PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LENVIMA 4 hard capsules

LENVIMA 10 hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LENVIMA 4: Each hard capsule contains lenvatinib mesilate equivalent to 4 mg lenvatinib.

LENVIMA 10: Each hard capsule contains lenvatinib mesilate equivalent to 10 mg lenvatinib.

LENVIMA is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

LENVIMA 4: 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: 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

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), 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 adult patients (> 18 years of age) with progressive, locally advanced or metastatic, radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC).

Renal Cell carcinoma (RCC)

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

LENVIMA is indicated in combination with everolimus for the treatment of adult patients (> 18 years of age) with advanced renal cell carcinoma whose disease has progressed following one prior vascular endothelial growth factor targeted therapy.

Hepatocellular carcinoma

LENVIMA is indicated for the first-line treatment of adult patients (> 18 years of age) with unresectable hepatocellular carcinoma (HCC).

4.2 Posology and method of administration

LENVIMA treatment should be supervised by a healthcare provider experienced in the use of anticancer therapies.

Posology

Starting dose in RAI – Refractory DTC

The recommended dose of LENVIMA is 24 mg (two 10 mg capsules plus one 4 mg capsule) taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (see dose adjustment section below).

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 dosage 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. The daily dose should be modified as needed according to the dose/toxicity management plan (see dose adjustment schedule below).

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

Previously treated RCC

The recommended daily dose of LENVIMA is 18 mg (one 10 mg capsule and two 4 mg capsules) once daily in combination with 5 mg everolimus once daily. The daily doses of LENVIMA, and if

necessary, everolimus are to be modified as needed according to the dose/toxicity management plan (see dose adjustment section below).

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 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. The daily dose is to be modified, as needed, according to the dose/toxicity management plan (see dose adjustment section below).

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. The daily dose should be modified, as needed, according to the dose/toxicity management plan (see dose adjustment section below). 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 or LENVIMA and everolimus if treating in the combination (see section 4.4).

Medical management of nausea, vomiting and diarrhoea should be optimised to reduce the risk of dehydration and renal failure (see section 4.4) prior to any LENVIMA therapy interruption or dose reduction.

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, interrupt one or both medicines, reduce dose 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.

For toxicities thought to be related to everolimus, when treating renal cell carcinoma using the combination of LENVIMA and everolimus, everolimus treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the everolimus PI for advice on specific adverse reactions).

For toxicities thought to be related to both LENVIMA and everolimus, when treating renal cell carcinoma using the combination, LENVIMA (see Table 1) should be reduced prior to reducing everolimus.

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Table 1 Dose modifications for adverse reactions

Adverse Reaction	**CTCAE Grade**	**Action**	**Dose reduce and resume LENVIMA**
Hypertension	Grade 3[a]	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
Nephrotic syndrome	**----**	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4[b]	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[b]	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[c]	Discontinue	Do not resume

[a] Grade 3 despite optimal antihypertensive therapy.

[b] Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)

[c] 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
Endometrial Carcinoma	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 hepatic impairment

No dose adjustment is recommended for patients with DTC or RCC and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC, ~~or~~ RCC, endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose for patients with DTC, RCC and endometrial carcinoma who have severe hepatic impairment (Child-Pugh C).

- 14 mg orally once daily for DTC
- 10 mg orally once daily for RCC
- 10 mg once daily for endometrial carcinoma

Further dose adjustments may be necessary on the basis of individual tolerability.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate or severe hepatic impairment. Use in this population is not recommended.

Dosage adjustment in renal impairment

No adjustment of the starting dose is required on the basis of renal function in patients with mild (CrCL 60-89 mL/min) or moderate (CrCL 30-59 mL/min) renal impairment. In patients with severe renal impairment (CrCL <30 mL/min), the recommended starting dose of LENVIMA should bereduced:

- 14 mg orally once daily for DTC
- 10 mg orally once daily plus 5 mg everolimus orally once daily for RCC
- 10 mg orally once daily for endometrial carcinoma

Further dose adjustments may be necessary based on the individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of LENVIMA in these patients is not recommended.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with LENVIMA and should be regularly monitored during treatment (see sections 4.4 and 4.8).

Use in the elderly

No adjustment of the starting dose is required on the basis of age. Limited data are available on the use in patients aged ≥ 75 years.

Paediatric population

The safety and efficacy of LENVIMA in children <18 years have not yet been established (see section 5.1).

Method of administration

LENVIMA should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water.

If unable to swallow the capsule whole place the capsule, without breaking or crushing, in a glass of approximately 25 mL of water or apple juice. The capsules must be left to disintegrate in the liquid for at least 10 minutes and then gently stirred for at least 3 minutes to dissolve the capsules shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (25 mL) must be added to the glass and swirled a few times. The additional liquid must be swallowed. Do not mix more than one medicine in the glass at the same time.

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 LENVIMA or to any of the excipients listed in section 6.1.

Patients with fistula(e), and/or patients at risk of developing fistula(e), such as after a major surgical procedure.

Patients with severe and/or uncontrolled hypertension (BP ≤150 mmHg, diastolic BP ≤ 95 mmHg).

Patients with severe thrombocytopenia (< 50 x 103 per µL) and/or active bleeding.

Patients due to undergo surgery or radiotherapy.

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). 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).

Gastrointestinal toxicity (including diarrhoea, nausea and vomiting) should be actively managed in order to reduce the risk of development of complications such as dehydration, electrolyte imbalances, and possible renal impairment or renal failure. Serious adverse events of both hypokalaemia and hyperkalaemia have occurred, as such, renal function and electrolytes should be monitored closely (see section 4.4 below).

Renal failure and impairment

Patients with baseline renal function <60 mL/minute experienced more adverse events, including fatal and serious adverse events of Grade 3 or 4, 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) 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). The primary risk factors identified were pre-existing renal impairment and dehydration and/or hypovolemia due to gastrointestinal toxicity (see section 4.4 below). 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).

If patients have severe renal impairment, the initial dose of LENVIMA should be adjusted (see section 4.2).

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). 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 medicine may be increased, if appropriate, or one or more medicines 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)
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). Monitor urine protein regularly. If urine dipstick proteinuria ≥ 2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). 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). 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).

