**Supplementary Appendix**

**Table S1.** Baseline demographic and disease characteristics of patients with central Ki-67 data available

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **AC🠪T** | | **AC🠪XT** | |
| **ITT**  **(*N* = 1,318)** | **Ki-67**  **(*N* = 763)** | **ITT**  **(*N* = 1,293)** | **Ki-67**  **(*N* = 751)** |
| Median age, y (range) | 51 (26–70) | 51 (26–69) | 50 (26–72) | 51 (26–70) |
| TNM stage, *n* (%) T  T1  T2  T3  T4 | 487 (37)  724 (55)  103 (8)  3 (<1) | 276 (36)  420 (55)  65 (9)  2 (<1) | 489 (38)  721 (56)  82 (6)  0 | 289 (39)  422 (56)  40 (5)  0 |
| Number of positive lymph nodes, *n* (%)  0  1–3  ≥4 | 403 (31)  631 (48)  284 (22) | 218 (29)  375 (49)  170 (22) | 389 (30)  627 (49)  277 (21) | 211 (28)  371 (49)  169 (23) |
| Histologic grade, *n* (%)  G1  G2  G3  G4  Unknown | 99 (8)  412 (31)  715 (54)  4 (<1) 85 (7) | 71 (9)  247 (32)  397 (52)  3 (<1) 43 (6) | 114 (9)  413 (32)  672 (52)  3 (<1) 84 (7) | 67 (9)  228 (30)  402 (54)  2 (<1) 48 (6) |
| ER/PgR status, *n* (%)  ER+/PgR+  ER+/PgR-  ER-/PgR+  ER-/PgR- | 688 (52)  139 (11)  21 (2)  470 (36) | 403 (53)  83 (11)  14 (2)  263 (34) | 660 (51)  139 (11)  22 (2)  472 (37) | 360 (48)  92 (12)  12 (2)  287 (38) |

A, doxorubicin; C, cyclophosphamide; ER, estrogen receptor; ITT, intent-to-treat; PgR, progesterone receptor; T, docetaxel; X, capecitabine.

**Table S2.** Concordance between central and local Ki-67 scores

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Local Ki-67 IHC** | **Central Ki-67 IHC, *n*** | | | | |
| **<10%** | | **10 to 20%** | **≥20%** | **Not done** |
| All patients, *n* | |  |  |  |  |
| <10% | | 89 | 60 | 47 | 130 |
| 10 to 20% | | 33 | 72 | 91 | 144 |
| ≥20% | | 20 | 57 | 373 | 404 |
| Not done | | 103 | 146 | 418 | 409 |
| ER+/HER2-, *n* | |  |  |  |  |
| <10% | | 77 | 52 | 32 | 0 |
| 10 to 20% | | 32 | 58 | 56 | 0 |
| ≥20% | | 15 | 42 | 97 | 0 |
| Total | | 92 | 114 | 154 | 0 |
| TNBC, *n* | |  |  |  |  |
| <10% | | 5 | 4 | 9 | 0 |
| 10 to 20% | | 0 | 4 | 17 | 0 |
| ≥20% | | 3 | 4 | 202 | 0 |
| Total | | 4 | 6 | 196 | 0 |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

**Table S3.** Percentage of patients with a DFS event or death in lobular versus ductal early breast cancer (exploratory analysis)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Histology** | **AC🠪T** | **AC🠪XT** | **AC🠪T** | **AC🠪XT** | **HR (95% CI)** | ***P* value** |
| DFS | |  |  |  |  |  |
| Ductal | 1,096 | 1,099 | 132 (12.0%) | 122 (11.1%) | 0.92 (0.72–1.17) | 0.48 |
| Lobular/mixeda | 176 | 179 | 27 (15.3%) | 16 (8.9%) | 0.55 (0.29–1.01) | 0.055 |
| OS |  |  |  |  |  |  |
| Ductal | 1,096 | 1,099 | 89 (8.1%) | 67 (6.1%) | 0.75 (0.54–1.02) | 0.07 |
| Lobular/mixeda | 176 | 179 | 15 (8.5%) | 6 (3.4%) | 0.38 (0.15–0.98) | 0.04 |

A, doxorubicin; C, cyclophosphamide; DFS, disease-free survival; ER, estrogen receptor; OS, overall survival; T, docetaxel; X, capecitabine. Data are number (%, 95% CI). aMixed includes lobular/ductal carcinoma.

