**Supplementary Table S1.** Growth inhibitory effects of CYC065 treatment

in a high throughput screening platform of 84 human lung cancer cell lines.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cell Line** | **kras** | **RSE** | **IC10** | **IC20** | **IC30** | **IC40** | **IC50** | **IC60** | **IC70** | **IC80** | **IC90** | **AUC** |
| **EBC1** | WT | 0.04 | 0.10 | 0.13 | 0.16 | 0.20 | 0.26 | 0.39 | 9.61 | 9.61 | 9.61 | 1.83 |
| **EKVX** | WT | 0.04 | 0.44 | 0.57 | 0.65 | 0.72 | 0.79 | 0.86 | 0.95 | 1.10 | 1.78 | 1.83 |
| **H125** | WT | 0.02 | 0.08 | 0.12 | 0.15 | 0.19 | 0.22 | 0.26 | 0.31 | 0.37 | 0.50 | 1.33 |
| **H1395** | WT | 0.06 | 0.28 | 0.30 | 0.32 | 0.34 | 0.36 | 0.40 | 9.61 | 9.61 | 9.61 | 2.09 |
| **H1437** | WT | 0.01 | 0.55 | 0.60 | 0.64 | 0.67 | 0.71 | 0.76 | 0.88 | 9.61 | 9.61 | 2.09 |
| **H1563** | WT | 0.02 | 0.15 | 0.21 | 0.27 | 0.33 | 0.41 | 0.52 | 0.71 | 1.46 | 9.61 | 1.75 |
| **H1651** | WT | 0.01 | 0.38 | 0.45 | 0.51 | 0.58 | 0.66 | 0.76 | 0.90 | 1.16 | 1.99 | 1.95 |
| **H1693** | WT | 0.05 | 0.35 | 0.40 | 0.44 | 0.49 | 0.55 | 0.65 | 0.98 | 9.61 | 9.61 | 2.09 |
| **H1819** | WT | 0.01 | 0.22 | 0.26 | 0.30 | 0.34 | 0.40 | 0.47 | 0.59 | 1.09 | 9.61 | 1.82 |
| **H2073** | WT | 0.03 | 0.31 | 0.38 | 0.44 | 0.50 | 0.57 | 0.71 | 9.61 | 9.61 | 9.61 | 2.11 |
| **H2077** | WT | 0.02 | 0.14 | 0.18 | 0.21 | 0.24 | 0.27 | 0.31 | 0.35 | 0.42 | 0.53 | 1.38 |
| **H2085** | WT | 0.08 | 0.43 | 0.50 | 0.56 | 0.64 | 0.75 | 1.07 | 9.61 | 9.61 | 9.61 | 2.53 |
| **H2087** | WT | 0.03 | 0.24 | 0.29 | 0.32 | 0.34 | 0.35 | 0.37 | 0.40 | 0.45 | 9.61 | 1.59 |
| **H2106** | WT | 0.04 | 0.16 | 0.20 | 0.26 | 0.36 | 0.53 | 0.88 | 1.82 | 6.52 | 9.61 | 1.88 |
| **H2126** | WT | 0.03 | 0.10 | 0.25 | 0.34 | 0.41 | 0.48 | 0.55 | 0.63 | 0.74 | 1.00 | 1.58 |
| **H2250** | WT | 0.02 | 0.30 | 0.36 | 0.41 | 0.45 | 0.50 | 0.56 | 0.63 | 0.76 | 1.39 | 1.76 |
| **H2405** | WT | 0.03 | 0.15 | 0.22 | 0.28 | 0.34 | 0.42 | 0.68 | 9.61 | 9.61 | 9.61 | 1.98 |
| **H2882** | WT | 0.03 | 0.10 | 0.19 | 0.27 | 0.35 | 0.44 | 0.55 | 0.74 | 1.18 | 9.61 | 1.65 |
| **H290** | WT | 0.04 | 0.10 | 0.16 | 0.22 | 0.28 | 0.34 | 0.40 | 0.48 | 0.57 | 0.73 | 1.46 |
| **H322** | WT | 0.02 | 0.22 | 0.27 | 0.33 | 0.38 | 0.46 | 0.55 | 0.71 | 1.07 | 9.61 | 1.92 |
