Lenvima®

Hard Capsules
4 mg, 10 mg

lenvatinib

1. NAME OF THE MEDICINAL PRODUCT

LENVIMA 4 mg hard capsules
LENVIMA 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains lenvatinib mesilate equivalent to 4 mg lenvatinib.
Each hard capsule contains lenvatinib mesilate equivalent to 10 mg lenvatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Differentiated Thyroid Cancer (DTC)

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

Renal Cell Carcinoma (RCC)

LENVIMA, in combination with pembrolizumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Hepatocellular Carcinoma (HCC)

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

Endometrial Carcinoma (EC)

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

4.2 Posology and method of administration

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

Posology

Adults

Differentiated Thyroid Cancer

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

Renal Cell Carcinoma

LENVIMA in combination with pembrolizumab

The recommended daily dose of LENVIMA is 20mg 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.
Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

LENVIMA in combination with everolimus

The recommended daily dose of LENVIMA is 18 mg in combination with 5 mg everolimus orally taken once daily.
Refer to the everolimus prescribing information for other everolimus dosing information.

Hepatocellular Carcinoma

The recommended dosage of LENVIMA is based on actual body weight:

- 12 mg for patients greater than or equal to 60 kg or
- 8 mg for patients less than 60 kg.

Take LENVIMA orally once daily until disease progression or until unacceptable toxicity.

Endometrial Carcinoma

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 unacceptable toxicity or disease progression.
Refer to the pembrolizumab prescribing information for recommended pembrolizumab dosing information.

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. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.
Optimal medical management for nausea, vomiting, and diarrhoea should be initiated prior to any interruption or dose reduction of LENVIMA. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or failure (see section 4.4 Renal failure and impairment).

Dose adjustment

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of the combination therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of the combination, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement of the reaction to Grade 0-1 or baseline.
Treatment should be discontinued in case of life-threatening reactions (eg, Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (eg, Grade 3). For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant, lenvatinib continuation without dose modification may be considered.

For toxicities thought to be related to lenvatinib (see Table 1), upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested in Table 2.

For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the

everolimus SmPC for advice on specific adverse reactions).

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced prior to reducing everolimus.

When used in combination with pembrolizumab, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued as appropriate. Withhold or discontinue pembrolizumab in accordance with the instructions in the prescribing information for pembrolizumab. No dose reductions are recommended for pembrolizumab.

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

Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of LENVIMA for adverse reactions.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modifications for LENVIMA
Hypertension	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	• Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 g of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation	Any Grade	• Permanently discontinue.
Fistula Formation	Grade 3 or 4	• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 adverse reaction	• Permanently discontinue.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

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

When administering LENVIMA in combination with everolimus for the treatment of renal cell carcinoma, reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

When administering LENVIMA in combination with pembrolizumab for the treatment of endometrial carcinoma, interrupt one or both drugs or dose reduce LENVIMA as appropriate. No dose reductions are recommended for pembrolizumab. Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab prescribing information.

Special populations

Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib (see section 4.8e). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended 24 mg dose for DTC and 18 mg dose for RCC, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see section 4.4).

Patients with hepatic impairment

In patients with DTC,RCC and EC, no adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose for DTC is 14 mg taken once daily; for RCC and endometrial carcinoma is 10 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.
Limited data are available for the combination of lenvatinib with pembrolizumab or everolimus in patients with hepatic impairment. Please refer to the respective prescribing information for pembrolizumab or everolimus for dosing in patients with hepatic impairment. 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

Patients with renal impairment

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose for DTC is 14 mg taken once daily; for RCC and endometrial carcinoma is 10 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Limited data are available for the combination of lenvatinib with pembrolizumab or everolimus in patients with renal impairment. Please refer to the respective prescribing information for pembrolizumab or everolimus for dosing in patients with renal impairment. There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

Elderly population

No adjustment of starting dose is required on the basis of age.

Paediatric population

Lenvatinib must not be used in children younger than 2 years of age because of safety concerns regarding organ growth and maturation (see section 5.3). The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.

Method of administration

Lenvatinib should be taken at about the same time each day, with or without food (see section 5.2). The capsules should be swallowed whole with water. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypertension

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

Table 3 Recommended Management of Hypertension

Blood Pressure Level	Recommended Action
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib 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 lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

BP, blood pressure.

Serious cases of artery dissection, some with a fatal outcome, have been reported in patients using vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), with or without hypertension.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment (see section 4.6). It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8.c). Monitor urine protein regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). Cases of nephrotic syndrome have been reported in patients using lenvatinib. LENVIMA should be discontinued in the event of nephrotic syndrome

Renal failure and impairment

Events of renal impairment (including renal failure) have been reported in patients treated with lenvatinib (see section 4.8). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or

discontinuation may be necessary (see section 4.2).
If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Cardiac dysfunction
Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (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).

Posterior reversible encephalopathy syndrome (PRES) / Reversible Posterior Leucoencephalopathy Syndrome (RPLS)
Events of posterior reversible encephalopathy syndrome (PRES, also known as RPLS) have been reported in patients treated with lenvatinib (<1%; see section 4.8). 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 Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Hepatotoxicity
Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8.c) have been reported in patients treated with lenvatinib. The hepatic failure events were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).
If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).
Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Haemorrhagic events
Serious haemorrhagic events have been reported in patients treated with lenvatinib (see section 4.8.c). Fatal intracranial haemorrhagic events have been reported in some patients with brain metastases. Serious tumour related bleeds, including fatal haemorrhagic events in LENVIMA-treated patients, have occurred in clinical trials and been reported in post-marketing experience. In post-marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumour types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Arterial thromboembolic events
Arterial thromboembolic events (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see section 4.8). Lenvatinib 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.

Gastrointestinal perforation and fistula formation
Events of gastrointestinal perforation or fistulae have been reported in patients treated with lenvatinib (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 lenvatinib. Cases of fistula formation or enlargement that involve areas of the body other 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 fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax. Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib 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. Lenvatinib may adversely affect the wound healing process as for other agents of the same class.

QT interval prolongation
QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see section 4.8). Electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. 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.

Impairment of thyroid stimulating hormone suppression/Thyroid dysfunction

Lenvatinib impairs exogenous thyroid suppression (see section 4.8c). Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Diarrhoea
Diarrhoea has been reported frequently in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.

Impaired wound healing
No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Withhold lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of lenvatinib after resolution of wound healing complications has not been established.

Osteonecrosis of the jaw (ONJ)
Cases of ONJ have been reported in patients treated with lenvatinib. Some cases were reported in patients who had received prior or concomitant treatment with antiresorptive bone therapy, and/or other angiogenesis inhibitors, e.g. bevacizumab, TKI, mTOR inhibitors. Caution should therefore be exercised when lenvatinib is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors.

Invasive dental procedures are an identified risk factor. Prior to treatment with lenvatinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Special populations
Limited data are available for patients of ethnic origin other than

Caucasian or Asian, and in patients aged ≥75 years. Lenvatinib should be used with caution in such patients, given the reduced tolerability of lenvatinib in Asian and elderly patients (see section 4.8e)

There are no data on the use of lenvatinib 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 medicinal products and other forms of interaction

Interaction with other medicinal products and other forms of interaction below are relevant to the use of lenvatinib monotherapy. Population pharmacokinetic analysis demonstrated that lenvatinib does not significantly affect the pharmacokinetics of either everolimus or pembrolizumab. When using lenvatinib in combination with everolimus or pembrolizumab, also refer to the manufacturer's prescribing information for everolimus or pembrolizumab.

Effect of other medicinal products on lenvatinib

CYP3A, P-gp, and BCRP substrates

No dose adjustment of lenvatinib is recommended when co-administering with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

Other chemotherapeutic agents

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

Effect of lenvatinib on other medicinal products

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

Oral contraceptives

It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method (see section 4.6).

4.6 Fertility, pregnancy and lactation

Information on fertility, pregnancy and lactation below is relevant to use of lenvatinib monotherapy. When using lenvatinib in combination with everolimus or pembrolizumab, please see below and also refer to the manufacturer's prescribing information for everolimus or pembrolizumab.

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits (see section 5.3).

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

Breastfeeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk (see section 5.3). A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breastfeeding (see section 4.3).

Fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys (see section 5.3).

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. Lenvatinib may cause side effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable effects

4.8.a. Summary of the safety profile (DTC, RCC, HCC EC)

The safety profile of lenvatinib is based on the combined safety data of 458 DTC patients, 496 HCC patients as monotherapy, 62 RCC patients in combination with everolimus, 497 RCC patients in combination with pembrolizumab,and 530 EC patients in combination with pembrolizumab (see section 5.1).

Differentiated Thyroid Cancer

The most frequently reported adverse reactions in (occurring in ≥30% of patients) are hypertension (73%), fatigue (67%), diarrhoea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), and palmar-plantar erythrodysaesthesia syndrome (PPE) (32%), abdominal pain (31%), and dysphonia (31%). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see section 4.8.c). The majority of Grade 3 or 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

In 261 patients with RAI-refractory DTC, dose reductions and discontinuations were the actions taken for an adverse reaction in 68% and 18% respectively. Adverse reactions that most commonly led to dose reductions (in ≥10% of patients) were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhoea (10%). Adverse reactions that most commonly led to discontinuation of lenvatinib were asthenia (1%), and hypertension (1%).

