

## Atezolizumab (TECENTRIQ) National Drug Monograph August 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

### FDA Approval Information

#### Description/Mechanism of Action

Atezolizumab is a fully humanized IgG1 monoclonal antibody that binds to Programmed Death-Ligand 1 (PD-L1) and blocks the interaction with the PD-1 and B7.1 receptors on T-lymphocytes. Blocking these receptors allows for restoration of anti-tumor T-cell activity. The FDA granted accelerated approval of atezolizumab for bladder cancer that has progressed following platinum-based therapy in May of 2016. In April 2016 it was granted fast track status for non-small cell lung cancer.

#### Indication(s) Under Review in this document ( may include off label)

Atezolizumab is a programmed death-ligand 1(PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or after platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Off-label: Patients with non-small cell lung cancer that progressed following 1 or 2 prior therapies.

#### Dosage Form(s) Under Review

Injection for intravenous use 1200 mg/20mL single-dose vial

#### REMS

REMS  No REMS  Postmarketing Requirements  
*See Other Considerations for additional REMS information*

#### Pregnancy Rating

Can cause fetal harm when administered to a pregnant woman. *See Warnings and Precautions*

### Executive Summary

#### Efficacy

- In locally advanced or metastatic urothelial carcinoma that progressed during or after platinum-based therapy or within 12 months of neoadjuvant or adjuvant therapy with platinum containing chemotherapy, atezolizumab produced an Objective Response Rate (ORR) of 15% in all patients, and ORR of 26% in patients with the highest expression of PD-L1 on tumor infiltrating immune cells.
- The median Duration of Response has not yet been reached in an updated analysis with a median follow-up of 14.4 months.

Safety	<ul style="list-style-type: none"> <li>• Relatively well tolerated in most patients.</li> <li>• Immune-related adverse events similar to those seen with PD-1 inhibitors.</li> <li>• Most non-endocrine immune-related adverse events reversible with corticosteroid use.</li> <li>• While greater than 40% of patients had grade 3 or 4 adverse events in clinical trials, discontinuation rates due to adverse events were low.</li> </ul>								
Other Considerations	<ul style="list-style-type: none"> <li>• Granted accelerated approval. No comparison in the phase 2 trial.</li> <li>• Include table for oncology NMEs</li> </ul> <table border="1"> <tr> <td><b>Outcome in clinically significant area</b></td> <td>Locally advanced or metastatic urothelial carcinoma: Objective Response Rate (ORR) Duration of Response (DOR)</td> </tr> <tr> <td><b>Effect Size</b></td> <td>ORR: 15% in all patients ORR: 26% in patients with the highest expression of PD-L1 on tumor-infiltrating immune cells. mDOR: not yet reached in any IC subgroup or all patients</td> </tr> <tr> <td><b>Potential Harms</b></td> <td>High Risk</td> </tr> <tr> <td><b>Net Clinical Benefit</b></td> <td>Not available (accelerated approval)</td> </tr> </table>	<b>Outcome in clinically significant area</b>	Locally advanced or metastatic urothelial carcinoma: Objective Response Rate (ORR) Duration of Response (DOR)	<b>Effect Size</b>	ORR: 15% in all patients ORR: 26% in patients with the highest expression of PD-L1 on tumor-infiltrating immune cells. mDOR: not yet reached in any IC subgroup or all patients	<b>Potential Harms</b>	High Risk	<b>Net Clinical Benefit</b>	Not available (accelerated approval)
<b>Outcome in clinically significant area</b>	Locally advanced or metastatic urothelial carcinoma: Objective Response Rate (ORR) Duration of Response (DOR)								
<b>Effect Size</b>	ORR: 15% in all patients ORR: 26% in patients with the highest expression of PD-L1 on tumor-infiltrating immune cells. mDOR: not yet reached in any IC subgroup or all patients								
<b>Potential Harms</b>	High Risk								
<b>Net Clinical Benefit</b>	Not available (accelerated approval)								
Projected Place in Therapy	<ul style="list-style-type: none"> <li>• The only FDA approved drug for use in locally advanced or metastatic urothelial carcinoma that as progressed during or following platinum-based chemotherapy or progressed within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy.</li> <li>• Accelerated approval based on a single-arm phase 2 trial.</li> <li>• Fast-track designation for previously treated non-small cell lung cancer following platinum based chemotherapy.</li> </ul>								

## Background

### Purpose for review

#### Issues to be determined:

- ✓ Evidence of need for atezolizumab for urothelial carcinomas
- ✓ Does atezolizumab offer advantages to currently available alternatives?
- ✓ Does atezolizumab offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does atezolizumab have specific characteristics best managed by the non-formulary process, prior authorization, or criteria for use?

