NEW ZEALAND DATA SHEET

1 PRODUCT NAME

LENVIMA 4 mg and 10 mg hard capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LENVIMA 4 mg hard capsule contains 4 mg lenvatinib (as mesilate).

Each LENVIMA 10 mg hard capsule contains 10 mg lenvatinib (as mesilate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

LENVIMA 4 mg hard capsule: A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 4 mg" on the body.

LENVIMA 10 mg hard capsule: A yellow body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Endometrial carcinoma (EC)

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Differentiated thyroid cancer (DTC)

LENVIMA is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.

Renal cell carcinoma (RCC)

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

LENVIMA, in combination with everolimus, is indicated for the treatment of adult patients with advanced renal cell carcinoma whose disease has progressed following one prior vascular endothelial growth factor targeted therapy.

Hepatocellular carcinoma (HCC)

LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

4.2 DOSE AND METHOD OF ADMINISTRATION

LENVIMA treatment should be supervised by a health care professional experienced in the use of anticancer therapies.

Starting dose in RAI – Refractory DTC

The recommended dose of LENVIMA is 24 mg once daily. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Starting dose in Advanced Renal Cell Carcinoma

First-line treatment of patients with advanced RCC

The recommended dose of LENVIMA is 20 mg orally once daily in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes until disease progression or until unacceptable toxicity.

Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

Previously treated RCC

The recommended daily dose of LENVIMA is 18 mg once daily in combination with 5 mg everolimus once daily. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Starting dose in Hepatocellular Carcinoma

The recommended daily dose of LENVIMA is based on actual body weight:

- 8 mg orally once daily for patients with a body weight of < 60 kg
- 12 mg orally once daily for patients with a body weight of ≥ 60 kg.

Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Starting dose in endometrial carcinoma

The recommended dose of LENVIMA is 20 mg orally once daily, in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Refer to the pembrolizumab product information for recommended pembrolizumab dosing information.

Dose adjustment during therapy

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of LENVIMA. For toxicities thought to be related to LENVIMA, general advice about dose management is included in Table 1, and specific daily dose modifications are in Table 2.

When administering LENVIMA in combination with pembrolizumab for the treatment of RCC or EC, for toxicities thought to be related to both drugs, interrupt one or both drugs, dose reduce or discontinue LENVIMA as appropriate. Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab product information. No dose reductions are recommended for pembrolizumab.

When administering LENVIMA in combination with everolimus for the treatment of renal cell carcinoma, for toxicities thought to be related to both drugs, LENVIMA should be reduced prior to reducing everolimus. For toxicities thought to be related to everolimus, everolimus treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the everolimus PI for advice on specific adverse reactions).

Medical management of nausea, vomiting and diarrhoea should be optimised to reduce the risk of dehydration and renal failure (See Section 4.4 Special warnings and precautions for use, Renal failure and impairment) prior to any LENVIMA therapy interruption or dose reduction.

Table 1 Dose modifications for adverse reactions

Adverse Reaction	CTCAE Grade[a]	Action	Dose Reduce and Resume LENVIMA
Hypertension	Grade 3[b]	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in Section 4.4 Special warnings and precautions for use, Hypertension section
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm/24 hours	Interrupt	Resolves to less than 2 gm/ 24 hours

Adverse Reaction	CTCAE Grade[a]	Action	Dose Reduce and Resume LENVIMA
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4[c]	Discontinue	Do not resume
Cardiac failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4[c]	Discontinue	Do not resume
Arterial thromboembolisms	Any Grade	Discontinue	Do not resume
Haemorrhage and Thrombocytopenia *	Grade 3	Interrupt	Resolves to Grade 0-1
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not resume
QT interval prolongation	> 500 ms	Interrupt	Resolves to < 480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4[d]	Discontinue	Do not resume

a Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
b Grade 3 despite optimal antihypertensive therapy.
c Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)
d Grade 4 despite medical management

Table 2 Recommended Dosage Reductions of LENVIMA for Adverse Reactions

Indication	First Dosage Reduction To	Second Dosage Reduction To	Third Dosage Reduction To
DTC	20 mg once daily	14 mg once daily	10 mg once daily
RCC	14 mg once daily	10 mg once daily	8 mg once daily
EC	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
• Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
• Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue

Special populations

Dosage adjustment in severe hepatic impairment

A reduced starting dose of LENVIMA is recommended for patients with DTC, RCC or EC who have severe hepatic impairment (Child-Pugh C):

- 14 mg LENVIMA orally once daily for DTC
- 10 mg orally once daily for RCC
- 10 mg orally once daily for EC

The available data do not allow for a dosing recommendation for patients with HCC and moderate hepatic impairment (Child-Pugh B). The available data do not allow for a dosing recommendation for patients with HCC and severe hepatic impairment (Child-Pugh C), and use in this population is not recommended.

Dosage adjustment in renal impairment

A reduced starting dose of LENVIMA is recommended for patients with DTC, RCC or EC who have severe renal impairment (CrCL < 30 mL/min):

- 14 mg orally once daily for DTC
- 10 mg orally once daily for RCC
- 10 mg orally once daily for EC

LENVIMA has not been studied in patients with end-stage renal disease, and use in this population is not recommended.

The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment, and use in this population is not recommended.

Paediatric population

LENVIMA should not be used in children younger than 2 years of age because of safety concerns identified in animal studies. The safety and efficacy of LENVIMA in children aged 2 to < 18 years have not yet been established (see Section 5.1 Pharmacodynamic properties, Clinical trials). No data are available.

Method of administration

LENVIMA should be taken at about the same time each day, with or without food.

LENVIMA capsules can be swallowed whole with water or administered as a suspension prepared by dispersing the whole capsule(s) in water, apple juice, or milk. The suspension may be administered orally or via a feeding tube. If administered via a feeding tube, then the suspension should be prepared using water (see Section 6.6 for preparation and administration of suspension).

Do not mix more than one medicine in the glass at the same time.

If not used at the time of preparation, LENVIMA suspension may be stored in a covered container and must be refrigerated at 2ºC to 8ºC for a maximum of 24 hours. After removal from the refrigerator the suspension should be shaken for approximately 30 seconds before use. If not administered within 24 hours, the suspension should be discarded.

The person preparing the suspension should ensure their hands are thoroughly washed on completion of preparation and taking of the medication.

If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastrointestinal toxicity: diarrhoea and dehydration

Diarrhoea has been reported frequently in patients treated with LENVIMA usually occurring early in the course of treatment (see Section 4.8 Adverse effects,). Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. LENVIMA should be discontinued in the event of persistent Grade 4 diarrhoea despite medical management (see Section 4.2 Dose and method of administration).

Gastrointestinal toxicity (including events of diarrhoea, nausea and vomiting) should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Serious adverse events of both hypokalaemia and hyperkalaemia have occurred, and renal function and electrolytes should be monitored closely. (See Section 4.4 Special warnings and precautions for use, Renal failure and impairment).

Renal failure and impairment

Patients with baseline renal function < 60 mL/minute experienced more adverse events, including fatal and serious adverse events and Grade 3 or 4 events, than those with normal renal function and were more likely to require a treatment interruption, dose reduction or discontinuation of treatment. The recommended starting dose is lower for patients with renal impairment (see Section 4.2 Dose and method of administration) and it is also recommended these patients be monitored closely during treatment. There is no clinical trial experience of patients with severe renal impairment.

Renal impairment (including renal failure) has been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects,). The primary risk factors identified were pre-existing renal impairment and dehydration and/or hypovolemia due to gastrointestinal toxicity. (See Section 4.4 Special warnings and precautions for use, Gastrointestinal toxicity: Diarrhoea and dehydration). Caution should be taken in patients receiving agents acting on the renin-angiotensin aldosterone system given a potentially higher risk for acute renal failure with the combination treatment. Dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

If patients have severe renal impairment, the initial dose of LENVIMA should be adjusted (see Section 4.2 Dose and method of administration).

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating LENVIMA, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Hypertension

Hypertension has been reported in patients treated with LENVIMA, usually occurring early in the course of treatment (see Section 4.8 Adverse effects,). Blood pressure (BP) should be well controlled prior to treatment with LENVIMA and, if patients are known to be hypertensive they should be on a stable dose of an antihypertensive therapy for at least 1 week prior to treatment with LENVIMA. The early detection and effective management of hypertension are important to minimise the need for LENVIMA dose interruptions and reductions. Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. Antihypertensives should be started as soon as elevated BP is confirmed. Blood pressure should be monitored after 1 week of treatment with LENVIMA, then every 2 weeks for the first 2 months and monthly thereafter. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 3.

Table 3 Recommended management of hypertension

Blood Pressure (BP) Level	Recommended Action
Systolic BP ≥ 140 mmHg up to < 160 mmHg or diastolic BP ≥ 90 mmHg up to < 100 mmHg	Continue LENVIMA and initiate antihypertensive therapy, if not already receiving OR Continue LENVIMA and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg despite optimal antihypertensive therapy	1. Withhold LENVIMA 2. When systolic BP ≤ 150 mmHg, diastolic BP ≤ 95 mmHg, and patient has been on a stable dose for at least 48 hours, resume LENVIMA at a reduced dose (see Section 4.2 Dose and method of administration)

Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue LENVIMA and institute appropriate medical management.

Proteinuria

Proteinuria has been reported in patients treated with LENVIMA, usually occurring early in the course of the treatment (see Section 4.8 Adverse effects,). Monitor urine protein regularly. If urine dipstick proteinuria ≥ 2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration). LENVIMA should be discontinued in the event of nephrotic syndrome.

Cardiac dysfunction

Cardiac failure and decreased left ventricular ejection fraction have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects,). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration). LENVIMA has not been studied in patients who have had cardiac failure within the previous 6 months and therefore should be used with caution in such patients.

Posterior reversible encephalopathy syndrome (PRES) / reversible posterior leucoencephalopathy syndrome (RPLS)

Posterior reversible encephalopathy syndrome (PRES, also known as RPLS) has been reported in patients treated with LENVIMA (observed in < 1% of patients; ADVERSE EFFECTS,). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (See Section 4.4 Special warnings and precautions for use, Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

Hepatotoxicity

In DTC and RCC, liver-related adverse reactions most commonly reported in patients treated with LENVIMA included increases in alanine aminotransferase (ALT), increases in aspartate aminotransferase (AST), and increases in blood bilirubin (see Section 4.8 Adverse effects,). Hepatic failure and acute hepatitis (observed in < 1% of patients) have been reported in patients with DTC and RCC treated with LENVIMA. The hepatic failure events were generally reported in patients with progressive metastatic liver disease.
Liver-related adverse reactions including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency in LENVIMA treated HCC

patients (see Section 4.8 Adverse effects, Hepatocellular carcinoma) compared to DTC see Section 4.8 Adverse effects, Radioactive iodine refractory differentiated thyroid cancer) and RCC see Section 4.8 Adverse effects, Renal cell carcinoma) patients. Patients with worse hepatic impairment and/or greater liver tumour burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure were reported in patients with disease progression.

Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

If patients have any degree of liver impairment they need to be monitored closely for liver related adverse reactions. For DTC and RCC patients with severe hepatic impairment, the initial dose of LENVIMA should be adjusted. The available data do not allow for a dosing recommendation for patients with HCC and moderate hepatic impairment (Child-Pugh B). LENVIMA has not been studied in patients with HCC and severe hepatic impairment (Child-Pugh C) and therefore the use of LENVIMA in these patients is not recommended.

Arterial thromboembolic events

Arterial thromboembolic events (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects,). LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk LENVIMA should be discontinued following an arterial thrombotic event (see Section 4.2 Dose and method of administration).

Haemorrhagic events and thrombocytopenia

Serious haemorrhagic events have been reported in patients treated with LENVIMA. The most frequently reported haemorrhagic event was mild epistaxis. Serious events of thrombocytopenia have also been reported in patients treated with LENVIMA and thrombocytopenia may increase risk of developing haemorrhagic events. (see Section 4.8 Adverse effects,)

Serious tumour related bleeds have been reported, including fatal haemorrhagic events in LENVIMA treated patients and there have been reports of haemorrhage associated with thrombocytopenia.

The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour

shrinkage/necrosis following LENVIMA therapy. In the case of haemorrhagic events/ thrombocytopenia, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

Wound healing complications

No formal studies of the effect of LENVIMA on wound healing have been conducted. Impaired wound healing has been reported in patients receiving LENVIMA. Temporary interruption of LENVIMA should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of LENVIMA following a major surgical procedure. Therefore, the decision to resume LENVIMA following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects,). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

Non-gastrointestinal fistula

Patients may be at increased risk for the development of fistulae when treated with LENVIMA. Cases of fistula formation or enlargement that involve other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of gastrointestinal perforation, fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. LENVIMA should not be started in patients with fistulae to avoid worsening and LENVIMA should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see Section 4.2 Dose and method of administration); limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. LENVIMA may adversely affect the wound healing process as do other agents of the same class.

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with LENVIMA than in patients treated with placebo (see Section 4.8 Adverse effects,). The median time to onset of QTc prolongation was 16.1 weeks in the DTC study, 31.1 weeks in the HCC study for patients on LENVIMA monotherapy and 30 weeks in the RCC study for

patients treated with LENVIMA in combination with everolimus. Electrocardiograms should be monitored in patients on an ongoing basis with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. LENVIMA should be withheld in the event of development of QT interval prolongation greater than 500 ms. LENVIMA should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline (see Section 4.2 Dose and method of administration).

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation; therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during LENVIMA treatment. LENVIMA dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression/thyroid dysfunction

LENVIMA impairs exogenous thyroid suppression (see Section 4.8 Adverse effects).

