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Phase II Trial of Eribulin and Lenvatinib in Advanced Solid Tumors (CTMS 15-2139)

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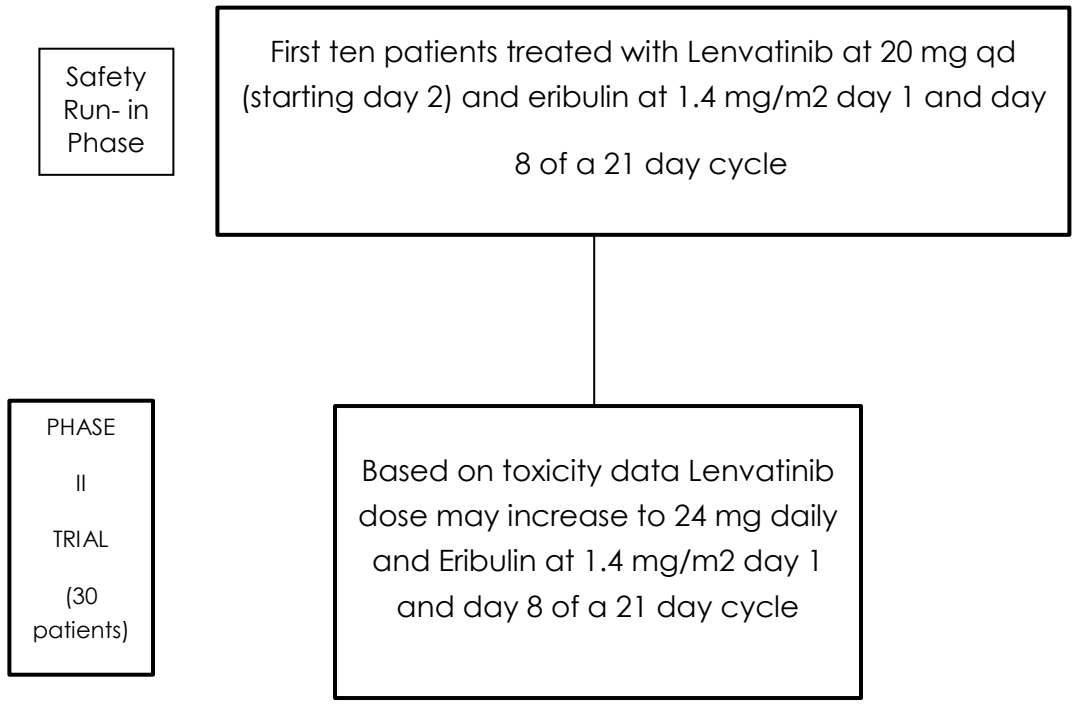
ABBREVIATIONS

AE	Adverse Event
AUC:	Area under the Curve
CAI	Corrective Action Item
DSB	Double Strand Breaks
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
DQA	Director of Quality Assurance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HRD	Homologous recombination deficiency
IDD	Institute for Drug Development
IDEAS	Informatics Data Exchange Acquisition System
IIS	Investigator Initiated Protocol
IND	Investigational New Drug
IRB	Institutional Review Board
MBC	Metastatic Breast Cancer
QAD	Quality Assurance Division
PI	Principal Investigator
PSD	Pharmacokinetic Sampling Department
SAE	Serious Adverse Event
SSB	Single Strand Breaks
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others

SYNOPSIS

Title	Phase II Clinical Trial on the Combination of Eribulin and Lenvatinib in patients with advanced solid cancers
Design	Non-randomized, open-label, multi-center, phase II, dose-escalation with a safety run-in phase.
Objectives	The overall purpose of this study is to determine the overall response rate, efficacy and safety of the combination of Eribulin and Lenvatinib. **The primary objectives are:** 1. Overall Response rate of the combination at MTD (Phase II) **Secondary objectives include:** 1. Determine the safety of Eribulin and Lenvatinib 2. Define the progression free survival 3. Expression profile of MicroRNA
Patient Population	The number of subjects in the safety run-in phase will be 10. In the phase II trial the number of patients will be 30.
Treatment Plan	This is a phase II clinical trial of the combination of Eribulin, and Lenvatinib. A cycle will be defined as 21 days. Eribulin will be given on days 1 and 8 of each cycle. Lenvatinib will be given daily during each cycle. Eribulin will be given on day 1 and day 8 at 1.4 mg/m2 and lenvatinib at a dose of 20 mg will be started on day 2 for the first ten patients. At that time and based on tolerability the PI will have a teleconference with the EISAI medical team and decide whether to increase the lenvatinib dose to 24mg/day. Then the dose of lenvatinib can increase to 24 mg/day for the remaining cycles.
Efficacy Assessment	Response rate will be measured by performance of imaging after every two cycles of therapy.


Safety Run- in Phase
First ten patients treated with Lenvatinib at 20 mg qd (starting day 2) and eribulin at 1.4 mg/m2 day 1 and day 8 of a 21 day cycle
PHASE II TRIAL (30 patients)
Based on toxicity data Lenvatinib dose may increase to 24 mg daily and Eribulin at 1.4 mg/m2 day 1 and day 8 of a 21 day cycle

Introduction – Background and Rationale

Vascular endothelial growth factor (VEGF) stimulates endothelial cell proliferation and is key to tumor angiogenesis and growth.[1] Targeting VEGF or its receptor (VEGFR) may limit tumor induced angiogenesis, vascular supply to the tumor and halt tumor growth. The therapeutic benefits of this strategy have been proven in several solid tumors including non-small cell lung cancer, colon cancer, and renal cell carcinoma.[2] [3]

The VEGF pathway can be inhibited with monoclonal antibodies against VEGF (e.g. bevacizumab) or the extracellular domain of the VEGFR (e.g. ramucirumab), as well as by several small molecule tyrosine kinase inhibitors targeting VEGFR (e.g. sorafenib, lenvatinib, sunitinib, pazopanib) among others.

The recombinant humanized monoclonal antibody bevacizumab is directed against the pro-angiogenic VEGF subgroup A. One explanation for the failure of bevacizumab monotherapy to induce enduring clinical responses may be the fact that bevacizumab targets VEGF-A exclusively, thus only one member of a large family of pro-angiogenic growth factors inducing angiogenesis is targeted. This would suggest that the blockage of the interaction of multiple growth factors with their receptors might improve therapeutic efficacy.[4]

Lenvatinib (LEN) is an oral tyrosine kinase inhibitor of the VEGFR1-3, FGFR1-4, PDGFRβ, RET, and KIT signaling networks. It has shown activity in many solid tumors, such as NSCLC and thyroid cancer. Data on xenograft models have shown activity of lenvatinib in breast cancer[5]. When compared with bevacizumab in breast cancer xenograft models lenvatinib provided better antitumor activity[6]. Lenvatinib is approved for use in thyroid cancer at a dose of 24 mg p.o. per day. Clinical trials are currently under way evaluating lenvatinib in patients with hepatocellular, lung and other cancers.

Phase I studies identified the maximum tolerated dose to be 25 mg daily that, in fasting treated patients, is rapidly absorbed with maximum concentrations achieved within 3 h of administration. In these studies, lenvatinib showed activity in solid tumors.

Chemotherapy agents acting on microtubules have demonstrated activity against multiple cancers, including breast cancer. Microtubules form an integral part of many intracellular processes, including maintenance of cell structure, transport of intracellular components, cell signaling, and mitosis[7]. These structures are tube-shaped filaments composed of α-tubulin and β-tubulin heterodimers, which form highly dynamic polymers. Exploitation of their vital importance in mitosis and cell division has led to development of some of the most effective systemic chemotherapy drugs, with the taxanes and vinca alkaloids being the most widely studied.

Eribulin is a microtubule inhibitor was derived from halichondrin B, a large polyether macrolide found in marine sponges including ***Halichondria okadai*** and is shown to improve overall survival (OS) in breast cancer and with activity is other solid tumors such as NSCLC[8] [9]. Eribulin has a unique mechanism of action, with a tubulin binding site that appears to be different from the taxane and vinca binding sites on

the positive end of the microtubule. In practical terms, Eribulin exerts its cytotoxic effect by inhibiting microtubule growth and sequestering tubulin, ultimately causing G_2-M cell cycle arrest and cell death through apoptosis. Eribulin has shown preclinical activity against a number of human cancer cell lines and xenografts with a wide therapeutic index, making it attractive for clinical development.

Recently data from Study 309 showed an improvement in OS in patients with advanced sarcoma with Eribulin compared with dacarbazine, a standard treatment in sarcoma (data not published yet). We propose a phase II clinical trial of the combination of Eribulin and lenvatinib in breast cancer, non-small cell lung cancer (NSCLC) and sarcoma.

Primary objective will be response rate with secondary objectives being toxicity, progression free survival, and overall survival. If the combination is deemed safe future randomized phase II trials will be designed.

1.0 Eribulin

Overview

The search for active agents for the treatment of metastatic breast cancer (MBC) has included a meticulous assessment of naturally occurring compounds from the oceans. One such agent is halichondrin B, a large polyether macrolide, which is derived from the marine sponge Halichondria okadai found off the coast of Japan[10]. Halichondrins are potent antimicrotubule cytotoxic agents with activity against a variety of tumor cells in vitro[11]. However, a major limitation to the use of many naturally occurring substances as anticancer agents is the availability of adequate quantities of the naturally occurring compound. Hence, the synthesis of eribulin mesylate, formerly E7389, a synthetic halichondrin analog, was a major step in the investigation of these substances as possible anticancer agents.[12]

1.1 Preclinical Studies with Eribulin

Preclinical studies showed that the cytotoxic effect of Eribulin was maintained in paclitaxel-resistant cell lines, including those with mutations in b-tubulin. [13] Furthermore, Eribulin inhibited the growth of human tumor xenografts, including breast cancer[14].This notable activity may be related to a somewhat novel mechanism of action. Similar to other microtubule agents, Eribulin seems to bind to a single site on tubulin, close to the vinca-binding site, and exerts a cytotoxic effect by blocking cell cycle progression at the G2–M phase, leading to apoptosis and ultimately resulting in tumor growth suppression. However, unlike other microtubule agents such as taxanes, vinca alkaloids, and epothilones, Eribulin seems to have no effect on tubule shortening and causes sequestration of tubulin into nonfunctional aggregates[15]. Taken together, these attributes make Eribulin an exciting compound for investigation in clinical studies.

1.2 Clinical Studies with Eribulin

Phase III trials

These encouraging results in heavily pretreated patients led to randomized phase III trials of Eribulin for MBC. As noted, anthracyclines and taxanes are the most active chemotherapy agents in breast cancer. For patients who experience disease progression despite these agents, numerous other active cytotoxic agents

have been investigated including gemcitabine, vinorelbine, capecitabine, and ixabepilone. However, for patients with heavily pretreated MBC, no standard of care exists and no individual agent has shown an OS benefit in clinical trials in this setting. Against this background, the Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin (EMBRACE) (305) study was conducted to compare single-agent Eribulin with standard chemotherapy for patients with heavily pretreated disease[16]. This was a large international phase III study comparing Eribulin with the 'treatment of physician's choice' (TPC). Eligible patients had received two to five prior chemotherapy regimens, at least two of which must have been for MBC. In addition, the patients were required to have received both anthracyclines and taxanes, to have progressed within 6 months of past chemotherapy, have baseline neuropathy less than or equal to grade 2, and Eastern Cooperative Oncology Group performance status less than or equal to 2. Patients were randomized 2 : 1 to intravenous Eribulin of 1.4mg/m2 given over 2–5 min on days 1 and 8 of a 21-day cycle or TPC, consisting of any monotherapy (cytotoxic chemotherapy/hormonal therapy/biologic therapy) or supportive care only. Baseline characteristics in the EMBRACE study were well matched between the treatment arms. In total, 762 patients were treated (508 with Eribulin and 254 with TPC) who were of a median age of 55.2 years (range: 27–85 years). Patients had received a median of four earlier chemotherapy regimens (range: 1–7). No patients randomized to the TPC arm received best supportive care or biological therapy alone. Furthermore, 96% of the patients in this arm received chemotherapy, consisting of vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxane (15%), and anthracyclines (10%) in decreasing frequency. The study met its primary endpoint; treatment with Eribulin was associated with an improvement in the median OS from 10.65 months to 13.12 months; hazard ratio 0.81 (95% CI, 0.66–0.99), P=0.041. In addition, the 1-year survival of patients treated with Eribulin was 53.9% as compared with 43.7% for patients who received TPC. In terms of secondary endpoints, on independent review of the intention to treat population, Eribulin showed a trend to improvement in median PFS from 2.2 months to 3.7 months (hazard ratio 0.87, 95% CI, 0.71–1.05), although this result was not statistically significant (P=0.14). However, Eribulin was associated with an increased response rate (12.2%) over TPC (4.7%) P=0.002, and the clinical benefit rate (response+stable disease $\geq$6 months) was 22.6% as compared with 16.8%. Furthermore, the toxicity profile seemed manageable and consistent with the earlier studies of Eribulin. For example, 25% of patients treated with Eribulin had a serious adverse event as compared with 25.9% of patients treated with TPC. Although Eribulin treatment was commonly associated with neutropenia (45.2% of patients grade 3), as reported earlier, this did not translate into a high rate of febrile neutropenia. Furthermore, as predicted from earlier clinical studies, the incidence of neuropathy was low (8.2% of patients $\geq$grade 3). This does not seem excessive considering that the patients were heavily pretreated and were eligible with less than or equal to grade 2 neuropathy at baseline. Therefore, this study shows that for patients with heavily pretreated MBC, Eribulin is associated with improved OS over standard chemotherapy and a manageable toxicity profile.

