אוגוסט 2023

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

<u>הנדון: לנווימה 4 מ"ג, 10 מ"ג- Lenvima 4 mg, 10mg, Hard Capsule</u>

חברת אסאיי ישראל בע"מ (Eisai Israel Ltd.) מבקשת להודיעכם כי העלונים לרופא של התכשירים שלהלן התעדכן ביולי 2023, בעקבות החלפת בעל רישום ועדכונים נוספים.

Lenvima 4 mg
Lenvima 10mg

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט ~~אדום עם קו חוצה~~).

ההתוויות המאושרות לתכשיר בישראל:

LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC) refractory to radioactive iodine (RAI).
LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.
LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
Lenvima, in combination with pembrolizumab, is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum containing therapy and who are not candidates for curative surgery or radiation.
LENVIMA is indicated in combination with pembrolizumab for the first-line treatment of adult patients with advanced RCC.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות ומצורף לפרסום זה. כמו כן, ניתן לקבל העתק מודפס שלו באמצעות פנייה לבעל הרישום: אסאיי ישראל בע"מ, ת.ד. 8049 כפר סבא, 4418001.

להלן העדכונים בעלון לרופא:

4.8 Undesirable effects

<u>Summary of the safety profile</u>

The safety profile of lenvatinib is based on pooled data from 497 RCC patients treated with lenvatinib in combination with pembrolizumab, including Study 307 (CLEAR)pooled data from 623 RCC patients treated with lenvatinib in combination with everolimus ~~in Study 205~~; 458 DTC patients and

496 HCC patients treated with lenvatinib as monotherapy. Also, the combination of lenvatinib with pembrolizumab has been evaluated in 530 patients with advanced EC receiving 20 mg lenvatinib once daily and 200 mg pembrolizumab every 3 weeks. ~~62 patients, allowing characterisation only of common adverse drug reactions in RCC patients from Study 205. The adverse reactions presented in this section are based on the combined safety data of 62 RCC patients from Study 205 (see section 5.1) and 458 DTC patients (see SmPC for Lenvima).~~

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Lenvatinib in combination with everolimus in RCC

The safety profile of lenvatinib in combination with everolimus is based on data from 623 patients.

The most frequently reported adverse reactions (occurring in ≥30% of patients) were diarrhoea (69.0%), fatigue (41.9%), hypertension (41.7%), decreased appetite (41.6%), stomatitis (40.6%), nausea (38.8%), proteinuria (34.2%), vomiting (32.7%) and weight decreased (31.3%).
The most common severe (Grade ≥3) adverse reactions (≥5%) were hypertension (19.3%), diarrhoea (13.8%), proteinuria (8.8%), fatigue (7.1%), decreased appetite (6.3%) and weight decreased (5.8%).

Discontinuation of lenvatinib, everolimus, or both due to an adverse reaction occurred in 27.0% of patients; 21.7% lenvatinib, and 18.7% both drugs. The most common adverse reactions (≥1%) leading to discontinuation of lenvatinib, everolimus, or both were proteinuria (2.7%), diarrhoea (1.0%) and decreased appetite (1.0%). Adverse reaction that most commonly led to discontinuation of lenvatinib (≥1%) was proteinuria (2.1%).

Dose interruptions of lenvatinib, everolimus, or both due to an adverse reaction occurred in 82.2% of patients; in patients where data on individual drug modifications were collected, lenvatinib was interrupted in 74.3%, and both drugs in 71.9% of patients. The most common adverse reactions (≥ 5%) resulting in dose reduction or interruption of lenvatinib were diarrhoea (30.4%), fatigue (15.3%), proteinuria (14.7%), appetite decreased (13.4%), stomatitis (13.2%), nausea (10.9%), vomiting (10.2%), hypertension (9.2%), asthenia (7.9%), platelet count decreased (5.7%), and weight decreased (5.1%).
~~reactions in the Study 205 RCC and DTC patient populations (occurring in ≥30% of patients) were diarrhoea (80.6%), hypertension (70.1%)*, fatigue (59.7%), decreased appetite (53.7%), weight decreased (52.6%)*, vomiting (48.4%), nausea (45.2%), proteinuria (38.9%)*, stomatitis (36.9%)*, headache (35.8%)*, dysphonia (35.6%)*, palmar-plantar erythrodysaesthesia syndrome (34.1%)*, peripheral oedema (33.9%), and hypercholesterolemia (30.6%). Hypertension and proteinuria tend to occur earlyduring lenvatinib treatment (see sections 4.4 and 4.8; the asterisked frequencies are from the DTC patient population).~~

