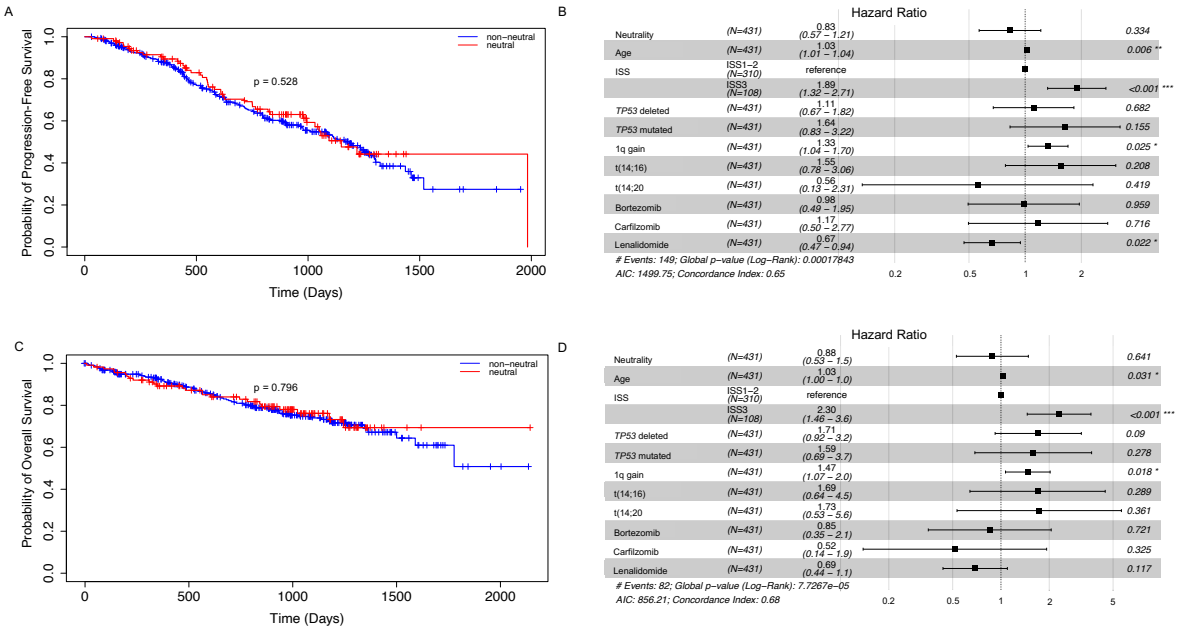
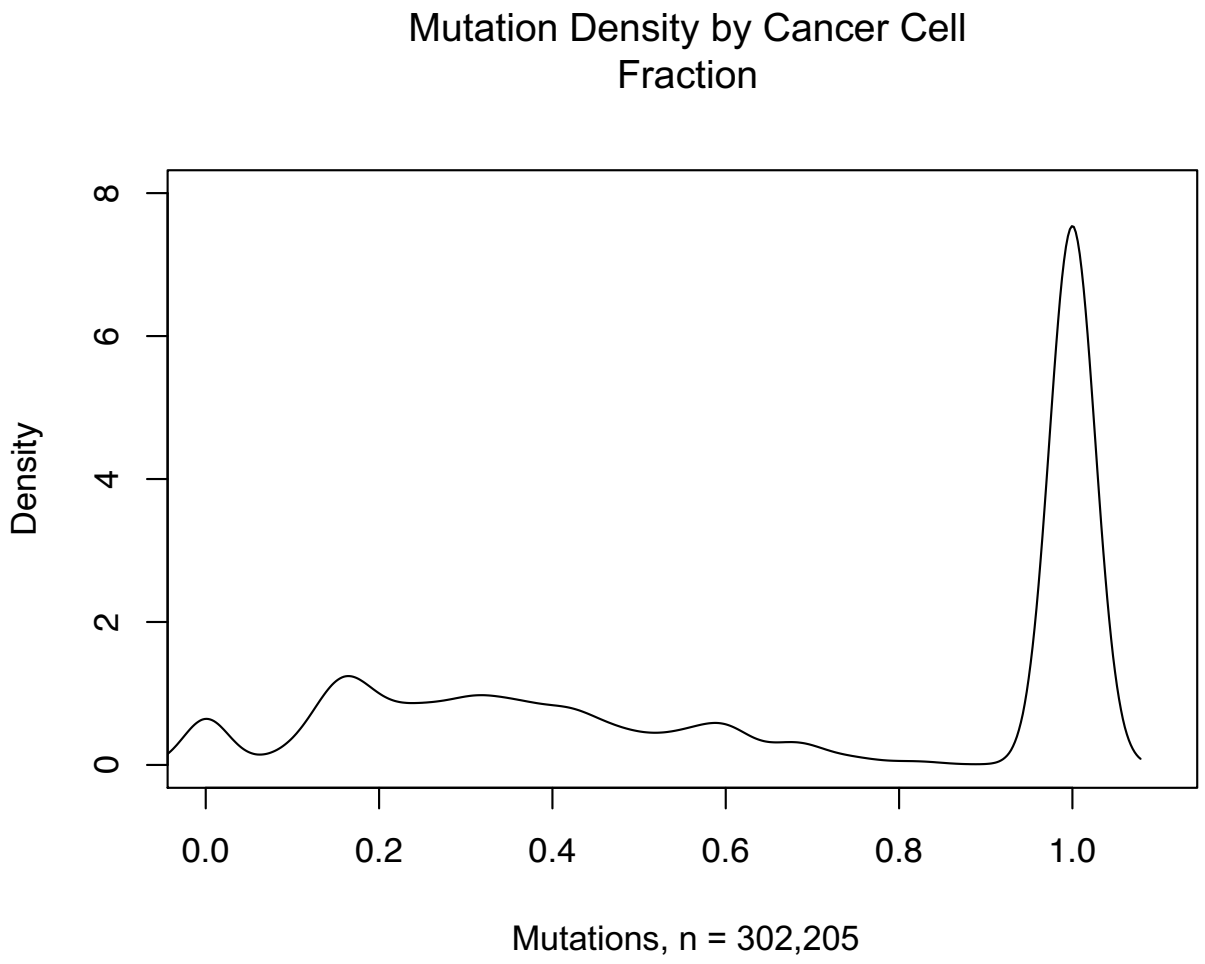
Supplementary Figures

