Pathways and molecules that play a role in cancer develpomentand being the targets of therapy

MED 213

The Genetic Bases of Cancer

Oncogenes
Tumor suppressor genes
Repair genes

Environmental mutagens
(biological, chemical, physical agents)

Genetic mechanisms in Familial vs Sporadic Cancers

Pathways in Carcinogenesis

Epigenetics and Cancer

Pathways and molecules that play a role in cancer develpomentand being the targets of therapy

Conventional cancer therapy

Works on two basic mechanisms of cell cycle arrest

DNA damage producing
Prevention DNA synthesis

Modern cancer therapy

Works on targeted molecules of cellular pathways

Disrupting ligand receptor relation
Preventing signal transduciton

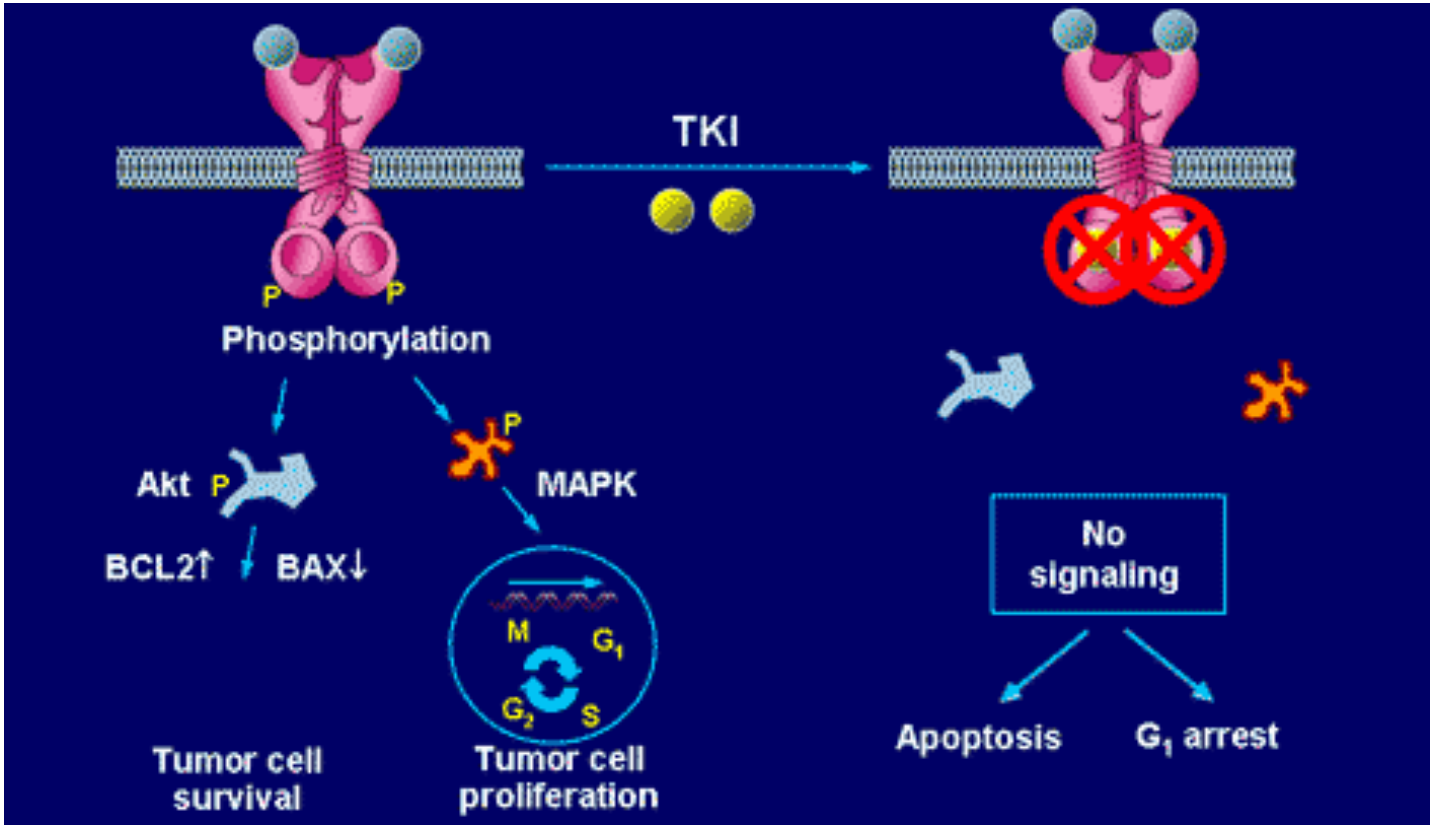
Molecular Targets for Cancer Therapy

Therapeutic Targets

Monoklonal antikorlar (-mab)	**Receptor tyrosine kinases**	ERBB *HER1/EGFR* *HER2/neu*	 (Cetuximab, Panitumumab) (Trastuzumab)
	Other (Solid tissüe tümors)	*EpCAM* *VEGF-A*	 (Bevacizumab)
	Other (leükemia/lymph oma)	Lenfoid *CD20* *CD52* Myeloid *CD33*	 (Ibritumomab, Ofatumumab, Rituximab, Tositumomab), (Alemtuzumab) (Gemtuzumab)
Tyrosine kinase inhibitors (-nib)	**Receptor tyrosine kinases**	ERBB *HER1/EGFR* *HER1 ve HER2* RTK clasIII *CKIT ve PGFR* *FLT3* *VEGFR*	 (Erlotinib, Gefitinib, Vandetanib) (BIBW 2992, Lapatinib, Neratinib) (Axitinib, Pazopanib, Sunitinib, Sorafenib, Toceranib) (Lestaurtinib) (Axitinib,Cediranib,Pazopanib,Regorafenib,Semaxanib,Sorafenib,Sunitin Toceranib, Vandetanib)
	Non receptor tyrosine kinases	*BCR/ABL* *SRC* *JAK2*	(Dasatinib, Imatinib, Nilotinib) (Bosutinib) (Lestaurtinib)
Others	**Füsion proteins**	*VEGF*	**F** (Aflibercept)
	Exzotoxins	*IL2*	(Denileukin diftitox)

