Avelumab

An HCP Tool From AIM with Immunotherapy

Avelumab (Bavencio) is a programmed death ligand -1 (PD-L1)–blocking antibody or immune checkpoint inhibitor. The drug has several FDA-approved indications; however, this toolkit is based on the indication of avelumab for the treatment of renal cell carcinoma. It is indicated for use as a first-line treatment, in combination with axitinib, for patients with advanced renal cell carcinoma.

Multiple indications

Avelumab has additional indications for adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma and certain patients with urothelial carcinoma. More specifically, avelumab is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. It is also indicated in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy. In addition, it is used for patients with urothelial carcinoma that have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Clinical trial results

The JAVELIN Renal 101 phase 3 clinical trial (NCT02684006) established the utility of avelumab plus axitinib in patients with advanced renal-cell carcinoma. It was compared against the standard-of-care, sunitinib.

- Among the patients with PD-L1–positive tumors, the median progression-free survival was significantly longer in those who received avelumab plus axitinib (13.9 months) than among those patients who received sunitinib (8.2 months).
- In the overall population, the median follow-up with avelumab plus axitinib was 73.7 months and 73.6 months with sunitinib.
- Among the overall population, not excluding those without PDL1-positive tumors, median progression-free survival was significantly longer with avelumab plus axitinib (13.9 months) than with sunitinib (8.5 months).
- Long term safety and efficacy results confirmed objective response rate of 59.7% with the combination of avelumab and axitinib compared to 32% with sunitinib. However, at the updated analyses, the median overall survival for the overall population was 44.8 months with avelumab plus axitinib and 38.9 months with sunitinib, but was not statistically significant.

DRUG DOSAGE AND ADMINISTRATION

Avelumab is administered as an intravenous infusion over 60 minutes. For renal cell carcinoma, 800 mg is given every 2 weeks in combination with oral axitinib (5 mg) given twice daily, 12 hours apart with or without food. The 2-week administration schedule continues until disease progression or unacceptable toxicity.

Pre-medication administration

Avelumab has a moderate risk for infusion-related reactions, particularly for the first and second doses. Pre-medications are typically administered for the first 4 infusions and then subsequently as needed for prevention of infusion-related reactions, with antihistamines and antipyretics. Premedication should be administered for subsequent doses based upon clinical judgment and presence or the severity of previous reactions.

Grade 3 and 4 immune-mediated adverse reactions

Avelumab is generally withheld for severe (Grade 3) immune-mediated adverse reactions. The drug is permanently discontinued for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Should avelumab require dose interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤Grade 1. Then initiate corticosteroid taper and continue to taper over at least 1 month.

SIDE EFFECTS AND MANAGEMENT

Severe or fatal immune-mediated toxicities may occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-L1 blocking antibody. Usually these occur during treatment with the drug, but they can also manifest after drug discontinuation. These may include the following immune-mediated reactions like colitis, dermatologic adverse reactions, endocrinopathies, hepatitis, pneumonitis, nephritis with renal dysfunction, and may result in solid organ transplant rejection.

Serious adverse reactions occurred in 35% of patients receiving avelumab in combination with axitinib.

In the JAVELIN Renal 101 clinical trial, 7% of patients treated with avelumab and axitinib experienced major cardiac adverse events. No overall difference in safety or efficacy were reported between elderly patients and younger patients.

The most common adverse reactions (> 20%) in patients treated with avelumab in combination with axitinib were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache.

For suspected Stevens-Johnson syndrome, toxic epidermal necrolysis, or Drug Rash with Eosinophilia and Systemic Symptoms, withhold the drug. For confirmed cases, permanently discontinue.

Infusion-related reactions

Infusion-related reactions are possible with anti-PD-L1 antibodies, such as avelumab, and pre-medications are recommended. These reactions are more common at the first dose and symptoms may be nonspecific but present as chills, itching, malaise, and pyrexia. Avelumab may also cause patients to experience feeling abnormal or cold, dysphonia, hyperhidrosis, insomnia, pain in the extremities, pallor, and tremors.

In one study, 50.0% (12/24) of patients that received an avelumab infusion had an infusion-related reaction. Seven of these patients had grade 2 reactions and five patients had grade 1. To premedicate patients for infusion-related reactions, antihistamines, antipyretics, and analgesics are recommended. After prophylaxis treatment, an international study demonstrated a substantial reduction in the number of patients experiencing grade 2 reactions (1/7) during their second infusion of avelumab.

