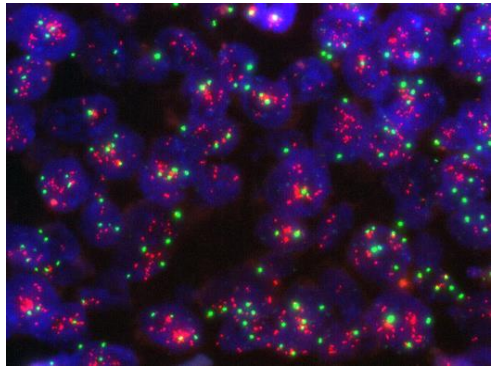
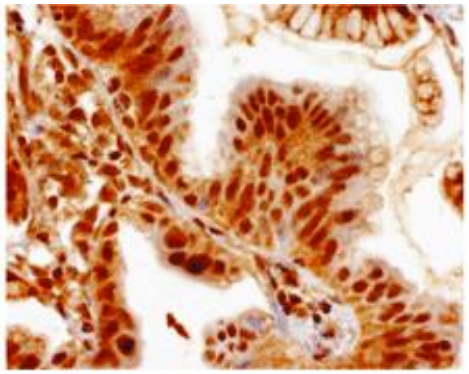
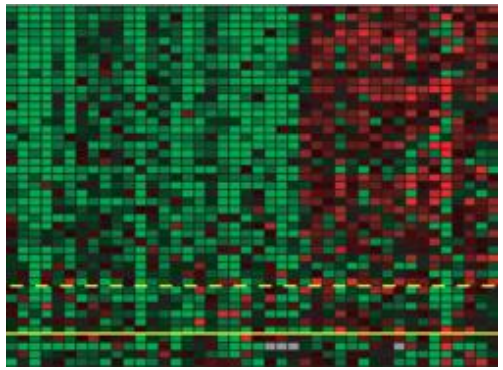
Principles of Laboratory Testing for Treatment Decision-Making in Metastatic Breast Cancer





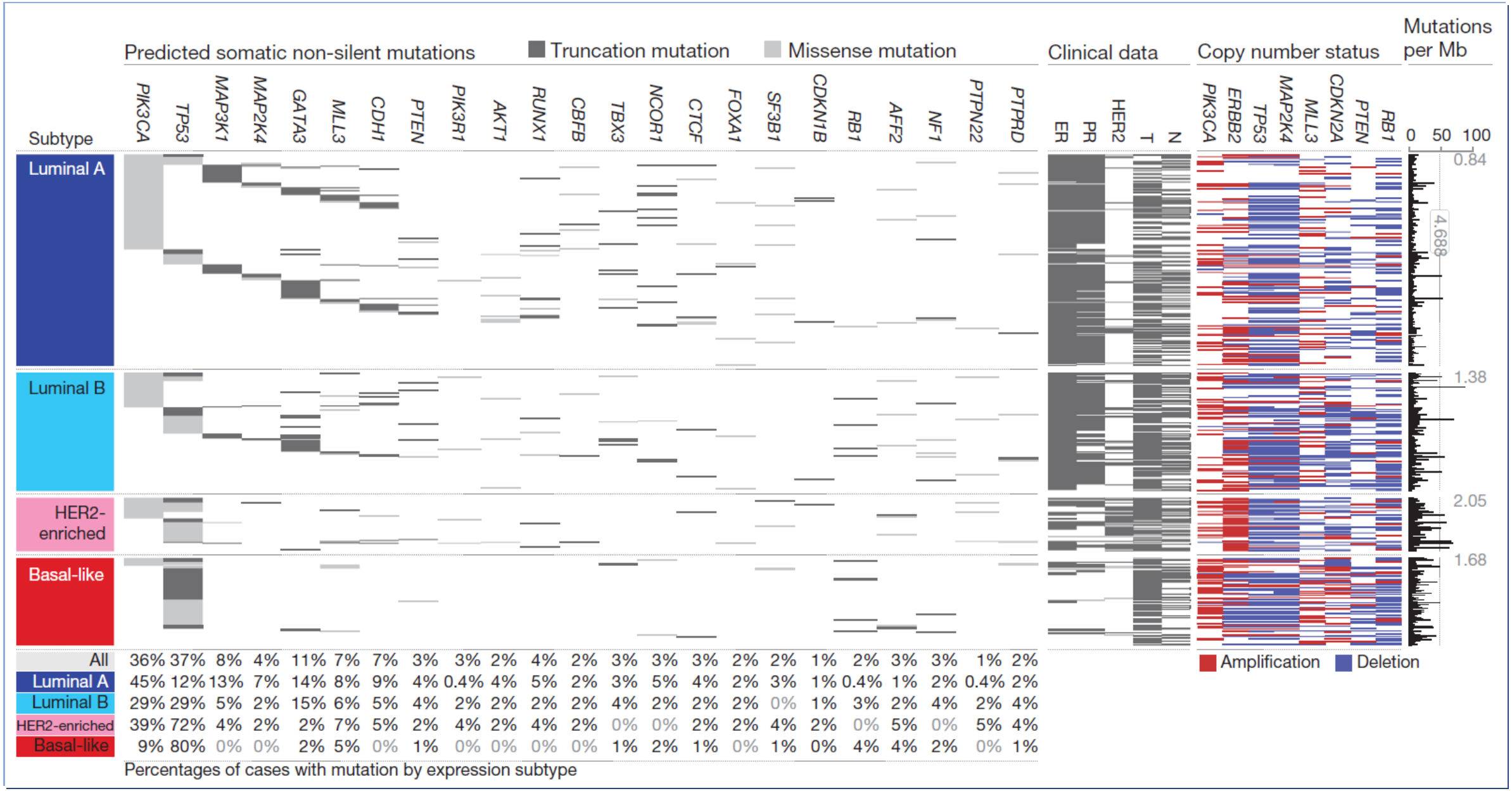


Debu Tripathy, MD

Department of Breast Medical Oncology

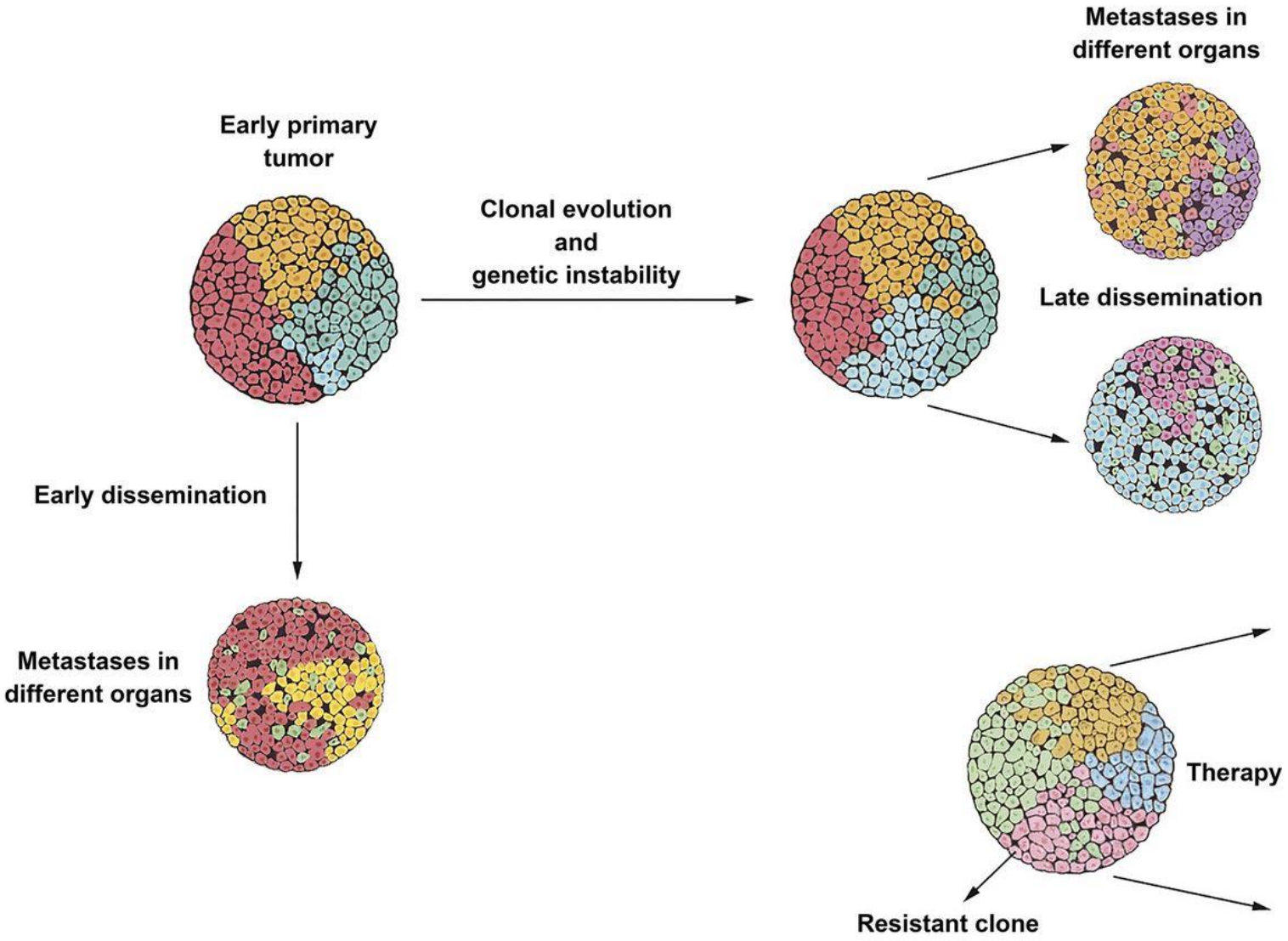
The University of Texas MD Anderson Cancer Center, Houston, TX

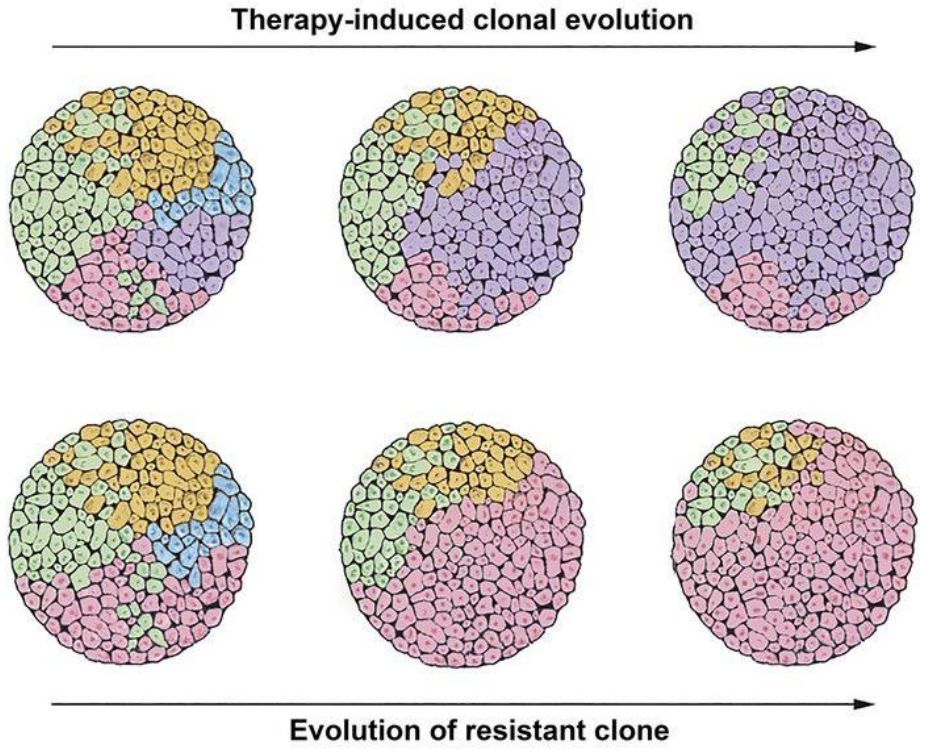
Genomic Landscape in Receptor Subtypes of Breast Cancer