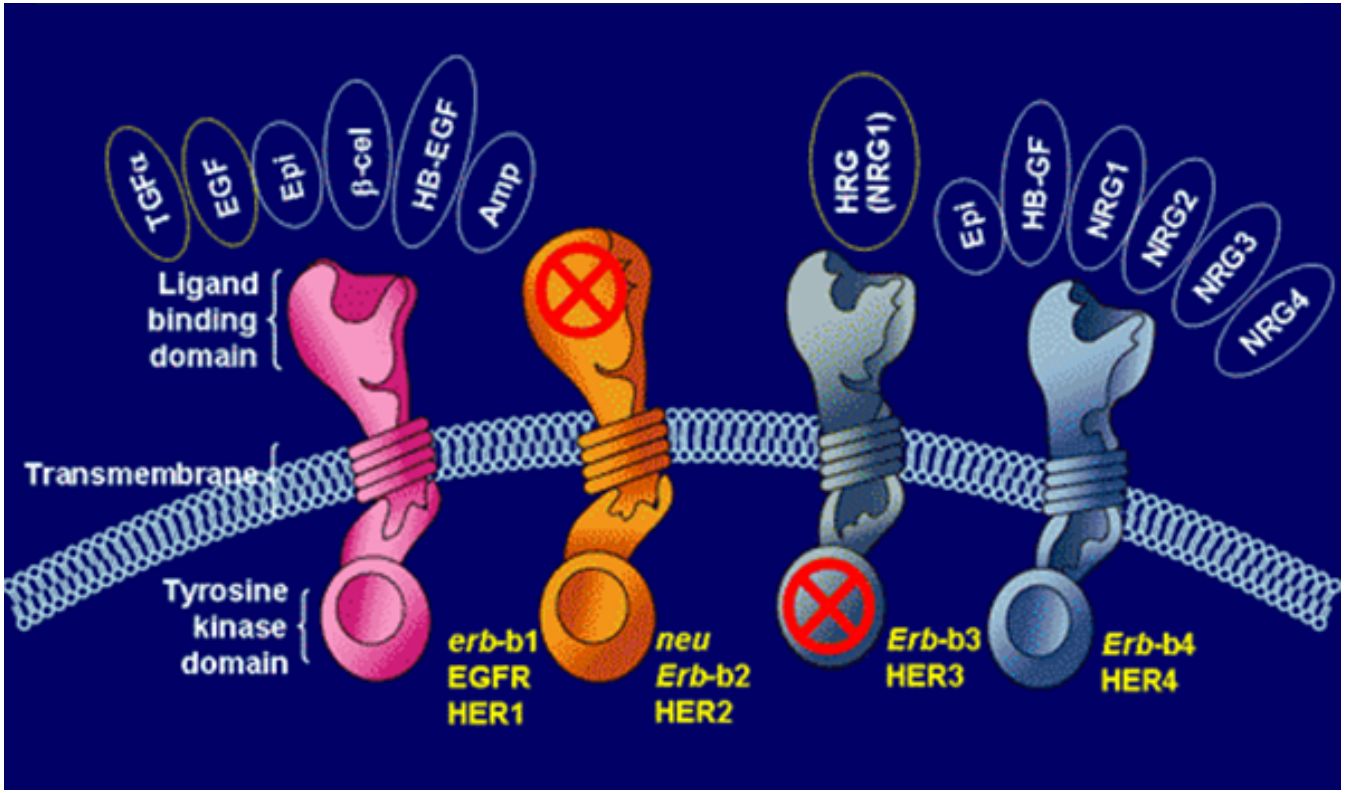
Trastuzumab (Herceptin)

Monoclonal antibody



High specifity humanized recombinant antibody against HER2

