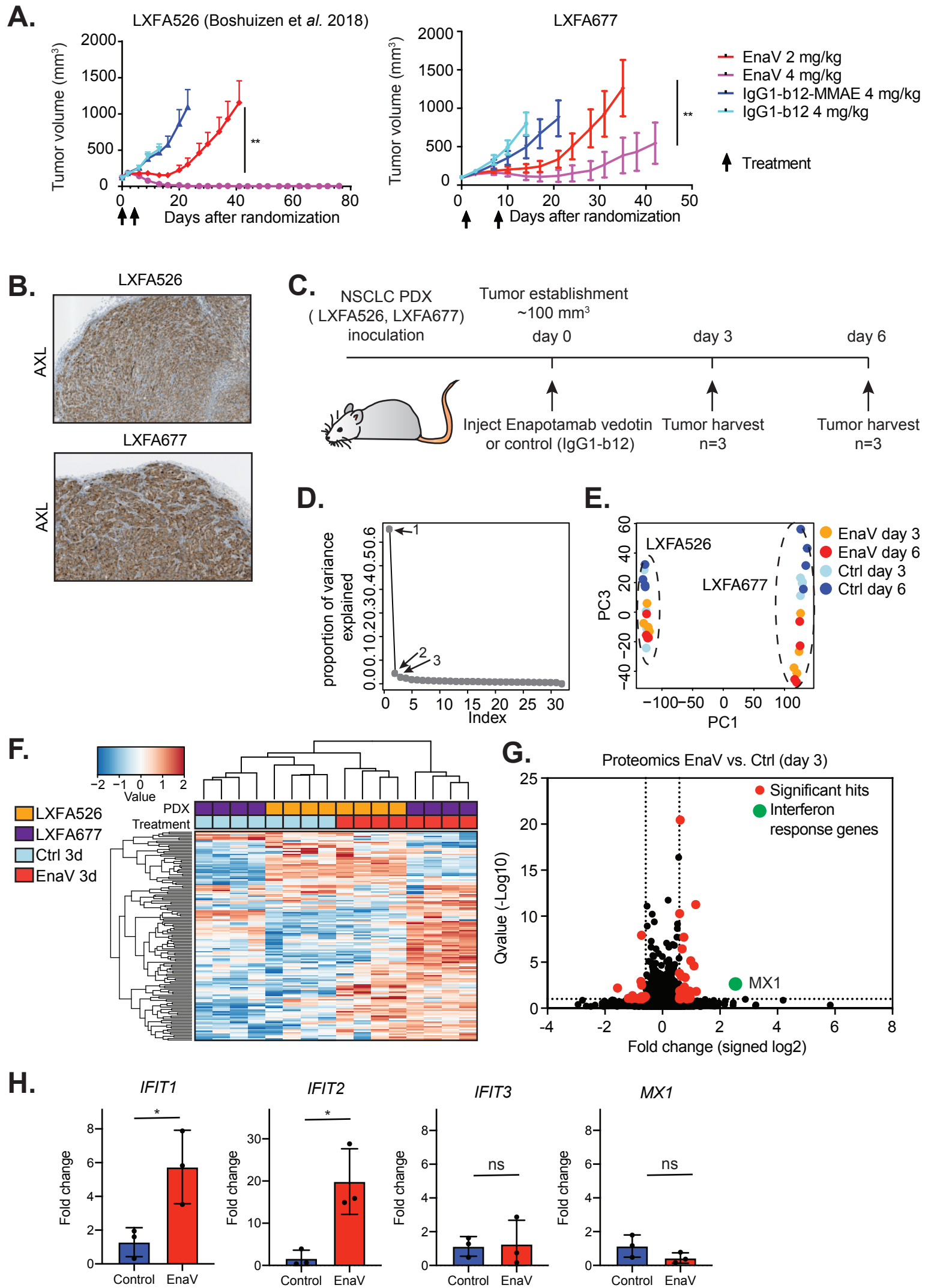
