

Table S1: *MMTV-R26^{Met}* tumor samples used for bulk RNAseq analysis.

Mouse #	Pathologic diagnosis	ER/PR/ HER 2 status
669789	IDC	-/-/-
671802	IDC	-/-/-
671607	IDC	-/-/-
671662	IDC	-/-/-

IDC: Invasive Ductal Carcinoma

Table S2: Available human TNBC cohorts used in this study.

GEO ID	Authors / Reference	Study description	Nb of TNBC patients	PMID
GSE76124	Brown	RNA profiling analysis conducted on 198 TNBC tumors	198	26921331 25208879
GSE96058	Brueffer - Sweden cohort	Clinical Value of RNA Sequencing–Based Classifiers for Prediction of the Five Conventional Breast Cancer Biomarkers: A Report From the Population-Based Multicenter Sweden Cancerome Analysis Network—Breast Initiative [cohort 3273]	395	32913985
GSE194040	Park	The I-SPY2-990 mRNA/RPPA Data Resource contains gene expression and clinical data for 987 patients from 10 arms of the neoadjuvant I-SPY2 TRIAL for aggressive early-stage breast cancer	364	35623341
GSE31448	Bertucci	mRNA expression in 353 invasive breast cancer samples.	101	22110708
GSE199633	Diaz	Gene expression data for 637 human primary breast tumors with recurrence, ER/PR/HER2 status, and overall survival	97	40361136
TCGA	BRCA-TNBC		192	

Table S3. Histopathological characterization of *MMTV-R26^{Met}* tumors (primary and syngeneic).

	Sample name	Mouse #	Pathologic diagnosis	Nottingham grade	Mitotic score	ER/PR/HER 2 status	Necrosis (%)	DCIS (grade)
PRIMARY tumors	T34	678711	IDC NST	2	2	-/-/-	No (NA)	Yes (2)
	T35	678968	IDC NST	2	2	-/-/ HER2-low	No (NA)	No (NA)
	T36	677580	Metaplastic carcinoma squamous	2	3	-/-/-	Yes (60)	No (NA)
	T37	678739	IDC NST	3	2	-/-/-	Yes (50)	No (NA)
	T38	677854	Metaplastic carcinoma squamous cells	2	1	-/-/-	No (NA)	No (NA)
	T39	678741	Metaplastic carcinoma spindle cells	3	3	-/-/-	Yes (10)	No (NA)
	T40	678473	IDC NST	3	3	-/-/-	Yes (5)	No (NA)
	T41	678844	IDC NST	1	2	-/-/-	No (NA)	No (NA)
SYNGENEIC tumors	S34-4G	678845	IDC NST	3	3	-/-/-	Yes (10)	No (NA)
	S34-7G	679616	IDC NST	3	3	-/-/-	No (NA)	No (NA)
	S35-4G	679522	IDC NST	3	3	-/-/-	Yes (10)	No (NA)
	S35-7G	679609	IDC NST	3	3	-/-/-	Yes (5)	No (NA)
	S37-4G	679617	IDC NST	3	3	-/-/-	Yes (35)	No (NA)
	S37-7G	679961	IDC NST	3	3	-/-/-	Yes (30)	No (NA)
	S39-4G	679757	Metaplastic carcinoma spindle cells	3	3	-/-/-	No (NA)	No (NA)
	S39-7G	679962	Metaplastic carcinoma spindle cells	3	3	-/-/-	No (NA)	No (NA)

IDC NST: Invasive Ductal Carcinoma of No Special Type

NA: Not Applicable

Table S6. Specific gene mutations identified in *MMTV-R26^{Met}* primary tumors.

Gene	Mutation in <i>MMTV-R26^{Met}</i>	Effect (OncoKB™/ Cancer Hotspots)	<i>MMTV-R26^{Met}</i> Tumors	Main function	Expected effect of mutation in Breast Cancer
<i>Gcsh</i>	S15N	unknown	36, 37	Mitochondrial Glycine degradation	Metabolic perturbation ¹⁸
<i>Cdk4</i>	V51I	unknown	34, 35, 36, 37, 39, 40	Cell cycle regulator	GOF: Uncontrolled cell proliferation ¹⁹
<i>Cdk6</i>	S57P	unknown	35, 40	Cell cycle regulator	GOF: Uncontrolled cell proliferation ²⁰
	G53D	unknown	40		
<i>Taf1</i>	R1181H	unknown	35	Transcription factor	Gene regulation alteration
<i>Ptpn11</i>	A461T	LOF	39	SHP2 phosphatase regulating signals critical for cell proliferation and survival	Oncogenic signals activation
<i>Ctnnb1</i>	G34R	GOF	36	Encodes β-catenin, key player in Wnt signaling	Aberrant β-catenin (<i>CTNNB1</i> mutation) deregulates Wnt pathway ²¹
	N387K	GOF	40		
<i>Fgf4</i>	I88N	unknown	40	Regulates cell proliferation and differentiation	Uncontrolled cell proliferation / differentiation
<i>Sp140</i>	F400I	unknown	34, 35, 36, 40	Transcriptional regulation and immune response modulator (repressor of genes implicated in inflammation)	Alteration of immune response modulation
	P350A	unknown	36, 40		
	T530S	unknown	35, 36		
<i>Spn</i>	A2184ATA	unknown	34, 36	Tumor suppressor	Perturbed cell proliferation ²²
<i>Rest</i>	D214H	unknown	34	Tumor suppressor	Loss of REST promotes TNBC ²³ Loss of REST promotes BC progression and aggressiveness ²⁴
<i>Lats1</i>	A226P	unknown	40	Tumor suppressor (part of the HIPPO pathway), maintains cell identity & metabolic state	LATS1 loss promotes the expression of basal-like features ²⁵

