מרץ 2020

Bavencio® (Avelumab),
concentrate for solution for infusion vial

רופא/ה, רוקח/ת וצוות רפואי נכבדים,

חברת Merck שמחה להודיעכם על אישור משרד הבריאות לתוספת ההתוויה וכן על שינוי במשטר המינון, עבור התכשיר Bavencio® (Avelumab).

להלן רשימת ההתוויות המלאה של התכשיר (התוויות חדשות מודגשות בצהוב):

Bavencio is indicated for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

Bavencio is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who:
Have disease progression during or following platinum-containing chemotherapy disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

משטר המינון המעודכן (מודגש בצהוב):

Recommended Dosage for MCC
The recommended dose of Bavencio is 800 mg administered intravenously over 60 minutes every 2 weeks.
…
Recommended Dosage for UC
The recommended dose of Bavencio is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Recommended Dosage for RCC
The recommended dose of Bavencio is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks in combination with axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity.
…

Merck Serono Ltd.
18 Kishon St.
Yavne, Israel 81220
Tel: +972 8 9382610
Fax: +972 8 9403152
office.israel@merckgroup.com
www.merckserono.co.il

סל הבריאות 2020 - Bavencio® (Avelumab) בלולה בסל הבריאות עבור:

- מטופלי קרצינומה גרורתית של תאי מרקל ללא הגבלת קו טיפולי
- טיפול בסרטן מתקדם מקומי או גרורתי של דרכי השתן בחולים העונים על אחד מאלה:
  - החולה קיבל טיפול כימותרפי קודם במשטר שכלל תרכובת פלטינום למחלתו הגרורתית
  - מחלת החולה התקדמה בתוך 12 חודשים מטיפול כימותרפי במשטר שכלל תרכובת פלטינום במסגרת משלימה (adjuvant) או (neoadjuvant).
- טיפול בסרטן כליה מתקדם בקו טיפול ראשון עבור חולים בדרגת סיכון intermediate או poor

ההחמרות והשינויים המהותיים בעלון לרופא הינם (טקסט שנוסף מודגש בצהוב, טקסט שנמחק מופיע עם ~~קו חוצה~~):

4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Table 1: Guidelines for withholding or discontinuation of Bavencio

Treatment-related adverse reaction	**Severity***	**Treatment modification**
Hepatitis For Bavencio in combination with axitinib, see below.	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN	Withhold until adverse reactions recover to Grade 0-1
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN	Permanently discontinue
Pancreatitis	Suspected pancreatitis	Withhold
	Confirmed pancreatitis	Permanently discontinue
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue
Other immune-related adverse reactions (including ~~myocarditis, pancreatitis,~~ myositis, hypopituitarism, uveitis, Guillain-Barré syndrome)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above.	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: • Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) • Recurrent Grade 3 immune-related adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue

Treatment modifications when Bavencio is used in combination with axitinib

If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN, both Bavencio and axitinib should be withheld until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), corticosteroid therapy with prednisone or equivalent followed by a taper should be considered. Rechallenge with Bavencio or axitinib or sequential rechallenge with both Bavencio and axitinib

after recovery should be considered. Dose reduction according to the axitinib product information should be considered if rechallenging with axitinib.

If ALT or AST ≥ 5 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN or total bilirubin ≥ 3 times ULN, both Bavencio and axitinib should be permanently discontinued and corticosteroid therapy should be considered.

Dose modification advice for axitinib when used with Bavencio
When Bavencio is administered in combination with axitinib, please refer to the axitinib product information for recommended dose modifications for axitinib.

4.4 Special warnings and precautions for use

…

Immune-related pancreatitis

Immune-related pancreatitis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related pancreatitis. In symptomatic patients, obtain gastroenterology consultation and laboratory investigations (including imaging) to ensure the initiation of appropriate measures at an early stage. Corticosteroids should be administered for immune-related pancreatitis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper).

Avelumab should be withheld in the event of suspected immune-related pancreatitis. Avelumab should be permanently discontinued if immune-related pancreatitis is confirmed (see section 4.2).

