יולי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

פרסום עדכון בעלון התכשיר :

Imfinzi® 120 mg/2.4 ml solution for infusion
Imfinzi® 500 mg/10 ml solution for infusion

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.

Small Cell Lung Cancer

IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment
of adult patients with extensive-stage small cell lung cancer (ES-SCLC)."

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

העדכון העיקרי בעלון לרופא הוא:

1. INDICATIONS AND USAGE

1.3 Small Cell Lung Cancer

IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)."

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing for Urothelial Carcinomaage

The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with chemotherapy are presented in Table 1 *[see Clinical Studies (14)]*.

IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended Dosages of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of Therapy
Urothelial Carcinoma	10 mg/kg every 2 weeks	Until disease progression or unacceptable toxicity
Unresectable stage III NSCLC	10 mg/kg every 2 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 months
ES-SCLC	1500 mg1 in combination with chemotherapy2 every 3 weeks (21 days) for 4 cycles,	Until disease progression or unacceptable toxicity
	followed by 1500 mg every 4 weeks as a single agent	

[1] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent until weight increases to greater than 30 kg.

[2] Administer IMFINZI prior to chemotherapy on the same day. When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information.

~~The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.~~

~~**2.2 Recommended Dosage for NSCLC**~~

~~The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression, unacceptable toxicity, or a maximum of 12 months~~

2.2 Dose Modifications for Adverse Reactions

Table ~~1~~2. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	Severity[1]	Dosage Modification
Hyperthyroidism or thyroiditis [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable
Other immune-mediated adverse reactions [see Warnings and Precautions (5.7)]	Grade ~~2 or~~ 3 ~~adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last IMFINZI dose~~	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent) [2].
	Grade 4	Permanently discontinue

2.4 Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. ~~IMFINZI is clear to opalescent, colorless to slightly yellow solution, free from visible particles.~~ Discard the vial if the solution is cloudy, discolored, or visible particles are observed.

WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

The frequency and severity of immune-mediated pneumonitis were similar whether IMFINZI was given as a single agent in patients with various cancers or in combination with chemotherapy in patients with ES-SCLC

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The data also reflects exposure to IMFINZI in combination with chemotherapy in 265 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC). In the CASPIAN study, IMFINZI was administered at a dose of 1500 mg every 3 or 4 weeks.

The data described in this section reflect exposure to IMFINZI in patients with locally advanced or metastatic urothelial carcinoma enrolled in Study 1108, ~~and~~ in patients with Stage III NSCLC enrolled in the PACIFIC study and in patients with ES-SCLC enrolled in the CASPIAN study.

Other adverse reactions occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.

Table 6 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.

~~**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.~~

~~Other adverse reactions occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.~~

~~Table 5 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.~~

Small Cell Lung Cancer

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was evaluated in CASPIAN, a randomized, open-label, multicenter, active-controlled trial. A total of 265 patients received IMFINZI 1500 mg in combination with chemotherapy every 3

weeks for 4 cycles followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants [see Clinical Studies (14.3)].

Among 265 patients receiving IMFINZI, 49% were exposed for 6 months or longer and 19% were exposed for 12 months or longer.

Among 266 patients receiving chemotherapy alone, 57% of the patients received 6 cycles of chemotherapy and 8% of the patients received PCI after chemotherapy.

IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each). Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%) and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue/asthenia and alopecia.

Table 7 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 7. Adverse Reactions Occurring in ≥ 10% Patients in the CASPIAN study

	IMFINZI with etoposide and either carboplatin or cisplatin N = 265		**Etoposide and either carboplatin or cisplatin N = 266**	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Respiratory, thoracic and mediastinal disorders				
Cough/Productive Cough	**15**	**0.8**	**9**	**0**
Gastrointestinal disorders				
Nausea	**34**	**0.4**	**34**	**1.9**
Constipation	**17**	**0.8**	**19**	**0**

Vomiting	15	0	17	1.1
Diarrhea	10	1.1	11	1.1
Endocrine disorders				
Hyperthyroidisma	10	0	0.4	0
Skin and subcutaneous tissue disorders				
Alopecia	31	1.1	34	0.8
Rashb	11	0	6	0
General disorders and administration site conditions				
Fatigue/Asthenia	32	3.4	32	2.3
Metabolism and nutrition disorders				
Decreased appetite	18	0.8	17	0.8