Hypothyroidism has been reported as very common in patients treated with LENVIMA in combination with everolimus (see Section 4.8 Adverse effects, Selected Adverse Reactions).

Thyroid function should be monitored before initiation of treatment, and periodically at least monthly throughout treatment with LENVIMA. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Osteonecrosis of the jaw (ONJ)

Events of osteonecrosis of the jaw (ONJ) have been observed with LENVIMA (see Section 4.8, Adverse effects). Invasive dental procedures are an identified risk factor for the development of ONJ. An oral dental examination and appropriate preventive dentistry should be considered prior to initiation of LENVIMA. Patients should be advised regarding periodic dental examinations and oral hygiene practice during LENVIMA therapy. Avoid invasive dental procedures during LENVIMA treatment, if possible. Use caution in patients receiving agents associated with ONJ, such as bisphosphonates and denosumab.

Special populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian. LENVIMA should be used with caution in such patients, given the reduced tolerability of LENVIMA in Asian patients (see Section 4.8 Adverse effects, Other Special Populations).

There are no data on the use of LENVIMA immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was of 4 weeks.

Patients with poor ECOG performance status

Patients with an ECOG performance status of 2 or higher were excluded from the RCC (LENVIMA in combination with everolimus) and HCC studies (see Section 5.1 Pharmacodynamic properties, Clinical trials). Patients with an ECOG performance 3 or higher were excluded from the DTC studies (see Section 5.1 Pharmacodynamic properties, Clinical trials). Benefit-risk in these patients has not been evaluated.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with LENVIMA, and should be regularly monitored during treatment (See Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects).

Use in hepatic impairment

See 4.2 Dose and method of administration, Dosage adjustment in hepatic impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Hepatic Impairment,

Use in renal impairment

See 4.2 Dose and method of administration, Dosage adjustment in renal impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment,

Use in the elderly.

Limited data are available in patients aged ≥ 75 years. LENVIMA should be used with caution in such patients, given the reduced tolerability of LENVIMA in elderly patients (see Section 4.8 Adverse effects, Other Special Populations).

Paediatric use

Clinical data are not yet available in this population.

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21. Mortality occurred at lower doses in neonatal rats (dosing initiated on PND7), or after a shorter duration of treatment in juvenile rats (dosing initiated on PND21). The exposure (as AUC) to lenvatinib in juvenile rats was lower compared to adults, suggesting increased susceptibility to the toxic effects of lenvatinib in young animals. Growth retardation, secondary delay of physical development, and lesions attributable to

pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

Effects on laboratory tests

No data available

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Effect of other medicinal products on LENVIMA

CYP3A, P-gp, and BCRP inhibitors or inducers

LENVIMA may be administered regardless of co-administration with CYP3A, P-gp, and BCRP inhibitors. In healthy subjects, ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ approximately 15% while C_{max} increased 19%. This is supported by a population PK analysis which found CYP3A4 inhibitors decreased Cl/F by 7.8%.

LENVIMA may be co-administered without dose adjustment with CYP3A and P-gp inducers, based on a study in which healthy subjects were administered repeated doses of rifampicin (600 mg for 21 days) and a single dose of lenvatinib (24 mg, Day 15). $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ decreased approximately 18% while C_{max} did not change. The effect of CYP3A induction alone was estimated by comparing the PK parameters for lenvatinib following single and multiple doses of rifampicin. Lenvatinib AUC and C_{max} were predicted to decrease by 30% and 15%, respectively, after strong induction in the absence of acute P-gp inhibition. This is supported by a population PK analysis which found CYP3A4 inducers increased Cl/F by 30%.

Gastric pH-altering agents

In a population pharmacokinetic analysis of patients receiving LENVIMA up to 24 mg once daily, agents which increase gastric pH (H2 receptor blockers, proton pump inhibitors, antacids) did not have a significant effect on lenvatinib exposure.

Other chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel had no significant impact on the pharmacokinetics of any of these 3 substances.

Effect of LENVIMA on other medicinal products

Cytochrome P450 or UGT enzyme substrates

Lenvatinib is considered neither a strong inhibitor nor an inducer of cytochrome P450 or uridine 5'-diphosphoglucuronosyl transferase (UGT) enzymes.

P-gp and BCRP substrates

Lenvatinib showed minimal inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed.

OAT, OCT, OATP, BSEP, MATE and aldehyde oxidase substrates

Lenvatinib showed inhibitory effects on organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, and bile salt export pump (BSEP), but minimal or no inhibitory effect on OATP1B3 and multidrug and toxin extrusion 2 (MATE2)-K. Lenvatinib weakly inhibits MATE1. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys.
No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular and ovarian changes were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4–week recovery period.

Use in pregnancy

Pregnancy Category D.

There is limited information on the use of LENVIMA in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits during organogenesis at exposures below the clinical exposure (based on body surface area) at the maximum recommended human dose. Fetal anomalies included parietal oedema, cryptophthalmia, abnormal tail (rats), retroesophageal subclavian artery, fused ribs, and vertebral abnormalities (rabbits). These embryofetal findings are probably related to the pharmacologic activity of lenvatinib as an antiangiogenic agent.

LENVIMA should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with LENVIMA and for at least one month after finishing treatment. It is currently unknown whether LENVIMA may reduce the effectiveness of

hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Use in lactation

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk and neonatal rats were more sensitive to the toxicity of lenvatinib compared to adults (See Section 4.4 Special warnings and precautions for use, Paediatric Use). Therefore, a risk to newborns or infants cannot be excluded and LENVIMA should not be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. LENVIMA may cause side effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 UNDESIRABLE EFFECTS

Clinical trials

Radioactive iodine refractory differentiated thyroid cancer

The safety of LENVIMA was evaluated in 392 patients from the Phase 3 SELECT trial with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) randomised to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the SELECT study, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhoea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysaesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA and 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhoea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 4 presents the incidence rates of treatment-emergent adverse events observed in the double-blind phase of the DTC study. All adverse events occurring with a treatment difference of at least 5% over placebo are included in the Table. Clinically significant events

(CSEs) that were observed more frequently than placebo are also included based on an assessment of the known pharmacology of LENVIMA and class effects.

Table 4 Treatment-emergent adverse events reported for LENVIMA in the double-blind phase of the DTC study*

System Organ Class Preferred Term	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood & Lymphatic System Disorders				
Thrombocytopenia[a]	13.8	1.9	2.3	0
Lymphopenia[b]	10.7	2.3	4.6	0.8
Splenic infarction	0.8	0	0	0
Cardiac Disorders				
Ejection fraction decreased	5.4	1.1	0.8	0
Myocardial infarction[c,d]	1.1	1.1	0.8	0.8
Cardiac failure	0.8	0	0	0
Endocrine Disorders				
Hypothyroidism	5.4	0	0	0
Gastrointestinal Disorders				
Diarrhoea	67.4	9.2	16.8	0
Nausea	46.7	2.3	25.2	0.8
Stomatitis[e]	41.0	4.6	8.4	0
Vomiting	35.6	1.9	14.5	0
Abdominal pain[f]	31.4	2.3	10.7	0.8
Constipation	28.7	0.4	15.3	0.8
Oral pain[g]	24.9	1.1	2.3	0
Dry mouth	16.9	0.4	8.4	0
Dyspepsia	13.0	0.4	3.8	0
Flatulence	6.1	0	0.8	0
Anal fistula	1.1	0.4	0	0
General Disorders and Administration Site Conditions				
Fatigue	42.5	4.6	24.4	1.5
Asthenia	25.3	6.1	13.0	2.3
Oedema peripheral	20.7	0.4	7.6	0
Malaise	5.4	0	0	0
Hepatobiliary Disorders				
Hepatocellular damage / hepatitis[h]	1.1	0.8	0	0
Infections and Infestations				
Urinary tract infection	11.5	1.1	5.3	0
Perineal abscess	0.8	0.8	0	0
Investigations				
Weight decreased	51.3	13.4	14.5	0.8
Electrocardiogram QT prolonged	8.8	1.5	1.5	0
Alanine aminotransferase increased	7.7	1.5	0	0
Blood creatinine increased	7.3	0	1.5	0
Aspartate aminotransferase increased	6.9	1.9	1.5	0
Blood thyroid stimulating hormone increased	6.5	0	0	0
Blood alkaline phosphatase increased	6.1	0.8	2.3	0.8
Blood urea increased	3.1	0	0	0
Hepatic function abnormal	2.3	0.4	0	0
Blood bilirubin increased	1.9	0	0	0
Gamma-glutamyl transferase increased	1.5	0.8	0.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	54.4	6.9	18.3	0.8
Hypokalaemia	13.8	3.4	3.8	0

Table 4 Treatment-emergent adverse events reported for LENVIMA in the double-blind phase of the DTC study*

System Organ Class Preferred Term	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hypocalcaemia	12.6	5.0	0	0
Hypoalbuminaemia	9.6	0.4	1.5	0
Dehydration	8.8	2.3	2.3	0.8
Hypomagnesaemia[i]	6.5	0.4	1.5	0
Hypercholesterolaemia[j]	5.0	0.4	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	26.1	0.4	6.9	0.8
Myalgia	19.2	1.5	4.6	0
Back pain	17.6	1.9	9.2	0
Musculoskeletal pain	16.1	0.4	8.4	0.8
Pain in extremity	15.3	1.1	6.9	1.5
Nervous System Disorders				
Headache	38.3	3.1	11.5	0.8
Dysgeusia	18.0	0	3.1	0
Dizziness	15.3	0.4	9.2	0
Monoparesis	1.1	0.8	0	0
Cerebrovascular accident	0.8	0.4	0	0
Transient ischemic attack	0.8	0	0	0
Reversible posterior leucoencephalopathy syndrome	0.4	0	0	0
Psychiatric Disorders				
Insomnia	11.9	0	3.1	0
Renal and Urinary Disorders				
Proteinuria	33.7	10.7	3.1	0
Renal failure events[d,k]	5.0	2.7	0.8	0.8
Renal impairment	1.9	0.4	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	31.4	1.1	5.3	0
Cough	23.8	0	17.6	0
Pulmonary embolism[d]	3.1	3.1	1.5	1.5
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	32.2	3.4	0.8	0
Rash	18.8	0.4	1.5	0
Alopecia	12.3	0	5.3	0
Hyperkeratosis	6.9	0	1.5	0
Palmar erythema	1.1	0	0	0
Vascular Disorders				
Haemorrhage[d, l]	34.9	1.5	18.3	3.1
Hypertension[m]	72.8	44.4	16.0	3.8
Hypotension	8.8	1.5	2.3	0

a Includes the following terms: thrombocytopenia, platelet count decreased
b Includes the following terms: lymphopenia, lymphocyte count decreased
c Includes the following terms: acute myocardial infarction, myocardial infarction
d Includes fatal events and these are counted in all Grade column
e Includes the following terms: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, mucosal inflammation
f Includes the following terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain
g Includes the following terms: oral pain, glossodynia, oropharyngeal pain
h Includes the following terms: drug-induced liver injury, cholestatic liver injury, hepatic steatosis
i Includes the following terms: hypomagnesaemia, blood magnesium decreased
j Includes the following terms: hypercholesterolaemia and blood cholesterol increased
k Includes the following terms: acute prerenal failure, renal failure, renal failure acute, renal tubular necrosis

Table 4 Treatment-emergent adverse events reported for LENVIMA in the double-blind phase of the DTC study*

System Organ Class Preferred Term	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

l Includes the following terms: epistaxis, haematuria, contusion, gingival bleeding, haematochezia, pulmonary haemorrhage, vaginal haemorrhage, rectal haemorrhage, haematoma, haemorrhoidal haemorrhage, laryngeal haemorrhage, petechiae, intracranial tumour haemorrhage, haemorrhagic stroke, pleural haemorrhage, splenic haemorrhage, blood urine present, conjunctival haemorrhage, eye haemorrhage, gastroduodenitis haemorrhagic, haematemesis, increased tendency to bruise, proctitis haemorrhagic, purpura, renal haematoma, skin haemorrhage, splinter haemorrhages

m Includes the following terms: hypertension, hypertensive crisis, blood pressure diastolic increased, blood pressure increased

*TEAEs reported at 4 months after the cut-off for the final PFS analysis

Renal cell carcinoma

First-line treatment of renal cell carcinoma in combination with pembrolizumab (CLEAR)

The safety of LENVIMA was evaluated in CLEAR, a study in which patients with advanced renal cell carcinoma (RCC) were randomised (1:1:1) to LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks (n=352), LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340) [see Clinical Studies (14.2)]. All patients on the LENVIMA plus pembrolizumab arm were started on LENVIMA 20 mg orally once daily. The median time to first dose reduction for LENVIMA was 1.9 months. The median average daily dose for LENVIMA was 14 mg. The median duration of study treatment was 17 months (range: 0.07 to 39.13 months). Pembrolizumab was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months.

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA and pembrolizumab, including arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, sepsis and subarachnoid haemorrhage.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in ≥2% of patients were haemorrhagic events (5%), diarrhoea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction (Grade 1-4) occurred in 36% of patients; 24% LENVIMA, and 12% both drugs. The most common adverse reactions (≥2%) leading to discontinuation of LENVIMA, pembrolizumab, or both were pneumonitis (3%), myocardial infarction (3%), rash (3%), and diarrhoea (2%). Refer to the pembrolizumab prescribing information for pembrolizumab discontinuation information.