### Other therapeutic options

Atezolizumab is the first drug in 20 years approved for bladder carcinoma.

Formulary Alternatives Locally advanced or metastatic urothelial carcinomas	Other Considerations	CFU, Restrictions or Other Guidance
Gemcitabine	1200 mg/m <sup>2</sup> Days 1,8,15 repeat every 28 days Not standard of care	No
Docetaxel	100 mg/m <sup>2</sup> every 21 days Not standard of care	No
Paclitaxel	200 mg/m <sup>2</sup> every 21 days Not standard of care	No
Paclitaxel	80 mg/m <sup>2</sup> every week Not standard of care	No

## Efficacy (FDA Approved Indications)

### Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to July 2016) using the search terms atezolizumab and MPDL3280A. The search was limited to the Pub Med Clinical Queries Filter for Therapy (specific/narrow and sensitive/broad) and studies performed in humans and published in the English language. Reference lists of review articles and evidence based databases were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

### Review of Efficacy

#### Locally advanced or metastatic urothelial carcinoma

- Single-arm two cohort trial in locally advanced or metastatic urothelial carcinoma (includes renal pelvis, ureter, urinary bladder, or urethra).
- Data is from Cohort 2 consisting of patients whose disease had progressed after previous platinum-based therapy.
- ECOG PS 0-1.
- Measurable disease as defined by RECIST.
- Labs within 14 days: ANC  $\geq 1500$ ; WBC  $\geq 2500$ ; lymphocytes  $\geq 300$ ; platelets  $\geq 100K$ ; Hgb  $\geq 9.0$  g/dL; AST ALT and Alk Phos  $\leq 2.5$  X ULN except for document liver metastases then AST and/or ALT  $\leq 5$  X ULN, and those with liver or bone metastases Alk Phos  $\leq 5$  X ULN; serum bilirubin  $\leq 1.5$  X ULN (except for Gilbert disease with serum bilirubin  $\leq 3$  X ULN).
- In cohort 2 fixed dose of atezolizumab 1200mg IV on day 1 of each 21 day cycle.
- Dose interruptions allowed for toxicity but dose reductions not allowed.
- Continued therapy after RECIST documented progressive disease if patient met prespecified clinical benefit to allow for unconventional responses (for example pseudoprogression followed by response).
- Primary outcome: Objective Response based on 2 methods: independent review via RECIST and investigator-assessed response according to immune-modified RECIST criteria.
- Secondary endpoints: duration of response, progression free survival, overall survival, 12 month overall survival.
- Tumors assessed for PD-L1 expression. PD-L1 tumor infiltrating immune cells (IC) status defined by percentage of PD-L1 positive cells in the tumor microenvironment: IC0 (<1%); IC1 ( $\geq 1\%$  but <5%); IC2/3 ( $\geq 5\%$ ).
- Excluded: history of autoimmune disease, HIV, active HBV/HCV, tuberculosis, active or steroid dependent brain metastases, or received live attenuated vaccine in the previous 28 days, or on immunosuppressive therapy.

**Table 1: Cohort 2 Locally advanced or metastatic urothelial carcinoma**

Study	Setting	Pts	ECOG PS	Treatment	Response (%)						
					IC	ORR %	CR %	PR %	SD %	PD %	
Rosenberg, et al <sup>1</sup>	Locally advanced or metastatic urothelial carcinoma	Cohort 2	0: 38%	Atezolizumab 1200 mg IV Day 1 every 21 days	N=100	2/3	26	11	15	16	44
		N=310									
Funding: F Hoffman-La Roche Ltd.	after platinum chemotherapy	Bladder: 74%	Visceral mets: 78%	Liver mets: 31%	N=207	1/2/3	18	6	12	16	52
		1 Prev therapy: 40%									
		2 Prev therapies: 21%			N=310	All	15	5	10	19	51
		3 Prev therapies: 13%									
						Modified RECIST by investigator					
						2/3	27	8	19	31	28
						1/2/3	22	7	15	28	36
						All	19	5	14	30	35

