**SUPPLEMENTARY METHODS**

**NCT03340935 trial**

***Patient selection***

The NCT03340935 study enrolled patients consenting to combine the FMD with their standard anticancer treatment, which was chosen by the treating oncologist before patient enrollment, and independently of it. Standard antitumor therapies included ChT, radiotherapy, immunotherapy, endocrine treatments, molecular targeted therapies and best supportive care (BSC). Main inclusion criteria were: age > 18 years; diagnosis of any malignant neoplasm, with the exception of small cell lung cancer treated with cytotoxic ChT; baseline BMI ≥ 20 kg/m2. Main exclusion criteria were: unintentional weight loss ≥ 5% in the last three months; diagnosis of diabetes mellitus treated with insulin or insulin secretagogues; pregnancy status; severe kidney, hearth, liver or lung comorbidities. The complete list of enrollment criteria can be found at <https://clinicaltrials.gov/ct2/show/NCT03340935>. A maximum of eight consecutive FMD cycles was allowed. The FMD was precociously interrupted in case of: 1) disease progression or patient death; 2) unacceptable AEs; 3) inability to reach a BMI of at least 20 kg/m2 within one month after the end of the last FMD cycle; 4) consent withdrawal for any reason. Patient weight was measured before and at the end of each FMD cycle; the BMI was calculated as the weight (Kg)/[height(m)2] ratio before and after each FMD cycle.

***Control groups***

Due to the lack of a formal control group in the NCT03340935 trial, to test if the observed biological effects were really caused by the FMD we evaluated peripheral blood metabolic and immunological profiles in two parallel cohorts of subjects: a) a cohort of 9 healthy volunteers undergoing the same five-day FMD regimen and blood/urine sampling before FMD initiation and at the end of the FMD; b) a cohort of 13 patients with advanced BC (mostly TNBC) who refused to take part in the NCT03340935 trial, and were enrolled in an observational study (INT 79/17; **Supplementary Table S3**); these patients received standard, first-line doublet ChT (mostly carboplatin-gemcitabine) without the FMD, and underwent blood/urine sampling two days before ChT administration and three days after ChT administration, i.e., at the same time points as patients undergoing the FMD (plus/minus ChT).

***Two-stage Green-Dahlberg design and* *sample size calculation***

In the first stage, 30 patients were accrued. If the number of patients with G3/G4 AEs related to the FMD was equal to or higher than 8, the study would have been stopped. Otherwise, at least 55 additional patients would have been accrued, up to a total minimum number of 85 patients. Assuming an attrition rate of approximately 10%, a minimum number of 95 were needed. Considering the final number of enrolled patients (n=101), a maximum number of 13 G3/G4 FMD-related AEs was acceptable to reject the null hypothesis. This design yields a type I error rate of at most 5% and power of at least 80% when the true rate of FMD-related AEs is 10%.

***FMD regimen and patient management***

The intake of water and non-caloric beverages was not restricted, while a minimum intake of 1.5 liters of water and/or non-caloric beverages was strongly recommended. The calorie content of foods and beverages included in the FMD scheme was calculated from the *nut.entreca.it* open access website, which is based on the dataset of the INRAN (National Institute of Research for foods and nutrition). The FMD was repeated every 21-28 days on the basis of the concomitant anticancer therapies, as well as of patient tolerability and weight recovery. Patients receiving concomitant intravenous treatments (ChT; immunotherapy) initiated the FMD two days before treatment administration, while patients treated with daily therapies (oral ChT, endocrine, targeted therapies) initiated the FMD simultaneously with their anticancer treatment.

To promote patient compliance with the dietary regimen and to monitor FMD tolerability, we established a dedicated multidisciplinary team composed of five oncologists (C.V., G.F., F.L., A.R., F.dB.), a nutritionist and a research nurse. Enrolled patients maintained a daily contact via email (or by phone in case of emergency symptoms) with one physician involved in the study for the communication of body weight, blood pressure, any occurring AEs and daily food diaries, in which the type and the amount of consumed foods (in grams) and beverages (in liters) was annotated. Patients were given advice on how to manage FMD-induced AEs at enrollment and during the FMD. To improve FMD tolerability, patients were advised to avoid exposure to high/low temperatures, to limit physical activity and energy expenditure, to monitor blood pressure regularly, to drink enough water or non-caloric beverages. Since this was the first large clinical trial that evaluated the safety and feasibility of such a severely calorie-restricted and potentially risky dietary intervention in a heterogeneous population of cancer patients treated with concomitant anticancer therapies (including many patients with advanced neoplasms), one physician was available 24 hours a day by phone during the five-day FMD.