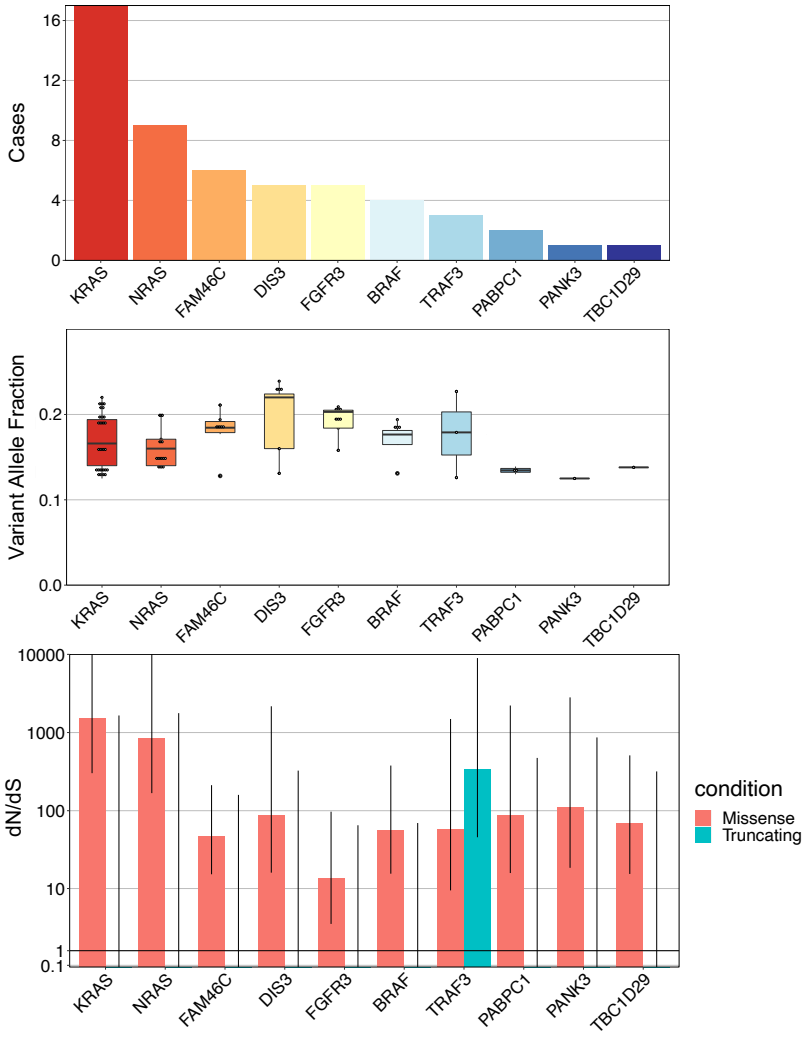
Supplementary Figure 1. Clinical outcomes in the MMRF CoMMpass cohort with regard to neutrality assessed by the *neutralitytestr* Package (n=431). A. Progression free survival for neutral vs. non-neutral tumors. B. Multivariate cox proportional hazards assessing the effect of neutrality, high-risk features, and treatment on progression free survival. C. Overall survival for neutral vs. non-neutral tumors. D. Multivariate cox proportional hazards assessing the effect of neutrality and high-risk features on overall survival.



