Treatment Guidelines

Avelumab Early Access – Single Patient Use

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Document Version	20-Jul-2016 / Version 3.0
Replaces Versions	29-Jun-2016 / Version 2.0 22-Apr-2016 / Version 1.0

Table of Contents

Table of Tables

Table of Figures

1 Treatment Guidance

1.1 Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal.

1.2 Avelumab Treatment

Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Generally, patients will receive avelumab treatment until confirmed progressive disease (PD) per RECIST 1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent (if applicable); however, patients may remain on avelumab beyond confirmed PD if the patient's Eastern Cooperative Oncology Group Performance Status (ECOG PS) has remained stable, and if in the opinion of the Physician, the patient will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms. It is recommended that patients receiving Avelumab through this process have a first radiological evaluation (CT scan of known disease sites) within 6 weeks to 10 weeks of beginning Avelumab, in order to assess response or progression.

Confirmed PD is defined as both an initial assessment of PD per RECIST 1.1 while receiving avelumab and a subsequent assessment, 4 to 8 weeks later, of PD while receiving avelumab.

Patients receiving avelumab who have experienced a complete remission (CR) should be treated for a minimum of 12 months after confirmation of response and / or until disease progression or unacceptable toxicity.

If a patient with a confirmed CR relapses after stopping treatment with avelumab, one re-initiation of treatment is allowed at the discretion of the Physician. In order to be eligible for retreatment, the patient must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy.

2 Which Patients Should Receive Avelumab

2.1 Patients Appropriate for Treatment

Patients, who are/have:

1. male or female patients aged ≥ 18 years

2. measurable metastatic Merkel cell carcinoma according to RECIST v1.1 who have failed at least one line of adequately dosed platinum-based chemotherapy in the metastatic setting and have subsequently progressed;

    - where adequate dosing of platinum-based chemotherapy is defined as a minimum of 3 cycles of platinum containing chemotherapy at therapeutic doses

3. not eligible for participation in any ongoing clinical trial for Merkel cell carcinoma including the Javelin Merkel 200 study (NCT02155647), or the Javelin Merkel 100 study (EMR 100070-006) currently being designed

4. adequate hematological function defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused)

5. adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range and AST and ALT levels $\leq 2.5 \times$ ULN for all patients

6. adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

7. negative serum pregnancy test prior to dosing for women of childbearing potential.

8. using a highly effective contraception for both male and female patients if the risk of conception exists. (Note: The effects of avelumab on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 28 days prior, throughout and for at least 60 days after avelumab treatment).

2.2 Patients Inappropriate for Treatment

Patients should not receive Avelumab, if they are/have:

1. brain metastases, except those meeting the following criteria:

    - Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to enrollment

    - No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)

    - Patients must be either off steroids or on a stable or decreasing dose of $\leq$10mg daily prednisone (or equivalent)

2. prior organ transplantation, including allogeneic stem-cell transplantation

3. significant acute or chronic infections including, among others:

- Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive)

4. active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

   a. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible

   b. Patients requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day

   c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

5. known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)

6. persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 is acceptable

7. pregnant or lactating

8. known alcohol or drug abuse

9. any other significant diseases (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Physician, might impair the patient's tolerance of treatment

10. any psychiatric condition that would prohibit the understanding or rendering of informed consent (if applicable)

11. had prior treatment with an anti-PD-L1 or anti-PD-1 agent for any disease

12. had a vaccination within 4 weeks of the first dose of avelumab and while on treatment except for administration of inactivated vaccines

13. currently on treatment with any other immunomodulating therapy

3 Avelumab Dosage and Administration

There are to be no dose reductions for avelumab. Patients will receive an IV infusion of avelumab at a dose of 10 mg/kg over the duration of 1 hour (-10 minutes / +20 minutes, that is, over 50 to

80 minutes) following pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to each drug infusion, once every 2 weeks.

Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Patients will receive drug once every 2 weeks until significant progressive disease or significant toxicity occurs which the treating physician feels would necessitate taking the patient off avelumab.

For patients receiving avelumab, treatment may continue past the initial determination of disease progression per RECIST 1.1 as long as the following criteria are met:

- Physician assessed clinical benefit, without rapid disease progression;
- Tolerance to avelumab;
- Stable ECOG PS;
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A first radiological evaluation on treatment (for example, a CT scan of known disease sites) should be performed within 6 weeks to 10 weeks of beginning avelumab, in order to assess response or progression (PD). A second radiographic assessment should be performed within 4 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

If the physician feels that the patient continues to achieve clinical benefit by continuing treatment, the patient should remain on treatment and continue to be monitored.

Further progression after the initial determination of PD is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and / or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Additionally, patients receiving avelumab who have experienced a CR should continue to receive avelumab for a minimum of 12 months after confirmation of response and/or until disease progression or unacceptable toxicity. In case a patient with a confirmed CR relapses after stopping

treatment, 1 re-initiation of treatment is allowed at the discretion of the physician. To be eligible for retreatment, the patient must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Patients who re-initiate treatment will stay on treatment and continue to be monitored.

4 Safety Considerations

4.1 Adverse Drug Reactions Requiring Avelumab Discontinuation or Dose Modifications

Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the physician, do not have any clinical correlate, and resolve within 7 days with adequate medical management

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to treatment according to the physician, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does not resolve to 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the patient should permanently discontinue treatment with avelumab.

- ADR (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same patient, treatment with avelumab has to be permanently discontinued.
- Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), and tumor lysis syndrome should be handled according to NCI guidelines (Table 1).

4.2 Special Precautions for Avelumab

Physicians should be aware of the possible occurrence of an anaphylactic / hypersensitivity reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension.