Immune-related myocarditis

Immune-related myocarditis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related myocarditis. In symptomatic patients, obtain cardiologic consultation and laboratory investigations to ensure the initiation of appropriate measures at an early stage. Corticosteroids should be administered for immune-related myocarditis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper). If no improvement within 24 hours on corticosteroids, additional immunosuppression (e.g., mycophenolate, infliximab, anti-thymocyte globulin) should be considered.

Avelumab should be withheld in the event of suspected immune-related myocarditis. Avelumab should be permanently discontinued if immune-related myocarditis is confirmed (see section 4.2).

…

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported in less than 1% of patients: ~~myocarditis including fatal cases, pancreatitis including fatal cases,~~ myositis, hypopituitarism, uveitis, and Guillain-Barré syndrome (see section 4.8).

…

Hepatotoxicity (in combination with axitinib)

Hepatotoxicity occurred in patients treated with avelumab in combination with axitinib with higher than expected frequencies of Grade 3 and Grade 4 ALT and AST elevation compared to avelumab alone (see section 4.8).

Patients should be more frequently monitored for changes in liver function and symptoms as compared to when avelumab is used as monotherapy.

Avelumab should be withheld for Grade 2 hepatotoxicity until resolution and permanently discontinued for Grade 3 or Grade 4 hepatotoxicity. Corticosteroids should be considered for Grade ≥ 2 events (see section 4.2).

4.8 Undesirable effects

Merkel cell carcinoma

Summary of the safety profile

The safety of avelumab as monotherapy has been evaluated in 1,738 patients with solid tumours including metastatic MCC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies.

…

Tabulated list of adverse reactions

Adverse reactions reported for 88 patients with metastatic MCC ~~treated with avelumab 10 mg/kg and adverse reactions reported~~and for 1,650 patients in a phase I study in ~~other~~solid tumours are presented in Table 2. In both studies, avelumab was administered at 10 mg/kg every 2 weeks.

…

Locally Advanced or Metastatic Urothelial Carcinoma

Table 3 describes adverse reactions reported in 242 patients with locally advanced or metastatic UC receiving Bavencio at 10 mg/kg every 2 weeks in the UC cohorts of the EMR100070-001trial. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. The median duration of exposure to Bavencio was 12 weeks (range: 2 weeks to 92 weeks).

Fourteen patients (6%) who were treated with Bavencio experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

Bavencio was permanently discontinued for Grade 1-4 adverse reactions in 30 (12%) patients. The adverse reaction that resulted in permanent discontinuation in > 1% of patients was fatigue. Bavencio was temporarily discontinued in 29% of patients for adverse reactions, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The adverse reactions that resulted in temporary discontinuation in > 1% of patients were diarrhoea, fatigue, dyspnoea, urinary tract infection, and rash.

Grade 1-4 serious adverse reactions were reported in 41% of patients. The most frequent serious adverse reactions reported in ≥ 2% of patients were urinary tract infection/urosepsis, abdominal pain, musculoskeletal pain, creatinine increased/renal failure, dehydration, haematuria/urinary tract haemorrhage, intestinal obstruction/small intestine obstruction, and pyrexia.

The most common Grade 3 and 4 adverse reactions (≥ 3%) were anaemia, fatigue, hyponatremia, hypertension urinary tract infection, and musculoskeletal pain.

The most common adverse reactions (≥ 20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction.

Table 3 summarizes the adverse reactions that occurred in at least 10% of patients with locally advanced or metastatic UC receiving Bavencio while Table 4 summarizes selected Grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with Bavencio.

Table 3: All Grade Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic UC in the EMR100070-001 Trial

Adverse Reactions	Bavencio (N=242)	
	All Grades (%)	Grade 3-4 (%)
Any	98	59
Gastrointestinal Disorders		
Nausea	24	1
Abdominal pain[a]	19	2
Diarrhea	18	2
Constipation	18	1
Vomiting/Retching	14	1
General Disorders and Administration Site Conditions		
Fatigue [b]	41	7
Infusion-related reaction [c]	30	0.4
Peripheral oedema [d]	17	0.4
Pyrexia/Temperature increased	16	1
Infections		
Urinary tract infection [e]	21	5
Investigations		
Weight decreased	19	0
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	21	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain [f]	25	3
Renal Disorders		
Creatinine increased/Renal failure [g]	16	3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea/Exertional dyspnoea	17	2
Cough/Productive cough	14	0
Skin and Subcutaneous Tissue Disorders		
Rash [h]	15	0.4
Pruritus/Generalized pruritus	10	0.4
Vascular Disorders		
Hypertension/Hypertensive crisis	10	5

