**Supplementary Data**

**Supplementary Table 1.** CirculatingBiomarker Levels at Baseline, Prior to Cycle 2, and Prior to Cycle 3 in Each Arm. Results are reported as the median and the lower and upper quartiles (Q1, Q3). P value was from Wilcoxon Rank Sum test comparing the two arms in terms of the ratio of the post-treatment levels divided by the baseline.

|  | Arm A | | |  | |  | | Arm B | | | |  | | P value | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | n | Median (Q1, Q3)  pg/mL | |  | |  | | n | | Median (Q1, Q3)  pg/mL | |  | |
|  | *Markers of Angiopoietin-Tie2 Pathway* | | | | | | | | | | |  | |  | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 3,909 (3,246, 4,863) |  | |  | | 15 | | 3,237 (2,424, 4,813) | |  | |  | |
| Prior to cycle 2 | 14 | 132,156 (110,775, 160,316) |  | |  | | 15 | | 120,956 (84,474, 131,643) | |  | | 0.86 | |
| Prior to cycle 3 | 9 | 125,928 (114,871, 141,528) |  | |  | | 11 | | 96,075 (84,200, 150,486) | |  | | 0.76 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 803 (510, 1,035) |  | |  | | 15 | | 835 (650, 1,094) | |  | |  | |
| Prior to cycle 2 | 14 | 783 (535, 1,041) |  | |  | | 15 | | 671 (571, 856) | |  | | 0.14 | |
| Prior to cycle 3 | 9 | 912 (263, 1,232) |  | |  | | 11 | | 753 (424, 912) | |  | | 0.069 | |
|  | *Markers of VEGF Pathway* | | | | | | | | | | |  | |  | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 27.3 (10.5, 48.4) |  | |  | | 15 | | 26.1 (19.6, 38.0) | |  | |  | |
| Prior to cycle 2 | 14 | 21.3 (10.5, 29.0) |  | |  | | 15 | | 33.4 (13.6, 48.2) | |  | | 0.19 | |
| Prior to cycle 3 | 9 | 20.7 (0.3, 34.2) |  | |  | | 11 | | 41.2 (26.1, 56.7) | |  | | 0.046 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 31.1 (26.1, 35.2) |  | |  | | 15 | | 30.7 (28.3, 46.7) | |  | |  | |
| Prior to cycle 2 | 14 | 30.5 (21.8, 36.0) |  | |  | | 15 | | 33.6 (29.9, 39.2) | |  | | 0.029 | |
| Prior to cycle 3 | 9 | 31.4 (30.5, 34.3) |  | |  | | 11 | | 31.5 (26.3, 41.8) | |  | | 0.20 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 873 (157, 1,073) |  | |  | | 15 | | 489 (50, 898) | |  | |  | |
| Prior to cycle 2 | 14 | 722 (117, 869) |  | |  | | 15 | | 50 (50, 321) | |  | | 0.11 | |
| Prior to cycle 3 | 9 | 489 (362, 954) |  | |  | | 11 | | 50 (50, 416) | |  | | 0.068 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 255 (72, 425) |  | |  | | 15 | | 283 (251, 380) | |  | |  | |
| Prior to cycle 2 | 14 | 209 (67, 340) |  | |  | | 15 | | 311 (247, 357) | |  | | 0.61 | |
| Prior to cycle 3 | 9 | 230 (45, 358) |  | |  | | 11 | | 311 (154, 503) | |  | | 0.27 | |
|  | *Markers of Alternative Pro-angiogenic Pathways* | | | | | | | | | | |  | |  | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 0.1 (0.1, 12.6) |  | |  | | 15 | | 0.1 (0.1, 4.0) | |  | |  | |
| Prior to cycle 2 | 14 | 3.6 (0.1, 17.5) |  | |  | | 15 | | 5.9 (0.1, 13.5) | |  | | 0.61 | |
| Prior to cycle 3 | 9 | 2.5 (0.1, 8.1) |  | |  | | 11 | | 0.4 (0.1, 17.3) | |  | | 0.49 | |
| ICAM – 1 |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 161,879 (103,645, 240,620) |  | |  | | 15 | | 243,594 (185,653, 601,003) | |  | |  | |
| Prior to cycle 2 | 14 | 193,335 (117,584, 247,434) |  | |  | | 15 | | 239,027 (160,295, 318,968) | |  | | 0.82 | |
| Prior to cycle 3 | 9 | 262,636 (221,161, 266,594) |  | |  | | 11 | | 200,959 (150,610, 276,615) | |  | | 0.069 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 965,554 (738,499, 1,421,550) |  | |  | | 15 | | 1,307,900 (982,643, 1,946,700) | |  | |  | |
| Prior to cycle 2 | 14 | 1,336,300 (955,663, 1,903,550) |  | |  | | 15 | | 1,850,000 (1,327,000, 2,555,600) | |  | | 0.34 | |
| Prior to cycle 3 | 9 | 982,488 (969,237, 1,581,000) |  | |  | | 11 | | 1,666,200 (1,351,500, 2,091,050) | |  | | 0.046 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 124 (105, 136) |  | |  | | 15 | | 120 (105, 136) | |  | |  | |
| Prior to cycle 2 | 14 | 112 (89, 131) |  | |  | | 15 | | 110 (95, 132) | |  | | 0.11 | |
| Prior to cycle 3 | 9 | 131 (104, 136) |  | |  | | 11 | | 120 (97, 133) | |  | | 0.23 | |
|  |  |  |  | |  | |  | |  | |  | |  | |
| Baseline | 15 | 351 (237, 788) |  | |  | | 15 | | 478 (112, 647) | |  | |  | |
| Prior to cycle 2 | 14 | 291 (190, 394) |  | |  | | 15 | | 262 (213, 829) | |  | | 0.37 | |
| Prior to cycle 3 | 9 | 264 (119, 710) |  | |  | | 11 | | 173 (105, 777) | |  | | 0.35 | |

**Supplementary Figure 1.** Circulating Biomarkers Levels at Baseline, Prior to Cycle 2, and Prior to Cycle 3 in Each Arm. Results are reported as median and lower and upper quartiles (Q1, Q3).

|  |  |
| --- | --- |
| **A. Angiopoietin-2.** | **B. Tie-2** |
|  |  |
| **C. VEGF-A** | **D. PlGF** |
|  |  |

|  |  |
| --- | --- |
| **E. VEGFR-3** | **F. VEGF-C** |
|  |  |
| **G. IL-8** | **H. ICAM-1** |
|  |  |

|  |  |
| --- | --- |
| **I. VCAM-1** | **J. FGF2** |
|  |  |
| **K. PDGF-AA** |  |
|  |  |