AVELUMAB MECHANISM OF ACTION

- Indications and Prescribing Information
- Immune Checkpoint Mediated Self-Tolerance and Tumor Immune Evasion
- Restoration of Anti-Tumor Immune Response by Avelumab
- Structure of Avelumab Antibody
- Anti-Tumor Immune Response
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- Innate and Adaptive Immune System

Please see the full BAVENCIO® (avelumab) US Prescribing Information available at https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

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For additional resources, please visit our US Medical Resources Website Oncology page at https://medical.emdserono.com/en_US/medinfo/therapeutic-areas/oncology.html

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AVELUMAB INDICATIONS AND PRESCRIBING INFORMATION

Please refer to the full Prescribing Information on important treatment considerations for BAVENCIO® (avelumab) via the following link: **https://www.emdserono.com/us-en/pi/bavencio-pi.pdf**.

Note: selected prescribing information is excerpted further in the document.

INDICATIONS[1]

BAVENCIO® (avelumab) is indicated for:

- The treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC)
- The maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy
- The treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

BAVENCIO® (avelumab) in combination with axitinib is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

SELECTED PRESCRIBING INFORMATION[1]

Avelumab is a programmed death ligand-1 (PD-L1) blocking antibody. Avelumab is a human IgG1 lambda monoclonal antibody produced in Chinese hamster ovary cells and has a molecular weight of approximately 147 kDa.

PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. Avelumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

LITERATURE SEARCH

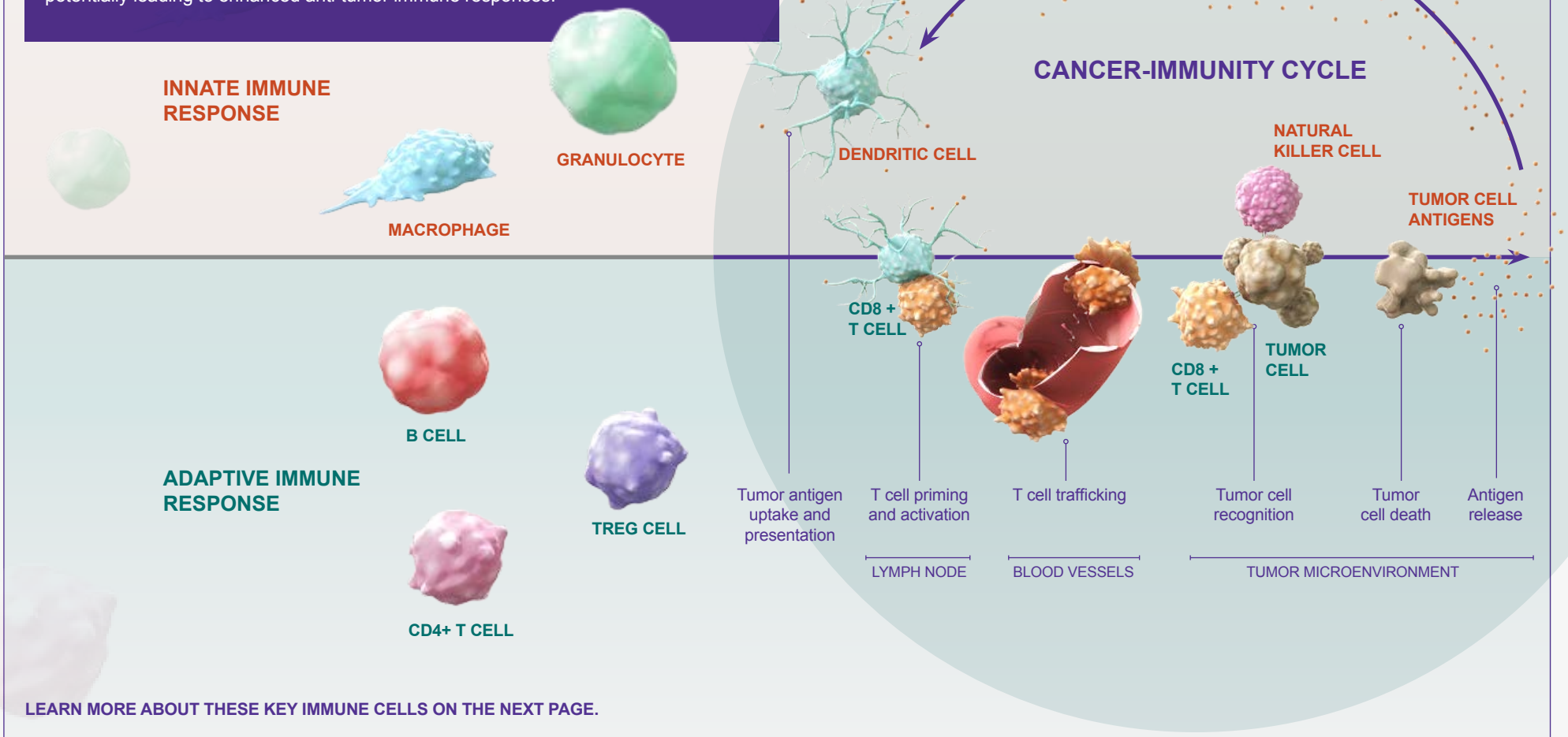
As of October 2025, a search of the published medical literature has identified several articles that discuss the mechanism of action of immune checkpoint inhibitors including avelumab. A review of these articles follows.

