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1. Supplementary Materials and Methods

Cell line and reagents

The HER2-positive mammary tumor cell line MI6 was established from the spontaneous primary mammary carcinomas of a transgenic FVB-Δ16HER2 mouse (1). The cells were maintained in complete culture medium (MammoCult™; Stemcell Technologies, cat no. 05620, Vancouver, Canada) supplemented with 1% fetal bovine serum (FBS; Gibco, Thermo Fisher Scientific, Waltham, MA, USA), penicillin 1 µg/ml, streptomycin 1 µg/ml (Sigma-Aldrich), hydrocortisone 0.48 µg/ml (Stemcell Technologies, cat no. 07925), and heparin 2 U/ml and cultured at 37°C in a 5% CO_2 atmosphere incubator. Mycoplasma testing was conducted using MycoAlert™ PLUS Mycoplasma Detection Kit (Lonza, cat no. LT07-703, Basel, Switzerland). The cells were used up to 6 passages after thawing and for no longer than 2 months.

Vancomycin hydrochloride (vancomycin; Cayman Chemical, cat no. 15327, MI, USA) and streptomycin sulfate salt (streptomycin; Sigma-Aldrich, cat no. S6501) were dissolved in the drinking water at a concentration of 200 mg/L. The antibiotic cocktail (ABX) was prepared using metronidazole (cat no. M3761), ampicillin sodium salt (cat no. A9518), and neomycin sulfate (cat no. 1458009) (Sigma-Aldrich) at a concentration of 1 g/L and vancomycin 500 mg/L dissolved in the drinking water. The ABX was administered to mice *ad libitum* starting at four weeks of age and changed every 48-72 hours with fresh solution.

Transgenic model of spontaneous tumorigenesis

A breeding colony of FVB Δ16HER2 transgenic mice [FVB/NHsd-Tg(Δ16HER2-LUC)6157Acam] was generated as described (2) and bred in the Animal Facility of Fondazione IRCCS Istituto Nazionale dei Tumori. Ear biopsies were harvested from four-week-old mice for routine genotyping. DNA was extracted using the Exgene Tissue DNA mini kit (GeneAll, Seoul, Korea) and analyzed by PCR (primers: F, 5′-GGCTCAGTGACCTGTTTTGG-3′ and R, 5′-TGATGAGGATCCCAAAGACC-3′), with an expected amplicon length of 231 bp. The positive female mice were randomized into two groups, and one group was administered vancomycin (200 mg/L) in the drinking water for the entire duration of the experiment. The mice were inspected weekly by palpation and, when the first tumor lesions reached a palpable volume, 8 mg/kg of trastuzumab, or saline (NaCl 0.9%), were administered i.p. once per week for 6 weeks. The anti-HER2 treatment efficacy was assessed by measuring the volume of the first tumor appeared.

Quantification of bacterial load by flow cytometry and qRT-PCR

The total bacterial load and the viability of fecal samples used for FMT were evaluated by flow cytometry. The fecal suspensions were double-stained with 1X SYBR green (Sigma-Aldrich, cat no. S9430) and propidium iodide (PI) 0.5 µg/ml (Sigma-Aldrich, cat no. 79214) at 37°C for 15 minutes in the dark to distinguish live, injured and dead cells based on fluorescence. The concentration and viability of the cells was determined by using an Accuri C6 flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

The bacterial DNA extracted form stool samples of antibiotic treated mice. The total 16S rRNA was quantified by using the SYBR^{TM} Green Master Mix (Applied Biosystem, Thermo Fisher Scientific, cat no. 4385612). *U16S-Forwar:* 5'-ACTCCTACGGGAGGCAGCAGT-3'; *U16S-Reverse:* 5'-ATTACCGCGGCTGCTGGC-3'.

Analysis of HER2 expression by western blot and immunohistochemistry

To assess HER2 protein expression tumors were homogenized in radio-immunoprecipitation assay (RIPA) protein lysis buffer containing protease inhibitors. Protein concentrations were determined using Bio-Rad Protein Assay Dye (Bio-Rad, cat no. 5000006, Hercules, CA, USA) and 30 µg of protein were resolved on 4-12% precast NuPage Bis-Tris gels (Thermo Fisher Scientific, cat no. NP0326BOX, Waltham, MA, USA) in reducing conditions. Acquired images were analyzed using Quantity One software (RRID:SCR_014280). The following antibodies were used: mouse monoclonal antibodies anti-HER2, clone Ab3 (Calbiochem, OP15L - RRID:AB_2099415); Phospho-HER2/ErbB2 (Tyr1248)/EGFR (Tyr1173) (Cell Signalling, 2244 - RRID:AB_331705); anti-vinculin, clone hVIN-1 (Sigma-Aldrich, V9131 - RRID:AB_477629).

The HER2 expression was analyzed in FFPE tumors, four-micrometer tumor slides were deparaffinized, serially rehydrated, subjected to antigen retrieval at 96°C for 6 min using 10 mM citrate buffer, pH 6.0, and stained with the primary antibody anti-p185 used in the HercepTest (1:150, Dako, Agilent, cat no. A0485, Santa Clara, CA, USA - RRID:AB_2335701). Quantification was performed using the publicly available ImageJ software (RRID:SCR_003070) for image processing and reported is the percentage of stained area (n=2 tumors/group of treatment).

Analysis of trastuzumab distribution

Trastuzumab detection within the tumor microenvironment was performed by immunofluorescence. The tumor samples were embedded in O.C.T. compound (Agar Scientific Ltd. cat no. AGR1180, Stansted, UK) and conserved at -80°C. Tissue specimens were cut on a cryostat microtome, and the cryostat sections were fixed with 4% paraformaldehyde for 20 minutes at room temperature. The tumor sections were then incubated with a blocking solution containing 3% BSA before staining with anti-human Alexa Flour®568 secondary antibodies (Thermo Fisher Scientific, cat no. A-21090; RRID:AB_2535746) at a concentration of 1:100 for 1 hour at room temperature. The nuclei were

counterstained with DAPI (Thermo Fisher Scientific, cat no. D1306). Sample imaging was performed in the microscopy facility of the Fondazione IRCCS Istituto Nazionale dei Tumori using a Leica TCS SP8 X confocal laser scanning microscope (Leica Microsystems GmbH, Mannheim, Germany). The fluorochrome was excited by a pulsed super continuum white light laser (470-670 nm; 1 nm tuning step size). In particular, Alexa Flour®568 was excited by selecting a 557 nm laser line and detected from 562 to 642 nm, and DAPI was excited with a 405 nm diode laser and detected from 422 nm to 488 nm. Three images were acquired for each sample in the 512x512 scan format using an HC PL APO 40X/1.3 CS2 oil immersion objective and a pinhole set to 1 airy unit. The data were analyzed using the publicly available ImageJ software for image processing.

Microbial metabolic analyses

Short-chain fatty acids (SCFAs) were measured in fecal sample as previously described in (3). Samples were stored at −20 °C until analysis. Determination of SCFAs concentration was achieved through ultraperfomance liquid chromatography-high resolution-mass spectrometry analysis (UPLC-HR-MS). UPLC-HR-MS analysis was carried out on an Acquity UPLC separation module (Waters, Milford, MA, USA) coupled with an Exactive Orbitrap MS with an HESI-II probe for electrospray ionization (Thermo Fisher Scientific).