IC=PD-L1 tumor infiltrating immune cells; ORR=Objective Response Rate; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors;

- Median Duration of Response not yet reached in any PD-L1 IC groups (range 2-13.7 months).
- Median time to onset of response: 2.1 months

- Of 121 patients treated beyond progression (pseudoprogression) for a median of 7.8 weeks, 17% experienced target lesion reduction of at least 30% from baseline.
- Response by metastatic site (ORR): Liver mets vs no liver mets: 5% vs 19%; Visceral mets vs no visceral mets: 10% vs 31%; ECOG 1 vs 0: 8% vs 25%;
- Complete response rate in absence of visceral mets disease (lymph-only disease) vs visceral mets: 18% vs 1%.
- Median Progression Free Survival: 2.1 months (95% CI 2.1-2.1) in all patients; similar across all IC groups; Median Progression Free Survival assessed by immune-modified RECIST: 4 months (95% CI 2.6-5.9) in IC2/3 group vs 2.9 months in IC1/2/3 and 2.7 months in ALL patients.
- Median Overall Survival 11.4 months in IC 2/3, 8.8 months in IC 1/2/3 group and 7.9 months in all patients.
- 12 month Overall Survival: 48% in IC2/3, 39% in IC1/2/3, and 36% in ITT population.

Patients

**Table 2: Updated responses in Cohort 2**

Study	RECIST ORR%	RECIST CR, n	mRECIST ORR %	mRECIST CR, n	mOS, mos 95%CI	1-yr OS, % 95%CI
Dreicer, et al. <sup>2</sup>						
IC 2/3	26	12	29	8	11.9 9.0, NYR	50 40, 60
IC 1/2/3	18	14	23	16	9.0 7.1, 10.9	40 33, 47
All	15	17	19	18	7.9 6.7, 9.3	37 31, 42

Median Duration of Response not yet reached in IC2/3, IC 1/2/3, and all patients.

### Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based.

- **First-line therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (Cohort 1):** Primary analysis of IMvigor210 cohort 1: ORR in all IC subgroups (range 19%-22%); Progression Free Survival range 2.3-2.9 months; median Overall Survival estimate 10.6 months.<sup>3</sup>
- **IMvigor211 Phase III in bladder carcinoma vs chemotherapy** Actively recruiting clinical trial
- **Previously treated non-small-cell lung cancer:** phase 2 randomized trial (POPLAR) post platinum chemotherapy (66% non-squamous). Patients randomized to atezolizumab 1200 mg IV day 1 every 21 days or docetaxel 75 mg/m<sup>2</sup> day 1 every 21 days. Primary outcome: Median Overall Survival 12.6 vs 9.7 months; HR 0.73 (95% CI 0.53-0.99). OS benefit increased with increasing PD-L1 expression on tumor cells, tumor-infiltrating immune cells, or both. Overall survival in patient with PD-L1 tumor cell expression of TCO (<1%) and PD-L1 tumor-infiltrating immune cell expression IC0 (<1%) in the atezolizumab group was similar to the overall survival in the docetaxel group. PFS 2.7 vs 3.0 months; HR 0.94; 95% CI 0.72-1.23. Objective responses: 15% in both groups.<sup>4</sup>
- **Squamous NSCLC vs gemcitabine plus cisplatin or carboplatin** actively recruiting clinical trial.
- **Renal Cell Carcinoma** phase Ia in metastatic renal cell carcinoma. (90% clear cell) to assess safety and tolerability and secondary outcome of antitumor activity. No dose limiting toxicities observed. 85% had a treatment-related adverse event. In all patients, 67% experienced a grade 1 or 2 AE. 12% experienced a treatment-related grade 3 AE. Most common immune-mediated AE was grade 1 rash in 20% and grade 2 hypothyroidism in 10%. Median PFS was 5.6 months and median Overall Survival was 23.9 months.<sup>5</sup>
- **Renal Cell Carcinoma in combination with bevacizumab** Actively recruiting clinical trial

### Safety

(for more detailed information refer to the product package insert)

	Comments
<b>Boxed Warning</b>	• None
<b>Contraindications</b>	• None
<b>Warnings/Precautions</b>	• Immune-related pneumonitis or interstitial lung disease requiring use of corticosteroids occurred in 2.6% of patients. Fatal pneumonitis occurred in 2 patients. Monitor for signs with radiographic imaging and symptoms. Administer steroids at a dose of 1-2 mg/kg/day prednisone equivalent for