Reference: 1.BAVENCIO® (avelumab). Prescribing Information. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

THE ANTI-TUMOR IMMUNE RESPONSE

Both innate and adaptive immune systems play important roles in the body's anti-tumor defense.[1] Cooperation of these two arms of the immune system increases its ability to recognize and destroy tumor cells.[1]

The interaction of tumor cells and the immune system has been modeled as a continuous process known as the Cancer-Immunity Cycle.[2] This cycle begins with the release of cancer antigens by the tumor cell, which, when presented by antigen-presenting cells (APCs) such as dendritic cells, lead to priming, activation and trafficking of T cells to the tumor site and ultimately tumor cell death.[2] Since immune-mediated tumor cell lysis leads to further cancer antigen release, this cycle continues, potentially leading to enhanced anti-tumor immune responses.[2]



LEARN MORE ABOUT THESE KEY IMMUNE CELLS ON THE NEXT PAGE.

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1. Zhang H, Chen J. Current status and future directions of cancer immunotherapy. Journal of Cancer. 2018;9(10):1773-81; 2. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity. 2013;39(1);1-10; 3. Monjazeb AM, Zamora AE, Grossenbacher SK, Mirsoian A, Sckisel GD, Murphy WJ. Immunoediting and antigen loss: overcoming the Achilles heel of immunotherapy with antigen non-specific therapies. Front Oncol. 2013;3:197.

INNATE AND ADAPTIVE IMMUNE SYSTEM

INNATE IMMUNE SYSTEM

The innate immune system is the first line of defense against foreign bodies, such as bacteria and parasites, primarily through the recognition of distinct patterns, including lipopolysaccharides (LSPs), peptidoglycan, bacterial flagellar proteins, or viral double-stranded RNA, exhibited only by these foreign pathogens.[1] In addition, the activity of innate effector cells can also be elicited through immunoglobulin G (IgG) antigen recognition and the consequent interaction of the crystallisable fragment (Fc) region on the IgG with the Fc receptor on the effector immune cell leading to selected cell death of the antigen-expressing cell.[2] This mechanism is important in processes such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).[2]

NK cells

Natural killer (NK) cells destroy virus-infected cells and tumor cells through release of enzymes and cytokines, such as INFγ, to initiate apoptosis.[3]

Granulocytes

Granulocytes are a group of leukocytes including neutrophils, basophils, eosinophils and mast cells, which are responsible for eliminating bacteria and parasites.[3]

Macrophages

Macrophages are responsible for elimination of foreign or damaged cells through phagocytosis and can activate and recruit other immune cells.[3]

Dendritic cells

Dendritic cells connect the innate and adaptive immune systems, and are commonly found in tissues exposed to the external environment. These cells are part of the antigen-presenting cell group, which ingest pathogens and present them on their cell surface via major histocompatibility complex (MHC) for recognition by lymphocytes.[3]

ADAPTIVE IMMUNE SYSTEM

The adaptive immune system has an overall slower response than the innate immune system. This is due to its specific nature and the lag time necessary for activation and direction of lymphocytes towards a particular target.[1] Part of the recognized foreign body, known as the antigen, is incorporated into APCs and presented to activate B cells and T cells. B cells respond by producing antibodies specific to these antigens.[1] Active T cells either eliminate infected cells (CD8+ cytotoxic T cells) through the release of effector proteins and cytokines, or recruit and support other branches of the immune systems (CD4+ helper T cells) via cytokine release, chemokine release or membrane-bound signals.[1,4,5] The adaptive immune system may recruit the activity of innate immune system effectors, such as NK cells, to amplify the response.[1]

B cells

B cells proliferate and differentiate into antibody-producing plasma cells and memory B cells when activated by an antigen via MHC II presentation. These memory B cells allow the immune system a quicker response with subsequent infection by the same pathogen.[1,3]

