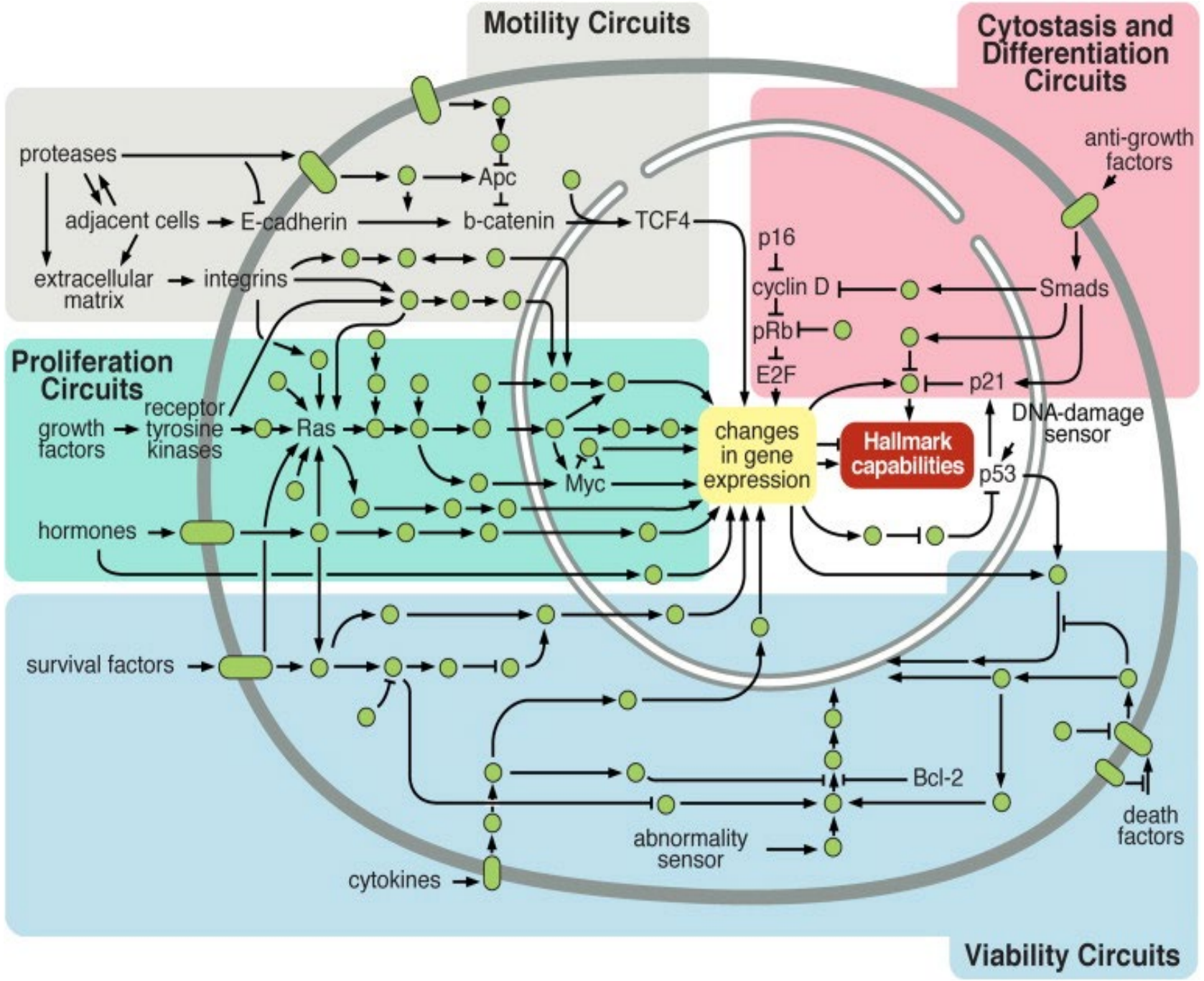
HER2 INHIBITORS

Lihua

Outlines

- History of Her2 **overexpression**
- Role in Cancer treatment （ Type of cancer, Driven gene, role of treatment ）
- Drug mechanism
- Indication
  - Clinical measurement
  - Followed up : Lab data
  - Drug studies and comparison (ORR, OS)
  - ADR
- Side effect management
- Education
- Conclusion



正常細胞內運行如同精細的集成電路，並經過重新編程以調節癌細胞內的標誌性功能。單獨的子電路（此處在不同顏色的區域中進行了描述）專用於協調各種功能。一方面，這種描述是簡單的，因為在這些子電路之間存在相當大的串擾(crosstalk)。此外，由於每個癌細胞都暴露於來自其微環境的信號的複雜混合物，因此這些子電路中的每一個都與來自腫瘤微環境中其他細胞的信號相連。

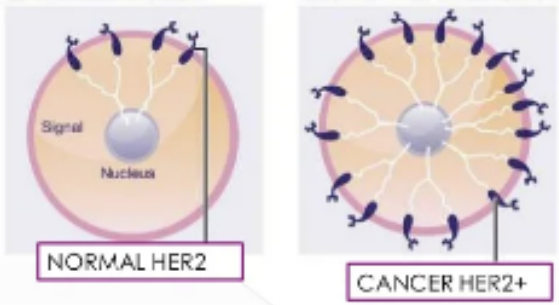
Cell 2011 Mar 4;144(5):646-74

HER2 gene

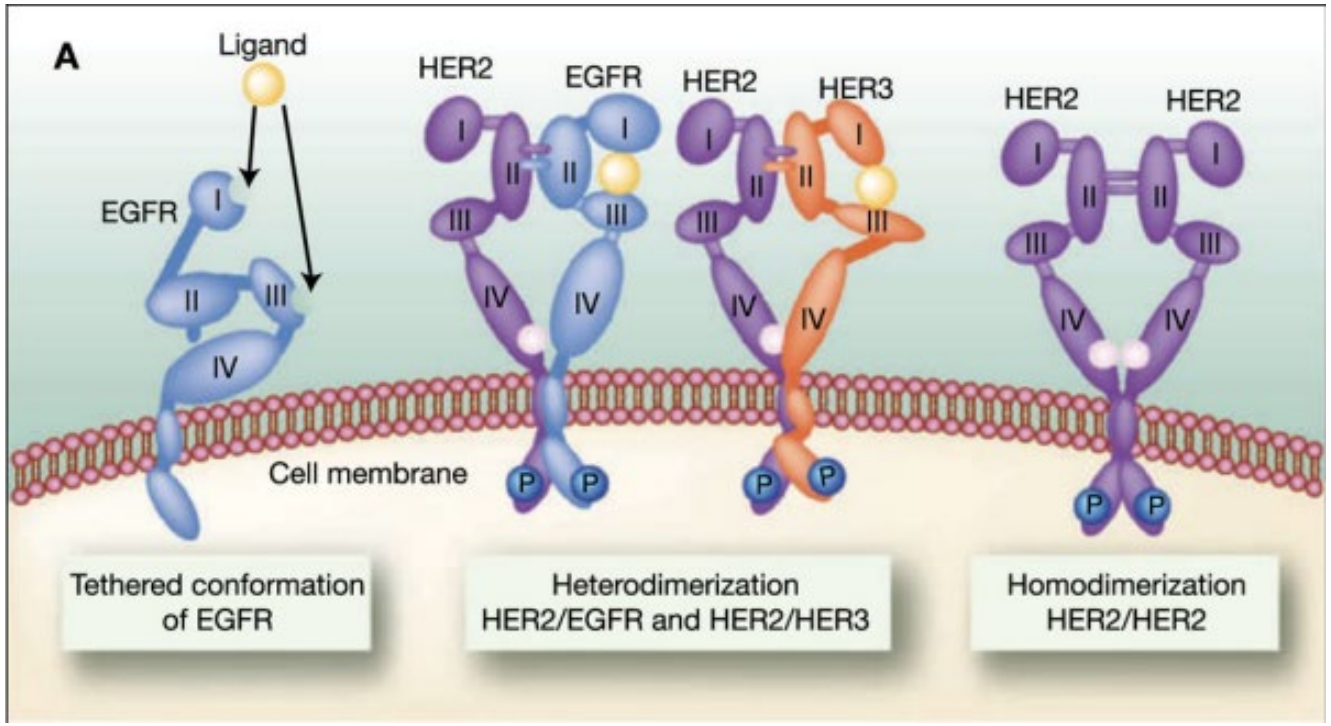
Normal vs. Cancerous HER2+

Yes, normal cells have HER2

The difference:

