Checkpoint inhibitors forge new treatment paradigm for metastatic bladder cancer

Last spring, the US Food and Drug Administration (FDA) granted accelerated approval to 3 different immune checkpoint inhibitors for the treatment of patients with metastatic urothelial carcinoma in the second-line setting, bringing the total number of approved members of this drug class for this indication to 5.

Avelumab and durvalumab, like atezolizumab, are monoclonal antibodies that target the programmed cell death protein ligand-1 (PD-L1) and prevent it from binding to and activating the programmed cell death protein-1 (PD-1) and CD80 receptors, which transmit inhibitory signals into T cells. In this way, it is hypothesized that their use reactivates the anti-tumor immune response conducted by tumor-infiltrating T cells.

Both drugs were approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are refractory to platinum-based chemotherapy, and the approvals provide additional treatment options for this group of patients who typically have poor prognosis.[1,2]

Avelumab trial findings

The approval of avelumab was based on the urothelial cancer cohorts of the JAVELIN Solid Tumor trial, a phase 1, open-label, dose-escalation study.[3] Patients aged 18 years and older, with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (range, 0-5; 0, fully active, and 5, dead), life expectancy of at least 3 months, and cytologically or histologically confirmed metastatic or locally advanced solid tumors were eligible.

Patients were excluded from the study if they had a history of or active central nervous system metastases, had other malignancies within the previous 5 years, had undergone organ transplant, had conditions requiring immune suppression, had active HIV or hepatitis B or C infection, or had autoimmune diseases other than type 1 diabetes, vitiligo, psoriasis, or thyroid disease that does not require immunosuppressive treatment.

Patients were also required to have adequate end organ function (white blood cell count, ≥3 x 10^9 cells/L; absolute neutrophil count, ≥1.5 x 10^9 cells/L; lymphocyte count, ≥0.5 x 10^9 cells/L; platelet count, ≥100 x 10^9 platelets/L; hemoglobin, ≥9 g/dL; total bilirubin concentration, ≤1.5 x upper limit of normal [ULN] range; aspartate- and alanine- aminotransferase (ALT/AST) concentrations, ≤2.5 x ULN); and estimated creatinine clearance, >50 mL/min.

A total of 242 patients were treated with a 10 mg/kg intravenous dose of avelumab every 2 weeks until disease progression or unacceptable toxicity. Before avelumab infusion, all patients received premedication with an antihistamine and acetaminophen.

The primary endpoint was objective response rate (ORR), which was 13.3% among 226 patients followed for at least 13 weeks, including 4% complete response (CR) rate, and 16.1% among 161 patients followed for at least 6 months, including 5.6% CR rate. The median time to response was 2 months and the median response duration had not been reached at the time of data cut-off. PD-L1 expression was evaluable in 84% of patients and there was no discernable variation in the response rates according to the levels of PD-L1 expression on the tumor.

The most common adverse events (AEs) that occurred in at least 20% of patients included fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite,

What's new, what's important

The monoclonal antibodies avelumab and durvalumab were approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are refractory to platinum-based chemotherapy. Avelumab was approved on the basis of findings from the urothelial cancer cohorts of the JAVELIN Solid Tumor trial in which 242 patients were treated with a 10 mg/kg IV dose of avelumab every 2 weeks until disease progression or unacceptable toxicity. ORR was 13.3% in 226 patients followed for at least 13 weeks, including 4% CR rate, and 16.1% in 161 patients followed for at least 6 months, including 5.6% CR rate.

Durvalumab's approval was based on results from the phase 1/2 Study 1108. It was administered as an IV infusion at a dose of 10 mg/kg every 2 weeks, for up to 12 months or until disease progression or unacceptable toxicity. PD-L1 expression was evaluated before treatment using the Ventana PD-L1 (SP263) assay, which was also approved. The ORR was 17.8%, including 7 CRs (3.7%). In patients with high PD-L1 expression, the ORR was 27.6%, compared with 5.1% in those with low or no PD-L1 expression. Responses were observed across all subgroups, including patients with a poor prognosis.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

Report prepared by Jane de Lartigue, PhD. JCSO 2018;16(1):e5–e7. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0379

Mechanism of action: avelumab and durvalumab

Re-establishing the anti-tumor immune response

Bladder cancer, which most often presents as urothelial carcinoma, is the most common cancer of the genitourinary system and the 5th most common type of cancer in the United States. For patients who present with metastatic disease, the standard of care is platinum-based chemotherapy, conferring a median overall survival of 9-15 months.

