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Supplementary information

The immunology of human breast cancer

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Supplementary Table 1 | Prognostic value of TMB and antigen presentation in patients with breast cancer

Variable	Subtype	Nº	Treatment	Technology	Effect	Notes	Ref
APP components	TNBC	34	Adjuvant CT	IHC	Prolonged RFS Prolonged OS	Validated with public datasets	1
APP components	TNBC	249 580	n/a	Transcriptomics*	Prolonged RFS	Not correlating with OS	1
HLA Class I	$HR^{+}HER2^{-}$	320	NACT	IHC	Increased pCR rate Shortened DFS	Correlating with TIL levels	2
HLA Class I	$HR^{+}HER2^{-}$ TNBC	196	NACT	IHC	Increased pCR rate Prolonged DFS	Interacting with TIL abundance	3
HLA Class I	$HER2^{+}$	42 71	Neoadjuvant HER2 blockers	IHC	Prolonged DFS	Independent of pCR rates	4
HLA Class I	TNBC	879	n/a	Transcriptomics*	Prolonged RFS Prolonged OS	Correlating with T cell markers	5
HLA-A HLA-B TAP1	TNBC	162	NACT + durvalumab	Transcriptomics*	Increased pCR rate	Limited to patients on ICIs	6
TMB	$HR^{+}HER2^{-}$	379	SOC	TGS	Shortened RFS Shortened OS	Based on cutoff at q90	7
TMB	TNBC	25	PD-1 or PD-L1 blockers	WES	Prolonged PFS Prolonged OS	Based on cutoff of ≥10 mut/Mb	8
TMB	TNBC	253	CT Pembrolizumab	n/a	Prolonged PFS Prolonged OS	Limited to patients on pembrolizumab	9
TMB TNA	TNBC	186	SOC	WES	Shortened DFS	Linked to tumor clonality	10
TNA	Not specified	441	SOC	WES	Prolonged OS	Correlating with driver mutations	11

APP, antigen processing and presentation; CT, chemotherapy; DFS, disease-free survival; HR, hormone receptor; IHC, immunohistochemistry; n/a, not available or not assessable; NACT, neoadjuvant chemotherapy; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; RFS, relapse-free survival; RNAseq, RNA sequencing; SOC, standard-of-care; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden; TGS, targeted genomic sequencing; TNA, tumor neoantigen; TNBC, triple-negative breast cancer; WES, whole-exome sequencing.

Supplementary Table 2 | Prognostic value of the intratumoral immune microenvironment in patients with breast cancer

Variable	Subtype	Nº	Treatment	Technology	Effect	Notes	Ref.
APC- and T cell-enriched niches	TNBC	34	Pembrolizumab → RT + pembrolizumab	scRNAseq and spatial proteomics	pCR	Emerging after neoadjuvant pembrolizumab	12
B cell and $CD8^+$ CTL clusters	TNBC	36	Surgery	IHC	Prolonged RFS	Potentially representing immature TLSs	13
B cell signatures	$HER2^+$ TNBC	144 140	SOC	Transcriptomics*	Prolonged MFS	Correlating with T cell signatures	14
B cells	$HER2^+$ TNBC	136 113	Adjuvant CT	IHC	Prolonged iDFS Prolonged OS	Often linked to TLS formation	15
B cells	TNBC	114	Surgery	IHC	Prolonged RFS Prolonged OS	Focused on stromal TILs	16
BCL2 competence	HR+	n/a	n/a	Various	Improved outcome	Potentially linked to suppressed type I IFN signaling	17
CCL19 levels	TNBC	19	NACT + pembrolizumab	RNASeq	Increased pCR rate	Lack of association with pCR in patients treated with NACT only	18
CCL19 levels	TNBC	30	Neoadjuvant camrelizumab	IHC	Increased ORR Response magnitude Prolonged PFS	Correlating with stromal TIL abundance	18
CCL19 levels	TNBC	33	NACT + camrelizumab	IHC	Increased pCR rate	Lack of association with pCR in patients treated with NACT only	18
$CD163^+$ TAMs	Multiple	238	n/a	IHC	Shortened OS	Linked to TGF-β and VEGFA signaling	19
CD24 levels	Multiple	204	SOC	IHC	Shortened DFS Shortened OS	Association with DFS independent of other variables	20
CD24 levels	Multiple	104	SOC	IHC	Shortened OS	No association with DFS	21
CD24 levels	Multiple	155	Surgery	IHC	Shortened DFS Shortened OS	Monitored as percentage of $CD24^+CD44^-$ cancer cells	22
CD24 levels	Multiple	1,080	n/a	Transcriptomics*	Shortened OS	Linked to defects in phagocytosis by macrophages	23
$CD3^+$ TILs	TNBC	36	Surgery	IHC	Prolonged RFS	Especially when associated with heterotypic LAs	13
$CD33^+$ MDSCs	Multiple	54	NACT	IHC	PD or SD	Confirmed on multivariate Cox regression (also for $IDO1^+CD33^+$ MDSCs)	24

