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Short communication

Emergence of *MET* hyper-amplification at progression to *MET* and *BRAF* inhibition in colorectal cancer

Running title: MET hyper-amplification drives therapy resistance

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Abstract

Background:

Combined MET and BRAF inhibition showed clinical benefit in a patient with rectal cancer carrying *BRAF*^{V600E} and *MET* amplification. However after four months, acquired resistance emerged and the patient deceased shortly after disease progression. The mechanism of resistance to this drug combination is unknown.

Methods:

We analysed plasma circulating tumour DNA obtained at progression by exome sequencing and digital PCR. *MET* gene and mRNA *in situ* hybridization analyses in two bioptic specimens obtained at progression were used to confirm plasma data.

Results:

We identified in plasma *MET* gene hyper-amplification as a potential mechanism underlying therapy resistance. Increased *MET* gene copy and transcript levels were detected in liver and lymph node metastatic biopsies. Finally, transduction of *MET* in *BRAF* mutant colorectal cancer cells conferred refractoriness to BRAF and *MET* inhibition.

Conclusions:

We identified in a rectal cancer patient *MET* gene hyper-amplification as mechanism of resistance to dual BRAF and *MET* inhibition.

Keywords: BRAF / colorectal cancer / crizotinib / drug resistance / target therapy / *MET*

The *MET* oncogene encodes for a receptor tyrosine kinase involved in the regulation of tumour growth, survival, angiogenesis, invasion and metastases (Birchmeier *et al*, 2003; Raghav *et al*, 2012). Its amplification is associated with sensitivity to MET inhibition in preclinical models as well as in a subset of patients (Camidge *et al*, 2014; Smolen *et al*, 2006). *MET* gene amplification may be present in subclones of tumour cells that are positively selected during anti-EGFR based therapy in both NSCLC and colorectal cancer (CRC) patients (Bardelli *et al*, 2013; Pietrantonio *et al*, 2016; Turke *et al*, 2010). *MET* amplification or copy gain occurs in a fraction of *BRAF* mutated tumors including CRC (Jardim *et al*, 2014; Pietrantonio *et al*, 2016). The combination of vemurafenib (*BRAF* inhibitor) with crizotinib (dual ALK-MET inhibitor) is being assessed in a phase I study ([NCT01531361](#)), but to date no mechanisms of primary or secondary resistance to combined *BRAF* and MET inhibitors have been characterized at pre-clinical or clinical level. Here, for the first time, we identified a molecular mechanism of clinical resistance to *BRAF* and MET inhibition by analysis of ctDNA from plasma alongside tissue taken at progression to this combination therapy in a rectal cancer patient.

MATERIALS AND METHODS

Patient Care. The study involved a 48-year-old patient with *BRAF*^{V600E} mutant microsatellite-stable mucinous metastatic rectal cancer. Biospecimens were collected in accordance with a Fondazione IRCCS Istituto Nazionale dei Tumori Review Board–approved protocol, to which the patient provided written informed consent, and all studies were conducted in accordance with the Declaration of Helsinki. The patient's insurance company covered the cost of crizotinib+vemurafenib off-label combination therapies, to which the patient gave written informed consent. CT scans were obtained as part of routine clinical care. Additional information about specimen collection and its process

(whole exome sequencing and digital PCR on plasma samples; DNA and RNA *in situ* hybridization) are reported in Supplementary File S1.

Cell lines. WiDr parental cells were obtained from Dr René Bernards (Amsterdam, The Netherlands) in July 2011. The genetic identity of parental cell lines and their resistant derivatives was confirmed by short tandem repeat profiling (Cell ID System; Promega) at 10 different loci. Cell lines were tested and resulted negative for Mycoplasma contamination with the VenorGeM Classic Kit (Minerva Biolabs). WiDr MET^{amp} cell line was generated as previously described (Pietrantonio *et al*, 2016). Additional information is reported in Supplementary File S1.

RESULTS

The first part of this molecular case study was previously published and involved the same *BRAF* mutated metastatic rectal cancer patient who became resistant to combined *BRAF* and *EGFR* blockade (vemurafenib+panitumumab) due to the emergence of *MET* amplification. The patient was shifted from *EGFR* to *MET* inhibition, and received the combination of vemurafenib and crizotinib achieving an early response (Pietrantonio *et al*, 2016). Then, partial response was confirmed after 2 months of treatment, although the computed tomography (CT) scan at 4 months showed progressive disease (PD) across all sites (Figure 1A).

In order to uncover potential mechanisms of acquired resistance, whole exome next-generation sequencing analysis of plasma circulating tumour DNA (ctDNA) obtained prior to crizotinib and vemurafenib treatment and at PD was performed. DNA isolated from PBMC was used to remove germline variants from the analysis. The number of sequencing reads supporting the presence of a *BRAF*^{V600E} mutation was comparable in the pre-treatment and post-resistance samples, indicating similar amounts

of tumour- derived circulating cell free DNA in both samples (Figure 1B). No acquired single nucleotide variants were observed in plasma ctDNA at PD (Supplementary Table S1). However, *MET* copy number variation (CNV) further increased in the plasma ctDNA sample obtained at progression (Figure 1B).

In order to validate these findings, *BRAF*^{V600E} mutation and *MET* gene copy were longitudinally monitored in plasma ctDNA by droplet digital PCR using 15 samples collected at regular intervals from initial receipt of vemurafenib+panitumumab (Figure 1C). A rapid decrease in *BRAF*^{V600E} mutation and *MET* CNV in ctDNA was observed within two weeks from the start of vemurafenib+crizotinib. The dynamics of mutant *BRAF*^{V600E} alleles anticipated radiological progression, as mutant *BRAF* in plasma increased again as early as 8 weeks after starting therapy. At progression, the percentage of *BRAF*^{V600E} alleles were comparable to the pre-treatment sample, while – proportionally – a notable increase in the number of *MET* copies was detected (Figure 1C), thus validating exome data.

To corroborate *MET* hyper-amplification, and to further exclude tumour burden-related *MET* CNV, we performed gene copy number analysis by *MET/CEP7* bright field *in situ* hybridization (ISH) in tissue specimens obtained before and after treatment. In the liver biopsy obtained after resistance to vemurafenib+panitumumab but prior to vemurafenib+crizotinib (Figure 2, indicated as baseline 2), heterogeneous *MET* gene copy number (ranging from 2 to 20) had previously been reported (Pietrantonio *et al*, 2016). Upon resistance to vemurafenib+crizotinib, the patient consented to liver and inguinal lymph node tumour biopsies, both of which displayed *MET* hyper-amplification by ISH. Of note, the pre- and post- treatment liver biopsies were taken from the same metastatic lesion. Exome analysis performed on DNA from the liver biopsy at resistance confirmed the presence of *MET* amplification and ruled out other genetic mechanisms of resistance (Supplementary Table S1). Collectively, the results in liquid and tissue biopsies suggest that clones with higher levels of *MET* gene amplification

had been selected by the treatment.

Since evaluation of MET activation has recently been proposed to better correlate with transcription rather than protein expression due to the rapid turnover of the activated protein (Bradley *et al*, 2016), we investigated *MET* transcript levels in tissues by RNA *in situ* hybridization (RNA ISH). While *MET* mRNA was undetectable in the rectal primary tumour tissue, low expression level was seen in the liver biopsy taken after vemurafenib+panitumumab. Notably, upon resistance to vemurafenib+crizotinib, both available re-biopsies demonstrated *MET* RNA overexpression.

In order to test whether MET overexpression is causally responsible for resistance to vemurafenib+crizotinib combination treatment, we conducted *in vitro* forward genetic experiments. We previously reported that a *BRAF* mutant CRC cell line, WiDr, which also has increased *MET* gene copy number (WiDr-MET^{ampl}), was sensitive to vemurafenib+crizotinib treatment (Pietrantonio *et al*, 2016). We found that exogenous hyper-expression of MET in the same WiDr-MET^{ampl} cells (called WiDr-hyper MET^{ampl}, Figure 2B) could confer resistance to dual BRAF and MET inhibition and prevented drug combination induced cytotoxicity (Figure 2C and 2D, Supplementary Figure S1).

DISCUSSION

Concomitant inhibition of BRAF and MET in CRC patients with *BRAF*^{V600E} and *MET* amplification could represent a rationale therapeutic strategy (Pietrantonio *et al*, 2016). Recent work correlated *MET* amplification with a higher prevalence of *BRAF*^{V600E} tumours (Jardim *et al*, 2014), which may increase the impact of this combination.

The patient reported in this work achieved 4 months of partial response under therapy with vemurafenib+crizotinib until drug resistance emerged. Our effort to uncover the gene

alteration(s) driving resistance was based on ctDNA plasma sequencing. This approach has the potential to capture the inter- and intra-tumour heterogeneity present in metastatic disease (Russo *et al*, 2016). Single nucleotide variants and CNV were comprehensively analysed by whole exome sequencing comparing plasma ctDNA taken prior to target treatment and at PD. No single nucleotide variants previously associated with resistance to BRAF inhibition in melanoma or CRC were observed (Ahronian *et al*, 2015; Hong *et al*, 2016; Oddo *et al*, 2016). We also did not detect secondary *MET* mutations affecting the crizotinib-binding region, which had been observed either by drug-protein co-crystal structure analysis or in *MET* amplified tumours after acquired resistance to MET inhibition (Bahcall *et al*, 2016; Cui *et al*, 2011; Heist *et al*, 2016; Qi *et al*, 2011).

In a previous study of a *MET* amplified gastric cancer cell line treated with increasing concentrations of MET inhibitors, resistance was correlated with increased *MET* amplification accompanied by increased KRAS expression (Cepero *et al*, 2010). Our analyses identified only *MET* hyper-amplification, detected both by ISH and mRNA ISH methodologies, as the most likely genetic alteration underlying clinical acquired resistance to BRAF and MET inhibition.

Even when precision oncology is successful, the efficacy of targeted strategies is generally transient. Since the patient died about two months following disease progression, we speculate that *MET* hyper-amplification coupled with *BRAF*^{V600E} mutation not only conferred resistance to vemurafenib+crizotinib, but could be also responsible for the particularly aggressive disease behaviour. Elucidating the molecular mechanisms underlying secondary resistance may help in designing further lines of therapy (Bahcall *et al*, 2016; Pietrantonio *et al*, 2016; Russo *et al*, 2016). We believe that the traits associated with the extremely high level of MET expression shown by the resistant tumour in this study could have been exploited as a Achilles' heel to rationally test as a further salvage line novel anti-MET antibody-drug conjugates, such as ABBV-399, which showed promising activity in *MET* amplified

cancer cells and non-small cell lung cancer patients (Strickler *et al*, 2016; Wang *et al*, 2017). However, the rapid deterioration of patient conditions prevented administration of further active treatments.

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CONFLICT OF INTEREST

F. Pietrantonio is a consultant for Bayer and Sanofi. F. Pietrantonio has received honoraria from the speakers bureaus of Roche and Amgen. F. de Braud is a consultant for Roche, Amgen and Novartis. A. Bardelli is an advisory board member for Biocartis, Horizon Discovery, and Trovogene. A. Bardelli and F. Di Nicolantonio have received research support from Trovogene. No potential conflicts of interest were disclosed by the other authors.

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Titles and legends to figures:

Figure 1. Emergence of *MET* gene hyper-amplification in plasma circulating tumour DNA of a *BRAF*^{V600E} metastatic colorectal cancer patient upon progression to crizotinib and vemurafenib combinatorial treatment.

A) Clinical course of the disease during treatment with vemurafenib+crizotinib. Computed tomography scans document the disease status before treatment (left panel), after the initial response (middle panel) and at disease progression (right panel). **B)** Exome analysis of circulating tumour DNA (ctDNA) by next-generation sequencing (NGS). Mutant *BRAF*^{V600E} allele frequencies of 46% and 50% were seen in the baseline 2 plasma sample and at resistance, respectively, indicating similar amounts of ctDNA in both samples. *MET* copy number variation (CNV) is increased when comparing ctDNA before therapy with vemurafenib+crizotinib and after disease progression. **C)** Analysis of ctDNA by digital droplet PCR (ddPCR). Time kinetics of the percentage of *BRAF*^{V600E} alleles (red line) or copies of *MET* gene copy number (blue line) show a decrease of both circulating markers during patient response to vemurafenib+crizotinib. At radiological disease progression, the percentage of *BRAF*^{V600E} alleles were comparable to the pre-treatment sample, while – proportionally – a notable increase in *MET* gene copy number was detected. Datapoints represent mean ± SD of 2 independent observations, each performed in duplicate. Abbreviations are as follows: PR, partial response; PD, progressive disease.

Figure 2. *MET* gene hyper-amplification and *MET* mRNA expression emerge in a patient with *BRAF*^{V600E} rectal cancer and confer resistance to BRAF and MET dual inhibition in WiDr cells. *In situ* hybridization analyses for *MET* gene and mRNA levels were performed on the primary tumour (baseline 1, panels A1 and B1), a liver biopsy

obtained upon resistance to vemurafenib+panitumumab but before vemurafenib+crizotinib (baseline 2, panels A2 and B2), as well as liver (panels A3 and B3) and inguinal lymph node (panels A4 and B4) biopsies obtained upon acquired resistance to vemurafenib+crizotinib. **A)** Dual colour bright field in situ hybridization (ISH) for *MET* gene (black dots) and *CEP7* (red dots). The baseline sample obtained prior to targeted treatments does not show *MET* amplification, even if a few clones display gain of *MET* gene copy number, with 18% of neoplastic cells bearing ≥ 5 *MET* gene copy number (A1). The sample obtained at acquired resistance to vemurafenib+panitumumab but prior to vemurafenib+crizotinib (baseline 2) shows *MET* amplification, with a mean gene copy number of 8.8 (range 2-20) (A2). Upon acquired resistance to vemurafenib+crizotinib, tumour cells display *MET* 'hyper-amplification', with a further increase of *MET* gene copy number in both liver re-biopsy (A3 – multiple copies and small and large clusters) and inguinal lymph node biopsy (A4 – small and large clusters). *In situ* hybridization for *MET* mRNA *MET* gene transcription is below level of detection (score = 0) in baseline 1 sample (B1); while an increased staining of *MET* gene transcription (score = 1) is present in the liver biopsy upon acquired resistance to vemurafenib+panitumumab (B2). This is further increased in samples obtained upon resistance to vemurafenib+crizotinib (B3-B4), with evidence of strong *MET* mRNA overexpression (score = 3 in liver biopsy; score = 4 in lymph node biopsy). Scale bar represent 12.5 μ m. **B)** *BRAF*^{V600E} mutant WiDr parental or its *MET* amplified derivative cell line (WiDr-MET^{ampl}) were transduced with either control (empty) or *MET*-expressing lentiviral vector (here called WiDr hyper-MET^{ampl}), respectively. Protein extraction and Western blotting with total *MET* antibodies revealed a gradient of *MET* protein expression among the three different cell lines. HSP90 is reported for normalization purposes. **C)** Cell viability by ATP assay of WiDr empty, MET^{ampl} and hyper-MET^{ampl} cells after treatment for 72 hours with the indicated molar concentrations of vemurafenib in association with constant 0.2 μ M crizotinib. **D)** WiDr empty, MET^{ampl} and hyper MET^{ampl} were treated for 72 hours with 1 μ M

vemurafenib and/or 0.2 μ M crizotinib in mono or combinatorial therapies. CellTox green cytotoxicity assay was performed to identify cells with compromised membrane integrity characteristic of cell death. Data are expressed as fold change relative to DMSO treated control cells. Results represent mean \pm SD of 2 independent observations, each performed in duplicate or triplicate. Statistical differences in *BRAF* mutant cell viability or cytotoxicity between MET^{ampl} and hyper- MET^{ampl} cells was determined with the Mann-Whitney *U* test (**P* < .05, ***P* < .01).