CD4+ T cells

CD4+ T cells, or helper T cells, are activated through antigen presentation via MHC II presentation.[1,3,4] Activated CD4+ T cells recruit and support activities of B cells, CD8+ T cells and macrophages in their execution of the immune response through the release of cytokines or chemokines, and via membrane-bound signals.[1,3,4] Helper T cells can also proliferate to form memory helper T cells, which can facilitate a quicker response with subsequent exposure to the same pathogen.[1,3,4]

CD8+ T cells

CD8+ T cells, or cytotoxic T cells, act to eliminate tumor cells, cells infected with a virus, and other pathogens through cytokine release.[1,3,5] Upon antigen recognition through MHC I presentation, these cells are either activated to effector function or can proliferate to form memory cytotoxic T cells.[1,3,5] Similar to memory B cells, memory T cells facilitate a quicker secondary immune response with subsequent exposure to the same pathogen.[1,3,5]

Tregs

Tregs are T cells that regulate immune activity through suppression of cells of the innate immune system, including NK cells, monocytes/macrophages, dendritic cells and granulocytes, and cells of the adaptive immune system such as B cells, CD4+ T cells and CD8+ T cells.[3,6] There are multiple types of Tregs, each secreting different cytokines with specific effects but which ultimately reduce immune system activity.[7] Treg-mediated suppression can be antigen-specific.[1]

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1. Chaplin D. Overview of the Immune Response. J Allergy Clin Immunol. 2010;125:S3-23; 2. Stewart R, Hammond RA, Oberst M, Wilkonson RW. The role of Fc gamma receptors in the activity of immunomodulatory antibodies for cancer. JITC. 2012;2(29); 3. Spiering MJ. Primer on the Immune System. Alcohol Res. 2015;37(2):171–175; 4. Alberts B, Johnson A, Lewis J, et al. Helper T Cells and Lymphocyte Activation. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002; 5. Janeway CA, Travers P, Walport M, et al. T cell-mediated cytotoxicity. Immunobiology: The Immune System in Health and Disease. New York: Garland Science; 2001; 6. Peterson RA. Regulatory T-Cells: Diverse Phenotypes Integral to Immune Homeostasis and Suppression. Toxicol Pathol. 2012;40(2): 186-204; 7. Jonuleit H, Schmitt E. The Regulatory T Cell Family: Distinct Subsets and their Interrelation. J Immunol. 2003;171(12):6323-6327.

IMMUNE CHECKPOINTS ALLOW FOR SELF-TOLERANCE AND TUMOR IMMUNE EVASION

REGULATION OF T CELL RESPONSE

Responses of the activated T cells, elicited with antigen association, are regulated through a balance of co-stimulatory and co-inhibitory signals.[1] These signals occur through ligand-receptor interaction of membrane proteins, known as immune checkpoints, present on native cells of the body and on immune cells.[1,2]