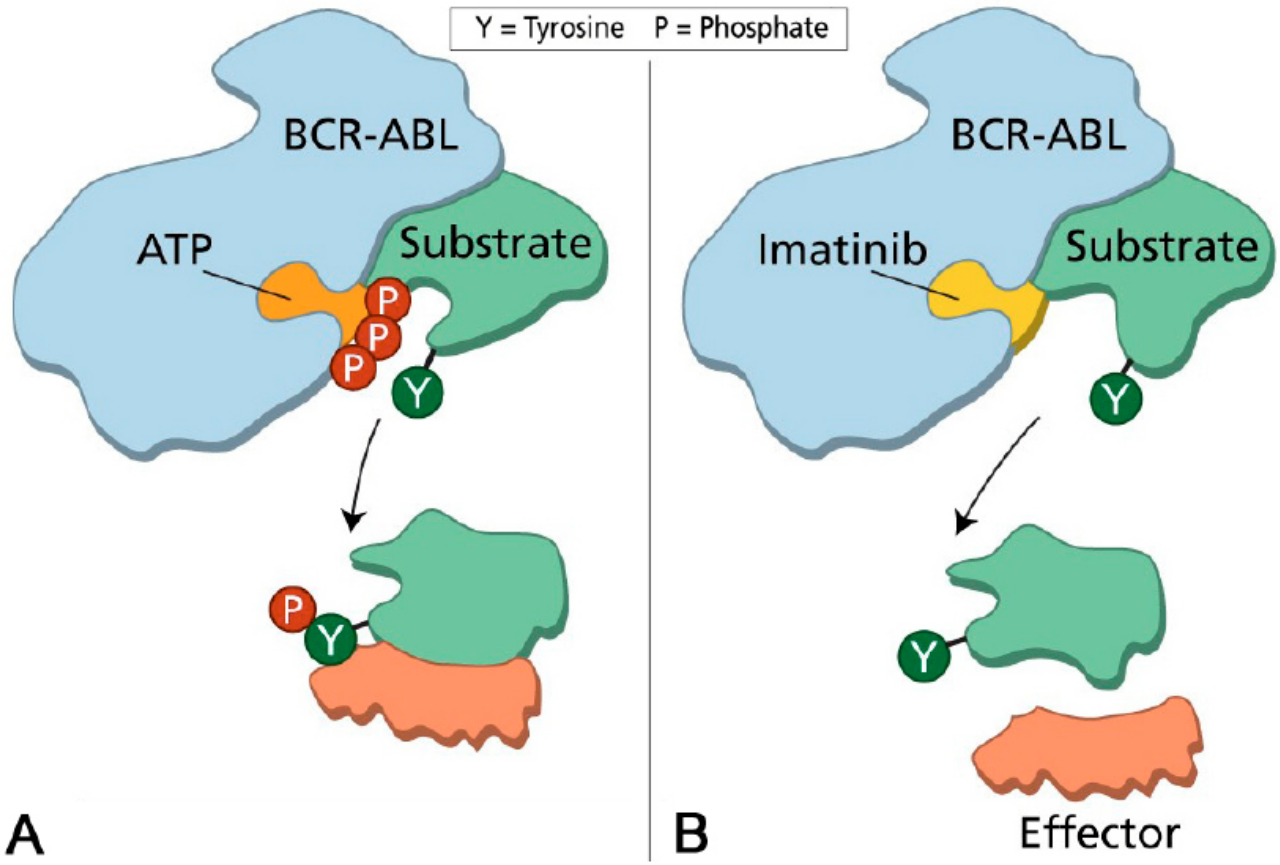
ErbB-1: EGFR (epidermal growth factor)
ErbB-2: HER2 or neu
ErbB-3: HER3
ErbB-4: HER4
ErbB protein family

