Tucatinib vs placebo in combination with trastuzumab and capecitabine for patients with locally advanced unresectable or HER2-positive metastatic breast cancer (HER2CLIMB): Outcomes by hormone receptor status

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Background Tucatinib (TUC) is a highly selective oral tyrosine kinase inhibitor of HER2 with minimal inhibition of EGFR. It was recently approved by the FDA for patients (pts) with HER2+ metastatic breast cancer (MBC), including pts with brain metastases (BM) whose cancers have progressed on at least 1 prior anti-HER2 regimen in the metastatic setting. In the HER2CLIMB (NCT02614794) pivotal trial, pts with HER2+ MBC previously treated with trastuzumab (T), pertuzumab, and trastuzumab emtansine (T-DM1) were randomized to receive TUC or placebo in combination with T and capecitabine (C). The addition of TUC resulted in clinically meaningful and statistically significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in HER2+ MBC pts. Primary methods and outcomes have been reported previously (Murthy, NEJM 2019). Here we present an exploratory analysis describing the outcomes in the HER2CLIMB trial based on hormone receptor (HR) status.

Methods Pts were randomized 2:1 to receive TUC or placebo in combination with T and C. All pts had a baseline brain MRI and randomization was stratified by presence of BM, ECOG status, and geographic region. All pts with HER2+ MBC who were positive for either or both estrogen receptor and progesterone receptor (≥1%) were assigned to the HR “positive” subgroup. Pts not meeting the above criteria were assigned to the HR “negative” subgroup. For the exploratory HR+HR- efficacy analysis presented here, PFS per RECIST 1.1 by blinded independent central review was evaluated in the first 480 pts enrolled. OS, PFS in pts with baseline BM, and confirmed ORR in pts with measurable disease were evaluated in the total study population. P values presented for PFS are nominal.

Results Overall, 612 pts were enrolled to HER2CLIMB; 370 pts (60%) had HR+ and 242 (40%) had HR- tumors. Baseline demographics and disease characteristics in HR+/HR- subgroups were generally balanced between treatment arms. In the HR+ group, there was a 42% reduction in the risk of progression or death in the TUC arm (hazard ratio: 0.58; 95% CI: 0.42, 0.80; P=0.0008); median (95% CI) PFS was 7.6 mo (7.4, 9.5) in the TUC arm vs 5.6 mo (4.3, 7.4) in the control arm. In the HR- group, there was a 46% reduction in the risk of progression or death in the TUC arm (hazard ratio: 0.54; 95% CI: 0.34, 0.86; P=0.0008); median (95% CI) PFS was 8.1 mo (7.0, 11.6) in the TUC arm vs 4.2 mo (3.1, 8.6) in the control arm. In the total population, median OS was 21.7 mo vs 18.2 mo in HR+ in the TUC arm vs control arm, respectively; median OS in HR- was 31.1 mo in the TUC arm vs 14.1 mo in the control arm. In pts with BM in the HR+ group (n=166 [45%]), there was a 52% reduction in the risk of progression or death (hazard ratio: 0.48; 95% CI: 0.31, 0.75; P=0.0008); median (95% CI) PFS was 7.5 mo (5.6, 9.5) in the TUC arm vs 5.1 mo (4.1, 5.7) in the control arm, and median OS was 18.1 mo vs 12.8 mo, respectively. In pts with BM in the HR- group (n=125 [52%]), there was a 50% reduction in the risk of progression or death (hazard ratio: 0.50; 95% CI: 0.27, 0.95; P=0.03); median (95% CI) PFS was 7.8 mo (6.1, 11.6) in the TUC arm vs 5.4 mo (2.9, 8.6) in the control arm, and median OS was 18.5 mo vs 11.5 mo, respectively. In the total population, ORR was numerically higher in the TUC arm vs the control arm regardless of HR status (HR+: 37.4% [95% CI: 30.8, 44.5] vs 27.1% [95% CI: 19.0, 36.6], respectively and HR-: 45.3% [95% CI: 36.7, 54.0] vs 15.6% [95% CI: 7.8, 26.9], respectively).

Conclusions Among pts with HER2+ MBC previously treated with T, pertuzumab, and T-DM1, the addition of TUC to T and C showed clinically meaningful improvements of PFS, OS, and ORR independent of HR status. Furthermore, pts with HR+ and HR- MBC with BM derived similar benefit from the addition of TUC to T and C.