CD47 levels	$HER2^+$	40	Neoadjuvant trastuzumab	IHC	Shortened OS	Limited to metastatic disease	25
CD47 levels	TNBC	57	Surgery	IHC	Shortened DFS	Correlating with multiple EMT markers	26
CD47 levels	Multiple	738 945	n/a	Transcriptomics*	Shortened dMFS Shortened RFS	Especially in the context of HER2 upregulation	27
$CD68^+$ TAMs	HR^+HER2^-	282	n/a	IHC	Shortened RFS	Limited to $CD47^+$ samples	28
$CD8^+$ CTL and NK cell signatures	HR^+HER2^-	16	CDK4/6 inhibitors	scRNAseq	Prolonged PFS	Validated with public datasets	29
$CD8^+$ CTLs	$HER2^+$	30	NACT	MIFM	pCR	Correlating with HER2 levels at baseline	30
$CD8^+$ CTLs	$HER2^+$ TNBC	14 18	Surgery	IHC	Prolonged OS	Metastatic brain lesions	31
$CX3CR1^+$ TAMs	HR^+HER2^-	12	Pembrolizumab → RT + pembrolizumab	scRNAseq	Decreased pCR rate	Exhibiting robust immunosuppressive features	32
$CX3CR1^+$ TAMs	HR^+HER2^-	86	CDK4/6 inhibitors	IHC	Tumor grade	Correlating with γδ T cells	32
CXCL13 levels	Multiple	794	Surgery only	Transcriptomics*	Increased pCR rate Prolonged DFS	No correlation with DFS in the TNBC set	33
$FOLR2^+$ TAM signatures	HR^+	1,107	SOC	Transcriptomics*	Prolonged OS	Inversely correlating with immunosuppressive TAM abundance	34
$FOLR2^+$ TAMs	Multiple	122 126	n/a	MIFM	Prolonged OS	Validated with multivariate Cox regression analysis	34
Granulocyte structures	HR^+	427	n/a	Spatial transcriptomics	Shortened OS	Upon adjustment for HER2 status	35
$GZMB^+$ TAMs	$HER2^+$	30	NACT	MIFM	pCR	Specifically when in proximity of malignant cells	30
IgG signature	$HER2^+$	205 151	NACT	Transcriptomics*	Prolonged EFS	Outperformed TIL assessments	36
IgG signature	Multiple	1904 1082	None	Transcriptomics*	Prolonged OS	In disease-free patients, correlating with TLS formation	37
Immunostimulatory TAMs	$HER2^+$	40	Neoadjuvant trastuzumab	IHC	Prolonged OS	Limited to metastatic disease	25
Immunosuppressive TAM signatures	HR^+	96	NACT	Transcriptomics*	Residual disease	Correlating with depletion of $CD8^+$ CTLs and TILs	38