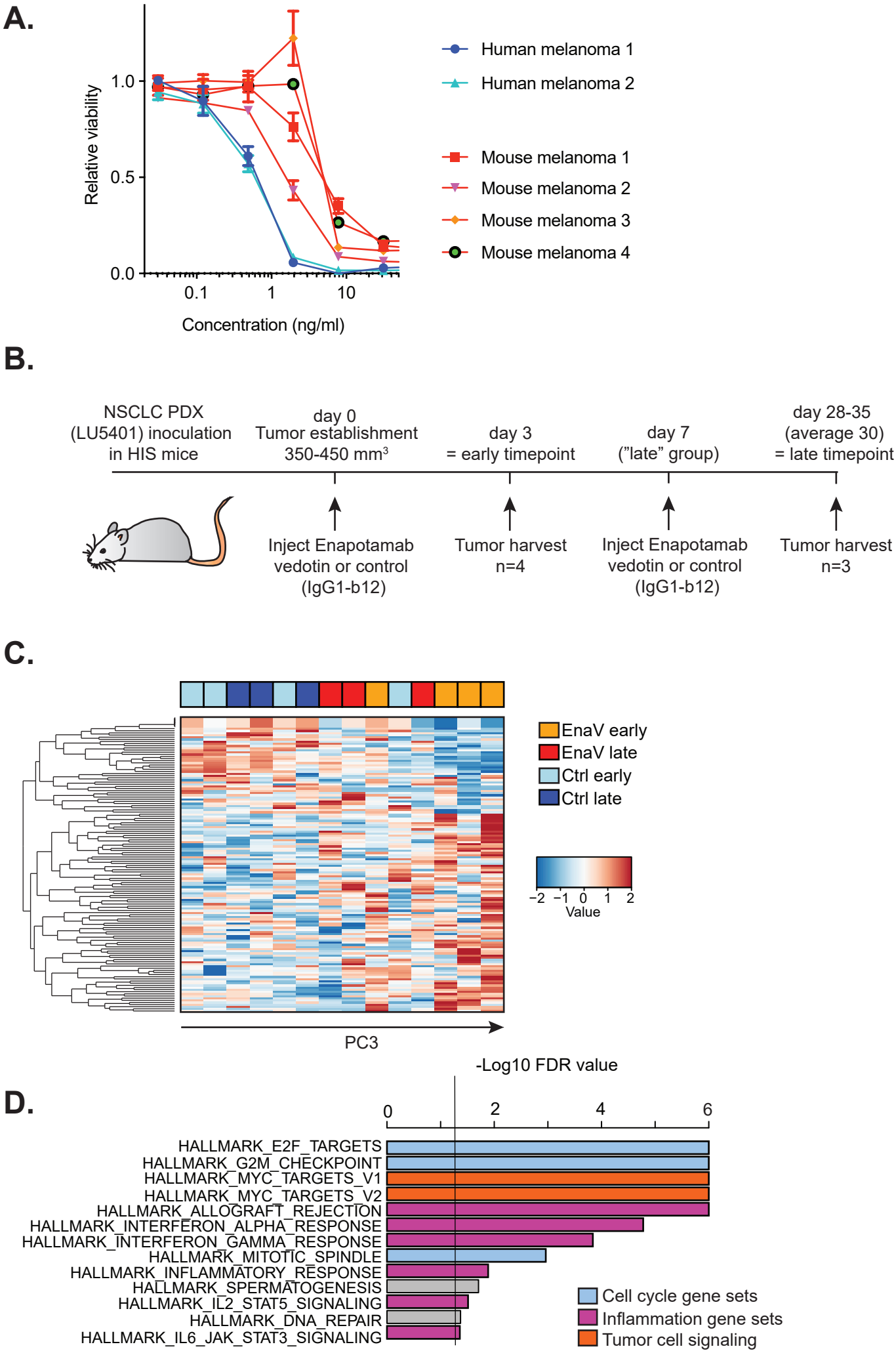
Suppl. Figure 1.



