**Supplemental Table 1. Clinical and pathologic characteristics of patients included in tissue microarrays**

The table shows clinical characteristics of patients and their tumors included in each tissue microarray. NSCLC cases were retrieved from the Department of Pathology archive at the Johns Hopkins Medical Institutes and were approved by the Johns Hopkins Institutional Review Board. The World Health Organization and International Association for the Study of Lung Cancer/American Thoracic Society classification criteria were used to determine histological subtypes of lung NSCLC ([1](#_ENREF_1), [2](#_ENREF_2)) and American Joint Committee on Cancer 7th edition was used to determine the pathological stage (pT) of the primary tumor at the time of initial diagnosis ([3](#_ENREF_3)). The tumor area for TMA construction was selected based on the review of the H&E stained tissue section by an American Pathology Board-certified pathologist (QKL). The lung carcinoma tissue microarray (0.6 mm in diameter, 3-4 cores per case) and tumor-matched normal lung tissue (0.6 mm in diameter, 2 cores per case) were constructed using surgically resected specimens. All tissues were fixed in 10% buffered formalin and embedded in paraffin. For tumor cases, 63 lung adenocarcinomas with quadruplicate cores for each case and 96 lung squamous cell carcinomas with triplicate cores for each case were included in this study. All tumor cases were annotated with available clinical information in a manner that protected patient identity. In addition, a variety of normal tissue such as liver, stomach, brain, lymph node and others, were also included as controls. A chi-squared analysis was performed to compare characteristics between adenocarcinoma (AD) and squamous cell carcinoma (SCC) samples.

**Supplementary Figure 1. B7-H4 expression is low in human and mouse lung cancer cell lines in vitro**

(A) Both human and mouse lung cancer cell lines were examined for membranous B7-H4 expression by flow cytometry. The graph represents averages from three separate experiments. (B) The H520 squamous cell carcinoma cell line was treated with 100 nM rapamycin for indicated time points and analyzed by flow cytometry and immunoblotting. The images are representative of two independent experiments.

**Supplementary Figure 2. B7-H1 expression does not change with MAPK or proliferation inhibition**

(A) NSCLC cell lines treated with 10 μM of the MEK inhibitor U0126 for the indicated time points. (B) 2.5x104 IO33 cells were plated and the cell number was determined again after 16 hr treatment with 10 μM U0126.

**Supplementary Figure 3. Scoring of PD-L1 and pS6 staining in lung adenocarcinoma and squamous cell carcinoma TMAs**

(A) Images represent the scale (0=<5%, 1+ (≥5-20%), 2+ (≥20-50%), 3+ (≥50%) used to score the number of cells positive for membrane and cytoplasmic PD-L1 expression in both TMAs. The length of the scale bar is 100 μM. (B) Quantification of scoring for membrane PD-L1 expression in tumor and normal tissues. A score for each set of tumor punches was determined by averaging the individual scores for each punch. (C) The immunohistochemical images are a representation of the scoring criteria for positive or negative pS6 staining in both TMAs. (D) Quantification of pS6 expression in both TMAs. All immunostained TMAs were scanned using Aperio’s ImageScope.

**Supplementary Figure 4. Co-expression of pS6 and PD-L1 staining in TMAs**

Representative images of a tumor sample with a similar staining pattern for PD-L1 and pS6. Positive staining was pseudocolored (green for PD-L1, pink for pS6) using Adobe Photoshop and colors were overlaid. The red color results from an additive blending of the pseudocolors, indicating overlapping staining patterns. The length of the scale bar is 100 μM.

**Supplemental Figure 5. The combination of rapamycin and anti-PD-1 antibody decreases KRAS-driven lung tumor growth**

(A) 1x106 IO33 cells were administered as sub-cutaneous tumors to syngeneic A/J mice. When tumors were 3-5mm in diameter treatment began and lasted for 21 days.The same dosing schedule and regimen was used as in the transgenic mouse study. (B) Tumor volume of syngeneic IO33 cells in A/J mice over a 22 d period. Length and width were measured QOD with digital calipers and the third dimension was estimated by averaging the length and width. Tumor volume was calculated by multiplying the three dimensions. The arrow indicates the first treatment day. N=6/group. (C) Image J quantified immunoblotting of tumor lysates are shown. PDL1 was normalized to α-tubulin. pS6 and pAKT were normalized to total levels of S6 and AKT, respectively. N=3/group (D) Populations of tumor infiltrating lymphocytes were analyzed by flow cytometry. Tumors were digested into single cells using mechanical separation and a triple-enzyme digestion mix. Tumor-infiltrating lymphocytes were isolated through a Ficoll gradient (Cellgro). Surface staining was completed prior to cell permeabilization and was done using the FoxP3 Fixation Permeabilization Concentrate and Diluent kit (eBio #00-5521-00) according to manufacturer’s recommended protocol. After blocking endogenous Fc receptors (BD #553142) the following conjugated antibodies were used: mCD8-PerCP (BD #553036), mCD4-PacBlue (BD #558107), mCD3-APC/Cy7 (BD #560590), mCD127-FITC (eBio #11-1271), mCD25-PE/Cy7 (eBio #25-0251) and mFoxP3-APC (eBio #17-5773). Compensation, isotype controls and primary staining were run on a FACS LSRII (BD Biosciences) and analyzed using FlowJo software. N=3/group. (E) The ratio of CD8 T cells over Tregs from (D). (F) Images represent IHC staining with markers of proliferation (Ki67), senescence (pHP1-γ), and apoptosis (cleaved caspase 3) in subcutaneous lung tumors. Quantification of staining is shown to the right. N=6. \*p≤0.05 using unpaired student’s t test.

**Supplementary Figure 6. The combination of rapamycin and αPD-1 blockade decreases NNK-derived syngeneic lung tumor growth.** (A) 1x106 IO33 cells were administered as sub-cutaneous tumors to syngeneic A/J mice. When tumors were 3-5mm in diameter treatment began and lasted for 21 days. All treatments were IP injections. (B) The average subcutaneous tumor volume of syngeneic IO33 cells in A/J mice 21 d after specified treatments. N=6/group. N=6/group. (C) Therapies alone or in combination were well tolerated and did not significantly mouse weight. (D) Quantified immunoblots of tumor lysates are shown using Image J software. PD-L1 was normalized to α-tubulin and pS6 was normalized to total levels of S6. N=6/group (E) Populations of tumor infiltrating lymphocytes were analyzed by flow cytometry. N=3/group. \*\*p≤0.05 compared to all groups by two way ANOVA.

**Supplemental References**

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