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 % or patients; ADVERSE EFFECTS, Selected Adverse Reactions). 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 above). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

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). 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) compared to DTC and RCC 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).

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). 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).

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).

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).

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). 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).

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); 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 medicines of the same class.

QT interval prolongation

The incidence of QT/QTc interval prolongation was higher in patients treated with LENVIMA than in patients treated with placebo (see section 4.8). 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 combination patients. Electrocardiograms should be monitored in patients on an ongoing basis with a special attention for those with congenital long QT syndrome, congestive heart failure, bradydysrhythmias, 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).

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).

Hypothyroidism has been reported as very common in patients treated with LENVIMA in the RCC trial (see section 4.8).

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). 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).

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.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines 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 medicines

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

Other chemotherapeutic medicines

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

Effect of LENVIMA on other medicines

Cytochrome P450 or UGT enzyme substrates

Lenvatinib (e.g. LENVIMA) 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 as contained in LENVIMA 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

Women of childbearing potential / Contraception in males and females

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.

Pregnancy

LENVIMA should not be used during pregnancy.

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. Foetal anomalies included parietal oedema, cryptophthalmia, abnormal tail (rats), retroesophageal subclavian artery, fused ribs, and vertebral abnormalities (rabbits). These embryofoetal findings are probably related to the pharmacologic activity of lenvatinib as an antiangiogenic medicine.

Breastfeeding

LENVIMA should not be used during breastfeeding.

It is not known whether LENVIMA 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).

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.

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 be cautious when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile (DTC, RCC, HCC and EC)

The safety profile of LENVIMA is based on the combined safety data of 623 RCC patients in combination with everolimus, 452 DTC patients and 496 HCC patients; allowing characterisation of common adverse drug reactions in DTC, RCC and HCC patients. The safety of lenvatinib in combination with pembrolizumab has been evaluated in 530 patients with advanced EC, and 497 RCC patients. The adverse reactions presented in this section are based on safety data of DTC, RCC and HCC patients.

Tabulated list of adverse reactions for EC, DTC, RCC and HCC studies

Table 4 shows the frequency categories of adverse reactions observed in clinical trials for EC, DTC, RCC and HCC, and reported from post-marketing use of LENVIMA. The adverse reaction frequency category represents the most conservative estimate of frequency from the three individual populations.

For additional safety information when lenvatinib is administered in combination, refer to the Professional Information for the respective combination therapy components.

Frequencies are defined as:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Table 4 Adverse reactions reported in patients treated with Lenvatinib

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab**
Infections and infestations			
Very common	Urinary tract infection		
Common		Urinary tract infection	Urinary tract infection
Uncommon	Perineal abscess	Perineal abscess	Perineal abscess
Blood and lymphatic disorders			
Very common	Thrombocytopenia‡ Lymphopenia‡	Thrombocytopenia‡ Lymphopenia‡	Thrombocytopenia‡ Lymphopenia‡

	Leukopenia‡ Neutropenia‡	Leukopenia‡ Neutropenia‡	Leukopenia‡ Neutropenia‡
Uncommon	Splenic infarction		
Endocrine disorders			
Very common	Hypothyroidism* Increased blood thyroid stimulating hormone*,‡	Hypothyroidism* Increased blood thyroid stimulating hormone*, ‡	Hypothyroidism* Increased blood thyroid stimulating hormone*, ‡
Common			Adrenal insufficiency
Uncommon	Adrenal insufficiency	Adrenal insufficiency	
Metabolism and nutrition disorders			
Very common	Hypocalcaemia*, ‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia‡ Decreased weight Decreased appetite	Hypocalcaemia‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia*, ‡ Decreased weight Decreased appetite	Hypocalcaemia‡ Hypokalaemia‡ Hypomagnesaemia‡ Hypercholesterolaemia*, ‡ Decreased weight Decreased appetite
Common	Dehydration	Dehydration	Dehydration
Psychiatric disorders			
Very common	Insomnia	Insomnia	Insomnia
Nervous system disorders			
Very common	Dizziness Headache Dysgeusia	Headache Dysgeusia	Dizziness Headache Dysgeusia
Common	Cerebrovascular	Dizziness	

	accident†		
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Cerebrovascular accident† Transient ischaemic attack	Cerebrovascular accident Posterior reversible encephalopathy syndrome Transient ischaemic attack
Cardiac disorders			
Common	Myocardial infarction[a,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Myocardial infarction[a,†] Cardiac failure† Prolonged electrocardiogram QT	Myocardial infarction[a] Prolonged electrocardiogram QT
Uncommon		Decreased ejection fraction	Cardiac failure† Decreased ejection fraction
Vascular disorders			
Very common	Haemorrhage[b, ∗, †] Hypertension[c,∗] Hypotension	Haemorrhage[b, ∗, †] Hypertension[c,∗]	Haemorrhage[b, ∗, †] Hypertension[c,∗]
Common		Hypotension	Hypotension
Not known	Aneurysms and artery dissections	Aneurysms and artery dissections	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders			

Very common	Dysphonia	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism Pneumothorax	Pulmonary embolism
Uncommon	Pneumothorax		Pneumothorax
Gastrointestinal disorders			
Very common	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase‡ Increased amylase‡	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Increased lipase‡ Increased amylase‡	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase‡ Increased amylase‡
Common	Anal fistula Flatulence	Dry mouth Flatulence	Pancreatitis[g] Colitis Flatulence
Uncommon	Pancreatitis[g] Colitis	Pancreatitis[g] Anal fistula Colitis	Anal fistula
Hepatobiliary disorders			
Very common	Increased blood bilirubin*, ‡ Hypoalbuminaemia*, ‡	Hypoalbuminaemia*, ‡ Increased alanine aminotransferase‡	Increased blood bilirubin ‡ Hypoalbuminaemia‡

	Increased alanine aminotransferase*, ‡ Increased aspartate aminotransferase*, ‡ Increased blood alkaline phosphatase‡ Increased gamma-glutamyltransferase‡	Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡	Increased alanine aminotransferase‡ Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡
Common	Hepatic failure[h,†] Hepatic encephalopathy[i, †] Cholecystitis Abnormal hepatic function	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase Increased blood bilirubin*, ‡	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[j]	Hepatic failure[h, †] Hepatic encephalopathy[i]	Hepatic failure[h,,†] Hepatic encephalopathy[i] Hepatocellular damage/hepatitis[j]
Skin and subcutaneous tissue disorders			
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia	Hyperkeratosis Alopecia

