**Supplementary Table 4.** Changes in candidate plasma metabolite pharmacodynamic biomarker concentrations over first 2 weeks in 17 patients treated with ≥330 mg once-daily of pictilisib. (p-values <0.05 are shaded dark grey and those with p-values <0.10 and ≥0.05 are shaded light grey.)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Metabolite** | **D8 Pre-dose** | | | | **D8 1h** | | | | **D15 Pre-dose** | | | | **D15 2h** | | | | **D15 8h** | | | | **D15 24h** | | | |
| 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 | 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 | -3.36 | -10.63 | 4.49 | 0.404 | -1.40 | -9.69 | 7.64 | 0.757 | -0.28 | -11.32 | 12.11 | 0.963 | 19.12 | 7.25 | 32.29 | **0.006** | 44.42 | 27.50 | 63.57 | **0.0001** | 13.75 | -2.38 | 32.51 | 0.127 |
| Citrulline | 1.14 | -5.87 | 8.67 | 0.761 | 0.57 | -9.00 | 11.14 | 0.913 | 12.17 | -1.85 | 24.27 | 0.108 | 12.60 | -0.11 | 23.72 | 0.081 | -8.67 | -27.41 | 14.83 | 0.453 | -21.10 | -42.83 | 8.73 | 0.176 |
| Glutamate | 3.29 | -10.14 | 18.72 | 0.655 | 14.16 | -1.76 | 32.63 | 0.104 | 2.04 | -15.64 | 23.38 | 0.838 | 20.71 | -0.76 | 46.78 | 0.082 | -1.66 | -18.03 | 17.94 | 0.860 | 1.98 | -11.84 | 17.94 | 0.796 |
| Histidine | -3.13 | -9.77 | 3.99 | 0.392 | 0.43 | -6.23 | 7.55 | 0.905 | -1.21 | -12.12 | 11.03 | 0.841 | 10.91 | 3.56 | 18.77 | **0.010** | 22.39 | 12.45 | 33.20 | **0.0004** | 7.09 | -4.01 | 19.45 | 0.241 |
| Isoleucine | -0.66 | -8.52 | 7.87 | 0.877 | 10.67 | -2.37 | 25.44 | 0.132 | 4.12 | -9.52 | 19.80 | 0.581 | 29.83 | 15.17 | 46.35 | **0.001** | 43.23 | 20.87 | 69.70 | **0.001** | 15.86 | 2.84 | 30.52 | **0.031** |
| Leucine | 2.74 | -6.22 | 12.55 | 0.569 | 10.54 | -2.94 | 25.88 | 0.150 | 0.96 | -11.26 | 14.84 | 0.887 | 27.60 | 14.21 | 42.55 | **0.001** | 30.86 | 7.76 | 58.88 | **0.017** | 8.33 | -8.93 | 28.83 | 0.382 |
| Phenylalanine | 0.98 | -7.21 | 9.90 | 0.823 | 6.84 | -2.51 | 17.08 | 0.176 | 1.30 | -8.06 | 11.60 | 0.798 | 21.45 | 13.92 | 29.47 | **0.00004** | 36.63 | 23.62 | 51.00 | **0.00003** | 12.77 | 1.09 | 25.80 | **0.051** |
| Serine | 1.09 | -6.22 | 8.96 | 0.781 | 1.84 | -5.59 | 9.85 | 0.644 | 7.51 | -3.87 | 20.23 | 0.224 | 18.19 | 8.23 | 29.05 | **0.002** | 27.35 | 13.43 | 42.97 | **0.001** | 11.17 | -1.21 | 25.09 | 0.102 |
| Threonine | -6.77 | -18.53 | 6.66 | 0.322 | -8.68 | -20.55 | 4.93 | 0.219 | -4.21 | -20.92 | 15.98 | 0.666 | 4.10 | -12.40 | 23.67 | 0.655 | 24.54 | -0.13 | 55.23 | 0.072 | 14.51 | -13.10 | 50.79 | 0.353 |
| Tryptophan | -2.10 | -11.86 | 8.73 | 0.697 | 5.70 | -4.31 | 16.74 | 0.291 | 2.99 | -9.79 | 17.56 | 0.669 | 19.68 | 10.58 | 29.52 | **0.001** | 24.44 | 12.24 | 37.94 | **0.001** | 13.66 | -0.83 | 30.25 | 0.089 |
| Valine | 1.63 | -6.11 | 10.00 | 0.694 | 3.36 | -4.77 | 12.18 | 0.440 | 1.97 | -5.96 | 10.55 | 0.644 | 13.97 | 4.62 | 24.14 | **0.010** | 20.31 | 8.65 | 33.21 | **0.003** | 7.05 | -1.24 | 16.02 | 0.121 |
| C3 AC | -3.12 | -15.71 | 11.33 | 0.661 | -4.65 | -20.13 | 13.78 | 0.605 | 5.56 | -12.43 | 27.20 | 0.579 | 2.27 | -15.03 | 23.04 | 0.816 | 15.45 | -3.74 | 38.42 | 0.144 | 27.82 | 8.56 | 50.47 | **0.011** |