Figure 1

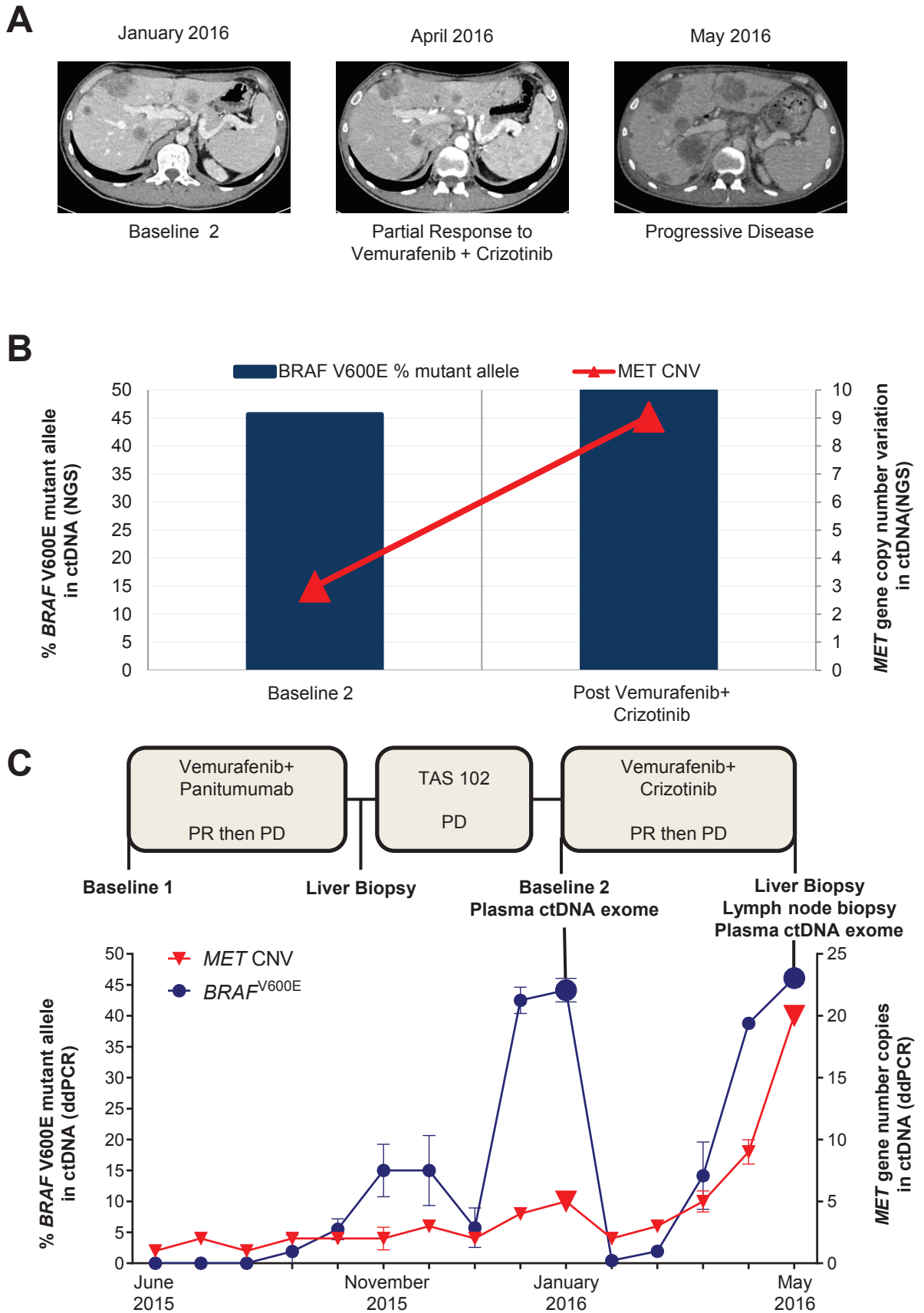
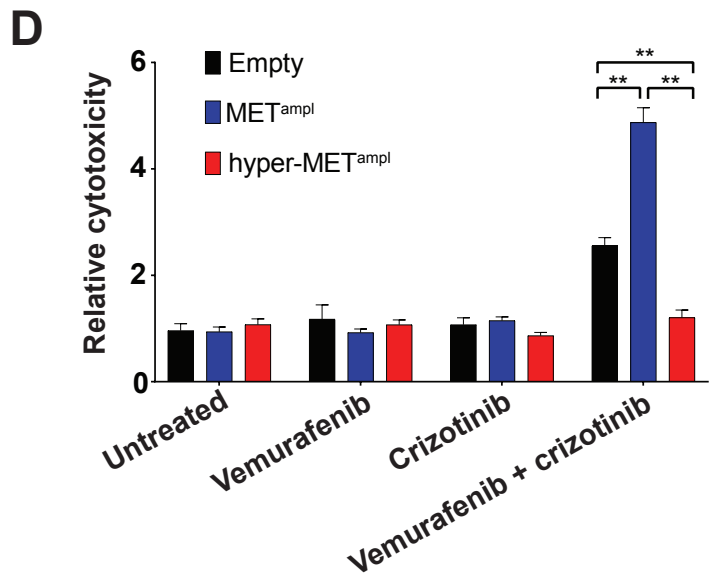
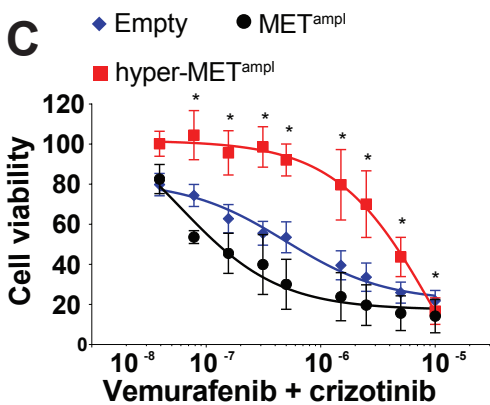
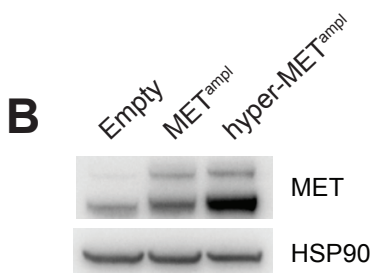
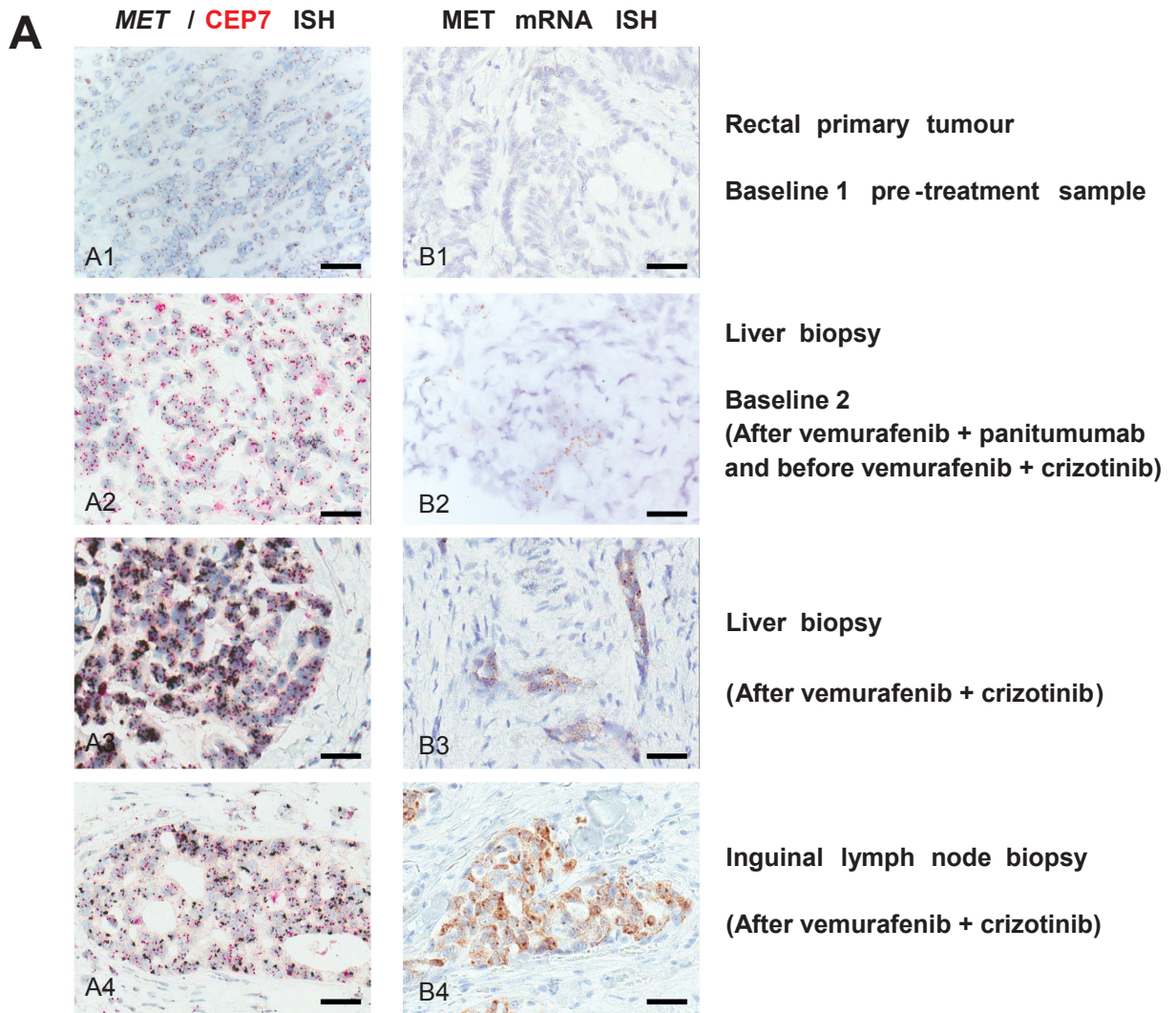


Figure 2



Supplementary File

Specimen Collection

Solid tumour tissues (rectum, liver and inguinal lymph node) and whole blood were collected in accordance with an Institutional Review Board–approved protocol, to which the patient provided written informed consent, and all studies were conducted in accordance with the Declaration of Helsinki. Patient was still alive when biospecimens were obtained.

A minimum of 10 ml of whole blood samples were obtained during therapy by direct venipuncture in antecubital area of the arm (or from central venous catheter devices) directly on standard EDTA tubes. Plasma was separated within 5 h through two different centrifugation steps (the first at room temperature for 10 min at 1,600g and the second at 3,000g for the same time and temperature), obtaining up to 3 ml of plasma. PBMC were also obtained which served as a reference control for germ-line genomic DNA. Plasma samples and PBMC were frozen and shipped in dry ice to IRCCS Candiolo, (Turin, Italy) and stored at -80°C upon arrival until ctDNA extraction. Solid tumour tissues were formalin-fixed in 10% neutral buffered formalin for 24 hours according to routine procedures and paraffin-embedded.

DNA extraction from plasma, PBMC and tissue

Germline DNA was extracted from PBMC using ReliaPrep Tissue Kit (Promega, #A2051). ctDNA for ddPCR analysis was extracted from 1 ml of plasma using the Maxwell® RSC ccfDNA Plasma Kit (Promega, #AS1480) with the automated Maxwell® RSC Instrument (Promega) according to the manufacturer's instructions. ctDNA samples for Next Generation Sequencing analysis were extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen, #55114) according to the manufacturer's instructions

and DNA yield measured with the Qubit® dsDNA HS Assay Kit (Thermo Fisher Scientific, #Q32851). Tissue DNA was extracted by ReliaPrep gDNA Tissue Miniprep System (Promega) according to manufacturer's directions.

Whole exome sequencing and bioinformatics

Libraries were prepared with Nextera Rapid Capture Exome Kit (Illumina Inc., San Diego, CA, USA), according to the manufacturer's protocol. Preparation of libraries was performed using up to 150 ng of plasma ctDNA and 100 ng of PBMC and fresh tissue DNA. DNA from PBMC and fresh tissues was fragmented using transposons, adding simultaneously adapter sequences, while ctDNA libraries preparation was performed using NEBNext® Ultra™ DNA Library Prep Kit for Illumina® (New England BioLabs Inc., Ipswich MA), with optimized protocol. DNA from PBMC and fresh tissues after the tagmentation step, and ctDNA were used as template for subsequent PCR to introduce unique sample barcodes. Fragments' size distribution of the DNA was assessed using the 2100 Bioanalyzer with a High Sensitivity DNA assay kit (Agilent Technologies, Santa Clara, CA). Equal amount of DNA libraries were pooled and subjected to targeted panel hybridization capture. Libraries were then sequenced using an Illumina Next-Seq-500 sequencer (Illumina Inc., San Diego, CA, USA). In order to analyze only good quality sequences, all nucleotides in the reads with a Phred quality score less than 30 were removed. FastQ files were then mapped to the human reference (assembly hg19) using the BWA-mem algorithm (Li & Durbin, 2010) and PCR duplicates were removed using the RMDUP command of SAMtools package (Li *et al*, 2009). Mutational discovery analyses were performed by a custom NGS pipeline, in order to call somatic variations, when supported by at least 1% allelic frequency and 5% significance level obtained with a Fisher test, as previously described (Siravegna *et al*, 2015). To identify insertions and deletions (indels), we further analyzed the alignment files by comparing pre-treatment and post-treatment

samples using Pindel software (Ye *et al*, 2009). The indels that were presents in germline sample or supported less than 4 reads were filtered out. Mutations and indels were annotated by a custom script printing out gene information, number of normal and mutated reads, the allelic frequencies and the variation effect. Each of these entries was associated with the corresponding number of occurrences in the COSMIC database (Forbes *et al*, 2015). Gene copy number (GCN) was obtained by calculating the ratio of the median gene read depth to the median read depth of all coding regions. Alterations of tumour sample with respect to normal were obtained by considering the ratio of the corresponding GCNs.

Droplet Digital PCR (ddPCR)

Circulating free DNA isolated from plasma was amplified using ddPCR™ Supermix for Probes (Bio-Rad) using *BRAF*^{V600E} assay (PrimePCR™ ddPCR™ Mutation Assay, Bio-Rad, #dHsaCP2000027) and *MET* vs *EIF2C1* (reference) for gene number copies (PrimePCR ddPCR Copy Number Assay, Bio-Rad, # dHsaCP250032- #dHsaCP1000002). ddPCR was then performed according to manufacturer's protocol and the results reported as number of copies and/or percentage or Fractional Abundance of mutant DNA alleles to total (mutant plus wild type) DNA alleles. 8 to 10 µl of DNA template was added to 10 µl of ddPCR™ Supermix for Probes (Bio-Rad) and 2 µl of the primer/probe mixture. Droplets were generated using Automated Droplet Generator (Bio-Rad, #186-4101) where the reaction mix was added together with Droplet Generation Oil for Probes (Bio-Rad, #1864110). Droplets were then transferred to a 96 well plate (Eppendorf, # H 0030 129 504) and then thermal cycled with the following conditions: 5 minutes at 95°C, 40 cycles of 94°C for 30s, 55°C for 1 minute followed by 98°C for 10 minutes (Ramp Rate 2°C/sec). Droplets were analyzed with the QX200™ Droplet Reader for fluorescent measurement of FAM and HEX probes. Gating was performed based on positive and negative controls, and mutant populations were identified. The ddPCR data were analyzed with

QuantaSoft™ analysis software (Bio-Rad) to obtain CNV and Fractional Abundance of the mutant DNA alleles in the wild-type (WT)/normal background. The quantification of the target molecule was presented as number of total copies (mutant plus WT) per sample in each reaction. Fractional Abundance is calculated as follows: F.A. % = $(N_{mut}/(N_{mut}+N_{wt})) * 100$, where N_{mut} is number of mutant events and N_{wt} is number of WT events per reaction. ddPCR analysis of normal control (from cell lines) and no DNA template controls were always included. Samples with positive events that were too low were repeated at least twice in independent experiments to validate the obtained results.

MET DNA silver In situ hybridization (SISH)

Bright field dual-color SISH analysis was performed on 3 µm formalin fixed and paraffin embedded (FFPE) tissue sections by using the MET DNP Probe along with the Chromosome 7 DIG Probe (Ventana Medical Systems, Tucson, AZ, USA) on a BenchMark Ultra Platform (Ventana Medical Systems) according to the manufacturer's protocol.

RNA *in situ* hybridisation (ISH) studies

MET mRNA expression was studied in FFPE tissue sections by means of ISH using the target probe Homo sapiens MET (Hs-MET) (Cat. No. 310051 - sequence region 1236–2257, Advanced Cell Diagnostics, Inc., Hayward, CA). For each case a negative control probe (bacterial gene 4-hydroxy-tetrahydrodipicolinate reductase [DapB]; # 310043, sequence region 139–989, Advanced Cell Diagnostics) and a positive control probe for evidence of preserved RNA (housekeeping gene ubiquitin C [UbC] #310041 - sequence region 342–1503, Advanced Cell Diagnostics) was included. ISH was performed manually using the RNAscope 2.5 High Definition detection kit (brown) (Advanced Cell Diagnostics) in accordance with the manufacturer's instructions.

Briefly, 5 µm FFPE tissue sections were incubated with hydrogen peroxide for 10 minutes at room temperature (RT). The slides then were boiled in Target Retrieval 1X buffer for 45 minutes, followed by incubation with Protease Plus for 20-30 minutes at 40°C, and then hybridised with the relevant probes for two hours at 40°C, followed by successive incubations with Amp1-Amp6 reagents, colour development with 3,3'-diaminobenzine (DAB), and counterstaining with haematoxylin. Positive staining signals were identified as brown, punctuate dots in the cytoplasm and/or nucleus.

MET mRNA ISH scoring

MET mRNA was analysed by using a scoring system that categorizes the cases into five grades depending on the number of dots visualised under a bright-field microscope: 0 = no staining or <1 dot every 10 cells; 1+: 1-3 dots/cell; 2+: 4-10 dots/cell with very few dot clusters; 3+: >10 dots/cell with <10% of positive cells having dot clusters; and 4+: >10 dots/cell with >10% of positive cells having dot clusters.

Cell lines and Drugs

WiDr parental and MET^{amp1} cell lines were cultured at 37°C and 5% CO₂ in RPMI 1640 (Invitrogen), supplemented with 10% fetal bovine serum, 2 mM L-glutamine and antibiotics (100 U/ml penicillin and 100 mg/ml streptomycin). Vemurafenib was purchased from Sequoia Chemicals; crizotinib was from ChemieTek.

Western Blot analysis

Total cellular proteins were extracted by lysing cells in boiling Laemmli buffer (1% SDS, 50 mM Tris-HCl [pH 7.5], 150 mM NaCl). The following primary antibodies were used: anti-

MET (rabbit polyclonal, clone D1C2, 1:1000, Cell Signaling Technology) and Actin (goat polyclonal, clone I-19, Santa Cruz Biotechnology; 1:3000).

Viral Infection

Lentiviral vector stock were produced by transient transfection of the pCCL-MET wild-type or lenti-control plasmid (a gift of Elisa Vigna, IRCCS, Candiolo, Turin) the packaging plasmid MDLg/pRRE and pRSV.REV, and the vesicular stomatitis virus (VSV) envelope plasmid pMD2.VSV-G (25, 2.5, 6.25 and 9 µg, respectively, for 15-cm dishes) in HEK-293T cells in presence of 1mM/L sodium butyrate (Sigma) and 10 ng/ml of Doxycycline. Cells were transduced in six well plates (3 x 10⁵ per well in 2 ml of medium) in the presence of polybrene (8 µg/ml) (Sigma).

Drug proliferation assays

Cell proliferation experiments were carried out in 96-well plates in duplicate. Cells were plated (3,000 cells/well) in 100 µl complete growth medium. At 24 hours post-seeding, 100 µl of serum-free medium was manually added to the cells. Vemurafenib and crizotinib were added directly on the plate by TECAN D300e digital dispenser (HP). After 72 hours' treatment cell viability was assessed by ATP content using CellTiter-Glo Luminescent Assay (Promega). Viability was normalized as a percentage of control untreated cells. Data from growth-inhibition assays were plotted using the nonlinear regression curve fit modelling from GraphPad Prism-5 (GraphPad Software).

Cell proliferation over time from day 0 to day 5 was estimated by ATP content using CellTiter-Glo Luminescent Cell Viability Assay (Promega) following manufacturer's instructions and according the experimental procedure describe above.

Cytotoxicity assays

For cytotoxicity assays cells were seeded at 4,000 cells/well in 96-well black optical-bottom plates (Nunc, Life Technologies). After 24 hours, cells were treated with vemurafenib (1 μ M) and/or crizotinib (0.2 μ M) in mono or combinatorial therapies. The CellTox Green cytotoxicity assay was performed according to manufacturer instructions and fluorescence was read by TECAN Spark 10M plate reader at 535 nm. As toxicity control, Lysis Solution was added (4 μ l per 100 μ l of cells) 30 minutes prior to reading. Subsequently, the amount of viable cells for each well was quantified by CellTiter-Glo Luminescent Assay (Promega). Data were first normalized to the amount of cells and after to untreated control.

Supplementary References

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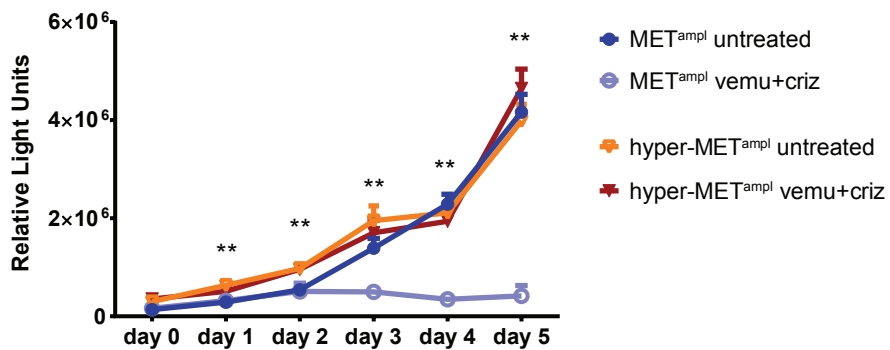
Legend to Supplementary Table:

Supplementary Table S1. List of gene mutation hotspots previously involved in resistance to BRAF inhibition or the crizotinib binding site of MET. For each hotspot, the numbers of reads supporting each allele in pre-treatment and post-treatment samples are shown. All counts were obtained from alignments files: reads from whole exome sequencing were mapped to the human reference (assembly hg19), PCR duplicates were removed and all bases with a Phred score less than 30 are filtered out.

Legend to Supplementary Figure:

Supplementary Figure S1. Hyper-MET^{ampl} cells under vemurafenib and crizotinib treatment proliferate similarly to the untreated cells. Proliferation rate of WiDr MET^{ampl} and hyper-MET^{ampl} cells was measured by ATP assay. Cells were cultured from day 0 to day 5 in absence or presence of the following drug combination: 1 μ M vemurafenib and 0.2 μ M crizotinib. Data are expressed as relative light units. Results represent mean \pm SD of 2 independent observations, each performed in triplicate. Statistical differences in *BRAF* mutant cell viability between MET^{ampl} and hyper-MET^{ampl} cells was determined with the Mann-Whitney *U* test (**P* < .05).

Supplementary Figure S1



Supplementary Table 1

Supplementary Table S1. List of gene mutation hotspots previously involved in resistance to BRAF inhibition or the crizotinib binding site of MET. For each hotspot, the numbers of reads supporting each allele in pre-treatment and post-treatment samples are shown. All counts were obtained from alignments files: reads from whole exome sequencing were mapped to the human reference (assembly hg19), P duplicates were removed and all bases with a Phred score less than 30 are filtered out.

