Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lenvatinib STADA 10 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lenvatinib STADA 10 mg hard capsules

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (Capsule).

Lenvatinib STADA 10 mg hard capsules

Hard capsule, size 2 (approx. 17.6 mm in length) with a golden body and brown cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Differentiated Thyroid Carcinoma (DTC)

Lenvatinib STADA as monotherapy is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Hepatocellular Carcinoma (HCC)

Lenvatinib STADA as monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 5.1).

Endometrial Carcinoma (EC)

Lenvatinib STADA 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.

Renal Cell Carcinoma (RCC)

Lenvatinib STADA is indicated for the treatment of adults with advanced renal cell carcinoma (RCC):

- in combination with pembrolizumab, as first-line treatment (see section 5.1).
- in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experienced in the use of anticancer therapies.

Optimal medical management (i.e., treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any lenvatinib therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure (see section 4.4).

Posology

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.

When Lenvatinib STADA is used in combination with pembrolizumab in RCC, lenvatinib treatment should continue until disease progression or unacceptable toxicity. Pembrolizumab should be continued until disease progression, unacceptable toxicity or the maximum duration of therapy as specified for pembrolizumab.

Differentiated thyroid cancer (DTC)

The recommended daily dose of lenvatinib is 24 mg (two 10-mg capsules and one 4-mg capsule) once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan.

Dose adjustments and discontinuations for DTC
Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management.
Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0 to 1 or baseline.

For lenvatinib-related toxicities (see Table 5), upon resolution/improvement of an adverse reaction to Grade 0 to 1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested in Table 1.

Table 1 Dose modifications from recommended lenvatinib daily dose in DTC patients[a]		
Dose level	**Daily dose**	**Number of capsules**
Recommended daily dose	24 mg orally once daily	Two 10-mg capsules plus one 4-mg capsule
First dose reduction	20 mg orally once daily	Two 10-mg capsules
Second dose reduction	14 mg orally once daily	One 10-mg capsule plus one 4-mg capsule
Third dose reduction	10 mg orally once daily [a]	One 10-mg capsule
Life-threatening toxicities (Grade 4): Discontinue[b]		

[a] Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.
[b] Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

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

Hepatocellular Carcinoma (HCC)

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Dose adjustments and discontinuation for HCC
Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. For lenvatinib-related toxicities, see Table 5. Details for monitoring, dose adjustment and discontinuation are provided in Table 2.

Table 2 Dose modifications from recommended lenvatinib daily dose in HCC patients			
Starting Dose		**≥ 60 kg BW** **12 mg (three 4-mg capsules orally once daily)**	**< 60 kg BW** **8 mg (two 4-mg capsules orally once daily)**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities[a]			
Adverse Reaction	**Modification**	**Adjusted Dose [b] (≥ 60 kg BW)**	**Adjusted Dose[b] (< 60 kg BW)**
First occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline[d]	8 mg (two 4-mg capsules) orally once daily	4 mg (one 4-mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg (one 4-mg capsule) orally once daily	4 mg (one 4-mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg (one 4-mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			

[a] Initiate medical management for nausea, vomiting, or diarrhoea prior to interruption or dose reduction
[b] Reduce dose in succession based on the previous dose level (12 mg, 8 mg, 4 mg or 4 mg every other day).
[c] Haematologic toxicity or proteinuria: no dose adjustment required for first occurrence.
[d] For haematologic toxicity, dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2 g/24 hours.
[e] Excluding laboratory abnormalities judged to be non-life-threatening, which should be managed as Grade 3.

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

Endometrial Carcinoma (EC)

The recommended dosage of lenvatinib 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 (see section 5.1).

Refer to the Summary of Product Characteristics (SmPC) for pembrolizumab for additional dosing information.

Dose adjustments and discontinuation for EC
For lenvatinib-related toxicities see Table 5. When administering lenvatinib in combination with pembrolizumab, interrupt, dose reduce, or discontinue lenvatinib as appropriate (see Table 3).
Withhold or discontinue pembrolizumab in accordance with the instructions in the SmPC for pembrolizumab. No dose reductions are recommended for pembrolizumab.

Table 3 Dose modifications from recommended lenvatinib daily dose in EC patients[a]		
Starting Dose in combination with pembrolizumab		20 mg orally once daily (two 10-mg capsules)
Persistent and Intolerable Grade 2 or Grade 3 Toxicities		
Adverse Reaction	**Modification**	**Adjusted Dose**
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once daily (one 10-mg capsule)
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	8 mg orally once daily (two 4-mg capsules)
Life-threatening toxicities (Grade 4): Discontinue[b]		

[a] Limited data are available for doses below 8 mg.
[b] Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

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

Renal Cell Carcinoma (RCC)

Lenvatinib in combination with pembrolizumab as first-line treatment
The recommended dose of lenvatinib is 20 mg (two 10-mg capsules) orally once daily in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The daily dose of lenvatinib is to be modified as needed according to the dose/toxicity management plan.

See the Summary of Product Characteristics (SmPC) for pembrolizumab for full pembrolizumab dosing information.

Lenvatinib in combination with everolimus as second-line treatment
The recommended daily dose of lenvatinib is 18 mg (one 10-mg capsule and two 4-mg capsules) orally once daily in combination with 5 mg of everolimus once daily. The daily dose of lenvatinib and, if necessary, everolimus is to be modified as needed according to the dose/toxicity management plan.

See the SmPC for everolimus for full everolimus dosing information.

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

Dose adjustments and discontinuation for RCC
For management of adverse reactions, refer to dose adjustments and discontinuation for DTC.

For toxicities thought to be related to lenvatinib (see Table 5), upon resolution/improvement of an adverse reaction to Grade 0 to 1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested in Table 4.

Table 4 Dose modifications from recommended lenvatinib daily dose in RCC patients[a]

	Lenvatinib dose in combination with pembrolizumab	**Lenvatinib dose in combination with everolimus**
Recommended daily dose	20 mg orally once daily (two 10-mg capsules)	18 mg orally once daily (one 10-mg capsule + two 4-mg capsules)
First dose reduction	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)
Second dose reduction	10 mg orally once daily (one 10-mg capsule)	10 mg orally once daily (one 10-mg capsule)
Third dose reduction	8 mg orally once daily (two 4-mg capsules)	8 mg orally once daily (two 4-mg capsules)
Life-threatening toxicities (Grade 4): Discontinue[b]		

[a] Limited data are available for doses below 8 mg.

[b] All treatments should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

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

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 SmPC for pembrolizumab. No dose reductions are recommended for pembrolizumab.

For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the SmPC for everolimus for dose adjustment recommendations regarding specific adverse reactions).

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced (see Table 4) prior to reducing everolimus.

All indications (DTC, HCC, EC, RCC)

Adverse reactions requiring dose modification

Table 5 Adverse reactions requiring dose modification of lenvatinib			
Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 6 in section 4.4.
	Grade 4	Discontinue	Do not resume.
Proteinuria	≥ 2 g / 24 hours	Interrupt	Resolves to less than 2 g / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume.
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume.
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume.
Posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS)	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume.
Arterial thromboembolisms	Any grade	Discontinue	Do not resume.
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume.
Gastrointestinal perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume.
Non-gastrointestinal fistula	Grade 4	Discontinue	Do not resume.
QT interval prolongation	> 500 ms	Interrupt	Resolves to < 480 ms or baseline.
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume.
* Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3).			

Special populations

DTC

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 4.8). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended 24-mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

HCC

Patients ≥ 75 years, of white race or female sex or those with worse baseline hepatic impairment (Child-Pugh A score of 6 compared to score of 5) appear to have reduced tolerability to lenvatinib.

HCC patients other than those with moderate and severe hepatic impairment or severe renal impairment should initiate treatment at the recommended starting dose of 8 mg (two 4-mg capsules) for body weight < 60 kg and 12 mg (three 4-mg capsules) for body weight ≥ 60 kg, following which the dose should be further adjusted on the basis of individual tolerability.

RCC

Patients of age ≥ 65 years, with baseline hypertension or those with renal impairment appear to have reduced tolerability to lenvatinib (see section 4.8).

No data for the combination of lenvatinib and everolimus are available for most of the special populations. The following information is derived from clinical experience of single agent lenvatinib in patients with differentiated thyroid cancer (DTC).

All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended dose of 20 mg of lenvatinib daily with pembrolizumab or 18 mg of lenvatinib with 5 mg of everolimus taken once daily as indicated, following which the dose should be further adjusted on the basis of individual tolerability.

For information about clinical experience with the combination treatment of lenvatinib and pembrolizumab, see section 4.8.

Patients with hypertension

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

Patients with hepatic impairment

DTC
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 is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability. Refer also to section 4.8.

HCC
In the patient populations enrolled in the HCC study no dose adjustments were required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A). The available very limited data are not sufficient to allow for a dosing recommendation for HCC patients with moderate hepatic impairment (Child-Pugh B). Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2). Lenvatinib has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is not recommended for use in these patients.

EC
Limited data are available for the combination of lenvatinib with pembrolizumab in patients with hepatic impairment. No adjustment of starting dose of the combination 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 of lenvatinib is 10 mg taken once daily. Please refer to the SmPC for pembrolizumab for dosing in patients with hepatic impairment. Further dose adjustments may be necessary on the basis of individual tolerability.

RCC
Limited data are available for the combination of lenvatinib with pembrolizumab in patients with hepatic impairment. No adjustment of starting dose of the combination 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 of lenvatinib is 10 mg taken once daily. Please refer to the SmPC for pembrolizumab for dosing in patients with hepatic impairment. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk (see section 4.8).

No data for the combination of lenvatinib with everolimus are available in patients with hepatic impairment. No adjustment of starting dose of the combination 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 of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the SmPC for everolimus. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk (see section 4.8).

Patients with renal impairment

DTC

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 is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability.
Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended (see section 4.8).

HCC
No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment.

EC
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 is 10 mg of lenvatinib taken once daily. Please refer to the SmPC for pembrolizumab for dosing in patients with renal impairment. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease have not been studied, therefore the use of lenvatinib in these patients is not recommended.

RCC
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 is 10 mg of lenvatinib taken once daily. Please refer to the SmPC for pembrolizumab or everolimus for dosing in patients with renal impairment. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease have not been studied, therefore the use of lenvatinib in these patients is not recommended (see section 4.8).

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥ 75 years (see section 4.8).

Paediatric population

The safety and efficacy of lenvatinib in children aged 2 to < 18 years have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3).

Ethnic origin

No adjustment of starting dose is required on the basis of race (see section 5.2). Limited data are available on use in patients from ethnic origins other than Caucasian or Asian (see section 4.8).

Body weight below 60 kg

RCC
No adjustment of starting dose is required on the basis of body weight. Limited data are available on treatment with lenvatinib in combination with everolimus in patients with a body weight below 60 kg with RCC (see section 4.8).

Performance status

RCC
Patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2 or higher were excluded from RCC Study 205 (see section 5.1). Patients with a KPS (Karnofsky Performance Status) < 70 were excluded from Study 307 (CLEAR). Benefit-risk in these patients has not been evaluated.

Method of administration

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2). Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Lenvatinib capsules should be swallowed whole with water.
For the patients with swallowing difficulties, that are not able to swallow the hard capsules, other medicinal products with lenvatinib should be used instead of Lenvatinib STADA.

For use in combination with pembrolizumab, refer to the SmPC for pembrolizumab.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

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). Blood pressure (BP) 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. BP 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 individualised to the patient's clinical circumstances and follow standard medical practice. For previously normotensive patients, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on an antihypertensive medicinal product, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 6.

Table 6 Recommended management of hypertension

Blood Pressure (BP) level	**Recommended action**
Systolic BP ≥ 140 mmHg up to < 160 mmHg or diastolic BP ≥ 90 mmHg up to < 100 mmHg	Continue 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.

Aneurysms and artery dissections

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

Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8). Urine protein should be monitored 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. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Hepatotoxicity

In DTC and RCC, liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin. Hepatic failure and acute hepatitis (<1 %; see section 4.8) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases.

In HCC patients treated with lenvatinib in the REFLECT trial, liver-related adverse reactions including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency (see section 4.8) compared to patients treated with sorafenib. Patients with worse hepatic impairment and/or greater liver tumour burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure and one third of the events of the hepatic encephalopathy were reported in patients with disease progression.

Data in HCC patients with moderate hepatic impairment (Child-Pugh B) are very limited and there are currently no data available in HCC patients with severe hepatic impairment (Child-Pugh C). Since lenvatinib is mainly eliminated by hepatic metabolism, an increase in exposure in patients with moderate to severe hepatic impairment is expected.

In EC, liver-related adverse reactions most commonly reported in patients treated with lenvatinib and pembrolizumab included increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Hepatic failure and hepatitis (< 1 %; see section 4.8) have been reported in patients with EC treated with lenvatinib and pembrolizumab.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see sections 4.2 and 5.2). Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

For dosing recommendations in patients with severe hepatic impairment see section 4.2. Please also see section 5.2.

