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פברואר 2025

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת מדיסון פארמה בע"מ שמחה להודיעכם על אישור משרד הבריאות לתוספות ההתוויות עבור התכשיר:

LIBTAYO **ליבטאיו**

Concentrate for solution for infusion

מרכיב פעיל : Cemiplimab

התוויות המאושרות (ההתוויות החדשות מסומנות בצהוב) :

Cutaneous Squamous Cell Carcinoma
LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

Basal Cell Carcinoma
LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

Non-Small Cell Lung Cancer

LIBTAYO as a single agent is indicated for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an approved test, with no EGFR, ALK or ROS1 aberrations, and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- metastatic.

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- metastatic.

ליבטאיו כמונותרפיה משמשת לטיפול במבוגרים:

- עם סרטן עור מסוג קרצינומה של תאי הקשקש (CSCC), גרורתי או בעל פולשנות מקומית, אשר אינם מועמדים לניתוח או הקרנה.
- עם סרטן עור מסוג קרצינומה של תאי הבסיס (BCC), גרורתי או בעל פולשנות מקומית, אשר קיבלו טיפול במעכב מסלול קיפוד (Hedgehog) והטיפול לא עבד כמצופה או לא היה נסבל.
- עם סרטן ריאה מסוג סרטן ריאה בעל תאים שאינם קטנים (NSCLC).

ליבטאיו עשוי להינתן כטיפול משולב עם כימותרפיה עבור סרטן ריאה בעל תאים שאינם קטנים (NSCLC). חשוב שתקרא

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גם את העלונים עבור הכימותרפיה הספציפית שאתה עשוי לקבל. אם יש לך שאלות בנוגע לתרופות אלו, שאל את הרופא שלך.

להלן המידע שהתעדכן בעלון לרופא המתייחס לתוספות ההתוויות:

4.2 Posology and method of administration

Non-Small Cell Lung Cancer
The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.
Refer to the Prescribing Information for the agents administered in combination with LIBTAYO for recommended dosing information, as appropriate.

Patient Selection for NSCLC
Select patients with locally advanced or metastatic NSCLC for treatment with LIBTAYO based on PD-L1 expression on tumor cells [see section 5.1].

[…]

4.4 Special warnings and precautions for use
[…]

4.8 Undesirable effects

Summary of the safety profile
Immune-mediated adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab (see "Description of selected adverse reactions" below).

Cemiplimab as monotherapy
The safety of cemiplimab as monotherapy has been evaluated in 1281 patients with advanced solid malignancies who received cemiplimab monotherapy in 5 clinical studies. The median duration of exposure to cemiplimab was 28 weeks (range: 2 days to 144 weeks).

Immune-mediated adverse reactions occurred in 21% of patients treated with cemiplimab in clinical trials including Grade 5 (0.3%), Grade 4 (0.6%), Grade 3 (5.7%), and Grade 2 (11.2%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 4.6% of patients. The most common immune-mediated adverse reactions were hypothyroidism (6.8%), hyperthyroidism (3.0%), immune-mediated pneumonitis (2.6%), immune-mediated hepatitis (2.4%), immune-mediated colitis (2.0%), and immune-mediated skin adverse reactions (1.9%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2).

Adverse events were serious in 32.4% of patients. Adverse events led to permanent discontinuation of cemiplimab in 9.4% of patients.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment (see section 4.4).

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Cemiplimab in combination with platinum-based chemotherapy
The safety of cemiplimab in combination with platinum-based chemotherapy has been evaluated in a clinical study of 465 patients with locally advanced or metastatic NSCLC. The median duration of exposure was 38.5 weeks (10 days to 102.6 weeks) in the cemiplimab and chemotherapy group, and 21.3 weeks (4 days to 95 weeks) in the chemotherapy group.

Immune-mediated adverse reactions occurred in 18.9% of patients including Grade 5 (0.3%), Grade 3 (2.6%), and Grade 2 (7.4%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 1.0% of patients. The most common immune-mediated adverse reactions were hypothyroidism (7.7%), hyperthyroidism (5.1%), increased blood thyroid stimulating hormone (4.2%), immune-mediated skin reaction (1.9%), immune-mediated pneumonitis (1.9%), and decreased blood thyroid stimulating hormone (1.6%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2).

Adverse events were serious in 25.3% of patients.

Adverse events led to permanent discontinuation of cemiplimab in 5.1% of patients.

