

**Prolonged Time to Adjuvant Chemotherapy Initiation Was Associated with  
Worse Disease Outcome in Triple Negative Breast Cancer Patients**

Lifen Cai<sup>#</sup>, Yiwei Tong<sup>#</sup>, Xiaoping Zhu, Kunwei Shen, Juanying Zhu<sup>\*</sup>, Xiaosong Chen<sup>\*</sup>

**Supplementary Tables**

**Supplementary Table S1. Patient baseline characteristics by study center**

|                          | All Patients | Study Center    |                   |          |
|--------------------------|--------------|-----------------|-------------------|----------|
| Characteristics          | (n=2611)     | Jiaxing (n=519) | Shanghai (n=2092) | <i>P</i> |
|                          | No. (%)      | No. (%)         | No. (%)           |          |
| Age at diagnosis, years  |              |                 |                   |          |
| Median age (IQR)         | 52 (45-60)   | 48 (44-56)      | 53 (46-60)        |          |
| <50                      | 1065 (40.8)  | 290 (55.9)      | 775 (37.0)        | <0.001   |
| ≥50                      | 1546 (59.2)  | 229 (44.1)      | 1317 (63.0)       |          |
| Comorbidity <sup>†</sup> |              |                 |                   | <0.001   |
| 0                        | 1869 (71.6)  | 430 (82.9)      | 1439 (68.8)       |          |
| 1                        | 537 (20.6)   | 74 (14.3)       | 463 (22.1)        |          |
| ≥2                       | 205 (7.9)    | 15 (2.9)        | 190 (9.1)         |          |
| Breast surgery           |              |                 |                   | <0.001   |
| Mastectomy               | 1989 (76.2)  | 470 (90.6)      | 1519 (72.6)       |          |
| BCS                      | 622 (23.8)   | 49 (9.4)        | 573 (27.4)        |          |
| Histologic type          |              |                 |                   | 0.763    |
| IDC                      | 2386 (91.4)  | 476 (91.7)      | 1910 (91.3)       |          |
| Non-IDC                  | 225 (8.6)    | 43 (8.3)        | 182 (8.7)         |          |
| Histologic grade         |              |                 |                   | <0.001   |
| I-II                     | 1275 (48.8)  | 378 (72.8)      | 897 (42.9)        |          |
| III                      | 1118 (42.8)  | 93 (17.9)       | 1025 (49.0)       |          |

|                          |             |            |             |                  |
|--------------------------|-------------|------------|-------------|------------------|
| Unknown                  | 218 (8.3)   | 48 (9.2)   | 170 (8.1)   |                  |
| Pathological tumor size  |             |            |             | <b>&lt;0.001</b> |
| T1                       | 1446 (55.4) | 354 (68.2) | 1092 (52.2) |                  |
| T2                       | 1106 (42.4) | 154 (29.7) | 952 (45.5)  |                  |
| T3-4                     | 59 (2.3)    | 11 (2.1)   | 48 (2.3)    |                  |
| Pathological node status |             |            |             | <b>&lt;0.001</b> |
| Negative                 | 1502 (57.5) | 359 (69.2) | 1143 (54.6) |                  |
| Positive                 | 1109 (42.5) | 160 (30.8) | 949 (45.4)  |                  |
| LVI                      |             |            |             | <b>&lt;0.001</b> |
| Negative                 | 2408 (92.2) | 445 (85.7) | 1963 (93.8) |                  |
| Positive                 | 203 (7.8)   | 74 (14.3)  | 129 (6.2)   |                  |
| ER status                |             |            |             | <b>&lt;0.001</b> |
| Negative                 | 879 (33.7)  | 133 (25.6) | 746 (35.7)  |                  |
| Positive                 | 1732 (66.3) | 386 (74.4) | 1346 (64.3) |                  |
| PR status                |             |            |             | <b>&lt;0.001</b> |
| Negative                 | 1250 (47.9) | 172 (33.1) | 1078 (51.5) |                  |
| Positive                 | 1361 (52.1) | 347 (66.9) | 1014 (48.5) |                  |
| HER2 status              |             |            |             | <b>&lt;0.001</b> |
| Negative                 | 1932 (74.0) | 441 (85.0) | 1491 (71.3) |                  |
| Positive                 | 679 (26.0)  | 78 (15.0)  | 601 (28.7)  |                  |
| Ki67, %                  |             |            |             | <b>&lt;0.001</b> |
| <14                      | 763 (29.2)  | 244 (47.0) | 518 (24.8)  |                  |
| ≥14                      | 1848 (70.8) | 274 (52.8) | 1574 (75.2) |                  |
| Molecular subtype        |             |            |             | <b>&lt;0.001</b> |
| Luminal A                | 349 (13.4)  | 149 (28.7) | 200 (9.6)   |                  |
| Luminal B/HER2-negative  | 1068 (40.9) | 202 (38.9) | 866 (41.4)  |                  |
| Luminal B/HER2-positive  | 317 (12.1)  | 36 (6.9)   | 281 (13.4)  |                  |
| TNBC                     | 515 (19.7)  | 90 (17.3)  | 425 (20.3)  |                  |