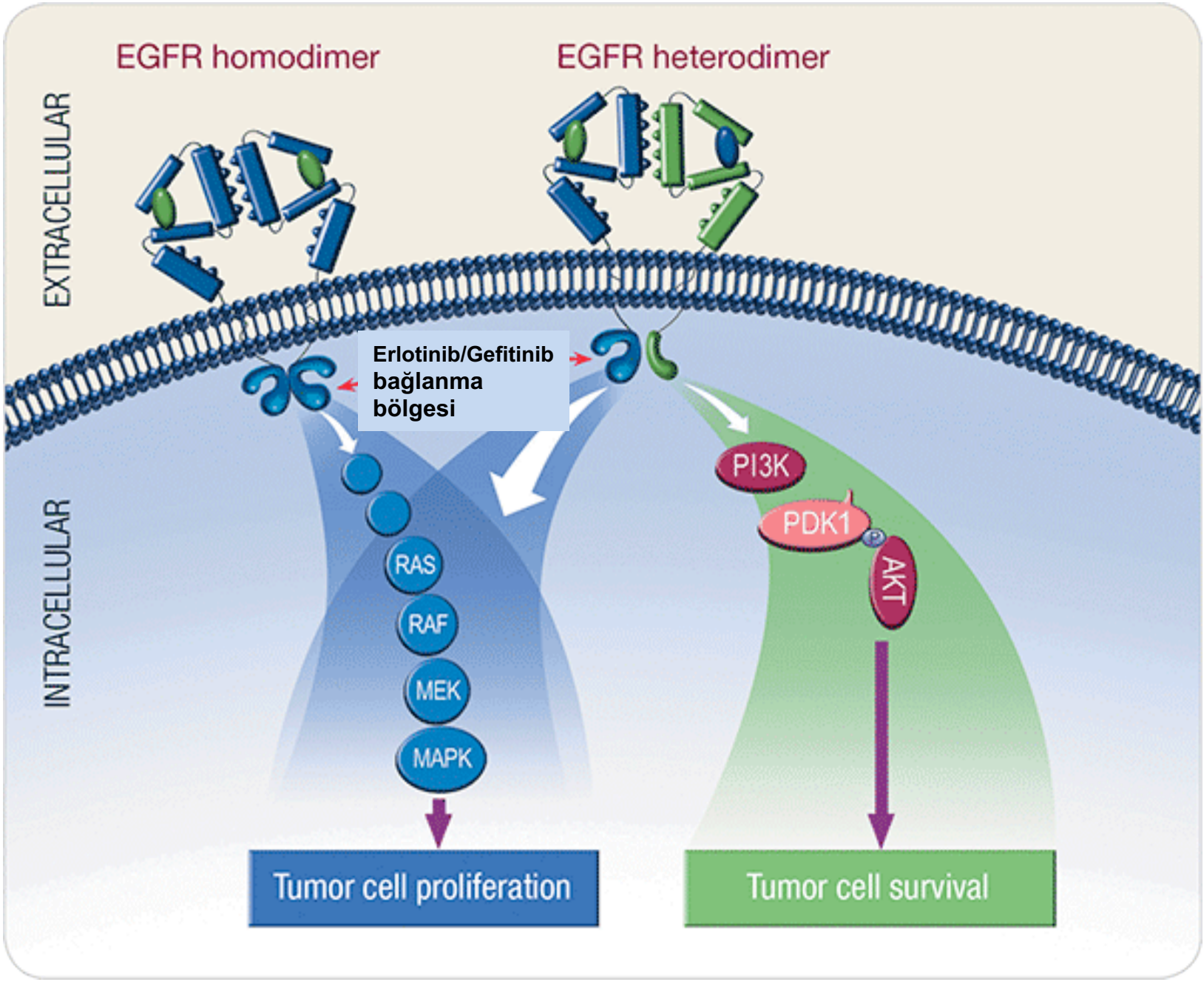


HER2 amplifications:
15% of primary breast cancer cases and 30% of metastatic cancers have

Imatinib (tyrosine kinase inhibitor)

Used for CML ve Gastrointestinal stromal tumor (GIST) therapy




EGFR homodimer