Renal failure and impairment

Renal impairment and 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. Caution should be taken in patients receiving agents acting on the renin-angiotensin aldosterone system given a potentially higher risk for acute renal failure with the combination treatment. Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

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

Diarrhoea

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

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 leucoencephalopathysyndrome (RPLS)

PRES, also known as RPLS, has 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).

Arterial thromboembolisms

Arterial thromboembolisms (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 thromboembolism 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. Lenvatinib should be discontinued following an arterial thrombotic event.

Haemorrhage

Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience (see section 4.8). In post-marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumour types. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumour shrinkage and fistula formation, e.g. tracheo-oesophageal fistulae. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported.
One fatal case of hepatic tumour haemorrhage in a patient with HCC has been reported.

Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with lenvatinib.

In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see section 4.2, Table 5).

Gastrointestinal perforation and fistula formation

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 fistulae 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 at baseline and periodically during treatment in all patients with particular attention to those with congenital long QT syndrome, congestive heart failure, bradyarrhythmia, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation > 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

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. Electrolytes

(magnesium, potassium and calcium) should be monitored periodically during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction

Hypothyroidism has been reported in patients treated with lenvatinib (see section 4.8). Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Lenvatinib impairs exogenous thyroid suppression (see section 4.8). 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.

Wound healing complications

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

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).

Tumour lysis syndrome (TLS)

Lenvatinib can cause TLS which can be fatal. Risk factors for TLS include but are not limited to high tumour burden, pre-existing renal impairment and dehydration. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

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.

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 4.8).

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 4 weeks.

In DCT, HCC and EC, patients with ECOG PS ≥ 2 were excluded from clinical studies (except for thyroid carcinoma).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on lenvatinib

Chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances.
Additionally, in patients with RCC the pharmacokinetics of lenvatinib was not significantly affected by concomitant everolimus.

Effect of lenvatinib on other medicinal products

CYP3A4 substrates

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.
Additionally, in patients with RCC the pharmacokinetics of everolimus was not significantly affected by concomitant 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

Women of childbearing potential/ Contraception in females

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 after a careful consideration of the needs of the mother and the risk to the foetus.

Breast-feeding

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 breast-feeding (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

Lenvatinib has minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

DTC, HCC, and EC

The safety profile of lenvatinib as monotherapy is based on data from 452 DTC patients and 496 HCC patients; allowing characterisation only of common adverse drug reactions in DTC and HCC patients (see section 5.1).

The safety profile of lenvatinib as combination therapy is based on data from 530 EC patients treated with lenvatinib in combination with pembrolizumab (see section 5.1).

DTC

The most frequently reported adverse reactions (occurring in ≥ 30 % of patients) are hypertension (68.6 %), diarrhoea (62.8 %), decreased appetite (51.5 %), decreased weight (49.1 %), fatigue (45.8 %), nausea (44.5 %), proteinuria 36.9 %), stomatitis (35.8 %), vomiting (34.5 %), dysphonia (34.1 %), headache (34.1 %), and palmar-plantar erythrodysaesthesia syndrome (PPE) (32.7 %). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see sections 4.4 and 4.8). The majority of Grade 3 to 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 important serious adverse reactions were renal failure and impairment (2.4 %), arterial thromboembolisms (3.9 %), cardiac failure (0.7 %), intracranial tumour haemorrhage (0.7 %), PRES / RPLS (0.2 %), hepatic failure (0.2 %), and arterial thromboembolisms (cerebrovascular accident (1.1 %), transient ischaemic attack (0.7 %), and myocardial infarction (0.9 %).

In 452 patients with RAI-refractory DTC, dose reduction and discontinuation were the actions taken for an adverse reaction in 63.1 % and 19.5 % of patients, respectively. Adverse reactions that most commonly led to dose reductions (in ≥ 5 % of patients) were hypertension, proteinuria, diarrhoea, fatigue, PPE, decreased weight, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism.

HCC

The most frequently reported adverse reactions (occurring in ≥ 30 % of patients) are hypertension (44.0 %), diarrhoea (38.1 %), decreased appetite (34.9 %), fatigue (30.6 %), and decreased weight (30.4 %).

The most important serious adverse reactions were hepatic failure (2.8 %), hepatic encephalopathy (4.6 %), oesophageal varices haemorrhage (1.4 %), cerebral haemorrhage (0.6 %), arterial thromboembolic events (2.0 %) including myocardial infarction (0.8 %), cerebral infarction (0.4 %) and cerebrovascular accident (0.4 %) and renal failure/impairment events (1.4 %). There was a higher incidence of decreased neutrophil count in patients with HCC (8.7 % on lenvatinib than in other non-HCC tumour types (1.4 %)), which was not associated with infection, sepsis or bacterial peritonitis.

In 496 patients with HCC, dose modification (interruption or reduction) and discontinuation were the actions taken for an adverse reaction in 62.3 % and 20.2 % of patients, respectively. Adverse reactions that most commonly led to dose modifications (in ≥ 5 % of patients) were decreased appetite, diarrhoea, proteinuria, hypertension, fatigue, PPE and decreased platelet count. Adverse reactions that most commonly led to discontinuation of lenvatinib were hepatic encephalopathy, fatigue, increased blood bilirubin, proteinuria and hepatic failure.

EC

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 %).

RCC

The safety profile of lenvatinib is based on pooled data from 497 RCC patients treated with lenvatinib in combination with pembrolizumab, including Study 307 (CLEAR); pooled data from 623 RCC patients treated with lenvatinib in combination with everolimus: 458 DTC patients and 496 HCC patients treated with lenvatinib as monotherapy.

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

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

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

Dose interruptions of lenvatinib, everolimus, or both due to an adverse reaction occurred in 82.2 % of patients; in patients where data on individual drug modifications were collected, lenvatinib was interrupted in 74.3 %, and both drugs in 71.9 % of patients. The most common adverse reactions (≥ 5 %) resulting in dose reduction or interruption of lenvatinib were diarrhoea

(30.4 %), fatigue (15.3 %), proteinuria (14.7 %), appetite decreased (13.4 %), stomatitis (13.2 %), nausea (10.9 %), vomiting (10.2 %), hypertension (9.2 %), asthenia (7.9 %), platelet count decreased (5.7 %), and weight decreased (5.1 %).

Tabulated list of adverse reactions

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

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

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.

DTC, HCC, and EC

Adverse reactions observed in clinical trials in DTC, HCC, and EC, and reported from post-marketing use of lenvatinib are listed in Table 7. The adverse reaction frequency category represents the most conservative estimate of frequency from the individual populations.

Table 7 Adverse reactions reported in DTC, HCC and EC patients treated with lenvatinib[§]

System Organ Class (MedDRA terminology)	Lenvatinib monotherapy	Combination with pembrolizumab
Infections and infestations		
Very common	Urinary tract infection	Urinary tract infection
Uncommon	Perineal abscess	Perineal abscess
Blood and lymphatic disorders		
Very common	Thrombocytopenia[a,‡] Lymphopenia[a,‡] Leukopenia[a,‡] Neutropenia[a,‡]	Thrombocytopenia[a,‡] Lymphopenia[a,‡] Leukopenia[a,‡] Neutropenia[a,‡] Anaemia
Uncommon	Splenic infarction	
Endocrine disorders		
Very common	Hypothyroidism Increased blood thyroid stimulating hormone[*,‡]	Hypothyroidism Increased blood thyroid stimulating hormone[*] Hyperthyroidism
Common		Adrenal insufficiency
Uncommon	Adrenal insufficiency	
Metabolism and nutrition disorders		
Very common	Hypocalcaemia[*,‡] Hypokalaemia[‡] Hypercholesterolaemia[b,‡] Hypomagnesaemia[b,‡] Decreased weight Decreased appetite	Hypocalcaemia[*,‡] Hypokalaemia[‡] Hypercholesterolaemia[b,‡] Hypomagnesaemia[b,‡] Decreased weight Decreased appetite
Common	Dehydration	Dehydration
Rare	Tumour lysis syndrome[†]	Tumour lysis syndrome[†]
Psychiatric disorders		

Very common	Insomnia	
Common		Insomnia
Nervous system disorders		
Very common	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
Cardiac disorders		
Common	Myocardial infarction[c,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Prolonged electrocardiogram QT
Uncommon		Myocardial infarction[c,†] Cardiac failure Decreased ejection fraction
Vascular disorders		
Very common	Haemorrhage[d,*,†] Hypertension[e,*] Hypotension	Haemorrhage[d,*,†] Hypertension[e,*]
Common		Hypotension
Unknown	Aneurysms and artery dissections	
Respiratory, thoracic and mediastinal disorders		
Very common	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism[†]
Uncommon	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[‡]
Common	Anal fistula Flatulence Gastrointestinal perforation	Pancreatitis[i] Flatulence Dyspepsia Colitis Gastrointestinal perforation
Uncommon	Pancreatitis[i] Colitis	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[‡]

Common	Hepatic failure[k,*,†] Hepatic encephalopathy[l,*,†] Abnormal hepatic function Cholecystitis	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[m]	Hepatic failure[k,*,†] Hepatic encephalopathy[l,†] Hepatocellular damage/hepatitis[m]
Skin and subcutaneous tissue disorders		
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia
Uncommon		Hyperkeratosis
Musculoskeletal and connective tissue disorders		
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia Myalgia Pain in extremity
Common		Musculoskeletal pain
Uncommon	Osteonecrosis of the jaw	
Renal and urinary disorders		
Very common	Proteinuria[*] Increased blood creatinine[‡]	Proteinuria[*] Increased blood creatinine[‡]
Common	Renal failure[n,*,†] Renal impairment[*] Increased blood urea	Renal failure[n,*,†]
Uncommon	Nephrotic syndrome	Renal impairment[*] Increased blood urea
General disorders and administration site conditions		
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral
Common	Malaise	Malaise
Uncommon	Impaired healing	Impaired healing
Not known	Non-gastrointestinal fistula [o]	

[§:] Adverse reaction frequencies presented in Table 7 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 4.8 Description of selected adverse reactions for further characterisation.
[†:] Includes cases with a fatal outcome.
[‡:] Frequency based on laboratory data.

The following terms have been combined:
[a:] 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.

[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.

RCC

Adverse reactions observed in clinical trials in RCC and reported from post-marketing use of lenvatinib are listed in Table 8.

Table 8 Adverse reactions reported in RCC patients treated with lenvatinib§

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

	Headache Dysgeusia	Dysgeusia	Headache Dysgeusia
Common	Cerebrovascular accident [†]	Dizziness	
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Cerebrovascular accident [†] Transient ischaemic attack	Cerebrovascular accident Posterior reversible encephalopathy syndrome Transient ischaemic attack
Cardiac disorders			
Common	Myocardial infarction[a,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Myocardial infarction[a,†] Cardiac failure [†] Prolonged electrocardiogram QT	Myocardial infarction[a] Prolonged electrocardiogram QT
Uncommon		Decreased ejection fraction	Cardiac failure[†] Decreased ejection fraction
Vascular disorders			
Very common	Haemorrhage[b,*,†] Hypertension[c,*] Hypotension	Haemorrhage[b,*,†] Hypertension[c,*]	Haemorrhage[b,*,†] Hypertension[c,*]
Common		Hypotension	Hypotension
Not known	Aneurysms and artery dissections	Aneurysms and artery dissections	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders			
Very common	Dysphonia	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism Pneumothorax	Pulmonary embolism
Uncommon	Pneumothorax		Pneumothorax
Gastrointestinal disorders			
Very common	Diarrhoea[*] Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase[‡]	Diarrhoea[*] Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Increased lipase[‡] Increased amylase[‡]	Diarrhoea[*] Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase[‡]
Common	Anal fistula Flatulence Gastrointestinal perforation	Dry mouth Flatulence Gastrointestinal perforation	Pancreatitis[g] Colitis Flatulence Gastrointestinal perforation
Uncommon	Pancreatitis[g] Colitis	Pancreatitis[g] Anal fistula Colitis	Anal fistula
Hepatobiliary disorders			
Very common	Increased blood bilirubin[*,‡] Hypoalbuminaemia[*,‡]	Hypoalbuminaemia[*,‡] Increased alanine aminotransferase[‡]	Increased blood bilirubin[‡] Hypoalbuminaemia[‡]

	Increased alanine aminotransferase[*,‡] Increased aspartate aminotransferase[*,‡] Increased blood alkaline phosphatase[‡] Increased gamma-glutamyltransferase[‡]	Increased aspartate aminotransferase[‡] Increased blood alkaline phosphatase[‡]	Increased alanine aminotransferase[‡] Increased aspartate aminotransferase[‡] Increased blood alkaline phosphatase[‡]
Common	Hepatic failure[h,†] Hepatic encephalopathy[i,†] Cholecystitis Abnormal hepatic function	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase Increased blood bilirubin[*,‡]	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[j]	Hepatic failure[h,†] Hepatic encephalopathy[i]	Hepatic failure[h,†] Hepatic encephalopathy[i] Hepatocellular damage/hepatitis[j]
Skin and subcutaneous tissue disorders			
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia	Hyperkeratosis Alopecia
Uncommon		Hyperkeratosis	
Musculoskeletal and connective tissue disorders			
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain
Common		Myalgia Pain in extremity Musculoskeletal pain	
Uncommon	Osteonecrosis of the jaw	Osteonecrosis of the jaw	
Renal and urinary disorders			
Very common	Proteinuria[*] Increased blood creatinine[‡]	Proteinuria[*] Increased blood creatinine[‡]	Proteinuria[*] Increased blood creatinine[‡]
Common	Renal failure[k,*,†] Renal impairment[*] Increased blood urea	Renal failure[k,*,†] Renal impairment[*] Increased blood urea	Renal failure[k,*] Increased blood urea
Uncommon	Nephrotic syndrome		Nephrotic syndrome Renal impairment[*]
General disorders and administration site conditions			
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral
Common	Malaise	Malaise	Malaise
Uncommon	Impaired healing	Impaired healing Non-gastrointestinal fistula[l]	Impaired healing Non-gastrointestinal fistula[l]
Not known	Non-gastrointestinal		

	fistula[l]		

[§:] Adverse reaction frequencies presented in Table 8 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 4.8 Description of selected adverse reactions for further characterisation.
[†:] Includes cases with a fatal outcome.
[‡:] Frequency based on laboratory data.