The Cancer Genome Atlas Network. Nature 2012

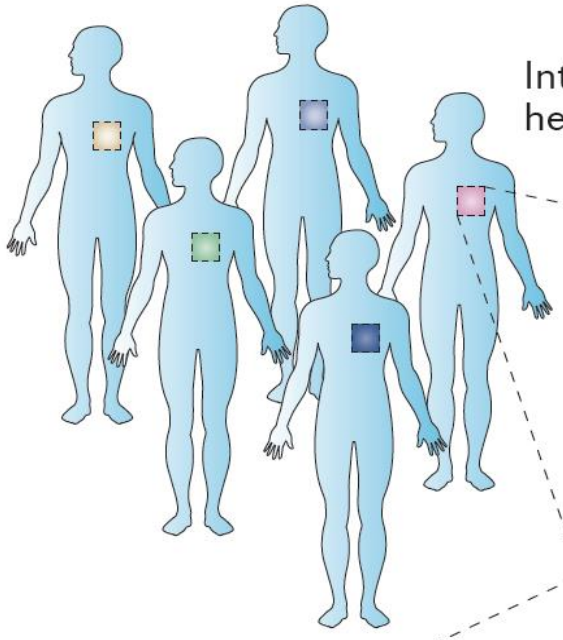
The Fluid State of the Tumor Micro-Ecosystem: Genomic Evolution and Adaptive Resistance





Santarpia L et al. The Oncologist 2016

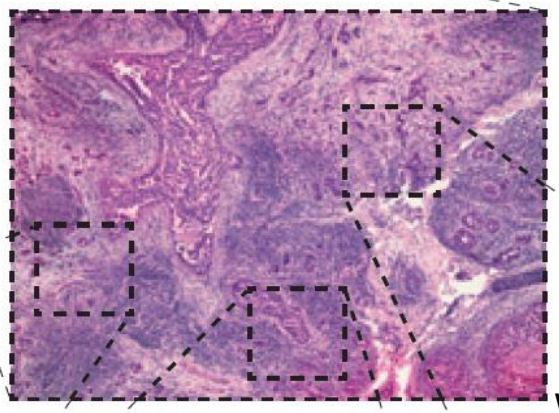
Breast Cancer Heterogeneity Patients and Tumors



Inter-tumour heterogeneity

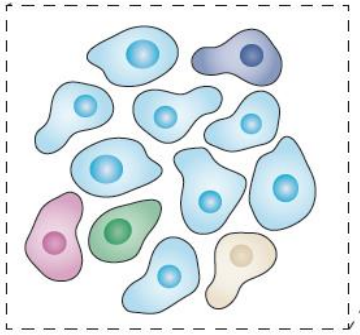
Between patients: **Subtypes and clinical courses**

Within a patient: **Evolution, divergent paths**

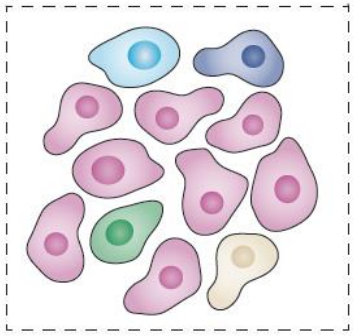


Intra-tumour heterogeneity

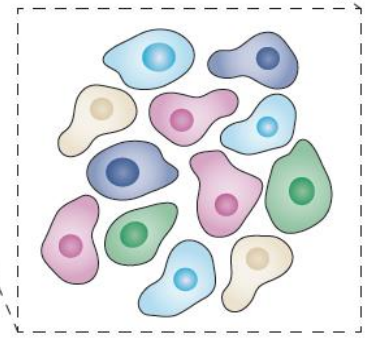
Within Tumours: subclones



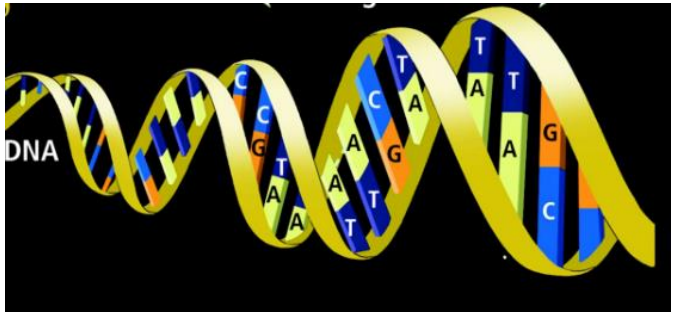
Dominance of clone 1



Dominance of clone 2



Mixed dominance



What, How, and Why Do We Test in Metastatic Breast Cancer?

Test	Material Measured	Purpose
Estrogen/Progesterone receptor	Protein	Effectiveness of hormonal (endocrine) therapies
HER2 receptor	Protein and/or DNA	Effectiveness of HER2-targeted therapies
PD-L1	Protein	Effectiveness of immunotherapy
Germline (Hereditary) gene mutations	Germline DNA	Genetic counseling, cancer prevention, Effectiveness of PARP inhibitors therapy
Tumor Mutations	Tumor DNA	Tumor gene mutations that show potential activity of specific targeted therapies
Tumor Gene Expression (RNA)	Tumor RNA	Expression profiles to optimize and personalize treatment (experimental)

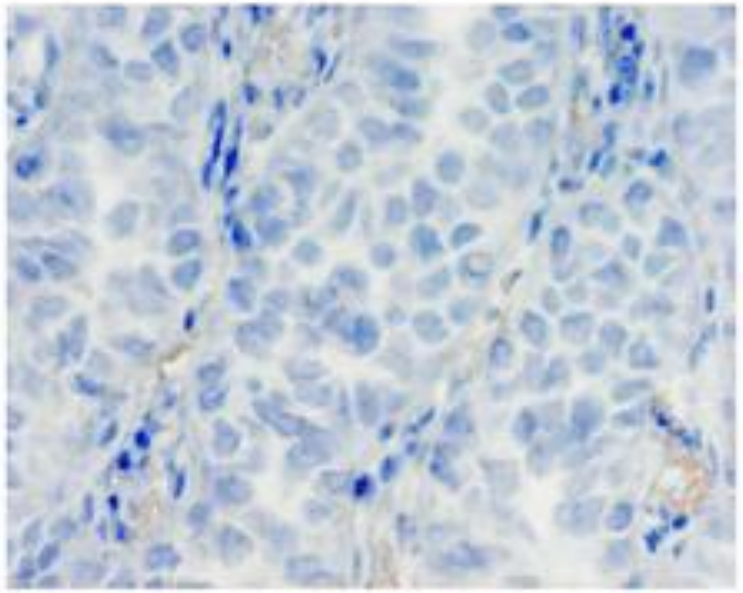
Recommendations for Testing in Metastatic Breast Cancer

- **Imaging (CT chest, abdomen, pelvis and bone scan or whole body PET/CT scan, if indicated brain MRI**
- **Genetic counseling and germline DNA testing**
- **Biopsy of metastatic lesion for histological confirmation of cancer, ER, PR and HER2 testing**
- **After 1st line therapy (or sooner), tumor gene next generation DNA and/or RNA sequencing**

Estrogen and Progesterone Receptor Immuno-Staining: Scoring by % Staining and Intensity