[a] Includes hyperthyroidismand Basedow's disease

[b] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash anddermatitis

Table 8 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 8. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%1 of Patients in the CASPIAN study

	IMFINZI with Etoposide and either Carboplatin or Cisplatin	Etoposide and either Carboplatin or Cisplatin
Laboratory Abnormality	Grade[2] 3 or 4 (%)[3]	Grade[2] 3 or 4 (%)[3]
Chemistry		

Hyponatremia	11	13
Hypomagnesemia	11	6
Hyperglycemia	5	5
Increased Alkaline Phosphatase	4.9	3.5
Increased ALT	4.9	2.7
Increased AST	4.6	1.2
Hypocalcemia	3.5	2.4
Blood creatinine increased	3.4	1.1
Hyperkalemia	1.5	3.1
TSH decreased < LLN4 and ≥ LLN at baseline	NA	NA
Hematology		
Neutropenia	41	48
Lymphopenia	14	13
Anemia	13	22
Thrombocytopenia	12	15

[1] The frequency cut off is based on any grade change frombaseline

[2] Graded according to NCI CTCAE version 4.03

[3] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 258 to 263) and chemotherapy (range: 253 to 262) except magnesium IMFINZI + chemotherapy(18) and chemotherapy(16)

[4] LLN = lower limit of normal

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant

medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to durvalumab ~~IMFINZI~~ to the incidence of antibodies to other products may be misleading.

Of ~~1570~~ 2280 patients ~~enrolled in Study 1108, the PACIFIC study or an additional open-label study,~~ who received IMFINZI 10 mg/kg every 2 weeks a or 20 mg/kg every 4 weeks as a single- agent, 69 patients (3%) tested positive for treatment-emergent~~nd evaluable for the presence of~~ anti-drug antibodies (ADA~~s~~), and ~~45~~12 (~~2.9~~0.5%) ~~patients~~ tested positive for for neutralizing antibodies~~treatment-emergent ADAs~~. The development of ~~treatment-emergent~~ ADA against durvalumab appears to have no clinically relevant effect on its pharmacokinetic profile or safety. ~~There are insufficient numbers of patients with ADA to determine whether ADA alters the safety or efficacy of durvalumab.~~

Of 201 patients in the CASPIAN study who received IMFINZI 1500 mg every 3 weeks in combination with chemotherapy for four doses followed by IMFINZI 1500 mg every 4 weeks no patients tested positive for treatment-emergent ADA.

8. USE IN SPECIFIC POPULATIONS

8.1 Geriatric Use

Of the 182 patients treated with IMFINZI in patients with urothelial carcinoma 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15% (17/112) and was 12% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older.

Of the 476 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older, while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

10. CLINICAL STUDIES

14.3 Small Cell Lung Cancer (SCLC)

The efficacy of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label trial (NCT03043872). Eligible patients had WHO Performance Status of 0 or 1 and were suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC. Patients with asymptomatic or treated brain metastases were eligible. Choice of platinum agent was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome; active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids were ineligible.

Randomization was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin). The evaluation of efficacy for ES-SCLC relied on comparison between:

- IMFINZI 1500 mg, and investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity, or

- Investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle, up to 6 cycles. After completion of chemotherapy, prophylactic cranial irradiation (PCI) as administered per investigator discretion.

Administration of IMFINZI as a single agent was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS) of IMFINZI plus chemotherapy vs. chemotherapy alone. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR), per RECIST v1.1.

The study population characteristics were: median age of 63 years (range: 28 to 82); 40% age 65 or older; 70% male; 84% White, 15% Asian, and 0.9% Black; 65% WHO/ECOG PS of 1; and 93% were former/current smokers. Ninety percent of patients had Stage IV disease and 10% had brain metastasis at baseline. A total of 25% of the patients received cisplatin and 74% of the patients received

carboplatin. In the chemotherapy alone arm, 57% of the patients received 6 cycles of chemotherapy, and 8% of the patients received PCI.

The OS results are summarized in Table 11 and Figure 2.