IMMUNE CHECKPOINTS ALLOW FOR HEALTHY CELL SURVIVAL

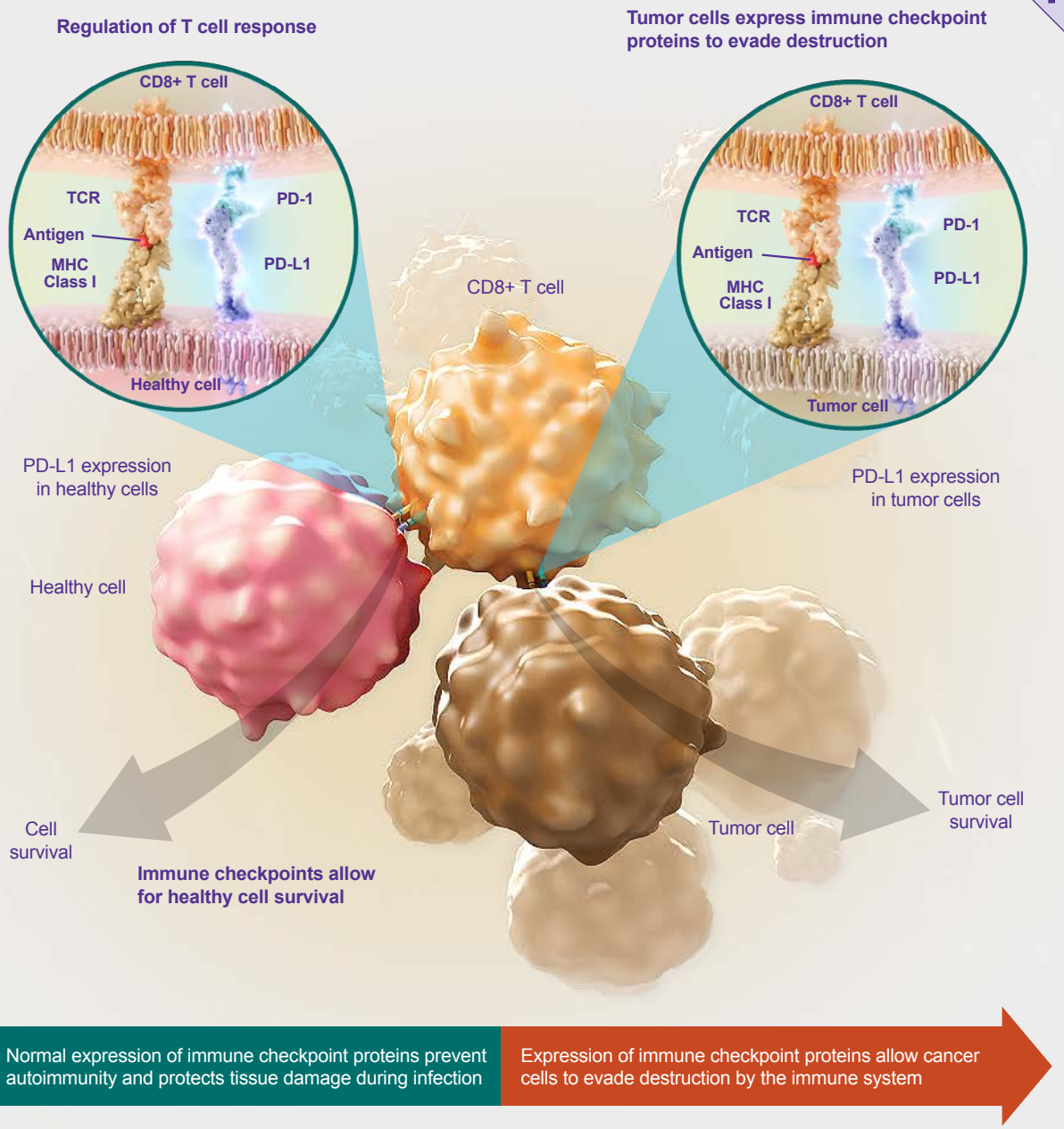
These immune checkpoints are crucial for the maintenance of self-tolerance (preventing autoimmunity) under normal physiological conditions, and for the protection of tissues from damage when the immune system is responding to pathogenic infection.[1]

One of the co-inhibitory immune checkpoint pathways that has been well studied is the PD-1/PD-L1 pathway. The PD-1 receptor is expressed on activated cytotoxic T cells and suppresses the cytotoxic response when PD-1 binds to PD-L1 expressed on, for example, normal tissue cells.[1]

TUMOR CELLS EXPRESS IMMUNE CHECKPOINT PROTEINS TO EVADE DESTRUCTION

Immune checkpoint proteins can be expressed by tumor cells as an important immune escape mechanism, thereby allowing tumor cells to evade recognition and destruction by the immune system.[1] One such mechanism to disrupt anti-tumor immunity is thought to be the cancer cell's ability to express the inhibitory immune checkpoint molecule, PD-L1, on its surface.[3] By interacting with PD-1 on the cytotoxic T cells, PD-L1 molecules expressed on the cancer cells may impair the anti-tumor response.[3]

The PD-1/PD-L1 pathway is being investigated as a therapeutic target in order to potentially restore anti-tumor immunity.[4,5]



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1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264; 2. Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies. Int Immunol. 2015;27(1):39-46; 3. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity. 2013;39(1);1-10; 4. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol. 2015;33(17):1974-1982; 5. Tan S, Chen D, Liu K, et al. Crystal clear: visualizing the intervention mechanism of the PD-1/PD-L1 interaction by two cancer therapeutic monoclonal antibodies. Protein Cell 2016;7(12):866-877; 6. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, Lyer AK. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol. 2017; 561. doi: 10.3389/fphar.2017.00561. eCollection 2017; 7.Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98-106.

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THE ANTI-PD-L1 ANTIBODY AVELUMAB