Dose interruptions of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 78% of patients; LENVIMA was interrupted in 73%, and both drugs in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions (≥ 5%) resulting in dose reduction or interruption of LENVIMA were diarrhoea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), PPE (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), and vomiting (6%), increased ALT (5%), and increased amylase (5%). Refer to the pembrolizumab prescribing information for pembrolizumab interruption information.

Table 5 presents the adverse reactions in ≥ 20% of patients in the LENVIMA with pembrolizumab arm.

Table 5: Adverse reactions in ≥ 20% of patients on LENVIMA plus pembrolizumab and sunitinib in CLEAR (RCC)

	LENVIMA 20 mg in combination with pembrolizumab 200mg N=352		**Sunitinib 50 mg N=340**	
Adverse Reactions	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General				
Fatigue[a]	63	9	56	8
Gastrointestinal				
Diarrhoea[b]	62	10	50	6
Stomatitis[c]	43	2	43	2
Nausea	36	3	33	1
Abdominal pain[d]	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and connective tissue				
Musculoskeletal pain[e]	58	4	41	3
Endocrine				
Hypothyroidism[f]	57	1	32	0
Vascular				
Hypertension[g]	56	29	43	20
Haemorrhagic events[h]	27	5	26	4
Metabolism				
Decreased appetite[i]	41	4	31	1
Skin and Subcutaneous Tissue				
Rash[j]	37	5	17	1
Palmar-plantar erythrodysesthesia syndrome[k]	29	4	38	4
Investigations				
Decreased weight	30	8	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	30	0	4	0
Renal and urinary				

Table 5: Adverse reactions in ≥ 20% of patients on LENVIMA plus pembrolizumab and sunitinib in CLEAR (RCC)				
	LENVIMA 20 mg in combination with pembrolizumab 200mg N=352		**Sunitinib 50 mg N=340**	
Adverse Reactions	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Proteinuria[l]	30	8	13	3
Nervous System				
Headache	23	1	16	1

a Includes asthenia, fatigue, lethargy and malaise
b Includes diarrhoea and gastroenteritis
c Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis
d Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain
e Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and pain in jaw
f Includes hypothyroidism, increased blood thyroid stimulating hormone and secondary hypothyroidism
g Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure
h Includes all haemorrhage terms. Haemorrhage terms that occurred in 1 or more subjects in either treatment group include: Anal haemorrhage, aneurysm ruptured, blood blister, blood loss anemia , blood urine present, catheter site haematoma, cerebral microhaemorrhage, conjunctival haemorrhage, contusion, diarrhoea haemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye haemorrhage, gastric haemorrhage, gastritis haemorrhagic, gingival bleeding, haemorrhage urinary tract, hemothorax, haematemesis , haematoma , haematochezia, haematuria, hemoptysis, hemorrhoidal haemorrhage , increased tendency to bruise, injection site haematoma, injection site haemorrhage, intra-abdominal haemorrhage, lower gastrointestinal haemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal haemorrhage, renal haemorrhage, retroperitoneal haemorrhage, small intestinal haemorrhage, splinter haemorrhages, subcutaneous haematoma, subdural haematoma, subarachnoid haemorrhage, thrombotic thrombocytopenic purpura, tumour haemorrhage, traumatic haematoma, and upper gastrointestinal haemorrhage
i Includes decreased appetite and early satiety
j Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular
k Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome and plantar erythema
l Includes haemoglobinuria, nephrotic syndrome, and proteinuria

Table 6 presents laboratory abnormalities occurring in ≥ 20% of patients (All Grades) or ≥ 3% (Grades 3-4) of patients with LENVIMA in combination with pembrolizumab.

Table 6: Laboratory abnormalities in ≥ 20% (All Grades) or ≥ 3% (Grades 3-4) of patients on LENVIMA plus pembrolizumab in CLEAR (RCC)				
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg		**Sunitinib 50 mg**	
Laboratory Abnormality[a]	**All Grades %[b]**	**Grades 3-4 %[b]**	**All Grades %[b]**	**Grade 3-4 %[b]**
Chemistry				
Hypertriglyceridaemia	80	15	71	15
Hypercholesterolaemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased aspartate aminotransferase (AST)	58	7	57	3
Hyperglycaemia	55	7	48	3

Table 6: Laboratory abnormalities in ≥ 20% (All Grades) or ≥ 3% (Grades 3-4) of patients on LENVIMA plus pembrolizumab in CLEAR (RCC)				
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg		**Sunitinib 50 mg**	
Laboratory Abnormality[a]	**All Grades %[b]**	**Grades 3-4 %[b]**	**All Grades %[b]**	**Grade 3-4 %[b]**
Increased alanine aminotransferase (ALT)	52	7	49	4
Hyperkalaemia	44	9	28	6
Hypoglycaemia	44	2	27	1
Hyponatraemia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcaemia	30	2	22	1
Hypophosphataemia	29	7	50	8
Hypomagnesaemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesaemia	23	2	22	3
Hypercalcaemia	21	1	11	1
Hypokalaemia	13	4	7	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

a With at least 1 grade increase from baseline

b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post

Baseline laboratory measurement for each parameter. LENVIMA/pembrolizumab (n= 343 to 349) and sunitinib (n= 329 to 335).

Previously treated renal cell carcinoma in combination with everolimus (Study 205)

The most common adverse reactions observed in the LENVIMA in combination with everolimus-treated group (> 30%) were, in order of decreasing frequency, diarrhoea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral oedema, cough, abdominal pain, dyspnoea, rash, weight decreased, haemorrhagic events, and proteinuria. The most common serious adverse reactions (≥ 5%) were renal failure (11%), dehydration (10%), anaemia (6%), thrombocytopenia (5%), diarrhoea (5%), vomiting (5%), and dyspnoea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA + everolimus and 54% in patients receiving everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the LENVIMA + everolimus-treated group were diarrhoea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus-treated group and 12% of patients in the everolimus-treated group.

Table 7 presents the adverse reactions in > 15% of patients in the LENVIMA + Everolimus arm.

Table 7 Grades 1-4 adverse reactions in > 15% of patients in the LENVIMA + everolimus arm

	LENVIMA 18 mg + Everolimus 5 mg (N=62)		Everolimus 10 mg (N=50)	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism	24	0	2	0
Gastrointestinal Disorders				
Constipation	16	0	18	0
Diarrhoea	81	19	34	2
Dyspepsia/Gastro-oesophageal reflux	21	0	12	0
Abdominal pain[a]	37	3	8	0
Nausea	45	5	16	0
Oral pain[b]	23	2	4	0
Stomatitis/Oral inflammation[c]	44	2	50	4
Vomiting	48	7	12	0
General Disorders and Administration Site Conditions				
Fatigue[d]	73	18	40	2
Peripheral oedema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Investigations				
Weight decreased	34	3	8	0
Metabolism and Nutrition Disorders				
Decreased appetite	53	5	18	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System Disorders				
Headache	19	2	10	2
Psychiatric Disorders				
Insomnia	16	2	2	0
Renal and Urinary Disorders				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	37	0	30	0
Dysphonia	18	0	4	0
Dyspnoea/Exertional dyspnoea	35	5	28	8
Skin and Subcutaneous Tissue Disorders				
Rash[g]	35	0	40	0
Vascular Disorders				
Haemorrhagic events[h]	32	6	26	2
Hypertension/Increased blood pressure	42	13	10	2

a Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
b Includes gingival pain, glossodynia, and oropharyngeal pain
c Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration
d Includes asthenia, fatigue, lethargy and malaise
e Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia
f Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment
g Includes erythema, erythematous rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, and septic rash

h Includes haemorrhagic diarrhea, epistaxis, gastric haemorrhage, haemarthrosis, haematoma, haematuria, haemoptysis, lip haemorrhage, renal haematoma, and scrotal haematocele

In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥ 3% of patients in the LENVIMA with everolimus arm are presented.

Table 8 Grade 3-4 laboratory abnormalities in ≥ 3% of patients in the LENVIMA + everolimus arm[a,b]

Laboratory Abnormality	LENVIMA 18 mg + everolimus 5 mg (N=62)	Everolimus 10 mg N=50
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Aspartate aminotransferase (AST) increased	3	0
Alanine aminotransferase (ALT) increased	3	2
Alkaline phosphatase increased	3	0
Hyperkalaemia	6	2
Hypokalaemia	6	2
Hyponatraemia	11	6
Hypocalcaemia	6	2
Hypophosphataemia	11	6
Hyperglycaemia	3	16
Hypertriglyceridaemia	18	18
Elevated cholesterol	11	0
Creatine kinase increased	3	4
Lipase increased	13	12
Hematology		
Haemoglobin decreased	8	16
Platelet count decreased	5	0
Lymphocyte count decreased	10	20

a With at least 1 grade increase from baseline
b Subject with at least 1 post baseline laboratory value

Hepatocellular carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomised (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=476) or sorafenib (n=475) (see Section 5.1, Pharmacodynamic properties, Clinical trials). The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥ 60 kg and 8 mg orally once daily for patients with a baseline body weight of < 60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was ≥ 6 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients (≥ 20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhoea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysaesthesia syndrome, proteinuria, dysphonia, haemorrhagic events, hypothyroidism, and nausea. The most common serious adverse reactions (≥ 2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥ 5%) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhoea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysaesthesia syndrome (5%).

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions (≥ 1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Table 9 summarises the adverse reactions that occurred in ≥ 10% of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 9.

Table 9 Adverse reactions occurring in ≥ 10% of patients in the LENVIMA arm in REFLECT (HCC)

	LENVIMA 8 mg/12 mg N=476		**Sorafenib 800 mg N=475**	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism[a]	21	0	3	0
Gastrointestinal Disorders				
Diarrhoea	39	4	46	4
Abdominal pain[b]	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites[c]	15	4	11	3
Stomatitis/Oral inflammation[d]	11	0.4	14	1
General Disorders and Administration Site Conditions				
Fatigue[e]	44	7	36	6
Pyrexia[f]	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Investigations				
Weight decreased	31	8	22	3
Metabolism and Nutrition Disorders				
Decreased appetite	34	5	27	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[g]	31	1	20	2
Nervous System Disorders				
Headache	10	1	8	0
Renal and Urinary Disorders				
Proteinuria[h]	26	6	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	24	0.2	12	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	27	3	52	11
Rash[i]	14	0	24	2

Vascular Disorders				
Hypertension[j]	45	24	31	15
Haemorrhagic events[k]	23	4	15	4

a Includes hypothyroidism, blood thyroid stimulating hormone increased.
b Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
c Includes ascites and malignant ascites
d Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis
e Includes asthenia, fatigue, lethargy and malaise
f Includes increased body temperature, pyrexia
g Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia
h Includes proteinuria, increased urine protein, and increased urine protein/creatinine ratio
i Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and rash
j Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension
k Includes all haemorrhage terms. Haemorrhage terms that occurred in 5 or more subjects in either treatment group include: epistaxis, haematuria, gingival bleeding, haemoptysis, esophageal varices haemorrhage, haemorrhoidal haemorrhage, mouth haemorrhage, rectal haemorrhage and upper gastrointestinal haemorrhage

In Table 10, Grade 3-4 laboratory abnormalities occurring in ≥ 2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 10 Grade 3-4 laboratory abnormalities occurring in ≥ 2% of patients in the LENVIMA arm[a,b] in REFLECT (HCC)

Laboratory Abnormality	LENVIMA (N=476) (%)	Sorafenib (N=475) (%)
Chemistry		
Alanine aminotransferase (ALT) increased	8	9
Albumin decreased	3	1
Alkaline phosphatase increased	7	5
Aspartate aminotransferase (AST) increased	12	18
Bilirubin increased	13	10
Creatinine increased	2	2
GGT increased	17	20
Hyperkalemia	3	2
Hypokalemia	3	4
Hyponatremia	15	9
Lipase increased	6	17
Haematology		
Haemoglobin decreased	4	5
Lymphocyte count decreased	8	9
Neutrophil count decreased	7	3
Platelet count decreased	10	8

a With at least 1 grade increase from baseline
b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=278 to 470) and sorafenib (n=260 to 473)

Endometrial carcinoma

The safety of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicenter, open-label, randomised (1:1), active-controlled trial in 827 patients with advanced EC previously treated with at least one prior platinum-based chemotherapy regimen

in any setting, including in the neoadjuvant and adjuvant settings. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received LENVIMA 20 mg orally once daily with pembrolizumab 200 mg intravenously every 3 weeks (n=406) or treatment of investigator's choice (n=388), consisting of 60 mg/m^2 doxorubicin every 3 weeks or 80 mg/m^2 paclitaxel given weekly, 3 weeks on/1 week off *[see Clinical Studies (14.4)]*.

The median duration of study treatment was 7.6 months (range 1 day to 26.8 months). The median duration of exposure to LENVIMA was 6.9 months (range 1 day to 26.8 months). Pembrolizumab was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months.

Dose reductions of LENVIMA due to adverse events occurred in 65.5% of patients. The median time to first dose reduction for any reason was 1.9 months (range 0.1 to 22.8 months). The median of the average daily dose of LENVIMA was 13.8 mg (range 3 to 20 mg).

Fatal adverse reactions occurred in 5.7% of patients treated with LENVIMA and pembrolizumab, including pneumonia, acute kidney injury, acute myocardial infarction, cerebrovascular accident, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, right ventricular dysfunction, urosepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in 53% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency ≥ 3% were hypertension (4.2%) and urinary tract infection (3.2%).

Discontinuation of LENVIMA, pembrolizumab or both due to an adverse reaction (Grade 1 to 4) occurred in 30% of patients; 27% LENVIMA, and 11% both drugs. The most common adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.7%), decreased appetite (1.5%), decreased weight (1.5%), diarrhea (1.2%), proteinuria (1.2%), intestinal obstruction (1%), and vomiting (1%), Refer to the pembrolizumab prescribing information for pembrolizumab discontinuation information.

