**Supplementary Table 1. Patient and tumor characteristics.** Comparison of distributions of patient and tumor characteristics among patientsin the original trial (n=391), the baseline cohort (n=294), and those who were excluded from the study (n=97).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Not included (N=97)** | **Included (N=294)** | **Total (N=391)** | **Chi-Square p-value** |
|   |  |  |  |  |
| **Treatment** |  |  |  | 0.08 |
|     Letrozole + Bevacizumab | 41 (42.3%) | 154 (52.4%) | 195 (49.9%) |   |
|  Letrozole only     | 56 (57.7%) | 140 (47.6%) | 196 (50.1%) |   |
|   |  |  |  |   |
| **Measurable disease** |  |  |  | 0.43 |
|     No | 40 (41.2%) | 108 (36.7%) | 148 (37.9%) |   |
|     Yes | 57 (58.8%) | 186 (63.3%) | 243 (62.1%) |   |
|   |  |  |  |   |
| **Race/Ethnicity** |  |  |  | 0.86 |
|     Unknown | 2 (2.1%) | 6 (2.0%) | 8 (2.0%) |   |
|     White | 86 (88.7%) | 262 (89.1%) | 348 (89.0%) |   |
|     Black or African American | 6 (6.2%) | 20 (6.8%) | 26 (6.6%) |   |
|     Asian | 3 (3.1%) | 4 (1.4%) | 7 (1.8%) |   |
|     Native Hawaiian or Pacific Islander | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |   |
|     More than one race | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |   |
|  |  |  |  |  |
|   |  |  |  |   |
| **Age** |  |  |  | 0.79 |
|     ≤30 | 1 (1.0%) | 2 (0.7%) | 3 (0.8%) |   |
|     31-40 | 5 (5.2%) | 31 (10.5%) | 36 (9.2%) |   |
|     41-50 | 17 (17.5%) | 54 (18.4%) | 71 (18.2%) |   |
|     51-60 | 30 (30.9%) | 81 (27.6%) | 111 (28.4%) |   |
|     61-70 | 31 (32.0%) | 87 (29.6%) | 118 (30.2%) |   |
|     71-80 | 9 (9.3%) | 30 (10.2%) | 39 (10.0%) |   |
|     80+ | 4 (4.1%) | 9 (3.1%) | 13 (3.3%) |   |
|   |  |  |  |   |
| **Age** |  |  |  | 0.67 |
|     Median | 57.2 | 57.7 | 57.7 |   |
|     Range | (29.0-87.0) | (24.7-85.3) | (24.7-87.0) |   |
|   |  |  |  |   |
| **ECOG performance status** |  |  |  | **<0.01** |
|  Missing | 4 | 2 | 6 |   |
|     0 | 51 (54.8%) | 191 (65.4%) | 242 (62.9%) |   |
|     1 | 39 (41.9%) | 101 (34.6%) | 140 (36.4%) |   |
|   |  |  |  |   |
|  |  |  |  |   |
| **Disease-free interval** |  |  |  | 0.71 |
|     ≤24mos | 48 (49.5%) | 152 (51.7%) | 200 (51.2%) |   |
|     >24mos | 49 (50.5%) | 142 (48.3%) | 191 (48.8%) |   |
|   |  |  |  |   |
| **Estrogen receptor status** |  |  |  | 0.57 |
|  Missing | 4 | 2 | 6 |   |
|     Negative | 0 (0.0%) | 1 (0.3%) | 1 (0.3%) |   |
|     Positive | 93 (100.0%) | 291 (99.7%) | 384 (99.7%) |   |
|   |  |  |  |   |
| **Progesterone receptor status** |  |  |  | 0.23 |
|     Missing | 4 | 2 | 6 |   |
|     Negative | 24 (25.8%) | 55 (18.8%) | 79 (20.5%) |   |
|     Positive | 69 (74.2%) | 234 (80.1%) | 303 (78.7%) |   |
|     Unknown | 0 (0.0%) | 3 (1.0%) | 3 (0.8%) |   |
|   |  |  |  |   |
| **HER2 status** |  |  |  | 0.06 |
|     Missing | 4 | 2 | 6 |   |
|     Positive | 81 (87.1%) | 272 (93.2%) | 353 (91.7%) |   |
|     Negative | 5 (5.4%) | 13 (4.5%) | 18 (4.7%) |   |
|  Unknown | 7 (7.5%) | 7 (2.4%) | 14 (3.6%) |   |
|   |  |  |  |   |
| **Prior chemotherapy** |  |  |  | 0.44 |
|     No | 62 (63.9%) | 175 (59.5%) | 237 (60.6%) |   |
|     Yes | 35 (36.1%) | 119 (40.5%) | 154 (39.4%) |   |
|   |  |  |  |   |
| **Any prior endocrine therapy** |  |  |  | 0.70 |
|     No | 52 (53.6%) | 151 (51.4%) | 203 (51.9%) |   |
|     Yes | 45 (46.4%) | 143 (48.6%) | 188 (48.1%) |   |
|   |  |  |  |   |
| **Prior aromatase inhibitor** |  |  |  | 0.93 |
|     No | 74 (76.3%) | 223 (75.9%) | 297 (76.0%) |   |
|     Yes | 23 (23.7%) | 71 (24.1%) | 94 (24.0%) |   |
|   |  |  |  |   |
| **Prior tamoxifen** |  |  |  | 0.85 |
|     No | 65 (67.0%) | 194 (66.0%) | 259 (66.2%) |   |
|     Yes | 32 (33.0%) | 100 (34.0%) | 132 (33.8%) |   |
|   |  |  |  |   |
| **No. of metastatic sites** |  |  |  | 0.89 |
|     Missing | 4 | 3 | 7 |   |
|     1 | 30 (32.3%) | 104 (35.7%) | 134 (34.9%) |   |
|     2 | 33 (35.5%) | 105 (36.1%) | 138 (35.9%) |   |
|     3 | 18 (19.4%) | 54 (18.6%) | 72 (18.8%) |   |
|     4 | 9 (9.7%) | 19 (6.5%) | 28 (7.3%) |   |
|     5 | 1 (1.1%) | 5 (1.7%) | 6 (1.6%) |   |
|     6 | 2 (2.2%) | 4 (1.4%) | 6 (1.6%) |   |

