**Supplementary Figure Legends**

**Supplementary Figure S1. Neoantigen landscape in tumors before and at acquired resistance to ICIs.** Distribution of neoantigens with strong, intermediate or weak predicted HLA I binding in paired pre-immunotherapy (P1) and immunotherapy resistant (IR) specimens **(A)** and overall in the cohort under investigation **(B)**.

**Supplementary Figure S2. Analysis of mutational signatures. (A)** Three mutational signatures discovered by the Bayes NMF algorithm for cases of resistance to immune checkpoint blockade and **(B)** the distribution of the three mutation signatures in the 14 patients in our cohort.

**Supplementary Figure S3. Copy number analysis of *B2M*.** Results of quantitative PCR experiments to determine *B2M* copy number in samples collected from case #23. Diagnostic, pre-immunotherapy and immunotherapy resistant samples showed progressive loss of *B2M* through treatment. Total loss of *B2M* was confirmed in a PDX sample derived from case #23 at the time of acquired resistance to ICIs. Normal tonsil DNA was used as a control.Data is the average of *B2M* copy number was evaluated using two independent assays and is presented as the average of these two assays + SEM.

**Supplementary Figure S4. Impaired antigen processing and presentation in specimens from case #23. (A-D)** Simultaneous multiplex quantitative immunofluorescence of antigen processing and presentation markers in pre-immunotherapy and immunotherapy resistant tumor tissues from case #23**. (A-B):** Bar graph depicting the level of HLA I in whole tumor sections from pre-immunotherapy and immunotherapy resistant samples measured using multiplex quantitative immunofluorescence and quantified with AQUA® software. Numbers in the individual bars represent total fields of view analyzed. Statistical significance was calculated using the Mann-Whitney test. \*\*\*\*p<0.0001. AU, arbitrary units. **(F)** Multiplex immunofluorescence image representing one field-of-view (FOV), showing the expression of HLA I (red) specifically in the tumor compartment represented by cytokeratin positive epithelial cells (green) and nuclear staining with DAPI (blue) respectively. **(C-D)** Bar graphs showing the levels of B2M and HLA I in the stromal compartment of whole tumor sections from pre-immunotherapy and immunotherapy resistant samples from case #23 as quantified using the AQUA® software. Numbers in the individual bars represent total FOVs analyzed. Statistical significance was calculated using Mann-Whitney test. \*\*\*\*p<0.0001. AU, arbitrary units.

**Supplementary Figure S5. Effect of IFN induction on ICI-resistant PDXs.** Western blot analysis ofPDXs generated from cases #23, #26, #8 and #7 at the time of resistance to ICIs following intratumoral injection of either PBS or IFN showing the levels of phosphorylated STAT1 and total B2M in the presence or in the absence of IFN- Each lane of the western blot represents an independent mouse tumor used for these studies.

**Supplementary Figure S6. Levels of HLA I and B2M measured using quantitative immunofluorescence in paired pre-immunotherapy tumor and immunotherapy resistant samples.** Levels of HLA I and B2M in whole tumor sections from pre-immunotherapy and immunotherapy resistant samples as quantified using the AQUA® software. Numbers in the individual bars represent total fields of view analyzed. Statistical significance was calculated using the Mann-Whitney test. P1- pre-immunotherapy and IR-immunotherapy resistant. \*\*\*\*p<0.0001, \*p<0.05.

**Supplementary Figure S7. The genomic landscape of interferon pathway genes.** Oncoprint generated from whole exome sequencing data. Mutated IFN genes are listed vertically in order of frequency of somatic single nucleotide mutations or copy number alterations. A case with a hypermutator phenotype (#17) sample was excluded from this analysis. Only genes with genetic alterations are shown. \*Of note, sample 26IR1 was collected from a site (adrenal metastasis) that responded to a short course of ICI, but progressed during a 2-month delay of treatment when steroids were administered for cerebral edema associated with new intracranial disease (sample 26IR3) and pneumonitis. This site subsequently regressed with re-introduction of ICI.

**Supplementary Figure S8. Quantitative immunofluorescence analysis showing the levels of the immune inhibitory molecule TIM-3 in paired pre-immunotherapy and immunotherapy resistant tumor samples.** Numbers in the individual bars represent total fields of view analyzed. Statistical significance was calculated using Mann-Whitney test. P1- pre-immunotherapy and IR- immunotherapy resistant. \*\*\*\*p<0.0001, \*\*\*p<0.001 \*\*p<0.01, \*p<0.05.