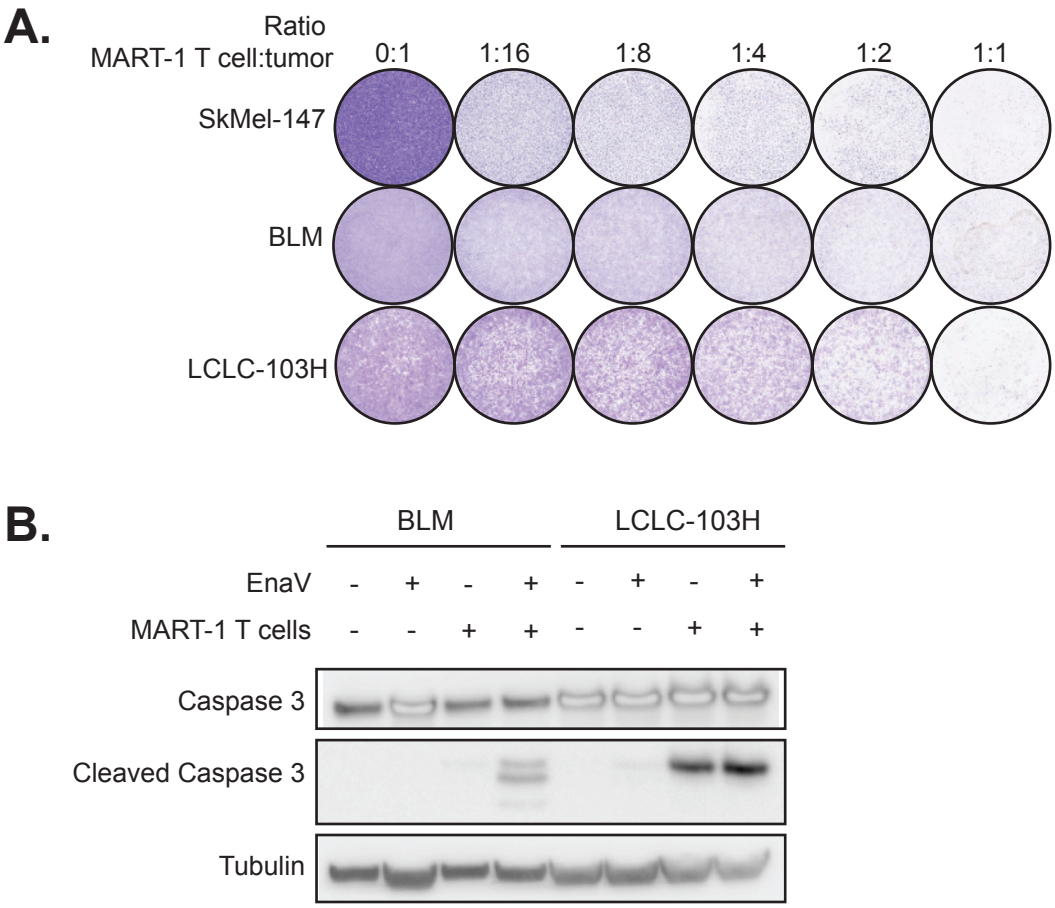
Suppl. Fig. 1. EnaV induces an inflammatory response in PDX models of lung cancer *in vivo*. (**A**) Growth curves of PDX LXFA526 and 677 *in vivo* and efficacy of EnaV (2 and 4 mg/kg). IgG1-b12-MMAE and IgG1-b12 were used as controls. Error bars represent SEM. Statistical analysis by Mann-Whitney test; ** $p<0.01$. (**B**) AXL positivity of the two tumor models of panel A. (**C**) Graphic overview of experiment performed for RNA + proteomic sequencing. (**D, E**) Principal component plots of the gene expression data combined for both PDX models, showing treatment-related separation in PC3. (**F**) Heat map of the EnaV gene expression signature in PDX tumors treated with Ctrl (IgG1-b12) or EnaV (4 mg/kg) for 3 days. (**G**) Proteomics analysis on day 3 after EnaV/Ctrl treatment of the same tumors used for RNA profiling. Q-value of <0.1 and fold change of >1.5 were used as cut-off. Green dot indicates significant hit in the interferon response pathways. (**H**) qPCR quantification of *IFIT1-3* and *MX1* in three LXFA526 tumors from the *in vivo* experiment as described in panel C. Mice were treated with EnaV or control IgG1-b12 and tumors were harvested after 6 days for RNA isolation.