Gene expression analysis

Gene expression profile was performed by the Genomic Facility of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan. After RNA extraction quality check and quantification were performed by 4200 TapeStation (Agilent) and a Qubit fluorometer with the Qubit RNA HS assay kit (Thermo Fischer Scientific, cat no. Q32852), respectively, the RNA expression was assessed using the mouse or human Affymetrix Clariom S Pico assay (Thermo Fisher Scientific, cat no. 902930 and 902929), respectively. A total of 100 ng of total RNA was used to generate the single-stranded cDNA samples for hybridization. Then, cDNA was enzymatically fragmented and biotinylated using the WT Terminal

Labeling kit (Thermo Fisher Scientific, cat no. 901647), combined with hybridization buffer, and injected into human Clariom S arrays targeting >20,000 well-annotated genes. The arrays were stained using the Affymetrix® GeneChip® Fluidics Station 450 and scanned with the 7G Affymetrix® GeneChip® Scanner 3000. Raw data were processed using Transcriptome Analysis Console software (Thermo Fisher Scientific). CEL files containing feature intensity values were converted into summarized expression values by Robust Multiarray Average (RMA), which consists of background adjustment and quantile normalization across all chips. All samples passed QC thresholds for hybridization, labeling and the expression of housekeeping gene controls.

Immunohistochemical analysis and flow cytometry

The characterization of the tumor immune infiltrate on FFPE samples was performed and analyzed in collaboration with the pathologists' group led by Dr. Tripodo at the Università di Palermo, Italy. The antigen unmasking was performed using Novocastra Epitope Retrieval Solutions (Novocastra, cat no. RE7119-CE, Newcastle upon Tyne, UK), pH 9, in a PT Link pretreatment module (Dako) at 98°C for 30 min. The sections were warmed to room temperature and washed with PBS. After neutralization of the endogenous peroxidase with 3% H_2O_2 and Fc blocking by a specific protein block, the slides were incubated overnight with the primary antibodies at 4°C. The following antibodies were used: rabbit polyclonal anti-mouse CD3 (1:100 pH 9, cat no. ab5690, Abcam, Cambridge, UK - RRID:AB_305055); rat monoclonal anti-mouse CD4 (Clone 4SM95, 1:100 pH 9, cat no. 14-9766, eBIOSCIENCE, Thermo Fisher Scientific - RRID:AB_2573007); rat monoclonal anti-mouse CD8a (Clone 4SM15, 1:100 pH 9, cat no. 14-0808, eBIOSCIENCE Thermo Fisher Scientific - RRID:AB_2572860); rabbit polyclonal anti-mouse CD45 (1:1000 pH 9, cat no. ab10558, Abcam - RRID:AB_442810); rabbit polyclonal anti-human Granzyme B (ready to use, pH 9, cat no. 760-4283, Ventana, cross reactive with mouse - RRID:AB_2335967); rat monoclonal anti-mouse Gr-1 (Clone RB6-8C5, 1:50 pH9, cat no. MAB1037-100, R&D System - RRID:AB_2232806); goat polyclonal anti-

mouse NKp46/NCR1 (1:50 pH6 cat no. AF2225, R&DSystem - RRID:AB_355192). Proteins' staining were revealed by AEC (3-amino-9-ethylcarbazole) substrate-chromogen following the manufacturer's instructions. The slides were counterstained with Harris hematoxylin (Novocastra, cat no. 3801560). The valuation of tumor immune infiltrate was carried out by two independent pathologists who were blinded to the treatment groups. All sections were analyzed under an AXIO Scope A1 optical microscope (ZEISS, Jena, Germany), and 5 sections were counted at 40x magnification. Microphotographs were collected through an Axiocam 503 Color digital camera (ZEISS) using Zen2 software.

For flow cytometry analysis, tumors and draining lymph nodes (dLN) were harvested at the end of the experiment. The dLNs were digested in HBSS with 0.5 % FBS containing DNAse I (100 µg/mL) and Collagenase IV (200 U/mL) for 20 min and smashed through a cell strainer (40 µm pore diameter), single cell suspensions were then used for flow cytometry staining. Tumors were cut into small pieces and smashed through a cell strainer (40 µm pore diameter) Red blood cells lysis was performed by incubating tumor cells with ACK (Gibo™, Thermo Fisher Scientific, cat no. A10492-01) on ice 5 min. Single cell suspensions were then used for flow cytometry staining. Antibodies used for the analysis through flow cytometry are listed in table S1 (Table S1). Stained samples were fixed 15 min at 4°C with 1 % formalin and run on a BD FACSCelesta system (BD Biosciences) at the flow cytometry facility of our Institute.

Table S1. List of the antibodies used for flow cytometry

Molecule	Conjugate	Clone	Brand and Cat. no	Dilution
Anti-CD45	BV786	30-F11	BD Horizon™ n. 564225; RRID:AB_2716861	1:300
Anti-CD3	BB700	145-2C11	BD Horizon™ n. 745836; RRID:AB_2743282	1:50
Anti-CD8	BV605	53-6.7	BD Horizon™ n. 563152; RRID:AB_2738030	1:100

Anti-CD4	BV510/BB700	RM4-5	BD Horizon™ n. 563106/566407; RRID:AB_2687550; RRID:AB_2744427	1:100
Anti-CD49b	BV421	DX5	BD Horizon™ n. 563063; RRID:AB_2737983	1:100
Anti-NKp46	PE-eFluor610	29A1.4	eBioscience n. 61-3351-82; RRID:AB_2574606	1:100
Anti-CD69	PE	H1.2F3	BD Horizon™ n. 553237; RRID:AB_394726	1:100
Anti-MHCII	FITC	2G9	BD Pharmingen n. 553623; RRID:AB_394958	1:1000
Anti-CD11c	BV605	HL3	BD Horizon™ n. 563057; RRID:AB_2737978	1:100
Anti-CD19	FITC	1D3	BD Pharmingen n. 553785; RRID:AB_395049	1:100
Anti-CD86	APC-R700	GL1	BD Horizon™ n. 565479; RRID:AB_2739258	1:200
L/D	Fixable viability Stain 780		BD Horizon™ n. 565388	1:1000

Quantification of plasma cytokines

Blood samples were collected from mice 48 hours after trastuzumab treatment in heparine (20 µL, 5000 U.I./mL). Sample were centrifuged at 1500 rpm for 5 min and then 3000 rpm for 10 min at 4° C. Plasma samples were stored at -80° C. Cytokines and chemokines detection was carried out using the ProCartaplex Immunoassay (Thermo Fisher Scientific, cat no. EPXR260-26088-901). Samples were processed according to manufacturer's instruction and read on a Bio-Plex® 200 Systems instrument (Bio-Rad, CA, USA).

Collection of patients' fecal samples and fecal microbiota transplantation (FMT) experiment