Unfortunately, for the large number of patients who subsequently relapse, or who are ineligible for chemotherapy because of their poor performance status, survival time is significantly shorter and few treatment options are available. Recently, immunotherapy has begun to fill that niche in bladder cancer; likely the high number of mutations in this cancer type makes it especially sensitive to this form of treatment.

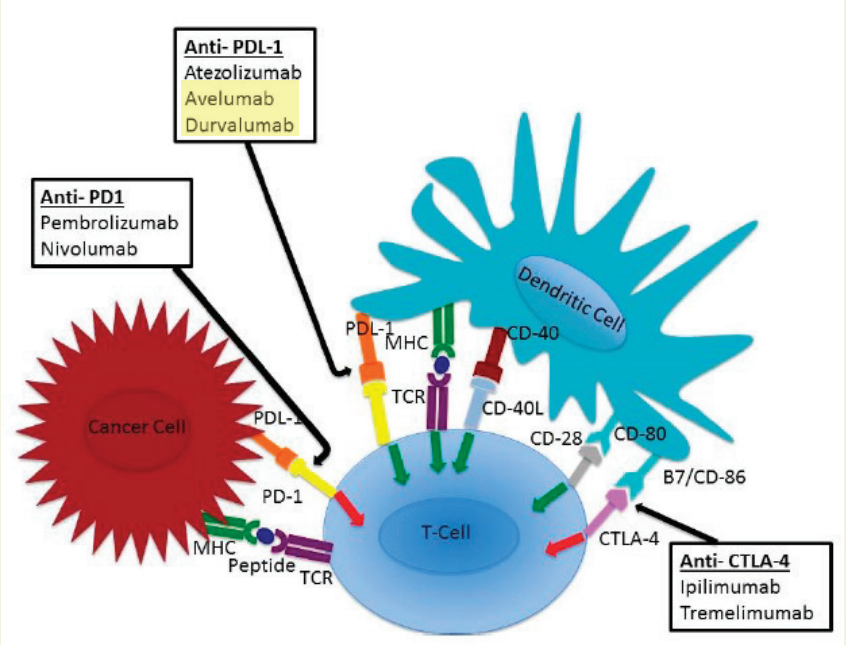
Tumors display foreign antigens on their surface as a result of these mutations and other molecular alterations, which provoke an anti-tumor immune response when they engage the major effectors of the immune system, the T cells, which patrol the body looking for abnormal or foreign cells. Tumors are able to suppress the immune system through numerous different mechanisms, and the goal of immunotherapy is to re-establish the anti-tumor immune response.

One of the best characterized mechanisms of tumor-mediated immunosuppression is the exploitation of signaling pathways that dampen T-cell activity, including the programmed cell death protein-1 (PD-1) pathway. Urothelial carcinomas often demonstrate high levels of expression of the PD-1 ligand, PD-L1, and this has been shown to correlate with more aggressive disease and poorer patient outcomes.

By expressing PD-L1, the tumor cells are in essence mimicking the signals released by healthy cells, engaging the PD-1 receptor on the surface of tumor-infiltrating T cells and sending an inhibitory signal into the cells and effectively switching them off.

The use of monoclonal antibodies that target either PD-1, such as nivolumab and pembrolizumab, or the ligand PD-L1, which include avelumab, durvalumab, and atezolizumab, has shown significant promise in the treatment of metastatic urothelial carcinoma. These antibodies block the interaction between the receptor and its ligand and help to re-establish the anti-tumor immune response by re-activating tumor-infiltrating T cells.

All 5 of these drugs are now approved by the FDA in this disease setting. Each has distinct binding properties and kinetics, which could ultimately mean they have different anti-tumor efficacy, though comparative studies have not yet been performed. As a class, they provide a much needed new treatment option for patients with this type of cancer.



Durvalumab and avelumab join atezolizumab, another PD-L1-targeting antibody and 2 PD-1-targeting drugs, nivolumab and pembrolizumab in the expanding immune checkpoint market for patients with metastatic urothelial carcinoma. These drugs block the T-cell inhibitory PD-1 pathway, reactivate tumor-infiltrating T cells, and re-establish the anti-tumor immune response.

Reproduced with permission: Goode EF, Smyth EC. Immunotherapy for gastroesophageal cancer. J Clin Med. 2016;5:84.

and urinary tract infection (UTI). Serious AEs occurred in 41% of patients and most commonly involved UTI, abdominal pain, musculoskeletal pain, creatinine increase/renal failure, dehydration, hematuria, intestinal obstruction, and pyrexia. Deaths owing to AEs occurred in 6% of patients and were related to pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal AEs.