~~*Tabulated list of adverse reactions*~~

~~*Adverse reactions observed in clinical studies of cemiplimab as monotherapy (N=1281) or reported from post-marketing use of cemiplimab are listed in Table 2. Adverse reactions are presented by system organ class and by 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); not known (cannot be estimated from available data).*~~

~~Table 2: Tabulated list of adverse reactions in patients treated with cemiplimab monotherapy (N=1281)~~

~~**System organ class Preferred term**~~	~~**Any Grade %**~~		~~**Grades 3-5 %**~~
~~**Infections and infestations**~~			
~~Upper respiratory tract infection[a]~~	~~Very Common~~	~~10.9~~	~~0.4~~
~~Urinary tract infection[b]~~	~~Common~~	~~8.4~~	~~2.3~~
~~**Blood and lymphatic system disorders**~~			
~~Anaemia~~	~~Very Common~~	~~15.0~~	~~5.2~~
~~Haemophagocytic lymphohistiocytosis[d]~~	~~Not Known~~	~~--~~	~~--~~
~~**Immune system disorders**~~			
~~Infusion-related reaction~~	~~Common~~	~~3.3~~	~~< 0.1~~
~~Thrombocytopaenia[c]~~	~~Uncommon~~	~~0.9~~	~~0~~

Sjogren's syndrome	Uncommon	0.2	0
Solid organ transplant rejection[d]	Not known	--	--
Endocrine disorders			
Hypothyroidism[e]	Common	6.8	< 0.1
Hyperthyroidism	Common	3.0	< 0.1
Thyroiditis[f]	Uncommon	0.6	0
Hypophysitis[g]	Uncommon	0.5	0.2
Adrenal insufficiency	Uncommon	0.5	0.5
Type 1 diabetes mellitus[h]	Rare	< 0.1	< 0.1
Nervous system disorders			
Headache	Common	8.0	0.3
Peripheral neuropathy[i]	Common	1.3	< 0.1
Meningitis[j]	Rare	< 0.1	< 0.1
Encephalitis	Rare	< 0.1	< 0.1
Myasthenia Gravis	Rare	< 0.1	0
Paraneoplastic encephalomyelitis	Rare	< 0.1	< 0.1
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	< 0.1	0
Eye disorders			
Keratitis	Rare	< 0.1	0
Uvetis	Rare	<0.1	<0.1
Cardiac disorders			
Myocarditis[k]	Uncommon	0.5	0.3
Pericarditis[l]	Uncommon	0.3	0.2
Vascular disorders			
Hypertension[m]	Common	5.7	2.6
Metabolism and nutrition disorders			
Decreased appetite	Very common	13.0	0.6
Respiratory, thoracic and mediastinal disorders			
Cough[n]	Very common	10.8	0.2
Dyspnoea[o]	Common	9.7	1.2
Pneumonitis[p]	Common	3.3	1.1
Gastrointestinal disorders			
Diarrhoea	Very common	16.3	0.7
Nausea	Very common	14.7	0.2

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Constipation	Very common	12.3	0.2
Abdominal pain[q]	Very common	11.5	0.7
Vomiting	Common	9.9	0.2
Colitis[r]	Common	2.0	0.8
Stomatitis	Common	1.8	< 0.1
Gastritis[s]	Uncommon	0.2	0
Hepatobiliary disorders			
Hepatitis[t]	Common	2.7	1.8
Skin and subcutaneous skin disorders			
Rash[u]	Very common	21.4	1.6
Pruritus[v]	Very common	12.7	0.2
Actinic keratosis	Common	3.7	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[w]	Very common	28.3	1.8
Arthritis[x]	Uncommon	0.9	0.2
Myositis[y]	Uncommon	0.3	< 0.1
Muscular weakness	Uncommon	0.2	0
Polymyalgia rheumatica	Uncommon	0.2	0
Renal and urinary disorders			
Nephritis[z]	Common	1.2	0.2
Noninfective cystitis	Not known	--	--
General disorders and administration site conditions			
Fatigue[aa]	Very common	29.9	2.6
Pyrexia[bb]	Common	8.7	0.2
Oedema[cc]	Common	7.9	0.4
Investigations			
Alanine aminotransferase increased	Common	4.6	0.5
Aspartate aminotransferase increased	Common	4.4	0.7
Blood alkaline phosphatase increased	Common	1.9	0.2
Blood creatinine increased	Common	1.6	0
Blood thyroid stimulating hormone increased	Uncommon	0.8	0
Transaminases increased	Uncommon	0.4	<0.1
Blood bilirubin increased	Uncommon	0.4	<0.1

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~~Blood thyroid stimulating hormone decreased~~	~~Rare~~	~~< 0.1~~	~~0~~

~~Version 4.03 of NCI CTCAE was used to grade toxicity.~~

~~a. Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, viral respiratory tract infection, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, and tracheitis.~~

~~b. Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, kidney infection, pyelonephritis acute, urosepsis, bacterial cystitis, escherichia urinary tract infection, pyelocystitis, bacterial urinary tract infection, and urinary tract infection pseudomonal.~~

~~c. Thrombocytopaenia includes thrombocytopaenia and immune thrombocytopaenia.~~

~~d. Post marketing event.~~

~~e. Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism.~~

~~f. Thyroiditis includes thyroiditis, autoimmune thyroiditis, and immune-mediated thyroiditis.~~

