A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04)

**Capecitabine for RESidual cancer as ADjuvant Therapy**

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**Background**

- Standard regimens of neoadjuvant chemotherapy (NAC) contain anthracycline and taxane.
- Patients (pts) with pathologic residual invasive disease after NAC have higher risk for relapse.
- It is unclear whether postoperative systemic chemotherapy following NAC is able to prolong survival.
- This trial was designed as a multicenter open-labeled randomized phase III trial evaluating the efficacy of adjuvant capecitabine (X) use for pts having residual invasive disease (non-pCR/ n+) after NAC.

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**CREATE-X: Trial Design**

HER2-

<table>
<thead>
<tr>
<th>NAC</th>
<th>Surgery</th>
</tr>
</thead>
</table>

Pathology:

- Non-pCR or node +

Control:

Standard therapy

Standard therapy + Capecitabine

(n=900)

Stratification factors:

ER, Age, NAC, ypN, SFU and institution

Standard therapy:

HR+: Hormone therapy

HR-: No further systemic treatment
Capecitabine Therapy

Capecitabine (X): 2,500 mg/m²/day, po, day 1-14
Repeat every 3 weeks for 8 cycles

According to the safety interim analysis of the first 50 pts treated with 6 cycles of X, the IDMC recommended extending X to 8 cycles.

Endpoints

- Primary endpoint:
  Disease free survival (DFS)

- Secondary endpoints:
  Overall survival (OS)
  Period from the first day of preoperative chemotherapy to recurrence or death
  Safety
  Cost-effectiveness
Statistics

- Sample size calculation: 5-year DFS
  Control 62%, Capecitabine 70.4%
- HR=0.74, α=0.05 (two-sided), β=0.2, exponential drop rate 5%
- Enrollment 5 years, follow-up 5 years
- 352 events were expected from 900 patients
- We planned one interim analysis on DFS at 2 years after all pts enrolled using Lan-DeMets alpha spending function method (O'Brein-Fleming type).
- Trial registration: UMIN00000843

Key Inclusion Criteria

- Age: 20-74
- ECOG PS 0 or 1
- Stage I – IIIB
- HER2-negative (IHC 0 or 1 and/or FISH negative)
- Non-pCR and/or node-positive after NAC with anthracycline (A) and taxane (T), A-containing or TC (docetaxel, cyclophosphamide)
- No prior treatment with oral FU
- Adequate organ functions
- No toxicity reactions of grade 2 or higher carried over from NAC
- Written informed consent
Consort Diagram and Trial Progress

In 2013, the safety analysis indicated that the postoperative 8 cycles X treatment was feasible. (SABCS2013MP3-12-03, Dhiran S et al.)

In 2015, the first pre-planned interim analysis was carried out at the point of two years follow-up from the last patient enrollment. The IDMC recommended that this study should be discontinued according to the protocol.

Patients & Tumor Characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Capcitabine (N=440)</th>
<th>Control (N=445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Pre (%)</td>
<td>Post (%)</td>
</tr>
<tr>
<td>Stage</td>
<td>I / IIA / IIB</td>
<td>IIIA / IIIB</td>
</tr>
<tr>
<td>ER &amp; PgR</td>
<td>ER(+) or PgR(+)</td>
<td>ER(-) &amp; PgR(-)</td>
</tr>
<tr>
<td>Nodal metastases</td>
<td>0</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Histological effect</td>
<td>0 / 1a / 1b</td>
<td>2 / 3</td>
</tr>
</tbody>
</table>

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Patients & Tumor Characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine (N=440)</th>
<th>Control (N=445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A containing*</td>
<td>18 (4.1)</td>
<td>16 (3.6)</td>
</tr>
<tr>
<td>A-T (sequential)*</td>
<td>357 (81.1)</td>
<td>371 (83.4)</td>
</tr>
<tr>
<td>AT (concurrent)*</td>
<td>60 (13.6)</td>
<td>53 (11.9)</td>
</tr>
<tr>
<td>TC*</td>
<td>5 (1.1)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>5FU containing regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>260 (59.1)</td>
<td>269 (60.4)</td>
</tr>
<tr>
<td>No</td>
<td>180 (40.9)</td>
<td>176 (39.6)</td>
</tr>
<tr>
<td>Adjuvant endocrine therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes for premenopausal</td>
<td>187 (42.5)</td>
<td>178 (40.0)</td>
</tr>
<tr>
<td>Yes for postmenopausal</td>
<td>108 (24.5)</td>
<td>127 (28.5)</td>
</tr>
<tr>
<td>No</td>
<td>145 (33.0)</td>
<td>140 (31.5)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>318 (72.3)</td>
<td>327 (73.5)</td>
</tr>
<tr>
<td>No</td>
<td>122 (27.7)</td>
<td>118 (26.5)</td>
</tr>
</tbody>
</table>