Uncommon		Hyperkeratosis	
Musculoskeletal and connective tissue disorders			
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain
Common		Myalgia Pain in extremity Musculoskeletal pain	
Uncommon	Osteonecrosis of the jaw	Osteonecrosis of the jaw	
Renal and urinary disorders			
Very common	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡
Common	Renal failure[k, *, †] Renal impairment* Increased blood urea	Renal failure[k, *, †] Renal impairment* Increased blood urea	Renal failure[k, *] Increased blood urea
Uncommon	Nephrotic syndrome		Nephrotic syndrome Renal impairment*
General disorders and administration site conditions			
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral
Common	Malaise	Malaise	Malaise

Uncommon	Impaired healing	Impaired healing Non-gastrointestinal fistula[l]	Impaired healing Non-gastrointestinal fistula[l]
Not known	Non-gastrointestinal fistula[l]		

*: See section 4.8 Description of selected adverse reactions for further characterisation.

†: Includes cases with a fatal outcome.

‡: Frequency based on laboratory data

The following terms have been combined:

a: Myocardial infarction includes myocardial infarction and acute myocardial infarction.

b: Includes all haemorrhage terms:

Haemorrhage terms that occurred in 5 or more patients were: epistaxis, haematuria, contusion, gingival bleeding, rectal haemorrhage, haemoptysis, ecchymosis, and haematochezia.

c: Hypertension includes: hypertension, hypertensive crisis, increased blood pressure diastolic, orthostatic hypertension and increased blood pressure.

d: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.

e: Oral inflammation includes: aphthous stomatitis, aphthous ulcer, gingival erosion, gingival ulceration, oral mucosal blistering, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

f: Oral pain includes: oral pain, glossodynia, gingival pain, oropharyngeal discomfort, oropharyngeal pain and tongue discomfort.

g: Pancreatitis includes: pancreatitis and acute pancreatitis.

h: Hepatic failure includes: hepatic failure, acute hepatic failure and chronic hepatic failure.

i: Hepatic encephalopathy includes: hepatic encephalopathy, coma hepatic, metabolic encephalopathy and encephalopathy.

j: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.

k: Renal failure includes: acute prerenal failure, renal failure, renal failure acute, acute kidney injury, and renal tubular necrosis.

l: Non-gastrointestinal fistula includes cases of fistula occurring outside of the stomach and intestines such as tracheal, tracheo-oesophageal, oesophageal, cutaneous fistula and female genital tract fistula.

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).

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 5 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 5 Treatment-Emergent Adverse Events reported for LENVIMA in the double-blind phase of the DTC Study*

System Organ Class (MedDRA terminology)	**LENVIMA 24 mg N=261**	
	All Grades (%)	**Grades 3-4 (%)**
Blood and lymphatic system disorders		
Thrombocytopenia	13,8	1,9
Lymphopenia	10,7	2,3
Splenic infarction	0,8	0
Cardiac disorders		
Ejection fraction decreased	5,4	1,1
Myocardial infarction	1,1	1,1
Cardiac failure	0,8	0
Endocrine disorders		
Hypothyroidism	5,4	0
Gastrointestinal disorders		
Diarrhoea	67,4	9,2
Nausea	46,7	2,3

Stomatitis	41,0	4,6
Vomiting	35,6	1,9
Abdominal pain	31,4	2,3
Constipation	28,7	0,4
Oral pain	24,9	1,1
Dry mouth	16,9	0,4
Dyspepsia	13,0	0,4
Flatulence	6,1	0
Anal fistula	1,1	0,4
General disorders and administration site conditions		
Fatigue	42,5	4,6
Asthenia	25,3	6,1
Peripheral oedema	20,7	0,4
Malaise	5,4	0
Hepatobiliary disorders		
Hepatocellular damage / hepatitis	1,1	0,8
Infections and infestations		
Urinary tract infection	11,5	1,1
Perineal abscess	0,8	0,8
Investigations		
Weight decreased	51,3	13,4
Electrocardiogram QT prolonged	8,8	1,5
Increased Alanine aminotransferase	7,7	1,5
Increased Blood creatinine	7,3	0
Increased Aspartate aminotransferase	6,9	1,9
Increased Blood thyroid stimulating hormone	6,5	0
Increased Blood alkaline phosphatase	6,1	0,8

Increased Blood urea	3,1	0
Hepatic function abnormal	2,3	0,4
Increased blood bilirubin	1,9	0
Increased Gamma-glutamyltransferase	1,5	0,8
Metabolism and nutrition disorders		
Decreased appetite	54,4	6,9
Hypokalaemia	13,8	3,4
Hypocalcaemia	12,6	5,0
Hypoalbuminaemia	9,6	0,4
Dehydration	8,8	2,3
Hypomagnesaemia	6,5	0,4
Hypercholesterolaemia	5,0	0,4
Musculoskeletal and connective tissue disorders		
Arthralgia	26,1	0,4
Myalgia	19,2	1,5
Back pain	17,6	1,9
Musculoskeletal pain	16,1	0,4
Pain in extremity	15,3	1,1
Nervous system disorders		
Headache	38,3	3,1
Dysgeusia	18,0	0
Dizziness	15,3	0,4
Monoparesis	1,1	0,8
Cerebrovascular accident	0,8	0,4
Transient ischemic attack	0,8	0
Reversible posterior leucoencephalopathy syndrome	0,4	0

Psychiatric disorders		
Insomnia	11,9	0
Renal and urinary disorders		
Proteinuria	33,7	10,7
Renal failure events	5,0	2,7
Renal impairment	1,9	0,4
Respiratory, thoracic, and mediastinal disorders		
Dysphonia	31,4	1,1
Cough	23,8	0
Pulmonary embolism	3,1	3,1
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	32,2	3,4
Rash	18,8	0,4
Alopecia	12,3	0
Hyperkeratosis	6,9	0
Palmar erythema	1,1	0
Vascular disorders		
Haemorrhage	34,9	1,5
Hypertension	72,8	44,4
Hypotension	8,8	1,5

*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 17.0 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 6 presents the adverse reactions in ≥20 % of patients in the LENVIMA with pembrolizumab arm.

