**Supplemantary Table 3.** Characteristics of dose-dependent changes in candidate plasma metabolite pharmacodynamic biomarker concentrations in 41 patients on day 1 of pictilisib clinical trial. (t test p-values <0.05 are shaded dark grey;p-values <0.10 and ≥0.05 are shaded light grey.)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Metabolite | Time post-dose (h) | Dose levels 45 to 60 mg |  | Dose levels 80 to 245 mg |  | Dose levels 330 to 450 mg |
| Rel. change (%) | 95%CI lower limit | 95%CI upper limit | p-value |  | Rel. change (%) | 95%CI lower limit | 95%CI upper limit | p-value |  | Rel. change (%) | 95%CI lower limit | 95%CI upper limit | p-value |
| Asparagine | 2 | -0.71 | -24.77 | 30.95 | 0.962 |  | 27.71 | 6.17 | 53.57 | **0.041** |  | 13.41 | 5.25 | 22.18 | **0.003** |
| 8 | -0.57 | -14.68 | 15.84 | 0.944 |  | 41.10 | 21.51 | 63.83 | **0.003** |  | 27.98 | 18.24 | 38.52 | **0.000002** |
| 24 | -4.56 | -19.44 | 13.04 | 0.612 |  | 79.49 | 14.84 | 180.23 | **0.037** |  | 29.09 | 14.00 | 46.15 | **0.0005** |
| Citrulline | 2 | 8.85 | -2.76 | 21.83 | 0.201 |  | -0.62 | -13.15 | 13.68 | 0.930 |  | 15.37 | 7.96 | 23.28 | **0.0003** |
| 8 | 10.59 | -4.18 | 27.62 | 0.227 |  | 4.19 | -12.53 | 24.08 | 0.659 |  | 13.72 | 4.67 | 23.54 | **0.005** |
| 24 | 6.27 | -9.45 | 24.71 | 0.490 |  | 0.88 | -16.97 | 22.53 | 0.933 |  | -0.74 | -9.49 | 8.85 | 0.876 |
| Glutamate | 2 | -5.36 | -13.73 | 3.80 | 0.295 |  | 52.16 | 15.62 | 100.15 | **0.024** |  | 29.24 | 13.48 | 47.16 | **0.001** |
| 8 | -5.27 | -25.39 | 20.21 | 0.675 |  | 31.57 | 2.92 | 68.13 | 0.065 |  | 20.00 | 6.63 | 35.02 | **0.006** |
| 24 | -11.82 | -30.20 | 11.33 | 0.339 |  | 30.50 | -5.02 | 79.17 | 0.152 |  | 27.20 | 11.42 | 45.20 | **0.002** |
| Histidine | 2 | 0.87 | -11.33 | 14.72 | 0.901 |  | 15.25 | -0.02 | 32.84 | 0.098 |  | 11.31 | 6.67 | 16.15 | **0.00004** |
| 8 | 0.07 | -12.02 | 13.80 | 0.992 |  | 17.96 | 4.46 | 33.19 | **0.032** |  | 21.61 | 16.01 | 27.46 | **0.00000001** |
| 24 | 0.99 | -9.60 | 12.79 | 0.869 |  | 29.37 | 14.89 | 45.65 | **0.004** |  | 15.52 | 8.74 | 22.71 | **0.0001** |
| Isoleucine | 2 | 1.53 | -22.49 | 32.90 | 0.917 |  | 35.39 | 3.28 | 77.38 | 0.071 |  | 30.86 | 20.71 | 41.86 | **0.000001** |
| 8 | 0.87 | -25.96 | 37.29 | 0.958 |  | 51.03 | 11.74 | 104.01 | **0.031** |  | 47.86 | 33.28 | 64.03 | **0.0000001** |
| 24 | -12.06 | -30.93 | 11.90 | 0.344 |  | 36.39 | -2.43 | 90.50 | 0.112 |  | 27.55 | 12.06 | 45.17 | **0.001** |
| Leucine | 2 | 2.88 | -23.62 | 38.44 | 0.859 |  | 29.40 | 2.67 | 63.02 | 0.072 |  | 27.60 | 16.57 | 39.66 | **0.00002** |
