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R&D INSIGHT REPORT

Lenvatinib: First Global Approval

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Abstract Lenvatinib (Lenvima™) is a multitargeted receptor kinase inhibitor that inhibits the kinase activities of vascular endothelial-derived growth factor receptors 1, 2 and 3, fibroblast growth factor receptors 1, 2, 3 and 4, platelet-derived growth factor receptor α, RET and KIT. In addition to their role in normal cellular function, these kinases have been implicated in pathogenic angiogenesis, tumour growth and cancer progression. Lenvatinib is being developed by Eisai Co. Ltd for the treatment of solid tumours, primarily for differentiated thyroid cancer, and other malignancies. A capsule formulation of the drug has received approval in the USA for use in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvatinib is in pre-registration for this indication in the EU, Australia, Brazil, Canada, Japan, South Korea, Russia, Singapore and Switzerland, and is in phase 3 development in Argentina, Chile and Thailand. Lenvatinib has orphan designation in the EU and Japan for use in differentiated thyroid cancer. In addition, an ongoing global, phase 3 trial is evaluating the use of lenvatinib as first-line treatment in unresectable hepatocellular carcinoma. This article summarizes the milestones in the development of lenvatinib leading to this first approval in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

1 Introduction

Thyroid cancer is one of the most prevalent endocrine malignancies, with an age-standardized rate of 15.1 per 100,000 females in North America and 5.8 per 100,000 females in Western Europe [1–3]. Thyroid cancers are categorized into four major histological types consisting of papillary (80–85 % of cases), follicular (11 %), medullary (3–4 %) and anaplastic (1–2 %) [1–3]. Most patients with thyroid cancer have a very good prognosis [5-year overall survival (OS) rate of 98 %], with treatment involving surgery, thyroid-stimulating hormone-suppressive therapy and, in patients with differentiated (i.e. papillary plus follicular) thyroid cancer, radioactive iodine (RAI) ablation [1]. However, for patients with RAI-refractory thyroid cancer, treatment options are limited and the prognosis is poor [1, 2].

An improved understanding of molecular signalling pathways involved in normal physiological cellular functions and also implicated in the pathogenesis of tumour growth and cancer progression, has led to the development of targeted therapies, including multikinase inhibitors for the treatment of RAI-refractory thyroid cancer (e.g. lenvatinib, pazopanib, sorafenib and vandetanib [1–3]. Receptor tyrosine kinases (RTKs) located in the cell membrane play a central in the activation of signal transduction pathways involved in the normal regulation of cellular processes, such as cell proliferation, migration, apoptosis and differentiation, and in

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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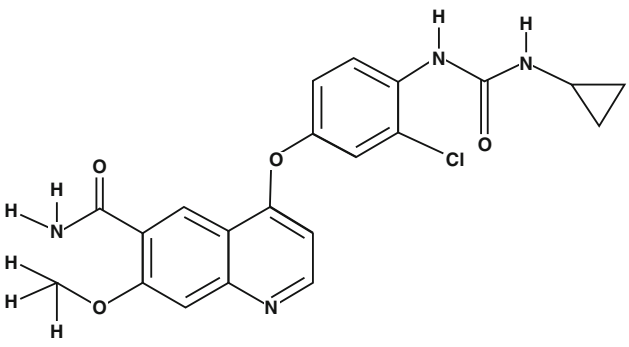
Features and properties of lenvatinib

Alternative names	E 7080; E-7080; E7080; ER 20349200; ER-203492-00; lenvatinib mesylate; Lenvima™
Class	Amides, Chlorobenzenes, Cyclopropanes, Phenyl-ethers, Quinolines, Small-molecules, Urea-compounds
Mechanism of action	Inhibits the kinase activities of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, KIT and RET
Route of administration	Oral
Pharmacodynamics	Inhibits multiple tyrosine kinases that have been implicated in pathogenic angiogenesis, tumour growth and cancer progression, in addition to their normal cellular functions, including 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, KIT and RET
Pharmacokinetics	Rapidly absorbed and slowly eliminated; metabolized by cytochrome P450 3A and aldehyde oxidase
Adverse reactions	
Most frequent (incidence ≥30 % in SELECT trial)	Hypertension, diarrhoea, fatigue or asthenia, decreased appetite, bodyweight decreased, nausea, stomatitis, palmar-plantar erythrodysesthaesia syndrome, proteinuria
ATC codes	
WHO ATC code	L01X-E (protein kinase inhibitors)
EphMRA ATC code	L1X4 (antineoplastic protein kinase inhibitors)
Chemical name	4-[3-chloro-4-(3-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide