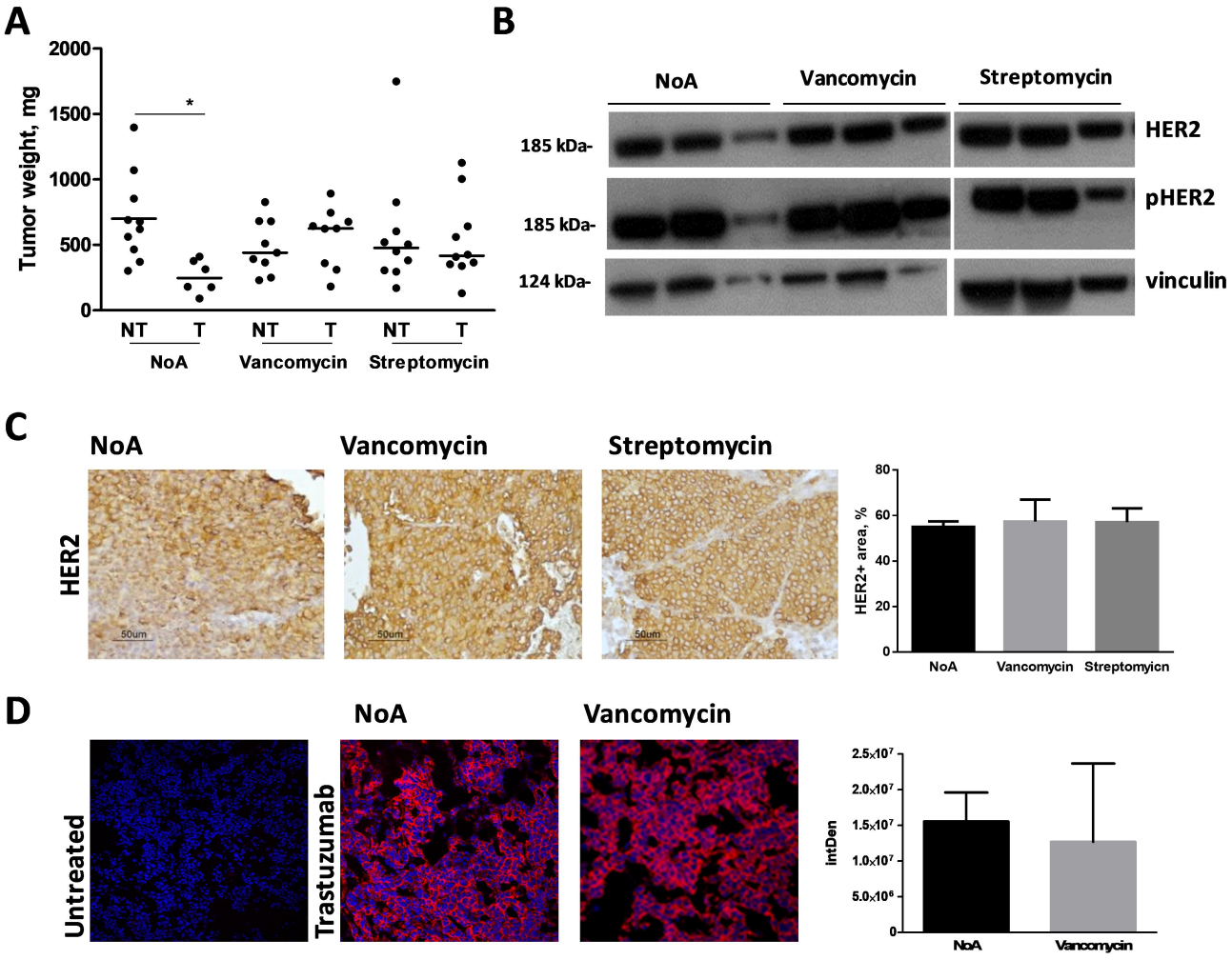
Fecal samples from patients were collected before the beginning of TH (taxanes and trastuzumab) treatment using the ANAEROGEN™ COMPACT system (Oxoid Microbiology Products, Thermo Fisher Scientific, cat no. AN0010C) to preserve anaerobic bacteria viability. Fecal samples for the 16S analysis were aliquoted and stored at -80°C. For the patient FMT experiments, the feces samples were frozen after being homogenized with autoclaved brain-heart-infusion media (BHI) (Sigma-Aldrich, cat

no. 1104930500) supplemented with 0.1% L-cysteine (Sigma-Aldrich, cat no. 30129) (2 g of feces in 10 ml of medium) and 15% glycerol and stored immediately at -80°C.

FMT using fecal samples from BC patients was performed by thawing the fecal material and by transferring 200 µl of suspension via oral gavage into each recipient mouse. FMT was performed a total of 5 times. Two gavages were performed at 24 hours before and 48 hours after tumor cell injection and then every 10 days for an additional 3 times. Trastuzumab treatment started when the tumor reached a palpable volume as previously described, and the mAb was administered twice a week for 3 weeks at a concentration of 5 mg/kg. Differences in tumor weights were evaluated by mixed effect linear model (implemented in the lme4 package of R) using treatment in mice as fixed effect and with random intercept.