EGFR heterodimer
EXTRACELLULAR
INTRACELLULAR
Erlotinib/Gefitinib bağlanma bölgesi
RAS
RAF
MEK
MAPK
PI3K
PDK1
P
AKT
Tumor cell proliferation
Tumor cell survival

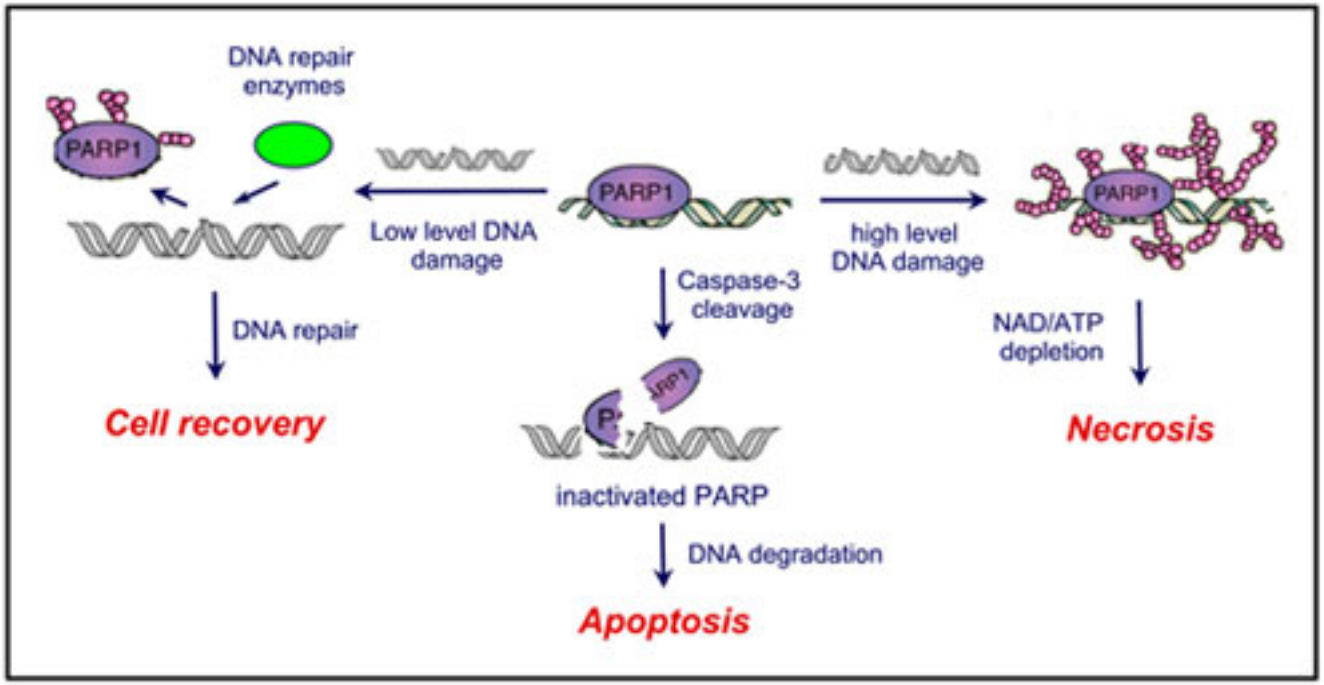
Examples of targeted drugs for cancer therapies