Dose interruptions of LENVIMA, pembrolizumab or both due to an adverse reaction occurred in 69% of patients; LENVIMA was interrupted in 59%, and both drugs in 31% of patients. The most common adverse reactions leading to interruption of LENVIMA (≥ 2%) were hypertension (11.1%), diarrhea (10.6%), proteinuria (5.9 %), vomiting (5.4%), decreased appetite (4.9%), fatigue (4.2%), nausea (3.4%), increased alanine aminotransferase (3.0%), urinary tract infection (2.7%), abdominal pain (2.5%), decreased weight (2.5%), asthenia (2.2%), hypothyroidism (2.0%), and increased aspartate aminotransferase (2.0%), Refer to the pembrolizumab prescribing information for pembrolizumab interruption information.

Table 11 and Table 12 summarise adverse reactions and laboratory abnormalities, respectively, in patients receiving LENVIMA in combination with pembrolizumab in Study 309.

Table 11 Adverse reactions in ≥ 20% of patients receiving LENVIMA plus pembrolizumab in Study 309 (EC)

Adverse Reaction	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=406		Doxorubicin or Paclitaxel N=388	
	All Grades[a] (%)	Grades 3-4 (%)	All Grades[a] (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism[b]	69	1	1	0
Vascular				
Hypertension[c]	65	38	6	2
Hemorrhagic events[d]	24	2	13	1
General				
Fatigue[e]	59	11	54	7
Gastrointestinal				
Diarrhea[f]	54	8	21	2
Nausea	50	3	46	1
Vomiting	37	3	21	2
Stomatitis[g]	35	3	25	1
Abdominal pain[h]	33	3	21	2
Constipation	26	1	25	1
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders[i]	52	5	26	1
Metabolism				
Decreased appetite[j]	45	8	21	1
Investigations				
Decreased weight	34	10	6	0
Renal and Urinary				
Proteinuria[k]	30	5	3	0
Infections				
Urinary tract infection[l]	29	5	12	1
Nervous System				
Headache	25	<1	9	0
Respiratory, Thoracic and Mediastinal				
Dysphonia	23	0	1	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia[m]	22	3	1	0
Rash[n]	20	2	4	0

a Graded per NCI CTCAE v4.03
b Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, and secondary hypothyroidism
c Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, and blood pressure fluctuation

d Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, injection site hemorrhage, melena, purpura, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, coital bleeding, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, and vessel puncture site bruise
e Includes fatigue, asthenia, malaise, and lethargy
f Includes diarrhea and gastroenteritis
g Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, and tongue ulceration
h Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, and epigastric discomfort
i Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw
j Includes decreased appetite and early satiety
k Includes proteinuria, protein urine present, hemoglobinuria
l Includes urinary tract infection, cystitis, and pyelonephritis
m Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, and skin reaction
n Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash 28opular, rash vesicular, and application site rash

Table 12 Laboratory abnormalities worsened from baseline[a] occurring in ≥ 20% (All Grades) or ≥ 3% (Grades 3-4) of patients receiving LENVIMA plus pembrolizumab in Study 309 (EC)

Laboratory Test[b]	LENVIMA 20 mg in combination with Pembrolizumab N=406		Doxorubicin or Paclitaxel N=388	
	All Grades[c] %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hypertriglyceridemia	69	7	43	2
Hypoalbuminemia	61	3	42	2
Increased aspartate aminotransferase	58	9	22	1
Hyperglycemia	57	8	45	4
Hypomagnesemia	46	<1	27	1
Increased alanine aminotransferase	53	8	21	1
Hypercholesteremia	53	3	22	1
Hyponatremia	47	14	27	7
Increased alkaline phosphatase	43	4	19	1
Hypocalcemia	40	4	20	2
Increased lipase	35	14	12	4
Increased creatinine	35	4	17	2
Hypokalemia	34	11	23	5
Hypophosphatemia	25	8	18	4
Increased amylase	25	7	7	1
Hyperkalemia	24	2	13	2
Increased creatine kinase	20	3	6	0
Increased bilirubin	19	3	6	2
Hypermagnesemia	7	3	4	2

Hematology				
Lymphopenia	52	18	66	24
Thrombocytopenia	50	7	30	5
Anemia	50	8	83	16
Leukopenia	44	3	83	42
Neutropenia	36	8	78	59

a With at least 1 grade increase from baseline
b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: LENVIMA/pembrolizumab (range: 312 to 404 patients) and doxorubicin or paclitaxel (280 to 380).
c Graded per NCI CTCAE v4.03

Post-marketing adverse drug reactions

The following adverse reactions have been identified during post approval use of LENVIMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: amylase increased, lipase increased, pancreatitis
Hepatobiliary Disorders: cholecystitis
General Disorders and Administration Site Conditions: impaired healing
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw
Renal and urinary disorders: nephrotic syndrome
Respiratory, thoracic and mediastinal disorders: pneumothorax
Vascular Disorders: aortic dissection, cases of aneurysms and artery dissections, sometimes fatal, have been reported with VEGF pathway inhibitors.

Other special populations

Elderly

In DTC, patients of age ≥ 75 years were more likely to experience Grade 3 or 4 hypertension, proteinuria, decreased appetite, and dehydration.

In CLEAR, patients of age ≥ 75 years had a higher (≥ 10% difference) incidence of proteinuria than patients of age < 65 years.

In HCC, patients of age ≥ 75 years were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness and hepatic encephalopathy. Arterial thromboembolic events also occurred at an increased incidence in this age group.

Sex

In DTC, females had a higher incidence of hypertension (including Grade 3 or 4 hypertension), proteinuria, and PPE, while males had a higher incidence of decreased ejection fraction and gastrointestinal perforation and fistula formation.

In HCC, females had a higher incidence of hypertension, fatigue and ECG QT prolongation. Hepatic failure events were observed in male patients only.

In CLEAR, males had a higher (≥ 10% difference) incidence than females of diarrhoea.

Race

In DTC, Asian patients had a higher incidence than Caucasian patients of oedema peripheral, hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased. Japanese patients had a higher incidence of Grade 3 or 4 hypertension, decreased appetite, fatigue, and thrombocytopenia compared with non-Japanese subjects.

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 HCC, Asian patients had a higher incidence than Caucasian patients of proteinuria and PPE syndrome, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy and acute kidney injury.

Baseline hypertension

In DTC, patients with baseline hypertension had a higher incidence of Grade 3 or 4 hypertension, proteinuria, diarrhoea, and dehydration, and experienced more serious events of dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting).

In CLEAR, patients with baseline hypertension had a higher incidence of proteinuria than patients without baseline hypertension.

Hepatic impairment

In DTC, patients with baseline hepatic impairment had a higher incidence of hypertension and PPE, and a higher incidence of Grade 3 or 4 hypertension, asthenia, fatigue, and hypocalcaemia compared with patients with normal hepatic function. There are limited data on patients with hepatic impairment in RCC.

In HCC, patients with a baseline Child Pugh (CP) score of 6 compared to a baseline CP score of 5 had a higher incidence of decreased appetite, fatigue, proteinuria, hepatic encephalopathy and hepatic failure. Hepatotoxicity events and haemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients.

Renal impairment

In DTC, patients with baseline renal impairment had a higher incidence of Grade 3 or 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, blood thyroid stimulating hormone increased and pneumonia compared with subjects with normal renal function. These patients also had a higher incidence of renal events and a trend towards a higher incidence of liver events.

See also Section 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

In HCC, patients with baseline renal impairment had a higher incidence of fatigue, hypothyroidism, dehydration, diarrhoea, decreased appetite, proteinuria and hepatic encephalopathy. These patients also had a higher incidence of renal reactions and arterial thromboembolic events.

Patients with body weight < 60 kg

In DTC, patients with low body weight (< 60 kg) had a higher incidence of PPE, proteinuria, Grade 3 or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite. There are limited data on patients with body weight < 60 kg in RCC.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactionshttps://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

There have been reports of overdose with LENVIMA including a single administration of 144 mg, 6 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of LENVIMA, or were without adverse reactions. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally. There is no specific antidote for overdose with LENVIMA, due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. In case of suspected overdose, LENVIMA should be withheld and appropriate supportive care given as required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX08

Mechanism of action

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

In addition, lenvatinib inhibited the proliferation of human hepatocellular carcinoma (HCC) cell lines dependent on FGFR signaling *in vitro* and caused a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

In syngeneic mouse tumour models, lenvatinib decreased tumour-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumour activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling *in vitro* and tumour volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

Pharmacodynamic effects

Cardiac electrophysiology

A single 32-mg dose of lenvatinib did not prolong the QT/QTc interval based on results from a thorough QT study in healthy volunteers; however, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with LENVIMA than in patients treated with placebo (see Section 4.8 Adverse effects, Selected Adverse Reactions).

Clinical efficacy and safety

Radioactive iodine refractory differentiated thyroid cancer

The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioactive iodine refractory differentiated thyroid cancer with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month window) prior to enrolment. Radioiodine-refractory status was defined as one or more measurable lesions either with a lack of iodine uptake or with progression in spite of radioactive-iodine (RAI) therapy, or having a cumulative activity of RAI of >600 mCi or 22 GBq with the last dose at least 6 months prior to study entry.

Randomisation was stratified by geographic region (Europe, North America, and Other), prior VEGF/VEGFR-targeted therapy (patients may have received 0 or 1 prior VEGF/VEGFR-targeted therapy), and age (≤65 years or >65 years). The main efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Secondary efficacy outcome measures included overall response rate and overall survival (OS). Patients in the placebo arm could opt to receive LENVIMA treatment at the time of confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomised 2:1 to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131). Baseline demographics and disease characteristics were well balanced for both treatment groups. Of the 392 patients randomised, 76.3% were naïve to prior VEGF/VEGFR-targeted therapies, 49.0% were female, 49.7% were European, and the median age was 63 years. Histologically, 66.1% had a confirmed diagnosis of papillary thyroid cancer and 33.9% had follicular thyroid cancer which included Hürthle cell 14.8% and clear cell 3.8%. Metastases were present in 99% of the patients: lungs in 89.3%, lymph nodes in 51.5%, bone in 38.8%, liver in 18.1%, pleura in 16.3%, and brain in 4.1%. The majority of patients (54%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0; 42.1% had a status of 1; 3.9% had a status above 1. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared with those receiving placebo ($p < 0.0001$). The positive effect on PFS was similar in the subgroups that received 0 or 1 prior VEGF/VEGFR-targeted therapy (see Table 13 and Figure 1). In addition, the positive effect on PFS was seen across the subgroups of age, sex, race, histological subtype, and geographic region. Following independent review confirmation of disease progression, 109 (83.2%) patients randomised to placebo crossed over to receive open-label LENVIMA.

There was no statistically significant difference in overall survival in the treatment arm compared to the placebo group at the primary analysis (HR (95% CI): 0.73 (0.59, 1.07)). However, the SELECT study was not powered to demonstrate an improvement in OS, and the high rate of crossover of patients in the placebo arm to the treatment arm after confirmed disease progression made demonstration of a statistically significant difference in OS difficult.

The median time to first dose reduction was 2.8 months. The median time to objective response was 2.0 (95% CI: 1.9, 3.5) months; however, of the patients who experienced a complete or partial response to LENVIMA, 70.4% were observed to develop the response on or within 30 days of being on the 24-mg dose.

The study did not measure quality of life (QoL). The effect of treatment on QoL can therefore not be assessed and QoL may not be improved with LENVIMA treatment.

Table 13 Efficacy results in radioactive iodine refractory differentiated thyroid cancer

	LENVIMA N=261	**Placebo N=131**
Progression-Free Survival (PFS)[a]		
Number of progressions or deaths (%)	107 (41.0)	113 (86.3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard Ratio (99% CI)[b,c]	0.21 (0.14, 0.31)	
P-value[b]	< 0.0001	
Patients who had received 0 prior VEGF/VEGFR-target therapy (%)	195(74.7)	104 (79.4)
Number of progressions or deaths	76	88
Median PFS in months (95%CI)	18.7 (16.4, NE)	3.6 (2.1, 5.3)
Hazard ratio (95% CI) [b,c]	0.20 (0.14, 0.27)	
Patients who had received 1 prior VEGF/ VEGFR - targeted therapy (%)	66 (25.3)	27 (20.6)
Number of progressions or deaths	31	25
Median PFS in months (95%CI)	15.1 (8.8, NE)	3.6 (1.9, 3.7)
Hazard ratio (95% CI) [b,c]	0.22 (0.12, 0.41)	
Overall Response Rate[a]		
Number of objective responders (%)	169 (64.8)	2 (1.5)
(95% CI)	(59.0, 70.5)	(0.0, 3.6)
P-value[b]	< 0.0001	
Number of complete responses	4	0
Number of partial responses	165	2
Median time to objective response,[d] months (95%CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Duration of response,[d] months, median (95% CI)	NE (16.8, NE)	NE (20.3, NE)
Overall Survival		
Number of Deaths (%)	71 (27.2)	47 (35.9)
Median OS in months (95% CI)	NE (22.0, NE)	NE (20.3, NE)
Hazard Ratio (95% CI)[b,e]	0.73 (0.50, 1.07)	
P-value[b,e]	0.1032	

CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time model; VEGF/VEGFR, vascular endothelial growth factor /vascular endothelial growth factor receptor.

a Independent radiologic review.