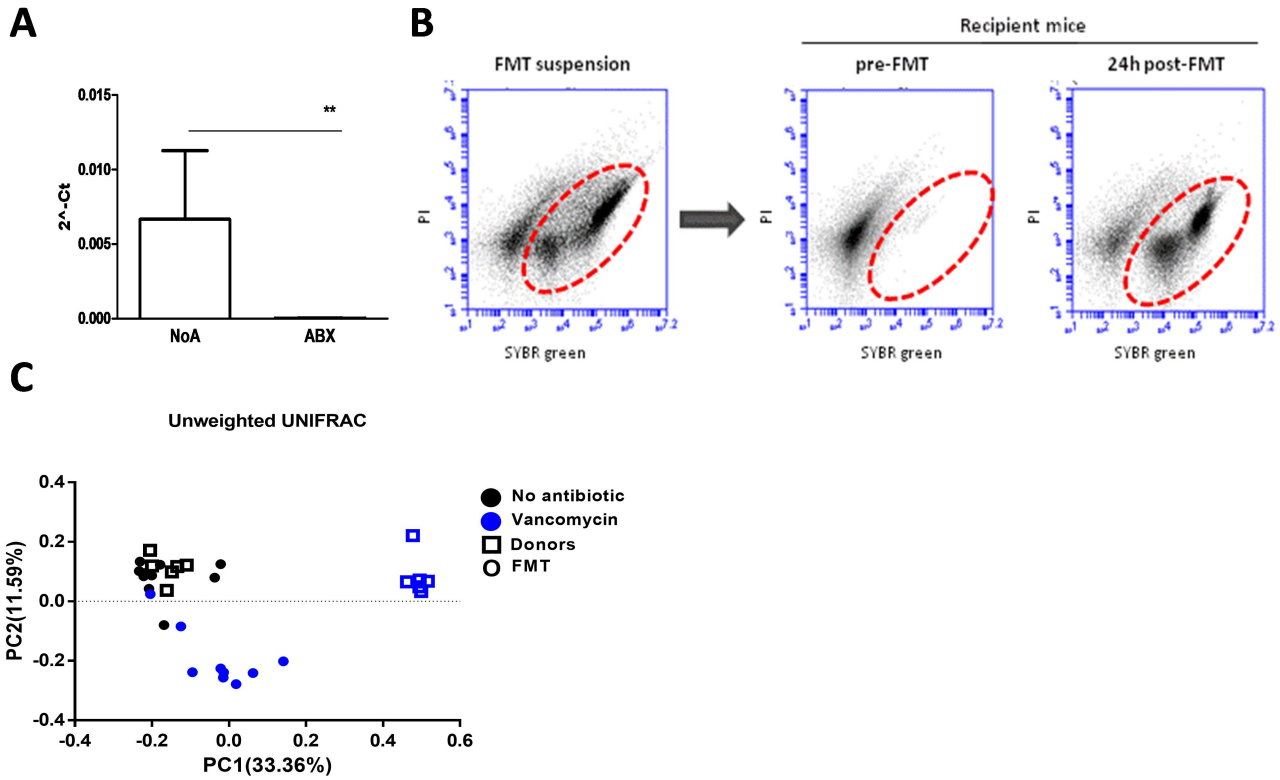
2. Supplementary Figures

Supplementary Fig. S1



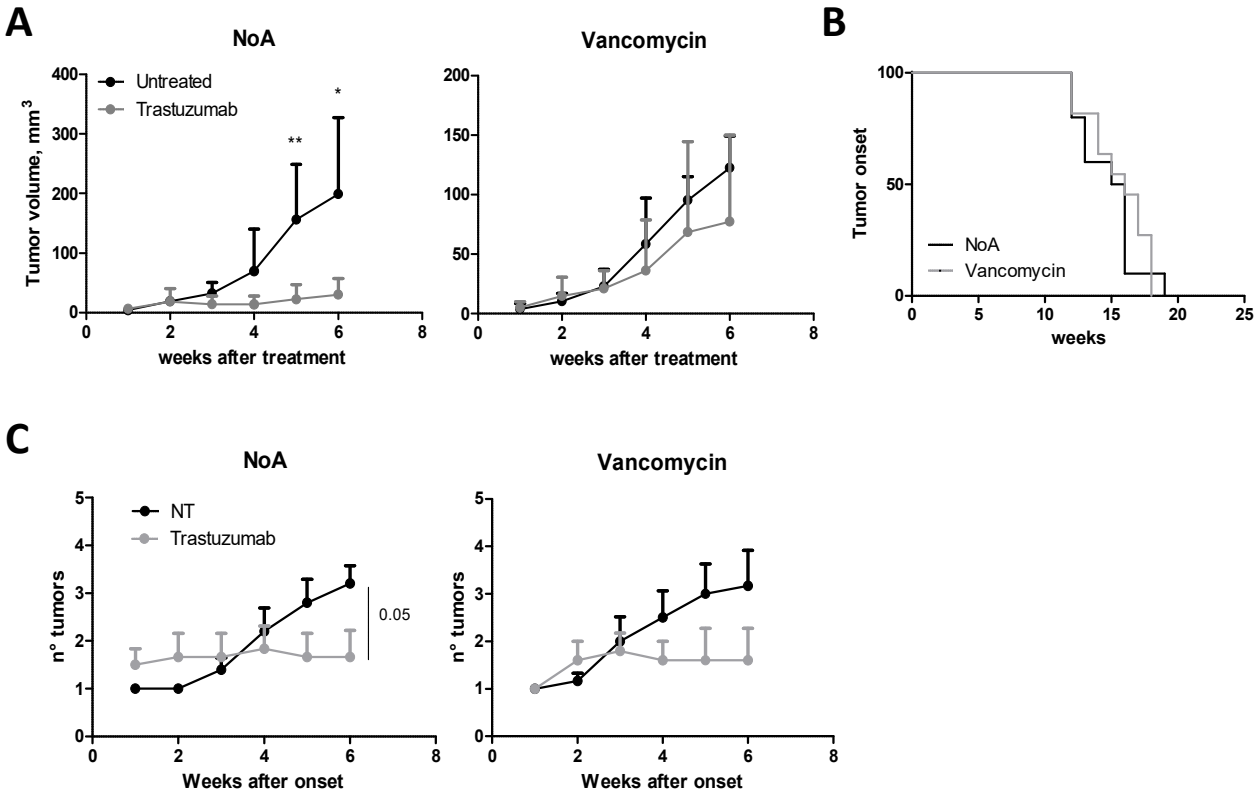
Supplementary Fig. S1. Impact of antibiotic treatment on trastuzumab efficacy and the tumor microenvironment. A) MI6 tumor weight measurement in control mice (NoA) and vancomycin-, or streptomycin (200 mg/L)-treated mice. MI6 tumors were treated or not (NT) with 5 mg/kg of trastuzumab twice a week (T). **B-C**) HER2 expression and activation as analyzed by WB (B) and HER2 staining as evaluated by IHC (C) in tumors derived from NoA- and antibiotic-treated animals. HER2 quantification was evaluated by ImageJ as the number of brown pixels. Scale bars: 50 µm. **D**) Trastuzumab diffusion within the tumor was evaluated by immunofluorescence using an anti-human IgG antibody. The IntDen is the number of red pixels as evaluated by ImageJ software in 3 images per group at 40x magnification. Blue: DAPI (data shown as the mean+SD). * $p<0.05$ by Student's t-test.

Supplementary Fig. S2



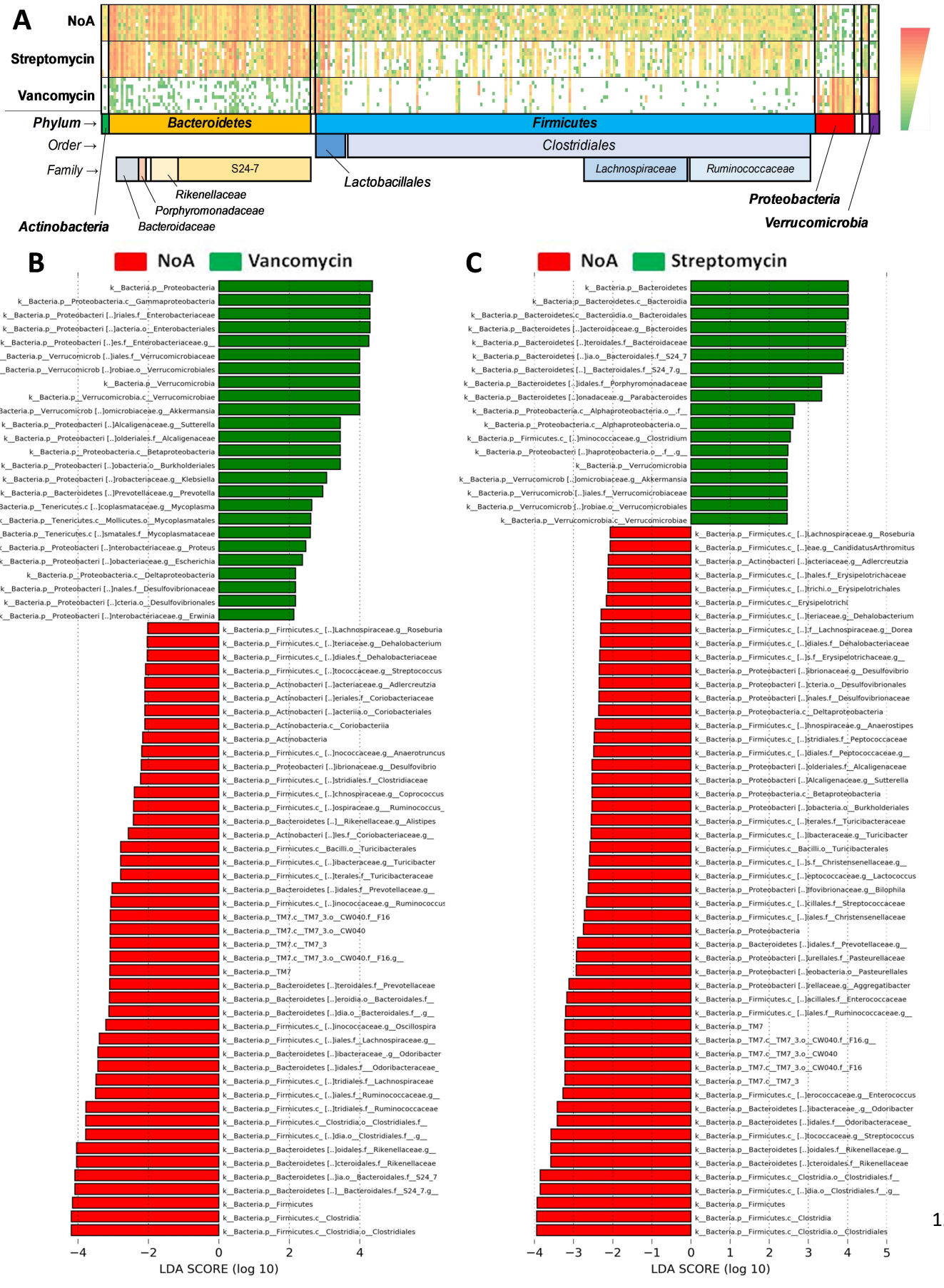
Supplementary Fig. S2. Depletion of commensal microbiota by antibiotic cocktail (ABX) treatment and fecal microbiota transplantation. Four-week-old FVB mice were treated with a cocktail of broad-spectrum antibiotics (metronidazole, ampicillin, neomycin 1 g/L, vancomycin 500 mg/L) administered in the drinking water for 28 days to deplete the mouse intestinal flora. The gut microbiota was then reconstituted by fecal microbiota transplantation (FMT) using stool suspensions from donor mice treated or not treated with vancomycin or streptomycin. **A)** Bacterial load quantification by qRT-PCR using universal primers for the 16S rRNA gene. DNA was extracted from one stool pellet per mouse. **B)** Flow cytometry analysis of the bacterial suspension: viability of the bacterial suspension from donor mice used for FMT (FMT suspension), in recipient mice before FMT (pre-FMT) and 24 h after FMT with stool suspension (24 h post-FMT). **C**) Principal coordinate analysis plot of microbial β-diversity between FMT-NoA (black) and FMT-vancomycin (blue) animals generated using unweighted UniFrac distance matrices using feces collected at the end of the experiment. The data from FMT mouse (●) and donor mouse (□) fecal samples are shown. ** $p<0.01$ by Student's t-test.