~~g. Hypophysitis includes hypophysitis and lymphocytic hypophysitis.~~

~~h. Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus.~~

~~i. Peripheral neuropathy includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, polyneuropathy, neuritis, and peripheral motor neuropathy.~~

~~j. Meningitis includes aseptic meningitis.~~

~~k. Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.~~

~~l. Pericarditis includes autoimmune pericarditis and pericarditis.~~

~~m. Hypertension includes hypertension and hypertensive crisis.~~

~~n. Cough includes cough, productive cough, and upper-airway cough syndrome.~~

~~o. Dyspnea includes dyspnea and dyspnea exertional.~~

~~p. Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis.~~

~~q. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain.~~

~~r. Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis.~~

~~s. Gastritis includes gastritis and immune-mediated gastritis.~~

~~t. Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinemia, hepatocellular injury, hepatic failure, and abnormal hepatic function.~~

~~u. Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, and parapsoriasis.~~

~~v. Pruritus includes pruritus and allergic pruritus.~~

~~w. Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort.~~

~~x. Arthritis includes arthritis, polyarthritis, autoimmune arthritis, and immune-mediated arthritis.~~

~~y. Myositis includes myositis and dermatomyositis.~~

~~z. Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, nephritis, renal failure, tubulointerstitial nephritis, and nephropathy toxic.~~

~~aa. Fatigue includes fatigue, asthenia, and malaise.~~

~~bb. Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.~~

~~cc. Edema includes peripheral edema, face edema, peripheral swelling, face swelling, localised edema, generalised edema, and swelling.~~

Tabulated list of adverse reactions

Table 2 lists the incidence of adverse reactions in the monotherapy safety dataset and in patients treated with cemiplimab in combination with chemotherapy. Adverse reactions are presented by system organ class and by 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); not known (cannot be estimated from available data).

Adverse reactions known to occur with cemiplimab or combination therapy components given alone may occur during treatment with these medicinal products in combination.

Table 2: Tabulated list of adverse reactions in patients treated with cemiplimab monotherapy and cemiplimab in combination with chemotherapy

	Cemiplimab Monotherapy			**Cemiplimab in Combination with Chemotherapy**		
System organ class Preferred term	Any Grade %		Grade 3-5 (%)	Any Grade %		Grade 3-5 (%)
Infections and infestations						
Upper respiratory tract infection[a]	Very common	10.9	0.4			
Urinary tract infection[b]	Common	8.4	2.3			
Blood and lymphatic system disorders						
Anaemia	Very common	15.0	5.2	Very common	43.6	9.9
Neutropaenia				Very common	15.4	5.8
Thrombocytopaenia				Very common	13.1	2.6
Haemophagocytic lymphohistiocytosis[d]	Not Known	--	--			
Immune system disorders						
Infusion-related reaction	Common	3.3	< 0.1	Uncommon	0.3	0
Thrombocytopaenia[c]	Uncommon	0.9	0			
Sjogren's syndrome	Uncommon	0.2	0			
Solid organ transplant rejection[d]	Not known	--	--			
Endocrine disorders						
Hypothyroidism[e]	Common	6.8	< 0.1	Common	7.7	0.3
Hyperthyroidism	Common	3.0	< 0.1	Common	5.1	0
Thyroiditis[f]	Uncommon	0.6	0	Uncommon	0.6	0
Hypophysitis[g]	Uncommon	0.5	0.2			
Adrenal insufficiency	Uncommon	0.5	0.5			
Type 1 diabetes mellitus[h]	Rare	< 0.1	< 0.1	Uncommon	0.3	0
Nervous system disorders						
Headache	Common	8.0	0.3			
Peripheral neuropathy[i]	Common	1.3	< 0.1	Very common	21.2	0
Meningitis[j]	Rare	< 0.1	< 0.1			
Encephalitis	Rare	< 0.1	< 0.1			
Myasthenia Gravis	Rare	< 0.1	0			
Paraneoplastic encephalomyelitis	Rare	< 0.1	< 0.1			
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	< 0.1	0			
Eye disorders						
Keratitis	Rare	< 0.1	0			
Uveitis	Rare	< 0.1	< 0.1			
Cardiac disorders						