The following terms have been combined:
[a:] Myocardial infarction includes myocardial infarction and acute myocardial infarction.
[b:] Includes all haemorrhage terms:
Haemorrhage terms that occurred in 5 or more patients with RCC in lenvatinib plus pembrolizumab were: epistaxis, haematuria, contusion, gingival bleeding, rectal haemorrhage, haemoptysis, ecchymosis, and haematochezia.
[c:] Hypertension includes: hypertension, hypertensive crisis, increased blood pressure diastolic, orthostatic hypertension and increased blood pressure.
[d:] Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
[e:] Oral inflammation includes: aphthous stomatitis, aphthous ulcer, gingival erosion, gingival ulceration, oral mucosal blistering, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
[f:] Oral pain includes: oral pain, glossodynia, gingival pain, oropharyngeal discomfort, oropharyngeal pain and tongue discomfort.
[g:] Pancreatitis includes: pancreatitis and acute pancreatitis.
[h:] Hepatic failure includes: hepatic failure, acute hepatic failure and chronic hepatic failure.
[i:] Hepatic encephalopathy includes: hepatic encephalopathy, coma hepatic, metabolic encephalopathy and encephalopathy.
[j:] Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
[k:] Renal failure includes: acute prerenal failure, renal failure, renal failure acute, acute kidney injury, and renal tubular necrosis.
[l:] Non-gastrointestinal fistula includes cases of fistula occurring outside of the stomach and intestines such as tracheal, tracheo-oesophageal, oesophageal, cutaneous fistula and female genital tract fistula.

Description of selected adverse reactions

Hypertension (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), hypertension (including hypertension, hypertensive crisis, increased diastolic blood pressure, and increased blood pressure) was reported in 72.8 % of lenvatinib-treated patients and 16.0 % of patients in the placebo-treated group. The median time to onset in lenvatinib-treated patients was 16 days. Reactions of Grade 3 or higher (including 1 reaction of Grade 4) occurred in 44.4 % of lenvatinib-treated patients compared with 3.8 % of placebo-treated patients. The majority of cases recovered or resolved following dose interruption or reduction, which occurred in 13.0 % and 13.4 % of patients, respectively. In 1.1 % of patients, hypertension led to permanent treatment discontinuation.

HCC
In the Phase 3 REFLECT trial (see section 5.1), hypertension (including hypertension, increased blood pressure, increased diastolic blood pressure and orthostatic hypertension) was reported in 44.5 % of lenvatinib-treated patients and Grade 3 hypertension occurred in 23.5 %. The median time to onset was 26 days. The majority of cases recovered following dose interruption or reduction, which occurred in 3.6 % and 3.4 % of patients, respectively. One subject (0.2 %) discontinued lenvatinib due to hypertension.

EC
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.

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

Proteinuria (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), proteinuria was reported in 33.7 % of lenvatinib-treated patients and 3.1 % of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7 % of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction, which occurred in 16.9 % and 10.7 % of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8 % of patients.

HCC
In the Phase 3 REFLECT trial (see section 5.1), proteinuria was reported in 26.3 % of lenvatinib-treated patients and Grade 3 reactions occurred in 5.9 %. The median time to onset was 6.1 weeks. The majority of cases recovered following dose interruption or reduction, which occurred in 6.9 % and 2.5 % of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.6 % of patients.

EC
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.

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

Renal failure and impairment (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), 5.0 % of patients developed renal failure and 1.9 % developed renal impairment (3.1 % of patients had a Grade ≥ 3 event of renal failure or impairment). In the placebo group 0.8 % of patients developed renal failure or impairment (0.8 % were Grade ≥ 3).

HCC
In the Phase 3 REFLECT trial (see section 5.1), 7.1 % of lenvatinib-treated patients developed a renal failure/impairment event. Grade 3 or greater reactions occurred in 1.9 % of lenvatinib-treated patients.

EC
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.

RCC
In the pooled RCC population treated with lenvatinib and everolimus, 1.3 % of patients developed renal failure (0.6 % were Grade ≥ 3) and 5.3 % developed acute kidney injury (2.7 % were Grade ≥ 3). Renal events were reported in 17.2 % of patients (4.3 % were Grade ≥ 3). In patients where data on individual drug modifications were collected, 5.5 % of patients with renal events had dose modifications of lenvatinib (2.3 % reduction and 4.0 % interruption) and led to permanent treatment discontinuation in 1.9 % of patients. The median time to onset of renal events in lenvatinib plus everolimus treated patients was 3.5 months.

Cardiac dysfunction (see section 4.4)

DTC
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).

HCC
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.

EC
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.

RCC
In the pooled RCC population treated with lenvatinib and everolimus, cardiac dysfunction events were reported in 3.5 % of patients (1.8 % were Grade ≥ 3). In patients where data on individual drug modifications were collected, 0.9 % of patients with cardiac dysfunction events had dose modifications of lenvatinib (0.4 % reduction and 0.8 % interruption) and led to permanent treatment discontinuation in 0.6 % of patients. The median time to onset of cardiac dysfunction events in lenvatinib plus everolimus treated patients was 3.6 months.

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

DTC
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.

HCC
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.

EC
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.

RCC
In the pooled RCC population treated with lenvatinib and everolimus, there was 1 event of PRES reported (Grade 2), occurring after 1.3 months of treatment for which no dose modifications or discontinuation were required.

Hepatotoxicity (see section 4.4)

DTC
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 reactions in lenvatinib-treated patients was 12.1 weeks. Liver-related reactions of Grade 3 or higher (including 1 Grade 5 case of hepatic failure) occurred in 5.4 % of lenvatinib-treated patients compared with 0.8 % in placebo-treated patients. Liver-related reactions led to dose interruptions and reductions in 4.6 % and 2.7 % of patients, respectively, and to permanent discontinuation in 0.4 %.

Amongst 1 166 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.

HCC

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 hepatotoxicity 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 trials in which 1 327 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 %).

EC
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.

RCC
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 pooled RCC population treated with lenvatinib and everolimus, the most commonly reported liver-related adverse reactions were elevations of liver enzyme levels, including increases in alanine aminotransferase (11.9 %), aspartate aminotransferase (11.4 %) and gamma-glutamyltransferase increased (2.7 %). Grade 3 liver related reactions occurred in 6.1 % of lenvatinib plus everolimus treated patients. In patients where data on individual drug modifications were collected, 6.0 % of patients with hepatotoxicity events had dose modifications of lenvatinib (2.8 % reduction and 4.2 % interruption) and led to permanent treatment discontinuation in 0.9 % of patients. The median time to onset of liver-related reactions in lenvatinib plus everolimus treated patients was 1.8 months.

Arterial thromboembolisms (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), arterial thromboembolic events were reported in 5.4 % of lenvatinib-treated patients and 2.3 % of patients in the placebo group.

HCC
In the Phase 3 REFLECT trial (see section 5.1), arterial thromboembolic events were reported in 2.3 % of patients treated with lenvatinib.

Amongst 1 823 patients treated with lenvatinib monotherapy in clinical trials, there were 10 cases (0.5 %) of arterial thromboembolisms (5 cases of myocardial infarction and 5 cases of cerebrovascular accident) with a fatal outcome.

EC
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.

RCC

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

Haemorrhage (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), haemorrhage was reported in 34.9 % (1.9 % were Grade ≥ 3) of lenvatinib-treated patients versus 18.3 % (3.1 % were Grade ≥ 3) of placebo-treated patients. Reactions 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 reactions (3.4 % vs. 3.8 %), reactions leading to premature discontinuation (1.1 % vs. 1.5 %), or reactions leading to dose interruption (3.4 % vs. 3.8 %) or reduction (0.4 % vs. 0).

HCC
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 trials 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.

EC
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.

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

Hypocalcaemia (see section 4.4)

DTC

In the pivotal Phase 3 SELECT trial (see section 5.1), hypocalcaemia was reported in 12.6 % of lenvatinib-treated patients vs. no cases in the placebo arm. The median time to first onset in lenvatinib treated patients was 11.1 weeks. Reactions of Grade 3 or 4 severity occurred in 5.0 % of lenvatinib-treated vs 0 placebo-treated patients. Most reactions 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.

HCC
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.

EC
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.

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

Gastrointestinal perforation and fistula formation (see section 4.4)

DTC
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.

HCC
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.

EC
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.

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

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

Non-gastrointestinal fistulae (see section 4.4)

Lenvatinib use has been associated with cases of fistulae including reactions resulting in death.

Reports of fistulae that involve areas of the body other than stomach or intestines were observed across various indications. Reactions were reported at various time points during treatment ranging from two weeks to greater than 1 year from initiation of lenvatinib, with median latency of about 3 months.

QT interval prolongation (see section 4.4)

DTC
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.

HCC
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 500 ms was 2.4 %.

EC
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.

RCC
In the pooled RCC population treated with lenvatinib and everolimus, QTcF interval increases greater than 60 ms were reported in 9.8 % of patients in the lenvatinib plus everolimus treated group. The incidence of QTc interval greater than 500 ms was 3.3 % in the lenvatinib plus everolimus-treated group. The median time to onset of QT prolongation events in lenvatinib plus everolimus treated patients was 3.0 months.

Increased blood thyroid stimulating hormone/hypothyroidism (see section 4.4)

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), 88 % of all patients had a baseline TSH level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57 % of lenvatinib-treated patients as compared with 14 % of placebo-treated patients.

HCC
In the Phase 3 REFLECT trial (see section 5.1), 89.6 % of patients had a baseline TSH level of less than the upper limit of normal. Elevation of TSH above the upper limit of normal was observed post baseline in 69.6 % of lenvatinib-treated patients.

EC
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.

RCC
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, 90.0 % 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 pooled RCC population treated with lenvatinib and everolimus, hypothyroidism occurred in 24.1 % of patients. In general, the majority of hypothyroidism events were of Grade 1 or 2. Grade 3 hypothyroidism was reported in 0.3 % of patients in the lenvatinib plus everolimus-treated patients. The median time to onset of hypothyroidism events in lenvatinib plus everolimus treated patients was 2.7 months. At baseline, 83.0 % of patients in the lenvatinib plus everolimus-treated group had TSH levels ≤ upper limit of normal. Elevations of TSH > upper limit of normal were observed post-baseline in 71.3 % of lenvatinib plus everolimus treated patients. In patients where data on individual drug modifications were collected, hypothyroidism events resulted in dose modification of lenvatinib (0.4 % dose reduction or 0.9 % dose interruption) in 1.3 % of patients. No discontinuations were reported.

Diarrhoea (see section 4.4)

DTC

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).

HCC

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).

EC

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.

RCC

In the pooled RCC population treated with lenvatinib and everolimus, diarrhoea was reported in 69.0 % of patients (13.8 % were Grade ≥ 3). In patients where data on individual drug modifications were collected, 30.4 % of patients had dose modifications of lenvatinib (17.7 % interruptions and 19.6 % reductions) and led to permanent treatment discontinuation in 0.6 % of patients.

Paediatric population

In the paediatric Studies 207, 216, 230, and 231 (see section 5.1), the overall safety profile of lenvatinib as a single agent or in combination with either ifosfamide and etoposide or everolimus was consistent with that observed in adults treated with lenvatinib.