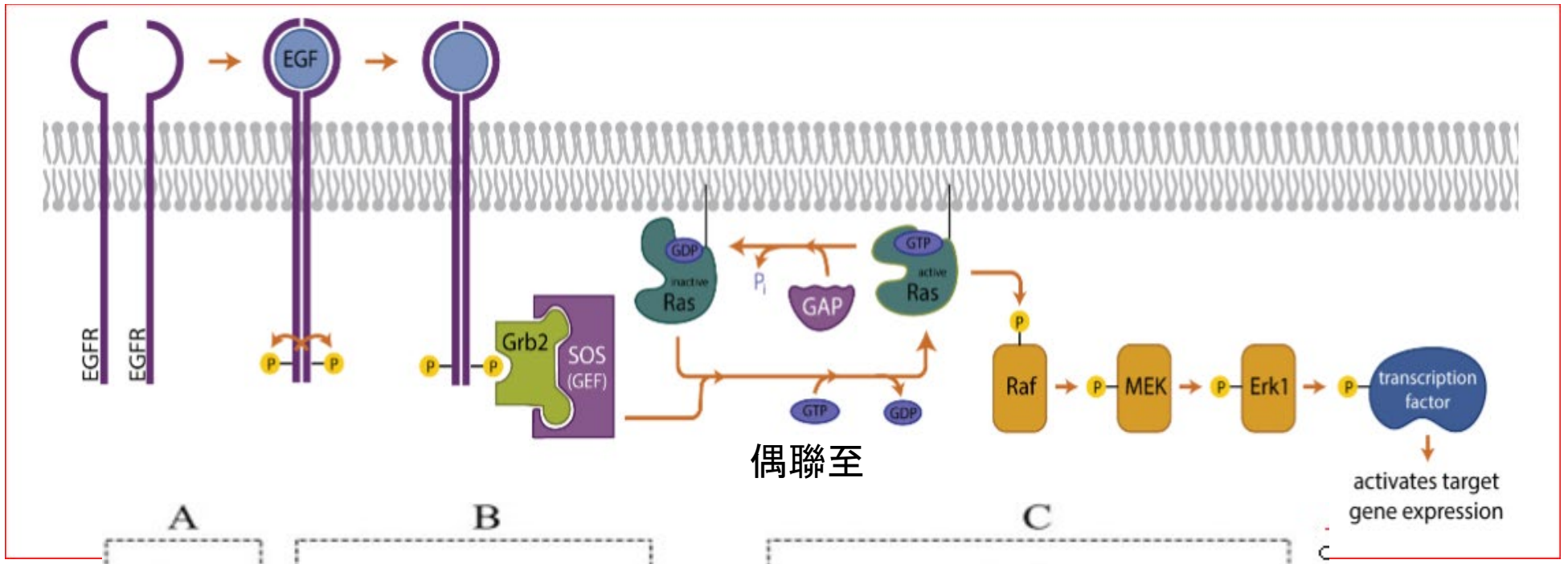


1.) receptor overexpression
2.) dysregulation of receptor activation

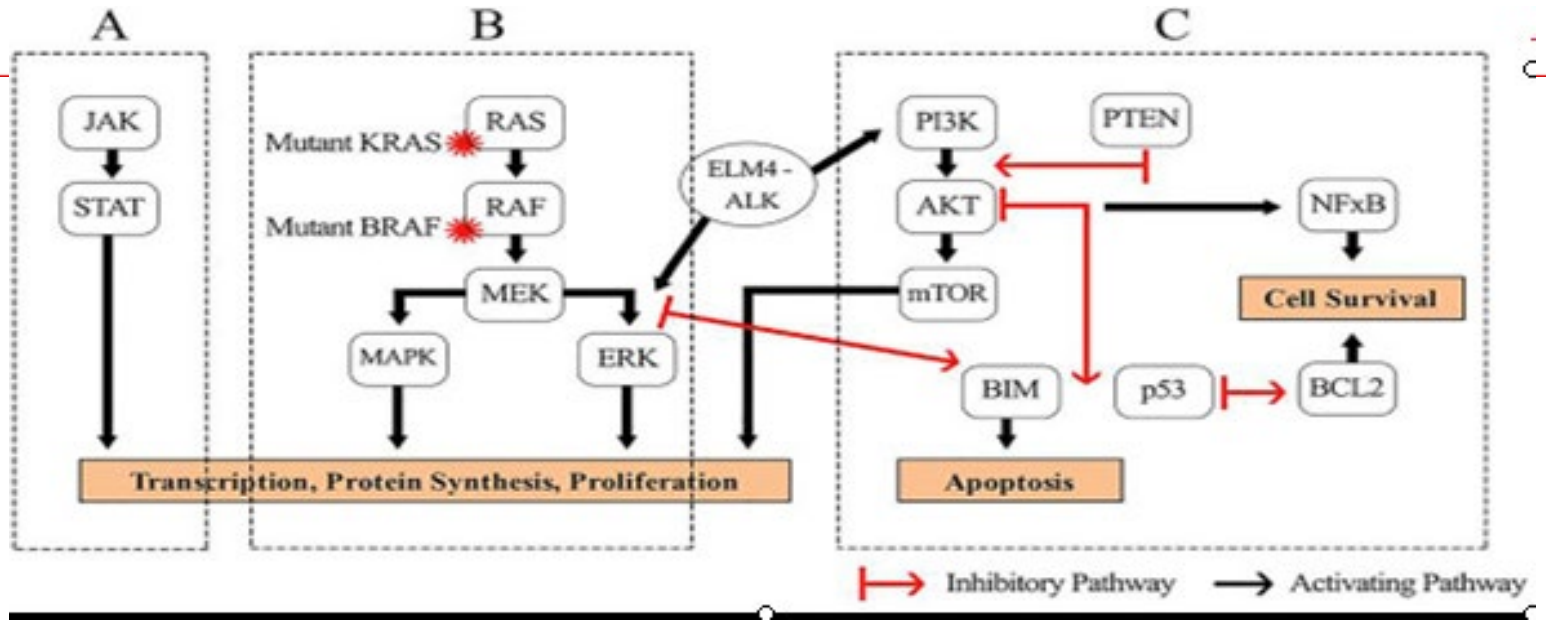


Clin Cancer Res (2009) 15 (24): 7479–7491

Regulation of cell growth (target)