| **H324** | WT | 0.05 | 0.21 | 0.29 | 0.36 | 0.43 | 0.50 | 0.59 | 0.72 | 0.92 | 1.48 | 1.71 |
| **H3255** | WT | 0.03 | 0.31 | 0.38 | 0.44 | 0.50 | 0.57 | 0.66 | 0.80 | 1.16 | 9.61 | 1.94 |
| **H520** | WT | 0.04 | 0.13 | 0.18 | 0.22 | 0.27 | 0.33 | 0.39 | 0.49 | 0.72 | 9.61 | 1.72 |
| **H522** | WT | 0.03 | 0.13 | 0.17 | 0.22 | 0.26 | 0.31 | 0.36 | 0.44 | 0.54 | 0.73 | 1.50 |
| **H661** | WT | 0.02 | 0.33 | 0.40 | 0.46 | 0.51 | 0.57 | 0.63 | 0.71 | 0.86 | 1.51 | 1.81 |
| **H820** | WT | 0.06 | 0.07 | 0.21 | 0.31 | 0.41 | 0.51 | 0.62 | 0.77 | 1.11 | 9.61 | 1.69 |
| **HCC1195** | WT | 0.03 | 0.16 | 0.20 | 0.23 | 0.28 | 0.32 | 0.38 | 0.47 | 0.60 | 0.91 | 1.63 |
| **HCC15** | WT | 0.02 | 0.20 | 0.29 | 0.37 | 0.46 | 0.56 | 0.75 | 9.61 | 9.61 | 9.61 | 2.03 |
| **HCC1897** | WT | 0.03 | 0.32 | 0.40 | 0.47 | 0.55 | 0.67 | 0.98 | 9.61 | 9.61 | 9.61 | 2.13 |
| **HCC2279** | WT | 0.03 | 0.18 | 0.25 | 0.30 | 0.36 | 0.42 | 0.49 | 0.59 | 0.75 | 1.15 | 1.62 |
| **HCC2302** | WT | 0.03 | 0.23 | 0.29 | 0.33 | 0.38 | 0.43 | 0.48 | 0.55 | 0.66 | 0.92 | 1.65 |
| **HCC2814** | WT | 0.04 | 0.09 | 0.12 | 0.15 | 0.17 | 0.19 | 0.22 | 0.25 | 0.30 | 0.41 | 1.28 |
| **HCC4006** | WT | 0.03 | 0.16 | 0.27 | 0.34 | 0.40 | 0.46 | 0.54 | 0.66 | 9.61 | 9.61 | 1.80 |
| **HCC4011** | WT | 0.04 | 0.29 | 0.34 | 0.39 | 0.44 | 0.49 | 0.56 | 0.65 | 0.83 | 9.61 | 1.83 |
| **HCC4017** | WT | 0.03 | 0.07 | 0.19 | 0.27 | 0.34 | 0.41 | 0.49 | 0.59 | 0.78 | 9.61 | 1.58 |
| **HCC827** | WT | 0.04 | 0.11 | 0.16 | 0.21 | 0.26 | 0.31 | 0.37 | 0.45 | 0.61 | 9.61 | 1.62 |
| **HCC95** | WT | 0.02 | 0.36 | 0.47 | 0.56 | 0.66 | 0.77 | 0.93 | 9.61 | 9.61 | 9.61 | 2.16 |
| **SKMES-1** | WT | 0.06 | 0.01 | 0.18 | 0.43 | 0.53 | 0.61 | 0.71 | 0.85 | 1.18 | 9.61 | 1.61 |
| **Calu3** | WT | 0.06 | 0.33 | 0.39 | 0.46 | 0.54 | 0.64 | 0.82 | 1.97 | 9.61 | 9.61 | 2.16 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **DFCI032** | WT | 0.06 | 0.02 | 0.13 | 0.22 | 0.31 | 0.40 | 0.49 | 0.60 | 0.75 | 1.00 | 1.43 |
| **H1299** | WT | 0.01 | 0.64 | 0.73 | 0.81 | 0.91 | 1.10 | 9.61 | 9.61 | 9.61 | 9.61 | 2.36 |
| **H1568** | WT | 0.03 | 0.07 | 0.09 | 0.10 | 0.12 | 0.13 | 0.15 | 0.17 | 0.20 | 0.25 | 1.10 |
| **H1648** | WT | 0.04 | 0.01 | 0.12 | 0.22 | 0.31 | 0.39 | 0.48 | 0.58 | 0.72 | 1.02 | 1.43 |