Intratumoral DCs	TNBC	60	Neoadjuvant pembrolizumab	IHC	pCR	No association with stromal DCs	39
LGALS2 levels	Multiple	1084 1904 3075 107	n/a	Transcriptomics*	Prolonged OS	Emerging from pre-developed TLS-associated DC signature	40
Mature TLSs	TNBC	63	NACT	IHC	Prolonged DFS	Correlating with TIL levels	41
Mature TLSs	Multiple	n/a	SOC	Transcriptomics*	Prolonged OS	Poorly represented in the HR^+ subset	41
MDSC signatures	TNBC	357	n/a	Transcriptomics*	Shortened OS	Correlating with scarce TILs and active glycolysis	42
Naïve TAM signatures	HR^+HER2^-	1,580	NACT	Transcriptomics*	Shortened DFS	No association in $HER2^+$ and TNBC	43
NK cells	$HER2^+$	42 71	Neoadjuvant HER2 blockers	IHC	Increased pCR rate Prolonged DFS	Correlating with CTL and DC signatures	4
pDCs	Multiple	152 103	SOC	IHC	Shortened DFS Shortened OS	Potentially linked to type I IFN signaling	44
PD-L1 levels	Multiple	68	NACT	IHC	Increased pCR rate	No association with survival	45
PD-L1 levels	Multiple	105	NACT	IHC	pCR	Correlating with TIL abundance	46
PD-L1 levels	TNBC	29	PD-1 or PD-L1 blockers ± CT or TT	Transcriptomics*	Prolonged PFS Prolonged OS	Correlating with markers of immunity	8
PD-L1 levels	TNBC	67	Neoadjuvant CT or RT → Nivolumab	IHC	Increased ORR	Based on ≥1% cutoff for cancer cells or ≥5% cutoff for ICs	47
PD-L1 levels	TNBC	116	Atezolizumab	IHC	Increased ORR Prolonged OS	Based on ≥1% cutoff for ICs	48
PD-L1 levels	TNBC	451	First-line CT + atezolizumab	IHC	Prolonged OS	Based on ≥1% cutoff for ICs	49,50
PD-L1 levels	TNBC	566	First-line CT + pembrolizumab	IHC	Prolonged PFS Prolonged OS	Based on CPS ≥10% cutoff	51,52
PD-L1 levels	TNBC	902	First-line CT + atezolizumab	IHC	Prolonged PFS Prolonged OS	Based on ≥1% cutoff	53
Plasma cells	TNBC	114	Surgery	IHC	Prolonged RFS	Focused on stromal TILs	54

Signature of inflamed tumors	TNBC	53	Neoadjuvant CT or RT → nivolumab	Transcriptomics*	DC	Signature developed from spatial data in another cohort	55
Signature of inflamed tumors	TNBC	579	Surgery	Transcriptomics*	Prolonged DFS	Especially in the context of IFN signaling signatures	56
TGFBR1 and TGFBR2 levels	$HER2^+$	166	n/a	Transcriptomics*	Prolonged dMFS	Paradoxically associated with poor prognostic factors	57
TGFBR1 and TGFBR2 levels	Multiple	574	Surgery	Transcriptomics*	Shortened PFS	Combined with IHC markers of TGF-β activity	58
TGFBR3 levels	Multiple	286	SOC	Transcriptomics*	Prolonged RFS	Linked to TGFBR3 shedding and suppressed TGF-β activity	59
TGF-β activity	Multiple	61	Surgery	IHC	Recurrence Shortened DFS	Based on TGF-β1 expression and IHC markers of activity	60
TGF-β signatures	Multiple	1,319	n/a	Transcriptomics*	Prolonged RFS	Strongest association in the HR^+HER2^- subtype	61
T_H1 and T_{FH} $CD4^+$ T cell signatures	Multiple	794	Surgery only	Transcriptomics*	Increased pCR rate Prolonged DFS	No correlation with DFS in the TNBC set	33
T_H1 $CD4^+$ T cell signatures	Multiple	1,004	SOC	Transcriptomics*	Prolonged dDFS Prolonged OS	Correlating with TMB	62
TILs	HR^+HER2^-	187	Surgery	H/E	Increased Oncotype DX score	Increased propensity for relapse	63
TILs	HR^+HER2^-	1,366	NACT	H/E	Increased pCR rate	Based on 10% and 60% TIL cutoffs	64
TILs	$HER2^+$	205 151	NACT	H/E	Increased pCR rate	Correlating with immune signatures	36
TILs	$HER2^+$	305 455	NACT	H/E	Prolonged EFS	In the context of a composite score including BCR diversity	65
TILs	$HER2^+$	232	NACT	H/E	Prolonged dDFS	Only in patients receiving trastuzumab	66
TILs	$HER2^+$	447	Adjuvant trastuzumab	H/E	Prolonged DFS	Restricted to HR^- patients	67
TILs	$HER2^+$	1,379	NACT	H/E	Increased pCR rate	Based on 10% and 60% TIL cutoffs	64
TILs	TNBC	157	Surgery	H/E	Prolonged DFS Prolonged OS	Focused on peripheral TILs	63
TILs	TNBC	778	NACT	H/E	Prolonged dDFS	Focused on stromal TILs	66