COORDINATES	GENE	AA CHANGE	REF	# READS											
				PLASMA AT BASELINE TO VEMURAFENIB-CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB-CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB-CRIZOTINIB			
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2
chr10:12325034	FGFR2	p.N590	A	590	0	0	0	776	0	0	0	742	1	0	0
chr10:123274774	FGFR2	p.C582	A	651	0	0	0	673	0	0	0	682	1	0	0
chr10:123274794	FGFR2	p.Y375	T	0	0	2	657	0	0	1	662	1	0	1	696
chr10:123274803	FGFR2	p.S372	G	0	0	703	0	0	0	678	1	0	0	693	2
chr10:123279503	FGFR2	p.K310	T	0	0	1	420	0	0	0	402	0	0	0	374
chr10:123279674	FGFR2	p.P263	G	0	0	259	0	0	0	299	0	0	0	237	0
chr10:123279677	FGFR2	p.S252	G	0	0	231	0	0	0	229	1	0	0	189	0
chr10:43609096	RET	p.C618	T	0	0	1	296	0	0	1	260	1	0	3	372
chr10:43609102	RET	p.C620	T	0	0	0	322	0	0	0	289	1	0	1	388
chr10:43609936	RET	p.C630	T	1	0	1	494	0	0	1	528	0	0	0	636
chr10:43609940	RET	p.D631	A	433	1	0	0	437	0	1	0	0	509	3	0
chr10:43609948	RET	p.C634	T	0	0	1	482	0	0	1	545	0	0	3	624
chr10:43609949	RET	p.C634	G	0	0	601	2	0	0	594	0	0	0	797	1
chr10:43609950	RET	p.C634	C	0	0	564	0	0	0	538	0	4	747	0	0
chr10:43613840	RET	p.E768	G	0	0	465	1	0	0	431	0	0	1	762	0
chr10:43615567	RET	p.V882	A	454	0	0	0	458	0	0	0	552	1	0	0
chr10:43615568	RET	p.A883	G	0	0	497	1	0	0	460	1	0	0	610	5
chr10:43615569	RET	p.A883	C	1	470	0	0	1	440	0	0	1	570	0	0
chr10:43617416	RET	p.M878	T	0	0	2	581	0	0	0	778	0	0	0	776
chr10:89624245	PTEN	p.E7	G	0	0	308	0	0	0	385	1	0	0	433	0
chr10:89624255	PTEN	p.S10	G	0	0	300	0	0	0	370	1	0	0	421	1
chr10:89624263	PTEN	p.R13	A	303	0	0	0	431	0	1	0	470	0	0	1
chr10:89624266	PTEN	p.R14	A	287	0	0	0	408	0	0	0	431	1	0	1
chr10:89624270	PTEN	p.R15	G	0	0	283	0	0	0	362	0	0	0	454	0
chr10:89624271	PTEN	p.R15	A	283	1	0	0	397	0	0	0	467	1	0	0
chr10:89624273	PTEN	p.Y16	A	279	0	0	0	404	1	0	1	455	2	0	0
chr10:89624275	PTEN	p.Q17	C	2	294	0	0	0	402	2	0	2	457	0	0
chr10:89625271	PTEN	p.F96	T	0	0	0	338	0	0	0	508	0	0	0	298
chr10:89625275	PTEN	p.L57	T	0	0	0	300	0	0	0	517	0	0	0	337
chr10:89685281	PTEN	p.S59	C	0	371	0	0	0	480	0	1	324	0	0	0
chr10:89685287	PTEN	p.H61	A	379	0	0	0	504	0	0	0	338	0	0	0
chr10:89685300	PTEN	p.V85	C	0	387	0	0	1	475	0	0	0	342	0	1
chr10:89685301	PTEN	p.K68	A	379	0	0	0	507	0	0	0	351	0	0	0
chr10:89685303	PTEN	p.K66	G	0	0	391	0	0	0	476	2	0	0	382	0
chr10:89685307	PTEN	p.V68	T	0	1	0	387	0	0	1	479	0	0	0	409
chr10:89685308	PTEN	p.V68	A	393	0	0	0	478	0	0	0	405	0	0	0
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chr10:896852831	PTEN	p.C105	T	2	2	0	486	0	0	1	702	0	0	1	731
chr10:896852835	PTEN	p.D107	G	0	0	525	0	0	0	698	0	0	0	752	2
chr10:896852839	PTEN	p.L108	T	0	0	0	571	0	1	0	783	0	0	1	803
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chr10:89682847	PTEN	p.W111	T	1	0	0	569	0	0	0	771	3	0	1	753
chr10:89682848	PTEN	p.W111	G	0	0	545	0	0	0	685	3	0	0	727	0
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chr10:89720711	PTEN	p.E268	G	0	0	231	0	0	0	342	0	0	0	313	0
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chr10:89720864	PTEN	p.F339	C	0	311	0	0	0	399	0	0	0	394	0	0
chr10:89720870	PTEN	p.F341	T	0	0	0	311	0	0	0	435	0	0	0	431
chr11:108117798	ATM	p.R337	C	1	846	0	0	0	974	0	0	0	590	0	2
chr11:108119823	ATM	p.V410	T	0	2	0	849	1	0	0	1184	0	0	1	671
chr11:108123551	ATM	p.P604	C	0</											

Supplementary Table 1

COORDINATES	GENE	AA	CHANGE	REF	# READS															
					PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB							
					A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2				
chr12:12888156	PTPN11	p.N58	A	990	2	0	0	1388	2	0	0	851	1	0	0	0				
chr12:12888162	PTPN11	p.G60	G	0	0	1093	1	0	0	1403	0	2	0	832	3	0				
chr12:12888163	PTPN11	p.G60	G	0	0	1115	0	0	0	1115	0	0	0	1436	2	2				
chr12:12888165	PTPN11	p.D61	C	2	0	1166	1	2	0	0	1517	2	0	877	0	0				
chr12:12888166	PTPN11	p.D61	A	1186	0	0	0	1592	0	0	0	0	0	940	0	1				
chr12:12888189	PTPN11	p.E69	G	0	0	1268	1	0	0	1569	0	0	0	873	2	0				
chr12:12888195	PTPN11	p.F71	T	3	0	0	1298	0	0	1	0	1702	0	0	0	960				
chr12:12888197	PTPN11	p.F71	T	0	0	0	0	0	0	1	0	1614	0	1	0	938				
chr12:12888198	PTPN11	p.A72	G	0	0	1343	2	0	0	0	1588	0	0	0	923	0				
chr12:12888199	PTPN11	p.A72	C	0	0	1261	0	2	5	1517	1	0	2	861	0	1				
chr12:12888202	PTPN11	p.T73	C	6	1287	0	0	4	1518	0	0	1	893	0	0	0				
chr12:12888210	PTPN11	p.E76	G	1	0	1303	0	0	0	0	1416	4	0	0	900	1				
chr12:12888211	PTPN11	p.E76	A	1321	0	2	0	1608	0	0	0	0	986	0	0	0				
chr12:12926852	PTPN11	p.F491	C	0	1096	0	0	2	1296	0	0	1	1152	0	0	0				
chr12:12926884	PTPN11	p.S502	T	1	0	1	1043	0	0	2	1299	0	0	0	4	980				
chr12:12926885	PTPN11	p.S502	C	0	1273	0	0	2	1550	1	0	1	1149	0	0	0				
chr12:12926888	PTPN11	p.S503	G	0	0	1280	0	0	0	1450	1	0	0	1125	3	0				
chr12:12926908	PTPN11	p.Q510	C	0	1337	0	0	2	1558	0	1	3	1241	1	0	0				
chr12:121431403	HNF1A	p.R203	C	0	351	0	0	0	342	0	0	0	405	0	0	0				
chr12:121431413	HNF1A	p.W206	G	0	0	313	1	0	0	355	0	0	1	388	1	0				
chr12:121431414	HNF1A	p.W206	G	0	0	309	1	0	0	329	1	0	0	374	0	0				
chr12:121431416	HNF1A	p.S207	G	1	0	323	1	0	0	331	0	0	0	405	0	1				
chr12:121431428	HNF1A	p.Q211	A	279	0	0	0	300	1	0	0	335	0	0	0	0				
chr12:121432032	HNF1A	p.T260	C	0	408	0	0	0	359	0	0	0	406	1	0	0				
chr12:121432040	HNF1A	p.R263	C	0	400	0	0	1	371	0	0	1	393	0	0	0				
chr12:121432068	HNF1A	p.R272	G	0	0	381	0	0	0	351	0	0	0	352	0	0				
chr12:121432070	HNF1A	p.K275	A	392	0	0	0	389	0	1	1	352	0	0	0	0				
chr12:25378560	KRAS	p.A146	T	1	0	0	588	0	0	0	728	0	0	0	667	0				
chr12:25378561	KRAS	p.A146	G	0	0	588	0	0	0	0	728	0	0	0	652	1				
chr12:25378562	KRAS	p.A146	C	0	570	0	0	1	701	0	0	0	629	0	0	0				
chr12:25378647	KRAS	p.K117	T	0	0	0	757	0	0	0	943	0	0	1	690	0				
chr12:25378648	KRAS	p.K117	T	0	0	0	774	2	0	0	968	0	0	1	669	0				
chr12:25378649	KRAS	p.K117	T	0	0	0	754	0	0	0	912	0	0	0	640	0				
chr12:25380275	KRAS	p.O61	T	0	0	1	499	1	0	0	718	0	0	2	611	0				
chr12:25380276	KRAS	p.O61	T	0	0	0	495	0	0	0	713	0	1	0	607	0				
chr12:25380277	KRAS	p.O61	G	0	0	487	0	0	0	0	678	0	0	0	589	0				
chr12:25380278	KRAS	p.G60	A	411	0	0	0	572	1	0	0	528	2	0	0	0				
chr12:25380281	KRAS	p.A59	T	0	0	0	471	0	0	0	641	0	0	0	541	0				
chr12:25380282	KRAS	p.A59	G	0	0	475	0	0	0	1	615	3	0	0	563	1				
chr12:25380293	KRAS	p.A59	C	0	457	0	0	4	582	0	0	0	565	0	0	0				
chr12:25380285	KRAS	p.T58	G	0	0	465	0	0	0	588	0	0	0	559	1	0				
chr12:25380255	KRAS	p.Q22	G	0	535	1	0	0	0	718	1	2	0	739	3	0				
chr12:25380262	KRAS	p.L19	C	0	543	0	0	3	710	0	0	2	789	0	0	0				
chr12:25380266	KRAS	p.A18	G	0	0	509	1	0	0	688	0	0	0	727	2	0				
chr12:25380276	KRAS	p.G15	C	0	497	0	0	0	640	0	0	3	769	0	0	0				
chr12:25380279	KRAS	p.V14	C	0	479	0	0	0	603	0	0	2	690	0	0	0				
chr12:25380280	KRAS	p.G13	G	0	0	465	1	2	0	679	0	0	0	731	1	0				
chr12:25380281	KRAS	p.G13	C	0	484	0	0	0	603	0	0	1	743	0	0	0				
chr12:25380282	KRAS	p.G13	C	0	483	0	0	0	607	0	0	0	744	0	0	0				
chr12:25380283	KRAS	p.G12	A	409	0	0	0	568	0	0	0	0	672	1	0	0				
chr12:25380284	KRAS	p.G12	C	0	483	0	1	0	612	0	0	0	769	0	0	0				
chr12:25380285	KRAS	p.G12	C	0	462	0	0	0	603	0	0	0	714	0	0	0				
chr12:25380287	KRAS	p.A11	C	0	442	0	0	0	607	0	0	1	735	0	0	0				
chr12:25380288	KRAS	p.A11	C	0	481	0	0	0	614	0	0	1	777	0	0	0				
chr12:25380295	KRAS	p.V8	T	0	0	0	451	0	0	0	609	0	0	0	727	0				
chr13:28592620	FLT3	p.Y842	T	0	0	0	321	0	0	0	0	0	0	0	251	0				
chr13:28592635	FLT3	p.M837	A	330	0	0	0	337	0	0	0	320	305	0	0	0				
chr13:28592636	FLT3	p.M837	T	0	0	0	339	0	0	0	0	0	0	0	323	0				
chr13:28592637	FLT3	p.I836	G	0	0	347	1	0	0	342	0	0	0	321	0	0				
chr13:28592638	FLT3	p.I836	A	349	0	0	0	354	0	0	0	320	0	0	0	0				
chr13:28592639	FLT3	p.I836	T	1	0	1	350	0	0	0	0	371	0	0	329	0				
chr13:28592640	FLT3	p.D835	A	345	0	0	0	371	0	0	0	332	0	0	0	0				
chr13:28592641	FLT3	p.D835	T	0	0	1	344	0	0	0	0	0	0	0	344	0				
chr13:28592642	FLT3	p.D835	C	0	353	0	0	0	358	0	0	0	332	0	0	0				
chr13:28592644	FLT3	p.R834	C	0	359	0	0	0	317	1	0	0	324	0	0	1				
chr13:28592653	FLT3	p.L931	C	0	364	0	0	0	377	0	0	0	396	0	0	0				
chr13:28602229	FLT3	p.A680	T	0	0	248	0	0	0	271	0	0	0	154	0	1				
chr13:28602600	FLT3	p.Y999	T	0	0	0	241	0	0	0	380	1	0	0	282	0				
chr13:28602601	FLT3	p.V992	A	271	0	0	0	407	0	0	0	283	1	0	0	0				
chr13:28603411	FLT3	p.Y572	T	0	0	0	278	0	0	0	0	449	0	0	0	225				
chr13:28610138	FLT3	p.S451	G	0	0	0	265	0	0	0	322	0	0	0	294	2				
chr13:48919244	RB1	p.E137	G	0	0	526	0	0	0	423	0	0	0	456	2	0				
chr13:48923148	RB1	p.L199	T	0	0	0	325	0	0	0	250	0	2	0	287	0				
chr13:48941648	RB1	p.R320	C	0	443	0	0	1	545	0	0	1	592	0	0	0				
chr13:48942695	RB1	p.R358	C	0	341	0	0	0	477	0	0	0	498	0	0	0				
chr13:48953700	RB1	p.R545	C	1	259	0	0	1	300	0	0	0	243	0	0	0				
chr13:48955538	RB1	p.R552	C	1	378	0	0	2	322	0	0	2	239	0	0	0				
chr13:48955560	RB1	p.R556	C	1	381	0	0	0	319	0	0	1	248	0	0	0				
chr13:49027168	RB1	p.R579	C	0	443	0	1	1	478	0	0	2	502	0	0	0				
chr13:49033844	RB1	p.R661	C	0	425	0	0	0	485	0	0	0	498	0	0	0				
chr13:49033916	RB1	p.D685	C	0	463	0	0	2	555	0	0	0	423	0	0	0				
chr13:49037877	RB1	p.C706	G	2	0	458	0	0	0	420	1	0	1	428	0	0				
chr13:49037903	RB1	p.K715	A	469	0	0	0	517	0	0	0	422	0	0	0	0				
chr13:49039104	RB1	p.E748	G	0	187	2	0	0	0	214	2	0	0	213	0	0				
chr13:49039183	RB1	p.K754	T	0	0	1	238	0	0	0	378	0	0	0	357	0				
chr14:105241444	AKT1	p.K179	T	0	0	0	142	0	0	0	0	201	0	0	0	198				
chr14:105241463	AKT1	p.G173	C	0	200	0	0	0	241	0	0	0	371	0	0	0				
chr14:105244455	AKT1	p.E49	C	0	179	0	0	0	189	0	0	0	254	0	0	0				
chr14:105244497	AKT1	p.F35	A	183	0	0	0	0	223	0	0	0	350	0	0	0				
chr14:105246551	AKT1	p.S17	C	0	135	0	0	0	148	0	0	3	253	0	0	0				
chr15:66727441	MAP2K1	p.F53	T	0	0	1	565	2	0	1	760	0	2	584	0	0				
chr15:66727442	MAP2K1	p.F53	T	0	0	0	563	0	0	0	800	0	0	1	624	0				
chr15:66727443	MAP2K1	p.F53	T	0	0	0	589	0	1	0	800	1	0	1	664	0				
chr15:66727450	MAP2K1	p.Q56	C	0	606	0	0	1	716	0	0	2	612	0	0	0				
chr15:66727451	MAP2K1	p.Q56	A	599	0	0	0	802												

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS															
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB								PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB			
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2				
chr15:66729190	MAP2K1	p.F133	T	0	0	0	585	0	0	4	796	0	0	0	0	0	0	517	0
chr15:66729191	MAP2K1	p.F133	C	2	657	0	0	4	871	0	2	661	0	2	661	0	0	0	0
chr15:6674155	MAP2K1	p.V211	C	0	0	612	0	0	0	623	2	0	1	742	0	1	742	1	0
chr15:6674156	MAP2K1	p.V211	T	0	0	2	464	0	1	0	1	501	0	0	10	546	0	0	0
chr15:6674157	MAP2K1	p.V211	C	0	586	0	0	3	633	0	0	2	721	0	0	0	0	0	0
chr15:6674167	MAP2K1	p.L215	C	0	568	0	0	2	601	1	0	2	734	0	0	0	0	0	0
chr15:6674168	MAP2K1	p.L215	T	0	0	1	506	0	0	1	571	0	0	3	649	0	0	0	0
chr15:6674169	MAP2K1	p.L215	C	1	559	0	0	1	587	0	0	0	656	0	0	0	0	0	0
chr15:66781568	MAP2K1	p.P326	C	0	466	0	0	0	570	0	0	0	496	0	0	0	0	0	0
chr15:66781569	MAP2K1	p.P326	C	0	414	0	0	0	545	0	0	2	460	0	0	0	0	0	0
chr15:66781570	MAP2K1	p.P326	C	0	428	0	0	0	530	1	0	0	453	0	0	0	0	0	0
chr15:66781574	MAP2K1	p.G328	G	0	0	454	2	0	0	554	2	0	0	0	0	0	517	0	0
chr15:66781575	MAP2K1	p.G328	G	0	0	484	1	0	0	588	0	0	0	0	0	0	528	0	0
chr15:66781576	MAP2K1	p.G328	A	472	0	0	0	619	1	0	0	541	0	0	0	0	0	0	0
chr15:66782873	MAP2K1	p.E368	G	0	0	497	1	0	0	651	0	0	608	2	0	0	0	0	0
chr15:66782874	MAP2K1	p.E368	A	459	0	0	0	684	0	0	0	615	1	0	1	0	0	0	0
chr15:66782875	MAP2K1	p.E368	A	449	0	0	0	661	0	0	0	601	0	0	0	0	0	0	0
chr15:90631837	IDH2	p.R172	C	1	505	0	0	0	531	0	0	1	732	0	0	0	0	0	0
chr15:90631838	IDH2	p.R172	C	0	509	0	0	1	522	0	0	3	744	0	0	0	0	0	0
chr15:90631839	IDH2	p.R172	T	0	0	0	483	0	0	0	514	0	0	0	705	0	0	0	0
chr15:90631841	IDH2	p.D171	C	0	495	0	0	0	518	0	0	0	739	0	0	0	0	0	0
chr15:90631881	IDH2	p.F158	G	0	0	460	1	0	0	494	2	1	0	687	0	0	0	0	0
chr15:90631934	IDH2	p.R140	C	0	385	0	0	2	442	0	0	2	615	0	0	0	0	0	0
chr15:90631935	IDH2	p.R140	G	0	0	394	0	0	452	0	0	0	649	1	0	0	0	0	0
chr15:90631938	IDH2	p.I139	T	0	0	0	363	0	0	1	503	0	0	1	675	0	0	0	0
chr16:88848086	CDH1	p.E333	G	0	0	725	0	0	0	795	0	0	802	0	0	0	0	0	0
chr16:88848137	CDH1	p.D370	G	0	0	674	0	0	0	747	1	0	0	625	2	0	0	0	0
chr16:88847282	CDH1	p.D402	G	1	0	436	2	0	0	509	1	0	0	423	1	0	0	0	0
chr17:2956931	NF1	p.E977	G	0	0	586	0	0	0	621	0	0	0	643	0	0	0	0	0
chr17:2956932	NF1	p.E977	A	541	2	0	0	602	1	0	0	594	2	0	0	0	0	0	0
chr17:2956933	NF1	p.E977	A	572	0	0	0	645	0	0	0	616	2	0	0	0	0	0	0
chr17:37872775	ERBB2	p.R522	A	178	1	0	0	121	0	0	0	250	0	0	0	0	0	0	0
chr17:37872776	ERBB2	p.R522	G	0	0	199	0	0	0	136	0	0	0	262	0	0	0	0	0
chr17:37872777	ERBB2	p.R522	G	0	0	188	0	0	0	139	0	0	0	258	0	0	0	0	0
chr17:37880219	ERBB2	p.L755	T	0	0	125	0	0	0	1	175	0	0	1	195	0	0	0	0
chr17:37880220	ERBB2	p.L755	T	0	0	0	129	0	0	1	173	0	0	1	213	0	0	0	0
chr17:37880257	ERBB2	p.I767	C	0	101	0	0	0	168	0	0	0	161	0	0	0	0	0	0
chr17:37880261	ERBB2	p.D769	G	0	0	96	0	0	0	143	2	0	0	157	0	0	0	0	0
chr17:37880987	ERBB2	p.G776	G	1	0	160	0	0	0	182	0	0	0	151	0	0	0	0	0
chr17:37880988	ERBB2	p.G776	C	0	0	172	0	0	0	178	0	0	0	156	0	0	0	0	0
chr17:37881000	ERBB2	p.V777	G	0	0	174	0	0	0	182	0	0	0	165	0	0	0	0	0
chr17:37881001	ERBB2	p.V777	T	0	0	1	137	0	0	0	159	0	0	123	0	0	0	0	0
chr17:37881332	ERBB2	p.H842	G	0	0	181	0	0	0	215	0	0	0	222	0	0	0	0	0
chr17:37881440	ERBB2	p.H878	C	0	0	176	0	2	176	203	0	0	182	0	0	0	0	0	0
chr17:7573931	TP53	p.S366	A	255	0	0	0	176	0	0	0	201	0	0	1	0	0	0	0
chr17:7573961	TP53	p.G356	C	0	304	0	0	0	243	0	0	0	257	0	0	0	0	0	0
chr17:7573966	TP53	p.Q354	T	0	0	301	0	0	0	0	241	0	0	0	231	0	0	0	0
chr17:7573982	TP53	p.E349	C	1	328	0	0	1	266	0	0	0	276	0	0	0	0	0	0
chr17:7573983	TP53	p.E349	C	0	328	0	0	0	276	0	0	0	267	0	0	0	0	0	0
chr17:7573984	TP53	p.L348	A	299	1	0	1	266	0	0	0	259	2	0	0	0	0	0	0
chr17:7573986	TP53	p.L344	A	303	0	0	0	283	0	0	0	262	0	0	0	0	0	0	0
chr17:7574000	TP53	p.E343	C	0	321	0	0	0	283	0	0	0	280	0	0	0	0	0	0
chr17:7574002	TP53	p.R342	C	0	303	0	0	2	276	0	0	0	289	0	0	0	0	0	0
chr17:7574003	TP53	p.R342	C	0	0	285	0	0	0	0	253	0	0	272	0	0	0	0	0
chr17:7574012	TP53	p.E339	C	0	281	0	0	1	283	0	0	0	270	0	0	0	0	0	0
chr17:7574017	TP53	p.R337	C	0	278	0	0	1	257	0	0	0	253	0	0	0	0	0	0
chr17:7574018	TP53	p.R337	G	0	0	280	0	0	1	270	0	0	0	268	0	0	0	0	0
chr17:7574021	TP53	p.E336	C	0	271	0	0	2	285	0	0	0	268	0	0	0	0	0	0
chr17:7574026	TP53	p.G334	C	0	272	0	0	1	260	0	0	0	264	0	0	0	0	0	0
chr17:7574022	TP53	p.R306	G	0	535	2	0	0	477	1	0	0	524	2	0	0	0	0	0
chr17:7574023	TP53	p.K305	C	0	530	0	0	0	478	0	0	1	553	0	0	0	0	0	0
chr17:7574024	TP53	p.K305	T	0	0	508	0	0	0	0	464	0	0	511	0	0	0	0	0
chr17:7574025	TP53	p.K305	T	3	0	0	504	0	0	0	518	0	0	3	536	0	0	0	0
chr17:7574027	TP53	p.T304	G	0	1	532	0	0	0	500	0	0	0	565	0	0	0	0	0
chr17:7574028	TP53	p.T304	T	1	0	0	492	0	0	0	495	0	0	2	499	0	0	0	0
chr17:7574030	TP53	p.S303	C	1	536	0	0	1	501	1	0	1	586	0	0	0	0	0	0
chr17:7574031	TP53	p.S303	C	0	0	530	0	0	0	0	467	0	0	1	510	0	0	0	0
chr17:7574032	TP53	p.G302	C	0	534	0	1	0	495	0	0	1	559	0	0	0	0	0	0
chr17:7574033	TP53	p.G302	C	0	531	0	0	0	477	0	0	1	542	0	0	0	0	0	0
chr17:7574035	TP53	p.P301	T	0	0	1	532	0	0	0	506	1	0	1	536	0	0	0	0
chr17:7574037	TP53	p.P301	G	0	0	529	0	0	1	474	1	0	0	529	0	0	0	0	0
chr17:7574039	TP53	p.P300	G	0	0	528	1	0	0	501	2	0	0	549	0	0	0	0	0
chr17:7574040	TP53	p.P300	G	0	0	540	0	0	0	528	0	0	0	545	3	0	0	0	0
chr17:7574045	TP53	p.E298	T	0	0	0	498	0	0	0	494	0	0	0	481	0	0	0	0
chr17:7574046	TP53	p.E298	C	0	561	0	0	0	528	1	0	1	536	0	0	0	0	0	0
chr17:7574049	TP53	p.H297	G	0	0	538	0	0	0	524	0	0	0	489	0	0	0	0	0
chr17:7574050	TP53	p.H296	G	0	0	569	0	0	0	541	0	0	0	538	0	0	0	0	0
chr17:7574051	TP53	p.H296	T	0	0	1	499	0	0	3	494	0	0	1	438	0	0	0	0
chr17:7574052	TP53	p.H296	G	0	0	572	0	1	508	1	0	538	1	0	0	0	0	0	0
chr17:7574053	TP53	p.P295	A	528	0	0	0	495	2	0	0	494	1	0	0	0	0	0	0
chr17:7574054	TP53	p.P295	G	0	0	572	0	1	507	0	0	522	0	0	0	0	0	0	0
chr17:7574055	TP53	p.P295	G	0	0	578	0	1	0	535	0	0	0	539	0	0	0	0	0
chr17:7574056	TP53	p.E294	C	0	586	0	0	0	537	1	0	0	536	0	0				