~~The most important serious adverse reactions included renal failure and impairment (11.3%), arterial thromboembolisms (3.9%)*, cardiac failure (1.6%), cerebral haemorrhage (1.6%), intracranial tumour haemorrhage (0.7%)*, PRES / RPLS (0.2%)*, and hepatic failure (0.2%)* (the asterisked frequencies are from the DTC patient population).~~

~~In RCC Study 205 (see section 5.1), adverse reactions led to dose reductions in 67.7% of patients and 18 (29.0%) patients discontinued the treatment. The most common adverse reactions (≥5%) resulting in dose reductions in the lenvatinib plus everolimus treated group were diarrhoea (21.0%), thrombocytopenia (6.5%), and vomiting (6.5%).~~

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Table 8 Adverse reactions reported in patients treated with lenvatinib §

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab (RCC)**	**Combination with pembrolizumab (EC)**
Infections and infestations				
Very common	Urinary tract infection			Urinary tract infection
Common		Urinary tract infection	Urinary tract infection	
Uncommon	Perineal abscess	Perineal abscess	Perineal abscess	Perineal abscess
Blood and lymphatic disorders				
Very common	Thrombocytopenia‡ Lymphopenia‡ Leukopenia‡ Neutropenia‡	Thrombocytopenia‡ Lymphopenia‡ Leukopenia‡ Neutropenia‡	Thrombocytopenia‡ Lymphopenia‡ Leukopenia‡ Neutropenia‡	Thrombocytopenia[a,‡] Lymphopenia[a,‡] Leukopenia[a,‡] Neutropenia[a,‡] Anaemia
Uncommon	Splenic infarction			
Endocrine disorders				
Very common	Hypothyroidism* Increased blood thyroid stimulating hormone*,‡,‡	Hypothyroidism* Increased blood thyroid stimulating hormone*, ‡	Hypothyroidism* Increased blood thyroid stimulating hormone*, ‡	Hypothyroidism* Increased blood thyroid stimulating hormone* Hyperthyroidism
Metabolism and nutrition disorders				
Very common	Hypocalcaemia*, ‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia‡ Decreased weight Decreased appetite	Hypocalcaemia‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia *, ‡ Decreased weight Decreased appetite	Hypocalcaemia‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia *, ‡ Decreased weight Decreased appetite	Hypocalcaemia*,‡ Hypokalaemia‡ Hypercholesterolaemia[b, *,‡] Hypomagnesaemia[b,‡] Decreased weight Decreased appetite
Common	Dehydration	Dehydration	Dehydration	Dehydration
Psychiatric disorders				
Very common	Insomnia	Insomnia	Insomnia	
Common				Insomnia
Nervous system disorders				
Very common	Dizziness Headache Dysgeusia	Headache Dysgeusia	Dizziness Headache Dysgeusia	Dizziness Headache Dysgeusia
Common	Cerebrovascular accident†	Dizziness		

System Organ Class (MedDRA terminology)	Lenvatinib monotherapy	Combination with everolimus	Combination with pembrolizumab (RCC)	Combination with pembrolizumab (EC)
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Cerebrovascular accident† Transient ischaemic attack	Cerebrovascular accident Posterior reversible encephalopathy syndrome Transient ischaemic attack	Posterior reversible encephalopathy syndrome Cerebrovascular accident† Monoparesis Transient ischaemic attack
Cardiac disorders				
Common	Myocardial infarction[a,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Myocardial infarction[a,†] Cardiac failure† Prolonged electrocardiogram QT	Myocardial infarction[a] Prolonged electrocardiogram QT	Prolonged electrocardiogram QT
Uncommon		Decreased ejection fraction	Cardiac failure† Decreased ejection fraction	Myocardial infarction[c,†] Cardiac failure Decreased ejection fraction
Vascular disorders				
Very common	Haemorrhage[b, *, †] Hypertension[c,*] Hypotension	Haemorrhage[b, *, †] Hypertension[c,*]	Haemorrhage[b, *, †] Hypertension[c,*]	Haemorrhage[d, *,†] Hypertension[e,*]
Common		Hypotension	Hypotension	Hypotension
Not known	Aneurysms and artery dissections	Aneurysms and artery dissections	Aneurysms and artery dissections	
Respiratory, thoracic and mediastinal disorders				
Very common	Dysphonia	Dysphonia	Dysphonia	Dysphonia
Common	Pulmonary embolism†	Pulmonary embolism Pneumothorax	Pulmonary embolism	Pulmonary embolism†
Uncommon	Pneumothorax		Pneumothorax	Pneumothorax
Gastrointestinal disorders				
Very	Diarrhoea*	Diarrhoea*	Diarrhoea*	Diarrhoea*

