FIGURE LEGENDS (Supplemental Figures)

Supplemental Figure 1

THU/DNMTi treatment reduces tumor burden and increases survival in ID8 *Trp53*$^{-/-}$ mouse model of OC; flow cytometry immunophenotyping data. A) Schematic of mouse experiment. Mice i.p. injected with 5e6 ID8 *Trp53*$^{-/-}$ tumor cells, with treatment beginning about three weeks post tumor injection. n = 10 per group. **B)** On day 1, mice were injected with tetrahydrouridine (THU) at 10 mg/kg and then after 30-60 minutes, injected with 0.1 mg/kg of Dac. On day 4, mice were injected with tetrahydrouridine (THU) at 10 mg/kg and then after 30-60 minutes, injected with 1 mg/kg of 5-Aza. This treatment schedule was repeated until the end of the experiment. **C)** Survival curve for Mock versus THU/DNMTi treatment groups. n = 10 per group. No animals were excluded or censored from the study. **D)** Schematic of mouse experiment. Mice were i.p. injected with 5e6 ID8 *Trp53*$^{-/-}$ tumor cells, with treatment beginning one week post tumor injection. n = 10 per group. **E)** Mice were injected with 0.5 mg/kg of 5-Aza reconstituted in PBS for five consecutive days in one week, followed by a week with no injections. This treatment schedule is repeated until the end of the experiment. **F)** Survival curve for Mock versus Aza treatment groups. n = 10 per group. No animals were excluded or censored from the study. **G-K)** Immunophenotyping was performed on ascites drained from mice in Figure 1 using flow cytometry. Lymphocyte panel gating strategy shown. **G)** CD8+IFNγ+ T Cells (% IFNγ+ of CD8+). CD8+PD-1+ T Cells (% PD-1+ of CD8+). **H)** NKT Cells (% NK1.1+ of CD3+). **I)** CD4+ T Cells (% CD4+ of CD3+). T_{reg} Cells (% FOXp3+ of CD4+). CD4+IFNγ+ T Cells (% IFNγ+ of CD4+). CD4+PD-1+ T Cells (% PD-1+ of CD4+). **J)** Central Memory CD4+ T Cells (% CD62L+CD44+ of

CD4+). Effector Memory CD4+ T Cells (% CD62L-CD44+ of CD4+). Naïve CD4+ T Cells (% CD62L+CD44- of CD4+). **K)** Central Memory CD8+ T Cells (% CD62L+CD44+ of CD8+). Effector Memory CD8+ T Cells (% CD62L-CD44+ of CD8+). Naïve CD4+ T Cells (% CD62L+CD44- of CD8+). **L)** Myeloid panel gating. **M**) Lymphocyte panel gating. A one-way ANOVA was performed for statistical significance. *p<0.05

Supplemental Table 1

Table showing identifier of each mouse, date of drain, ascites tap number, volume of ascites (mL), live cell concentration (cells/mL), total live cells, and percentage of live cells using trypan blue exclusion and an automated cell counter. Ascites was drained and stained when enough mice had accumulated ascites for flow analysis: Week 7 (12/10/2020) and Week 11 (1/8/2021) post-tumor injection. All mice that were still alive had an attempted ascites drain on those two dates.

Supplemental Figure 2

Raw numbers of migrated T cells and the calculation of migration index.

A) Dac treatment. **B)** Experimental schematic. T cells were isolated from spleens of IFNγ GFP reporter mice (C57BL/6J genetic background). T cells were then activated with CD3/CD28 Dynabeads and cultured for 6 days with Complete RPMI media supplemented with 2-mercaptoethanol, murine recombinant IL-2, and murine recombinant IL-7 prior to using in transwell migration/chemotaxis assay. Subsequently, murine ID8 *Trp53*$^{-/-}$ Adar1 knockdown (shAdar1) or control cells (shGFP) were plated in 6 well dishes and treated with DMSO (Mock) or Dac for three consecutive days without

media change (each condition performed in triplicate). On day 4, -CCL5 and +CCL5 control conditions were also setup in wells with media only (control conditions performed in duplicate), and the activated T cells were placed on the transwell inserts for 2 hours for each well. All cells (T cells and tumor cells) below the transwell insert were then quantified using flow cytometry (cells left in transwell insert were discarded). Schematic created using Biorender.com. **C)** Raw numbers of migrated T cells (not normalized to the number of tumor cells). **D)** Formulas for the calculation of migration index/fold change. A one-way ANOVA was performed for statistical significance. *p<0.05

Supplemental Figure 3

A) This is the same data graphed in Figure 3C, but shown with different statistical comparisons. **B)** This is the same data graphed in Figure 3D, but shown with different statistical comparisons.

