NET of lung/GI origin remain an area of significant unmet medical need. RADIANT-4 evaluated the efficacy and safety of EVE in this NET population.

Methods: Patients (pts) with advanced, progressive, well-differentiated, nonfunctional lung/GI NET were randomized (2:1) to EVE (10 mg/d) or placebo (PBO), both with best supportive care. Pts were stratified by tumor origin, WHO performance status (PS), and prior somatostatin analogue (SSA) treatment. Primary endpoint was progression-free survival (PFS) assessed by central radiology review (modified RECIST 1.0). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: 302 pts were randomized to EVE (n = 205) or PBO (n = 97); median age, 63 y; 53% females; G1/G2: 64%/35%; WHO PS: 0, 74% or 1, 26%; majority (76%) were Caucasian; most common tumor sites: lung (30%), ileum (24%). The two arms were well balanced with respect to prior SSA therapy (53% in EVE vs 56% in PBO), chemotherapy (26% vs 24%), and locoregional and radiotherapy (22% vs 20%). Median PFS by central review was 11.0 mo (95% CI, 9.2–13.3) in EVE and 3.9 mo (95% CI, 3.6−7.4) in PBO arm (HR, 0.48; 95% CI, 0.35–0.67; P < 0.001). Investigator-assessed PFS was consistent with the central review: 14.0 mo (95% CI, 11.2–17.7) with EVE vs 5.5 mo (95% CI, 3.7−7.4) with PBO (HR, 0.39; 95% CI, 0.28–0.54; P < 0.001). Subgroup analyses of PFS by stratification factors were consistent with the primary efficacy analysis. Per central review, ORR (all partial responses) was 2% (4 pts) in EVE vs 1% (1 pt) in PBO. DCR was higher in EVE vs PBO (82% vs 65%). 9% in EVE vs 27% pts in PBO arm had progressive disease as best outcome; tumor response was unknown in the remaining pts. A pre-planned interim OS analysis showed an HR of 0.64 (95% CI, 0.40–1.05; P = 0.037) in favor of EVE. The difference in OS does not achieve statistical significance (threshold P-value for significance, 0.000213). Adverse events (AEs) were mainly G1/2; most common AEs included stomatitis, diarrhea, peripheral edema, fatigue, and rash. Most frequent G3/4 AEs (EVE vs PBO): diarrhea (9% vs 2%), stomatitis (7% vs 0), abdominal pain (5% in each), and anemia (5% vs 2%).

Conclusions: RADIANT-4, the first large, PBO-controlled, phase 3 study in pts with advanced, progressive, nonfunctional lung/GI NET, provided unequivocal evidence for the efficacy of EVE in this population. Results as per central radiology review demonstrated a statistically significant 52% risk reduction in favor of EVE with a clinically meaningful 7.1-month prolongation of PFS vs PBO. EVE was well tolerated and AEs were consistent with the known safety profile.

Conflict of interest: *Advisory Board: James C. Yao: Consulting or Advisory Role − Ipsen, Lexicon, Novartis; Nicola Fazio: Consulting or Advisory Role − Celgene, Ipsen, Lexicon, Novartis; Simron Singh: Consulting or Advisory Role − Novartis; Edward M. Wolin: Consulting or Advisory Role − Celgene, Ipsen, Novartis; Markus Raderer: Consulting or Advisory Role − Celgene, Ipsen, Novartis, Roche; Harald Lahner: Consulting or Advisory Role − Novartis, Pfizer; Juan W. Valle: Consulting or Advisory Role − Novartis; Gianfranco Delle Fave: Consulting or Advisory Role − Novartis; Jonathan R. Strosberg: Consulting or Advisory Role − Ipsen, Lexicon, Novartis; Matthew Kulke: Consulting or Advisory Role − Ipsen, Novartis; Marianne E. Pavel: Consulting or Advisory Role − Ipsen, Lexicon, Novartis, Pfizer. Corporate-sponsored Research: James C. Yao: Research Funding to Institute − Novartis; Nicola Fazio: Research Funding to Institute − Novartis; Simron Singh: Research Funding to Institute − Novartis; Roberto Buzzoni: Research Funding to Institute − Italfarmaco, Novartis, Otsuka; Jiri Tomasek: Research Funding to Institute − Novartis; Harald Lahner: Research Funding to Institute − Novartis; Juan W. Valle: Research Funding to Institute − Novartis; Gianfranco Delle Fave: Research Funding to Institute − Novartis; Eric Van Cutsem: Research Funding to Institute − Novartis; Yasuhiro Shimada: Research Funding to Institute − Chugai Pharma, Lilly, Novartis, Taiho Pharmaceutical; Jonathan R. Strosberg: Research Funding to Institute − Novartis, Pfizer; Marianne E. Pavel: Research Funding to Institute − Novartis. Other Substantive Relationships:. Nicola Fazio: Honoraria − Ipsen, Novartis Travel, Accommodations, Expenses − Ipsen, Novartis; Simron Singh: Honoraria − Novartis Travel, Accommodations, Expenses − Novartis; Roberto Buzzoni: Travel, Accommodations, Expenses − Ipsen Italfarmaco Novartis; Jiri Tomasek: Honoraria − Novartis Travel, Accommodations, Expenses − Novartis; Markus Raderer: Honoraria − Celgene, Ipsen, Novartis, Roche; Harald Lahner: Honoraria − Ipsen, Novartis, Pfizer Travel, Accommodations, Expenses − Ipsen, Novartis, Pfizer; Maurizio Voi: Employment − Novartis Stock and Other Ownership Interests − Novartis; Lida Pacaud: Employment − Novartis Stock and Other Ownership Interests − Novartis; Jeremie Lincy: Employment − Novartis Stock and Other Ownership Interests − Novartis; Carolin Sachs: Employment − Novartis Stock and Other Ownership Interests − Novartis; Juan W. Valle: Honoraria − Novartis; Jonathan R. Strosberg: Honoraria − Novartis Speakers' Bureau − Bayer, Genentech; Marianne E. Pavel: Honoraria − Ipsen, Lexicon, Novartis, Pfizer Travel, Accommodations, Expenses − Ipsen, Novartis.*

