**Supplementary Tables**

|  |  |
| --- | --- |
| Supplementary Table 1. Chemotherapy treatment | |
| Name of regiments | Treatment |
| The AC regimen | EPI 90 mg/ on day 1 and CTX 600 mg/ on day 1 and repeated every 21 days for 4-6 cycles |
| The EC-T(H) regimen and dose-density EC-T(H) | EPI 90 mg/ and CTX 600 mg/ on day 1, repeated every 14 (dose-density) or 21 days for 4 cycles, followed by PTX 175 mg/ on day 1 and repeated every 14 days (and trastuzumab 2 mg/kg on day 1 and repeated every 7 days) for 4 cycles |
| The TC regimen | DTX 75 mg/ and CTX 600 mg/ on day 1, repeated every 21 days for 4-6 cycles |
| The TCb(H) regimen | DTX 75 mg/ on day 1 (and trastuzumab 2 mg/ on day 1 and repeated every 7 days), carboplatin area under receiver-operating curve (AUC) = 5 mg/mL on day 2 and repeated every 21 days for 6 cycles |
| The AT regimen | EPI 75 mg/ or on day 1 and PTX 175 mg/ on day 2, which was repeated every 21 days for 6 cycles |
| The TH regimen | PTX 80 mg/ on day 1 and trastuzumab 2 mg/kg on day 1, which was repeated every 7 days for 12 cycles |
| EPI:epirubicin; PTX: paclitaxel; DTX: docetaxel | |

|  |
| --- |
| Supplementary Table 2. Univariate analysis of risk factors of reduction of overall cardiac toxicity |

