**Supplementary Table 1: List of genes sequenced in melanoma, saliva, and bone marrow mononuclear cells.**

| | | | | | | |
|---|---|---|---|---|---|---|
| ABL1 | CDK8 | ERBB4 | IDH1 | MLH1 | PIK3CB | SMO |
| ABL2 | CDKN1A | ERG | IDH2 | MLL | PIK3CD | SOCS1 |
| AKT1 | CDKN2A | ESR1 | IGF1R | MLL2 | PIK3CG | SOX2 |
| AKT2 | CDKN2B | ETV1 | IGFBP7 | MLL3 | PIK3R1 | SPOP |
| AKT3 | CDKN2C | ETV6 | IKBKE | MLST8 | PIK3R2 | SRC |
| ALK | CEBPA | EZH2 | IKZF1 | MPL | PIK3R3 | SRSF2 |
| ALOX12B | CHEK1 | FAM123B | IL7R | MSH2 | PKM2 | STAG2 |
| APC | CHEK2 | FAM46C | INPP4A | MSH6 | PLK2 | STK11 |
| AR | CIC | FAS | INPP4B | MTOR | PNRC1 | SUFU |
| ARAF | CREBBP | FAT1 | INSR | MYB | PPP2R1A | TBK1 |
| ARHGAP26 | CRKL | FBXO11 | IRS1 | MYC | PRDM1 | TEK |
| ARID1A | CRLF2 | FBXW7 | IRS2 | MYCL1 | PREX2 | TERT |
| ARID2 | CSF1R | FGFR1 | JAK1 | MYCN | PRKAA2 | TET1 |
| ASXL1 | CTNNB1 | FGFR2 | JAK2 | MYD88 | PRKAR1A | TET2 |
| ATM | CYLD | FGFR3 | JAK3 | NCOA2 | PRKCI | TGFBR2 |
| ATRX | DAXX | FGFR4 | JUN | NF1 | PTCH1 | TMPRSS2 |
| AURKA | DDR2 | FH | KCNJ5 | NF2 | PTEN | TNFAIP3 |
| BAP1 | DICER1 | FLCN | KDM5C | NFE2L2 | PTPN11 | TNFRSF14 |
| BCL2L1 | DIS3 | FLT1 | KDM6A | NFKB1 | PTPRD | TOP1 |
| BCL2L11 | DNMT1 | FLT3 | KDR | NFKB2 | PTPRS | TP53 |
| BCL6 | DNMT3A | FLT4 | KEAP1 | NKX2-1 | PTPRT | TP63 |
| BCOR | DNMT3B | FOXL2 | KIT | NOTCH1 | RAF1 | TSC1 |
| BIRC2 | E2F3 | FUBP1 | KLF6 | NOTCH2 | RARA | TSC2 |
| BRAF | EGFR | GATA1 | KRAS | NOTCH3 | RB1 | TSHR |
| BRCA1 | EIF4EBP1 | GATA2 | LDHA | NOTCH4 | REL | U2AF1 |
| BRCA2 | EP300 | GATA3 | LGR6 | NPM1 | RET | VHL |
| BUB1B | EPHA10 | GLI1 | LMO1 | NRAS | RICTOR | WAS |
| CARD11 | EPHA2 | GLI3 | MAGI2 | NTRK1 | RNF43 | WNK1 |
| CBL | EPHA3 | GNA11 | MAP2K1 | NTRK2 | ROR2 | WT1 |
| CBLB | EPHA4 | GNAQ | MAP2K2 | NTRK3 | ROS1 | XPO1 |
| CBLC | EPHA5 | GNAS | MAP2K4 | PAK7 | RPTOR | YAP1 |
| CCND1 | EPHA6 | GOLPH3 | MAP3K1 | PALB2 | RUNX1 | YES1 |
| CCNE1 | EPHA7 | GRIN2A | MAP3K8 | PARK2 | SDHB | ZRSR2 |
| CD79B | EPHA8 | GRM3 | MCL1 | PARP1 | SETD2 | |
| CDC42EP2 | EPHB1 | GSK3B | MDM2 | PAX5 | SF3B1 | |
| CDC73 | EPHB2 | HDAC2 | MDM4 | PBRM1 | SHQ1 | |
| CDH1 | EPHB3 | HIF1A | MED12 | PDGFRA | SMAD2 | |
| CDH11 | EPHB4 | HMGA2 | MEF2B | PDGFRB | SMAD3 | |
| CDK12 | EPHB6 | HNF1A | MEN1 | PHOX2B | SMAD4 | |
| CDK4 | ERBB2 | HRAS | MET | PIK3C2G | SMARCA4 | |
| CDK6 | ERBB3 | HSP90AA1 | MITF | PIK3CA | SMARCB1 | |