Immune-mediated

Management of administration with notable side effects of avelumab

Adverse event	Common management guidance
Pneumonitis	Grade 2: Withhold Grade 3 or 4: Permanently discontinue
Colitis	Grade 2: Withhold Grade 3: Withhold or permanently discontinue Grade 4: Permanently discontinue
Endocrinopathies	Grade 3 or 4: Withhold until stable or permanently discontinue depending on severity
Hepatitis	Withhold: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases to ≥ 3 times the upper limit normal (ULN) but less than 5 times the ULN or total bilirubin increases to ≥ 1.5 and up to 3 times ULN, withhold both avelumab and axitinib until these adverse reactions recover to Grades 0-1. If persistent (> 5 days), consider corticosteroid therapy [initial dose of 0.5 to 1 mg/kg/day] prednisone or equivalent followed by a taper. Reduce axitinib dose if rechallenging with axitinib. Permanently discontinue: ALT or AST increases to ≥ 5 times ULN or total bilirubin increases to more than 3 times the ULN. Permanently discontinue avelumab and axitinib. Also consider corticosteroid therapy [initial dose 1 to 2 mg/kg/day prednisone or equivalent followed by a taper].
Intestinal Perforation	Any Grade: Permanently discontinue
Myocarditis	Grade 2, 3 or 4: Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine: Withhold Grade 4 increased blood creatinine: Permanently discontinue

Other side effects

The table below shows management strategies for other side effects associated with avelumab.

Management of other notable side effects of avelumab

Adverse event	Common management guidance
Complications of allogenic healthy stem cell transplant (HSCT)	Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Health care providers should closely monitor patients for evidence of graft-versus-host-disease (GVHD) and related conditions. Intervention is required.
Embryo-fetal toxicity	May case fetal harm. Advise females of reproductive potential to use effective contraception during treatment with avelumab due to the risk to the fetus and then one month after the last dose of the drug. There is an increased risk of immune-mediated rejection of the developing fetus, which will result in death of the fetus.
Major adverse cardiovascular events	Grade 3 or 4: Optimize management of cardiovascular risk factors. Discontinue in combination with axitinib for grade 3-4 events. MACE occurred in 7% of patients with advanced RCC treated with avelumab in combination with axitinib.

KEY TAKEAWAYS ABOUT AVELUMAB

- Educate patients and caregivers about side effects and the importance of reporting symptoms as soon as possible. Remind patients about the importance of staying on schedule.

QUESTIONS & ANSWERS

Q. How long will patients stay on avelumab and axitinib for first-line treatment?

A. The prescribing information indicates until disease progression (unless the patient is otherwise deriving clinical benefit) or unacceptable toxicity.

Q. Are there standard dose reductions for adverse events?

A. It depends on the reaction. The dose is either withheld until the Grade 2 or Grade 3 event resolves sufficiently (typically to Grade 0 or Grade 1) or, if the event is Grade 4, avelumab is discontinued permanently.

Q. How do you modify doses in a patient experiences a severe adverse event?

A. Patients who experience severe (Grade 3) reactions will have the drug withheld. Sometimes, Grade 2 reactions, in the case of colitis, will also result in the drug being withheld. There are no dose modifications for this drug. It is permanently discontinued in the case of Grade 4 adverse reactions. Doses are not escalated.

Q. How often do patients discontinue avelumab due to adverse events?

A. There is a low rate of discontinuation due to adverse events. In the clinical trial, 7% of patients discontinued avelumab due to hepatotoxicity. In that study, grade 3 or 4 hepatotoxicity occurred in 9% of patients.

In the JAVELIN Renal 101 clinical trial (NCT02684006), treatment-related adverse events of any grade occurred in 99.5% of patients in the avelumab (with axitinib) group and in 99.3% of patients in the sunitinib-treated group. For the treatment-related adverse events that were grade ≥3 occurred in 71.2% of patients in the avelumab (with axitinib) group and in 71.5% of patients in the sunitinib-treated group.

Q. What are the chances of infusion reactions with avelumab??

A. The likelihood for infusion reactions is highest with the first 2 doses, and premedication is recommended for the first 4 infusions.