Potential Risks of Eribulin

Eribulin seems to have a manageable side-effect profile. In the Phase I study by Goel et al., the most common adverse events included fatigue, nausea and anorexia, seen in 53, 41 and 38% of patients, respectively. Most of these toxicities were grade 1 or 2, and none was grade 4. Grade 3 or 4 neutropenia occurred in six patents and fatigue in four patients. Grade 1 neuropathy was reported in eight patients, and

two patients experienced grade 2 neuropathy. There were no reports of grade 3 or 4 neuropathy. The most frequent adverse effects seen in the Phase I study by Tan et al. were neutropenia, fatigue and alopecia, in 38, 33 and 33% of patients, respectively. Seven patients experienced nine serious adverse effects that were considered to be related to treatment. These adverse effects included one case of hyponatremia, six cases of grade 4 neutropenia and one grade 3 infection. One patient on study died of progressive disease. Fatigue and alopecia were all of either grade 1 or 2. Grade 1 nausea was seen in 19% of patients. Of note, neuropathy was seen as a grade 1 toxicity in one patient at a dose higher than the MTD as per Tan et al. Eribulin remained well tolerated in the Phase II studies among women with metastatic breast cancer (MBC). In the Phase II study of 291 women by Vahdat et al., the most common grade 3/4 toxicities were neutropenia, febrile neutropenia, leucopenia and fatigue, seen in 54, 5.5, 14- and 10% of women, respectively. There were no cases of grade 4 neuropathy, and grade 3 peripheral neuropathy was noted in 5.5% of patients as referred in Vahdat et al. Similarly, results from the second Phase II study of 103 women by Vahdat et al., demonstrate the most common grade 3/4 toxicities of Eribulin to be neutropenia, leucopenia, fatigue, peripheral neuropathy and febrile neutropenia, seen in 64, 18, 5, 5 and 4% of women, respectively. There was no incidence of grade 4 neuropathy. Nineteen per cent of patients received granulocyte growth factors during the first cycle of drug. Alopecia was reported in 41% of patients, but the presence of alopecia at baseline was not recorded. The 21-day cohort seemed to be better tolerated, with less anemia, thrombocytopenia and anorexia.

2.0 Lenvatinib

Overview

Lenvatinib 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, tumortumor growth and cancer progression. An improved understanding of molecular signaling pathways involved in normal physiological cellular functions and also implicated in the pathogenesis of tumortumor growth and cancer progression, has led to the investigation of targeted therapies, including multikinase inhibitors for the management of several solid tumors.

2.1 Preclinical studies with Lenvatinib

In preclinical in vitro studies in human cancer cell lines and in vivo studies involving a broad spectrum of human tumortumor xenograft models, including thyroid, melanoma and hepatocellular xenograft models and a *RET* gene fusion-driven tumortumor model (with *RET* gene fusions associated with thyroid and lung cancers), lenvatinib exhibited potent antitumortumor activity via inhibition of tyrosine kinase activities of VEGFR 1–3 and other pro-angiogenic and oncogenic pathway-related RTKs[17 18]. In an in vitro assay of angiogenesis, lenvatinib inhibited VEGFR- and FGFR-induced proliferation and tube formation of human umbilical vein endothelial cells.[19] As described by Matsui et al, Inhibition of VEGF-R3 kinase with Lenvatinib effectively decreased lymphatic vessel density within MDA-MB-231 tumors,

which express VEGF-C. Simultaneous inhibition of both VEGF-R2 and VEGF-R3 kinases by Lenvatinib may be a promising new strategy to control regional lymph node and distant lung metastases.

2.2 Clinical studies with Lenvatinib

Phase 1 trials

In phase 1 and 2 studies, oral lenvatinib exhibited antitumor activity against a variety of tumor types.[20] In a phase 1 trial conducted by Molina et al, with Lenvatinib and everolimus in the management of metastatic renal cell cancer, twenty patients (mean 58.4 years) received lenvatinib [12 mg (n = 7); 18 mg (n = 11); 24 mg (n = 2)] plus everolimus 5 mg. MTD was established as once daily lenvatinib 18 mg plus everolimus 5 mg. The most common treatment-related treatment-emergent adverse events (all dosing cohorts) were fatigue 60 % (Grade ≥3: 10 %), mucosal inflammation 50 %, proteinuria (Grade ≥3: 15 %), diarrhea (Grade ≥3: 10 %), vomiting (Grade ≥3: 5 %), hypertension, and nausea, each 40 %. In MTD and lowest-dose cohorts (n = 18), best responses of partial response and stable disease were achieved in 6 (33 %) and 9 (50 %) patients, respectively.

In a phase 1 study by Boss et al[21], Eighty-two patients received Lenvatinib in dose cohorts from 0.2 to 32 mg. Dose-limiting toxicities (DLTs) were grade 3 proteinuria (two patients) at 32 mg, and the MTD was defined as 25 mg. The most frequently observed cumulative toxicities (all grades) again noted were hypertension (40% of patients), diarrhea (45%), nausea (37%), stomatitis (32%) and vomiting (23%). Seven patients (9%) had a partial response and 38 patients (46%) had stable disease as best response. Lenvatinib has dose-linear kinetics with no drug accumulation after 4 weeks' administration.

Another Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors by Yamada et al[22], twenty-seven patients (median age 53 years, performance status 0/1) were enrolled. E7080 was escalated from 0.5 to 1, 2, 4, 6, 9, 13, 16, and 20 mg bid by conventional 3-patient cohorts. During cycle 1, no grade 3/4 toxicity was observed up to 13 mg bid. DLTs included grade 3 AST/ALT increase in 1 patient at 16 mg bid and grade 3 platelet count decrease in 2 patients at 20 mg bid. The MTD of 13 mg bid was determined. After repeated doses, C(max) and area under the plasma concentration-time curve increased in a dose-dependent manner. After 14 days of treatment, c-kit(+) CEPs and CECs significantly decreased in cycle 1, but c-kit(-) CEPs and CECs did not. Change from baseline in c-kit(+) CEC ratio in cycle 1 and baseline SDF1α, c-kit(+) CEPs and c-kit(+) CEP ratio significantly correlated with the E7080 therapeutic effect.

Phase II trials

In a phase II trial by Schlumberger et al[23] for the management of medullary thyroid cancers, 59 pts were enrolled (med age: 52; Male: 63%;) and are evaluable for response. 54% of pts required dose reduction for management of toxicity, and 22% were withdrawn from therapy due to toxicity. The most common treatment-related adverse events again were proteinuria 58% (Gr3: 2%), diarrhea 56% (Gr3: 5%), hypertension 48% (Gr3: 7%), fatigue 44% (Gr3: 5%), decreased appetite 41% (Gr3: 5%), nausea 34% (Gr3: 0), and weight decreased 32% (Gr3: 3%). No Gr4 events were reported for these event categories. Confirmed PRs were observed in 21pts (RR: 36%, 95% CI: 24-49) based on independent imaging review

(IIR) and 29 pts (RR: 49%, 95% CI: 36-62) based on investigator assessment. For patients who received prior VEGFR-directed treatment (n=26) RR=35% (IIR); with no prior VEGFR-directed treatment (n=33) RR=36 % (IIR). Median PFS by IRR is 9.0 months (95% CI: 7.0-) (based on minimum 8 month. f/u, 46% events observed). There was no clear difference in treatment response between RET-mutant (RET-mu) and RET-wild type (RET-wt) patients. Low baseline levels of ANG2, sTie-2, HGF and IL-8 were associated with greater tumor shrinkage and prolonged PFS whereas high baseline levels of VEGF and sVEGFR3 were associated with greater tumor shrinkage.

In the Phase II trial conducted by O'day et al[24], eligible patients (pts) had stage IV or unresectable stage III BRAF wild type (wt) melanoma with ≥1 prior treatment (26/96 [27%] pts received ≥3 treatments) and no prior VEGF-targeted therapy. Lenvatinib 24 mg once daily with dose reduction for toxicity was administered until disease progression or unmanageable toxicities. Primary endpoint was response rate (RR) by independent review (IRR) using RECIST 1.1. Archival tumor tissue and baseline and post treatment serum samples were collected for molecular analysis.

Results: 93 patients were treated (median [m] age: 64 years; male: 69%; 95% AJCC stage IV). Confirmed partial responses (PRs) were observed in 8 patients (9%) with a clinical benefit rate (CR+PR+durable SD ≥23 wks) of 32% by IRR. Median PFS (mPFS) was 3.7 months (95% CI, 2.5-4.0) by IRR and median OS (mOS) was 9.5 months (95% CI, 8.3-12.9); 46% pts required dose reduction for management of toxicity; 12% were withdrawn from therapy due to toxicity. Treatment-related adverse events reported in ≥20% pts included hypertension 59% (34% Gr 3/4), fatigue 58% (16% Gr 3/4), nausea 44% (3% Gr 3/4), diarrhea 43% (2% Gr 3/4), decreased appetite 38%, vomiting 29% (2% Gr 3), dysphonia 27%, and proteinuria and headache 26% each (4% and 1% Gr 3/4). Serum biomarker analysis showed baseline levels of serum angiogenic factors, such as angiopoietin-2, correlated with OS.

In a phase II trial of lenvatinib conducted in endometrial cancer by Vergote et al[25], Patients had metastatic/unresectable EC after 1 or 2 prior platinum-based treatments ≤2 prior chemotherapies, and ECOG PS ≤2. Patients received lenvatinib 24 mg once daily until disease progression or development of unmanageable toxicities. Primary endpoint was objective response rate (ORR: complete + partial response [CR+PR]) by RECIST 1.1. 133 pts were treated (median age: 62 years) and evaluated for safety, efficacy, and molecular correlative analysis. Dose reduction (31%) or treatment discontinuation (31%) occurred for toxicity. Median treatment duration was 112 days. The most common adverse events were hypertension 55% (Gr 3/4: 33%), fatigue 42% (Gr 3: 12.8%), diarrhea 35% (Gr 3: 5.3%), decreased appetite 35% (Gr 3: 2.3%), and nausea 32% (Gr 3: 3%); 1 patient had Gr 5 asthenia. Bowel obstruction, fistula formation, and perforation occurred in 3.8%, 2.3%, and 1.5%, respectively. Confirmed CR+PRs were observed in 19 patient (14.3%) by independent review (IRR) and 29 patients (21.8%) by investigator assessment (Inv). mPFS was 5.4 months and mOS was 10.6 moths. Among 50 serum factors tested, only BL plasma Ang-2 correlated with maximal tumor shrinkage, R = 0.36 (Spearman), $p < 0.001$; ORR; PFS; and OS. The 24 patients with low BL Ang-2 plasma levels (cut-off value <2082 pg/mL) were compared with the 98 pts with high BL Ang-2 (>2082 pg/mL) and improved ORR (61% vs 18%), mPFS (9.5 vs 3.7 months), and mOS (23 vs 8.9 months) were observed.

Phase III trials

In a Phase III randomized, double-blind, multicenter study involving patients with progressive thyroid cancer with disease refractory to iodine-131 (I-131) by Schlumberger et al [26], 261 patients were randomly assigned to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and I-131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival (PFS). Secondary end points included the response rate (RR), overall survival (OS), and safety.

The median progression-free survival (mPFS) was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. The response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses) and 1.5% in the placebo group (P<0.001). The median overall survival was not reached in either group. Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related.

A Multicenter, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma is currently in recruitment phase.

2.2.1 Potential risks of Lenvatinib

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 as mentioned by Schlumberger et al. In this study, 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.

The most common (incidence ≥30 %) TRAEs of any grade occurring in lenvatinib recipients were hypertension (67.8 vs. 9.2 % in the placebo group), diarrhea (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 erythrodysaesthesia syndrome (31.8 vs. 8.0 %) and proteinuria (31.0 vs. 1.5 %)

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 diarrhea (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, hypocalcemia, reversible posterior leucoencephalopathy syndrome (three cases across clinical studies; n = 1108 lenvatinib recipients), haemorrhagic events and impairment of thyroid stimulating hormone (TSH) suppression.

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.[27]

2.3 Rationale for combining Lenvatinib and Eribulin

Lenvatinib (LEN) is an oral tyrosine kinase inhibitor of the VEGFR1-3,FGFR1-4, PDGFRβ, RET, and KIT signaling networks[1]. It has shown activity in many solid tumors, such as NSCLC and thyroid cancer. Data on xenograft models have shown activity of lenvatinib in breast cancer as mentioned in Matsui et al. When compared with bevacizumab in breast cancer xenograft models lenvatinib provided better antitumor activity as described by Yano et al. Lenvatinib is approved for use in thyroid cancer. Clinical trials are currently under way evaluating lenvatinib in patients with hepatocellular, lung, and other cancers. Eribulin is a microtubule inhibitor shown to improve OS in breast cancer and with activity in other solid tumors such as NSCLC. Recently data from Study 309 showed an improvement in OS in patients with advanced sarcoma with Eribulin compared with dacarbazine, a standard treatment in sarcoma (data not published yet). We propose a phase II clinical trial of the combination of Eribulin and lenvatinib in breast cancer, non-small cell lung cancer (NSCLC) and sarcoma.