|               |              |             |                  |
|---------------|--------------|-------------|------------------|
| HER2-positive | 362 (13.9)   | 42 (8.1)    | 320 (15.3)       |
| TTC           |              |             | <b>&lt;0.001</b> |
| ≤4            | 1900 (72.77) | 519 (100.0) | 1381 (66.1)      |
| >4            | 711 (27.23)  | 0 (0.0)     | 711 (33.9)       |

Abbreviations: IQR, interquartile range; BCS, breast-conserving surgery; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; TTC, time to adjuvant chemotherapy.

<sup>†</sup> Comorbidity score was calculated according to Charlson Comorbidity Index.

**Supplementary Table S2. Adjuvant treatment information by TTC**

| Treatment            | All Patients | TTC (weeks) |            | <i>P</i> |
|----------------------|--------------|-------------|------------|----------|
|                      | (n=2611)     | ≤4 (n=1900) | >4 (n=711) |          |
|                      | No. (%)      | No. (%)     | No. (%)    |          |
| Chemotherapy regimen |              |             |            |          |
| EC                   | 277 (10.6)   | 217 (11.4)  | 60 (8.4)   | <0.001   |
| TC                   | 710 (27.2)   | 437 (23.0)  | 273 (38.4) |          |
| EC-T                 | 1593 (61.0)  | 1228 (64.6) | 365 (51.3) |          |
| Others               | 31 (1.1)     | 18 (0.9)    | 13 (1.8)   |          |
| Radiation therapy    |              |             |            | 0.353    |
| No                   | 1269 (48.6)  | 934 (49.2)  | 335 (47.1) |          |
| Yes                  | 1342 (51.4)  | 966 (50.8)  | 376 (52.9) |          |
| Targeted therapy     |              |             |            | <0.001   |
| No                   | 2137 (81.8)  | 1613 (84.9) | 524 (73.7) |          |
| Yes                  | 474 (18.2)   | 287 (15.1)  | 187 (26.3) |          |
| Endocrine therapy    |              |             |            | 0.147    |
| No                   | 947 (36.3)   | 705 (37.1)  | 242 (34.0) |          |
| Yes                  | 1664 (63.7)  | 1195 (62.9) | 469 (66.0) |          |

Abbreviations: TTC, time to chemotherapy; EC, epirubicin and cyclophosphamide; TC, taxane and cyclophosphamide; T, taxane.



