Urothelial carcinoma is the most common subtype of bladder cancer, accounting for more than 90% of bladder cancer diagnoses in the United States.¹ In 2017, more than 79,000 bladder cancer cases were diagnosed in the United States, and more than 16,000 people died from this disease.² The prognosis is favorable for patients with localized disease, with a 5-year relative survival rate of 78% for all stages of bladder cancer, which decreases to 5% for patients with distant disease.²

Lung cancer is the second most frequently diagnosed cancer in the United States, with an estimated 234,030 new cases projected for 2018.³ Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer.⁴

Tecentriq Approved for First-Line Treatment of Urothelial Carcinoma

On April 17, 2017, the US Food and Drug Administration (FDA) granted accelerated approval to atezolizumab (Tecentriq; Genentech), a monoclonal antibody intravenous (IV) inhibitor of programmed-cell death ligand-1 (PD-L1), as detected by the FDA-approved test, as a front-line treatment for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin chemotherapy.⁵

“IT is encouraging to see continued progress in the treatment of advanced bladder cancer, which until last year had not seen any major advancements in more than 30 years,” said Andrea Maddox Smith, Chief Executive Officer, Bladder Cancer Advocacy Network. “We are excited that TECENTRIQ is now a treatment option for people with advanced bladder cancer who are unable to receive a cisplatin-based chemotherapy as an initial treatment.”⁶

Atezolizumab initially received accelerated approval in May 2016 for the treatment of locally advanced or metastatic urothelial carcinoma that progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.⁶,⁷ This was the first FDA approval of a PD-L1 inhibitor for any malignancy.⁶ The 2 approvals for urothelial carcinoma are contingent on results from ongoing phase 3 clinical trials.⁸

In October 2016, the FDA approved atezolizumab for the treatment of metastatic NSCLC that progressed during or after platinum-containing chemotherapy.⁹ Patients with NSCLC and EGFR or ALK mutations should have disease progression during FDA-approved treatment for these mutations before receiving atezolizumab.⁹

Mechanism of Action

PD-L1 on tumor cells and tumor-infiltrating immune cells contributes to the inhibition of the body’s antitumor immune response in the tumor microenvironment. The binding of PD-L1 to PD-1 and B7.1 receptors on T-cells and antigen-presenting cells results in cytotoxic T-cell activity, T-cell proliferation, and the suppression of cytokine production.⁸

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.⁸

Dosing and Administration

The recommended dosage of atezolizumab is 1200 mg, administered once daily via IV infusion for 60 minutes every 3 weeks until disease progression or until unacceptable toxicity.⁸

Pivotal Clinical Trials

IMvigor 210 in Urothelial Carcinoma

The efficacy of atezolizumab as front-line treatment for cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma was established in a cohort of the open-label, multicenter, phase 2 IMvigor 210 clinical trial.¹⁰ Patients were considered cisplatin-ineligible if they had impaired renal function (creatinine clearance of >30 mL/min but <60 mL/min), Eastern Cooperative Oncology Group performance status 2, hearing loss...
of ≥25 dB at 2 contiguous frequencies, or grade ≥2 peripheral neuropathy. Key efficacy measures were objective response rate (ORR), duration of response, and overall survival (OS).\textsuperscript{10}

After a median of 14.4 months of atezolizumab therapy, the ORR was 23.5% (95% confidence interval [CI], 16.2-32.2), with 6.7% of patients achieving a complete response (Table 1).\textsuperscript{8,10} The median duration of response had not been reached for the full patient population at the most recent analysis (range, approximately 3.7-16.6 months).\textsuperscript{8,10}

**POPLAR and OAK Studies in NSCLC**

The efficacy of atezolizumab in patients with NSCLC was established in 2 multicenter, international, randomized, open-label clinical trials in patients with metastatic disease that progressed during or after a platinum-containing regimen.\textsuperscript{11,12} The POPLAR study enrolled 287 patients.\textsuperscript{11} The OAK study included 1225 patients, with a primary analysis population of 850 patients with metastatic NSCLC.\textsuperscript{12} All patients were stratified by PD-L1 expression status, number of previous chemotherapy regimens, and histology.\textsuperscript{11,12} In both studies, the primary end point was OS. Other efficacy measures in the POPLAR study were ORR and duration of response.\textsuperscript{8}

In the OAK study, after a median follow-up of 21 months, patients who received atezolizumab had significantly longer OS (13.8 months; 95% CI, 11.8-15.7) versus docetaxel (9.6 months; 95% CI, 8.6-11.2).\textsuperscript{8,12}

In the POPLAR study, after a median follow-up of 22 months, patients who received atezolizumab had significantly longer OS versus patients who received docetaxel: 12.6 months (95% CI, 9.7-16.0) versus 9.7 months (95% CI, 8.6-12.0), respectively (Table 2).\textsuperscript{11} Although the ORR findings were similar, the duration of response was significantly longer in patients who received atezolizumab (18.6 months) than in patients who received docetaxel (7.2 months).\textsuperscript{11}

