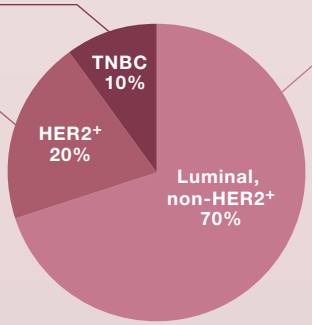
SnapShot: Breast Cancer

Kornelia Polyak and Otto Metzger Filho
Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02215 USA

Cancer Cell

Frequency of breast cancer subtypes

TNBC Triple-negative breast cancers are ER$^-$PR$^-$HER2$^-$ and show significant, but not complete, overlap with the basal-like subtype of breast cancer (which is defined by differentiation state and gene expression profile).



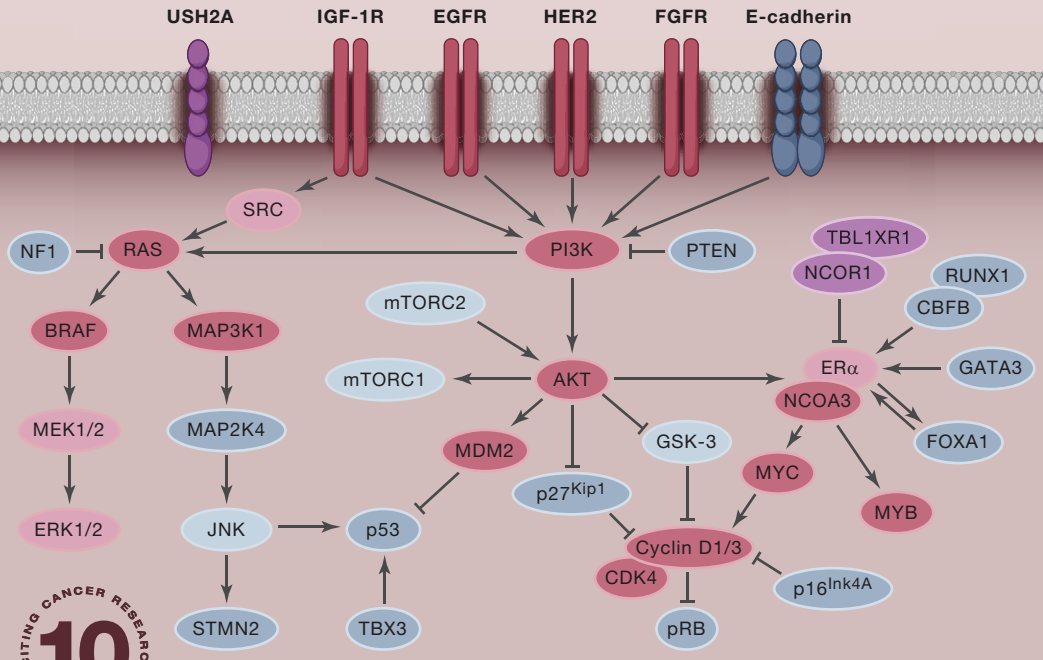
HER2$^+$ breast cancers have luminal features and are characterized by *ERBB2* gene amplification and overexpression leading to a dependency on HER2 signaling.

Luminal (non-HER2$^+$) tumors are typically estrogen receptor positive, displaying high ERα levels. These tumors are dependent on estrogen for growth and, therefore, respond to endocrine therapy.

Subtype	Stage	5 year OS (%)	10 year OS (%)
*DCIS	0	99	98
Luminal (non-HER2+)	I	98	95
	II	91	81
	III	72	54
	IV	33	17
**HER2+	I	98	95
	II	92	86
	III	85	75
	IV	40	15
TNBC	I	93	90
	II	76	70
	III	45	37
	IV	15	11

*Preinvasive stage
**Estimated overall survival (OS) using HER2-targeted therapies

Key signaling pathways in breast cancer based on somatic mutation data



Colors indicate tumor suppressors (blue), oncogenes (red), or mutant genes with unclear roles (purple), and lighter shading marks pathway components in which somatic mutations have not been identified.