DRUG	TUMOR	TARGET
Trastuzumab	Breast cancer	ERBB2 (RTK) inhibition
Cetuximab	Colon, head neck, etc. solid tissue tumors	EGFR (RTK) inhibition
Erlotinib	NSCLC (non small cell lung cancer)	EGFR (RTK) inhibition
Gefitinib	NSCLC effective 10% of cases	EGFR (RTK) inhibition
İmatinib	CML, GIST	BCR-ABL, PDGFR
Vemurafenib	Advanced melanoma	RAS pathwayBRAF inhibition (V600E mutation + cases)
Ruxolitinib	Myeloproliferative disorders	JAK/STAT pathway- signal inhibition
Rapamisin (sirolimus)	Combined therapies	mTOR pathway
Rapamisin türevi (everolimus)	Advanced renal cancers, pancreatic neuroendoctin tumors	mTOR pathway
Bevacizumab	Advanced colon kcancers, NSCLC, ovarium, renal cancers, glioblastoma multiforme	mTOR pathway HIF1a>VEGFA inhibition
Ramucirumab	Advanced gastric and eosophagal cancers	HIF1a>VEGFA inhibition

Genetic alterations causing drug resistance

Drug	Tumor	Resistance mutation
IMATINIB	Gastrointestinal Stromal Tumors (GIST)	cKIT gene EKZON 9, 11, 13 and 17 mutations
		PDGFRA genie EKZON 12 and 18 mutations
GEFITINIB	NSCLC	EGFR gene T790M
TRASTUZUMAB	Breast cancer	PTEN loss
RITUKXIMAB	B-cell non-Hodgkin lymphoma (NHL)	FCGR3A
DOXORUBİCİN	Breast cancer	*MRD1* C3435T
DOXORUBİCİN	Pleomorfik Lyposarcoma	Long telomere

PARP1 inhibitors



Olaparib, Rucaparib: BRCA related breast-ovary cancers
Niraparib: epithelial ovary, primary peritoneal cancers