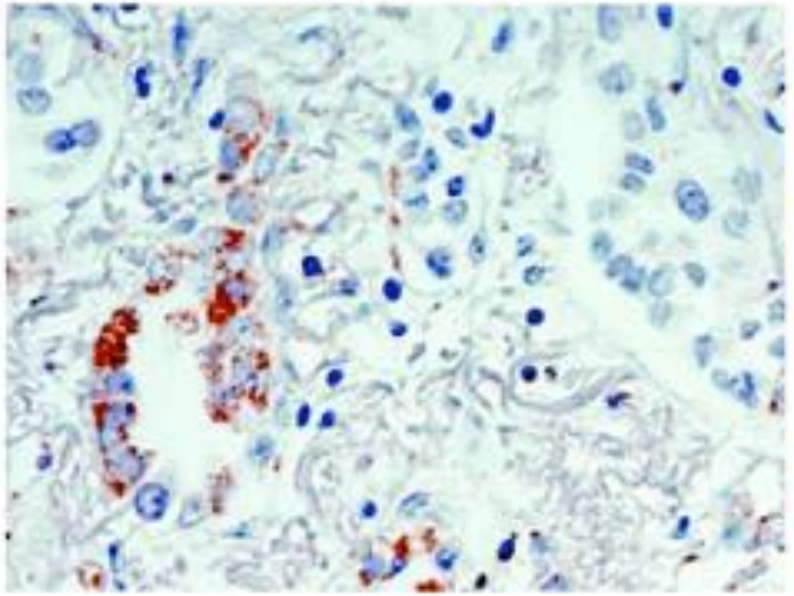
Estrogen Receptor Assay Examples

Negative



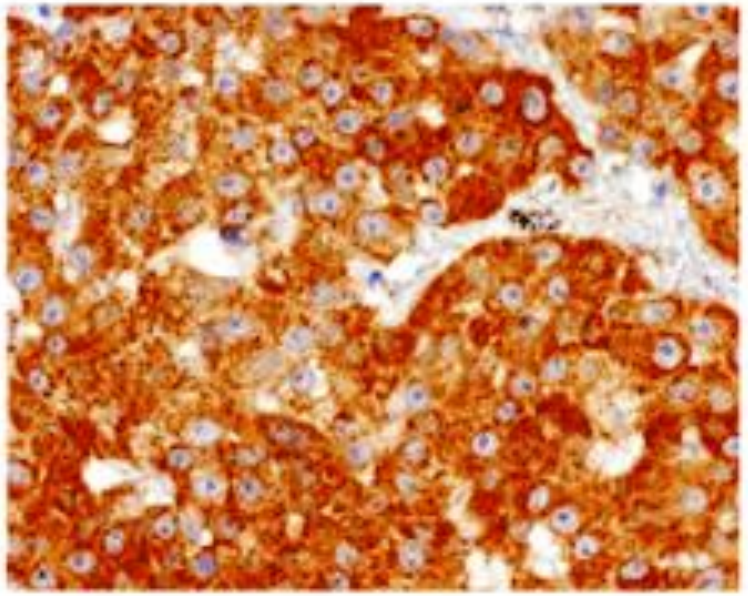
0 + 0 = 0

Weak



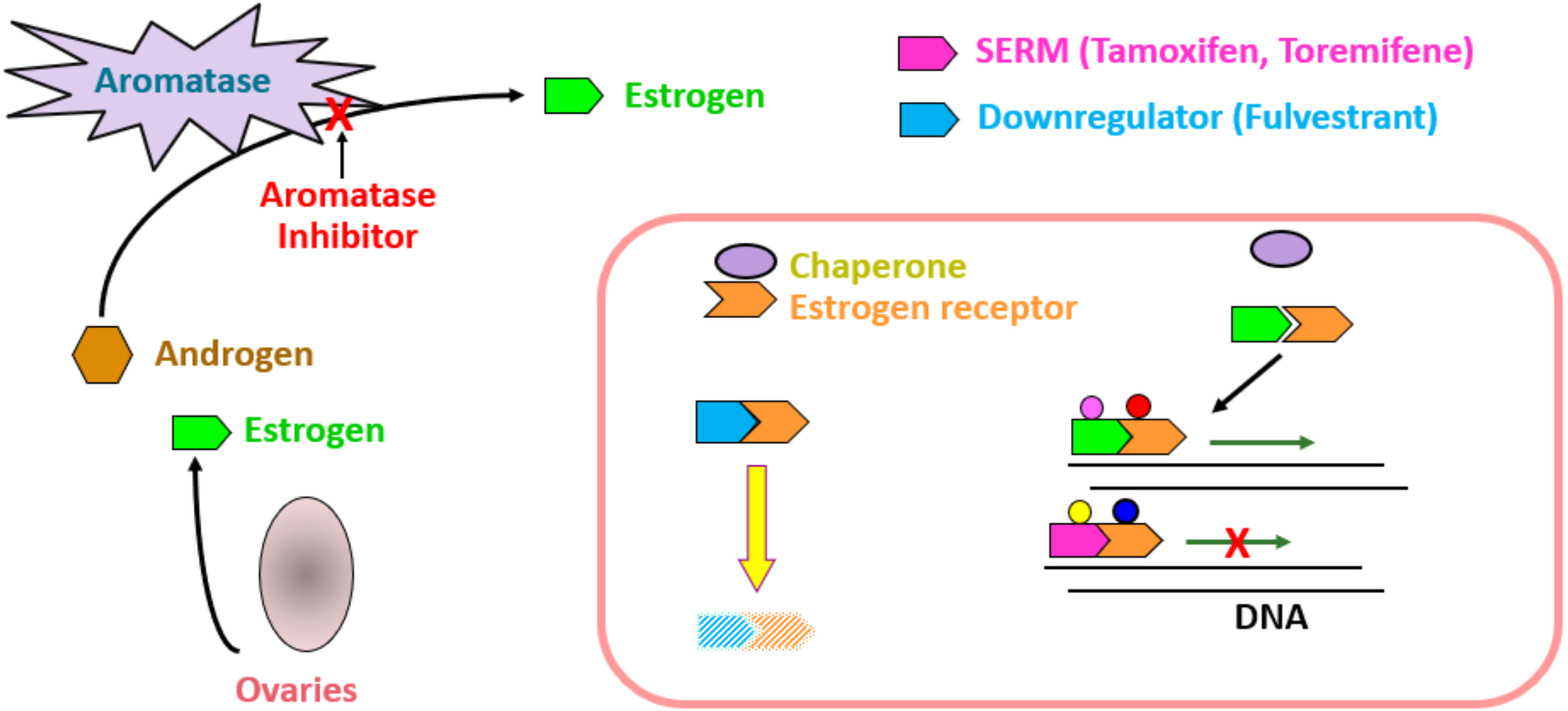
2 + 1 = 3

Strong

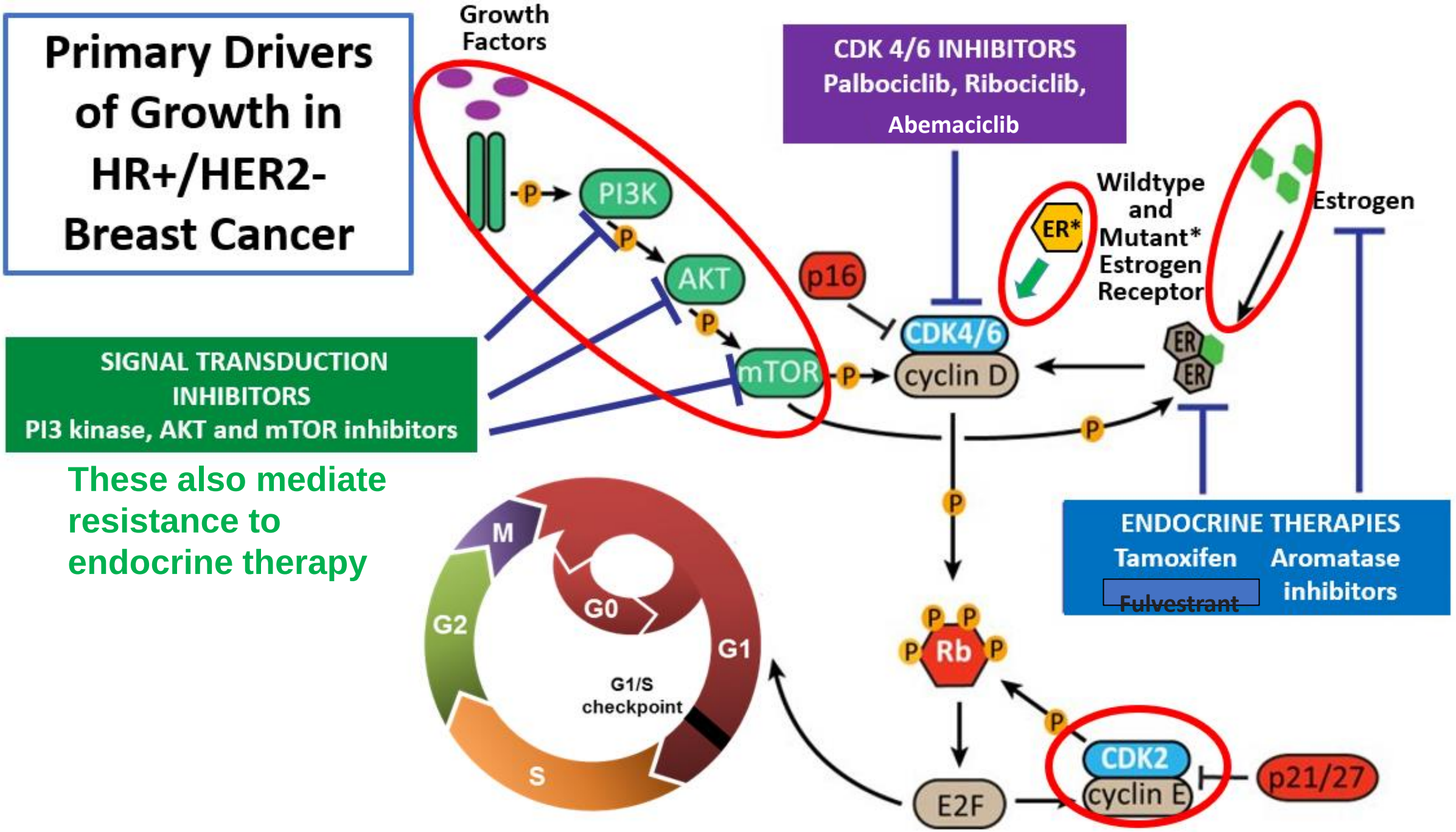


3 + 5 = 8

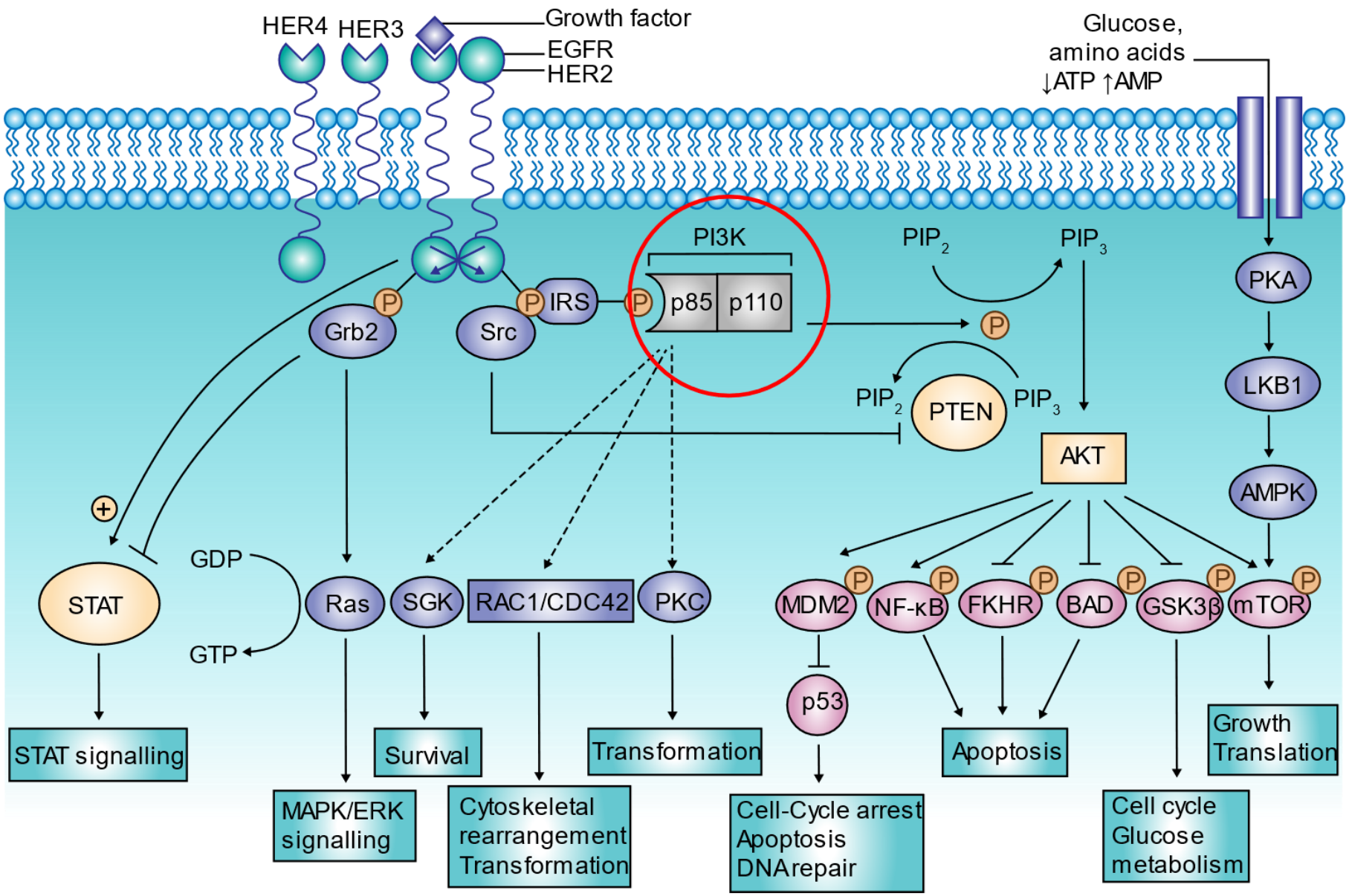
Estrogen, Estrogen Receptor and Different Endocrine Therapies Activities in HR+ Breast Cancer



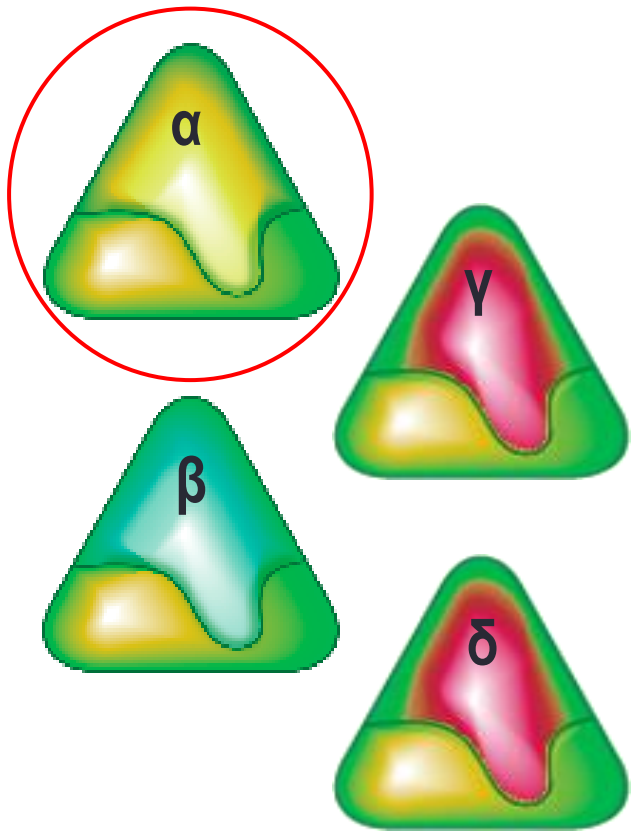
Primary Drivers of Growth in HR+/HER2- Breast Cancer