Top 21 most commonly mutated genes in breast cancer			
Gene	All (%)	Luminal	TNBC
TP53	35	26	54
PIK3CA	34	44	8
GATA3	9	13	0
MAP3K1	8	11	0
MLL3	6	8	3
CDH1	6	8	2
USH2A	5	4	8
PTEN	3	3	3
RUNX1	3	4	0
MAP2K4	3	4	1
NCOR1	3	3	1
RB1	3	2	5
TBX3	2	3	1
PIK3R1	2	3	2
CTCF	2	2	1
NF1	2	2	1
SF3B1	2	2	0
AKT1	2	2	0
CBFB	1	2	1
FOXA1	1	1	1
CDKN1B	1	1	0

Mutation frequencies (%) in all tumors, or just within luminal (including HER2$^+$) and TNBC subtypes.

ER	HER2	PI3K Pathway (PI3K, AKT, mTOR)		IGF, IGF-1R	Angiogenesis (VEGFR, PDGFR, KIT)		PARP	Others (Target)
Anastrozole	Afatinib	AZD8055[b]	INK1117	BMS-754807	Aflibercept	Olaratumab	BMN-673	Cabozantinib[e], Foretinib[e], Onartuzumab (MET)
Estradiol	Canertinib	BEZ235[c]	INK128[b]	Cixutumumab	Axitinib	Pazopanib	CEP-9722	
Exemestane	Dacomitinib	BGT226	MK2206[b]	Dalotuzumab	Bevacizumab	Ponatinib	E7016	AZD4547, BGJ398, Dovitinib, E-3810[e], HGS1036 (FGFR)
Fulvestrant	Lapatinib	BKM120	PF-04691502[c]	Figitumumab	Brivanib	Sorafenib	INO-1001	
Megestrol	MM-121	BYL719	PKI-587[c]	Ganitumab	Lenvatinib	Sunitinib	MK4827	AUY922, Retaspimycin, Tanespimycin (HSP90)
Letrozole	Neratinib	Everolimus[b]	PX-866	Linsitinib	MEDI-575	Semaxanib	Olaparib	
Raloxifene[a]	Pertuzumab	GDC-0032	Temsirolimus[b]	MEDI-573	Motesanib	Vandetanib	Rucaparib	Ruxolitinib (JAK)
Tamoxifen	Trastuzumab	GDC-0068[d]	XL147		Nintedanib	Vatalanib	Veliparib	Denosumab (RANKL)
Toremifene	T-DM1	GDC-0941	XL765[c]	[a] Raloxifene is used for breast cancer prevention, not treatment, [b] mTOR inhibitor, [c] dual PI3K/mTOR inhibitor, [d] AKT inhibitor, [e] also inhibits VEGFR.				
		GDC-0980[c]						

See online version for legend and references.

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Breast cancer is the most commonly diagnosed cancer and the principle cause of cancer-related mortality in women worldwide. Breast tumors are highly heterogeneous and are classified based on: (1) histology into ductal or lobular carcinomas, (2) differentiation state/gene expression profiles into luminal and basal-like subtypes, and (3) the expression of estrogen and progesterone receptors and HER2 into ER^+, $HER2^+$, and $ER^-PR^-HER2^-$ (triple-negative breast cancer, TNBC) subtypes. $HER2^+$ and ER^+ tumors all have luminal features, whereas TNBCs show significant but not complete overlap with basal-like subtype. The categorization of breast tumors based on hormone receptor and HER2 status and the use of antihormonal and HER2-targeted therapy, respectively, are among the first examples for molecular-based classification and personalized cancer treatment that made a significant difference in clinical outcomes. The widespread use of mammograms has lead to increased diagnosis of early stage disease, including ductal carcinoma in situ (DCIS), which also contributed to a decrease in mortality rates. The pie chart in the adjacent figure shows frequencies of various clinically relevant breast cancer subtypes, and the top table summarizes the prognoses of these subtypes.