| 8 | -10.08 | -31.43 | 17.82 | 0.476 |  | 29.43 | -0.63 | 68.50 | 0.097 |  | 31.30 | 16.06 | 48.53 | **0.0002** |
| 24 | -14.34 | -34.98 | 12.75 | 0.320 |  | 28.78 | -2.71 | 70.36 | 0.120 |  | 15.26 | 0.92 | 31.62 | **0.046** |
| Phenylalanine | 2 | -2.54 | -15.99 | 13.04 | 0.748 |  | 22.93 | 6.16 | 42.32 | **0.033** |  | 20.53 | 14.73 | 26.61 | **0.0000001** |
| 8 | -2.63 | -17.56 | 14.96 | 0.766 |  | 36.53 | 15.95 | 60.73 | **0.007** |  | 37.98 | 28.80 | 47.81 | **0.000000001** |
| 24 | -10.75 | -23.77 | 4.46 | 0.216 |  | 35.14 | 12.70 | 62.00 | **0.014** |  | 18.91 | 9.29 | 29.38 | **0.0004** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Serine | 2 | 0.66 | -15.11 | 19.33 | 0.943 |  | 15.76 | -0.73 | 34.95 | 0.111 |  | 14.62 | 6.14 | 23.77 | **0.002** |
| 8 | 5.04 | -5.99 | 17.35 | 0.425 |  | 17.65 | 5.26 | 31.49 | **0.024** |  | 23.82 | 15.27 | 33.00 | **0.000** |
| 24 | -9.11 | -20.38 | 3.74 | 0.216 |  | 25.59 | 8.25 | 45.68 | **0.020** |  | 19.92 | 11.56 | 28.89 | **0.000** |
| Threonine | 2 | 5.77 | -9.73 | 23.89 | 0.519 |  | 12.80 | -4.52 | 33.24 | 0.206 |  | 6.11 | -3.06 | 16.13 | 0.210 |
| 8 | 8.80 | -0.15 | 18.55 | 0.112 |  | 34.03 | 7.97 | 66.34 | **0.033** |  | 16.03 | 4.78 | 28.48 | **0.008** |
| 24 | 4.45 | -8.63 | 19.38 | 0.552 |  | 55.14 | 2.32 | 134.97 | 0.077 |  | 8.44 | -5.65 | 24.63 | 0.264 |
| Tryptophan | 2 | 0.58 | -10.91 | 13.53 | 0.929 |  | 28.33 | 5.28 | 56.38 | **0.049** |  | 21.90 | 15.37 | 28.79 | **0.0000002** |
| 8 | 2.05 | -12.20 | 18.58 | 0.802 |  | 37.12 | 14.13 | 64.70 | **0.012** |  | 32.47 | 22.25 | 43.53 | **0.0000003** |
| 24 | -7.67 | -21.45 | 8.50 | 0.377 |  | 32.79 | 11.60 | 57.97 | **0.015** |  | 17.59 | 7.82 | 28.24 | **0.001** |
| Valine | 2 | -0.55 | -15.42 | 16.90 | 0.950 |  | 17.24 | -1.19 | 39.09 | 0.118 |  | 11.75 | 6.18 | 17.60 | **0.0002** |
| 8 | 1.20 | -19.44 | 27.05 | 0.923 |  | 27.51 | 3.91 | 56.41 | 0.053 |  | 20.21 | 12.13 | 28.87 | **0.00002** |
| 24 | -11.59 | -24.59 | 3.62 | 0.189 |  | 19.68 | -0.18 | 43.47 | 0.094 |  | 9.54 | 0.50 | 19.39 | **0.048** |
| C3 AC | 2 | -2.10 | -13.51 | 10.81 | 0.751 |  | 23.16 | -9.32 | 67.15 | 0.231 |  | 4.71 | -5.19 | 15.64 | 0.372 |
| 8 | 8.30 | -16.19 | 39.86 | 0.568 |  | 58.84 | 17.93 | 113.83 | **0.019** |  | 29.83 | 16.83 | 44.25 | **0.00005** |
| 24 | -4.76 | -23.84 | 19.04 | 0.686 |  | 52.84 | 8.13 | 115.87 | **0.047** |  | 42.25 | 27.95 | 58.15 | **0.000001** |
| C5 AC | 2 | 11.08 | -11.65 | 39.58 | 0.409 |  | 25.38 | -9.19 | 72.97 | 0.218 |  | 5.85 | -4.14 | 16.88 | 0.271 |