In patients with relapsed/refractory osteosarcoma, pneumothorax was reported at a frequency higher than that observed in adults with DTC, HCC, RCC and EC. In Study 207, pneumothorax occurred in 6 patients (10.9 %) treated with single-agent lenvatinib and 7 patients (16.7 %) treated with lenvatinib in combination with ifosfamide and etoposide. Overall, 2 patients discontinued study treatment due to pneumothorax. In Study 230, pneumothorax was reported in a total of 14 patients (11 patients [28.2 %] treated with lenvatinib plus ifosfamide and etoposide, and 3 patient [7.7 %] treated with ifosfamide and etoposide). In Study 216, pneumothorax was reported in 3 patients (4.7 %) with Ewing sarcoma, rhabdomyosarcoma (RMS) and Wilms tumour; all 3 patients had lung metastases at baseline. In Study 231, pneumothorax was reported in 8 patients (6.3 %) with spindle cell sarcoma, undifferentiated sarcoma, RMS, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell carcinoma, and malignant fibromyxoid ossifying tumour; all 8 patients had lung metastases or primary disease in the chest wall or pleural cavity at baseline. For Studies 216 and 230, no patient discontinued study treatment due to pneumothorax; in Study 231, one patient discontinued study treatment due to pneumothorax. Pneumothorax occurrence appeared to be mainly associated with pulmonary metastases and underlying disease.

In the single-agent dose-finding cohort of Study 207, the most frequently (≥ 40 %) reported adverse drug reactions were decreased appetite, diarrhoea, hypothyroidism, vomiting, abdominal pain, pyrexia, hypertension, and weight decreased; and in the single-agent expansion cohort of patients with relapsed or refractory osteosarcoma, the most frequently (≥ 40 %) reported adverse drug reactions were decreased appetite, headache, vomiting, hypothyroidism, and proteinuria.

In the combination dose-finding cohort of Study 207, the most frequently (≥ 50 %) reported adverse drug reactions were vomiting, anaemia, nausea, diarrhoea, hypothyroidism, abdominal pain, arthralgia, epistaxis, neutropenia, constipation, headache, and pain in extremity; and in the combination expansion cohort, the most frequently (≥ 50 %) reported adverse drug reactions were anaemia, nausea, white blood cell count decreased, diarrhoea, vomiting, and platelet count decreased.

In Phase 1 (combination dose-finding cohort) of Study 216, the most frequently (≥ 40 %) reported adverse drug reactions were hypertension, hypothyroidism, hypertriglyceridemia, abdominal pain, and diarrhoea; and in Phase 2 (combination expansion cohort), the most frequently reported (≥ 35 %) adverse drug reactions were hypertriglyceridemia, proteinuria, diarrhoea, lymphocyte count decreased, white blood cell count decreased, blood cholesterol increased, fatigue, and platelet count decreased.

In the OLIE study (Study 230), the most frequently (≥ 35 %) reported adverse drug reactions were hypothyroidism, anaemia, nausea, platelet count decreased, proteinuria, vomiting, back pain, febrile neutropenia, hypertension, constipation, diarrhoea, neutrophil count decreased, and pyrexia.

In Study 231, the most frequently reported (≥ 15 %) adverse drug reactions were hypothyroidism, hypertension, proteinuria, decreased appetite, diarrhoea, and platelet count decreased.

Other special populations

Elderly

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

HCC
Patients of age ≥75 years were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness, malaise, peripheral oedema, pruritus and hepatic encephalopathy.
Hepatic encephalopathy occurred at more than twice the incidence in patients aged ≥ 75 years (17.2 %) than in those < 75 years (7.1 %). Hepatic encephalopathy tended to be associated with adverse disease characteristics at baseline or with the use of concomitant medicinal products. Arterial thromboembolic events also occurred at an increased incidence in this age group.

EC
Patients of age ≥ 75 years were more likely to experience urinary tract infections and Grade ≥ 3 hypertension (≥ 10 % increase compared to patients of age < 65 years).

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

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

Gender

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.

HCC
Females had a higher incidence of hypertension, fatigue, ECG QT prolongation and alopecia. Men had a higher incidence (26.5 %) of dysphonia than women (12.3 %), decreased weight and decreased platelet count. Hepatic failure events were observed in male patients only.

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

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

Ethnic origin

DTC
Asian patients had a higher (≥ 10 % difference) incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, stomatitis, thrombocytopenia, 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. A larger proportion of Asian patients had a lenvatinib dose reduction compared to Caucasian patients. the median time to first dose reduction and the average daily dose taken were lower in Asian than in Caucasian patients.

HCC
Asian patients had a higher incidence than Caucasian patients of proteinuria, decreased neutrophil count, decreased platelet count, decreased white blood count and PPE, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy, acute kidney injury, anxiety, asthenia, nausea, thrombocytopenia and vomiting.

EC
Asian patients had a higher (≥ 10 % difference) incidence than Caucasian patients of anaemia, malaise, neutrophil count decrease, stomatitis, platelet count decreased, proteinuria and PPE while Caucasian patients had a higher incidence of mucosal inflammation, abdominal pain, diarrhoea, urinary tract infection, weight decreased, hypomagnesaemia, dizziness, asthenia and fatigue.

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

Baseline hypertension

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

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

Baseline diabetes

RCC
In the pooled RCC population treated with lenvatinib and everolimus, patients with baseline diabetes had a higher incidence (≥ 10 % difference) of proteinuria than those without baseline diabetes.

Hepatic impairment

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.

HCC
Patients with a baseline Child-Pugh (CP) score of 6 (about 20 % patients in the REFLECT study) had a higher incidence of decreased appetite, fatigue, proteinuria, hepatic encephalopathy and hepatic failure compared to patients with a baseline CP score of 5. Hepatotoxicity events and haemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients.

RCC
There are limited data on patients with hepatic impairment in RCC.

Renal impairment

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

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

RCC
In RCC patients treated with lenvatinib and everolimus, patients with baseline renal impairment had higher incidence of thrombocytopenia or platelet count decreased compared with patients with normal renal function.

Patients with body weight < 60 kg

DTC
Patients with low body weight (< 60 kg) had a higher incidence of PPE, proteinuria, of Grade 3 or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite.

RCC
In RCC patients treated with lenvatinib and everolimus, those with low body weight (< 60 kg) had a higher incidence (≥ 10 % difference) of platelet count decreased and hypertension.

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

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.

In addition, lenvatinib had selective, direct antiproliferative activity in hepatocellular cell lines dependent on activated FGFR signalling, which is attributed to the inhibition of FGFR signalling by lenvatinib.

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

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.

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

The mechanism of action for the worsening of hypercholesterolaemia with the combination of lenvatinib and everolimus has not been studied directly and is not fully elucidated.

Although not studied directly, the MOA for the worsening of diarrhoea with the combination of lenvatinib and everolimus is postulated to be mediated by the impairment of intestinal function related to the MOAs for the individual agents – VEGF/VEGFR and c-KIT inhibition by lenvatinib coupled with mTOR/NHE3 inhibition by everolimus.

Clinical efficacy

Radioiodine-refractory differentiated thyroid cancer

The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioiodine-refractory differentiated thyroid cancer with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month window) prior to enrolment. Radioiodine-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 therapies. Following independent review confirmation of disease progression, 109 (83.2 %) patients randomised to placebo had 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 responsive 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.

The 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 Overall Survival (OS) had not been reached for either the lenvatinib group or the placebo crossover group.

Table 9 Efficacy results in DTC patients

	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,c]	0.73 (0.50, 1.07)	
P value[b,c]	0.1032	

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

[a] Independent radiologic review.

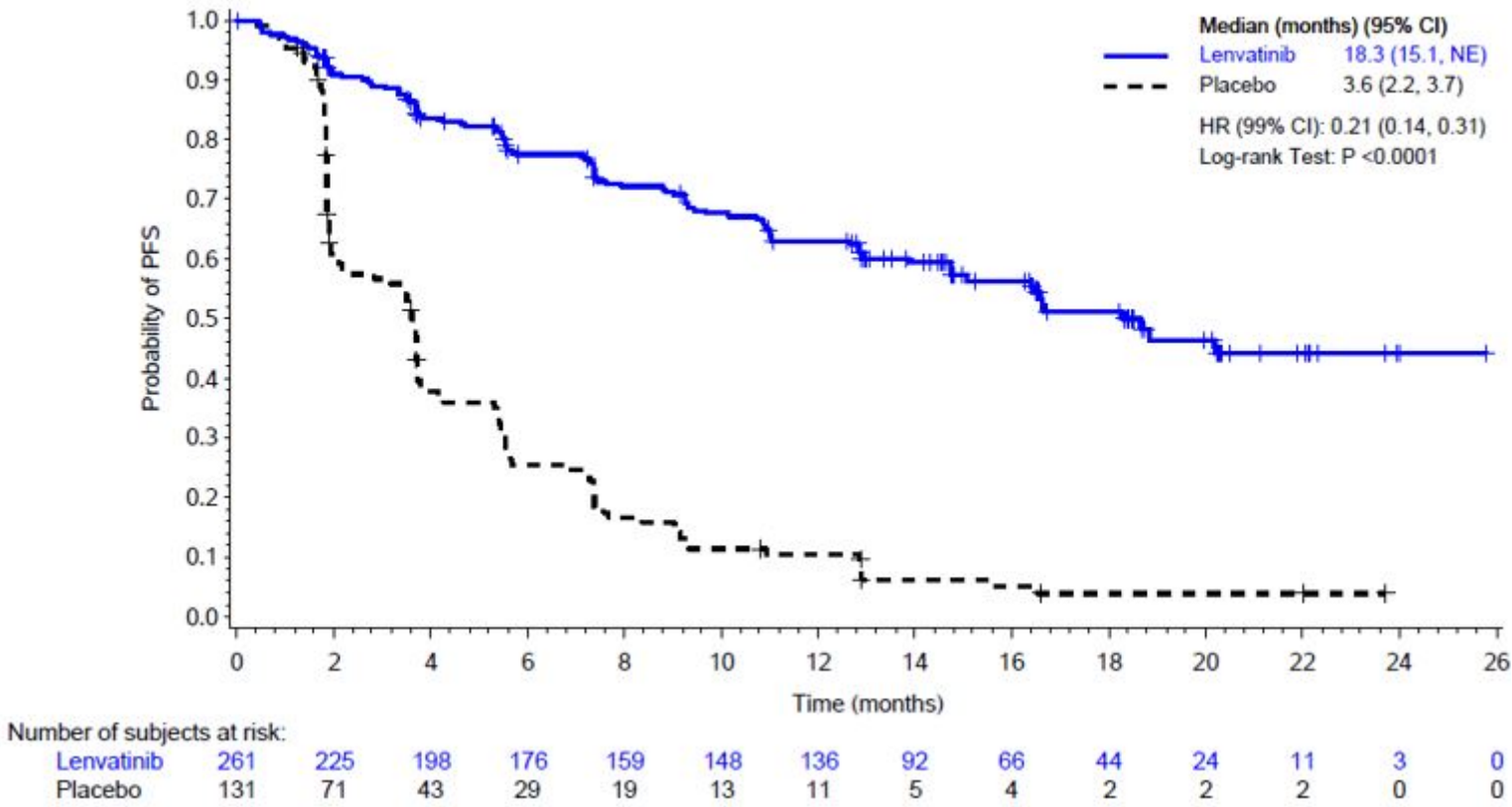
[b] Stratified by region (Europe vs. North America vs. Other), age group (≤ 65 years vs > 65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

[c] Estimated with Cox proportional hazard model.

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

[e] Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Curve of Progression-Free Survival - DTC



CI, confidence interval; NE, not estimable.

Hepatocellular carcinoma

The clinical efficacy and safety of lenvatinib have been evaluated in an international, multicentre, open-label, randomised phase 3 study (REFLECT) in patients with unresectable hepatocellular carcinoma (HCC).

In total, 954 patients were randomised 1:1 to receive either lenvatinib (12 mg [baseline body weight ≥ 60 kg] or 8 mg [baseline body weight < 60 kg]) given orally once daily or sorafenib 400 mg given orally twice daily.

Patients were eligible to participate if they had a liver function status of Child-Pugh class A and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1. Patients were excluded who had prior systemic anticancer therapy for advanced/unresectable HCC or any prior anti-VEGF therapy. Target lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression. Patients with ≥ 50 % liver occupation, clear invasion into the bile duct or a main branch of the portal vein (Vp4) on imaging were also excluded.