***Analysis of patient compliance with the FMD***

Daily food diaries were analyzed at the end of each FMD cycle to assess patient compliance based on the incidence of minor and major deviations from the prescribed dietary regimen. Minor deviations were defined as lower than 50% increase in daily caloric intake (with either allowed or not-allowed foods/beverages) with respect to the total caloric intake allowed as per study protocol. Major deviations were defined as equal to or higher than 50% increase in daily calorie intake (with either allowed or not-allowed foods/beverages) with respect to the allowed daily caloric intake. Consuming non-caloric foods/beverages not explicitly included in the dietary scheme was considered a minor deviation as well. Two minor deviations occurring during the same FMD cycle were considered as a major deviation. Major and minor deviations were defined in a conservative way, i.e., by calculating the amount of calories consumed during each day of FMD, and not the total amount of calories consumed during the entire FMD cycle.

Patients undergoing at least one major deviation during at least one day of a FMD cycle, or two minor deviations during two different days of the same FMD cycle, were defined as non-compliant during the whole FMD cycle. At the end of the study, we calculated the percentage of patients who were compliant during the whole study (full compliance during all FMD cycles), as well as the rate of compliance during individual FMD cycles. In the time interval between subsequent FMD cycles, patients were recommended to adhere to International Guidelines for Cancer Prevention and Cancer Survivors (1,2).

***Incidence and grading of FMD-related AEs***

AEs occurring during each FMD cycle were retrieved from patient daily reports. The following AEs were attributed to the FMD if they occurred during the diet: fatigue, headache, insomnia, somnolence, constipation, muscle cramps, dizziness, nausea, vomiting, syncope, pre-syncope, tachycardia, epigastric pain, hot flushes, chills, tremor, weight loss, hypoglycemia. The following biochemical alterations were also considered to be FMD-related AEs if they were detected before the initiation of the following FMD cycle (i.e., if they persisted 3-4 weeks after the end of the previous cycle): weight loss, increased concentration of blood cholesterol, triglyceride, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine levels. Other AEs occurring during or after the FMD were not attributed to the experimental dietary intervention. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (<https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0>).

***Metabolic and other biochemical analyses***

All patients underwent blood and urine sampling after at least 8-hour complete fasting on: a) the morning of FMD initiation (day 1); b) the morning of FMD completion (day 6), i.e., just before re-starting their normal diet (**Fig. 1A**). Metabolic parameters measured before and after the FMD were compared to quantify FMD-induced modifications. We routinely analyzed the following parameters: plasma glucose, serum insulin and insulin-like growth factor 1 (IGF-1), urinary ketone bodies, total plasma cholesterol and plasma triglycerides. Blood cell counts (white blood cells, hemoglobin, red blood cells, platelets, neutrophils, lymphocytes), liver (AST, ALT) and kidney (creatinine) parameters were also measured before each FMD cycle. The Paired Wilcoxon test was used to assess changes in BMI and other metabolic parameters before and after each FMD cycle in cancer patients, as well as BMI measurements before consecutive FMD cycles. The Paired Wilcoxon test was also used to assess changes in metabolic parameters before and after the first ChT cycle in 13 advanced breast cancer patients treated with ChT without the FMD, as well as before and after one FMD cycle in healthy volunteers.

BMI and metabolic parameters were illustrated through box plots showing median values, with the boundaries of the rectangle representing the first and third quartiles, while whiskers extend to the extreme data points that are no more than 1.5 times the interquartile range.