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- Grade 2 or greater. For Grade 2, withhold therapy until resolution. For Grades 3 or 4, permanently discontinue therapy.
- Immune-related hepatitis requiring steroids occurred in 1.3% of patients. Elevations in liver function tests occurred in 1.6-2.5% of patients. One patient died from hepatitis. Median time to onset 1.1 months. Monitor for signs and symptoms of hepatitis including liver function tests periodically. Administer steroids at a dose of 1-2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations with or without bilirubin elevation followed by taper. Withhold therapy for Grade 2 and permanently discontinue for Grades 3 or 4.
  - Immune-related colitis requiring steroids occurred in 18.7-19.7% of patients. Ten patients had Grade 3 or 4 diarrhea. Monitor for signs and symptoms. Withhold therapy for Grade 2 diarrhea or colitis. If symptoms persist for more than 5 days administer 1-2 mg/kg/day prednisone or equivalent. For Grade 3 diarrhea or colitis withhold therapy and administer IV methylprednisolone 1-2 mg/kg per day and convert to oral steroids once patient improves. For Grades 2 or 3 diarrhea or colitis, when symptoms improve to Grade 0 or 1, taper steroids. Resume atezolizumab if the event improves to Grade 0 or 1 within 12 weeks and steroids have been reduced to  $\leq 10$  mg oral prednisone or equivalent. Permanently discontinue for Grade 4 diarrhea or colitis.
  - Immune-related Endocrinopathies
    - Hypophysitis: administer steroids and hormone replacement as clinically indicated.
    - Thyroid disorders: monitor thyroid function periodically. For symptomatic hypothyroidism, withhold atezolizumab and initiate thyroid replacement therapy. For symptomatic hyperthyroidism, withhold atezolizumab and initiate anti-thyroid drug as needed. Resume atezolizumab when symptoms of hypo or hyperthyroidism are controlled and thyroid function is improving.
    - Adrenal insufficiency: if symptomatic, withhold atezolizumab and administer methylprednisolone 1-2 mg/kg IV per day followed by prednisone 1-2 mg/kg/day or equivalent once symptoms improve. Taper steroids when symptoms improve to  $\leq$  Grade 1. Resume atezolizumab if event improves to  $\leq$  Grade 1 within 12 weeks and steroids are reduced to equivalent of  $\leq 10$  mg/kg/day oral prednisone and patient is stable on replacement therapy.
    - Diabetes mellitus: New onset diabetes with ketoacidosis has occurred. Initiate insulin for type 1 diabetes. For Grade  $\geq 3$  hyperglycemia, withhold atezolizumab and resume when metabolic control achieved on insulin therapy.
  - Other Immune Related Reactions: included meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barre, ocular inflammatory toxicity, and pancreatitis in  $\leq 1.0\%$  of patients.
    - Meningitis/Encephalitis: Permanently discontinue atezolizumab for any grade meningitis or encephalitis. Treat with IV steroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) once symptoms improve. When symptoms improve to  $\leq$  Grade 1, taper steroids.
    - Motor and sensory neuropathy: Permanently discontinue atezolizumab for any grade myasthenic syndrome/myasthenia gravis or Guillain-Barre syndrome. Start medical intervention as appropriate. Consider systemic steroids at a dose of 1-2 mg/kg/day prednisone.
    - Pancreatitis: Withhold atezolizumab for  $\geq$  Grade 3 serum amylase or
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lipase levels (>2.0 ULN) or Grade 2 or 3 pancreatitis. Treat with 1-2 mg/kg IV methylprednisolone or equivalent per day and convert to oral prednisone 1-2 mg/kg/day or equivalent when symptoms improve. Restart atezolizumab if serum amylase and lipase levels improve to ≤Grade 1 within 12 weeks, symptoms of pancreatitis have resolved, and steroids have been reduced to ≤10 mg oral prednisone or equivalent per day. Permanently discontinue atezolizumab for Grade 4 or any grade of recurrent pancreatitis.