6LBA LATE-BREAKING ABSTRACT

177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: Results of the phase III NETTER-1 trial

J. Strosberg[1], E. Wolin[2], B. Chasen[3], M. Kulke[4], D. Bushnell[5], M. Caplin[6], R.P. Baum[7], E. Mittra[8], T. Hobday[9], A. Hendifar[10], K. Oberg[11], M. Lopera Sierra[12], P. Ruszniewski[13], D. Kwekkeboom[14]. *[1]H. Lee Moffitt Cancer Center & Research Institute, Medical Oncology and Hematology, Tampa, USA; [2]Markey Cancer Center − University of Kentucky, GI − Carcinoid and Neuroendocrine Cancer, Lexington, USA; [3]University of Texas MD Anderson Cancer Center, Department of Nuclear Medicine, Houston, USA; [4]Dana-Farber Cancer Institute, Neuroendocrine and Carcinoid Tumors, Boston, USA; [5]University of Iowa Carver College of Medicine, Division of Nuclear Medicine, Iowa City, USA; [6]Royal Free Hospital, Gastroenterology and Gastrointestinal Neuroendocrinology, London, United Kingdom; [7]Zentralklinik, Center for Neuroendocrine Tumors, Bad Berka, Germany; [8]Stanford University Medical Center, Radiology and Nuclear Medicine, Stanford, USA; [9]Mayo Clinic College of Medicine, Hematology and Oncology, Rochester, USA; [10]Cedars Sinai Medical Center, Gastrointestinal Oncology, Los Angeles, USA; [11]Uppsala University Hospital, Endocrine Oncology, Uppsala, Sweden; [12]Advanced Accelerator Applications, Clinical Development, New York, USA; [13]Hopital Beaujon, Gastroenterology and Pancreatology, Clichy, France; [14]Erasmus Medical Center, Nuclear Medicine, Rotterdam, Netherlands*

Background: Currently, there are limited therapeutic options for patients with advanced midgut neuroendocrine tumours (20−45% of NETs) progressing on first-line somatostatin analogue therapy. Since 2000, thousands of patients have been treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera®) peptide receptor radionuclide therapy (PRRT) with promising results.

Material and Methods: NETTER-1 is the first Phase III multicentric, stratified, open, randomized, controlled trial evaluating Lutathera® in patients with inoperable, progressive, somatostatin receptor positive midgut NETs. 230 patients with Grade 1−2 metastatic midgut NETs were randomized to receive Lutathera 7.4 GBq every 8 weeks (x4 administrations) with renal protection (amino acid solution infusion) versus Octreotide LAR 60 mg every 4-weeks. The primary endpoint was PFS per RECIST 1.1 criteria, with objective tumour assessment performed by an independent reading center every 12 weeks until tumour progression. Secondary objectives included objective response rate, overall survival, TTP, safety, tolerability and health-related quality of life. An independent Data Safety Monitoring Board regularly assessed the safety outcome.

Results: Enrolment was completed in February 2015, with a target of 230 patients randomized (1:1) in 35 European and 15 sites in the United States. At the time of statistical analysis, the median PFS was not reached for Lutathera and was 8.4 months with 60 mg Octreotide LAR [95% CI: 5.8–11.0 months], p < 0.0001, with a hazard ratio of 0.21 [95% CI: 0.13–0.34]. The number of centrally confirmed disease progressions or deaths was 23 in the Lutathera group and 67 in the Octreotide LAR 60 mg group. The safety profile observed in the study was consistent with the safety information generated in the Phase I-II clinical trial.

Conclusions: The Phase III NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS in patients with advanced midgut neuroendocrine tumours treated with Lutathera.

No conflict of interest.