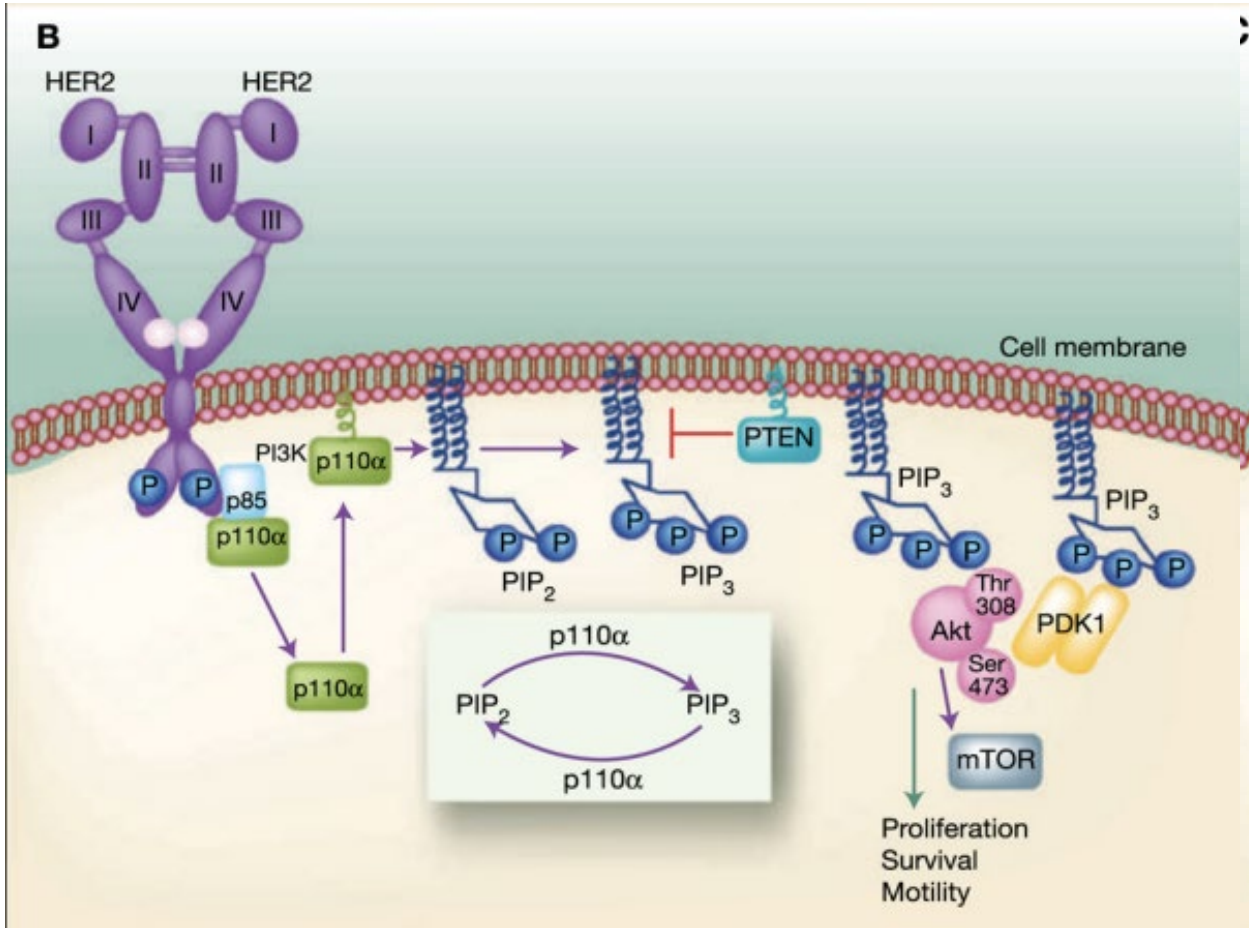


偶聯至

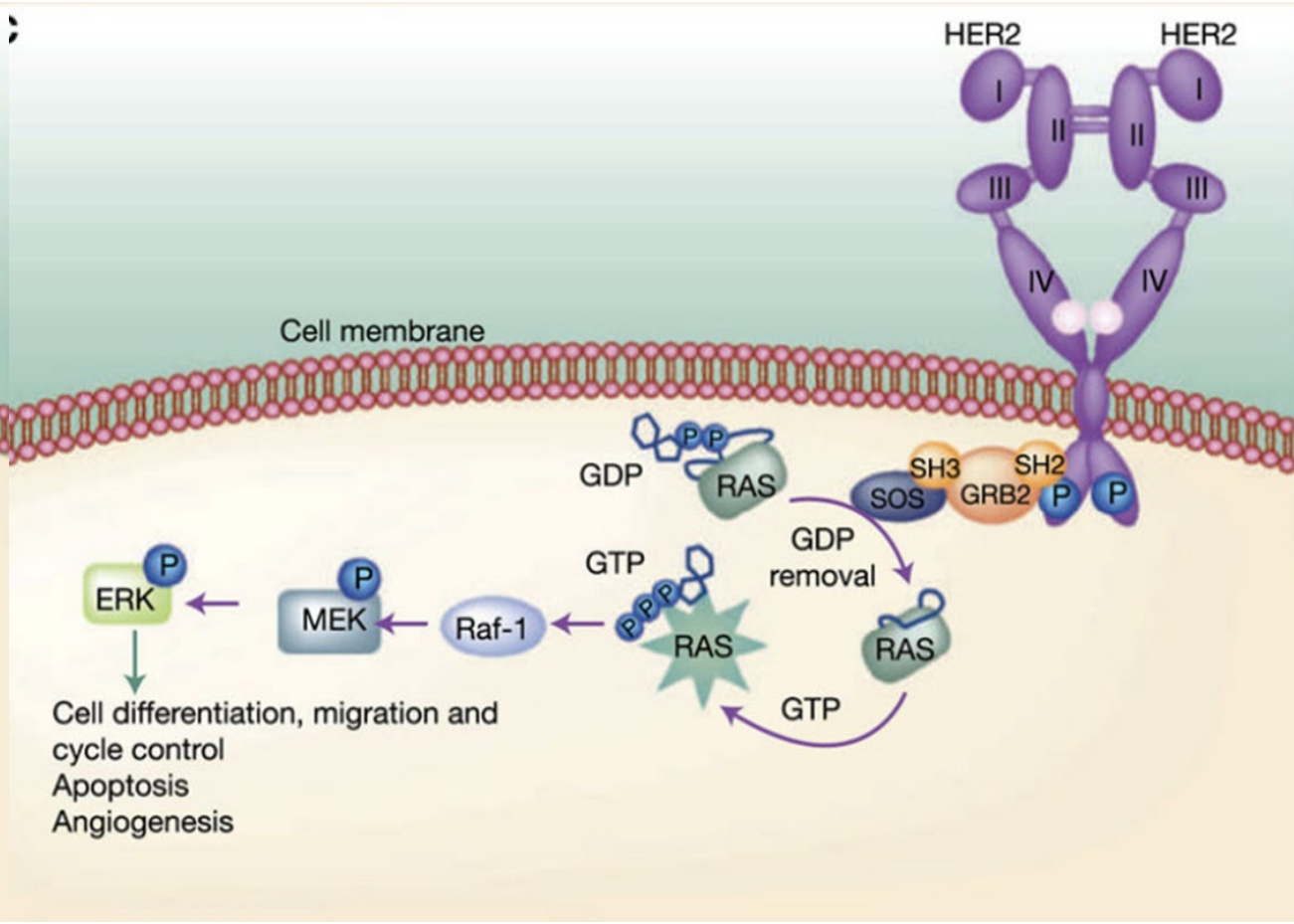


SOS：“Son of Sevenless”

PTEN（Phosphatase and Tensin Homolog Deleted on Chromosome Ten）。



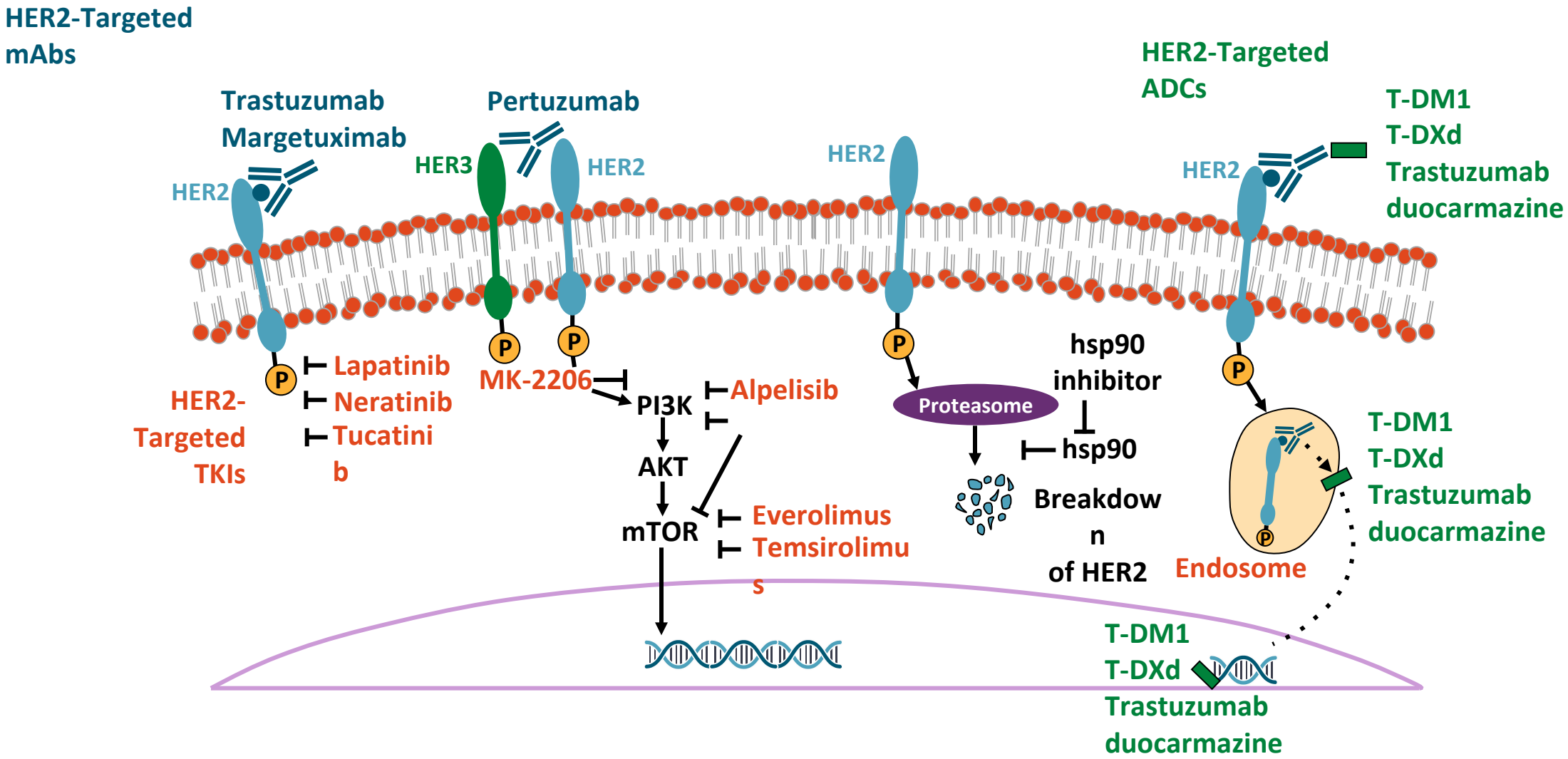
activation of PI3K/Akt pathway



RAS/Raf/ MAPK signaling cascade

Clin Cancer Res (2009) 15 (24): 7479–7491

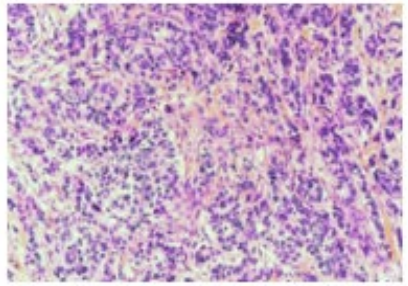
Targeted Therapies for HER2+ Breast Cancer



Gajria. Expert Rev Anticancer Ther. 2011;11:263. Pernas. Ther Adv Med Oncol. 2019:11:1758835919833519.