[a] Includes abdominal discomfort, abdominal pain upper and lower, and gastrointestinal pain
[b] Includes asthenia and malaise
[c] Infusion-related reaction is a composite term that includes chills, pyrexia, back pain, flushing, dyspnoea, and hypotension
[d] Includes oedema, generalized oedema, and peripheral swelling
[e] Includes urosepsis, cystitis, kidney infection, pyuria, and urinary tract infection due to fungus, bacterial, and enterococcus
[f] Includes back pain, myalgia, neck pain, and pain in extremity
[g] Includes acute kidney injury and glomerular filtration rate decreased
[h] Includes dermatitis acneiform, eczema, erythema, erythema multiforme, erythematous, macular, maculo-papular, papular, and pruritic rash

Table 4: Selected Laboratory Abnormalities* (Grade 3-4) in ≥ 1% of Patients with Locally Advanced or Metastatic UC Receiving Bavencio in the EMR100070-001Trial

Laboratory Tests	Grade 3-4 (N=242)** %
Chemistry	
Hyponatremia	16
GGT increased	12
Hyperglycaemia	9
Increased alkaline phosphatase	7
Increased lipase	6
Hyperkalaemia	3
Increased aspartate aminotransferase (AST)***	3
Increased creatinine	2
Increased amylase	2
Increased bilirubin	1
Hematology	
Lymphopenia	11
Anaemia	6

* Including Grade 3 and 4 lab abnormalities worsening from and unchanged since baseline.

** The number of patients with on study available laboratories varies between 188 and 235.

*** Increased alanine aminotransferase (ALT) was reported in 0.9% (Grade 3-4) of platinum-pretreated patients with locally advanced or metastatic UC.

Renal cell carcinoma

Summary of the safety profile

The safety of avelumab in combination with axitinib has been evaluated in 489 patients with advanced RCC receiving 10 mg/kg avelumab every 2 weeks and axitinib 5 mg orally twice daily in two clinical studies.

In this patient population, the most common adverse reactions were diarrhoea (62.8%), hypertension (49.3%), fatigue (42.9%), nausea (33.5%), dysphonia (32.7%), decreased appetite (26.0%), hypothyroidism (25.2%), cough (23.7%), headache (21.3%), dyspnoea (20.9%), and arthralgia (20.9%).

Tabulated list of adverse reactions

Adverse reactions reported for 489 patients with advanced RCC treated in two clinical studies with avelumab in combination with axitinib are presented in Table 5.

These reactions are presented by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 5: Adverse reactions in patients treated with avelumab in combination with axitinib in clinical studies B9991002 and B9991003

Frequency	Adverse reactions
Infections and infestations	
Uncommon	Rash pustular
Blood and lymphatic system disorders	
Common	Anaemia, thrombocytopenia
Uncommon	Lymphopenia, eosinophilia
Immune system disorders	
Common	Hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	Hyperthyroidism, adrenal insufficiency, thyroiditis
Uncommon	Autoimmune thyroiditis, hypophysitis
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyperglycaemia
Uncommon	Diabetes mellitus, Type 1 diabetes mellitus
Nervous system disorders	
Very common	Headache, dizziness
Common	Neuropathy peripheral
Cardiac disorders	
Uncommon	Myocarditis
Vascular disorders	
Very common	Hypertension
Common	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Dysphonia, cough, dyspnoea
Common	Pneumonitis
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, constipation, vomiting, abdominal pain
Common	Dry mouth, colitis
Uncommon	Autoimmune colitis, autoimmune pancreatitis, enterocolitis, ileus, pancreatitis necrotizing
Hepatobiliary disorders	
Common	Hepatic function abnormal
Uncommon	Hepatitis, hepatotoxicity, immune-mediated hepatitis, liver disorder
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Rash pruritic, rash maculo-papular, pruritus generalized, dermatitis acneiform, erythema, rash macular, rash papular, rash erythematous, dermatitis, eczema, rash generalized
Uncommon	Drug eruption, erythema multiforme, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, back pain, myalgia
Renal and urinary disorders	
Common	Acute kidney injury
General disorders and administrative site conditions	
Very common	Fatigue, chills, asthenia, pyrexia
Common	Oedema peripheral, influenza like illness