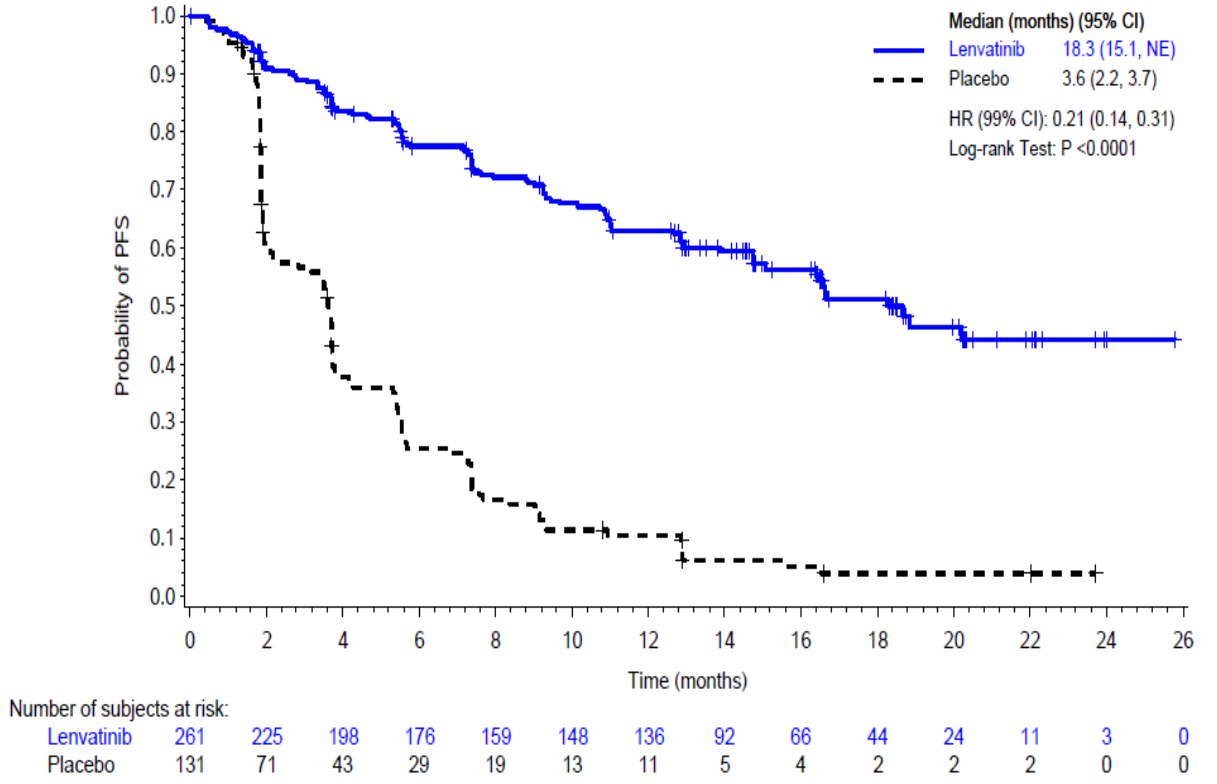
b Stratified by region (Europe vs. North America vs. Other), age group (≤ 65 year vs > 65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

c Estimated with Cox proportional hazard model.

d Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.

e Not adjusted for crossover effect.

Figure 1 Kaplan-Meier curve of progression-free survival - DTC



Renal cell carcinoma

First-Line treatment of patients with RCC in combination with Pembrolizumab (CLEAR)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in CLEAR (NCT02811861), a multicenter, open-label, randomised trial that enrolled 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by geographic region (North America and Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable, intermediate and poor risk).

Patients were randomised to LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=355), or LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=357), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=357). Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by independent radiologic review committee (IRC) using RECIST 1.1.

Administration of LENVIMA with pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab dosing was continued for a maximum of 24

months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 8 weeks.
The overall study population characteristics were: median age of 62 years (range: 29 to 88 years); 42% age 65 or older, 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC (International Metastatic RCC Database Consortium) risk categories was 33% favourable, 56% intermediate, and 10% poor, and MSKCC risk categories was 27% favourable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The primary efficacy outcome measure was PFS based on RECIST 1.1 per IRC. Key secondary efficacy outcome measures included OS and ORR. LENVIMA in combination with pembrolizumab demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. At a median overall survival follow-up time of 26.6 months, efficacy results for CLEAR are summarised in Table 14 and Figure 2 and Figure 3. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups, and PD-L1 tumour expression status.

Table 14: Efficacy results[a] in renal cell carcinoma per IRC in CLEAR

	LENVIMA 20 mg with Pembrolizumab 200 mg N=355	**Sunitinib 50 mg N=357**
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45.1%)	205 (57.4%)
Progressive disease	145 (40.8%)	196 (54.9%)
Death	15 (4.2%)	9 (2.5%)
Median PFS in months (95% CI)[b]	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard Ratio (95% CI)[c,d]	0.39 (0.32, 0.49)	
p-Value[d]	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (22.5%)	101 (28.3%)
Median OS in months (95% CI)	NR (33.6, NE)	NR (NE, NE)
Hazard Ratio (95% CI)[c,d]	0.66 (0.49, 0.88)	
p-Value[d]	0.0049	
Overall Survival Rate (%) (95% CI) at[e]		
12 months	91.4% (87.9, 93.9)	80.2% (75.5, 84.1)
18 months	87.1% (83.1, 90.3)	74.4% (69.3, 78.8)
24 months	79.2% (74.1, 83.3)	70.4% (65.0, 75.2)
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	252 (71.0%)	129 (36.1%)
(95% CI)	(66.3, 75.7)	(31.2, 41.1)
Number of complete responses, n (%)	57 (16.1%)	15 (4.2%)
Number of partial responses, n (%)	195 (54.9%)	114 (31.9%)
p-Value[f]	<0.0001	
Duration of Response[b]		
Median in months (range)	26 (1.6+, 36.8+)	15 (1.6+, 33.2+)

Tumour assessments were based on RECIST 1.1; only confirmed responses are included for ORR.
Data cutoff date = 28 Aug 2020
CI = confidence interval; NE= Not estimable; NR= Not reached
a Based on pre-specified interim analysis (primary analysis)
b Quartiles are estimated by Kaplan-Meier method.
c Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.

Table 14: Efficacy results[a] in renal cell carcinoma per IRC in CLEAR

	LENVIMA 20 mg with Pembrolizumab 200 mg N=355	Sunitinib 50 mg N=357

d Stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) in IxRS. Two-sided p-value based on stratified log-rank test.

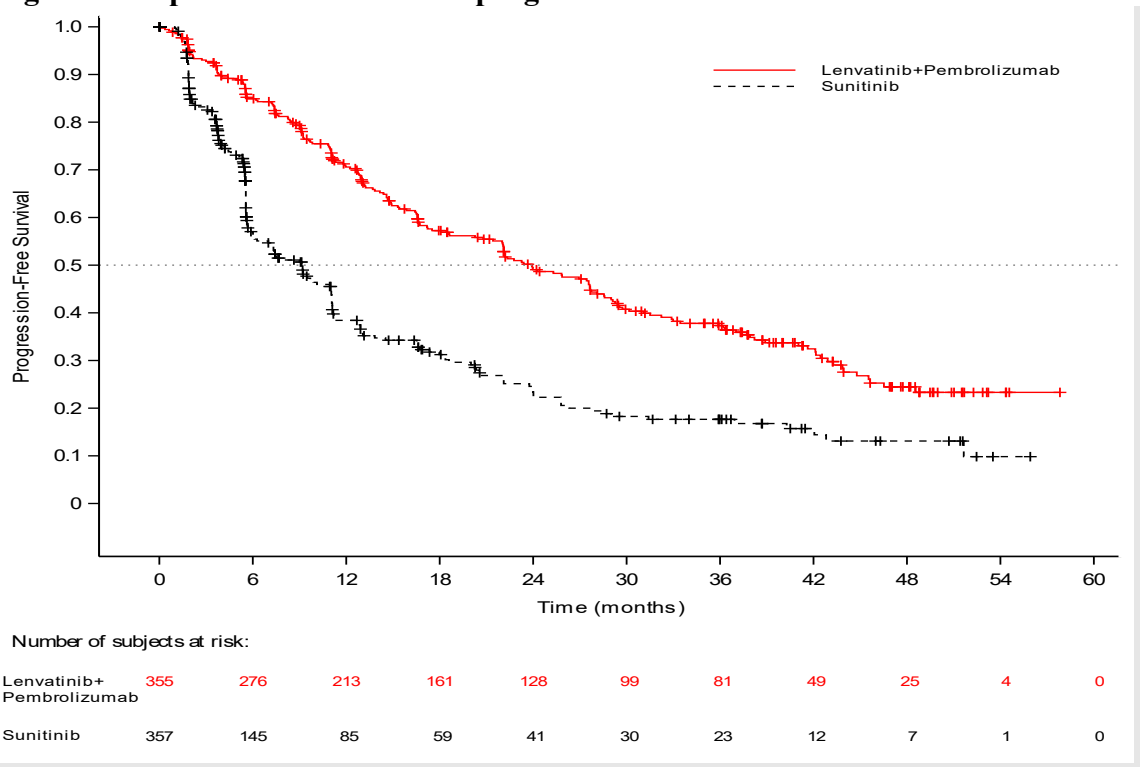
e Overall survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.

f Nominal p-value. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing LENVIMA plus pembrolizumab with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-value < 0.0001).

At the protocol-specified final analysis, median PFS for LENVIMA in combination with pembrolizumab was 23.9 months (95% CI: 20.8, 27.7) compared to 9.2 months (95% CI: 6.0, 11.0) for sunitinib, with an HR of 0.47 (95% CI: 0.38, 0.57); median OS for LENVIMA in combination with pembrolizumab was 53.7 months (95% CI: 48.7, NE) compared to 54.3 months (95% CI: 40.9, NE) for sunitinib with an HR of 0.79 (95% CI: 0.63, 0.99); ORR of 71% for LENVIMA in combination with pembrolizumab and 37% for sunitinib. The complete response rates were 18% for LENVIMA in combination with pembrolizumab and 5% for sunitinib.

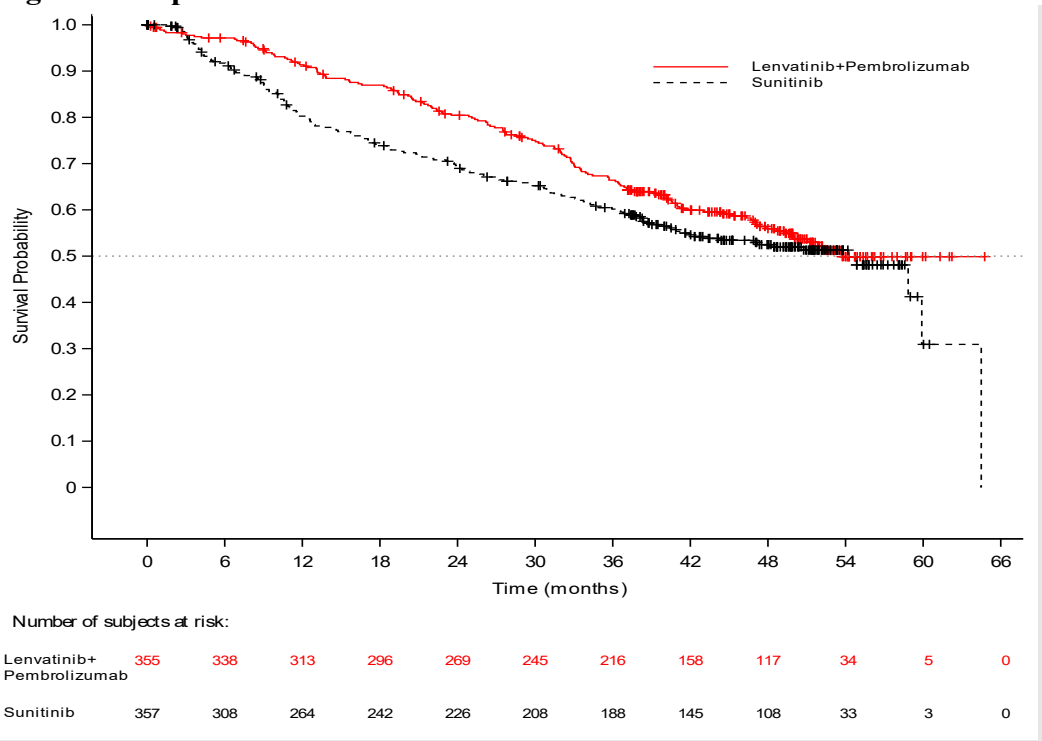
The OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54.6%) subjects in the sunitinib arm and 56/355 (15.8%) subjects in the lenvatinib plus pembrolizumab arm receiving subsequent anti-PD-1/PD-L1 therapy. OS may be confounded by the difference in subsequent therapies.

Figure 2: Kaplan-Meier curves for progression-free survival in CLEAR*



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
*Based on updated PFS analysis conducted at the time of the protocol-specified final analysis.

Figure 3: Kaplan-Meier curves for overall survival in CLEAR*



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
* Based on the protocol-specified final analysis; the OS analysis was not adjusted to account for subsequent therapies. Among those who discontinued treatment or who were randomised but had never been treated, 154/290 (53.1%) patients in the sunitinib arm subsequently received an anti-PD-(L)1 treatment versus 29/213 (13.6%) in the lenvatinib plus pembrolizumab arm. OS may be confounded by the difference in subsequent therapies.