Primary objective will be response rate with secondary objectives toxicity, progression free survival, and overall survival. If the combination is deemed safe future randomized phase II trials will be designed.

2.4 Rationale for patient population

Patients with stage IV cancer will be included in this trial. Data on xenograft models has shown activity of Lenvatinib and recently it has been approved for use in radioiodine resistant thyroid cancer with significantly improved PFS. Furthermore, Eribulin is a microtubule inhibitor which has already shown to improve overall survival in breast cancer, and recently has shown activity in Sarcoma. Given the above

data, we have elected to include stage 4 breast cancer, sarcoma and Non small cell lung cancer patients in our trial.

2.4.1 Micro RNA assay

Our goal is also to quantify serum levels of microRNAs pre- and post-treatment, with the goal of correlating levels with patient response to treatment.

RNA isolation. RNA will be isolated using the mirVanaTM miRNA Isolation Kit (Ambion) and quantified using a Nanodrop spectrophotometer. RNA quality will be determined on an Agilent 2100 Bioanalyzer. miRNA expression profiling will be determined by NGS. We will use the HiSeq 2000 Sequencing System (Illumina) at the GCCRI Genomics Facility to measure miRNA expression profiles. Samples will be barcoded to allow multiplex sequencing and subjected to a second round of Q/C.

Data analysis. Adaptor sequences will be removed and reads of the length ≤ 15 or ≥ 30 are removed as they are not likely to originate from mature miRNAs. Duplicate reads will be removed with the remaining unique reads stored in FASTA format along with the read count. Unique reads will be aligned to the reference human genome (hg19) using the Bowtie short read aligner (0.12.9). Reads mapped to known miRNA loci as defined by miRbase (v21) will be kept for expression profiling. miRNA expression will be derived from counting reads perfectly matching known miRNA loci, normalized to the total number of uniquely mapped reads per sample.

Expected results. Expression profiles of serum miRNAs in 10 responders and 10 non-responders, which can then be compared by t-test to identify differentially expressed miRNAs that correlate with patient response to treatment.

3.0 Objective

The overall purpose of this study is to determine the efficacy and safety of the combination of Eribulin, and Lenvatinib in stage 4 breast, NSCLC and sarcoma.

Primary objective

To determine the overall response rate of the combination of lenvatinib and Eribulin

Secondary objectives

1) Determine the safety of Eribulin and lenvatinib
2) Define the progression free survival
3) Expression profile of MicroRNA

3.1 Selection of Patients

The target population for this study is patients with stage IV breast, NSCLC lung cancers and Sarcoma.

This will be a multi-center trial conducted by Mays Cancer Center. At Mays Cancer Center, patients will be recruited by the clinical team in the Breast Center; lung center and sarcoma center. Potential patients may be referred to the Principal Investigator, Virginia Kaklamani, MD, at (210) 450-3830.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

Inclusion Criteria

- Stage IV breast cancer, stage IV NSCLC, stage IV sarcoma
- ECOG PS 0-2
- Measurable disease
- No more than 4 prior chemotherapeutic regimens for metastatic disease
- Patients must be ≥ 18 years.
- Patients may not have received Eribulin or lenvatinib previously
- Patients must have a life expectancy of greater than 12 weeks.
- Patients may have had a prior diagnosis of cancer if it has been > 5 years since their last treatment and are considered free of disease.
- Patients must have normal organ and marrow function as defined below:
    - Leukocytes ≥ 3,000/μL
    - Absolute neutrophil count ≥ 1,500/μL
    - Platelets ≥ 100,000/μL
    - Child Pugh score ≤ 10
- Patients must be able to swallow and retain oral medication.
- All patients must have given signed, informed consent prior to registration on study.

Exclusion Criteria

- Women who are pregnant or lactating are not eligible for study treatment.
- Patients who are undergoing concomitant radiotherapy are NOT eligible for participation.
- Patients who are receiving any other investigational agents or concurrent anticancer therapy are NOT eligible for participation. Previous systemic treatment and/or radiation therapy is allowed with a 14 day washout period prior to registration.
- Lesions that have been radiated previously cannot be considered target lesions
- Prior treatment related side effects must have resolved to < Grade 2 severity per Common Terminology Criteria for Adverse Events (CTCAE version 4.03), except alopecia and infertility.
- Patients who are taking any herbal (alternative) medicines are NOT eligible for participation. Patients must be off any such medications by the time of registration.
- Patients with known brain metastases are NOT eligible for participation unless the brain metastases are treated (either with surgical excision, stereotactic radiosurgery or radiotherapy) and have been stable based on the physician's assessment, the patient is asymptomatic and has discontinued corticosteroids if taken for that purpose.
- Patients with any of the following conditions or complications are NOT eligible for participation:
    1. GI tract disease resulting in an inability to take oral medication
    2. Malabsorption syndrome
    3. Require IV alimentation
    4. History of prior surgical procedures affecting absorption
    5. Uncontrolled inflammatory GI disease (e.g., Crohn's, ulcerative colitis).
    6. Hypersensitivity of any of the components of Eribulin or lenvatinib
    7. History of significant neurological (no neuropathy more than grade 2) or psychiatric disorders

8. Significant non neoplastic liver disease (Cirrhosis, active chronic hepatitis)
9. Immunocompromised subjects, including patients with human immunodeficiency virus
10. Significant non neoplastic renal disease
11. Active infection requiring systemic therapy.
12. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug; or cardiac arrhythmia requiring medical treatment
13. Prolongation of QTc interval to more than 480 milliseconds when electrolyte balance is normal
14. Major surgery within 4 weeks prior to first dose of the study drug.

4.0 Treatment plan

4.1 Overview

This will be a phase II, non-randomized trial to determine the efficacy and safety of the combination of Eribulin, and lenvatinib in patients with metastatic breast cancer, non-small cell lung cancer and sarcoma. Treatments will be given in cycles of 3 weeks (21 days) and staging scans(CT Scans) will be performed every 2 cycles. Bone scans and MRI brain will be optional. Toxicity assessment will take place after each cycle.

Eribulin will be administered on cycle days 1 and 8; lenvatinib is an orally administered medication which will be given daily throughout each cycle (on cycle 1 lenvatinib will be started on day 2). On days when both drugs are administered, Eribulin will be administered immediately prior to lenvatinib.

Patients will be followed after treatment discontinuation until disease recurrence or death. An evaluable patient for toxicity is any patient who has received at least 1 dose of any of the study drugs. An evaluable patient for efficacy is any patient who has received at least 2 cycles of therapy.

There will be a safety run-in phase. Ten patients will receive lenvatinib at 20 mg daily and Eribulin at 1.4 mg/m^2 day 1 and day 8 of a 21 day cycle. Eribulin will be given on day 1 and lenvatinib at 20 mg daily will be started on day 2. After completion of 1 cycle of therapy for the first 10 patients the PI will have a teleconference with the medical team at EISAI and decide whether to continue at the same dose or increase the dose to 24 mg daily of lenvatinib and Eribulin at 1.4 mg/m^2 day 1 and day 8 of a 21 day cycle.

4.2 Study Drug Administration

Eribulin

Eribulin will be administered intravenously (IV) on days 1 and 8 of each cycle at a dose of 1.4 mg/m^2 over a 2-5 minute time period; on cycle day 1 in the Phase II portion of the trial; this will be immediately prior to Lenvatinib administration. Eribulin will be administered to the patient in the clinic (for drug preparation instructions, see section 7.0). Each cycle will last 21 (+/- 3) days. Laboratory tests will be performed within 2 days prior to days 1 and 8 of all cycles to assess toxicity and confirm that it is safe to proceed with treatment (see Section 7.0 for a complete listing of assessments). The dose of Eribulin will be calculated based on the BSA at study entry and *should only be recalculated if there is >10% change in body weight from baseline.* The actual body weight will be used for these calculations.

Lenvatinib

Lenvatinib will be self-administered by patients orally once a day during the study period. Patients will self-administer lenvatinib at home, except on study visit days. On these visit days, patients should take lenvatinib after chemotherapy is administered. Patients will be instructed to take each dose orally once daily, with or without food, starting on day 2 of cycle 1. The capsules should be swallowed whole without chewing, dissolving, or opening them. Patients should be instructed to take their dose of study drug at the same time each day. If the usual dosing time is missed, the patient should take the dose that day as soon as they remember as long as this is within 12 hours of the usual time the patient takes the dose. If it has been over 12 hours then this will be considered a missed dose. Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed. Patients will be given a medication diary to record all doses taken, missed/skipped, or vomited. This diary will be reviewed with study personnel prior to dispensing medication for the next cycle.

4.3 Supportive Care Guidelines

Supportive therapy for neutropenia:

If grade 3 or 4 neutropenia develops (ANC<1000/ul), G-CSF (Neupogen) can be administered, at the discretion of the treating investigator, until resolution of neutropenia. Neulasta (PEG-filgrastim) 6mg SC for 1 dose is recommended. If Neulasta is given, chemotherapy cannot be administered within 14 days. Neupogen can also be given at the discretion of the treating investigator. NOTE: Neupogen can be given any time before or after chemo. HOWEVER, Neulasta cannot be given within 14 days of chemotherapy.

Supportive therapy for neuropathy

Gabapentin or similar medications can be given at the discretion of the treating physician per institutional practice.

Dose Delays & Dose Modifications

Toxicities will be graded using NCI CTCAE version 4.03 (see Appendices). Dose delays and modification of lenvatinib and Eribulin are summarized below (for post-DLT period in phase II patients only). Individual patient dose reductions are also provided in separate tables.

Dose Delay& Modification for Eribulin and Lenvatinib

Toxicity	Adverse event	Dose Reduction/Delay	
		Eribulin	Lenvatinib
Hematologic toxicity attributed to any or all treatment	Platelets 75000-99999/mm^3 within 24 hrs prior to scheduled therapy	If Day 1: Hold until recovery of platelets >100,000/mm^3. Resume at the same level after recovery If Day 8: No intervention	No dose modification necessary
	ANC <1000/mm3 or Platelets 25000-74999/mm^3 within 24 hrs prior to scheduled therapy	If Day 1: Hold until recovery to ANC >1000/mm^3 and Platelets 100000/mm^3. Resume at same level after recovery If Day 8: Hold until recovery to ANC >1000/mm^3 and Platelets 75000/mm^3. Resume at same level after recovery	Hold until recovery to ANC >500/mm3 and platelets more than 25000, Resume at same level after recovery.
	Platelets <25000/mm^3 or Platelets 25000-50000/mm3complicated by bleeding, easy bruising, petechiae, or requiring platelet transfusion	If Day 1: Hold until recovery to Platelets 100000/mm^3. Resume at same level after recovery If Day 8: Hold until recovery to Platelets 75000/mm^3. Resume at same level after recovery	Hold until recovery of Platelets 25000/mm3. Resume at current dose level.

	Prolonged neutropenia (ANC<500/mm^3 for >7 days)	Hold until recovery to ANC>1000/mm^3. Resume at one dose level below current dose level	Hold until recovery to ANC>500/mm^3. Resume at same level dose.
	Febrile neutropenia (ANC <1000/mm^3 with temperature of >38.5^oC)	Hold until recovery to ANC>1000/mm^3. Resume at one dose level below current dose level	Hold until recovery to ANC>1000/mm^3. Resume at same dose level
	Anemia	No reduction or delay	No reduction of delay
Hepatic toxicity	Grade 4 AST, ALT or Total Bilirubin Child Pugh Score	For patients with known liver dysfunction and Child Pugh score A, Eribulin should be started at a dose of 1.1mg/m2. For patients with known liver dysfunction and Child Pugh score B, Eribulin should be started at a dose of 0.7mb/m^2. Eribulin should not be administered in patients with Child Pugh score C. If during treatment there is grade 3,4 liver toxicity then dose reduce by 1 dose level.	Hold until recovery to Grade 1 or baseline. Resume at reduced dose of 20 mg po daily if first occurrence, reduce to 14 mg po daily on second occurrence and 10 mg po daily on third occurrence.