Supplementary Fig. S3



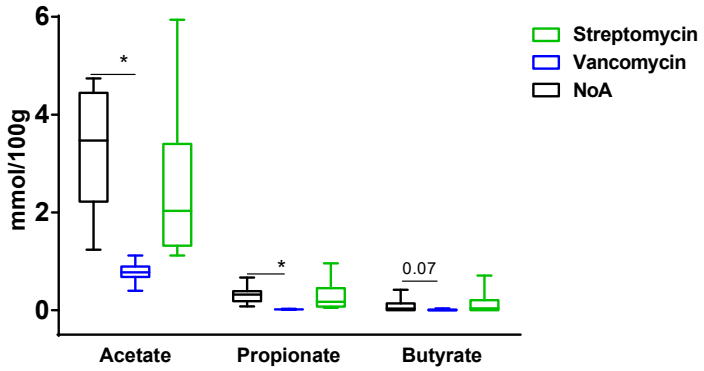
Supplementary Fig. S3. Impact of vancomycin on trastuzumab efficacy in Δ16HER2 transgenic FVB mice. Female Δ16HER2 transgenic FVB mice were treated or not treated with vancomycin (200 mg/L) starting at 4 weeks of age. After onset of the first tumor, the mice were treated with 8 mg/kg trastuzumab once a week for 6 weeks. **A**) Antitumor activity of trastuzumab. The tumor volume of the first tumor is shown. **B**) Tumor onset. **C**) Tumor multiplicity. Data are shown as the mean+SD (n=5-6 mice per group of treatment). * $p<0.05$ and ** $p< 0.01$ by an unpaired Student's t-test.

Supplementary Fig. S4



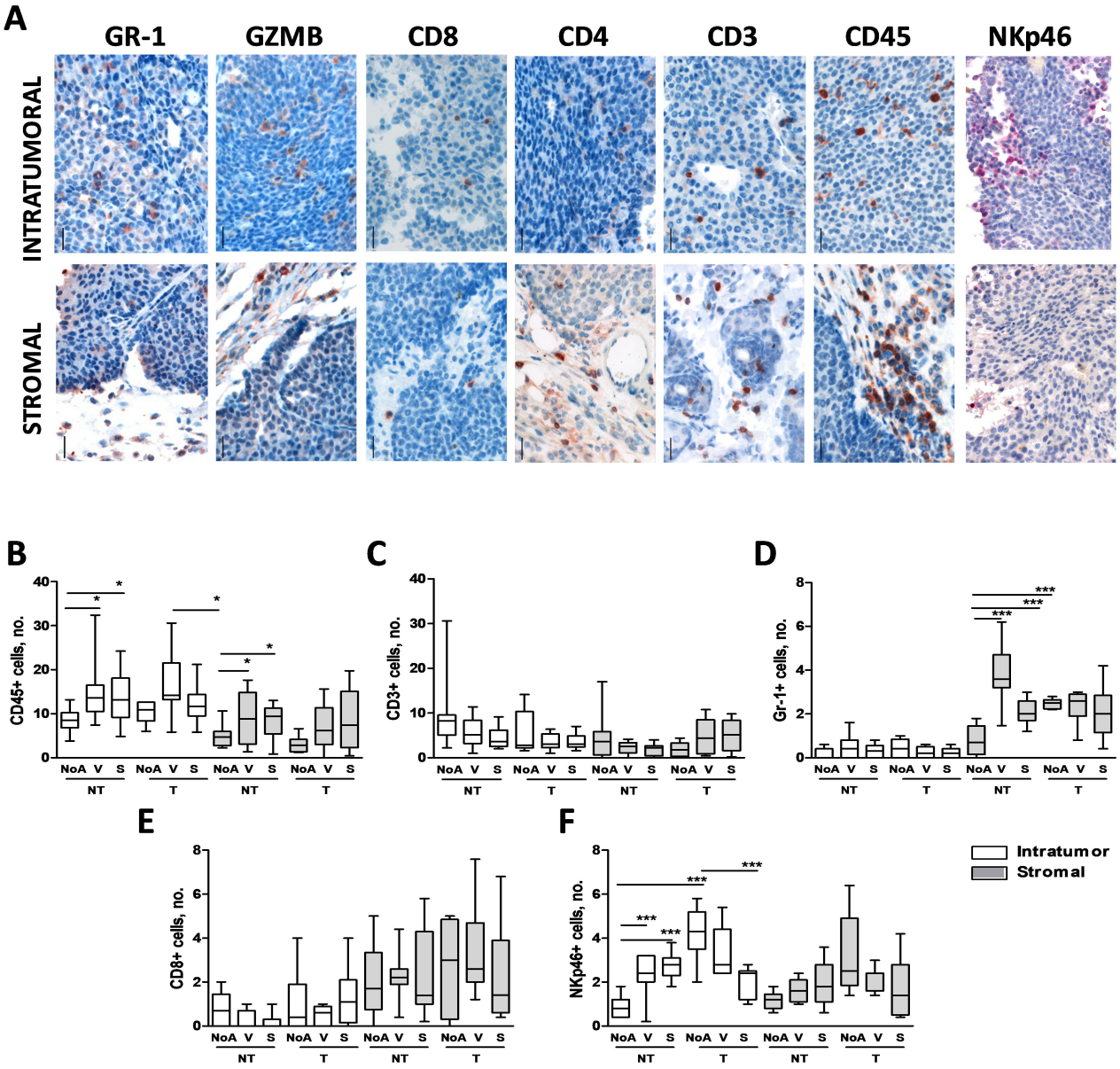
Supplementary Fig. S4. Differentially abundant bacteria in the gut microbiota of antibiotic-treated mice. A) Heatmap of bacterial taxa relative abundance for the three treatment groups. Minimum to maximum relative abundances are indicated as green-yellow-red; white, not detected. **B-C**) Linear discriminant analysis (LDA) scores computed for differentially abundant taxa in the fecal microbiomes of NoA (red) and vancomycin- or streptomycin (green)-treated mice.