**Supplementary Table 2.** Multivariable Cox regression analysis to determine correlation between circulating tumor cell (CTC)-positivity at baseline vs. progression-free survival (PFS) and overall survival (OS).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PFS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC (positive vs. negative) | 1.79 | 1.35 | 2.36 | **<0.01** |
| Arm (Let + Bev vs. Let) | 0.73 | 0.56 | 0.95 | **0.02** |
| Age (continuous)  | 1.00 | 0.99 | 1.01 | 0.46 |
| Measurable disease (Yes vs. No) | 1.19 | 0.90 | 1.56 | 0.22 |
| Disease-free interval (>24 vs. ≤ 24 months) | 0.86 | 0.66 | 1.12 | 0.27 |
| HER2 (positive vs. negative) | 0.51 | 0.28 | 0.94 | **0.03** |
|  |  |  |  |  |
| **OS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC (positive vs. negative) | 2.72 | 1.98 | 3.73 | **<0.01** |
| Arm (Let + Bev vs. Let) | 0.79 | 0.58 | 1.08 | 0.14 |
| Age (continuous)  | 1.02 | 1.00 | 1.03 | **0.02** |
| Measurable disease (Yes vs. No) | 1.23 | 0.89 | 1.70 | 0.22 |
| Disease-free interval (>24 vs. ≤ 24 months) | 1.29 | 0.94 | 1.78 | 0.11 |
| HER2 (positive vs. negative) | 0.88 | 0.44 | 1.77 | 0.73 |

**Supplementary Table 3.** Multivariable Cox regression analysis to determine correlation between circulating tumor cell (CTC) status at baseline (T0) and 3 weeks after initiation of treatment (T1) vs. progression-free survival (PFS) and overall survival (OS).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PFS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC-CTC+ vs. CTC-CTC- | 1.44 | 0.72 | 2.90 | 0.30 |
| CTC+CTC- vs. CTC-CTC- | 1.45 | 0.97 | 2.17 | 0.07 |
| CTC+CTC+ vs. CTC-CTC- | 2.15 | 1.43 | 3.23 | **<0.01** |
| Arm (Let vs. Let+Bev) | 1.40 | 1.03 | 1.91 | 0.03 |
| Age (continuous)  | 1.00 | 0.99 | 1.01 | 0.80 |
| Measurable disease (Yes vs. No) | 0.84 | 0.61 | 1.16 | 0.30 |
| Disease-free interval (>24 vs. ≤ 24 months) | 1.23 | 0.90 | 1.68 | 0.20 |
| HER2 (positive vs. negative) | 2.94 | 1.49 | 5.80 | **<0.01** |
|  |  |  |  |  |
| **OS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC-CTC+ vs. CTC-CTC- | 3.20 | 1.57 | 6.51 | **<0.01** |
| CTC+CTC- vs. CTC-CTC- | 1.97 | 1.20 | 3.25 | **0.01** |
| CTC+CTC+ vs. CTC-CTC- | 2.70 | 1.66 | 4.38 | **<0.01** |
| Arm (Let vs. Let+Bev) | 1.30 | 0.88 | 1.93 | 0.20 |
| Age (continuous)  | 1.01 | 1.00 | 1.03 | 0.12 |
| Measurable disease (Yes vs. No) | 0.76 | 0.50 | 1.16 | 0.20 |
| Disease-free interval (>24 vs. ≤ 24 months) | 0.83 | 0.56 | 1.23 | 0.40 |
| HER2 (positive vs. negative) | 0.89 | 0.35 | 2.27 | 0.80 |

**Supplementary Table 4.** Multivariable Cox regression analysis to determine correlation between circulating tumor cell (CTC) status during therapy vs. progression-free survival (PFS) and overall survival (OS).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PFS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC (positive vs. negative) |  2.20 | 1.58 | 3.07 | **<0.01** |
| Arm (Let vs. Let+Bev) |  1.46 | 1.11 | 1.91 | **0.01** |
| Age (continuous)  |  1.00 | 0.99 | 1.01 | 0.70 |
| Measurable disease (Yes vs. No) |  0.89 | 0.67 | 1.19 | 0.40 |
| Disease-free interval (>24 vs. ≤ 24 months) |  1.11 | 0.84 | 1.46 | 0.50 |
| HER2 (positive vs. negative) |  2.58 | 1.40 | 4.73 | **<0.01** |
|  |  |  |  |  |
| **OS** | **Hazard ratio** | **Lower 95%** | **Upper 95%** | **Adjusted likelihood-ratio (p-value)** |
| CTC (positive vs. negative) |  3.40 | 2.36 | 4.88 | **<0.01** |
| Arm (Let vs. Let+Bev) |  0.85 | 0.59 | 1.23 | 0.40 |
| Age (continuous)  |  1.02 | 1.00 | 1.03 | 0.05 |
| Measurable disease (Yes vs. No) |  0.85 | 0.59 | 1.23 | 0.40 |
| Disease-free interval (>24 vs. ≤ 24 months) |  0.81 | 0.57 | 1.14 | 0.20 |
| HER2 (positive vs. negative) |  0.63 | 0.27 | 1.50 | 0.30 |