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Myocarditis[k]	Uncommon	0.5	0.3			
Pericarditis[l]	Uncommon	0.3	0.2			
Vascular disorders						
Hypertension[m]	Common	5.7	2.6			
Metabolism and nutrition disorders						
Decreased appetite	Very common	13.0	0.6	Very common	17.0	1.0
Hyperglycaemia				Very common	17.6	1.9
Hypoalbuminaemia				Very common	10.3	0.6
Respiratory, thoracic and mediastinal disorders						
Cough[n]	Very common	10.8	0.2			
Dyspnoea[o]	Common	9.7	1.2	Very common	12.8	2.2
Pneumonitis[p]	Common	3.3	1.1	Common	4.2	0.6
Gastrointestinal disorders						
Nausea	Very common	14.7	0.2	Very common	25.0	0
Diarrhoea	Very common	16.3	0.7	Very common	10.6	1.3
Constipation	Very common	12.3	0.2	Very common	13.8	0.3
Abdominal pain[q]	Very common	11.5	0.7			
Vomiting	Common	9.9	0.2	Very common	12.2	0
Colitis[r]	Common	2.0	0.8	Common	1.0	0.3
Stomatitis	Common	1.8	< 0.1			
Gastritis[s]	Uncommon	0.2	0			
Hepatobiliary disorders						
Hepatitis[t]	Common	2.7	1.8			
Psychiatric Disorders						
Insomnia				Very common	10.9	0
Skin and subcutaneous skin disorders						
Rash[u]	Very common	21.4	1.6	Very common	12.5	1.3
Pruritus[v]	Very common	12.7	0.2	Common	3.5	0
Actinic keratosis	Common	3.7	0			
Alopecia				Very common	36.9	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[w]	Very common	28.3	1.8	Very common	26.9	1.3
Arthritis[x]	Uncommon	0.9	0.2	Common	1.0	0
Myositis[y]	Uncommon	0.3	< 0.1			
Muscular weakness	Uncommon	0.2	0			
Polymyalgia rheumatica	Uncommon	0.2	0			
Renal and urinary disorders						
Nephritis[z]	Common	1.2	0.2	Common	2.6	0
Noninfective cystitis	Not known	--	--			
General disorders and administration site conditions						
Fatigue[aa]	Very common	29.9	2.6	Very common	23.4	3.8
Pyrexia[bb]	Common	8.7	0.2			
Oedema[cc]	Common	7.9	0.4			
Investigations						
Alanine aminotransferase increased	Common	4.6	0.5	Very common	16.3	2.2

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Aspartate aminotransferase increased	Common	4.4	0.7	Very common	14.7	0.3
Blood alkaline phosphatase increased	Common	1.9	0.2	Common	4.5	0
Blood creatinine increased	Common	1.6	0	Common	8.7	0
Blood thyroid stimulating hormone increased	Uncommon	0.8	0	Common	4.2	0
Transaminases increased	Uncommon	0.4	< 0.1			
Blood bilirubin increased	Uncommon	0.4	< 0.1	Common	1.6	0.3
Blood thyroid stimulating hormone decreased	Rare	< 0.1	0	Common	1.6	0
Weight decreased				Very common	11.2	1.3
Gamma-glutamyltransferase increased				Uncommon	0.6	0.3

Version 4.03 of NCI CTCAE was used to grade toxicity.

a. *Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, viral respiratory tract infection, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, and tracheitis.*
b. *Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, kidney infection, pyelonephritis acute, urosepsis, bacterial cystitis, escherichia urinary tract infection, pyelocystitis, bacterial urinary tract infection, and urinary tract infection pseudomonal.*
c. *Thrombocytopaenia includes thrombocytopaenia and immune thrombocytopaenia.*
d. *Post-marketing event.*
e. *Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism.*
f. *Thyroiditis includes thyroiditis, autoimmune thyroiditis, and immune-mediated thyroiditis.*
g. *Hypophysitis includes hypophysitis and lymphocytic hypophysitis.*
h. *Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus.*
i. *Peripheral neuropathy includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, polyneuropathy, neuritis, and peripheral motor neuropathy.*
j. *Meningitis includes aseptic meningitis.*
k. *Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.*
l. *Pericarditis includes autoimmune pericarditis and pericarditis.*
m. *Hypertension includes hypertension and hypertensive crisis.*
n. *Cough includes cough, productive cough, and upper-airway cough syndrome.*
o. *Dyspnea includes dyspnea and dyspnea exertional.*
p. *Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis.*
q. *Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain.*
r. *Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis.*
s. *Gastritis includes gastritis and immune-mediated gastritis.*
t. *Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinemia, hepatocellular injury, hepatic failure, and abnormal hepatic function.*
u. *Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, and parapsoriasis.*
v. *Pruritus includes pruritus and allergic pruritus.*
w. *Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort.*

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x. *Arthritis includes arthritis, polyarthritis, autoimmune arthritis, and immune-mediated arthritis.*
y. *Myositis includes myositis and dermatomyositis.*
z. *Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, nephritis, renal failure, tubulointerstitial nephritis, and nephropathy toxic.*
aa. *Fatigue includes fatigue, asthenia, and malaise.*
bb. *Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.*
cc. *Edema includes peripheral edema, face edema, peripheral swelling, face swelling, localised edema, generalised edema, and swelling.*

Description of selected adverse reactions

The selected adverse reactions described below are based on safety of cemiplimab in 1281 patients in clinical studies in monotherapy.

These selected adverse reactions were consistent when cemiplimab was administered in monotherapy or in combination with chemotherapy.