Renal Cell Carcinoma

Lenvatinib in combination with pembrolizumab in RCC

The safety profile of lenvatinib in combination with pembrolizumab is based on data from 497 RCC patients. The most frequently reported adverse reactions (occurring in ≥30% of patients) were diarrhoea (61.8%), hypertension (51.5%) fatigue (47.1%), hypothyroidism (45.1%), decreased appetite (42.1%), nausea (39.6%), stomatitis (36.6%), proteinuria (33.0%), dysphonia (32.8%), and arthralgia (32.4%).

The most common severe (Grade ≥3) adverse reactions (≥5%) were hypertension (26.2%), lipase increased (12.9%), diarrhoea (9.5%), proteinuria (8.0%), amylase increased (7.6%), weight decreased (7.2%), and fatigue (5.2%).

Discontinuation of lenvatinib, pembrolizumab, or both due to an adverse reaction occurred in 33.4% of patients; 23.7% lenvatinib, and 12.9 % both drugs. The most common adverse reactions (≥1%) leading to discontinuation of lenvatinib, pembrolizumab, or both were myocardial infarction (2.4%), diarrhoea (2.0%), proteinuria (1.8%), and rash (1.4%). Adverse reactions that most commonly led to discontinuation of lenvatinib (≥1%) were myocardial infarction (2.2%), proteinuria (1.8%), and diarrhoea (1.0%).

Dose interruptions of lenvatinib, pembrolizumab, or both due to an adverse reaction occurred in 80.1% of patients; lenvatinib was interrupted in 75.3%, and both drugs in 38.6% of patients. Lenvatinib was dose reduced in 68.4% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of lenvatinib were diarrhoea (25.6%), hypertension (16.1%), proteinuria (13.7%), fatigue (13.1%), appetite decreased (10.9%), palmar-plantar erythrodysaesthesia syndrome (PPE) (10.7%), nausea (9.7%), asthenia (6.6%), stomatitis (6.2%), lipase increased (5.6%), and vomiting (5.6%).

Lenvatinib in combination with everolimus in RCC

The most frequently reported adverse reactions in the LENVIMA with everolimus-treated group (occurring in ≥30% of patients) are

diarrhoea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, haemorrhagic events, and proteinuria. The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhoea (5%), vomiting (5%), and dyspnea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients of patients receiving LENVIMA with everolimus. The most common adverse reactions (≥5%) in the LENVIMA with everolimus-treated group resulting in dose reductions were diarrhoea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA with everolimus-treated group.*Hepatocellular Carcinoma*
The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic 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%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia 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%).

Endometrial Carcinoma
The safety of lenvatinib in combination with pembrolizumab has been evaluated in 530 patients with advanced EC receiving 20 mg lenvatinib once daily and 200 mg pembrolizumab every 3 weeks. The most common (occurring in ≥20% of patients) adverse reactions were hypertension (63%), diarrhoea (57%), hypothyroidism (56%), nausea (51%), decreased appetite (47%), vomiting (39%), fatigue (38%), decreased weight (35%), arthralgia (33%), proteinuria (29%), constipation (27%), headache (27%), urinary tract infection (27%), dysphonia (25%), abdominal pain (23%), asthenia (23%), palmar-plantar erythrodysaesthesia syndrome (23%), stomatitis (23%), anaemia (22%), and hypomagnesaemia (20%).

The most common (occurring in ≥5% of patients) severe (Grade ≥3) adverse reactions were hypertension (37.2%), decreased weight (9.1%), diarrhoea (8.1%), increased lipase (7.7%), decreased appetite (6.4%), asthenia (6%), fatigue (6%), hypokalaemia (5.7%), anaemia (5.3%), and proteinuria (5.1%).

Discontinuation of lenvatinib occurred in 30.6% of patients, and discontinuation of both lenvatinib and pembrolizumab occurred in 15.3% of patients due to an adverse reaction. The most common (occurring in ≥1% of patients) adverse reactions leading to discontinuation of lenvatinib were hypertension (1.9%), diarrhoea (1.3%), asthenia (1.3%), decreased appetite (1.3%), proteinuria (1.3%), and decreased weight (1.1%).

Dose interruption of lenvatinib due to an adverse reaction occurred in 63.2% of patients. Dose interruption of lenvatinib and pembrolizumab due to an adverse reaction occurred in 34.3% of patients. The most common (occurring in ≥5% of patients) adverse reactions leading to interruption of lenvatinib were hypertension (12.6%), diarrhoea (11.5%), proteinuria (7.2%), vomiting (7%), fatigue (5.7%), and decreased appetite (5.7%).

Dose reduction of lenvatinib due to adverse reactions occurred in 67.0% of patients. The most common (occurring in ≥5% of patients) adverse reactions resulting in dose reduction of lenvatinib were hypertension (16.2%), diarrhoea (12.5%), palmar-plantar erythrodysaesthesia syndrome (9.1%), fatigue (8.7%), proteinuria (7.7%), decreased appetite (6.6%), nausea (5.5%), asthenia (5.1%), and decreased weight (5.1%).

4.8.b. Tabulated list of adverse reactions
The safety profile of lenvatinib monotherapy and lenvatinib in combination with everolimus is based on data from 458 DTC patients, 496 HCC patients and 62 RCC patients where the most conservative frequency for each ADR is used.

The safety profile of lenvatinib as combination therapy is based on data from 530 EC and 497 RCC patients treated with lenvatinib in combination with pembrolizumab.

Similar adverse reactions were observed in clinical trials in DTC, RCC with lenvatinib in combination with everolimus, and HCC. Adverse reactions that occur more frequently with combination therapy with everolimus compared to lenvatinib monotherapy are hypothyroidism, (including increased blood thyroid stimulating hormone), hypercholesterolaemia, and severe diarrhoea. Adverse reactions that occurred more frequently in RCC with lenvatinib and pembrolizumab combination therapy compared to lenvatinib monotherapy were hypothyroidism (including increased blood thyroid stimulating hormone), hypercholesterolaemia, diarrhoea, lipase increased, amylase increased, rash (including maculopapular rash), and blood creatinine increased.

Table 4 shows the frequency categories of adverse reactions observed in clinical trials for subjects taking lenvatinib monotherapy (subjects with DTC or HCC) and subjects taking lenvatinib in combination with everolimus (RCC) or pembrolizumab (RCC or EC). The adverse reaction frequency category represents the most conservative estimate of frequency from the individual populations.

Adverse reactions known to occur with lenvatinib or combination therapy componentsgiven alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy.

For additional safety information when lenvatinib is administered in combination, refer to the product information for the respective combination therapy component (pembrolizumab or everolimus).

Frequencies are defined as:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency category, undesirable effects are presented in order of decreasing seriousness.

Table 4 Adverse reactions reported in patients treated with lenvatinib[§]

System Organ Class (MedDRA terminology)	**Monotherapy/ Combination with everolimus**	**Combination with pembrolzumab in EC**	**Combination with pembrolizumab in RCC**
Infections and infestation			
Very common	Urinary tract infection	Urinary tract infection	
Common			Urinary tract infection
Uncommon	Perineal abscess	Perineal abscess	Perineal abscess
Blood and lymphatic disorders			
Very common	Thrombocytopenia[a, ‡] Lymphopenia[a,‡]	Thrombocytopenia[a,‡] Lymphopenia[a,‡]	

