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Efficacy of neratinib in patients with HER2-positive (HER2+) early-stage breast cancer: Final overall survival (OS) analysis from the randomized phase 3 ExteNET trial

Frankie Ann Holmes,[1] Beverly Moy,[2] Janine Mansi,[3] Michael Gnant,[4] Carlos Barrios,[5] Robert Separovic,[6] Angel Guerrero-Zotano,[7] Ira Gore,[8] John Smith,[9] Richard Bryce,[10] Feng Xu,[10] Alvin Wong,[10] Miguel Martin,[11] Arlene Chan[12]

1 Texas Oncology/US Oncology Research, The Woodlands, TX; 2 Massachusetts General Hospital Cancer Center, Boston, MA, USA; 3 Guy's and St Thomas Hospital NHS Foundation Trust and Biomedical Research Centre, King's College, London, UK; 4 Department of Surgery and Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria; 5 Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil; 6 Klinicki bolnicki centar "Sestre milosrdnice, Zagreb, Croatia; 7 Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; 8 Birmingham Hematology and Oncology Associates, Birmingham, AL, USA; 9 Compass Oncology – USOR, Portland, OR, USA; 10 Puma Biotechnology Inc., Los Angeles, CA, USA; 11 Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain; 12 Breast Cancer Research Centre-WA & Curtin University, Perth, Australia

Introduction: Neratinib (NERLYNX®) is an irreversible pan-HER inhibitor that improves invasive disease-free survival (iDFS) vs placebo as extended adjuvant therapy in HER2+ early breast cancer after trastuzumab-based adjuvant therapy. In the phase 3 ExteNET trial (NCT00878709), an absolute iDFS benefit of 2.5% and distant disease-free survival (DDFS) benefit of 1.7% were observed with neratinib after 5y. Patients with hormone receptor-positive (HR+) disease who initiated neratinib <1y after trastuzumab (HR+/≤1y) experienced an absolute iDFS benefit of 5.1% and DDFS benefit of 4.7% at 5y. In HR+/≤1y patients with residual disease after neoadjuvant therapy, absolute 5y iDFS and DDFS benefits were 7.4% and 7.0%, respectively. We report the protocol-defined OS analysis from ExteNET and descriptive analyses in higher-risk subgroups.

Materials and methods: ExteNET evaluated neratinib in women with early-stage HER2+ breast cancer who had completed adjuvant (+/– neoadjuvant) trastuzumab + chemotherapy. Patients were randomized to oral neratinib 240 mg/day or placebo for 1y. The OS analysis was event-driven and powered for the intention-to-treat (ITT) population (target 248 events). Descriptive analyses were performed in the HR+/≤1y subgroup per the EU-approved indication and in higher-risk patients [HR+/≤1y with residual disease, i.e. no pathologic complete response (pCR)].

Results: 2840 patients were randomized (1420 per group). After median follow-up of 8.1y, 127 (8.9%) and 137 (9.6%) patients in the neratinib and placebo ITT groups had died, respectively. 8-y OS rates were 90.1% (95% CI 88.3–91.6) for neratinib and 90.2% (95% CI 88.4–91.7) for placebo (absolute difference at 8y –0.1%; stratified HR=0.95; 95% CI 0.75–1.21; p=0.6914). A positive trend was seen in the HR+ subgroup (n=1631; absolute difference at 8y 1.5%; HR=0.80; 95% CI 0.58–1.12); descriptive

analyses suggested greater benefits with neratinib in the HR+/≤1y subgroup (n=1334; absolute difference at 8y 2.1%; HR=0.79; 95% CI 0.55–1.13) and in the HR+/≤1y subset with no pCR after neoadjuvant therapy (n=295; absolute difference at 8y 9.1%; HR=0.47; 95% CI 0.23–0.92). No new safety signals were reported.

Conclusions: There were fewer deaths with neratinib vs placebo (ITT population), but the results did not reach statistical significance. Analyses suggested greater OS improvements with neratinib in subgroups including HR+/≤1y and HR+/≤1y no pCR.