**Supplementary Table S3. Multivariate analysis of factors associated with RFS and OS**

**in the whole population and by molecular subtype**

| Characteristics                | RFS              |                  | OS               |                  |
|--------------------------------|------------------|------------------|------------------|------------------|
|                                | HR (95% CI)      | <i>P</i>         | HR (95% CI)      | <i>P</i>         |
| <b><i>Whole population</i></b> |                  |                  |                  |                  |
| Age at diagnosis, years        |                  | 0.882            |                  | 0.229            |
| ≥50 vs <50                     | 0.98 (0.75-1.28) |                  | 1.26 (0.87-1.82) |                  |
| Comorbidity                    |                  | 0.125            |                  | 0.502            |
| 1 vs 0                         | 1.31 (0.97-1.75) | 0.075            | 1.22 (0.82-1.81) | 0.331            |
| ≥2 vs 0                        | 1.36 (0.89-2.08) | 0.160            | 1.30 (0.73-2.32) | 0.379            |
| Histologic grade               |                  | <b>0.004</b>     |                  | <b>0.006</b>     |
| III vs I-II                    | 1.56 (1.19-2.05) | 0.001            | 1.83 (1.26-2.66) | 0.001            |
| Unknown vs I-II                | 1.52 (0.97-2.38) | 0.065            | 1.52 (0.83-2.78) | 0.173            |
| Pathological tumor size        |                  | <b>&lt;0.001</b> |                  | <b>&lt;0.001</b> |
| T2 vs T1                       | 1.82 (1.41-2.35) | <0.001           | 1.68 (1.18-2.39) | 0.004            |
| T3-4 vs T1                     | 3.23 (1.81-5.77) | <0.001           | 3.89 (1.92-7.91) | <0.001           |
| Pathological node status       |                  | <b>&lt;0.001</b> |                  | <b>&lt;0.001</b> |
| Positive vs Negative           | 2.19 (1.70-2.83) |                  | 2.93 (2.05-4.20) |                  |
| LVI                            |                  | 0.087            |                  | 0.089            |
| Positive vs Negative           | 1.41 (0.95-2.07) |                  | 1.53 (0.94-2.51) |                  |
| Molecular subtype              |                  | <b>0.026</b>     |                  | <b>0.019</b>     |

|                          |                   |       |                    |       |
|--------------------------|-------------------|-------|--------------------|-------|
| LumB/HER2- vs LumA       | 1.57 (1.00-2.47)  | 0.051 | 1.50 (0.82-2.76)   | 0.193 |
| LumB/HER2+ vs LumA       | 0.92 (0.51-1.65)  | 0.768 | 0.87 (0.39-1.93)   | 0.732 |
| TNBC vs LumA             | 1.78 (1.08-2.93)  | 0.024 | 2.18 (1.13-4.20)   | 0.019 |
| HER2+ vs LumA            | 1.51 (0.89-2.56)  | 0.129 | 1.18 (0.56-2.48)   | 0.668 |
| <b><i>Luminal A</i></b>  |                   |       |                    |       |
| Age at diagnosis, years  |                   | 0.389 |                    | 0.780 |
| ≥50 vs <50               | 0.66 (0.25-1.71)  |       | 1.19 (0.35-4.13)   |       |
| Comorbidity              |                   | 0.259 |                    | 0.419 |
| 1 vs 0                   | 1.56 (0.53-4.60)  | 0.423 | 1.63 (0.39-6.79)   | 0.504 |
| ≥2 vs 0                  | 3.76 (0.74-19.08) | 0.110 | 4.68 (0.44-50.27)  | 0.202 |
| Histologic grade         |                   | 0.554 |                    | 0.964 |
| III vs I-II              | 1.79 (0.63-5.11)  | 0.277 | 1.24 (0.26-5.93)   | 0.788 |
| Unknown vs I-II          | 0.00 (0.00- )     | 0.973 | 0.00 (0.00- )      | 0.986 |
| Pathological tumor size  |                   | 0.207 |                    | 0.182 |
| T2 vs T1                 | 1.72 (0.74-4.00)  | 0.207 | 2.27 (0.70-7.343)  | 0.172 |
| T3-4 vs T1               | 5.42 (0.59-49.65) | 0.135 | 9.36 (0.62-141.87) | 0.107 |
| Pathological node status |                   | 0.862 |                    | 0.222 |
| Positive vs Negative     | 1.08 (0.44-2.64)  |       | 0.44 (0.12-1.64)   |       |
| LVI                      |                   | 0.798 |                    | 0.591 |
| Positive vs Negative     | 1.23 (0.26-5.77)  |       | 1.67 (0.26-10.94)  |       |
| TTC                      |                   | 0.698 |                    | 0.813 |