- Infection: Severe infections (sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage) reported in patients receiving atezolizumab. Infections reported in 38.4% of patients in clinical trials and 37.7% of patients with urothelial carcinoma. Grade 3 or 4 infection occurred in 11.5% and three patients died due to infection. Urinary tract infections were most common Grade 3 or higher infection, occurring in 7.1%. In non-small cell lung cancer, infections were more common in atezolizumab (42%) versus docetaxel (33%). Treat patients with antibiotics for suspected or confirmed bacterial infections. Withhold atezolizumab for ≥Grade 3 infection.
- Infusion-related reactions: Reported in 1.3% across all clinical trials and 1.7% in urothelial carcinoma. Interrupt or slow infusion rate in mild to moderate infusion reactions. Permanently discontinue for Grade 3 or 4 reactions.
- Embryo-fetal toxicity: May cause fetal harm if administered to pregnant woman based on its mechanism of action. In animals, inhibition of the PD-L1/PD-1 pathway lead to increased risk for immune-rejection of fetus resulting in fetal death. If used during pregnancy or if patient becomes pregnant while taking drug, advise patient of potential risk to fetus. Advise female patients of child-bearing potential to use effective contraception during treatment and for at least 5 months after the last dose of atezolizumab.

### Safety Consideration

- Tolerated in most patients in clinical trials.
- Immune associated adverse reactions similar to those seen with PD-1 inhibitors.
- Non-endocrine immune-mediated toxicities mostly reversible with the use of corticosteroids.
- Further evaluation of hypothyroidism is required.

### Adverse Reactions

Common adverse reactions	In ≥20%: fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation.
Death/Serious adverse reactions	Grade 3 or 4 adverse reactions in ≥2%: urinary tract infections, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia. Death in three patients: sepsis, pneumonitis, intestinal obstruction
Discontinuations due to adverse reactions	Urothelial carcinoma: 4% Non-small cell lung cancer: 8% versus 22% docetaxel

### Drug Interactions

#### Drug-Drug Interactions

None noted

**Risk Evaluation**

As August 2016

		<b>Comments</b>			
Sentinel event advisories		<ul style="list-style-type: none"> <li>None</li> <li>Sources: ISMP, FDA, TJC</li> </ul>			
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Atezolizumab 1200mg/20mL Inj	Alemtuzumab Nivolumab Pembrolizumab	None	None	Atazanavir
	Tecentriq	None	None	None	Tecfidera Technivie Cometriq
(Lexi-Comp, First Databank, and ISMP Confused Drug Name List)					

**Other Considerations**

- Postmarketing requirements:
  - Phase III trial comparing atezolizumab to chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure of platinum-containing chemotherapy
  - Develop and validate assay to detect atezolizumab neutralizing antibodies in the presence of atezolizumab levels.
  - Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function and clinical thyroid disease.
- No REMS is indicated. The safe use can be managed through accurate labeling and routine pharmacovigilance. A Medication Guide is available for distribution but is not required.
- Pharmacokinetic/pharmacodynamics considerations
  - Half-life 27 days
  - Gender, body weight, tumor burden, serum albumin, anti-therapeutic antibody status, mild and moderate renal impairment, and mild hepatic impairment did not impact pharmacokinetics.
  - AUC did not predict response or probability of and adverse event.
  - No evidence from clinical data of a potential to delay ventricular repolarization.

<b>Outcome in clinically significant area</b>	Locally advanced or metastatic urothelial carcinoma: Objective Response Rate (ORR) Duration of Response (DOR)
<b>Effect Size</b>	ORR: 15% in all patients ORR: 26% in patients with the highest expression of PD-L1 on tumor-infiltrating immune cells. mDOR: not yet reached in any IC subgroup or all patients
<b>Potential Harms</b>	High Risk
<b>Net Clinical Benefit</b>	Not available (accelerated approval)

Definitions

**Outcome in clinically significant area:** morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

**Effect Size:** odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

**Potential Harms:** Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

**Net Clinical Benefit:** Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

**Dosing and Administration**

- The recommended dose of atezolizumab is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus.