System Organ Class (MedDRA terminology)	Lenvatinib monotherapy	Combination with everolimus	Combination with pembrolizumab (RCC)	Combination with pembrolizumab (EC)
common	Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase‡ Increased amylase‡	Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Increased lipase‡ Increased amylase‡	Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase‡ Increased amylase‡	Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dry mouth Increased lipase Increased amylase‡
Common	Anal fistula Flatulence	Dry mouth Flatulence	Pancreatitis[g] Colitis Flatulence	Pancreatitis[i] Flatulence Dyspepsia Colitis
Uncommon	Pancreatitis[g] Colitis	Pancreatitis[g] Anal fistula Colitis	Anal fistula	Anal fistula
Hepatobiliary disorders				
Very common	Increased blood bilirubin*, ‡ Hypoalbuminaemia*, ‡ Increased alanine aminotransferase*, ‡ Increased aspartate aminotransferase*, ‡ Increased blood alkaline phosphatase‡ Increased gamma-glutamyltransferase‡	Hypoalbuminaemia*, ‡ Increased alanine aminotransferase‡ Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡	Increased blood bilirubin ‡ Hypoalbuminaemia‡ Increased alanine aminotransferase‡ Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡	Increased blood bilirubin[j,*,‡] Hypoalbuminaemia[j,*,‡] Increased alanine aminotransferase*, ‡ Increased aspartate aminotransferase*, ‡ Increased blood alkaline phosphatase‡
Common	Hepatic failure[h,†] Hepatic encephalopathy[i, †] Cholecystitis Abnormal hepatic function	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase Increased blood bilirubin*, ‡	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[j]	Hepatic failure[h, †] Hepatic	Hepatic failure[h,,†] Hepatic	Hepatic failure[k,*†] Hepatic

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab (RCC)**	**Combination with pembrolizumab (EC)**
		encephalopathy[i]	encephalopathy[i] Hepatocellular damage/hepatitis[j]	encephalopathy[l,†,*] Hepatocellular damage/hepatitis[m]
Skin and subcutaneous tissue disorders				
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia	Hyperkeratosis Alopecia	Alopecia
Uncommon		Hyperkeratosis	~~Palmar erythema~~	Hyperkeratosis
Musculoskeletal and connective tissue disorders				
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia Myalgia Pain in extremity
Common		Myalgia Pain in extremity Musculoskeletal pain		Musculoskeletal pain
Uncommon	Osteonecrosis of the jaw	Osteonecrosis of the jaw		
Renal and urinary disorders				
Very common	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡
Common	Renal failure[k,*,†] Renal impairment* Increased blood urea	Renal failure[k,*,†] Renal impairment* Increased blood urea	Renal failure[k,*] Increased blood urea	Renal failure[n,*,†]
Uncommon	Nephrotic syndrome		Nephrotic syndrome Renal impairment*	Renal impairment* Increased blood urea
General disorders and administration site conditions				
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Asthenia Oedema peripheral
Common	Malaise	Malaise	Malaise	Malaise

System Organ Class (MedDRA terminology)	Lenvatinib monotherapy	Combination with everolimus	Combination with pembrolizumab (RCC)	Combination with pembrolizumab (EC)
Uncommon	Impaired healing	Impaired healing Non-gastrointestinal fistula[l]	Impaired healing Non-gastrointestinal fistula[l]	Impaired healing
Not known	Non-gastrointestinal fistula[l]			

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Description of selected adverse reactions

Hypertension (see section 4.4)

RCC

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In the pooled RCC population treated with lenvatinib and everolimus, hypertension was reported in 42.5% of patients (the incidence of Grade 3 or Grade 4 hypertension was 19.7%). In patients where data on individual drug modifications were collected, 9.8% of patients with hypertension had dose modifications of lenvatinib (5.3% dose reduction and 6.2% dose interruption) and led to permanent treatment discontinuation in 0.9% of patients. The median time to onset of hypertension events in lenvatinib plus everolimus treated patients was 0.5 months.

~~RCC study 205 (see section 5.1), hypertension was reported in 41.9% of patients in the lenvatinib plus everolimus-treated group (the incidence of Grade 3 or Grade 4 hypertension was 12.9%) and 10.0% of patients in the everolimus-treated group (the incidence of Grade 3 or Grade 4 hypertension was 2.0%). The median time to onset was 4.9 weeks (any grade) and 6.9 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group.~~

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Proteinuria (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, proteinuria was reported in 34.8% of patients (9.0% were Grade ≥3). In patients where data on individual drug modifications were collected, 15.1% of patients with proteinuria had dose modifications of lenvatinib (9.6% reduction and 9.8% interruption) and led to permanent treatment discontinuation in 2.1% of patients. The median time to onset of proteinuria events in lenvatinib plus everolimus treated patients was 1.4 months.