	Leukopenia[a,‡] Neutropenia[a,‡]	Leukopenia[a,‡] Neutropenia[a,‡] Anaemia	
Common			Thrombocytopenia[a] Leukopenia[a] Neutropenia[a] Lymphopenia[a]
Uncommon	Splenic infarction		
Endocrine disorders			
Very common	Hypothyroidism Increased blood thyroid stimulating hormone*[,‡]	Hypothyroidism Increased blood thyroid stimulating hormone* Hyperthyroidism	Hypothyroidism Blood thyroid stimulating hormone increased*
Metabolism and nutrition disorders			
Very common	Hypocalcaemia*[,‡] Hypokalaemia[‡] Hypercholesterolaemia[b,‡] Decreased weight Decreased appetite	Hypocalcaemia*[,‡] Hypokalaemia[‡] Hypercholesterolaemia[b,‡] Hypomagnesaemia[b,‡] Decreased weight Decreased appetite	Decreased appetite Decreased weight Hypercholesterolaemia[b]
Common	Dehydration Hypomagnesaemia[b]	Dehydration	Hypocalcaemia* Hypokalaemia Dehydration Hypomagnesaemia[b]
Psychiatric disorders			
Very common	Insomnia		Insomnia
Common		Insomnia	
Nervous system disorders			
Very common	Dizziness Headache Dysgeusia	Dizziness Headache Dysgeusia	Dizziness Headache Dysgeusia
Common	Cerebrovascular accident[†]		
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Posterior reversible encephalopathy syndrome Cerebrovascular accident[†] Monoparesis Transient ischaemic attack	Cerebrovascular accident Posterior reversible encephalopathy syndrome Transient ischaemic attack
Cardiac disorders			
Common	Myocardial infarction[c,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Prolonged electrocardiogram QT	Myocardial infarction[c,†] Prolonged electrocardiogram QT
Uncommon		Myocardial infarction[c,†] Cardiac failure Decreased ejection fraction	Cardiac failure[†] Decreased ejection fraction
Vascular disorders			
Very common	Haemorrhage[d,*,†] Hypertension[e,*] Hypotension	Haemorrhage[d,*,†] Hypertension[e,*]	Haemorrhage[d,†,*] Hypertension[e,†,*]
Common		Hypotension	Hypotension
Unknown	Aneurysms and artery dissections		Aneurysms and artery dissections[†]
Respiratory, thoracic and mediastinal disorders			
Very common	Dysphonia	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism[†]	Pulmonary embolism[†]
Uncommon	Pneumothorax	Pneumothorax	Pneumothorax
Gastrointestinal disorders			
Very common	Diarrhoea Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase	Diarrhoea Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dry mouth Increased lipase Increased amylase[‡]	Diarrhoea* Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth Increased lipase Increased amylase[‡]
Common	Anal fistula Flatulence	Pancreatitis[i] Flatulence Dyspepsia	Pancreatitis[i] Flatulence
Uncommon	Pancreatitis[i]	Anal fistula	Anal fistula
Hepatobiliary disorders			
Very common	Increased blood bilirubin[j,*,‡] Hypoalbuminaemia[j,*,‡] Increased alanine aminotransferase*[,‡] Increased aspartate aminotransferase*[,‡] Increased blood alkaline phosphatase[‡] Increased gamma-glutamyltransferase[‡]	Increased blood bilirubin[j,*,‡] Hypoalbuminaemia[j,*,‡] Increased alanine aminotransferase*[,‡] Increased aspartate aminotransferase*[,‡] Increased blood alkaline phosphatase[‡]	Increased aspartate aminotransferase*[,‡] Increased alanine aminotransferase[‡]
Common	Hepatic failure[k,*,†] Hepatic encephalopathy[l,*,†] Abnormal hepatic function Cholecystitis	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase	Cholecystitis Hepatic function abnormal Hypoalbuminaemia* Blood bilirubin increased[j,‡] Blood alkaline phosphatase increased Gamma-glutamyltransferase increased
Uncommon	Hepatocellular damage/hepatitis[m]	Hepatic failure[k,*,†] Hepatic encephalopathy[l,†] Hepatocellular damage/hepatitis[m]	Hepatic failure[k,†,*] Hepatic encephalopathy[l,*] Hepatocellular damage and hepatitis[m]
Skin and subcutaneous tissue disorders			
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar Erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia	Alopecia Hyperkeratosis
Uncommon		Hyperkeratosis	Palmar erythema
Musculoskeletal and connective tissue disorders			
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia Myalgia Pain in extremity	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain
Common		Musculoskeletal pain	
Uncommon	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[n, *,†] Renal impairment* Increased blood urea	Renal failure[n, *,†]	Renal failure[n] Increased blood urea
Uncommon	Nephrotic syndrome	Renal impairment* Increased blood urea	Renal impair ment* Nephrotic syndrome
General disorders and administration site conditions			
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema periph-Eral
Common	Malaise	Malaise	Malaise
Uncommon	Impaired healing	Impaired healing	Non-gastrointestinal fistula[o] Impaired healing
Not known	Non-gastrointestinal fistula		

§: Adverse reaction frequencies presented in Table 4 may not be fully attributable to lenvatinib alone, but may contain contributions from the underlying disease or from other medicinal products used in a combination.

*: See section 4.8c, 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: Thrombocytopenia includes thrombocytopenia and decreased platelet count. Neutropenia includes neutropenia and decreased neutrophil count. Leukopenia includes leukopenia and decreased white blood cell count. Lymphopenia includes lymphopenia and lymphocyte count decreased.

b: Hypomagnesaemia includes hypomagnesaemia and decreased blood magnesium. Hypercholesterolaemia includes hypercholesterolaemia and increased blood cholesterol.

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

d: Includes all haemorrhage terms.

Haemorrhage terms that occurred in 5 or more subjects with DTC were: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechial, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma and vaginal haemorrhage.

Haemorrhage terms that occurred in 5 or more subjects with HCC were: epistaxis, haematuria, gingival bleeding, haemoptysis, oesophageal varices haemorrhage, haemorrhoidal haemorrhage, mouth haemorrhage, rectal haemorrhage and upper gastrointestinal haemorrhage.

Haemorrhage term that occurred in 5 or more subjects with EC was: vaginal haemorrhage.

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

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

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

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

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

i: Pancreatitis includes: pancreatitis and acute pancreatitis.

j: Increased blood bilirubin includes: hyperbilirubinaemia, increased blood bilirubin, jaundice and increased bilirubin conjugated. Hypoalbuminaemia includes hypoalbuminaemia and decreased blood albumin.

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

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

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

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

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

4.8.c. Description of selected adverse reactions

Hypertension (see section 4.4)

Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.

In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure ≥160 mmHg occurred in 29% of patients and diastolic blood pressure ≥100 mmHg occurred in 21%.

In CLEAR (see section 5.1), hypertension was reported in 56.3% of patients in the lenvatinib plus pembrolizumab-treated group and 42.6% of patients in the sunitinib-treated group. The exposure-adjusted frequency of hypertension was 0.65 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.73 episodes per patient year in the sunitinib-treated group. The median time to onset in lenvatinib plus pembrolizumab-treated patients was 0.7 months. Reactions of Grade 3 or higher occurred in 28.7% of lenvatinib plus pembrolizumab-treated group compared with 19.4% of the sunitinib-treated group. 16.8% of patients with hypertension had dose modifications of lenvatinib (9.1% dose interruption and 11.9% dose reduction). In 0.9% of patients, hypertension led to permanent treatment discontinuation of lenvatinib.

In the Phase 3 Study 309 (see section 5.1), hypertension was reported in 65% of patients in the lenvatinib plus pembrolizumab group. Reactions of Grade 3 or higher occurred in 38.4% of patients in the lenvatinib plus pembrolizumab group. The median time to onset in the lenvatinib plus pembrolizumab group was 15 days. Dose interruption, reduction and discontinuation of lenvatinib occurred in 11.6%, 17.7% and 2.0% of patients, respectively.

Proteinuria (see section 4.4)

Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus.

In the Phase 3 Study 309 (see section 5.1), proteinuria was reported in 29.6% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 5.4% of patients. The median time to onset was 34.5 days. Dose interruption, reduction and discontinuation of lenvatinib occurred in 6.2%, 7.9% and 1.2% of patients, respectively.

Hepatotoxicity (see section 4.4)

In the pivotal Phase 3 SELECT trial (see section 5.1), the most commonly reported liver-related adverse reactions were hypoalbuminaemia (9.6% lenvatinib vs. 1.5% placebo) and elevations of liver enzyme levels, including increases in alanine aminotransferase (7.7% lenvatinib vs. 0 placebo), aspartate aminotransferase (6.9% lenvatinib vs. 1.5% placebo), and blood bilirubin (1.9% lenvatinib vs. 0 placebo). The median time to onset of liver events in lenvatinib-treated patients was 12.1 weeks. Liver-related events of Grade 3 or higher (including 1 Grade 5 event of hepatic failure) occurred in 5.4% of lenvatinib-treated patients compared with 0.8% in placebo-treated patients. Liver-related events led to dose interruptions and reductions in 4.6% and 2.7% of patients, respectively, and to permanent discontinuation in 0.4%.

Amongst 1108 patients treated with lenvatinib, there were 3 cases (0.3%) of hepatic failure, all with a fatal outcome. One occurred in a patient with no liver metastases. There was also a case of acute hepatitis in a patient without liver metastases.

The incidence of ALT and AST elevation was similar in Study 2 in RCC. In Study 2, 3% of LENVIMA + everolimus-treated patients

experienced an increase in ALT and 3% experienced an increase in AST that was Grade 3 or greater. Two percent of patients in the everolimus-treated group experienced an increase in ALT and none experienced an increase in AST that was Grade 3 or greater.
In the Phase 3 REFLECT trial (see section 5.1), the most commonly reported hepatotoxicity adverse reactions were increased blood bilirubin (14.9%), increased aspartate aminotransferase (13.7%), increased alanine aminotransferase (11.1%), hypoalbuminaemia (9.2%), hepatic encephalopathy (8.0%), increased gamma-glutamyltransferase (7.8%) and increased blood alkaline phosphatase (6.7%). The median time to onset of hepatotoxocity adverse reactions was 6.4 weeks. Hepatotoxicity reactions of ≥ Grade 3 occurred in 26.1% of lenvatinib-treated patients. Hepatic failure (including fatal events in 12 patients) occurred in 3.6% of patients (all were ≥ Grade 3). Hepatic encephalopathy (including fatal events in 4 patients) occurred in 8.4% of patients (5.5% were ≥ Grade 3). There were 17 (3.6%) deaths due to hepatotoxicity events in the lenvatinib arm and 4 (0.8%) deaths in the sorafenib arm. Hepatotoxicity adverse reactions led to dose interruptions and reductions in 12.2% and 7.4% of lenvatinib-treated patients respectively, and to permanent discontinuation in 5.5%.