- Demographic and baseline disease characteristics were similar between the lenvatinib and the sorafenib groups and are shown below for all 954 randomised patients:
- Median age: 62 years
- Male: 84 %
- White: 29 %, Asian: 69 %, Black or African American: 1.4 %
- Body weight: < 60 kg -31 %, 60-80 kg – 50 %, >80 kg - 19 %
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0: 63 %, ECOG PS of 1: 37 %
- Child-Pugh A: 99 %, Child-Pugh B: 1 %
- Aetiology: Hepatitis B (50 %), Hepatitis C (23 %), alcohol (6 %)
- Absence of macroscopic portal vein invasion (MPVI): 79 %
- Absence of MPVI, extra-hepatic tumour spread (EHS) or both: 30 %
- Underlying cirrhosis (by independent imaging review): 75 %
- Barcelona Clinic Liver Cancer (BCLC) stage B: 20 %; BCLC stage C: 80 %
- Prior treatments: hepatectomy (28 %), radiotherapy (11 %), loco-regional therapies including transarterial (chemo)embolisation (52 %), radiofrequency ablation (21 %) and percutaneous ethanol injection (4 %)

The primary efficacy endpoint was Overall Survival (OS). Lenvatinib was non-inferior for OS to sorafenib with HR = 0.92 [95 % CI of (0.79, 1.06)] and a median OS of 13.6 months vs 12.3 months (see Table 10 and Figure 2). The results for surrogate endpoints (PFS and ORR) are presented in Table 10 below.

Table 10 Efficacy Results from the REFLECT study in HCC

Efficacy parameter	Hazard ratio[a,b] (95 % CI)	P value[d]	Median (95 % CI)[e]	
			Lenvatinib (N= 478)	Sorafenib (N=476)
OS	0.92 (0.79,1.06)	NA	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
PFS[g] (mRECIST)	0.64 (0.55, 0.75)	<0.00001	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
			Percentages (95 % CI)	
ORR[c,f,g] (mRECIST)	NA	<0.00001	41 % (36 %, 45 %)	12 % (9 %, 15 %)

Data cut-off date: 13 Nov 2016.

[a] Hazard ratio (HR) is for lenvatinib vs. sorafenib, based on a Cox model including treatment group as a factor.

[b] Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (< 60 kg, ≥ 60 kg).

[c] Results are based on confirmed and unconfirmed responses.

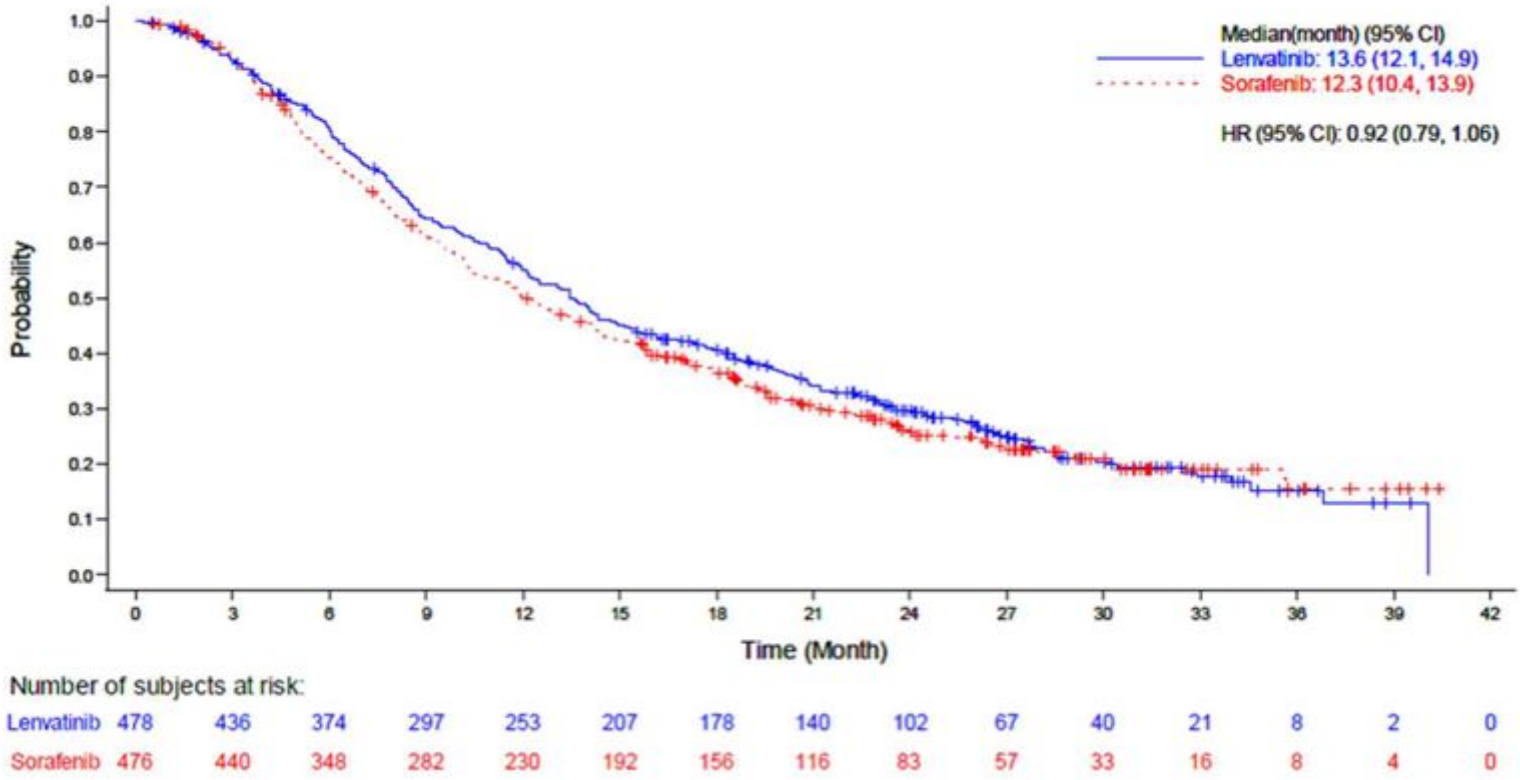
[d] P- value is for the superiority test of lenvatinib versus sorafenib.

[e] Quartiles are estimated by the Kaplan-Meier method, and the 95 % CIs are estimated with a generalised Brookmeyer and Crowley method

[f] Response rate (complete or partial response)

[g] Per independent radiology review retrospective analysis. The median duration of objective response was 7.3 (95 % CI 5.6, 7.4) months in the lenvatinib arm and 6.2 (95 % CI 3.7, 11.2) months in the sorafenib arm.

Figure 2 Kaplan-Meier Curve of Overall Survival - HCC



1. Data cut-off date = 13 Nov 2016.
2. Noninferiority margin for hazard ratio (HR: lenvatinib vs sorafenib = 1.08).
3. Median was estimated with the Kaplan-Meier method and the 95 % confidence interval was constructed with a generalised Brookmeyer and Crowley method.

4. HR was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
5. + = censored observations.

In subgroup analyses by stratification factors (presence or absence of MPVI or EHS or both, ECOG PS 0 or 1, BW < 60 kg or ≥ 60 kg and region) the HR consistently favoured lenvatinib over sorafenib, with the exception of Western region [HR of 1.08 (95 % CI 0.82, 1.42], patients without EHS [HR of 1.01 (95 % CI 0.78, 1.30)] and patients without MPVI, EHS or both [HR of 1.05 (0.79, 1.40)]. The results of subgroup analyses should be interpreted with caution.

The median duration of treatment was 5.7 months (Q1: 2.9, Q3: 11.1) in the lenvatinib arm and 3.7 months (Q1: 1.8, Q3: 7.4) in the sorafenib arm.

In both treatment arms in the REFLECT study, median OS was approximately 9 months longer in subjects who received post-treatment anticancer therapy than in those who did not. In the lenvatinib arm, median OS was 19.5 months (95 % CI: 15.7, 23.0) for subjects who received post-treatment anticancer therapy (43 %) and 10.5 months (95 % CI: 8.6, 12.2) for those who did not. In the sorafenib arm, median OS was 17.0 months (95 % CI: 14.2, 18.8) for subjects who received posttreatment anticancer therapy (51 %) and 7.9 months (95 % CI: 6.6, 9.7) for those who did not. Median OS was longer by approximately 2.5 months in the lenvatinib compared with the sorafenib arm in both subsets of subjects (with or without post-treatment anticancer therapy).

Endometrial carcinoma

The efficacy of lenvatinib in combination with pembrolizumab was investigated in Study 309, a randomised, multicentre, 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. Participants may have received up to 2 platinum-containing therapies in total, as long as one was given in the neoadjuvant or adjuvant treatment setting. The study excluded patients with endometrial sarcoma (including carcinosarcoma), or patients who had active autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by mismatch repair (MMR) status (dMMR or pMMR [not dMMR]) using a validated IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomised (1:1) to one of the following treatment arms:

- 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/m^2 every 3 weeks, or paclitaxel 80 mg/m^2 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. A total of 121/411 (29 %) of the lenvatinib and pembrolizumab-treated patients received continued study therapy beyond RECIST-defined disease progression. The median duration of post-progression therapy was 2.8 months. Assessment of tumour status was performed every 8 weeks.

A total of 827 patients were enrolled and randomised 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 tumour status, and 16 % with dMMR tumour 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 median duration of study treatment was 7.6 months (range 1 day to 26.8 months). The median duration of exposure to lenvatinib was 6.9 months (range 1 day to 26.8 months).

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. At the pre-specified interim analysis, with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), the study demonstrated a statistically significant improvement in OS and PFS in the all-comer population.

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

The pre-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. The efficacy results in the all-comer population are summarised in Table 11. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 3 and 4, respectively.

Table 11 Efficacy Results in Endometrial Carcinoma in Study 309		
Endpoint	**Lenvatinib with pembrolizumab N=411**	**Doxorubicinor Paclitaxel N=416**
OS		
Number (%) of patients with event	276 (67 %)	329 (79 %)
Median in months (95 % CI)	18.7 (15.6, 21.3)	11.9 (10.7, 13.3)
Hazard ratio[a] (95 % CI)	0.65 (0.55, 0.77)	
P value[b]	<0.0001	
PFS[d]		
Number (%) of patients with event	281 (68 %)	286 (69 %)
Median in months (95 % CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio[a] (95 % CI)	0.56 (0.47, 0.66)	
P value[c]	<0.0001	
ORR[d]		
ORR[e] (95 % CI)	32 % (27, 37)	15 % (11,18)
Complete response	7 %	3 %
Partial response	25 %	12 %
P value[f]	<0.0001	
Duration of Response[d]		
Median in months[g] (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

[a] Based on the stratified Cox regression model

[b] One-sided nominal p-Value based on stratified log-rank test (final analysis). At the pre- specified interim analysis of OS with a median follow-up time of 11.4 months (range:0.3 to 26.9 months), statistically significant superiority was achieved for OS comparing the combination of lenvatinib and pembrolizumab with doxorubicin or paclitaxel (HR: 0.62 [95 %CI: 0.51, 0.75] p-Value <0.0001).

[c] One-sided p-Value based on stratified log-rank test

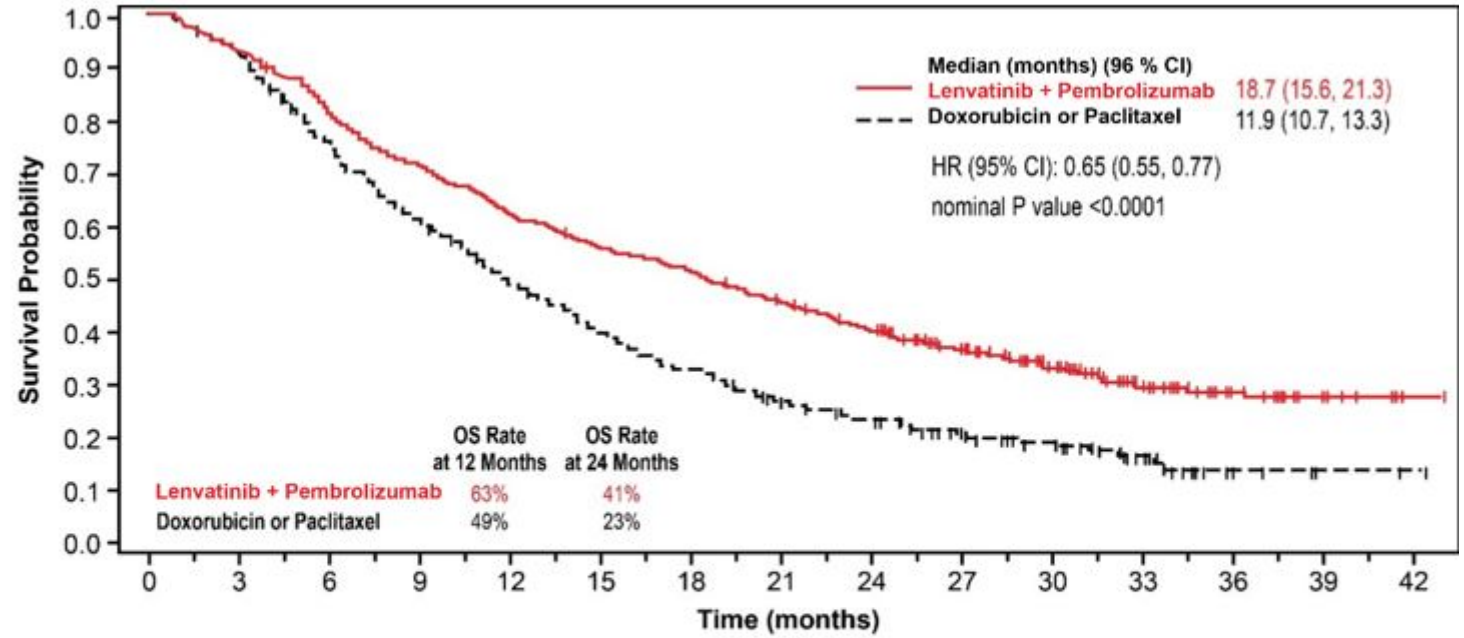
[d] At pre-specified interim analysis

[e] Response: Best objective response as confirmed complete response or partial response

[f] Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation.