| 8 | 20.46 | -11.46 | 63.77 | 0.289 |  | 50.82 | 18.88 | 91.27 | **0.012** |  | 32.59 | 19.61 | 46.97 | **0.00001** |
| 24 | 5.25 | -16.29 | 32.28 | 0.679 |  | 38.58 | -10.81 | 115.04 | 0.190 |  | 20.92 | 5.60 | 38.45 | **0.011** |
| C16 AC | 2 | -10.45 | -23.77 | 5.17 | 0.236 |  | -15.47 | -30.83 | 3.25 | 0.151 |  | -5.12 | -12.08 | 2.39 | 0.188 |
| 8 | -20.82 | -34.26 | -4.67 | 0.057 |  | -33.61 | -49.39 | -13.00 | **0.021** |  | -16.55 | -22.56 | -10.09 | **0.0001** |
| 24 | -5.01 | -28.15 | 25.47 | 0.732 |  | -25.10 | -41.13 | -4.78 | **0.050** |  | -18.42 | -26.88 | -9.00 | **0.001** |
| C16:1-OH AC | 2 | -3.11 | -36.90 | 48.49 | 0.890 |  | -13.39 | -26.55 | 2.11 | 0.138 |  | -8.76 | -20.14 | 4.22 | 0.189 |
| 8 | -0.94 | -25.54 | 31.68 | 0.951 |  | -11.63 | -31.70 | 14.26 | 0.377 |  | -7.68 | -16.15 | 1.63 | 0.115 |
| 24 | -14.33 | -37.57 | 17.43 | 0.381 |  | -18.33 | -39.44 | 10.03 | 0.225 |  | -19.44 | -27.06 | -11.04 | **0.0002** |
| C18 AC | 2 | 28.79 | 4.66 | 58.44 | 0.062 |  | -4.53 | -20.78 | 15.01 | 0.643 |  | 7.92 | -6.78 | 24.90 | 0.317 |
| 8 | 10.34 | -17.88 | 48.12 | 0.542 |  | -10.95 | -24.16 | 4.54 | 0.199 |  | 2.40 | -9.30 | 15.58 | 0.705 |
| 24 | -3.51 | -27.67 | 28.62 | 0.817 |  | -17.56 | -33.75 | 2.52 | 0.126 |  | 1.95 | -8.87 | 14.05 | 0.738 |
| C18:1 AC | 2 | -6.28 | -18.36 | 7.56 | 0.398 |  | -31.22 | -47.63 | -9.76 | **0.035** |  | -14.96 | -23.10 | -5.97 | **0.004** |
| 8 | -33.79 | -50.01 | -12.42 | **0.034** |  | -47.27 | -62.62 | -25.78 | **0.008** |  | -29.34 | -36.19 | -21.78 | **0.0000004** |
| 24 | -22.24 | -44.12 | 8.05 | 0.194 |  | -39.74 | -55.38 | -18.76 | **0.013** |  | -32.26 | -42.27 | -20.54 | **0.0001** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| C18:1-OH AC | 2 | 8.25 | -21.38 | 48.91 | 0.647 |  | -25.39 | -51.16 | 13.72 | 0.222 |  | -16.24 | -29.60 | -0.37 | 0.056 |
| 8 | 10.58 | -27.03 | 67.32 | 0.655 |  | -20.84 | -45.05 | 13.85 | 0.248 |  | -24.01 | -33.31 | -13.43 | **0.0003** |
| 24 | -1.74 | -38.33 | 56.22 | 0.944 |  | -29.99 | -55.00 | 8.61 | 0.156 |  | -35.78 | -54.63 | -9.26 | **0.019** |
| lysoPCaC18:1 | 2 | 11.67 | -4.45 | 30.50 | 0.224 |  | -1.10 | -14.32 | 14.13 | 0.884 |  | 3.00 | -7.75 | 14.98 | 0.604 |
| 8 | 32.80 | 16.63 | 51.18 | **0.008** |  | 17.72 | 5.87 | 30.87 | **0.020** |  | 21.12 | 8.85 | 34.76 | **0.002** |
| 24 | 9.92 | -4.22 | 26.13 | 0.236 |  | 28.47 | 12.68 | 46.45 | **0.007** |  | 11.60 | 0.22 | 24.27 | 0.056 |
| lysoPCaC20:3 | 2 | 7.85 | -7.19 | 25.30 | 0.369 |  | 8.10 | -14.34 | 36.37 | 0.536 |  | 3.33 | -6.50 | 14.19 | 0.526 |
| 8 | 25.11 | 3.46 | 51.26 | 0.069 |  | 20.73 | -1.80 | 48.39 | 0.117 |  | 27.83 | 16.14 | 40.68 | **0.00003** |