Across clinical studies in which 1327 patients received lenvatinib monotherapy in indications other than HCC, hepatic failure (including fatal events) was reported in 4 patients (0.3%), liver injury in 2 patients (0.2%), acute hepatitis in 2 patients (0.2%), and hepatocellular injury in 1 patient (0.1%).

In CLEAR (see section 5.1), the most commonly reported liver related adverse reactions in the lenvatinib plus pembrolizumab treated group were elevations of liver enzyme levels, including increases in alanine aminotransferase (11.9%), aspartate aminotransferase (11.1%) and blood bilirubin (4.0%). Similar events occurred in the sunitinib-treated group at rates of 10.3%, 10.9% and 4.4% respectively. The median time to onset of liver events was 3.0 months (any grade) in the lenvatinib plus pembrolizumab treated group and 0.7 months in the sunitinib-treated group. The exposure-adjusted frequency of hepatoxicity events was 0.39 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.46 episodes per patient year in the sunitinib-treated group. Grade 3 liver related reactions occurred in 9.9% of lenvatinib plus pembrolizumab treated patients and 5.3% of sunitinib-treated patients. Liver related reactions led to dose interruptions and reductions of lenvatinib in 8.5% and 4.3% of patients, respectively, and to permanent discontinuation of lenvatinib in 1.1% of patients.

In the Phase 3 Study 309 (see section 5.1), hepatotoxicity was reported in 33.7% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 12.1% of patients. The median time to onset was 56.0 days. Dose interruption, reduction and discontinuation of lenvatinib occurred in 5.2%, 3.0% and 1.2% of patients, respectively.

Arterial thromboembolisms (see section 4.4)
In CLEAR (see section 5.1), 5.4% of patients in the lenvatinib plus pembrolizumab treated group reported arterial thromboembolic events (of which 3.7% were Grade ≥ 3) compared with 2.1% of patients in the sunitinib-treated group (of which 0.6% were Grade ≥ 3). No events were fatal. The exposure-adjusted frequency of arterial thromboembolic event episodes was 0.04 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.02 episodes per patient year in the sunitinib-treated group. The most commonly reported arterial thromboembolic events in the lenvatinib plus pembrolizumab treated group was myocardial infarction (3.4%). One event of myocardial infarction (0.3%) occurred in the sunitinib-treated group. The median time to onset of arterial thromboembolic events was 10.4 months in the lenvatinib plus pembrolizumab treated group.

In RCC Study 205 (see section 5.1), 1.6% of patients in the lenvatinib plus everolimus-treated group reported arterial thromboembolic events. The time to onset was 69.6 weeks. In the everolimus group, 6.0% of patients reported an arterial thromboembolism (4.0% were Grade ≥ 3). In the DTC study (see SmPC for Lenvima SmPC), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

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

In the Phase 3 Study 309 (see section 5.1), arterial thromboembolisms were reported in 3.7% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 2.2% of patients. The median time to onset was 59.0 days. Dose interruption and discontinuation of lenvatinib occurred in 0.2% and 2.0% of patients, respectively.

Renal Failure or Impairment (see section 4.4)
Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study. In Study 205 (RCC), renal impairment or renal failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients.

In the Phase 3 Study 309 (see section 5.1), 18.2% of lenvatinib plus pembrolizumab-treated patients developed a renal failure/impairment event. Grade ≥ 3 reactions occurred in 4.2% of patients. The median time to onset was 86.0 days. Dose interruption, reduction and discontinuation of lenvatinib occurred in 3.0%, 1.7% and 1.2% of patients, respectively.

Cardiac dysfunction (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), decreased ejection fraction/cardiac failure was reported in 6.5% of patients (1.5% were Grade ≥ 3) in the lenvatinib treated group, and 2.3% in the placebo group (none were Grade ≥ 3).

In the Phase 3 REFLECT trial (see section 5.1), cardiac dysfunction (including congestive cardiac failure, cardiogenic shock, and cardiopulmonary failure) was reported in 0.6% of patients (0.4% were Grade ≥ 3) in the lenvatinib-treated group.

In the Phase 3 Study 309 (see section 5.1), cardiac dysfunction was reported in 1.0% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 0.5% of patients. The median time to onset was 112.0 days. Dose reduction and discontinuation of lenvatinib both occurred in 0.2% of patients.

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group and no reports in the placebo group.

In the Phase 3 REFLECT trial (see section 5.1), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group.

Amongst 1,823 patients treated with lenvatinib monotherapy in clinical trials, there were 5 cases (0.3%) of PRES (0.2% were Grade 3 or 4), all of which resolved after treatment and/or dose interruption, or permanent discontinuation.

In the Phase 3 Study 309 (see section 5.1), there was one event of PRES (Grade 1) in the lenvatinib plus pembrolizumab-treated group for which lenvatinib was interrupted.

Diarrhea (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), diarrhoea was reported in 67.4% of patients in the lenvatinib-treated group (9.2% were Grade ≥ 3) and in 16.8% of patients in the placebo group (none were Grade ≥ 3).

In Study 205 (RCC), diarrhea occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%.

In the Phase 3 REFLECT trial (see section 5.1), diarrhoea was reported in 38.7% of patients treated with lenvatinib (4.2% were Grade ≥ 3).

In the Phase 3 Study 309 (see section 5.1), diarrhoea was reported in 54.2% of lenvatinib plus pembrolizumab-treated patients (7.6% were Grade ≥ 3). Dose interruption, reduction and discontinuation of lenvatinib occurred in 10.6%, 11.1% and 1.2% of patients, respectively.

Haemorrhagic events (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), haemorrhagic events were reported in 34.9% of lenvatinib-treated patients versus 18.3% of placebo-treated patients. Events that occurred at an incidence of ≥0.75% above placebo were: epistaxis (11.9%), haematuria (6.5%), contusion (4.6%), gingival bleeding (2.3%), haematochezia (2.3%), rectal haemorrhage (1.5%), haematoma (1.1%), haemorrhoidal haemorrhage (1.1%), laryngeal haemorrhage (1.1%), petechiae (1.1%), and intracranial tumour haemorrhage (0.8%). In this trial, there was 1 case of fatal intracranial haemorrhage among 16 patients who received lenvatinib and had CNS metastases at baseline.
The median time to first onset in lenvatinib-treated patients was 10.1 weeks. No differences between lenvatinib- and placebo-treated patients were observed in the incidences of serious adverse events (3.4% vs. 3.8%), events leading to premature discontinuation (1.1% vs. 1.5%), or events leading to dose interruption (3.4% vs. 3.8%) or reduction (0.4% vs. 0).
In Study 2 in RCC, haemorrhagic events occurred in 34% of patients in the LENVIMA + everolimus-treated group and 26% of patients in the everolimus-treated group. The most frequently reported haemorrhagic event was epistaxis (LENVIMA + everolimus 23% and everolimus 24%). Grade 3 or greater events occurred in 8% of LENVIMA + everolimus-treated patients and in 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated patients, this included one fatal cerebral haemorrhage. Discontinuation due to a haemorrhagic event occurred in 3% of patients in the LENVIMA + everolimus-treated group.

In the Phase 3 REFLECT trial (see section 5.1), haemorrhage was reported in 24.6% of patients and 5.0% were Grade ≥ 3. Grade 3 reactions occurred in 3.4%, Grade 4 reactions in 0.2% and 7 patients (1.5%) had a grade 5 reaction including cerebral haemorrhage, upper gastrointestinal haemorrhage, intestinal haemorrhage and tumour haemorrhage. The median time to first onset was 11.9 weeks. A haemorrhage event led to dose interruption or reduction in 3.2% and 0.8% patients respectively and to treatment discontinuation in 1.7% of patients.
Across clinical studies in which 1,327 patients received lenvatinib monotherapy in indications other than HCC, Grade ≥ 3 or greater haemorrhage was reported in 2% of patients, 3 patients (0.2%) had a Grade 4 haemorrhage and 8 patients (0.6%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial haemorrhage, intracranial tumour haemorrhage, haematemesis, melaena, haemoptysis and tumour haemorrhage.

In the Phase 3 Study 309 (see section 5.1), haemorrhage was reported in 24.4% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 3.0% of patients. The median time to onset was 65.0 days. Dose interruption, reduction and discontinuation of lenvatinib occurred in 1.7%, 1.2% and 1.7% of patients, respectively.
Hypocalcaemia (see section 4.4, QT interval prolongation)
In the pivotal Phase 3 SELECT trial (see section 5.1), hypocalcaemia was reported in 12.6% of lenvatinib-treated patients vs. no events in the placebo arm. The median time to first onset in lenvatinib-treated patients was 11.1 weeks. Events of Grade 3 or 4 severity occurred in 5.0% of lenvatinib-treated vs 0 placebo-treated patients. Most events resolved following supportive treatment, without dose interruption or reduction, which occurred in 1.5% and 1.1% of patients, respectively; 1 patient with Grade 4 hypocalcaemia discontinued treatment permanently.