Peripheral neuropathy	Grade 3 or 4	Hold until recover to ≤grade 2. Reduce dose by one dose level. If neuropathy fails to recover to grade 2 within 3 weeks, Eribulin should be discontinued.	No modifications necessary
Non-hematologic toxicity grade 3 or 4 attributed to any or all treatment (except for neuropathy)	Grade 3 or 4 nausea/vomiting despite optimal antiemetic treatment	Hold until nausea/vomiting have resolved to ≤grade 1. Resume at same dose level	Hold until nausea/vomiting have resolved to ≤grade 1. Resume at same dose.
	>Grade 2 stomatitis	Hold until stomatitis has resolved to ≤grade 1. Resume at one dose level below current dose level	Hold until recovery to ≤grade 1. Resume at the same dose level
Hypertension	Grade 3 Hypertension Or life threatening Hypertension	No dose modification necessary.	Withhold lenvatinib for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at one dose level below current dose level. Discontinue for life threatening hypertension.
Cardiac dysfunction or Hemorrhage.	Grade 3 or Grade 4 events	No dose modification necessary	Withhold lenvatinib for development of Grade 3 event until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of the adverse event.
Proteinuria	>2 gms or less than 2 gms	No dose modification necessary.	Withhold lenvatinib for ≤2 grams of proteinuria/24 hours. Resume at next dose level below current dose level; 2) when proteinuria is >2 gm/24 hours. Discontinue lenvatinib for nephrotic syndrome.
QTc Prolongation	Grade 3 or greater	No dose modification necessary	Monitor and correct electrolyte abnormalities in all patients. Withhold lenvatinib for the development of Grade 3 or greater QT interval prolongation. Resume lenvatinib at a one dose level below previous dose level when QT prolongation resolves to Grade 0 or 1 or baseline.

Day 8 dose of Eribulin may be delayed for a maximum of 1 week. If toxicities do not improve enough after 1 week delay then omit day 8 dose of Eribulin. If day 8 of Eribulin is omitted two consecutive cycles Eribulin should be resumed at one dose below current dose level.

Eribulin Dose Modifications
Starting dose and dose modifications for unacceptable toxicity that is thought to be related to Eribulin are listed below. Dose adjustments are to be made according to the greatest degree of toxicity. The most common toxic effects of Eribulin are fatigue, neutropenia (including neutropenic fever), peripheral neuropathy, and alopecia.

Eribulin Dose Modifications, TABLE 1

0	1.4
-1	1.1
-2	0.7

NOTE: Patients requiring a third dose reduction should be taken off study unless in the opinion of the investigator and/or the DSMB there is reason to believe that the patient is still experiencing clinical benefit(in such cases the DSMB will issue written approval).

Lenvatinib Dose Modifications
Recommended Dose Modifications for Persistent and Intolerable Grade 2
or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities, TABLE 2

0	20
-1	14
Note: *Based on toxicity data of 1st 10 patients in Phase 2, starting Lenvatinib dose was not increased to 24 mg daily*	

Other Toxicities with Lenvatinib

In the SELECT trial, QT/QTc interval prolongation was reported in 9% of lenvatinib-treated patients and 2% of patients in the placebo group. The incidence of QT interval prolongation of Grade 3 or greater was 2% in lenvatinib-treated patients compared to no reports in the placebo group. In the same trial, events of gastrointestinal perforation or fistula were reported in 2% of lenvatinib-treated patients and 0.8% of patients in the placebo group. 9% of lenvatinib-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction.

Across clinical studies in which 1108 patients received lenvatinib, there were 3 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). It is recommended to confirm the diagnosis with MRI and hold Lenvatinib until the resolution of the RPLS.

Lenvatinib impairs exogenous thyroid suppression. In the SELECT trial, 88% of all patients had a baseline thyroid stimulating hormone (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 patients receiving placebo. It is recommended to monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

GI perforation and fistula formation has been reported in 2 % of the patients compared to 0.8 % patients in the placebo group. It is recommended to discontinue Lenvatinib in patient who had life threatening perforation or fistula formation.

4.4 Concomitant medications

All concomitant treatments, including blood and blood products, must be reported in the patient's electronic medical record.

4.5 Not Permitted

Patients who are taking any herbal (alternative) medicines are NOT eligible for participation. Patients must be off any such medications by the time of registration. Patients who are undergoing concomitant radiotherapy or chemotherapy are NOT eligible for participation. Patients may not have received Eribulin or lenvatinib previously. Length of the washout period from prior chemotherapy or radiation therapy will be 14 days.

4.6 Permitted

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the treating physician. Concurrent treatment with bisphosphonates or denosumab is allowed. Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines. G-CSF should be administered according to the guidelines in this protocol.

4.7 Duration of Therapy

Patients may continue on study therapy until disease progression or until unacceptable toxicity occurs. Patients will go off study therapy if any of the following occurs:

- The patient experiences any grade 4 toxicity after 2 dose modifications, as recommended by the protocol. If treatment is held for 2 consecutive treatment cycles due to toxicity, the patient must go off treatment.
- The patient withdraws consent from treatment or from the study as a whole.
- There is disease progression.
- The treating physician feels it is necessary (e.g. due to patient non-compliance or other safety concerns).

4.8 Follow-up Post Therapy

Patients will be followed every 6 months at the time of routine clinic visit or via phone call with study personnel after completion of treatment until death.

Treatment after study completion will be left to the discretion of the treating physician(s) and will not be considered part of this study. However, patients should still be followed for study endpoints including date of progression and survival status.

5.0 Response Assessment

Patients with measurable disease are eligible for the study. Response to treatment will be assessed using RECIST 1.1 guidelines. Response and progression will be assessed in this study via physical exam and imaging.

5.1 Definitions

5.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan.

5.1.2 Non measurable disease

All other lesions or sites of disease, including small lesions (those with a longest diameter of < 20 mm with conventional techniques or < 10 mm with spiral CT scan) as well as those that can be assessed as to changes in size but cannot be clearly measured, are considered non-measurable disease. Other examples include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI).

5.1.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

5.1.4 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

5.2 Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

5.2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

5.2.2 Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (PD).

5. 3 Response Criteria

Response will be based on evaluation of target and non-target lesions. To be assigned a best response of partial response (PR) or complete response (CR), changes in tumor measurements must be confirmed by repeat studies that should be performed at a minimum of 4 weeks after the criteria for response are first met. A best response of SD will not require a confirmatory measurement; however, best overall response of SD will not be assessed unless a patient has received at least 2 complete cycles of treatment.

5.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

5.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by Dr. Kaklamani and the UTHSA Data Safety Monitoring Committee assigned to this protocol.

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

5.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 6.4).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

5.3.4 Endpoint Assessment

The overall response rate (ORR) will be defined as response after scans assessed after two cycles of therapy (1 cycle = 3 weeks). Clinical response will be assessed by the treating physician as outlined above. All patients who are on study after 2 cycles will be considered evaluable for the response endpoints.

Progression-free survival (PFS) will be defined as the time from the first study treatment to the first occurrence of progression or death. All patients who receive at least one dose of each drug will be evaluable for this endpoint.

Toxicity will be assessed NCI CTCAE v 4.03. The incidence, nature, and severity of adverse events will be determined. All patients who receive at least one dose of study drug will be considered evaluable for toxicity and safety endpoints.

6.0 Study Parameters

Procedures	Screening & Baseline	Cycle 1	Every cycle[2]	Every 2 cycles or at study termination	End of study visit[7]	Follow-Up[6]
Tissue procurement[1]	X			X[5]		
Informed consent	X					
Eribulin administration			X (Days 1 & 8)			
Lenvatinib			X once daily (starting on day 2 of cycle 1)			
Medical history[3]	X		X		X	
Physical exam[3]	X		X		X	
CBC w/ diff	X[3]		X		X	
Comprehensive chemistry panel	X[3]		X			
TSH	X		X			
Serum pregnancy test	X					
EKG	X		X[10]			
Blood draw for micro RNA assay[9]		X			X	

Procedures	Screening & Baseline	Cycle 1	Every cycle[2]	Every 2 cycles or at study termination	End of study visit[7]	Follow-Up[6]
Urine analysis[11]	X			X		
Imaging[8]	X[4]			X		
Toxicity assessment			X			
Biopsy				X[5]		
Survival status						X

[1]Archival tissue or a fresh biopsy will be required to procure tissue for study purposes. Biopsy does not need to be repeated for study purposes if archived tissue is available. Tissue procurement is voluntary

[2]A cycle is defined as 3 weeks or 21 days (+/- 3 days). Eribulin will be given on cycle days 1 and 8 and lenvatinib starting on day 2 of cycle one and then continuously.

[3]Pre-study laboratory tests, medical history, and physical exam (including performance status and review of systems) must be completed within 28 days prior to registration. Pre-study CBC and CCP will be repeated on day 1 prior to treatment administration.

[4]Pre-study imaging must be performed within 28 days prior to registration.

[5]At the initiation and completion of study treatment (or at the time of early withdrawal), tissue samples should be obtained for correlative studies. This is voluntary and will only be done on patients who consent to it.

[6]Patients will be followed every 6 months, at the time of routine clinic visit or via phone, until death, to document disease progression and survival.

[7]Within 30 days of last dose of study medications.

[8]Imaging modality is left to the discretion of the investigator. However the same imaging modality should be used every two cycles to assess disease status.

[9]Blood samples for microRNA assay will be collected on Cycle 1, Day 1 and at the end of treatment.

[10]Repeat EKG with every cycle in patients with congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics.

[11]Lenvatinib may cause proteinuria. Patients with 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. If 24hr urine protein $\geq$2 g then suspend lenvatinib until it decreases to <2g and dose reduce by one dose level. IIf nephrotic syndrome then permanently discontinue lenvatinib.

7.0 Drug formulation and Procurement

7.1 Eribulin

Other Names
Halaven; eribulin mesylate

Classification
Eribulin is a non-taxane, synthetic analogue of halichondrin B (a product isolated from the marine sponge Halichondria okadai).

Mode of Action
Eribulin is a non-taxane microtubule dynamics inhibitor. Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

Storage & Stability
Vials should be stored in their original cartons at 25°C (77°F); excursions are permitted to 15°-30°C (59°-86°F). Do not freeze. Undiluted Eribulin may be stored for up to 4 hours at room temperature, or for up to 24 hours under refrigeration (4°C or 40°F). Diluted solutions of Eribulin may be stored for up to 4 hours and room temperature or up to 24 hours under refrigeration. Discard unused portions of the vial.

Protocol Dose
Eribulin will be given at a dose of 1.4 mg/m2 administered intravenously over 2-5 minutes.

Preparation
Eribulin will be supplied in commercially-labeled vials as a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of Eribulin mesylate as a 0.5 mg/ml solution in ethanol: water (5:95). Eribulin should be administered undiluted or diluted in 100 mL of 0.9% sodium chloride injection, USP.

Protocol Administration
Eribulin will be administered via intravenous infusion over 2-5 minutes. Treatments will be administered on cycle days 1 and 8.

Incompatibilities
Eribulin should not be diluted in, or administered through, an intravenous line containing solutions with dextrose.

Availability
Eribulin will be supplied by Eisai, Inc in vials labeled for clinical use containing 1 mg/2mL Eribulin mesylate as a 0.5 mg/ml solution in ethanol: water (5:95). To order drug, please contact EISAI IIS Department at Phone: 866-434-8176 or Eisai_iisgrants@eisai.com

Side Effects
Detailed information regarding side effects and rates of adverse events of Eribulin can be found in the package insert. Some of the most common side effects include:

Hematologic: The most common hematologic toxicities (occurring in ≥ 25% of patients) are neutropenia and anemia. The most common serious adverse events were febrile neutropenia (4%) and neutropenia (2%).

Gastrointestinal: Most common are nausea and constipation (occurring in ≥ 25% of patients). Other GI adverse events include diarrhea and vomiting.

Neurologic: Peripheral neuropathy (incidence of ≥ 25%) is the most common.

Other: Asthenia/fatigue and alopecia are the most common (occurring in ≥ 25% of patients) miscellaneous adverse events.

Nursing Implications
Monitor CBC and platelet counts.
Monitor for signs of neuropathy.
Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities.

7.2 Lenvatinib

Other names
Lenvima

Classification
LENVIMA, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamidemethanesulfonate.

Mode of action
Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

Storage and Stability
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F)

Protocol dose
Lenvatinib is administered at a dose of 20 mg orally.

Preparation
LENVIMA 4 mg capsules are supplied as hard hyperomellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 4 mg" on the body.

LENVIMA 10 mg capsules are supplied as hard hyperomellose capsules with yellow body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 10 mg" on the body.

Protocol administration
Lenvatinib is administered orally 20 mg po daily. It will be administered immediately after the Eribulin administration.

Incompatibilities
None

Availability
Lenvima will be supplied by Eisai, Inc in cards containing 10 mg and 4 mg capsules. To order drug, please contact EISAI IIS Department at Phone: 866-434-8176 or Eisai_iisgrants@eisai.com

Side effects
Detailed information regarding side effects and rates of adverse events of lenvatinib can be found in the package insert. Some of the most common side effects include:

Hypertension
The median time to onset of new or worsening hypertension was 16 days for LENVIMA-treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVIMA-treated patients and none in the placebo group.

Cardiac dysfunction
Cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of LENVIMA-treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in LENVIMA-treated patients were based on findings of decreased ejection fraction as assessed by echocardiography

Hepatic toxicity
4% of LENVIMA-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was Grade 3 or greater. No patients in the placebo group experienced Grade 3 or greater increases in ALT or AST. Across clinical studies in which 1108 patients received LENVIMA, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient.

Other adverse effects include renal failure or improvement, proteinuria, gastro intestinal fistula and perforation, arterial thrombotic events, QT interval prolongation, PRES, hypocalcemia and hemorrhagic events.

