

**S5 Table.** Adverse events in study groups and PALOMA-2 data

|                           | Group 1<br>(n=174) | Group 2<br>(n=128) | Group 3<br>(n=102) | Group 4<br>(n=30) | Total<br>(n=434) | PALOMA-2 <sup>a)</sup><br>(n=444) | p-value<br>(group 1 vs.<br>group 2) | p-value<br>(all groups) |
|---------------------------|--------------------|--------------------|--------------------|-------------------|------------------|-----------------------------------|-------------------------------------|-------------------------|
| Neutropenia               | 172 (98.8)         | 126 (98.4)         | 64 (62.7)          | 30 (100)          | 392 (90.3)       | 353 (79.5)                        | > 0.99 <sup>b)</sup>                | < 0.0001 <sup>b)</sup>  |
| Fatigue                   | 27 (15.5)          | 24 (18.7)          | 24 (23.5)          | 6 (20.0)          | 81 (18.7)        | 166 (37.4)                        | 0.4587                              | 0.0141 <sup>b)</sup>    |
| Oral mucositis            | 33 (19.0)          | 29 (22.7)          | 21 (20.6)          | 7 (23.3)          | 90 (20.7)        | 68 (15.3)                         | 0.4326                              | 0.0455 <sup>b)</sup>    |
| Anemia                    | 56 (32.2)          | 59 (46.1)          | 23 (22.5)          | 14 (46.7)         | 152 (35.0)       | 107 (24.1)                        | 0.0139                              | 0.0021                  |
| Thrombocytopenia          | 47 (27.0)          | 38 (29.7)          | 22 (21.6)          | 10 (33.3)         | 117 (27.0)       | 69 (15.5)                         | 0.6093                              | 0.5788                  |
| Alopecia                  | 18 (10.3)          | 6 (4.7)            | 5 (4.9)            | 1 (3.3)           | 30 (6.9)         | 146 (32.9)                        | 0.0725                              | 0.1595                  |
| Skin rash                 | 10 (5.7)           | 8 (6.2)            | 5 (4.9)            | 1 (3.3)           | 24 (5.5)         | 79 (17.8)                         | 0.8553                              | 0.9323                  |
| Pruritus                  | 7 (4.0)            | 5 (3.9)            | 5 (4.9)            | 1 (3.3)           | 18 (4.1)         |                                   | 0.9591                              | 0.9634 <sup>b)</sup>    |
| Nausea                    | 5 (2.9)            | 14 (10.9)          | 12 (11.8)          | 1 (3.3)           | 32 (7.4)         | 156 (35.1)                        | 0.0043                              | 0.0086                  |
| Anorexia                  | 5 (2.9)            | 10 (7.8)           | 5 (4.9)            | 2 (6.7)           | 22 (5.1)         | 66 (14.9)                         | 0.0509                              | 0.2155 <sup>b)</sup>    |
| Diarrhea                  | 10 (5.7)           | 5 (3.9)            | 7 (6.9)            | 2 (6.7)           | 24 (5.5)         | 116 (26.1)                        | 0.4688                              | 0.7418                  |
| Myalgia                   | 10 (5.7)           | 7 (5.5)            | 10 (9.8)           | 2 (6.7)           | 29 (6.7)         | 53 (11.9)                         | 0.9174                              | 0.4644                  |
| Dizziness                 | 5 (2.9)            | 1 (0.8)            | 2 (2.0)            | 0                 | 8 (1.8)          | 63 (14.2)                         | 0.2470 <sup>b)</sup>                | 0.5827 <sup>b)</sup>    |
| Dyspepsia                 | 5 (2.9)            | 0                  | 1 (1.0)            | 0                 | 6 (1.4)          | 41 (9.2)                          | 0.0750 <sup>b)</sup>                | 0.1976 <sup>b)</sup>    |
| Abdominal pain            | 3 (1.7)            | 1 (0.8)            | 2 (2.0)            | 0                 | 6 (1.4)          | 50 (11.3)                         | 0.6399 <sup>b)</sup>                | 0.8505 <sup>b)</sup>    |
| Liver enzyme<br>elevation | 10 (5.7)           | 7 (5.5)            | 4 (3.9)            | 2 (6.7)           | 23 (5.3)         |                                   | 0.9174                              | 0.9303                  |
| Arthralgia                | 14 (8.0)           | 11 (8.6)           | 8 (7.8)            | 6 (20.0)          | 39 (9.0)         | 148 (33.3)                        | 0.8644                              | 0.1975                  |
| Neuropathy                | 3 (1.7)            | 1 (0.8)            | 0                  | 0                 | 4 (0.9)          | 75 (16.9)                         | 0.6399 <sup>b)</sup>                | 0.6792 <sup>b)</sup>    |
| Fever                     | 1 (0.6)            | 4 (3.1)            | 3 (2.9)            | 3 (10.0)          | 11 (2.5)         | 55 (12.4)                         | 0.1667 <sup>b)</sup>                | 0.0196 <sup>b)</sup>    |

