La biologia del carcinoma mammario: comprendere i meccanismi molecolari per individuarne le vulnerabilità

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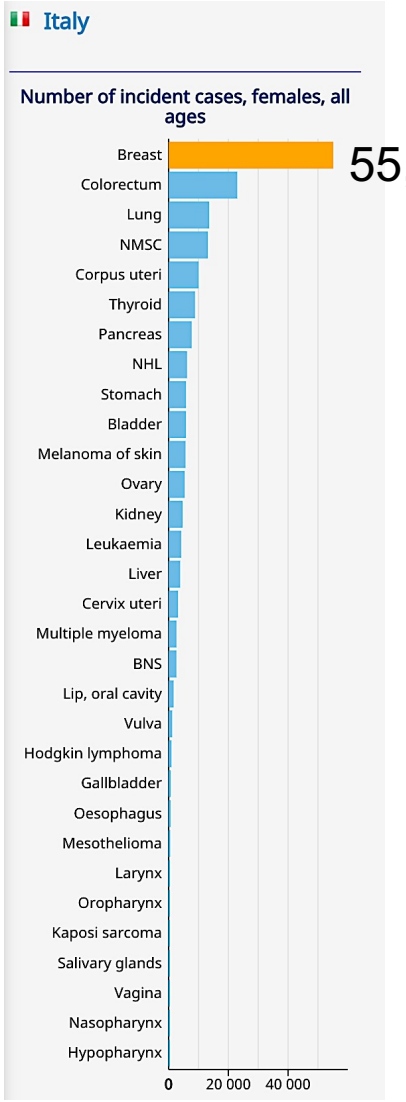
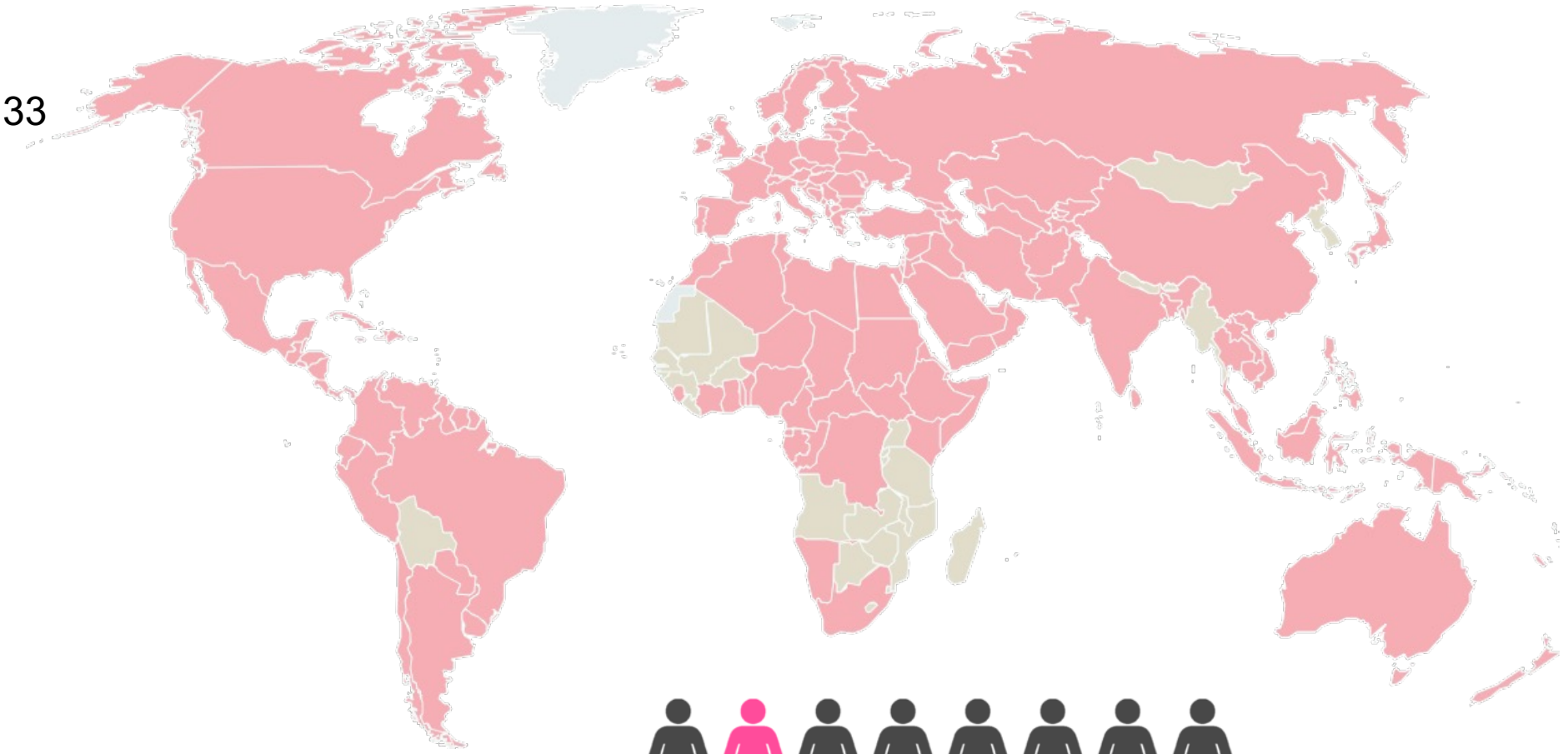
WHAT IS BREAST CANCER?

• 11.7% of cancer cases diagnosed in adults in 2020 were breast cancer (Worldwide), 24.5% in women. This is 2,261,419 cases.

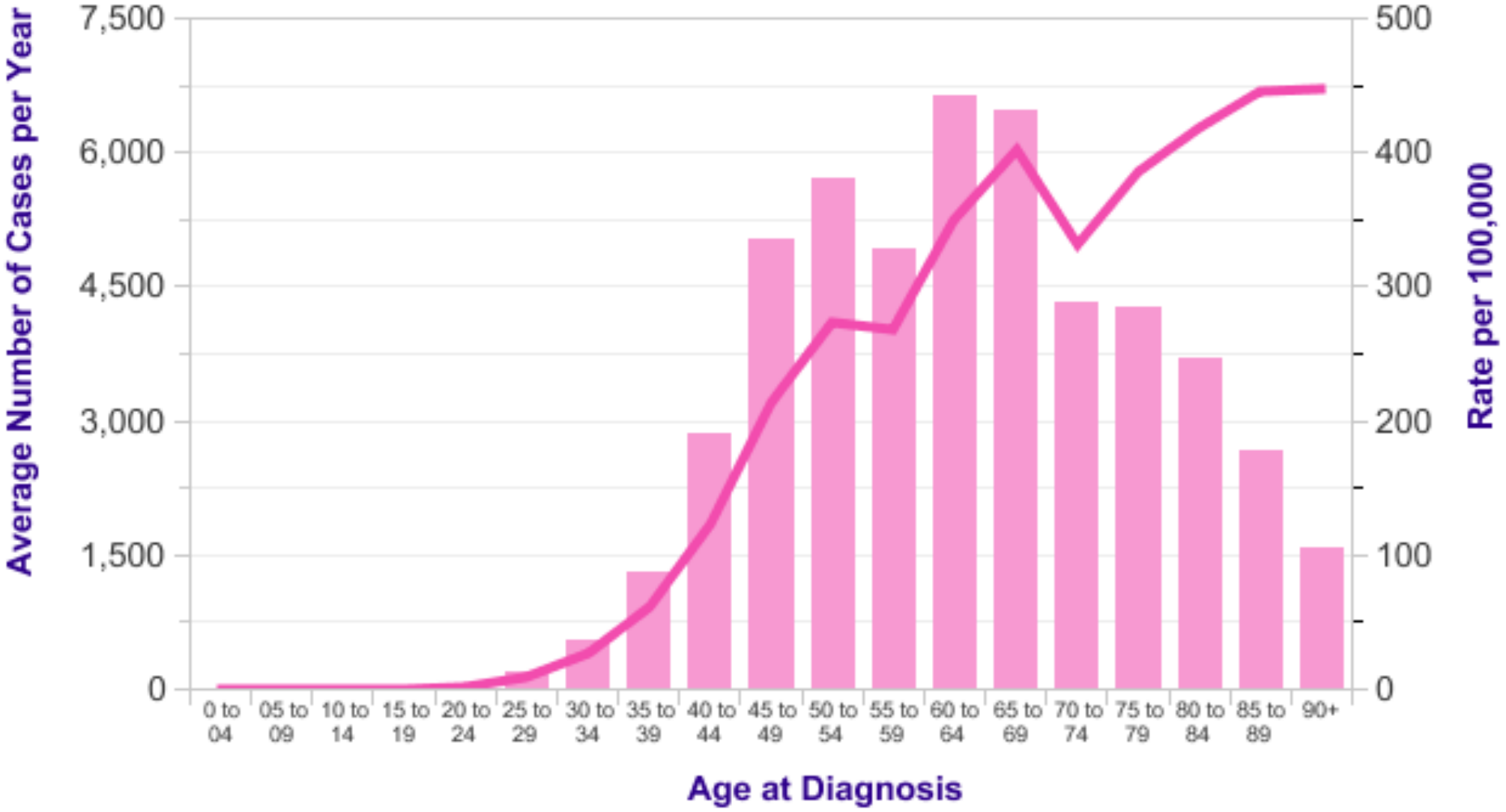


55,133

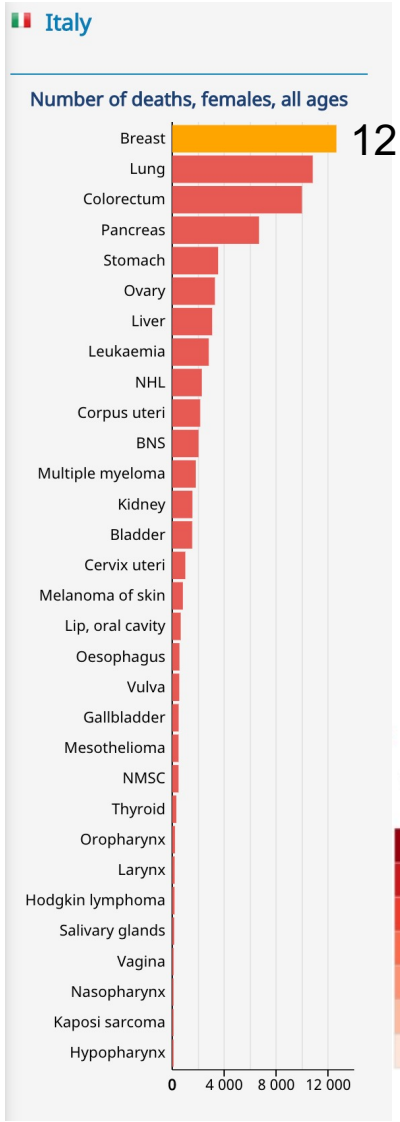


1 in 8 women will receive a breast cancer diagnosis during their life.

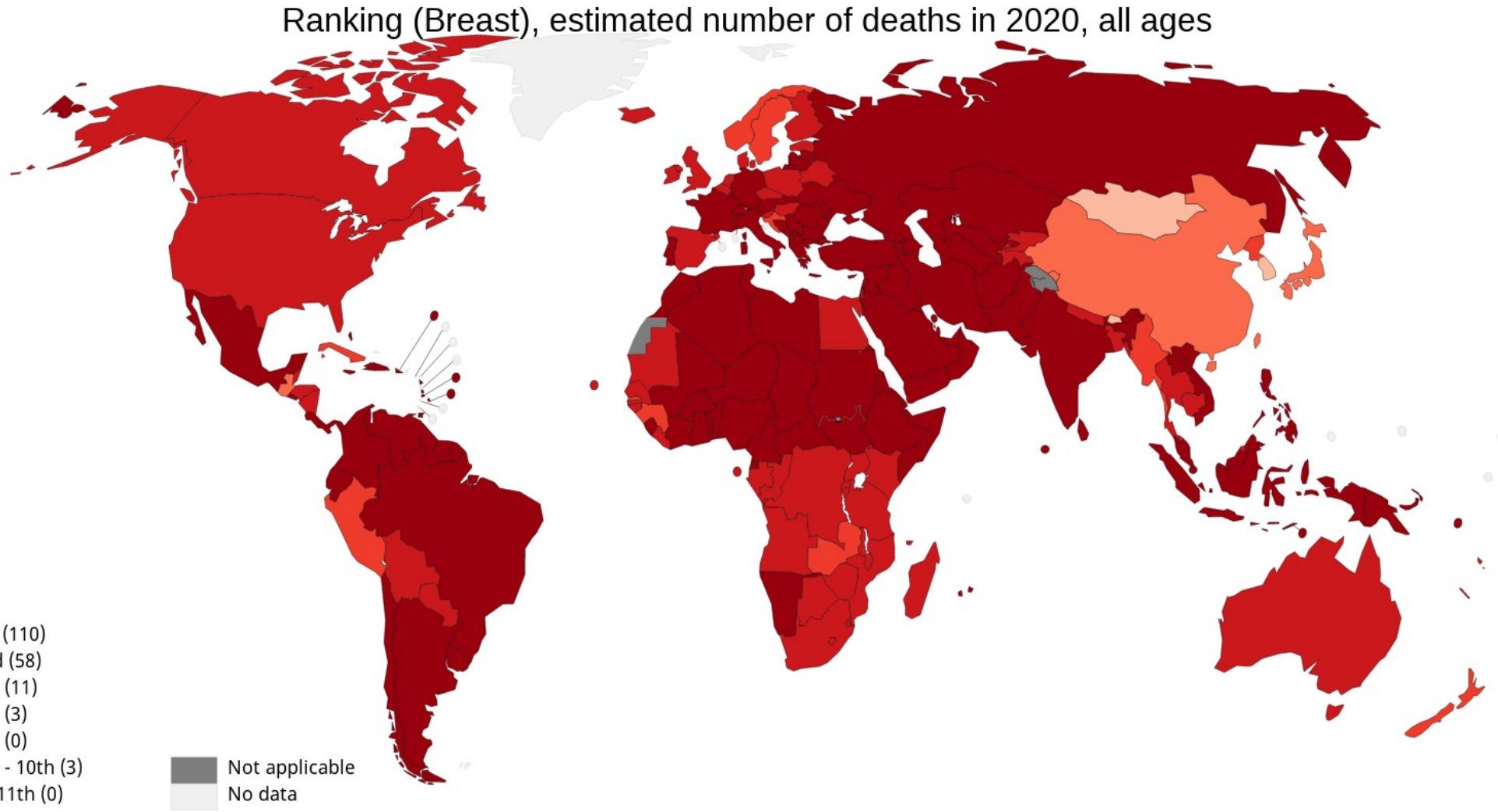
- breast cancer incidence is strongly related to age
- female breast cancer death rates have fallen by 40% in the UK



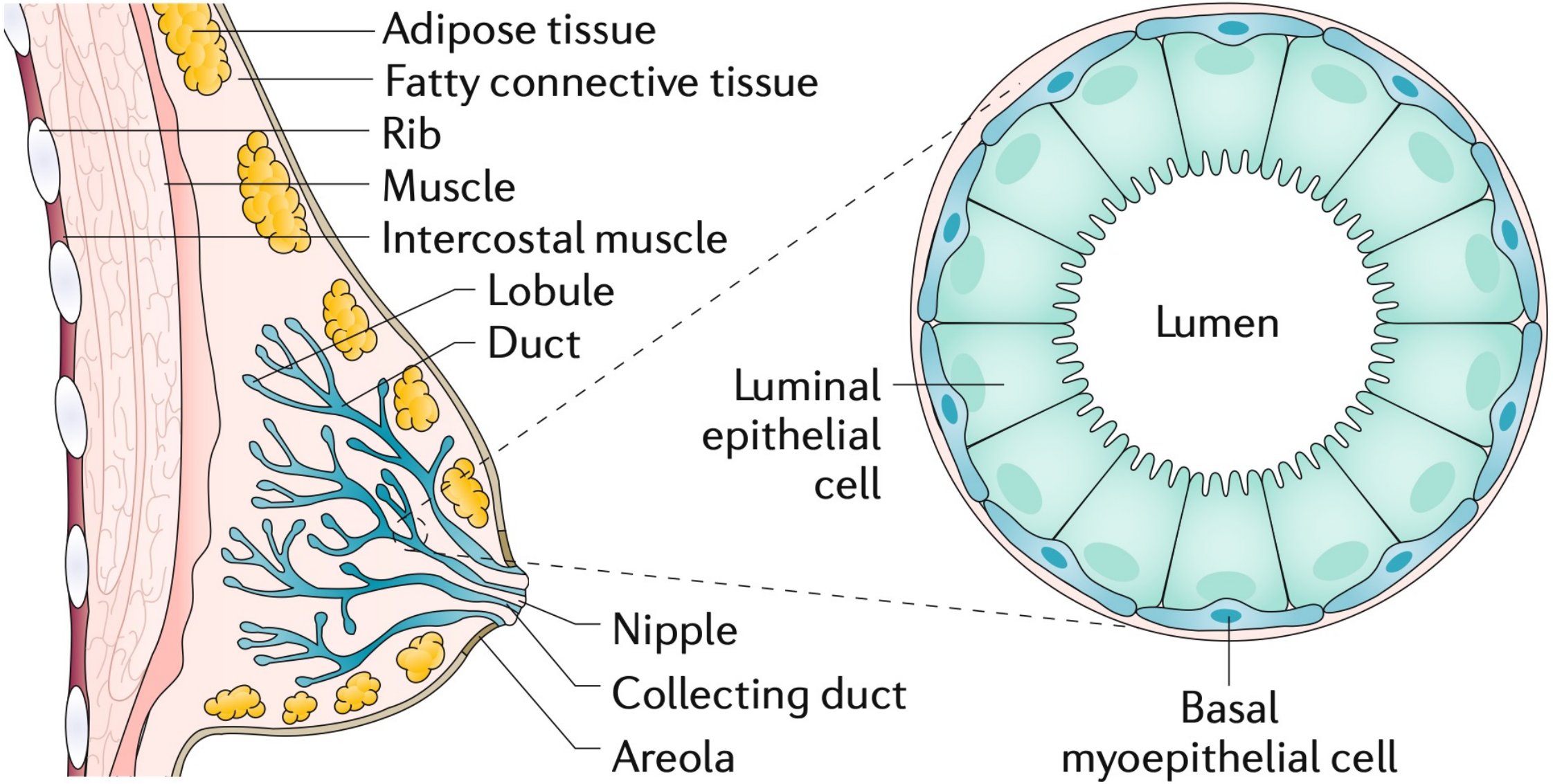
- 6.9% of cancer deaths in adults in 2020 were breast cancer (Worldwide), 15.5% in women.
- This is **684,996** cases.