Nursing complications
Advise nursing women to discontinue breastfeeding during treatment with LENVIMA

8.0 Statistical Considerations

8.1 Proposed sample size

8.1.1 Safety run in phase

The number of subjects in the safety run-in phase will be 10. In the phase II trial the number of patients will be 30. Three patients will receive lenvatinib at 20 mg qd and Eribulin at 1.4 mg/m2 day 1 and day 8 of a 21 day cycle. Eribulin will be given on day 1 and lenvatinib will be started on day 2. If no DLTs are experienced, then the Phase II trial will be initiated at a dose of 24 mg daily of lenvatinib and Eribulin at 1.4 mg/m2 day 1 and day 8 of a 21 day cycle. If there is a DLT, then three more patients will be treated at that dose level. If no more DLTs are observed, then the phase II trial can commence at lenvatinib dose of 20 mg qd and Eribulin at 1.4 mg/m^2 day one and day 8 of a 21 day cycle. If there is another DLT, then there will be a dose reduction of lenvatinib to 14 mg daily.

8.1.2 Phase II

We will use group of n= 30 patients at the MTD. The expected poor response rate is p=0.20 or less, while p>=0.4 or more would be considered successful/good. We intend to proceed by calculating a response rate and providing a 95% confidence interval in the experimental group. This interval will have an approximate half width 2x [0.5/sqrt(30)]= 0.18 or less. We will test the hypothesis that the response rate is larger than 0.2 in the following way: if the lower bound of the one sided 90% exact confidence interval for underlying p is greater than 0.2, we will consider this evidence that p>0.2 i.e. of good response, and worthy of further investigation. Equivalently, using a one sided exact test of H0: p=0.2 versus H1: p>0.2, with power at p=0.4 being over 80%, we have the power analysis below.

Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

Power	N	Given H0 (P0)	Given H1 (P1)	Difference (P1 - P0)	Target Alpha	Actual Alpha	Beta	Reject H0 If R>=This
0.8237	30	0.2000	0.4000	0.2000	0.1000	0.0611	0.1763	10

8.2 Data analysis

Data will be analyzed by the PI and Dr Michalek using Stata statistical software. We will provide descriptive statistics and confidence intervals for all variables of interest for which data are collected.

8.3 Correlative science

Objective. To quantify serum levels of microRNAs pre- and post-treatment, with the goal of correlating levels with patient response to treatment.

RNA isolation. RNA will be isolated using the mirVanaTM miRNA Isolation Kit (Ambion) and quantified using a Nanodrop spectrophotometer. RNA quality will be determined on an Agilent 2100 Bioanalyzer.

miRNA expression profiling by NGS. We will use the HiSeq 2000 Sequencing System (Illumina) at the GCCRI Genomics Facility to measure miRNA expression profiles. Samples will be barcoded to allow multiplex sequencing and subjected to a second round of Q/C.

Data analysis. Adaptor sequences will be removed and reads of the length ≤ 15 or ≥ 30 are removed as they are not likely to originate from mature miRNAs. Duplicate reads will be removed with the remaining unique reads stored in FASTA format along with the read count. Unique reads will be aligned to the reference human genome (hg19) using the Bowtie short read aligner (0.12.9). Reads mapped to known miRNA loci as defined by miRbase (v21) will be kept for expression profiling. miRNA expression will be derived from counting reads perfectly matching known miRNA loci, normalized to the total number of uniquely mapped reads per sample.

Expected results. Expression profiles of serum miRNAs in 10 responders and 10 non-responders, which can then be compared by t-test to identify differentially expressed miRNAs that correlate with patient response to treatment.

Blood samples for microRNA assay will be collected on Cycle 1, Day 1 of treatment, and at the end of treatment. QIAGEN PAXgene Blood RNA tubes will be used to collect the samples.

Blood samples will be sent to Dr Pertsemlidis's lab:

Xiuye Ma (ma@uthscsa.edu)
Greehey Children's Cancer Research Institute
UT Health Science Center at San Antonio
8403 Floyd Curl Drive, MC 7784
San Antonio, TX 78229-3900
T (210) 562-9062

Tissue specimens from before and after treatment will be stained for markers of both angiogenesis and of hypoxia, CD-36 and carbonic anhydrase 9 (CA9) respectively, to see if the combination is effective at reducing hypoxia and the effects on angiogenesis. We will also look at the effects on reversal of EMT by performing IHC for E-cadherin, N-cadherin and vimentin to see if there is a reversion with treatment as has been seen in vitro and in animal models.

All IHC will be performed in Dr Susan Moobery's lab:

UT Health San Antonio

7703 Floyd Curl Drive, Mail Code 7764

San Antonio, TX 78229-3900

Phone: 210-567-4788

9.0 Adverse Events Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using

similar agents. Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death occurs.

Therapeutic monitoring should be performed following dose modification in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.

9.2 Definitions & Descriptions

9.2.1Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. A “drug-related toxicity" includes as events, any toxicity considered related, probably related, or possibly related to study drugs. Toxicities clearly not related to the drug, such as disease progression, environmental, unrelated trauma may not be considered “drug related toxicity”.

9.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v. 4.03 is available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

9.2.3 Serious Adverse events

All SAEs, regardless of attribution, occurring during the study or within 30 days of the last administration of study drug must be reported upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE. A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death. If death results from (progression of) the disease, the disease should be reported as the event (SAE) itself.
- Is life-threatening. The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24hours.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
- Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event". Examples: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

9.2.4 Exceptions to the Definition of SAE

Certain hospitalizations or prolongation of hospitalizations should not be considered SAEs, including those that meeting the following criteria:

- An admission resulting in a hospital stay of less than 12 hours.
- An admission that is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study).
- An admission that is not associated with an AE (i.e. social hospitalization for purposes of respite care)

9.2.5 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

A UPIRSO includes events that meet ALL of the following criteria:

- Are unanticipated in terms of nature, severity, or frequency
- Place the research subject or others at a different or greater risk of harm, AND
- Are deemed to be related or possibly related to participation in the study

10.0 Adverse event reporting

Steps to determine if expedited reporting is required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Identify the type of adverse event using the NCI CTCAE v 4.03.
Grade the adverse event using the NCI CTCAE v 4.03.

Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

Definite: AE is clearly related to the study treatment (attribution should be separated by each study drug)
Probable: AE is likely related to the study treatment (attribution should be separated by each study drug)
Possible: AE may be related to the study treatment (attribution should be separated by each study drug)
Unrelated: AE is clearly NOT related to the study treatment (attribution should be separated by each study drug

Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the specific agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current protocol, the drug package insert;
- or the current Investigator's Brochure.

10.1 Expedited Reporting of SAEs

Reporting
All SAEs must be reported following the DSMB outlined in the appendix of this protocol within 24 hours of becoming aware of the event. Completion of the Mays Cancer Center SAE Form is required. The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number
- Patient's Identification Number
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Hospital Discharge Summary (if available)

All SAEs will be reported to, and reviewed by, the DSMB at their next meeting.

Reporting to Eisai

All SADRs must also be reported to Eisai within 24 hours of becoming aware of the event. The report should use the FDA Medwatch. Reports can be sent to:

Eisai Medical Services
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: -1-732-791-1111
Email: ESI_Safety@eisai.com
Reporting to the UT Health San Antonio IRB

Any death of a subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the UT Health San Antonio Mays Cancer Center Regulatory Affairs Division

for reporting within 24 hours of notification. Other SAE's that are life threatening, but not fatal, should be reported to Mays Cancer Center Regulatory Affairs within 7 days of notification.

The following SAEs will be reported to the Mays Cancer Center Regulatory Affairs for reporting to the UT Health San Antonio IRB at the time of continuing review:

The following SAEs will be reported to the Mays Cancer Center Regulatory Affairs for reporting to the UT Health San Antonio IRB at the time of continuing review:

- All deaths of UT Health San Antonio subjects that were not previously reported
- All deaths of non-UT Health San Antonio subjects that are deemed to be unanticipated in nature and unrelated to participation
- Other UPIRSO's
- All other SAEs not previously reported to the UT Health San Antonio IRB as UPIRSOs

In addition, participating sites should follow local guidelines for reporting of SAEs to their IRB as required.

In addition, participating sites should follow local guidelines for reporting of SAEs to their IRB as required.

Reporting to the FDA:

The Mays Cancer Center Regulatory Affairs division will notify FDA within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening. The Mays Cancer Center Regulatory Affairs Division will notify the FDA within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMB). In these instances, an FDA Med Watch Form will be completed.

10.2 Routine Reporting

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the Schedule of Events. Routine AEs will be reviewed by the assigned DSMB for the study in accordance with the Cancer Therapy and Research Center's Multi-site DSMP Procedures. These will be reviewed by the DSMB on an on-going basis. A summary of all these events will be reported annually to the UT Health San Antonio IRB as part of the continuing review process.

11.0 Study Management

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be centralized through the Research/Nurse Coordinator of this study at the Institute for Drug Development at the Mays Cancer Center of the UT Health San Antonio. Please contact the assigned Mays Cancer Center Research/Nurse Coordinator for questions regarding patient registration procedures.

11.1.1 Access to IDEAS

Eligible patients will be registered to the study via the web-based application IDEAS. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the IDEAS system.

11.1.2 Registering a Patient for the Safety run in Portion of the Study

For potential patients for the phase I portion of this study, please email the UT Health San Antonio Nurse/Research Coordinator *prior to consenting a patient* to determine whether a slot is available on the current cohort. An email confirming the reservation and expiration date will be sent by the UT Health San Antonio Nurse/Research Coordinator. In order for registrations to be processed efficiently, study teams are asked to inform the UT Health San Antonio Nurse/Research Coordinator of the date and time that the patient will need to be registered. Detailed instructions and project coordinator contact information regarding registration procedures will be provided separately from this protocol.

To register a patient, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility checklist (signed and dated by the treating physician
- Signed and dated informed consent document
- Pathology Report

Affiliates sites are required to de-identify, scan, and e-mail the following source documents in order to confirm eligibility prior to registration for phase I patients:

- Complete medical and surgical history, current medications, history of clinically significant infections, and physical exam [including weight, height, ECOG PS, vital signs (pulse, temperature, respiratory rate, blood pressure, oxygen saturation)]
- Lab results (baseline CBC w/diff, baseline CMP)
- Documentation that archival tissue is available or documentation that a biopsy will be done
- Negative serum pregnancy test (if applicable)
- Copy of baseline imaging report

UT Health San Antonio study teams are NOT required to submit a separate email for UT Health San Antonio participants, provided that the required documentation listed above is readily available in the patient's electronic medical record (EMR). However, any information that is not available in the EMR must be de-identified and retained in the subject's research record.

The Nurse/Research Coordinator will review all source documentation required to confirm eligibility with the PI. Once confirmed, the Nurse/Research Coordinator will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of registration to the study team. Registration will then be complete and the patient may begin study treatment.

11.1.3 Registering a Patient to the Phase II Portion of the Study

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility checklist (signed and dated by the treating physician)
- Signed and dated informed consent document
- Pathology Report

The Nurse/Research Coordinator will review the submission with the PI, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

12.0 Data Management and Monitoring

This study will be monitored as an Investigational Initiated study, which requires auditing after the first patient has completed 1 cycle of treatment at each site and at least an annual audit, as outlined in the Cancer Therapy and Research Center's DSMP. Please refer to Appendix III for more specific details on the monitoring plan. Data submission requirements can be found in Appendix IV for both phase I patients and phase II patients.

Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, the coordinating site must be notified of the event within five business days of making the change.

Other Protocol Deviations

According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation is considered an instance of promptly reportable event if the occurrence:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: Study personnel will promptly report all deviations to the Mays Cancer Center Regulatory Affairs Division at: regulatoryaffairs@uthscsa.edu after becoming aware of the event using the Mays Cancer Center Protocol Deviation Tracking Form.

Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

13.0 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.0 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records or de identified documents to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator at each site and will require his/her final signature to verify the accuracy of the data.

14.1 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in by the PI of this study prior to release. If the investigator's wish to obtain monitored data prior to this point (or prior to the point dictated by study design), the investigator must send a written request for data to the PI of this study that includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The investigators are expected to use only monitored, accurate and approved data in all publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

15.0 Pathology Requirements

Biopsy proven disease by confirmation of biopsy specimen at the treating institution pathology department is required for enrollment to the study. Biopsy material will be reviewed by the pathology department at the treating institution.

16.0 Samples for Correlative Studies

Correlative studies will be conducted as secondary outcome measures to provide information on response prediction. We will perform assays to detect micro RNA and correlate response pre and post treatment.

We will use the HiSeq 2000 Sequencing System (Illumina) at the GCCRI Genomics Facility to measure miRNA expression profiles. Samples will be barcoded to allow multiplex sequencing and subjected to a second round of Q/C.

Blood Sample Collections

1. Red-top vacutainer tubes (not SST), upright at RT for 30 minutes, then centrifuged in a horizontal rotor for 20 min at 1100-1300g. Within 1 hour of centrifugation, pipette aliquots of 150 to 250 ul serum into labeled cryovials. These need to be stored at -80ºC and transported on dry ice.
2. Blood samples for microRNA assay will be collected on Cycle 1, Day 1 of treatment, and at the end of treatment. QIAGEN PAXgene Blood RNA tubes will be used to collect the samples and will and stored at -20ºC.