~~RCC study 205 (see section 5.1), proteinuria was reported in 30.6% of patients in the lenvatinib plus everolimus-treated group (8.1% were Grade ≥ 3) and 14.0% of patients in the everolimus-treated group (2.0% were Grade ≥3). The median time to onset of proteinuria was 6.1 weeks (any grade) and 20.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Proteinuria led to permanent treatment discontinuation in 4.8% of patients.~~

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Renal failure and impairment (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, 1.3% of patients developed renal failure (0.6% were Grade ≥3) and 5.3% developed acute kidney injury (2.7% were Grade ≥3). Renal events were reported in 17.2% of patients (4.3% were Grade ≥3). In patients where data on

individual drug modifications were collected, 5.5% of patients with renal events had dose modifications of lenvatinib (2.3% reduction and 4.0% interruption) and led to permanent treatment discontinuation in 1.9% of patients. The median time to onset of renal events in lenvatinib plus everolimus treated patients was 3.5 months.
~~In RCC study 205 (see section 5.1), 8.1% of patients in the lenvatinib plus everolimus treated group developed renal failure and 3.2% developed renal impairment, (9.7% of patients had a Grade 3 event of renal failure or impairment). In the everolimus monotherapy group 2.0% of patients developed renal failure (2.0% were Grade 3).~~

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Cardiac dysfunction (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, cardiac dysfunction events were reported in 3.5% of patients (1.8% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.9% of patients with cardiac dysfunction events had dose modifications of lenvatinib (0.4% reduction and 0.8% interruption) and led to permanent treatment discontinuation in 0.6% of patients. The median time to onset of cardiac dysfunction events in lenvatinib plus everolimus treated patients was 3.6 months.
~~In RCC study 205 (see section 5.1), decreased ejection fraction/cardiac failure was reported in 4.8% of patients (3.2% were Grade ≥ 3) in the lenvatinib plus everolimus treated group, and 4.0% in the everolimus group (2.0% were Grade ≥ 3). The median time to onset of decreased ejection fraction and cardiac failure was 15.7 weeks (any grade) and 32.8 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group.~~

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Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, there was 1 event of PRES reported (Grade 2), occurring after 1.3 months of treatment for which no dose modifications or discontinuation were required.
~~In RCC study 205 (see section 5.1), there was 1 event of PRES (Grade 3) in the lenvatinib-treated group, occurring after 18.4 weeks of treatment. There were no reports in the lenvatinib plus everolimus or everolimus monotherapy groups.~~

Hepatotoxicity (see section 4.4)

RCC

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In the pooled RCC population treated with lenvatinib and everolimus, the most commonly reported liver-related adverse reactions were elevations of liver enzyme levels, including increases in alanine aminotransferase (11.9%), aspartate aminotransferase (11.4%) and gamma-glutamyltransferase increased (2.7%). Grade 3 liver related reactions occurred in 6.1% of lenvatinib plus everolimus treated patients. In patients where data on individual drug modifications were collected, 6.0% of patients with hepatotoxicity events had dose modifications of lenvatinib (2.8% reduction and 4.2% interruption) and led to permanent treatment discontinuation in 0.9% of patients.

~~In RCC Study 205 (see section 5.1), the most commonly reported liver-related adverse reactions in the lenvatinib plus everolimus-treated group were elevations of liver enzyme levels, including increases in alanine aminotransferase (9.7%), aspartate aminotransferase (4.8%), alkaline phosphatase (4.8%), and blood bilirubin (3.2%). The median time to onset of liver events was 6.7 weeks (any grade) and 14.2 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Grade 3 liver-related reactions occurred in 3.2% of lenvatinib plus everolimus-treated patients. Liver-related reactions led to dose interruptions and reductions in 1.6% and 1.6% of patients, respectively, and to permanent discontinuation in 3.2% of patients.~~

Arterial thromboembolisms (see section 4.4)

RCC

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In the pooled RCC population treated with lenvatinib and everolimus, arterial thromboembolic events were reported in 2.7% of patients (2.2% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.6% of patients with arterial thromboembolic events had dose modifications of lenvatinib (0.6% interruption) and led to permanent treatment discontinuation in 1.5% of patients. The most commonly reported arterial thromboembolic event in the lenvatinib plus everolimus-treated group was myocardial infarction (1.3%). The median time to onset of arterial thromboembolic events in lenvatinib plus everolimus treated patients was 6.8 months.

