יולי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלון התכשיר :</u>
<u>Imfinzi® 120 mg/2.4 ml solution for infusion</u>
<u>Imfinzi® 500 mg/10 ml solution for infusion</u>

הרכב:

Durvalumab 120 mg, 500 mg.

התוויה:

Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with PD-L1 high (Tumor cell ≥ 25% or IC ≥ 25%) locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.

Non-Small Cell Lung Cancer

IMFINZI is indicated for the treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **יולי 2020.**

העדכון העיקרי בעלון לרופא הוא:

~~HCP guide~~

~~This product is marketed with HCP guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.~~

2.3 Dose Modifications for Adverse Reactions

3 Table 1. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	**Severity[1]**	**Dosage Modification**	**~~IMFINZI Treatment Modification~~**	**~~Corticosteroid Treatment Unless Otherwise Specified~~**
Pneumonitis [see Warnings and Precautions (5.1)]	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).	~~Withhold dose[b]~~	~~Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper~~
	Grade 3 or 4	Permanently discontinue	~~Permanently discontinue~~	~~Initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper~~
Hepatitis [see Warnings and Precautions (5.2)]	~~Grade 2 ALT or AST >3-5xULN or total bilirubin >1.5-3xULN~~	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).	~~Withhold dose[b]~~	~~Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper~~
	For ALT or AST greater than 3 but less than or equal to 8 times the ULN or Total bilirubin greater than 1.5 but less than or equal to 5 times the ULN ~~Grade 3 ALT or AST ≤8xULN or total bilirubin ≤5xULN~~			
	ALT or AST greater than 8 times the ULN or total bilirubin greater than 5 times the ULN or Concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause~~Grade 3 ALT or AST >8xULN or total bilirubin >5xULN Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause~~	Permanently discontinue	~~Permanently discontinue~~	
Colitis or diarrhea [see Warnings and Precautions (5.3)]	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).	~~Withhold dose[b]~~	~~Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper~~
	Grade 3 or 4	Permanently discontinue	~~Permanently discontinue~~	
~~Hypothyroidism [see Warnings and Precautions (5.4)]~~	~~Grade 2-4~~			~~Initiate thyroid hormone replacement as clinically indicated~~
Hyperthyroidism	Grade 2-4	Withhold dose until	~~Withhold~~	~~Symptomatic management~~

[see Warnings and Precautions (5.4)]		clinically stable	~~dose until clinically stable~~	
Adrenal insufficiency, Hypophysitis/Hypopituitarism [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable	~~Withhold dose until clinically stable~~	~~Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated~~
Type 1 Diabetes Mellitus [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable	~~Withhold dose until clinically stable~~	~~Initiate treatment with insulin as clinically indicated~~
Nephritis [see Warnings and Precautions (5.5)]	For Creatinine greater than 1.5 to 3 times the ULN~~Grade 2 Creatinine >1.5-3x ULN~~	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).	~~Withhold dose[b]~~	~~Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper~~
	For Creatinine greater than 3 times the ULN~~Grade 3 Creatinine >3-6x ULN Grade 4 Creatinine >6x ULN~~	Permanently discontinue	~~Permanently discontinue~~	
Rash or dermatitis (including Pemphigoid) [see Warnings and Precautions (5.~~5~~6)]	Grade 2 for longer than 1 week or Grade 3~~Grade 2 for >1 week Grade 3~~	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).	~~Withhold dose[b]~~	~~Consider initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper~~
	Grade 4	Permanently discontinue	~~Permanently discontinue~~	
Infection [see Warnings and Precautions (5.~~6~~8)]	Grade 3 or 4	Withhold dose until clinically stable	~~Withhold dose~~	~~Symptomatic management; treat with anti-infectives for suspected or confirmed infections~~
Infusion-related reactions [see Warnings and Precautions (5.~~7~~9)]	Grade 1 or 2	Interrupt or slow the rate of infusion	~~Interrupt or slow the rate of infusion~~	~~Consider pre-medications with subsequent doses~~
	Grade 3 or 4	Permanently discontinue	~~Permanently discontinue~~	
Other immune-mediated adverse reactions [see Warnings and Precautions (5.7)]~~Other~~	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last IMFINZI dose~~Grade 3~~	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent) 2.	~~Withhold dose[b]~~	~~Symptomatic management~~
	Grade 4	Permanently discontinue	~~Permanently discontinue~~	~~Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper~~
Persistent Grade	Grade 2 or 3 adverse	Permanently discontinue		

