**Supplementary Methods**

**Multiplexed quantitative immunofluorescence**

Three simultaneous multiplexing protocols were carried out to detect: (1) tumor infiltrating lymphocytes (TILs), (2) immune inhibitory receptors, and (3) antigen processing and presentation markers. The TIL staining protocol was performed as described previously by our group (42). Protocols #2 and #3 were each performed using 5-color multiplex fluorescence with simultaneous detection of 5 markers labeled using isotype specific antibodies for PD-1, TIM-3 and LAG-3 specifically in CD3 cells (protocol #2) and HLA Class I and B2M specifically in CK positive cells (protocol #3). These protocols were carefully titrated, validated and tested for reproducibility (Datar et al., unpublished). Both these protocols are an adaptation of the TIL multiplexing protocol (42). Briefly, fresh histology sections from the cases were deparaffinized and subjected to antigen retrieval using EDTA buffer (Sigma-Aldrich, St Louis, MO) pH=8.0 and boiled for 20 min at 97°C in a pressure-boiling container (PT module, Lab Vision). Slides were then incubated with dual endogenous peroxidase block (DAKO #S2003, Carpinteria, CA) for 10 min at room temperature and subsequently with a blocking solution containing 0.3% bovine serum albumin in 0.05% Tween solution for 30 minutes. Slides were stained with 4', 6-Diamidino-2-Phenylindole (DAPI), CD3, PD-1, TIM-3, and LAG-3. Primary antibodies for protocol #2 included: CD3 (rabbit polyclonal, Dako), PD-1 (clone EH33, CST), LAG-3 (Clone 17B4, Abcam) and TIM-3 (clone D5D5R, CST). Primary antibodies for protocol #3 included: cytokeratin-488 (Clone AE1/AE3, eBioscience), HLA I mAb HC-10 (that recognizes HLA-B, HLA-C and some HLA-A molecules) and B2M (Clone D8P1H, CST). For protocol #2, secondary antibodies and fluorescent reagents used were anti-rabbit Envision (K4003, DAKO) with fluorescein-tyramide (Perkin-Elmer), anti-mouse IgG2a antibody (Abcam) with Cy3 plus (Perkin-Elmer), goat anti-rabbit (Abcam) with biotinylated tyramide/Streptavidine-Alexa750 conjugate (Perkin-Elmer), anti-mouse Envision (K40001) with Cy5-tyramide (Perkin-Elmer). For protocol #3, secondary antibodies and fluorescent reagents used were anti-rabbit Envision (K4003, DAKO) with biotinylated tyramide/Streptavidin-Alexa 750 conjugate, anti-mouse IgG2a antibody (Abcam) with Cy3 plus (Perkin-Elmer), anti-mouse Envision (K40001) with Cy5-tyramide (Perkin-Elmer). Residual horseradish peroxidase activity between incubations with secondary antibodies was eliminated by exposing the slides twice for 10 minutes to a solution containing benzoic hydrazide (0.136 mg) and hydrogen peroxide (50 µl).

**Tissue fluorescence measurement, scoring and statistical analysis**

Quantitative measurement of the fluorescent signal was performed using the AQUA® method that enables objective and sensitive measurement of targets within user-defined tissue compartments (42,43). Briefly, the quantitative immunofluorescent score of each target (i.e. CD3+ cells (protocol #2) and CK+ cells (protocol #3)) was calculated by dividing the target pixel intensities by the area of CD3 positivity or cytokeratin positivity in the sample. Scores were normalized to the exposure time and bit depth at which the images were captured, allowing scores collected at different exposure times to be comparable. For the statistical analysis, the Mann Whitney test was carried out to calculate the statistical significance between the pre-ICI and ICI-resistant patient samples.

**Interferon gamma treatment**

Patient derived xenografts were established in >28 day old NOD-*scid* IL2Rgammanull (NSG) mice. All animals were kept in pathogen-free micro-isolator housing under BSL2 guidelines under a Yale IACUC-approved animal protocol. Initial patient tumor biopsy material was manually dissociated, suspended in Matrigel (Corning) and subcutaneously injected in the right flank using an 18G needle. To propagate the engrafted patient derived xenograft (PDX) tissue, measureable tumors were harvested asceptically, manually dissociated, re-suspended in Matrigel and re-injected into additional NSG mice. A sample of the tumor at each *in vivo* passage was submitted to The Molecular Diagnostics Laboratory in the Section of Comparative Medicine at Yale to test for mouse biological contaminants.At approximately 100mm3, established patient derived xenografts were injected intratumorally with 125,000 units/mouse of recombinant human Interferon gammaR&D, 285-IF). Intratumoral injections were performed every 24 hours for two days with a 3rd injection one hour before mice were euthanized for tumor collection.