Table 6: Adverse Reactions in ≥20 % of Patients on LENVIMA plus Pembrolizumab and Sunitinib in CLEAR (RCC)		
	Lenvima 20 mg in combination with Pembrolizumab 200 mg N = 352	
Adverse Reactions	All Grades (%)	Grads 3-4 (%)
General		
Fatigue[a]	63	9
Gastrointestinal		
Diarrhoea[b]	62	10
Stomatitis[c]	43	2
Nausea	36	3
Abdominal pain[d]	27	2
Vomiting	26	3
Constipation	25	1
Musculoskeletal and connective tissue		
Musculoskeletal pain[e]	58	4
Endocrine		
Hypothyroidism[f]	57	1
Vascular		
Hypertension[g]	56	29
Haemorrhagic events[g]	27	5

Metabolism		
Decreased appetite[i]	41	4
Skin and subcutaneous Tissue		
Rash[j]	37	5
Palmar-plantar erythrodysesthesia syndrome[k]	29	4
Investigations		
Decreased weight	30	8
Respiratory, Thoracic and Mediastinal		
Dysphonia	30	0
Renal and urinary		
Proteinuria[l]	30	8
Nervous System		
Headache	23	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 anaemia , 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, haemothorax, haematemesis , haematoma , haematochezia, haematuria, haemoptysis, haemorrhoidal 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

Previously treated Renal Cell Carcinoma in combination with Everolimus

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 %), thrombocytopaenia (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 Events 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 (MedDRA terminology)	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 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

Table 7 Grades 1-4 Adverse Events 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 (MedDRA terminology)	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
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				
Decreased weight	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				

Table 7 Grades 1-4 Adverse Events 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 (MedDRA terminology)	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
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 diarrhoea, epistaxis, gastric haemorrhage, haemarthrosis, haematoma, haematuria, haemoptysis, lip haemorrhage, renal haematoma, and scrotal haematocele

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

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 (%)**
Lipase increased	13	12
Haematology		
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). 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 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.

Table 9 Adverse reactions occurring in ≥10 % of patients in the LENVIMA arm in REFLECT (HCC)		
	LENVIMA 8 mg/ 12 mg N=476	
System Organ Class **(MedDRA terminology)**	**Grade 1-4** **(%)**	**Grade 3-4 (%)**
Endocrine disorders		
Hypothyroidism	21	0
Gastrointestinal disorders		
Diarrhoea	39	4
Abdominal pain	30	3
Nausea	20	1
Vomiting	16	1
Constipation	16	1
Ascites	15	4
Stomatitis/Oral inflammation	11	0,4
General disorders and administration site conditions		

Fatigue	44	7
Pyrexia	15	0
Peripheral oedema	14	1
Investigations		
Decreased weight	31	8
Metabolism and nutrition disorders		
Decreased appetite	34	5
Musculoskeletal and connective tissue disorders		
Arthralgia/ Myalgia	31	1
Nervous system disorders		
Headache	10	1
Renal and urinary disorders		
Proteinuria	26	6
Respiratory, thoracic, and mediastinal disorders		
Dysphonia	24	0,2
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	27	3
Rash	14	0
Vascular disorders		
Hypertension	45	24
Haemorrhagic events	23	4

Table 10 Grade 3-4 Laboratory abnormalities occurring in ≥2 % of patients in the LENVIMA arm in REFLECT (HCC)

Laboratory Abnormality	**LENVIMA (N=476) (%)**
Chemistry	

Alanine aminotransferase (ALT) increased	8
Albumin decreased	3
Alkaline phosphatase increased	7
Aspartate aminotransferase (AST) increased	12
Bilirubin increased	13
Creatinine increased	2
GGT increased	17
Hyperkalemia	3
Hypokalemia	3
Hyponatremia	15
Lipase increased	6
Haematology	
Haemoglobin decreased	4
Lymphocyte count decreased	8
Neutrophil count decreased	7
Platelet count decreased	10

Endometrial Carcinoma

The safety of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicentre, open-label, randomised (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings (See Section 5.1, Clinical trials, Endometrial Carcinoma (EC)). Patients with endometrial carcinoma that are not MSI-H or dMMR received LENVIMA 20 mg orally once daily with pembrolizumab 200 mg intravenously every 3 weeks (n=342); or received doxorubicin or paclitaxel (n= 325).

For patients with not MSI-H or dMMR status, the median duration of study treatment was 7.2 months (range 1 day to 26.8 months) and the median duration of exposure to LENVIMA was 6.7 months (range: 1 day to 26.8 months).

Fatal adverse reactions among these patients occurred in 4.7 % of those treated with LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal haemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50 % of these patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency ≥3 % were hypertension (4.4 %), and urinary tract infection (3.2 %).

Discontinuation of LENVIMA due to an adverse reaction occurred in 26 % of these patients. The most common (≥1 %) adverse reactions leading to discontinuation of LENVIMA were hypertension (2 %), asthenia (1.8 %), diarrhoea (1.2 %), decreased appetite (1.2 %), proteinuria (1.2 %), and vomiting (1.2 %).

Dose reductions of LENVIMA due to adverse reactions occurred in 67 % of patients. The most common (≥5 %) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhoea (11 %), palmar-plantar erythrodysesthesia syndrome (9 %), proteinuria (7 %), fatigue (7 %), decreased appetite (6 %), asthenia (5 %), and weight decreased (5 %).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58 % of these patients. The most common (≥2 %) adverse reactions leading to interruption of LENVIMA were hypertension (11 %), diarrhoea (11 %), proteinuria (6 %), decreased appetite (5 %), vomiting (5 %), increased alanine aminotransferase (3.5 %), fatigue (3.5 %), nausea (3.5 %), abdominal pain (2.9 %), weight decreased (2.6 %), urinary tract infection (2.6 %), increased aspartate aminotransferase (2.3 %), asthenia (2.3 %), and palmar-plantar erythrodysesthesia (2 %).