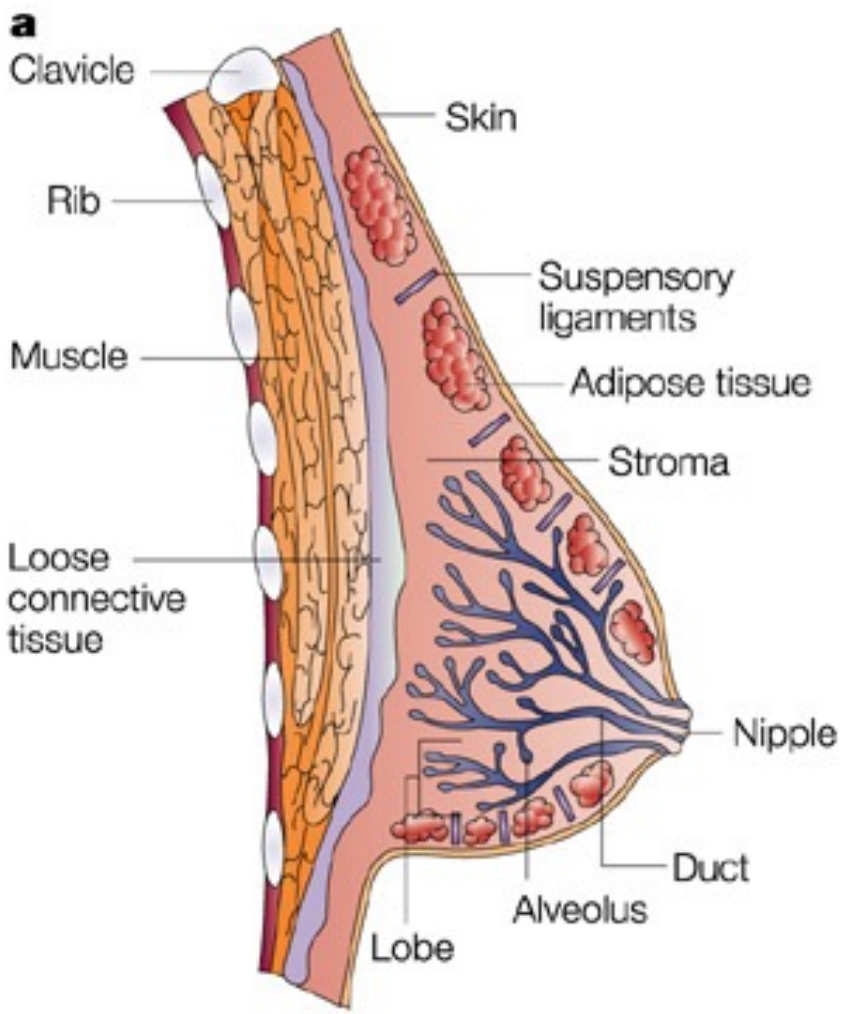
12,633

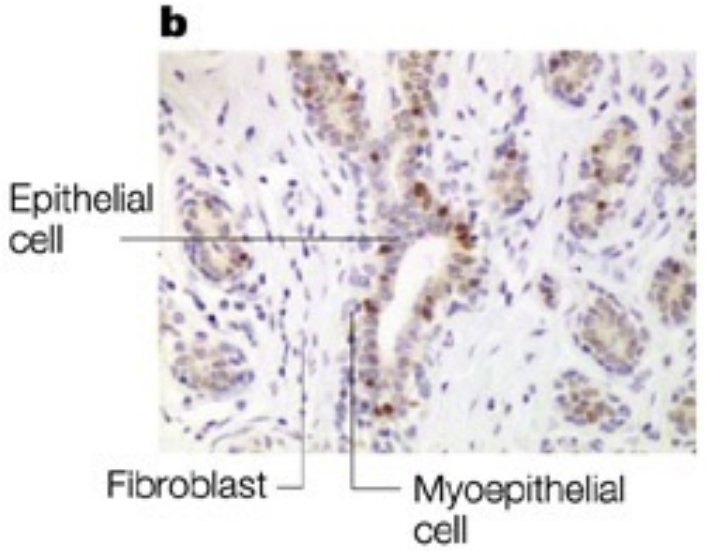


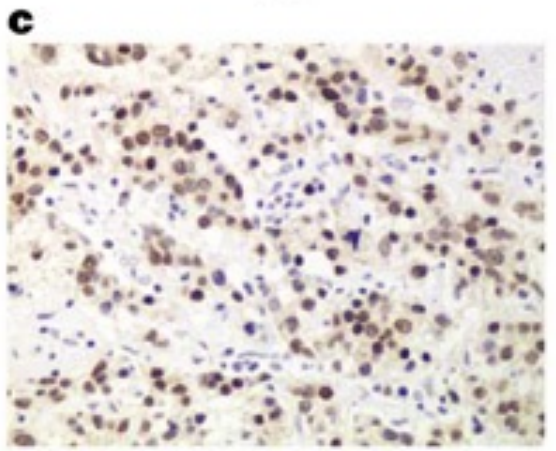
All breast cancers arise in the terminal duct lobular units (the functional unit of the breast) of the collecting duct



Mechanism and Pathophysiology

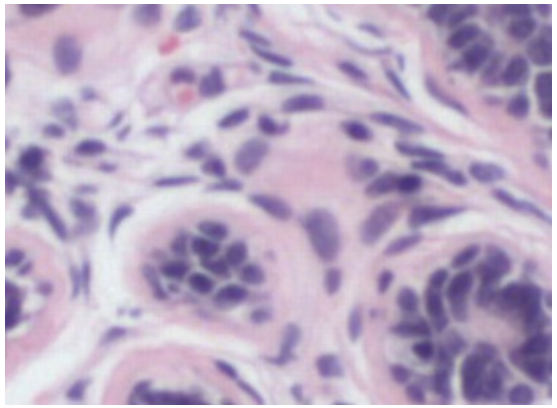
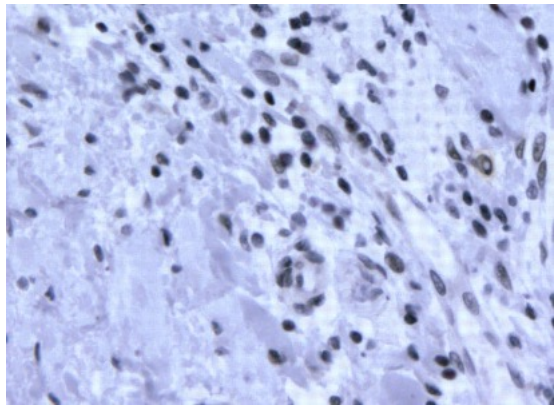
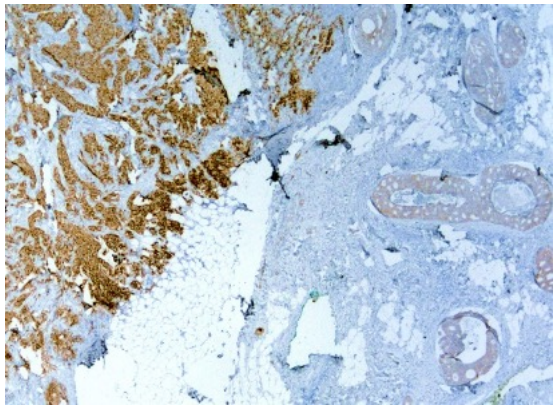
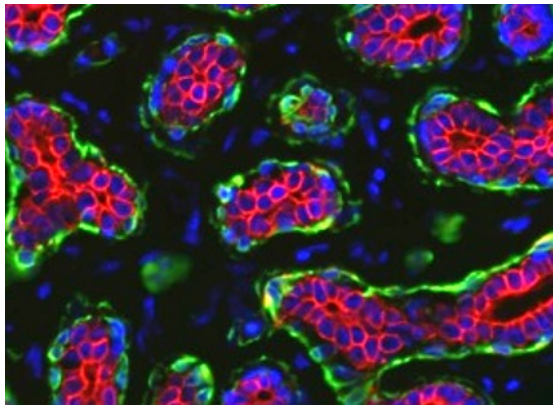






Nature Reviews | Cancer

Breast Cancer under the microscope

Predict behaviour

- histological types
- grade
- size
- lymph node status

Cancer biology

- hormone receptors
- HER2
- proliferation

Breast cancer is a family of diseases

Histological subtypes

Preinvasive

Ductal carcinoma in situ (DCIS)

- Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral

Lobular carcinoma in situ (LCIS)

- Does not distort ductal architecture; can be bilateral
- Risk factor rather than precursor

Invasive

Ductal carcinoma no special type (NST)

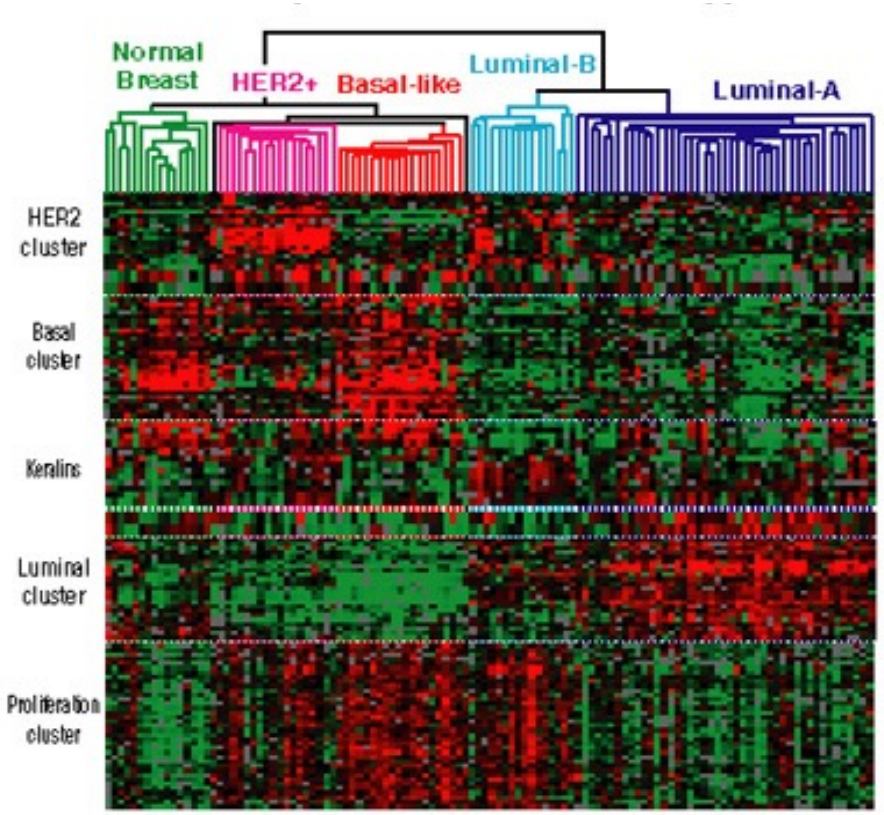
- Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood

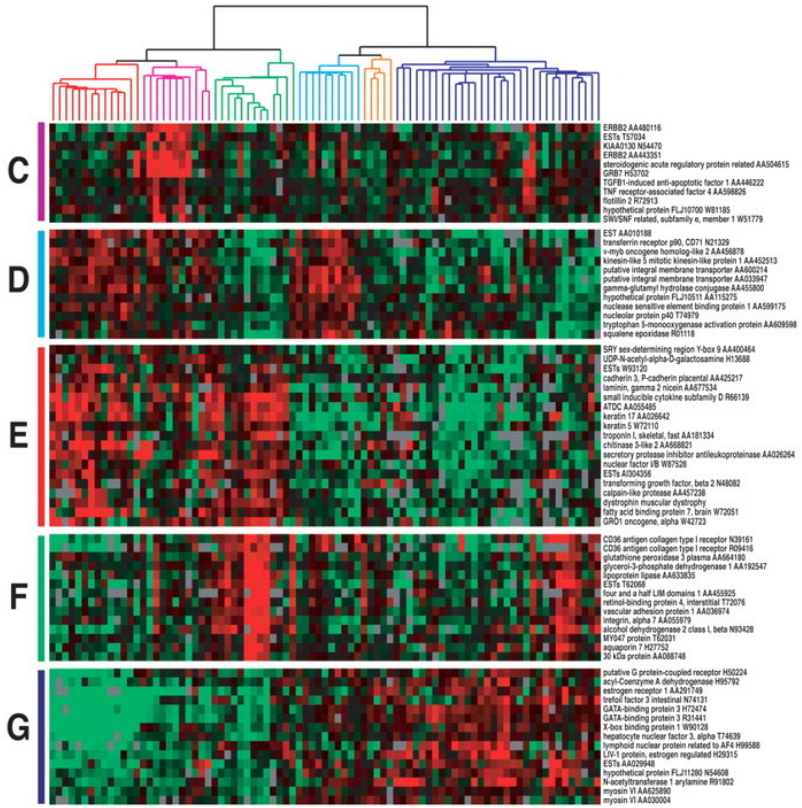
Lobular carcinoma (ILC)

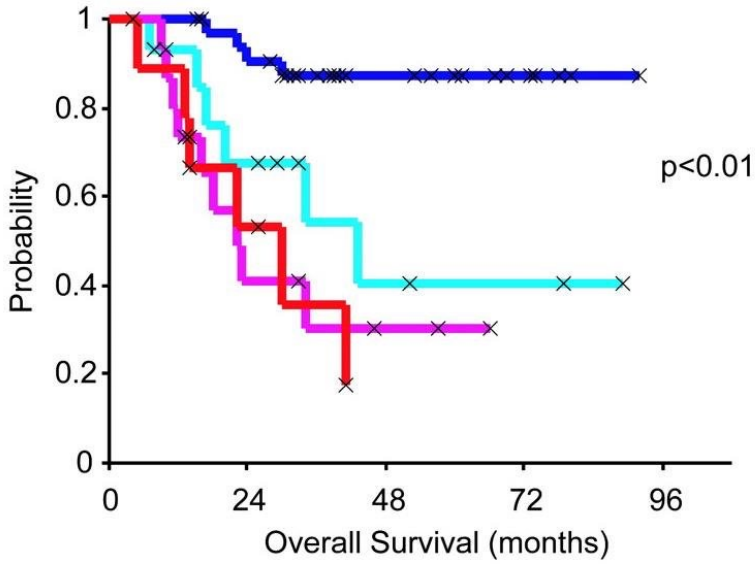
- Isolated tumor cells (*CDH1* mutations) minimal fibrous response; metastasizes preferentially via viscera

Harbeck et al, *Nature Reviews 2019*

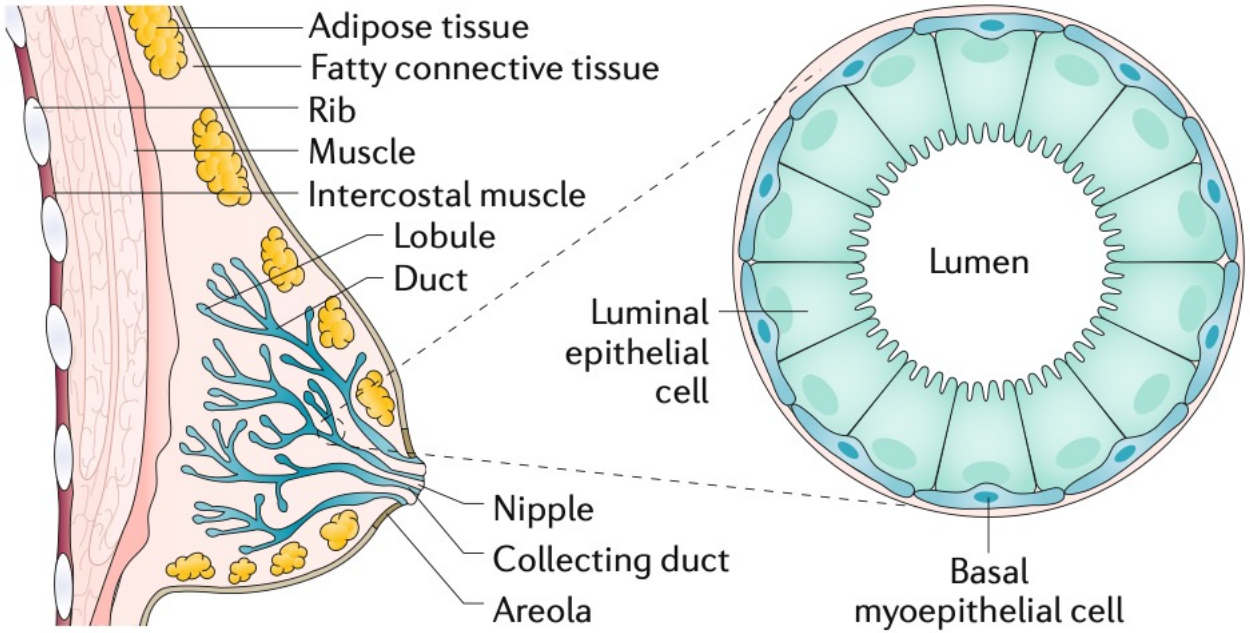
Diversity of breast tumour subtypes







Perou et al, *Nature* 2000; Sørlie T et al. *PNAS* 2001



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Intrinsic subtypes (PAM50)

Basal-like
TP53 mutations; genetic instability; *BRCA* mutations; medullary-like histology poorly differentiatied

Claudin-low
Largely triple-negative; metaplastic

HER2-enriched
HER2 amplification; *GRB7* amplification; *PIK3CA* mutations; *TOPO2* and/or *MYC* amplification; NST, pleiomorphic lobular and micropapillary histology

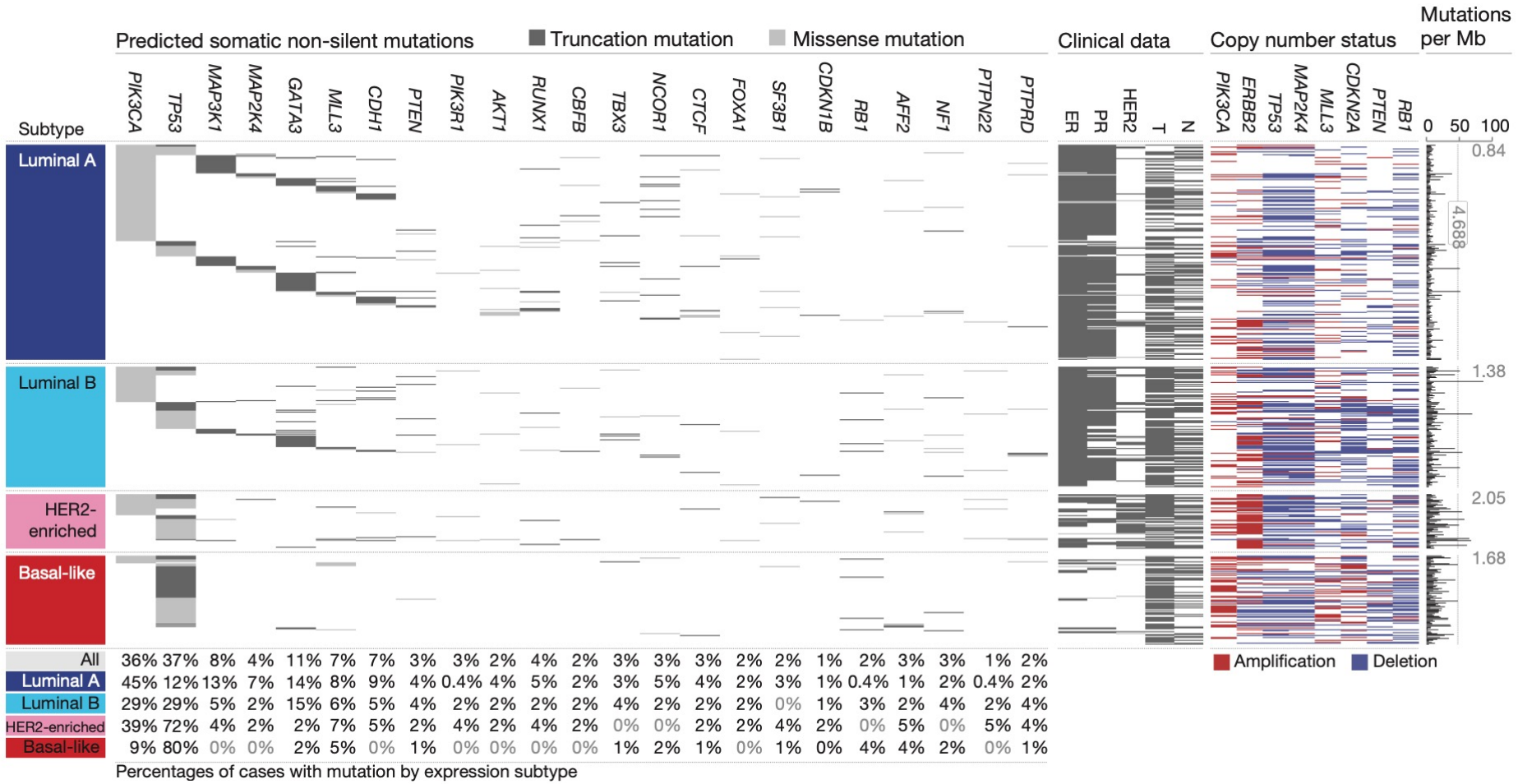
Normal-like[b]