Patients must be observed for 2 hours post infusion, in an area with resuscitation equipment and emergency agents. At all times during treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of drug will be stopped in case of Grade $\geq$ 2 hypersensitivity, inflammatory response, or infusion-related reaction. The treatment recommendations for infusion-related reactions, severe hypersensitivity reactions, and tumor lysis syndrome according to the NCI guidelines (Table 1).

Physicians should also monitor patients closely for potential immune-related adverse events (irAEs), which may become manifest earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like anti-nuclear antibodies or anti-neutrophil cytoplasmic antibodies.

4.3 Management of Avelumab-Specific Adverse Events or Adverse Drug Reactions

4.3.1 Infusion-Related Reactions

A. Symptoms

- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

B. Management

Treatment of infusion-related reactions should follow guidelines set forth in Table 1 below.

Table 1 Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening. The total infusion time for study drug should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Stop drug infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the study infusion immediately and disconnect infusion tubing from the patient. Patients have to be withdrawn immediately from drug treatment and must not receive any further drug treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

If the patient has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the patient should be removed from treatment. If a patient experiences a Grade 3 or 4 infusion-related reaction at any time, the patient must discontinue drug.

4.3.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms

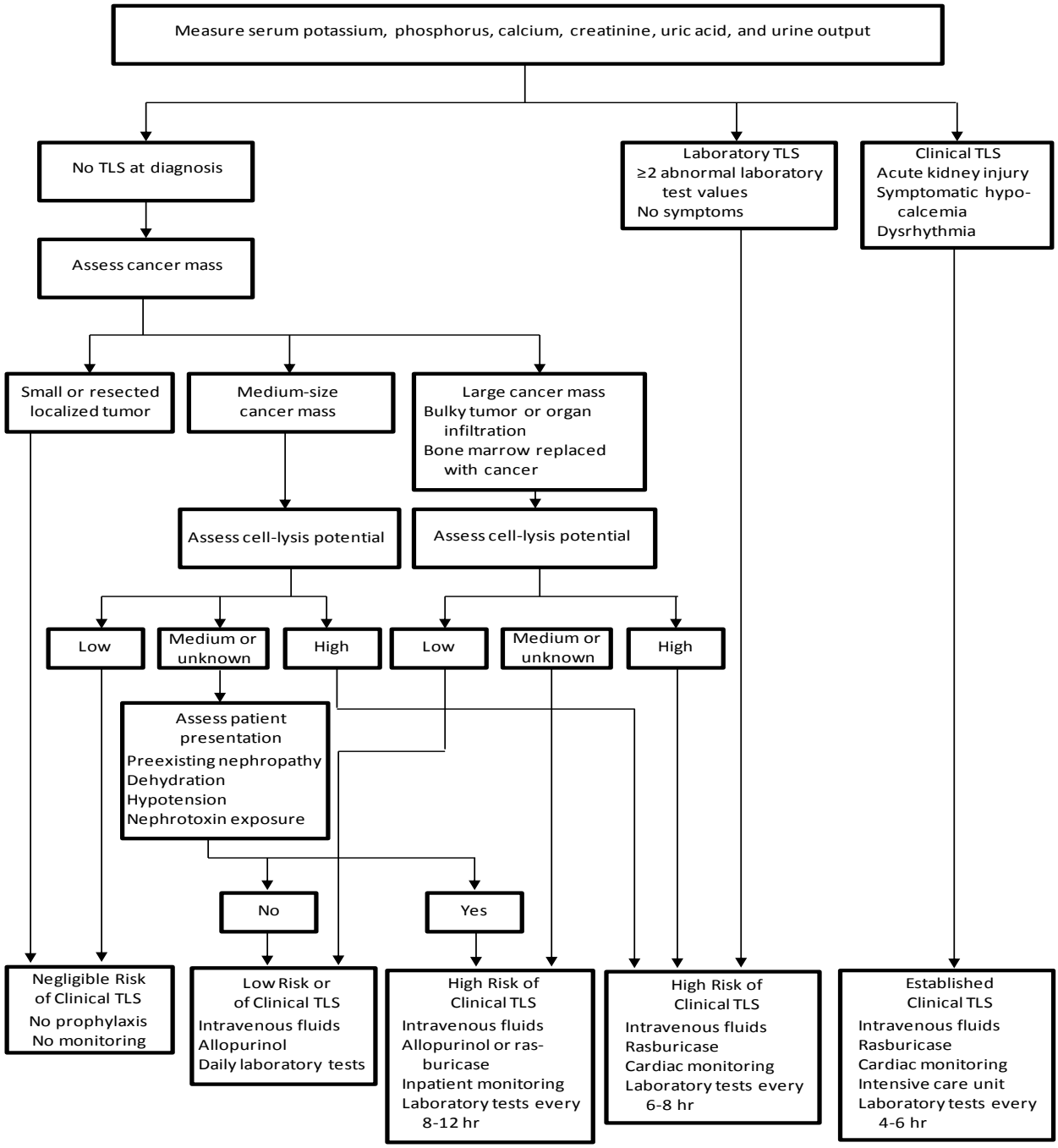
If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the physician immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to patients at the discretion of the physician.

4.3.3 Tumor Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated per the local guidelines and the management algorithm below (Howard et al. N Engl J Med 2011; 364:1844-1854).

Figure 1 Assessment and Initial Management of Tumor Lysis Syndrome



TLS = tumor lysis syndrome

4.3.4 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- **Grade 1 to 2:** treat symptomatically or with moderate dose steroids, more frequent monitoring
- **Grade 1 to 2 (persistent):** manage similar to high grade AE (Grade 3 to 4)
- **Grade 3 to 4:** treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in Table 2 below.

Table 2 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4

Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; IV=intravenous; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.