Slide credit: clinicaloptions.com

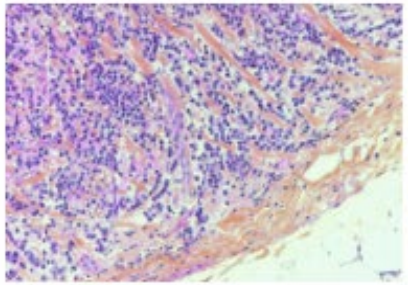
Generally ER+, HER2–, luminal-like



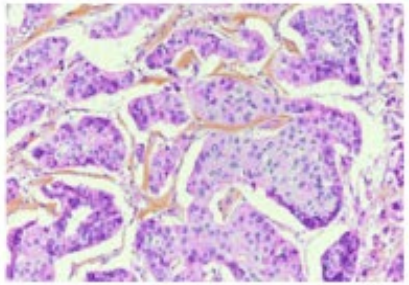
Lobular pleiomorphic (<2%)

ERBB2 amplification (25%)

CDH1 mutations (85%); *PIK3CA*, *AKT1* or *PTEN* alterations (50%); *ERBB2* and *ERBB3* mutations (8.5%)



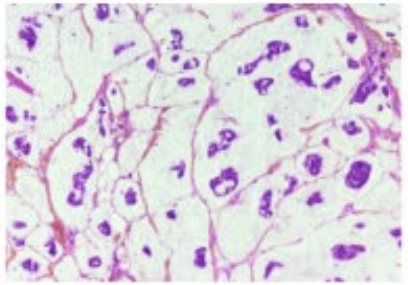
Lobular classical (12%)



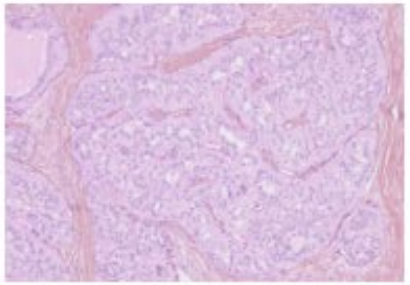
Micropapillary (3–6%)

PIK3CA and *MAP3K1* mutations (45%); *GATA3* mutations (27%)

Lymphophyllic



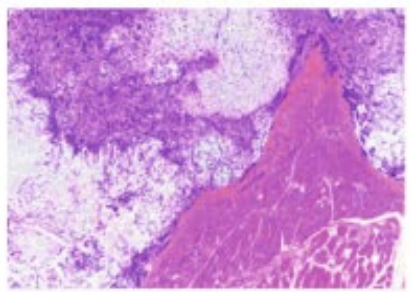
Mucinous (~2%)



Tall cell carcinoma with reverse polarity (<0.1%)

Triple-negative (60%; weak and focal ER expression in 40%); *IDH2* mutations (84%); *PIK3CA* mutations (67%)

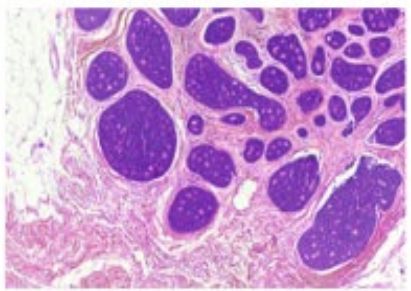
Generally ER–, HER2–, basal-like



Metaplastic (0.2–5%)

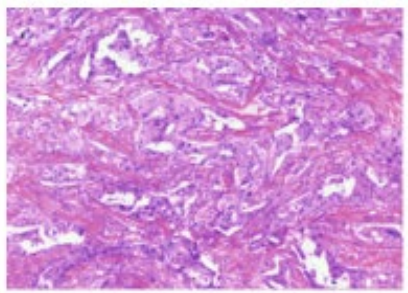
TP53 mutations (70%); *PIK3CA* mutations (>50%); WNT pathway activation

Claudin-low



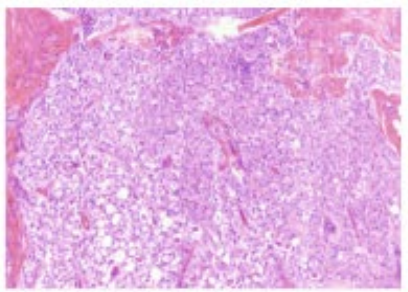
Adenoid cystic (<1%)

Lack of *TP53* and *PIK3CA* mutations; alterations of *MYB* or *MYBL*, including *MYB–NFIB* fusion (60%)



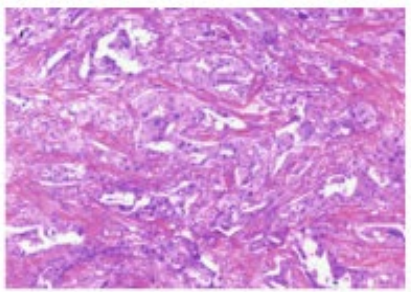
Adenocarcinoma with lymphoid-rich stroma (<1%)

TP53 mutations (87%); *BRCA* inactivated (>50%)



Secretory (~1%)

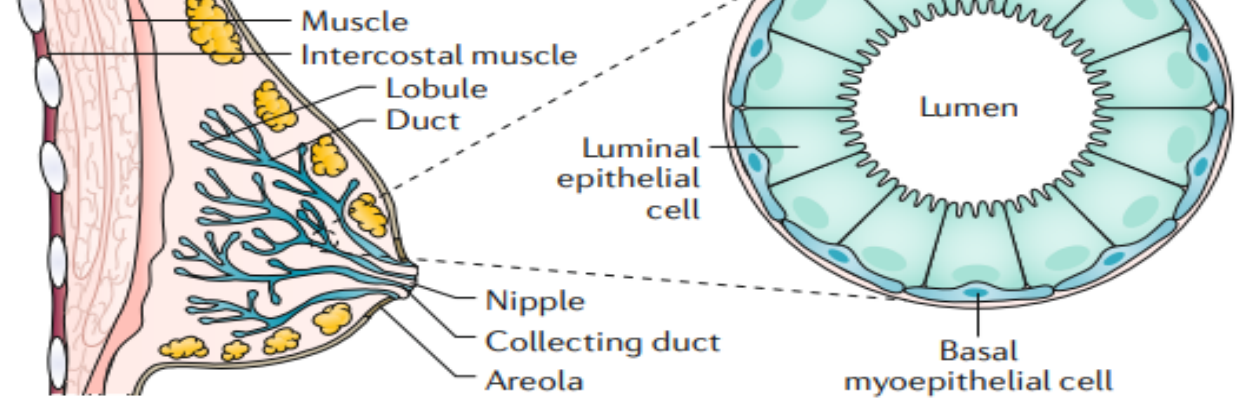
NTRK3–ETV6 fusion



Apocrine (~1%)

PI3KCA or *PTEN* mutations (>60%); *ERBB2* amplification (30%); androgen receptor activation (90%); molecular apocrine

☐ Histotype (frequency) ☐ Molecular features (occurrence) ☐ Other features



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

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

Breast cancer. *Nat Rev Dis Primers* **5,** 67 (2019).

Surrogate intrinsic subtypes

Triple-negative
ER–, PR–, HER2–; high grade; high Ki67 index; NST histology; special type histology (metaplastic, adenoid cystic, medullary-like and secretory); poor prognosis except for some special types

HER2-enriched (non-luminal)
ER–, PR–, HER2+; high grade; high Ki67 index; NST histology; aggressive disease but responds to targeted therapies; intermediate prognosis

Luminal B-like HER2+
ER+ but lower ER and PR expression than luminal A-like; HER2+; higher grade; high Ki67 index; NST and pleiomorphic; responds to targeted therapies; intermediate prognosis

Luminal B-like HER2–
ER+ but ER and PR expression lower than in luminal A-like; HER2–; higher grade; high Ki67 index; high-risk GES; NST, micropapillary and lobular pleiomorphic histology; intermediate prognosis

Luminal A-like
Strongly ER+ and PR+; HER2–; low proliferation rates; typically low grade; low Ki67 index; low-risk GES; NST, tubular cribriform and classic lobular histology; good prognosis

10–15% **13–15%** **10–20%** **60–70%**

Proliferation
High grade
Basal-like genes
ER expression
HER2 expression
Low grade

Biomarkers validated for therapy decision-making

Biomarker	Method and threshold	Use	LOE
ER	IHC; positive if ≥1%	• Essential for the characterization of the IHC luminal group • Poor prognostic marker if negative • Predictive marker for endocrine treatment • Mandatory for endocrine treatment prescription	I
PR	IHC; positive if ≥1%	• If negative, tumour classified as IHC luminal B • Strong poor prognostic marker if negative • Predictive marker for endocrine treatment	I
HER2	• IHC; positive if >10% complete membrane staining (3+) • Single-probe ISH; positive if HER2 ≥6 copies • Dual-probe ISH; positive if HER2 and CEP17 ≥2 and HER2 ≥4 copies, or HER2 and CEP17 <2 and HER2 ≥6 copies	• Essential to characterize HER2-enriched (ER-negative) disease and luminal B, HER2-positive • Prognostic marker • Predictive marker for anti-HER2 treatment • Mandatory for anti-HER2 therapy	I (IHC) and I (ISH)
Ki67	IHC; no final consensus on cut-off value but values <10% are considered low and >30% are considered high[a]	Absence of international consensus for scoring and threshold	I
		Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant tumour residues)	I
		Absence of prognostic value in HER2-positive disease or TNBC	I
		Predictive of response to neoadjuvant endocrine therapy[a]	I
		Predictive of response to neoadjuvant chemotherapy	Expert opinion
		If elevated, chemotherapy is often prescribed in ER-positive, HER2-negative tumours	Expert opinion
		Part of the IHC definition of luminal tumours whereby when Ki67 is low, luminal A tumour likely and when Ki67 high, luminal B tumour likely	Expert opinion
Intrinsic subtypes	Gene expression profile, N-Counter technology	Prognostic	II and III
		Predictive; different responses to neoadjuvant chemotherapy and anti-HER2 therapy according to subtype	I