5.1 Pharmacodynamic properties

[…]

NSCLC

First-line treatment of NSCLC with LIBTAYO in combination with platinum-based chemotherapy

The safety of LIBTAYO in combination with platinum-based chemotherapy was evaluated in 465 patients with locally advanced or metastatic NSCLC in Study 16113 [see Clinical Studies (14.3)]. Patients received LIBTAYO 350 mg every 3 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles (n=312), or placebo every 3 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles (n=153). Among patients who received LIBTAYO, 70% were exposed for 6 months or longer and 35% were exposed for greater than one year. The safety population characteristics were: median age of 63 years (25 to 82 years), 41% of patients 65 or older, 86% male, 86% White, 14% Asian, 86% had metastatic disease and 14% had locally advanced disease and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 (16%) and 1 (83%). Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions that occurred in at least 2% of patients were pneumonia, anemia, and neutropenia. Fatal adverse reactions occurred in 6% of patients who received LIBTAYO in combination with chemotherapy, including death not otherwise specified (2.9%), sudden death (1.0%), acute hepatitis (0.3%), acute respiratory distress syndrome (0.3%), mesenteric artery thrombosis (0.3%), pneumonia (0.3%), pneumonitis (0.3%), and pulmonary hemorrhage (0.3%). LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients. Adverse reactions resulting in permanent discontinuation in at least 2 patients were increased alanine aminotransferase and anemia. Dosage interruptions of LIBTAYO due to an adverse reaction occurred in 33% of patients. Adverse reactions which required dosage interruptions in at least 2% of patients were anemia, pneumonia, neutropenia, thrombocytopenia, fatigue, COVID-19 infection, and pyrexia. The most common (≥ 15%) adverse reactions were alopecia, musculoskeletal pain, nausea, fatigue, peripheral neuropathy, and decreased appetite. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were anemia, neutropenia, lymphopenia, leukopenia, hyponatremia, thrombocytopenia, hyperglycemia, hypophosphatemia, increased alanine aminotransferase, hypocalcemia, hyperkalemia, hypermagnesemia, hypokalemia, and increased creatinine.

The efficacy of LIBTAYO in combination with platinum-based chemotherapy was evaluated in Study 16113 (NCT03409614), a randomized, multi-center, double-blind, active-controlled trial in 466 patients

with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation or with metastatic NSCLC who had not previously received systemic treatment for metastatic NSCLC. Patients were eligible regardless of tumor PD-L1 expression status.

Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; or ongoing or recent autoimmune disease that required systemic therapy were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization.

Randomization was stratified by histology (non-squamous vs squamous) and PD-L1 expression

(<1% versus 1% to 49% versus ≥ 50%) according to the VENTANA PD-L1 (SP263) assay. Patients were randomized (2:1) to receive either:

- LIBTAYO 350 mg intravenously (IV) every 3 weeks for 108 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles, or
- placebo IV every 3 weeks for 108 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles.

Platinum-based chemotherapy in either arm consisted of carboplatin AUC of 5 or 6 and paclitaxel 200 mg/m^2; cisplatin 75 mg/m^2 and paclitaxel 200 mg/m^2; carboplatin AUC of 5 or 6 and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2. Maintenance pemetrexed was mandatory for patients with non-squamous NSCLC who received a pemetrexed- containing chemotherapy regimen in the first 4 treatment cycles.

Study treatment continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or 108 weeks. Assessment of tumor status was performed every 9 weeks during year 1 and every 12 weeks after year 1. The major efficacy outcome measure was overall survival (OS).
Additional efficacy outcome measures were progression-free survival (PFS) and overall response rate (ORR) as assessed by blinded independent central review (BICR).

The study population characteristics were: median age of 63 years (range: 25 to 84), 40% age 65 or older; 84% male; 87% White, 13% Asian. Fifteen percent had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 84% had ECOG PS 1; 85% had metastatic disease and 15% had stage IIIB or IIIC disease and were not candidates for surgical resection or definitive chemoradiation per investigator assessment; 57% had non-squamous and 43% had squamous histology; and 7% had history of treated brain metastases at baseline.

The trial demonstrated a statistically significant improvement in OS for patients randomized to LIBTAYO in combination with chemotherapy compared with placebo in combination with chemotherapy.

Efficacy results are presented in Table 5 and Figure 1.