Patient-reported outcomes (PROs) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). From baseline to a mean follow-up time of 46 weeks, patients treated with LENVIMA in combination with pembrolizumab had better physical functioning scores compared to the sunitinib group. When compared to sunitinib, LENVIMA in combination with pembrolizumab showed a more than 12 week delay in the median time to development or worsening of the following patient reported symptoms with no subsequent recovery: fatigue (51 weeks), insomnia (30 weeks), dyspnea (27 weeks), nausea and vomiting (16 weeks), and pain (14 weeks). The patient-reported delay in onset or worsening may be an under-or over-estimation, because patients were not blinded to treatment assignment.

Open-label trial of LENVIMA plus pembrolizumab in patients with advanced/metastatic non-clear cell RCC in the first line setting

The efficacy of LENVIMA in combination with pembrolizumab was investigated in KEYNOTE-B61, a multicenter, open-label, single-arm trial that enrolled 160 patients with advanced/metastatic non-clear cell RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received LENVIMA 20 mg orally once daily in combination with pembrolizumab 400 mg every 6 weeks up to 24 months. Treatment continued until unacceptable toxicity or disease progression. Administration of LENVIMA with pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit. LENVIMA could be continued beyond 24 months; however, pembrolizumab was continued for a maximum of 24 months.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years); 71% male; 86% White, 8% Asian, and 3% Black; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories was 35% favourable, 54% intermediate, and 10% poor. Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included DOR and PFS (as assessed by BICR using RECIST 1.1) and OS. Clinical activity was observed regardless of the histological subtype. Efficacy results are summarised in Table 15.

Table 15 Efficacy results in Study-B61

Endpoint	**LENVIMA and pembrolizumab 400 mg every 6 weeks n=158**
Objective Response Rate*	
ORR†, (95% CI)	51% (43%, 59%)
Complete response	8%
Partial response	42%
Stable disease	32%
Disease control rate	82%
Response Duration*,‡	
Median in months (range)	19.5 (1.5+, 23.5+)
% with duration ≥ 6 months	89%
% with duration ≥ 12 months	76%
% with duration ≥ 18 months	51%
Time to Response	
Median in months (range)	2.8 (2.5, 15.2)
PFS*,‡	
Median in months (95% CI)	17.9 (15.1, 22.1)
12-month PFS rate (95% CI)	64% (56, 71)
18-month PFS rate (95% CI)	48% (39, 56)
OS	
Median in months (95% CI)	NR (NR, NR)
12-month OS rate (95% CI)	82% (75, 87)
18-month OS rate (95% CI)	73% (65, 79)

* Assessed by BICR using RECIST 1.1
† Based on patients with a best overall response as confirmed complete or partial response
‡ Based on Kaplan-Meier estimates
NR = not reached

Previously treated RCC in combination with everolimus (Study 205)

A multicentre, randomised, open-label, trial was conducted to determine the safety and efficacy of LENVIMA administered alone or in combination with everolimus in subjects with unresectable advanced or metastatic Renal Cell Carcinoma (RCC). The study consisted of a Phase 1b dose finding and a Phase 2 portion. The Phase 1b portion included 11 patients who received the combination of 18 mg of LENVIMA plus 5 mg of everolimus. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic RCC, who had previously received 1 prior VEGF-targeted treatment, 1:1:1 to LENVIMA 18 mg plus everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of predominant clear cell RCC, and ECOG Performance Status of 0 or 1. Patients were stratified by haemoglobin level (≤ 13 g/dL vs. > 13 g/dL for males and ≤ 11.5 g/dL vs > 11.5 g/dL for females) and corrected serum calcium (≥ 10 mg/dL vs. < 10 mg/dL).

Of the 101 patients randomly allocated to the LENVIMA plus everolimus arm and everolimus monotherapy, 72% were male, the median age was 60 years, 31% were 65 years or older, and 96% were Caucasian. All patients were classified as having Stage IV RCC. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across the 2 treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) favourable, intermediate, and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA plus everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

The primary efficacy outcome measure was investigator assessed PFS evaluated according to RECIST 1.1. Efficacy results are summarised in Table 16 and Figure 4 and Figure 5. The treatment effect of the combination on PFS was supported by a retrospective independent blinded review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm.

Table 16 Efficacy results following one prior VEGF targeted therapy in RCC Study 205 (investigator assessment)

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	**Everolimus 10 mg (N=50)**
Progression-Free Survival (PFS)[ab]		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[c] LENVIMA + Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival[d]		
Number of deaths, n (%)	32 (63)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI)[c] LENVIMA + Everolimus vs Everolimus	0.59 (0.36, 0.97)	-

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)
Objective Response Rate (Confirmed)[b]		
Objective response rate, n (%)	19 (37)	3 (6)
(95% CI)	(24, 52)	(1, 17)
Number of complete responses, n (%)	1 (2)	0
Number of partial responses (%)	18 (35)	3 (6)

Tumour assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR.
CI = confidence interval
a Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
b Data cutoff date = 13 Jun 2014
c Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and haemoglobin and corrected serum calcium as strata.
d Data cutoff date = 31 Jul 2015

Figure 4 Kaplan-Meier curve of progression-free survival (investigator assessment - RCC)

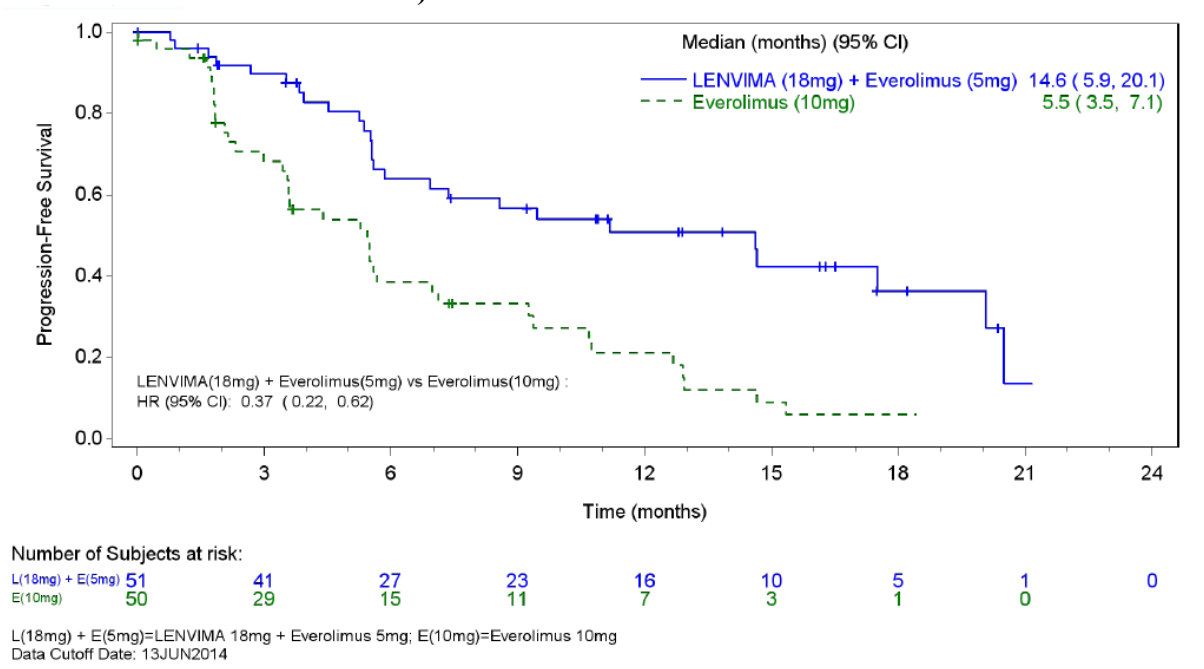
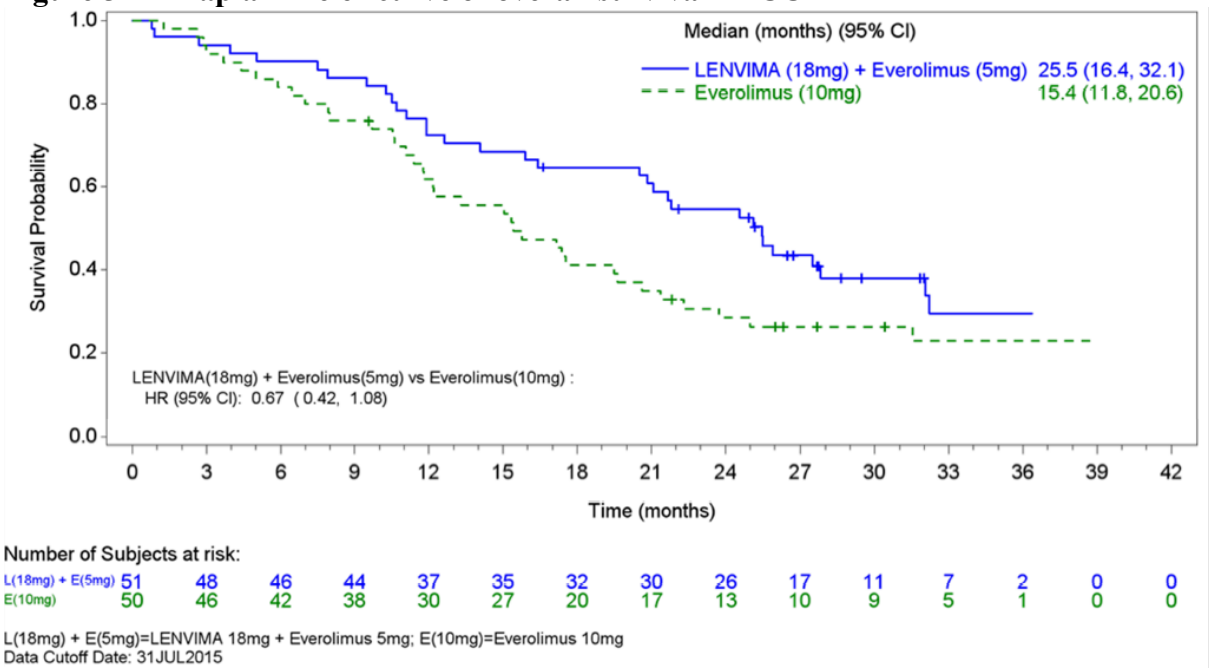


Figure 5 Kaplan-Meier curve of overall survival - RCC



Hepatocellular carcinoma

A multicenter, open-label study was conducted in 954 patients with unresectable hepatocellular carcinoma who were randomised to LENVIMA or sorafenib. The starting dose of LENVIMA, given once daily, was based on baseline body weight: 12 mg for patients with a body weight ≥ 60 kg and 8 mg for patients with a body weight < 60 kg. The dose of sorafenib was 400 mg given orally twice daily.

Patients were required to have a histologically or cytologically confirmed diagnosis of unresectable HCC, or a clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria, including cirrhosis of any etiology, or with chronic hepatitis B or C infection. Patients could have BCLC stage B or C disease, and could only have Child Pugh category A liver dysfunction (i.e., a score of 5-6). Patients had at least 1 measureable target hepatic or nonhepatic lesion according to mRECIST, and adequate liver, bone marrow, blood coagulation, renal, and pancreatic function. Patients were stratified by region, presence or absence of macroscopic portal vein invasion (MPVI) or extrahepatic spread (EHS) or both, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and BW (< 60 kg or ≥ 60 kg). The majority of patients in both treatment arms had an ECOG PS of 0 at Baseline (63%), Child-Pugh score of 5 (76%), and weighed ≥ 60 kg (69%). The median age was 62 years, 84% were male, 16% were female, 69% were Asian, 1% were black, and 29% were white. Approximately 80% of patients in Study 304 had BCLC stage C disease at study entry. This percentage was similar between the treatment arms (LENVIMA 374/478, 78.2%; sorafenib 384/476, 80.7%).

LENVIMA was non-inferior for Overall Survival (OS) to sorafenib. Median OS was 13.6 months compared to 12.3 months for sorafenib with HR = 0.92 [95% CI of (0.79, 1.06)].

Based on investigator assessment evaluated according to mRECIST, LENVIMA treatment resulted in statistically significant (P< 0.00001) and clinically meaningful improvement over sorafenib in the secondary endpoints of PFS and ORR. LENVIMA treatment significantly prolonged TTP compared to sorafenib, with a median TTP that was more than twice as long as that of sorafenib. Retrospective independent review of imaging corroborated the secondary endpoints of PFS, TTP and ORR. These efficacy results are summarised in Table 17 and Figure 6, Figure 7 and Figure 8.