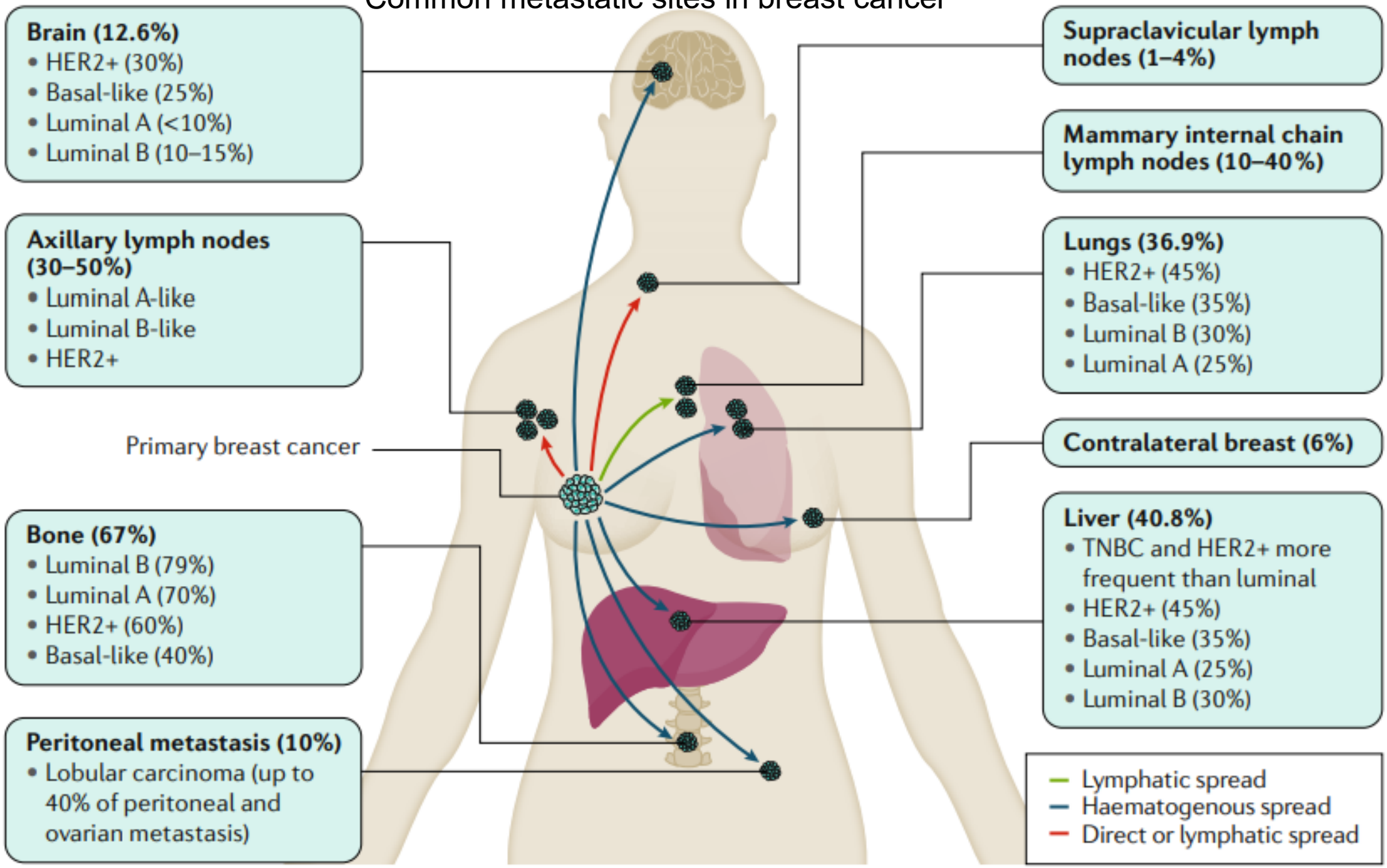
Breast cancer. *Nat Rev Dis Primers* **5,** 67 (2019).

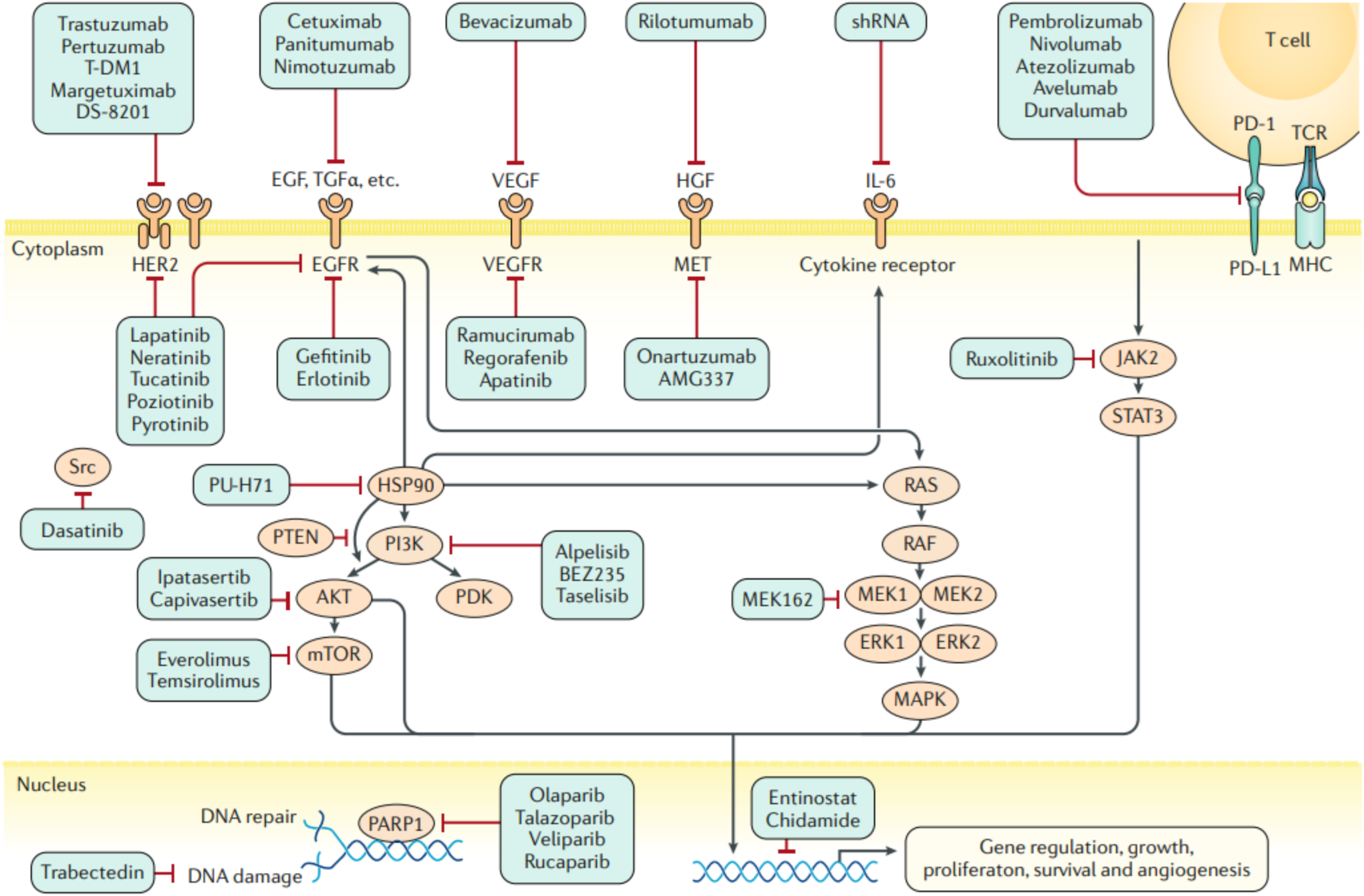
First-generation signatures (MammaPrint and OncotypeDx)	Gene expression profile, RT-PCR	• Prognostic for ER-positive, HER2-negative tumours (with 0–3 involved lymph nodes) • Chemotherapy is indicated if high risk or high score	Ia
Second-generation signatures (Prosigna and Endopredict)	N-Counter technology, RT-PCR	• Prognostic for ER-positive, HER2-negative tumours (with 0–3 involved lymph nodes), include T size and N status in their final score • Chemotherapy is indicated if high risk or high score	Ib
PIK3CA mutations	Mutations detected by PCR or NGS in exons 9 or 20 from cancer biopsy specimen or liquid biopsies	Predictive marker for specific PI3KCA inhibitors (such as alpelisib) in luminal A and luminal B metastatic breast cancer	Ia[284]
Germline *BRCA* mutation	NGS on blood lymphocytes or on tumour cells	• Predictive marker for PARP inhibitors in metastatic breast cancer (evidence-based for HER2-negative disease) • Germline mutations imply family counselling • Predictive impact of somatic mutations is under evaluation	Ia[30]
PD-L1	IHC; positive if expression in immune cells ≥1% in tumour specimens (metastatic or primary)	Predictive for immunotherapy with atezolizumab combined with nab-paclitaxel in TNBC	Ia[249]

CEP17, chromosome enumeration probe 17; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LOE, level of evidence; N, node; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death 1 ligand 1; PR, progesterone receptor; RT-PCR, PCR with reverse transcription; T, tumour; TNBC, triple-negative breast cancer. Data from REFS[111,128,225]. [a]According to the International Ki67 Working Group Guidelines[114].

Breast cancer. *Nat Rev Dis Primers* **5,** 67 (2019).