The Importance of the PI3K Pathway in HR+ Breast Cancer

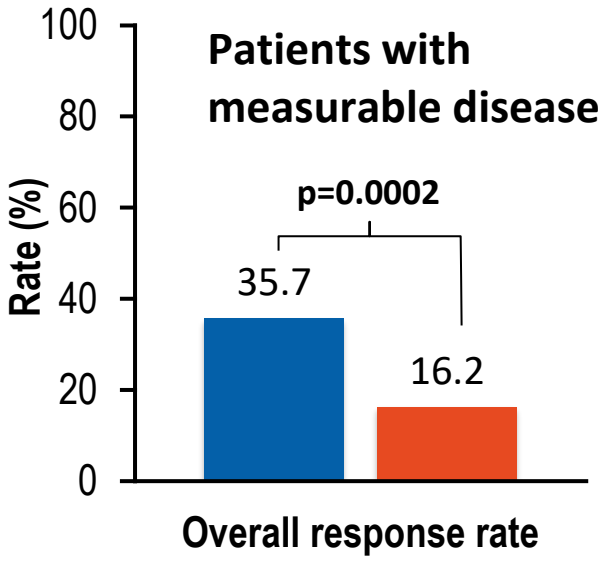


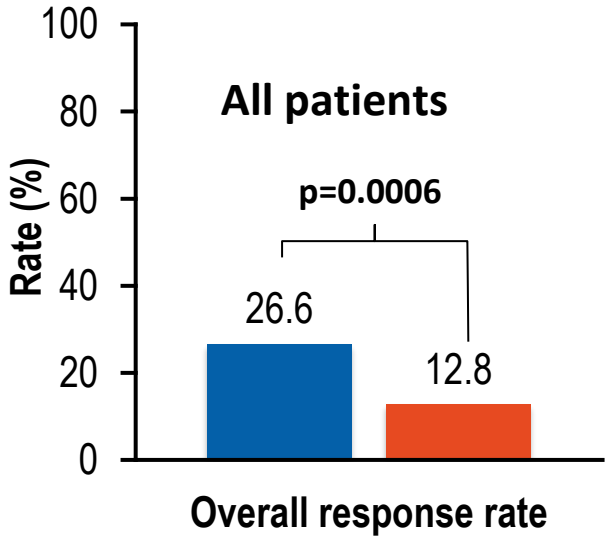
PI3K isoforms

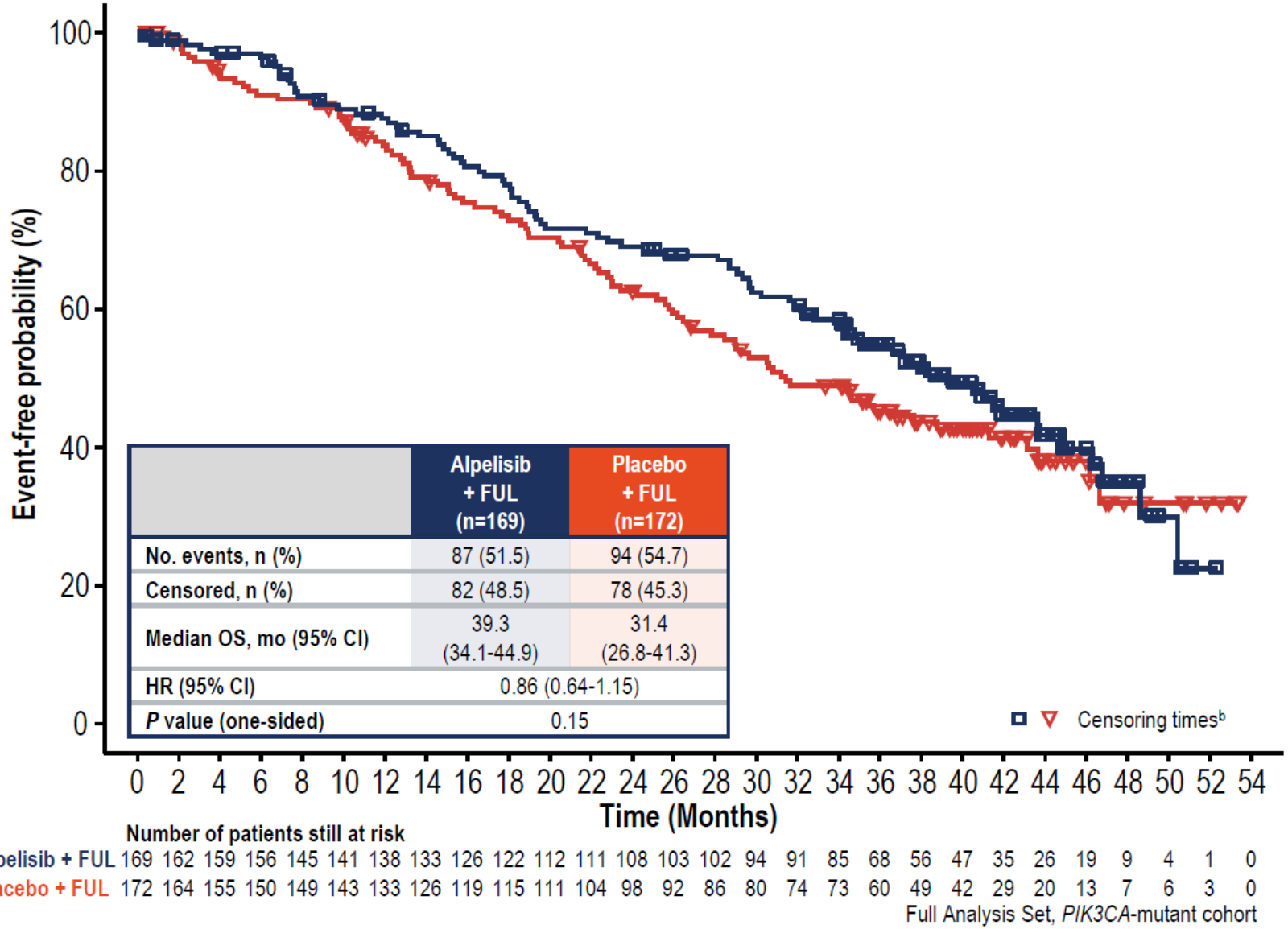


Bosch A, et al. Sci Transl Med 2015

Overall Response Rates and Survival in the *PIK3CA*-Mutant Cohort







Alpelisib + fulvestrant Placebo + fulvestrant

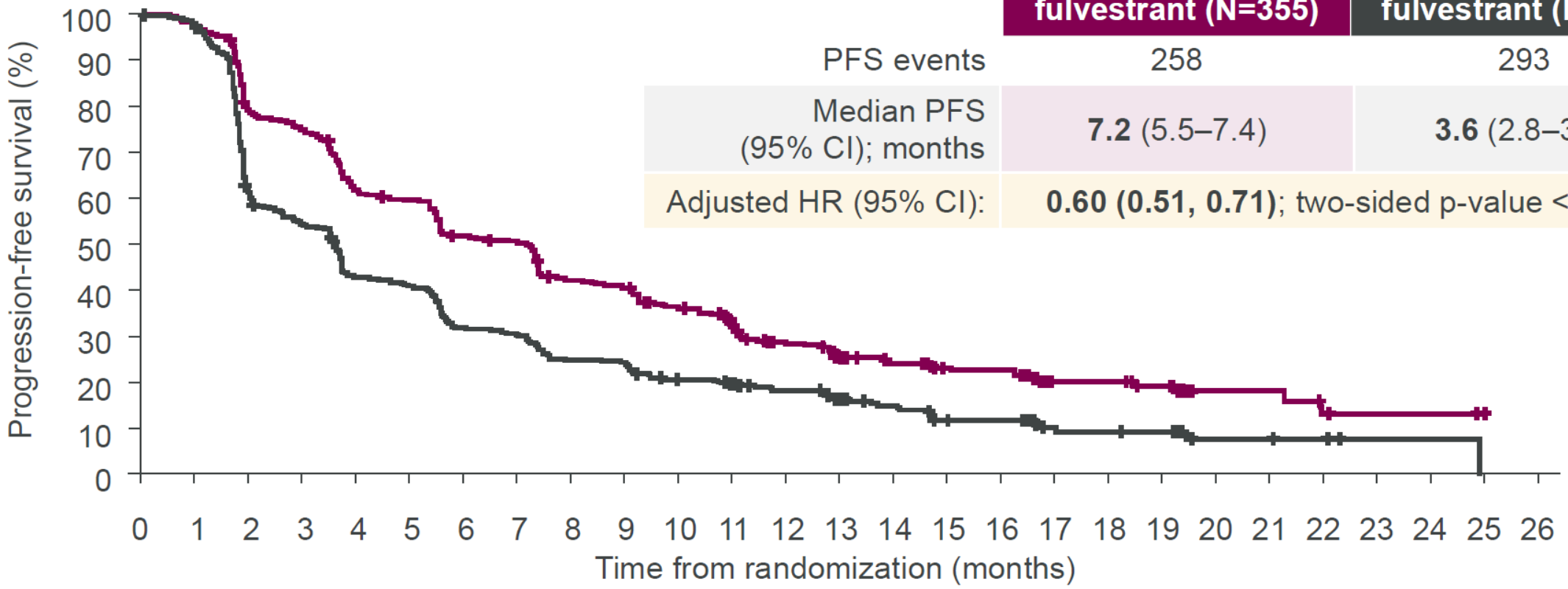
André F, et al. NEJM 2019; Andre F, et al. Ann Oncol 2021

CAPItello-291 Trial: Fulvestrant +/- Capivasertib (AKT Inhibitor)

- Men and pre/postmenopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

Dual primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



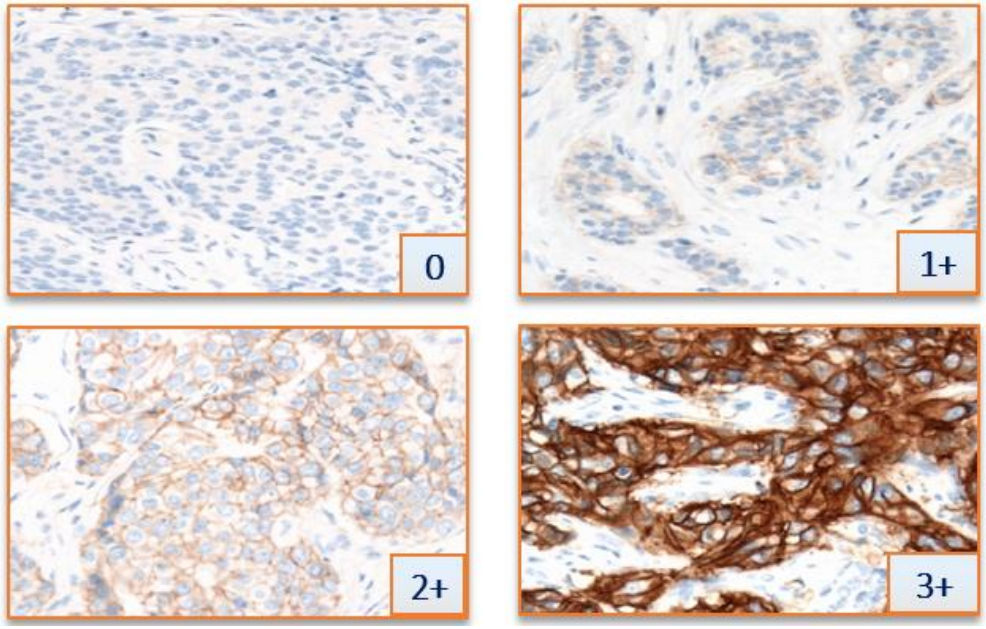
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

