

SUPPLEMENTARY METHODS

Data collection

Informed consent was obtained for all patients included in the study. Patients' medical and pathological records were analyzed for demographic and clinical characteristics, treatments received, and survival.

Whole exome and RNA sequencing

For the patient #1, DNA and RNA have been simultaneously purified with AllPrep DNA/RNA/miRNA Universal Kit for frozen tissue and AllPrep DNA/RNA FFPE Kit for FFPE cores, according to the manufacturer's instructions (Qiagen). Their concentrations were determined by the NanoDrop ND-1000 spectrophotometer at 260/280 nm (NanoDrop Technologies, Inc.). The nucleic acids quality and integrity were analyzed with the Agilent TapeStation 2200 system.

The whole exome sequencing procedure was performed following the manufacturer's recommendations (SureSelect Human Exon Kit v5, 75 MB; Agilent) as previously described [1]. The generated reads were mapped to reference genome hg38 (GRCh38). Identification of SNVs (Single Nucleotide Variations) and small insertions/deletions was performed via the Broad Institute's MuTect tool 2.0 for somatic DNA [2]. The somatic mutations were filtered as follows: Total Reads > 10, Somatic score > 3, Mutated Allele Frequency in Tumor tissue \geq 5%, Mutated Allele Count in Tumor tissue \geq 3, Mutated Allele Frequency in Constitutional tissue < 4%. Somatic repetitive mutations were identified using the MSICare program (<https://github.com/MSI.CRSA/MSICare>). The Next Generation Sequencing (NGS) MSI status was determined using the MSISensor program [3].

RNA sequencing procedure was performed following the manufacturer's recommendations (quantseq-3mrna-sequencing; Lexogen). The generated reads were mapped using STAR [4] to the reference genome hg38 (GRCh38) and normalized using the DESeq2 normalization method

[5]. Immune infiltrate and stromal cells were estimated using MCP-counter [6]. Immune checkpoint and modulator genes were selected from our previous publication [7].

Supplementary references

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SUPPLEMENTARY FIGURES

Supplementary Figure S1: Radiological evolution of the adrenal glands under immune checkpoint inhibition

Supplementary Figure S2: Progressive adrenal, colon or liver tumors displaying the microsatellite instability phenotype

(A) Bar plots represent the number of mutations per megabase (Nb mutations/Mb) across the whole exome for 3 tumor sites of patient #1 in repetitive DNA sequences (R, light blue) and in non-repetitive DNA sequences (NR, dark blue). The median mutation rate in all types of CRC was described previously [25] and is indicated by the red dotted line.

(B) Distribution of MSISensor scores. Dots represent the percentage of mutated microsatellites (MSISensor score) obtained from whole exome sequencing of 3 tumor sites of patient #1. The cutoff of MSISensor score at 10 (FDA recommendation) was used to differentiate MSS from MSI tumors (green dotted line).

Supplementary Figure S3: Overlapping mutational signature. Venn diagram showing the overlap between colon, liver, and adrenal tumors in DNA non-repetitive (A) and repetitive DNA sequences (B) of patient #1.

Supplementary Figure S4: Schematic diagram illustrating the potential mechanism of immune escape of antigen presentation pathways genes in the adrenal tumors of patient #1.