pathogenic angiogenesis, lymphogenesis, tumour growth and cancer progression. Key intracellular signalling pathways involved in the development of thyroid cancers include the mitogen-activated protein kinase (MAPK) pathway, the rat sarcoma (RAS)/B-type rapidly accelerated fibrosarcoma (BRAF)/mitogen-activated protein kinase (ERK)/extracellular signal-activated protein kinase (MEK) pathway and the phosphatidylinositol-3 kinase (P13K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. The binding of specific ligands to RTKs triggers these intracellular signal transduction pathways, with mutations at various steps in these pathways potentially associated with dysregulation of normal physiological function. RTKs involved in the MAPK, RAS/BRAF/ERK/MEK and P13K–AKTmTOR pathways include vascular endothelial-derived growth factor receptors (VEGFR; pivotal pro-angiogenic factor), rearranged during transcription tyrosine kinase (RET) and fibroblast growth factor receptors (FGFR) [1–3]. Lenvatinib (Lenvima™) is a small molecule, multikinase inhibitor that inhibits the kinase activities of VEGFR1 [also known as fms-related tyrosine kinase 1 (FLT1)], VEGFR2 (or kinase insert domain receptor) and VEGFR3 (or FLT4), FGFR 1–4, platelet-derived growth factor (PDGF) receptor α, KIT (or stem cell factor receptor or CD117) and RET [4–7].

Lenvatinib is being developed by Eisai Co. Ltd as an anticancer agent and was approved by the US FDA in February 2015 for locally recurrent or metastatic, progressive, RAI-refractory differentiated thyroid cancer in the USA at an oral dosage of 24 mg once daily [4, 8]. Its approval in the USA in this indication was based on the phase 3, double-blind, multinational SELECT trial [9]. The drug is also in pre-registration for this indication in Australia, Brazil, South Korea, Japan, Switzerland, Canada, Singapore, Russia and Europe [10], and is in phase 3 development in Argentina, Chile and Thailand. Lenvatinib has orphan designation for use in differentiated thyroid cancer in the EU and Japan [11, 12]. In addition, an ongoing global, phase 3 trial (NCT01761266) is evaluating the use of lenvatinib as first-line treatment in unresectable hepatocellular carcinoma, and global phase 2 and phase 1/2 trials are evaluating its use for several other malignancies, including melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC) [10].



Chemical structure of lenvatinib

1.1 Company Agreements

Eisai entered into a strategic collaboration agreement with Quintiles in October 2009 to develop six anticancer compounds [13]. Quintiles will conduct phase 1b/2 proof-of-concept studies for 11 tumour indications and Eisai will continue ongoing development for 18 other cancer indications. Lenvatinib is one of the six anticancer compounds included in this collaboration [13].

In September 2011, Eisai entered into a collaborative development agreement with SFJ Pharma, a wholly-owned subsidiary of SFJ Pharmaceuticals Group, to help provide funding for phase 3 studies of lenvatinib in thyroid cancer [14]. Under this agreement, Eisai will conduct the studies and SFJ Pharma will wholly fund them. Eisai will make milestone payments to SFJ Pharma only if lenvatinib receives regulatory approval. Commercial rights will remain with Eisai [14].

In February 2015, Eisai announced that Biologics Inc. was selected as a speciality pharmacy provider for lenvatinib, within its limited distribution network, for the treatment of radioactive iodine-refractory thyroid cancer [15].