THE AVELUMAB VARIABLE REGION

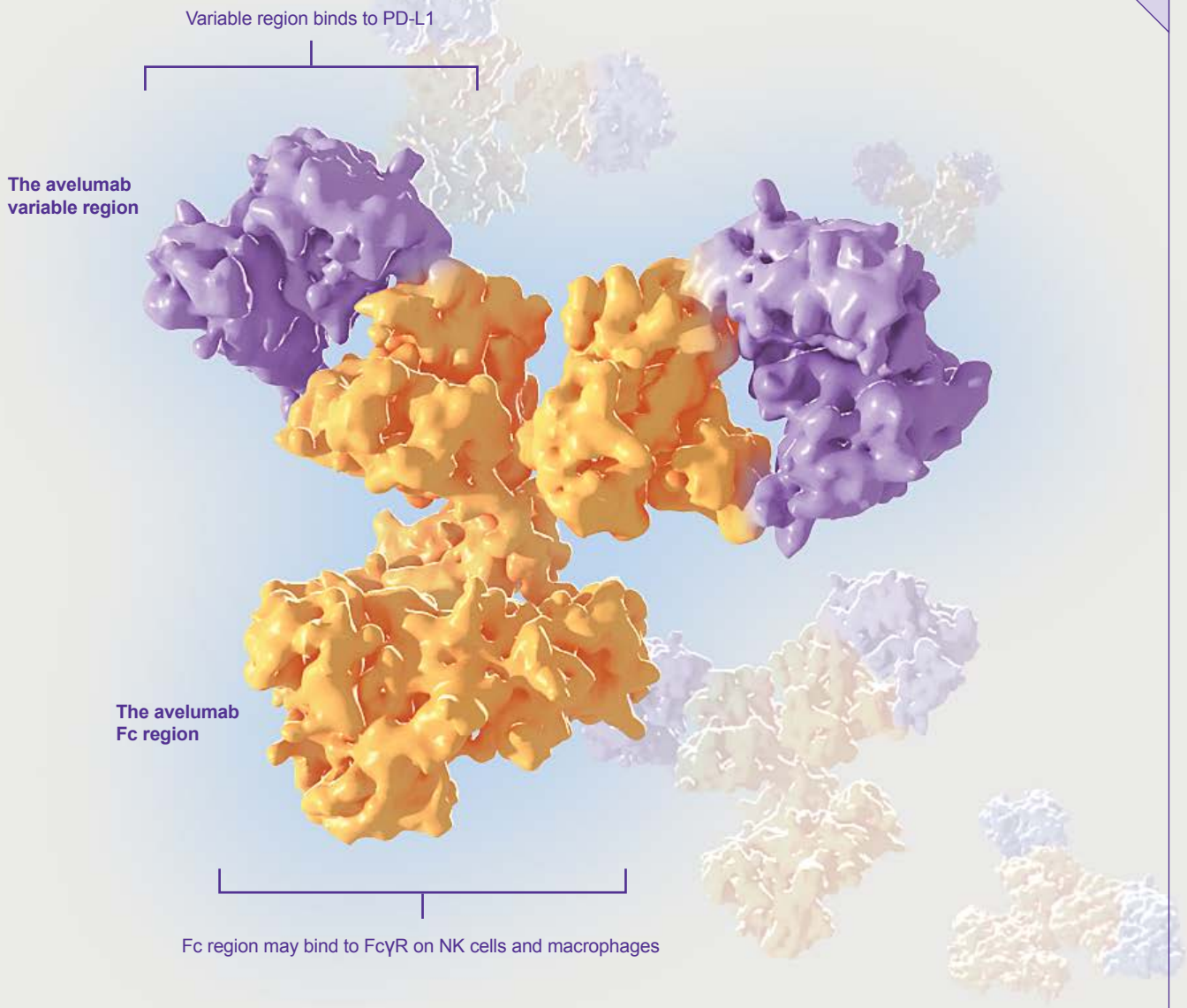
Avelumab is a human immunoglobulin G1 (IgG1) lambda monoclonal antibody against PD-L1. When bound to PD-L1, avelumab blocks the interaction between PD-L1 and its receptors PD-1 and B7.1, while leaving the PD-L2/PD-1 interaction intact.[1,2]

THE AVELUMAB FC REGION

Avelumab retains the fragment crystallizable region (Fc region) of the IgG antibody, allowing it to bind Fc-gamma receptors (FcγR) on natural killer (NK) cells and macrophages.[2-5]

This interaction may lead to antibody-dependent cell-mediated cytotoxicity (ADCC), in which the antigen-expressing cell is eliminated through direct killing via NK cells, as demonstrated in preclinical studies.[4]

Avelumab is one of several immune checkpoint inhibitors being investigated to treat various types of cancers. Structural differences exist between currently marketed PD-1/PD-L1 antibodies.[5] Avelumab is the only approved PD-1/PD-L1 inhibitor that has been shown to induce ADCC *in vitro*.[2,6]



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AVELUMAB MAY ALLOW FOR RESTORATION OF THE ANTI-TUMOR IMMUNE RESPONSE

Avelumab has been shown to induce cell death in multiple tumor cell lines *in vitro*.[1,2]
In cancer mouse models, avelumab treatment reduced tumor growth and improved mouse survival.[3,4]