Table 5: Efficacy Results from Study 16113 in Non-Small Cell Lung Cancer

Endpoints	LIBTAYO and Chemotherapy N=312	Placebo and Chemotherapy N=154
Overall Survival		
Deaths, n (%)	132 (42)	82 (53)
Median in months (95% CI)[a]	21.9 (15.5, NE)	13.0 (11.9, 16.1)
Hazard ratio (95% CI)[b]	0.71 (0.53, 0.93)	
p-value[c]	0.0140	
Progression-free Survival per BICR		

Events, n (%)	204 (65)	122 (79)
Median in months (95% CI)[a]	8.2 (6.4, 9.3)	5.0 (4.3, 6.2)
Hazard ratio (95% CI)[b]	0.56 (0.44, 0.70)	
p-value[c]	<0.0001	
Overall Response Rate per BICR (%)		
ORR (95% CI)[d]	43 (38, 49)	23 (16, 30)
Complete response (CR) rate	2.6	0
Partial response (PR) rate	41	23
p-value[c]	<0.0001	
Duration of Response per BICR		
Median in months[a] (range)	15.6 (1.7, 18.7+)	7.3 (1.8, 18.8+)

BICR: blinded independent central review, CI: confidence interval; NE: Not evaluable; +: Ongoing response

a. Based on Kaplan-Meier method
b. Based on stratified proportional hazards model
c. Based on a two-sided p-value
d. Clopper-Pearson exact confidence interval

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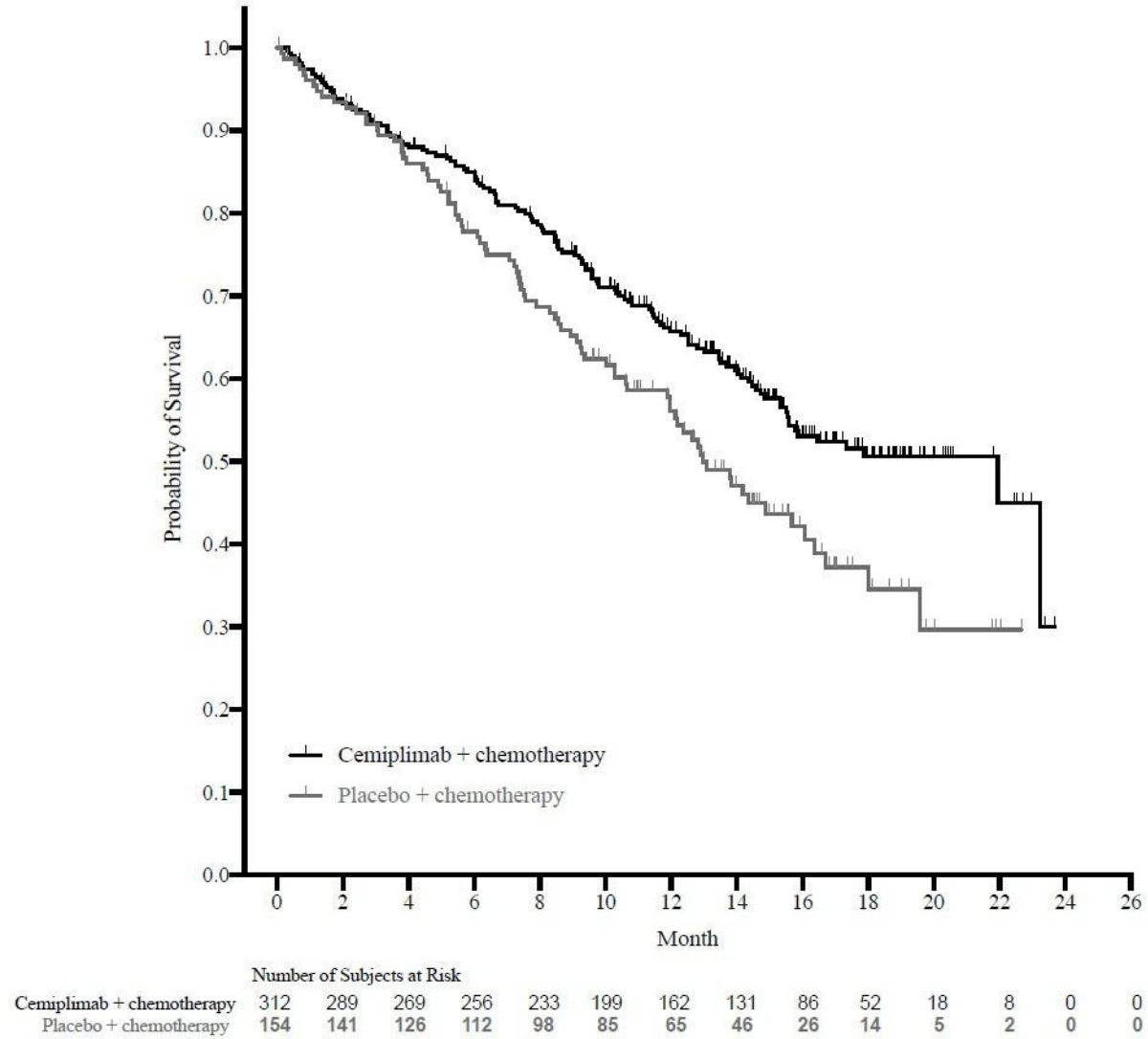
Figure 1: Kaplan-Meier Curves for OS from Study 16113



First-line treatment of NSCLC with LIBTAYO as a single agent

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Studies (14.3)]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator's choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥ 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86%White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions

resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

The efficacy of LIBTAYO was evaluated in Study 1624 (NCT03088540), a randomized, multi- center, open-label, active-controlled trial in 710 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC.