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS												
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2	
chr17:757113	TP53	p.C275	A	448	0	0	0	465	3	0	0	456	1	0	0	1
chr17:757114	TP53	p.C275	C	1	486	0	0	0	493	0	0	0	521	0	0	0
chr17:757115	TP53	p.C275	A	454	0	0	0	461	0	0	0	467	0	0	0	0
chr17:757116	TP53	p.V274	A	441	0	0	0	481	0	0	0	473	0	0	0	0
chr17:757117	TP53	p.V274	A	438	0	0	0	450	1	0	0	479	3	0	0	1
chr17:757118	TP53	p.V274	C	1	485	0	0	0	479	0	0	1	500	0	0	0
chr17:757120	TP53	p.R273	C	4	464	0	0	1	444	0	0	2	491	0	0	0
chr17:757121	TP53	p.R273	G	1	0	445	0	0	0	425	1	0	0	454	1	0
chr17:757123	TP53	p.V272	A	386	0	0	1	415	1	1	0	398	0	0	0	0
chr17:757124	TP53	p.V272	C	0	452	2	0	0	436	0	0	0	495	0	0	0
chr17:757125	TP53	p.E271	C	0	461	0	0	2	452	0	0	0	464	0	0	0
chr17:757126	TP53	p.E271	T	0	0	0	434	0	0	1	442	0	0	0	0	472
chr17:757127	TP53	p.E271	C	0	459	0	0	1	438	0	0	1	468	0	0	0
chr17:757128	TP53	p.F270	A	442	0	0	0	451	0	0	0	459	2	0	0	0
chr17:757129	TP53	p.F270	A	420	1	0	1	402	0	0	0	460	1	0	0	0
chr17:757130	TP53	p.F270	A	434	1	0	0	388	0	0	0	470	2	0	0	0
chr17:757131	TP53	p.S269	G	0	0	470	0	0	0	426	0	0	0	497	1	0
chr17:757132	TP53	p.S269	C	0	454	0	0	1	433	0	0	0	489	0	0	0
chr17:757133	TP53	p.S269	T	0	0	1	436	0	0	1	412	0	0	0	0	457
chr17:757134	TP53	p.N268	G	0	0	440	0	0	0	415	0	0	0	452	1	0
chr17:757136	TP53	p.N268	T	1	0	0	401	0	0	1	410	0	0	1	452	0
chr17:757137	TP53	p.R267	C	1	445	1	0	1	394	0	0	2	456	0	0	0
chr17:757138	TP53	p.R267	C	1	434	0	0	0	375	0	0	2	429	0	0	0
chr17:757139	TP53	p.R267	G	0	0	452	0	0	0	392	0	0	0	462	1	0
chr17:757141	TP53	p.G266	C	0	447	0	0	2	421	0	0	1	458	0	0	0
chr17:757142	TP53	p.G266	G	0	418	0	0	0	403	0	0	0	446	0	0	0
chr17:757144	TP53	p.L265	A	424	0	0	0	447	0	0	0	444	1	0	0	0
chr17:757145	TP53	p.L265	G	0	0	444	0	0	0	423	1	0	0	460	0	0
chr17:757151	TP53	p.L256	T	0	0	0	306	0	0	0	338	0	0	1	365	0
chr17:757157	TP53	p.L255	A	356	1	0	0	410	0	0	0	414	0	0	2	0
chr17:757158	TP53	p.L255	T	0	0	0	334	0	0	2	363	0	0	2	397	0
chr17:757159	TP53	p.L254	A	356	0	0	0	397	0	0	0	408	2	0	0	0
chr17:757161	TP53	p.L254	T	0	0	1	341	0	0	2	359	0	0	1	389	0
chr17:757162	TP53	p.L253	G	0	0	372	1	0	0	372	0	0	0	408	0	0
chr17:757163	TP53	p.L253	G	0	0	381	0	0	0	368	0	0	0	446	0	0
chr17:757164	TP53	p.L253	T	0	0	1	303	0	0	1	340	0	0	2	365	0
chr17:757166	TP53	p.L252	A	370	0	0	0	389	0	0	0	427	3	0	0	0
chr17:757167	TP53	p.L252	G	1	0	406	1	0	0	394	0	0	1	445	1	0
chr17:757168	TP53	p.L251	G	0	0	396	0	0	0	388	0	0	0	450	2	0
chr17:757169	TP53	p.L251	A	370	1	0	0	377	0	0	0	434	1	0	0	0
chr17:757170	TP53	p.L251	T	0	0	0	333	0	0	1	344	0	0	2	394	0
chr17:757171	TP53	p.P250	G	0	0	376	0	0	0	388	1	1	1	422	0	0
chr17:757172	TP53	p.P250	G	0	1	382	0	0	1	393	1	0	0	440	0	0
chr17:757173	TP53	p.P250	G	0	0	409	0	0	0	400	2	0	0	454	5	0
chr17:757174	TP53	p.R249	C	0	0	376	0	0	0	412	0	0	1	458	1	0
chr17:757175	TP53	p.R249	C	0	0	377	0	0	0	380	0	0	0	429	0	0
chr17:757176	TP53	p.R249	T	0	0	2	349	0	0	1	370	0	0	2	406	0
chr17:757177	TP53	p.R248	C	0	367	0	0	0	386	0	0	0	436	0	0	0
chr17:757178	TP53	p.R248	C	0	0	371	0	0	3	380	0	0	0	442	3	0
chr17:757179	TP53	p.R248	G	0	0	400	1	0	0	368	0	0	0	457	2	0
chr17:757180	TP53	p.N247	G	0	0	403	0	0	0	405	3	0	0	487	1	0
chr17:757181	TP53	p.N247	T	0	0	0	312	0	0	1	332	0	2	4	357	0
chr17:757182	TP53	p.N247	T	0	0	0	325	0	0	0	364	0	0	3	445	0
chr17:757183	TP53	p.M246	C	0	383	0	0	0	401	0	0	2	455	0	0	0
chr17:757184	TP53	p.M246	A	368	0	0	1	371	1	0	0	424	1	0	0	0
chr17:757185	TP53	p.M246	T	0	0	0	381	0	0	0	407	0	0	1	471	0
chr17:757186	TP53	p.G245	G	0	0	410	0	0	0	427	0	2	0	469	1	0
chr17:757187	TP53	p.G245	C	1	377	0	0	0	1	394	0	0	0	452	0	0
chr17:757188	TP53	p.G245	C	1	369	0	0	4	387	0	1	0	0	471	0	0
chr17:757189	TP53	p.G244	G	0	0	383	1	0	0	389	0	0	0	463	2	0
chr17:757190	TP53	p.G244	C	0	392	0	0	1	397	0	0	1	480	0	0	0
chr17:757191	TP53	p.G244	C	0	349	0	0	0	387	0	0	0	425	0	0	0
chr17:757192	TP53	p.M243	C	0	359	0	0	0	371	0	0	0	1	445	0	0
chr17:757193	TP53	p.M243	A	341	0	0	1	369	0	0	0	431	0	0	0	0
chr17:757194	TP53	p.M243	T	0	0	1	347	0	0	0	364	1	0	0	444	0
chr17:757195	TP53	p.C242	G	0	0	380	0	0	0	391	0	0	0	456	0	0
chr17:757196	TP53	p.C242	G	0	0	368	0	0	0	376	0	1	0	459	0	0
chr17:757197	TP53	p.C242	A	364	0	0	1	400	0	0	0	458	0	0	0	0
chr17:757198	TP53	p.S241	G	0	0	397	0	0	0	386	0	2	0	465	1	0
chr17:757199	TP53	p.S241	G	0	0	376	1	0	0	392	0	0	0	476	1	0
chr17:757200	TP53	p.S241	A	368	1	0	0	398	0	0	0	437	0	3	0	0
chr17:757201	TP53	p.S240	A	334	0	1	0	373	2	0	0	399	1	0	0	0
chr17:757202	TP53	p.S240	C	0	371	0	0	0	406	0	0	0	1	495	0	0
chr17:757203	TP53	p.S240	T	2	0	1	365	0	0	0	406	0	0	0	479	0
chr17:757204	TP53	p.N239	G	0	0	382	0	0	0	408	0	0	0	496	0	0
chr17:757205	TP53	p.N239	T	0	0	0	355	0	0	1	358	0	0	1	453	0
chr17:757206	TP53	p.N239	T	0	0	0	359	0	0	1	420	0	0	0	498	0
chr17:757207	TP53	p.C238	A	356	0	0	0	412	0	0	0	479	1	0	0	2
chr17:757208	TP53	p.C238	C	0	351	0	0	0	384	0	0	3	471	0	0	1
chr17:757209	TP53	p.C238	A	343	0	0	1	385	0	0	0	496	0	0	0	0
chr17:757210	TP53	p.M237	C	0	347	0	0	0	359	0	0	2	467	0	0	0
chr17:757211	TP53	p.M237	A	345	0	0	1	402	0	0	0	480	2	0	0	0
chr17:757212	TP53	p.M237	T	0	0	0	357	0	0	1	413	0	0	0	448	0
chr17:757213	TP53	p.Y236	G	0	0	374	0	0	1	393	0	0	0	481	0	0
chr17:757214	TP53	p.Y236	T	1	0	0	347	0	0	0	392	0	0	3	478	0
chr17:757215	TP53	p.Y236	A	347	0	0	0	403	0	0	0	472	0	0	0	0
chr17:757216	TP53	p.N235	T	0	0	0	319	0	0	0	352	0	1	3	438	0
chr17:757217	TP53	p.N235	T	0	0	1	329	0	0	1	375	0	0	2	463	0
chr17:757218	TP53	p.Y234	G	0	0	364	0	0	0	411	1	0	0	492	0	0
chr17:757219	TP53	p.Y234	T	0	0	359	0	0	0	398	0	0	0	449	0	0
chr17:757220	TP53	p.Y234	A	335	0	0	0	391	0	0	0	458	0	0	0	0
chr17:757221	TP53	p.H233	G	0	0	380	0	0	0	418	2	0	0	498	0	0
chr17:757222	TP53	p.H233	T	0	0	0	289	0	0	0	367	2	0	2	409	0
chr17:757223	TP53	p.H233	G	0	0	354	0	0	0	403	0	0	0	450	1	0
chr17:757224	TP53	p.L232	A	316	0	0	0	379	0	0	0	439	1	0	0	0
chr17:757225	TP53	p.L232	T	0	0	1	290	0	0	1	35					

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS											
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB			
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2
chr17:7578213	TP53	p.F212	A	497	0	0	0	610	0	0	0	563	0	0	0
chr17:7578214	TP53	p.F212	A	492	0	0	0	575	0	0	0	537	0	0	0
chr17:7578215	TP53	p.F212	A	479	0	0	0	566	0	0	0	530	0	0	0
chr17:7578216	TP53	p.T211	A	450	0	0	0	579	0	0	0	533	0	1	0
chr17:7578217	TP53	p.T211	G	0	0	491	1	0	0	557	1	0	0	541	2
chr17:7578218	TP53	p.T211	T	0	0	0	466	0	0	1	561	0	0	1	519
chr17:7578220	TP53	p.N210	T	0	0	4	420	0	0	0	521	2	0	1	494
chr17:7578223	TP53	p.R209	C	0	524	0	0	0	0	592	0	0	570	0	0
chr17:7578224	TP53	p.R209	T	1	2	0	488	1	0	1	593	0	0	1	570
chr17:7578225	TP53	p.D208	G	0	0	491	0	0	0	579	0	0	0	557	1
chr17:7578226	TP53	p.D208	T	0	0	0	457	0	0	2	549	0	0	0	519
chr17:7578227	TP53	p.D208	C	1	501	0	0	0	0	576	0	0	549	1	0
chr17:7578229	TP53	p.R207	T	0	1	0	490	0	0	0	598	0	0	1	602
chr17:7578232	TP53	p.L206	A	493	1	0	0	609	0	0	0	628	0	0	0
chr17:7578234	TP53	p.Y205	A	486	0	0	0	579	2	0	0	590	2	0	0
chr17:7578235	TP53	p.Y205	T	1	0	0	515	0	0	1	610	0	0	0	608
chr17:7578236	TP53	p.Y205	A	472	0	0	0	563	0	0	0	614	1	0	0
chr17:7578237	TP53	p.E204	C	0	536	0	0	2	596	0	0	0	639	0	0
chr17:7578238	TP53	p.E204	T	0	0	0	505	0	0	0	594	0	1	0	611
chr17:7578239	TP53	p.E204	C	0	513	0	0	3	560	0	0	1	593	0	0
chr17:7578240	TP53	p.V203	C	0	500	0	0	0	546	0	0	2	562	0	0
chr17:7578241	TP53	p.V203	A	420	1	0	0	494	1	0	1	533	1	0	1
chr17:7578242	TP53	p.V203	C	1	525	0	0	0	574	0	0	1	600	0	0
chr17:7578243	TP53	p.R202	A	425	1	0	1	515	0	0	0	528	2	0	0
chr17:7578244	TP53	p.R202	C	2	534	0	0	0	568	0	0	2	602	0	0
chr17:7578245	TP53	p.R202	G	0	0	484	0	0	0	539	5	0	0	551	1
chr17:7578246	TP53	p.L201	C	0	536	0	0	0	577	0	0	0	611	0	0
chr17:7578250	TP53	p.N200	T	1	0	0	494	0	0	0	582	1	0	2	636
chr17:7578252	TP53	p.G199	T	0	0	0	517	1	0	0	609	0	0	0	642
chr17:7578253	TP53	p.G199	C	1	529	0	0	1	588	0	0	2	646	0	0
chr17:7578254	TP53	p.G199	C	0	515	0	0	0	582	0	0	2	591	0	0
chr17:7578257	TP53	p.E198	C	0	521	0	0	0	547	0	0	1	611	0	0
chr17:7578258	TP53	p.V197	C	0	502	0	0	1	517	0	0	0	581	0	1
chr17:7578259	TP53	p.V197	A	429	2	0	0	485	2	0	0	561	2	0	0
chr17:7578260	TP53	p.V197	C	0	495	0	0	0	518	0	0	0	634	0	0
chr17:7578261	TP53	p.R196	T	0	0	0	492	0	0	0	553	0	0	0	623
chr17:7578262	TP53	p.R196	C	0	502	0	0	0	520	0	0	2	595	0	0
chr17:7578263	TP53	p.R196	G	0	0	478	1	0	0	496	0	0	0	568	1
chr17:7578264	TP53	p.I195	G	0	0	473	1	0	0	503	0	0	0	608	0
chr17:7578265	TP53	p.I195	A	476	0	0	0	568	0	0	0	659	1	0	0
chr17:7578266	TP53	p.I195	T	1	0	2	470	0	0	0	539	0	0	0	626
chr17:7578267	TP53	p.L194	A	456	0	0	0	543	0	0	0	622	0	0	0
chr17:7578268	TP53	p.L194	A	464	1	0	2	547	0	0	0	644	1	0	1
chr17:7578269	TP53	p.L194	G	0	0	483	1	0	0	528	0	0	0	651	0
chr17:7578270	TP53	p.H193	A	458	0	2	0	506	2	0	0	642	6	0	0
chr17:7578271	TP53	p.H193	T	2	0	0	449	0	0	0	531	0	1	0	651
chr17:7578272	TP53	p.H193	G	0	0	487	2	0	0	503	0	0	0	656	2
chr17:7578273	TP53	p.O192	C	0	508	0	0	2	509	0	0	1	652	0	0
chr17:7578274	TP53	p.O192	T	1	0	1	432	0	0	1	480	0	0	4	602
chr17:7578275	TP53	p.O192	G	0	1	1	487	0	0	0	526	0	0	0	658
chr17:7578277	TP53	p.P191	G	1	0	0	484	0	0	0	499	0	0	0	674
chr17:7578278	TP53	p.P191	G	0	1	491	0	0	0	499	0	0	0	665	0
chr17:7578280	TP53	p.P190	C	0	0	486	0	0	0	505	0	0	0	619	0
chr17:7578281	TP53	p.P190	C	0	0	471	0	0	0	470	1	0	0	581	0
chr17:7578282	TP53	p.A189	G	0	0	491	1	0	0	486	1	0	1	632	1
chr17:7578283	TP53	p.A189	G	0	0	476	0	1	0	510	0	0	0	651	3
chr17:7578284	TP53	p.A189	C	3	483	0	0	1	507	0	0	1	654	0	0
chr17:7578289	TP53	p.E189	C	1	489	0	0	1	487	0	0	0	672	0	0
chr17:7578371	TP53	p.G187	C	0	441	0	0	2	459	0	0	0	550	0	0
chr17:7578372	TP53	p.D186	A	418	1	0	0	435	0	0	0	507	2	0	1
chr17:7578374	TP53	p.D186	C	1	465	0	0	0	482	0	0	1	587	0	0
chr17:7578375	TP53	p.S185	G	0	469	0	0	0	469	0	0	0	572	0	0
chr17:7578377	TP53	p.S185	T	0	1	0	452	0	0	1	499	0	0	0	575
chr17:7578378	TP53	p.D184	A	443	2	0	0	500	0	0	0	550	1	0	0
chr17:7578380	TP53	p.D184	C	0	457	0	0	0	485	0	0	0	585	0	0
chr17:7578382	TP53	p.S183	G	0	0	436	0	0	0	484	0	0	0	538	1
chr17:7578383	TP53	p.S183	A	411	0	1	456	0	1	0	0	468	3	0	0
chr17:7578384	TP53	p.C182	G	0	471	0	0	0	0	474	0	0	0	536	2
chr17:7578385	TP53	p.C182	C	0	468	0	0	0	486	0	0	0	566	0	0
chr17:7578386	TP53	p.C182	A	434	0	0	0	467	1	0	0	525	0	0	0
chr17:7578387	TP53	p.R181	C	0	0	470	1	0	0	469	2	0	0	557	0
chr17:7578388	TP53	p.R181	C	1	459	0	1	0	459	0	0	0	537	0	0
chr17:7578389	TP53	p.R181	G	0	0	440	0	0	0	407	0	0	0	492	0
chr17:7578390	TP53	p.E180	C	0	452	0	0	0	479	0	0	1	565	0	0
chr17:7578392	TP53	p.E180	C	2	437	0	0	0	492	0	0	0	529	0	0
chr17:7578393	TP53	p.H179	A	455	1	0	0	0	503	0	0	543	0	1	0
chr17:7578394	TP53	p.H179	T	0	0	0	438	0	0	1	504	0	0	3	546
chr17:7578395	TP53	p.H179	G	0	0	447	0	0	0	469	0	0	0	537	0
chr17:7578396	TP53	p.H178	T	0	0	454	0	0	0	479	1	0	0	527	1
chr17:7578397	TP53	p.H178	G	0	0	438	1	0	0	470	1	0	0	519	401
chr17:7578398	TP53	p.H178	G	0	0	439	0	0	0	483	1	0	0	511	17
chr17:7578399	TP53	p.P177	G	0	0	445	1	0	0	459	0	0	0	475	1
chr17:7578400	TP53	p.P177	G	0	0	431	0	0	0	443	1	0	0	465	0
chr17:7578401	TP53	p.P177	G	0	0	444	0	0	2	467	0	0	0	508	0
chr17:7578402	TP53	p.C176	G	0	0	448	0	0	0	478	1	0	0	503	0
chr17:7578403	TP53	p.C176	C	2	450	0	0	0	0	478	0	0	0	512	0
chr17:7578404	TP53	p.C176	A	406	0	0	0	459	3	0	0	425	4	0	0
chr17:7578405	TP53	p.R175	G	1	0	449	0	0	0	476	1	0	0	483	0
chr17:7578406	TP53	p.R175	C	1	457	0	0	2	463	0	0	0	478	0	0
chr17:7578407	TP53	p.R175	G	0	0	434	0	0	0	470	0	0	0	464	0
chr17:7578408	TP53	p.R174	C	0	430	0	0	0	448	0	0	0	518	0	1
chr17:7578409	TP53	p.R174	C	0	449	0	0	0	474	0	0	1	506	0	0
chr17:7578410	TP53	p.R174	T	0	0	2	369	0	0	2	431	0	0	1	420
chr17:7578411	TP53	p.V173	C	1	447	0	0	0	507	0	0	0	0	487	0
chr17:7578412	TP53	p.V173	A	417	0	0	0	465	1	0	0	415	3	0	0
chr17:7578413	TP53	p.V173	C	0	433	0	1	1	493	0	0	0	476	0	0
chr17:7578414	TP53	p.V172	A	410	1	0	0	493	0	0	0	443	2	0	1
chr17:7578415	TP53	p.V172	A	370	0	0	0	433	4	0	0	421	2	0	1
chr17:7578416	TP53	p.V172	G	0	444	0	0	0	487	0	0	0	495	0	0
chr17:7578418	TP53	p.E171	T	0	0	0	423	0	0						