Luminal B
PI3KCA mutations (40%); *ESR1* mutations (30–40%)[a]; *ERBB2* and *ERBB3* mutations; NST, micropapillary and atypical lobular histology

Luminal A
Activation of *ERS1*, *GATA3*, *FOXA1*, *XBP1*; NST, tubular cribriform and classic lobular histology

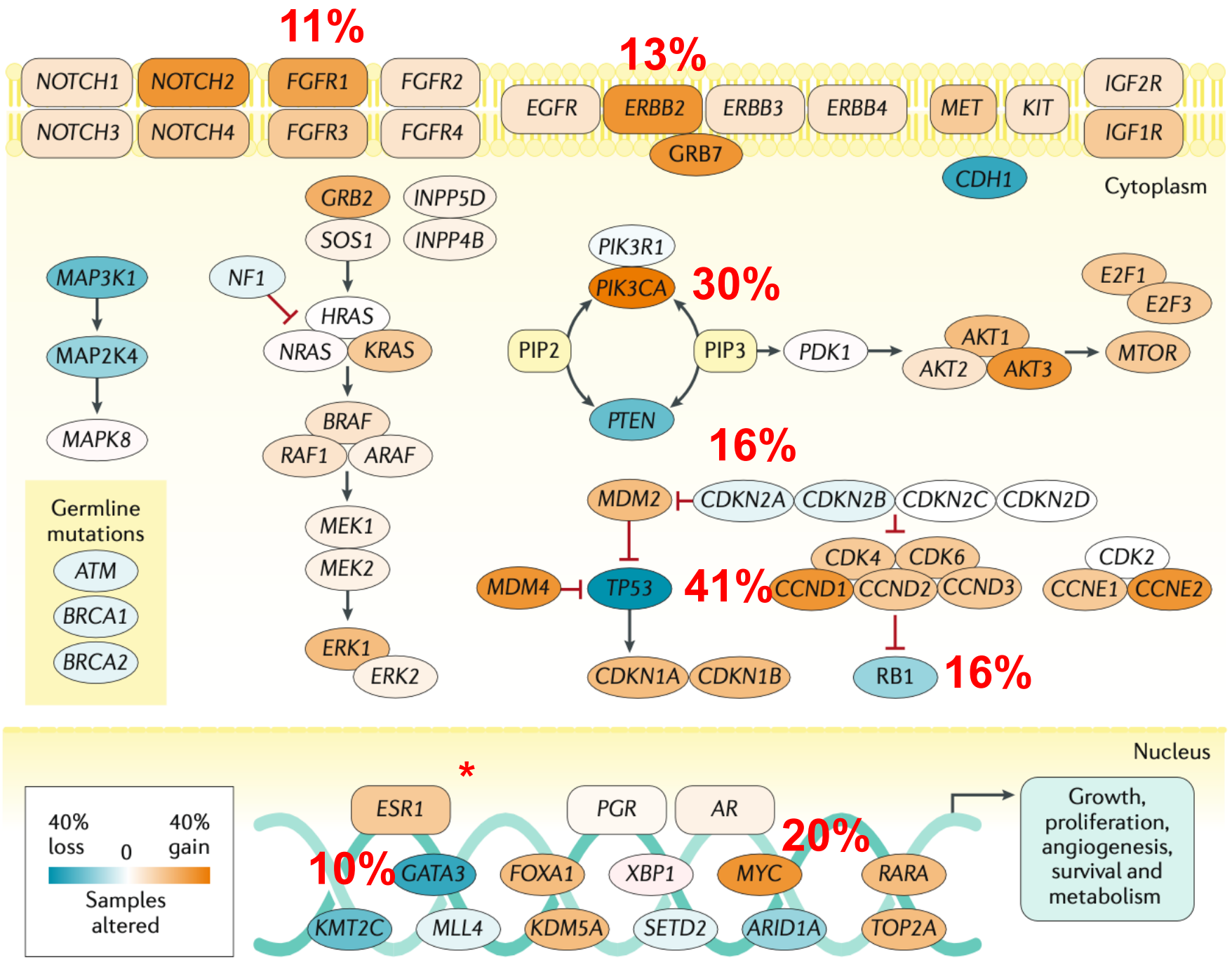
Comprehensive molecular portraits of human breast tumours

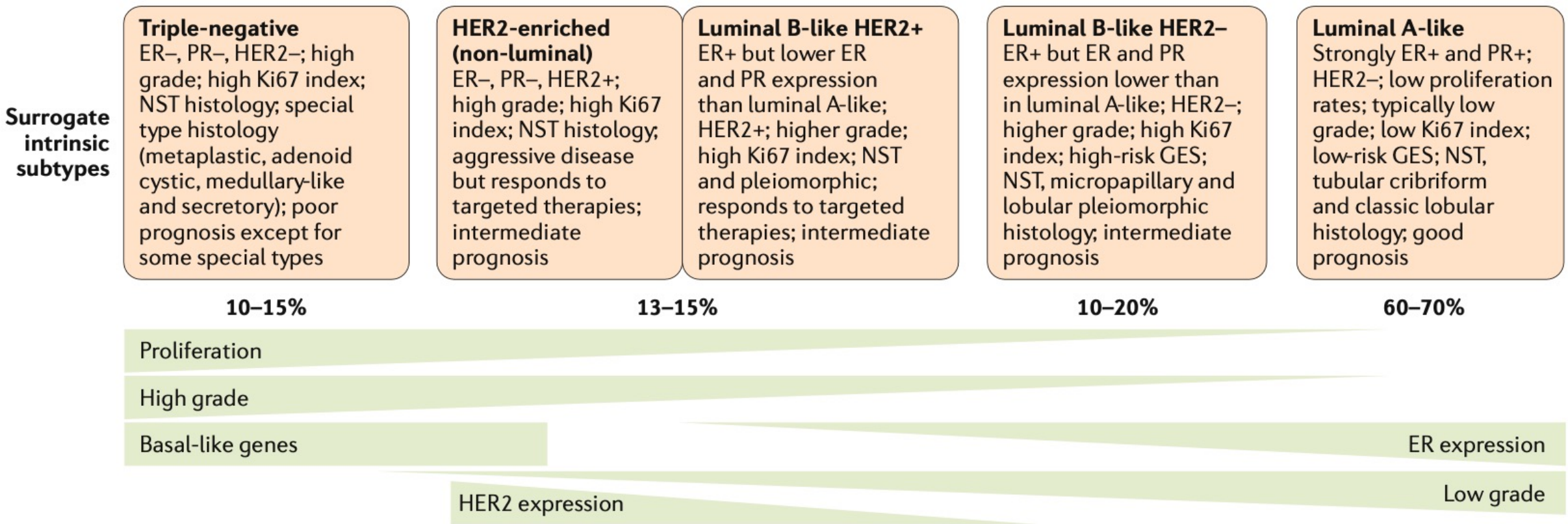
The Cancer Genome Atlas Network*



>50% of mutations are present in < 10% of breast cancer

TCGA, *Nature* 2012


11%
13%
NOTCH1
NOTCH2
FGFR1
FGFR2
NOTCH3
NOTCH4
FGFR3
FGFR4
EGFR
ERBB2
ERBB3
ERBB4
MET
KIT
IGF2R
IGF1R
GRB7
CDH1
Cytoplasm
GRB2
INPP5D
SOS1
INPP4B
MAP3K1
NF1
HRAS
NRAS
KRAS
MAP2K4
MAPK8
BRAF
RAF1
ARAF
MEK1
MEK2
ERK1
ERK2
PIK3R1
PIK3CA
30%
PIP2
PIP3
PDK1
PTEN
AKT1
AKT2
AKT3
MTOR
E2F1
E2F3
16%
MDM2
CDKN2A
CDKN2B
CDKN2C
CDKN2D
CDK4
CDK6
CDK2
MDM4
TP53
41%
CCND1
CCND2
CCND3
CCNE1
CCNE2
CDKN1A
CDKN1B
RB1
16%
Germline mutations
ATM
BRCA1
BRCA2
Nucleus
*
ESR1
PGR
AR
10%
GATA3
FOXA1
XBP1
MYC
20%
RARA
KMT2C
MLL4
KDM5A
SETD2
ARID1A
TOP2A
40% loss
0
40% gain
Samples altered
Growth, proliferation, angiogenesis, survival and metabolism



Harbeck et al, *Nature Reviews 2019*

Breast cancer progression (theory *vs* real life)

