**Supplementary Legends for Figures and Tables**

**Supplementary Figure S1** **LRRC15 RNA expression in additional solid tumor indications and metastatic protein expression.** RNA Seq data from TCGA analyzed using OmicSoft ArrayStudio™ software (<https://www.omicsoft.com>) showing LRRC15 RNA expression for multiple solid tumor indications relative to the corresponding normal tissue of origin.

**Supplementary Figure S2 Cancer expression of LRRC15 and confirmation of LRRC15 antibody specificity.** **A,** Examples of mesenchymal cell lines from glioblastoma, melanoma and sarcoma that stain positive for LRRC15 when cultured *in vitro*, pelleted and made as FFPE-blocks for IHC. LRRC15 negative cells lines PANC1 and EBC-1 (used in cancer negative, stromal positive mouse models) are shown for comparison. **B,** LRRC15 expression (Ab5) by immunofluorescence and immunohistochemistry on fixed HCT116 parental and HCT116-LRRC15 transfectant cells. **C,** LRRC15 cell surface receptor numbers across glioblastoma, melanoma, and sarcoma cell lines, estimated by flow cytometry. **D,** LRRC15 expression by flow cytometry using fluor labeled antibodies (isotype, LRRC15 Ab1) on U118MG cells treated with control siRNA (pool or single oligonucleotide) or 4 distinct LRRC15 siRNA oligonucleotides. **E,** LRRC15 stromal expression in primary versus metastatic tissue. LRRC15 stromal protein expression (IHC, brown) in a patient-matched primary tumor (head and neck) and metastatic tissue (lymph node).

**Supplementary Figure S3 Evaluation of LRRC15 antibody activity *in vivo*.**  **A,** EBC-1 xenograft tumors were treated at 6 mg/kg (i.p.) with the reagents as shown, including LRRC15 naked antibody (Ab1). **B,** ADCC assay was performed using U118MG cells as LRRC15 positive target cells and NK92-V158 cells as effectors at a 9:1 E:T ratio. Cetuximab was used as a positive control for ADCC activity. Cells incubated without antibody were used to determine background lysis from effector:target co-incubation. Data shown is representative of results from two independent experiments*.*

**Supplementary Figure S4 Evaluation of varying drug-to-antibody ratios (DAR) and combinations with standard of care therapies on LRRC15-ADC efficacy.** **A,** LRRC15 cancer positive xenograft model U118MG (glioblastoma) was treated with isotype-ADC or LRRC15-ADC as indicated with enriched drug loading of approximately 2 MMAE molecules per antibody (E2), 4 MMAE molecules per antibody (E4) or a broad distribution of 0,2,4,6,8 averaging to DAR4. Groups were dosed at equivalent MMAE levels. **B,** Tumor growth curve of ABBV-085 combined with docetaxel in the LRRC15 cancer negative / stromal positive squamous NSCLC model EBC-1, **C,** ABBV-085 combined with cetuximab in LRRC15 cancer negative / stromal positive head & neck cancer model SCC-15. All agents were dosed as indicated.

**Supplementary Figure S5 *In vitro* cell cycle mitotic arrest and cell killing induced by LRRC15-ADCs.A,** DNA cell-cycle flow cytometry analysis of U118-MG (LRRC15 cancer positive, GBM cells) treated with ABBV-085 or isotype controls for 24 h. **B,** Cell killing of LRRC15 positive cell line (HCT-116-huLRRC15) with anti-LRRC15 ADC’s conjugated with either MMAE or MMAF payloads.

**Supplementary Figure S6 Flow cytometry gating for EBC1 tumors treated with ABBV-085.**  Representative dot-plot gating used for *ex vivo* EBC1 tumor staining for EPCAM, FAPα and F4/80 as shown in Fig 6e.

**Supplementary Figure S7 RNASeq data of tumor versus normal for LRRC15 and FAP in breast cancer.** TCGA RNASeq data showing disease vs normal expression of LRRC15 (top) and FAP (bottom) for all breast cancer samples (left column) or triple negative breast cancers only (right column).

**Supplementary** **Table S1**  **Cross species binding and tolerability of ABBV-085.** **A,** Binding of ABBV-085 and LRRC15 (Ab1) by ELISA to LRRC15-Fc fusion protein for each species and flow cytometry binding to LRRC15 transfectant cell lines for each species (human, cynomolgus monkey, rat, mouse), reported as EC50 (nM) binding. **B,** tolerability comparison of LRRC15-ADCs with varying DAR in rats. A comparison of LRRC15-ADC as indicated with enriched drug loading of approximately 2 MMAE molecules per antibody (E2) or a broad distribution of 0,2,4,6,8 averaging to DAR4. Five male and five female rats were dosed per group as indicated, and the observations listed.