***PBMCs isolation, staining procedures and populations of living myeloid cells, MDSC subsets and lymphoid cell subsets analyzed.***

PBMCs were isolated by Ficoll gradient (Leuco-sep polypropylene tubes, Thermo Fisher Scientific) within 2 hours from withdrawal; one aliquot was tested directly by multicolor flow cytometry analysis, while the remaining cells were frozen and stored in liquid nitrogen for subsequent analyses. Monoclonal fluorochrome-conjugated antibodies were used to detect the expression of CD11b, CD14, CD15, CD33, HLA-DR and PD-L1 for the identification of the following populations of living myeloid cells and MDSC subsets: total monocytes (CD11b+CD33+CD14+, here indicated as CD14+), PMN-MDSCs (CD11b+CD14negCD15+, here indicated as CD15+), M-MDSCs (CD11b+CD33+CD14+HLA-DRneg, here indicated as CD14+HLA-DRneg) and PD-L1+ immunosuppressive monocytes (CD11b+CD33+CD14+PD-L1+, here indicated as CD14+PD-L1+). Frequencies of CD14+ (CD11b+CD33+CD14+) and CD15+ (CD11b+CD14negCD15+) cells were calculated as percentages in total PBMCs, while CD14+HLA-DRneg and CD14+PD-L1+ cell frequencies were calculated as percentages in total CD14+ (CD11b+CD33+CD14+) cells. These myeloid cell populations were selected based on previous works that associated their frequency to worse cancer patient prognosis and poor response to treatments (3-6).

Regarding lymphoid populations, we used different markers to define the following T and NK cell subsets: CD3, CD4 and CD8 T cell markers, the activation marker CD69 and the high-affinity IL-2 receptor CD25, the immune checkpoints PD1, TIM3 and LAG3, the FcR CD16 and the glycoprotein CD56/NCAM, the cytolytic molecule granzyme B (GZMB), the proliferation marker Ki-67 and the cytokine IFNγ, the latter measured after 18 hour exposure of PBMCs to anti-CD3 agonist antibody (1μg/ml OKT3, Orthoclone) in the presence of GolgiStop (BD Biosciences, Cat# 554724). GZMB, Ki-67 and IFNγ were quantified through an intracellular staining in previously permeabilized cells (BD Biosciences, Cat# 554714). We assessed the frequency of the following T cell subpopulations: cytotoxic T cells (CD3+CD8+PD1+CD69+, here indicated as CD8+PD1+CD69+) among CD3+CD69+ cells, T cells expressing CD25 (high-affinity IL-2 receptor) among CD3+ cells (here indicated as CD3+CD25+), as well as the frequency of cytolytic NK cells (CD3negCD16+CD56dim amongCD3neg cells). In a subset of 12 patients undergoing the FMD without ChT (to avoid confounding effects), we also evaluated the expression of markers associated with T cell activation and/or proliferation (GZMB, Ki-67, IFNγ after TCR triggering, all detected among CD8+PD1+ cells and reported in CD3+ cells) or exhaustion (LAG-3, TIM-3), detected as LAG-3negTIM-3neg cells among CD8+PD1+ cells) (3,4), as well as the frequency of CD3+CCR7negCD45RAneg effector/memory T cells among CD3+ cells and CD4+CD127negCD25+FOXP3+ Tregs among CD4+ cells. Gating strategies for myeloid and lymphoid cells are depicted in **Supplementary Fig. S4A-S4F**. FMO (Fluorescence Minus One) samples were used as controls (**Supplementary Fig. S4G**).

Regarding staining procedures performed in fresh PBMCs, cell viability was checked by Trypan blue cell count, and it was routinely higher than 95%. When thawed PBMCs were used, cell viability was assessed through Live/Dead Cell Viability Assay (Termofisher, Cat# L23101 and Cat#L34955). Samples were acquired by Gallios Beckman Coulter FC 500 or Cytoflex S (Villepinte, France) flow cytometers and analyzed with Kaluza software (Beckman Coulter; <https://www.beckman.it/flow-cytometry/software/kaluza/downloads>). The complete list of antibodies and other reagents is provided in **Supplementary Table S17**. Distinct cell subsets were quantified in terms of frequencies rather than absolute numbers, as the latter are affected by sampling manipulation procedures that are unrelated to biological patterns. The Paired Wilcoxon test was used to assess changes in immune cell populations before and after each FMD cycle in cancer patients. The Paired Wilcoxon test was also used to assess changes in immune cell populations before and after the first ChT cycle in 13 advanced breast cancer patients treated with ChT without the FMD, and before and after one FMD cycle in healthy volunteers. Frequencies of immune cell populations in PBMCs were illustrated through box plots and through dot plots indicating the value of the parameter in each subject.