~~In RCC Study 205 (see section 5.1), 1.6% of patients in the lenvatinib plus everolimus-treated group reported arterial thromboembolic events. The time to onset was 69.6 weeks. In the everolimus group, 6.0% of patients reported an arterial thromboembolism (4.0% were Grade ≥ 3).~~

~~Amongst 1,166 patients treated with lenvatinib, there were 5 cases (0.4%) of arterial thromboembolisms (3 cases of myocardial infarction and 2 cases of cerebrovascular accident) with a fatal outcome.~~

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Haemorrhage (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, haemorrhage events were reported in 28.6% of patients (3.2% were Grade ≥3). In patients where data on individual drug modifications were collected, 4.9% of patients with haemorrhage events had dose modifications of lenvatinib (4.2% interruption and 0.8% reduction) and led to permanent treatment discontinuation in 0.6% of patients. The most commonly reported haemorrhage events in the lenvatinib plus everolimus-treated group were epistaxis (19.4%) and haematuria (4.2%). The median time to onset of haemorrhage events in lenvatinib plus everolimus treated patients was 1.9 months.

~~In RCC study 205 (see section 5.1), haemorrhage was reported in 38.7% (8.1% were Grade ≥ 3) of patients in the lenvatinib plus everolimus-treated group. Reactions that occurred at an incidence of ≥2.0% were: epistaxis (22.6%), haematuria (4.8%), haematoma (3.2%), and gastric haemorrhage (3.2%). The median time to first onset of was 10.2 weeks (any grade) and 7.6 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. The incidence of serious haemorrhage was 4.8% (cerebral haemorrhage, gastric haemorrhage and haemarthrosis). Discontinuation due to haemorrhagic events occurred in 3.2% of patients in the lenvatinib plus everolimus-treated group.~~

~~There was one case of fatal cerebral haemorrhage in the lenvatinib plus everolimus-treated group and one case of fatal intracranial haemorrhage in the lenvatinib-treated group.~~

DTC

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~~Amongst 1,166 patients treated with lenvatinib, Grade 3 or greater haemorrhage was reported in 2% of patients, 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.4%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial tumour haemorrhage, haemoptysis and tumour haemorrhage.~~

Hypocalcaemia (see section 4.4, QT interval prolongation)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, hypocalcaemia was reported in 4.8% of patients (1.1% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.8% of patients with hypocalcaemia had dose modifications of lenvatinib (0.6% dose interruption and 0.4% dose reduction) and led to permanent treatment discontinuation in no patients. The median time to onset of hypocalcaemia events in lenvatinib plus everolimus treated patients was 2.9 months.

~~In RCC study 205 (see section 5.1), hypocalcaemia was reported in 8.1% of patients in the lenvatinib plus everolimus-treated group (3.2% were Grade ≥ 3) and 4.0% of patients in the everolimus-treated group (none were Grade ≥ 3). The median time to onset of hypocalcaemia was 28.3 weeks (any grade) and 45.9 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. There was one Grade 4 TEAE. No events of hypocalcaemia required dose reduction or interruption, and no patients discontinued treatment due to hypocalcaemia.~~

Gastrointestinal perforation and fistula formation (see section 4.4)

~~Clear cell RCC~~

~~In RCC study 205 (see section 5.1), 1.6% of cases of perforated appendicitis (of Grade 3) occurred in the lenvatinib plus everolimus-treated group; there were no reports in the lenvatinib or everolimus groups.~~

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RCC

In the pooled RCC population treated with lenvatinib and everolimus, GI perforation events were reported in 3.7% of patients (2.9% were Grade ≥3). In patients where data on individual drug modifications were collected, 2.1% of patients with GI perforations had dose modifications of lenvatinib (1.5% interruption and 0.6% reduction) and led to permanent treatment discontinuation in 1.1% of patients. The median time to onset of GI perforation events in lenvatinib plus everolimus treated patients was 3.6 months.

In the pooled RCC population treated with lenvatinib and everolimus, fistula formation events were reported in 1.0% of patients (0.5% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.8% of patients with GI perforations had dose modifications of lenvatinib (0.8% interruption) and led to permanent treatment discontinuation in 0.4% of patients. The median time to onset of fistula formation events in lenvatinib plus everolimus treated patients was 3.7 months.

QT interval prolongation (see section 4.4)

RCC

In the pooled RCC population treated with lenvatinib and everolimus, QTcF interval increases greater than 60 ms were reported in 9.8% of patients in the lenvatinib plus everolimus treated group.

The incidence of QTc interval greater than 500 ms was 3.3% in the lenvatinib plus everolimus-treated group. The median time to onset of QT prolongation events in lenvatinib plus everolimus treated patients was 3.0 months.
~~In the clear cell RCC study (see section 5.1), QTc interval increases greater than 60 ms were reported in 11% of patients in the lenvatinib plus everolimus-treated group. The incidence of QTc interval greater than 500 ms was 6% in the lenvatinib plus everolimus-treated group. No reports of QTc interval prolongation greater than 500 ms or increases greater than 60 ms occurred in the everolimus-treated group.~~