Supplementary Fig. S5



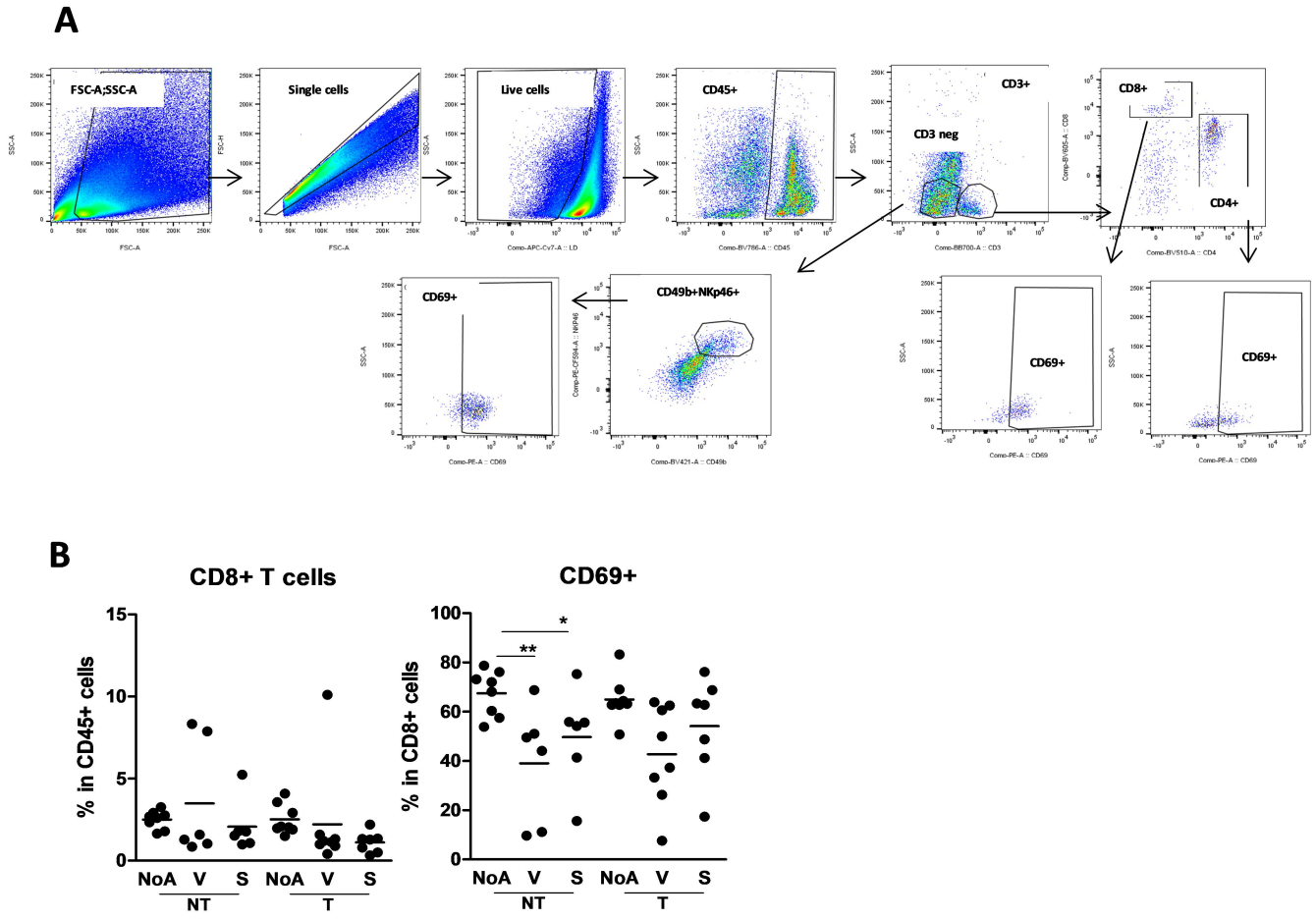
Supplementary Fig. S5. Short-chain fatty acids (SCFAs) quantification in fecal samples from antibiotic-treated mice. The analysis was performed by ultraperformance liquid chromatography-high-resolution-mass spectrometry (UPLC-HR-MS). *$p<0.05$ by an unpaired Student's t-test.

Supplementary Fig. S6



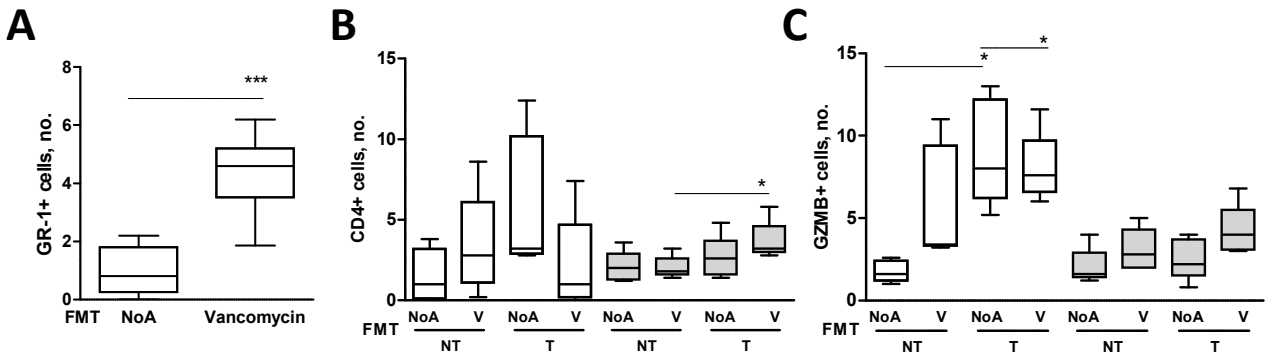
Supplementary Fig. S6. Analysis of intratumor and stromal cell staining in tumors of antibiotic-treated mice. A) Representative images of intratumor and stromal staining of tumor immune infiltrate. **B-E**) Counts of intratumor (white) and stromal (gray) CD45+ cells (B), CD3 lymphocytes (C), Gr1+ cells (D), CD8+ T cells (E) and NKp46+ cells (F). Control (NoA), vancomycin (V)- or streptomycin (S)-treated mice treated with trastuzumab (T) or untreated (NT). Cells were counted in 5 sections at an original magnification of 40x. Scale bars: 50 µm (data shown as box-and-whiskers, min to max). * $p<0.05$ and *** $p<0.001$ by an unpaired Student's t-test.