In Study 2 in RCC, 6% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group experienced Grade 3 or greater hypocalcemia. No patients discontinued due to hypocalcemia.
In the Phase 3 REFLECT trial (see section 5.1), hypocalcaemia was reported in 1.1% of patients, with grade 3 reactions occurring in 0.4%. Lenvatinib dose interruption due to hypocalcaemia occurred in one subject (0.2%) and there were no dose reductions or discontinuations.

In the Phase 3 Study 309 (see section 5.1), hypocalcaemia was reported in 3.9% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 1.0% of patients. The median time to onset was 148.0 days. No lenvatinib dose modifications were reported.

Gastrointestinal perforation and fistula formation (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients and 0.8% of patients in the placebo group.

In the Phase 3 REFLECT trial (see section 5.1), events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients.

In the Phase 3 Study 309 (see section 5.1), events of fistula formation were reported in 2.5% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 2.5% of patients. The median time to onset was 117.0 days. Discontinuation of lenvatinib occurred in 1.0% of patients. Events of gastrointestinal perforation were reported in 3.9% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 3.0% of patients. The median time to onset was 42 days. Dose interruption and discontinuation of lenvatinib occurred in 0.5% and 3.0% of patients, respectively.

QT interval prolongation (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), QT/QTc interval prolongation was reported in 8.8% of lenvatinib-treated patients and 1.5% of patients in the placebo group. The incidence of QT interval prolongation of greater than 500 ms was 2% in the lenvatinib-treated patients compared to no reports in the placebo group.

In the Phase 3 REFLECT trial (see section 5.1), QT/QTc interval prolongation was reported in 6.9% of lenvatinib-treated patients. The incidence of QTcF interval prolongation of greater than 500ms was 2.4%.

In the Phase 3 Study 309 (see section 5.1), QT interval prolongation was reported in 3.9% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 0.5% of patients.
The median time to onset was 115.5 days. Dose interruption and reduction of lenvatinib occurred in 0.2% and 0.5% of patients, respectively.

Blood thyroid stimulating hormone increased/Thyroid dysfunction (see section 4.4)
In the pivotal Phase 3 SELECT (DTC) trial (see section 5.1), 88% of all patients had a baseline TSH level ≤ 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level > 0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients.

Grade 1 or 2 hypothyroidism occurred in 24% of patients receiving LENVIMA with everolimus in Study 205 (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 70% of patients receiving LENVIMA in REFLECT and 60% of patients receiving LENVIMA with everolimus in Study 205.

In CLEAR (see section 5.1), hypothyroidism occurred in 47.2% of patients in the lenvatinib plus pembrolizumab treated group and 26.5% of patients in the sunitinib treated group. The exposure-adjusted frequency of hypothyroidism was 0.39 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.33 episodes per patient year in the sunitinib-treated group. In general, the majority of hypothyroidism events in the lenvatinib plus pembrolizumab treated group were of Grade 1 or 2. Grade 3 hypothyroidism was reported in 1.4% of patients in the lenvatinib plus pembrolizumab treated group versus none in the sunitinib-treated group. At baseline, 90% of patients in the lenvatinib plus pembrolizumab-treated group and 93.1% of patients in the sunitinib-treated group had baseline TSH levels ≤ upper limit of normal. Elevations of TSH > upper limit of normal were observed post baseline in 85.0% of lenvatinib plus pembrolizumab treated patients versus 65.6% of sunitinib-treated patients. In lenvatinib plus pembrolizumab-treated patients, hypothyroidism events resulted in dose modification of lenvatinib (reduction or interruption) in 2.6% patients and discontinuation of lenvatinib in 1 patient.

In the Phase 3 Study 309 (see section 5.1), hypothyroidism was reported in 68.2% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 1.2% of patients. The median time to onset was 62.0 days. Dose interruption and reduction of lenvatinib occurred in 2.2% and 0.7% of patients, respectively.
Blood TSH increased was reported in 12.8% of lenvatinib plus pembrolizumab-treated patients with no patients reporting Grade ≥3 reactions. Dose interruption occurred in 0.2% of patients.

4.8.f. Paediatric population
Clinical data are not yet available in this population (see section 4.2).

4.8.g. Other special populations
Elderly
In CLEAR, patients of age ≥75 years had a higher (≥ 10% difference) incidence of proteinuria than patients of age <65 years.

There are limited data on patients of age ≥75 years with RCC. However, in DTC, patients of age ≥75 years were more likely to experience Grade 3 to 4 hypertension, proteinuria, decreased appetite, and dehydration.

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

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

Race
In CLEAR, Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of palmar-plantar erythrodysaesthesia syndrome, proteinuria and hypothyroidism (including blood thyroid hormone increased) while Caucasian patients had a higher incidence of fatigue, nausea, arthralgia, vomiting, and asthenia.

There are limited data on Asian patients with RCC Study 205. However, in DTC, Asian patients had a higher incidence than Caucasian patients of oedema peripheral, fatigue, PPE, proteinuria, thrombocytopenia, stomatitis and myalgia; while Caucasian patients had a higher incidence of diarrhoea, weight decreased, nausea, vomiting, constipation, asthenia, abdominal pain, pain in extremity, and dry mouth. Japanese patients had a higher incidence of Grade 3 to 4 hypertension, decreased appetite, fatigue, and thrombocytopenia compared with non-Japanese patients.

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

In DTC, patients with baseline hypertension had a higher incidence of Grade 3 to 4 hypertension, proteinuria, diarrhoea, and dehydration, and experienced more serious events of dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting). In RCC Study 205, patients with baseline hypertension had a higher incidence of Grade 3 or 4 dehydration, fatigue, and hypertension.

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

Renal impairment
In DTC, patients with baseline renal impairment had a higher incidence of Grade 3 to 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, and blood thyroid stimulating hormone increased, pneumonia compared with patients with normal renal function. These patients also had a higher incidence of renal events and a trend towards a higher incidence of liver events. In RCC Study 205, patients with baseline renal impairment had a higher incidence of Grade 3 fatigue.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

4.9 Overdose
The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhoea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. There have also been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.
Symptoms and Management
There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib 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

Lenvatinib is a multikinase inhibitor which has shown mainly antiangiogenic properties in vitro and *in vivo*, and direct inhibition of tumour growth was also observed in *in vitro* models.

Mechanism of action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively 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. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

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

The combination of lenvatinib and everolimus showed increased anti-angiogenic and antitumour activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling *in vitro*, and by decreases in tumour volume in mouse xenograft models of human renal cell cancer that were greater than those with either drug alone.

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus.

The mechanism of action for hypothyroidism is not fully elucidated.

Clinical efficacy

The clinical safety and efficacy of LENVIMA have been studied in patients with differentiated thyroid cancer, renal cell carcinoma amd hepatocellular carcinoma.

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 (+1month window) prior to enrollment. Radioactive iodine-refractory 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. Patients in the placebo arm could opt to receive lenvatinib treatment at the time of confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomised 2:1 to receive lenvatinib 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 had an 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 lenvatinib-treated patients compared with those receiving placebo (p<0.0001) (see figure 1). The positive effect on PFS was seen across the subgroups of age (above or below 65 years), sex, race, histological subtype, geographic region, and those who received 0 or 1 prior VEGF/VEGFR-targeted therapy (see Table 5). Following independent review confirmation of disease progression, 109 (83.2%) patients randomised to placebo crossed over to open-label lenvatinib at the time of the primary efficacy analysis.

The objective response rate (complete response [CR] plus partial response [PR]) per independent radiological review was significantly (p<0.0001) higher in the lenvatinib-treated group (64.8%) than in the placebo-treated group (1.5%). Four (1.5%) subjects treated with lenvatinib attained a CR and 165 subjects (63.2%) had a PR, while no subjects treated with placebo had a CR and 2 (1.5%) subjects had a PR.

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 lenvatinib, 70.4% were observed to develop the response on or within 30 days of being on the 24-mg dose.

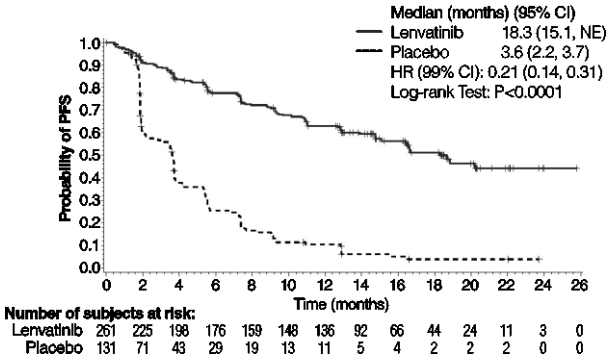
An overall survival analysis was confounded by the fact that placebo-treated subjects with confirmed disease progression had the option to cross over to open-label lenvatinib. There was no statistically significant difference in overall survival between the treatment groups at the time of the primary efficacy analysis (HR=0.73; 95%CI: 0.50, 1.07, p=0.1032). The median OS had not been reached for either the lenvatinib group or the placebo crossover group.