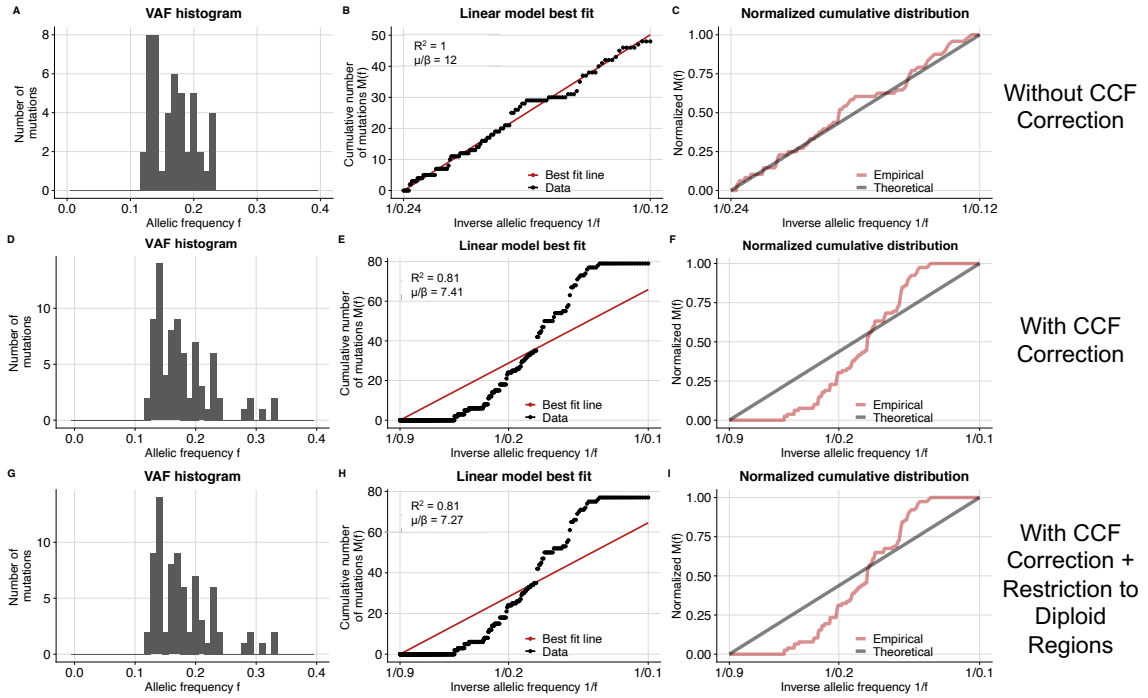
Supplementary Figure 2. Density of all SNVs as classified by cancer cell fraction. Mutations with a cancer cell fraction >0.9 are determined to be represented in the trunks of each tumor phylogeny (i.e, clonal).