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

American Cancer Society
Patient programs, services, 24/7 hotline, etc
https://www.cancer.org/

National Cancer Institute
Information about cancer types, treatment, side effects, find a clinical trial, etc
https://www.cancer.gov/

FINANCIAL ASSISTANCE

Cancer Financial Aid Coalition
Facilitates communication, educates and advocates for patients.
www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)
Apply to determine if you are eligible for government assistance.
www.cms.gov or www.medicare.gov
800-633-4227

Lazarex Foundation
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.
www.lazarex.org

Needymeds
Database to search for free or low-cost medications, help with medical transportation and other resources.
www.needymeds.org

Patient Advocate Foundation
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.
www.patientadvocate.org
1-800-532-5274

The Sam Fund for Young Adult Survivors of Cancer
Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.
www.thesamfund.org
info@thesamfund.org

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation
Helps with the cost of medication. Availability of funds for patients with specific cancers is subject to availability.
www.cancercarecopay.org
1-866-552-6729

Medicine Assistance Tool
Database to search for patient assistance resources offered by pharmaceutical companies.
www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief
Provides direct financial support to patients who medically qualify. Funds subject to availability.
https://copays.org
1-866-512-3861

Good Days
Provides assistance with insurance co-pays, and prescription medications. Funds subject to availability.
www.mygooddays.org

Health Well Foundation
For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Funds for patients subject to availability. Patient must also meet eligibility for financial assistance.
www.healthwellfoundation.org or grants@healthwellfoundation.org
1-800-675-8416

The Assistance Fund, Inc
Provides prescription copay and financial assistance, including health insurance premiums. Funds subject to availability.
www.theassistancefund.org
https://tafcares.org
1-855-845-3663

PAN Foundation
Provides financial assistance to cover out-of-pocket treatment costs. Funds subject to availability.
www.panfoundation.org
1-866-316-PANF (7263)

Patient Assistance Program
Comprehensive database of patient assistance programs offering free medications.
www.rxassist.org
info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge
Provides free housing during treatment appointments. Requires a referral from your social worker.
www.cancer.org/
1-800-227-6333.

American Cancer Society – Extended Stay America
Partnership to offer discounted rooms for patients who have to be away from home for cancer treatment.
https://www.cancer.org/about-us/our-partners/extended-stay-america.html
1-800-227-2345

Healthcare Hospitality Network
Connects patients and their caregivers looking for lodging near their healthcare provider
https://members.hhnetwork.org/locate-a-house
1-800-318-8861

Joe's House
Helping patients with cancer find lodging throughout the U.S.
https://www.joeshouse.org/lodging?state=0
1-877-563-7468

National Council of State Housing Agencies
Emergency rental assistance programs available by state. Federal grants still available in some areas.
https://www.ncsha.org/emergency-housing-assistance/

TRANSPORTATION (AIR AND GROUND)

Air Charity Network
Provides access for people in need who are seeking free air transportation to specialized health care facilities
http://aircharitynetwork.org/
1-877-621-7177

Corporate Angel Network
Nonprofit organization that helps cancer patients by arranging free travel on corporate aircraft
https://www.corpangelnetwork.org/
info@corpangelnetwork.org
1-914-328-1313

Medicaid
Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.
1-877-633-8747

Mercy Medical Angels
Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.
www.mercymedical.org/

Pilots for Patients
Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.
www.pilotsforpatients.org
318-322-5112

ADDITIONAL RESOURCES

ASCO Daily News from the 2024 ASCO Annual Meeting. JAVELIN Renal-101 Follow-Up Finds No Significant Overall Survival Benefit With Avelumab/Axitinib in Advanced Renal Cell Carcinoma. Available at: https://dailynews.ascopubs.org/do/javelin-renal-101-follow-up-finds-no-significant-overall-survival-benefit-avelumab. Updated June 3, 2024. Accessed July 12, 2024.

Bavencio (avelumab) [prescribing information]. Rockland, MA, U.S.A. and Darmstadt, Germany: EMD Serono, Inc. and Merck; 2017. Available at: https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. Accessed July 7, 2024.

Hata K, Nakamura K, Maeda S et al. Infusion-Related Reactions Subsequent to Avelumab, Durvalumab, and Atezolizumab Administration: A Retrospective Observational Study. *Clin Pract*. 2024;14(2):377-387. doi: 10.3390/clinpract14020029.

Larkin J, Oya M, Martignoni M et al. Avelumab Plus Axitinib as First-Line Therapy for Advanced Renal Cell Carcinoma: Long-Term Results from the JAVELIN Renal 100 Phase Ib Trial. *Oncologist*. 2023; 28(4): 333–340. doi: 10.1093/oncolo/oyac243.

Motzer RJ, Penkov K, Haanen J et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1103-1115. doi: 10.1056/NEJMoa1816047.