Suppl. Figure 2.



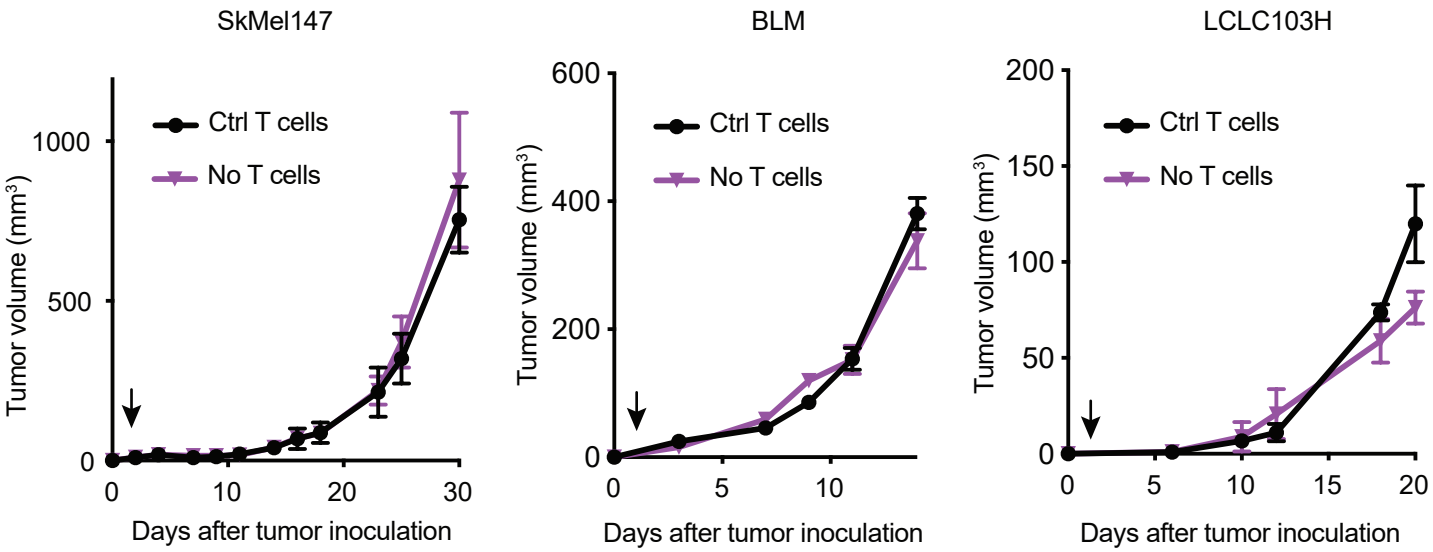
Suppl. Fig. 2. Profiling of lung cancer PDX LU5401 in HIS mice. (**A**) Sensitivity to free MMAE of human (blue) and mouse (red) cell lines. (**B**) Graphic overview of experiment performed for RNA sequencing. Tumors were used for the analysis of panels B and C. (**C**) Heat map of the EnaV signature in LU5401 PDX tumors treated with either Ctrl (IgG1-b12) or EnaV (4 mg/kg) for 3 days or an average of 30 days (range 28-35). (**D**) GSEA of comparison between Ctrl ADC (IgG1-b12-MMAE) versus EnaV treatment in LU5401 PDX tumors, showing significantly induced inflammation-associated hallmark gene sets.

Suppl. Figure 3.