Supplementary Fig. S7



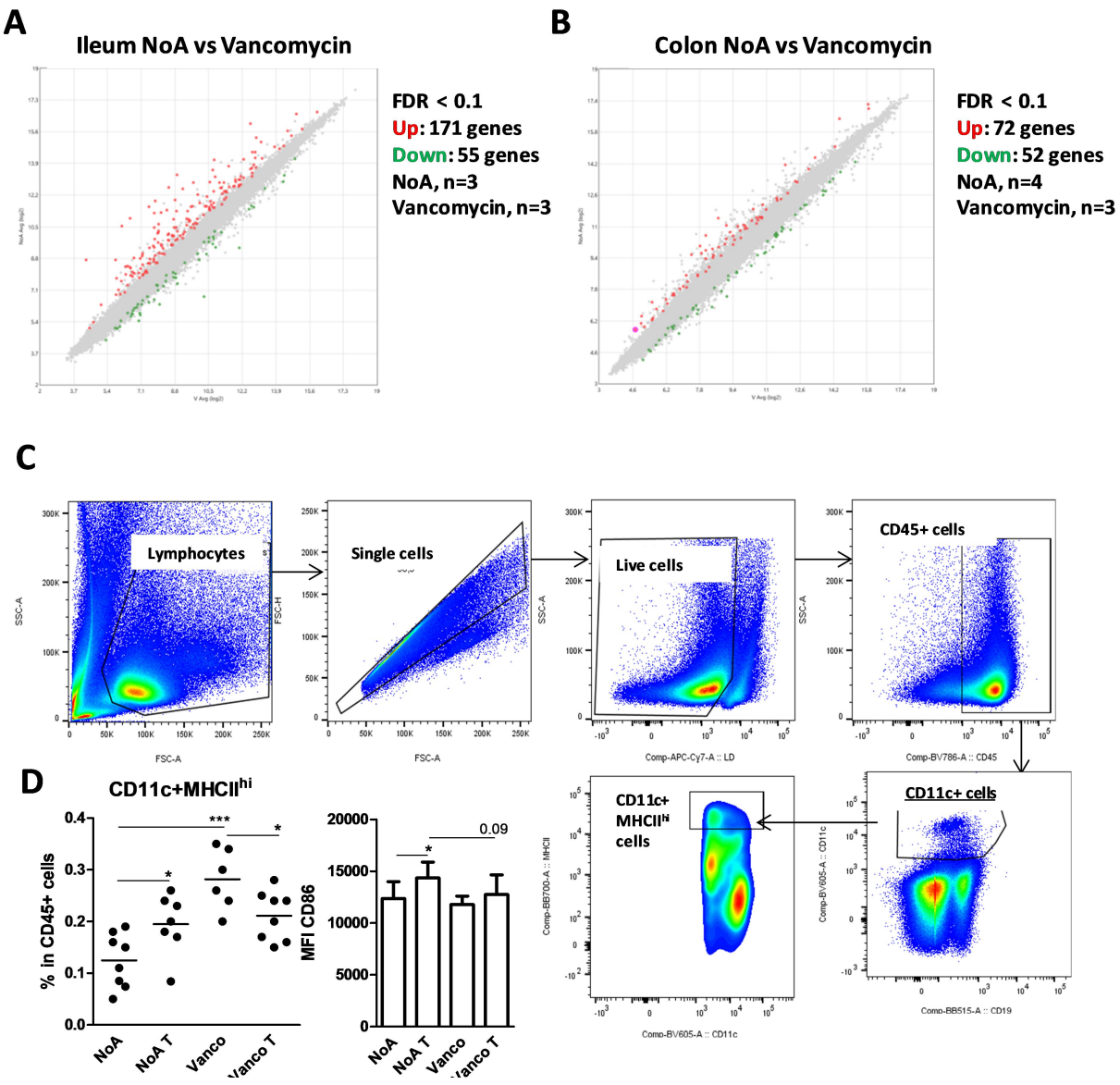
Supplementary Fig. S7. Impact of antibiotic treatment on tumor immune infiltrate. Tumor samples collected at the end of the experiment were homogenized and characterized for immune infiltrates by flow cytometry. **A**) Population gating strategy. **B**) Frequencies of CD8+ T cell (CD3+; CD8+) (left) and activated (CD69+) CD8+ T cell (right) immune populations found in tumors grown in control (NoA), vancomycin (V) or streptomycin (S) mice treated with trastuzumab (T) or untreated (NT). * $p<0.05$ and ** $p<0.01$ by an unpaired Student's t-test.

Supplementary Fig. S8



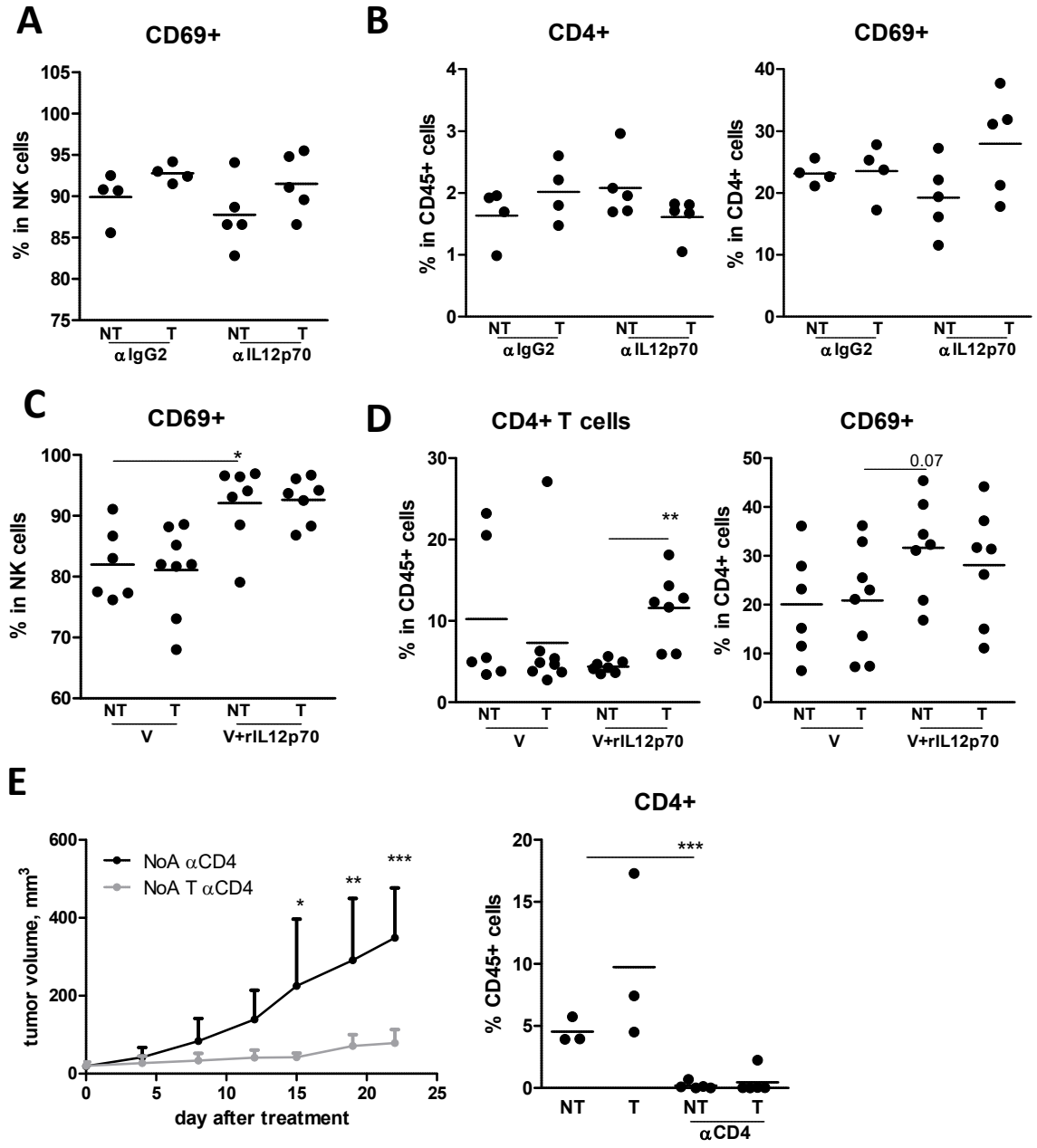
Supplementary Fig. S8. Analysis of intratumor and stromal cell staining in tumors from FMT mice. A-C) Count of total Gr-1+ cells (A) and intratumor (white) and stromal (gray) staining of CD4+ T cells (B) and GZMB-positive cells (C) in the tumor microenvironment of FMT mice. Control (FMT-NoA), vancomycin (FMT-V) mice treated with trastuzumab (T) or untreated (NT). Cells were counted in 5 sections at an original magnification of 40x. Scale bars: 50 μm (data shown as box-and-whiskers, min to max). * $p<0.05$ and *** $p<0.001$ by an unpaired Student's t-test.