**Table S4.** 7-year DFS and OS by central Ki-67 scores (exploratory analysis)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient group** | **Patients** | **AC🠪T** | **AC🠪XT** | **AC🠪T** | **AC🠪XT** | **HR (95% CI)** | ***P* value** |
| DFS | | |  |  |  |  |  |
| All patients | 2,611 | 1,304 | 1,307 | 186 | 160 | 0.84 (0.68–1.04) | 0.11 |
| Ki-67 |  |  |  |  |  |  |  |
| <10% | 245 (9.4%) | 114 | 131 | 7 | 13 | 1.61 (0.64–4.04) | 0.31 |
| ≥10% | 1269 (48.6%) | 643 | 626 | 111 | 100 | 0.90 (0.69–1.18) | 0.45 |
| <20% | 581 (22.2%) | 278 | 303 | 30 | 35 | 1.05 (0.64–1.71) | 0.84 |
| ≥20% | 933 (35.7%) | 479 | 454 | 88 | 78 | 0.91 (0.67–1.23) | 0.54 |
| Unknown | 1097 (42.0%) | 547 | 550 | 68 | 47 | 0.68 (0.47–0.99) | 0.041 |
| ER+/HER2- | 824 |  |  |  |  |  |  |
| <10% | 216 (26.2%) | 99 | 117 | 6 | 11 | 1.53 (0.56–4.13) | 0.4 |
| ≥10% | 608 (73.8%) | 317 | 291 | 52 | 42 | 0.87 (0.58–1.30) | 0.49 |
| <20% | 483 (58.6%) | 234 | 249 | 25 | 28 | 1.04 (0.61–1.78) | 0.89 |
| ≥20% | 341 (41.4%) | 182 | 159 | 33 | 25 | 0.85 (0.51–1.44) | 0.55 |
| OS |  |  |  |  |  |  |  |
| All patients | 2,611 | 1,304 | 1,307 | 133 | 94 | 0.69 (0.53–0.90) | 0.0064 |
| Ki-67 |  |  |  |  |  |  |  |
| <10% | 245 (9.3%) | 114 | 131 | 3 | 4 | 1.15 (0.26–5.15) | 0.85 |
| ≥10% | 1269 (48.6%) | 643 | 626 | 83 | 64 | 0.77 (0.55–1.06) | 0.11 |
| <20% | 581 (22.2%) | 278 | 303 | 16 | 13 | 0.73 (0.35–1.51) | 0.39 |
| ≥20% | 933 (35.7%) | 479 | 454 | 70 | 55 | 0.80 (0.56–1.14) | 0.22 |
| Unknown | 1097 (42.0%) | 547 | 550 | 47 | 26 | 0.55 (0.34–0.89) | 0.014 |
| ER+/HER2- | 824 |  |  |  |  |  |  |
| <10% | 216 (26.2%) | 99 | 117 | 2 | 4 |  |  |
| ≥10% | 608 (73.8%) | 317 | 291 | 35 | 23 | 0.69 (0.41–1.17) | 0.17 |
| <20% | 483 (58.6%) | 234 | 249 | 12 | 11 | 0.85 (0.37–1.93) | 0.7 |
| ≥20% | 341 (41.4%) | 182 | 159 | 25 | 16 | 0.70 (0.37–1.31) | 0.26 |

A, doxorubicin; C, cyclophosphamide; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; T, docetaxel; X, capecitabine.

**Table S5.** 5-year DFS and OS by local Ki-67 scores (exploratory analysis)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient group** | **Patients** | | **AC🠪T** | | **AC🠪XT** | **HR (95% CI)** |
| DFS | | |  |  |  |  |
| All patients | 2,611 | | 164 | | 140 | 0.84 (0.67–1.05) |
| Ki-67 (all patients) | | |  | |  |  |
| <10% | 326 (12.5%) | | 9 | | 12 | 1.34 (0.57–3.19) |
| ≥10% | 1194 (45.7%) | | 84 | | 57 | 0.70 (0.50–0.98) |
| Not done | 1076 (41.2%) | | 71 | | 71 | 0.91 (0.65–1.26) |
| ER+/HER2- | 1,443 | |  | |  |  |
| <10% | 273 (18.9%) | | 6 | | 9 | 1.47 (0.52–4.15) |
| ≥10% | 570 (39.5%) | | 34 | | 21 | 0.66 (0.38–1.13) |
| Unknown | 600 (41.6%) | | 32 | | 33 | 0.95 (0.58–1.54) |
| OS |  |  |  |  |  |  |
| All patients | 2,611 | | 108 | | 75 | 0.68 (0.51–0.92) |
| Ki-67 (all patients) | | |  | |  |  |
| <10% | 326 (12.5) | | 7 | | 5 | 0.72 (0.23–2.27) |
| ≥10% | 1,194 (45.7) | | 56 | | 28 | 0.52 (0.33–0.82) |
| Not done | 1,076 (41.2) | | 45 | | 42 | 0.85 (0.56–1.30) |
| ER+/HER2- | 1,443 | |  | |  |  |
| <10% | 273 (18.9) | | 5 | | 4 | 0.79 (0.21–2.94) |
| ≥10% | 570 (39.5) | | 18 | | 5 | 0.30 (0.11–0.81) |
| Unknown | 600 (41.6) | | 17 | | 17 | 0.92 (0.47–1.81) |

A, doxorubicin; C, cyclophosphamide; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; T, docetaxel; X, capecitabine.

**Figure S1.** Forest plot of hazard ratios by subgroup in the ITT population (planned analysis) for (A) DFS and (B) OS

DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor; T, docetaxel; X, capecitabine.

**Figure S2.** Distribution of central Ki-67 scores in (A) ER-positive/HER2-negative breast cancer (*n* = 824) and (B) TNBC (*n* = 454)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

**Figure S3.** Subpopulation Treatment Effect Pattern Plot for 5-year DFS between the two treatment arms within predefined patient subgroups based on Ki-67 levels in (A) ER-positive/HER2-negative breast cancer and (B) TNBC (exploratory analysis).

The x-axis shows the Ki-67 cutoff used to categorize patients into low and high groups, with the actual Ki-67 value noted in parentheses. Dashed and solid lines represent T and XT arms, respectively.

A, doxorubicin; C, cyclophosphamide; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; T, docetaxel; TNBC, triple-negative breast cancer; X, capecitabine.