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS															
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB							
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2				
chr17:7578455	TP53	p.A159	C	0	362	0	0	0	0	402	0	0	1	0	361	0	0		
chr17:7578456	TP53	p.R158	G	0	0	345	0	0	0	401	0	401	1	0	0	361	1		
chr17:7578457	TP53	p.R158	G	0	334	0	0	0	0	410	0	0	0	0	359	0	0		
chr17:7578458	TP53	p.R158	G	0	0	326	0	0	0	0	386	0	0	0	0	348	1		
chr17:7578459	TP53	p.V157	G	0	0	357	0	0	2	0	436	0	0	0	0	378	0		
chr17:7578460	TP53	p.V157	A	284	1	0	0	0	380	2	0	0	0	302	2	0	0		
chr17:7578461	TP53	p.V157	C	0	334	0	0	0	1	390	0	0	0	0	349	0	0		
chr17:7578462	TP53	p.R156	G	0	0	339	0	0	0	0	392	0	0	0	0	351	0		
chr17:7578463	TP53	p.R156	C	0	326	0	0	0	2	383	0	0	1	320	0	0	0		
chr17:7578464	TP53	p.R156	G	0	0	315	0	0	1	0	351	3	2	0	316	1	1		
chr17:7578465	TP53	p.T155	G	0	0	326	0	0	0	0	377	1	0	0	0	327	1		
chr17:7578466	TP53	p.T155	G	0	0	334	0	0	0	0	398	0	0	0	0	324	0		
chr17:7578467	TP53	p.T155	T	0	0	1	230	0	0	0	1	305	0	0	0	2	219		
chr17:7578468	TP53	p.G154	G	0	0	306	0	0	1	0	390	1	0	0	0	322	0		
chr17:7578469	TP53	p.G154	C	1	284	0	0	0	1	387	0	0	0	0	290	0	0		
chr17:7578470	TP53	p.G154	C	1	279	0	0	0	0	360	0	0	1	293	0	0	0		
chr17:7578471	TP53	p.P153	G	0	0	298	0	0	0	0	340	0	0	0	0	278	0		
chr17:7578472	TP53	p.P153	G	0	0	297	0	0	0	0	379	0	0	0	0	296	0		
chr17:7578473	TP53	p.P153	G	0	0	294	0	0	0	0	369	0	0	0	0	297	0		
chr17:7578474	TP53	p.P152	C	2	284	0	0	0	3	369	0	0	2	312	0	0	0		
chr17:7578475	TP53	p.P152	G	0	0	258	0	0	0	0	294	2	0	0	0	270	0		
chr17:7578476	TP53	p.P152	G	0	0	278	0	0	0	0	360	1	0	0	0	306	0		
chr17:7578477	TP53	p.P151	G	0	0	282	0	0	0	0	351	0	0	0	0	305	0		
chr17:7578523	TP53	p.Q136	T	1	0	0	207	0	0	0	0	330	0	0	0	0	236		
chr17:7578524	TP53	p.Q136	G	0	0	228	0	0	0	0	321	2	0	0	241	2	0		
chr17:7578525	TP53	p.C135	G	0	0	229	0	0	0	0	330	0	0	0	0	243	0		
chr17:7578526	TP53	p.C135	C	0	230	0	0	0	0	332	0	0	0	0	286	0	0		
chr17:7578527	TP53	p.C135	A	210	0	0	0	0	338	0	0	0	0	223	0	0	0		
chr17:7578528	TP53	p.F134	A	204	0	0	0	0	354	0	0	0	0	246	0	0	0		
chr17:7578529	TP53	p.F134	A	202	0	0	0	0	344	0	0	0	0	231	0	0	0		
chr17:7578530	TP53	p.F134	A	193	0	0	0	0	320	0	0	0	0	238	0	0	0		
chr17:7578531	TP53	p.M133	C	0	221	0	0	0	0	337	0	0	0	1	251	0	0		
chr17:7578532	TP53	p.M133	A	205	0	0	0	0	337	0	0	0	0	260	0	0	0		
chr17:7578534	TP53	p.K132	C	0	210	0	0	0	0	343	0	0	0	0	258	0	0		
chr17:7578535	TP53	p.K132	T	0	0	206	0	0	0	0	0	347	0	0	0	0	264		
chr17:7578536	TP53	p.K132	T	0	0	0	194	0	0	0	0	0	340	0	0	1	253		
chr17:7578538	TP53	p.N131	T	0	0	1	177	0	0	0	1	326	0	0	0	0	259		
chr17:7578539	TP53	p.N131	T	0	0	1	184	0	0	0	0	319	0	0	0	0	255		
chr17:7578540	TP53	p.L130	G	0	0	197	0	0	0	0	322	0	0	0	0	259	0		
chr17:7578541	TP53	p.L130	A	193	0	0	0	0	327	0	0	0	0	251	0	0	0		
chr17:7578542	TP53	p.L130	G	0	0	206	0	0	0	0	318	0	0	0	0	244	0		
chr17:7578544	TP53	p.A129	G	0	0	214	0	0	0	0	311	0	0	0	0	261	0		
chr17:7578545	TP53	p.A129	C	0	203	0	0	0	0	303	0	0	0	0	249	0	0		
chr17:7578547	TP53	p.F128	G	0	0	204	0	0	0	204	0	0	0	0	0	265	0		
chr17:7578548	TP53	p.F128	G	0	0	201	1	0	0	0	307	0	0	0	0	243	1		
chr17:7578549	TP53	p.S127	G	0	0	191	1	0	0	0	310	0	0	0	0	248	0		
chr17:7578550	TP53	p.S127	G	0	1	187	0	0	0	0	303	0	0	0	0	268	0		
chr17:7578551	TP53	p.S127	A	179	0	0	0	0	317	0	0	0	0	258	1	0	0		
chr17:7578552	TP53	p.Y126	T	0	0	190	0	0	0	0	310	0	0	0	0	275	0		
chr17:7578553	TP53	p.Y126	T	0	0	1	169	0	0	0	0	0	297	0	0	5	249		
chr17:7578554	TP53	p.Y126	A	177	0	0	0	0	322	0	0	0	0	0	260	0	0		
chr17:7579358	TP53	p.R110	C	0	261	2	0	0	0	251	1	0	0	1	216	0	0		
chr17:7579359	TP53	p.R110	G	0	0	246	0	0	0	0	236	1	0	0	0	207	0		
chr17:7579361	TP53	p.F109	A	230	0	0	0	0	257	0	0	0	0	184	1	0	0		
chr17:7579365	TP53	p.G108	C	0	263	0	0	0	1	237	0	0	0	1	192	0	0		
chr17:7579366	TP53	p.Y107	G	0	0	268	0	0	0	0	248	0	0	0	0	199	1		
chr17:7579368	TP53	p.Y107	A	237	0	0	0	0	241	0	0	0	0	193	1	0	0		
chr17:7579369	TP53	p.S106	G	0	0	267	0	0	0	0	253	1	0	0	0	214	0		
chr17:7579374	TP53	p.G105	C	0	224	1	0	0	0	219	0	0	0	1	178	0	0		
chr17:7579377	TP53	p.Q104	G	0	0	242	0	0	0	0	239	1	0	0	0	186	1		
chr17:7579378	TP53	p.Y103	G	0	0	252	0	0	0	0	235	0	0	0	0	199	0		
chr17:7579382	TP53	p.T102	G	0	0	252	0	0	0	0	0	231	2	0	0	189	1		
chr17:7579385	TP53	p.K101	T	0	0	0	245	0	0	0	0	0	225	0	0	0	162		
chr17:7579389	TP53	p.Q100	G	0	0	266	0	0	0	0	227	1	0	0	0	194	1		
chr17:7579391	TP53	p.S99	G	0	0	254	0	0	0	0	213	0	0	0	0	185	0		
chr17:7579394	TP53	p.F98	G	0	0	262	0	0	0	0	226	0	0	0	0	202	0		
chr17:7579395	TP53	p.F98	G	0	0	262	0	0	0	0	223	1	0	0	0	189	1		
chr17:7579400	TP53	p.S96	G	0	0	256	0	0	0	0	209	0	0	0	0	206	0		
chr17:7579403	TP53	p.S95	G	0	0	250	1	0	0	0	225	1	0	0	0	208	0		
chr17:7579406	TP53	p.S94	G	0	0	250	0	0	0	0	212	0	0	0	0	186	1		
chr17:7579407	TP53	p.S94	A	205	1	0	0	0	160	2	0	0	0	150	1	0	0		
chr17:7579414	TP53	p.W91	C	0	265	0	0	0	0	226	0	0	0	0	0	199	0		
chr17:7579415	TP53	p.W91	C	0	236	0	0	0	0	223	0	0	0	0	0	175	0		
chr17:7579422	TP53	p.F89	G	0	0	268	0	0	0	0	231	0	0	0	0	180	0		
chr17:7579427	TP53	p.F87	G	0	0	264	0	0	1	0	245	1	0	0	0	181	0		
chr17:7579434	TP53	p.F85	G	0	0	286	0	0	0	0	266	0	0	0	0	196	0		
chr17:7579436	TP53	p.A84	G	0	0	256	0	0	0	0	238	0	0	0	0	187	0		
chr17:7579442	TP53	p.F82	G	0	0	283	0	0	0	0	248	0	0	0	0	177	0		
chr17:7579445	TP53	p.T81	G	0	0	253	0	0	0	0	258	0	0	0	0	198	0		
chr17:7579454	TP53	p.A78	G	0	0	264	0	0	0	0	242	0	0	0	0	167	0		
chr17:7579458	TP53	p.F77	G	0	0	276	0	0	1	0	249	0	0	0	0	197	0		
chr17:7579463	TP53	p.P75	G	0	0	301	0	0	0	0	280	0	0	0	0	219	0		
chr17:7579470	TP53	p.V73	C	0	216	0	0	0	0	222	1	0	0	0	0	177	0		
chr17:7579472	TP53	p.R72	G	0	76	231	0	0	0	82	221	0	0	0	61	168	0		
chr17:7579473	TP53	p.R72	C	0	0	320	0	0	0	0	0	325	0	0	0	237	0		
chr17:7579882	TP53	p.E11	C	0	439	0	0	0	0	467	0	0	0	0	313	0	0		
chr18:48575159	SMAD4	p.A118	C	0	247	0	0	0	0	255	0	1	0	0	267	1	0		
chr18:48575671	SMAD4	p.S144	C	0	169	0	0	1	257	0	0	0	0	0	145	0	0		
chr18:48581198	SMAD4	p.C168	G	0	0	209	0	0	0	0	163	0	0	0	0	243	0		
chr18:48584600	SMAD4	p.Q245	C	1	282	0	0	0	0	294	0	0	0	0	344	0	0		
chr18:48582622	SMAD4	p.Q311	C	0	258	0	0	0	0	255	0	0							