Supplementary Fig. S9



Supplementary Fig. S9. Impact of vancomycin treatment on intestinal and systemic immune features. **A-B**) Scatter plot of differentially expressed genes (DEGs) (FDR <0.1) in the ileum (A) and colon (B) of mice. Red, DEGs increased in NoA mice; green, DEGs increased in mice under vancomycin treatment. **C-D**) Flow cytometry analysis of tumor-draining lymph nodes in NoA- and vancomycin-treated mice. Population gating strategy (C). Frequency and activation (CD86 MFI) of $CD11c^{+}MHCII^{hi}$ DCs in control (NoA) and vancomycin (Vanco)-treated mice treated with trastuzumab (T) or untreated (NT). * $p<0.05$ and ***$p<0.001$ by an unpaired Student's t-test.

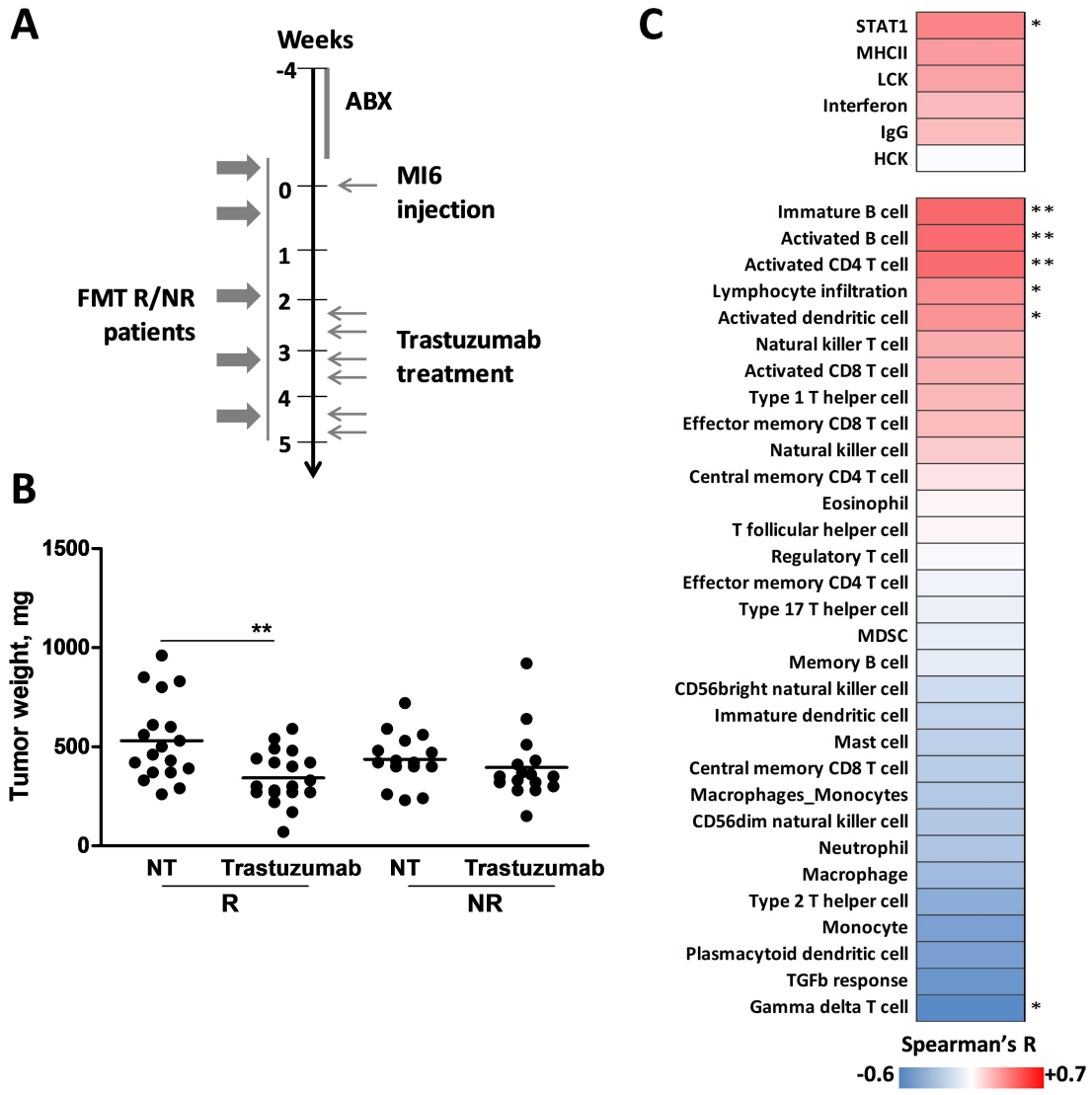
Supplementary Fig. S10



Supplementary Fig. S10. Impact of IL12p70 and CD4+ cell depletion on trastuzumab antitumor efficacy and on tumor immune infiltrate. A-B) Tumor samples collected at the end of the experiment were homogenized and characterized for immune infiltrates by flow cytometry. NK cell activation status (CD69+) (A); frequencies of CD4+ T cells (CD3+;CD4+) (left) and activation status (right) (B) in NoA mice treated with anti-IL12p70 mAb (1 mg before trastuzumab injection, then 500 µg i.p. twice a week). **C-D**) NK cell activation status (CD69+) (C); frequencies of CD4+ T cells (CD3+;CD4+) (left) and activation status (right) (D) in mice under the vancomycin regimen (200 mg/L) and treatment or no

266 treatment with recombinant IL12p70 (rIL12p70) (500 ng i.p. three times a week). **E**) Trastuzumab (T)
267 antitumor activity in NoA mice depleted of CD4+ T cells (αCD4) by an anti-CD4 mAb (400 µg i.p.
268 twice a week) (right) and frequencies of intratumor CD4+ T cells analyzed by flow cytometry.
269 *$p<0.05$; ** $p<0.01$ and ***$p<0.001$ by an unpaired Student's t-test.
270

Supplementary Fig. S11



Supplementary Fig. S11. Causal role of human commensal bacteria in immune-mediated trastuzumab antitumor efficacy. A-B) FVB mice were gavaged with fecal material from R (n=5) and NR (n=4) patients after depletion of their intestinal flora by an antibiotic cocktail (ABX). MI6 cells were injected into the mammary fat pads of treated mice. Fecal material from patients was transplanted 48 h before and after tumor cell injection and then every 10 days for a total of 5 FMTs (7-8 mice/patient were used). Treatment with trastuzumab was started when the tumors reached palpable volumes. The mAb was administered twice a week for 3 weeks at a concentration of 5 mg/kg body weight (A). The weight of tumors collected at the end of the experiment is reported (B). Differences in tumor weights were evaluated by a mixed effect linear model, which calculated the significance of

differences between NT and T tumor weights considering the variability among patients and the variability in transplantation, using treatment in mice as a fixed effect and with a random intercept (**p<0.01). **C)** Correlation between Rody immune metagenes (4) or infiltrating immune cell subsets (5) and PC1 values of β-diversity in profiled cases of HER2-positive BC cohort. The Spearman correlation coefficient (R) is color coded, and relative p-values are shown (*p<0.05, ** p<0.01).

3. Supplementary References

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2. Marchini C, Gabrielli F, Iezzi M, Zanobi S, Montani M, Pietrella L, et al. The human splice variant delta16HER2 induces rapid tumor onset in a reporter transgenic mouse. PLoS ONE 2011;6:e18727.

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5. Charoentong P, Finotello F, Angelova M, Mayer C, Efremova M, Rieder D, et al. Pan-cancer Immunogenomic Analyses Reveal Genotype-Immunophenotype Relationships and Predictors of Response to Checkpoint Blockade. Cell Rep 2017;18:248-62.