|                                       |                  |                  |                  |                  |
|---------------------------------------|------------------|------------------|------------------|------------------|
| >4 vs ≤4                              | 0.80 (0.26-2.46) |                  | 0.82 (0.16-4.23) |                  |
| <b><i>Luminal B/HER2-negative</i></b> |                  |                  |                  |                  |
| Age at diagnosis, years               |                  | 0.694            |                  | 0.061            |
| ≥50 vs <50                            | 1.09 (0.72-1.64) |                  | 1.83 (0.97-3.43) |                  |
| Comorbidity                           |                  | 0.472            |                  | 0.573            |
| 1 vs 0                                | 1.16 (0.74-1.83) | 0.514            | 1.36 (0.75-2.47) | 0.310            |
| ≥2 vs 0                               | 1.44 (0.78-2.65) | 0.242            | 1.28 (0.53-3.11) | 0.586            |
| Histologic grade                      |                  | <b>&lt;0.001</b> |                  | <b>&lt;0.001</b> |
| III vs I-II                           | 1.97 (1.31-2.95) | 0.001            | 2.40 (1.33-4.33) | 0.004            |
| Unknown vs I-II                       | 3.08 (1.71-5.53) | <0.001           | 4.29 (3.06-8.96) | <0.001           |
| Pathological tumor size               |                  | <b>0.002</b>     |                  | 0.111            |
| T2 vs T1                              | 1.59 (1.07-2.34) | 0.020            | 1.07 (0.63-1.84) | 0.794            |
| T3-4 vs T1                            | 3.60 (1.61-8.08) | 0.002            | 3.12 (1.07-9.12) | 0.038            |
| Pathological node status              |                  | <b>0.001</b>     |                  | <b>0.003</b>     |
| Positive vs Negative                  | 1.90 (1.29-2.80) |                  | 2.34 (1.35-4.06) |                  |
| LVI                                   |                  | 0.876            |                  | 0.478            |
| Positive vs Negative                  | 1.05 (0.55-2.04) |                  | 0.65 (0.20-2.12) |                  |
| TTC                                   |                  | 0.339            |                  | 0.590            |
| >4 vs ≤4                              | 1.22 (0.81-1.82) |                  | 1.17 (0.66-2.06) |                  |
| <b><i>Luminal B/HER2-positive</i></b> |                  |                  |                  |                  |
| Age at diagnosis, years               |                  | 0.999            |                  | 0.886            |

|                              |                   |              |                   |              |
|------------------------------|-------------------|--------------|-------------------|--------------|
| $\geq 50$ vs $< 50$          | 1.00 (0.38-2.72)  |              | 0.90 (0.23-3.59)  |              |
| Comorbidity                  |                   | 0.087        |                   | 0.235        |
| 1 vs 0                       | 2.30 (0.88-6.01)  | 0.088        | 3.10 (0.81-11.95) | 0.100        |
| $\geq 2$ vs 0                | 3.70 (0.94-14.56) | 0.062        | 2.88 (0.30-27.82) | 0.362        |
| Histologic grade             |                   | 0.981        |                   | 0.773        |
| III vs I-II                  | 0.99 (0.38-2.54)  | 0.976        | 0.82 (0.22-3.06)  | 0.770        |
| Unknown vs I-II              | 1.15 (0.24-5.53)  | 0.862        | 1.87 (0.19-18.52) | 0.592        |
| Pathological tumor size      |                   | 0.319        |                   | 0.203        |
| T2 vs T1                     | 2.11 (0.80-5.55)  | 0.131        | 4.32 (0.87-21.59) | 0.074        |
| T3-4 vs T1                   | 0.00 (0.00- )     | 0.981        | 0.00 (0.00- )     | 0.991        |
| Pathological node status     |                   | <b>0.030</b> |                   | 0.170        |
| Positive vs Negative         | 2.84 (1.10-7.32)  |              | 2.68 (0.66-10.92) |              |
| LVI                          |                   | 0.202        |                   | <b>0.034</b> |
| Positive vs Negative         | 2.14 (0.67-6.89)  |              | 5.02 (1.13-22.31) |              |
| TTC                          |                   | 0.457        |                   | 0.289        |
| $> 4$ vs $\leq 4$            | 0.69 (0.26-1.83)  |              | 0.43 (0.09-2.05)  |              |
| <b><i>HER2-amplified</i></b> |                   |              |                   |              |
| Age at diagnosis, years      |                   | <b>0.037</b> |                   | 0.292        |
| $\geq 50$ vs $< 50$          | 0.49 (0.25-0.96)  |              | 0.57 (0.20-1.62)  |              |
| Comorbidity                  |                   | 0.367        |                   | 0.153        |
| 1 vs 0                       | 0.73 (0.31-1.71)  | 0.469        | 0.22 (0.03-1.75)  | 0.153        |