Table 17 Efficacy results in hepatocellular carcinoma

	LENVIMA (N= 478)	Sorafenib (N=476)
Overall Survival		
Number of deaths, n (%)	351 (73.4)	350 (73.5)
Median OS in months (95% CI) [a]	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Hazard Ratio (95% CI)[b, c]	0.92 (0.79,1.06)	
Progression-Free Survival (PFS) per Investigator Assessment (mRECIST)		
Number of events, n (%)	349 (73.0)	367 (77.1)
Progressive disease, n (%)	308 (64.4)	343 (72.1)
Death, n (%)	41 (8.6)	24 (5.0)
Median PFS in months (95% CI)[a]	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
Hazard Ratio (95% CI) [b, c]	0.66 (0.57, 0.77)	
P-value [c,d]	<0.00001	
Time to Progression per Investigator Assessment (mRECIST)		
Subjects with Disease Progression, n (%) [e]	308 (64.4)	343 (72.1)
Censored Subjects, n (%)	170 (35.6)	133 (27.9)
Median (95% CI) [a]	8.9 (7.4, 9.2)	3.7 (3.6, 5.4)
Hazard Ratio (95% CI) [b, c]	0.63 (0.53, 0.73)	
P-value [c,d]	<0.00001	
Objective Response Rate per Investigator Assessment (mRECIST)		
Objective response rate, n (%)	115 (24.1)	44 (9.2)
(95% CI) [f]	(20.2, 27.9)	(6.6, 11.8)
Complete responses, n (%)	6 (1.3)	2 (0.4)
Partial responses, n (%)	109 (22.8)	42 (8.8)
Odds ratio (95% CI) [g]	3.13 (2.15, 4.56)	
P-value [g]	<0.00001	
Objective Response Rate per Independent Review (mRECIST)		
Objective response rate, n (%)	194 (40.6)	59 (12.4)
(95% CI) [f]	(36.2, 45.0)	(9.4, 15.4)
Odds ratio (95% CI) [g]	5.01 (3.59, 7.01)	
P-value [g]	<0.00001	
Objective Response Rate per Independent Review (RECIST 1.1)		
Objective response rate, n (%)	90 (18.8)	31 (6.5)
(95% CI) [f]	(15.3, 22.3)	(4.3, 8.7)
Odds ratio (95% CI) [g]	3.34 (2.17, 5.14)	
P-value [g]	<0.00001	

Data cutoff date: 13 Nov 2016.
The noninferiority margin for the HR of LENVIMA versus sorafenib is 1.08. Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set.
CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; OS = overall survival

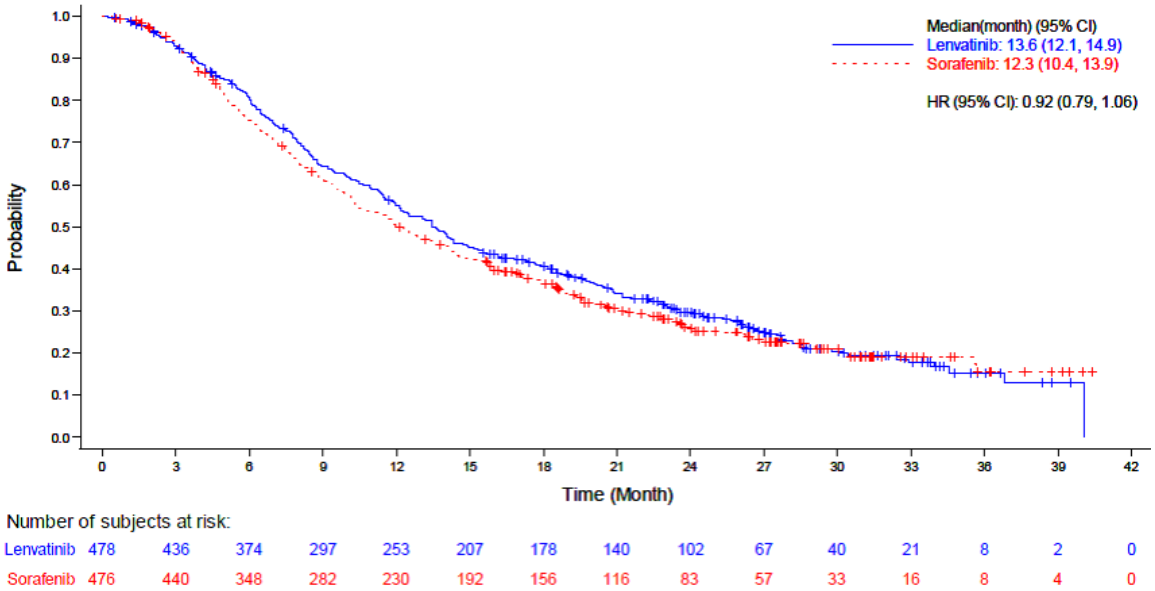
a Quartiles are estimated by the Kaplan-Meier method, and the 95% CIs are estimated with a generalised Brookmeyer and Crowley method.
b Hazard ratio is for LENVIMA vs. sorafenib, based on a Cox model including treatment group as a factor.
c Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (< 60 kg, ≥ 60 kg).
d P-value is for the superiority test of LENVIMA versus sorafenib.

Table 17 Efficacy results in hepatocellular carcinoma

	LENVIMA (N= 478)	Sorafenib (N=476)

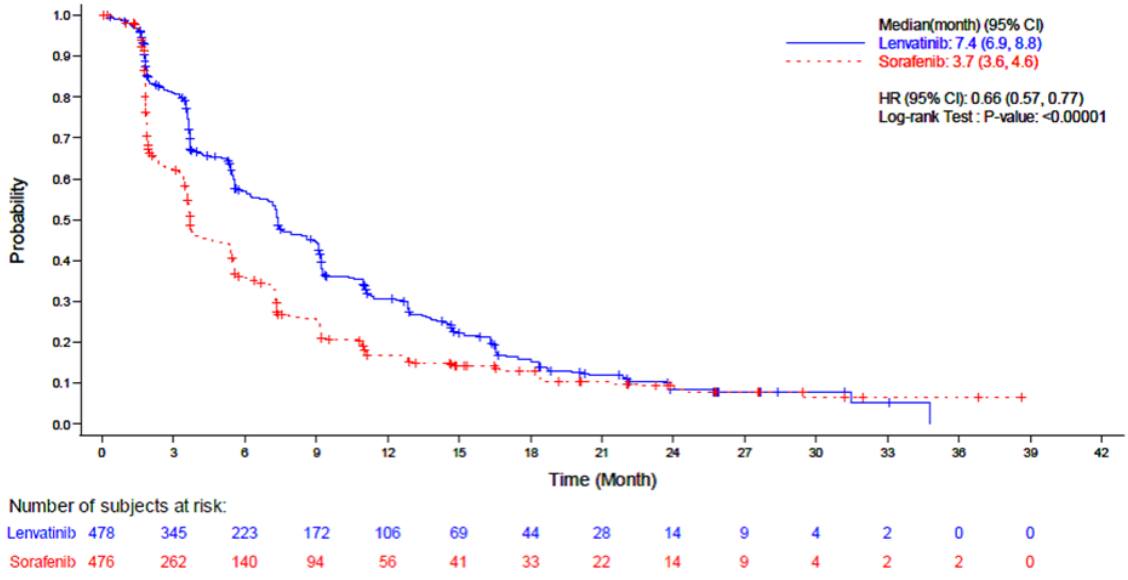
e Deaths were not counted as progression events in this analysis.
f 95% CI was calculated using asymptotic normal approximation.
g Odds ratio and P-value (for superiority test) were calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors.

Figure 6 Kaplan-Meier curve of overall survival – HCC



Data cut-off date = 13 Nov 2016.
Noninferiority margin for hazard ratio (HR: LENVIMA vs sorafenib = 1.08).
Median was estimated with the Kaplan-Meier method and the 95% confidence interval was constructed with a generalised Brookmeyer and Crowley method.
HR was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
+ = censored observations
CI = confidence interval; HR = hazard ratio; IxRS = interactive response system.

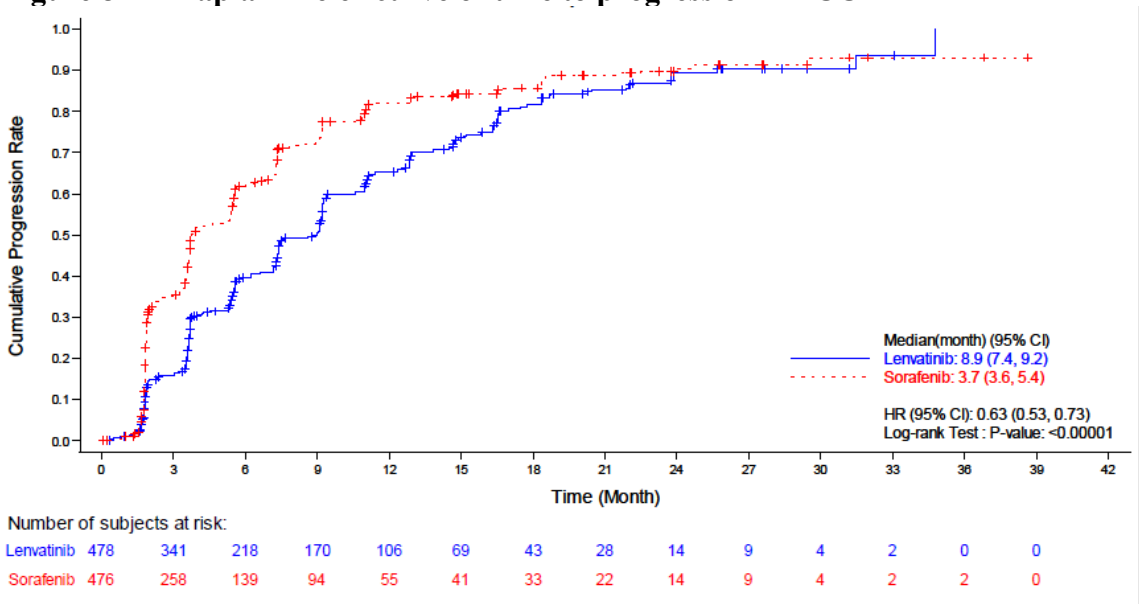
Figure 7 Kaplan-Meier curve of progression-free survival – HCC



Data cut-off date = 13 Nov 2016.
Median was estimated with the Kaplan-Meier method and the 95% CI was constructed with a generalised Brookmeyer and Crowley method.

Hazard ratio is expressed as LENVIMA: sorafenib and was estimated from the Cox proportional hazard model with treatment as an independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
P-value was for superiority test (LENVIMA vs. Sorafenib) and was calculated using log-rank test stratified by IxRS stratification factors.
+ = censored observations.
CI = confidence interval; HR = hazard ratio; IxRS = interactive response system.

Figure 8 Kaplan-Meier curve of time to progression – HCC



Data cut-off date: 13 Nov 2016.
The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalised Brookmeyer and Crowley method.
Hazard ratio is expressed as LENVIMA: sorafenib and was estimated from the Cox proportional hazard model with treatment as an independent variable, and stratified by IxRS stratification factors. Efron method was used for ties.
P-value is for the superiority test of LENVIMA vs sorafenib and was calculated using the log-rank test stratified by IxRS stratification factors.
CI = confidence interval; HR = hazard ratio; IxRS = interactive voice/web response system.

Assessment on Quality of Life (QoL) in patients with HCC

Three QoL questionnaires were administered EORTC QLQ-C30, EORTC QLQ-HCC18 and the EQ-5D-3L.

Compared to patients treated with LENVIMA, those treated with sorafenib experienced greater risks of more rapid time to clinically meaningful worsening of symptoms and function for the domain of Diarrhoea (nominal $p < 0.0001$) from the EORTC QLQ-C30.

Endometrial carcinoma

The efficacy of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicenter, open-label, randomised, active-controlled trial that enrolled 827 patients with advanced EC who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Randomization was stratified according to MMR status (dMMR or pMMR [not dMMR]) using an immunohistochemistry (IHC) test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomised (1:1) to one of the following treatment arms:

- LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks.
- Investigator's choice consisting of either doxorubicin 60 mg/m^2 every 3 weeks, or paclitaxel 80 mg/m^2 given weekly, 3 weeks on/1 week off.

Treatment with LENVIMA and pembrolizumab continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumour status was performed every 8 weeks. The primary efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DOR, as assessed by BICR.

A total of 827 patients were enrolled and randomised to LENVIMA in combination with pembrolizumab (n= 411) or investigator's choice of doxorubicin (n= 306) or paclitaxel (n= 110). The study population characteristics were: median age of 65 years (range: 30 to 86), 50% age 65 or older; 61% White, 21% Asian, and 4% Black; 59% ECOG PS of 0 and 41% ECOG PS of 1; and 84% with pMMR tumour status. The histologic subtypes were endometrioid carcinoma (60%), serous (26%), clear cell carcinoma (6%), mixed (5%), and other (3%). All 827of these patients received prior systemic therapy for EC: 69% had one, 28% had two, and 3% had three or more prior systemic therapies. 37% of patients received only prior neoadjuvant or adjuvant therapy.

The median follow-up time for this trial was 11.4 months (range 0.3 to 26.9 months). The trial demonstrated statistically significant superiority in OS and PFS for patients randomised to LENVIMA in combination with pembrolizumab compared to investigator's choice of doxorubicin or paclitaxel. The trial also demonstrated statistically significant superiority in ORR. Efficacy results are summarised in Table 18 and Figure 9 and Figure 10.