| **Risk Factors** | | **Univariate analysis** | | |
| --- | --- | --- | --- | --- |
| **OR (95% CI)** | **P** | |
| **Clinical variables**  **Clinical variables** | Age (≥60 vs. <60) | 0.892（0.551-1.444） | | 0.642 |
| Laterality |  | | 0.484 |
| Left | 3.664（0.403-33.342） | | 0.249 |
| Right | 3.340（0.336-30.481） | | 0.285 |
| Bilateral | Reference | | Reference |
| Stage |  | |  |
| I | 0.907（0.525-1.566） | | 0.725 |
| II | 1.054（0.645-1.723） | | 0.834 |
| III | Reference | | Reference |
| Histology (IDC vs. Non-IDC) | 0.160（0.020-1.316） | | 0.088 |
| Molecular subtypes |  | |  |
| Luminal A | 1.048（0.465-2.359） | | 0.911 |
| Luminal B (HER-2 negative) | 0.870（0.527-1.435） | | 0.586 |
| Luminal B (HER-2 postive) | 0.524（0.227-1.211） | | 0.131 |
| Her-2 postive | 1.702（0.641-4.522） | | 0.286 |
| Triple Negative | Reference | | Reference |
| Operative method(Non breast conserving surgery v Breast conserving surgery) | 0.942（0.592-1.498） | | 0.800 |
| Comorbidity |  | |  |
| Hypertension | 0.827（0.506-1.352） | | 0.449 |
| Diabetes mellitus | 1.005（0.533-1.898） | | 0.987 |
| Coronary heart disease | 0.503（0.152-1.660） | | 0.259 |
| Hyperlipemia | 0.833（0.328-2.118） | | 0.701 |
| Smoking history | 1.156（0.072-18.622） | | 0.918 |
| Drinking history | 1.156（0.072-18.622） | | 0.918 |
| BMI (≥28 v ＜28) | 1.356（0.845-2.175） | | 0.206 |
| Menstrual conditions (Premenopausal v Postmenopausal) | 1.317（0.875-1.983） | | 0.186 |
| Adjuvamt chemotherapy (Targeted therapy) regimen |  | |  |
| Anthracycline + Taxane + Trastuzumab | 1.880（0.782-4.522） | | 0.158 |
| Anthracycline + Taxane | 1.514（0.9-27-2.471） | | 0.097 |
| Taxane + Trastuzumab | 0.795（0.374-1.691） | | 0.552 |
| Anthracycline Only | 1.477（0.753-2.897） | | 0.256 |
| Taxane Only | Reference | | Reference |
| Anthracycline containing chemotherapy | 1.636（1.080-2.479） | | 0.020 |
| Trastuzumab containing chemotherapy | 0.851（0.497-1.457） | | 0.557 |
| Elavation of homocysteine level (>25umol/L)\* | 1.158（0.231-5.811） | | 0.858 |
| Elavation of blood glucose (>6.7mmol/L)\* | 1.044（0.534-2.042） | | 0.899 |
| Elavation of TC (>5.2 mmol/L)\* | 0.955（0.638-1.431） | | 0.823 |
| Elavation of TG (>1.7mmol/L)\* | 0.815（0.510-1.302） | | 0.392 |
| Decrease of HDL (<1.3mmol/L)\* | 0.965（0.642-1.449） | | 0.965 |
| Elavation of LDL (>3.3mmol/L)\* | 0.894（0.589-1.356） | | 0.598 |
| Elavation of D-Dimer (>0.55ug/ml)\* | 0.780（0.523-1.163） | | 0.222 |
| Elavation of CK-MB (>25U/L)\* | 0.864（0.191-3.915） | | 0.864 |
| Elavation of BNP(pro-BNP) (BNP>100 pg/ml or pro-BNP>17.5 pmol/L)\* | 0.693（0.337-1.428） | | 0.320 |
| E/A ratio (<1)\* | 0.916（0.595-1.412） | | 0.692 |
| **Genetic variables**†  **Genetic variables**†  **Genetic variables**† | rs1056892 |  | | 0.733 |
| GG | 0.980（0.542-1.772） | | 0.946 |
| GA | 1.158（0.662-2.026） | | 0.608 |
| AA | Reference | | Reference |
| rs1058808 |  | | 0.822 |
| GG | 1.144（0.637-2.054） | | 0.653 |
| CG | 1.152（0.727-1.826） | | 0.547 |
| CC | Reference | | Reference |
| rs10836235 |  | | 0.709 |
| CC | 0.748（0.343-1.632） | | 0.748 |
| CT | 0.843（0.382-1.863） | | 0.674 |
| TT | Reference | | Reference |
| rs10838611 |  | | 0.242 |
| GG | 0.541（0.264-1.110） | | 0.094 |
| CG | 0.577（0.280-1.189） | | 0.136 |
| CC | Reference | | Reference |
| rs1136201 |  | | 0.34 |
| GG | 1.040（0.310-3.485） | | 0.949 |
| GA | 1.440（0.885-2.344） | | 0.142 |
| AA | Reference | | Reference |
| rs13181 |  | | 0.603 |
| GG | 2.371（0.213-26.429） | | 0.483 |
| GT | 1.221（0.724-2.059） | | 0.455 |
| TT | Reference | | Reference |
| rs1695 |  | | 0.301 |
| GG | 0.420（0.130-1.357） | | 0.420 |
| GA | 1.076（0.707-1.638） | | 0.733 |
| AA | Reference | | Reference |
| rs1786814 |  | | 0.943 |
| GG | 0.855（0.053-13.778） | | 0.912 |
| GA | 0.952（0.056-16.279） | | 0.973 |
| AA | Reference | | Reference |
| rs1799983 |  | | 0.617 |
| GG | 2.524（0.260-24.526） | | 0.425 |
| GT | 2.914（0.289-29.414） | | 0.365 |
| TT | Reference | | Reference |
| rs1883112 |  | | 0.720 |
| GG | 1.319（0.635-2.741） | | 0.458 |
| GA | 0.975（0.6340-1.484） | | 0.905 |
| AA | Reference | | Reference |
| rs2232228 |  | | 0.694 |
| GG | 0.996（0.574-1.728） | | 0.989 |
| GA | 1.190（0.746-1.898） | | 0.465 |
| AA | Reference | | Reference |
| rs2235047 |  | | 0.297 |
| AA | 0.765（0.460-1.272） | | 0.302 |
| CA | 0.574（0.284-1.162） | | 0.123 |
| CC | Reference | | Reference |
| rs2282143 |  | | 0.467 |
| CC | 0.490（0.140-1.708） | | 0.263 |
| CT | 0.439（0.118-1.625） | | 0.217 |
| TT | Reference | | Reference |
| rs2290271 |  | | 0.821 |
| AA | 1.180（0.657-2.120） | | 0.579 |
| CA | 1.180（0.684-2.036） | | 0.552 |
| CC | Reference | | Reference |
| rs2305364 |  | | 0.33 |
| CC | 0.844（0.469-1.521） | | 0.573 |
| CT | 1.194（0.694-2.055） | | 0.522 |
| TT | Reference | | Reference |
| rs246221 |  | | 0.88 |
| CC | 0.915（0.526-1.592） | | 0.754 |
| CT | 0.887（0.556-1.416） | | 0.616 |
| TT | Reference | | Reference |
| rs2631372 |  | | 0.016 |
| GG | 1.447（0.774-2.705） | | 0.247 |
| CG | 2.257（1.232-4.135） | | 0.008 |
| CC | Reference | | Reference |
| rs316019 |  | | 0.341 |
| AA | 0.548（0.049-6.110） | | 0.625 |
| CA | 0.691（0.412-1.159） | | 0.161 |
| CC | Reference | | Reference |
| rs3743527 |  | | 0.167 |
| CC | 0.757（0.424-1.351） | | 0.346 |
| CT | 1.180（0.690-2.016） | | 0.545 |
| TT | Reference | | Reference |
| rs3749172 |  | | 0.583 |
| AA | 0.686（0.337-1.397） | | 0.299 |
| CA | 0.929（0.606-1.422） | | 0.734 |
| CC | Reference | | Reference |
| rs3887137 |  | | 0.522 |
| CC | 1.4737（0.742-2.782） | | 0.282 |
| CT | 1.225（0.637-2.358） | | 0.543 |
| TT | Reference | | Reference |
| rs4148808 |  | | 0.272 |
| CC | 1.767（0.737-4.240） | | 0.202 |
| CT | 2.447（0.443-13.532） | | 0.305 |
| TT | Reference | | Reference |
| rs4673 |  | |  |
| GG | 1.148（0.673-1.957） | | 0.613 |
| GA | Reference | | Reference |
| AA | None | | None |
| rs4982753 |  | | 0.457 |
| CC | 0.698（0.372-1.310） | | 0.263 |
| CT | 0.690（0.378-1.261） | | 0.228 |
| TT | Reference | | Reference |
| rs7542939 |  | | 0.901 |
| GG | 1.196（0.371-3.859） | | 0.765 |
| GA | 1.288（0.382-4.343） | | 0.683 |
| AA | Reference | | Reference |
| rs7627754 |  | | 0.911 |
| AA | 1.040（0.478-2.264） | | 0.921 |
| AT | 0.949（0.437-2.057） | | 0.894 |
| TT | Reference | | Reference |
| rs7853758 |  | | 0.069 |
| GG | 4.784（0.553-41.412） | | 0.155 |
| GA | 2.805（0.309-25.490） | | 0.36 |
| AA | Reference | | Reference |
| rs885004 |  | | 0.037 |
| GG | 3.974（0.439-35.966） | | 0.220 |
| GA | 2.189（0.234-20.509） | | 0.493 |
| AA | Reference | | Reference |