**Supplementary Table 2. Somatic mutations detected in melanoma and bone marrow mononuclear cells.**

| Sample | Chr | Start | Ref | Alt | Gene Symbol | Protein Change | #Variant Reads/Total # Reads | Saliva Variant Frequency | #Variant Reads/Total # Reads | Tumor Variant Frequency |
|---|---|---|---|---|---|---|---|---|---|---|
| Melanoma | 1 | 22903137 | C | T | *EPHA8* | p.S196F | 0/315 | 0 | 33/205 | 0.16098 |
| | 2 | 212812260 | G | A | *ERBB4* | p.R106C | 1/350 | 0.00286 | 28/197 | 0.14213 |
| | 3 | 96706664 | C | T | *EPHA6* | p.T314I | 0/359 | 0 | 23/150 | 0.15333 |
| | 3 | 96706780 | C | T | *EPHA6* | p.P353S | 0/206 | 0 | 15/149 | 0.10067 |
| | 3 | 96963128 | G | A | *EPHA6* | p.D535N | 0/184 | 0 | 40/203 | 0.19704 |
| | 3 | 134968266 | C | A | *EPHB1* | p.Q927K | 0/351 | 0 | 28/191 | 0.1466 |
| | 5 | 35873595 | C | T | *IL7R* | p.S184F | 1/339 | 0.00295 | 21/149 | 0.14094 |
| | 6 | 32188537 | C | T | *NOTCH4* | p.W306* | 1/344 | 0.00291 | 36/340 | 0.10588 |
| | 6 | 135515030 | C | T | *MYB* | p.P273S | 0/209 | 0 | 40/250 | 0.16 |
| | 7 | 140453136 | AC | TT | *BRAF* | p.V600K | 0/392 | 0 | 150/361 | 0.41551 |
| | 8 | 69028055 | G | A | *PREX2* | p.D1072N | 1/369 | 0.00271 | 25/180 | 0.13889 |
| | 9 | 8331661 | C | T | *PTPRD* | p.G1819R | 0/364 | 0 | 43/241 | 0.17842 |
| | 9 | 8485816 | C | T | *PTPRD* | p.G1001R | 0/290 | 0 | 28/212 | 0.13208 |
| | 9 | 8518111 | C | T | *PTPRD* | p.R427Q | 1/253 | 0.00395 | 29/185 | 0.15676 |
| | 9 | 8521384 | C | T | *PTPRD* | p.G285E | 0/368 | 0 | 28/173 | 0.16185 |
| | 12 | 49445373 | GT | AA | *MLL2* | p.T698L | 0/242 | 0 | 28/148 | 0.18919 |
| | 13 | 28893589 | C | T | *FLT1* | p.G1086E | 0/341 | 0 | 39/257 | 0.15175 |
| | 14 | 95590573 | TA | T | *DICER1* | p.I445fs | 0/357 | 0 | 53/204 | 0.2598 |
| | 16 | 65016180 | C | T | *CDH11* | p.A342T | 0/200 | 0 | 28/132 | 0.21212 |
| | 19 | 10599930 | G | A | *KEAP1* | p.P549L | 1/370 | 0.0027 | 67/339 | 0.19764 |
| | 19 | 15271654 | G | A | *NOTCH3* | p.S2262F | 0/407 | 0 | 31/207 | 0.14976 |
| | 19 | 15295201 | C | T | *NOTCH3* | p.G824D | 1/337 | 0.00297 | 47/242 | 0.19421 |
| | 19 | 15297931 | G | A | *NOTCH3* | p.P609S | 0/244 | 0 | 29/141 | 0.20567 |
| | 19 | 19257116 | C | T | *MEF2B* | p.G290S | 0/203 | 0 | 13/102 | 0.12745 |
| | 19 | 45293278 | G | A | *CBLC* | p.G312E | 0/372 | 0 | 24/144 | 0.16667 |
| | 20 | 9543602 | C | T | *PAK7* | p.E518K | 0/429 | 0 | 40/213 | 0.18779 |
| | 20 | 9546752 | G | A | *PAK7* | p.P424S | 0/172 | 0 | 21/132 | 0.15909 |
| | 21 | 39795414 | C | T | *ERG* | p.M109I | 0/220 | 0 | 38/226 | 0.16814 |
| Leukemia (pre-GDC-0973) | 1 | 115258748 | C | G | *NRAS* | p.G12R | 13/200 | 0.065 | 145/295 | 0.492 |
| | 4 | 106193931 | C | T | *TET2* | p.R1465* | 23/274 | 0.084 | 157/358 | 0.439 |
| | 4 | 106196324 | C | T | *TET2* | p.Q1553* | 42/341 | 0.123 | 227/463 | 0.49 |
| | 7 | 148523560 | C | T | *EZH2* | p.P298_splice | 12/321 | 0.037 | 41/504 | 0.081 |
| | 7 | 148543621 | G | A | *EZH2* | p.R63* | 30/324 | 0.093 | 213/464 | 0.459 |
| | 15 | 90631934 | C | T | *DIH2* | p.R140Q | 0/299 | 0 | 26/427 | 0.061 |
| Leukemia (during vemurafenib + GDC-0973) | 1 | 115258748 | C | G | *NRAS* | p.G12R | 13/200 | 0.065 | 274/578 | 0.47 |
| | 4 | 106193931 | C | T | *TET2* | p.R1465* | 23/274 | 0.084 | 432/933 | 0.46 |
| | 4 | 106196324 | C | T | *TET2* | p.Q1553* | 42/341 | 0.123 | 374/806 | 0.46 |
| | 7 | 148523560 | C | T | *EZH2* | p.P298_splice | 12/321 | 0.037 | 125/928 | 0.13 |
| | 7 | 148543621 | G | A | *EZH2* | p.R63* | 30/324 | 0.093 | 656/942 | 0.69 |
| | 15 | 90631934 | C | T | *DIH2* | p.R140Q | 0/299 | 0 | 33/760 | 0.04 |