Durvalumab approval

The agency's approval of durvalumab rested on the results of an ongoing single-arm phase 1/2 trial (Study 1108).[4] Eligibility criteria were the same as for the avelumab study. Patients were ineligible for the trial if they had received any immunotherapy within the previous 4 weeks, any monoclonal antibody within the previous 6 weeks, or had received concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy.

Durvalumab was administered as an intravenous infusion at a dose of 10 mg/kg every 2 weeks, for up to 12 months or until disease progression or unacceptable toxicity. PD-L1 expression was evaluated by immunohistochemistry in tumor tissue obtained before treatment using the Ventana PD-L1 (SP263) assay (Ventana Medical Systems), which was approved by the FDA alongside durvalumab as a companion diagnostic. The first 20 patients were enrolled regardless of their PD-L1 expression, and the subsequent 43 patients were required to have PD-L1 expression of at least 5% of their tumor cells, but that requirement was removed at an interim analysis when objective responses occurred in patients with a PD-L1 expression of less than 5%.

In the most up-to-date analysis, published after FDA approval, a total of 191 patients had been treated. The ORR as assessed by blinded independent central review per RECIST-1.1, was 17.8%, including 7 CRs (3.7%). In patients with high PD-L1 expression, the ORR was 27.6%, compared with 5.1% in those with low or no PD-L1 expression. Responses were observed across all subgroups, including patients with a poor prognosis. The ORRs in patients with visceral and liver metastases were 15.3% and 7.3%, respectively. The median time to response was 1.41 months, and the median duration of response had not yet been reached.

The most common AEs experienced by patients treated with durvalumab included fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and UTI. Serious treatment-related AEs occurred in 4.7% of patients, and treatment-related AEs leading to death occurred in 2 patients owing to autoimmune hepatitis and pneumonitis.

Toxicities and warnings for both therapies

Avelumab is marketed as Bavencio by EMD Serono, and durvalumab as Imfinzi by AstraZeneca. According to the prescribing information for both drugs, the recommended dose is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks.[5,6]

Both drugs are associated with serious or potentially life-threatening toxicities for which warnings and precautions are detailed in the prescribing information, predominantly for immune-mediated toxicities such as pneumonitis, hepatitis, colitis, nephritis, and endocrinopathy. Patients should be monitored for signs and symptoms of these toxicities and managed appropriately. Avelumab and durvalumab should both be withheld for grade 2 or higher pneumonitis, hepatitis, colitis, severe or life-threatening adrenal insufficiency, thyroid disorders or hyperglycemia, and moderate or severe nephritis or renal dysfunction.

These drugs should be permanently discontinued in the event of life-threatening or recurrent AEs. Immune-mediated pneumonitis, colitis, and hepatitis and adrenal insufficiency can be managed with corticosteroids; hypothyroidism, with hormone-replacement therapy; and hyperglycemia, with hyperglycemics or insulin.

To manage infusion-related reactions, patients should be premedicated with antihistamines and acetaminophen before the first 4 infusions and closely monitored for symptoms such as pyrexia, chills, flushing, hypotension, and dyspnea. Infusion can be interrupted or slowed for mild to moderate infusion-related reactions, but should be stopped and the drug discontinued for severe or life-threatening reactions.

Durvalumab is also associated with a risk of infection and patients should be monitored for signs and symptoms of infection and treated with anti-infectives. Durvalumab should be withheld for grade 3 infections. Patients being treated with durvalumab or avelumab should also be warned of the potential for embryofetal toxicity and advised to take appropriate precautions.

References

1. United States Food and Drug Administration. FDA grants accelerated approval to avelumab for urothelial carcinoma. US FDA Web site. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm557162.htm. Last updated May 9, 2017. Accessed September 15, 2017.
2. United States Food and Drug Administration. Durvalumab (Imfinzi). US FDA Web site. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555930.htm. Last updated May 1, 2017. Accessed September 15, 2017
3. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, et al. Avelumab for metastatic or locally advanced previously treated solid tumors (JAVELIN Solid Tumos): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol. 2017;18(5):587-598.
4. Powles T, O'Donnell PH, Massard C, Arkenau H-T, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma. Updated results from a phase 1/2 open-label study. JAMA Oncol. 2017;3(8):e172411.
5. Bavencio (avelumab) injection, for intravenous use. Prescribing information. EMD Serono Inc. https://www.bavencio.com/en_US/document/Prescribing-Information.pdf. Revised October 2017. Accessed September 18th, 2017.
6. Imfinzi (durvalumab) injection, for intravenous use. Prescribing information. AstraZeneca Pharmaceuticals. https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1. Revised May 2017. Accessed September 18, 2017.