***Panel of plasmatic cytokines and chemokines***

In 34 patients, selected cytokines and chemokines were measured in plasma samples by Cytometric Bead Array. Samples were analyzed by Cytoflex flow cytometer and the FCAP Array v3.0 Software (BD Biosciences Cat# 652099) was used. In particular, we dosed C-C Motif Chemokine Ligand 2 (CCL2, BD Biosciences Cat# 558287, RRID:AB\_2869139), CD62L (BD Biosciences Cat# 560420, RRID:AB\_2869343), Fas Ligand (FasL, BD Biosciences Cat#558330), Granulocyte Colony-Stimulating Factor (G-CSF, BD Biosciences Cat# 558326, RRID:AB\_2869156), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF, BD Biosciences Cat# 558335, RRID:AB\_2869163), Granzyme B (GRZb, BD Biosciences Cat# 560304, RRID:AB\_2869331), Interferon alpha (IFNa, BD Biosciences Cat# 560379, RRID:AB\_2869336), Interferon gamma (IFNg, BD Biosciences Cat# 558269, RRID:AB\_2869127), Interleukin 2 (IL2, BD Biosciences Cat# 558270, RRID:AB\_2869128), Interleukin 5 (IL5, BD Biosciences Cat# 558278, RRID:AB\_2869134), Interleukin 6 (IL6, BD Biosciences Cat# 558276, RRID:AB\_2869132), Interleukin 8 (IL8, BD Biosciences Cat# 558277, RRID:AB\_2869133), Interleukin 10 (IL10, BD Biosciences Cat# 558274, RRID:AB\_2869131), Interferon gamma-induced protein 10 (IP10, BD Biosciences Cat# 558280, RRID:AB\_2869136), Tumor Necrosis Factor alpha (TNFa, BD Biosciences Cat# 558273, RRID:AB\_2869130) and Vascular-Endothelial Growth Factor (VEGF, BD Biosciences Cat# 558336, RRID:AB\_2869164). The concentration of plasmatic cytokines/chemokines were illustrated through box plots and through dot plots indicating the value of the corresponding parameter before and after the FMD cycle. The Paired Wilcoxon test was used to assess changes in plasmatic cytokines/chemokines before and after the first FMD cycle.

**DigesT (NCT03454282) trial**

***Metabolic and other biochemical analyses***

Patients underwent blood and urine collection after at least 8-hour complete fasting on the morning of FMD initiation (T1), on the morning of FMD completion (T2), the day of surgery (T3) and ~30 days after surgery (T4) (**Fig. 3A**). We reported data about plasma glucose, serum insulin and IGF-1 and urinary ketone bodies. The Paired Wilcoxon test was used to assess changes in the metabolic parameters between T1 and T2. Metabolic parameters were illustrated through box plots showing median values, with the boundaries of the rectangle representing the first and third quartiles, while whiskers extend to the extreme data points that are no more than 1.5 times the interquartile range.

***RNA extraction and RNA sequencing libraries preparation from tumor samples***

Formalin-fixed and paraffin-embedded (FFPE) breast cancer specimens were identified by two pathologists (A.V. and G.P.). Tumor areas with a cellularity ≥ 70% were macrodissected. Cellular RNA was extracted using the MasterPure™ Complete DNA and RNA Purification Kit (Lucigen, LGC Biosearch Technologies, Novato, USA, Cat# MC85200) following manufacturer’s instructions. RNA quality was evaluated using Agilent RNA 6000 Nano Kit (Agilent Technologies, Santa Clara, USA, Cat# 5067-1511) on the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, USA). RNA sequencing libraries were prepared using TruSeq Stranded Total RNA Library Prep Gold (Illumina, San Diego, CA, USA, Cat# 20020598) according to the manufacturer's protocol and sequenced using 50bp paired end-sequencing mode on Illumina Novaseq 6000 platform (Illumina, San Diego, CA, USA).

***Differential gene expression and deconvolution analyses***

RNA-seq experiment reads were aligned to the GRCh38/hg38 assembly human reference genome using the STAR aligner (7) with default settings. Then size factor normalized data (DESeq2) was log2 transformed and all downstream analysis was performed using RStudio (Version 1.4, RStudio Inc.). Differential gene expression analysis was performed using negative binomial distribution and Benjamini-Hochberg (B-H) FDR with the Bioconductor package DESeq2 (8). Cell type enrichment analysis from gene expression data was performed using the *xCell* webtool (9) according to a set of pan-cancer metagenes for 28 immune cell sub-populations (9,10). Additional gene signatures were used to stratify macrophages into M1-like and M2-like subtypes (9). For each immune cell population, two-tailed Wilcoxon signed rank test comparing post-FMD *versus* pre-FMD distributions of the score of paired samples was performed, retaining only those that passed statistical significance (p < 0.05).

