SUPPLEMENTARY METHODS

Whole-exome and targeted massively parallel sequencing

Tumor and matched normal DNA samples were subjected to whole-exome sequencing (n=9) or massively parallel sequencing (n=15) using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay targeting all exons of 341 key cancer genes, as previously described [1,2]. Sequence reads were aligned to the human reference genome GRCh37 using the Burrows-Wheeler Aligner (BWA, v0.7.10) [3], and local realignment, duplicate removal and base quality recalibration were performed using the Genome Analysis Toolkit (GATK, v3.1.1) [4]. Variant calling was performed as previously described [2,5]. In brief, single nucleotide variants (SNVs) were identified using MuTect (v1.0) [6], small insertions and deletions (indels) using Strelka (v2.0.15) [7] and VarScan 2 (v2.3.7) [8], and copy number alterations and loss of heterozygosity (LOH) using FACETS [9]. Mutation hotspots were assigned according to Chang *et al* [10]. Cancer cell fractions of each mutation and whether these mutations were clonal or subclonal were inferred using ABSOLUTE (v1.0.6) [11], as previously described [2,5]. Mutational signatures were defined for cases with at least 20 somatic mutations using deconstructSigs [12].

Supplementary References

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