Systematic characterization of breast cancer genomes has identified somatic mutations in several key signaling pathways depicted in the adjacent figure. The top 21 genes with the most frequent nucleotide sequence changes are summarized in the middle table. The increased activities of these signaling pathways serve both as therapeutic targets and as biomarkers guiding the selection of patients who would most likely benefit from particular therapies. Current pathways and compounds used for rationally designed targeted therapy in breast cancer are listed in the bottom table.

Estrogen Receptor Alpha

The estrogen receptor alpha (ERα) nuclear hormone receptor, encoded by *ESR1*, is a ligand-dependent transcription factor. Upon estrogen binding, ERα directly and indirectly activates the expression of numerous genes. ERα's activity is modulated by coactivators, including NCOA3. Whereas ERα is expressed in only a small subset of cells in normal breast epithelium, where it plays an important role in breast development and differentiation, 65%–70% of breast tumors display high ERα levels and estrogen dependency for growth. Therefore, these ER^+ tumors respond to endocrine therapy. Several therapeutic approaches have been designed to modulate ER activity, including competitive antagonists, downregulators of ER protein levels, and inhibitors of the aromatase enzyme that produces estrogen.

HER2

HER2, encoded by the *ERBB2* proto-oncogene, is a receptor tyrosine kinase (RTK) and a member of the epidermal growth factor receptor (EGFR) family. HER2 forms heterodimers with all three other members of the EGFR family, yielding different complexes with different kinase activities and physiologic functions. *ERBB2* is amplified and overexpressed in ~20%–25% of breast carcinomas, leading to their dependency on HER2 signaling. The number of HER2-targeted therapies has increased significantly in recent years; these therapies include simple or drug-conjugated antibodies and small-molecule inhibitors of RTK activity specific for HER2 or broader for additional EGFR family members. These therapies have significantly improved disease-specific and overall survival of patients with $HER2^+$ breast cancer.

PI3K, AKT, and PTEN

PIK3CA encodes the 110 kDa catalytic subunit of a class I phosphatidylinositol 3-kinase (PI3K). The 85 kDa regulatory subunit acts as an adaptor and mediates the activation of PI3K by RTKs and other kinases. PI3K phosphorylates phosphatidylinositol 4-phosphate and phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 plays a key role in regulating the activity of signaling cascades involved in cell growth, survival, proliferation, metabolism, motility, and morphology by recruiting PH-domain-containing proteins, including AKT1 and PDPK1, to the cell membrane. A large fraction of human malignancies, including ~30% of breast carcinomas, have somatic mutations in *PIK3CA* leading to constitutive activation of the downstream signaling pathway. The activity of PI3K is antagonized by the PTEN tumor suppressor. PTEN is a dual-specificity phosphatase that dephosphorylates PIP3, leading to inhibition of AKT kinase activity, and can also antagonize the MAP kinase pathway via its protein phosphatase function. Germline mutations in *PTEN* play a role in Cowden disease and Bannayan-Zonana syndrome leading to increased cancer risk. Somatic inactivation of *PTEN* is common in a wide range of human cancers, including breast cancer. Approximately 50% of breast carcinomas have an activated PI3K/AKT pathway due to mutations in one of its components, making this kinase signaling cascade an attractive therapeutic target. Small-molecule inhibitors targeting PI3K, AKT, mTOR, or their combination are in various phases of clinical development.

MAP3K1, MAP2K4, and JNK1

MAP3K1 is a mitogen-activated protein kinase (MAPK) kinase kinase that regulates the ERK and JNK MAPK pathways, the NF-κB transcription factor, and the p300 transcriptional coactivator. MAP2K4 is another member of the MAPK-JNK signaling pathway functioning between MAP3K1 and JNK. Frequent somatic mutations in *MAP3K1* and *MAP2K4* have recently been reported in breast cancer, identifying MAPK-JNK signaling as a key pathway in breast cancer.

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