**Supplementary Table S1.** In vitro pharmacology profile of LY3009120, LSN3074753 and vemurafenib

|  |  |  |  |
| --- | --- | --- | --- |
| **In vitro Pharmacology of RAF Inhibitors** | | | |
| Activities (nM) | LY3009120 | LSN3074753 | Vemurafenib |
| BRAF V600E | 5.8 | 7.7 | 6.1 |
| BRAF WT | 15 | 39 | 32 |
| CRAF | 15 | 18 | 414 |
| p38 | 27 | 30 | 1700 |
| PDGFRα | 61 | 58 | 3300 |
| PDGFRβ | 13 | 19 | 989 |
| KIT | 21 | 7.9 | 1600 |
| VEGFR2 | 3900 | 746 | 365 |
| pERK in A375 (cell activity) | 37 | 22 | 68 |
| pERK in HCT116 (cell activity) | 150 | 161 | Activating |

**Supplementary Table S2.** Major genetic mutations and EGFR copy numbers and expression in CRC PDX models

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MODEL\* | BRAF | KRAS | NRAS | APC | P53 | EGFR | PIK3CA | PTEN | PIK3R1 | CTNNB1 | EGFR-COPY\_NUMBER | EGFR EXPRESSION (RNA seq, RPM) |
| CTG0061 |  | G12D |  | C1249\*, Q1367\* | Q167\* |  | E542K |  |  |  | 2.70 | 6.1701 |
| CTG0062 |  | G13D |  | 1487fs, 816fs | R175H |  |  |  |  |  | 2.14 | 4.2055 |
| CTG0063 |  | G12V |  | F1491fs |  |  |  | I50T, R233\* |  |  | 2.33 | 5.1318 |
| CTG0064 | G469E | G12V |  | C1410\* | G245S |  | N345S |  |  |  | 2.88 | 5.7389 |
| CTG0066 |  | G13D |  | 1079fs | K132R, R273C |  | M1043I |  |  |  | 2.00 | 5.2675 |
| CTG0067 |  |  |  |  | 121fs |  | G1049R | 319fs |  |  | 1.86 | 2.3552 |
| CTG0068 |  | G12D |  | Q1447\* |  |  |  | 319fs |  |  | 1.83 | 5.792 |
| CTG0069 |  | G12D |  | 1556fs, L1129S |  |  |  |  |  |  | 2.09 | 5.285 |
| CTG0075 |  |  |  | coding-splice |  |  |  |  |  |  | 3.99 | 7.0924 |
| CTG0079 |  | G12D |  | 758fs, E1408\* |  |  |  |  |  |  | 1.95 | 4.0347 |
| CTG0082 |  | Q61H |  |  | K132N |  |  |  |  |  | 2.39 | 5.6458 |
| CTG0104 |  | G13D |  |  | R273H |  |  |  |  |  | 2.27 | 5.4119 |
| CTG0117 | V600E |  |  |  | 88fs, I255T, IT255T, TI253T |  |  |  |  |  | 2.01 | 5.7913 |
| CTG0125 |  |  |  |  | Q52\* |  |  |  |  |  | 2.20 | 4.4989 |
| CTG0129 |  | G12V |  |  | R181H |  | E545A, R88Q |  |  |  | 2.38 | 3.7251 |
| CTG0356 |  |  |  | 1140fs | R273C |  |  |  |  |  | 3.17 | 6.0611 |
| CTG0358 | G596V |  | G13R |  | 229Y |  | E542K |  | P116L |  | 1.79 | 3.9658 |
| CTG0359 | G12S |  |  | Q1406\*;Q1388\* |  |  |  |  |  |  | 2.09 | 5.0568 |