***Pathway analyses***

Preranked gene set enrichment analysis (GSEA) for evaluating pathway enrichment in post-FMD *vs.* pre-FMD transcriptional data was carried out using the Bioconductor package fgsea (https://www.biorxiv.org/content/10.1101/060012v3), taking advantage of the KEGG gene sets available from the GSEA Molecular Signatures Database (http://www.gsea-msigdb.org/gsea/msigdb/collections.jsp). Moderated t-statistic was used to rank the genes. P values were calculated as the number of random genes with the same or more extreme ES value divided by the total number of generated gene sets. (R version 4.0.3; fgsea version 1.16.0). Visualization Plots of Immunological pathways with genes significantly modulated by FMD (p value < 0.05; Wald test assuming a zero-centered Normal distribution) were created starting from the list of differentially expressed genes using the Pathview Bioconductor package (11), a tool set for pathway-based data integration and visualization (R version 4.0.3; pathview version 1.30.0).

***Immunohistochemistry analysis***

The presence of tumor-infiltrating CD8+ T lymphocytes was assessed by immunohistochemistry (IHC) analysis in 22 paired breast cancer specimens. For this analysis, 3-µm thick sections were obtained from FFPE specimens and stained for CD8 (clone C8/144B, Dako, Agilent, Santa Clara, CA, US, 1:20, RRID:AB\_2075537), CD68 (clone KP1, Dako, 1:3000, RRID:AB\_2661840), Perforin 1 (clone 5B10, Leica Biosystems, Wetzlar, Germany, 1:20, RRID:AB\_563955), Granzyme B (clone 11F1, Leica Biosystems, 1:50, RRID:AB\_563751), IGF1R (clone F-1, Santa Cruz Biotechnology, Dallas, TX, US, 1:100, Cat# sc-390130), phospho-IGF1R (polyclonal, Abcam, Cambridge, UK, 1:200, RRID:AB\_731544), following manufacturer's recommendations. Antigen retrieval was achieved using 96°C EDTA for 15 min in a Dako pt link (Dako, Agilent, Santa Clara, US); thereafter the slides were loaded on automated IHC stainer (Dako Link 48 Autostainer, Agilent, Santa Clara, US) under manufacturer recommendations. The primary antibody was incubated for 30 min at room temperature and signal was developed through 3,3'-Diaminobenzidine substrate chromogen (Dako, Agilent, Santa Clara, US, Cat# K3468).

CD8+ T cell infiltration was assessed semi-quantitatively with the scoring system commonly used for the evaluation of tumor-infiltrating lymphocytes (TILs) (12), which reports the percentage of tumor stromal area occupied by CD8+ T cells. We also performed absolute intratumor CD8+ T cell quantification by evaluating the average number of CD8+ T cells per high power field (HPF, 400x magnification with 22 mm ocular, corresponding to 0,237 mm2 area) both in tumor stroma and in intraepithelial areas (i.e., in direct contact with tumor cells). Perforin 1- and Granzyme B-positive T cells, as well as CD68+ macrophage densities, were quantified by reporting the average number of positive cells per HPF. In diagnostic biopsies, the whole tumor area was evaluated, while in surgical samples at least 10 random HPF were assessed, and average IHC scores/counts in each sample were reported. IGF1R and phospho-IGF1R immunoreactivity was evaluated by H score, which takes into account both quantitative (i.e., membranous staining intensity, as classified as weak, moderate and strong) and qualitative (i.e., the prevalence of cells staining positive) , and which is calculated through the following formula: % of weakly stained cells + 2 x % of moderate stained cells + 3 x % of strongly stained cells. IHC scores were illustrated through box plots and through dot plots indicating parameter values in each patient before (T1) and after (T3) the FMD cycle. The Paired Wilcoxon test was used to assess changes in IHC parameters before (T1, tumor biopsies) and after (T3, surgical samples) the FMD.