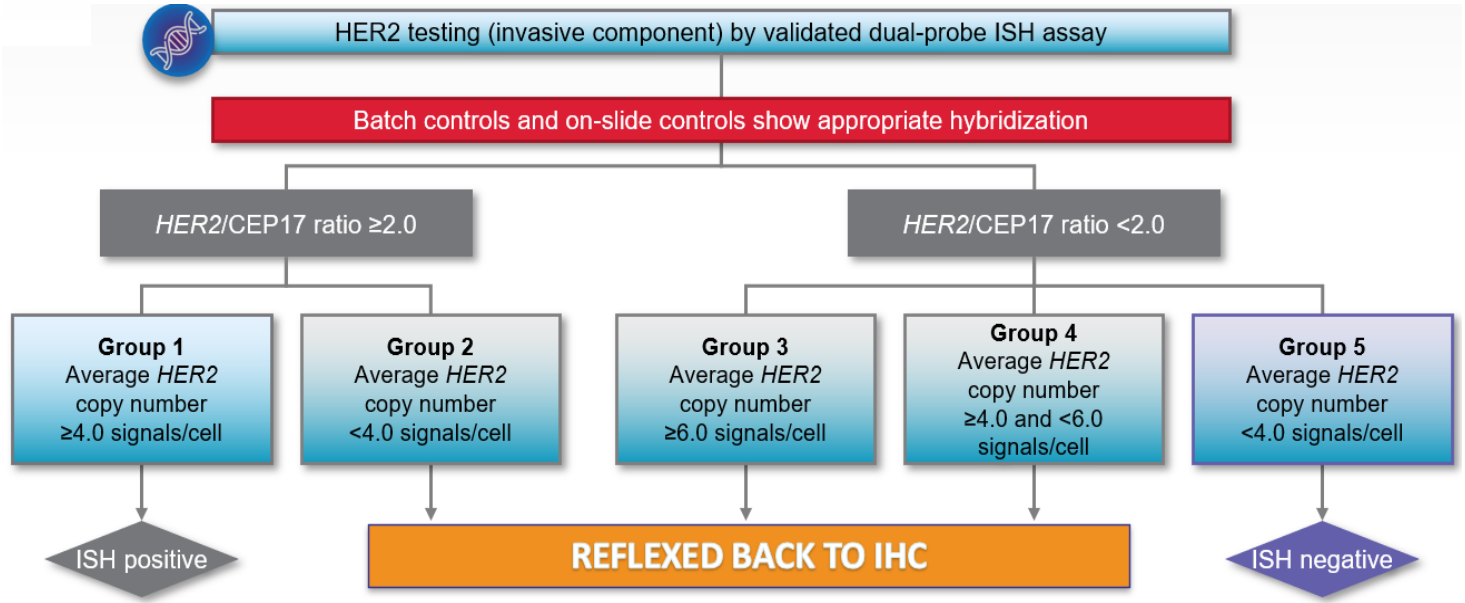
Turner N, et al. NEJM 2023

HER2 Testing: Technique and Interpretation are Critical

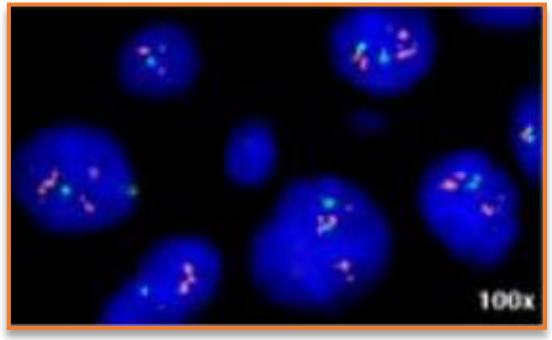
Immunohistochemistry



Interpretation of Dual Probe ISH based

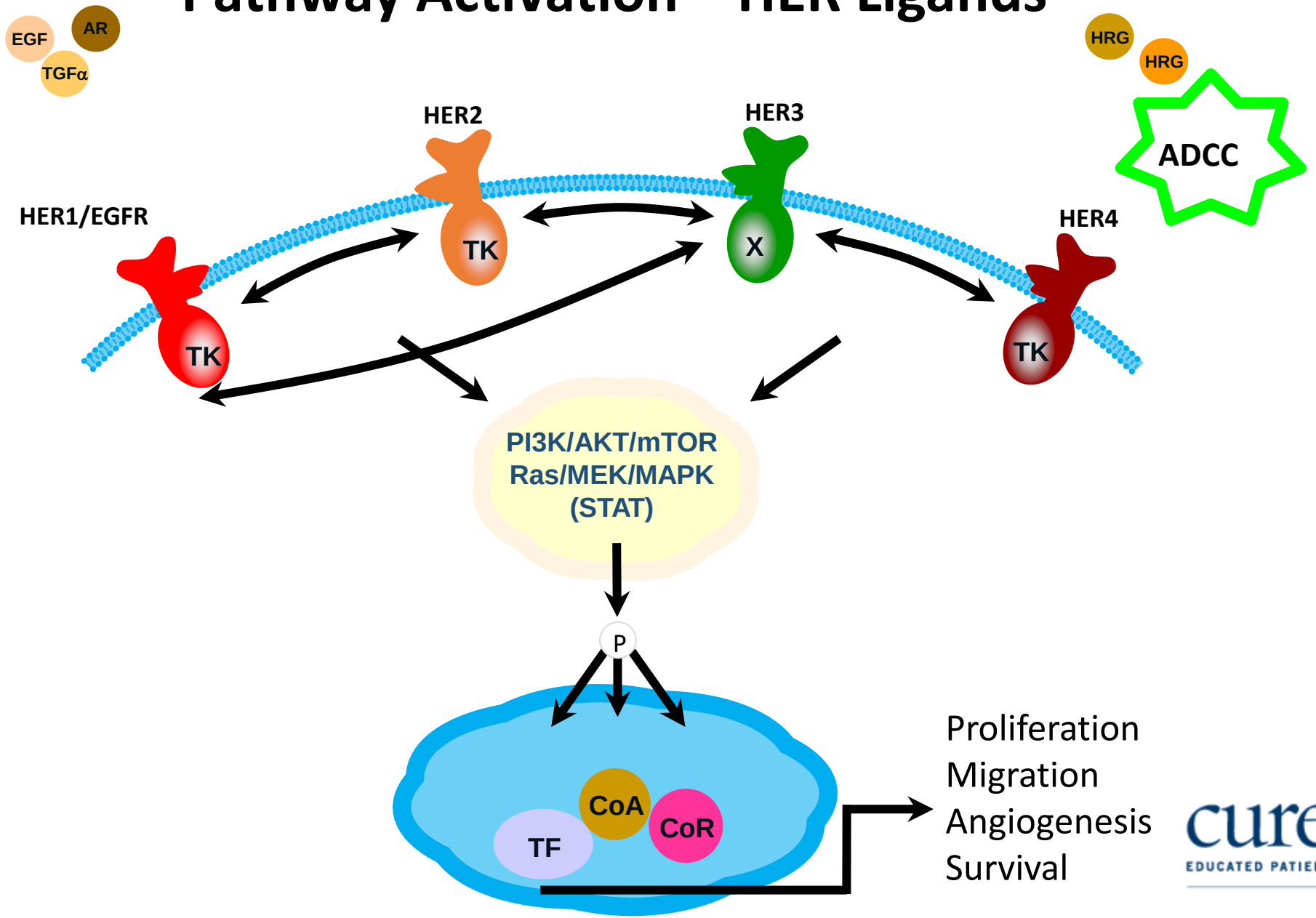


2+ cases are "reflexed" to ISH (in situ hybridization



*Note – Next-generation tumor DNA sequencing can also call HER2 amplification, but both antibody and ISH analysis should be done to confirm

Pathway Activation – HER Ligands



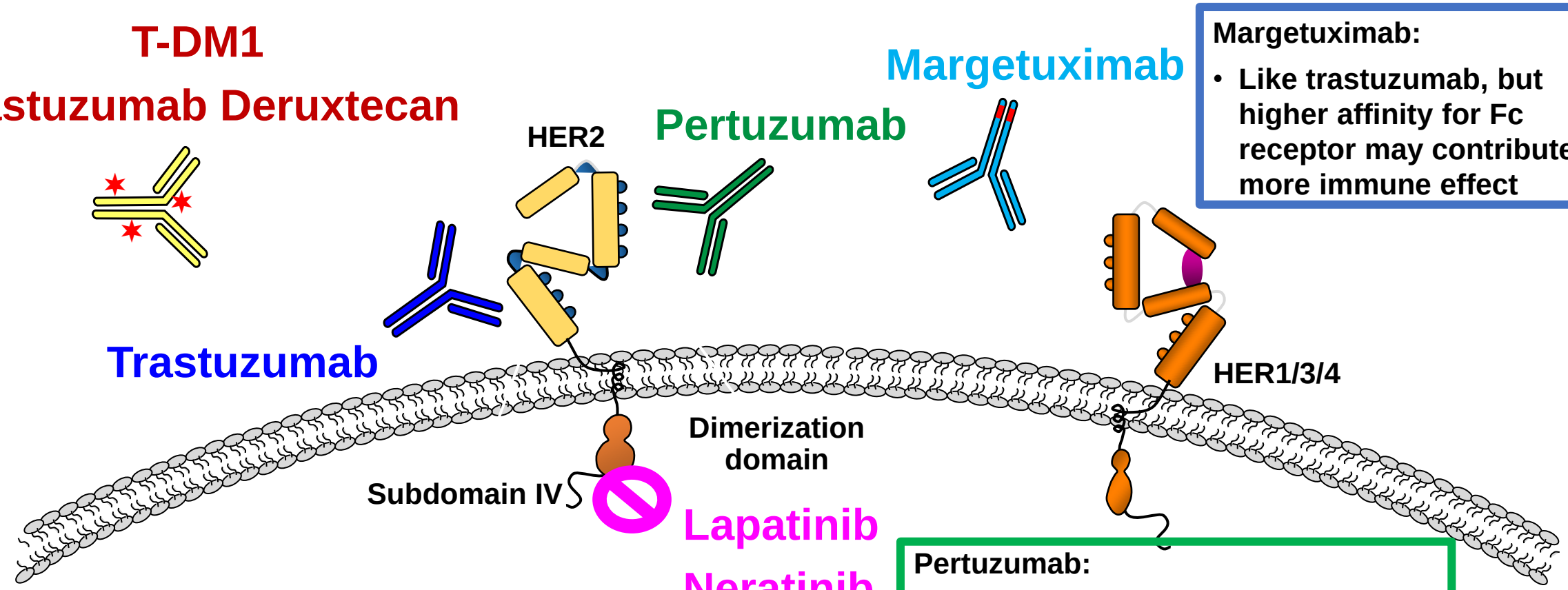
Trastuzumab

Humanized Anti-HER2 Monoclonal Antibody

- Targets HER2 protein
- Selectively binds with high affinity (K_d ≤0.5 nM)
- 95% human, 5% murine
- IgG1 isotype able to activate antibody-dependent cytotoxicity

Carter P et al. PNAS 1992

Trastuzumab, Pertuzumab, Lapatinib and T-DM1: Complementary Mechanisms



Margetuximab:

- Like trastuzumab, but higher affinity for Fc receptor may contribute more immune effect

Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

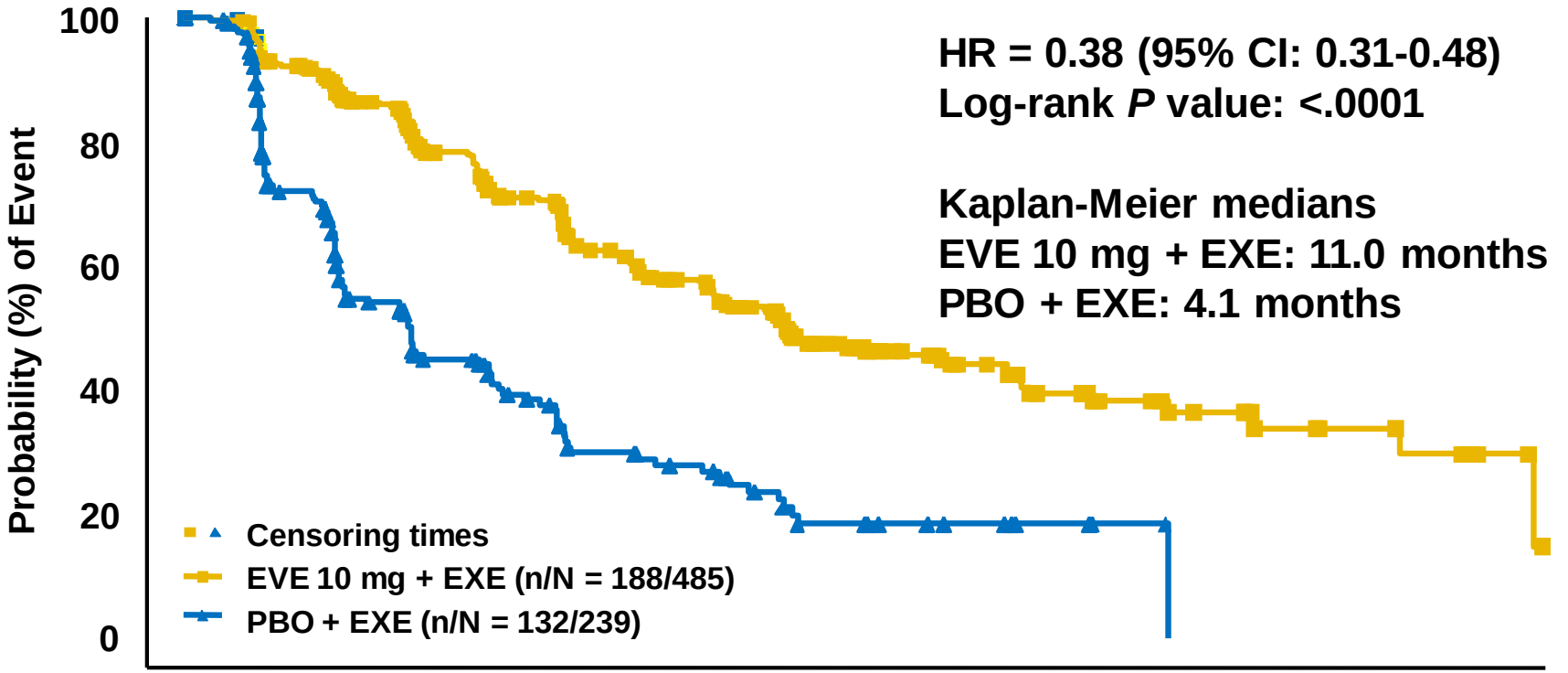
Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Lapatinib, Neratinib, Tucatinib:

- Inhibit intracellular kinase domain of HER2, HER1 (EGFR)

Exemestane +/- mTOR Inhibitor Everolimus: BOLERO-2 18 Month Followup



Number of patients still at risk

EVE 10 mg + EXE	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
PBO + EXE	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

