59PD Final analysis of serum biomarkers in patients (pts) from the phase III study of lenvatinib (LEN) vs sorafenib (SOR) in unresectable hepatocellular carcinoma (uHCC) [REFLECT]

R.S. Finn[1], M. Kudo[2], A-L. Cheng[3], L. Wyrwicz[4], R. Ngan[5], J.F. Blanc[6], A.D. Baron[7], A. Vogel[8], M. Ikeda[9], F. Pisciaglia[10], K-H. Han[11], S. Qin[12], Y. Minoshima[13], M. Kanekiyo[14], M. Ren[14], R. Dairiki[13], T. Tamai[14], C.E. Dutcus[14], Y. Funahashi[13], T.R.J. Evans[15]

[1]*Division of Hematology/Oncology, Geffen School of Medicine, UCLA Medical Center, Santa Monica, CA, USA,* [2]*Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan,* [3]*National Taiwan University Hospital, Taipei, Taiwan,* [4]*Centrum Onkologii-Instytut im., M. Sklodowskiej Curie, Warsaw, Poland,* [5]*Queen Elizabeth, Hospital, Kowloon, Hong Kong, China,* [6]*University of, Bordeaux, Bordeaux, France,* [7]*California Pacific, Medical Center, San Francisco, CA, USA,* [8]*Hannover Medical, School, Hannover, Germany,* [9]*Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan,* [10]*Medical and Surgical Sciences, University of Bologna, Bologna, Italy,* [11]*Severance Hospital, Yonsei University, Seoul, Democratic People's Republic of Korea,* [12]*Nanjing Bayi Hospital, Nanjing, Jiangsu, China,* [13]*Eisai Co., Ltd., Tsukuba, Ibaraki, Japan,* [14]*Eisai, Inc, Woodcliff Lake, NJ, USA,* [15]*Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK*

Background: LEN is a multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT. In a phase 3 randomized, open-label, first-line study in pts with uHCC, LEN demonstrated a treatment effect on overall survival (OS) by statistical confirmation of noninferiority to SOR, with an improved objective response rate.(Kudo et al. Lancet 2018) Preliminary biomarker analyses (n = 114) have been presented.(Finn et al. ESMO 2017) We now present the final biomarker analyses and correlations with efficacy for all pts with serum samples (n = 407).

Methods: 954 Pts with uHCC were randomized 1:1 to LEN (≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) or SOR 400 mg BID. Serum samples were collected (LEN, n = 279; SOR, n = 128) at baseline and during the study; VEGF, ANG2, FGF19, FGF21, and FGF23 were assayed by ELISA. Correlations with tumor response (by independent imaging review per mRECIST: complete or partial responses [CR/PR] vs others) were analyzed using Wilcoxon rank-sum tests. Baseline biomarker levels were analyzed by quartiles: low (0–25%), middle (25–75%), or high (75–100%). Correlations with OS were examined by Cox regression, Kaplan-Meier plots, and log-rank tests. All P-values are nominal.

Results: Both treatments increased VEGF levels, but only LEN increased FGF19 and FGF23 levels. In the LEN arm, pts with CR/PR had a greater increase in FGF19 and FGF23 from baseline vs nonresponders (FGF19: 55.2% vs 18.3%, P = 0.0140; FGF23: 48.4% vs 16.4%; P = 0.0022). Higher VEGF, ANG2, and FGF21 baseline levels were associated with worse OS in both arms. However, for pts with high baseline FGF21 (LEN, n = 70; SOR, n = 27), OS was longer for LEN vs SOR (median, 10.9 vs 6.8 months; HR, 0.528; 95% CI, 0.328–0.849; P = 0.0075), and correlations with OS and treatments were observed between high and low–middle groups ($P^{interaction}$=0.0397).

Conclusions: Differences in biomarker changes between treatments may reflect distinct target engagements for LEN and SOR. Increased baseline VEGF, ANG2, and FGF21 may be prognostic for shorter OS with both treatments, and increased FGF21 may be predictive for reduced OS with SOR. These results are hypothesis-generating and warrant further study.

Clinical trial identification: NCT01761266.

Editorial acknowledgement: Ediorial assistance was provided by Oxford PharmaGenesis of Newtown, PA, USA, which was funded by Eisai Inc.

Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.

Disclosure: R.S. Finn: Grants, personal fees, non-financial support: Eisai, Inc, during the conduct of the study; Grants, personal fees and non-financial support: Bayer, Pfizer, Novartis, Bristol-Myers Squibb, Merck, outside the submitted work. M. Kudo: Honoraria: Bayer, Eisai, MSD, EA pharma. A-L. Cheng: Personal fees: BMS, Ono, Novartis, Bayer, Merck, MSD, during the conduct of the study. R. Ngan: Travel, accommodations, expenses: Eisai, Merck Serono, Novartis, Pfizer, Roche. J.F. Blanc: Personal fees: Bayer SP, Lilly Oncology, Novartis, BMS, outside the submitted work. A.D. Baron: Research funding for data management: Eisai. M. Ikeda: Honoraria: Abbott Japan, Bayer Yakuhin, Bristol-Myers Squibb Japan, Chugai Pharma, Daiichi Sankyo, Eisai, Lilly Japan, Nobelpharma, Novartis, Otsuka, Taiho Pharmaceutical, Yakult Honsha; Consulting or advisory role: Bayer Yakuhin, Eisai, Kyowa Hakko Kirin, NanoCarrier, Novartis, Shire; Research funding: Aslan Pharmaceuticals, AstraZeneca, Baxter, Bayer Yakuhin, Bristol-Myers Squibb, Chugai Pharma, Eisai, Kowa, Kyowa Hakko Kirin, Lilly Japan, Merck Serono, NanoCarrier, Ono Pharmaceutical, Taiho Pharmaceutical, Yakult, Zeria Pharmaceutical. F. Pisciaglia: Personal fees: Eisai, during the conduct of the study; Grants and personal fees: Bayer; Personal fees: Bracco, outside the submitted work. K-H. Han: Consultant work and grants: Eisai Co., during the conduct of the study; Consultant work and grants: Kowa; Consultant work: Bayer, outside the submitted work. Y. Minoshima, R. Dairiki: Employee: Eisai Co., Ltd. M. Kanekiyo, M. Ren, T. Tamai: Employee: Eisai, Inc. C.E. Dutcus: Employee: Eisai, Inc,. Y. Funahashi: Employee: Eisai Co., Ltd. T.R.J. Evans: Financial support for clinical trials of novel anti-cancer drugs, honoraria for consultancies/speaker s fees, support to attend international conferences: Eisai, during the conduct of the study. Outside the submitted work: Financial support for clinical trials of novel anti-cancer drugs, and honoraria for consultancies/speaker's fees, support to attend international conferences: Bristol-Myers Squibb; Support for clinical trials to institution, honorarium for advisory board: Clovis; Scientific Advisory Board to institution: Karus Therapeutics; Advisory board honorarium to institution: Baxalta; Support for clinical trials, advisory board

honorarium to institution: Bayer, Celgene, GlaxoSmithKline, Otsuka, Roche/Genentech; Advisory board honorarium to institution: Immunova; Support for clinical trials from: TC Biopharm, Basilea, e-Therapeutics, Immunocore, Vertex, Verastem, Daiichi, Merck. All other authors have declared no conflicts of interest.