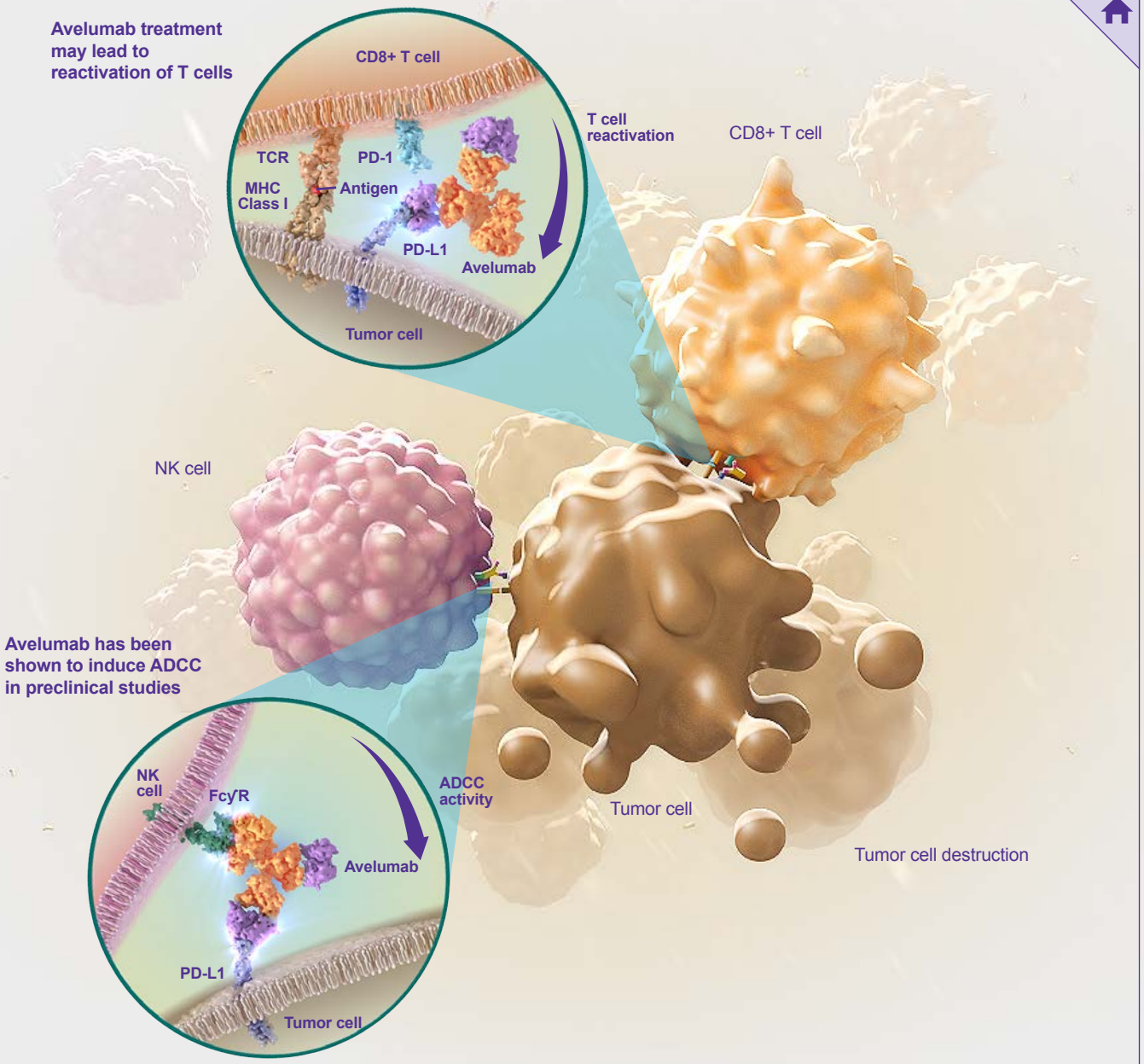
AVELUMAB TREATMENT MAY LEAD TO REACTIVATION OF T CELLS

The adaptive immune system has been implicated in the avelumab-mediated tumor response based on preclinical studies.