| CTG0360 | 401fs, S399T, V600E | Y157H |  | E243D, G362V, I495T, K957N, N1797Kfs, R1040G, Y796\* | W146\* |  | F430L, K111E, N822D, new-start, P757L, Q731R |  | G118V, I29L, Q435\* |  | 1.98 | 5.8153 |
| CTG0379 |  |  |  | E1034\* | R175H |  |  |  |  |  | 5.10 | 7.3805 |
| CTG0439 |  | Q61L |  | EKI1309fs | 102fs |  |  |  |  |  | 2.51 | 4.7949 |
| CTG0440 | A404V | G13D |  | E1577\*, K1226N, R2204\*, R554Q, S1252P, S2026Y, S2621Y, S836\* |  |  | I816S, L831I | E18D, E99\* |  | R587Q | 2.01 | 4.922 |
| CTG0489 |  |  |  |  |  |  |  |  |  |  | NA |  |
| CTG0652 | 401fs, V600E |  |  |  |  |  | E726K |  |  |  | 3.59 | 8.0185 |
| CTG0654 |  | G12D |  | Q1367\* | R282W |  |  |  |  |  | 3.48 | 6.0245 |
| CTG0661 |  | G12S |  | Q1406\* | C242F |  |  |  |  |  | 2.12 | 4.6313 |
| CTG0681 |  | G12D |  | 1434fs | R248W |  |  |  |  |  | 2.67 | 4.4465 |
| CTG0689 |  |  |  | 1431fs, R499\* |  |  |  |  | LH179Y |  | 3.36 | 5.8728 |
| CTG0722 |  | S41R |  | Q1480\*, R876\* |  |  |  |  |  |  | 2.88 | 5.1306 |
| CTG0772 |  | G12D |  |  | coding-splice |  |  |  |  | S23I | 2.02 | 3.2982 |
| CTG0784 |  |  |  | Y935\* | R175H |  |  |  |  |  | 2.32 | 5.843 |
| CTG0812 |  |  |  | R554\* |  |  |  |  |  |  | 3.46 | 5.8955 |
| CTG0826 |  |  | Q61K | EKI1309fs, K1199\*, N32S | coding-splice |  |  |  |  |  | 2.63 | 6.2022 |
| CTG0835 |  | G13D |  | R302\* | 204fs |  | E545K |  | T283A |  | 2.60 | 5.4795 |
| CTG0887 |  |  |  | 625fs | R249S, R306\* |  |  |  |  |  | 2.70 | 5.5929 |
| CTG0899 |  | G12S |  |  | R342\* |  |  |  |  |  | 3.14 | 6.6391 |
| CTG0934 |  | G12D |  | 1493fs, 1494fs, R1114\* | R248Q |  |  |  |  |  | 2.03 | 5.1593 |
| CTG0951 |  | G13D |  | R283\* | R273H |  |  |  |  |  | 2.70 | 5.7309 |
| CTG0971 |  |  |  | 1414fs, 887fs | G245S |  |  |  |  |  | 2.04 | 4.6156 |
| CTG0978 | V600E |  |  |  | L257R, P152L |  |  |  |  |  | 2.90 | 6.599 |
| CXF1034 |  | G13D |  | R414H |  |  | R741\* | del63 |  |  | 1.99 | 5.194 |
| CXF1044 |  | G12A |  | C1387\*, D432E, ins432, ins433 | R248Q |  |  |  |  |  | 1.92 | 5.5758 |
| CXF1086 |  | G12D |  | R283\* | A161T |  |  |  |  |  | 2.20 | 3.4476 |
| CXF1096 |  |  |  | del1307 | R175H |  |  |  |  |  | 2.82 | 5.5605 |
| CXF1103 |  | G12D |  | R876\* |  |  |  |  |  |  | 3.10 | 5.5717 |
| CXF1256 |  |  |  | EKI1309fs |  |  |  |  |  |  | NA | 6.07 |
| CXF1297 |  | G12V |  | del590 | R248Q |  | H1047R | F279del |  |  | 2.55 | 5.002 |
| CXF158 |  |  |  | R213\* | del342 |  |  |  |  |  | 3.14 | 5.4341 |