Piccart M, et al ASCO 2012

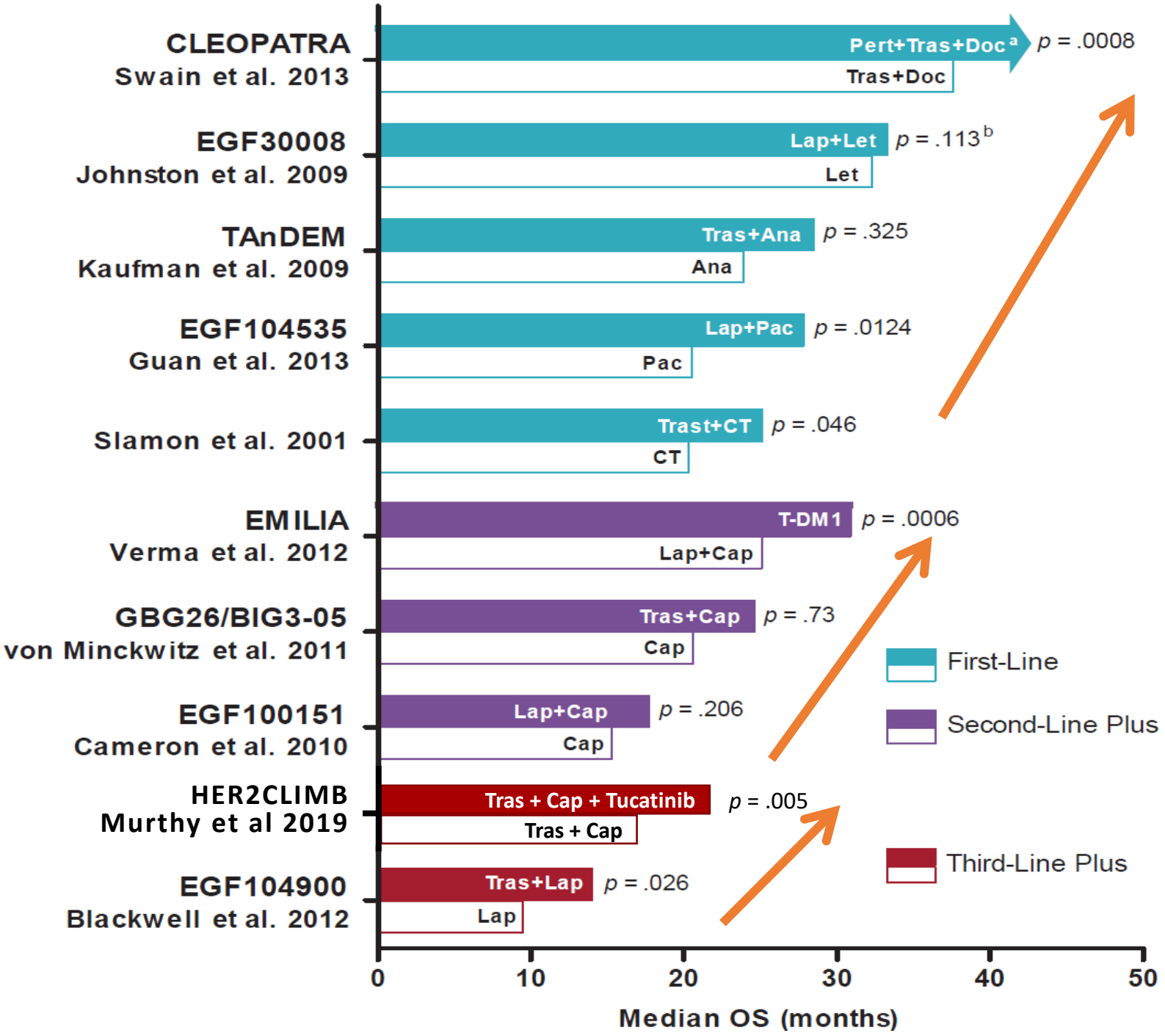
Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7*	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (close)
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

*PFS/OS data reported for approved AI subset. Abbreviations: CDK=Cyclin-dependent kinase; Rx=therapy; PFS=progression-free survival; HR=hazard ratio; OS=overall survival; AI=aromatase inhibitor; Fulv=fulvestrant; NR=not reported

References:

i. PALOMA-2: Finn R, et. al. New Engl J Med 2016; Rugo H, et al. Breast Cancer Res Treat, 2019; Finn R, et. al. ASCO 2022.
ii. MONALEESA-2: Hortobagyi G, et al. New Engl J Med 2016; Hortobagyi G, et al. Ann Oncol 2018; Hortobagyi G, et al. New Engl J Med 2022.
iii. MONALEESA-7: Tripathy D, et al. Ann Oncol 2018; Im S-A, et al New Engl J Med 2019. [Note PFS/OS data reported for approved AI subset].
iv. MONARCH-3: Goetz M, et al. J Clin Oncol 2017; Johnson S, et al. npj Breast Cancer 2019; Goetz M, et al. ESMO 2022.
v. PALOMA-3: Turner N, et al. New Engl J Med 2015; Cristofanilli M, et al. Lancet Oncol 2016; Turner N, et al New Engl J Med 2018.
vi. MONARCH-2: Sledge G, et al. J Clin Oncol. Sledge G, et al. JAMA Oncol 2019.
vii. MONALEESA-3: Slamon D, et al. J Clin Oncol 2018; Slamon D, et al New Engl J Med 2020.



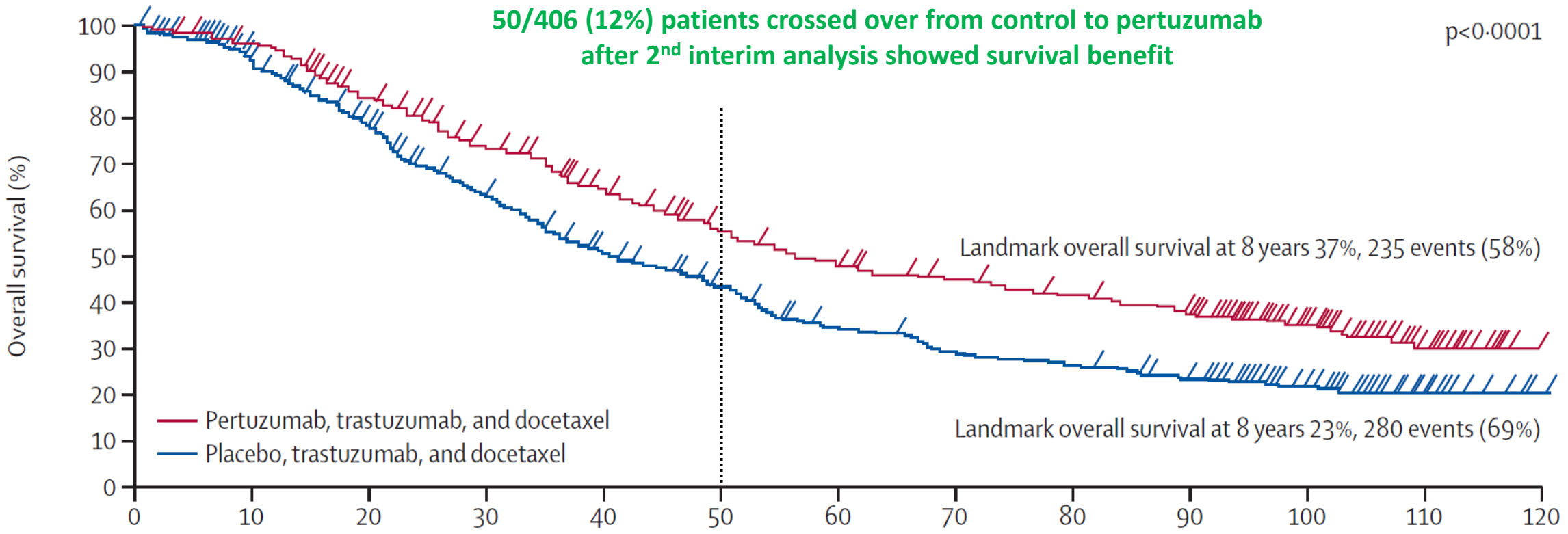
HER2+ Metastatic Breast Cancer:

Serial Improvements in Survival with Newer Agents and Combinations

BUT…. Rare "Cures"

Modified from:
Verma S, et al. Oncologist 2013

Updated Data from CLEOPATRA Trial: Docetaxel + Trastuzumab +/- Pertuzumab in First Line



Number at risk (number censored)													
Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

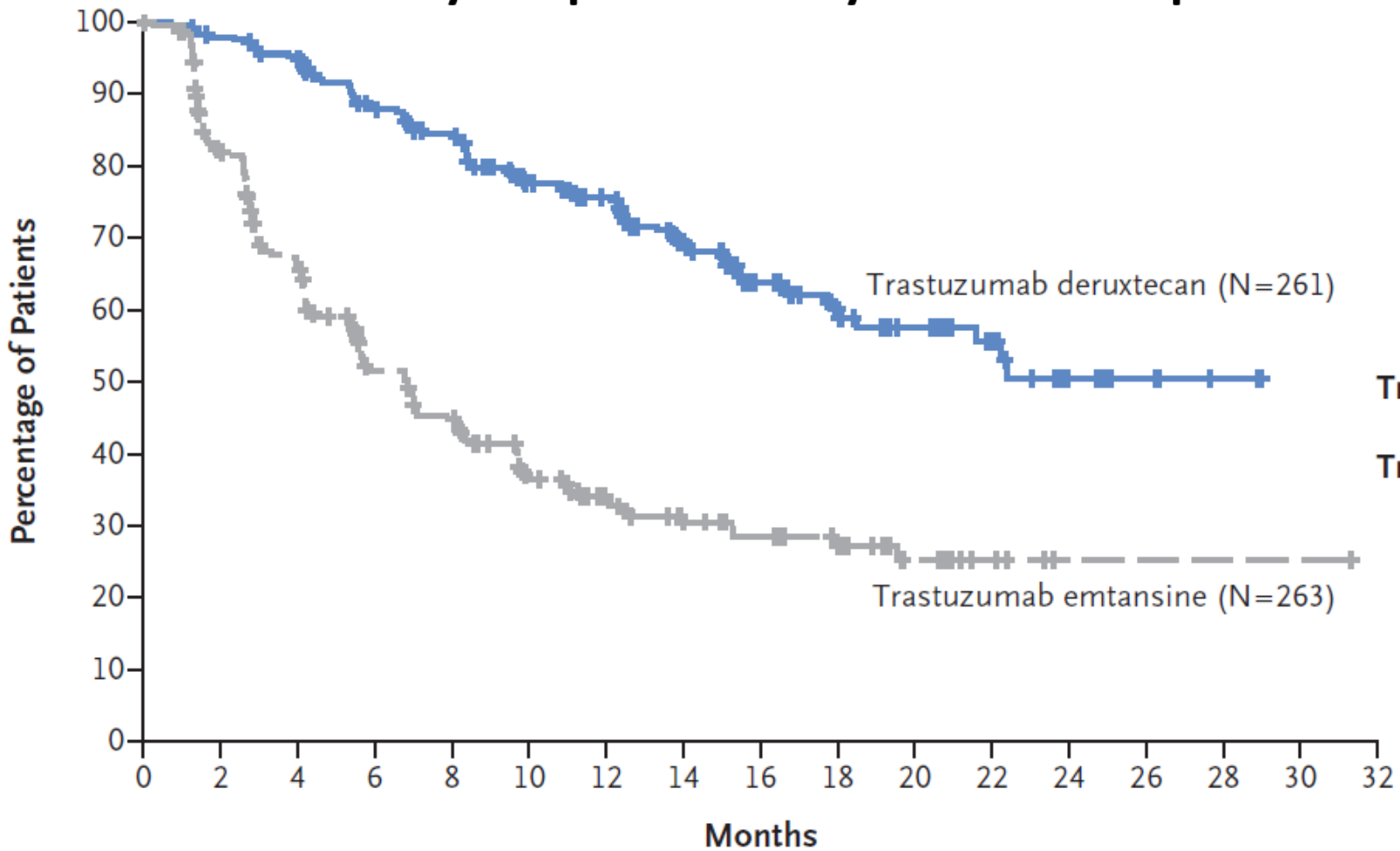
Median Progression-Free Survival: THP=18.8 mo; TH=12.4 mo (HR=0.69; 95% CI 0.59-0.81)

Median Overall Survival: THP=57.1 mo; TH=40.8 mo (HR=0.69; 95% CI 0.58-0.82)