Increased blood thyroid stimulating hormone (see section 4.4 Impairment of thyroid stimulating hormone suppression)
RCC
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In the pooled RCC population treated with lenvatinib and everolimus, hypothyroidism occurred in 24.1% of patients. In general, the majority of hypothyroidism events were of Grade 1 or 2. Grade 3 hypothyroidism was reported in 0.3% of patients in the lenvatinib plus everolimus-treated patients. The median time to onset of hypothyroidism events in lenvatinib plus everolimus treated patients was 2.7 months. At baseline, 83.0% of patients in the lenvatinib plus everolimus-treated group had TSH levels ≤ upper limit of normal. Elevations of TSH > upper limit of normal were observed post-baseline in 71.3% of lenvatinib plus everolimus treated patients. In patients where data on individual drug modifications were collected, hypothyroidism events resulted in dose modification of lenvatinib (0.4% dose reduction or 0.9% dose interruption) in 1.3% of patients. No discontinuations were reported.
~~In the clear cell RCC study (see section 5.1), hypothyroidism occurred in 24% of patients in the lenvatinib plus everolimus-treated group and 2% of patients in the everolimus-treated group. All events of hypothyroidism in the lenvatinib plus everolimus-treated group were of Grade 1 or 2. In patients with a normal TSH at baseline, an elevation of TSH level was observed post baseline in 60.5% of lenvatinib plus everolimus-treated patients as compared with none in patients receiving everolimus alone.~~

Diarrhoea (see section 4.4)

RCC
In the pooled RCC population treated with lenvatinib and everolimus, diarrhoea was reported in 69.0% of patients (13.8% were Grade ≥3). In patients where data on individual drug modifications were collected, 30.4% of patients had dose modifications of lenvatinib (17.7% interruptions and 19.6% reductions) and led to permanent treatment discontinuation in 0.6% of patients.
~~In RCC study 205 (see section 5.1), diarrhoea was reported in 80.6% of patients in the lenvatinib plus everolimus-treated group (21.0% were Grade ≥ 3) and in 34.0% of patients in the everolimus-treated group (2.0% were Grade ≥ 3). The median time to onset was 4.1 weeks (any grade) and 8.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Diarrhoea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhoea resulted in discontinuation in one patient.~~
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Other special populations

Elderly
RCC
In CLEAR, elderly patients (≥75 years) had a higher (≥ 10% difference) incidence of proteinuria than younger patients (<65 years).
In the pooled RCC population treated with lenvatinib and everolimus, elderly patients (≥75 years) had a higher (≥10% difference) incidence of platelet count decreased, weight decreased, proteinuria and hypertension than younger patients (<65 years).
~~There are limited data on patients of age ≥75 years with RCC.~~

Gender
RCC
In CLEAR, males had a higher (≥ 10% difference) incidence than females of diarrhoea.
In the pooled RCC population treated with lenvatinib and everolimus, females had a higher (≥10% difference) incidence than males of nausea, vomiting, asthenia and hypertension.

Ethnic origin

RCC
In CLEAR, Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of palmar-plantar erythrodysaesthesia syndrome, proteinuria and hypothyroidism (including blood thyroid hormone increased) while Caucasian patients had a higher incidence of fatigue, nausea, arthralgia, vomiting, and asthenia.
In the pooled RCC population treated with lenvatinib and everolimus, Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of hypothyroidism, stomatitis, platelet count decreased, proteinuria, dysphonia, PPE and hypertension while Caucasian patients had a higher incidence of nausea, asthenia, fatigue and hypercholesterolemia.
~~There are limited data on Asian patients with RCC study 205.~~

Baseline diabetes
Clear cell RCC
In the pooled RCC population treated with lenvatinib and everolimus, patients with baseline diabetes had a higher incidence (≥10% difference) of proteinuria than those without baseline diabetes.
~~Patients with baseline diabetes had a higher incidence of Grade 3 or 4 hypertension, hypertriglyceridemia and acute renal failure.~~

Renal impairment

RCC
In RCC patients treated with lenvatinib and everolimus, patients with baseline renal impairment had higher incidence of thrombocytopenia or platelet count decreased compared with patients with normal renal function. ~~Study 205, patients with baseline renal impairment had a higher incidence of Grade 3 fatigue.~~

Patients with body weight <60 kg

Clear cell RCC
In RCC patients treated with lenvatinib and everolimus, those with low body weight (<60 kg) had a higher incidence (≥10% difference) of platelet count decreased and hypertension.
There are limited data on patients with body weight <60 kg in clear cell RCC.

5.1 Pharmacodynamic properties

...
The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. At the pre-specified interim analysis, with a median follow-up time of 11.4 months

(range: 0.3 to 26.9 months). ~~Efficacy results by MMR subgroups were consistent with overall~~ the study in OS and PFS in the all-comer population.

Efficacy results by MMR subgroups were consistent with overall study results.

The pre-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. The efficacy results in the all-comer population are summarised in Table 13. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 5 and 6, respectively.