2 Scientific Summary

2.1 Pharmacodynamics

Based on x-ray crystallography and kinetic interaction studies, lenvatinib binds to the adenosine 5′-triphosphate binding site of VEGFR2 and to a neighbouring region via a cyclopropane ring and thereby inhibits tyrosine kinase activity and associated signalling pathways, with this binding differing from that of other VEGFR2 kinase inhibitors [16]. Lenvatinib bound with an equilibrium dissociation constant of 2.1 nmol/L (vs. 33 and 30 nmol/L with sorafenib and sunitinib) and had a residence time of 17 min (vs. 64 and <2.9 min, respectively) [16].

In preclinical in vitro studies in human cancer cell lines and in vivo studies involving a broad spectrum of human tumour xenograft models, including thyroid, melanoma and hepatocellular xenograft models and a *RET* gene fusion-driven tumour model (with *RET* gene fusions associated with thyroid and lung cancers), lenvatinib exhibited potent antitumour activity via inhibition of tyrosine kinase activities of VEGFR 1–3 and other pro-angiogenic and oncogenic pathway-related RTKs [5–7, 17–20]. In an in vitro assay of angiogenesis, lenvatinib inhibited VEGFR- and FGFR-induced proliferation and tube formation of human umbilical vein endothelial cells [18]. Lenvatinib treatment also inhibited angiogenesis and FGFR and RET signalling pathways in human differentiated, anaplastic and medullary thyroid cancer xenograft mouse models [17]. In cultured thyroid cancer cell lines, lenvatinib inhibited cell proliferation in 2 of 11 lines, and inhibited phosphorylation of FGFR1 and its downstream effector FGFR substrate 2 (FRS2) [17]. Lenvatinib (typically at concentrations of 30–100 nmol/L) inhibited pro-oncogenic *RET* gene fusion signalling in human thyroid and lung cancer cell lines, including inhibition of anchorage-dependent and -independent growth and oncogenic activity of these *RET* gene transformed cell lines [19]. Lenvatinib also suppressed tumour growth and significantly decreased microvessel density in mouse *RET* gene fusion driven tumour models. In ex vivo analyses, lenvatinib treatment reduced phosphorylation of KIFB-RET and MAPK (also known as extracellular signal-regulated kinases; ERK) in mice with NIH3T3/KIF5B-RET tumours [19]. Lenvatinib also reduced microvessel density and inhibited angiogenesis in human sarcoma xenografts resistant to at least one or more clinically relevant reference drugs (doxorubicin, cisplatin or ifosfamide given at the maximum tolerated dose) [20]. Since lenvatinib inhibits both VEGFRs and FGFRs, the drug may provide a mechanism of overcoming resistance to drugs that only inhibit VEGF/VEGFR [2]

In phase 1 and 2 studies, oral lenvatinib exhibited antitumour activity against a variety of tumour types [21–27], including unresectable advanced medullary thyroid cancer [22] and advanced hepatocellular carcinoma [26]. Results from these trials, most of which are ongoing, are discussed in Sect. 2.3. In phase 1 dose-escalation study in patients with advanced solid tumours, oral lenvatinib was associated with tumour shrinkage and changes in plasma angiogenic proteins (potential biomarkers for lenvatinib-induced antitumour activity), including increasing plasma VEGF and stromal cell-derived factor 1α (SDF1α) levels and decreasing plasma levels of soluble VEGFR2 [28]. These changes occurred in a dose-dependent manner, with maximum tumour shrinkage correlated with increases in plasma SDF1α levels [28].

In a thorough QT study, lenvatinib (single 32 mg dose; i.e. 1.3× recommended daily dose) had no clinically relevant effect on the corrected QT interval in healthy volunteers [29]. However, QT interval prolongation was observed in the phase 3 SELECT trial in patients with RAI-refractory thyroid cancer [4], as discussed in Sect. 2.4.