Swain S, et al. Lancet Oncology 2020

Destiny-Breast03 Randomized trial T-DXd vs. T-DM1

Primary Endpoint: PFS by blinded independent central review



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

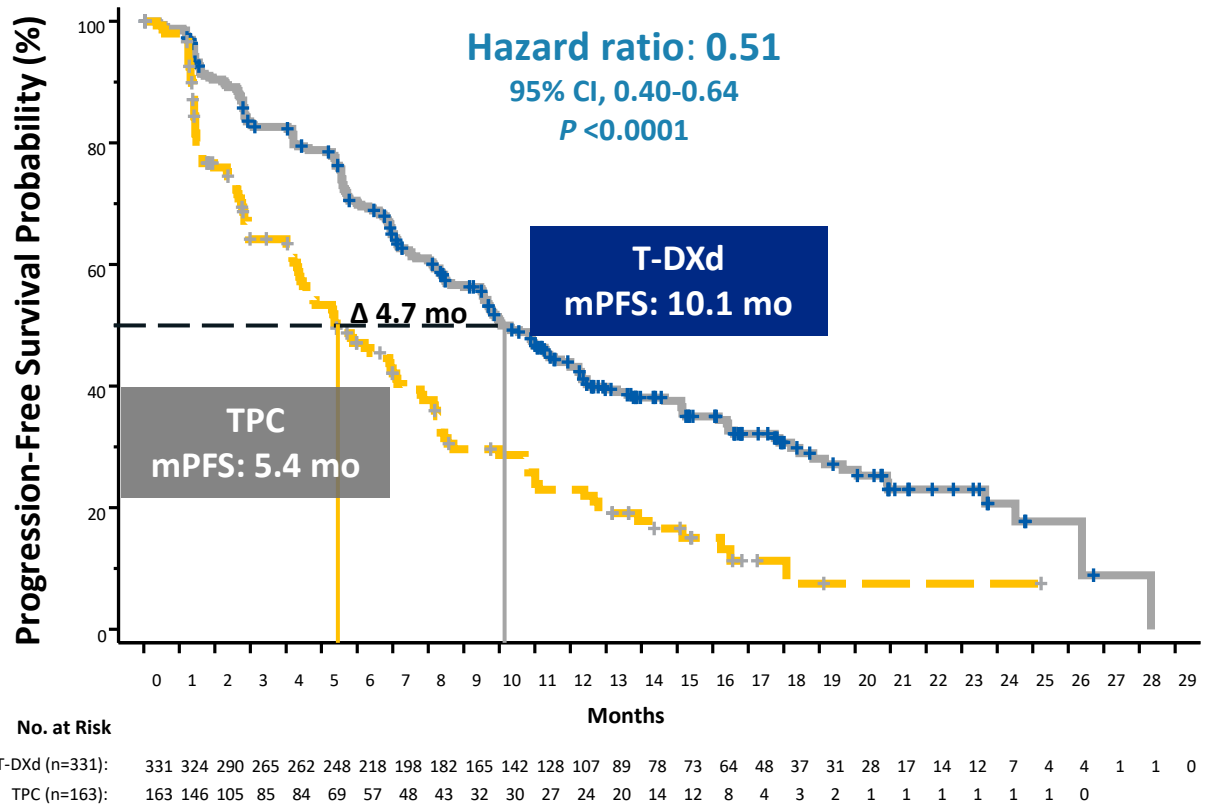
No. at Risk

Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	1	0

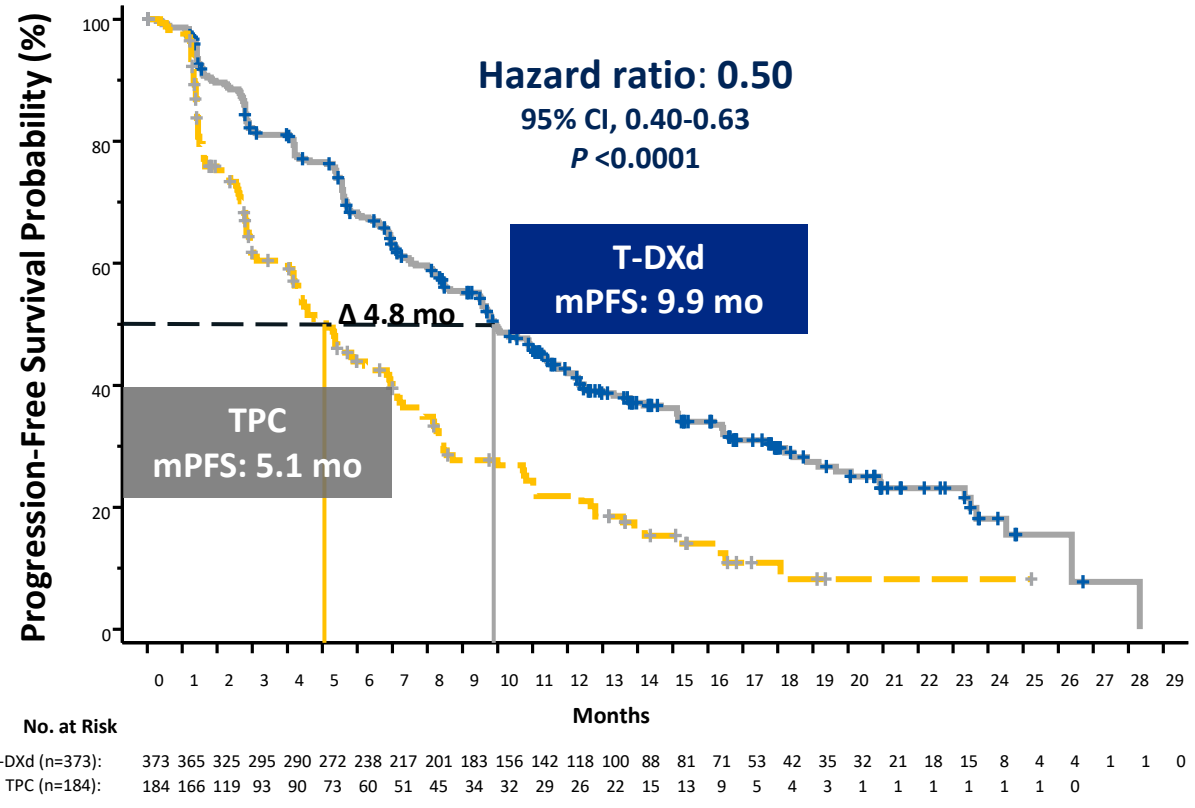
Cortés J, et al. NEJM 2022

Progression-Free Survival in HR+ and All Patients

Hormone receptor-positive



All patients



PFS by blinded independent central review.

HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S, et al. NEJM 2022

Mechanisms of DNA Repair

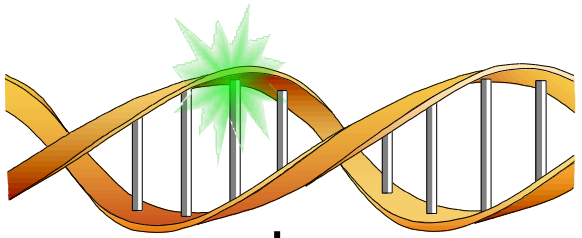
Environmental factors
(UV, radiation, chemicals)

Normal physiology
(DNA replication, ROS)

Chemotherapy
(alkylating agents, antimetabolites)

Radiotherapy

DNA DAMAGE



Cell Death

MAJOR DNA REPAIR PATHWAYS

Single Strand Breaks

- Nucleotide excision repair
- Base excision repair

  PARP1

Double Strand Breaks

- Non-homologous end-joining
- Homologous recombination

  BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

Replication Lesions

- Base exci[illegible] repa

  PARP1

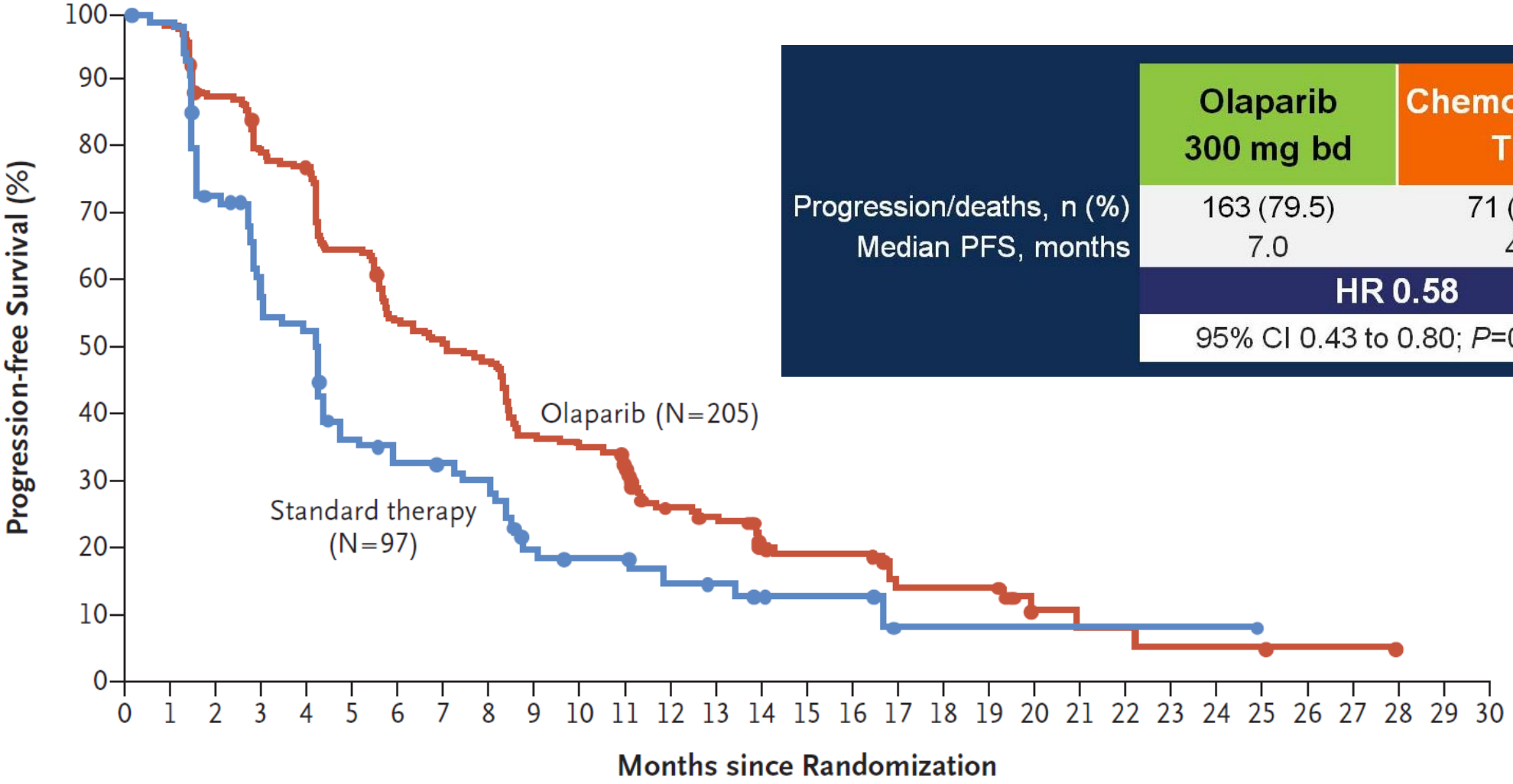
DNA Adducts/Base Damage

- Alkyltransferases
- Nucleotide excision repair
- Base excision repair

  PARP1

Helleday et al. Nature Reviews. 2008

OlympiAD: Olaparib vs. Chemotherapy of Physician's Choice*
Progression-Free Survival



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

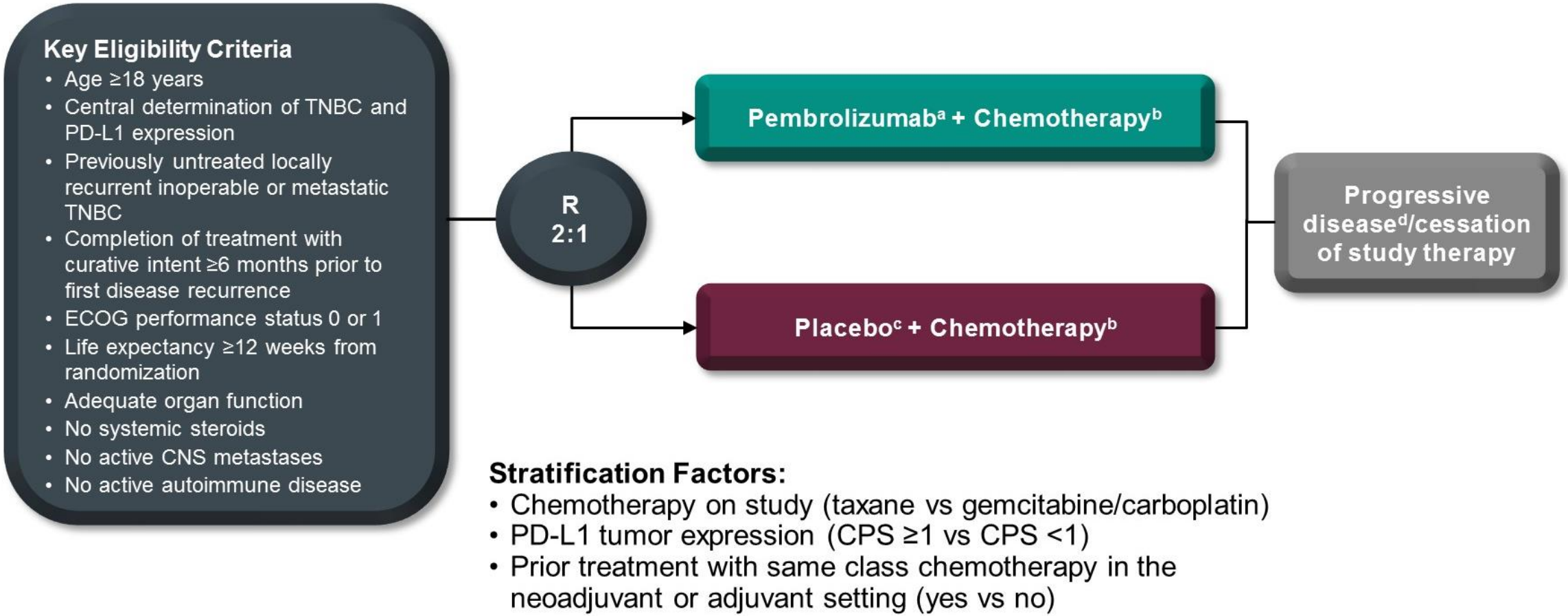
No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

