SUPPLEMENTAL METHODS:

Cell Culture, Transfection, and Drug Treatments:
GANT61 (Sigma-Aldrich) dissolved in dimethylsulfoxide (DMSO) was used for GLI inhibition at a final concentration of 10μM. For VEGF-C neutralization experiments, 5-10μg/ml VEGF-C antibody (SC-374628) or normal mouse immunoglobulin G (IgG) (SC-2025) from Santa Cruz Biotechnology was added to the media [54]. On-TARGET plus SMART pool small interfering RNAs (Dharmacon) were used for transient knockdown of SIX1, VEGF-C and NRP2. MISSION® shRNA Lentiviral Transduction Particles were used for stable KD of VEGF-C and NRP2, the sequences of shRNA are listed in Supplementary table 1. DB7-luc cells were generated by transducing the cells with an MSCV-IRES-luciferase-hygro plasmid. Conditioned medium (CM) was harvested as previously described [14].

Immunocytochemistry. Cells were seeded in eight-well chamber slides (Nunc Lab-Tek, 155409) (1×10^4 cells/well) with normal medium or different CM for 48 hours at 37°C. The cells were fixed in 4% paraformaldehyde in PBS for 15 min at room temperature. Next, cells were permeabilized with 0.1% Triton X-100 and blocked using 5% goat serum for 30 min. After fixation, cells were incubated at 4°C overnight with primary antibodies as outlined in the text. The next day, cells were incubated with secondary antibodies as outlined and slides were mounted with Fluoroshield™ with DAPI (Sigma-Aldrich, F6057). Quantification of membranous E-cad was performed by dividing the number of cells with membranous E-cad by the number of DAPI stained cells.
**Cell Proliferation Assays:** For IncuCyte ZOOM™ assays, 1500 cells incubated with various CMs were seeded in 96-well plates. The percent cell confluence was continuously measured using IncuCyte-ZOOM according to the manufacturer’s instructions.

**GLI Reporter Assays.** $20 \times 10^4$ cells were seeded in 6-well plates in respective CM and transfected with a 7x-GLI-GFP reporter which contains 7 repeats of the Gli binding site followed by GFP. A separate well of cells for each condition was transfected with an EFS-GFP vector [55], as a positive control to normalize for transfection efficiency. After 48 hours, the percentage of GLI-GFP positive cells (reflecting activation of GLI signaling) in each condition was measured using flow cytometry. Normalization was performed by dividing the percentage of GLI-GFP positive cells by the percentage of EFS-GFP positive cells. All the experiments were performed in triplicate at least two separate times.

**Mouse Experiments:** For the FVB mouse experiment, 30 mice were divided into 3 groups. Mixtures of tumor cells in 100ul serum-free medium were injected orthotopically in the fourth mammary fat pad of the mice. The injected cell conditions were as follows: 4:1 ratio of 400,000 DB7-luc: 100,000 untagged DB7-SCR cells, 4:1 ratio of 400,000 DB7-luc: 100,000 untagged Met1-SCR cells, 4:1 ratio of 400,000 DB7-luc: 100,000 untagged Met1-shVegfc cells. Tumor volume and luminescence signal were measured weekly. After 4 weeks, the primary tumors were removed and the luminescence signal at distant sites was monitored weekly.

For the immunocompromised mouse experiments, 48 nude mice were divided into 6 groups randomly. Mixtures of tumor cells in 100ul serum-free medium were injected orthotopically in the fourth mammary fat pad of the mice. The injected cell conditions were as follows: 4:1 ratio
of 400,000 DB7-SCR-luc: 100,000 untagged DB7-SCR cells, 4:1 ratio of 400,000 DB7-SCR-luc: 100,000 untagged Met1-SCR cells, 4:1 ratio of 400,000 DB7-SCR-luc: 100,000 untagged Met1-shVegfc KD1 cells, 4:1 ratio of 400,000 DB7-SCR-luc: 100,000 untagged Met1-shVegfc KD2 cells, 4:1 ratio of 400,000 DB7-shNrp2 KD1-luc: 100,000 untagged Met1-SCR cells and 4:1 ratio of 400,000 DB7-shNrp2 KD2-luc: 100,000 untagged Met1-SCR cells. Tumor volume and luminescence signal were measured weekly. After 3 weeks, the primary tumors were removed and the luminescence signal at distant sites was monitored weekly. Primary tumors were removed at the same time, and thus the different groups tumors sizes were different, which may contribute to metastatic disease. In order to investigate the role of Nrp2 in the survival of DB7 cells in vivo, 15 NOD scid gamma mice were equally divided into 3 groups and injected either with DB7-SCR cells, DB7-shNrp2 KD1 cells and DB7-shNrp2 KD2 cells. 5x10⁵ luciferase tagged cells in100ul serum-free medium were injected orthotopically into the fourth mammary fat pad of the female mice. Tumor volume was measured weekly using calipers.

GraphPad Prism 7.0 software (GraphPad Software) was used for the statistical analyses. Two group comparisons were conducted using the Student t test, three or more groups were compared using one-way ANOVA non-parametric followed by the Tukey–Kramer post hoc analysis. The proliferation data and tumor growth curves were analyzed with two-way ANOVA followed by Bonferroni posttest, or a mixed model function used previously [56]. Survival data were compared using log-rank test or the Wilcoxon test. P values <0.05 were considered statistically significant, and all p-values are listed in the figures.

Datasets for Gene Correlations:
The TCGA BRCA RNAseq dataset was obtained from the NCI GDC Data Portal [REF: https://portal.gdc.cancer.gov/projects/TCGA-BRCA].

MSigDB Hallmarks gene set collection dataset contains Gene-level expression values (HTSEQ FPKM-UQ) for 1222 samples, and comparison for specific genes was also done (ref: https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/Expression_mRNA_Pipeline/#mrna-expression-workflow).