Common metastatic sites in breast cancer




Trastuzumab
Pertuzumab
T-DM1
Margetuximab
DS-8201
Cetuximab
Panitumumab
Nimotuzumab
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
Onartuzumab
AMG337
Ruxolitinib
JAK2
STAT3
Src
Dasatinib
PU-H71
HSP90
RAS
PTEN
PI3K
Alpelisib
BEZ235
Taselisib
RAF
Ipatasertib
Capivasertib
AKT
PDK
MEK162
MEK1
MEK2
ERK1
ERK2
Everolimus
Temsirolimus
mTOR
MAPK
Nucleus
DNA repair
PARP1
Olaparib
Talazoparib
Veliparib
Rucaparib
Entinostat
Chidamide
Trabectedin
DNA damage
Gene regulation, growth,
proliferaton, survival and angiogenesis

Major Strides in HER2 Blockade for Metastatic Breast Cancer

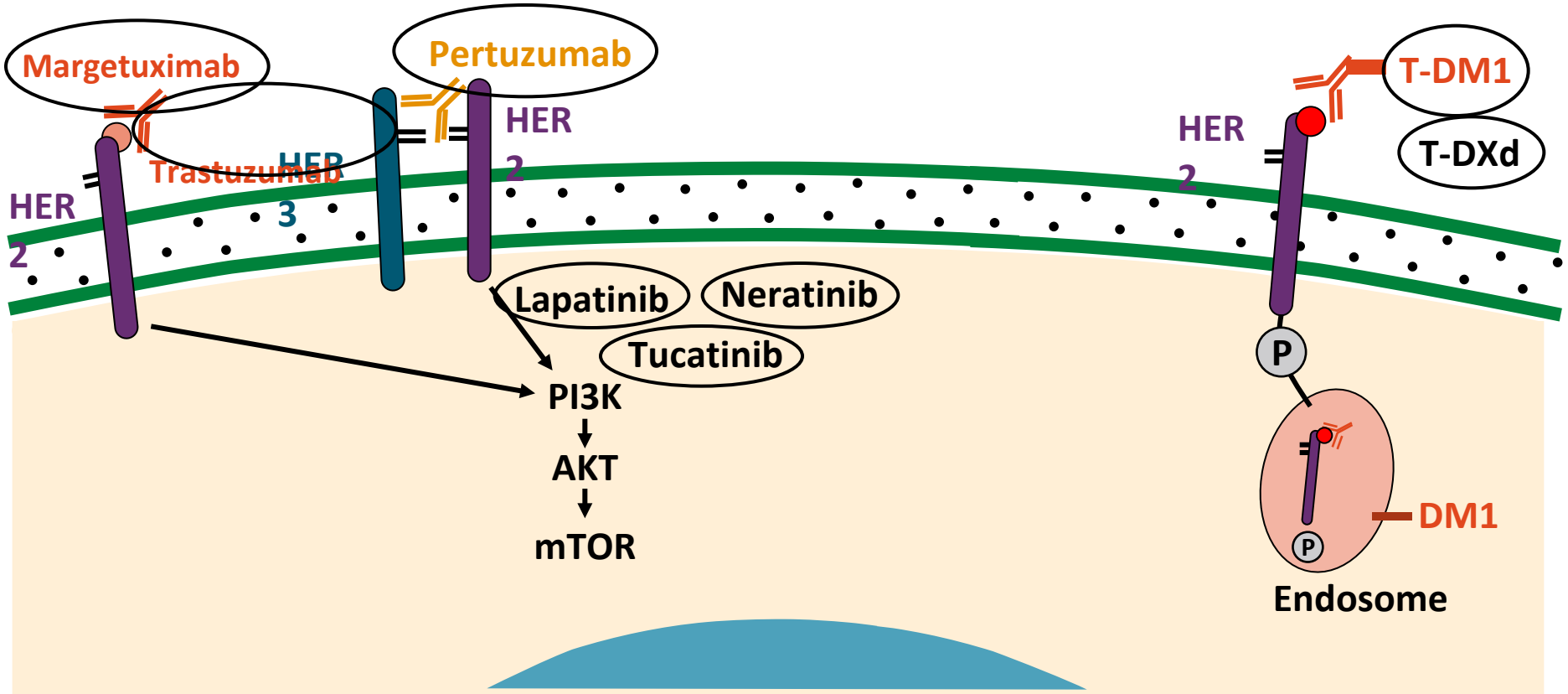
- The increasing availability of HER2-targeted agents in HER2 (+) metastatic breast cancer
  - overall survival rose from a median of 38.7 months to 51.1 months from 2008 through 2012.
- DESTINY-trastuzumab deruxtecan (topoisomerase I inhibitor)
  - A higher drug-to-antibody ratio than trastuzumab emtansine (8 to 1 vs. 3 to 1)
  - a median of six lines of prior therapy for advanced HER2-positive breast cancer.
  - Objective response rate : 60.9% and a median duration of progression-free survival of 16.4 months in a heavily pretreated population (100% of the pts had received TDM1(trastuzumab emtansine).

Eur J Cancer 2018;96:17-24, NEJM 2020; 382:669-671

Breast cancer the most important Drugs : Her2 and hormone therapy

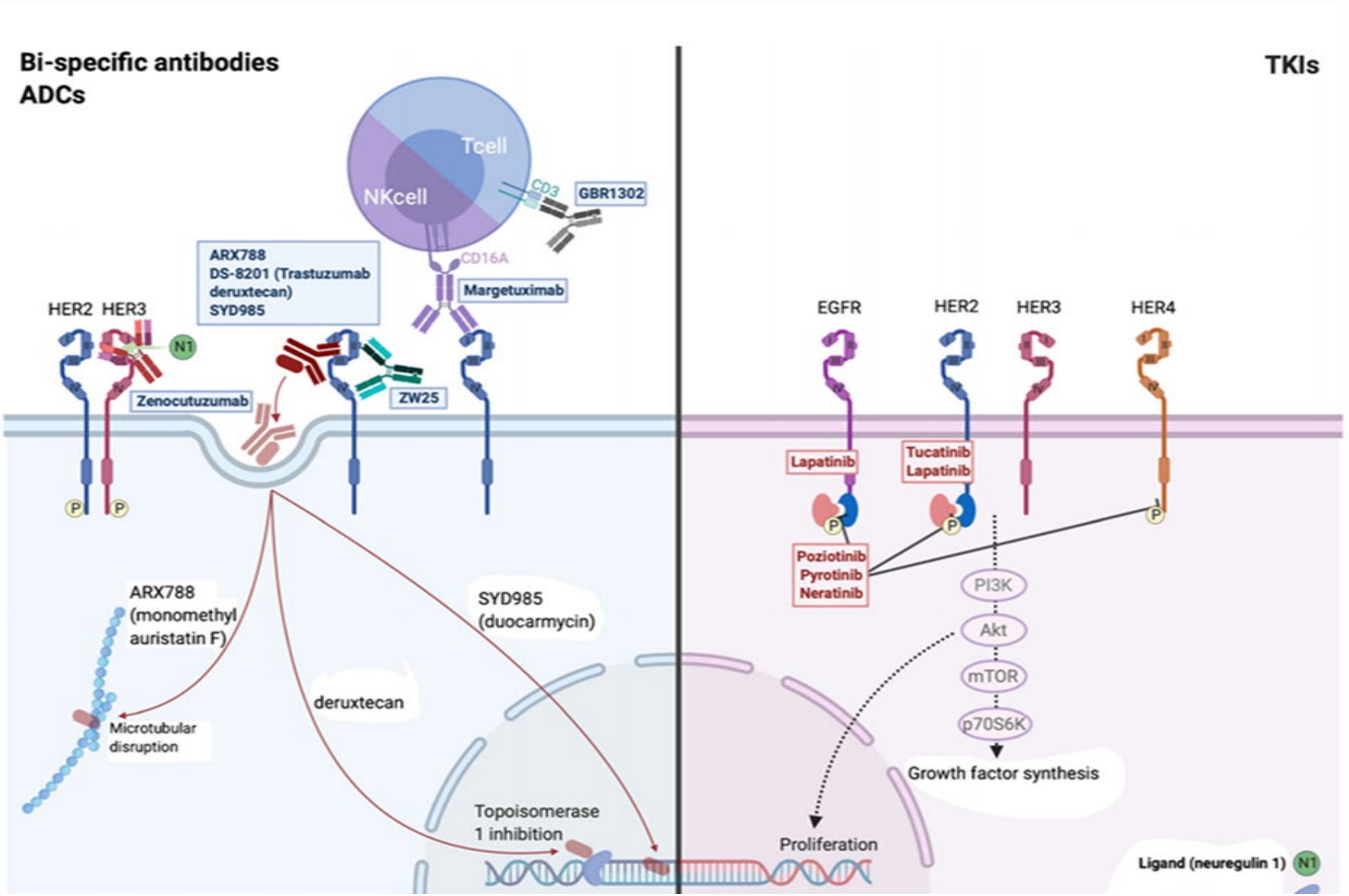
- Monoclonal antibody
  - Trastuzumab, Pertuzumab
  - Margetuximab (Fc engineered)
- New oral tyrosine kinase inhibitors (HER2)
  - Lapatinib (HER2/HR3 reversible)
  - Tucatinib (HER2, irreversible, less side effect)
  - Neratinib (HER2 irreversible)
  - Pyrotinib
- Antibody drug conjugates (HER2 antibody+ chemotherapy)
  - Tratuzumab Emtansine (taxane)
  - Trastuzumab deruxtecan (topoisomerase 1 inhibitor)
  - Trastuzumab duocarmazine
- Hormone therapy
  - Tamoxifen
  - Anastrozole, Letrozole (aromatase inhibitor)
  - Exemestane
  - Fulvestrant
- CDK4/6 Inhibitors
  - Palbociclib, Abemaciclib, Ribociclib
- mTOR inhibitor
  - Everolimus +endocrine therapy
- PI3K inhibitor
  - Alpelisib+ Endocrine therapy
- PARP inhibitors

2021: 8 FDA-Approved HER2-Targeted Agents for MBC



Adapted from Gajria. *Expert Rev Anticancer Ther*. 2011;11:263.