|                      |         |         |         |         |          |            |                      |                      |
|----------------------|---------|---------|---------|---------|----------|------------|----------------------|----------------------|
| Dyspnea              | 2 (1.1) | 0       | 6 (5.9) | 1 (3.3) | 9 (2.1)  | 66 (14.9)  | 0.5100 <sup>b)</sup> | 0.0073 <sup>b)</sup> |
| Insomnia             | 8 (4.6) | 1 (0.8) | 1 (1.0) | 0       | 10 (2.3) | 66 (14.9)  | 0.0839 <sup>b)</sup> | 0.1526 <sup>b)</sup> |
| Creatinine elevation | 2 (1.1) | 2 (1.6) | 0       | 0       | 4 (0.9)  |            | > 0.99 <sup>b)</sup> | 0.7671 <sup>b)</sup> |
| Constipation         | 2 (1.1) | 4 (3.1) | 5 (4.9) | 0       | 11 (2.5) | 86 (19.4)  | 0.4070 <sup>b)</sup> | 0.2121 <sup>b)</sup> |
| Febrile neutropenia  | 1 (0.6) | 2 (1.6) | 0       | 1 (3.3) | 4 (0.9)  |            | 0.5761 <sup>b)</sup> | 0.2526 <sup>b)</sup> |
| Edema                | 5 (2.9) | 2 (1.6) | 1 (1.0) | 1 (3.3) | 9 (2.1)  | 50 (11.3)  | 0.7029 <sup>b)</sup> | 0.6253 <sup>b)</sup> |
| Vomiting             | 4 (2.3) | 2 (1.6) | 0       | 0       | 6 (1.4)  | 69 (15.5)  | > 0.99 <sup>b)</sup> | 0.6260 <sup>b)</sup> |
| Tonsillitis          | 1 (0.6) | 1 (0.8) | 0       | 0       | 2 (0.5)  | 59 (13.3)  | > 0.99 <sup>b)</sup> | > 0.99 <sup>b)</sup> |
| Kidney infection     | 5 (2.9) | 2 (1.6) | 1 (1.0) | 0       | 8 (1.8)  | 53 (11.9)  | 0.7029 <sup>b)</sup> | 0.8115 <sup>b)</sup> |
| Hand foot syndrome   | 0       | 0       | 3 (2.9) | 0       | 3 (0.7)  | 68 (15.3)  | NA                   | 0.0324 <sup>b)</sup> |
| Cough                | 4 (2.3) | 3 (2.3) | 1 (1.0) | 0       | 8 (1.8)  | 111 (25.0) | > 0.99 <sup>b)</sup> | 0.8961 <sup>b)</sup> |
| Pneumonitis          | 1 (0.6) | 0       | 0       | 0       | 1 (0.2)  |            | > 0.99 <sup>b)</sup> | > 0.99 <sup>b)</sup> |

Values are presented as number (%). Blanks indicate data not mentioned in the article. NA, not applicable. <sup>a)</sup>A phase III study with palbociclib plus letrozole versus letrozole alone administered to patients with previously untreated, estrogen receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer. The adverse event data were from 444 patients who received palbociclib plus letrozole, <sup>b)</sup>Fisher's exact test.