[g] Based on Kaplan-Meier estimation

Figure 3 Kaplan-Meier Curves for Overall Survival in Study 309*

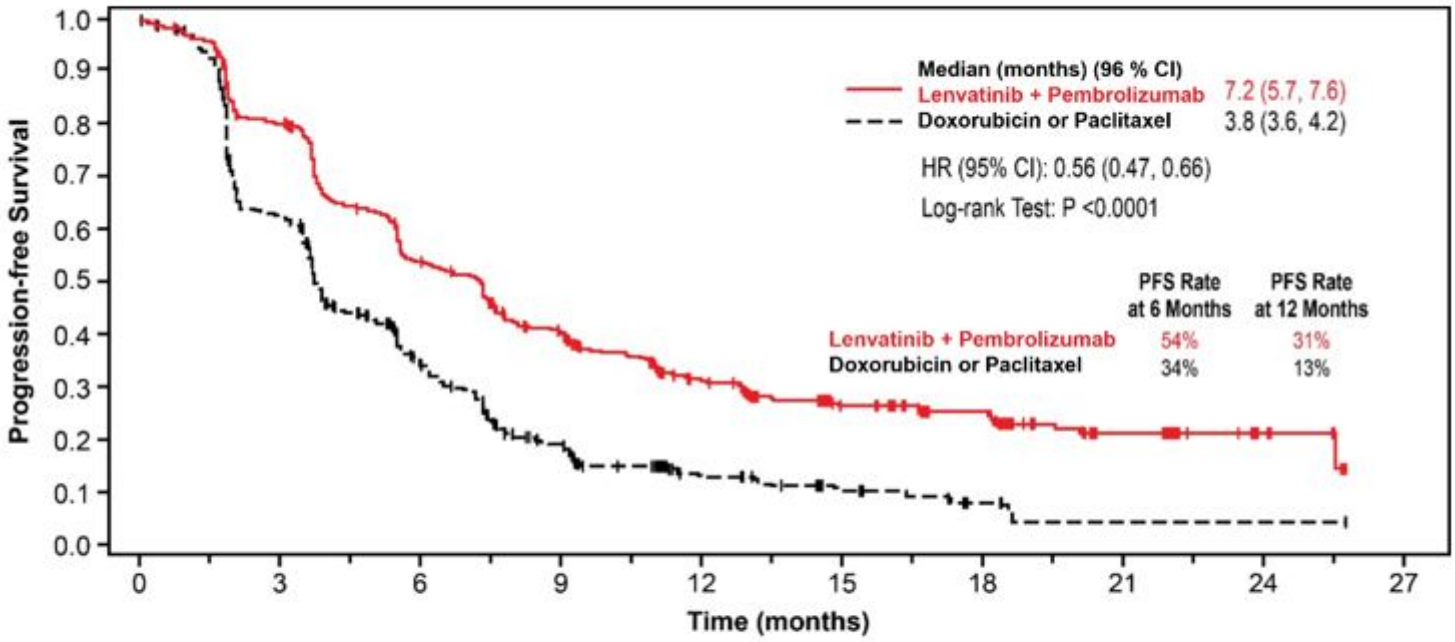


Number of subjects at risk:

Lenvatinib + Pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Doxorubicin or Paclitaxel	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

* Based on the protocol-specified final analysis

Figure 4 Kaplan-Meier Curves for Progression-Free Survival in Study 309



Number of subjects at risk:

Lenvatinib + Pembrolizumab	411	316	202	144	86	56	43	17	6	0
Doxorubicin or Paclitaxel	416	214	95	42	18	10	4	1	1	0

First-line treatment of patients with RCC (in combination with pembrolizumab)

The efficacy oflenvatinib in combination with pembrolizumab was investigated in Study 307(CLEAR), a multicentre, open-label, randomised trial that enrolled 1069patients with advanced RCC with clear cell component including otherhistological features such as sarcomatoid and papillary in the first-linesetting. Patients were enrolled regardless of PD-L1 tumour expression status.Patients with active autoimmune disease or a medical condition that requiredimmunosuppression were ineligible. Randomisation was stratified by geographicregion. (North America and Western Europe versus "Rest of theWorld") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups(favourable, 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 Tumours 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 was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 8 weeks.

The study population (355 patients in the lenvatinib with pembrolizumab arm and 357 in the sunitinib arm) characteristics were: median age of 62 years (range: 29 to 88 years); 41 % age 65 or older, 74 % male; 75 % White, 21 % Asian, 1 % Black, and 2 % other races; 17 % and 83 % of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC (International Metastatic RCC Database Consortium) risk categories was 33 % favourable, 56 % intermediate and 10 % poor, and MSKCC prognostic groups was 27 % favourable, 64 % intermediate and 9 % poor. Metastatic disease was present in 99 % of the patients and locally advanced disease was present in 1 %. Common sites of metastases in patients were lung (69 %), lymph node (46 %), and bone (26 %).

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 at the prespecified interim analysis (final analysis for PFS). The median PFS for lenvatinib in combination with pembrolizumab was 23.9 months (95 % CI: 20.8, 27.7) compared with 9.2 months (95 % CI: 6.0, 11.0) for sunitinib, with HR 0.39 (95 % CI: 0.32, 0.49; P value < 0.0001). For OS, HR was 0.66 (95 % CI: 0.49, 0.88; P value 0.0049) with the median OS follow-up time of 26.5 months and the median duration of treatment for lenvatinib plus pembrolizumab of 17.0 months. The ORR for lenvatinib in combination with pembrolizumab was 71 % (95 % CI: 66, 76) vs 36 % (95 % CI: 31, 41) P value < 0.0001 for sunitinib. Efficacy results for PFS, OS and ORR at the protocol-specified final analysis (median follow-up time of 49.4 months) are summarised in Table 12, Figure 5 and Figure 6. PFS results were consistent across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status. Efficacy results by MSKCC prognostic group are summarised in Table 13.

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

Table 12 Efficacy Results in Renal Cell Carcinoma Per IRC in CLEAR		
	Lenvatinib 20 mg with Pembrolizumab 200 mg N=355	**Sunitinib 50 mg N=357**
Progression-Free Survival (PFS)*		
Number of events, n (%)	207 (58 %)	214 (60 %)
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]	0.47 (0.38, 0.57)	
*P*value[c]	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	149 (42 %)	159 (45 %)
Median OS in months (95 % CI)[a]	53.7 (48.7, NE)	54.3 (40.9, NE)
Hazard Ratio (95 % CI)[b,c]	0.79 (0.63, 0.99)	
*P*value[c]	0.0424	
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	253 (71.3 %)	131 (36.7 %)
(95 % CI)	(66.6, 76.0)	(31.7, 41.7)
Number of complete responses (CR), n (%)	65 (18.3 %)	17 (4.8 %)

Number of partial responses (PR), n (%)	188 (53.0 %)	114 (32 %)
*P*value[d]	<0.0001	
Duration of Response[a]		
Median in months (range)	26.7 (1.64+, 55.92+)	14.7 (1.64+, 54.08+)

Tumour assessments were based on RECIST 1.1; only confirmed responses are included for ORR. Data cutoff date (DCO) = 31 July 2022

CI = confidence interval; NE= Not estimable

[*] The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.

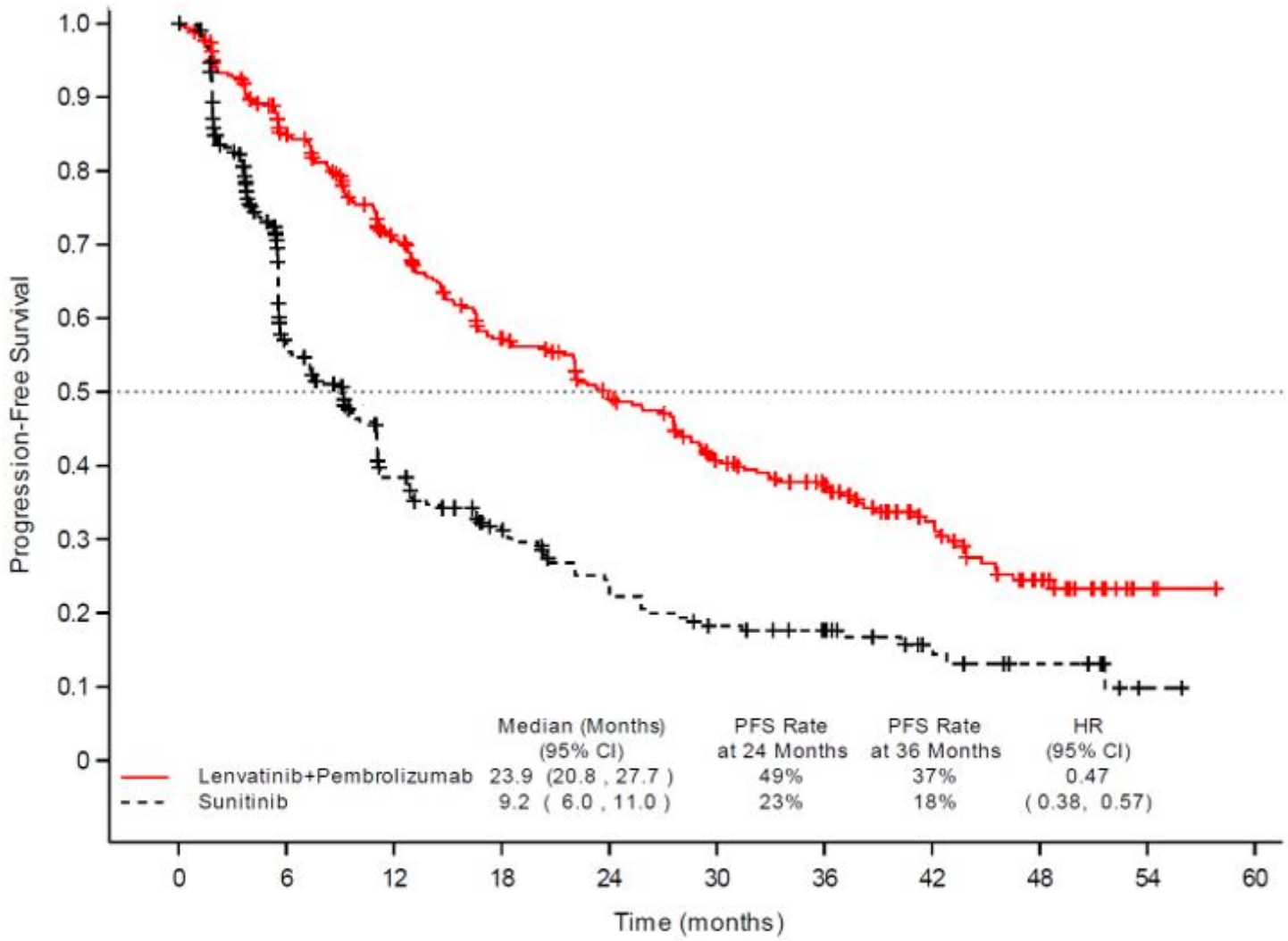
[a] Quartiles are estimated by Kaplan-Meier method.

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

[c] Stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) in IxRS. Nominal two-sided *P* value based on stratified log-rank test.

[d] Nominal two-sided *P*value based on the stratified Cochran-Mantel-Haenszel (CMH) test. 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).