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS											
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB			
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2
chr1:115256529	NRAS	p.Q61	T	1	0	0	271	0	0	0	285	0	0	0	333
chr1:115256530	NRAS	p.Q61	G	0	0	270	0	0	0	260	0	0	0	310	0
chr1:115256531	NRAS	p.Q60	T	0	0	0	253	0	0	0	269	0	0	0	319
chr1:115256532	NRAS	p.Q60	C	0	264	0	0	0	0	255	0	0	0	296	0
chr1:115256728	NRAS	p.A18	T	1	0	1	404	0	0	1	524	0	2	3	652
chr1:115256729	NRAS	p.A18	G	0	0	454	0	0	0	557	0	0	0	733	0
chr1:115256730	NRAS	p.A18	C	1	444	0	0	0	530	0	2	0	0	679	0
chr1:115256743	NRAS	p.G13	A	382	0	0	0	0	513	4	0	0	0	650	5
chr1:115256744	NRAS	p.G13	C	0	0	0	0	0	577	0	1	0	0	749	0
chr1:115256745	NRAS	p.G13	C	0	0	458	0	0	3	555	0	0	0	674	0
chr1:115256746	NRAS	p.G12	A	381	1	0	0	0	521	1	0	0	0	607	3
chr1:115256747	NRAS	p.G12	C	3	457	0	0	0	1	571	0	0	0	722	0
chr1:115256748	NRAS	p.G12	C	0	477	0	0	0	2	560	0	0	0	712	0
chr1:115256751	NRAS	p.A11	C	0	472	0	0	0	0	570	0	0	0	722	0
chr1:43814979	MPL	p.S505	G	0	0	166	0	0	0	164	0	0	0	234	0
chr1:43814981	MPL	p.A506	G	0	0	168	0	0	0	158	0	0	0	252	0
chr1:43815008	MPL	p.W515	T	0	0	1	140	0	0	0	1	0	0	1	151
chr1:43815009	MPL	p.W515	G	0	0	171	0	0	0	170	0	0	0	186	0
chr1:43815010	MPL	p.W515	G	0	0	165	0	0	0	164	0	0	0	182	0
chr1:43815020	MPL	p.A519	G	0	0	157	0	0	0	153	0	0	0	138	0
chr20:57484162	SRG	p.G531	C	0	249	0	0	0	1	258	0	0	0	307	0
chr20:57484420	GNAS	p.R201	C	0	665	0	0	0	4	793	0	0	0	927	0
chr20:57484421	GNAS	p.R201	G	0	0	687	0	0	0	1	819	3	0	1	973
chr20:57484595	GNAS	p.Q227	C	0	687	0	0	0	0	768	1	0	1	979	0
chr20:57484596	GNAS	p.Q227	A	641	2	0	0	0	738	0	0	0	0	919	5
chr20:57484597	GNAS	p.Q227	G	0	0	710	0	0	0	771	0	0	1	1023	1
chr20:57484615	GNAS	p.K233	G	0	0	708	0	0	0	764	1	0	0	1089	0
chr22:24133967	SMARCB1	p.R40	C	0	502	0	0	0	0	446	0	1	0	732	0
chr22:24133990	SMARCB1	p.Y47	C	0	578	0	0	0	1	557	0	0	0	0	0
chr22:24134006	SMARCB1	p.N53	G	0	595	0	0	0	2	544	0	0	0	876	0
chr22:24134320	SMARCB1	p.R158	C	0	355	0	0	0	0	371	0	0	0	427	0
chr22:24145582	SMARCB1	p.R201	C	0	507	0	0	1	467	0	0	1	0	672	0
chr22:24176339	SMARCB1	p.R377	G	0	0	266	0	0	0	260	0	0	0	533	0
chr2:209113106	IDH1	p.A134	G	0	0	235	0	0	0	343	3	0	1	390	0
chr2:209113108	IDH1	p.R133	A	241	0	0	0	392	0	0	0	400	1	1	1023
chr2:209113111	IDH1	p.R132	A	253	0	0	1	366	1	0	0	0	344	0	0
chr2:209113112	IDH1	p.R132	C	0	293	0	0	1	390	0	0	1	0	379	0
chr2:209113113	IDH1	p.R132	G	0	2	276	0	0	0	0	359	1	0	373	4
chr2:209113117	IDH1	p.L30	T	0	0	0	287	0	0	0	0	414	0	0	386
chr2:209113139	IDH1	p.G123	C	1	393	0	0	1	486	0	0	3	364	0	0
chr2:209113140	IDH1	p.G123	C	1	387	0	0	3	491	0	0	3	357	0	0
chr2:209113151	IDH1	p.R119	C	0	425	0	0	4	477	1	0	0	0	348	0
chr2:209113160	IDH1	p.N116	T	0	0	0	412	0	0	0	0	554	0	0	394
chr2:209113192	IDH1	p.G105	G	0	0	468	0	0	0	443	0	0	0	452	0
chr2:21228940	ERBB4	p.G936	C	0	637	0	0	0	799	0	0	2	0	863	0
chr2:21228942	ERBB4	p.K935	T	1	0	0	635	0	0	0	851	2	0	1	865
chr2:21228955	ERBB4	p.D931	C	0	642	0	0	3	807	0	0	0	0	852	0
chr2:21253006	ERBB4	p.H618	T	0	0	0	447	0	0	1	509	0	0	1	833
chr2:21253135	ERBB4	p.D936	T	0	0	0	1	686	0	0	1	0	0	1	813
chr2:212576857	ERBB4	p.V348	C	0	584	0	0	2	721	0	0	0	0	515	0
chr2:212576877	ERBB4	p.S341	G	0	509	0	0	0	0	680	0	0	0	521	1
chr2:212578341	ERBB4	p.R306	G	0	1	198	0	0	0	338	0	1	0	337	1
chr2:212578349	ERBB4	p.S333	G	0	0	175	0	0	0	343	0	0	0	342	0
chr2:212587147	ERBB4	p.T285	T	0	0	0	556	0	0	2	0	0	0	0	774
chr2:212589811	ERBB4	p.T244	G	0	506	0	0	0	0	631	1	0	0	621	0
chr2:212625674	ERBB4	p.N181	T	1	0	0	461	0	0	0	502	0	0	1	726
chr2:212812157	ERBB4	p.L140	G	0	0	517	0	0	0	1	520	0	0	0	644
chr2:294432664	ALK	p.L1275	C	0	352	0	0	0	0	415	0	0	0	470	0
chr2:29443631	ALK	p.L1196	G	0	0	486	0	0	0	405	0	0	0	557	0
chr2:29443695	ALK	p.F1174	G	0	524	0	0	0	0	539	2	0	0	657	1
chr2:29443696	ALK	p.F1174	A	539	0	0	0	585	0	0	0	692	1	0	0
chr2:29443697	ALK	p.F1174	A	509	0	0	0	568	0	0	0	676	1	0	0
chr3:10183772	VHL	p.R81	C	0	145	0	0	0	217	0	0	0	0	358	0
chr3:10183775	VHL	p.R82	C	0	148	0	0	0	206	0	0	1	0	350	0
chr3:10183776	VHL	p.R82	G	0	151	0	0	0	0	216	0	0	0	338	0
chr3:10183785	VHL	p.L85	T	0	0	0	123	0	0	0	188	0	0	2	290
chr3:10183787	VHL	p.R96	C	0	145	0	0	0	0	211	0	0	0	370	0
chr3:10183788	VHL	p.R96	C	0	146	0	0	0	0	185	0	0	0	361	1
chr3:10183793	VHL	p.W88	T	0	0	0	116	0	1	0	183	0	0	1	286
chr3:10183794	VHL	p.W88	G	0	0	150	0	0	0	203	0	1	0	323	0
chr3:10183795	VHL	p.W88	G	0	0	152	0	0	0	201	0	0	0	333	1
chr3:10183797	VHL	p.L89	T	0	0	0	121	0	0	0	170	0	0	2	242
chr3:10183800	VHL	p.N90	A	120	1	0	0	156	0	0	0	247	1	0	0
chr3:10183808	VHL	p.G93	G	0	0	141	0	0	0	196	0	0	0	327	0
chr3:10183815	VHL	p.P95	C	0	138	0	0	0	0	201	0	0	0	354	0
chr3:10183817	VHL	p.Q26	C	0	145	0	0	0	0	201	0	0	0	367	0
chr3:10183824	VHL	p.Y98	A	95	0	0	0	140	0	0	0	277	4	0	0
chr3:10183825	VHL	p.Y98	C	0	138	0	0	0	0	188	0	0	0	364	0
chr3:10183832	VHL	p.L101	C	0	150	0	0	0	0	181	0	0	0	328	0
chr3:10183833	VHL	p.L101	T	0	0	1	124	0	0	1	0	160	0	0	231
chr3:10188198	VHL	p.G114	G	0	377	0	0	0	0	392	0	0	0	396	0
chr3:10188200	VHL	p.H115	C	0	409	0	0	0	0	412	0	0	0	375	0
chr3:10188206	VHL	p.W117	T	0	0	0	393	0	0	0	474	2	0	0	407
chr3:10188207	VHL	p.W117	G	0	0	413	0	0	0	446	0	0	0	400	0
chr3:10188208	VHL	p.W117	G	0	0	400	0	0	0	421	0	0	0	394	2
chr3:10188210	VHL	p.L118	T	0	0	0	364	0	0	0	0	440	0	0	376
chr3:10188214	VHL	p.F119	C	0	423	0	0	0	461	0	0	0	0	390	0
chr3:10188218	VHL	p.D121	G	0	0	436	0	0	0	461	0	0	0	416	0
chr3:10188219	VHL	p.D121	A	394	0	0	0	429	1	0	1	367	2	0	0
chr3:10188220	VHL	p.D121	T	0	0	407	0	0	0	463	0	0	0	407	0
chr3:10188222	VHL	p.A122	C	0	423	0	0	3	474	1	0	0	0	399	0
chr3:10188234	VHL	p.D126	A	430	0	0	0	505	1	0	0	474	1	0	0
chr3:10188240	VHL	p.L128	T	0	0	391	0	0	0	0	469	1	0	0	472
chr3:10188245	VHL	p.V130	G	0	0	438	1	0	0	0	512	0	0	492	1
chr3:10188250	VHL	p.N131	C	0	465	0	0	0	0	516	0	1	0	488	0
chr3:10188251	VHL	p.O132	C	0	474	0	0	0	0	508	0	0	0	473	0
chr3:10188257	VHL	p.E134	G	0	0	465	0	0	0	0	520	0	0	501	1
chr3:10188263	VHL	p.F136	T	0	0	0	459	0	0	0	564	1	0	0	531
chr3:10188270	VHL	p.F136	C	0	447	0	0	0	0	507	0	0	0	457	0
chr3:10188274	VHL	p.S139	T	0	0	0	463	0	0	1	546	1	0	1	522
chr3:10188286	VHL	p.D143	C	0	460	0	2	1							

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS													
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB					
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2		
chr3:178916875	PIK3CA	p.R88	C	0	299	0	0	1	476	0	0	0	0	0	365	0	0
chr3:178916876	PIK3CA	p.R88	G	0	0	290	0	0	1	467	0	0	0	0	345	1	1
chr3:178916877	PIK3CA	p.R88	A	273	1	0	0	451	0	0	1	358	0	0	1	0	0
chr3:178916890	PIK3CA	p.R93	C	0	251	0	0	0	401	0	0	0	0	297	0	0	
chr3:178916891	PIK3CA	p.R93	G	0	0	242	0	0	1	378	1	0	0	0	293	1	1
chr3:178916892	PIK3CA	p.R93	G	0	0	240	0	0	0	391	1	0	0	0	296	2	2
chr3:178916935	PIK3CA	p.R108	C	0	192	0	0	3	267	0	0	1	248	0	0	0	0
chr3:178916936	PIK3CA	p.R108	G	0	0	187	0	0	0	288	1	0	0	0	254	0	0
chr3:178916937	PIK3CA	p.R108	T	0	0	0	165	0	0	0	307	0	0	0	1	230	0
chr3:178916941	PIK3CA	p.E110	G	0	0	179	0	0	0	300	0	0	0	0	253	0	0
chr3:178916944	PIK3CA	p.K111	A	164	1	0	0	304	0	0	0	232	0	0	0	0	0
chr3:178916945	PIK3CA	p.K111	A	167	0	0	0	305	0	0	0	244	0	0	0	0	0
chr3:178916946	PIK3CA	p.K111	G	0	0	160	0	0	0	296	0	0	0	0	241	0	0
chr3:178916948	PIK3CA	p.I112	T	0	0	0	160	0	0	0	278	0	0	0	1	241	1
chr3:178916957	PIK3CA	p.R115	G	1	0	137	0	0	0	210	1	0	0	0	238	1	1
chr3:178916965	PIK3CA	p.G118	G	0	0	111	0	0	1	173	0	0	0	0	197	2	2
chr3:178917478	PIK3CA	p.G118	G	0	0	300	0	0	0	348	0	0	1	431	0	0	0
chr3:178917479	PIK3CA	p.G118	T	0	0	0	274	0	0	0	344	0	0	0	2	425	0
chr3:178921489	PIK3CA	p.T324	C	0	489	0	0	0	577	0	0	0	0	565	0	0	0
chr3:178921549	PIK3CA	p.V344	T	0	0	0	230	0	0	0	289	0	0	1	405	0	0
chr3:178921551	PIK3CA	p.N345	A	254	0	0	0	319	0	0	0	375	0	0	0	0	0
chr3:178921552	PIK3CA	p.N345	A	225	0	0	0	291	0	0	0	374	0	0	0	0	0
chr3:178921553	PIK3CA	p.N345	T	0	0	0	230	0	0	1	299	1	0	0	365	0	0
chr3:178927451	PIK3CA	p.S405	C	0	206	0	0	0	276	0	0	0	0	289	0	0	0
chr3:178927458	PIK3CA	p.L407	C	0	192	0	0	0	258	0	0	0	0	282	0	0	0
chr3:178927974	PIK3CA	p.E418	G	0	0	114	0	0	0	143	0	0	0	84	1	1	1
chr3:178927980	PIK3CA	p.C420	T	0	0	0	113	0	0	0	171	0	0	0	103	0	0
chr3:178927981	PIK3CA	p.C420	G	0	0	112	0	0	0	165	0	0	0	112	0	0	0
chr3:178927982	PIK3CA	p.C420	T	0	0	0	109	0	0	0	176	0	0	0	113	0	0
chr3:178928079	PIK3CA	p.E453	G	0	0	122	0	0	0	204	0	0	0	181	0	0	0
chr3:178928080	PIK3CA	p.E453	A	126	0	0	0	217	0	0	0	184	1	0	0	0	0
chr3:178928093	PIK3CA	p.N457	C	0	102	0	0	0	1	186	0	0	0	163	0	0	0
chr3:178928118	PIK3CA	p.P466	C	0	88	0	0	2	146	0	0	1	143	0	0	0	0
chr3:178930073	PIK3CA	p.P539	C	0	371	0	0	0	427	0	0	0	0	252	0	0	0
chr3:178936074	PIK3CA	p.P539	C	0	380	0	0	0	425	0	0	0	0	248	0	0	0
chr3:178936075	PIK3CA	p.P539	T	0	0	0	382	0	0	0	439	0	0	1	265	0	0
chr3:178936082	PIK3CA	p.E542	G	0	0	369	0	0	0	446	0	0	0	251	0	0	0
chr3:178936083	PIK3CA	p.E542	A	368	0	0	0	439	0	0	0	252	1	0	0	0	0
chr3:178936084	PIK3CA	p.E542	A	359	0	0	0	444	0	0	0	261	0	0	0	0	0
chr3:178936089	PIK3CA	p.T544	C	0	377	0	0	0	420	0	0	0	245	0	0	0	0
chr3:178936091	PIK3CA	p.E545	G	0	0	368	0	0	0	418	0	0	0	252	0	0	0
chr3:178936092	PIK3CA	p.E545	A	336	0	0	0	403	0	0	0	217	0	0	0	0	0
chr3:178936093	PIK3CA	p.E545	G	0	0	358	0	0	0	402	0	0	0	237	0	0	0
chr3:178936094	PIK3CA	p.O546	C	0	351	0	0	0	390	0	0	0	241	0	0	0	0
chr3:178936095	PIK3CA	p.O546	A	356	0	0	0	437	0	0	0	237	0	0	0	0	0
chr3:178936096	PIK3CA	p.O546	G	0	0	356	0	0	0	408	0	0	0	244	1	1	1
chr3:178936103	PIK3CA	p.D549	G	0	0	351	0	0	0	421	0	0	0	231	1	1	1
chr3:178936104	PIK3CA	p.D549	A	331	0	0	0	0	0	0	0	237	0	0	0	0	0
chr3:178936105	PIK3CA	p.D549	T	0	0	0	317	0	0	0	0	301	0	0	0	205	0
chr3:178938860	PIK3CA	p.H701	A	248	0	0	0	323	0	0	0	252	2	0	0	0	0
chr3:178947827	PIK3CA	p.C901	G	0	2	330	1	0	0	0	428	0	0	0	312	0	0
chr3:178947850	PIK3CA	p.F909	T	0	0	0	344	0	0	0	498	0	0	0	465	0	0
chr3:178947852	PIK3CA	p.F909	C	0	0	355	0	0	0	469	0	0	0	466	0	0	0
chr3:178952004	PIK3CA	p.A1020	C	2	450	0	0	3	554	0	0	0	556	0	0	0	0
chr3:178952006	PIK3CA	p.Y1021	T	0	0	0	454	2	0	0	605	0	0	0	582	0	0
chr3:178952007	PIK3CA	p.Y1021	A	435	0	0	0	611	0	0	0	597	1	0	0	0	0
chr3:178952008	PIK3CA	p.Y1021	C	0	441	0	0	0	578	0	0	1	554	0	0	0	0
chr3:178952013	PIK3CA	p.T023	G	4	0	433	0	0	0	0	527	0	0	0	535	2	2
chr3:178952018	PIK3CA	p.T1025	A	412	0	0	0	496	0	1	0	514	2	0	0	0	0
chr3:178952019	PIK3CA	p.T1025	C	1	439	0	0	0	532	0	0	3	557	0	0	0	0
chr3:178952020	PIK3CA	p.T1025	C	0	416	0	0	2	502	0	0	4	498	0	0	0	0
chr3:178952030	PIK3CA	p.D1029	C	0	0	461	0	0	0	564	0	0	0	576	2	2	2
chr3:178952049	PIK3CA	p.A1035	C	0	2	406	0	2	549	0	0	1	522	0	0	0	0
chr3:178952060	PIK3CA	p.F1039	T	0	0	0	350	0	0	0	532	0	0	0	508	0	0
chr3:178952065	PIK3CA	p.M1040	G	0	0	361	0	0	0	494	0	0	0	477	1	1	1
chr3:178952072	PIK3CA	p.M1043	A	322	1	0	0	491	1	0	0	487	0	0	0	0	0
chr3:178952073	PIK3CA	p.M1043	T	0	0	0	320	0	0	0	409	0	0	0	507	0	0
chr3:178952074	PIK3CA	p.M1043	G	0	0	316	0	0	0	460	0	0	0	470	1	1	1
chr3:178952075	PIK3CA	p.N1044	A	311	0	0	0	471	0	0	0	480	0	0	0	0	0
chr3:178952077	PIK3CA	p.N1044	T	0	0	0	319	0	0	0	463	1	0	0	498	1	1
chr3:178952078	PIK3CA	p.D1045	G	0	0	0	316	0	0	0	425	0	0	0	463	0	0
chr3:178952081	PIK3CA	p.A1046	G	0	0	304	0	0	0	400	0	0	0	431	3	3	3
chr3:178952082	PIK3CA	p.A1046	C	1	298	0	0	1	390	0	0	1	441	0	0	0	0
chr3:178952084	PIK3CA	p.H1047	C	1	273	0	0	0	372	0	0	0	458	0	0	0	0
chr3:178952085	PIK3CA	p.H1047	A	275	1	0	0	408	0	0	0	465	0	0	0	0	0
chr3:178952086	PIK3CA	p.H1047	T	0	0	0	281	0	0	1	409	0	0	1	469	1	1
chr3:178952088	PIK3CA	p.H1048	A	272	0	0	1	409	0	0	2	439	0	0	0	0	0
chr3:178952090	PIK3CA	p.G1049	G	0	0	257	0	0	0	355	0	0	0	380	3	3	3
chr3:178952091	PIK3CA	p.G1049	G	0	0	258	0	0	0	356	0	0	0	414	0	0	0
chr3:178952092	PIK3CA	p.G1049	T	0	0	0	224	0	0	0	355	0	0	2	391	0	0
chr3:178952152	PIK3CA	p.I069	A	113	0	1	0	190	0	0	0	243	1	0	0	0	0
chr3:178952240	MLH1	p.V384	T	0	0	1	377	0	0	0	378	0	0	0	416	0	0
chr3:41268040	CTNNB1	p.A13	G	0	0	524	0	0	0	602	1	0	0	586	0	0	0
chr3:41268046	CTNNB1	p.E15	G	0	2	536	1	0	0	625	0	0	0	599	1	1	1
chr3:41268052	CTNNB1	p.A20	C	1	557	0	0	0	627	0	0	0	587	0	0	0	0
chr3:41268064	CTNNB1	p.A21	G	0	0	563	0	0	2	656	4	0	0	617	2	2	2
chr3:41268067	CTNNB1	p.V22	G	0	0	572	0	0	1	675	0	0	0	643	1	1	1
chr3:41268068	CTNNB1	p.V22	T	0	0	0	528	0	0	0	689	0	0	1	596	0	0
chr3:41268070	CTNNB1	p.S23	A	572	1	0	0	748	0	0	0	667	1	0	2	0	0
chr3:41268077	CTNNB1	p.W26	G	0													