2 or 3 adverse reaction (excluding endocrinopathies)	reaction that does not recover to Grade 0 or 1 within 12 weeks after last IMFINZI dose			
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after the last IMFINZI dose	Permanently discontinue		
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue		

[1]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[2] For myasthenia gravis permanently discontinue IMFINZI if the adverse reaction does notresolve to ≤ Grade 1
within 30 days or if there are signs of respiratoryand/or autonomic insufficiency.

~~[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.~~

~~[b] Based on severity of the adverse reactions, IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or other systemic immunosuppressants if there is worsening or no improvement. Corticosteroid taper should be initiated when adverse reaction improves to < Grade 1 and should be continued over at least 1 month. For adverse reactions that do not result in permanent discontinuation, resume treatment when adverse reaction returns to ≤ Grade 1 and the corticosteroid dose has been reduced to <10 mg prednisone or equivalent per day.~~

5.6 Immune-Mediated Dermatologic Reactions

IMFINZI can cause immune-mediated rash; or dermatitis (including Pemphigoid), ~~bullous dermatitis~~, other dermatologic reactions have occurred with other products in this class. Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) ~~have occurred with other products in this class~~ *[see Warnings and Precautions (5.7)]*.

Monitor for signs and symptoms of rash. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) rash or dermatitis lasting for more than 1 week or severe (Grade 3-4) rash or dermatitis followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity *[see Dosage and Administration (2.3)]*.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI *[see Adverse Reactions (6.1)]*, 26% of patients developed rash or dermatitis ~~and 0.4% of the patients developed vitiligo~~. Rash or dermatitis led to discontinuation of IMFINZI in 0.1% of the

1889 patients. Rash resolved in 62% of patients. Systemic corticosteroids were required in 2.0% of patients, including high-dose corticosteroids in 1% of patients.

5.7 Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis *[see Adverse Reactions (6.1)]*. In patients who received IMFINZI in clinical studies outside of the pooled dataset, myasthenia gravis occurred at an incidence of less than 0.1%.

The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, systemic inflammatory response syndrome, rhabdomyolysis, ~~myasthenia gravis,~~ histiocytic necrotizing lymphadenitis, vasculitis, hemolytic anemia, iritis, encephalitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome and Vogt-Koyanagi-Harada syndrome.

Table 2. Adverse Reactions in ≥10% of Patients in study 1108 UC Cohort

	IMFINZI (N=182)	
Adverse Reaction	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders		
Constipation	21	1.1
Nausea	16	~~2~~1.6
Abdominal pain[1]	14	~~3~~2.7
Diarrhea/Colitis	13	~~1~~1.1
General Disorders and Administration		
Fatigue[2]	39	6
Peripheral edema[3]	15	~~2~~1.6
Pyrexia/Tumor associated fever	14	~~1~~0.5
Infections		
Urinary tract infection[4]	15	~~4~~4.4
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	~~1~~0.5
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	24	~~4~~3.8
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2.2
Cough/Productive Cough	10	0

Skin and Subcutaneous Tissue Disorders		
Rash[6]	11	~~1~~0.5

Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥1% Patients ~~in UC~~ in Study 1108 Urothelial Carcinoma Cohort ~~Cohort Study 1108~~

Laboratory Abnormality ~~Test~~	Grade 3 – 4 %
Hyponatremia	12
Lymphopenia	11
Anemia	8
Increased alkaline phosphatase	4.1
Hypermagnesemia	4.2
Hypercalcemia	3
Hyperglycemia	3
Increased AST	2.4
Increased ALT	~~1~~0.6
Hyperbilirubinemia	1.2
Increased creatinine	1.2
Neutropenia	1.2
Hyperkalemia	1.2
Hypokalemia	1.2
Hypoalbuminemia	1.2

Immune-mediated rash

In the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 30 (1.6%) patients, including Grade 3 in 7 (0.4%) patients. The median time to onset was 74 days (range: 1-365 days). Eleven of the 30 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 2 patients. Resolution occurred in 18 patients.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,

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