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 pus Pembrolizumab		
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342	
Adverse Reaction	**All Grades[a] (%)**	**Grades 3-4 (%)**
Endocrine		
Hypothyroidism[b]	67	0.9
Vascular		
Hypertension[c]	67	39
Haemorrhagic events[d]	25	2.6
General		
Fatigue[e]	58	11
Gastrointestinal		
Diarrhoea[f]	55	8
Nausea	49	2.9
Vomiting	37	2.3
Stomatitis[g]	35	2.6
Abdominal Pain[h]	34	2.6
Constipation	27	0
Musculoskeletal and Connective Tissue		
Musculoskeletal disorders[i]	53	5
Metabolism		
Decreased Appetite[j]	44	7
Investigations		

Decreased weight	34	10
Renal and Urinary		
Proteinuria[k]	29	6
Infections		
Urinary tract infection[l]	31	5
Nervous System		
Headache	26	0.6
Respiratory, Thoracic and Mediastinal		
Dysphonia	22	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia[m]	23	2.9
Rash[n]		

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 haemorrhage, haematuria, gingival bleeding, metrorrhagia, rectal haemorrhage, contusion, haematochezia, cerebral haemorrhage, conjunctival haemorrhage, gastrointestinal haemorrhage, haemoptysis, haemorrhage urinary tract, lower gastrointestinal haemorrhage, mouth haemorrhage, petechiae, uterine haemorrhage, anal haemorrhage, blood blister, eye haemorrhage, haematoma, haemorrhage intracranial, haemorrhagic stroke, injection site haemorrhage, melena, purpura, stoma site haemorrhage, upper gastrointestinal haemorrhage, wound haemorrhage, blood urine present, coital bleeding, ecchymosis, haematemesis, haemorrhage subcutaneous, hepatic haematoma, injection site bruising, intestinal haemorrhage, laryngeal haemorrhage, pulmonary haemorrhage, subdural haematoma, umbilical haemorrhage, 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, haemoglobinuria

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 papular, 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)

	Endometrial Carcinoma (not MSI-H or dMMR)	
Laboratory Test[b]	**LENVIMA 20 mg in combination with Pembrolizumab N=342**	
	All Grades[c] (%)	**Grades 3-4**
Chemistry		
Hypertriglyceridemia	70	6
Hypoalbuminaemia	60	2.7

Increased aspartate aminotransferase	58	9
Hyperglycaemia	58	8
Increased alanine aminotransferase	55	9
Hypercholesterolaemia	53	3.2
Hyponatraemia	46	15
Increased alkaline phosphatase	43	4.7
Hypocalcaemia	40	4.7
Increased lipase	36	14
Increased creatinine	35	4.7
Hypokalaemia	34	10
Hypophosphatemia	26	8
Increased amylase	25	7
Hyperkalaemia	23	2.4
Increased creatine kinase	19	3.7
Increased bilirubin	18	3.6
Haematology		
Lymphopenia	50	16
Thrombocytopenia	50	8
Anaemia	49	8
Leukopenia	43	3.5
Neutropenia	31	6
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: 263 to 340 patients) and doxorubicin or paclitaxel (240 to 322).		

c Graded per NCI CTCAE v4.03

Table 13 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 medicine exposure.

Gastrointestinal disorders:	increased amylase, increased lipase, pancreatitis
Hepatobiliary disorders:	cholecystitis
General disorders and administration site conditions:	impaired healing
Renal and urinary disorders:	nephrotic syndrome
Respiratory, thoracic and mediastinal disorders:	pneumothorax
Vascular Disorders:	aortic dissection

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 dialysable. In case of suspected overdose, LENVIMA should be withheld and appropriate supportive care given as required.

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 signalling *in vitro* and caused a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

The combination of lenvatinib and everolimus showed increased antiangiogenic and anti-tumour 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 medicine 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).

Clinical trials

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 11). 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 14 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)[bc]	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)[bc]	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)

Table 14 Efficacy Results in radioactive iodine refractory differentiated thyroid cancer		
	LENVIMA **N=261**	**Placebo** **N=131**
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.

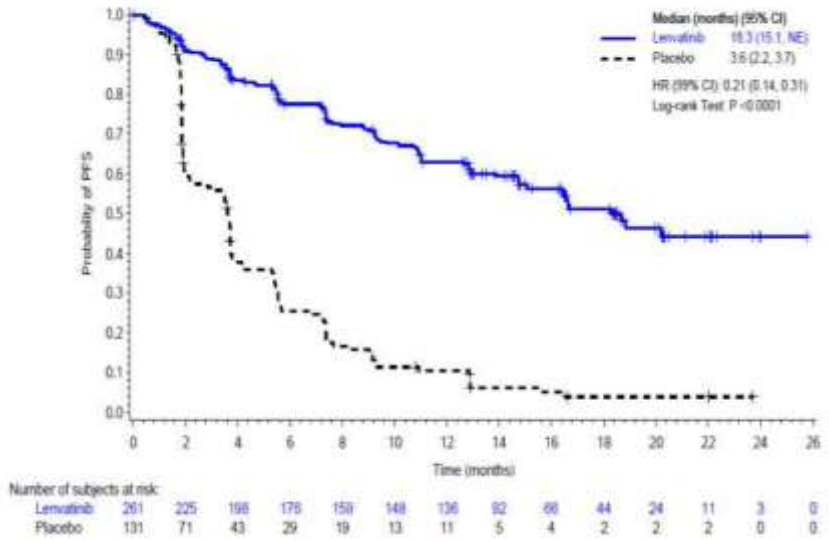
b) Stratified by region (Europe vs. North America vs. Other), age group (≤ 65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

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 Curveof 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 multicentre, 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 % favorable, 56 % intermediate, and 10 % poor, and MSKCC risk categories was 27 % favorable, 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, Figure 2 and Figure 3. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups, and PD-L1 tumour expression status.

