

ADDITIONAL EXPLORATORY ANALYSIS OF PHASE II TRIAL SUGGESTS ANTICANCER AGENT LENVATINIB EXTENDS OVERALL SURVIVAL IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today the latest results of an additional exploratory analysis of a Phase II clinical trial (Study 703) of its in-house developed anticancer agent lenvatinib mesylate (brand name in the U.S.: Lenvima™, "lenvatinib") in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had failed at least two systemic anticancer regimens.

Study 703 is a Phase II, randomized, double-blind, placebo-controlled study of lenvatinib in patients with locally advanced or metastatic, non-squamous, NSCLC who had failed at least two systemic anticancer regimens. The study enrolled 135 patients who were randomized in a 2:1 ratio to receive orally either lenvatinib (24 mg) or placebo once-daily in addition to best supportive care.

According to primary analysis of the study (67% of registered patients having experienced an OS event), lenvatinib exhibited a trend of extension in OS compared to placebo ($p=0.065$; median OS in the lenvatinib group: 38.4 weeks, median OS in the placebo group: 24.1 weeks; Hazard Ratio 0.7 [95% CI: 0.45-1.03]), and these results were presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2014¹. Survival information continued to be followed and an additional exploratory analysis of OS (90% of registered patients having experienced an OS event) was recently completed. The results of the exploratory analysis generated consistent outcomes with those from the primary analysis. The lenvatinib group maintained a similar trend of extension in OS compared to placebo (nominal p -value=0.029). The most common treatment-related adverse events reported in the lenvatinib group were hypertension, proteinuria, decreased appetite, stomatitis and diarrhea.

Lung cancer is the leading cause of cancer-related mortality in both men and women, with 1.8 million new cases diagnosed every year and 1.6 million deaths reported annually worldwide. NSCLC accounts for approximately 85% of all lung cancer cases. As there is no approved standard treatment for advanced NSCLC in a third-line or greater setting, development of an effective new treatment is needed. Eisai will utilize the outcome from this study to design its lenvatinib development strategy for NSCLC upon consultation with regulatory authorities.

Lenvatinib is an oral molecular targeted agent that selectively inhibits the activities of several different molecules including VEGFR, FGFR, RET, KIT and PDGFR. In particular, lenvatinib possesses a new binding mode (Type V) to VEGFR2, as confirmed through X-ray crystal structural analysis, and exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis².

Lenvatinib was approved in the United States on February 13 as Lenvima, indicated for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. In addition, Eisai has already submitted regulatory applications for lenvatinib seeking indication approval for refractory thyroid cancer to health authorities in Japan and the EU, and is filing subsequent applications in other countries worldwide. Meanwhile, Eisai is also conducting a global Phase III trial of lenvatinib in hepatocellular carcinoma as well as Phase II studies of lenvatinib in several other tumor types.

Eisai is committed to exploring the potential clinical benefits of lenvatinib in order to further contribute to patients with cancer and their families.

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[Notes to editors]

1. About Lenvatinib (E7080)

Lenvatinib, discovered and developed by Eisai, is an oral molecular targeted agent that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4)), and fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4 in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFR α ; KIT; and RET) involved in tumor proliferation. In particular, lenvatinib possesses a new binding mode (Type V) to VEGFR2, as confirmed through X-ray crystal structural analysis, and exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis².

Lenvatinib was approved as Lenvima on February 13, 2015, for the treatment of refractory thyroid cancer in the United States, and is currently undergoing regulatory review for this indication in Japan, the EU, Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil. Meanwhile, Eisai is currently conducting clinical studies of lenvatinib in several types of cancer including hepatocellular carcinoma (Phase III), renal cell carcinoma (Phase II), non-small cell lung cancer (Phase II) and endometrial cancer (Phase II). Furthermore, lenvatinib has been granted Orphan Drug Designation in Japan (for thyroid cancer), the United States (for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer), and Europe (for follicular and papillary thyroid cancer).

2. About Lenvatinib's Novel Binding Mode (Type V)²

Kinase inhibitors are categorized into several types (Type I to Type V) depending on the binding site and the conformation of the targeted kinase in complex with them. Most of the currently approved tyrosine kinase inhibitors are either Type I or Type II, however according to X-ray crystal structural analysis, lenvatinib was found to possess a new Type V binding mode of kinase inhibition that is distinct from existing compounds. In addition, lenvatinib was confirmed via kinetic analysis to exhibit rapid and potent inhibition of kinase activity, and it is suggested that this may be attributed to its novel binding mode.

3. About Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer-related mortality in both men and women, with 1.8 million new cases diagnosed every year and 1.6 million deaths reported annually worldwide. The majority of lung cancers are related to smoking, and regional incidence variations directly reflect smoking prevalence. NSCLC accounts for approximately 85% of all lung cancer cases, and the major histopathological subtypes are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Whilst surgery remains the single most consistent curative option for patients with NSCLC, many patients present with advanced disease, having metastases at the time of diagnosis which are not amenable to surgery. As there is no approved standard treatment for advanced NSCLC in a third-line or greater setting, development of an effective new treatment is needed and therefore it remains a disease with significant unmet medical needs.

4. About the Study 703 Results Presented at the 50th Annual Meeting of the American Society of Clinical Oncology¹

Abstract number: 8043

Title: E7080 (lenvatinib) in Addition to Best Supportive Care (BSC) Versus BSC Alone in Third-line or Greater Nonsquamous, Non-Small Cell Lung Cancer (NSCLC)

Target: 135 patients with locally advanced or metastatic, non-squamous, NSCLC who had failed at least two systemic anticancer regimens

Treatment: In addition to BSC, either lenvatinib (24 mg) or placebo taken once daily

Study Location: Europe, the United States and other countries

Primary Endpoint: Overall Survival

Secondary Endpoints: Progression-Free Survival and others.

Results: OS: lenvatinib median OS: 38.4 weeks, placebo median OS: 24.1 weeks;
Hazard Ratio 0.7 (95% CI=0.45-1.03); p=0.065

PFS: lenvatinib median PFS: 20.9 weeks, placebo median PFS: 7.9 weeks;
Hazard Ratio 0.4 (95% CI=0.29-0.62); p<0.001

Incidence Rate of Adverse Events of Grade 3 or higher (Common Terminology Criteria for Adverse Events): 68.5% in the lenvatinib group, 50.0% in the placebo group

Most commonly reported Treatment-Related Adverse Events:
Hypertension (45%), proteinuria (37%), decreased appetite (35%),
stomatitis (32%), diarrhea (30%)

*This study was conducted as a joint development project under a strategic collaboration agreement with Quintiles

¹ Havel L, et al. E7080 (lenvatinib) in Addition to Best Supportive Care (BSC) Versus BSC Alone in Third-line or Greater Nonsquamous, Non-Small Cell Lung Cancer (NSCLC). *ASCO Meet. Abstr.* 2014, 8043.

² Okamoto K, et al. Distinct Binding Mode of Multikinase Inhibitor Lenvatinib Revealed by Biochemical Characterization. *ACS Med. Chem. Lett.* 2015; 6, 89–94