**Adjuvant capecitabine in breast cancer patients with pathologic residual disease after neoadjuvant chemotherapy: First safety analysis of CREATE-X (JBCRG-04)**

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**Background**

Patients (pts) without pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) have a poor prognosis compared with pts achieving a pCR with NAC. It is not clear whether further systemic chemotherapy is beneficial for pts with no pCR. CREATE-X (UMIN000000843) is an ongoing collaborative Korean (KRN)/Japanese (JPN) prospective multicenter open-label randomized phase III trial evaluating this clinical question using capecitabine (X) in pts with no pCR after NAC. We report first safety results, focusing on hand-foot syndrome (HFS), the timing of radiotherapy (RT) and hormone therapy (HT), and differences between KRN and JPN pts.

**Methods**

Pts with residual invasive cancer after anthracycline- and/or taxane-containing NAC were randomized to standard post-surgical treatment (RT, HT as appropriate) with or without 8 cycles of X (1250 mg/m$^2$ bid, days 1–14 q3w). RT was given before or after X. Pts with hormone receptor (HR)-positive disease received HT either with or after X, according to each center's prespecified standard practice. After evaluation of the tolerability of 6 cycles of X in the first 50 pts, the independent data monitoring committee recommended extending X to 8 cycles.

**Results**

Between Feb 2007 and Jul 2012, 910 pts were enrolled (304 in Korea, 606 in Japan). At the time of data cut-off (May 20, 2013), data were available from 866 pts. Median age was 48 years in both arms. In the investigational arm, RT was given before X in 260 pts and after X in 33 pts; 73 pts received prophylactic vitamin B6 (VB6). In HR-positive pts HT was given with X in 200 pts and after X in 24 pts. The relative dose intensity of X was 85.7% in JPN pts and 95.2% in KRN pts. Grade (G) 3/4 neutropenia, HFS (G3 only), fatigue, and diarrhea were significantly ($p<0.05$) more common with X than no X. G3 HFS occurred in 11.1% of pts receiving X, and was significantly more common in JPN vs KRN pts ($p=0.016$). No significant difference in HFS was observed between pts who received vs did not receive VB6 ($p=0.392$). G3/4 alanine aminotransferase (ALT) abnormalities were significantly

more common in pts receiving RT after vs before X ($p<0.001$) and in pts receiving HT after vs concurrently with X ($p<0.001$).

| | n/N (%) | | |
|---|---|---|---|
| | **Investigational arm** | | **Control arm** |
| | **(n=430)** | | **(n=436)** |
| **HR status** | | | |
| Positive | 275/430 (64) | | 275/436 (63) |
| Negative | 141/430 (33) | | 143/436 (33) |
| Unknown | 14/430 (3) | | 18/436 (4) |
| **Grade 3/4 toxicity** | | | |
| Neutropenia | 36/385 (9) | | 5/326 (2) |
| Fatigue | 6/426(1) | | 0/417(0) |
| Diarrhea | 12/426 (3) | | 1/417 (<1) |
| HFS (G3) | 47/424 (11) | | 0 |
| | JPN | 40/296 (14) | 0 |
| | KRN | 7/128 (5) | 0 |
| | VB6 | 6/73 (8) | - |
| | No VB6 | 41/351 (12) | - |
| ALT abnormality | 10/409 (2) | | 3/391 (<1) |
| | with RT | 8/285 (3) | 1/280 (<1) |
| | X → RT | 8/31 (26) | - |
| | RT → X | 0/254 (0) | - |
| | without RT | 2/124 (2) | 2/111 (2) |
| | with HT | 2/214 (1) | 1/267 (<1) |
| | X + HT | 0/190 (0) | - |

| | | | |
|---|---|---|---|
| | X → HT | 2/24 (8) | - |
| | without HT | 8/195 (4) | 2/124 (2) |

**Conclusions**

Addition of 8 cycles of X to standard adjuvant therapy is feasible and tolerable, resulting in a modest yet acceptable increase in toxicities. The timing of RT and HT administration relative to X influenced the incidence of adverse events. HFS was more common in JPN than KRN pts, although further investigation of the potential cause of this difference is required. These findings should be interpreted in light of efficacy data, expected in 2015.