Table 15: Efficacy results in Renal Cell Carcinoma per IRC in CLEAR

	LENVIMA 20 mg with Pembrolizumab 200 mg N = 355
Progression-Free Survival (PFS)	
Number of events, n (%)	160 (45.1 %)
Progressive disease	145 (40.8 %)
Death	15 (4.2 %)
Median PFS in months (95 % CI)[a]	23.9 (20.8, 27.7)

Hazard Ratio (95 % CI)[b,c]	0.39 (0.32, 0.49)
p-Valuec	<0.0001
Overall Survival (OS)	
Number of deaths, n (%)	80 (22.5 %)
Median OS in months (95 % CI)	NR (33.6, NE)
Hazard Ratio (95 % CI)[b,c]	0.66 (0.49, 0.88)
p-Value[c]	0.0049
Overall Survival Rate (%) (95 % CI) at[d]	
12 months	91.4 % (87.9, 93.9)
18 months	87.1 % (83.1, 90.3)
24 months	79.2 % (74.1, 83.3)
Objective Response Rate (Confirmed)	
Objective response rate, n (%)	252 (71.0 %)
(95 % CI)	(66.3, 75.7)
Number of complete responses, n (%)	57 (16.1 %)
Number of partial responses, n (%)	195 (54.9 %)
p-Valuee	<0.0001
Duration of Response[a]	
Median in months (range)	26 (1.6+, 36.8+)

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 Quartiles are estimated by Kaplan-Meier method.

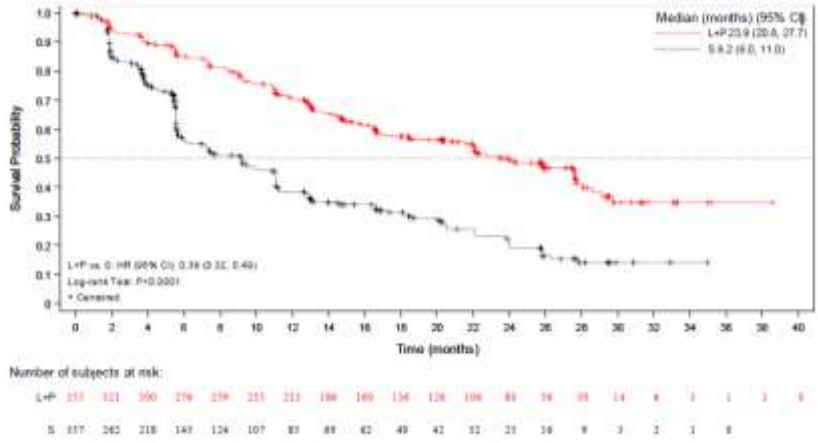
b Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.

c 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.

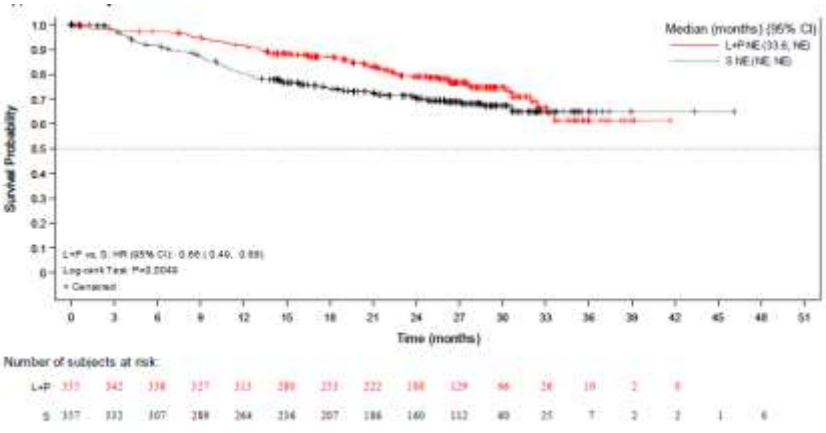
d Overall survival rate and 95 % CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.

e 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).

Figure 2; Kaplan-Meier Curves for progress-Free Survival in CLEAR



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
Data cutoff date: 28 Aug 2020



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib. NE = Not estimable.
Data cutoff date: 28 Aug 2020

* The OS analysis was not adjusted to account for subsequent therapies. Among those who discontinued treatment or who were randomized 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.

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 12 and Figure 2 and Figure 3. 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 in renal cell carcinoma (investigator assessment)		
	LENVIMA 18 mg + Everolimus 5 mg (N=51)	**Everolimus10 mg (N=50)**
Progression-Free Survival (PFS)[ab]		
Number of events, n (%)	25 (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)	-
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-FreeSurvival (Investigator Assessment – RCC)

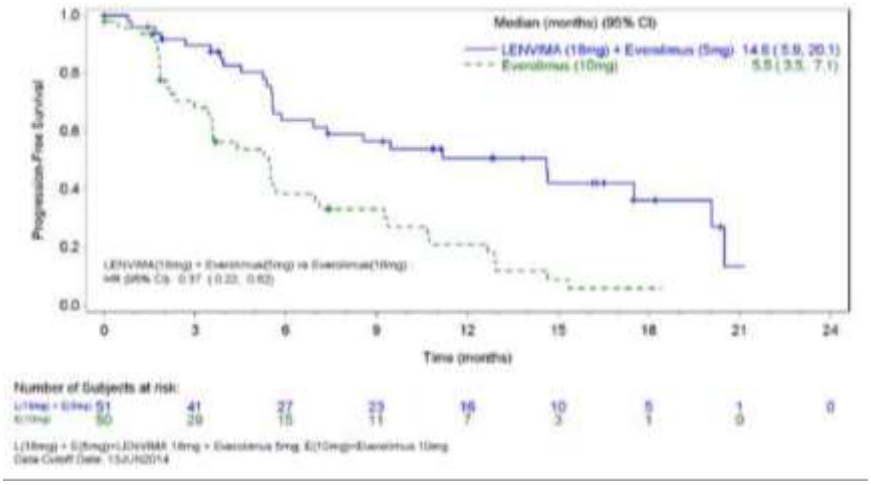
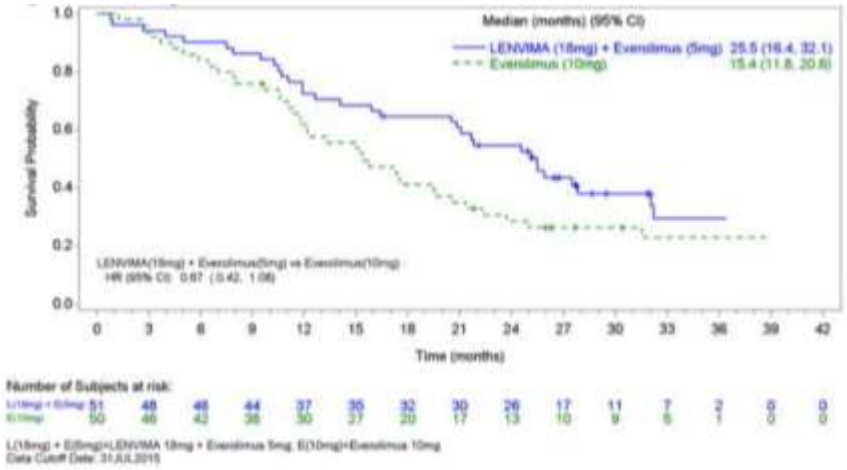