TILs	TNBC	906	NACT	H/E	Increased pCR rate	Based on 10% and 60% TIL cutoffs	64
TILs	TNBC	2,148	NACT	H/E	Prolonged iDFS Prolonged dDFS Prolonged OS	Focused on stromal TILs	68
TILs	Multiple	68	NACT	H/E	Increased pCR rate	No association with survival	45
TILs	Multiple	218 840	NACT	H/E	Increased pCR rate	Especially intratumoral TILs	69
TLS- and T cell-enriched niches	TNBC	34	Pembrolizumab → RT + pembrolizumab	scRNAseq and spatial proteomics	pCR	In baseline samples, correlating with HLA Class I expression	12
T_{reg} and T_{EX} structures	HR^+	427	n/a	Spatial transcriptomics	Shortened OS	Upon adjustment for HER2 status	35
T_{reg} cell/$CD8^+$ CTL ratio	HR^+HER2^-	28	Surgery	IHC	Shortened OS	Metastatic brain lesions	31
T_{reg} cells	Multiple	54	NACT	IHC	PD or SD	Not confirmed on multivariate Cox regression	24
T_{reg} cells	Multiple	62	Surgery	IHC	Increased RR	Focused on DCIS	70
T_{reg} cells	Multiple	237	SOC	IHC	Shortened RFS Shortened OS	Based on 15/core cutoff	70
Type I IFN signatures	Multiple	110 161 292	RT or adjuvant CT	Transcriptomics*	Shortened MFS	No association in patients not receiving adjuvant CT or RT, or receiving ET	71
Type I IFN signatures	Multiple	1,422	n/a	Transcriptomics*	Shortened OS	Associated with signatures of apoptosis signaling	72
$V\delta1^+$ γδ T cells	TNBC	11	Surgery	DNAseq	Prolonged PFS Prolonged OS	Not observed with γδ T cells at large	73
γδ T cell signatures IL-17 signatures	HR^-	381	SOC	Transcriptomics*	Prolonged DSS	Contrary to the HR^+ subset	32
γδ T cell signatures IL-17 signatures	HR^+	1,042	SOC	Transcriptomics*	Shortened DSS Shortened OS	Correlating with tumor grade	32
γδ T cells	HR^+HER2^-	86	CDK4/6 inhibitors	IHC	Tumor grade	Mostly localized within tumor nest	32
γδ T cell signatures	HR^+ TNBC	4,906 1,555	NACT	Transcriptomics*	Increased pCR rate Prolonged DFS	Alongside many other associations with outcome	43

