 2, IMvigor 210 clinical trial, which included 310 patients with locally advanced or metastatic urothelial cancer that progressed during or after a platinum-containing chemotherapy regimen or within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant regimen.\textsuperscript{14,17}

Patients’ PD-L1 expression status was assessed using the Ventana PD-L1 (SP142) assay. Overall, 32% of the 310 patients had PD-L1 expression of ≥5%, which was defined as PD-L1–stained immune cells that covered at least 5% of the tumor area. The remaining 68% of patients had PD-L1 expression <5%.\textsuperscript{14,17}

After a median treatment duration of 14.4 months with atezolizumab, the objective response rate (ORR) was 14.8% (95% confidence interval [CI], 11.1-19.3), including 5.5% complete responses (Table 1).\textsuperscript{14,17} The median duration of response has not been reached for the full patient population at the most recent analysis (range, approximately 2.1-13.8 months).\textsuperscript{14,17}

The ORR was 26% (95% CI, 17.7-35.7) in patients with PD-L1 expression ≥5% versus 9.5% (95% CI, 5.9-14.3) in patients with PD-L1 expression <5%; the duration of response in the latter group was 12.7 months (Table 1). The ORR was 22% (95% CI, 12.3-34.7) among 59 patients whose disease progressed after neoadjuvant or adjuvant chemotherapy.\textsuperscript{14,17}

OAK and POPLAR: Relapsed NSCLC

The efficacy of atezolizumab in NSCLC was established in 2 multicenter, international, randomized, open-label clinical trials in patients with metastatic NSCLC that progressed during or after a platinum-containing regimen.\textsuperscript{14,18,19} The OAK study included 1225 patients, with a primary analysis population that included 850 patients.\textsuperscript{19} The POPLAR study enrolled 287...
patients with metastatic NSCLC. In both studies, patients were stratified based on their PD-L1 expression status and the number of previous chemotherapy regimens and histology. Patients were randomized to receive atezolizumab (1200 mg IV every 3 weeks) until unacceptable toxicity or until radiographic or clinical disease progression, or docetaxel (75 mg/m² IV every 3 weeks) until unacceptable toxicity or until disease progression.

The major efficacy measure in the OAK study was overall survival (OS) in the first 850 randomized patients. In the POPLAR study, it was OS in the intent-to-treat population. Other efficacy measures included investigator-assessed ORR and duration of response.

After a median follow-up of 21 months, the OAK study had significantly longer OS (13.8 months; 95% CI, 11.8-15.7) than patients who received docetaxel (9.6 months; 95% CI, 8.6-11.2). In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, patients whose tumor expressed PD-L1 were more likely to benefit from atezolizumab. The hazard ratio for OS was 0.41 (95% CI, 0.27-0.64) in the high PD-L1 expression subgroup versus 0.82 (95% CI, 0.68-0.98) in patients without high PD-L1 expression.

In the POPLAR study, after a median follow-up of 22 months, the OS was 12.6 months (95% CI, 9.7-16.0) with atezolizumab versus 9.7 months (95% CI, 8.6-12.0) with docetaxel. The duration of response was significantly longer (18.6 months) with atezolizumab than with docetaxel (7.2 months; Table 2).

### Adverse Events

The safety of single-agent atezolizumab in urothelial carcinoma was based on data from 310 patients. The median duration of treatment with atezolizumab at the time of the data analysis was 12.3 weeks (range, 0.1-46 weeks). The most common (≥20% of patients) grade 1 or 2 adverse reactions included fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common (≥2% of patients) grade 3 or 4 adverse reactions included nausea (2%), abdominal pain (4%), fatigue (6%), urinary tract infection (9%), back or neck pain (2%), hematuria (3%), and dyspnea (4%).

Serious adverse reactions occurred in 45% of patients who received atezolizumab. Overall, 3% of patients discontinued therapy because of adverse reactions, and treatment interruption was required in 27% of patients.

The safety of atezolizumab in relapsed NSCLC was based on data from 277 patients who were enrolled in the POPLAR clinical trial. The median duration of exposure to atezolizumab was 3.7 months (range, 0-19 months) versus 2.1 months with docetaxel. The most common (≥20% of patients) all-grade adverse reactions with atezolizumab included fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common (≥2% of patients) grade 3 or 4 adverse reactions were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, increases in aspartate transaminase levels, increases in alanine transaminase levels, dysphagia, and arthralgia.