Figure 5 Kaplan-Meier Curve of Overall Survival – RCC



Hepatocellular Carcinoma

A multicentre, open-label study was conducted in 954 patients with unresectable hepatocellular carcinoma who were randomized 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 aetiology, 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 measurable target hepatic or non-hepatic 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 13 and Figure 4, Figure 5 and Figure 6.

Table 17 Efficacy Results in Hepatocellular Carcinoma		
	LENVIMA (N= 478)	**Sorafenib (N=476)**
Overall Survival		
Number of events, n (%)	351 (73,4)	351 (73,4)
Median OS in months (95 % CI) [a]	13,6 (12,1; 14,9)	13,6 (12,1; 14,9)
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)		

Table 17 Efficacy Results in Hepatocellular Carcinoma		
	LENVIMA (N= 478)	**Sorafenib (N=476)**
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	

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).

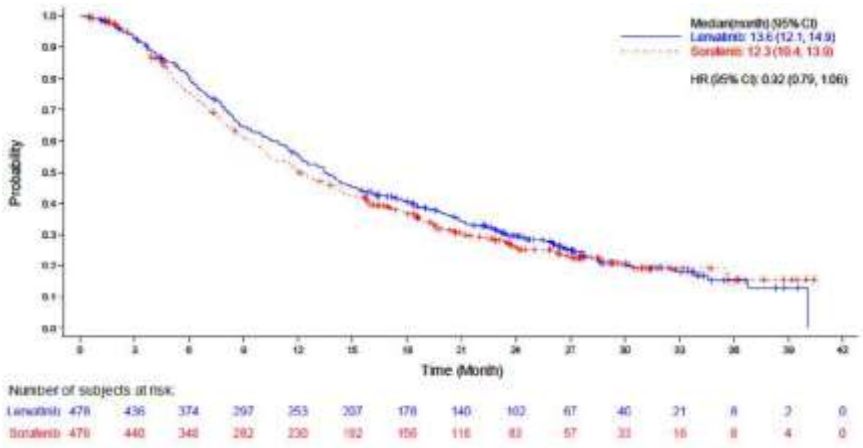
d P-value is for the superiority test of LENVIMA versus sorafenib.

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 cutoff date = 13 Nov 2016.

Noninferiority margin for hazard ratio (HR: LENVIMA vs sorafenib = 1.08).

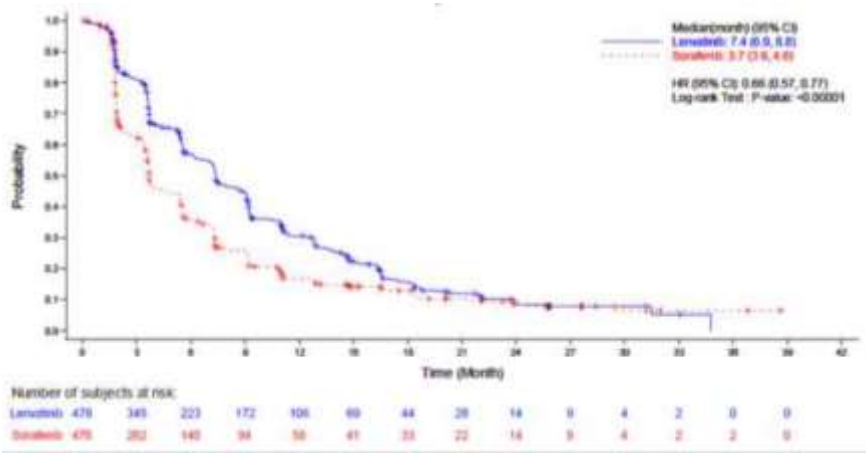
Median was estimated with the Kaplan-Meier method and the 95 % confidence interval was constructed with a generalised Brookmeyer and Crowley method.

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 cutoff date = 13 Nov 2016.

Median was estimated with the Kaplan-Meier method and the 95 % CI was constructed with a generalized Brookmeyer and Crowley method.

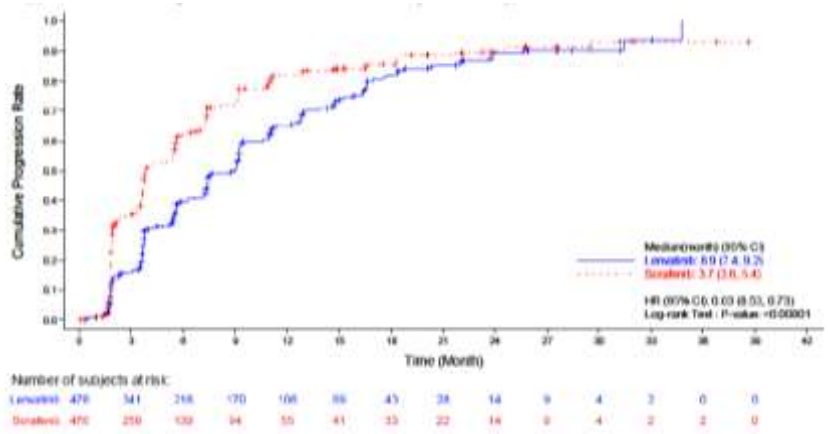
Hazard ratio is expressed as LENVIMA: sorafenib and was estimated from the Cox proportional hazard model with treatment as an independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.