|                          |                   |              |                   |              |
|--------------------------|-------------------|--------------|-------------------|--------------|
| $\geq 2$ vs 0            | 1.71 (0.63-4.69)  | 0.295        | 2.17 (0.55-8.46)  | 0.267        |
| Histologic grade         |                   | 0.523        |                   | 0.778        |
| III vs I-II              | 0.68 (0.35-1.33)  | 0.257        | 0.69 (0.25-1.93)  | 0.478        |
| Unknown vs I-II          | 0.74 (0.17-3.35)  | 0.699        | 0.00 (0.00- )     | 0.982        |
| Pathological tumor size  |                   | 0.454        |                   | 0.191        |
| T2 vs T1                 | 1.30 (0.66-2.55)  | 0.449        | 1.56 (0.52-4.74)  | 0.431        |
| T3-4 vs T1               | 2.45 (0.54-11.19) | 0.248        | 4.85 (0.88-26.63) | 0.069        |
| Pathological node status |                   | <b>0.005</b> |                   | <b>0.004</b> |
| Positive vs Negative     | 2.65 (1.35-5.21)  |              | 6.74 (1.84-24.66) |              |
| LVI                      |                   | 0.958        |                   | 0.683        |
| Positive vs Negative     | 0.97 (0.33-2.88)  |              | 1.31 (0.03-1.75)  |              |
| TTC                      |                   | 0.885        |                   | 0.438        |
| $>4$ vs $\leq 4$         | 1.05 (0.52-2.12)  |              | 0.60 (0.16-2.20)  |              |

Abbreviations: RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BCS, breast-conserving surgery; LVI, lymphovascular invasion; LumB, Luminal B; HER2, human epidermal growth factor receptor 2; LumA, Luminal A; TNBC, triple negative breast cancer; TTC, time to chemotherapy.