Frequency	Adverse reactions
Investigations	
Very common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased
Common	Blood creatinine increased, amylase increased, lipase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood thyroid stimulating hormone decreased, transaminases increased
Uncommon	Liver function test increased
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

Description of selected adverse reactions

Data for immune-related adverse reactions for avelumab as a monotherapy are based on 1,650 patients in the phase I study EMR100070-001 in solid tumours and 88 patients in study EMR100070-003, and for avelumab in combination with axitinib are based on 489 patients in study B9991002 and B9991003 (see section 5.1).

Immune-related pneumonitis

In patients treated with avelumab as monotherapy, 1.2% (21/1,738) of patients developed immune-related pneumonitis. Of these patients there was 1 (0.1%) patient with a fatal outcome, 1 (0.1%) patient with Grade 4, and 5 (0.3%) patients with Grade 3 immune-related pneumonitis.

…

In patients treated with avelumab in combination with axitinib, 0.6% (3/489) of patients developed immune-related pneumonitis. Of these patients, none experienced immune-related pneumonitis Grade ≥ 3.

The median time to onset of immune-related pneumonitis was 3.7 months (range: 2.7 months to 8.6 months). The median duration was 2.6 months (range: 3.3 weeks to more than 7.9 months).

Immune-related pneumonitis did not lead to discontinuation of avelumab in any patient. All 3 patients with immune-related pneumonitis were treated with high-dose corticosteroids for a median of 3.3 months (range: 3 weeks to 22.3 months). Immune-related pneumonitis resolved in 2 (66.7%) of the 3 patients at the time of data cut-off.

Immune-related hepatitis

In patients treated with avelumab as monotherapy, 0.9% (16/1,738) of patients developed immune-related hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 11 (0.6%) patients with Grade 3 immune-related hepatitis.

…

In patients treated with avelumab in combination with axitinib, 6.3% (31/489) of patients developed immune-related hepatitis. Of these patients, there were 18 (3.7%) patients with Grade 3 and 3 (0.6%) patients with Grade 4 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 2.3 months (range: 2.1 weeks to 14.5 months). The median duration was 2.1 weeks (range: 2 days to 8.9 months).

Avelumab was discontinued in 4.7% (23/489) of patients due to immune-related hepatitis. All 31 patients with immune-related hepatitis were treated for hepatitis including 30 (96.8%) patients treated with corticosteroids and 1 patient with a non-steroidal immunosuppressant. Twenty-eight (90.3%) of the 31 patients received high dose corticosteroids for a median of 2.4 weeks (range: 1 day to 10.2 months). Immune-related hepatitis resolved in 27 (87.1%) of the 31 patients at the time of data cut-off.

Immune-related colitis

In patients treated with avelumab as monotherapy, 1.5% (26/1,738) of patients developed immune-related colitis. Of these patients, there were 7 (0.4%) patients with Grade 3 immune-related colitis.

…

In patients treated with avelumab in combination with axitinib, 2.7% (13/489) of patients developed immune-related colitis. Of these patients, there were 9 (1.8%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 5.1 months (range: 2.3 weeks to 14 months). The median duration was 1.6 weeks (range: 1 day to more than 9 months).

Avelumab was discontinued in 0.4% (2/489) of patients due to immune-related colitis. All 13 patients with immune-related colitis were treated with corticosteroids and 12 (92.3%) of the 13 patients received high-dose corticosteroids for a median of 2.3 weeks (range: 5 days to 4.6 months). Immune-related colitis resolved in 10 (76.9%) of 13 patients at the time of data cut-off.

Immune-related pancreatitis

In patients treated with avelumab as monotherapy, immune-related pancreatitis occurred in less than 1% (1/4,000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune-related myocarditis

In patients treated with avelumab as monotherapy, immune-related myocarditis occurred in less than 1% (5/4,000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune-related endocrinopathies

Thyroid disorders

In patients treated with avelumab as monotherapy, 6% (98/1,738) of patients developed immune-related thyroid disorders, including 90 (5%) patients with hypothyroidism, 7 (0.4%) with hyperthyroidism, and 4 (0.2%) with thyroiditis. Of these patients, there were 3 (0.2%) patients with Grade 3 immune-related thyroid disorders.