Only patients whose tumors had high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible.
Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. Randomization was stratified by histology (non-squamous vs squamous) and geographic region (Europe vs Asia vs Rest of world). Patients were randomized (1:1) to receive LIBTAYO 350 mg intravenously (IV) every 3 weeks for up to 108 weeks or a platinum-doublet chemotherapy regimen for 4 to 6 cycles followed by optional pemetrexed maintenance for patients with non- squamous histology who received a pemetrexed containing regimen.

Treatment with LIBTAYO continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or up to 108 weeks. Patients who experienced IRC-assessed RECIST 1.1- defined progressive disease on LIBTAYO therapy were permitted to continue treatment with LIBTAYO (up to an additional 108 weeks) with the addition of 4 cycles of histology-specific chemotherapy until further progression was observed. Of the 203 patients randomized to receive chemotherapy who had IRC-assessed RECIST 1.1- defined disease progression, 150 (74%) patients crossed over to treatment with LIBTAYO. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS). An additional efficacy outcome measure was overall response rate (ORR).

The study population characteristics were: median age of 63 years (range: 31 to 84), 45% age 65 or older; 85% male; 86% White, 11% Asian; and 0.6% Black. Nine percent were Hispanic or Latino. Twenty-seven percent had ECOG PS 0 and 73% had ECOG PS 1; 84% had metastatic disease and 16% had stage IIIB or IIIC disease and were not candidates for surgical resection or definitive chemoradiation per investigator assessment; 56% had non-squamous and 44% had squamous histology; and 12% had history of treated brain metastases at baseline.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to LIBTAYO as compared with chemotherapy.

Efficacy results are presented in Table 6 and Figure 2.

Table 6: Efficacy Results from Study 1624 in Non-Small Cell Lung Cancer

Endpoints	LIBTAYO N=356	Chemotherapy N=354
Overall Survival		
Number of deaths (%)	108 (30)	141 (40)
Median in months (95% CI)[a]	22.1 (17.7, NE)	14.3 (11.7, 19.2)
Hazard ratio (95% CI)[b]	0.68 (0.53, 0.87)	
p-value	0.0022	
Progression-free Survival per BICR		

Number of events (%)	201 (57)	262 (74)
Median in months (95% CI)[a]	6.2 (4.5, 8.3)	5.6 (4.5, 6.1)
Hazard ratio (95% CI)[b]	0.59 (0.49, 0.72)	
p-value	<0.0001	
Overall Response Rate per BICR (%)[c]		
ORR (95% CI)	37 (32, 42)	21 (17, 25)
Complete response (CR) rate	3	1
Partial response (PR) rate	33	20
Duration of Response per BICR		
Median in months (range)	21.0 (1.9+, 23.3+)	6.0 (1.3+, 16.5+)

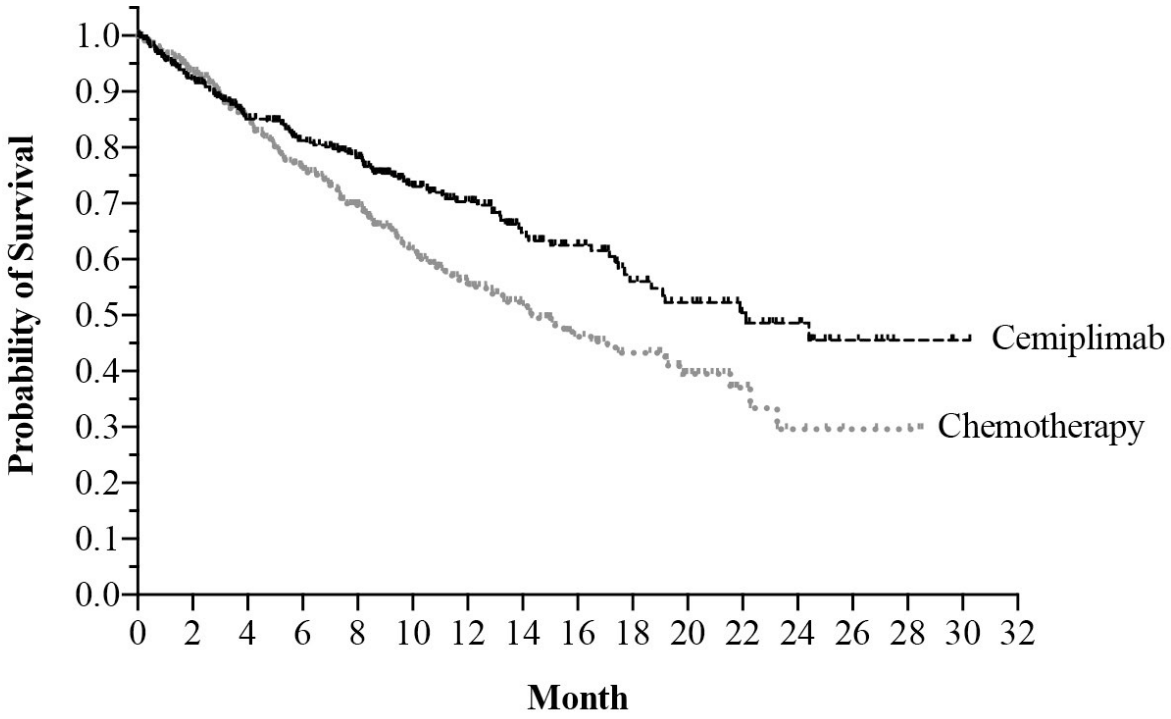
BICR: blinded independent central review, CI: confidence interval; NE: Not evaluable; +: Ongoing response