**Supplementary Table S4. Univariate analysis of factors influencing RFS and OS in**

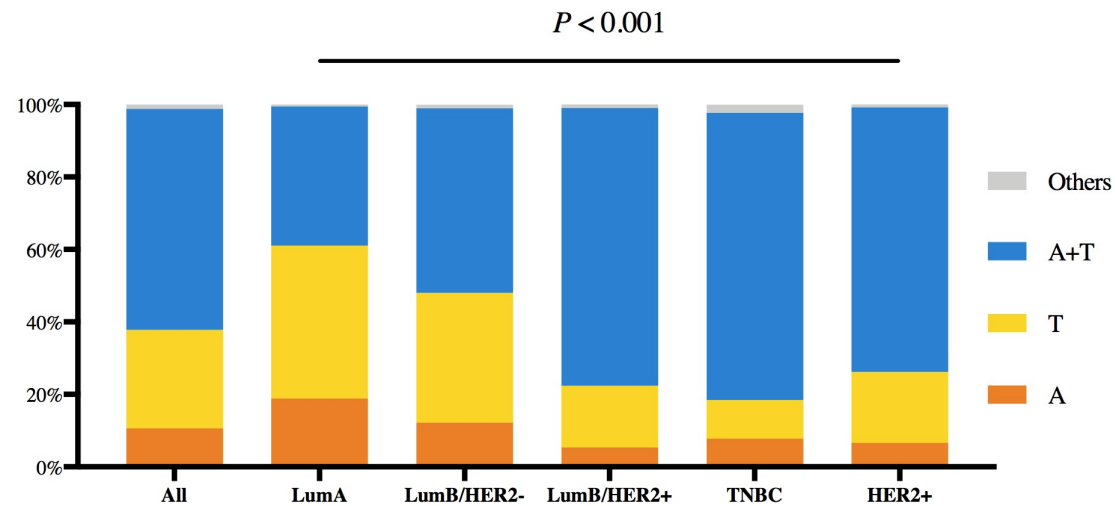
**TNBC patients**

| Characteristics           | RFS               |          | OS                |          |
|---------------------------|-------------------|----------|-------------------|----------|
|                           | HR (95% CI)       | <i>P</i> | HR (95% CI)       | <i>P</i> |
| Age at diagnosis, years   |                   | 0.721    |                   | 0.918    |
| ≥50 vs <50                | 1.10 (0.65-1.86)  |          | 0.97 (0.51-1.83)  |          |
| Comorbidity               |                   | 0.144    |                   | 0.815    |
| 1 vs 0                    | 1.54 (0.90-2.65)  | 0.115    | 1.21 (0.60-2.43)  | 0.603    |
| ≥2 vs 0                   | 0.58 (0.18-1.86)  | 0.357    | 0.85 (0.26-2.79)  | 0.782    |
| Breast surgery            |                   | 0.214    |                   | 0.181    |
| BCS vs Mastectomy         | 0.69 (0.38-1.24)  |          | 0.59 (0.27-1.28)  |          |
| Histologic type           |                   | 0.835    |                   | 0.426    |
| Non-IDC IDC               | 0.92 (0.44-1.94)  |          | 0.66 (0.23-1.85)  |          |
| Histologic grade          |                   | 0.068    |                   | 0.030    |
| III vs I-II               | 2.11 (1.07-4.18)  | 0.032    | 2.55 (1.07-6.09)  | 0.035    |
| Unknown vs I-II           | 1.25 (0.46-3.45)  | 0.662    | 0.69 (0.14-3.93)  | 0.643    |
| Pathological tumor size   |                   | 0.001    |                   | 0.022    |
| T2 vs T1                  | 2.76 (1.59-4.81)  | <0.001   | 2.39 (1.23-4.65)  | 0.010    |
| T3-4 vs T1                | 4.49 (1.32-15.24) | 0.016    | 3.74 (0.84-16.58) | 0.082    |
| Pathological nodal status |                   | <0.001   |                   | <0.001   |
| Positive vs Negative      | 3.52 (2.13-5.82)  |          | 5.16 (2.70-9.83)  |          |

|                      |                  |        |                  |
|----------------------|------------------|--------|------------------|
| LVI                  |                  | <0.001 | <0.001           |
| Positive vs Negative | 3.41 (1.78-6.55) |        | 4.38 (2.09-9.19) |
| TTC, weeks           |                  | 0.035  | 0.012            |
| >4 vs ≤4             | 1.81 (1.04-3.12) |        | 2.29 (1.20-4.37) |

Abbreviations: RFS, relapse-free survival; OS, overall survival; TNBC, triple-negative breast cancer; HR, hazard ratio; CI, confidence interval; BCS, breast-conserving surgery; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; TTC, time from definitive surgery to initiation of adjuvant chemotherapy.