Normal

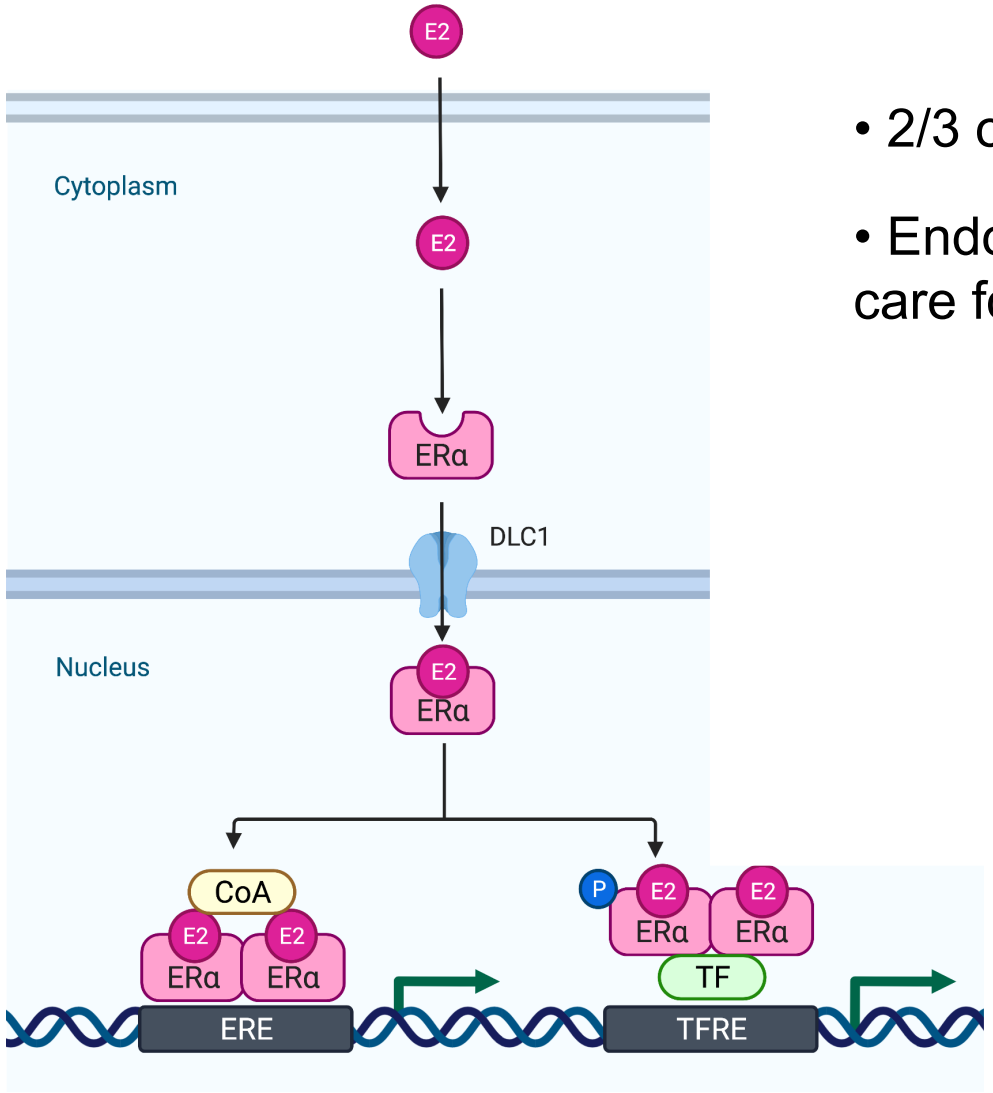
Hyperplasia

DCIS

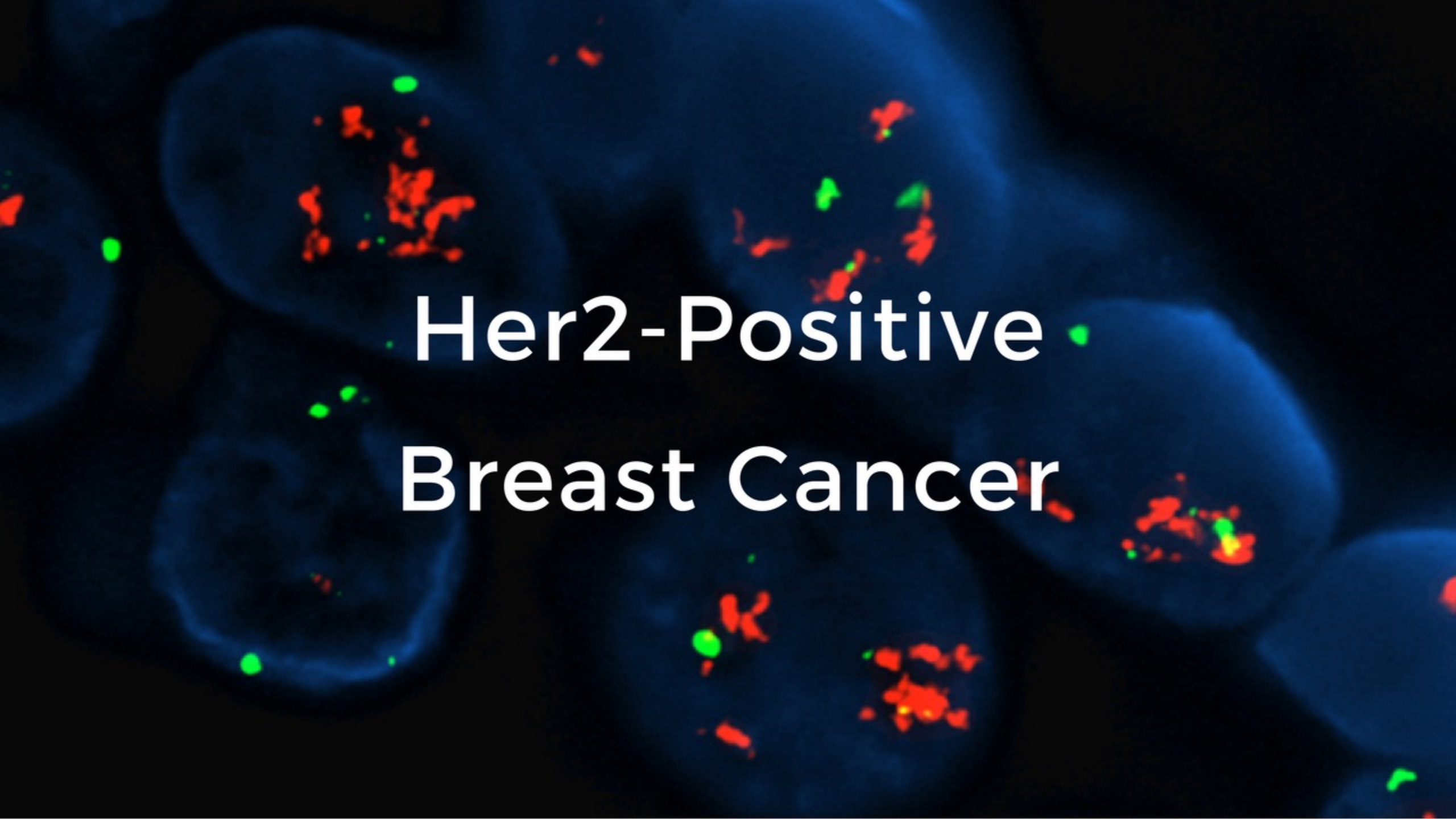
Microinvasion

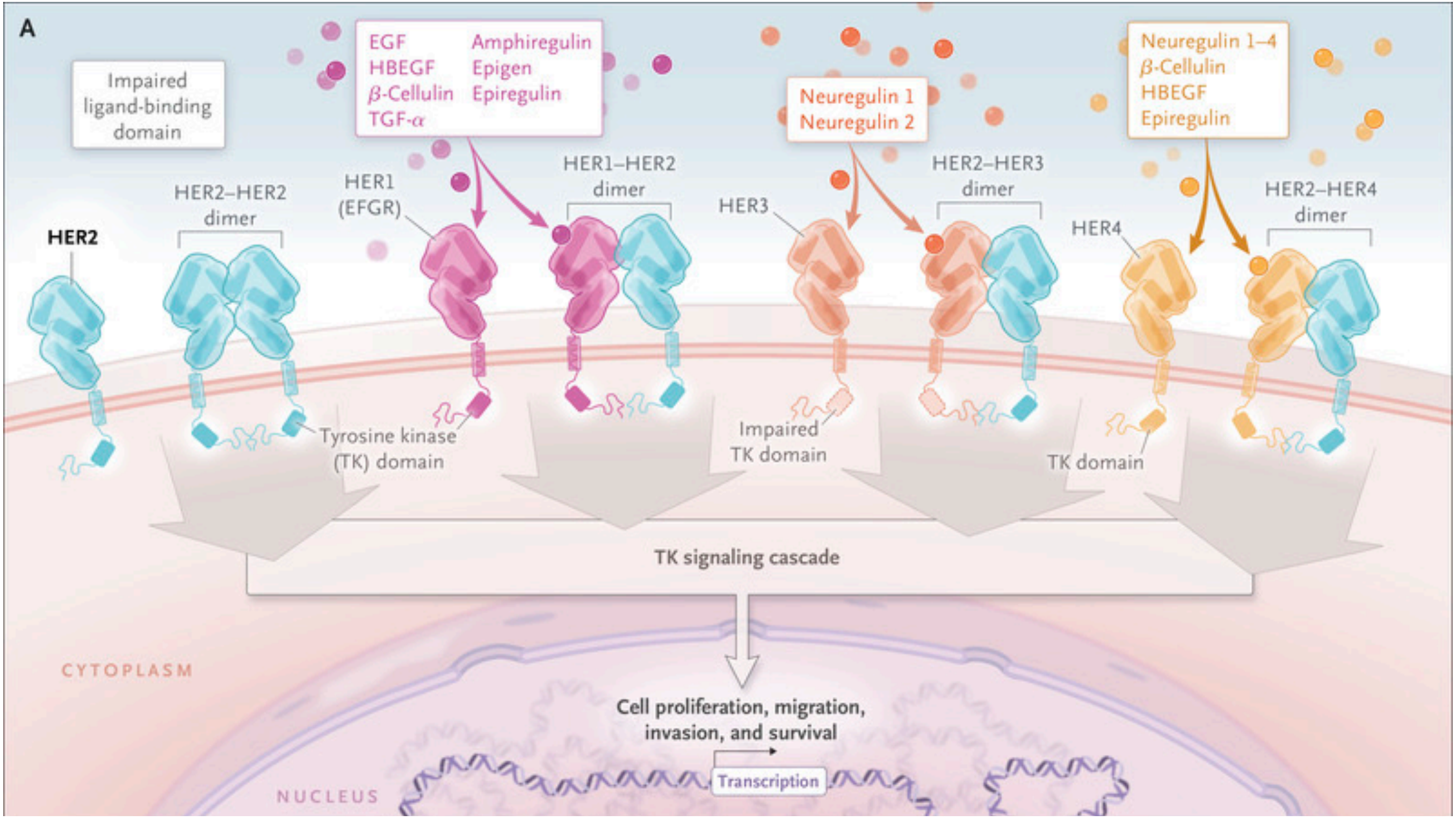
Invasive Cancer

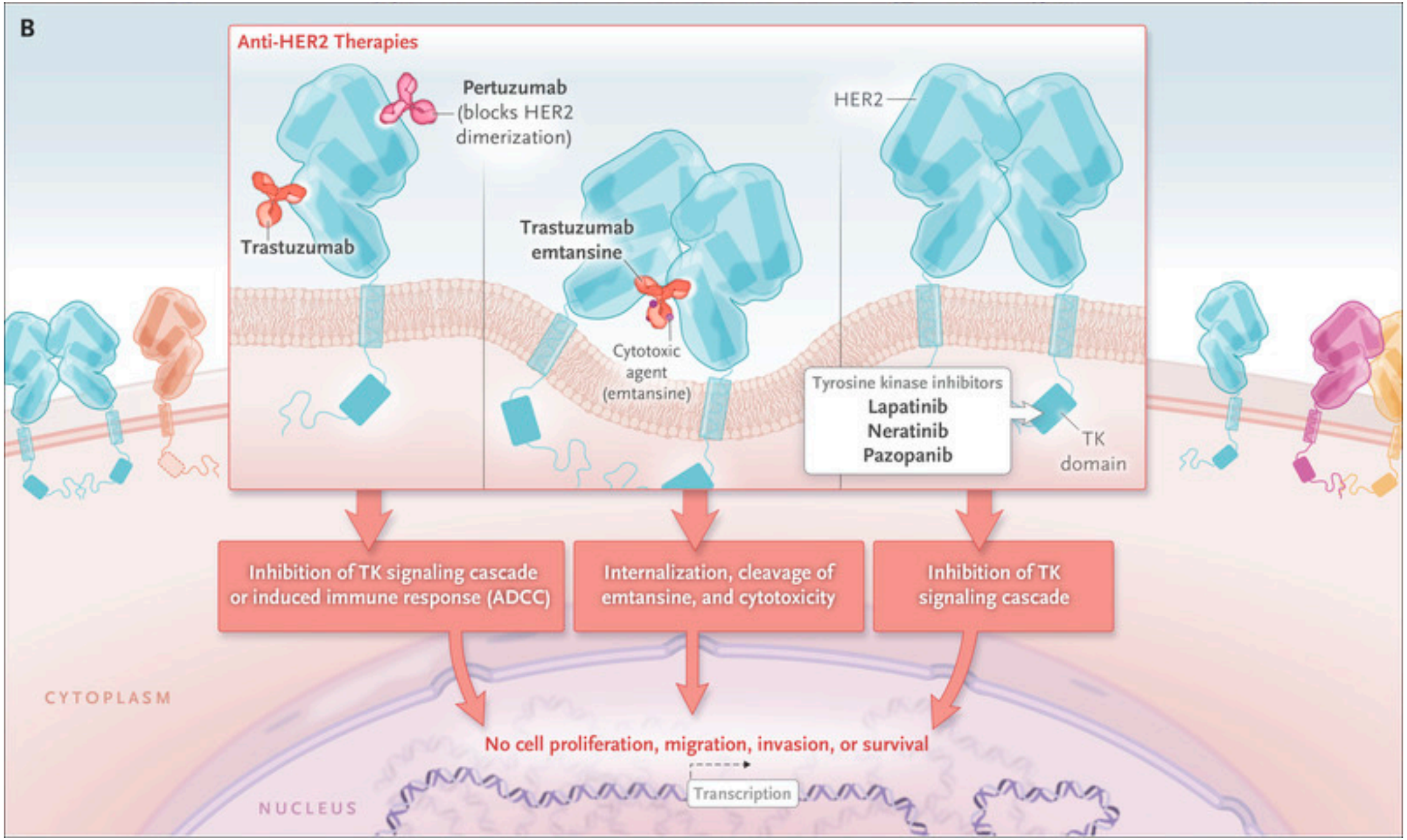
ER+ breast cancers



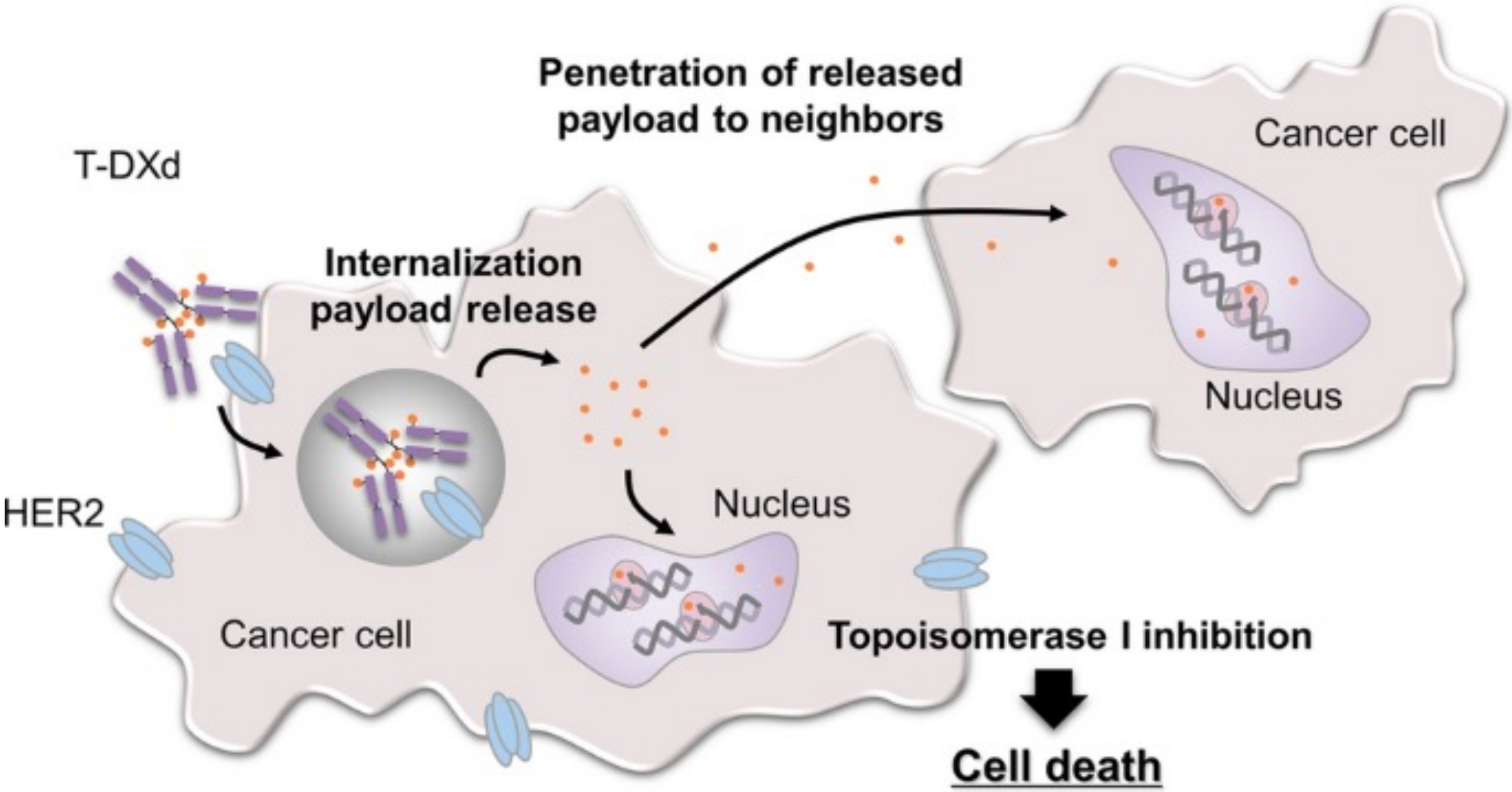
- 2/3 of breast cancers are ER+
- Endocrine therapy is the standard of care for these cancers


Her2-Positive
Breast Cancer


A
Impaired ligand-binding domain
EGF
HBEGF
β-Cellulin
TGF-α
Amphiregulin
Epigen
Epiregulin
Neuregulin 1
Neuregulin 2
Neuregulin 1–4
β-Cellulin
HBEGF
Epiregulin
HER2
HER2–HER2 dimer
HER1 (EFGR)
HER1–HER2 dimer
HER3
HER2–HER3 dimer
HER4
HER2–HER4 dimer
Tyrosine kinase (TK) domain
Impaired TK domain
TK domain
TK signaling cascade
CYTOPLASM
Cell proliferation, migration, invasion, and survival
Transcription
NUCLEUS


B
Anti-HER2 Therapies
Pertuzumab
(blocks HER2
dimerization)
Trastuzumab
Trastuzumab
emtansine
Cytotoxic
agent
(emtansine)
HER2
Tyrosine kinase inhibitors
Lapatinib
Neratinib
Pazopanib
TK
domain
Inhibition of TK signaling cascade
or induced immune response (ADCC)
Internalization, cleavage of
emtansine, and cytotoxicity
Inhibition of TK
signaling cascade
CYTOPLASM
No cell proliferation, migration, invasion, or survival
Transcription
NUCLEUS

ADC in HER2 positive cancer – mechanism of action



HER2 EXPRESSION IN BC

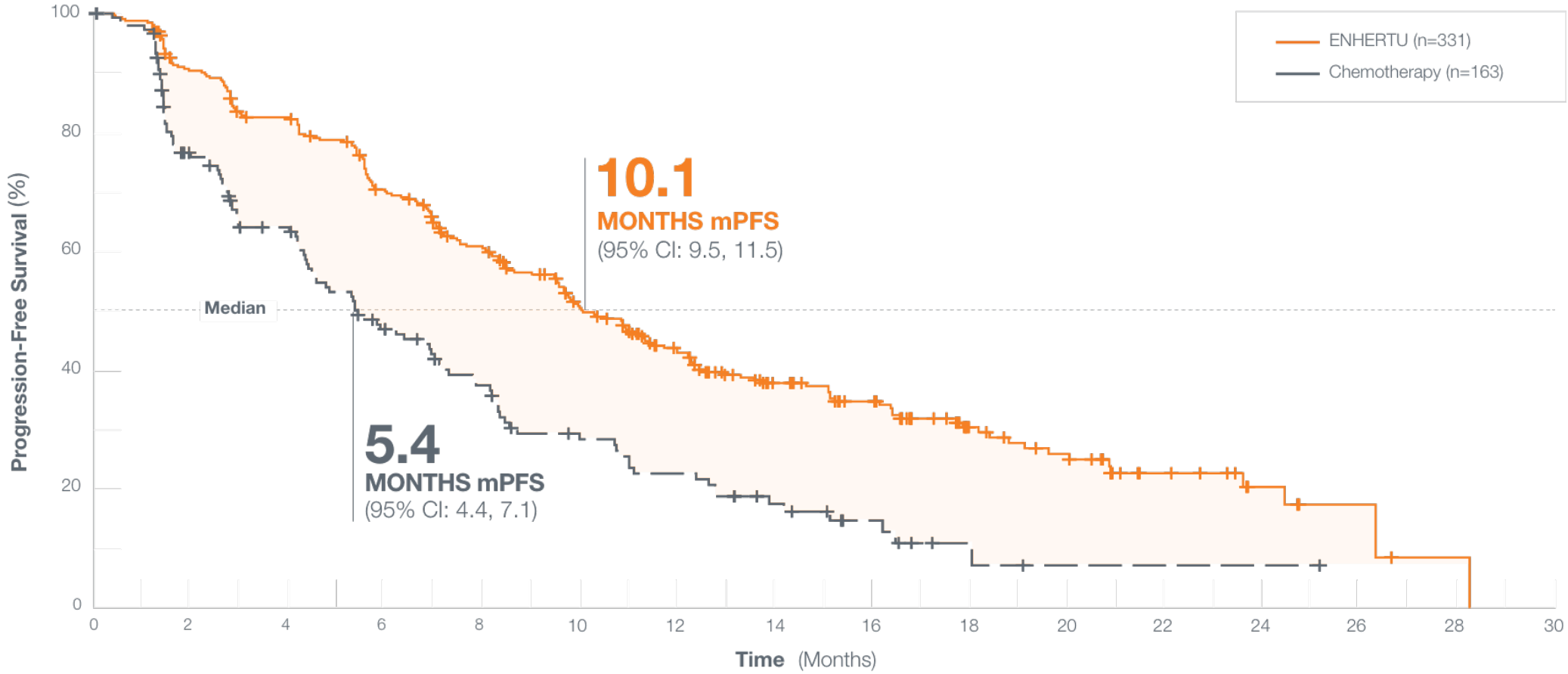
~15% HER2-positive

~85% HER2-negative
(IHC 0, IHC 1+, or IHC 2+/ISH–)

~60%
of patients with
HER2-negative BC have
low levels of HER2 expression
(IHC 1+ or IHC 2+/ISH–)[1,2]

~40% IHC 0

Destiny Breast04 – Trial Efficacy in HR+/HER2-low mBC

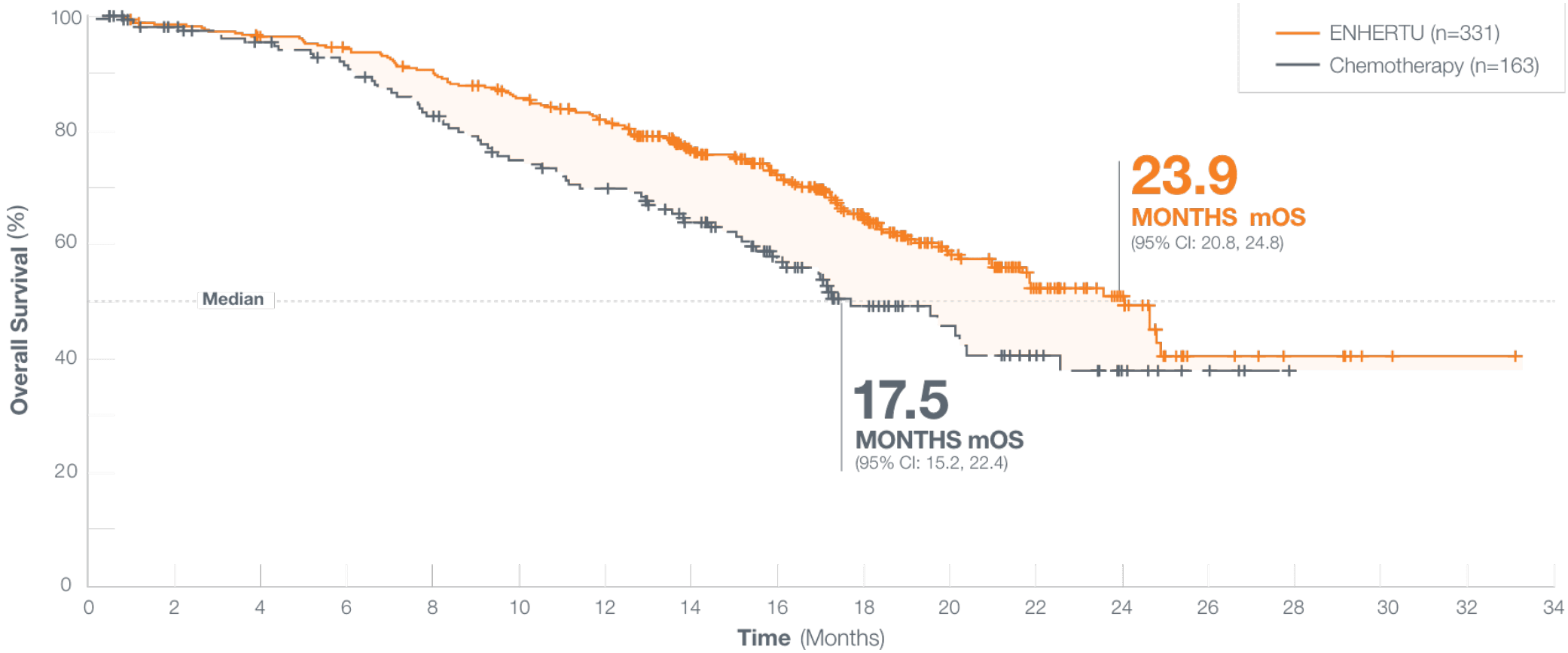


Number at Risk

ENHERTU	331	290	262	218	182	142	107	78	64	37	28	14	7	4	1	0
Chemotherapy	163	105	84	57	43	30	24	14	8	3	1	1	1	0		

Modi et al, *NEJM* 2022

>6 months longer overall survival vs chemotherapy



Number at Risk

ENHERTU	331	323	314	303	285	268	250	199	168	116	81	51	26	9	6	2	1	0
Chemotherapy	163	145	139	130	115	104	96	80	56	37	25	16	7	3	0			

Modi et al, *NEJM* 2022

Basal (Triple Negative) Breast Cancer

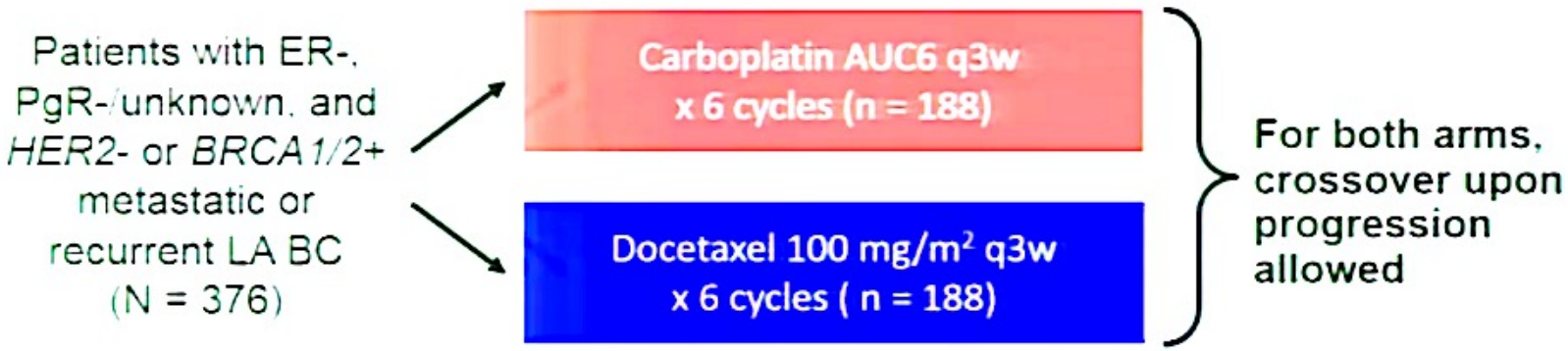
ER, PR, HER2 negative

High nuclear grade and proliferative index

BRCA1/2 positive

Chemosensitive (but poor prognosis)