Table 13 Efficacy Results in Endometrial Carcinoma in Study 309		
Endpoint	**LENVIMA with pembrolizumab N=411**	**Doxorubicin or Paclitaxel N=416**
OS		
Number (%) of patients with event	276 (67%) ~~188 (46%)~~	329 (79%) 245 (59%)
Median in months (95% CI)	18.7 (15.6, 21.3) ~~(15.2, 20.5)~~	11.9 (10.7, 13.3) ~~11.4 (10.5, 12.9)~~
Hazard ratio[a] (95% CI)	0.65 (0.55, 0.77) ~~0.62 (0.51, 0.75)~~	
…		

להלן העדכונים בעלון לצרכן:

4. **תופעות לוואי:**

...

תופעות לוואי נוספות:

תופעות הלוואי הבאות עלולות להופיע עם השימוש בלנווימה ~~עם או ללא אברוליזומב~~ כטיפול יחיד:

תופעות לוואי שכיחות (משפיעות על עד 1 מתוך 10 מטופלים)

- ...
- בעיות לבביות או קרישי דם בריאות (קשיי נשימה, כאבים בחזה) או באיברים אחרים שעלולים לכלול כאבים או לחץ בחזה, כאב בזרועות, גב, צוואר או לסת, קוצר נשימה, קצב לב מהיר או לא סדיר, שיעול, הכחלה של השפתיים והאצבעות ותחושת עייפות רבה.
- ...
- סימני שבץ מוחי, כולל אובדן תחושה או חולשה בצד אחד של הגוף, כאב ראש חמור, פרכוסים, בלבול, קשיים בדיבור, שינויים בראייה או תחושת סחרחורת.
- פיסטולה בפי הטבעת (תעלה קטנה שנוצרת בין פי הטבעת לבין העור שמסביב)

תופעות לוואי שאינן שכיחות: (משפיעות על עד 1 מתוך 100 מטופלים)

- זיהום כואב או גירוי באזור פי הטבעת
- מיני שבץ (אירוע איסכמי חולף)
- קשיי נשימה חמורים וכאבים בחזה, הנגרמים על ידי דליפת אוויר מהריאות אל תוך בית החזה, המקשה על התנפחות הריאות
- ...

<u>תופעות הלוואי הבאות עלולות להופיע בשילוב של לנווימה עם אברולימוס:</u>

תופעות לוואי שכיחות מאוד: (משפיעות על יותר מ-1 מתוך 10 מטופלים)

- לחץ דם גבוה ~~או נמוך~~
- ..
- פה ~~יבש~~, כואב או דלקתי, תחושת טעם מוזרה בפה
- כאבי מפרקים או שרירים
- ~~תחושת סחרחורת~~
- ~~נשירת שיער~~
- דימום (לרוב דימומים מהאף אך גם סוגי דימום אחרים כגון דם בשתן, חבורות, דימום מהחניכיים או מדופן המעיים)
- הפרעות בשינה
- שינויים בתוצאות בדיקות שתן: רמת חלבון (גבוהה~~) וזיהומים בדרכי שתן (השתנה תכופה וכאבים בעת מתן שתן)~~
- כאב גב וכאב ראש
- אדמומיות, כאבים ונפיחות של העור בכפות הידיים והרגליים (תסמונת כף-יד/רגל)
- תת פעילות של בלוטת התריס (עייפות, עלייה במשקל, עצירות, תחושת קור, עור יבש~~) ושינוי ברמת ההורמון המגרה של בלוטת התריס (TSH) (גבוהה)~~
- ...

תופעות לוואי שכיחות: (משפיעות על עד 1 מתוך 10 מטופלים)

- זיהומים בדרכי שתן (השתנה תכופה וכאבים בעת מתן שתן)
- אובדן נוזלים בגוף (התייבשות)
- תחושת סחרחורת
- ...
- בעיות לבביות או קרישי דם בריאות (קשיי נשימה, כאבים בחזה) או באיברים אחרים שעלולים לכלול כאבים או לחץ בחזה, כאב בזרועות, גב, צוואר או לסת, קוצר נשימה, קצב לב מהיר או לא סדיר, שיעול, הכחלה של השפתיים והאצבעות ותחושת עייפות רבה.
- לחץ דם נמוך
- קשיי נשימה חמורים וכאבים בחזה, הנגרמים על ידי דליפת אוויר מהריאות אל תוך בית החזה, המקשה על התנפחות הריאות
- פה יבש
- ~~כשל בכבד~~
- ~~נמנום, בלבול, ריכוז ירוד, ואובדן הכרה שעשויים להיות סימנים לכשל בכבד~~
- תחושה כללית רעה
- דלקת בכיס המרה
- נשירת שיער
- ~~פיסטולה בפי הטבעת~~