*A: Anthracycline containing, T:Taxane (Docetaxel or Paclitaxel), TC: Docetaxel + Cyclophosphamide

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Compliance of capecitabine

<table>
<thead>
<tr>
<th></th>
<th>Total (N=439)</th>
<th>Cases planned for 6 cycles (N=159)</th>
<th>Cases planned for 8 cycles (N=280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion</td>
<td>92 (58.0)</td>
<td>106 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Reduction</td>
<td>38 (23.9)</td>
<td>104 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Discontinued</td>
<td>29 (18.2)</td>
<td>70 (25.0)</td>
<td></td>
</tr>
<tr>
<td>RDI* (%) Mean (SD)</td>
<td>87.9 (21.6)</td>
<td>79.1 (29.0)</td>
<td></td>
</tr>
</tbody>
</table>

*RDI: Relative dose intensity
### Safety

<table>
<thead>
<tr>
<th>≥G3 (N, %)</th>
<th>Capecitabine arm (N=440)</th>
<th>Control arm (N=445)</th>
<th>Capecitabine administrated Hand-Foot-Syndrome (N=440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia *</td>
<td>29 (6.6)</td>
<td>7 (1.6)</td>
<td>Grade 0 122 (27.7)</td>
</tr>
<tr>
<td>Diarrhea *</td>
<td>13 (3.0)</td>
<td>2 (0.4)</td>
<td>Grade 1 160 (36.4)</td>
</tr>
</tbody>
</table>

- significantly higher in the capecitabine arm (Neutropenia: p<0.001, Diarrhea: p=0.004)
- All grade incidence is significantly higher in the capecitabine arm as below,
  - Leucopenia, Neutropenia, Anemia, Thrombocytopenia
  - Elevated AST/ALT, Total bilirubin
  - Appetite loss, Diarrhea, Stomatitis and Fatigue

(Ohnami S, et al. SABCS200310P: 32-33)

### Disease Free Survival

![Disease Free Survival Graph]

- 5yr DFS
  - 82.8% Capecitabine
  - 74.0% Control

One-sided p=0.00564 < 0.00671

HR (95%CI) 0.70 (0.53-0.93)

<table>
<thead>
<tr>
<th>Time from randomization (year)</th>
<th>Disease Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine</td>
<td>440 385 329 266 175 19</td>
</tr>
<tr>
<td>Non-Capcitabine</td>
<td>440 367 329 256 150 19</td>
</tr>
</tbody>
</table>
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**Overall Survival**

- 94.0% for Capcitabine
- 89.2% for Control

HR (95% CI): 0.60 (0.40 - 0.92)

One-sided p < 0.01

- Time from randomization (year):
  - Capcitabine: 440, 489, 391, 212, 179, 43
  - Non-Capcitabine: 445, 487, 376, 288, 130, 27

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**Subgroup Analysis for DFS**

- Category (n) HR (95%CI)
  - Total (885) 0.70 (0.53 - 0.93)
  - Age: 50-59 (351) 0.72 (0.50 - 1.03)
  - 60-69 (354) 0.68 (0.45 - 1.04)
  - HR+ (561) 0.84 (0.57 - 1.23)
  - HR- (296) 0.58 (0.39 - 0.87)
  - ypN0 (345) 0.88 (0.48 - 1.62)
  - ypN1 (339) 0.54 (0.36 - 0.83)
  - ypN2 or 3 (199) 0.82 (0.52 - 1.29)
  - Path grade 0-1 (482) 0.63 (0.45 - 0.88)
  - by NAC: 2,3 (385) 0.84 (0.52 - 1.34)
  - Path grade 2 (385) 0.84 (0.52 - 1.34)
  - Taxane (+) (849) 0.70 (0.53 - 0.93)
  - (-) (385) 0.87 (0.52 - 1.42)
  - 5FU containing (+) (529) 0.74 (0.52 - 1.04)
  - (-) (356) 0.65 (0.42 - 1.02)
  - Japanese (599) 0.74 (0.53 - 1.02)
  - Korean (286) 0.63 (0.37 - 1.05)
Conclusions

- After standard neoadjuvant chemotherapy containing A and/or T, postoperative adjuvant use of capecitabine improved DFS significantly in HER2-negative primary breast cancer patients with pathologically proven residual invasive disease.
- OS was significantly improved by capecitabine adjuvant therapy for non-pCR or node-positive patients after NAC.
- The balance of benefit and toxicity would favor the use of capecitabine in the post-NAC situation, but prediction for the therapeutic benefit needs to be investigated further.
- The cost-effectiveness analysis will be carried out.

Acknowledgements

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