Supplemental Figure 4. A) Assessment of proliferation showing shGFP and shAdar1: Mock, Dac or 5-Aza treated (each condition performed in triplicate). This is the same data as **Figure 4D** but shown as cell count with the mock condition rather than % live cells treated compared to mock. **B-C)** We seeded shGFP and shAdar1 ID8 *Trp53*$^{-/-}$ cells on day 0, added anti-IFNAR1 or isotype control (10 ug/mL), and then added murine recombinant IFN-β one hour later. We harvested cells 24 hours after IFN stimulation, extracted RNA and performed RT-qPCR. **B)** Schematic for experiment. **C)** RT-qPCR. **D)** ID8 *Trp53*$^{+/+}$, ID8 *Trp53*$^{-/-}$ and HGS2 (*Trp53*$^{-/-}$ *Pten*$^{-/-}$ *BrCa2*$^{-/-}$) cells were transduced

with lentiviral short-hairpin RNA vectors targeting GFP (shGFP for control) and Adar1 (shAdar1 for Adar1 knockdown) and selected with 3 μg/ml puromycin. To validate Adar1 knockdowns, cells were cultured with and without murine recombinant IFN-β to show induced and baseline levels of Adar1 p150 respectively. Western blot was then performed, using β-actin as the loading control. **E)** Growth inhibition assays showing DNMTi (Dac and 5-Aza), or IFN-β compared to Mock across all three cell lines (each condition performed in triplicate). **F)** Colony formation assays showing Mock, Dac, 5-Aza and IFN-β across all three cell lines (each condition performed in triplicate). ID8 *Trp53*$^{-/-}$ from Figure 6G is shown here again for direct comparison with other cell lines. **G)** IFN-β cytokine levels normalized by number of live cells in ID8 *Trp53*$^{+/+}$ cell line, ID8 *Trp53*$^{-/-}$ cell line, and HGS2 (*Trp53*$^{-/-}$*Pten*$^{-/-}$*BrCa2*$^{-/-}$) cell line. **H)** IFN-β cytokine levels (raw concentration) in ID8 *Trp53*$^{+/+}$ cell line, ID8 *Trp53*$^{-/-}$ cell line, and HGS2 (*Trp53*$^{-/-}$ *Pten-/- BrCa2-/-*) cell line. **I)** The last plot shows data from all three cell lines again, but on the same graph (stats not shown) for the purposes of representing scale for direct comparisons. **J)** CCl2, CCL5, CXCL10 chemokine levels normalized by number of live cells in ID8 *Trp53*$^{+/+}$ cell line, ID8 *Trp53*$^{-/-}$ cell line, and HGS2 (*Trp53*$^{-/-}$*Pten*$^{-/-}$*BrCa2*$^{-/-}$) cell line. The last row of plots shows data from all three cell lines again, but on the same graph (stats not shown) for the purposes of representing scale for direct comparisons. **K)** CCl2, CCL5, CXCL10 chemokine levels (raw concentration) in ID8 *Trp53*$^{+/+}$ cell line, ID8 *Trp53*$^{-/-}$ cell line, and HGS2 (*Trp53*$^{-/-}$ *Pten-/- BrCa2-/-*) cell line. The last row of plots shows data from all three cell lines again, but on the same graph (stats not shown) for the purposes of representing scale for direct comparisons. A one-way ANOVA was performed for statistical significance. *p<0.05