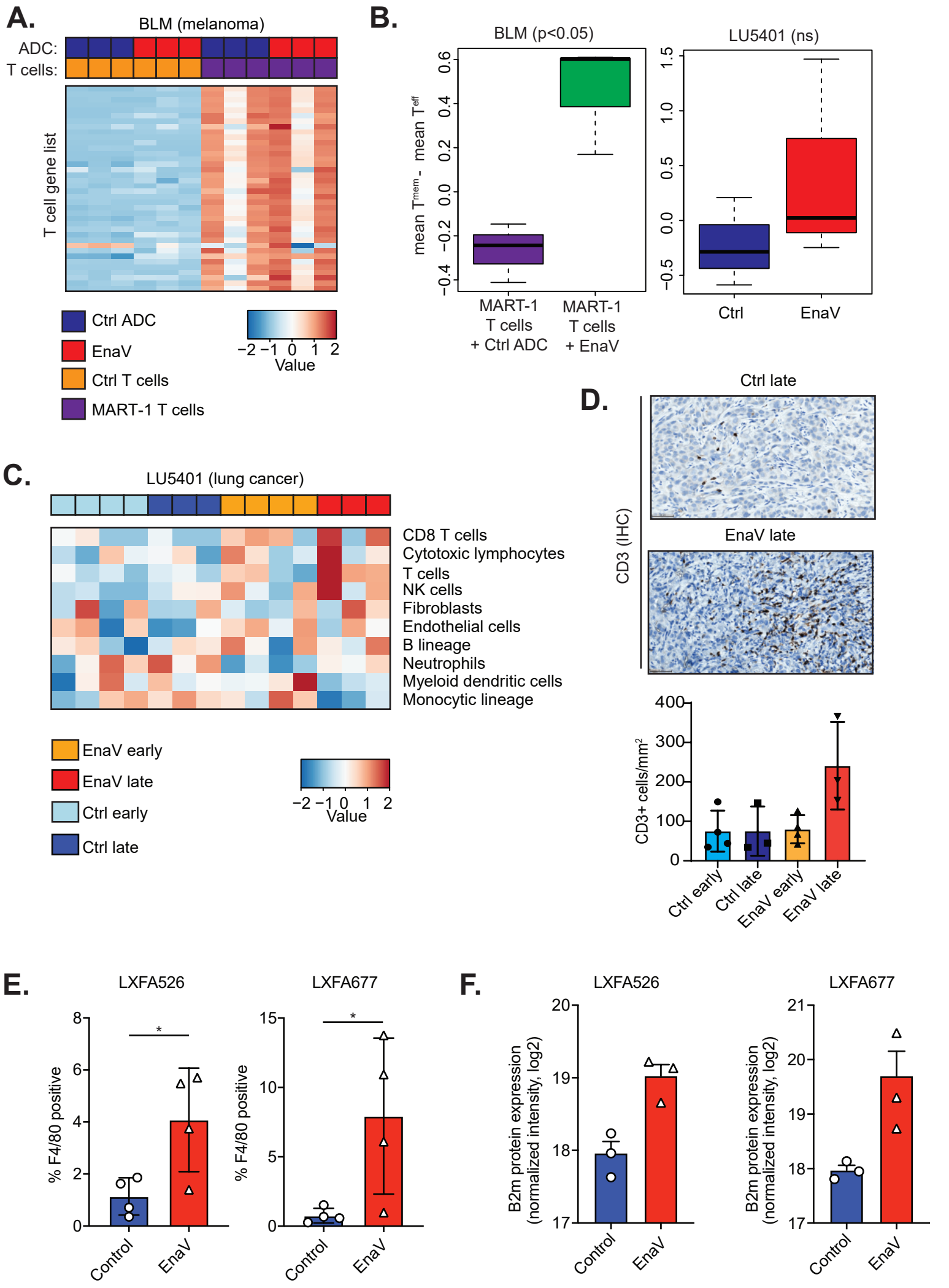
Suppl. Fig. 3. Cell lines treated with EnaV and/or tumor-specific T cells. (A) Colony formation assay of three cell lines, transduced with MART-1+HLA-A2, treated with MART-1 specific T cells for 24 hours in the indicated ratios. After- wards, T cells were washed away and plates were stained with crystal violet after 3 days. **(B)** Western Blot analysis of cleaved Caspase 3 in melanoma (BLM) and lung cancer (LCLC-103H) cells treated with EnaV (2 µg/ml) or MART-1-specific T cells (in a 1:4 T cell: tumor cell ratio), their respective control treatments (IgG1-b12-MMAE or Ctrl T cells), or the combination for 20 hours. Tubulin was used as a loading control.

Suppl. Figure 4.



Suppl. Fig. 4. Sensitivity of melanoma and lung tumors *in vivo* to untransduced versus no T cells.

Suppl. Figure 5.



Suppl. Fig. 5. Immune infiltration in melanoma and lung tumors *in vivo.* (A) Heat map of T cell gene sets in EnaV +/- MART-1 T cell treated mice bearing melanoma BLM tumors. **(B)** Mean log value of T memory versus T effector gene set in models from panel A and B. The "late" timepoint of 28-35 days is plotted for LU5401. **(C)** Heat map of immune cell gene sets in EnaV-treated HIS mice bearing LU5401 lung cancer PDX tumors. Immune signature abundance was imputed using MCP counter. (**D**) Representative IHC images of CD3 expressing T cells infiltrating in LU5401 tumors, showing a control tumor at day 30; and an EnaV-treated tumor at day 30. Below: quantification of CD3+ cells per surface area (mm^2) in indicated conditions. (**E**) Quantification of F4/80 positive cells by IHC in two lung cancer PDX models, as depicted also in Supplementary Figure 1C. Statistical analysis by unpaired t-test; * $p<0.05$. (**F**) Quantification of mouse B2m expression by proteomics in two lung cancer PDX models.