The interaction of avelumab with PD-L1 can block the PD-L1/PD-1 association, releasing the inhibitory effect on T cell mediated cytotoxic activity.[5] This may lead to restoration of immune responses, including the anti-tumor immune response.[5]

AVELUMAB HAS BEEN SHOWN TO INDUCE ADCC IN PRECLINICAL STUDIES

The innate immune system has also been implicated in tumor response to avelumab treatment based on preclinical studies.
Avelumab has been shown to induce NK cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.[1-3]



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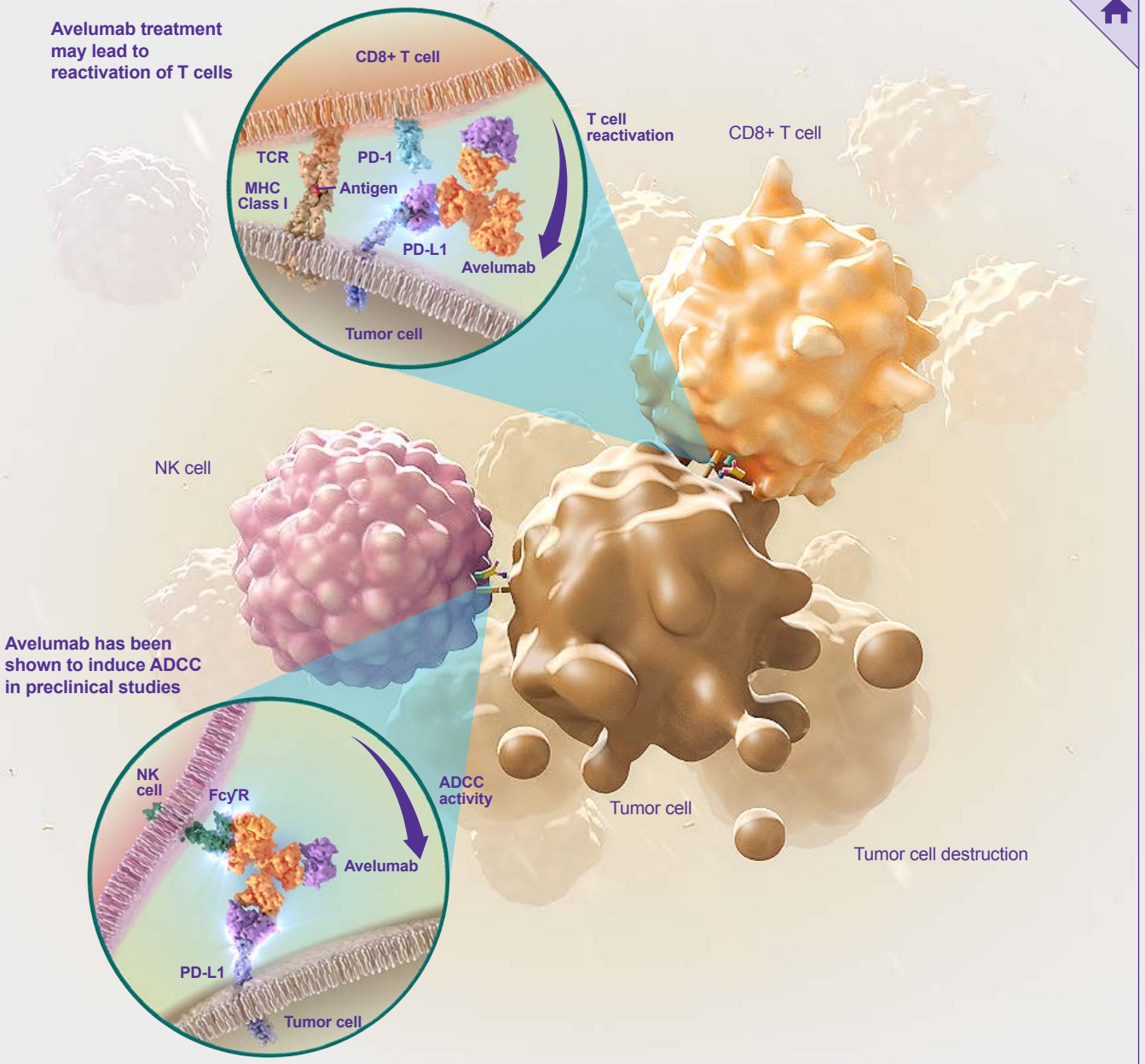
PRECLINICAL DATA

AVELUMAB TREATMENT MAY LEAD TO REACTIVATION OF T CELLS.

1. Avelumab reduced tumor growth in mouse models of cancer in a CD4+ T cell- and CD8+ T cell-dependent manner.[1,2] In one model, this response was long lasting and led to reduced death of mice.[1]
2. In an *in vitro* assay, avelumab increased the number of activated CD8+ T cells, measured by the capability to produce IFNγ and expression of the degranulation marker CD107a, in peripheral blood mononuclear cells harvested from both healthy donors and patients with cancer.[3]
3. Finally, response to avelumab was associated with PD-1 expression on CD8+ T cells and PD-L1 expression on dendritic cells.[3]

AVELUMAB HAS BEEN SHOWN TO INDUCE ADCC IN PRECLINICAL STUDIES

Avelumab treatment led to ADCC-mediated cell death in vitro in multiple cancer cell lines, as well as in a cancer mouse model. This effect was dependent on NK cells and was irrespective of whether these NK effectors came from healthy individuals or cancer patients.[2,4,5]



References:

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AVELUMAB IMPORTANT SAFETY INFORMATION

Avelumab can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for avelumab is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue avelumab depending on severity. In general, withhold avelumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue avelumab 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. In general, if avelumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

Avelumab can cause **immune-mediated pneumonitis**. Withhold avelumab for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.1% (21/1854) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

Avelumab can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (27/1854) of patients, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions. Systemic corticosteroids were required in all (27/27) patients with colitis.