Blood samples will be sent to Dr Pertsemlidis's lab:

Xiuye Ma
Greehey Children's Cancer Research Institute
UT Health San Antonio
8403 Floyd Curl Drive, MC 7784
San Antonio, TX 78229-3900
T: (210) 562-9062
Email: ma@uthscsa.edu

Tissue specimens from before and after treatment will be stained for markers of both angiogenesis and of hypoxia, CD-36 and carbonic anhydrase 9 (CA9) respectively, to see if the combination is effective at reducing hypoxia and the effects on angiogenesis. We will also look at the effects on reversal of EMT by performing IHC for E-cadherin, N-cadherin and vimentin to see if there is a reversion with treatment as has been seen in vitro and in animal models. Ten unstained slides thickness of 5 micron will be requested from pathology

All IHC will be performed in Dr Susan Moobery's lab:

UT Health San Antonio
7703 Floyd Curl Drive, Mail Code 7764
San Antonio, TX 78229-3900
Phone: 210-567-4788

I Appendix Lenvatinib Package Insert

LENVIMA (lenvatinib) capsules, for oral use

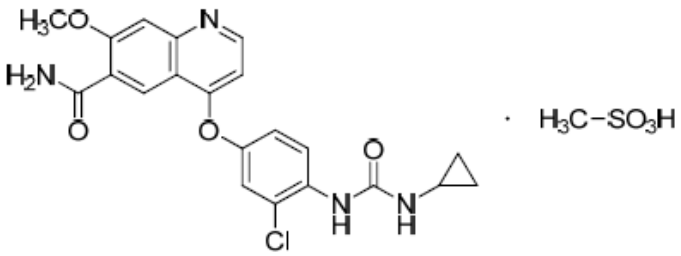
Initial U.S. Approval: 2015

Recommended Dose

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food [*see Clinical Pharmacology (12.3)*].
Continue LENVIMA until disease progression or until unacceptable toxicity occurs.
Take LENVIMA at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.
Severe Renal or Hepatic Impairment
The recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockroft-Gault equation) or severe hepatic impairment (Child-Pugh C).

11 DESCRIPTION

LENVIMA, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.30.

Each LENVIMA capsule contains lenvatinib mesylate equivalent to 4 mg or 10 mg of lenvatinib, and the following inactive ingredients: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropyl cellulose (type H), and talc. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A single 32 mg dose (1.3 times the recommended daily dose) of lenvatinib did not prolong the QT/QTc interval in a thorough QT study in healthy subjects. However, QT prolongation was observed in Study 1 *[see Warnings and Precautions (5.8)]*.

12.3 Pharmacokinetics

Absorption: After oral administration of LENVIMA, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.

In patients with solid tumors administered single and multiple doses of LENVIMA once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration- time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 μg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 μg/mL).

Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination: Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism: CYP3A is one of the main metabolic enzymes of lenvatinib. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion: Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Specific Populations:

Renal Impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), and severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of LENVIMA, the $AUC_{0\text{-}inf}$ for subjects with renal impairment were similar compared to those for healthy subjects [*see Dosage and Administration (2.1), Warnings and Precautions (5.6), Use in Specific Populations (8.6)*].

Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose of LENVIMA were evaluated in subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively [*see Dosage and Administration (2.1), Use in Specific Populations (8.7)*].

14 CLINICAL STUDIES

A multicenter, randomized (2:1), double-blind, placebo-controlled trial was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Radioactive iodine-refractory was defined as 1 or more measurable lesions with no iodine uptake on RAI scan, iodine uptake with progression within 12 months of RAI therapy, or having received cumulative RAI activity of >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic

region, prior VEGF/VEGFR-targeted therapy, and age. The major efficacy outcome measure was progression-free survival as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Independent review confirmation of disease progression was required prior to discontinuing patients from the randomization phase of the study. Other efficacy outcome measures included objective response rate and overall survival. Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression.

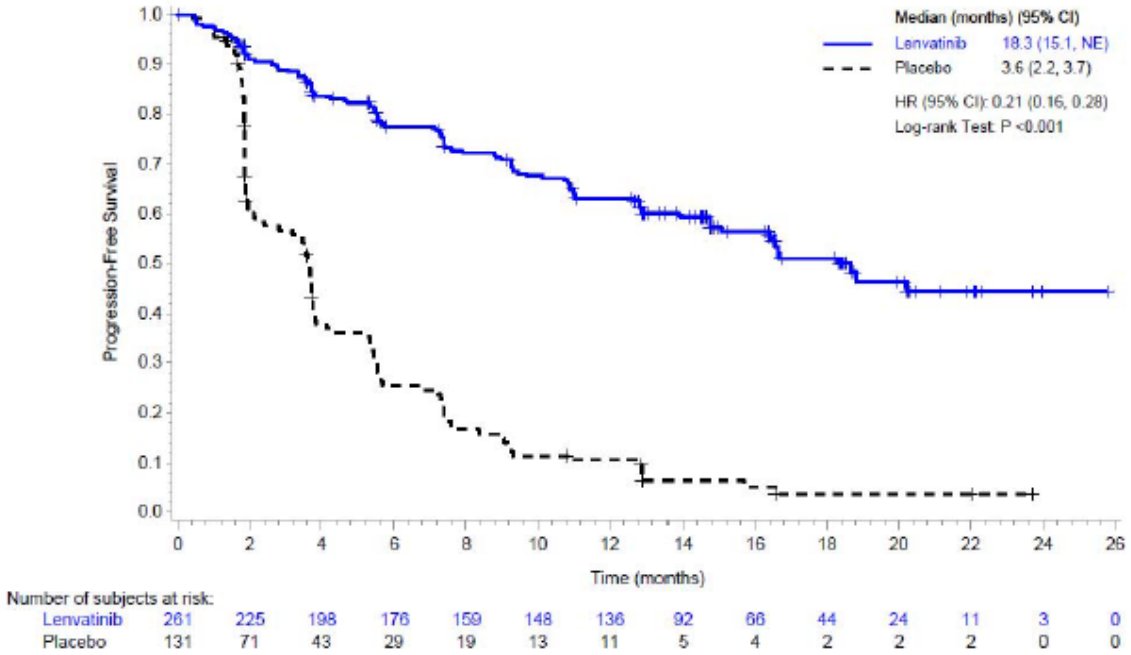
Of the 392 patients randomized, 51% were male, the median age was 63 years, 40% were older than 65 years, 79% were White, 54% had an ECOG performance status of 0, and 24% had received 1 prior VEGF/VEGFR-targeted therapy. Metastases were present in 99% of the patients: lungs in 89%, lymph nodes in 52%, bone in 39%, liver in 18%, and brain in 4%. The histological diagnoses were papillary thyroid cancer (66%) and follicular thyroid cancer (34%); of those with follicular histology, 44% had Hürthle cell and 11% had clear cell subtypes. In the LENVIMA arm, 67% of patients did not demonstrate iodine uptake on any radioiodine scan compared to 77% in the placebo arm. Additionally, 59% of patients on the LENVIMA arm and 61% of patients on placebo arm progressed, according to RECIST 1.1, within 12 months of prior ^{131}I therapy; 19.2% of patients on the LENVIMA arm and 17.6% of patients on placebo arm received prior cumulative activity of >600 mCi or 22 gigabecquerels (GBq) ^{131}I, with the last dose administered at least 6 months prior to study entry. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo (see Table 4 and Figure 1). Upon confirmation of progression, 109 (83%) patients randomly assigned to placebo crossed over to receive open-label LENVIMA.

	LENVIMA N=261	**Placebo N=131**
Progression-free Survival[a]		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI)[b]	0.21 (0.16, 0.28)	
P-value[c]	<0.001	
Objective Response Rate[a]		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value[d]	<0.001	
Overall Survival[e]		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b]	0.73 (0.50, 1.07)	
P-value[b]	0.10	

[a] Independent radiologic review
[b] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)
[c] Log-rank test 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)
[d] Cochran-Mantel-Haenszel chi-square test
[e] NE = Not estimable

Figure 1 Kaplan-Meier Plot of Progression-Free Survival



INDICATIONS

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

CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

In Study 1 hypertension was reported in 73% of LENVIMA-treated patients and 16% of patients in the placebo group [*see Adverse Reactions (6.1)*]. The median time to onset of new or worsening hypertension was 16 days for LENVIMA-treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVIMA-treated patients and none in the placebo group.

Control blood pressure prior to treatment with LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled at less than or equal to Grade 2. Discontinue LENVIMA for life-threatening hypertension [*see Dosage and Administration (2.2)*].

5.2 Cardiac Dysfunction

In Study 1, cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of LENVIMA-treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in LENVIMA-treated patients (14 of 17 cases) were based on findings of decreased ejection fraction as assessed by echocardiography. Six of 261 (2%) LENVIMA-treated patients in Study 1 had greater than 20% reduction in ejection fraction as measured by echocardiography compared to no patients who received placebo.

Monitor patients for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for development of Grade 3 cardiac dysfunction until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of cardiac dysfunction. Discontinue LENVIMA for Grade 4 cardiac dysfunction [*see Dosage and Administration (2.2)*].

5.3 Arterial Thromboembolic Events

In Study 1, arterial thromboembolic events were reported in 5% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of arterial thromboembolic

events of Grade 3 or greater was 3% in LENVIMA-treated patients and 1% in the placebo group.

Discontinue LENVIMA following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months [*see Dosage and Administration (2.2)*].

5.4 Hepatotoxicity

In Study 1, 4% of LENVIMA-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was Grade 3 or greater. No patients in the placebo group experienced Grade 3 or greater increases in ALT or AST. Across clinical studies in which 1108 patients received LENVIMA, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient.

Monitor liver function before initiation of LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold LENVIMA for the development of Grade 3 or greater liver impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hepatotoxicity. Discontinue LENVIMA for hepatic failure [*see Dosage and Administration (2.2)*].

5.5 Proteinuria

In Study 1, proteinuria was reported in 34% of LENVIMA-treated patients and 3% of patients in the placebo group [*see Adverse Reactions (6.1)*]. The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 11% compared to none in the placebo group.

Monitor for proteinuria before initiation of, and periodically throughout treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24 hour urine protein. Withhold LENVIMA for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 gm/24 hours. Discontinue LENVIMA for nephrotic syndrome [*see Dosage and Administration (2.2)*].

5.6 Renal Failure and Impairment

In Study 1, events of renal impairment were reported in 14% of LENVIMA-treated patients compared to 2% of patients in the placebo group. The incidence of Grade 3 or greater renal failure or impairment was 3% in LENVIMA-treated patients and 1% in the placebo group. The primary risk factor for severe renal impairment in LENVIMA-treated patients was dehydration/hypovolemia due to diarrhea and vomiting.

Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of renal impairment [*see Dosage and Administration (2.2)*].

5.7 Gastrointestinal Perforation and Fistula Formation

In Study 1, events of gastrointestinal perforation or fistula were reported in 2% of LENVIMA-treated patients and 0.8% of patients in the placebo group.

Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula [*see Dosage and Administration (2.2)*].

5.8 QT Interval Prolongation

In Study 1, QT/QTc interval prolongation was reported in 9% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of QT interval prolongation of Grade 3 or greater was 2% in LENVIMA-treated patients compared to no reports in the placebo group. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics.

Monitor and correct electrolyte abnormalities in all patients. Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation. Resume LENVIMA at a reduced dose when QT prolongation resolves to Grade 0 or 1 or baseline [*see Dosage and Administration (2.2), Clinical Pharmacology (12.2)*].

5.9 Hypocalcemia

In Study 1, 9% of LENVIMA-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction [*see Adverse Reactions (6.1)*].

Monitor blood calcium levels at least monthly and replace calcium as necessary during LENVIMA treatment. Interrupt and adjust LENVIMA dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia [*see Dosage and Administration (2.2)*].

Across clinical studies in which 1108 patients received LENVIMA, Grade 3 or greater hemorrhage was reported in 2% of patients. In Study 1, there was 1 case of fatal intracranial hemorrhage among 16 patients who received lenvatinib and had CNS metastases at baseline.

Withhold LENVIMA for the development of Grade 3 hemorrhage until resolved to Grade 0 to 1. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hemorrhage. Discontinue LENVIMA in patients who experience Grade 4 hemorrhage [*see Dosage and Administration (2.2)*].

5.12 Impairment of Thyroid Stimulating Hormone Suppression

LENVIMA impairs exogenous thyroid suppression. In Study 1, 88% of all patients had a baseline thyroid stimulating hormone (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 LENVIMA-treated patients as compared with 14% of patients receiving placebo.

Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

5.13 Embryofetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)*].

5.10 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies in which 1108 patients received LENVIMA, there were 3 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). Confirm the diagnosis of RPLS with MRI. Withhold for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms [*see Dosage and Administration (2.2)*].