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 cutoff date: 13 Nov 2016.

The median was estimated using the Kaplan-Meier method and the 95 % CI was constructed with a generalized 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 (EC)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicentre, open-label, randomised, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma 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. Patients with endometrial carcinoma that were not MSI-H or dMMR were 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/m2 every 3 weeks, or paclitaxel 80 mg/m2 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.

Among the 697 not MSI-H or dMMR patients, 346 patients were randomised to LENVIMA in combination with pembrolizumab, and 351 patients were randomised to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The population characteristics of these patients were: median age of 65 years (range: 30 to 86), 52 % age 65 or older; 62 % White, 22 % Asian, and 3 % Black; 60 % ECOG PS of 0 and 40 % ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55 %), serous (30 %), clear cell carcinoma (7 %), mixed (4 %), and other (3 %). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67 % had one, 30 % had two, and 3 % had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

Efficacy results are summarised in Table 18, Figure 9 and Figure 10.

Table 18 Efficacy results in Endometrial Carcinoma in Study 309

	Endometrial Carcinoma (not MSI-H or dMMR)	
Endpoint	LENVIMA with pembrolizumab N=346	Doxorubicin or Paclitaxel N=351
OS		
Number (%) of patients with event	165 (48 %)	203 (58 %)
Median in months (95 % CI)	Median in months (95 % CI)	12.0 (10.8, 13.3)
Hazard ratio[a] (95 % CI)	0.68 (0.56, 0.84)	
p-Value[b]	0.0001	
PFS[c]		
Number (%) of patients with event	247 (71 %)	238 (68 %)
Median in months (95 % CI)	6.6 (5.6, 7.4)	6.6 (5.6, 7.4)
Hazard ratio[a] (95 % CI)	0.60 (0.50, 0.72)	
p-Value[b]	<0.0001	

Objective Response Rate		
ORR[c] (95 % CI)	30 % (26, 36)	15 % (12,19)
Complete response	5 %	3 %
Partial response	25 %	13 %
p-Value[d]	<0.0001	
Duration of Response	N=105	N=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

a Based on the stratified Cox regression model

b Based on stratified log-rank test

c Per independent radiology review

d Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

Figure 9 Kaplan-Meier Curves for Overall Survival in Study 309 (not MI-H or dMMR)

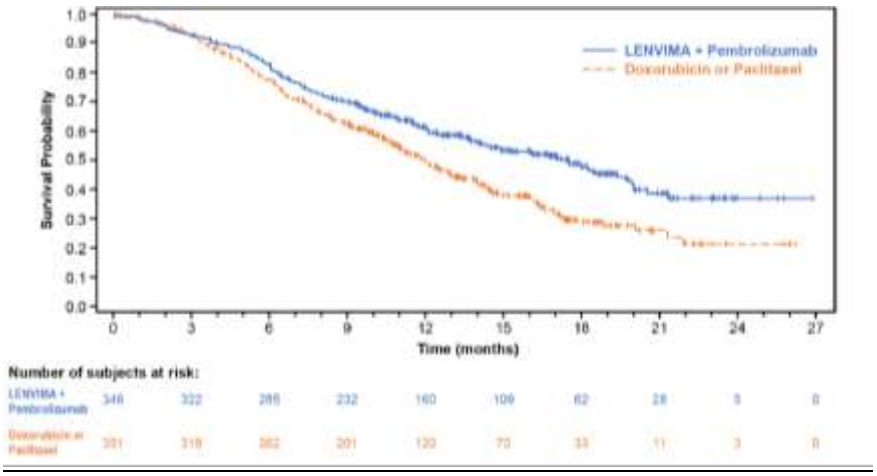
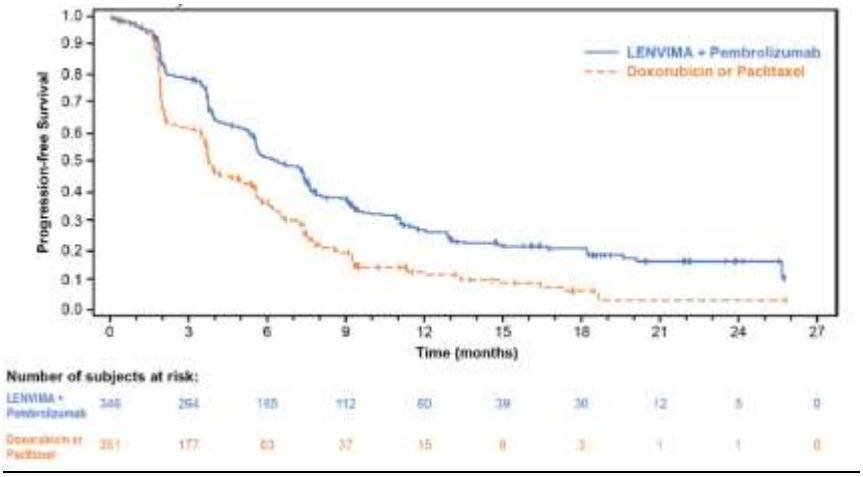


Figure 10 Kaplan-Meier Curves for Progression-Free Survival in Study 309 (not MSI-H or dMMR)



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.

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.

Metabolism

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). 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-t}, unbound and AUC_{0-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-t} and AUC_{0-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).

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-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-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). No dosage recommendations are available for HCC patients with severe renal impairment (see section 4.2). 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 i*n 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

Capsule

Calcium carbonate

Hydroxypropylcellulose

Low-substituted hydroxypropylcellulose

Mannitol

Microcrystalline cellulose

Purified talc

Capsule shell

Hypromellose

Iron oxide red

Iron oxide yellow

Titanium dioxide

Printing ink

Iron oxide black (E172)

Potassium hydroxide

Propylene glycol

Shellac

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container until required for use.

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.

The LENVIMA capsules are furthermore packaged in a carton board.

6.6 Special precautions for disposal and other handling

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

Do not open the capsule. Caregivers should avoid repeated exposure to the contents of the capsule.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

LENVIMA 4: 50/26/0375

LENVIMA 10: 50/26/0376

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 12 May 2020

10. DATE OF REVISION OF THE TEXT

27 June 2025