HER2+MBC both in early and late phase of their clinical course. Treatment duration to trastuzumab may be one of a marker to predict a response to lapatinib.

5066 POSTER

A Clinical Study to Assess Pharmacokinetics and Safety of Neratinib in Subjects With Chronic Hepatic Impairment and Matched Healthy Subjects

R. Abbas-Borhan[1], S. Chalon[2], C. Leister[1], M. El Gaaloul[2], V. Parks[2], D. Sonnichsen[1]. [1]*Pfizer Inc, Department of Clinical Pharmacology, Collegeville PA, USA;* [2]*Pfizer Global Research and Development, Department of Clinical Pharmacology, Paris, France*

Background: Neratinib (NER; HKI-272) is a potent, low molecular weight, orally administered, irreversible pan-ErbB receptor tyrosine kinase inhibitor in development for the treatment of erbB-2-positive breast cancer. The objective of this study was to evaluate the pharmacokinetics (PK) and safety of NER in subjects with chronic hepatic impairment (HI) and in matched healthy subjects.
Materials and Methods: This was an open-label, single-dose, parallel-group study (NCT00781430, completed, Pfizer) conducted in subjects with chronic HI (Child-Pugh classes A, B, and C; n = 6 each) and healthy subjects (n = 9) matched by sex, age, BMI and, if possible, smoking habit. All subjects received a single oral dose of NER 120 mg immediately after a standard breakfast. Plasma samples obtained through 72 hours postdose were analyzed for NER by liquid chromatography/tandem mass spectrometry.
Results: 27 subjects aged 37−65 years enrolled and completed. Following oral administration of NER 120 mg, mean (CV%) C_{max} and AUC were 18.5 ng/mL (65%) and 296 ng·h/mL (61%) in healthy subjects, 31.2 ng/mL (66%) and 394 ng·h/mL (83%) in Child-Pugh A subjects, 17.1 ng/mL (58%) and 286 ng·h/mL (78%) in Child-Pugh B subjects, and 47.0 ng/mL (59%) and 767 ng·h/mL (46%) in Child-Pugh C subjects, respectively. NER oral clearance decreased in Child-Pugh C subjects compared with healthy subjects. There were no effects of body weight on the oral clearance or apparent volume of distribution of NER in either HI or healthy subjects. The elimination half life of NER in Child-Pugh C subjects increased 3-fold compared to healthy subjects. Adverse events (AEs) were reported by 7 subjects (25.9%), and all were treatment emergent AEs (Child-Pugh B group, n = 2 [33.3%]; Child-Pugh C group, n = 3 [50.0%]; healthy subjects, n = 2 [22.2%]). The most commonly reported AEs were mild diarrhea and hematuria and were reported by Child-Pugh C subjects (n = 2 [33.3%] each). There were no reports of serious AEs, or AE-related discontinuations during the study.
Conclusions: Following a single oral dose of NER 120 mg in subjects with HI, NER exposures (C_{max} and AUC) and oral clearance in the Child-Pugh A and B groups were similar to those in healthy subjects; in the Child-Pugh C group, the exposure was approximately 3-fold higher and the oral clearance was approximately 36% lower than in healthy subjects. A single oral dose of NER 120 mg is safe and generally well tolerated in both hepatically impaired and healthy subjects.

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A Phase 1 Study of Neratinib in Combination With Vinorelbine in Japanese Patients With Advanced or Metastatic Solid Tumours

Y. Onozawa[1], J. Watanabe[2], N. Yamamoto[3], N. Boku[4], M. Suzuki[5], N. Takenaka[6], Y. Ito[7], M. Yokoyama[7], S. Takahashi[7], K. Hatake[7]. [1]*Shizuoka Cancer Center, Division of Clinical Oncology, Shizuoka, Japan;* [2]*Shizuoka Cancer Center, Department of Breast Oncology, Shizuoka, Japan;* [3]*Shizuoka Cancer Center, Division of Thoracic Oncology, Shizuoka, Japan;* [4]*Shizuoka Cancer Center, Division of Gastrointestinal Oncology, Shizuoka, Japan;* [5]*Pfizer Inc, Department of Oncology Clinical R&D, Tokyo, Japan;* [6]*Pfizer Inc, Department of Clinical Pharmacology Clinical R&D, Tokyo, Japan;* [7]*The Cancer Institute of the Japanese Foundation for Cancer Research, Department of Medical Oncology, Tokyo, Japan*