**Supplementary Figure 1: Effect of treatment on spleen length as measured by CT scan.**

**Supplementary Figure 2: Sensitivity of digital PCR assay for detection of $BRAF^{V600K}$ and $NRAS^{G12R}$ mutations.** Specified amounts of DNA containing BRAFV600K (Panel A) or NRASG12R (Panel B) mutations were placed into a large excess of 5ng of BRAF/NRAS wildtype genomic DNA followed by detection of mutant target DNA. Displayed is the correlation between the detected amounts of mutant DNA and input mutant DNA.

**Supplementary Figure 3: Response of melanoma as assessed by CT scans.** Effect of treatment on the subcarinal mass (Panel A). Currently, only a 1.1 cm lymphoid mass remains detectable. After 11 months of treatment with vemurafenib alone, a pericardial nodule appeared (red circle) which regressed upon addition of cobimetinib (Panel B). Size of the spleen (asterisk) increased on vemurafenib but shrunk once cobimetinib was added (Panel C).

**Supplementary Figure 4: Effect of vemurafenib and combined vemurafenib plus cobimetinib on ERK activation in CD14+ cells during therapy.** (A) Flow cytometric staining of peripheral blood mononuclear cells (PBMCs) for $CD14^+$ cells before (week 3.3 according to Figure 1) and after treatment with vemurafenib (week 4.6) shows an increase in the number of $CD14^+$ cells consistent with stimulation by vemurafenib (top row) . Phospho-flow analysis (bottom row) shows an increase in pERK levels in $CD14^+$ cells. (B) In contrast, combined vemurafenib plus cobimetinib therapy (collected on week 73 according to Figure 1) resulted in a decrease in both the frequency of $CD14^+$ cells amongst PBMCs (top row) as well as a decrease in pERK expression in $CD14^+$ cells (bottom row) compared to PBMC collected off all treatment 2 weeks earlier (week 71).