2.2 Pharmacokinetics

In patients with solid tumours, exposure to lenvatinib was dose-proportional after single and multiple doses across a dose range of 3.2–32 mg, with a medium accumulation

index of 0.96 (20 mg dose) to 1.54 (6.4 mg dose) [4]. Maximum plasma concentrations (C_{max}) were typically attained 1–4 h postdose. In vitro, lenvatinib was highly protein bound (98–99 %) and the blood-plasma ratio ranged from 0.59 to 0.61 [4]. In healthy volunteers, the pharmacokinetics of lenvatinib did not differ to a clinically relevant extent between the fasted and fed state [30]. Lenvatinib is primarily metabolized in humans via enzymatic [primarily cytochrome P450 (CYP) 3A4; also aldehyde oxidase] and non-enzymatic processes [4]. Plasma levels of lenvatinib decline bi-exponentially after C_{max} is attained, with a terminal elimination half-life ($t_{½}$) of ~28 h [4]. In patients with solid tumours, ~64 % of radioactive lenvatinib was eliminated in the faeces and ~25 % in the urine [4, 31].

Lenvatinib has a low potential for drug–drug interactions, based on clinical [32, 33] and in vitro studies [4]. In vitro studies indicated that lenvatinib is a substrate for P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP), but not for organic anion transporters (OAT1 and OAT3), organic anion transporting polypeptides (OATP1B1 and OAT1B3), organic cation transporters (OCT1 and OCT2) or the bile salt export pump [4]. No dosage adjustments are required when lenvatinib is coadministered with CYP3A4 (e.g. ketoconazole [32]), P-gp (e.g. rifampicin [33]) and BCRP inhibitors, and CYP3A4 and P-gp inducers (e.g. rifampicin [33]) [4].

In patients with severe hepatic impairment, exposure to lenvatinib (single 5 mg dose) was increased by 170 % and $t_{½}$ was prolonged (37 vs. 23 h in healthy volunteers) [34]; thus, in patients with severe hepatic impairment, the recommended dosage is 14 mg once daily [4]. No dosage adjustments are required in patients with mild or moderate hepatic or renal impairment [4]. After a single 24 mg dose, exposure to lenvatinib was similar in patients with renal impairment to that in healthy volunteers; patients with end-stage renal disease were not studied [4]. In patients with severe renal impairment, the recommended dosage is 14 mg once daily [4].

2.3 Therapeutic Trials

2.3.1 Thyroid Cancer

In SELECT, patients with RAI-refractory thyroid cancer and confirmed radiographical evidence of disease progression within the previous 13 months were randomized to oral lenvatinib 24 mg once daily ($n = 261$) or placebo ($n = 131$) in 28-day cycles, with treatment continuing until the occurrence of unacceptable disease progression. Incremental dosage reductions were permitted based on tolerability. Eligible patients were stratified according to age, geographic region, and whether or not they had previously received tyrosine kinase inhibitor (TKI) therapy. Placebo recipients with radiographical evidence of disease progression could elect to enter the open-label lenvatinib phase. The primary endpoint was progression-free survival (PFS), based on Kaplan–Meier methods, with the primary analysis conducted after at least 214 progression events or deaths had occurred (220 events had occurred at the time of the primary analysis) [9].

Lenvatinib treatment significantly prolonged median PFS compared with placebo at the time of the primary analysis [18.3 vs. 3.6 months; hazard ratio (HR) for progression or death 0.21; 95 % CI 0.14–0.31; $p < 0.001$] [9]. Sensitivity analyses showed that median PFS was prolonged in all prespecified subgroups, including based on age, sex, race, prior or no prior treatment with a TKI, geographic region, histological findings (papillary, poorly differentiated, follicular and Hürthle-cell) and baseline thyrotropin level. Overall response rates were significantly higher in the lenvatinib group than in the placebo group (64.8 vs. 1.5 %; odds ratio 28.87; 95 % CI 12.46–66.86; $p < 0.001$), with 1.5 % and no patients achieving a complete response, 63.2 and 1.5 % achieving a partial response and 23.0 and 54.2 % having stable disease. The median OS time had not been reached in either treatment group at the time of this primary analysis. In evaluable patients who entered the open-label phase, median PFS was 10.1 months and the overall response rate was 52.3 %, including one complete response and 56 partial responses [9].