Background: Neratinib (NER) is an orally administered, small-molecule, irreversible pan-erbB receptor inhibitor that is being evaluated in the treatment of breast cancer and other solid tumours. The primary objective was to confirm the safety and tolerability of NER in combination with vinorelbine (VIN) at the maximally tolerated dose (MTD) as determined in an earlier study. Secondary objectives were to obtain preliminary antitumour activity and pharmacokinetic (PK) data in Japanese patients (pts).
Materials and Methods: This was an open-label, phase 1 study of multiple oral doses of NER in combination with intravenous VIN in pts with advanced or metastatic solid tumours (NCT00958724; completed; Pfizer). Pts received NER 240 mg/day starting Day 2 of 1st cycle and then daily at each subsequent 3-wk cycle and VIN 25 mg/m^2 on Days 1 and 8 q3w. Adverse events (AEs) and dose-limiting toxicities (DLTs) were assessed, anti-tumour activity was measured every 6 wks, and PK analyses were conducted for VIN alone (Day 1/Cycle 1) and NER + VIN (Day 8/Cycle 1).
Results: 6 pts (breast cancer, n = 3; head/neck cancer, n = 3) were enrolled, received study drug, and were included in safety and efficacy evaluations. The median duration of treatment for NER was 18.5 wks and 17.1 wks for VIN; median total exposure was 30,240 mg for NER and 299.9 mg/m^2 for VIN. One DLT was reported (grade 3 blood sodium level decreased). The most common treatment-emergent AEs (any grade/grade $\geqslant$3) were neutropenia (100%/67%), leukopenia (100%/50%), and diarrhea (100%/33%); no pt withdrew because of an AE and no deaths were reported. The overall response rate was 16.7% (95% confidence interval [CI], 0.4%, 64.1%); 1 pt with breast cancer (baseline HER2 status of 3+) had a partial response with duration of 12.0 weeks. 5 pts had stable disease (SD) with a median duration of 18.3 (95% CI, 18.0, 30.0) wks, and 1 of 5 pt had SD $\geqslant$24 wks. Median progression-free survival was 18.2 (95% CI, 18.0, 24.1) wks. There were no obvious differences between VIN concentration-time profiles following administration of VIN alone and NER + VIN. VIN C_{max} was decreased upon concomitant administration with NER (mean ratio [VIN:NER + VIN], 0.682); there were no remarkable change in AUC (mean ratio, 0.925). NER exposures were comparable to previous studies.
Conclusions: NER was well tolerated at oral doses of 240 mg daily in combination with VIN in Japanese pts with advanced or metastatic solid tumours.

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Chemosensitivity to Neoadjuvant Chemotherapy of Breast Cancer Subtypes

J.S. Lee[1], J.R. Kim[1], E.S. Chang[1]. [1]*Chungnam National University, General Surgery, Daejeon, Korea*

Background: Human breast tumours are diverse in their natural history and in their responsiveness to treatment. We examined the relationship of neoadjuvant chemotherapy response to outcome among these breast cancer subtypes.
Materials and Methods: We used immunohistochemical markers [(1) HER2+/HR− for HER2+/ER−, (2) HR−/HER2− for basal-like, (3) HER2−/HR+ for luminal A and (4) HER2+/HR+ for luminal B] to subtype a prospectively maintained data set of patients with breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy. Patients received neoadjuvant docetaxel/doxorubicin chemotherapy were enrolled in this study. We analyzed each subtype for clinical and pathologic response to neoadjuvant chemotherapy and examined the relationship of response to disease free survival and overall survival.
Results: Of the 110 patients tested, 31 (28.2%) were basal-like, 19 (17.3%) were HER2+/ER−, 12 (10.9%) were luminal A, and 48 (43.6%) were luminal B. Pathologic complete response rate occurred in 7 (6.4%) of basal-like, 1 (0.9%) of luminal B and 3 (2.7%) of luminal A subtypes (p = 0.04). Patients with the HER2+/ER− and luminal B subtypes had worse disease-free survival and overall survival than those with the luminal A and basal-like subtypes.
Conclusions: Luminal B and HER2+/ER− subtypes are more sensitive to docetaxel/doxorubicin neoadjuvant chemotherapy than luminal A and basal like subtypes. HER2+ phenotype was associated with shorter survival, even though it was associated with a higher response rate to neoadjuvant chemotherapy.

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Phase II Study Assessing Lapatinib Added to Letrozole in Patients With Progressive Disease Under Aromatase Inhibitor in Metastatic Breast Cancer − Study BES 06

C. Villanueva[1], L. Chaigneau[1], G. Romieu[2], J. Salvat[3], T. N'Guyen[1], Y. Merrouche[4], M.H. Dramard[5], A. Goetscheld[5], F. Bazan[1], X. Pivot[1]. [1]*CHU de Besançon − Hopital Jean Minjoz, Doubs, Besançon, France;* [2]*CRLC Val d'Aurelle, Hérault, Montpellier, France;* [3]*EMRC Haute Savoie Nord, Haute Savoie, Thonon les Bains, France;* [4]*Institut de Cancérologie de la Loire, Loire, Saint Priest en Jarez, France;* [5]*GSK, Yvelines, Marly-le-Roi, France*

Purpose: The role of type I receptors epidermalgrowth factor receptor (EGFR) and human epidermal growth factor receptor 2(HER2) in cross-talk with estrogen receptor signaling pathway has been demonstrated in pre-clinical studies. This cross-talk may cause endocrine resistance in breast cancer. On the other hand various inhibitors of such HER1/HER2receptors have yielded additive or synergistic effects when combined with endocrine agents. This trial evaluated the effect of adding lapatinib, a dual tyrosine kinase inhibitor blocking EGFR and HER2, to letrozole after a clinical