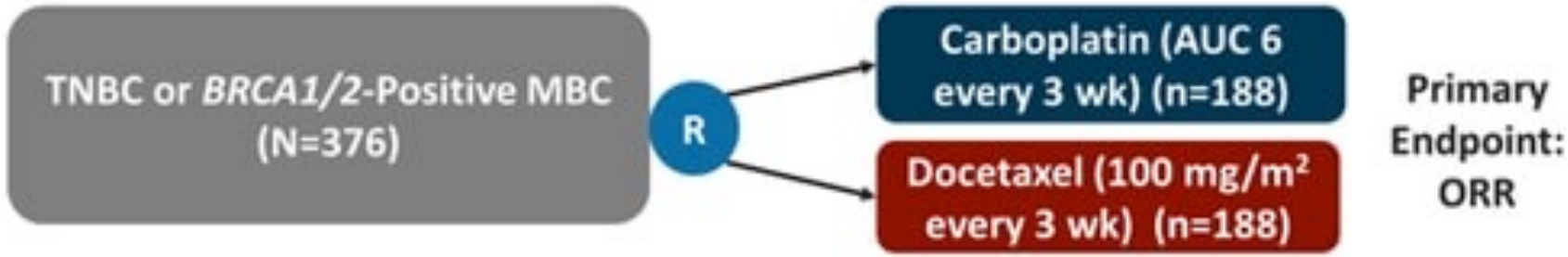
TNT: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2*+ BC



- Primary endpoint: ORR in ITT population
- Secondary endpoints: PFS, OS, ORR (crossover), toxicity
- Subgroup analyses: *BRCA1/2* mutation, basal-like subgroups, HRD biomarkers

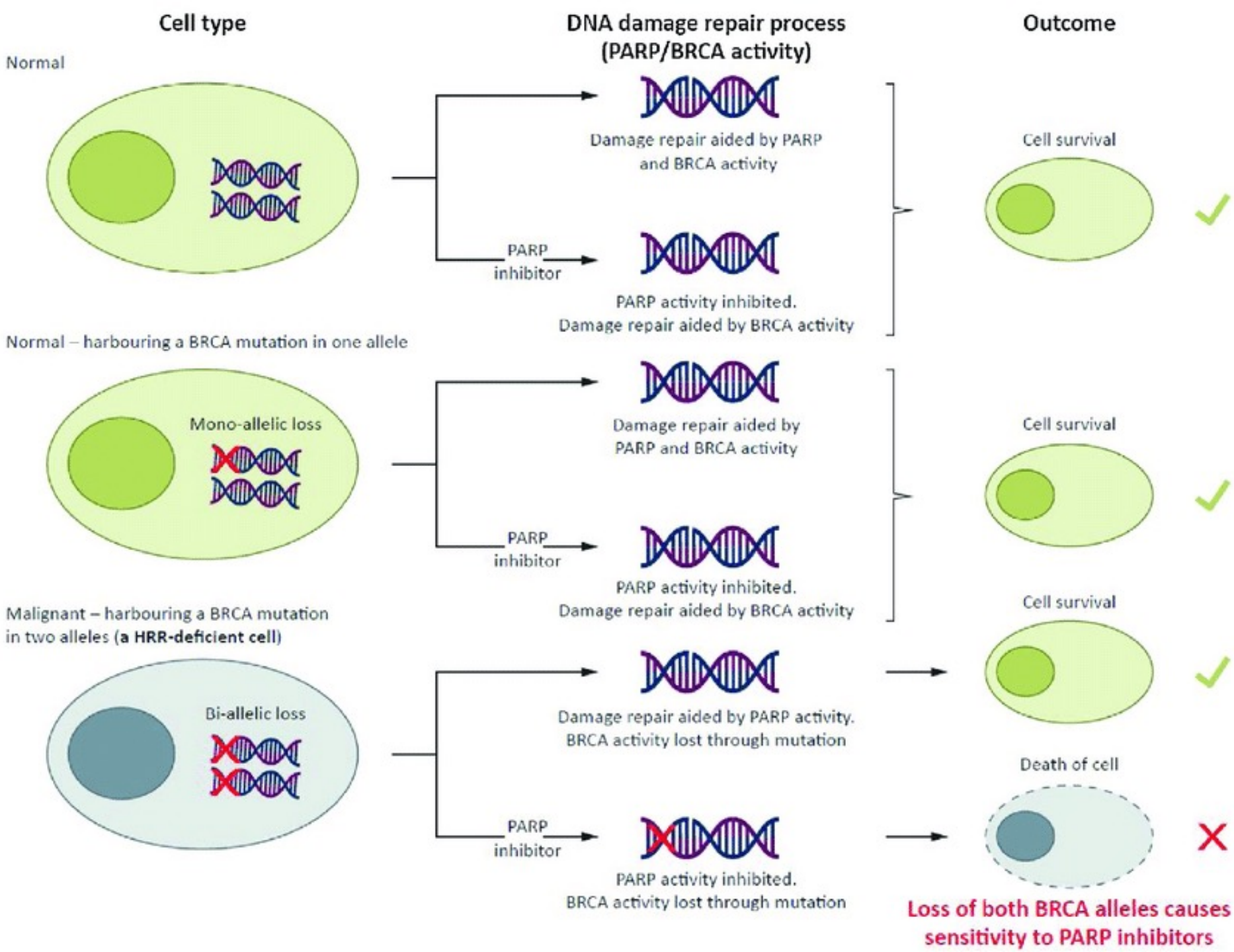
Tutt A, et al. SABCS 2014. Abstract S3-01.

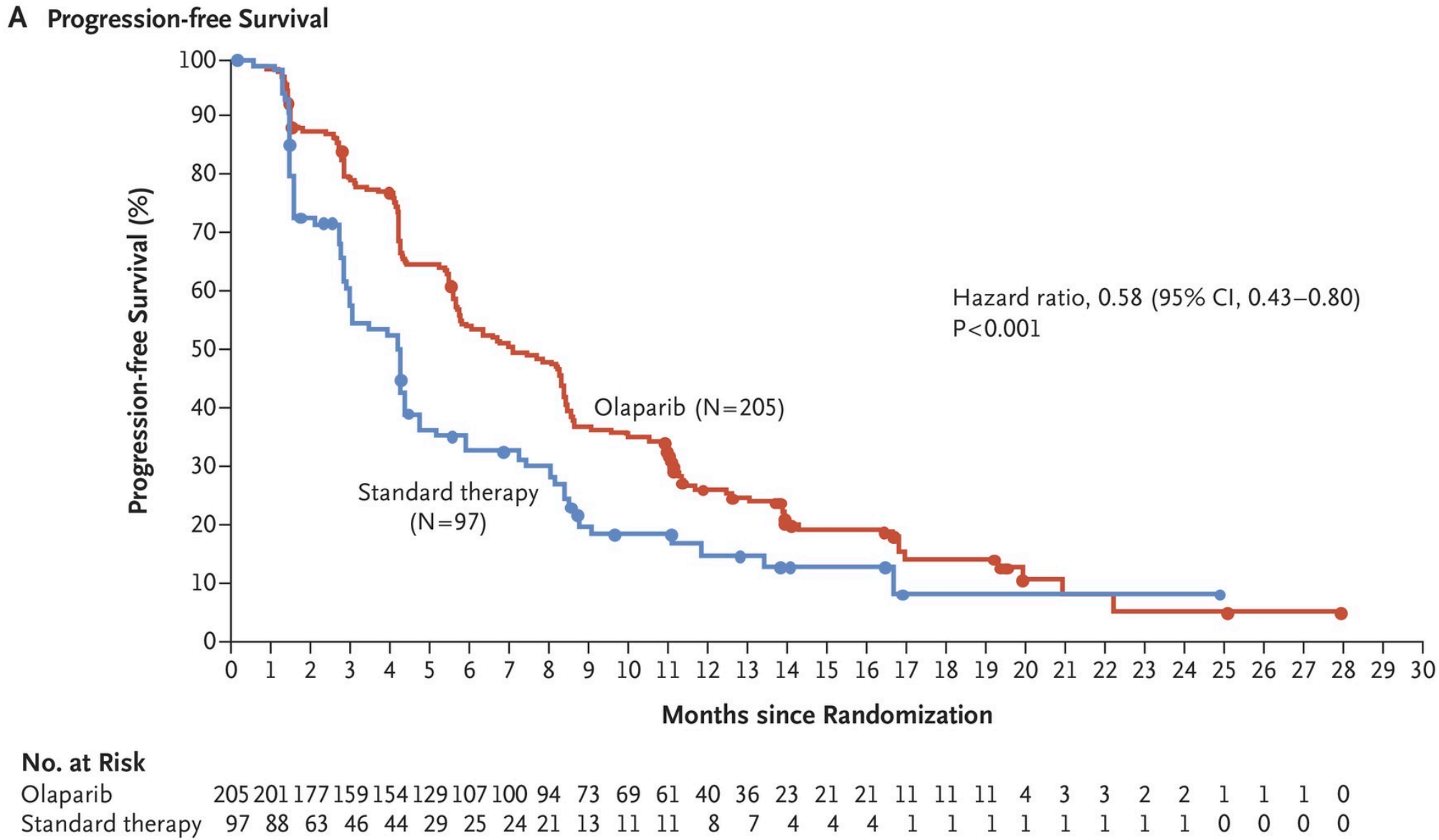
TNT Study: Carboplatin vs Docetaxel in Advanced TNBC or *BRCA1/2*-Positive MBC



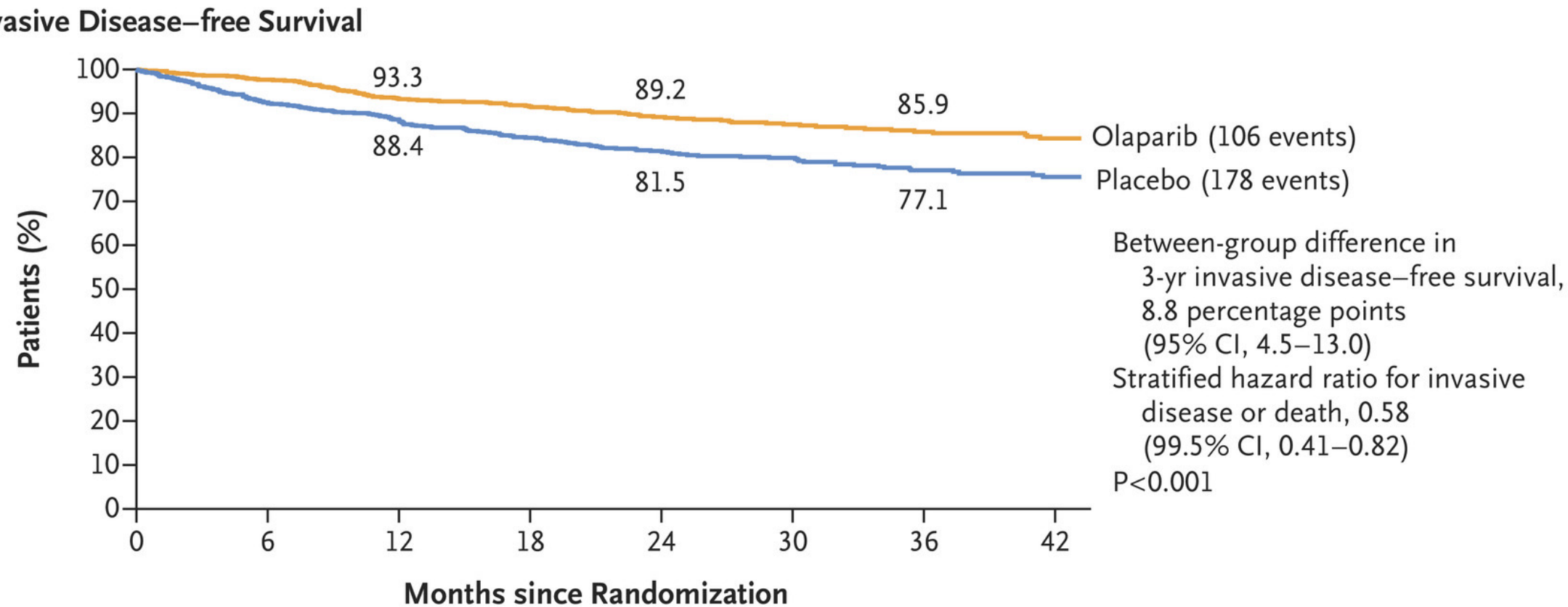
	Carboplatin	Docetaxel	*P* value
ORR, %	31.4	35.6	.44
BRCA1/2 mutated	68	33	.03
BRCA1/2 nonmutated	28.1	36.6	.16
Median PFS, mo	3.1	4.5	
BRCA1/2 mutated	6.8	4.8	
BRCA1/2 nonmutated	3.1	4.6	

Tutt A, et al. SABCS 2014. Abstract S3-01.


Cell type
DNA damage repair process (PARP/BRCA activity)
Outcome
Normal
Damage repair aided by PARP and BRCA activity
PARP inhibitor
PARP activity inhibited. Damage repair aided by BRCA activity
Cell survival
Normal – harbouring a BRCA mutation in one allele
Mono-allelic loss
Damage repair aided by PARP and BRCA activity
PARP inhibitor
PARP activity inhibited. Damage repair aided by BRCA activity
Cell survival
Malignant – harbouring a BRCA mutation in two alleles (a HRR-deficient cell)
Bi-allelic loss
Damage repair aided by PARP activity. BRCA activity lost through mutation
Cell survival
PARP inhibitor
PARP activity inhibited. BRCA activity lost through mutation
Death of cell
Loss of both BRCA alleles causes sensitivity to PARP inhibitors



Robson et al., NEJM 2017

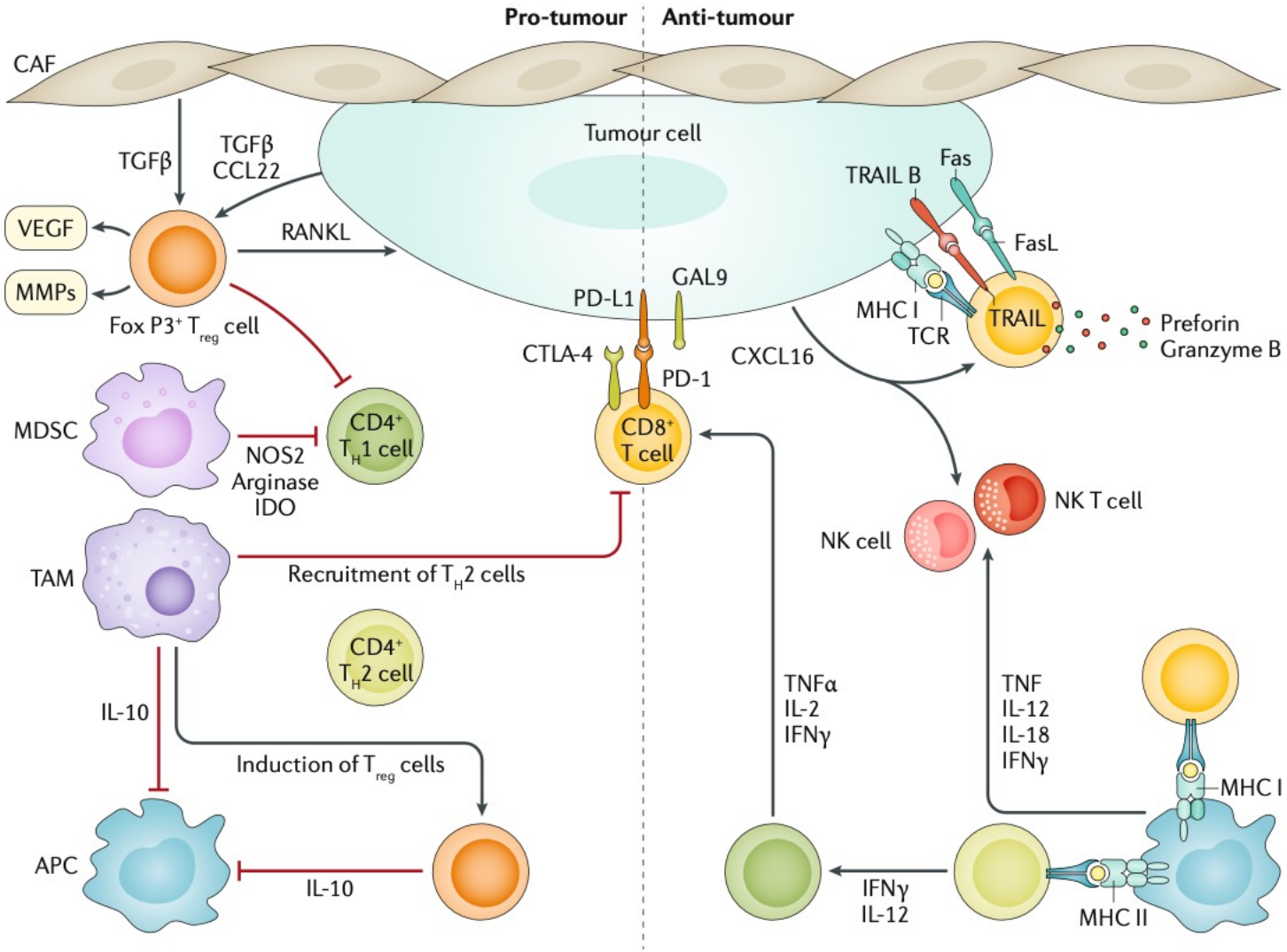


No. at Risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Tutt et al., NEJM 2021

Immune crosstalk in breast cancer



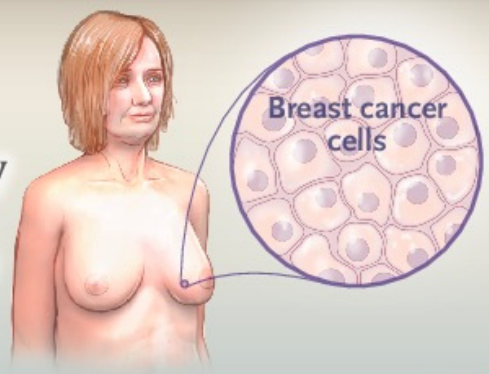
Harbeck et al, *Nature Reviews 2019*

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for Triple-Negative Breast Cancer