*Capecitabine (45%); eribulin (37%); vinorelbine (18%)

Robson M, et al. NEJM 2017

KEYNOTE-355 Study Design (NCT02819518)

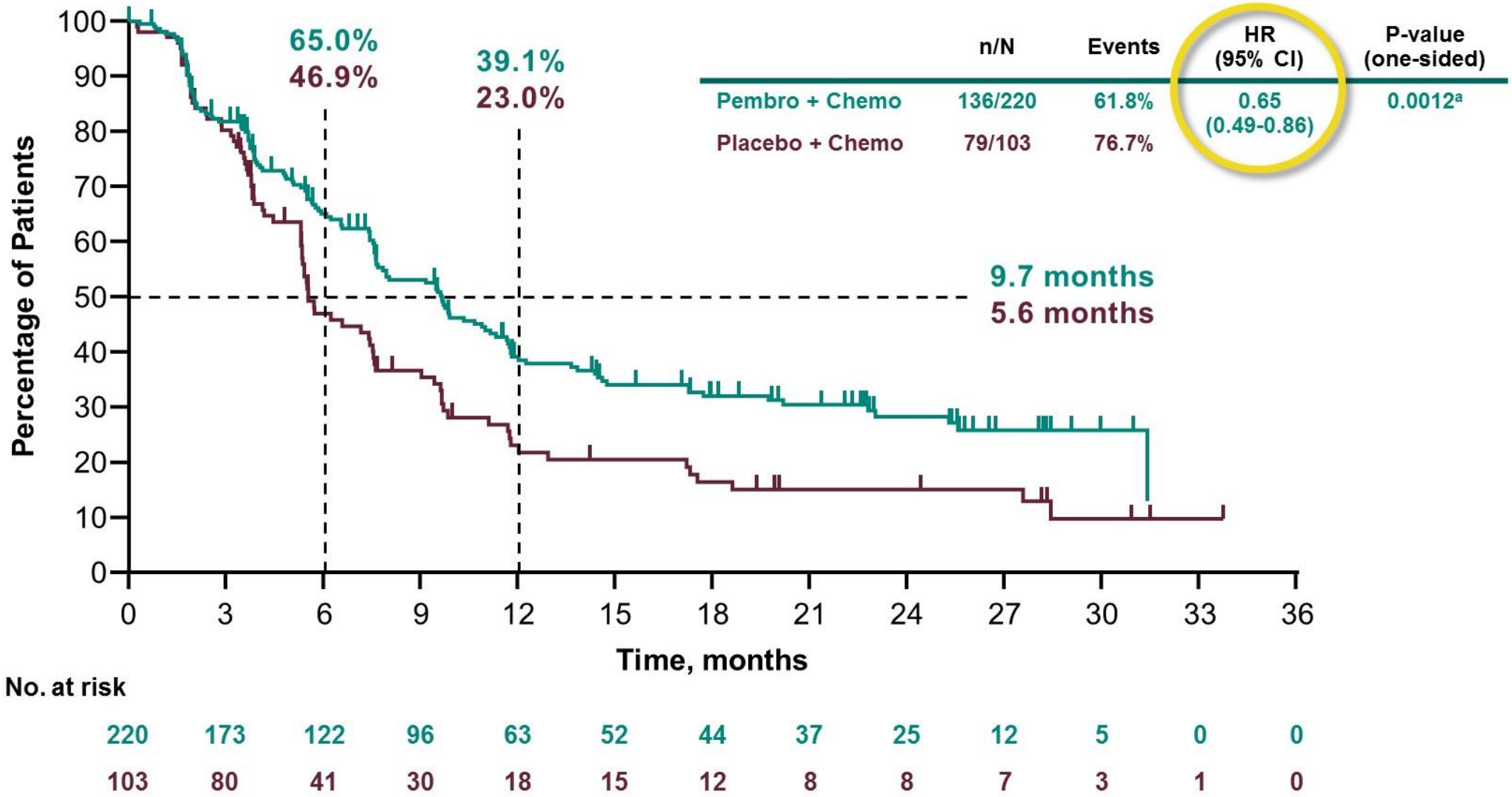


[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Cortes J, et al. ASCO 2020

Progression-Free Survival: PD-L1 CPS ≥10



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

[a]Prespecified *P* value boundary of 0.00411 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Cortes J, et al. Lancet 2020

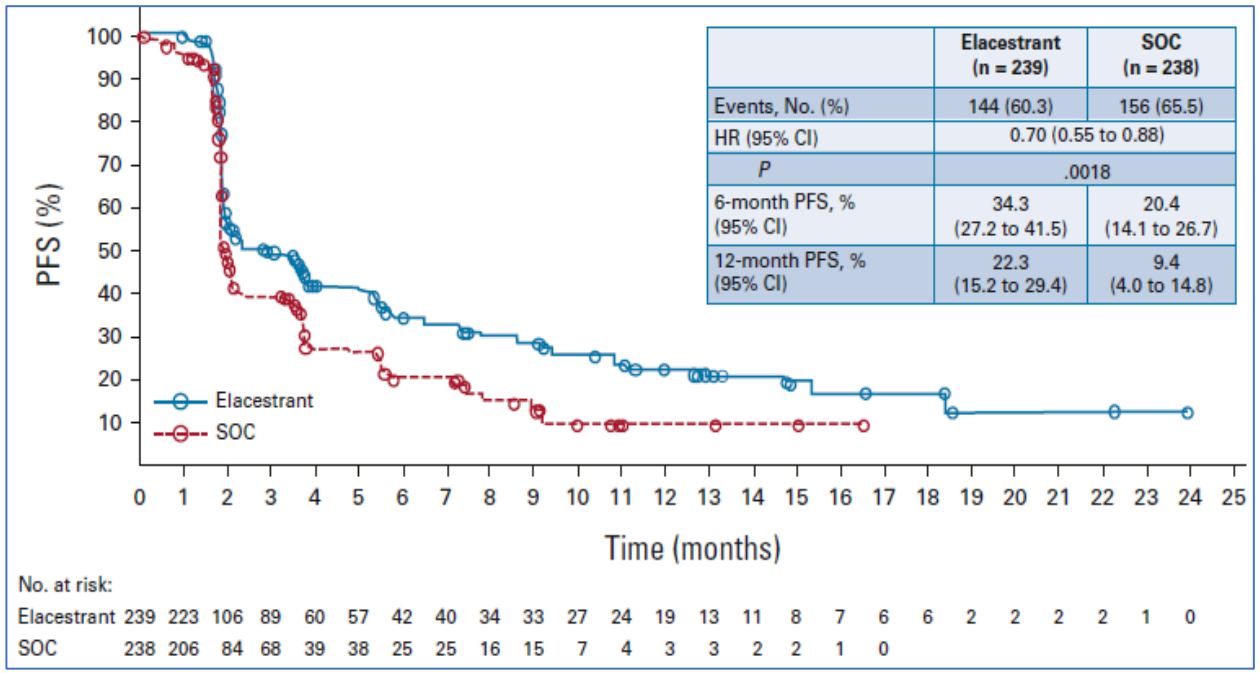
Genomic Aberrations in Breast Cancer that Guide Precision Medicine in Breast Cancer

Gene	Aberration	Frequency	Targeted Drug(s)
EVIDENCE BASED (from randomized or Phase II trials)			
HER2	Amplification	20%	Trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib, more
BRCA 1/2	Inactivation mutations (germline)	5%	Olaparib, talozoparib
PIK3CA	Activating mutations	30-40%	Alpelisib
BRAF	Activating mutation (V600E)	2-3% (TNBC)	Dabrafenib and trametinib
Several	Microsatellite instability	1-2%	Pembrolizumab
NTRK	Gene fusion	<1%	Larotrectinib
RET	Gene fusion/rearrangements/SNV	<1.5%	Selpercatinib
HER2	Activating mutations (non-amplified HER2)	2-10%	Neratinib (not FDA-approved)
EMERGING			
FGFR1-4	Amplification	10%	FGFR inhibitors
ESR1	Mutation (after AI exposure)	30-40%	Fulvestrant, other SERDs (elacestrant in randomized trial)
AKT	Activating mutations	2%	AKT, mTOR inhibitors (capivasertib, everolimus)
PTEN	Inactivating mutations/silencing	20%	PI3K (non alpha-selective), Akt, mTOR inhibitors
Myc	Amplification	16%	BET inhibitors
c-MET	Amplification/mutation	15%	Met inhibitors (cabozantinib)
CDH1	Inactivating mutations/silencing	7%	Wnt inhibitors, ALK/ROS inhibitors

Abbreviations IHC=immunohistochemistry; AI = aromatase inhibitor; SERD=selective estrogen receptor downregulator

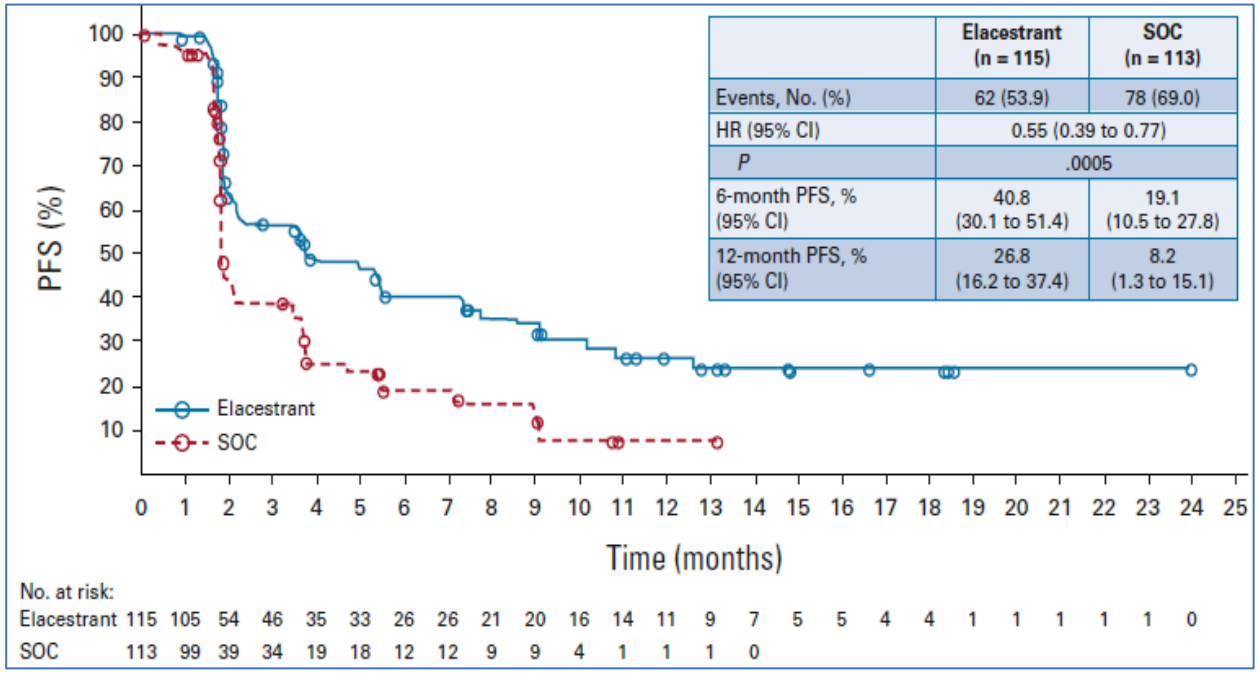
EMERALD Trial
PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

All Patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

Patients With Tumors Harboring *mESR1*



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Elacestrant demonstrated a significant improvement versus Fulvestrant as SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

Approved on 1/27/2023 for HR+/HER2, 2nd/3rd line, ESR1-mutated cancer

Bardia A, et al. J Clin Oncol 2022


THANK YOU