In a phase II trial, response rates based on an independent imaging review and investigator assessments were 36 % (95 % CI 24–49) and 49 % (95 % CI 36–62), respectively, in patients receiving lenvatinib 24 mg once daily [22]. This study enrolled patients with unresectable advanced medullary thyroid cancer who had disease progression in the previous 12 months ($n = 59$) [22].

2.3.2 Hepatocellular Cancer

In a phase 1/2 study conducted in Japan and Korea in patients with advanced hepatocellular cancer and Child-Pugh class A liver function ($n = 42$ evaluable), 14 patients treated with lenvatinib (initial dosage 12 mg once daily) had confirmed partial responses, as assessed by investigators in an initial analysis [26]. In a subsequent analysis ($n = 46$), the median time-to-progression was 12.8 months and median OS time was 18.7 months [35].

Based on results from this phase 1/2 study, an open-label, multinational, phase 3 trial (NCT01761266) will evaluate the noninferiority or superiority of lenvatinib to sorafenib as first-line treatment in patients with unresectable hepatocellular cancer (estimated enrolment of 940 patients) [35]. Patients will be randomized to oral lenvatinib 8 or 12 mg once daily (based on bodyweight) or sorafenib 400 mg twice daily. The primary endpoint is median OS [35].

2.3.3 Other Cancers

Lenvatinib has also been evaluated in multicentre (typically multinational), phase 1 or 2 trials ($n = 20$–135) in patients with advance solid tumours [27, 36], advanced NSCLC [23, 37], metastatic renal cell carcinoma [21], stage III and/or IV melanoma (NCT01133977 [38, 39]; NCT01136967 [24, 40]), or advanced or recurrent endometrial cancer [25]. Based on results from these trials, further studies are warranted to investigate the efficacy of lenvatinib in these patient populations.

In an ongoing, double-blind, phase II study in patients with nonsquamous NSCLC who had failed at least two prior treatments, median OS with lenvatinib plus best supportive care (BSC; $n = 89$) was 38.4 weeks compared with 24.1 weeks in the placebo plus BSC group ($n = 46$) (primary endpoint) [23]. Median PFS was significantly prolonged in lenvatinib versus placebo recipients (20.9 vs. 7.9 weeks; $p < 0.001$), with no between-group difference in the objective response rate (10.1 vs. 2.1 %). This interim analysis was conducted after 90 deaths had occurred [23].

As first-line treatment in patients with stage IV melanoma ($n = 78$), median PFS was significantly prolonged in the lenvatinib plus dacarbazine group compared with the dacarbazine group in a phase II study (19.1 vs. 7.0 weeks; HR 0.4; 95 % CI 0.23–0.75; $p = 0.0033$), as assessed by independent review (primary endpoint) [38]. In this ongoing study (NCT01133977), patients received lenvatinib 20 mg once daily plus dacarbazine 1000 mg/m^2 once every 21 days combination therapy or dacarbazine 1000 mg/m^2 once every 21 days [38]. In a cohort of patients with stage III unresectable or stage IV *BRAF* wild-type melanoma who had received at least one prior treatments ($n = 93$), eight lenvatinib recipients achieved a partial response in an ongoing, phase II trial (primary endpoint; assessed by independent review; NCT01136967) [24]. The median PFS and OS were 3.7 and 9.5 months, with a clinical benefit rate (complete plus partial responses plus durable stable disease of ≥23 weeks) of 32 %. In this study, which also evaluated a cohort of patients who were *BRAF* mutant advanced melanoma (data not reported), patients received lenvatinib 24 mg once daily [24].

In an ongoing, open-label, phase II trial in patients with metastatic or recurrent endometrial cancer ($n = 133$), the independent review and investigator assessed overall objective response rates with lenvatinib 24 mg once daily were 14.3 and 28.1 %, respectively (primary endpoint) [25]. The median PFS was 5.4 months and the median OS was 10.6 months [25].