| C5 AC | -7.87 | -19.55 | 5.49 | 0.252 | -8.25 | -23.82 | 10.45 | 0.377 | 2.39 | -17.36 | 26.80 | 0.832 | -8.64 | -19.88 | 4.16 | 0.198 | 13.04 | -6.09 | 36.04 | 0.216 | 12.40 | -3.84 | 31.34 | 0.166 |
| C16 AC | -4.44 | -16.41 | 9.21 | 0.514 | -11.64 | -21.20 | -0.94 | **0.050** | -17.47 | -26.86 | -6.90 | **0.007** | -13.11 | -17.91 | -8.02 | **0.0003** | -34.08 | -42.06 | -25.03 | **0.0000** | -24.32 | -34.04 | -13.18 | **0.002** |
| C16:1-OH AC | 1.90 | -15.46 | 22.77 | 0.846 | -0.21 | -19.62 | 23.82 | 0.985 | -8.20 | -22.16 | 8.22 | 0.324 | 2.44 | -14.12 | 22.15 | 0.793 | -5.69 | -19.86 | 10.95 | 0.492 | -2.95 | -14.35 | 9.95 | 0.646 |
| C18 AC | -0.24 | -16.23 | 18.77 | 0.979 | 0.09 | -14.07 | 16.55 | 0.991 | -7.13 | -20.57 | 8.54 | 0.367 | -3.92 | -16.13 | 10.05 | 0.573 | -15.32 | -28.76 | 0.62 | 0.080 | -10.67 | -26.50 | 8.52 | 0.277 |
| C18:1 AC | 3.84 | -7.75 | 16.87 | 0.541 | -8.58 | -21.65 | 6.63 | 0.270 | -17.58 | -26.70 | -7.35 | **0.005** | -26.11 | -37.45 | -12.75 | **0.003** | -40.97 | -52.70 | -26.38 | **0.0003** | -33.86 | -43.73 | -22.30 | **0.000** |
| C18:1-OH AC | 2.57 | -12.29 | 19.92 | 0.754 | -36.59 | -63.11 | 8.49 | 0.116 | -6.67 | -22.83 | 12.83 | 0.487 | -10.44 | -25.58 | 7.73 | 0.262 | -21.48 | -35.71 | -4.16 | **0.032** | -18.76 | -35.38 | 2.06 | 0.098 |
| lysoPCaC18:1 | -3.44 | -15.69 | 10.57 | 0.619 | -11.28 | -25.36 | 5.41 | 0.193 | -2.93 | -18.07 | 14.98 | 0.736 | 4.65 | -12.93 | 25.74 | 0.635 | 17.49 | -5.65 | 46.23 | 0.172 | 5.10 | -17.89 | 34.45 | 0.699 |
| lysoPCaC20:3 | -6.72 | -18.44 | 6.67 | 0.324 | -12.46 | -25.41 | 2.71 | 0.122 | -11.60 | -20.76 | -1.39 | **0.043** | -0.81 | -16.20 | 17.37 | 0.926 | 3.88 | -12.87 | 23.82 | 0.678 | -1.80 | -19.84 | 20.26 | 0.864 |
| lysoPCaC20:4 | -0.79 | -12.98 | 13.09 | 0.907 | -5.15 | -18.83 | 10.80 | 0.515 | 1.95 | -8.57 | 13.67 | 0.733 | 13.96 | -1.57 | 31.90 | 0.102 | 31.03 | 14.28 | 50.21 | **0.002** | 13.20 | -4.08 | 33.57 | 0.166 |
| PCaeC401 | -4.35 | -19.05 | 12.98 | 0.607 | -8.82 | -21.06 | 5.29 | 0.227 | 18.68 | 1.97 | 38.09 | **0.043** | 11.26 | -8.26 | 34.90 | 0.297 | 32.61 | 11.37 | 57.85 | **0.007** | 24.57 | 3.45 | 49.96 | **0.037** |
| PCaeC423 | -0.35 | -9.03 | 9.15 | 0.941 | -8.94 | -17.28 | 0.23 | 0.074 | 3.99 | -6.10 | 15.15 | 0.464 | 4.02 | -5.61 | 14.63 | 0.439 | 14.10 | 2.23 | 27.33 | **0.034** | 9.03 | -3.71 | 23.42 | 0.196 |
| PCaeC424 | -0.71 | -9.20 | 8.57 | 0.878 | -7.77 | -15.53 | 0.69 | 0.090 | -6.21 | -15.23 | 3.76 | 0.233 | -4.65 | -14.44 | 6.24 | 0.403 | -5.62 | -15.44 | 5.34 | 0.320 | 3.30 | -5.03 | 12.36 | 0.462 |
| AAA | -0.73 | -7.31 | 6.31 | 0.836 | 3.98 | -3.15 | 11.62 | 0.298 | 1.44 | -8.78 | 12.80 | 0.795 | 18.67 | 11.57 | 26.22 | **0.0001** | 29.34 | 18.95 | 40.64 | **0.00003** | 12.89 | 2.74 | 24.03 | **0.026** |
| BCAA | 1.47 | -5.91 | 9.43 | 0.710 | 6.85 | -2.96 | 17.66 | 0.196 | 1.89 | -7.59 | 12.33 | 0.713 | 20.72 | 10.18 | 32.27 | **0.001** | 27.70 | 11.26 | 46.56 | **0.004** | 8.97 | -2.52 | 21.79 | 0.155 |

(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.)