Overall, 9 (6%) patients who received atezolizumab died from pulmonary embolism (2 patients), pneumonia (2 patients), pneumothorax (1 patient), ulcer hemorrhage (1 patient), cachexia secondary to dysphagia (1 patient), myocardial infarction (1 patient), or large intestinal perforation (1 patient). Overall, 4% of patients who received atezolizumab discontinued treatment because of adverse reactions, and 24% of patients required the interruption of atezolizumab therapy. Serious adverse reactions occurred in 37% of patients; the most frequent serious adverse reactions were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism.

Atezolizumab has no contraindications.

### Warnings and Precautions

Patients taking atezolizumab should be assessed for the signs and symptoms of pneumonitis. Steroids should be administered for grade ≥2 pneumonitis, followed by a taper. Atezolizumab should be withheld until resolution of grade 2 pneumonitis, and discontinued for grade 3 or 4 pneumonitis.

Patients should be assessed for elevations in alanine aminotransferase levels, aspartate aminotransferase levels, and total bilirubin levels. Steroids should be admin-

---

**Table 2**

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Atezolizumab (N = 144)</th>
<th>Docetaxel (N = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, N (%)</td>
<td>90 (63)</td>
<td>110 (77)</td>
</tr>
<tr>
<td>Median overall survival, mo</td>
<td>12.6 (95% CI 9.7-16.0)</td>
<td>9.7 (95% CI 8.6-12.0)</td>
</tr>
<tr>
<td>Hazard ratio*</td>
<td>0.69 (95% CI 0.52-0.92)</td>
<td></td>
</tr>
<tr>
<td>Objective response, %</td>
<td>15 (95% CI 10-20)</td>
<td>15 (95% CI 9-23)</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Median duration of response, mo (range)</td>
<td>18.6 (11.6-NE)</td>
<td>7.2 (5.6-12.5)</td>
</tr>
</tbody>
</table>

*Stratified by PD-L1 expression in tumor-infiltrating immune cells, the number of previous chemotherapy regimens, and histology.

© 2017 by Green Hill Healthcare Communications, LLC; protected by U.S. copyright law.
istered for grade ≥2 hepatitis, followed by a taper. Atezolizumab should be withheld until resolution of grade 2 hepatitis and discontinued for grade 3 or 4 immune-mediated hepatitis.14

Atezolizumab should be withheld for grade 2 diarrhea or colitis. Steroids followed by a taper are warranted if symptoms persist for more than 5 days or if colitis recurs. Patients with grade 3 diarrhea or colitis should receive IV methylprednisolone, and atezolizumab should be withheld. Atezolizumab should be discontinued for grade 4 diarrhea or colitis.14

Patients receiving atezolizumab had thyroid disorders, adrenal insufficiency, hypophysis, and type 1 diabetes mellitus, including diabetic ketoacidosis; patients should be monitored for these complications.14

Infection was observed in 38% of patients with urothelial carcinoma and 43% of patients with NSCLC who received atezolizumab. Atezolizumab should be withheld for severe infections.14

Severe infusion reactions were noted in 1.3% of patients involved in clinical trials of atezolizumab.14

Use in Specific Populations

Atezolizumab therapy can cause fetal harm when administered to a pregnant woman. Women of reproductive age should use effective contraception during therapy and for 5 months after the last dose. Female fertility may be compromised with atezolizumab therapy.14

Women should not breast-feed with atezolizumab therapy, and for ≥5 months after the last dose.14

Atezolizumab has not been studied in children. No differences in the safety and effectiveness of atezolizumab were observed between patients aged ≥65 years and younger patients.14

No dose adjustment is needed for patients with renal impairment. Dose adjustment is not necessary in patients with mild hepatic impairment. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment.14

Conclusion

Atezolizumab is the first PD-L1 inhibitor approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial cancer that progressed after a platinum-containing regimen in the neoadjuvant, adjuvant, or advanced-disease setting. In this setting, atezolizumab demonstrated high response rates and durable responses, with a median duration of response not yet reached after approximately 14 months of follow-up. Atezolizumab is also the first PD-L1 inhibitor approved for patients with metastatic NSCLC that progressed during or after platinum-containing chemotherapy. Atezolizumab demonstrated a significant OS advantage compared with docetaxel in this patient population.

Combinations of atezolizumab with standard chemotherapy and other novel agents may improve outcomes for patients with cancer. Researchers are evaluating the activity of atezolizumab monotherapy and atezolizumab-based combinations in patients with urothelial carcinoma or with NSCLC, as well as in other solid and liquid tumors.20

References