**Adverse Reactions**

The safety of atezolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma was based on data from 119 patients. The most common (≥20%) adverse events included fatigue (52%), decreased appetite (24%), diarrhea (24%), and nausea (22%).\textsuperscript{8} The most common (≥2%) grade 3 or 4 adverse events included fatigue, urinary tract infection, anemia, diarrhea, increased blood creatinine levels, intestinal obstruction, increased alanine aminotransferase (ALT) levels, hyponatremia, decreased appetite, sepsis, back or neck pain, renal failure, and hypotension.\textsuperscript{8} Overall, 4.2% of patients discontinued therapy because of adverse reactions, and treatment interruption was required in 35% of patients.\textsuperscript{8}

The safety of atezolizumab in patients with metastatic NSCLC, regardless of PD-L1 expression, was based on data from 142 patients. The most common (≥20%) adverse events with atezolizumab included fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%).\textsuperscript{8} The most common (≥2%) grade 3 or 4 adverse events included dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, increase in aspartate aminotransferase levels, increase in ALT levels, dysphagia, and arthralgia.\textsuperscript{8} Overall, 4% of patients discontinued atezolizumab therapy because of adverse reactions, and treatment interruption was required in 24% of patients.\textsuperscript{8}

Atezolizumab has no contraindications.\textsuperscript{8}

**Use in Specific Populations**

Atezolizumab can cause fetal harm. Women of reproductive age should use effective contraception during

---

**Table 1** IMvigor 210: Atezolizumab in Cisplatin-Ineligible Patients with Advanced Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>All patients (N = 119)</th>
<th>Patients with PD-L1 expression ≤5% (N = 87)</th>
<th>Patients with PD-L1 expression &gt;5% (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, %</td>
<td>23.5 (95% CI, 16.2-32.2)</td>
<td>21.8 (95% CI, 13.7-32.0)</td>
<td>28.1 (95% CI, 13.8-46.8)</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>6.7</td>
<td>6.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>16.6</td>
<td>14.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Median duration of response, mo (range)</td>
<td>NR (3.7-16.6+)</td>
<td>NR (3.7-16.6+)</td>
<td>NR (8.1-15.6+)</td>
</tr>
</tbody>
</table>

*PD-L1 expression in tumor-infiltrating immune cells.*

CI indicates confidence interval; NR, not reached; PD-L1, programmed-cell death ligand-1.

**Table 2** POPLAR: Atezolizumab versus Docetaxel in Patients with Relapsed NSCLC

<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>Hazard ratio\textsuperscript{a}</td>
<td>12.6 (95% CI, 9.7-16.0)</td>
<td>9.7 (95% CI, 8.8-12.0)</td>
</tr>
<tr>
<td>Objective response rate, N (%)</td>
<td>22 (15)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Complete response, N (%)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response, N (%)</td>
<td>21 (15)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Median duration of response, mo (range)</td>
<td>16.6 (11.6-NR)</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 prior chemotherapy regimens, and histology.*

CI indicates confidence interval; NR, not reached; PD-L1, programmed-cell death ligand-1.

Source: Tecentriq (atezolizumab) injection prescribing information; March 2018.

---
atezolizumab therapy and for 5 months after the last dose. Female fertility may be compromised with atezolizumab therapy.8

Women should not breastfeed while using atezolizumab and for at least 5 months after the last dose.8

Atezolizumab has not been studied in children. No differences in its safety and effectiveness were observed between patients aged ≥65 years with urothelial carcinoma and younger patients, or between patients with NSCLC aged ≥75 years and younger patients.8

No dose adjustment is needed in patients with renal impairment or with mild hepatic impairment. Atezolizumab has not been studied in moderate or severe hepatic impairment.8

**Warnings and Precautions**

Patients using atezolizumab should be assessed for the signs and symptoms of several immune-mediated conditions, including pneumonitis, interstitial lung disease, hepatitis, diarrhea, colitis, pancreatitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré, or meningococcal meningitis. Treatment should be withheld or permanently discontinued with these conditions.8

Atezolizumab should be withheld for moderate ocular inflammatory toxicity and permanently discontinued with severe reaction.8

Patients who received atezolizumab reported thyroid disorders; adrenal insufficiency; hypophysitis; type 1 diabetes mellitus, including diabetic ketoacidosis; and other immune-related reactions. Patients should be monitored for these complications.8

Infection was observed in 38.4% of patients who received atezolizumab across clinical trials. Atezolizumab should be withheld for severe infections.8

Infusion reactions were reported in 1.3% of patients who received atezolizumab in clinical trials.8

**Conclusion**

The new indication for atezolizumab, a PD-L1 inhibitor, as first-line treatment for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, provides a new immunotherapy option for patients, regardless of PD-L1 expression. Atezolizumab is also approved for the treatment of patients with advanced or metastatic urothelial carcinoma that progressed during or after platinum-containing chemotherapy and those with metastatic NSCLC.

**References**