Supplemental Figure 5

A) We analyzed ADAR1 wildtype, ADAR1 KO, and ADAR1p150 KO HEK293T cells treated with mock or IFN**-**b (data deposited at the Gene Expression Omnibus accession number GSE99249 (66). Inosine bases ("I") are read as guanine bases ("G") by sequencing technology, therefore, adenosine to inosine (A-to-I) edits are outputted as the "A2G Editing Index" with the RNA Editing Indexer tool (38). *Alu* editing index is shown. LTR editing index is shown. A one-way ANOVA was performed for statistical significance. *p<0.05 compared to Wildtype – Mock; #p<0.05 compared to Wildtype – IFNb; +p<0.05 compared to ADAR1p150 KO- Mock; ‡p<0.05 compared to ADAR1p150 KO – IFNb. **B-C)** Mock and 5-Aza treatment is the same as in Figure 5. For the IFN-β condition, TykNu cells were treated in three replicates with a final concentration of 10 ng/mL human recombinant IFN-β for 24 hours prior to harvesting. RNA was isolated from three treatment replicates each, and Illumina sequencing libraries were prepared and sequenced, resulting in paired-end, stranded reads. **B)** ERV, LINE, and LINE-1 editing index for TykNu. **C)** ERV, LINE, and LINE-1 editing index for isogenic Hey cell lines. **D)** A2780, TykNu, Hey, Hey TP53 wild-type CRISPR control (HC2), and Hey TP53 mutant (HH23) cells were transduced with lentiviral short-hairpin scrambled/non-targeting RNA vectors (shSCR for control) and ADAR1 (shADAR1 for ADAR1 knockdown) and selected with 400 μg/ml neomycin. To validate ADAR1 knockdowns, cells were cultured with and without murine recombinant IFN-β to show induced and baseline levels of ADAR1 p150 respectively. Western blot was then performed, using β-actin as the loading control. **E)** Colony formation assays showing Mock, IFN-β Dac +/-

IFN-β, 5-Aza +/- IFN-β and across Hey TP53 wild-type shSCR or shADAR1 (each condition performed in triplicate). **F)** Colony formation assays showing Mock, IFN-β Dac +/- IFN-β, 5-Aza +/- IFN-β and across A2780 (TP53 wild-type) shSCR or shADAR1 (each condition performed in triplicate). **H-K)** shSCR and shADAR1 cells (TykNu, Hey TP53 mutant, TP53 wild-type, or A2780) were plated on day 0, treated with mock (DMSO), 1um 5-Aza, or 100 nM Dac for three days and then passaged on day 4. Cells were then harvested on day 7 and RNA was isolated for q-RT-qPCR for the assessment of interferon-stimulated gene (ISG) expression. **H)** RT-qPCR for TykNU ISGs: IFI27, ISG15, IFN-β, CCL5. **I)** RT-qPCR for Hey TP53 mutant ISGs: IFI27, ISG15, IFN-β, CCL5. **J)** RT-qPCR for Hey TP53 wild-type ISGs: IFI27, ISG15, IFN-β, CCL5. **K)** RT-qPCR for A278-ISGs: IFI27, ISG15, IFN-β, CCL5.

Supplemental Figure 6

A) Survival curve for mice that received shAdar1 tumors with THU/DNMTi treatment and either: 1) isotype control, 2) anti-IFNAR, 3) anti-CD8a, or 4) anti-NK1.1 antibodies. No animals were excluded or censored from the study (n = 10 per group). ID8 *Trp53*$^{-/-}$ shAdar1 knockdown tumor cells were grown in tissue culture dishes and then 5e6 cells were i.p. injected into mice 1 day after the first injections of antibodies. THU/DNMTi treatment began around week 2. **B)** Survival curve from Supplemental Figure 6A, but with the shGFP + THU/DNMTi curve overlay from Figure 1B (solid red line). **C)** Validation of CD8+ T cell depletion from experiment in Figure 6A. **D)** Validation of NK cell depletion from experiment in Figure 6A. A one-way ANOVA was performed for statistical significance on box-and-whisker graphs. Gehan-Breslow-Wilcoxon method was performed for statistical significance on Kaplan-Meier survival curve. *p<0.05

Supplemental Figure 7

A) This is the same data graphed in Figure 3C, but shown with different statistical comparisons. **B-J)** Ascites was drained from mice in the experiment from Figure 6A-D and analyzed for chemokines and cytokines present in the TME. **B)** IFN-γ protein concentration in ascites supernatant. **C)** IFN-α protein concentration in ascites supernatant. **D)** IFN-β protein concentration in ascites supernatant. **E)** CCL2 protein concentration in ascites supernatant. **F)** CXCL1 protein concentration in ascites supernatant. **G)** IL-12p70 protein concentration in ascites supernatant. **H)** GM-CSF protein concentration in ascites supernatant. **I)** IL-4 protein concentration in ascites supernatant. **J)** TNFα protein concentration in ascites supernatant. **K)** Concentrations of IgG1, IgG2b, IgG2b, IgG3, and IgA antibody isotypes in the ascites supernatant.