5.11 Hemorrhagic Events

In Study 1, hemorrhagic events occurred in 35% of LENVIMA-treated patients and in 18% of the placebo group. However, the incidence of Grade 3-5 hemorrhage was similar between arms at 2% and 3%, respectively. The most frequently reported hemorrhagic event was epistaxis (11% Grade 1 and 1% Grade 2). Discontinuation due to hemorrhagic events occurred in 1% of LENVIMA-treated patients.

- Impairment of Thyroid Stimulating Hormone Suppression

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

- Hypertension [*see Warnings and Precautions (5.1)*]
- Cardiac Dysfunction [*see Warnings and Precautions (5.2)*]
- Arterial Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Hepatotoxicity [*see Warnings and Precautions (5.4)*]
- Proteinuria [*see Warnings and Precautions (5.5)*]
- Renal Failure and Impairment [*see Warnings and Precautions (5.6)*]
- Gastrointestinal Perforation and Fistula Formation [*see Warnings and Precautions (5.7)*]
- QT Interval Prolongation [*see Warnings and Precautions (5.8)*]
- Hypocalcemia [*see Warnings and Precautions (5.9)*]
- Reversible Posterior Leukoencephalopathy Syndrome [*see Warnings and Precautions (5.10)]*
- Hemorrhagic Events [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data obtained in 1108 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize risks of serious adverse drug reactions [*see Warnings and Precautions (5.4, 5.10, 5.11)*]. The median age was 60 years (range 21-89 years). The dose range was 0.2 mg to 32 mg. The median duration of exposure in the entire population was 5.5 months.

The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVIMA (n=261) or placebo (n=131) [*see Clinical Studies (14)*]. The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.

In Study 1, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

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

Table 2 presents the percentage of patients in Study 1 experiencing adverse reactions at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the DTC study.

Table 2 **Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% All Grades or Greater than or Equal to 2% Grades 3 and 4**

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular Disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal Disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General Disorders and Administration Site Conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric Disorders				
Insomnia	12	0	3	0
Infections and Infestations				
Dental and oral infections[h]	10	1	1	0
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0

Table 2 Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% All Grades or Greater than or Equal to 2% Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

[a] Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure

[b] Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation

[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain

[d] Includes oral pain, glossodynia, and oropharyngeal pain

[e] Includes asthenia, fatigue, and malaise

[f] Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia

[g] Includes rash macular, rash maculo-papular, rash generalized, and rash

[h] Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

A clinically important adverse reaction occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of less than 5% was pulmonary embolism (3%, including fatal reports vs 2%, respectively).

Table 3 Laboratory Abnormalities with a Difference of at Least ≥2% in Grade 3 - 4 Events and at a Higher Incidence in LENVIMA-Treated Patients[a]

Laboratory Abnormality	LENVIMA 24 mg N=258[b]	Placebo N=131[b]
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Creatinine increased	3	0
Alanine aminotransferase (ALT) increased	4	0
Aspartate aminotransferase (AST) increased	5	0
Hypocalcemia	9	2
Hypokalemia	6	1
Lipase increased	4	1
Hematology		
Platelet count decreased	2	0

[a] With at least 1 grade increase from baseline

[b] Subject with at least 1 post baseline laboratory value

In addition the following laboratory abnormalities (all Grades) occurred in greater than 5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

10 OVERDOSAGE

There is no specific antidote for overdose with LENVIMA. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*.Adverse reactions in patients receiving single doses of LENVIMA as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food [*see Clinical Pharmacology (12.3)*]. Continue LENVIMA until disease progression or until unacceptable toxicity occurs.

Take LENVIMA at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

Severe Renal or Hepatic Impairment

The recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockroft-Gault equation) or severe hepatic impairment (Child-Pugh C) [*see Warning and Precaution (5.4, 5.6), Use in Specific Populations (8.6, 8.7)*].

2.2 Dose Modifications

Hypertension

- Assess blood pressure prior to and periodically during treatment. Initiate or adjust medical management to control blood pressure prior to and during treatment.
- Withhold LENVIMA for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at a reduced dose (*see Table 1*) when hypertension is controlled at less than or equal to Grade 2.
- Discontinue LENVIMA for life-threatening hypertension.

Cardiac dysfunction or hemorrhage

- Discontinue for a Grade 4 event.
- Withhold LENVIMA for development of Grade 3 event until improved to Grade 0 or 1 or baseline.
- Either resume at a reduced dose (*see Table 1*) or discontinue LENVIMA depending on the severity and persistence of the adverse event.

Arterial thrombotic event

- Discontinue LENVIMA following an arterial thrombotic event.

Renal failure and impairment or hepatotoxicity

- Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment or hepatotoxicity until resolved to Grade 0 to 1 or baseline.

- Either resume at a reduced dose (*see Table 1*) or discontinue LENVIMA depending on the severity and persistence of renal impairment or hepatotoxicity.
- Discontinue LENVIMA for hepatic failure.

Proteinuria
- Withhold LENVIMA for ≥2 grams of proteinuria/24 hours.
- Resume at a reduced dose (*see Table 1*) when proteinuria is <2 gm/24 hours.
- Discontinue LENVIMA for nephrotic syndrome.

Gastrointestinal perforation or fistula formation
- Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula.

QT prolongation
- Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation.
- Resume LENVIMA at a reduced dose (*see Table 1*) when QT prolongation resolves to Grade 0 or 1 or baseline.

Reversible posterior leukoencephalopathy syndrome (RPLS)
- Withhold for RPLS until fully resolved.
- Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms.

Manage other adverse reactions according to the instructions in Table 1. Based on the absence of clinical experience, there are no recommendations on resumption of dosing in patients with Grade 4 clinical adverse reactions that resolve.

Table 1 Recommended Dose Modifications for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily

[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA

[b] Reduce dose in succession based on the previous dose level (24 mg, 20 mg, or 14 mg per day)

[c] Refers to the same or a different adverse reaction that requires dose modification

3 DOSAGE FORMS AND STRENGTHS

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits *[see Data]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses greater than or equal to 0.3 mg/kg [approximately 0.14 times the recommended human dose based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended human dose based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the human dose of 24 mg based on body surface area). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma *[see*

Data]. Because of the potential for serious adverse reactions in nursing infants from LENVIMA, advise women to discontinue breastfeeding during treatment with LENVIMA.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Infertility

Females

LENVIMA may result in reduced fertility in females of reproductive potential *[*see *Nonclinical Toxicology (13.1)]*.

Males

LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration *[*see *Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of LENVIMA in pediatric patients have not been established.

Juvenile Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the clinical exposure by AUC at the recommended human dose). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

8.5 Geriatric Use

Of 261 patients who received LENVIMA in Study 1, 118 (45.2%) were greater than or equal to 65 years of age and 29 (11.1%) were greater than or equal to 75 years of age. No overall

16 HOW SUPPLIED/STORAGE AND HANDLING

LENVIMA 4 mg capsules are supplied as hard hypromellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 4 mg" on the body.

LENVIMA 10 mg capsules are supplied as hard hypromellose capsules with yellow body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 10 mg" on the body.

LENVIMA capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card as follows:

- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Manufactured by:
Patheon Inc.
Mississauga, Ontario, Canada

Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

LENVIMA™ is a trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc.

II. Appendix – Common Toxicity Criteria for Adverse Events

Toxicity will be graded according to the NCI's Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE version 4.03 can be accessed at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

III. Appendix – Data Safety & Monitoring Plan

Data and Safety Monitoring Oversight

A Data and Safety Monitoring Plan is required for all an individual protocols conducted at Mays Cancer Center. All protocols conducted at Mays Cancer Centerare covered under the auspices of the Mays Cancer CenterInstitutional Data Safety Monitoring Plan (DSMP).

The Mays Cancer Center Institutional DSMP global policies provide individual trials with:

- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the Mays Cancer Center Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- independent monitoring and source data verification by the Mays Cancer Center QA Monitor/Auditor
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS) ,
- oversight by the Data Safety Monitoring Committee (DSMC), and
- Verification of protocol adherence via annual audit for all Investigator Initiated Studies by the Mays Cancer Center Quality Assurance Division.

Monitoring Progress and Safety

Due to the risks associated with participation in this protocol, the Mays Cancer Center DSMB #2 in conjunction with the Principal Investigator will perform assessment of adverse events, adverse event trends and treatment effects on this study. The Mays Cancer Center DSMB #2 acts as an independent Data Safety Monitoring Board (DSMB) for IIS conducted at Mays Cancer Center. The Mays Cancer Center DSMB #2 will monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. An additional layer of review is provided by the Mays Cancer Center Data Safety Monitoring Committee (DSMC) who will review DSMB quarterly reports.

Baseline events and adverse events will be captured using the Mays Cancer Center Master Adverse Events Document for each patient using CTCAE V. 4.03 for the grading and attribution of adverse events. Usage of the Mays Cancer Center Master Adverse Events Document centrally documents:

- the event and grades the seriousness of the event,
- if the event was a change from baseline,
- the determination of the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- What actions were taken as a result of the event.

Safety Definitions:

For this study, the following safety definitions will be applicable:

Adverse Event Definition: An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research For this study, all adverse events will be documented starting with cycle 1 day 1 and ending 30 days after the last dose of study drug is received.

Serious Adverse Event Definition: is any adverse event that:
1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);
definitely related or probably related to participation in the research; and
suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Reporting Requirements

For this study, the Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a monthly basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- dose modification,
- suspending enrollment due to safety or efficacy, or
- termination of the study due to a significant change in risks or benefits.

The PI will provide the DSMB #2 with the monthly findings for discussion and review during their meetings.

Serious adverse events will be revised as they occur to determine if a DLT and the MTD has been reached. Adverse events and serious adverse events from all sites will be reviewed by DSMB#2 to determine if it is appropriate to escalate to the next dose level prior to opening the next cohort or determine that dose expansion at the current dose level is warranted.

For this protocol the number, frequency, and severity of adverse events and dose-limiting toxicities (DLTs) will be recorded (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE v 4.03). The MTD will be defined as the dose level at which ≤ 1 (out of 3 or 6 patients) exhibit a DLT.

Dose-Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

DLT evaluation will occur weekly for the first cycle (1 cycle = 21 days).

Any enrolled and treated patient should be evaluated for DLT purposes.

The DLT period as a whole will be the first cycle of treatment. (Adverse events, however, will continue to be collected for the duration of treatment).

In general, a non-hematologic DLT is defined as any Grade ≥ 3 toxicity, and a hematologic DLT is defined as any Grade ≥ 4 toxicity, both by CTCAE v4.03 criteria.

In addition, the following criteria and exceptions apply:

- ANC < 500/mm^3 for > 7 days despite GCSF support is a DLT.
- Platelet count < 20,000/mm^3 for more than 3 days that is considered drug-related is a DLT.
- For nausea, vomiting, or diarrhea, patients must have Grade 3 or 4 toxicity that persists at this level despite use of optimal symptomatic treatment (per local institutional guidelines), in order for these to be considered a DLT.
- Grade 3 thromboembolic events are not considered DLT.
- Any Grade 3 rash that resolves to Grade ≤ 2 within a 10 day period (including with symptomatic treatment) will not be considered a DLT.
- Cases involving hyperbilirubinemia that is primarily indirect, and considered not reflective of underlying liver disease (ie, resulting from transfusion of red blood cells), will not be considered a DLT.
- A DLT must be attributed to one of the two investigational drugs. A “drug-related toxicity" includes as events, any toxicity considered related, probably related, or possibly related to study drugs. Toxicities clearly not related to the drug, such as disease progression, environmental, unrelated trauma may not be considered “drug related toxicity”

- As per the Mays Cancer Center DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to the DSMB #2 and all members of the research team at UT Health San Antonio and all affiliate sites. Furthermore, the PI of this study will promptly notify all study affiliates, the UT Health San Antonio IRB, the Mays Cancer Center DSMC, and the FDA via a FDA Form 3500Aa written IND safety report of any adverse events that are either serious and/or unexpected. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance who will promptly notify the sponsor and the UT Health San Antonio IRB.

- The PI will review data on adverse events from case report forms from all sites on a monthly basis and serious adverse events per occurrence to determine the significance of the reported events and will provide findings to DSMB#2. The DSMB #2 will review the information provided by the PI and report to the Mays Cancer Center DSMC on a quarterly basis, unless an emergent issue has been identified. The Investigator Initiated Study Quarterly DSMB Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality) dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the Mays Cancer Center DSMB for independent review outside of the quarterly reporting cycle, which begins quarterly after the end of the first subject's DLT evaluation period. The DSMB #2 will also provide its findings to the Mays Cancer Center's Regulatory Affairs Division so that it may be provided to the UT Health San Antonio IRB and affiliate sites with the protocol's annual progress report. Conflict of interest is avoided by the independent reviews of the Mays Cancer Center DSMB #2, Mays Cancer Center DSMC, and by ongoing independent review of UPIRSO trends by the Director of Quality Assurance.