Figure 5 Kaplan-Meier Curves for Progression-Free Survival in CLEAR*

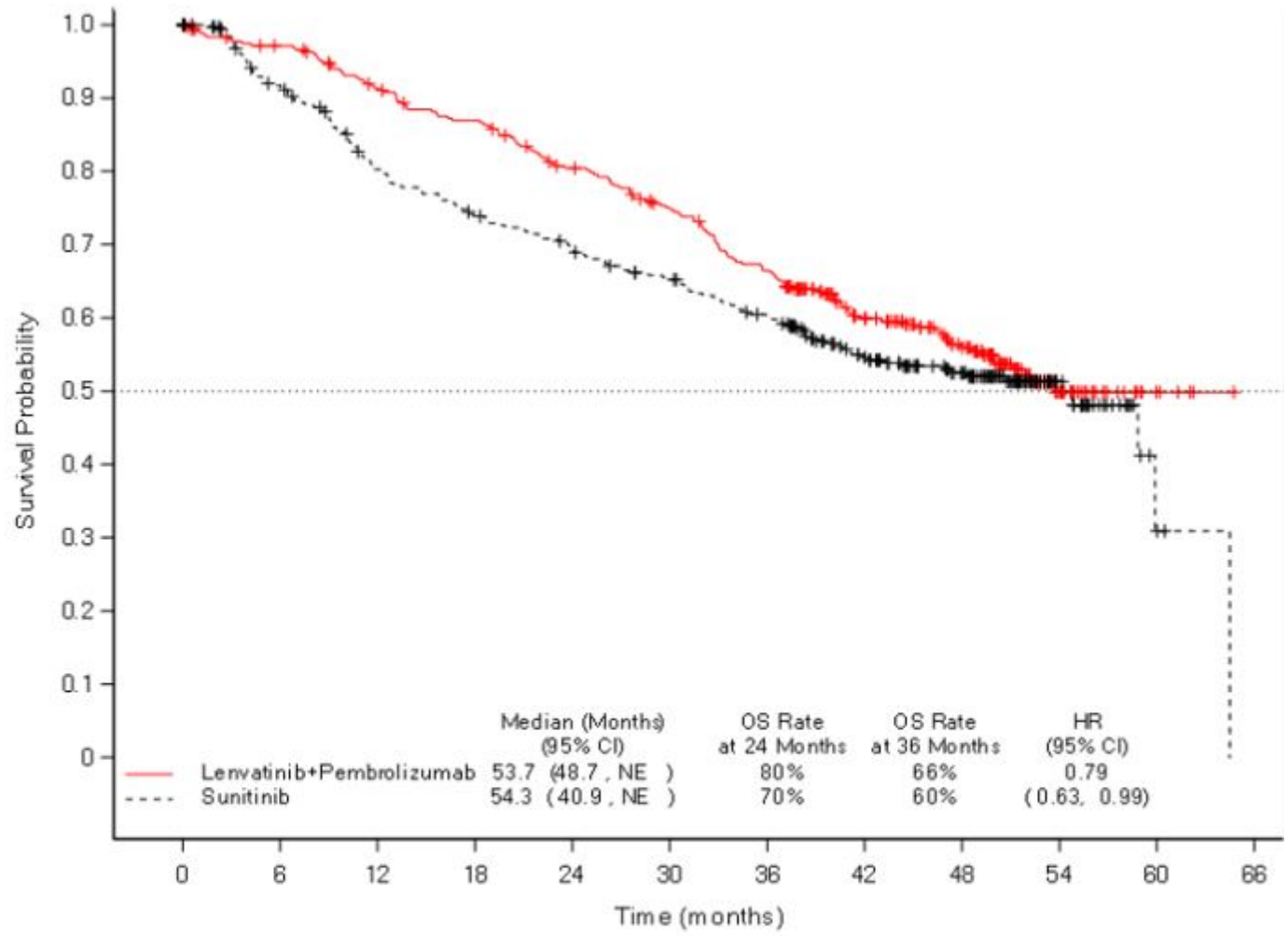


Number of subjects at risk:

Lenvatinib+ Pembrolizumab	355	276	213	161	128	99	81	49	25	4	0
Sunitinib	357	145	85	59	41	30	23	12	7	1	0

DCO: 31 July 2022
*Based on updated PFS analysis conducted at the time of the protocol-specified final OS analysis.

Figure 6 Kaplan-Meier Curves for Overall Survival in CLEAR*



NE = Not estimable.
DCO: 31 July 2022
*Based on the protocol-specified final OS analysis

The CLEAR study was not powered to evaluate efficacy of individual subgroups. Table 13 summarises the efficacy measures by MSKCC prognostic group based on the final OS analysis at a median follow-up of 49.4 months.

Table 13 Efficacy Results in CLEAR by MSKCC Prognostic Group

	Lenvatinib + Pembrolizumab (N=355)		Sunitinib (N=357)		Lenvatinib + Pembrolizumab vs. Sunitinib
	Number of Patients	Number of Events	Number of Patients	Number of Events	
Progression-Free Survival (PFS) by IRC[a]					**PFSHR(95 %CI)**
Favourable	96	56	97	65	0.46 (0.32, 0.67)
Intermediate	227	129	228	130	0.51 (0.40, 0.65)
Poor	32	22	32	19	0.18 (0.08, 0.42)
Overall Survival (OS)[a]					**OSHR(95 %CI)**
Favourable	96	27	97	31	0.89 (0.53, 1.50)
Intermediate	227	104	228	108	0.81 (0.62, 1.06)
Poor	32	18	32	20	0.59 (0.31, 1.12)

[a] Median follow up 49.4 months (DCO - 31 July 2022)

Open-label, single arm Phase 2 study

Additional data are available from the open-label, single-arm, Phase 2 study KEYNOTE-B61 of lenvatinib (20 mg OD) in combination with pembrolizumab (400 mg every 6 weeks) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158) including 59 % papillary, 18 % chromophobe, 4 % translocation, 1 % medullary, 13 % unclassified, and 6 % other. The ORR was 50.6 % (95 % CI (42.6, 58.7)), and the median duration of response was 19.5 months (95 % CI 15.3, NR).

Second-line treatment of patients with RCC (in combination with everolimus)

Study 205, a multicentre, randomised, open-label, trial was conducted to determine the safety and efficacy of lenvatinib administered alone or in combination with everolimus in patients with unresectable advanced or metastatic RCC. The study consisted of a Phase 1b dose finding and a Phase 2 portion. The Phase 1b portion included 11 patients who received the combination of 18 mg of lenvatinib plus 5 mg of everolimus. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic RCC following 1 prior VEGF-targeted treatment. A total of 62 patients received the combination of lenvatinib and everolimus at the recommended dose. Patients were required, among others, to have histological confirmation of predominant clear cell RCC, radiographic evidence of disease progression according to RECIST 1.1, one prior VEGF-targeted therapy and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.

Patients were randomly allocated to one of 3 arms: 18 mg of lenvatinib plus 5 mg of everolimus, 24 mg of lenvatinib or 10 mg of everolimus using a 1:1:1 ratio. Patients were stratified by haemoglobin level (≤ 13 g/dL vs. > 13 g/dL for males and ≤ 11.5 g/dL vs > 11.5 g/dL for females) and corrected serum calcium (≥ 10 mg/dL vs. < 10 mg/dL). The median of average daily dose in the combination arm per patient was 13.5 mg of lenvatinib (75.0 % of the intended dose of 18 mg) and 4.7 mg of everolimus (93.6 % of the intended dose of 5 mg). The final dose level in the combination arm was 18 mg for 29 % of patients, 14 mg for 31 % of patients, 10 mg for 23 % of patients, 8 mg for 16 % of patients and 4 mg for 2 % of patients.

Of the 153 patients randomly allocated, 73 % were male, the median age was 61 years, 37 % were 65 years or older, 7 % were 75 years or older, and 97 % were Caucasian. 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 (55 %) or 1 (45 %) with similar distribution across the 3 treatment arms.
Memorial Sloan Kettering Cancer Centre (MSKCC) poor risk was observed in 39 % of patients in the lenvatinib plus everolimus arm, 44 % in the lenvatinib arm and 38 % in the everolimus arm.
International mRCC Database Consortium (IMDC) poor risk was observed in 20 % of patients in the lenvatinib plus everolimus arm, 23 % in the lenvatinib arm, and 24 % in the everolimus arm. The median time from diagnosis to first dose was 32 months in the lenvatinib plus everolimus-treatment arm, 33 months in the lenvatinib arm and 26 months in the everolimus arm. All patients had been treated with 1 prior VEGF-inhibitor; 65 % with sunitinib, 23 % with pazopanib, 4 % with tivozanib, 3 % with bevacizumab, and 2 % each with sorafenib or axitinib.

The primary efficacy outcome measure, based on investigator assessed tumour response, was PFS of the lenvatinib plus everolimus arm vs the everolimus arm and of the lenvatinib arm vs the everolimus arm. Other efficacy outcome measures included OS and investigator-assessed ORR. Tumour assessments were evaluated according to RECIST 1.1.

The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm (see Table 14 and Figure 7). Based on the results of a post-hoc exploratory analysis in a limited number of patients per subgroup, the positive effect on PFS was seen regardless of which prior VEGF-targeted therapy was used: sunitinib (Hazard ratio [HR] = 0.356 [95 % CI: 0.188, 0.674] or other therapies (HR = 0.350 [95 % CI: 0.148, 0.828]).
The lenvatinib arm also showed an improvement in PFS compared with the everolimus arm. Overall survival was longer in the lenvatinib plus everolimus arm (see Table 14 and Figure 8). The study was not powered for the OS analysis.

The treatment effect of the combination on PFS and ORR was also supported by a post-hoc retrospective independent blinded review of scans. The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm. Results for ORR were consistent with that of the investigators' assessments, 35.3 % in the lenvatinib plus everolimus arm, with one complete response and 17 partial responses; no patient had an objective response in the everolimus arm (P < 0.0001) in favour of the lenvatinib plus everolimus arm.

Table 14 Efficacy results following one prior VEGF targeted therapy in RCC Study 205

	lenvatinib 18 mg+ everolimus 5 mg (N=51)	**lenvatinib 24 mg (N=52)**	**everolimus 10 mg (N=50)**
Progression-free survival (PFS) [a] by investigator assessment			
Median PFS in months (95 % CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Hazard Ratio (95 % CI)[b] lenvatinib + everolimus vs everolimus	0.40 (0.24, 0.67)	-	-
*P*value lenvatinib + everolimus vs everolimus	0.0005	-	-
Progression-free survival (PFS)[a] by post-hoc retrospective independent review			
Median PFS in months (95 % CI)	12.8 (7.4, 17.5)	9.0 (5.6, 10.2)	5.6 (3.6, 9.3)
Hazard Ratio (95 % CI)[b] lenvatinib + everolimus vs everolimus	0.45 (0.26, 0.79)	-	-
*P*value lenvatinib + everolimus vs everolimus	0.003	-	-
Overall Survival[c]			
Number of deaths, n (%)	32 (63)	34 (65)	37 (74)
Median OS in months (95 % CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Hazard Ratio (95 % CI)[b] lenvatinib + everolimus vs everolimus	0.59 (0.36, 0.97)	-	-
Objective Response Rate n(%) by investigator assessment			
Complete responses	1 (2)	0	0
Partial responses	21 (41)	14 (27)	3 (6)
Objective Response Rate	22 (43)	14 (27)	3 (6)
Stable disease	21 (41)	27 (52)	31 (62)
Duration of response, months, median (95 % CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)

Tumour assessment was based on RECIST 1.1 criteria. Data cut-off date = 13 Jun 2014
Percentages are based on the total number of patients in the Full Analysis Set within relevant treatment group.
CI = confidence interval, NE = not estimable

[a] Point estimates are based on Kaplan-Meier method and 95 % CIs are based on the Greenwood formula using log-log transformation.

[b] Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and haemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.