<i>Kmt2d</i>	A4417V	unknown	40	Lysine methyltransferase 2D (epigenetic regulator)	Altered gene expression The most frequently mutated histone methyltransferase in BC (10–20% of BC) ²⁶
<i>Muc4</i>	Multiple sites	unknown	34, 35, 36, 37, 39, 40	Cell signaling regulator	Frequently mutated in BC ²⁷ Anti-apoptotic signaling, increased cell migration and metastasis ²⁸
<i>Ptrh2</i>	R74* Q105*	unknown	34, 35, 36, 37, 39, 40	Protein synthesis and apoptosis regulator	Apoptotic mechanisms dysregulation
<i>Ndufc2</i>	P6Q	unknown	36, 37	Mitochondrial energy production	Dysregulation of mitochondrial activity ²⁹
	P29L		37		
<i>Kat6b</i>	A1664V	unknown	39	Histone acetyltransferase	Gene regulation alteration <i>KAT6B</i> loss enhances cancer growth ³⁰

Table S7. Antibodies used for immunohistochemistry.

Antibody	Company	Reference	Dilution	Used for	Antigen retrieval	Incubation	RRID#
CD45	Cell Signaling	70257	1:200	IHC	pH 6.5	1 h RT	AB_2799780
ER	Proteintech	212441-AP	1:200	IHC	pH 7.8	1 h RT	AB_11042600
F4/80	Invitrogen	14-4801-82	1:100	IHC	pH 8-8,5	1 h 37°C	AB_467558
HER2	Cell Signaling	2165	1 :200	IHC	pH 7.8	1 h RT	AB_10692490
Ki67	Abcam	15580	1:500	IHC	pH 6.5	20 min 37°C	AB_443209
Ly6G	Bioxcell	BE0075-1	1:400	IHC	pH 8-8,5	1h37°C	AB_1107721
MET	Assay Design	905-076	1:50	IHC	pH 6.5	1 h RT	AB_90259
OmniMap anti-Rb HRP	Roche	05269679 001	Ready to use	IHC	-	16 min RT	AB_2811043
PD-1	R&D Systems	AF1021	1:20	IHC	pH 6.0	1h37°C	AB_354541
PR	Abcam	101688	1:400	IHC	pH 6.5	1 h RT	AB_10715248

IHC: immunohistochemistry, RT: room temperature

Table S8. Antibodies used for spectral analysis.

Antibody	Fluorophore	Clone	Company	Reference	Dilution	RRID#
Anti-mouse CD3	APCVio770	REA641	Miltenyi	130-119-793	1:200	AB_2751847
Anti-mouse CD8a	BUV563	53-6.7	BD Biosciences	748535	1:100	AB_2872946
Anti-mouse CD11b	BUV 395	M1/70	BD Biosciences	563553	1:800	AB_2738276
Anti-mouse CD11c	PE-Cy7	N418	Biolegend	117317	1:800	AB_493569
Anti-mouse CD34	AF700	RAM34	LifeTechnologies	56-0341-82	1:200	AB_493998
Anti-mouse CD24	Viogreen	REA743	Miltenyi	130-110-694	1:200	AB_2656545
Anti-mouse CD31	VioBB515	REA784	Miltenyi	130-11-544	1:800	AB_2657302
Anti-mouse CD44	Vioblue	IM7.8.1	Miltenyi	130-116-531	1:200	AB_2727594
Anti-mouse CD45	BV786	30-F11	BD Biosciences	564225	1:500	AB_2716861
Anti-mouse CD45R (B220)	BV711	RA36B2	BioLegend	103255	1:300	AB_2563491
Anti-mouse CD88	BUV805	20/70	BD Biosciences	748611	1:100	AB_2873018
Anti-mouse Ly6C	PE-CF594	AL-12	BD Biosciences	562728	1:800	AB_2737749
Anti-mouse Ly-6G	BV421	1A8	Biolegend	127628	1:200	AB_2562567
Anti-mouse MHCII	PE	M5/114.15.2	Biolegend	107607	1:1800	AB_313323
Anti-mouse NK1.1	BV650	PK136	BD Biosciences	564143	1:200	AB_2738617
Anti-mouse PTK7	AF647	1H6	Homemade	None	1:200	NA
Anti-mouse PD-1	BV605	29F.1A12	BioLegend	135220	1:200	AB_2562616

NA: not applicable