Table 5 Efficacy Results in DTC in SELECT

	Lenvatinib 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-targeted therapy (%)	195 (74.7)	104 (79.4)
Number of progressions or deaths	76	88
Median PFS in months (95% CI)	18.7 (16.4, NE)	3.6 (2.1, 5.3)
Hazard ratio (95% CI)[b,c]	0.20 (0.14, 0.27)	
Patients who had received 1 prior VEGF/VEGFR-targeted therapy (%)	66 (25.3)	27 (20.6)
Number of progressions or deaths	31	25
Median PFS in months (95% CI)	15.1 (8.8, NE)	3.6 (1.9, 3.7)
Hazard ratio (95% CI)[b,c]	0.22 (0.12, 0.41)	
Objective Response Rate[a]		
Number of objective responders (%)	169 (64.8)	2 (1.5)
(95% CI)	(59.0, 70.5)	(0.0, 3.6)
P-value[b]	<0.0001	
Number of complete responses	4	0
Number of partial responses	165	2
Median time to objective response,[d] months (95% CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Duration of response,[d] months, median (95% CI)	NE (16.8, NE)	NE (NE, 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; VEGF/VEGFR, vascular endothelial growth factor / vascular endothelial growth factor receptor.
a: Independent radiologic review.
b: Stratified by region (Europe vs. North America vs. Other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).
c: Estimated with Cox proportional hazard model.
d: Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.
e: Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Curves for Progression-free Survival in SELECT



CI, confidence interval; NE, not estimable.

Renal cell carcinoma

In combination with pembrolizumab

First-line treatment (Study 307)

The efficacy of lenvatinib in combination with pembrolizumab was investigated in (CLEAR, Study 307), a multicenter, open-label, randomized trial that enrolled 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region. (North America and Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, and poor risk).

Patients were randomized to lenvatinib 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=355), or lenvatinib 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). All patients on the lenvatinib plus pembrolizumab arm were started on lenvatinib 20 mg orally once daily. The median time to first dose reduction for lenvatinib was 1.9 months. The median average daily dose for lenvatinib was 14 mg. Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by independent radiologic review committee (IRC) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).

Administration of lenvatinib 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 lenvatinib could be continued beyond 24 months. Assessment of tumor 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%).

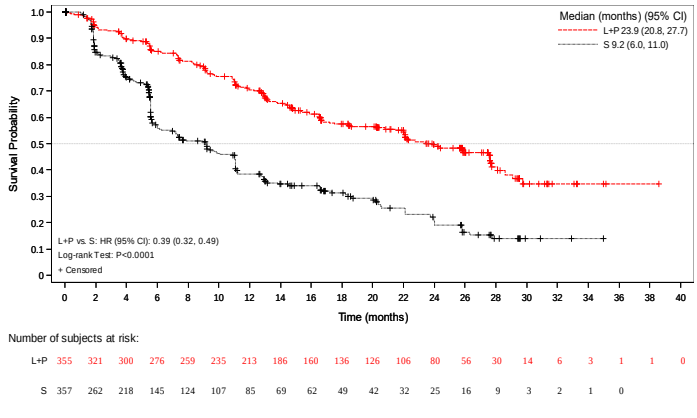
The primary efficacy outcome measure was progression free survival (PFS) based on RECIST 1.1 per IRC. Key secondary efficacy outcome measures included overall survival (OS) and objective response rate (ORR). Lenvatinib in combination with pembrolizumab demonstrated statistically significant improvements in PFS, OS and ORR compared with sunitinib. Efficacy results for CLEAR are summarized in Table 6 and Figures 2, 3 and 4, at a median OS follow-up time of 26.6 months. Progressive disease as best overall response was observed in 5.4% of patients treated with lenvatinib in combination with pembrolizumab compared with 14.0% of patients treated with sunitinib. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumor expression status (see Figure 3).

Table 6: Efficacy Results in Renal Cell Carcinoma Per IRC in Study 307 (RCC)

	Lenvatinib 20 mg with Pembrolizumab 200mg N=355	**Sunitinib 50mg N=357**
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45.1%)	205 (57.4%)
Progressive disease	145 (40.8%)	196 (54.9%)
Death	15 (4.2%)	9 (2.5%)
Median PFS in months (95% CI)[a]	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard Ratio (95% CI)[b, c]	0.39 (0.32, 0.49)	
P-value[c]	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (22.5%)	101 (28.3%)
Median OS in months (95% CI)	NR (33.6, NE)	NR (NE, NE)
Hazard Ratio (95% CI)[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)	80.2% (75.5, 84.1)
18 months	87.1% (83.1, 90.3)	74.4% (69.3, 78.8)
24 months	79.2% (74.1, 83.3)	70.4% (65.0, 75.2)
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	252 (71.0%)	129 (36.1%)
(95% CI)	(66.3, 75.7)	(31.2, 41.1)
Number of complete responses (CR), n (%)	57 (16.1%)	15 (4.2%)
Number of partial responses (PR), n (%)	195 (54.9%)	114 (31.9%)
P-value[e]	<0.0001	
Time to Response		
Median in months (range)	1.9 (1.41, 18.50)[f]	1.9 (1.61, 16.62)[g]
Duration of Response[a]		
Median in months (range)	25.8 (1.6+, 36.8+)	14.6 (1.6+, 33.1+)

Tumor 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 (favorable, 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 lenvatinib plus pembrolizumab with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), *P*-value <0.0001).
f Based on patients with objective responses per IRC (n=252)
g Based on patients with objective responses per IRC (n=129)

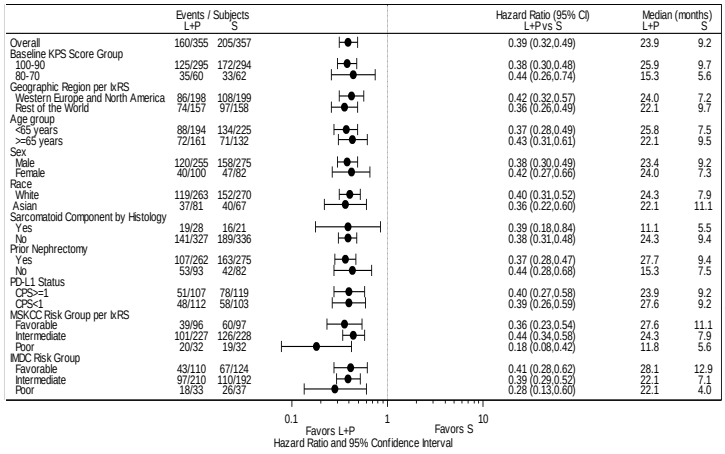
Figure 2 Kaplan-Meier Curves of Progression-Free Survival in Study 307 (RCC)



L+P=Lenvatinib + Pembrolizumab; S = Sunitinib.

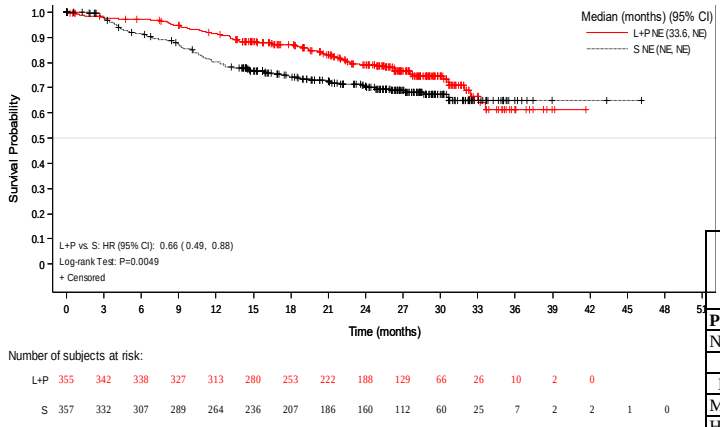
Data cutoff date: 28 Aug 2020

Figure 3 Forest Plot of Progression-Free Survival per IRC in Study 307 (RCC)



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis.
The subgroups/strata with sample size less than 5% of the treatment group are not displayed.
Source: ADTTE
Data cutoff date: 28 Aug 2020

Figure 4 Kaplan-Meier Curves of Overall Survival in Study 307 (RCC)



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.

Assessment of Quality of Life (QoL) in patients with RCC
Patient-reported outcomes (PRO) were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 and Kidney Cancer Symptom Index (FKSI-DRS). From baseline to a mean follow-up time of 46 weeks, patients treated with lenvatinib in combination with pembrolizumab had better physical functioning, fatigue, dyspnea, and constipation scores compared to the sunitinib group.