γδ T cell signatures	$HER2^+$	1,580	NACT	Transcriptomics*	Increased pCR rate Prolonged DFS Prolonged OS	Alongside many other associations with outcome	43
γδ T cell signatures	TNBC	169	SOC	Transcriptomics*	Prolonged OS	No association with $CD8^+$ CTL signatures	74
γδ T cells	TNBC	162	Surgery	IHC	Prolonged RFS Prolonged OS	Limited to *PI3KCA* wild-type tumors	75

APC, antigen-presenting cell; CPS, combined positive score; CT, chemotherapy; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DCIS, ductal carcinoma in situ; dDFS, distant disease-free survival; DFS, disease-free survival; dMFS, distant metastasis-free survival; DNAseq, DNA sequencing; DC, disease control; DSS, disease-specific survival; EFS, event-free survival; EMT, epithelial-to-mesenchymal transition; H/E, hematoxylin/eosin; IC, immune cell; iDFS, invasive disease-free survival; LA, lymphoid aggregate; MDSC, myeloid-derived suppressor cell; MFS, metastasis-free survival; MIFM, multispectral immunofluorescence microscopy; n/a, not available or not assessable; NK, natural killer; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PD, progressive disease; pDC, plasmacytoid DC; PFS, progression-free survival; RFS, relapse-free survival; scRNAseq, single-cell RNA sequencing; SD, stable disease; SOC, standard-of-care; TAM, tumor-associated macrophage; T_{EX}, exhausted T; T_{FH}, follicular helper T; TIL, tumor-infiltrating lymphocyte; TLS, tertiary lymphoid structure; TMB, tumor mutational burden; TNBC, triple-negative breast cancer; T_{reg}, regulatory T; TT, targeted therapy. *as per microarray or bulk RNA sequencing.

Supplementary Table 3 | Promising strategies with immunotherapeutic activity currently under evaluation in patients with breast cancer*

Target	Drug(s)	Subtype(s)	Phase	Status	Co-treatment(s)	Notes	Ref.
AKT	Afuresertib	HR^+HER2^-	III	Recruiting	Fulvestrant	Following recurrence or progression on or after endocrine therapy (up to 2 lines) and CDK4/6 inhibitors (1^{st} line) or chemotherapy (1^{st} line)	NCT04851613
AKT	Capivasertib	HR^+HER2^-	IIIb	Active, not recruiting	Fulvestrant	Following recurrence or progression on or after endocrine therapy and CDK4/6 inhibitors	NCT06764186
AKT	Capivasertib	HR^+HER2^-	III	Recruiting	Fulvestrant	Following recurrence or progression on or after endocrine therapy and CDK4/6 inhibitors	NCT06982521
AKT	Capivasertib	HR^+HER2^-	III	Recruiting	CDK4/6 inhibitors Fulvestrant	Following recurrence or progression on ET-containing regimens	NCT04862663
AKT	Capivasertib	HR^+HER2^-	III	Recruiting	Fulvestrant	Following recurrence or progression on ET-containing regimens	NCT06635447
CDK4	Atirmociclib	HR^+HER2^-	III	Recruiting	Letrozole	As first line intervention, compared with FDA-approved CDK4/6 inhibitors + letrozole	NCT06760637
PD-1 VEGFA	Ivonescimab	TNBC	III	Not yet recruiting	Nab-paclitaxel	As first line intervention, compared with placebo plus nab-paclitaxel	NCT06767527
PD-L1 VEGFA	PM8002	TNBC	III	Recruiting	Nab-paclitaxel	As first line intervention, compared with placebo plus nab-paclitaxel	NCT06419621

FDA, Food and Drug Administration; TNBC, triple-negative breast cancer. *As per www.clinicaltrials.gov, last updated on Mar 23, 2026; limited to Phase III or higher with status “Active, not recruiting”, “Not yet recruiting” and “Recruiting” and testing immunotherapeutic agents that are currently not approved by the FDA for use in patients with cancer.

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