Key clinical trials of lenvatinib (Eisai Inc./Eisai Co. Ltd)

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier
LEN vs. PL	Radioactive iodine-refractory differentiated thyroid cancer	3	Ongoing; primary analysis completed	Multinational	SELECT; NCT01321554; Eudra CT2010-023783-41
LEN	Radioactive iodine-refractory differentiated thyroid cancer	EXP	Ongoing	USA	NCT02211222
LEN	Radioactive iodine-refractory differentiated thyroid cancer	2	Completed	Multinational	NCT00784303
LEN	Radioactive iodine-refractory differentiated thyroid cancer	2	Recruiting	Japan	NCT01728623
LEN vs. SOR	Unresectable hepatocellular cancer	3	Recruiting	Multinational	NCT01761266; Eudra CT2012-002992-33
LEN	Advanced hepatocellular carcinoma	2	Ongoing	Japan	NCT00946153
LEN	Advanced endometrial cancer	2	Ongoing	Multinational	NCT01111461
LEN	Unresectable stage III or IV melanoma	2	Ongoing	Multinational	NCT01136967
LEN + DAC	Stage IV melanoma	1/2	Ongoing	Multinational	NCT01133977
LEN + E7050	Recurrent glioblastoma/unresectable stage III or IV melanoma	2 + expansion cohort	Ongoing	USA	NCT01433991
LEN ± EVE	Unresectable advanced or metastatic renal cell carcinoma	1/2	Ongoing	Multinational	NCT01136733
LEN	KIF5B-RET-positive lung adenocarcinoma	2	Recruiting	Multinational	NCT01877083
LEN + BSC	Advanced or metastatic non-squamous NSCLC	2	Ongoing	Multinational	NCT01529112; Eudra CT2011-002347-10

BSC best supportive care, *DAC* dacarbazine, *EVE* everolimus, *EXP* expanded access, *LEN* lenvatinib, *NSCLC* non-small cell lung cancer, *PL* placebo, *RI* radioactive iodine, *SELECT* Study of (E7080) LEnvatinib in differentiated Cancer of the Thyroid, *SOR* sorafenib

2.4 Adverse Events

Oral lenvatinib had a manageable safety and tolerability profile in clinical trials. In patients with RAI-refractory differentiated thyroid cancer participating in SELECT, treatment-related adverse events (TRAE) of any grade occurred in 97.3 % of lenvatinib recipients and 59.5 % of placebo recipients, with TRAEs of grade 3 or higher occurring in 75.9 and 9.9 % of patients [9]. Serious TRAEs occurred in 30.3 and 6.1 % of lenvatinib and placebo recipients. Treatment-emergent adverse events that lead to death occurred in 7.7 % of lenvatinib recipients and 4.6 % of placebo recipients, with 2.3 % of those occurring in the lenvatinib group considered to be treatment-related [9].

The most common (incidence ≥30 %) TRAEs of any grade occurring in lenvatinib recipients were hypertension (67.8 vs. 9.2 % in the placebo group), diarrhoea (59.4 vs. 8.4 %), fatigue or asthenia (59.0 vs. 27.5 %), decreased appetite (50.2 vs. 11.5 %), decreased bodyweight (46.4 vs. 9.2 %), nausea (41.0 vs. 13.7 %), stomatitis (35.6 vs. 3.8 %), palmar-plantar erythrodysethaesia syndrome (31.8 vs. 8.0 %) and proteinuria (31.0 vs. 1.5 %) [9]. TRAEs led to discontinuation of the study drug in 14.2 % of lenvatinib recipients and 2.3 % of placebo recipients, with the most frequent of these being asthenia and hypertension (each of which occurred in 1.1 % of lenvatinib recipients). Dosage reductions (67.8 vs. 4.6 %) or interruptions (82.4 vs. 18.3 %) occurred more frequently in the lenvatinib than in the placebo group. The most common adverse effects associated with dosage discontinuations or interruptions of lenvatinib were diarrhoea (22.6 %), hypertension (19.9 %), proteinuria (18.8 %) and decreased appetite (18.0 %).