…

In patients treated with avelumab in combination with axitinib, 24.7% (121/489) of patients developed immune-related thyroid disorders, including 111 (22.7%) patients with hypothyroidism, 17 (3.5%) with hyperthyroidism, and 7 (1.4%) with thyroiditis. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 3.6 weeks to 19.3 months). The median duration was not estimable (range: 8 days to more than 23.9 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 15 (12.4%) of the 121 patients at the time of data cut-off.

Adrenal insufficiency

In patients treated with avelumab as monotherapy, 0.5% (8/1,738) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (0.1%) patient with Grade 3 immune-related adrenal insufficiency.

…

In patients treated with avelumab in combination with axitinib, 1.8% (9/489) of patients developed immune-related adrenal insufficiency. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 5.5 months (range: 3.6 weeks to 8.7 months). The median duration was 2.8 months (range: 3 days to more than 15.5 months).

Immune-related adrenal insufficiency did not lead to discontinuation of avelumab in any patient. Eight (88.9%) patients with immune-related adrenal insufficiency were treated with corticosteroids and 2 (25%) of the 8 patients received high-dose corticosteroids (≥ 40 mg prednisone or equivalent) for a median of 8 days (range: 5 days to 11 days). Adrenal insufficiency resolved in 4 (44.4%) of the 9 patients at the time of data cut-off.

Type 1 diabetes mellitus
In patients treated with avelumab as monotherapy, Type 1 diabetes mellitus without an alternative aetiology occurred in 0.1% (2/1,738) of patients including two Grade 3 reactions that led to permanent discontinuation of avelumab.

In patients treated with avelumab in combination with axitinib, Type 1 diabetes mellitus without an alternative aetiology occurred in 1.0% (5/489) of patients. Of these patients, there was 1 (0.2%) patient with Grade 3 Type 1 diabetes mellitus.

The median time to onset of Type 1 diabetes mellitus was 1.9 months (range: 1.1 months to 7.3 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to Type 1 diabetes mellitus. All 5 patients with Type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus did not resolve in any of the patients at the time of data cut-off.

Immune-related nephritis and renal dysfunction
In patients treated with avelumab as monotherapy, immune-related nephritis occurred in 0.1% (1/1,738) of patients receiving avelumab leading to permanent discontinuation of avelumab.

In patients treated with avelumab in combination with axitinib, immune-related nephritis occurred in 0.4% (2/489) of patients. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related nephritis.

The median time to onset of immune-related nephritis was 1.2 months (range: 2.9 weeks to 1.8 months). The median duration was 1.3 weeks (range: more than 4 days to 1.3 weeks).

Immune-related nephritis did not lead to discontinuation of avelumab in any patient. All 2 patients with immune-related nephritis were treated with high-dose corticosteroids for a median of 1.1 weeks (range: 3 days to 1.9 weeks). Immune-related nephritis resolved in 1 (50%) of the 2 patients at the time of data cut-off.

Hepatotoxicity (in combination with axitinib)
In patients treated with avelumab in combination with axitinib, Grades 3 and Grade 4 increased ALT and increased AST were reported in 9% and 7% of patients, respectively.

In patients with ALT ≥ 3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%.

Among the 73 patients who were rechallenged with either avelumab (59%) or axitinib (85%) monotherapy or with both (55%), 66% had no recurrence of ALT ≥ 3 times ULN.

Immunogenicity
…

Of the 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (14.6%) tested positive. A new ADA method with improved sensitivity and drug tolerance was used in the RCC population. Overall, there was no evidence of altered pharmacokinetic

profile, increased incidence of infusion reactions or effects on efficacy with anti-avelumab antibody development.

יש לציין כי בעלון לרופא ישנם שינויים נוספים אשר אינם מהווים החמרה. למידע המלא יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות.

העלון לרופא מפורסים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום מרק סרונו בע"מ, רח' הקישון 18, יבנה 81220, טל' 09-9510737

בברכה,

אורית פוקס
רוקחת ממונה