**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*  |  |  |
| $$Angiopoietin-2$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$Tie-2$$ |  |  |  |  |  |  |  |  |
|  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* |  |  |
| $$VEGF-A$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$PlGF$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$VEGFR-3$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$VEGF-C$$ |  |  |  |  |  |  |  |  |
|  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*  |  |  |
| $$IL-8$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$VCAM-1$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$FGF2$$ |  |  |  |  |  |  |  |  |
|  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 |
| $$PDGF-AA$$ |  |  |  |  |  |  |  |  |
|  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).

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| **A. Angiopoietin-2.** | **B. Tie-2** |
|  |  |
| **C. VEGF-A** | **D. PlGF** |
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| --- | --- |
| **E. VEGFR-3** | **F. VEGF-C** |
|  |  |
| **G. IL-8** | **H. ICAM-1** |
|  |  |

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