Table 18 Efficacy results[a] in EC in Study 309

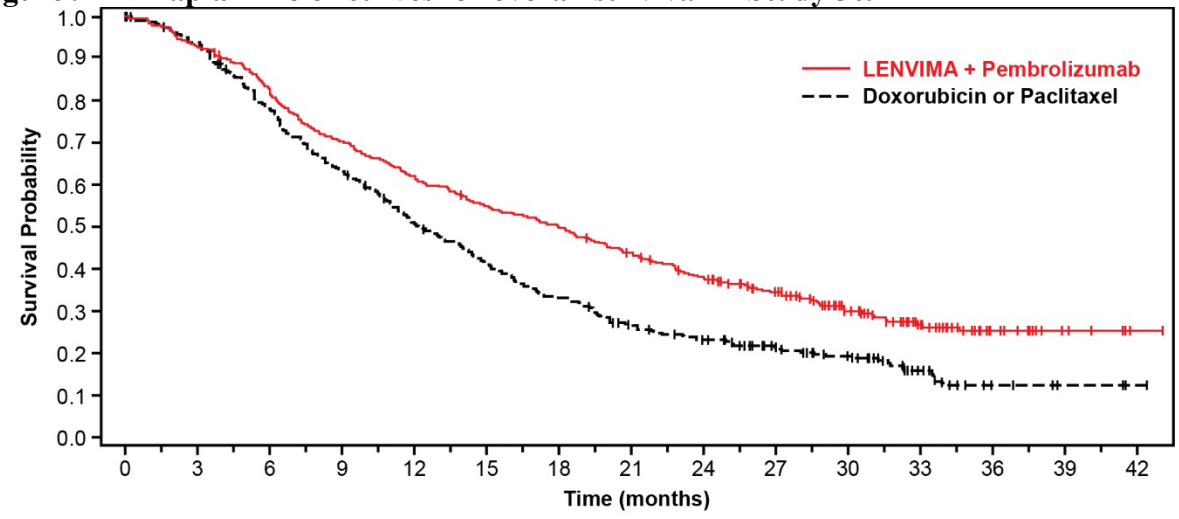
Endpoint	**LENVIMA with pembrolizumab N=411**	**Doxorubicin or Paclitaxel N=416**
OS		
Number (%) of patients with event	188 (46%)	245 (59%)
Median in months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
Hazard ratio[b] (95% CI)	0.62 (0.51, 0.75)	
p-Value[c]	<0.0001	

PFS[d]		
Number (%) of patients with event	281 (68%)	286 (69%)
Median in months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio[b] (95% CI)	0.56 (0.47, 0.66)	
p-Value[c]	<0.0001	
Objective Response Rate		
ORR[d] (95% CI)	32% (27, 37)	15% (11,18)
Complete response	7%	3%
Partial response	25%	12%
p-Value[e]	<0.0001	
Duration of Response	N=131	N=61
Median in months (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

a Based on pre-specified interim analysis
b Based on the stratified Cox regression model
c Based on stratified log-rank test
d Response: Best objective response as confirmed complete response or partial response
e Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

At the protocol-specified final OS analysis, the median OS for LENVIMA in combination with pembrolizumab was 18.0 months (95% CI: 14.9, 20.5) compared to 12.2 months (95% CI: 11.0, 14.1) for doxorubicin or paclitaxel, with an HR of 0.70 (95% CI: 0.58, 0.83). At the time of the protocol-specified final OS analysis, the median PFS for LENVIMA in combination with pembrolizumab was 6.7 months (95% CI: 5.6, 7.4) compared to 3.8 months (95% CI: 3.6, 5.0) for doxorubicin or paclitaxel, with an HR of 0.60 (95% CI: 0.50, 0.72).

Figure 9 Kaplan-Meier curves for overall survival in Study 309*

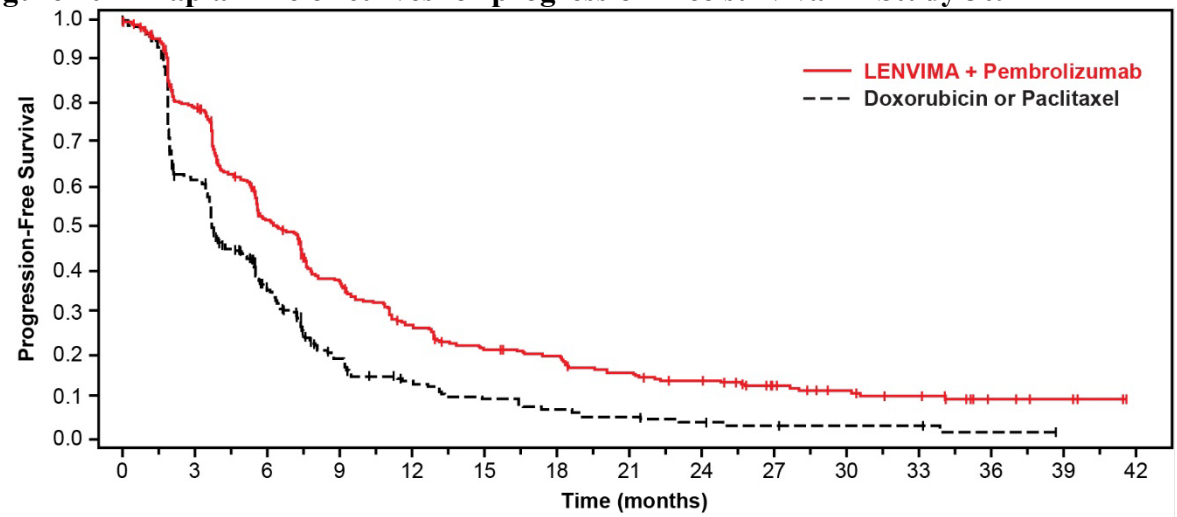


Number of subjects at risk:

LENVIMA + Pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Doxorubicin or Paclitaxel	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

*Based on the protocol-specified final OS analysis

Figure 10 Kaplan-Meier curves for progression-free survival in Study 309*



Number of subjects at risk:

LENVIMA + Pembrolizumab	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Doxorubicin or Paclitaxel	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0

*Based on updated PFS analysis conducted at the time of the protocol-specified OS final analysis

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Lenvatinib is rapidly absorbed after oral administration with T_{max} typically observed from 1 to 4 hours post-dose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours.

A high degree of inter-individual variability in average exposure at steady state was observed, with a 6-fold range when used as monotherapy at the 24 mg dose, and 7-fold range when LENVIMA 18 mg dose is administered in combination with 5mg everolimus. In HCC subjects, the inter-individual variability in average exposure at steady state was 6-fold and 5-fold range when used as monotherapy at 8 mg and 12 mg doses, respectively.

Distribution

In vitro binding of lenvatinib to human plasma proteins was high and ranged from 98% to 99% (0.3 – 30 µg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. A similar plasma protein binding (97% to 99%) with no dependencies on lenvatinib concentrations (0.2 to 1.2 µg/mL) was observed in plasma from hepatically impaired, renally impaired, and matching healthy subjects.

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 - 10 µg/mL, mesilate). *In vitro* studies indicate that lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K or the BSEP.

Biotransformation

In vitro, cytochrome P450 3A4 was the predominant (> 80%) cytochrome isoform involved in the P450- mediated metabolism of lenvatinib. *In vivo,* inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see Section 4.5 Interactions with other medicines). Patients should avoid strong inducers of CYP 3A4 and exercise caution with mild or moderate inhibitors or inducers when using everolimus (see Everolimus Product Information) in combination with LENVIMA.

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on AUC $_{(0-inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (eg, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials.

Elimination

Plasma concentrations decline bi-exponentially following C_{max}. The mean terminal exponential half-life of lenvatinib is approximately 28 hours.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The M2 metabolite was the predominant analyte in excreta (~ 5% of the dose) with lenvatinib the second most prominent (~ 2.5%).

Linearity/non-linearity

Dose proportionality and accumulation

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (C_{max} and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily (QD).

Lenvatinib displays minimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg). In patients with HCC, the mean accumulation ratio was 1.49 in those with higher Child-Pugh scores (7-8) receiving 8 mg lenvatinib.

Special populations

Hepatic impairment

The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5-mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10-mg dose. The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (< 2.16% across treatment cohorts).

Lenvatinib exposure, based on dose-adjusted $AUC_{0\text{-}t,unbound}$ and $AUC_{0\text{-}inf,unbound}$, was approximately 65%, 122%, and 273% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. Based on the analogous $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ data, lenvatinib exposure was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively (see Section 4.2 Dose and method of administration).

Renal impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in 6 subjects each with mild, moderate, or severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied. The percentage of unbound lenvatinib was similar between subjects with normal renal function (8% ± 3%, mean ± SD) and those with severely impaired renal function (9% ± 2%). $AUC_{0\text{-}inf,unbound}$ estimates for subjects with mild, moderate, or severe renal impairment were 54%, 129% and 184%, respectively, compared with normal subjects. Additionally, a linear equation was fit to the creatinine clearance vs. $AUC_{0\text{-}inf,unbound}$ data and exposure was predicted. Subjects with severe renal impairment were predicted to have a 2.4-fold increase in exposure. Therefore dosage needs to be reduced in DTC and RCC patients with severe renal impairment (see Section 4.2 Dose and method of administration). No dosage recommendations are available for HCC patients with severe renal impairment (See DOSAGE AND ADMINISTRATION). Use in HCC patients with severe renal impairment is not recommended.

Age, sex, weight, race

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg LENVIMA once daily, including HCC patients weighing < 60 kg and ≥ 60 kg receiving 8 mg and 12 mg, respectively, weight showed a statistically significant effect. The final PK model for lenvatinib included body-weight effect as an allometric constant on both clearance (CL/F) and volume parameters, whereby parameters increased with increasing body weight. The decrease in CL/F in subjects with low body weight resulted in an increase in lenvatinib exposure (AUC) whereby subjects weighing < 60 kg had approximately 35% higher exposure to lenvatinib than subjects weighing ≥ 60 kg when receiving the same dose. Based on the individual lenvatinib AUC at steady state for subjects with HCC, the median value and range of AUC are comparable between the group of starting dose of 8 mg for body weight < 60 kg and 12 mg for body weight ≥ 60 kg, which supports the starting doses of 8 mg and 12 mg for body weight < 60 kg and ≥ 60 kg, respectively, in HCC patients.

After accounting for body weight, neither age, sex or race (Japanese vs. other, Chinese vs other, white vs. other) influenced lenvatinib PK.

Paediatric population

Paediatric patients have not been studied.

Genomic assessment of lenvatinib pharmacokinetic parameters

Because of lenvatinib's extensive metabolism, the effect of selected drug-metabolising enzyme phenotypes on lenvatinib clearance was investigated using data derived from the Affymetrix drug-metabolising enzyme and transporter (DMET Plus) microarray genotyping platform. None of the phenotypes for CYP3A5, CYP1A2, CYP2A6, or CYP2C19 had a significant impact on lenvatinib clearance.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lenvatinib was not mutagenic in the in vitro Ames and mouse lymphoma tests and not clastogenic in an in vivo micronucleus assay in rats. These studies indicate a low genotoxic potential for LENVIMA.

Carcinogenicity

Carcinogenicity studies have not been conducted with LENVIMA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsules contain the excipients Calcium carbonate, Mannitol, Microcrystalline cellulose, Hydroxypropyl cellulose and Purified talc. The capsule shell contains the excipients Hypromellose, Titanium dioxide, Iron oxide yellow and Iron oxide red. The printing ink on the capsules contains the excipients Shellac, Iron oxide black, Potassium hydroxide and Propylene glycol.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

LENVIMA 4 mg and 10 mg hard capsules: 48 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LENVIMA 4 mg hard capsules are available in polyamide/aluminium/PVC/aluminium blisters of 30 capsules.

LENVIMA 10 mg hard capsules are available in polyamide/aluminium/PVC/aluminium blisters of 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Preparation and administration of suspension

- The suspension may be prepared using water, apple juice, or milk. If administered via a feeding tube, then the suspension should be prepared using water.
- Place the capsule(s) corresponding to the prescribed dose (up to 5 capsules) in a small container (approximately 20 mL (4 tsp) capacity) or oral syringe (20 mL); do not break or crush the capsules.
- Add 3 mL of liquid to the container or oral syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until the capsules are fully disintegrated.

    - If using an oral syringe, cap the syringe, remove plunger and use a second syringe or calibrated dropper to add the liquid to the first syringe, then replace plunger prior to mixing.
- Administer the entire contents of the container or oral syringe. The suspension may be administered from the container directly into the mouth, or from the oral syringe directly into the mouth or via feeding tube.
- Next, add an additional 2 mL of liquid to the container, or oral syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least twice and until there is no visible residue to ensure all of the medication is taken.
- For feeding tubes larger than > 5 French diameter (PVC and PUR tubing) or > 6 French diameter (silicone tubing), at least three rinses of 2 mL water or at least one 4 mL flush is needed to ensure all of the medication is taken.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube), at least 6 French diameter (silicone tube) and up to 16 French diameter for polyvinyl chloride, polyurethane, or silicone tubing.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISON STANDARD)

Prescription Medicine.

8 SPONSOR

Eisai New Zealand Ltd.
Simpson Grierson, Level 27
88 Shortland Street, Auckland Central
Auckland, 1010, NZ
Telephone: 0800 00 52 06
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9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine:

09 April 2020.

10 DATE OF REVISION OF THE TEXT

28 March 2025.

Summary Table of changes

Version Number	Section changed	Summary of new information
1.1		New Data Sheet
1.2	4.4, 4.8	Addition of precaution and post-marketing adverse event of osteonecrosis of the jaw.
1.3	4.4, 4.8	Addition of precaution and post-marketing adverse event of aneurysms and artery dissections.
2	4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Addition of text to support extension of indication for the first line treatment of patients with renal cell carcinoma.
3	4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Addition of text to support new indication for the treatment of patients with endometrial carcinoma.
3.1	5.1, 4.2	Addition of final overall survival (OS) and progression free survival (PFS) data for Study E7080-G000-309 (endometrial carcinoma) and Study E7080-G000-307 (renal cell carcinoma). Addition of pembrolizumab alternate dosage regimen for first line renal cell carcinoma and endometrial carcinoma.
3.2	4.2, 4.4, 4.8, 5.1, 6.6, 8, All	Addition of text to support preparation, administration and refrigeration of lenvatinib suspension in Section 4.2. Addition of final overall survival (OS) and progression free survival (PFS) data for non-clear cell RCC data based on KEYNOTE-B61 for patients with advanced/metastatic non-clear cell renal cell carcinoma in the first-line setting in Section 5.1. Updated Section 4.4 to clarify text. Condensed information in Section 4.8. Updated special precautions for disposal and other handling in Section 6.6. Replaced telephone number with NZ toll free number in Section 8 Sponsor details and other editorial corrections.
3.3	4.8	Corrections to Table 12.