| 24 | 0.56 | -12.92 | 16.12 | 0.942 |  | 20.83 | 4.87 | 39.20 | **0.035** |  | 4.77 | -6.52 | 17.41 | 0.430 |
| lysoPCaC20:4 | 2 | 12.40 | -4.31 | 32.00 | 0.214 |  | 9.59 | -6.82 | 28.86 | 0.311 |  | 12.47 | 1.18 | 24.99 | **0.039** |
| 8 | 39.36 | 19.04 | 63.13 | **0.009** |  | 34.92 | 14.63 | 58.78 | **0.009** |  | 41.15 | 28.39 | 55.17 | **0.0000001** |
| 24 | 6.48 | -7.54 | 22.59 | 0.423 |  | 27.53 | 11.95 | 45.25 | **0.008** |  | 19.13 | 6.67 | 33.03 | **0.005** |
| PCaeC40:1 | 2 | -3.47 | -23.60 | 21.90 | 0.779 |  | 22.49 | -3.43 | 55.30 | 0.145 |  | 4.45 | -8.26 | 18.91 | 0.517 |
| 8 | -6.25 | -54.90 | 93.75 | 0.869 |  | 12.76 | -12.36 | 45.00 | 0.381 |  | 22.88 | 9.64 | 37.70 | **0.002** |
| 24 | 12.31 | -20.42 | 58.34 | 0.538 |  | 16.39 | -17.24 | 63.52 | 0.411 |  | 18.30 | 3.83 | 34.76 | **0.018** |
| PCaeC42:3 | 2 | 1.93 | -9.87 | 15.26 | 0.773 |  | 0.57 | -4.74 | 6.17 | 0.845 |  | 4.58 | -3.33 | 13.14 | 0.274 |
| 8 | -1.66 | -21.99 | 23.91 | 0.893 |  | -1.91 | -11.30 | 8.46 | 0.717 |  | 5.44 | -2.05 | 13.49 | 0.171 |
| 24 | 11.46 | -14.47 | 45.16 | 0.458 |  | 1.92 | -6.79 | 11.43 | 0.689 |  | 9.63 | 1.65 | 18.23 | **0.025** |
| PCaeC42:4 | 2 | -1.90 | -20.56 | 21.08 | 0.865 |  | -6.18 | -19.54 | 9.38 | 0.447 |  | 3.37 | -4.39 | 11.76 | 0.413 |
| 8 | -0.86 | -15.00 | 15.59 | 0.916 |  | -14.04 | -25.11 | -1.36 | 0.068 |  | 1.95 | -7.18 | 11.96 | 0.690 |
| 24 | -10.24 | -20.33 | 1.10 | 0.135 |  | -8.74 | -18.66 | 2.38 | 0.163 |  | 1.61 | -5.03 | 8.70 | 0.648 |
| AAA | 2 | -1.39 | -13.12 | 11.90 | 0.836 |  | 19.78 | 3.10 | 39.12 | 0.056 |  | 17.09 | 11.98 | 22.43 | **0.0000002** |
| 8 | -0.73 | -12.59 | 12.71 | 0.914 |  | 31.17 | 12.57 | 52.80 | **0.010** |  | 31.77 | 24.03 | 40.00 | **0.000000002** |
| 24 | -4.77 | -15.34 | 7.12 | 0.453 |  | 34.30 | 13.52 | 58.86 | **0.011** |  | 20.00 | 11.38 | 29.28 | **0.0001** |
| BCAA | 2 | 1.01 | -19.04 | 25.96 | 0.933 |  | 24.25 | 1.00 | 52.79 | 0.086 |  | 19.96 | 12.36 | 28.08 | **0.00001** |
| 8 | -2.57 | -24.36 | 25.43 | 0.848 |  | 32.36 | 4.34 | 67.84 | 0.054 |  | 28.56 | 17.62 | 40.50 | **0.00001** |
| 24 | -12.71 | -29.15 | 7.50 | 0.257 |  | 25.73 | -1.11 | 59.77 | 0.104 |  | 14.69 | 3.05 | 27.63 | **0.019** |

(a, acyl; aa, acyl-acyl; ae, acyl-alkyl; Cx:y, where x is the number of carbons in the fatty acid side chain; y is the number of double bonds in the fatty acid side chain; AC, acylcarnitine; DC, decarboxyl; M, methyl; OH, hydroxyl; PC, phosphatidylcholine; AAA, sum of aromatic amino acids; BCAA, sum of branched chain amino acids.)