- Dose modifications: No dose reductions are recommended.
  - Withhold for any of the following (see Warnings/Precautions)
    - Grade 2 pneumonitis
    - AST or ALT greater than 3 and up to 5 times ULN or total bilirubin greater than 1.5 and up to 3 times ULN
    - Grade 2 or 3 diarrhea or colitis
    - Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or Grade 3 or 4 hyperglycemia
    - Grade 2 ocular inflammatory toxicity
    - Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels (greater than 2 times ULN)
    - Grade 3 or 4 infection
    - Grade 2 infusion-related reactions
    - Grade 3 rash
- Resume atezolizumab if adverse reactions recover to Grade 0-1.
- Permanently discontinue for any of the following (see Warnings/Precautions)
    - Grade 3 or 4 pneumonitis
    - AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
    - Grade 4 diarrhea or colitis
    - Grade 4 hypophysitis
    - Myasthenic syndrome/myasthenia gravis, Guillain-Barre or meningoencephalitis (all grades)
    - Grade 3 or 4 ocular inflammatory toxicity
    - Grade 4 or any grade recurrent pancreatitis
    - Grade 3 or 4 infusion-related reactions
    - Grade 4 rash

### Special Populations (Adults)

	Comments
<b>Elderly</b>	<ul style="list-style-type: none"> <li>• None. 59% of patients in urothelial carcinoma trial were 65 years old or older. No differences in safety or efficacy noted compared to those &lt;65 years old.</li> </ul>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• Based on its mechanism, may cause fetal harm if given to a pregnant woman. No data on use in pregnant females. No animal reproduction studies. Central function of PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt fetal tolerance and result in increased risk for rates of abortion or stillbirth. No malformations related to blockade of PD-L1/PD-1 signaling, but based on mechanism may increase risk of developing immune-mediated disorders or altering normal immune response.</li> </ul>
<b>Lactation</b>	<ul style="list-style-type: none"> <li>• No information regarding presence of atezolizumab in human milk, effects on breastfed infant, or effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to infant is unknown. Because of potential for serious adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment and for at least 5 months after the last dose.</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>• None in mild hepatic impairment. No data in patients with moderate or severe hepatic impairment.</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Females and Males of Reproductive Potential</b>	<ul style="list-style-type: none"> <li>• Contraception: Females of reproductive potential should use effective contraception during therapy and for at least 5 months following the last dose due to risk for fetal harm.</li> </ul>



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- Infertility: In females, atezolizumab may impair fertility during therapy based on animal studies.
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### Projected Place in Therapy<sup>6,7,8,9</sup>

- Urothelial carcinoma (includes renal pelvis, ureter, urinary bladder, or urethra) accounts for 16,000 deaths per year in the USA and 165,000 deaths worldwide.
- Most urothelial carcinomas are non-muscle invasive at diagnosis and managed with surgical interventions or local topical therapies (bladder).
- Approximately 10-15% of patients develop locally advanced or metastatic disease despite local treatment, and about 10% have advanced disease at initial diagnosis.
- The first-line standard of care for locally advanced or metastatic disease is a platinum-containing chemotherapy regimen such as gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin.
- Almost all patients experience disease progression or intolerance to therapy.
- While multiple agents have been studied in the second-line setting, most produce response rates of less than 20% and do not affect survival. In the US, there are no FDA approved drugs or standard of care for second-line therapy. Currently second-line options result in a PFS of 2-4 months and an OS of 6-9 months. Gemcitabine or one of the taxanes is commonly used for palliation. There have been no major advances in the treatment of urothelial carcinoma in the past 30 years.
- PD-L1 is expressed in multiple tissues including T and B cell, dendritic cells, macrophages, and many human cancer types. PD-L1 is the ligand for PD-1, expressed on the surface of T cells. Binding of PD-L1 to PD-1 results in an inhibitory signal that reduces cytokine production and T cell proliferation.
- Across multiple cancer types, responses to atezolizumab increased with increased expression of PD-L1 in tumor samples. A stronger association was seen with tumor-infiltrating immune cell PD-L1 expression and treatment response.
- In an expanded cohort of patients with urothelial bladder carcinoma in a phase 1 trial, treatment with MPDL3280A (atezolizumab) produced rapid responses and a high response rate with a favorable toxicity profile including a lack of renal toxicity.
- In a cohort of patients with locally advanced or metastatic urothelial carcinoma who progressed after previous platinum-based chemotherapy (including neoadjuvant and adjuvant therapy), atezolizumab demonstrated durable clinical efficacy and was well tolerated. Objective Response Rate in all comers was 15% with a median Duration of Response not yet reached. In patients with the highest levels of PD-L1 expression in tumor infiltrating immune cells, the objective response rate was 26%.
- Although activity was seen in all subgroups, rates of response increased with increased PD-L1 tumor infiltrating immune cell status.
- Some patients have an atypical response to immune targeted therapy. They may experience an initial increase in size of tumor lesions or a decrease in target lesions in the presence of new lesions followed by subsequent delayed decrease in tumor burden. Such pseudo-progression and immune-related patterns of response pose a challenge and may require treatment beyond progression of disease in order to observe more typical objective response rates.
- Atezolizumab was approved via an accelerated approval for locally advanced or metastatic urothelial carcinoma that progressed after platinum based therapy based on a single-arm trial. There are no other FDA approved drugs for this indication. Use for this indication in appropriate patients is warranted. However, confirmation of these results from the ongoing phase III trial comparing atezolizumab to chemotherapy will best determine the place in therapy. Clinical trials in this setting are still necessary and an important choice.
- For previously treated non-small cell lung cancer, the median overall survival from a randomized phase II trial is similar to that seen with PD-1 inhibitors. This indication has received a fast tract designation by FDA. Awaiting further clinical trial data.