***PBMCs isolation, staining procedures, sample acquisition and data analysis***

PBMCs were isolated by Ficoll gradient (Leuco-sep polypropylene tubes, Thermo Fisher Scientific) within 2 hours from withdrawal and tested directly by multicolor flow cytometry analysis, while the remaining cells were frozen and stored in liquid nitrogen. Cell viability was assessed through Live/Dead Cell Viability Assay (Termofisher). Samples were acquired by Beckman Coulter Cytoflex S (Villepinte, France) flow cytometer and analyzed with Kaluza software (Beckman Coulter; https://www.beckman.it/flow-cytometry/software/kaluza/downloads). Samples for high dimensional flow-cytometry were collected before the initiation of the FMD (T1) and at different time points after FMD (T2: at the end of the FMD; T3: the day of surgery; T4: ~30 days after surgery). Multiple lymphoid and myeloid markers’ expression were analyzed to define a total of 120 cell subsets (see **Supplementary Fig. S11-13**). The complete list of flow cytometry antibodies and other reagents is provided in **Supplementary Table S18**. The non-parametric paired Wilcoxon test was used to compare the diverse immune cell frequencies at T2 *vs.* T1, T3 *vs.* T1 and T4 *vs.* T1; PBMC subpopulations undergoing modifications passing the significance cut-off of at least one time point (p < 0.05, Benjamini-Hochberg FDR <0.1) were visually represented in a heatmap (**Fig. 5A**). Loess regression curves of representative immune cell subsets were also reported to illustrate modulation across time (**Fig. 5B**). Correlations between statistically significantly modulated PBMC subsets (p < 0.05, FDR < 0.1) at T3 *vs.* T1 and statistically significantly modulated intratumor immune cell subset estimates (p< 0.05, FDR < 0.1) at T3 *vs.* T1 were performed by Spearman’s correlation and corrected using Benjamini-Hochberg FDR.

***Functional and prognostic-predictive immune signatures***

We compiled a list of 25 immune-related signatures pathways with prognostic or predictive significance retrieved from the literature. A first set of signatures consists in immune signatures capturing crucial mechanisms involved in cancer-immune interactions assembled by the TCGA Pan-Cancer Immune Working Group (13,14): "IFNG\_score\_21050467" (15), "Interferon\_19272155" (16), "MHC.I\_19272155" (16), "MHC.II\_19272155" (16), "STAT1\_19272155" (16), "Interferon\_Cluster\_21214954" (17), "IFN\_21978456" (18), "STAT1\_score", "Module3\_IFN\_score", "APM1", "APM2" and "IFIT3" (13,19), and the Immunologic Constant of Rejection “ICR”, which has been associated with better prognosis (20-23) and responsiveness to immunotherapy in breast cancer patients (24). Other prognostic/predictive signatures include opposing IFN-gamma signatures: "IFNG.GS" and "ISG.RS" (25), the Tumor Inflammation Signatures "TIS" (26) and additional signature retrieved through the literature: "T\_Cell\_Palmer" (27), "T\_Cells\_Bindea" (28), "T\_Cell\_cluster\_Iglesia" (29), "CD8\_Palmer" (27), "CD8\_cluster\_Iglesia" (29), "LCK\_Rody" (16), "TNBC\_T-Cell\_Rody" (18), "CD8\_TRM\_Signature\_Up" (30) and "CD4\_Th1\_signature" (31). In addition, we compiled gene lists including transcripts cytokines/chemokines retrieved from the literature (N=23), and transcripts of T-cell exhaustion, co-stimulatory and inhibitory molecules (Immune checkpoints) (N=36), which were used for annotation purposes. Overall, 967 unique genes were included in these gene lists encompassing prognostic immune signatures, cytokine/chemokines and immune checkpoints; these genes were collectively referred to as “immune-related genes”. Gene annotations are reported in **Supplementary Table S10.**

To estimate the enrichment score (ES) of the 25 prognostic/predictive signatures, single sample Gene Set Enrichment analysis (ssGSEA) (32), implemented in the “GSVA package”, was performed. Enrichment scores (ESs) were calculated by ssGSEA on the log2 transformed, normalized data. Differences in ESs between post- and pre-FMD samples were determined using the paired Wilcoxon-test (Wilcoxon test p <0.05 and Benjamini-Hochberg FDR < 0.1). Correlation between ES and IHC data were performed using Spearman’s correlations. All statistical tests that were performed were two-tailed.

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