Supplementary Figure 3. Subclonal mutations, identified via variant allele frequency thresholds outlined by Williams et al., 2016, classified as drivers under positive selection by *dndscv* in MMRF CoMMpass tumors designated as neutral (n=114). Top panel shows number of cases, middle shows boxplots of the variant allele frequency, and bottom panel shows the dN/dS ratio for each of missense or truncating variants with 95% interval of confidence represented as vertical lines. Q values for all dN/dS ratios were <0.05.



Supplementary Figure 4. Allelic frequency histograms with fit to the $M(f) \propto 1/f$ linear model. After correction for cancer cell fraction, subclonal mutations from example patient MMRF_2480 no longer fit the neutral model with R^2 values falling below 0.98.



Supplementary Table

Supplementary Table 1. Pairwise discovery analysis of neutrality calls compared to frequent driver mutations and copy number abnormalities using Fisher's exact test. Q values were calculated via false discovery rate analysis. Asterisk denotes continuous variables for which pairwise analysis was performed with Wilcoxon ranked sum test.

Event	p value	q value
ACTG1	1	1
ARID2	1	1
BCL7A	0.033	0.449
BHLHE41	0.441	1
BRAF	0.028	0.449
BTG1	0.681	1
CCND1	1	1
CYLD	0.537	1
DIS3	0.038	0.449
DTX1	1	1
DUSP2	0.492	1
EGR1	0.175	0.73
EHD1	1	1
FAM46C	1	1
FGFR3	1	1
FUBP1	1	1
HIST1H1B	0.728	1
HIST1H1D	1	1
HIST1H1E	0.768	1
HLA.DRB1	0.577	1
IGLL5	0.477	1
INTS6	0.172	0.73
IRF1	1	1
IRF4	1	1
KLHL6	0.214	0.744
KMT2B	0.342	0.937
KRAS	0.806	1
LCE1D	1	1
LTB	0.131	0.671
MAX	0.041	0.449
MYO1E	1	1
NFKB2	0.342	0.937
NFKBIA	1	1
NRAS	0.51	1
PABPC1	0.302	0.905
PIM1	0.728	1
POT1	0.388	0.937
PRDM1	0.681	1
PRKD2	0.02	0.449
PTPN11	0.657	1

RASA2	1	1
RB1	0.216	0.744
RBBP7	0.388	0.937
RPL10	0.192	0.744
RPL5	1	1
RPRD1B	1	1
RPS3A	1	1
SAMHD1	0.091	0.606
SETD2	1	1
SLC35G5	1	1
SP140	0.385	0.937
TBC1D29	1	1
TCL1A	0.681	1
TGDS	1	1
TP53	0.158	0.73
TRAF2	1	1
TRAF3	0.577	1
TRIM73	0.058	0.565
WDR45	1	1
ZNF292	0.491	1
del4p15	0.081	0.606
del12p13	1	1
del12q21	0.578	1
gain1q21	0.131	0.671
del8p22	0.09	0.606
gain6p22	0.494	1
del20p12	0.115	0.671
ampMYC	0.863	1
delRB1	0.912	1
del6q	0.567	1
delCDKN2C	0.13	0.671
delTP53	0.38	0.937
delFAM46c	0.551	1
delCYLD	0.231	0.744
delTRAF3	1	1
del13q34	0.822	1
del14q23	0.295	0.905
delBIRC	0.176	0.73
extra1q	0.014	0.449
HRD	0.034	0.449
t_CCND1	0.223	0.744
t_MMSET	0.088	0.606
t_MAFB	0.388	0.937
t_MAF	0.222	0.744
t_CCND3	1	1
t_MYC	1	1
purity*	0.705	NA
coverage*	0.075	NA