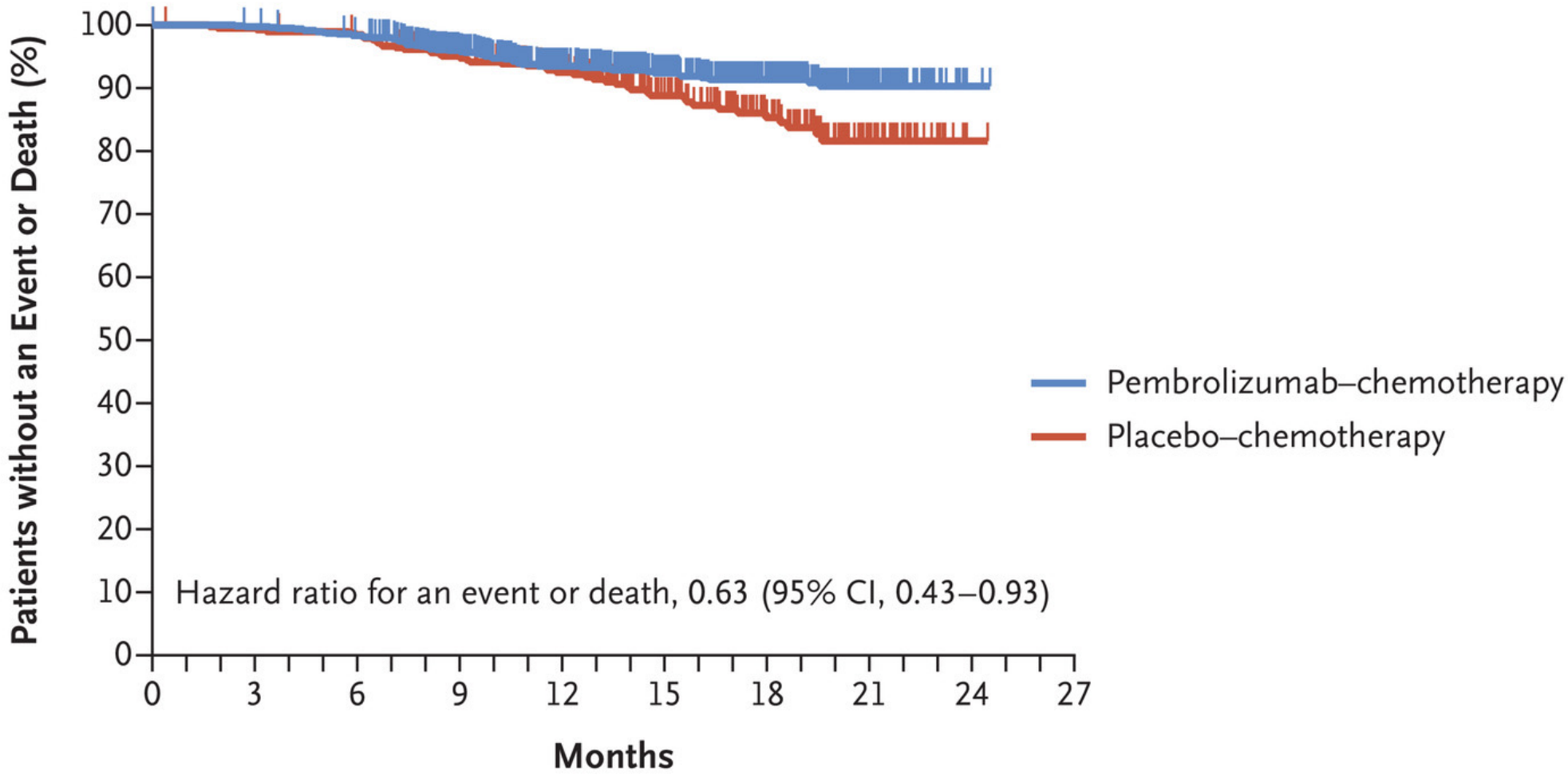
RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

1174 Patients with previously untreated triple-negative breast cancer



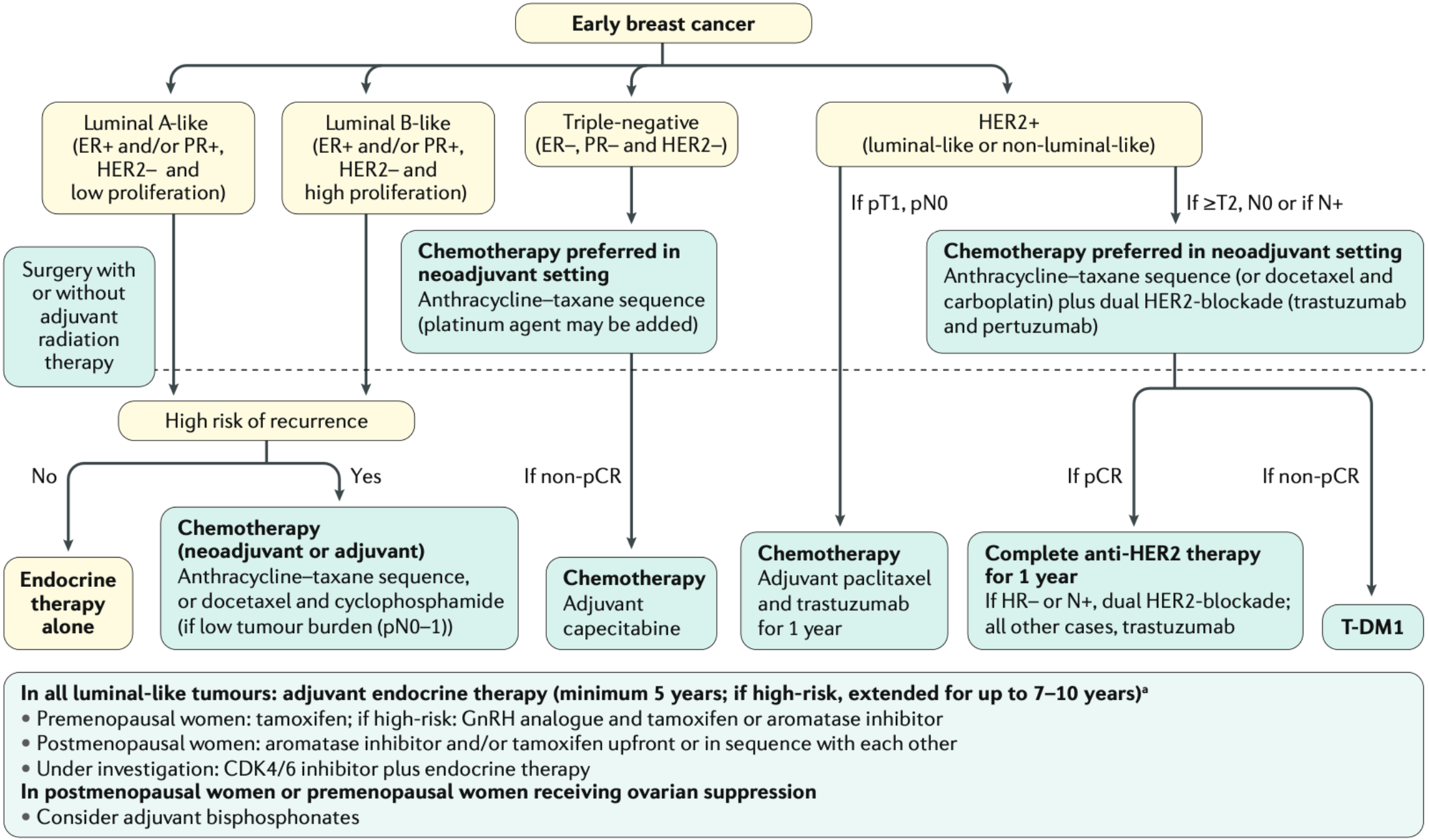
	Neoadjuvant **Pembrolizumab** + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784)	Neoadjuvant **Placebo** + chemotherapy, followed by surgery and adjuvant placebo (N=390)
Pathological complete response at time of surgery	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

P. Schmid et al. 10.1056/NEJMoa1910549



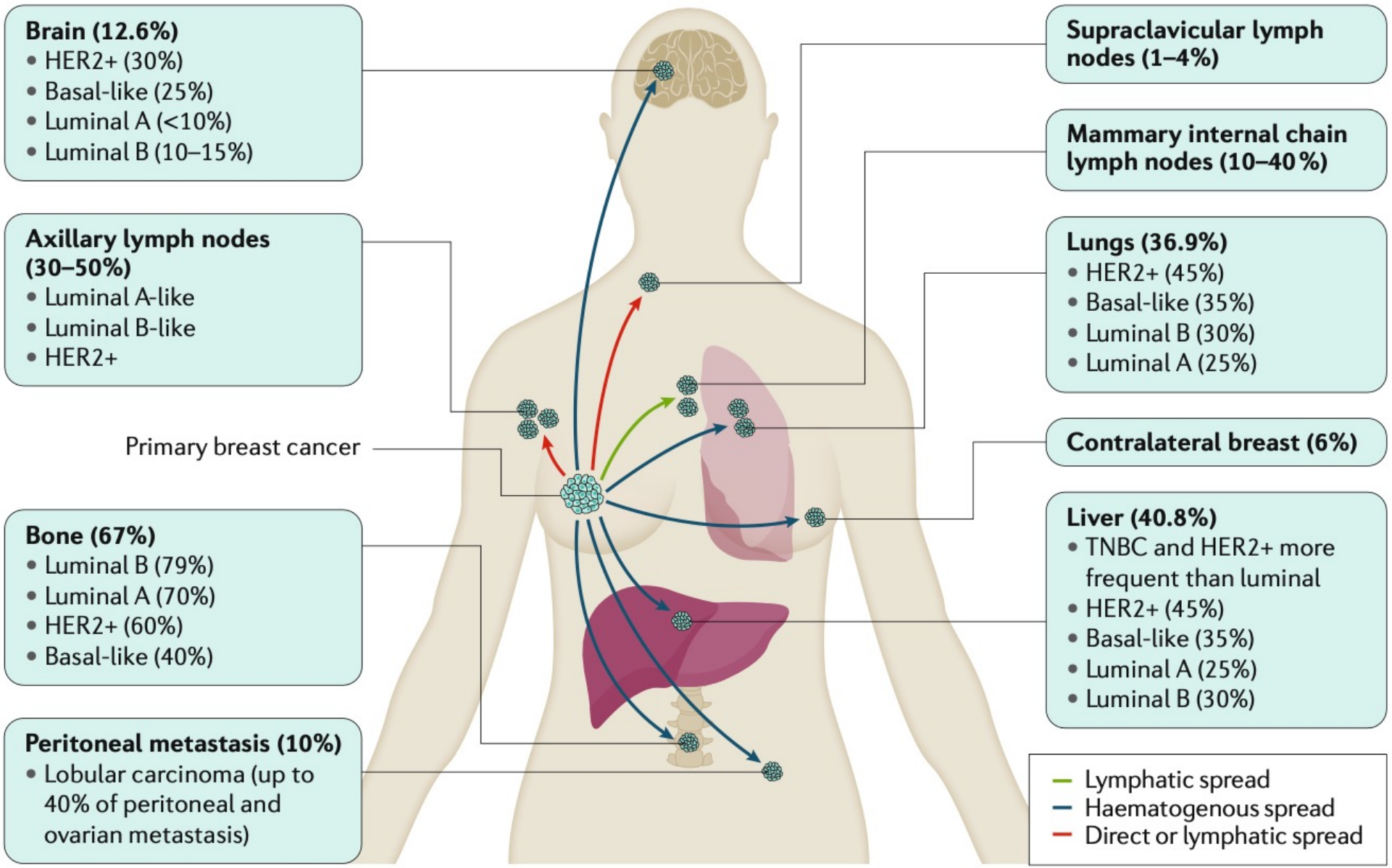
No. at Risk

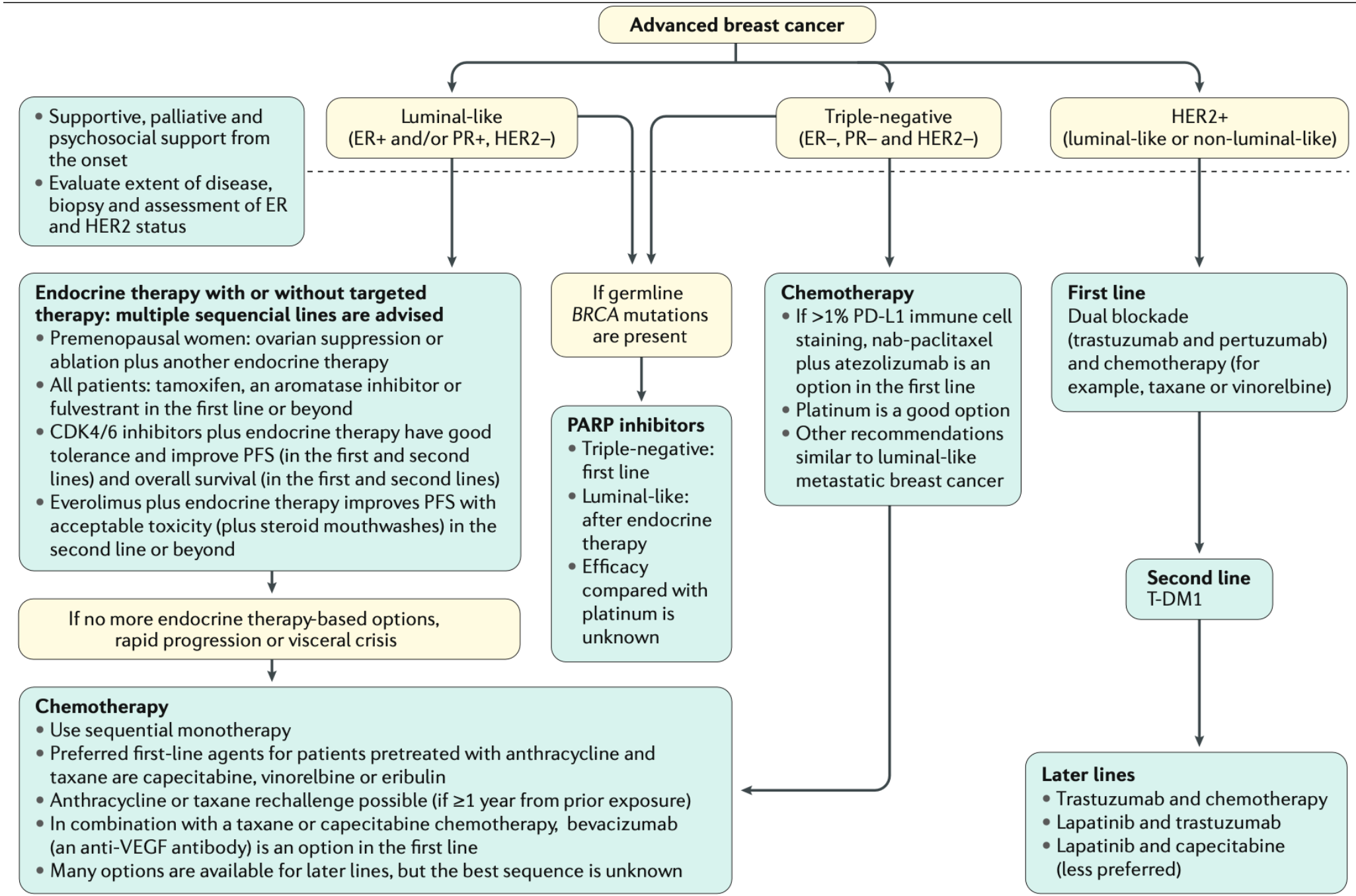
Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0



Harbeck et al, *Nature Reviews 2019*

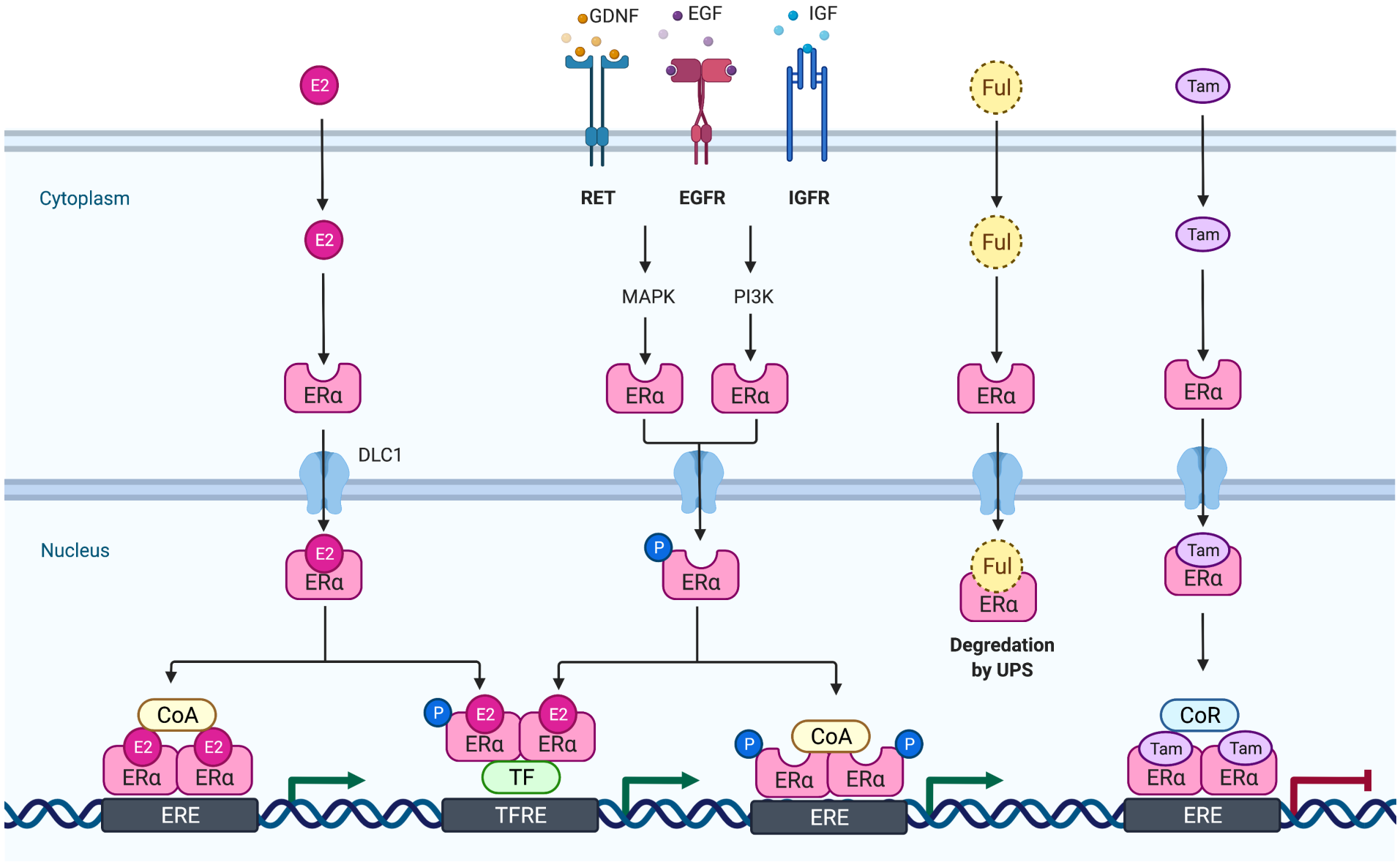
Common metastatic sites in breast cancer