Avelumab can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue avelumab based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with avelumab as a single agent in 1.1% (20/1854) of patients, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in all (20/20) patients with hepatitis.

Avelumab **in combination with axitinib** can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to avelumab alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold or permanently discontinue both avelumab and axitinib based on severity of AST, ALT, or total bilirubin elevation, and consider administering corticosteroids as needed. Consider rechallenge with Avelumab or axitinib, or sequential rechallenge with both avelumab and axitinib, after recovery. In patients treated with avelumab in combination with axitinib in the advanced RCC trials, increased ALT and increased AST were reported in 9% (Grade 3) and 7% (Grade 4) of patients. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant.

Avelumab can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency.

Avelumab can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction.

Reference: 1. BAVENCIO® (avelumab). Prescribing Information. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

AVELUMAB IMPORTANT SAFETY INFORMATION, continued

Avelumab can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1854) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (8/1854) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (97/1854) of patients, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions. Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism.

Avelumab can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions.

Avelumab can cause **immune-mediated nephritis with renal dysfunction**. Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 100% of patients with nephritis with renal dysfunction.

Avelumab can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold avelumab for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions. Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions.

Avelumab can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received Avelumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue Avelumab for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold avelumab for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

Avelumab can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue avelumab for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 26% of patients, including 3 (0.2%) Grade 4 and 10 (0.5%) Grade 3 infusion-related reactions. Eleven (85%) of the 13 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Avelumab **in combination with axitinib** can cause **major adverse cardiovascular events (MACE)** including severe and fatal events. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Permanently discontinue avelumab and axitinib for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with avelumab in combination with axitinib compared to 3.4% treated with sunitinib in a randomized trial. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%).

Avelumab can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab. It is not known whether avelumab is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants.

Reference: 1. BAVENCIO® (avelumab). Prescribing Information. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

AVELUMAB IMPORTANT SAFETY INFORMATION, continued

The most common adverse reactions (all grades, ≥20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (47%), musculoskeletal pain (29%), infusion-related reaction (26%), rash (25%), nausea (23%), constipation (22%), cough (22%), and diarrhea (21%).

Laboratory abnormalities worsening from baseline (all grades, ≥20%) in patients with **metastatic MCC** were decreased lymphocyte count (51%), decreased hemoglobin (40%), increased aspartate aminotransferase (31%), decreased platelet count (23%), increased alanine aminotransferase (22%), and increased lipase (21%).

A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving avelumab + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with avelumab experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The most common adverse reactions (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving avelumab + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving avelumab, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ≥20%) worsening from baseline in patients with **locally advanced or metastatic UC** receiving avelumab + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving avelumab in combination with axitinib. These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

The most common adverse reactions (all grades, ≥20%) in patients with **advanced RCC** receiving avelumab in combination with axitinib (vs sunitinib) were diarrhea (62% vs 48%), fatigue (53% vs 54%), hypertension (50% vs 36%), musculoskeletal pain (40% vs 33%), nausea (34% vs 39%), mucositis (34% vs 35%), palmar-plantar erythrodysesthesia (33% vs 34%), dysphonia (31% vs 3.2%), decreased appetite (26% vs 29%), hypothyroidism (25% vs 14%), rash (25% vs 16%), hepatotoxicity (24% vs 18%), cough (23% vs 19%), dyspnea (23% vs 16%), abdominal pain (22% vs 19%), and headache (21% vs 16%).

Selected laboratory abnormalities (all grades, ≥20%) worsening from baseline in patients with **advanced RCC** receiving avelumab in combination with axitinib (vs sunitinib) were blood triglycerides increased (71% vs 48%), blood creatinine increased (62% vs 68%), blood cholesterol increased (57% vs 22%), alanine aminotransferase increased (ALT) (50% vs 46%), aspartate aminotransferase increased (AST) (47% vs 57%), blood sodium decreased (38% vs 37%), lipase increased (37% vs 25%), blood potassium increased (35% vs 28%), platelet count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

Please see full Prescribing Information for additional information.

Reference: 1. BAVENCIO® (avelumab). Prescribing Information. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.