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS													
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB					
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2		
chr4:1803575	FGFR3	p.H251	C	0	88	0	0	0	0	75	0	0	0	0	146	0	0
chr4:1806088	FGFR3	p.A369	G	0	0	71	0	0	0	82	0	0	0	0	83	0	0
chr4:1806089	FGFR3	p.G370	G	0	0	77	0	0	0	81	0	0	0	86	0	0	
chr4:1806092	FGFR3	p.S371	A	67	0	0	0	0	85	0	0	0	0	71	0	1	
chr4:1806099	FGFR3	p.Y373	A	68	0	0	0	0	84	1	0	0	0	101	1	0	
chr4:1806119	FGFR3	p.G380	G	0	0	94	0	0	0	105	0	0	0	0	109	0	
chr4:1806131	FGFR3	p.F384	T	0	0	0	103	0	0	0	0	111	0	0	0	90	
chr4:1806153	FGFR3	p.A391	C	0	0	116	0	0	0	122	0	0	0	0	111	0	
chr4:1807862	FGFR3	p.D641	G	0	0	238	0	0	0	200	0	0	0	0	276	0	
chr4:1807889	FGFR3	p.K650	A	280	0	0	1	246	0	0	0	0	228	0	0	0	
chr4:1807890	FGFR3	p.K650	A	263	0	0	0	199	0	0	0	0	222	0	0	0	
chr4:1808331	FGFR3	p.G697	G	0	0	355	0	0	0	307	1	0	0	0	414	0	
chr4:1808949	FGFR3	p.L784	T	0	0	0	0	291	0	0	0	263	0	0	0	432	
chr4:55141036	PDGFRA	p.V561	T	0	0	1	352	0	0	1	420	0	0	0	4	579	
chr4:55144146	PDGFRA	p.N659	A	364	0	0	0	551	1	2	0	311	1	0	0	0	
chr4:55144148	PDGFRA	p.N659	C	0	393	0	0	0	547	0	0	0	0	342	0	0	
chr4:55145457	PDGFRA	p.L744	C	0	0	313	0	0	0	401	0	0	0	0	444	0	
chr4:55152040	PDGFRA	p.V824	C	0	140	0	312	1	140	1	376	1	151	1	402	0	
chr4:55152092	PDGFRA	p.D842	G	0	0	467	0	0	0	480	0	0	0	0	547	0	
chr4:55152093	PDGFRA	p.D842	A	412	0	0	0	471	0	0	0	519	2	0	0	0	
chr4:55152094	PDGFRA	p.D842	C	0	437	1	0	0	454	0	0	0	507	0	0	0	
chr4:55152095	PDGFRA	p.I843	A	435	0	0	1	482	0	0	0	504	2	1	0	0	
chr4:55152096	PDGFRA	p.I843	T	0	0	0	0	431	0	0	0	459	0	0	1	515	
chr4:55152097	PDGFRA	p.I843	C	1	438	0	0	0	454	0	0	0	494	0	0	0	
chr4:55152098	PDGFRA	p.M844	A	433	1	0	0	462	0	0	0	487	1	0	0	0	
chr4:55152099	PDGFRA	p.M844	T	0	0	0	423	0	0	0	471	2	0	1	498	0	
chr4:55152100	PDGFRA	p.M844	G	0	0	436	0	0	0	447	0	0	0	476	2	0	
chr4:55152101	PDGFRA	p.H845	C	0	429	0	0	0	444	0	0	2	478	0	0	0	
chr4:55152102	PDGFRA	p.H845	A	416	0	0	0	469	0	0	0	485	1	0	1	0	
chr4:55152103	PDGFRA	p.H845	T	0	0	0	398	0	0	0	0	462	0	0	469	0	
chr4:55152104	PDGFRA	p.D846	G	0	0	425	0	0	0	448	0	0	0	449	0	0	
chr4:55152105	PDGFRA	p.D846	A	413	0	0	0	469	1	0	1	479	1	0	0	0	
chr4:55152106	PDGFRA	p.D846	T	0	2	0	402	0	1	0	453	0	0	2	454	0	
chr4:55561763	KIT	p.G51	C	0	339	0	0	1	363	0	0	1	352	0	2	454	
chr4:55561764	KIT	p.D52	G	0	0	338	0	1	0	0	361	0	0	329	0	0	
chr4:55592202	KIT	p.K509	A	908	0	0	0	608	0	0	0	654	0	0	0	0	
chr4:55593431	KIT	p.V530	G	0	0	339	1	0	1	538	1	0	0	624	1	0	
chr4:55593464	KIT	p.M541	A	276	118	0	0	513	150	2	0	596	229	0	0	0	
chr4:55593481	KIT	p.K546	A	453	0	0	0	734	0	0	0	868	2	0	0	0	
chr4:55593596	KIT	p.F551	C	498	0	0	0	666	0	0	0	780	0	0	0	0	
chr4:55593588	KIT	p.M552	A	519	0	0	0	737	0	0	0	813	1	0	0	0	
chr4:55593591	KIT	p.Y553	T	2	1	0	517	0	0	0	726	0	0	0	871	0	
chr4:55593594	KIT	p.E554	G	0	0	516	0	0	0	688	0	0	0	829	1	0	
chr4:55593597	KIT	p.V555	G	0	0	495	0	0	0	666	1	0	0	865	0	0	
chr4:55593603	KIT	p.W557	T	0	0	3	468	0	0	0	619	0	0	3	753	0	
chr4:55593604	KIT	p.W557	G	0	0	485	1	0	0	596	0	0	0	737	1	0	
chr4:55593605	KIT	p.W557	G	0	0	499	0	0	0	616	0	0	0	775	4	0	
chr4:55593606	KIT	p.K558	A	482	1	0	0	662	0	0	0	749	1	0	0	0	
chr4:55593607	KIT	p.K558	A	457	0	0	0	607	0	0	0	708	0	0	0	0	
chr4:55593608	KIT	p.K558	G	0	0	481	1	0	0	602	0	0	0	727	2	0	
chr4:55593609	KIT	p.V559	G	0	0	486	2	0	0	613	1	0	0	742	2	0	
chr4:55593610	KIT	p.V559	T	1	0	0	415	0	0	1	561	0	0	3	674	0	
chr4:55593613	KIT	p.V560	T	1	0	0	436	1	0	0	0	594	0	0	680	0	
chr4:55593614	KIT	p.V560	T	0	0	0	444	0	0	1	620	0	0	1	709	0	
chr4:55593615	KIT	p.E561	G	0	1	471	0	0	0	583	0	0	0	703	4	0	
chr4:55593617	KIT	p.E561	G	0	0	462	0	0	0	573	0	0	0	669	4	0	
chr4:55593618	KIT	p.E562	G	0	0	466	0	0	0	568	2	0	0	699	4	0	
chr4:55593630	KIT	p.N566	A	429	0	0	0	579	0	0	0	659	2	0	0	0	
chr4:55593632	KIT	p.N566	C	2	471	0	0	0	0	565	0	0	3	699	0	0	
chr4:55593635	KIT	p.N567	T	0	0	0	462	0	0	0	599	0	0	0	741	0	
chr4:55593636	KIT	p.V568	T	0	0	0	453	0	0	0	567	0	0	0	710	0	
chr4:55593648	KIT	p.D572	G	0	0	453	0	0	0	542	0	0	0	699	2	0	
chr4:55593652	KIT	p.F573	C	0	0	434	0	0	2	513	0	0	2	633	0	0	
chr4:55593660	KIT	p.L576	C	0	485	0	0	4	0	548	1	0	0	646	0	0	
chr4:55593661	KIT	p.L576	T	0	0	0	472	0	0	576	0	0	568	1	0	633	
chr4:55593663	KIT	p.F577	C	1	488	0	0	3	548	0	0	2	612	0	0	0	
chr4:55593679	KIT	p.W582	G	0	0	486	0	0	0	644	2	0	0	570	0	0	
chr4:55593680	KIT	p.W582	G	0	2	465	0	0	0	482	0	0	0	567	1	0	
chr4:55593685	KIT	p.F584	T	0	0	1	448	1	0	0	555	0	0	1	551	0	
chr4:55593689	KIT	p.F585	C	0	459	0	0	2	504	0	0	0	534	0	0	0	
chr4:55594221	KIT	p.K642	A	539	0	0	0	604	1	0	0	682	0	0	0	0	
chr4:55594225	KIT	p.V643	T	0	0	1	527	0	0	1	559	0	0	1	669	0	
chr4:55594258	KIT	p.V654	T	0	0	0	620	0	0	0	616	0	0	0	484	0	
chr4:55595518	KIT	p.L670	A	407	0	0	0	584	0	0	0	522	0	0	0	1	
chr4:55595519	KIT	p.L670	C	0	421	0	0	0	538	0	0	0	496	0	0	0	
chr4:55599307	KIT	p.F811	T	1	0	0	539	0	0	0	661	0	0	0	554	0	
chr4:55599320	KIT	p.D816	G	0	0	551	0	0	0	614	3	0	0	578	0	0	
chr4:55599321	KIT	p.D816	A	524	0	0	1	635	0	0	0	571	0	0	2	0	
chr4:55599322	KIT	p.D816	C	0	562	0	0	0	624	0	0	3	544	0	0	0	
chr4:55599327	KIT	p.K816	A	553	0	0	0	644	0	0	0	966	0	0	0	0	
chr4:55599332	KIT	p.D820	G	0	559	0	0	0	1	635	0	0	0	535	0	0	
chr4:55599333	KIT	p.D820	A	539	0	0	0	661	0	0	0	558	1	0	0	0	
chr4:55599334	KIT	p.D820	T	0	0	0	509	0	0	1	648	0	0	0	524	0	
chr4:55599338	KIT	p.N822	A	515	0	0	0	643	0	0	0	538	0	0	0	0	
chr4:55599340	KIT	p.N822	C	0	0	0	502	0	0	629	0	0	0	0	543	0	
chr4:55599341	KIT	p.Y823	T	1	0	0	507	0	1	0	636	0	0	0	552	0	
chr4:55599342	KIT	p.Y823	A	490	1	0	2	599	0	0	0	514	1	0	0	2	
chr4:55599347	KIT	p.V825	G	0	0	510	0	0	0	569	0	0	0	551	1	0	
chr4:55599348	KIT	p.V825	T	0	0	0	423	1	0	0	545	1	1	0	487	0	
chr4:55602694	KDR	p.E830	K	0	0	564	0	0	0	688	0	0	0	641	0	0	
chr4:55602737	KIT	p.W853	G	0	0	569	0	0	0	657	3	0	0	685	1	0	
chr4:55642657	KDR	p.G1308	C	0	421	0	0	0	392	0	0	0	433	0	0	1	
chr4:55953807	KDR	p.P1210	G	0	0	352	1	0	0	338	1	1	0	345	0	0	
chr4:55985111	KDR	p.G1145	C	0	0	351	0	0	0	386	0	0	2	482	0	0	
chr4:55985127	KDR	p.L1140	G	0	0	342	0	1	0	0	356	0	0	0	555	0	
chr4:55980089	KDR	p.S984	C	0	405	0	0	0	370	0	0	0	0	529	0</		

Supplementary Table 1

COORDINATES	GENE	AA	CHANGE	REF	# READS															
					PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB							
					A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2				
chr5:112175399	APC	p.K1370	A	443	1	0	0	435	0	0	0	486	2	0	0	0				
chr5:112175411	APC	p.E1374	G	0	0	424	1	0	0	395	0	0	0	454	0	0				
chr5:112175419	APC	p.Y1376	T	0	0	0	1	2	0	0	0	431	0	1	480	0				
chr5:112175423	APC	p.O1378	C	0	0	453	0	0	3	418	0	0	0	501	0	0				
chr5:112175426	APC	p.E1379	G	0	0	432	0	0	0	391	0	0	1	483	1	0				
chr5:112175576	APC	p.Q1429	C	1	434	0	0	2	359	0	0	1	292	0	0	0				
chr5:112175586	APC	p.P1432	C	0	428	0	0	2	338	0	0	0	279	0	0	0				
chr5:112175587	APC	p.P1432	A	372	0	0	0	0	292	1	0	240	1	0	1	0				
chr5:112175594	APC	p.R1435	A	414	0	0	1	347	0	0	0	298	0	0	0	0				
chr5:112175617	APC	p.P1442	T	0	0	0	429	0	0	1	361	0	1	0	346	0				
chr5:112175620	APC	p.P1443	T	0	0	3	425	0	0	0	370	0	0	1	354	0				
chr5:112175621	APC	p.Q1444	C	0	461	0	0	0	370	0	0	2	337	0	0	0				
chr5:112175630	APC	p.Q1447	C	0	442	0	0	1	352	0	0	0	346	0	0	0				
chr5:112175639	APC	p.R1450	C	0	446	0	0	1	325	0	0	0	350	0	0	0				
chr5:112175642	APC	p.E1451	G	0	0	455	0	0	0	352	2	1	0	358	0	0				
chr5:112175651	APC	p.K1454	A	442	1	0	0	392	0	0	0	385	0	0	0	0				
chr5:112176672	APC	p.E1461	G	0	0	449	0	1	0	359	0	0	0	382	0	0				
chr5:112176681	APC	p.E1464	G	0	0	454	0	0	0	354	0	0	0	370	0	0				
chr5:112176696	APC	p.Q1469	C	0	432	0	0	0	330	0	0	0	351	0	0	0				
chr5:112176754	APC	p.L1488	T	0	0	0	370	0	0	0	433	0	0	0	269	0				
chr5:112176775	APC	p.S1485	G	0	0	406	0	0	1	430	1	0	0	299	0	0				
chr5:112176796	APC	p.G1499	G	0	0	397	1	0	0	404	1	0	0	246	0	0				
chr5:112176828	APC	p.E1513	G	0	0	437	0	0	0	485	0	0	0	352	2	0				
chr5:112176930	APC	p.E1547	G	0	0	659	0	0	0	816	1	0	0	488	0	0				
chr5:112176945	APC	p.E1552	G	0	0	704	0	0	0	922	0	0	0	563	0	0				
chr5:112176992	APC	p.L1564	T	2	2	0	699	0	0	0	1059	0	0	0	545	0				
chr5:112176920	APC	p.E1577	G	0	0	683	2	0	1	858	2	0	0	464	0	0				
chr5:149433644	CSF1R	p.Y969	A	274	1	0	0	374	0	0	0	506	1	0	0	0				
chr5:149433645	CSF1R	p.Y969	T	0	0	1	255	0	0	0	359	0	0	0	496	0				
chr5:149433648	CSF1R	p.Y969	A	262	1	0	0	366	0	0	0	417	0	0	0	0				
chr5:149433044	CSF1R	p.L301	A	146	2	0	0	158	0	0	0	182	0	0	0	0				
chr5:170837552	NPM1	p.W290	T	0	0	1	124	0	0	0	206	0	0	0	169	0				
chr7:128845101	SMO	p.R199	C	0	617	0	0	0	633	0	0	2	633	0	0	0				
chr7:128848040	SMO	p.A324	G	0	0	224	0	0	0	201	0	0	0	230	0	0				
chr7:128848374	SMO	p.Y404	G	0	0	319	0	0	0	368	0	0	0	355	1	0				
chr7:128850341	SMO	p.W535	G	0	0	416	0	0	0	368	0	0	0	497	0	0				
chr7:128851593	SMO	p.T640	A	265	0	0	1	370	2	0	1	322	2	0	0	0				
chr7:140453112	BRAF	p.H608	T	0	0	0	947	0	0	0	1129	0	0	0	784	0				
chr7:140453118	BRAF	p.G606	C	0	920	0	0	3	1060	0	0	2	793	0	0	0				
chr7:140453121	BRAF	p.S605	C	2	1045	0	0	0	1160	2	0	2	866	0	0	0				
chr7:140453122	BRAF	p.S605	T	0	0	0	1009	0	0	0	1253	0	0	0	884	0				
chr7:140453125	BRAF	p.W604	A	1005	0	0	0	1195	1	0	0	859	2	0	0	0				
chr7:140453128	BRAF	p.R603	G	0	0	988	1	0	0	1074	3	0	0	758	0	0				
chr7:140453132	BRAF	p.K601	T	0	0	1	977	0	0	1187	1	1	1	860	0	0				
chr7:140453133	BRAF	p.K601	T	0	0	0	980	2	1	0	1229	1	0	0	857	0				
chr7:140453134	BRAF	p.K601	T	0	0	0	1009	0	0	0	1218	0	0	1	857	0				
chr7:140453135	BRAF	p.V600	C	2	1027	0	0	2	1169	1	0	2	838	1	1	0				
chr7:140453136	BRAF	p.V600	A	531	2	0	0	448	599	2	1	599	470	1	0	362				
chr7:140453137	BRAF	p.S599	T	1	1029	0	0	1009	0	1189	0	0	824	0	0	0				
chr7:140453138	BRAF	p.T599	T	1	0	0	1009	0	0	0	1265	2	0	1	815	0				
chr7:140453139	BRAF	p.T599	G	0	0	994	0	0	1	1162	0	0	0	811	0	0				
chr7:140453140	BRAF	p.T599	T	1	0	0	999	0	0	0	1252	1	0	2	842	0				
chr7:140453142	BRAF	p.A598	G	0	0	1007	0	0	0	1160	2	0	0	831	2	0				
chr7:140453144	BRAF	p.L597	T	0	2	0	995	0	0	0	1264	1	2	2	881	0				
chr7:140453145	BRAF	p.L597	A	993	1	1	1	0	1265	0	0	2	884	0	0	0				
chr7:140453146	BRAF	p.L597	G	0	0	1003	0	0	0	1198	1	0	0	818	2	0				
chr7:140453148	BRAF	p.C596	C	1	984	0	0	2	1150	0	0	2	816	0	0	0				
chr7:140453149	BRAF	p.C596	C	1	947	0	0	0	1090	0	0	1	768	1	1	0				
chr7:140453150	BRAF	p.F595	A	978	1	0	0	0	1249	0	0	0	778	0	1	0				
chr7:140453151	BRAF	p.F595	A	987	1	0	0	0	1278	0	0	0	815	1	0	0				
chr7:140453152	BRAF	p.F595	A	967	2	0	1	1	1249	1	1	0	866	1	0	0				
chr7:140453153	BRAF	p.D594	A	969	4	0	0	0	1208	1	0	0	826	5	0	2				
chr7:140453154	BRAF	p.D594	T	0	0	0	1011	0	0	0	1288	0	0	0	875	0				
chr7:140453155	BRAF	p.D594	C	0	999	0	0	3	1181	0	0	9	814	0	0	0				
chr7:140453159	BRAF	p.I592	T	0	0	1	903	0	0	0	1084	0	0	1	763	0				
chr7:140453161	BRAF	p.I592	T	0	0	0	956	0	0	0	1187	0	0	2	843	0				
chr7:140453174	BRAF	p.D587	G	0	0	942	0	0	0	1011	0	0	0	837	0	0				
chr7:140453175	BRAF	p.D587	T	0	0	1	859	0	1	2	982	0	0	1	755	0				
chr7:140453177	BRAF	p.E586	T	0	0	0	897	0	0	0	1101	0	0	2	838	0				
chr7:140453179	BRAF	p.E586	C	1	924	0	0	2	1049	0	1	798	0	0	0	0				
chr7:140453183	BRAF	p.L584	A	897	0	0	2	1084	0	0	0	816	0	0	0	0				
chr7:140453185	BRAF	p.L584	G	0	0	907	1	0	0	1029	0	0	0	818	0	0				
chr7:140453186	BRAF	p.F583	A	882	0	0	0	1035	0	0	0	828	0	0	0	0				
chr7:140453189	BRAF	p.I582	T	0	0	0	926	0	0	1	1065	0	0	0	853	0				
chr7:140453193	BRAF	p.N581	T	0	0	0	915	1	0	1	1043	0	0	0	892	0				
chr7:140451397	BRAF	p.A271	C	0	829	0	0	0	952	0	0	2	608	0	0	0				
chr7:140481401	BRAF	p.G469	T	0	0	0	807	0	0	1	1043	1	0	0	648	0				
chr7:140481402	BRAF	p.G469	C	1	854	0	0	1	1016	0	0	0	622	0	0	0				
chr7:140481403	BRAF	p.G469	C	0	850	0	1	0	1014	1	0	1	619	0	0	0				
chr7:140481410	BRAF	p.G466	C	0	0	0	882	0	0	0	1125	0	0	0	661	0				
chr7:140481411	BRAF	p.G466	C	2	898	0	0	2	1084	0	1	648	0	0	0	0				
chr7:140481412	BRAF	p.G466	C	2	891	0	0	2	1006	1	0	2	610	0	0	0				
chr7:140481416	BRAF	p.G464	T	0	0	0	930	0	0	0	1179	1	0	2	667	0				
chr7:140481417	BRAF	p.G464	C	0	935	0	0	2	1085	0	0	0	629	0	0	0				
chr7:140481419	BRAF	p.G464	C	1	909	0	0	0	1079	0	0	0	649	0	0	0				
chr7:140481423	BRAF	p.R462	C	0	960	0	0	3	1139	1	0	0	699	0	0	0				
chr7:140481451	BRAF	p.F453	G	0	0	895	3	0	0	1059	0	0	0	676	2	0				
chr7:140481478	BRAF	p.R444	G	0	869	2	0	0	0	1011	1	0	0	722	2	0				
chr7:148508727	EZH2	p.T946	T	0	0	0	325	0	0	0	374	0	0	0	330	0				
chr7:148508728	EZH2	p.T946	A	328	0	0	0	375	0	0	0	355	0	0	0	0				
chr7:148508744	EZH2	p.N640	A	396	0	0	0	458	0	0	0	369	1	0	0	0				
chr7:148508757	EZH2	p.P636	G	0	0	395	1	0	0	422	1	0	0	367	0	0				
chr7:55211033	EGFR	p.L93	C	0	434	0	0	0	494	0	0	1	0	897	0	0				
chr7:55211034	EGFR	p.L93	C	1	438	0	0	0	514	0	0	1	677	0	0	0				
chr7:55211035																				