Compared to sunitinib, lenvatinib in combination with pembrolizumab showed a more than 12 week delay in median time to worsening in global health status (GHS), physical functioning and patient reported symptoms with no subsequent recovery: EORTC QLQ-C30 GHS (114 vs. 75 weeks, HR=0.6 [95%CI: 0.47, 0.77]), physical functioning (134 vs 78 weeks, HR=0.52 [95% CI: 0.41, 0.67]), fatigue (110 vs. 59 weeks, HR=0.54 [95% CI: 0.43, 0.67]), insomnia (156 vs. 126 weeks, HR=0.63 [95% CI: 0.47. 0.85]), dyspnea (153 vs. 126 weeks, HR=0.56 [95% CI: 0.41, 0.76]), nausea and vomiting (147 vs 131 weeks, (HR=0.53 [95% CI: 0.39, 0.74]), pain (119 vs. 105 weeks, HR=0.68 [95% CI: 0.53, 0.87]) and FKSI-DRS (134 vs. 117 weeks, HR=0.7 [95% CI: 0.53, 0.92]).

In combination with everolimus
Second-line treatment (Study 205)

A multicenter study (Study 205) randomized 153 patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy 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 clear cell RCC and ECOG Performance Status of 0 or 1. Patients were stratified by hemoglobin level (≤ or > 13 g/dL for males and ≤ or > 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 + everolimus arm and everolimus monotherapy arm, 72% were male, the median age was 60 years, 31% were older than 65 years, 96% were White. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. 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) favorable, intermediate, and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA + everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST 1.1. Efficacy results from Study 2 are summarized in Table 7 and Figures 5 and 6. The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm.

Table 7: Efficacy Results in Renal cell Carcinoma Per Investigator Assessment in Study 205

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	**Everolimus 10 mg (N=50)**
Progression-Free Survival (PFS)[a]		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] LENVIMA + Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival[c]		
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)[b] LENVIMA + Everolimus vs Everolimus	0.67 (0.42, 1.08)	-
Objective Response Rate (Confirmed)		
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. Data cutoff date = 13 Jun 2014
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 Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata.
c Data cutoff date = 31 Jul 2015

Figure 5 Kaplan-Meier Curves for Progression-Free Survival In Study 205

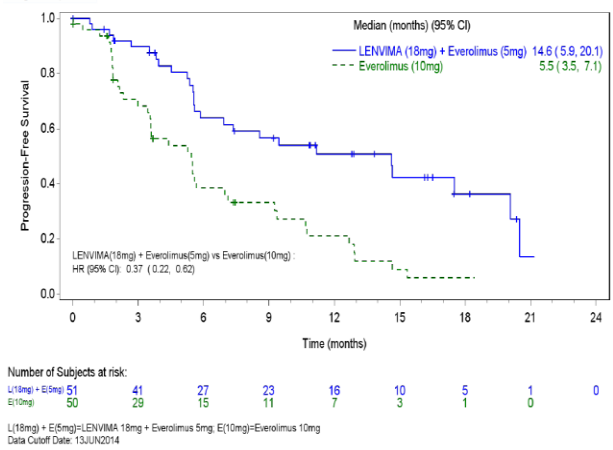
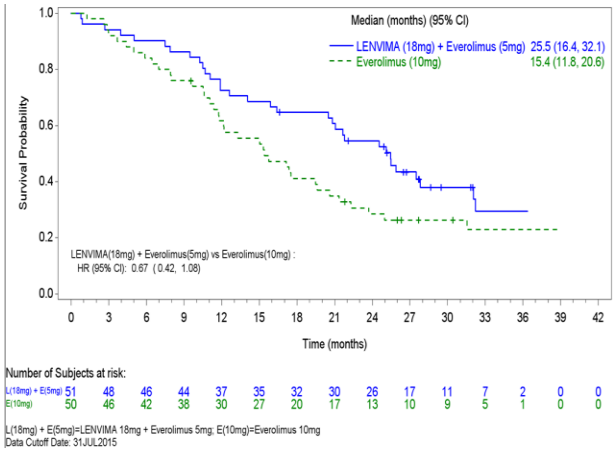


Figure 6 Kaplan-Meier Curves for Overall Survival in Study 205



Hepatocellular carcinoma

The efficacy of LENVIMA was evaluated in a randomized, open-label, multicenter, international study (REFLECT; NCT01761266) conducted in patients with previously untreated unresectable hepatocellular carcinoma (HCC). The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) Stage C or B HCC who were ineligible for local liver-directed therapy; had an ECOG PS of 0 or 1; had received no prior systemic therapy for HCC; and had at least one measurable target lesion according to modified RECIST for HCC.

Patients were randomized (1:1) to receive LENVIMA (12 mg for baseline body weight ≥60 kg or 8 mg for baseline body weight <60 kg) orally once daily or sorafenib 400 mg orally twice daily until radiological disease progression or unacceptable toxicity. Randomization was stratified by region (Western vs Asia Pacific), presence of macroscopic portal vein invasion or extrahepatic spread (yes vs no), ECOG PS (0 vs 1), and body weight (<60 kg vs ≥60 kg). The major efficacy outcome measure was overall survival (OS). REFLECT was designed to show the non-inferiority of LENVIMA to sorafenib for OS. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR) according to modified RECIST for HCC.

A total of 954 patients were randomized, 478 to the LENVIMA arm and 476 to the sorafenib arm. The demographics of the study population were: median age of 62 years (range: 20 to 88 years); 84% male; 69% Asian and 29% White; 63% ECOG PS of 0; and 69% weighed ≥60 kg. Of the 590 (62%) patients with at least one site of documented distant metastatic disease, 52% had lung metastasis, 45% had lymph node metastasis, and 16% had bone metastasis.

Macroscopic portal vein invasion, extra-hepatic spread, or both were present in 70% of patients. HCC was categorized as Child-Pugh A and BCLC Stage C in 79% and Child-Pugh A and BCLC Stage B in 21% of patients. Seventy-five percent (75%) of patients had radiographic evidence of cirrhosis at baseline. Investigator-documented primary risk factors for the development of HCC were hepatitis B (50%), hepatitis C (23%), alcohol use (6%), other (7%), and unknown (14%).

REFLECT demonstrated that LENVIMA was non-inferior to sorafenib for OS. REFLECT did not demonstrate a statistically significant improvement in OS for patients randomized to LENVIMA as compared to those in the sorafenib arm. LENVIMA was statistically significantly superior to sorafenib for PFS and ORR. Efficacy results are summarized in Table 8 and Figure 7.

Table 8: Efficacy Results in Hepatocellular Carcinoma in REFLECT

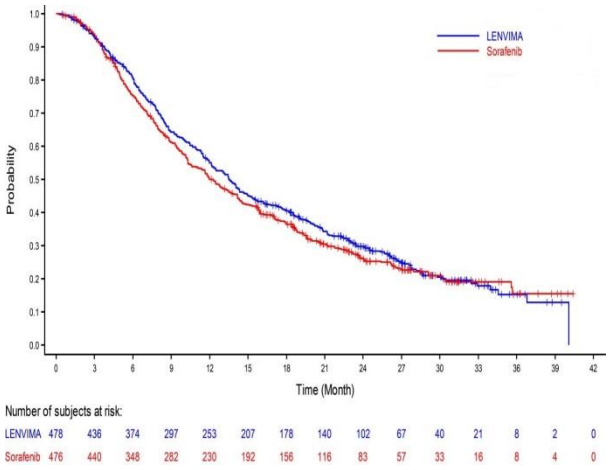
	LENVIMA N= 478	Sorafenib N=476
Overall Survival		
Number of deaths (%)	351 (73)	350 (74)
Median OS in months (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Hazard Ratio (95% CI)[a]	0.92 (0.79, 1.06)	
Progression-Free Survival[b] (mRECIST)		
Number of Events (%)	311 (65)	323 (68)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Hazard Ratio (95% CI)	0.64 (0.55, 0.75)	
P-value	<0.001	
Objective Response Rate[b] (mRECIST)		
Objective response rate	41%	12%
Complete responses, n (%)	10 (2.1)	4 (0.8)
Partial responses, n (%)	184 (38.5)	55 (11.6)
95% CI	(36%, 45%)	(10%, 16%)
P-value	<0.001	
Progression-Free Survival[b] (RECIST 1.1)		
Number of Events (%)	307 (64)	320 (67)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.9)
Hazard Ratio (95% CI)	0.65 (0.56, 0.77)	
Objective Response Rate[b] (RECIST 1.1)		
Objective response rate	19%	7%
Complete responses, n (%)	2 (0.4)	1 (0.2)
Partial responses, n (%)	88 (18.4)	30 (6.3)
95% CI	(15%, 22%)	(4%, 9%)

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; OS = overall survival.

a Based on stratified Cox-model. Non-inferiority margin for HR (lenvatinib vs sorafenib) is 1.08.

b Per independent radiology review.

Figure 7 Kaplan-Meier Curves for Overall Survival in REFLECT



Endometrial Carcinoma (EC)

The efficacy of lenvatinib in combination with pembrolizumab was investigated in Study 309, a randomized, multicenter, open-label, active-controlled study conducted in patients with advanced EC who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. The study excluded patients with endometrial sarcoma (including carcinosarcoma), or patients who had active autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by MMR status (dMMR or pMMR [not dMMR]) using an IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomizsed (1:1) to one of the following treatment arms:

- lenvatinib 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 lenvatinib and pembrolizumab continued until RECIST v1.1-defined progression of disease as verified by blinded independent central review (BICR), unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Administration of study treatment was permitted beyond RECIST-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks.