Slide credit: clinicaloptions.com


Bi-specific antibodies
ADCs
TKIs
Tcell
NKcell
CD3
GBR1302
CD16A
Margetuximab
ARX788
DS-8201 (Trastuzumab deruxtecan)
SYD985
HER2
HER3
N1
Zenocutuzumab
ZW25
P
ARX788 (monomethyl auristatin F)
Microtubular disruption
SYD985 (duocarmycin)
deruxtecan
Topoisomerase 1 inhibition
EGFR
HER2
HER3
HER4
Lapatinib
Tucatinib
Lapatinib
Poziotinib
Pyrotinib
Neratinib
PI3K
Akt
mTOR
p70S6K
Growth factor synthesis
Proliferation
Ligand (neuregulin 1)
N1

Principle (codes from studies)

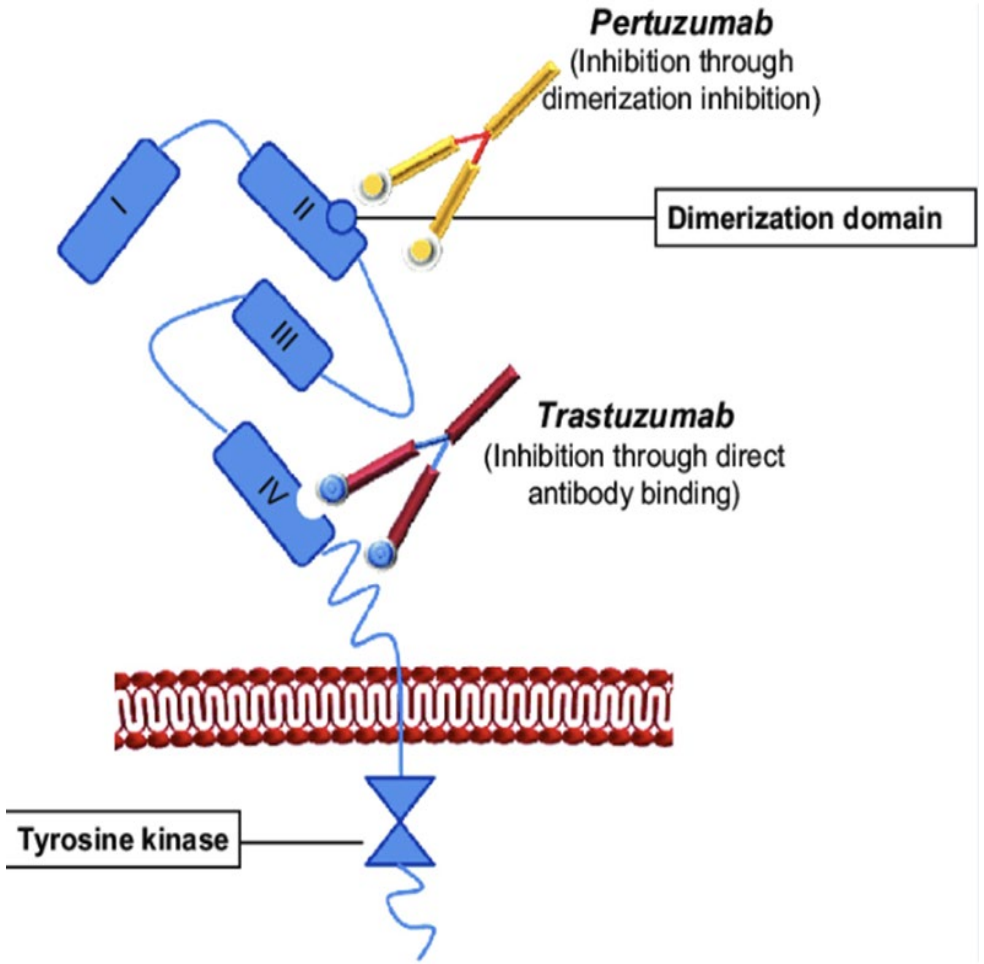
- HER2 and HR (**resistance**) are kings , one will dominate (driven gene)
- Hormone therapy never goes with chemotherapy /HER2 blocker always go with chemotherapy
- Double HER2 blockers +Chemotherapy is better than 1 HER2 blocker +chemotherapy
- Antibody drug conjugates (HER2 antibody+ chemotherapy) always alone (TDM-1, TDXd) (>TKI/ **Capecitabine**)
- HER2-targeted tyrosine kinase inhibitors (TKIs)/capecitabine (brain mets)
- CDK4/6 Inhibitors always go with hormone
- HR + mTOR inhibitors, HR+PI3K inhibitors. (less ORR, more side effect)
- Triple negative : chemotherapy, immunotherapy, PARPI, Sacituzumab Govitecan

Principle (codes from studies)

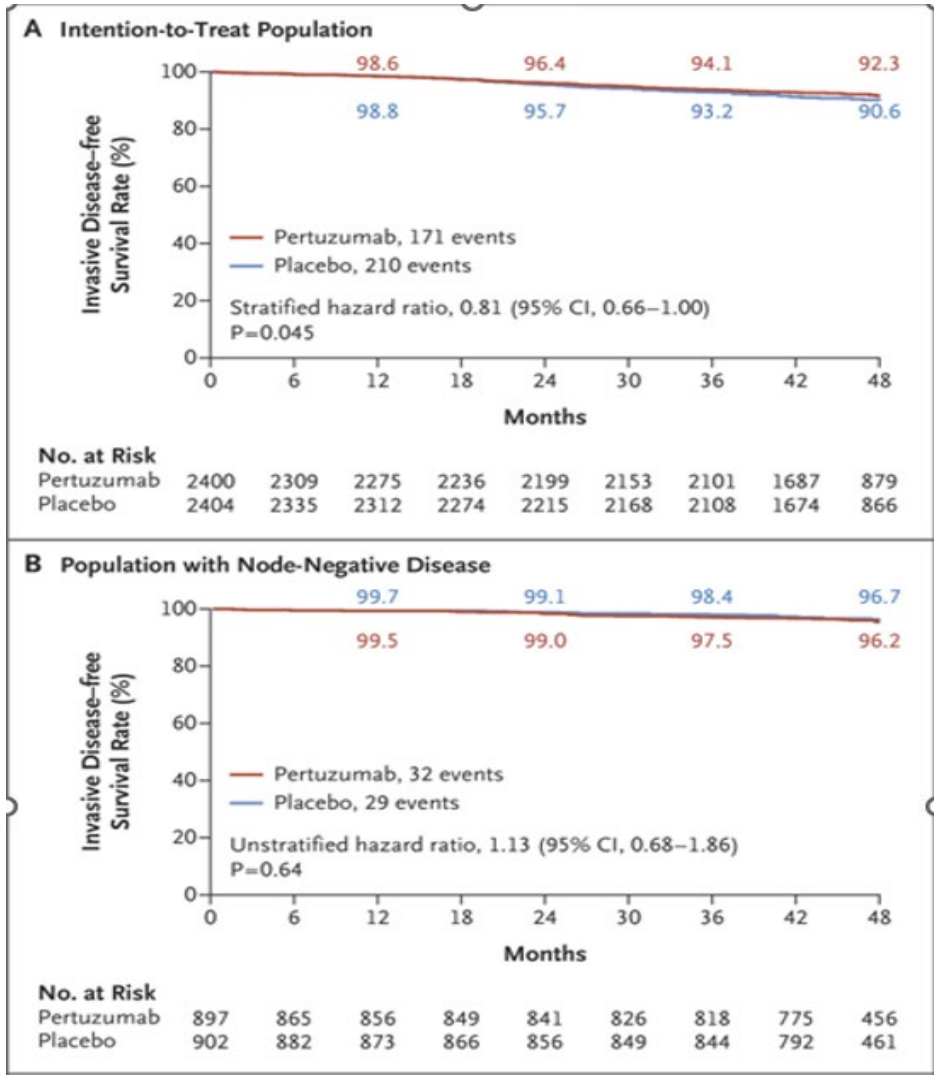
- Master gene in breast cancer : HER2 , HR , unknown (triple negative breast cancer) , one will dominate (driven gene)
- Target therapy (tyrosine kinase and signal): not curable, pregnancy (x)
- Hormone therapy never goes with chemotherapy /HER2 blocker always go with chemotherapy
- Double HER2 blockers +Chemotherapy is better than 1 HER2 blocker +chemotherapy
- Antibody drug conjugates (HER2 antibody+ chemotherapy) always alone (TDM-1, TDXd) (>TKI/ **Capecitabine**)
- HER2-targeted tyrosine kinase inhibitors (TKIs)/capecitabine (brain mets)
- CDK4/6 Inhibitors always go with hormone
- HR + mTOR inhibitors, HR+PI3K inhibitors. (less ORR, more side effect)
- Triple negative : chemotherapy, immunotherapy, PARPI, Sacituzumab Govitecan