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS													
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB					
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2		
chr7:55242418	EGFR	p.L730	C	0	666	0	0	0	0	737	0	0	0	810	0	0	0
chr7:55242423	EGFR	p.W731	G	0	0	634	1	0	0	0	701	1	0	0	781	1	0
chr7:55242427	EGFR	p.P733	C	2	615	0	0	1	702	0	0	3	0	732	0	0	
chr7:55242428	EGFR	p.P733	C	0	625	0	0	1	731	0	0	1	0	735	0	0	
chr7:55242430	EGFR	p.E734	G	0	1	640	0	0	0	763	0	0	0	759	2	0	
chr7:55242433	EGFR	p.G735	G	0	613	0	0	0	0	703	0	0	0	716	3	0	
chr7:55242443	EGFR	p.V738	T	0	0	1	612	0	0	1	765	0	0	739	0	0	
chr7:55242452	EGFR	p.T741	C	0	601	0	0	0	660	0	0	2	0	683	1	0	
chr7:55242455	EGFR	p.V742	T	0	0	0	552	0	0	4	688	1	0	6	683	0	
chr7:55242457	EGFR	p.A743	G	0	0	634	0	0	0	683	1	0	0	725	3	0	
chr7:55242464	EGFR	p.K745	A	631	1	0	0	0	785	0	0	780	1	0	0	0	
chr7:55242466	EGFR	p.E746	G	0	0	627	0	0	1	725	1	0	0	749	0	0	
chr7:55242467	EGFR	p.E746	A	671	0	0	0	0	826	0	0	855	0	2	0	0	
chr7:55242468	EGFR	p.E746	A	618	2	0	1	791	1	0	0	817	1	0	0	0	
chr7:55242469	EGFR	p.L747	T	0	0	1	629	0	0	0	796	0	0	0	812	0	
chr7:55242470	EGFR	p.L747	T	0	0	0	637	0	0	0	830	0	0	0	812	0	
chr7:55242471	EGFR	p.L747	A	623	0	0	0	0	810	0	0	771	1	0	0	0	
chr7:55242472	EGFR	p.R748	A	656	0	0	0	0	818	0	0	792	1	0	0	0	
chr7:55242473	EGFR	p.R748	G	0	0	660	0	0	0	757	1	0	0	763	1	0	
chr7:55242474	EGFR	p.R748	A	656	0	0	0	0	794	0	0	777	0	0	0	0	
chr7:55242475	EGFR	p.E749	G	0	0	662	1	0	0	763	0	0	2	747	1	0	
chr7:55242476	EGFR	p.E749	A	608	0	0	1	750	0	0	0	733	0	1	0	0	
chr7:55242477	EGFR	p.E749	A	595	1	0	0	754	1	0	0	735	3	0	0	0	
chr7:55242478	EGFR	p.A750	G	0	0	640	2	0	2	718	0	0	0	756	2	0	
chr7:55242479	EGFR	p.A750	C	1	670	0	0	2	728	0	0	0	775	0	0	0	
chr7:55242480	EGFR	p.A750	A	845	1	1	0	781	1	0	0	753	0	1	0	0	
chr7:55242481	EGFR	p.T751	A	597	1	0	2	739	0	0	0	725	0	0	0	0	
chr7:55242482	EGFR	p.T751	C	0	673	0	0	0	741	0	0	1	796	0	0	0	
chr7:55242483	EGFR	p.T751	A	606	2	0	0	741	0	0	0	762	1	0	0	0	
chr7:55242484	EGFR	p.S752	T	0	0	0	650	0	0	0	748	0	0	2	778	0	
chr7:55242485	EGFR	p.S752	C	0	676	0	0	0	736	0	0	0	771	0	0	0	
chr7:55242486	EGFR	p.S752	T	0	0	0	658	0	0	0	761	0	0	0	767	0	
chr7:55242487	EGFR	p.P753	C	0	664	0	0	0	692	1	0	3	755	0	0	0	
chr7:55242488	EGFR	p.P753	C	2	658	0	0	1	640	0	2	2	703	0	0	0	
chr7:55242489	EGFR	p.P753	G	0	0	1	0	0	0	668	1	0	0	724	4	0	
chr7:55242490	EGFR	p.K754	A	619	0	0	0	691	2	0	0	734	0	0	0	0	
chr7:55242491	EGFR	p.K754	A	599	1	1	0	712	0	0	0	708	2	0	0	0	
chr7:55242492	EGFR	p.K754	A	576	1	0	0	695	1	0	0	683	5	1	0	0	
chr7:55242493	EGFR	p.A755	G	0	3	626	3	0	0	663	0	0	0	717	2	0	
chr7:55242494	EGFR	p.A755	C	0	620	0	0	0	2	682	0	0	740	0	0	0	
chr7:55242495	EGFR	p.A755	C	2	608	0	0	1	651	0	0	0	744	0	0	0	
chr7:55242496	EGFR	p.A756	A	575	0	0	0	704	1	0	0	716	0	0	0	0	
chr7:55242497	EGFR	p.A756	A	552	0	0	0	668	0	0	0	686	0	0	0	0	
chr7:55242498	EGFR	p.A756	C	0	0	0	0	0	682	0	0	0	0	0	0	0	
chr7:55242499	EGFR	p.K757	A	592	0	0	0	698	0	0	0	719	2	0	0	0	
chr7:55242500	EGFR	p.K757	A	584	0	0	1	701	1	0	0	746	3	0	0	0	
chr7:55242501	EGFR	p.K757	G	0	0	566	1	0	0	667	1	0	0	679	1	0	
chr7:55242502	EGFR	p.E758	G	0	0	589	1	0	0	679	3	0	0	706	2	0	
chr7:55242503	EGFR	p.E758	A	599	0	0	0	753	0	0	0	785	2	0	0	0	
chr7:55242504	EGFR	p.E758	A	548	4	1	0	701	0	0	0	688	2	0	0	0	
chr7:55242505	EGFR	p.I759	A	511	2	0	0	672	0	0	0	668	1	0	0	0	
chr7:55242506	EGFR	p.I759	T	0	0	0	566	0	0	1	686	0	0	1	714	0	
chr7:55242511	EGFR	p.D761	A	0	0	578	0	0	0	618	2	0	0	684	0	0	
chr7:55242512	EGFR	p.D761	A	554	0	0	0	643	0	0	0	695	0	2	0	0	
chr7:55242513	EGFR	p.V765	G	0	281	1	0	0	0	340	0	0	0	614	1	0	
chr7:55242514	EGFR	p.V765	G	0	295	0	0	0	0	346	0	0	0	637	0	0	
chr7:55242515	EGFR	p.V765	G	0	0	299	0	0	0	364	0	0	0	645	0	0	
chr7:55242516	EGFR	p.V765	G	0	0	305	0	0	0	347	1	0	0	632	0	0	
chr7:55242517	EGFR	p.D770	G	0	0	304	0	0	0	359	0	0	0	636	0	0	
chr7:55242518	EGFR	p.H773	A	245	1	1	0	282	4	0	0	543	2	0	0	0	
chr7:55242519	EGFR	p.V774	G	0	0	308	0	0	0	334	1	1	0	644	2	0	
chr7:55242520	EGFR	p.C775	G	0	0	320	0	0	1	0	0	359	0	0	653	1	
chr7:55242521	EGFR	p.R776	C	1	296	0	0	0	0	309	0	0	3	616	0	0	
chr7:55242522	EGFR	p.R776	G	0	0	292	0	0	2	0	0	330	0	0	617	1	
chr7:55242523	EGFR	p.G779	G	0	0	282	0	1	0	0	304	0	0	0	576	0	
chr7:55242524	EGFR	p.G779	G	0	0	292	0	0	0	0	339	0	0	0	616	0	
chr7:55242525	EGFR	p.S784	T	0	0	0	352	0	0	0	366	0	0	0	655	0	
chr7:55242526	EGFR	p.S784	C	0	386	0	0	1	407	0	0	2	699	0	0	0	
chr7:55242527	EGFR	p.V786	G	0	0	384	0	0	0	389	1	0	0	633	4	0	
chr7:55242528	EGFR	p.T790	A	378	1	0	1	384	1	0	0	579	6	0	0	0	
chr7:55242529	EGFR	p.T790	C	0	449	0	0	0	0	414	0	1	0	673	0	0	
chr7:55242530	EGFR	p.T790	C	1	0	0	436	1	0	0	406	1	0	0	650	0	
chr7:55242531	EGFR	p.L792	T	1	0	0	467	0	0	0	448	0	0	1	678	0	
chr7:55242532	EGFR	p.G810	G	0	0	569	0	0	0	489	0	0	0	815	0	0	
chr7:55242533	EGFR	p.G810	G	0	0	576	0	0	0	499	1	0	0	832	0	0	
chr7:55242534	EGFR	p.L814	T	1	0	2	572	0	0	2	540	0	0	0	803	0	
chr7:55242535	EGFR	p.V819	G	0	0	614	0	0	0	527	0	0	0	821	0	0	
chr7:55242536	EGFR	p.L821	T	2	0	2	518	0	0	0	477	0	0	2	753	0	
chr7:55242537	EGFR	p.L856	C	2	664	0	0	0	640	0	0	0	898	0	0	0	
chr7:55242538	EGFR	p.L856	T	0	0	0	578	0	0	0	590	1	0	2	844	0	
chr7:55242539	EGFR	p.L856	G	0	0	613	0	0	0	612	0	0	0	897	0	0	
chr7:55242540	EGFR	p.A859	G	0	0	614	1	0	0	607	1	0	1	926	2	0	
chr7:55242541	EGFR	p.L859	T	0	0	0	632	0	0	0	682	0	0	3	924	0	
chr7:55242542	EGFR	p.C863	G	0	0	630	0	0	0	618	1	0	0	939	2	0	
chr7:55242543	EGFR	p.A864	G	0	0	612	2	0	0	612	384	0	0	893	0	0	
chr7:55242544	EGFR	p.E868	A	546	0	0	0	577	0	1	0	867	4	0	0	0	
chr7:55242545	EGFR	p.H870	C	0	545	0	0	3	529	0	0	1	717	0	0	0	
chr7:55242546	EGFR	p.H870	A	543	1	1	0	540	0	0	0	767	1	0	0	0	
chr7:55242547	EGFR	p.A871	G	0	0	557	0	0	2	535	0	0	0	811	2	0	
chr7:55242548	EGFR	p.A871	C	0	559	0	0	2	515	0	1	0	0	825	0	0	
chr7:55242549	EGFR	p.G873	G	1	0	563	0	0	0	535	1	0	0	819	3	0	
chr7:55242550	EGFR	p.G874	G	0	0	530	0	0	0	502	1	0	0	779	1	0	
chr8:38282209	FGFR1	p.P252	G	0	0	199	1	0	1	205	0	0	0	127	0	0	
chr8:38282210	FGFR1	p.S125	G	0	0	472	0	0	0	541	0	0	0	517	2	0	
chr9:133738330	ABL1	p.M244	A	237	0	0	1	354	2	0	0	398	2	0	0	0	
chr9:133738342	ABL1	p.L248	C	0	231	0	0	0	31								

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS															
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB							
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2				
chr9:21970980	CDKN2A	p.V126	G	0	0	265	0	0	1	0	288	0	0	0	0	407	1		
chr9:21970982	CDKN2A	p.V126	C	0	257	0	0	0	0	299	0	0	2	444	0	0	0		
chr9:21970985	CDKN2A	p.D125	C	0	253	0	0	0	0	292	0	0	0	419	0	0	0		
chr9:21970987	CDKN2A	p.R124	C	0	255	0	0	0	0	288	0	0	1	427	0	0	0		
chr9:21970989	CDKN2A	p.H123	A	235	0	0	0	0	251	0	0	0	366	3	0	0	0		
chr9:21970992	CDKN2A	p.G122	G	0	0	261	0	0	0	0	285	0	0	0	422	0	0		
chr9:21970993	CDKN2A	p.G122	C	0	265	0	0	0	0	290	0	0	1	431	0	0	0		
chr9:21970994	CDKN2A	p.G122	C	0	257	0	0	0	0	293	0	0	0	433	0	0	0		
chr9:21971000	CDKN2A	p.E120	C	0	256	0	0	0	0	289	0	0	2	471	0	0	0		
chr9:21971003	CDKN2A	p.E119	C	2	260	0	0	1	276	0	0	0	0	472	0	0	0		
chr9:21971012	CDKN2A	p.D116	C	0	246	0	0	1	266	0	0	0	0	530	0	0	0		
chr9:21971015	CDKN2A	p.V115	C	0	236	0	0	0	249	0	0	0	0	502	0	0	2		
chr9:21971017	CDKN2A	p.F114	G	0	0	230	1	0	0	223	0	0	0	438	0	0	0		
chr9:21971018	CDKN2A	p.F114	G	0	0	234	1	0	0	251	0	0	0	487	0	0	0		
chr9:21971024	CDKN2A	p.R112	G	0	0	214	0	0	0	219	0	0	0	467	0	0	0		
chr9:21971028	CDKN2A	p.W110	C	0	220	0	0	0	0	233	0	0	0	497	0	0	0		
chr9:21971029	CDKN2A	p.W110	C	0	229	0	0	0	0	238	0	0	0	540	0	0	0		
chr9:21971036	CDKN2A	p.D108	C	0	212	0	0	1	226	0	0	0	0	496	0	0	0		
chr9:21971040	CDKN2A	p.V106	C	0	209	0	0	2	217	0	0	1	509	0	0	0	0		
chr9:21971042	CDKN2A	p.V106	C	0	215	0	1	0	229	0	0	0	0	530	0	0	0		
chr9:21971053	CDKN2A	p.A102	G	0	0	222	0	1	0	223	1	0	0	489	0	0	0		
chr9:21971055	CDKN2A	p.G101	C	0	216	0	0	0	221	0	0	0	0	509	0	0	0		
chr9:21971060	CDKN2A	p.A100	C	0	221	0	0	0	237	0	0	1	533	0	0	0	0		
chr9:21971107	CDKN2A	p.D84	T	0	0	0	187	0	0	3	151	0	0	6	340	0	0		
chr9:21971108	CDKN2A	p.D84	C	0	241	0	0	0	218	0	0	0	0	500	0	0	0		
chr9:21971110	CDKN2A	p.H83	T	0	0	2	175	0	0	2	168	1	0	3	365	0	0		
chr9:21971111	CDKN2A	p.H83	G	0	0	230	0	0	0	212	0	0	0	503	0	0	0		
chr9:21971114	CDKN2A	p.V82	C	0	210	0	0	1	191	0	0	1	441	0	0	0	0		
chr9:21971116	CDKN2A	p.P81	G	0	0	219	0	0	0	205	0	0	0	483	0	0	0		
chr9:21971119	CDKN2A	p.R80	C	0	216	0	0	0	192	0	0	0	0	395	0	0	0		
chr9:21971120	CDKN2A	p.R80	G	0	0	208	0	0	0	189	0	0	0	431	0	0	0		
chr9:21971121	CDKN2A	p.T79	G	0	0	214	0	0	0	206	0	0	0	466	0	0	0		
chr9:21971122	CDKN2A	p.T79	G	0	0	216	0	0	0	212	0	0	0	489	0	0	0		
chr9:21971131	CDKN2A	p.A76	G	0	0	205	0	0	0	207	0	0	0	465	1	0	0		
chr9:21971134	CDKN2A	p.A76	G	0	0	202	0	0	0	204	0	0	0	438	0	0	0		
chr9:21971136	CDKN2A	p.D74	G	0	0	205	0	0	0	207	0	0	0	459	0	0	0		
chr9:21971137	CDKN2A	p.D74	T	0	0	165	0	0	0	2	142	0	0	6	274	0	0		
chr9:21971138	CDKN2A	p.D74	C	0	205	0	1	0	211	0	0	0	0	418	0	0	0		
chr9:21971142	CDKN2A	p.C72	G	0	0	205	1	1	0	190	0	0	0	426	0	0	0		
chr9:21971145	CDKN2A	p.N71	G	0	0	210	0	0	0	193	0	0	0	464	0	0	0		
chr9:21971149	CDKN2A	p.P70	G	0	0	197	0	0	0	213	0	2	0	433	1	0	0		
chr9:21971152	CDKN2A	p.E69	T	0	0	0	169	0	0	0	164	0	0	3	335	0	0		
chr9:21971153	CDKN2A	p.E69	C	0	197	0	0	1	205	0	0	0	0	420	0	0	0		
chr9:21971154	CDKN2A	p.A68	C	0	204	0	0	0	199	0	0	1	396	0	0	0	0		
chr9:21971155	CDKN2A	p.A68	G	0	0	198	0	0	0	206	0	0	0	428	0	0	0		
chr9:21971156	CDKN2A	p.A68	C	1	202	0	0	0	206	0	0	0	0	426	0	0	0		
chr9:21971158	CDKN2A	p.G67	C	0	192	0	2	0	192	0	0	0	0	405	0	0	0		
chr9:21971159	CDKN2A	p.G67	C	0	198	0	0	0	194	0	0	0	0	391	0	0	0		
chr9:21971161	CDKN2A	p.H66	T	0	0	158	0	0	0	157	0	157	0	1	2	306	0		
chr9:21971164	CDKN2A	p.L65	A	160	0	0	0	163	0	0	0	0	349	1	0	0	0		
chr9:21971166	CDKN2A	p.L64	C	0	192	0	0	0	202	0	0	2	439	0	0	0	0		
chr9:21971170	CDKN2A	p.L63	A	156	1	0	1	157	1	0	0	325	0	0	0	0	0		
chr9:21971171	CDKN2A	p.L63	G	0	0	193	0	0	0	195	0	0	1	0	414	0	0		
chr9:21971177	CDKN2A	p.E61	C	0	184	0	0	0	178	0	0	0	0	399	0	0	0		
chr9:21971179	CDKN2A	p.A60	G	0	0	198	0	0	0	194	1	0	0	422	1	0	0		
chr9:21971186	CDKN2A	p.R58	G	0	0	190	0	0	0	151	0	0	0	372	0	0	0		
chr9:21971187	CDKN2A	p.A57	G	0	0	190	0	0	0	170	0	0	0	399	0	0	0		
chr9:21971188	CDKN2A	p.A57	G	0	0	194	0	0	0	188	0	0	0	426	0	0	0		
chr9:21971189	CDKN2A	p.A57	C	0	194	0	1	0	184	0	0	0	0	427	0	0	0		
chr9:21971202	CDKN2A	p.M52	C	0	198	0	1	183	0	0	2	392	0	0	0	0	0		
chr9:21971203	CDKN2A	p.M52	A	176	0	0	0	156	0	0	0	361	0	0	0	0	0		
chr9:21971206	CDKN2A	p.V51	A	156	0	0	0	129	0	0	0	317	3	0	0	0	0		
chr9:21971207	CDKN2A	p.V51	C	0	193	0	0	0	170	0	0	0	0	386	0	0	0		
chr9:5073752	JAK2	p.L611	T	0	0	0	303	0	0	0	385	0	0	2	313	0	0		
chr9:5073769	JAK2	p.C616	T	0	0	0	271	0	0	0	349	0	0	0	254	0	0		
chr9:5073770	JAK2	p.V617	G	0	0	263	0	0	0	323	0	0	0	255	0	0	0		
chr9:5073773	JAK2	p.C616	T	0	0	0	175	0	0	0	343	0	0	0	213	0	0		
chr9:5073781	JAK2	p.D620	C	0	236	0	0	1	272	0	0	0	0	165	0	0	0		
chr9:80409487	GNAQ	p.Q209	T	0	0	0	165	0	0	0	240	0	0	0	284	0	0		
chr9:80409488	GNAQ	p.Q209	T	0	0	0	159	0	0	0	236	0	0	0	279	0	0		
chr9:80409489	GNAQ	p.Q209	G	0	0	168	0	0	168	0	208	0	0	275	0	0	0		
chrX:47429340	ARAF	p.S490	T	0	0	0	172	0	0	1	170	0	0	0	205	0	0		
chrX:47429341	ARAF	p.S490	C	0	202	0	0	0	198	0	1	229	0	0	0	0	0		
chrX:47429342	ARAF	p.S490	A	187	0	0	0	191	0	0	0	225	0	0	0	0	0		
chrX:70341430	MED12	p.C289	C	0	183	0	0	0	291	0	0	2	319	0	0	0	0		
chrX:70341431	MED12	p.C289	A	181	0	0	0	181	0	0	0	319	0	0	0	0	0		
chrX:70341432	MED12	p.C289	G	0	0	187	0	0	0	299	1	0	0	326	1	0	0		
chrX:70346290	MED12	p.E881	G	0	0	283	0	0	0	296	0	0	0	427	2	0	0		
chrX:70346291	MED12	p.E881	A	249	0	2	0	292	0	0	0	407	1	0	0	0	0		
chrX:70346292	MED12	p.E881	A	244	0	0	2	308	0	0	0	430	0	0	0	0	0		
chrX:70350002	MED12	p.R1329	C	0	160	0	0	125	0	2	2	135	0	0	0	0	0		
chrX:70350003	MED12	p.R1329	G	0	0	158	0	0	0	118	0	0	0	136	0	0	0		
chrX:70350004	MED12	p.R1329	A	142	3	0	0	114	0	0	0	123	0	0	0	0	0		
chrX:70352768	MED12	p.E1497	G	0	0	130	0	0	0	124	0	0	0	153	0	0	0		
chrX:70352769	MED12	p.E1497	A	121	0	0	0	121	0	0	0	148	0	0	0	0	0		
chrX:70352770	MED12	p.E1497	G	0	0	131	0	0	0	123	1	0	0	148	0	0	0		
chrX:70355014	MED12	p.R1646	C	1	273	0	0	0	213	0	0	1	127	0	0	0	0		
chrX:70355015	MED12	p.R1646	G	0	0	268	0	0	0	217	0	0	0	132	0	0	0		
chrX:70355016	MED12	p.R1646	A	271	1	0	0	224	0	0	0	132	0	0	0	0	0		
chrX:70356107	MED12	p.W1688	T	0	0	0	255	0	0	0	340	0	0	0	327	0	0		
chrX:70356168	MED12	p.W1688	G	0	0	265	0												

Supplementary Table 1

COORDINATES	GENE	AA_CHANGE	REF	# READS											
				PLASMA AT BASELINE TO VEMURAFENIB+CRIZOTINIB				PLASMA AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB				LIVER BIOPSY AT RESISTANCE TO VEMURAFENIB+CRIZOTINIB			
				A1	C1	G1	T1	A2	C2	G2	T2	A2	C2	G2	T2
chr7:116423413	MET	p.Y1248	T	0	0	0	1265	1	0	3	5250	0	0	2	1519
chr7:116423414	MET	p.Y1248	A	1233	1	0	0	5126	1	2	1	1488	1	0	0
chr7:116423415	MET	p.Y1248	T	0	0	0	1278	0	0	2	5159	1	0	0	1528
chr7:116423428	MET	p.Y1253	T	1	0	0	1223	0	0	1	5259	0	0	0	1648
chr7:116423474	MET	p.M1268	T	0	0	3	1358	0	1	5	5709	0	0	4	1481