[c] Data cut-off date = 31 Jul 2015

Figure 7 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment)

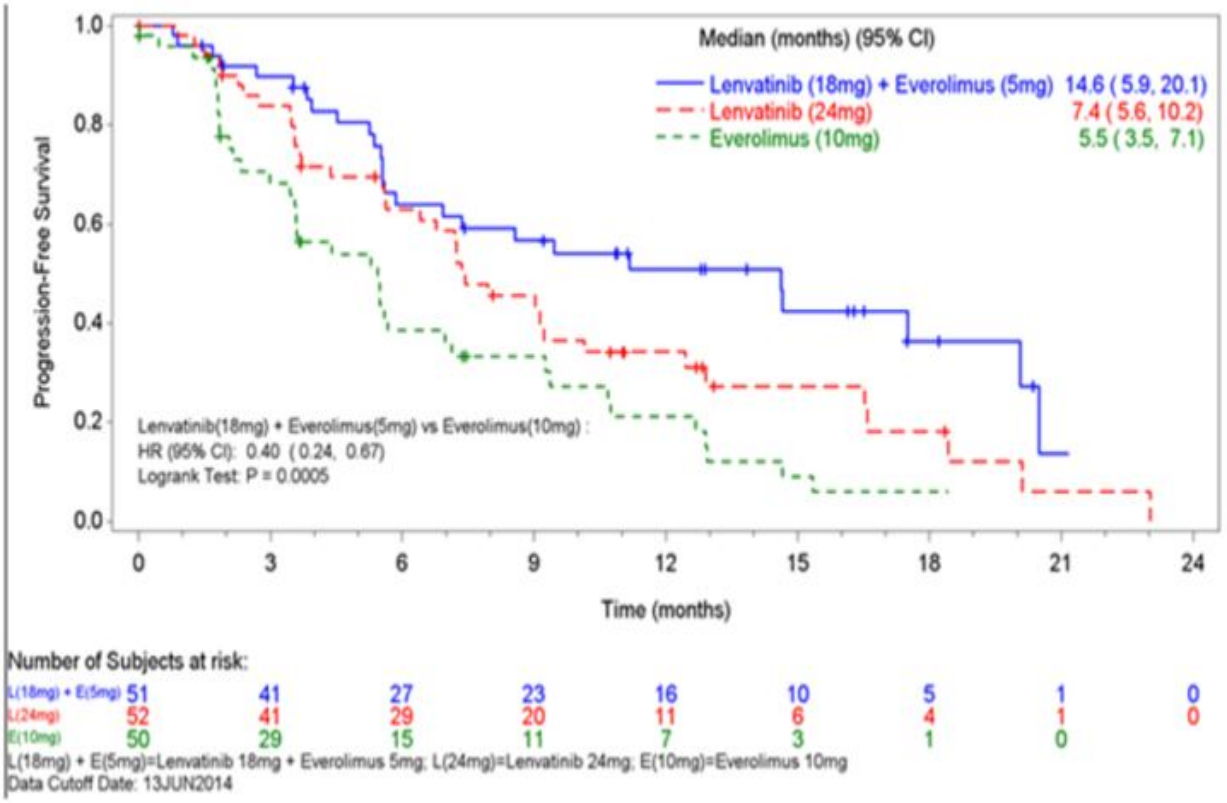
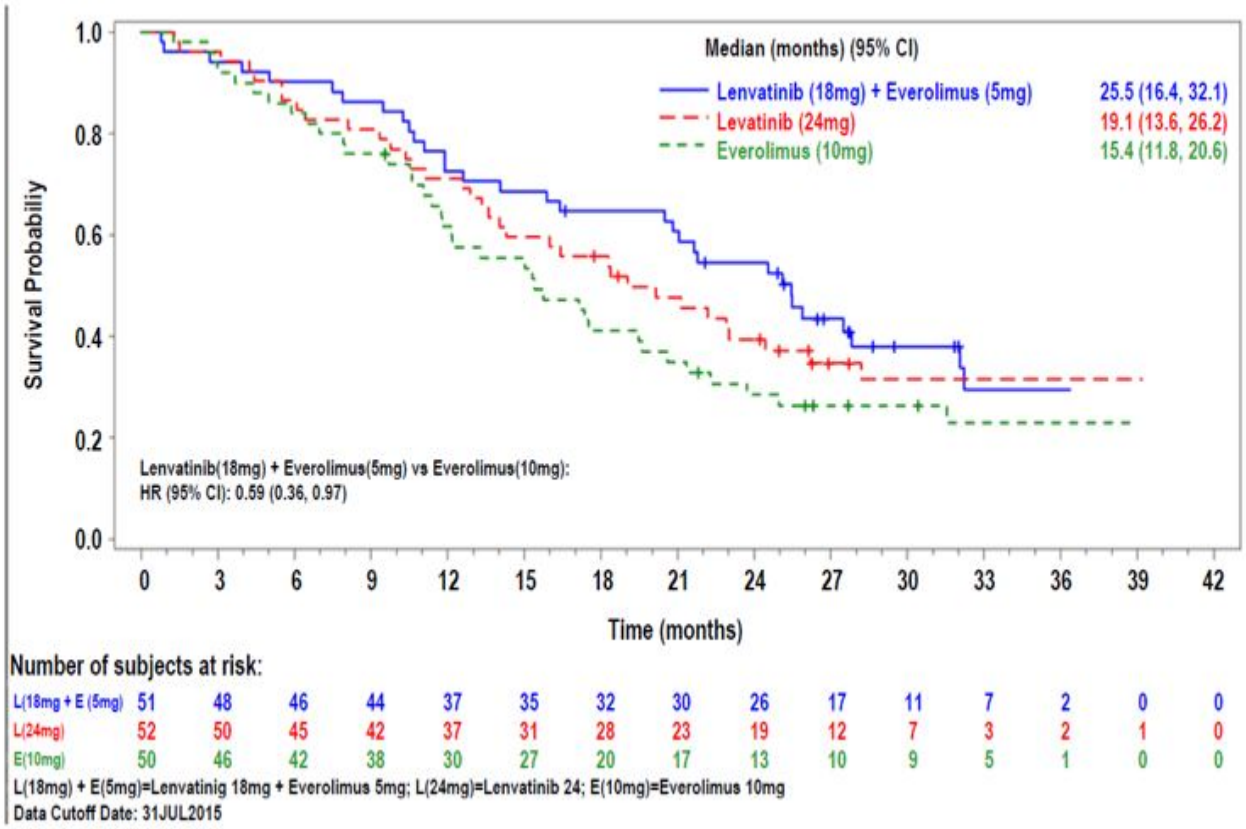


Figure 8 Kaplan-Meier Plot of Overall Survival



QT interval prolongation

A single 32-mg dose of lenvatinib did not prolong the QT/QTc interval based on results from a thorough QT study in healthy volunteers; however, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see sections 4.4 and 4.8).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with the reference medicinal product containing lenvatinib in one or more subsets of the paediatric population in the treatment of hepatocellular carcinoma (HCC), endometrial carcinoma (EC) and renal cell carcinoma (RCC) (see section 4.2 for information on paediatric use).

Paediatric studies

The efficacy of lenvatinib was assessed but not established in four open-label studies:

Study 207 was a Phase 1/2, open-label, multi-centre, dose-finding and activity-estimating study of lenvatinib as a single agent and in combination with ifosfamide and etoposide in paediatric patients (aged 2 to < 18 years; 2 to ≤ 25 years for osteosarcoma), with relapsed or refractory solid tumours. A total of 97 patients were enrolled. In the lenvatinib single agent dose-finding cohort, 23 patients were enrolled and received lenvatinib orally, once daily, across 3 dose levels (11, 14, or 17 mg/m^2). In the lenvatinib in combination with ifosfamide and etoposide dose-finding cohort, a total of 22 patients were enrolled and received lenvatinib across 2 dose levels (11 or 14 mg/m^2). The recommended dose (RD) of lenvatinib as a single agent, and in combination with ifosfamide and etoposide was determined as 14 mg/m^2 orally, once daily.

In the lenvatinib single agent expansion cohort of relapsed or refractory DTC, the primary efficacy outcome measure was objective response rate (ORR; complete response [CR] + partial response [PR]). One patient was enrolled, and this patient achieved a PR. In both the lenvatinib single agent, and combination with ifosfamide and etoposide expansion cohorts of relapsed or refractory osteosarcoma, the primary efficacy outcome measure was progression-free survival rate at 4 months (PFS-4); the PFS-4 by binomial estimate including all 31 patients treated with lenvatinib as a single agent was 29 % (95 %CI: 14.2, 48.0); the PFS-4 by binomial estimate in all 20 patients treated in the lenvatinib in combination with ifosfamide and etoposide expansion cohort was 50 % (95 %CI: 27.2, 72.8).

Study 216 was a multicentre, open-label, single-arm, Phase 1/2 study to determine the safety, tolerability, and antitumour activity of lenvatinib administered in combination with everolimus in paediatric patients (and young adults aged ≤ 21 years) with relapsed or refractory solid malignancies, including CNS tumours. A total of 64 patients were enrolled and treated. In Phase 1 (combination dose-finding), 23 patients were enrolled and treated: 5 at Dose Level –1 (lenvatinib 8 mg/m^2 and everolimus 3 mg/m^2) and 18 at Dose Level 1 (lenvatinib 11 mg/m^2 and everolimus 3 mg/m^2). The recommended dose (RD) of the combination was lenvatinib 11 mg/m^2 and everolimus 3 mg/m^2, taken once daily. In Phase 2 (combination expansion), 41 patients were enrolled and treated at the RD in the following cohorts: Ewing Sarcoma (EWS, n=10), Rhabdomyosarcoma (RMS, n=20), and High-grade glioma (HGG, n=11). The primary efficacy outcome measure was objective response rate (ORR) at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for patients with HGG). There were no objective responses observed in the EWS and HGG cohorts; 2 partial responses (PRs) were observed in the RMS cohort for an ORR at Week 16 of 10 % (95 % CI: 1.2, 31.7).

The OLIE study (Study 230) was a Phase 2, open-label, multi-centre, randomised, controlled trial in patients (aged 2 to ≤ 25 years) with relapsed or refractory osteosarcoma. A total of 81 patients were randomized in a 1:1 ratio (78 treated; 39 in each arm) to lenvatinib 14 mg/m^2 in combination with ifosfamide 3 000 mg/m^2 and etoposide 100 mg/m^2 (Arm A) or ifosfamide 3 000 mg/m^2 and etoposide 100 mg/m^2 (Arm B). Ifosfamide and etoposide were administered intravenously on Days 1 to 3 of each 21-day cycle for a maximum of 5 cycles. Treatment with lenvatinib was permitted until RECIST v1.1-defined disease progression as verified by Blinded Independent Central Review (BICR) or unacceptable toxicity. The primary efficacy outcome measure was progression-free survival (PFS) per RECIST 1.1 by BICR. The trial did not demonstrate a statistically significant difference in median PFS: 6.5 months (95 % CI: 5.7, 8.2) for lenvatinib in combination with ifosfamide and etoposide versus 5.5 months (95 % CI: 2.9, 6.5) for ifosfamide and etoposide (HR=0.54 [95 % CI: 0.27, 1.08]). Study 230 was not powered to detect a statistically significant difference in OS. At the end of study analysis, the HR was 0.93 (95 % CI: 0.53, 1.62) for the comparison of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide, with median OS 12.4 months (95 % CI 10.4, 19.8) versus 17.2 months (95 % CI 11.1, 22.3), respectively, and median follow-up time 24.1 months and 29.5 months, respectively.

Study 231 is a multicentre, open-label, Phase 2 basket study to evaluate the antitumour activity and safety of lenvatinib in children, adolescents, and young adults between 2 to ≤ 21 years of age with relapsed or refractory solid malignancies, including EWS, RMS, and HGG. A total of 127 patients were enrolled and treated at the lenvatinib RD (14 mg/m2) in the following cohorts: EWS (n=9), RMS (n=17), HGG (n=8), and other solid tumours (n=9 each for diffuse midline glioma, medulloblastoma, and ependymoma; all other solid tumours n=66). The primary efficacy outcome measure was ORR at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for patients with HGG). There were no objective responses observed in patients with HGG, diffuse midline glioma, medulloblastoma, or ependymoma. Two PRs were

observed in both the EWS and RMS cohorts for an ORR at Week 16 of 22.2 % (95 % CI: 2.8, 60.0) and 11.8 % (95 % CI: 1.5, 36.4), respectively. Five PRs (in patients with synovial sarcoma [n=2], kaposiform haemangioendothelioma [n=1], Wilms tumour nephroblastoma [n=1], and clear cell carcinoma [n=1]) were observed among all other solid tumours for an ORR at Week 16 of 7.7 % (95 % CI: 2.5, 17.0).

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 post dose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours.
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, lenvatinib 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, lenvatinib 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 demonstrated as 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 $IC_{50} > 50 \times C_{max,unbound}$.

Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and breast cancer resistance protein (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.

Please also see distribution section.

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.

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.

Specialpopulations

Hepaticimpairment

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 AUC_{0-t} and AUC_{0-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 lenvatinib 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 $AUC_{(0-inf)}$ 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, ethnic origin

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no clinically relevant effects on clearance (see section 4.2).

Paediatric population

Based on a population pharmacokinetics analysis in paediatric patients of 2 to 12 years old, which included data from 3 paediatric patients aged 2 to < 3 years, 28 paediatric patients aged ≥ 3 to < 6 years and 89 paediatric patients aged 6 to ≤ 12 years across the lenvatinib paediatric program, lenvatinib oral clearance (CL/F) was affected by body weight but not age. Predicted exposure levels in terms of area under the curve at steady-state (AUCss) in paediatric patients receiving 14 mg/m^2 were comparable to those in adult patients receiving a fixed dose of 24 mg. In these studies, there were no apparent differences in the pharmacokinetics of active substance lenvatinib among children (2 – 12 years), adolescents, and young adult patients with studied tumour types, but data in children are relatively limited to draw definite conclusions (see section 4.2).

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 was not genotoxic.

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 embryo lethality and teratogenicity in 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 PND7) 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 content

Microcrystalline cellulose (E460)
Mannitol (E421)
Hydroxypropylcellulose, low-substituted (E463)
Potassium hydrogen carbonate (E501)
Talc (E553b)

Capsule shell

Hypromellose
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Store below 25°C.

6.5 Nature and contents of container

oPA/Alu/PVC//Alu blisters containing 30, 60 or 90 hard capsules or oPA/Alu/PVC//Alu perforated unit dose blisters containing 30 x 1, 60 x 1 or 90 x 1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA0593/051/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2026

10 DATE OF REVISION OF THE TEXT