| **H1650** | WT | 0.02 | 0.43 | 0.51 | 0.60 | 0.70 | 0.82 | 1.03 | 9.61 | 9.61 | 9.61 | 2.48 |
| **H1703** | WT | 0.02 | 0.26 | 0.34 | 0.40 | 0.47 | 0.53 | 0.60 | 0.68 | 0.78 | 0.95 | 1.79 |
| **H1755** | WT | 0.04 | 0.09 | 0.20 | 0.31 | 0.42 | 0.54 | 0.69 | 0.90 | 1.47 | 9.61 | 1.75 |
| **H1770** | WT | 0.06 | 0.05 | 0.10 | 0.14 | 0.18 | 0.22 | 0.28 | 0.39 | 0.60 | 1.38 | 1.34 |
| **H1975** | WT | 0.00 | 0.31 | 0.37 | 0.42 | 0.46 | 0.51 | 0.57 | 0.64 | 0.78 | 9.61 | 1.80 |
| **H1993** | WT | 0.06 | 0.24 | 0.28 | 0.30 | 0.32 | 0.34 | 0.36 | 0.40 | 9.61 | 9.61 | 1.71 |
| **H2052** | WT | 0.03 | 0.11 | 0.15 | 0.18 | 0.21 | 0.26 | 0.31 | 0.40 | 0.63 | 9.61 | 1.56 |
| **H2170** | WT | 0.02 | 0.01 | 0.01 | 0.01 | 0.10 | 0.15 | 0.19 | 0.24 | 0.39 | 9.61 | 1.09 |
| **H2172** | WT | 0.04 | 0.01 | 0.29 | 0.38 | 0.45 | 0.53 | 0.62 | 0.75 | 1.11 | 9.61 | 1.68 |
| **H2228** | WT | 0.02 | 0.31 | 0.34 | 0.38 | 0.44 | 9.61 | 9.61 | 9.61 | 9.61 | 9.61 | 2.30 |
| **H226** | WT | 0.02 | 0.35 | 0.38 | 0.40 | 0.41 | 0.43 | 0.46 | 0.52 | 9.61 | 9.61 | 1.90 |
| **H28** | WT | 0.03 | 0.25 | 0.33 | 0.39 | 0.45 | 0.52 | 0.62 | 1.02 | 9.61 | 9.61 | 2.01 |
| **H838** | WT | 0.01 | 0.56 | 0.82 | 1.20 | 1.82 | 2.84 | 4.60 | 7.76 | 9.61 | 9.61 | 2.39 |
| **HCC193** | WT | 0.06 | 0.01 | 0.13 | 0.24 | 0.34 | 0.44 | 0.55 | 0.69 | 0.92 | 9.61 | 1.54 |
| **HCC3051** | WT | 0.03 | 0.18 | 0.21 | 0.24 | 0.27 | 0.30 | 0.34 | 0.39 | 0.48 | 0.67 | 1.52 |
| **HOP92** | WT | 0.03 | 0.49 | 0.55 | 0.60 | 0.66 | 0.75 | 9.61 | 9.61 | 9.61 | 9.61 | 2.26 |
| **HCC1171** | G12C | 0.05 | 0.46 | 0.54 | 0.62 | 0.76 | 9.61 | 9.61 | 9.61 | 9.61 | 9.61 | 2.51 |
| **H1573** | G12A | 0.04 | 0.13 | 0.16 | 0.19 | 0.22 | 0.27 | 0.35 | 0.50 | 1.02 | 9.61 | 1.64 |
| **H2009** | G12A | 0.01 | 0.60 | 0.69 | 0.77 | 0.86 | 0.98 | 1.26 | 9.61 | 9.61 | 9.61 | 2.26 |
| **H2030** | G12C | 0.01 | 0.23 | 0.28 | 0.32 | 0.36 | 0.41 | 0.47 | 0.58 | 9.61 | 9.61 | 1.83 |
| **H2122** | G12C | 0.02 | 0.44 | 0.47 | 0.49 | 0.51 | 0.53 | 0.56 | 0.60 | 9.61 | 9.61 | 1.95 |
| **H23** | G12C | 0.03 | 0.08 | 0.11 | 0.13 | 0.16 | 0.18 | 0.21 | 0.24 | 0.28 | 0.34 | 1.24 |
| **Hop62** | G12C | 0.02 | 0.32 | 0.40 | 0.47 | 0.53 | 0.60 | 0.69 | 1.05 | 9.61 | 9.61 | 2.05 |