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

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. The median follow-up time was 11.4 months (range: 0.3 to 26.9 months). Efficacy results for Study 309 are summarized in Table 9 and Figures 8, 9, and 10.

Table 9: Efficacy Results in Endometrial Carcinoma in Study 309

Endpoint	LENVIMA with pembrolizumab N=411	Doxorubicin or Paclitaxel N=416
OS		
Number (%) of patients with event	188 (46%)	245 (59%)
Median in months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
Hazard ratio[a] (95% CI)	0.62 (0.51, 0.75)	
P-value[b]	<0.0001	
PFS		
Number (%) of patients with event	281 (68%)	286 (69%)
Median in months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio[a] (95% CI)	0.56 (0.47, 0.66)	
P-value[b]	<0.0001	
Objective Response Rate		
ORR[c] (95% CI)	32% (27, 37)	15% (11,18)
Complete response	7%	3%
Partial response	25%	12%
P-value[d]	<0.0001	
Duration of Response[e]	N=131	N=61
Median in months (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)
% with duration ≥6 months	72	43
% with duration ≥12 months	51	35

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

Figure 8 Kaplan-Meier Curves of Overall Survival in Study 309

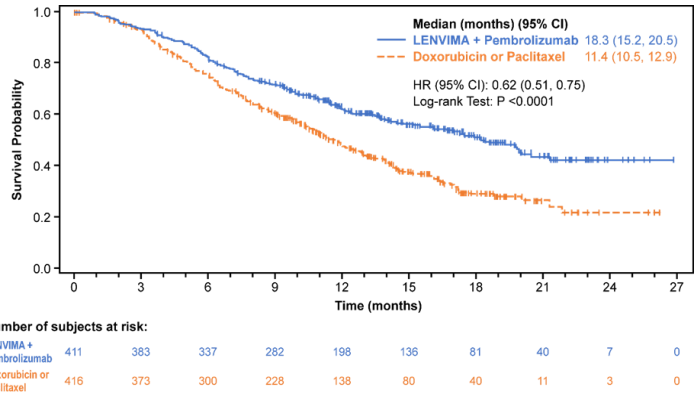


Figure 9 Kaplan-Meier Curves of Progression-Free Survival in Study 309

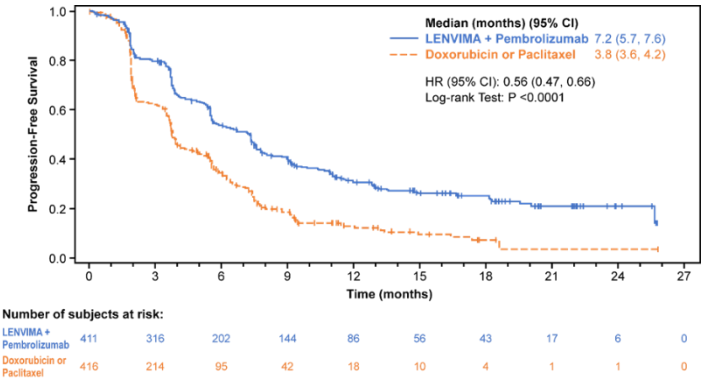
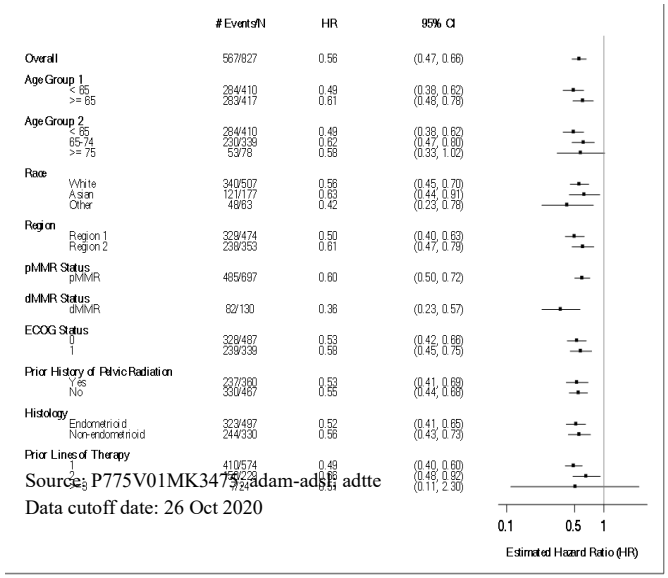


Figure 10 Forest Plot of Progression-Free Survival in Study 309



Source: P775V01MK3475adam-adsl adtte
Data cutoff date: 26 Oct 2020

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lenvatinib have been studied in healthy adult subjects, adult subjects with hepatic impairment, renal impairment, and solid tumours.

Absorption

Lenvatinib is rapidly absorbed after oral administration with t_{max} typically observed from 1 to 4 hours postdose. 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. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests that it is in the order of 85%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Distribution

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

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL, mesilate).

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 bile salt export pump BSEP.

In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation

In vitro, cytochrome P450 3A4 was the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo*, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see section 4.5).

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 (chlorophenyl moiety), and combinations of these pathways followed by further biotransformations (e.g., 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.

In vitro transporter studies

For the following transporters, OAT1, OAT3, OATP1B1, OCT1, OCT2, and BSEP, clinically relevant inhibition was excluded based on a cutoff of IC_{50}> 50 x $C_{max.unbound}$.

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

Lenvatinib showed minimal or no inhibitory effect on OATP1B3 and MATE2-K. Lenvatinib weakly inhibits MATE1. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

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-quarter of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4% of the dose).

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). The Rac in HCC subjects with mild and moderate liver impairment was similar to that reported for other solid tumours.

Special populations

Hepatic impairment

The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild and 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. Lenvatinib exposure, based on dose-adjusted AUC0-t and AUC0-inf data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It has been determined that plasma protein binding in plasma from hepatically impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed. See section 4.2 for dosing recommendation.

There are not sufficient data for HCC patients with Child-Pugh B (moderate hepatic impairment, 3 patients treated with lenvima in the pivotal trial) and no data available in Child Pugh C HCC patients (severe hepatic impairment). Lenvatinib is mainly eliminated via the liver and exposure might be increased in these patient populations.

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).

Renal impairment
The pharmacokinetics of lenvatinib following a single 24-mg dose were evaluated in 6 subjects each with mild, moderate, and severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied

Lenvatinib exposure, based on $AUC_{0\text{-}inf}$ data was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It has been determined that plasma protein binding in plasma from renally impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed. See section 4.2 for dosing recommendation.

Age, sex, weight, race, tumor type
Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily as monotherapy (DTC), up to 18 mg once daily in combination with 5 mg everolimus (RCC), and up to 20 mg once daily in combination with pembrolizumab (RCC and EC), age, sex, weight, race (Japanese vs. other, Caucasian vs. other) and tumor type had no significant effects on clearance (see section 4.2).

Paediatric Population
Paediatric patients have not been studied.

5.3 Preclinical safety data
In the repeated-dose toxicity studies (up to 39 weeks), lenvatinib caused toxicologic changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib including glomerulopathy, testicular hypocellularity, ovarian follicular atresia, gastrointestinal changes, bone changes, changes to the adrenals (rats and dogs) and arterial (arterial fibrinoid necrosis, medial degeneration, or haemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Elevated transaminase levels associated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity
Lenvatinib mesilate was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the *in vitro* mouse lymphoma thymidine kinase assay or the *in vivo* micronucleus assay in rats.

Carcinogenicity
Carcinogenicity studies have not been conducted with lenvatinib.

Reproductive and developmental toxicity
No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) 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.

Administration of lenvatinib during organogenesis resulted in embryolethality and teratogenicity in both rats (foetal external and skeletal anomalies) at exposures below the clinical exposure (based on AUC) at the maximum tolerated human dose, and rabbits (foetal external, visceral or skeletal anomalies) based on body surface area; mg/m^2 at the maximum tolerated human dose These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent. Lenvatinib and its metabolites are excreted in rat milk.

Juvenile animal toxicity studies
Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age. Therefore mortality may be attributed to complications related to primary duodenal lesions with possible contribution from additional toxicities in immature target organs.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND 7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats at 10 mg/kg compared with adult rats administered the same dose level. Growth retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents
Calcium carbonate
Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose
Talc

Capsule shell
Hypromellose
Titanium dioxide
Yellow iron oxide
Red iron oxide

Printing ink containing:
Shellac
Black iron oxide
Potassium hydroxide
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30ºC

6.5 Nature and contents of container
Aluminium/aluminium foil blisters
4 mg – packs of 20
10 mg – packs of 20

6.6 Special precautions for disposal and other handling
Any unused medicinal product 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. PRODUCT OWNER

Eisai Co., Ltd.
4-6-10 Koishikawa, Bunkyo-ku,
Tokyo, Japan

8. PRODUCT LICENCE NUMBER

SIN14982P
SIN14983P

[DATE OF REVISION OF PACKAGE INSERT]
October 2021

Eisai Co., Ltd.
TOKYO, JAPAN