\* at baseline

†rs2631370 and rs13240755 were excluded due to detection success rate less than 95%

Abbreviations: IDC, Invasive ductal carcinoma; TC, Total cholesterol; TG, Total triglyceride; HDL-c, high density lipoprotein cholesterol ; LDL-c, low density lipoprotein cholesterol; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CK-MB, Creatine kinase isoenzymes-MB.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Supplementary Table 3. Multivariate analysis of clinical risk factors alone for cardiac toxicity | | | | |
| Cardiotoxicity event | Risk fators | OR | CI | P |
| Overall cardiac toxicity\* | Anthracycline containing chemotherapy | 1.848 | 1.135-3.008 | 0.014 |
| 10% reduction of SF(absolute value)\*\* | Total cholesterol ＞5.2 mmol/L at baseline | 2.991 | 1.129-7.929 | 0.028 |
| BNP(NT-proBNP) elevated\*\*\* | Menstrual conditions (Postmenopausal vs Premenopausal) | 0.146 | 0.041-0.517 | 0.003 |
| Anthracycline containing chemotherapy | 7.665 | 1.517-38.745 | 0.014 |
| Trastuzumab containing chemotherapy | 5.072 | 1.451-17.734 | 0.011 |
| \*Model 1: adjustment factors: age (≥60), BMI (≥28) ,stage, pathology, molecular subtype, concomitant diseases, smoking history, drinking history, menstrual status, chemotherapy regimen containing anthracycline; \*\* Model 2: adjustment factors: age (≥60), BMI (≥28), stage, molecular subtype, concomitant diseases, menstrual status, elavation of total cholesterol, E / A ratio <1; \*\*\* Model 3: adjustment factors: age (≥60), BMI (≥28) stage, molecular subtype, concomitant diseases, menstrual status, chemotherapy regimen containing anthracycline, regimen containing herceptin, elavation of blood glucose, elavation of total triglyceride | | | | |