TRAEs that occurred in clinical trials and for which there is a warning/precaution in US manufacturer's prescribing information were hypertension, cardiac dysfunction (decreased left or right ventricular function, cardiac failure or pulmonary oedema), arterial thromboembolic events, hepatotoxicity, proteinuria, renal failure and impairment, gastrointestinal perforation and fistula formation (incidence in SELECT: 2 % in the lenvatinib group vs. 0.8 % in the placebo group), QT interval prolongation, hypocalcaemia, reversible posterior leucoencephalopathy syndrome (three cases across clinical studies; $n = 1108$ lenvatinib recipients), haemorrhagic events and impairment of thyroid stimulating hormone (TSH) suppression [4]. In SELECT, the incidences of these adverse events that were of grade 3 or higher in the lenvatinib and placebo groups were: hypertension (~44 vs. 4 %), cardiac dysfunction (2 vs. 0 %), arterial thromboembolic events (3 vs. 1 %), hepatotoxicity (4 vs. 0 % for an increase in alanine aminotransferase level; 5 vs. 0 % for an increase in aspartate aminotransferase level), proteinuria (11 vs. 0 %), renal failure or impairment (3 vs. 1 %), QT interval prolongation (2 vs. 0 %), hypocalcaemia (9 vs. 2 %) and haemorrhagic events (2 vs. 3 %). In patients who had normal TSH levels (≤0.5 mU/mL) at baseline in SELECT, 57 % of lenvatinib recipients and 14 % of placebo recipients had elevations in TSH level of >0.5 mU/mL [4].

Based on the mechanism of action of lenvatinib and results from animal reproduction studies, which showed embryotoxicity, foetotoxicity and teratogenicity at lenvatinib doses below the recommended dose in humans, females of reproductive potential should be advised to use effective contraception during treatment and for at least 2 weeks following completion of therapy [4].

2.5 Ongoing Clinical Trials

The pivotal phase 3 SELECT trial, which is evaluating the efficacy of lenvatinib treatment in patients with RAI-refractory thyroid cancer, is ongoing (NCT01321554; Eudra CT2010-023783-41); the primary analysis has been completed [9]. In addition, a US expanded access study is ongoing in patients with RAI-refractory thyroid cancer (NCT02211222), with a Japanese phase 2 study in this setting currently recruiting patients (NCT01728623).

A multinational phase 3 trial (NCT01761266; Eudra CT-2012-002992-33) and a Japanese phase 2 trial (NCT00946153) are currently recruiting patients with unresectable hepatocellular cancer. The phase 3 trial will evaluate the noninferiority or superiority of lenvatinib to sorafenib as first-line treatment in patients with unresectable hepatocellular cancer.

The efficacy of lenvatinib is also being evaluated in ongoing, multinational, phase 2 trials in patients with advanced endometrial cancer (NCT01111461), unresectable stage III or IV melanoma with or without V600E BRAF mutations (NCT01136967), or advanced or metastatic non-squamous NSCLC (NCT01529112; Eudra CT2011-002347-10). A multinational phase 2 trial in patients with KIF5B-RET-postive lung adenocarcinoma is currently recruiting patients to evaluate the efficacy of lenvatinib in this setting (NCT01877083). An ongoing, multinational, phase 1/2 trial is evaluating combination lenvatinib plus everolimus therapy in patients with unresectable or advanced renal cell carcinoma (NCT01136733). An ongoing, multinational, phase 1/2 trial is evaluating the efficacy of lenvatinib plus dacarbazine versus dacarbazine monotherapy as first-line treatment in patients with stage IV melanoma (NCT01133977). A US phase 2 and expansion cohort study is evaluating the efficacy of E7050 plus lenvatinib in patients with recurrent glioblastoma or unresectable stage III or IV melanoma after prior systemic therapy (NCT0143399).

3 Current Status

Lenvatinib received its first global approval on 13 February 2015 in the USA for the treatment of locally recurrent or metastatic, progressive, RIA differentiated thyroid cancer.

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