| CXF1729 |  |  |  | del1046 | del127 |  |  |  |  |  | 4.21 | 6.7374 |
| CXF1753 | R362Q |  | G12D | S1465fs |  |  | E542K |  |  |  | 2.37 | 4.8058 |
| CXF1783 |  | A146V |  | E1408\*, R876\* |  |  |  |  |  |  | 3.05 | 5.0267 |
| CXF1784 |  |  |  | del703 | del111 |  |  |  |  |  | 4.21 | 7.2721 |
| CXF1991 |  | Q61H |  | Y1376\* | G245S |  | E542Q |  |  |  | 2.71 | 4.8012 |
| CXF2025 |  |  |  |  | R248Q |  |  |  |  |  | 3.03 | 5.5348 |
| CXF2029 |  | G12D |  | Q1367\* | G245D |  |  |  |  |  | 2.84 | 6.7703 |
| CXF2032 |  | G13D |  | E1295\* | G245S |  |  |  |  |  | 2.22 | 3.3236 |
| CXF2039 |  |  |  | del1493, R499\* | Y236C |  |  |  |  |  | 6.07 | 6.7201 |
| CXF2061 |  |  |  | del1450 | M246V |  |  |  |  |  | 2.65 | 4.4971 |
| CXF2065 |  |  |  | del1295 | R175H |  |  |  | ED169D |  | 3.24 | 6.1501 |
| CXF2066 |  |  |  | del1326 | R213\* |  | E545K |  |  |  | 4.25 | 5.3249 |
| CXF2067 |  |  |  | R302\* | L264del |  |  |  |  |  | 3.64 | 6.58 |
| CXF2070 |  | G12D |  | ins1487, ins991, S992G, S992R | R175H |  |  |  |  |  | 2.94 | 5.555 |
| CXF2073 |  | G12A |  | V1605M |  |  | E545K |  |  |  | 2.22 | 4.8339 |
| CXF2083 |  | G12V |  | E893\* |  |  | G363A | S287\* |  |  | 2.63 | 5.5678 |
| CXF2102 |  |  |  |  | R175H |  |  |  |  |  | 2.41 | 5.1701 |
| CXF2127 |  |  | G13R |  | S261I |  | H1047R |  |  |  | 2.79 | 5.4827 |
| CXF2129 |  | G12D |  | R216\*;; |  |  | E545K |  |  |  | 1.98 | 4.3192 |
| CXF2163 |  | G12C |  | R876\* | ins326N, R213\* |  |  |  |  |  | 3.22 | 5.3027 |
| CXF2261 |  | G12D |  | S1356\* | R342\* |  |  |  |  |  | 2.29 | 5.5323 |
| CXF233 | A561V, V600E |  |  |  | S366P | V651M | ED453D, I633L, K111E |  |  |  | 1.93 | 5.5932 |
| CXF243 |  | G12D |  | L779\* | R196\* |  |  |  |  |  | 3.60 | 5.172 |
| CXF504 | V600E |  |  | IA544TA | R282W |  |  |  |  |  | 2.00 | 4.6402 |
| CXF533 |  |  |  |  | R175H |  |  | 267fs |  |  | 2.63 | 6.6724 |
| CXF609 | V111L | G12D |  | Q1378\* | P278L |  |  |  |  |  | 2.71 | 5.3493 |
| CXF647 |  | G12D |  | del1319 | Y220C |  |  | C105S, I101T |  |  | 1.96 | 4.0031 |
| CXF676 |  | G12V |  | S1315\* | ins83 |  |  |  |  |  | 2.75 | 5.4779 |
| CXF742 | V600E |  |  |  | R273C |  |  |  |  |  | 3.57 | 5.5774 |
| CXF883 |  |  |  |  |  |  | C420R, P2H, R808Q | 267fs, coding-splice |  | T41A | 2.80 | 6.0231 |
| CXF975 |  | G12D |  | del773 | R213\* |  |  |  |  |  | 2.02 | 5.0142 |