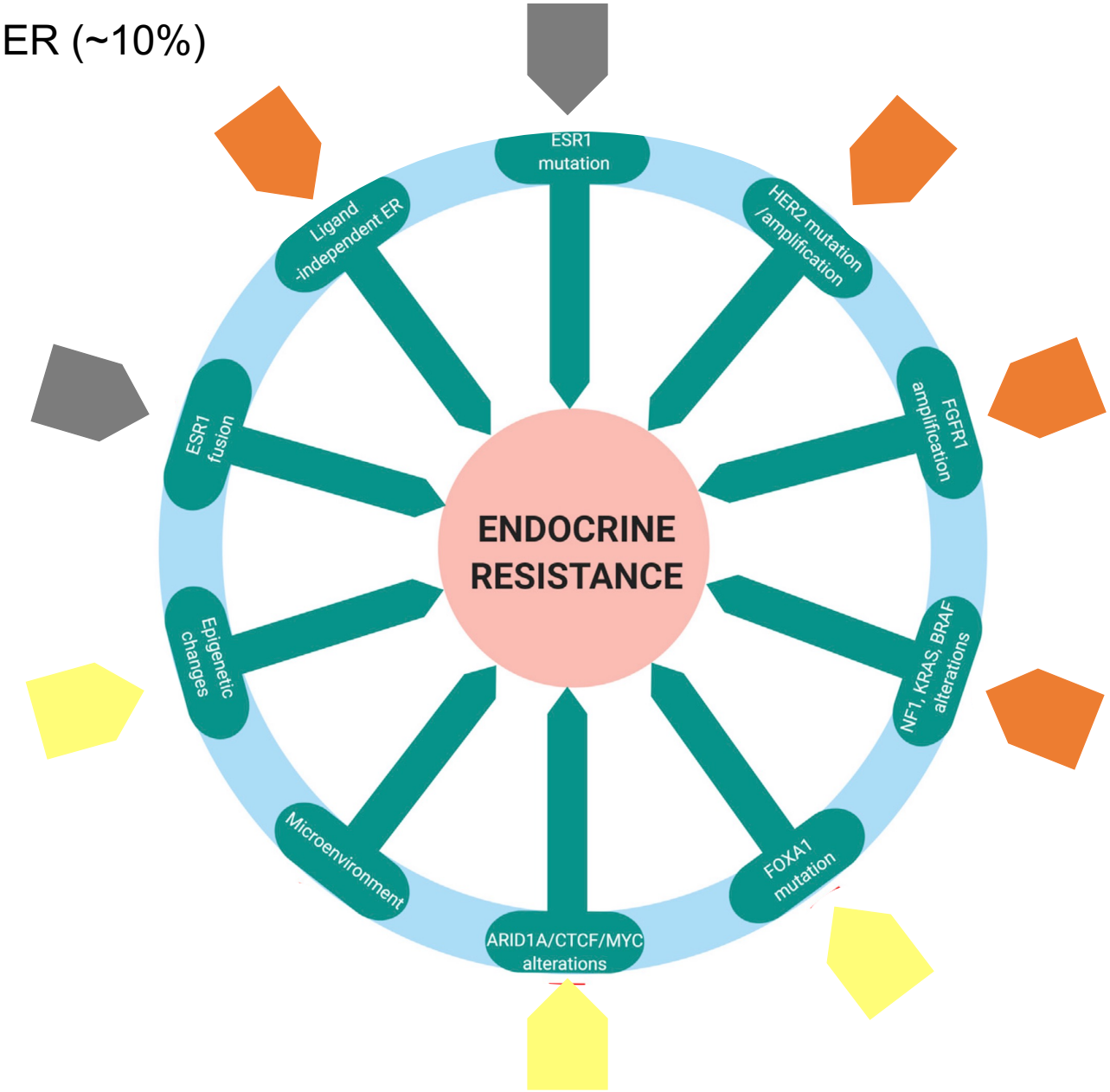
Harbeck et al, *Nature Reviews 2019*

Therapeutic Options



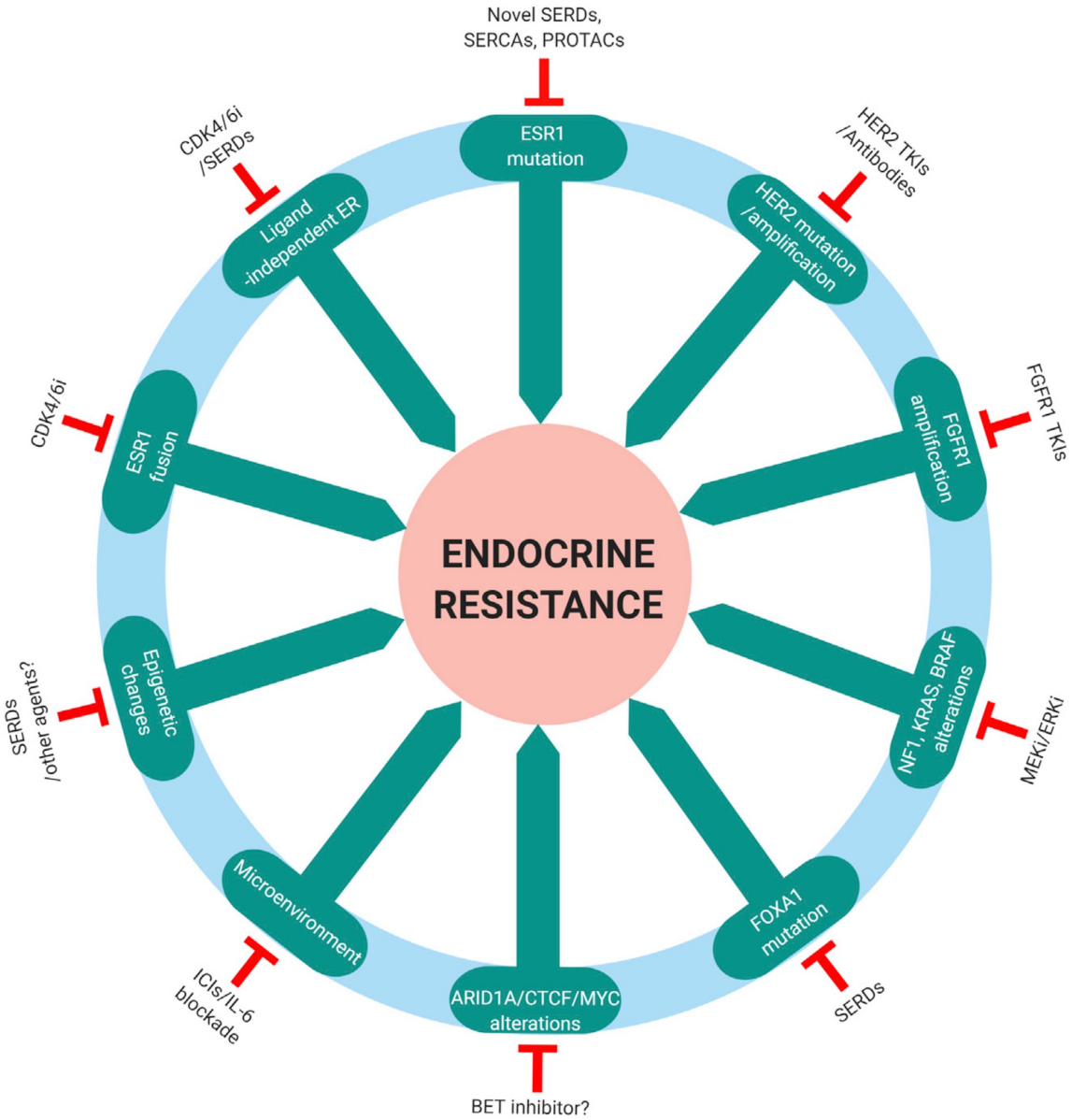
Mechanisms of therapy resistance

Loss of ER (~10%)



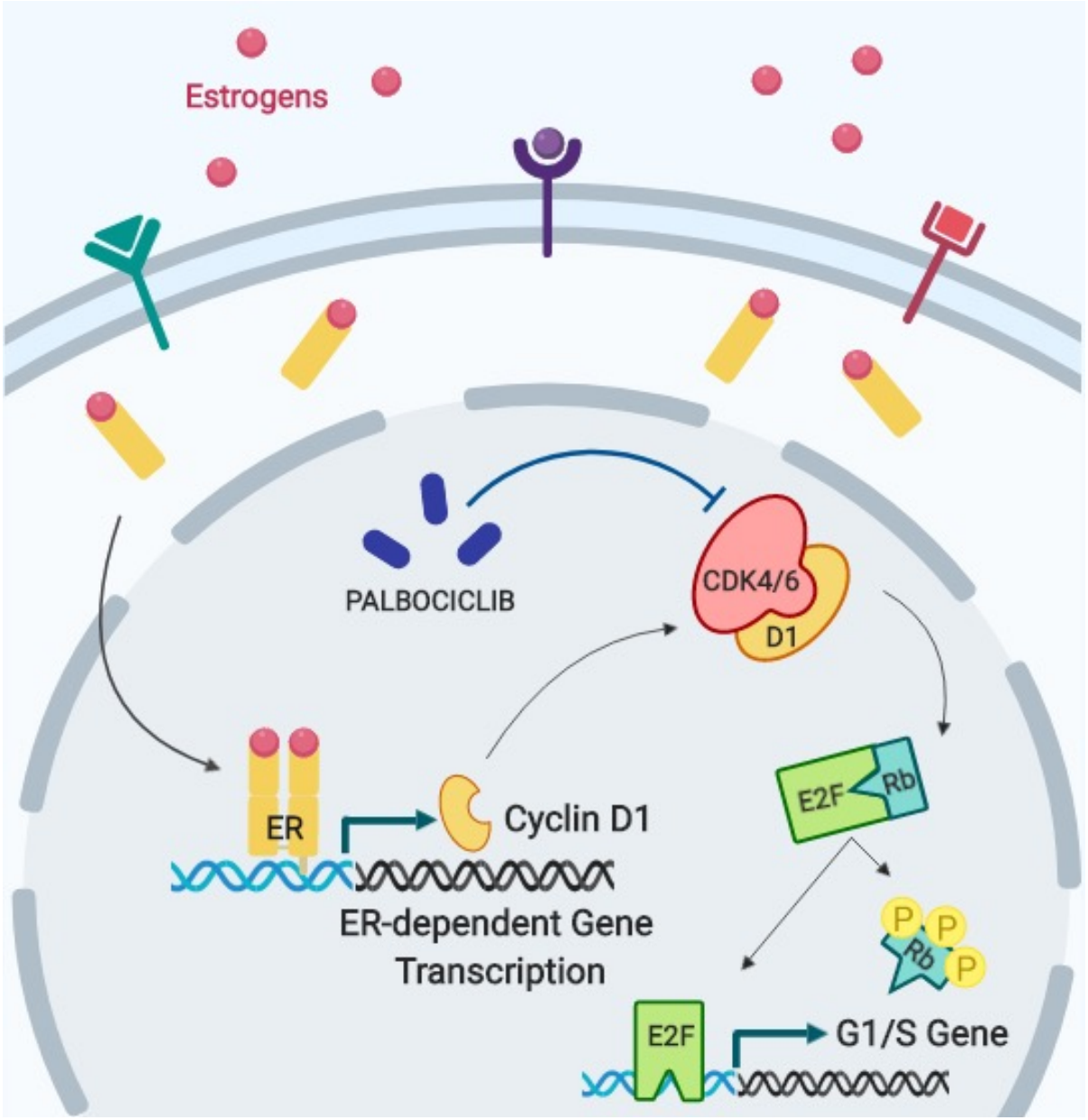
Cancer Cell 37, April 13, 2020

Mechanisms of therapy resistance and therapeuti approaches



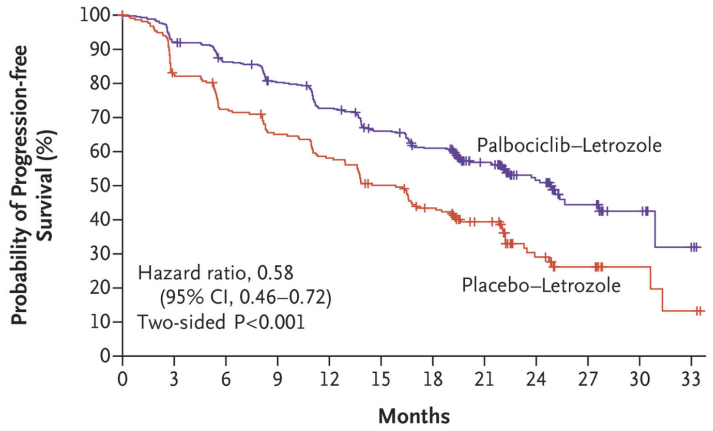
Cancer Cell 37, April 13, 2020

Therapeutic options – Palbociclib (CDK4/6i)



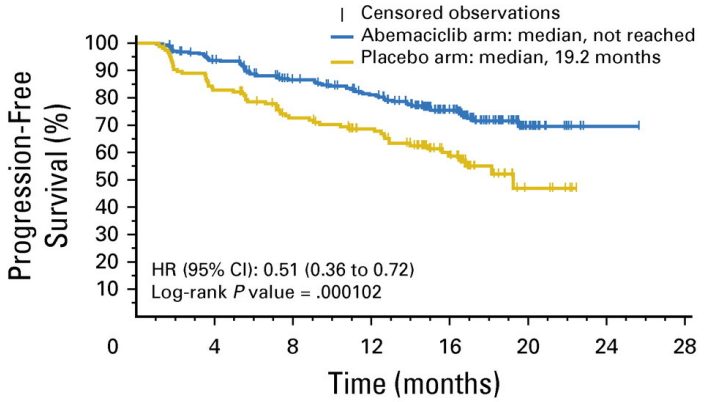
Clinical trials showing superior outcome in patients treated with a combination of ET and a CDK4/6 inhibitor

PALOMA2



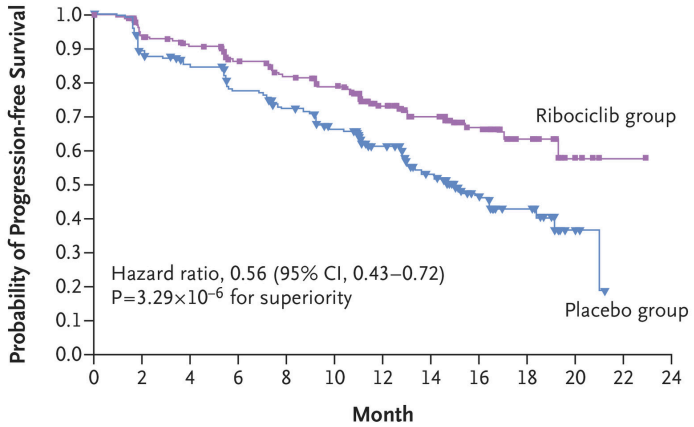
No. at Risk												
Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

MONARCH3



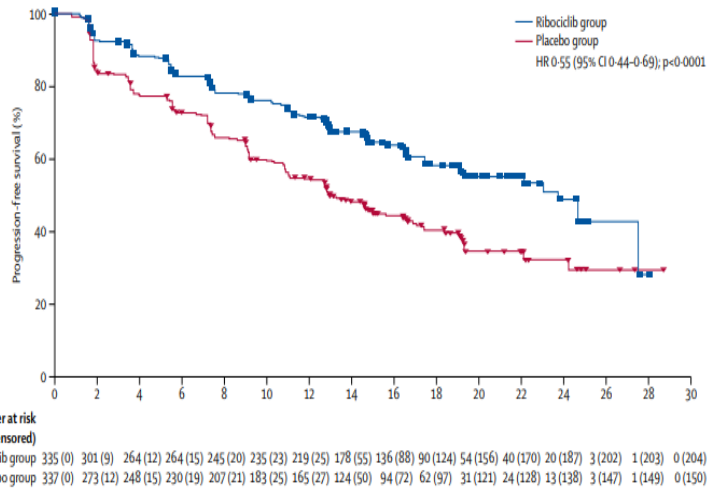
No. at risk:								
Abemaciclib arm	328	271	230	203	124	26	1	0
Placebo arm	165	121	95	79	45	6	0	0

MONALEESA2



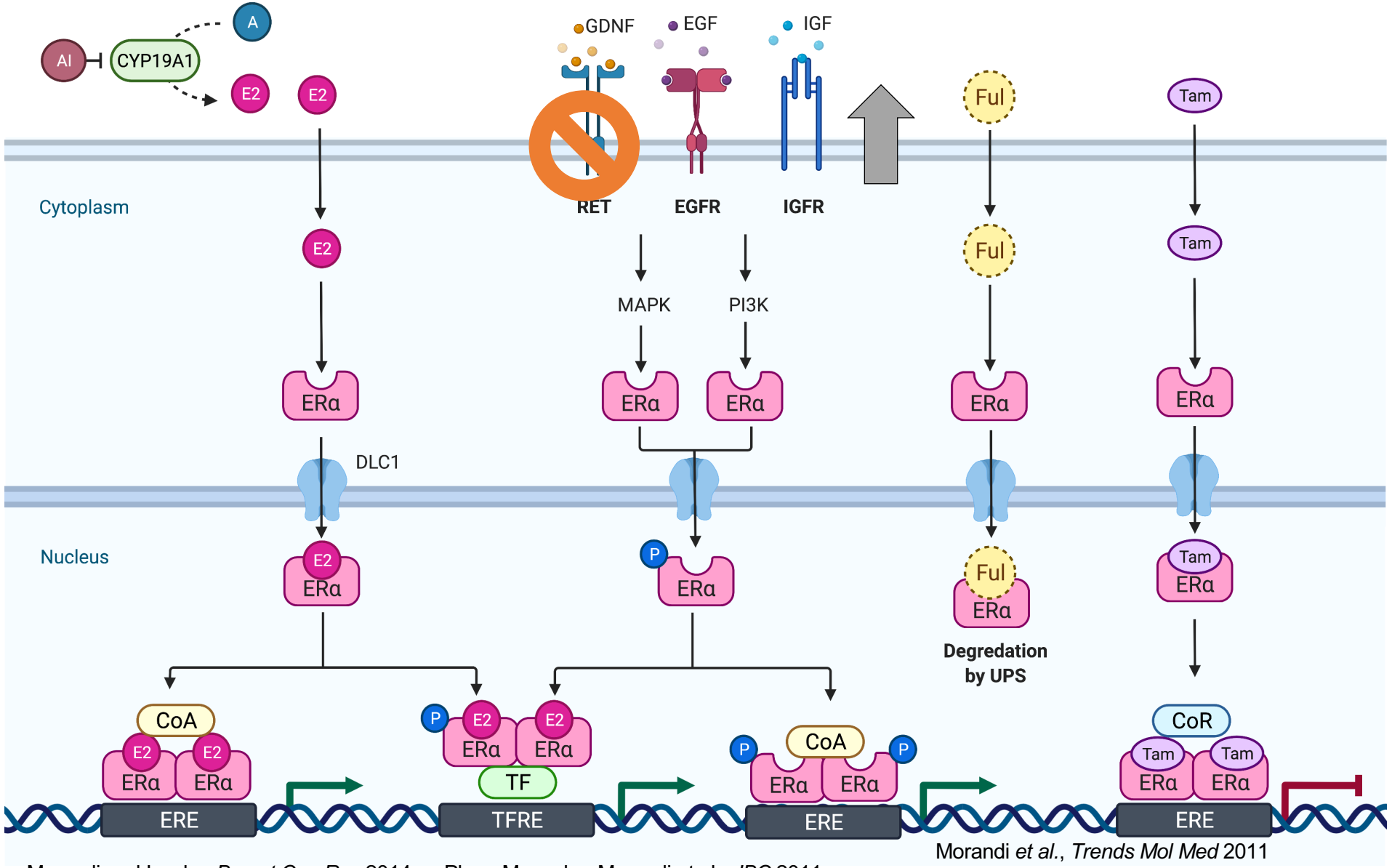
No. at Risk												
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

MONALEESA7



Finn *et al,* NEJM 2016; Hortobagyi *et al,* NEJM 2016; Di Leo *et al,* JCO 2017; Tripathy *et al,* Lancet Oncol 2018