| **SW1573** | G12C | 0.02 | 0.15 | 0.21 | 0.26 | 0.33 | 0.50 | 9.61 | 9.61 | 9.61 | 9.61 | 2.07 |
| **Calu 1** | G12C | 0.02 | 0.19 | 0.31 | 0.42 | 0.54 | 0.69 | 0.92 | 9.61 | 9.61 | 9.61 | 2.03 |
| **H1792** | G12C | 0.02 | 0.65 | 0.74 | 0.82 | 0.93 | 1.16 | 9.61 | 9.61 | 9.61 | 9.61 | 2.38 |
| **H358** | G12C | 0.03 | 0.13 | 0.19 | 0.24 | 0.28 | 0.34 | 0.40 | 0.51 | 9.61 | 9.61 | 1.76 |
| **SKLU1** | G12D | 0.04 | 0.31 | 0.42 | 0.51 | 0.59 | 0.68 | 0.78 | 0.91 | 1.24 | 9.61 | 1.97 |
| **H157** | G12R | 0.03 | 0.20 | 0.26 | 0.31 | 0.36 | 0.40 | 0.44 | 0.50 | 0.60 | 9.61 | 1.70 |
| **A549** | G12S | 0.02 | 0.36 | 0.39 | 0.42 | 0.46 | 0.48 | 0.52 | 0.59 | 0.67 | 0.79 | 2.25 |
| **H292** | G12S | 0.03 | 0.48 | 0.53 | 0.57 | 0.61 | 0.65 | 0.70 | 0.77 | 0.87 | 1.10 | 2.06 |
| **H2887** | G12V | 0.03 | 0.01 | 0.32 | 0.42 | 0.51 | 0.68 | 9.61 | 9.61 | 9.61 | 9.61 | 2.05 |
| **H441** | G12V | 0.03 | 0.34 | 0.42 | 0.49 | 0.54 | 0.61 | 0.70 | 1.06 | 9.61 | 9.61 | 2.06 |
| **H1355** | G13C | 0.02 | 0.11 | 0.17 | 0.23 | 0.28 | 0.33 | 0.40 | 0.50 | 9.61 | 9.61 | 1.69 |
| **H1944** | G13D | 0.04 | 0.23 | 0.25 | 0.27 | 0.28 | 0.29 | 0.31 | 0.33 | 0.36 | 9.61 | 1.54 |
| **HCC515** | G13D | 0.04 | 0.26 | 0.32 | 0.38 | 0.45 | 0.54 | 0.71 | 9.61 | 9.61 | 9.61 | 2.04 |
| **HCC2374** | mut | 0.04 | 0.01 | 0.22 | 0.35 | 0.45 | 0.55 | 0.68 | 0.95 | 9.61 | 9.61 | 1.77 |
| **H1155** | Q61H | 0.02 | 0.16 | 0.28 | 0.38 | 0.47 | 0.56 | 0.66 | 0.78 | 1.01 | 9.61 | 1.76 |
| **H460** | Q61H | 0.04 | 0.31 | 0.34 | 0.36 | 0.37 | 0.39 | 0.40 | 0.43 | 0.46 | 9.61 | 1.68 |
| **CALU6** | Q61K | 0.02 | 0.09 | 0.27 | 0.36 | 0.44 | 0.52 | 0.63 | 9.61 | 9.61 | 9.61 | 1.85 |

**Supplementary Table S2.** Histopathologic and clinical features of lung cancers used for PDX models.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** | **tumor type** | **Age** | **Gender** | **smoking** | **KRAS** | **TP53** |
| **TC383** | squamous | 76 | M | yes | WT | WT |
| **TC386** | adenocarcinoma | 56 | F | no | WT | WT |
| **TC464** | adenocarcinoma | 66 | F | yes | WT | G105V |
| **TC286** | pleomorphic | 66 | M | unknown | G12D | Del101-105 |
| **TC303** | adenocarcinoma | 55 | M | yes | G12C | R175H |
| **TC494** | adenocarcinoma | 75 | M | yes | G12V | WT |