## Supplementary Figures

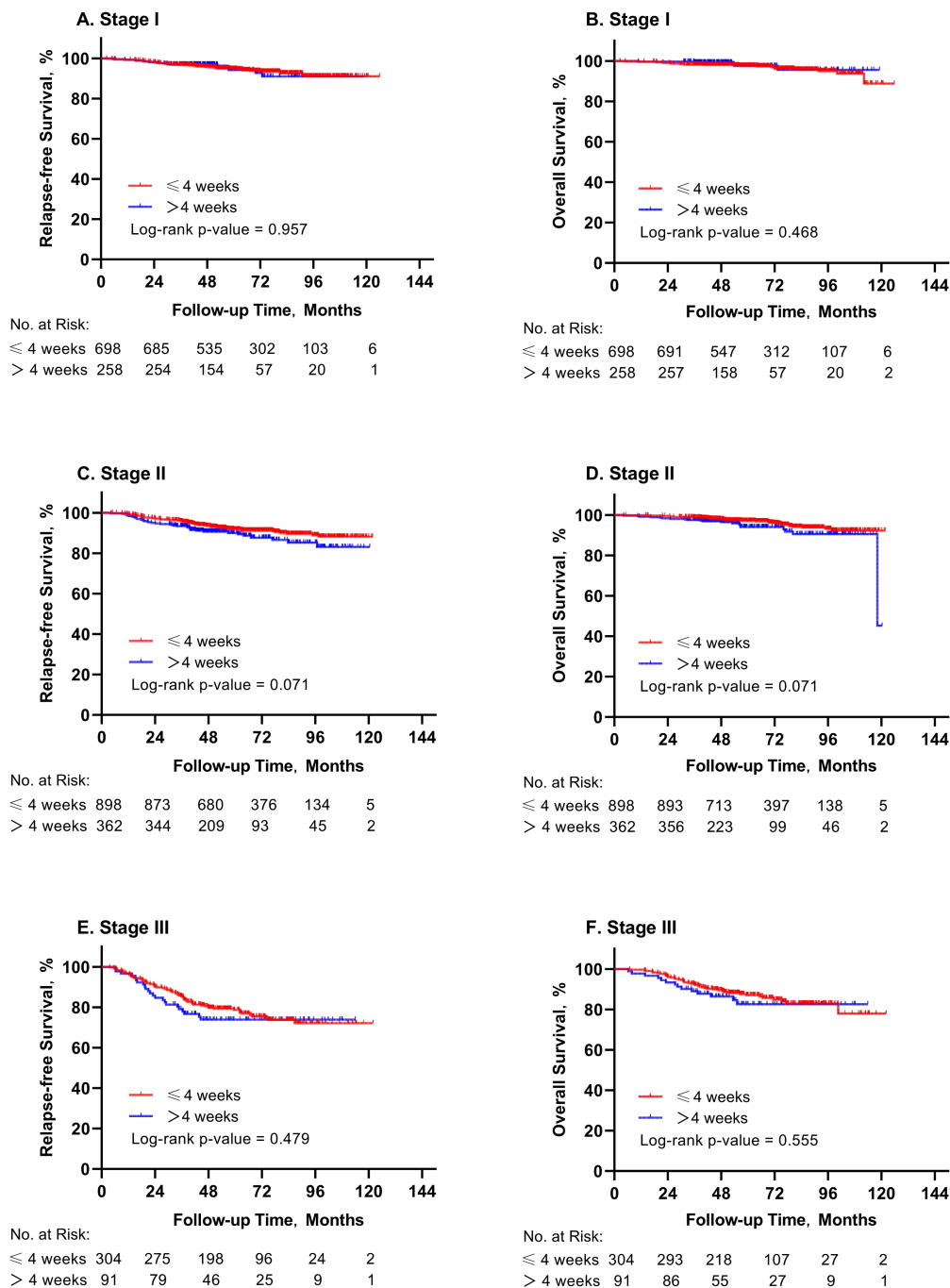


### Supplementary Figure S1. Chemotherapy regimen by molecular subtypes.

Chemotherapy regimen in the whole population, in patients with Luminal A, Luminal B/HER2-negative, Luminal B/HER2-positive, TNBC and HER2-positive tumors.

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; A, anthracyclins; T, taxanes; A+T, anthracyclins and taxanes.