Disrupts base excision repair mechanism

Synthetic letal effect

PARP inhibition therapy

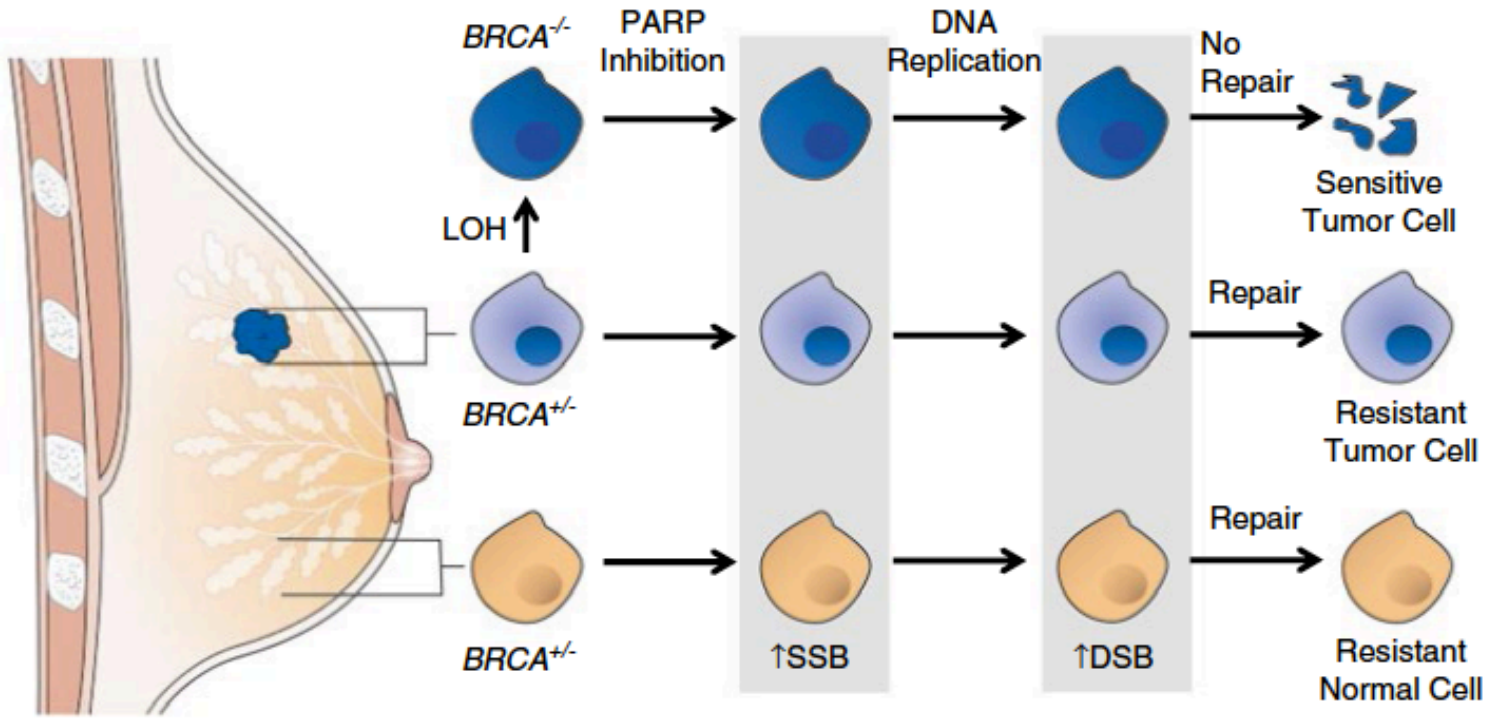


Fig. 8.3 Synthetic lethality of BRCA-deficient cancer cells treated with a PARP inhibitor. Breast cancers arise at an elevated rate in women who harbor heterozygous mutations (*BRCA*$^{+/-}$) in either *BRCA1* or *BRCA2*. Many tumor cells undergo loss of heterozygosity at the relevant locus and thereby become completely BRCA-deficient (*BRCA*$^{-/-}$). Systemic treatment with a PARP inhibitor results in the transient accumulation of single-strand breaks (*SSB*) in all cells. During DNA replication, unrepaired SSB are converted to double-strand breaks (*DSB*). Normal cells and tumor cells that retain *BRCA* heterozygosity are capable of repairing DSB via the pathway of homologous recombination. BRCA-deficient cells lack this capability, and will accumulate lethal levels of DSBs. Breast tumor image from Cancer Research UK

NEW DRUG EXPERIMENTS
PIK3/AKT
WNT/APC