## References

- <sup>1</sup> Rosenberg JE, Hoffman-Censits J, Powles T, 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;387:1909-20.
- <sup>2</sup> Dreicer R, Hoffman-Centis JH, Flaig TW, et al. Updated efficacy and >1-y follow up from IMvigor210: atezolizumab (atezo) in platinum (plat) treated locally advanced/metastatic urothelial carcinoma (mUC). *J Clin Oncol* 2016;34 (suppl):abstract 4515.
- <sup>3</sup> Balar AV, Galsky MD, Loriot Y, et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): primary analysis of IMvigor210 cohort 1. *J Clin Oncol* 2016; 34 (suppl): Abstract LBA4500.
- <sup>4</sup> Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicenter, open-label, phase 2 randomised controlled trial. *Lancet* 2016; 387:1837-46.
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**Appendix A: GRADEing the Evidence**

## Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.

## Appendix B: Approval Endpoints (use for oncology NMEs)

**Table 1. A Comparison of Important Cancer Approval Endpoints**

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding not essential</li> </ul>	<ul style="list-style-type: none"> <li>• Universally accepted direct measure of benefit</li> <li>• Easily measured</li> <li>• Precisely measured</li> </ul>	<ul style="list-style-type: none"> <li>• May involve larger studies</li> <li>• May be affected by crossover therapy and sequential therapy</li> <li>• Includes noncancer deaths</li> </ul>
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> <li>• Randomized blinded studies</li> </ul>	<ul style="list-style-type: none"> <li>• Patient perspective of direct clinical benefit</li> </ul>	<ul style="list-style-type: none"> <li>• Blinding is often difficult</li> <li>• Data are frequently missing or incomplete</li> <li>• Clinical significance of small changes is unknown</li> <li>• Multiple analyses</li> <li>• Lack of validated instruments</li> </ul>
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding preferred</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller sample size and shorter follow-up necessary compared with survival studies</li> </ul>	<ul style="list-style-type: none"> <li>• Not statistically validated as surrogate for survival in all settings</li> <li>• Not precisely measured; subject to assessment bias, particularly in open-label studies</li> <li>• Definitions vary among studies</li> </ul>
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Can be assessed in single-arm studies</li> <li>• Assessed earlier and in smaller studies compared with survival studies</li> <li>• Effect attributable to drug, not natural history</li> </ul>	<ul style="list-style-type: none"> <li>• Not a direct measure of benefit in all cases</li> <li>• Not a comprehensive measure of drug activity</li> <li>• Only a subset of patients with benefit</li> </ul>
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Can be assessed in single-arm studies</li> <li>• Durable complete responses can represent clinical benefit</li> <li>• Assessed earlier and in smaller studies compared with survival studies</li> </ul>	<ul style="list-style-type: none"> <li>• Not a direct measure of benefit in all cases</li> <li>• Not a comprehensive measure of drug activity</li> <li>• Small subset of patients with benefit</li> </ul>
Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding preferred</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller sample size and shorter follow-up necessary compared with survival studies</li> <li>• Measurement of stable disease included</li> <li>• Not affected by crossover or subsequent therapies</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Not statistically validated as surrogate for survival in all settings</li> <li>• Not precisely measured; subject to assessment bias particularly in open-label studies</li> <li>• Definitions vary among studies</li> <li>• Frequent radiological or other assessments</li> <li>• Involves balanced timing of assessments among treatment arms</li> </ul>

\*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

**Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.** U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.