- All SAE and UPRISO's will be reported following Mays Cancer Center, UT Health San Antonio institutional and FDA guidelines

UTHSCSA SAE/UPRISO REPORTING REQUIREMENTS For IIS that the PI holds the IND		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory Affairs and DQA	ASAP
All AE, SAE and UPIRSO	FDA on form 3500A	within 7 calendar days by telephone and 15 calendar days using the Form 3500A
SAE	PI at UTHSCSA	within 24 hours
SAE	UTHSCSA IRB	Annually
UPIRSO - all	PI at UTHSCSA	within 24 hours
UPIRSO - all	FDA	within 7 days
UPIRSO - life threatening	UTHSCSA IRB/UTHSCSA OCR	within 48 hours
UPIRSO - non-life threatening	UTHSCSA IRB/UTHSCSA OCR	within 7 days

AE's and SAE events that occur during clinical trials with or without an Investigational New Drug (IND) application are mandatory reports submitted to FDA via **Medwatch FDA F3500A** ***within 15 days for events that have at least a possible relationship with the drug.***

Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at Mays Cancer Center, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Each site will be audited for accuracy after the end of the first cycle for the first patient enrolled. Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the Mays Cancer Center DSMC.

Mays Cancer Center DSMB Membership

The Mays Cancer Center has two DSMB's with a primary set of members specific to the histology of the study consisting of UT Health San Antonio faculty and staff. This Protocol is under the jurisdiction of DSMB#2 for Solid Tumor Studies.

As per NCI guidelines and to eliminate conflict of interest (financial, intellectual, professional, or regulatory in nature), the Mays Cancer Cente rDSMB specific to this study will not treat patients on this protocol. Usage of the DSMB specific to the histology has been created to ensure that experts in that histology are represented on the DSMB assembled for this protocol, but may be expanded, at the PI's discretion, to include other members which may include:

- experts in the fields of medicine and science that are applicable to the study (if not currently represented on the DSMB),
- statistical experts,
- lay representatives,
- multidisciplinary representation, from relevant specialties including experts such as bioethicists, biostatisticians and basic scientists, and
- others who can offer an unbiased assessment of the study progress.

Additional or alternate membership of in the DSMB is selected by the DSMC chair, in conjunction with the PI of this protocol.

Mays Cancer Center DSMB Charter and Responsibilities

The Mays Cancer Center DSMB will provide information on the membership composition, including qualifications and experience to both the UT Health San Antonio IRB and Mays Cancer Center PRC for review. The Mays Cancer Center DSMB for this study will act as an independent advisory board to the PI and will report its findings and recommendations to the PI, the UT Health San Antonio IRB and the Mays Cancer Center DSMC. Mays Cancer Center DSMB reports will utilize the Investigator Initiated Study Quarterly DSMB Report Form and meetings will occur on a monthly basis to review any updates from the prior meeting.

Once the protocol is activated, if not already established elsewhere in the protocol the Mays Cancer Center DSMB will establish and provide:

- procedures for maintaining confidentiality;
- statistical procedures including monitoring guidelines, which will be used to monitor the identified primary, secondary, and safety outcome variables;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- plans for changing frequency of interim analysis as well as procedures for recommending protocol changes;
- recommendation of dose escalation, MTD recommendation of early termination based on efficacy results;
- recommendation of termination due to unfavorable benefit-to-risk or inability to answer study questions;
- recommendation of continuation of ongoing studies;
- recommend modification of sample sizes based on ongoing assessment of event rates; and
- review of final results and publications.

IV Appendix - Data Collection & Submission

Study-specific instructions regarding the entry and submission of data using paper CRFs or eCRFs using an electronic data system (e.g. REDCap or Excel), will be provided at the time of training prior to study activation.

Mays Cancer CenterMulti-site Compliance Policies of the Mays Cancer Center at the UT Health Science San Antonio DSMP regarding data collection and submission will be strictly enforced.

Study Chart

In addition to the regular hospital chart, a separate patient folder will be kept which includes the patient's signed, dated informed consent document.

PLEASE NOTE: FOR SAFETY RUN-IN PATIENTS, ACCRUAL MAY BE SUSPENDED IF DATA IS NOT SUBMITTED BY THE DUE DATES SPECIFIED BELOW

Case Report Forms to be submitted prior to registration

Please refer to Section 12.3 for all forms/data to be submitted prior to registration.

Case Report Forms to be submitted within 5 days of registration:

- Concomitant Medications Form: *This should be updated to reflect the patients' information at the time of registration. From that point, it should be updated as needed*.
- Master Adverse Event Form: *Update to reflect the adverse events that are present at baseline.*
- RECIST Disease Measurements Form: *Should reflect disease measurements at baseline.*

- On-Study Form: *Will include dates and results of all tests and labs required to be performed prior to registration.*

Case Report Forms to be submitted during the 21 day DLT Evaluation Period (THIS IS ONLY A REQUIREMENT FOR PHASE I PATIENTS)

- Lab Results *No more than 48 hours after the 21 day DLT period ends*
- Adverse Events Form: *No more than 48 hours after the 21 day DLT period ends*
- Patient Vitals Form: *Each exam conducted during the DLT period, no more than 48 hours after the 21 day DLT period ends*
- Concomitant Medications Form: *Updated as necessary*
- Treatment Cycle Summary Form: *No later than 48 hours after the end of 21 day DLT period*

Case Report Forms to be submitted at the end of each cycle:

- Labs Results r Form
- Master Adverse Events Form
- Patient Vitals Form
- Concomitant Medications Form: *Updated as needed*
- Treatment Cycle Summary Form

Case Report Forms to be submitted after every 2 cycles, when disease is assessed

- RECIST Disease Measurements Form: *Complete measurements for each assessment.*

Case Report Forms to be submitted no later than 1 week after End of Treatment Visit:

- Off-treatment Form:
- Patient Vitals Form
- Lab Results Form
- Master Adverse Events Form: *All AEs should be finalized within 30 days of last dose*

Case Report Forms to be completed during follow-up:

- Survival Status Form: Survival status and date of disease progression (if/when applicable) should be completed every 6 months until death.

V. Appendix – Table of Assessments

V. APPENDIX - DATA SUBMISSION TABLE

	Prior to registration	Within 5 days of registration	DLT Period- Only for Phase I Patients	After Each Cycle	After Every 2 cycles	End of Treatment Visit	Follow-Up
Eligibility Form	X						
Informed Consent Form	X						
Pathology Report	X						
On-Study Form		X					
Concomitant Medications Form		X[2]		X[4]			
Patient Vitals Form			X[3]	X		X[5]	
Labs Results Form			X[3]	X			
AE Form		X[1]	X[3]	X		X[5]	
Treatment form			X[3]	X			
Disease Measurement Form		X		X	X		
Off-Treatment Form						X[5]	X[6]
Survival Status Form							X[6]

1 Should reflect all AEs present at baseline
2 Should reflect medications taken at baseline
3 Should be entered no more than 48 hours after the end of 21 day DLT period
4 Update as required
5 To be entered within 1 week of the end of treatment visit
6 Survival status and date of disease progression will be entered q 6 months until death or until pt withdraw

VI. Appendix SAE Reporting Form

VI. APPENDIX – EISAI SAE REPORT FORM

EISAI CLINICAL STUDY REPORT FORM FOR SERIOUS ADVERSE EVENTS & EVENTS OF SPECIAL INTEREST

PLEASE COMPLETE IN CAPITALS

Version 1.0 (July 2013) Page 1 of 4

A. STUDY INFORMATION

1. Product:	2. Protocol:	3 ☐ Initial ☐ Follow up	4 Country:

B. SUBJECT INFORMATION

1 Initials:	4 Sex: ☐ Male ☐ Female	5 Age:	7 Weight: ☐ kg ☐ lb	8 Height: ☐ cm ☐ in	9 Pregnancy: ☐ Yes ☐ No 10 ( ) wks	11 At the onset of SAE: ☐ Outpatient ☐ Inpatient 12 Admission date: (DD/MMM/YYYY)
2 Subject ID no:		6 Date of birth (DD/MMM/YYYY)				
3 Randomization no:						
13 Protocol indication					14 Date of indication diagnosis: (DD/MMM/YYYY)	
15 Disease(s) present at baseline, and ongoing at time of event, including allergies/risk factors						
16 Past Medical History						

C. EVENT INFORMATION

1. Event(s)	2. Onset date (DD/MMM/YYYY)	3. Relationship to Study Drug	4. Severity Or CTC Grade (CTC 5 is death use Outcome)	5. Seriousness (See below)	6. Outcome (Date: DD/MMM/YYYY)	7. Dechallenge Did Event Diminish After Study Drug Stopped or Dose Reduced	8. Rechallenge Did Event Reappear after Study Drug Reintroduced
		Is there a reasonable possibility that the study drug caused the AE? ☐ Yes (Related) ☐ No (Not Related)	☐ Mild 1 ☐ Moderate ☐ 2 ☐ Severe ☐ 3 ☐ 4	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8	(Date) ☐ Recovered ☐ Death ☐ Recovering ☐ Unknown ☐ Not recovered ☐ Recovered with sequelae	☐ Yes (Positive) ☐ No (Negative) ☐ Not applicable ☐ Unknown	☐ Yes (Positive) ☐ No (Negative) ☐ Not applicable ☐ Unknown Dose of Rechallenge ( )

EISAI CLINICAL STUDY REPORT FORM FOR SERIOUS ADVERSE EVENTS & EVENTS OF SPECIAL INTEREST

PLEASE COMPLETE IN CAPITALS

		Is there a reasonable possibility that the study drug caused the AE? ☐ Yes (Related) ☐ No (Not Related)	☐ Mild 1 ☐ Moderate ☐ 2 ☐ Severe ☐ 3 ☐ 4	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8	(Date) ☐ Recovered ☐ Death ☐ Recovering ☐ Unknown ☐ Not recovered ☐ Recovered with sequelae	☐ Yes (Positive) ☐ No (Negative) ☐ Not applicable ☐ Unknown	☐ Yes (Positive) ☐ No (Negative) ☐ Not applicable ☐ Unknown Dose of Rechallenge ( )

Seriousness: Check the applicable numbers into the above "Seriousness" box
1. Death 2. Life-threatening 3. Involved hospitalization 4. Prolonged hospitalization 5. Persistent or significant disability/incapacity 6. Congenital anomaly
7. Important medical event (see instructions) 8. Non-serious (does not meet above criteria)

EISAI CLINICAL STUDY REPORT FORM FOR SERIOUS ADVERSE EVENTS & EVENTS OF SPECIAL INTEREST

PLEASE COMPLETE IN CAPITALS

Version. 1.0 (July 2013) Page 2 of 4

C. EVENT INFORMATION (continued)

9. Description of the event: Include signs, symptoms and treatment of the event

10. Did the subject dropout from the study due to AE? ☐ No ☐ Yes 11. Date of dropout: (DD/MMM/YYYY)

If outcome of event was death 12. Death date: (DD/MMM/YYYY)
14. Autopsy: ☐ No ☐ Yes 15. Autopsy date: (DD/MMM/YYYY)
16. Autopsy results:

13. Cause of Death:

17. Has the subject experienced this sign(s)/symptom(s)/disease(s) in the past? ☐ No ☐ Yes
18. If so, provide details:

19. Has the subject had a prior SAE reported ☐ No ☐ Yes
20. If so, for what event(s) and when reported:

D. DRUG INFORMATION

For each drug please include all of the information detailed below. It is particularly important to include all of the information for the study drug, including the start and stop date when the dose of the study drug is changed, whether the change is per protocol, or as a result of an AE or SAE. Use a separate line for each change in the dose of the study drug.

1. Drugs	2. Dose, Frequency (e.g. 10 mg bid)	3. Route	Date of administration		6. Indication	7. If Suspect, tick box
			4. Start date (DD/MMM/YYYY)	5. End date (DD/MMM/YYYY) or continuing (write C)		
8. Study treatment:						
Action taken with study treatment: Dose maintained ☐ Dose increased ☐ Dose reduced ☐ Drug discontinued ☐ Not applicable ☐ Unknown ☐						
8. Study treatment:						
Action taken with study treatment: Dose maintained ☐ Dose increased ☐ Dose reduced ☐ Drug discontinued ☐ Not applicable ☐ Unknown ☐						
8. Study treatment:						
Action taken with study treatment: Dose maintained ☐ Dose increased ☐ Dose reduced ☐ Drug discontinued ☐ Not applicable ☐ Unknown ☐						
9. Other drugs:						☐
						☐
						☐
						☐
						☐
						☐
						☐

E. LABORATORY TESTS RESULTS (PLEASE ATTACH RESULTS WHEN POSSIBLE)

(Baseline, During administration, At the time of AE, F-up, etc.)

EISAI CLINICAL STUDY REPORT FORM FOR SERIOUS ADVERSE EVENTS & EVENTS OF SPECIAL INTEREST

PLEASE COMPLETE IN CAPITALS

Version. 1.0 (July 2013)

F. REPORTING INVESTIGATOR'S COMMENT FOR CAUSALITY

G. REPORTING INVESTIGATOR INFORMATION

1. Investigator Name:	2. Centre	3. Center no:				
4. Address:						
5 Telephone:						
6. Investigator's signature:	7. Signed date: (DD/MMM/YYYY)					

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a. Date this report initially received by Eisai: (DD/MMM/YYYY)	b. ARISg No:	c. Local No:

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