A prospective multicenter randomized phase II neo-adjuvant study of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by docetaxel, cyclophosphamide and trastuzumab (TCH) versus TCH followed by FEC versus TCH alone, in patients (pts) with operable HER2 positive breast cancer: JBCRG-10 study

Background: The current standard treatment of primary systemic therapy (PST) in HER2 positive breast cancer is anthracyclines (A) and/or taxanes combined with trastuzumab (H) which demonstrates high pathological complete response (pCR). The pCR is considered as a predictive marker of prognosis although results are slightly different depending on the hormone receptor status. We conducted a randomized phase II study to examine sequence of treatments and necessity of A in the treatments using TCH to improve outcome and reduce cardiac toxicity in Japanese HER2 positive pts.

Methods: Pts were treated with FEC (5FU 500 mg/m2, epirubicin 100 mg/m2, cyclophosphamide 500 mg/m2) and/or TCH (docetaxel 75 mg/m2, cyclophosphamide 600 mg/m2, H 6 mg/kg, loading by 8 mg) in 3 groups: 4 cycles of FEC followed by 4 cycles of TCH (A-TCH); 4 cycles of TCH followed by 4 cycles of FEC (TCH-A) or 6 cycles of TCH. An unplanned interim analysis was conducted due to one death by interstitial lung disease (ILD) in the A-TCH after completion of 8 cycles. The pCR results suggested A containing regimens did not exceed benefit from the current standard regimen. The study was continued by limiting allocation only to the TCH group considering efficacy and safety. The primary endpoint was pCR and secondary endpoints were overall response rate (ORR) and safety.

Results: A total of 103 pts were enrolled between Sep. 2009 and Sep. 2011; 21 pts in the A-TCH, 22 pts in the TCH-A and 60 pts in the TCH including pts enrolled after termination of random allocation. Characteristics of the 103 pts were; median age of 54 (range, 33-70), median tumor size of 35 mm (range, 12-80), 42 pts with N(+) (40.8%) and 62 ER positive pts (60.2%). Characteristics of pts in the TCH were; median age of 54.5 (range, 33-67), median tumor size of 35.5 mm (range, 12-80), 25 pts with N(+) (41.7%) and 34 ER positive pts (56.7%). No major difference was reported between groups treated with or without A. Per protocol population was 59 pts in the TCH and its pCR rate was 45.8% (95% CI, 32.2-59.3: ER negative, 61.5%; ER positive, 33.3%). ORR was 86.4% assessed by MRI or CT. Although it is an exploratory analysis, the pCR rate of A containing regimens was 39.0% (ER negative, 57.1%; ER positive, 29.6%). Adverse

events grade 3 were reported in 50 pts (48.5%). Reported ILD was in 5 pts (A-TCH,1; TCH-A, 1; TCH, 3). The mean left ventricular ejection fraction (LVEF) decreased from 70.0% to 69.0% after treatment (A-TCH, 65.9%; TCH-A, 70.4%; TCH, 69.0%). Decrease of LVEF in the A-TCH was significant ($p<0.01$).

Conclusion: The pCR rate of the TCH group was similar to previous reports on A including regimens. Although ILD had been occurred during the treatment containing the TCH, no other new safety issues were reported. We were not able to conclude preferable sequence of A and T since statistical power was not sufficient. However, the result of LVEF suggested TCH followed by A or TCH were preferable. Six cycles of TCH could be one of treatment options as a PST in HER2 positive breast cancer to exclude A. (UMIN000002365)

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