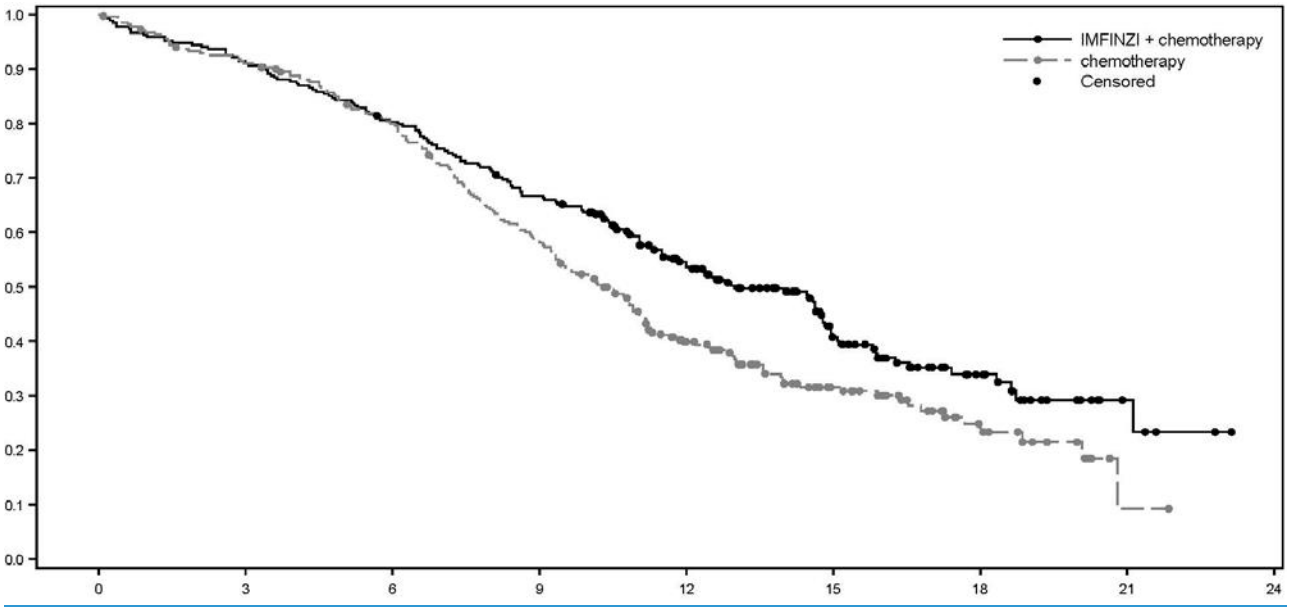
Table 11. OS Result for the CASPIAN Study

Endpoint	IMFINZI with Etoposide and either Carboplatin or Cisplatin (n=268)	Etoposide and either Carboplatin or Cisplatin (n=269)
Overall Survival (OS)		
Number of deaths (%)1	155 (58)	181 (67)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)
Hazard Ratio (95% CI)[2]	0.73 (0.59, 0.91)	
p-value[1]	0.0047	

[1] At a pre-specified interimanalysis, 336 OS events (79% of total planned events) were observed, and the boundary for declaring efficacy (0.0178) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary

[2] The analysis was performed using the stratified log-rank test, adjusting for planned platinumtherapy in Cycle 1 (carboplatin or cisplatin) and using the rank tests of association approach

Figure 2. Kaplan-Meier Curves of Overall Survival in the CASPIAN Study



Time from randomisation (months)

Number of patients at risk	0	3	6	9	12	15	18	21	24
IMFINZI + chemotherapy	268	244	214	177	116	57	25	5	0
chemotherapy	269	242	209	153	82	44	17	1	0

Investigator-assessed PFS (96% of total planned events) showed a HR of 0.78 (95% CI: 0.65, 0.94), with median PFS of 5.1 months (95% CI: 4.7, 6.2) in the IMFINZI plus chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) in the chemotherapy alone arm. The investigator-assessed confirmed ORR was 68% (95% CI: 62%, 73%) in the IMFINZI plus chemotherapy arm and 58% (95% CI: 52%, 63%) in the chemotherapy alone arm.

In the exploratory subgroup analyses of OS based on the planned platinum chemotherapy received at cycle 1, the HR was 0.70 (95% CI 0.55, 0.89) in patients who received carboplatin, and the HR was 0.88 (95% CI 0.55, 1.41) in patients who received cisplatin.

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

בכבוד רב,

אורה סטוליק

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