Mechanisms of therapy resistance

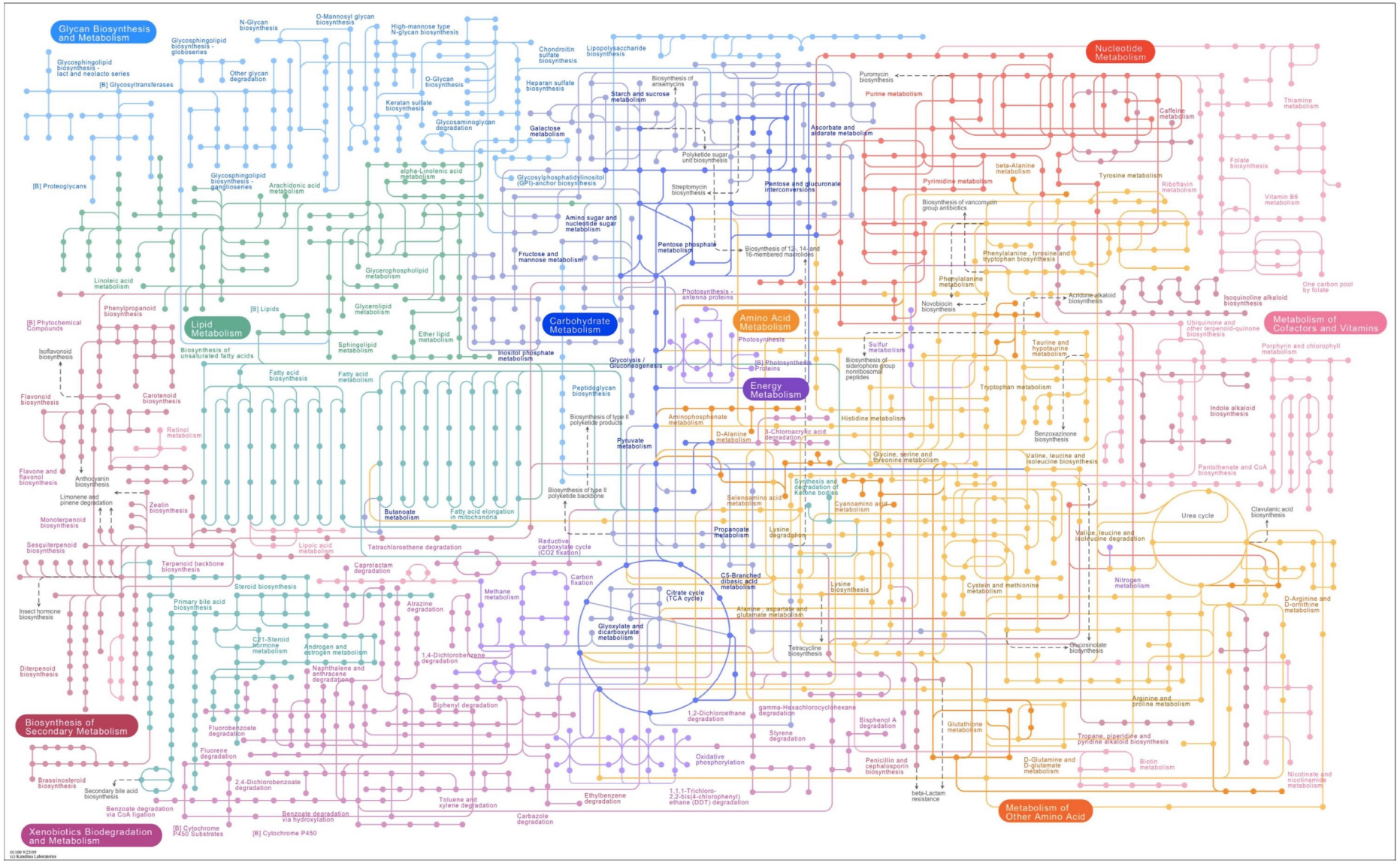


Morandi and Isacke, *Breast Can Res* 2014
Morandi *et al.*, *Cancer Research* 2013

Plaza-Menacho, Morandi et al., *JBC* 2011
Plaza-Menacho, Morandi *et al.*, *Oncogene* 2010

Morandi *et al.*, *Trends Mol Med* 2011
Mologni et al., *MCE* 2013
Andreucci, Francica,…, Morandi *Oncotarget* 2016

Targeting the engine and not the drivers of resistance



Metabolic targeting agents in cancer therapy

TABLE 1. Cancer Therapies/Drugs That Target Metabolic Pathways

METABOLIC PATHWAY	TARGET[a]	DRUG	STAGE OF DEVELOPMENT	REFERENCES
Nucleic acid synthesis	Thymidylate synthase (TS)	5-Fluorouracil, capecitabine, pemetrexed, raltitrexed	Approved	Heidelberger 1957,[97] Jackman 1991,[98] Chin 1997,[99] Miwa 1998[100]
	Dihydrofolate reductase (DHFR)	Methotrexate, pemetrexed	Approved	Chin 1997,[99] Myer 1950,[101] Wright 1951[102]
	Glycinamide ribonucleotide formyltransferase (GARFT)	Pemetrexed	Approved	Chin 1997[99]
	Dihydroorotate dehydrogenase (DHODH)	Brequinar, leflunomide	Phase 1/2	Sykes 2018[103]
	Ribonucleotide reductase (RNR)	Gemcitabine, clofarabine, fludarabine, cladribine, cytarabine	Approved	Xie & Plunkett 1996,[104] Heinemann 1990,[105] Greene 2020,[106] Evans 1961,[107] Hertel 1990[108]
	5-Phosphoribosyl-1-pyro-phosphatase (PRPP) amidotransferase	Mercaptopurine, thioguanine	Approved	Skipper 1954,[109] Atkinson & Murray 1965,[110] Hill & Bennett 1969[111]
Glycolysis	GLUT1	WZB117, BAY-876	Preclinical	Ma 2018,[112] Liu 2012[113]
	Hexokinase	2-Deoxyglucose	Phase 1/2	Dwarakanath 2009[114]
	Pyruvate Kinase M2 (PKM2)	TEPP-46	Preclinical	Anastasiou 2012[115]
	Lactate dehydrogenase A (LDHA)	Quinoline, 3-sulfonamides, FX11, PSTMB	Preclinical	Kim 2019,[116] Billiard 2013,[117] Le 2010[118]
	Monocarboxylate transporter 1 (MCT1)	AZD3965	Phase 1	Marchiq & Pouyssegur 2016[119]
Glutamine metabolism	Glutaminase 1 (GLS1)	CB-839, IPN60090	Phase 1/2	Xiang 2015,[120] Gross 2014,[121] Soth 2020[122]
	ASCT2 (SLC1A5)	GPNA	Preclinical	Yoo 2020,[123] Esslinger 2005[124]
	Multiple targets	JHU-083	Preclinical	Leone 2019,[95] Hanaford 2019[125]
Amino acid transport and biosynthesis	Phosphoglycerate dehydrogenase (PHGDH)	CBR-5884, NCT-503	Preclinical	Wang 2017,[126] Pacold 2016,[127] Mullarky 2016[128]
	Indoleamine-2,3-dioxygenase-1 (IDO1)	Epacadostat, indoximod	Phase 3	Prendergast 2017[129]
	Circulating asparagine	L-Asparaginase	Approved	Clavell 1986[130]
	Large neutral amino acid transporter (LAT1)	JPH203	Preclinical	Enomoto 2019,[131] Oda 2010[132]
Mitochondrial metabolism	Pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase	CPI-613	Phase 2	Zachar 2011[133]
	Electron transport chain complex 1	Metformin, IACS-010759	Phase 1-3	Molina 2018,[134] Yam 2019[135]
Lipid metabolism	ATP-citrate lyase (ACLY)	SB-204990	Preclinical	Hatzivassiliou 2005,[136] Shah 2016[137]
	Acetyl-CoA carboxylase (ACC)	Soraphen-A	Preclinical	Svensson 2016,[138] Corominas 2014[139]
	fatty acid synthase (FASN)	TVB-2640	Phase 2	Mullen & Yet 2015[140]
Enzymes mutated in cancer	Mutant isocitrate dehydrogenase 1 (IDH1)	AG-120, BAY1436032, LY3410738, FT-2102	Phase 1-3	DiNardo 2018,[141] Heuser 2020[142]
	Mutant isocitrate dehydrogenase 2 (IDH2)	AG-221	Phase 3	Stein 2017[143]

[a]Key targets of nucleoside analogs are shown; however, most nucleoside analogs inhibit multiple nucleic acid and DNA synthesis/repair enzymes, including DNA polymerase.

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Article

Fasting-mimicking diet and hormone therapy induce breast cancer regression

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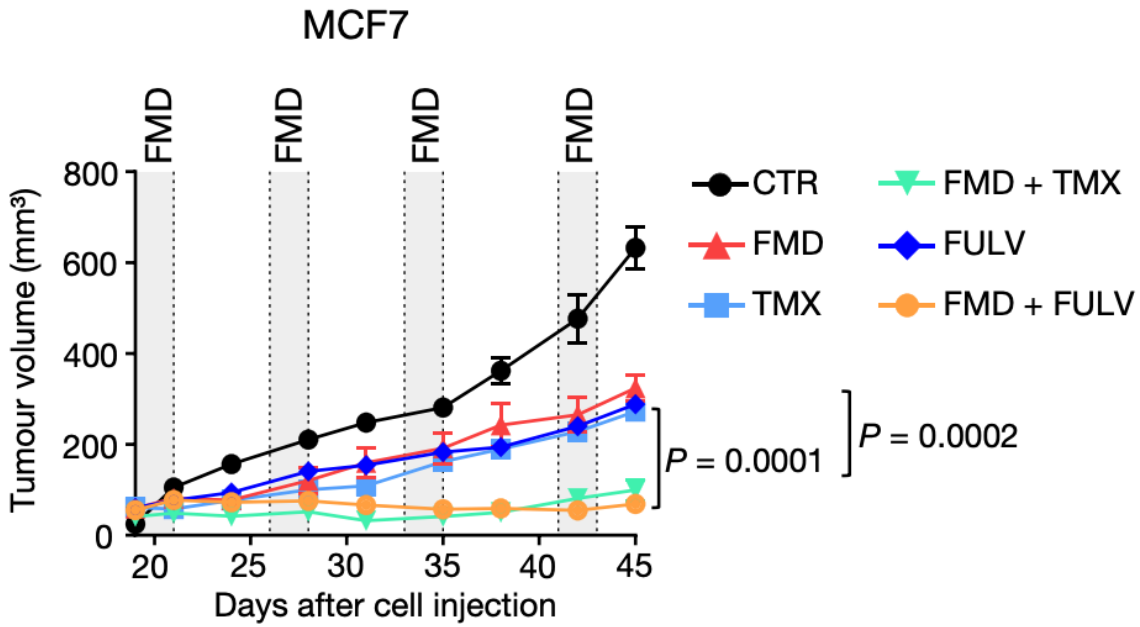
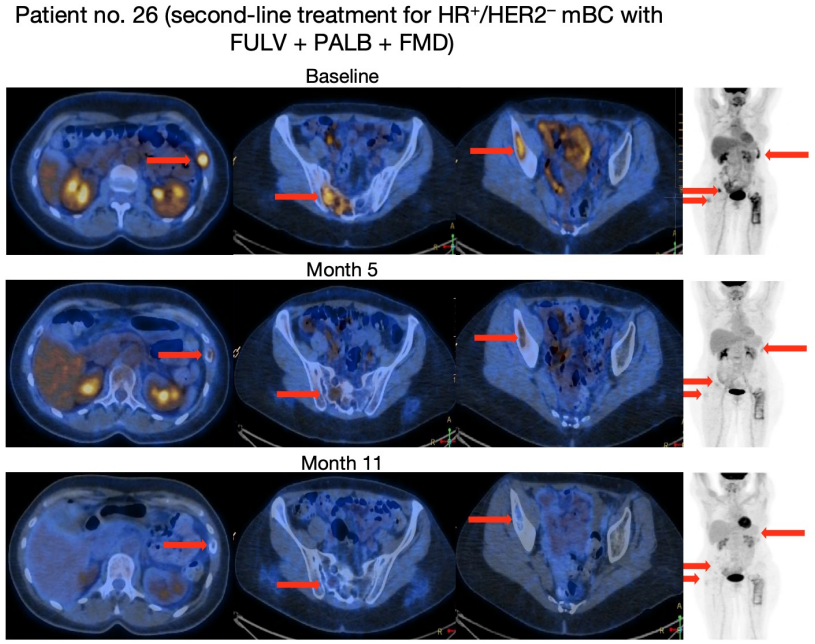
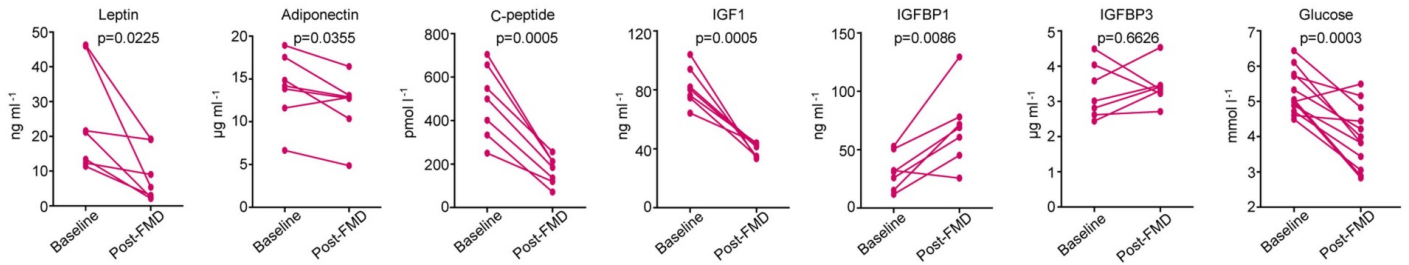
Irene Caffa[1,14], Vanessa Spagnolo[2,3,14], Claudio Vernieri[3,4], Francesca Valdemarin[1,5], Pamela Becherini[1,5], Min Wei[6], Sebastian Brandhorst[6], Chiara Zucal[7], Else Driehuis[8,9], Lorenzo Ferrando[5], Francesco Piacente[1,5], Alberto Tagliafico[10], Michele Cilli[1], Luca Mastracci[1,11], Valerio G. Vellone[1,11], Silvano Piazza[7], Anna Laura Cremonini[1,5], Raffaella Gradaschi[1], Carolina Mantero[1], Mario Passalacqua[12], Alberto Ballestrero[1,5], Gabriele Zoppoli[1,5], Michele Cea[1,5], Annalisa Arrighi[5], Patrizio Odetti[1,5], Fiammetta Monacelli[1,5], Giulia Salvadori[2,3], Salvatore Cortellino[3], Hans Clevers[8,9,13], Filippo De Braud[2,4], Samir G. Sukkar[1], Alessandro Provenzani[7], Valter D. Longo[3,6,15] ✉ &







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nature reviews cancer

Review Article | Published: 25 May 2022

Developing dietary interventions as therapy for cancer

Samuel R. Taylor, John N. Falcone, Lewis C. Cantley & Marcus D. Goncalves ✉

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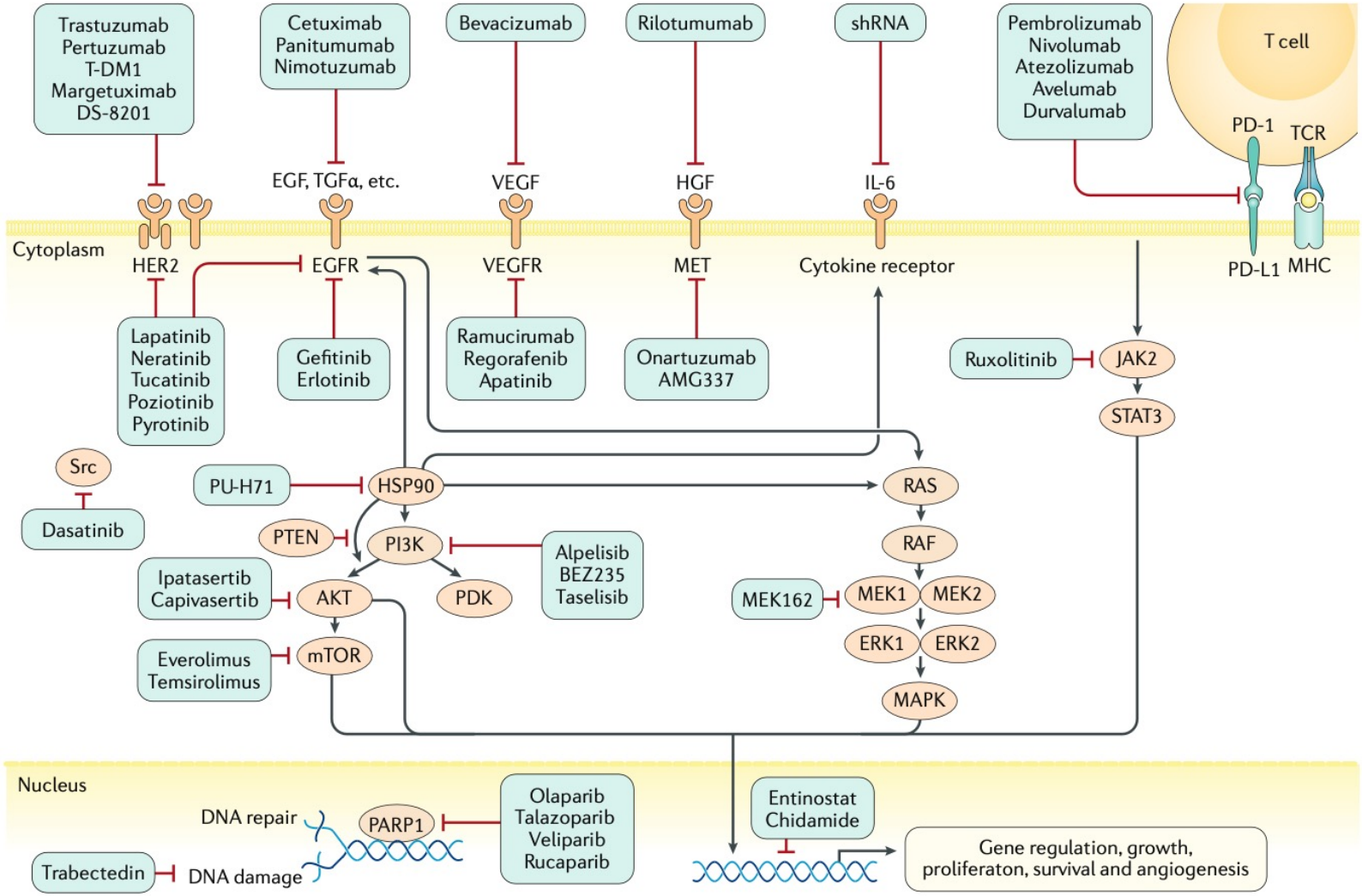
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Margetuximab
DS-8201
Cetuximab
Panitumumab
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Bevacizumab
Rilotumumab
shRNA
Pembrolizumab
Nivolumab
Atezolizumab
Avelumab
Durvalumab
T cell
PD-1
TCR
EGF, TGFα, etc.
VEGF
HGF
IL-6
Cytoplasm
HER2
EGFR
VEGFR
MET
Cytokine receptor
PD-L1
MHC
Lapatinib
Neratinib
Tucatinib
Poziotinib
Pyrotinib
Gefitinib
Erlotinib
Ramucirumab
Regorafenib
Apatinib
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STAT3
Src
Dasatinib
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