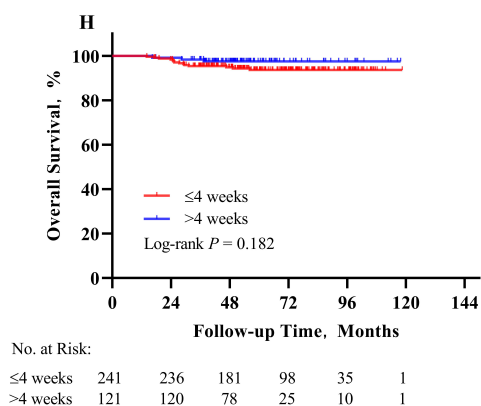
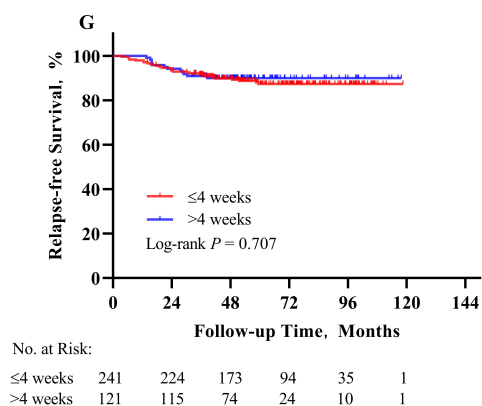
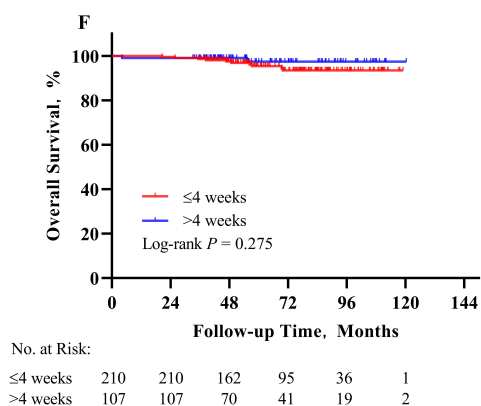
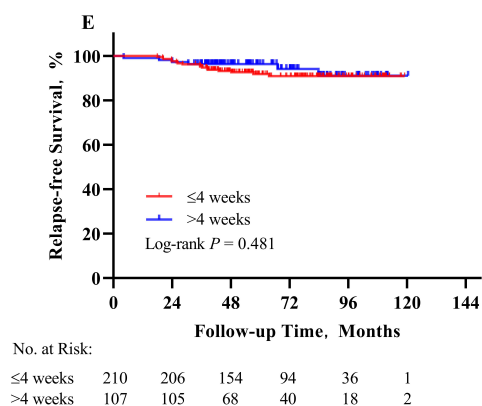
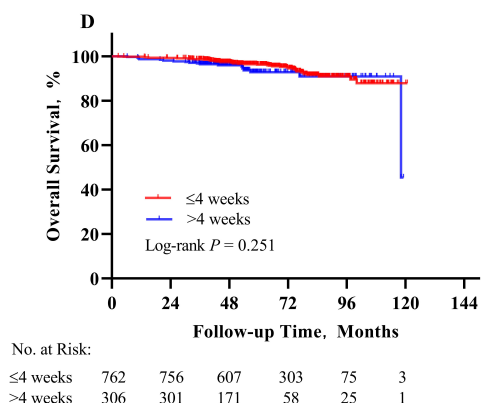
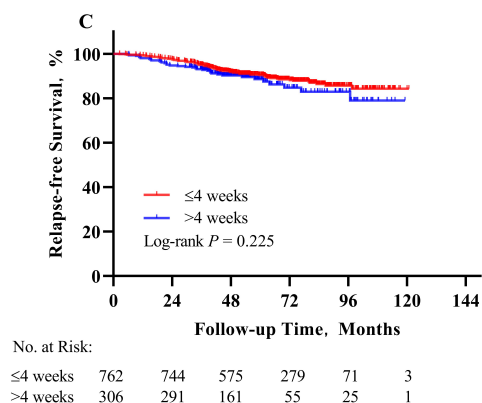
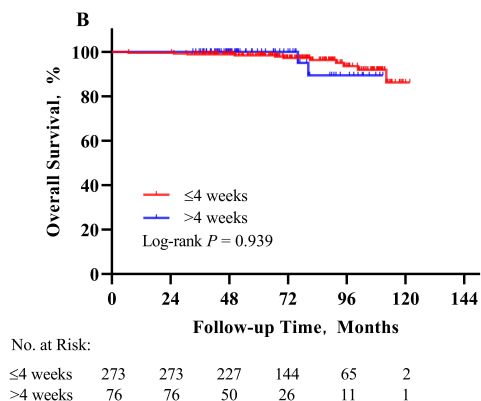
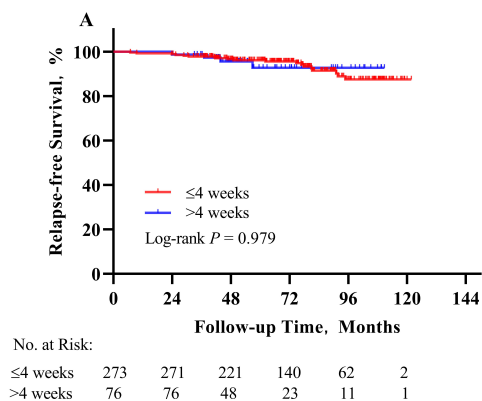




**Supplementary Figure S2. RFS and OS according to TTC by disease stage.**

Kaplan-Meier curves of RFS and OS according to TTC groups in patients with stage I (A, B), stage II (C, D), and stage III (E, F) diseases.

Abbreviations: RFS, relapse-free survival; OS, overall survival; TTC, time to adjuvant chemotherapy; HER2, human epidermal growth factor receptor 2; No., number.



**Supplementary Figure S3. RFS and OS according to TTC by molecular subtypes.**

Kaplan-Meier curves of RFS and OS according to TTC groups in patients with Luminal A (A, B), Luminal B/HER2-negative (C, D), Luminal B/HER2-positive (E, F) and HER2-positive (J, H) tumors.

Abbreviations: RFS, relapse-free survival; OS, overall survival; TTC, time to adjuvant chemotherapy; HER2, human epidermal growth factor receptor 2; No., number.