תופעות לוואי שאינן שכיחות: (משפיעות על עד 1 מתוך 100 מטופלים)

- זיהום כואב או גירוי באזור פי הטבעת
- סימני שבץ מוחי, כולל אובדן תחושה או חולשה בצד אחד של הגוף, כאב ראש חמור, פרכוסים, בלבול, קשיים בדיבור, שינויים בראייה או תחושת סחרחורת.
- מיני שבץ (אירוע איסכמי חולף)
- כשל כבדי או סימנים של נזק לכבד, לרבות עור צהבהב או הצהבה של לובן העין (צהבת) או נמנום, בלבול, ירידה בריכוז
- ~~כאב חזק בחלק העליון השמאלי של הבטן שעלול להיות מלווה בחום, צמרמורות, בחילות והקאות (אופן של הטחול)~~
- דלקת בלבלב
- פיסטולה בפי הטבעת (תעלה קטנה שנוצרת בין פי הטבעת לבין העור שמסביב)

- בעיות בריפוי פצעים
- נזק לעצם של הלסת (נמק של העצם)
- דלקת במעי הגס (קוליטיס)
- סוגים אחרים של פיסטולה (חיבור לא תקין בין איברים שונים בגוף או בין העור לאזורים הצמודים לו, כמו הגרון וקנה הנשימה). התסמינים תלויים במקום שבו הפיסטולה ממוקמת. שאל את הרופא שלך אם אתה חש בתסמינים חדשים או חריגים כלשהם כגון שיעול בזמן הבליעה.

תופעות לוואי ששכיחותן אינה ידועה: (על תופעות הלוואי שלהלן התקבלו דיווחים מאז שהחל השיווק של לנווימה, אבל שכיחות הופעתן אינה ידועה)

- ~~סוגים אחרים של פיסטולה (חיבור לא תקין בין איברים שונים בגוף או בין העור לאזורים הצמודים לו, כמו הגרון וקנה הנשימה). התסמינים תלויים במקום שבו הפיסטולה ממוקמת. שאל את הרופא שלך אם אתה חש בתסמינים חדשים או חריגים כלשהם כגון שיעול בזמן הבליעה.~~
- התרחבות והיחלשות של דופן כלי הדם או קרע בדופן כלי הדם (מפרצת (אנוריזמה) ומפרצת (אנוריזמה) או בתירה (דיסקציה) בכלי דם עורקי).

<u>תופעות הלוואי הבאות עלולות להופיע בשילוב של לנווימה עם פמברוליזומב לטיפול בסרטן כליה מתקדם:</u>

תופעות לוואי שכיחות מאוד: (משפיעות על יותר מ-1 מתוך 10 מטופלים)

- רמות נמוכות של טסיות בדם אשר עלולות להוביל לחבלות וקושי בריפוי פצעים
- ירידה במספר תאי הדם הלבנים
- תת פעילות של בלוטת התריס (עייפות, עלייה במשקל, עצירות, תחושת קור, עור יבש) ושינויים בתוצאות בדיקת דם עבור ההורמון המגרה של בלוטת התריס (TSH) (רמות גבוהות)
- שינויים בבדיקות דם לרמות אשלגן (נמוכות) ורמות סידן (נמוכות)
- שינויים בבדיקות דם למגנזיום (נמוך) ושינויים בתוצאות בדיקת דם לרמות כולסטרול (גבוהות)
- חוסר תיאבון או ירידה במשקל
- ~~שינויים בתוצאות בדיקת דם לרמות כולסטרול (גבוהות)~~
- ...

תופעות לוואי שכיחות: (משפיעות על עד 1 מתוך 10 מטופלים)

- דלקות בשתן (עליה בתכיפות מתן שתן וכאב בעת מתן שתן)
- ~~רמות נמוכות של טסיות בדם אשר עלולות להוביל לחבלות וקושי בריפוי פצעים~~
- ~~ירידה במספר תאי הדם הלבנים~~
- ~~שינויים בבדיקות דם לרמות אשלגן (נמוכות) ורמות סידן (נמוכות)~~
- ~~שינויים בבדיקות דם למגנזיום (נמוך)~~
- ...

תופעות לוואי שאינן שכיחות: (משפיעות על עד 1 מתוך 100 מטופלים)

- זיהום כואב או גירוי סביב פי הטבעת
- סימנים של שבץ, הכוללים אובדן תחושה ~~תחושת שיתוק~~ או חולשה בצד אחד של הגוף, כאב ראש חמור ~~חזק~~, פרכוס, בלבול, קושי בדיבור, שינויים בראיה או תחושת סחרחורת
- ...

בברכה,
אלינה ורמן, רוקחת ממונה
אסאיי ישראל בע"מ