a. Based on Kaplan-Meier method

b. Based on stratified proportional hazards model

c. Clopper-Pearson exact confidence interval

Figure 2: Kaplan-Meier Curve for OS from Study 1624



Number of Subjects at Risk

Cemiplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
Chemotherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

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Elderly population

Monotherapy
Of the 1281 patients treated with cemiplimab monotherapy in clinical studies, 52.2% (669/1281) were less than 65 years, 25.9% (332/1281) were 65 to less than 75 years, and 21.9% (280/1281) were 75 years or older.

No overall differences in efficacy were observed between elderly patients and younger patients. There was a trend towards a higher frequency of serious adverse events and discontinuations due to adverse events in patients 65 years and older compared with patients aged less than 65 years treated with cemiplimab monotherapy.

Combination therapy
Of the 312 patients treated with cemiplimab in combination with chemotherapy, 59% (184/312) were less than 65 years, 35.3% (110/312) were 65 to less than 75 years, and 5.8% (18/312) were 75 years or older.

No overall differences in safety or efficacy were observed between elderly patients and younger patients treated with cemiplimab in combination with platinum-based chemotherapy.

להלן המידע שהתעדכן בעלון לצרכן המתייחס לתוספות ההתוויות:

4. תופעות לוואי

[...]
התופעות הבאות דווחו בניסויים קליניים במטופלים שטופלו בסמיפלימאב בשילוב עם כימותרפיה:

תופעות לוואי שכיחות מאוד (מופיעות ביותר מ- 1 מתוך 10 משתמשים):
- ירידה במספר תאי הדם האדומים
- נשירת שיער
- כאב בשרירים או בעצמות
- בחילה
- תחושת עייפות
- דלקת בעצבים הגורמת לדקירה/עקצוץ, חוסר תחושה, חולשה או כאב צורב של הזרועות או הרגליים
- רמות סוכר גבוהות
- ירידה בתחושת הרעב
- עלייה ברמות אנזימי כבד בדם
- ירידה במספר תאי הדם הלבנים (נויטרופילים)
- עצירות
- ירידה במספר הטסיות בדם
- קוצר נשימה

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- פריחה
- הקאות
- ירידה במשקל
- קשיים בשינה
- שלשול
- רמות נמוכות בדם של חלבון הנקרא "אלבומין"

תופעות לוואי שכיחות (מופיעות בעד 1 מתוך 10 משתמשים)

- תוצאות לא תקינות בבדיקת תפקודי כליה
- בעיות בבלוטת התריס (פעילות יתר של בלוטת התריס (היפרתירואידיזם) ותת פעילות של בלוטת התריס (היפותירואידיזם))
- שיעול, דלקת ברקמת הריאות
- גרד
- דלקת בכליות
- דלקת במעי (שלשול, תנועות מעי רבות יותר מהמצב הרגיל, צואה שחורה או דומה לזפת, כאב חמור או רגישות בבטן)
- כאב במפרקים, נפיחות, רב-שיגרון (פוליארתריטיס) ותפליט (Effusion) של המפרקים.

תופעות לוואי שאינן שכיחות (מופיעות בעד 1 מתוך 100 משתמשים):

- דלקת בבלוטת התריס
- תגובות הקשורות לעירוי
- סוכרת מסוג 1, העשויה לכלול עלייה בתחושת רעב או צמא לעומת המצב הרגיל, צורך במתן שתן בתדירות גבוהה מהרגיל, ירידה במשקל ותחושת עייפות

תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה):

- מחלת צליאק (מאופיינת בתסמינים כגון כאבי בטן, שלשולים ונפיחות לאחר צריכת מזונות המכילים גלוטן).
- חוסר או הפחתה של אנזימי עיכול המיוצרים על ידי הלבלב (אי ספיקה אקסוקרינית של הלבלב).

העלון לרופא ולצרכן נמצאים בקישור וכן הועברו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בברכה,
מדיסון פארמה בע"מ

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