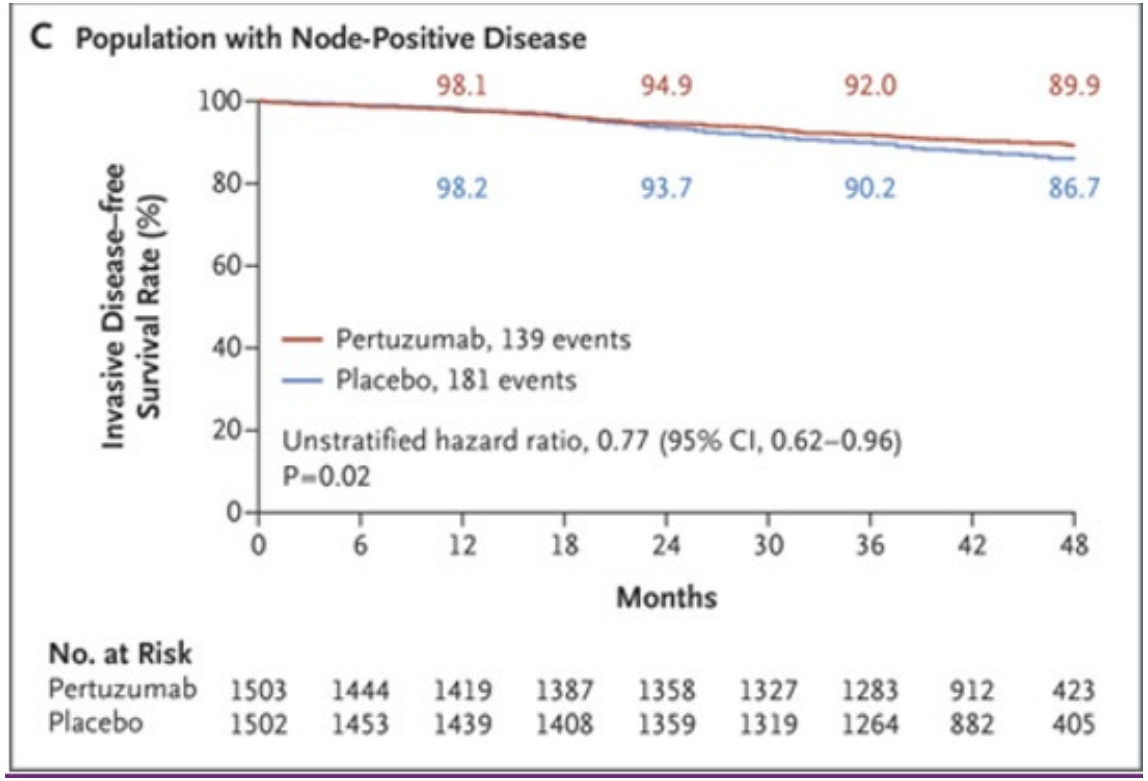
Code 1
Double HER2 blockers +Chemotherapy is better than 1 HER2 blocker +chemotherapy

- 2 HER2-Targeted mAbs (CLEOPATRA study : trastuzumab,pertuzumab)
- Tyrosine kinase inhibitor+ HER2-targeted mAbs (HER2CLIMB study, TUC+TRAS+Cape)



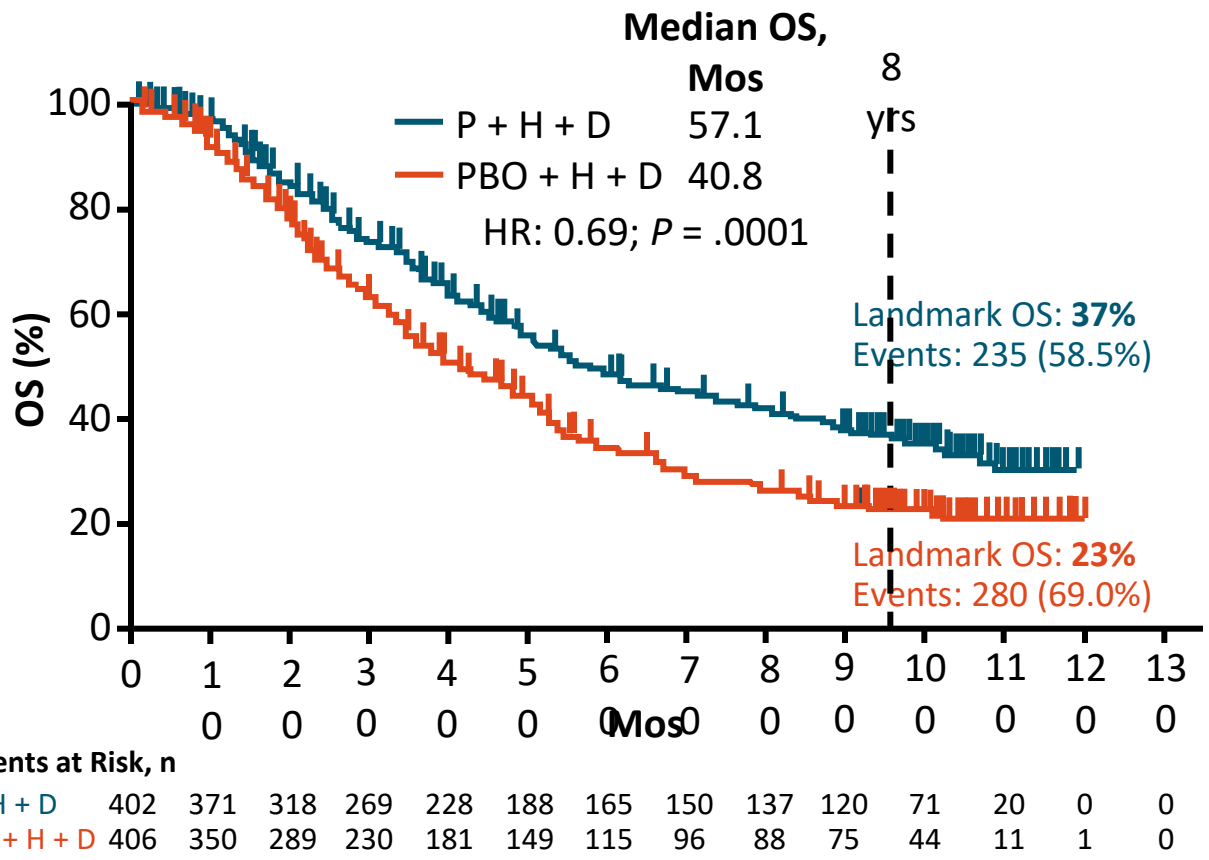
Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

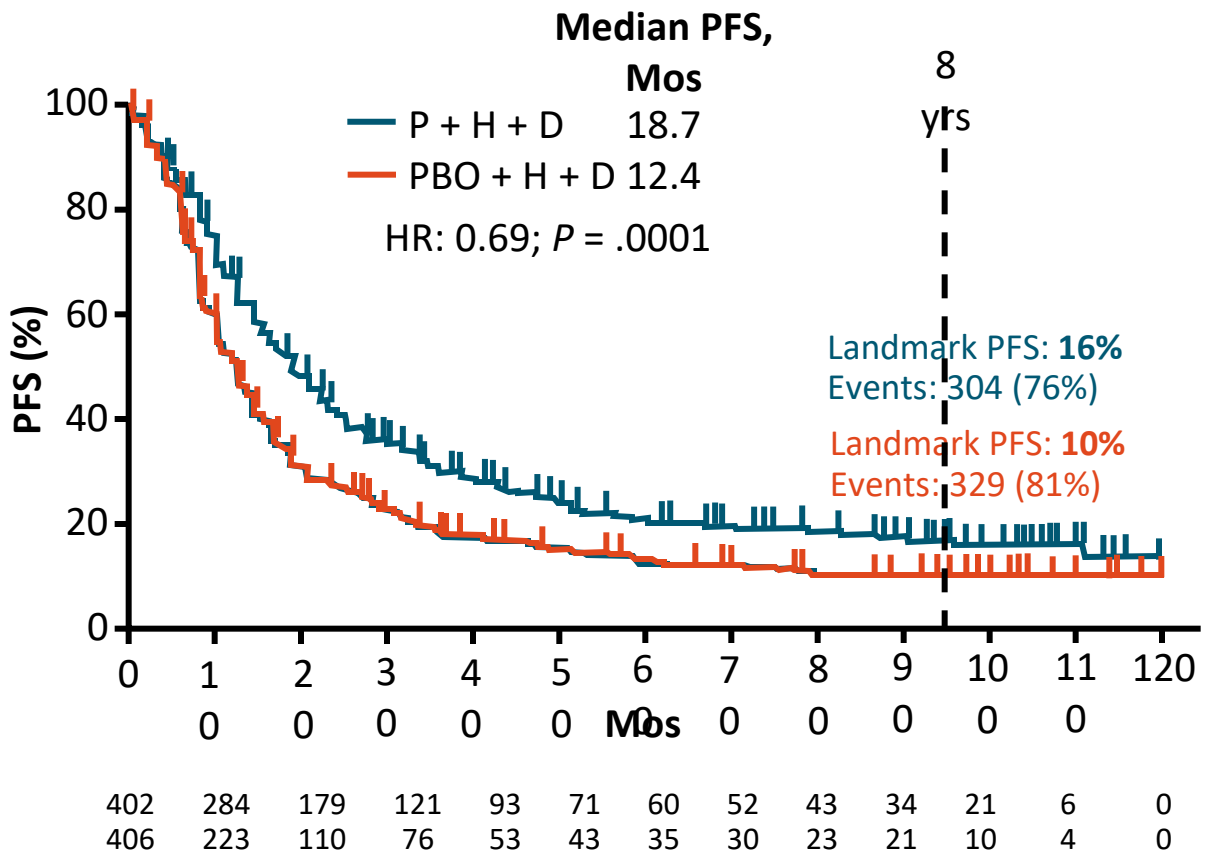




N Engl J Med 2017; 377:122-131

CLEOPATRA: HER2+ MBC Tx With Pertuzumab, Trastuzumab, and Docetaxel: Survival





Swain. Lancet Oncol. 2020;21:519

Slide credit: clinicaloptions.com

CLEOPATRA study

- Adding pertuzumab to trastuzumab and docetaxel improved median overall survival (OS) by almost 16 months vs placebo plus trastuzumab and docetaxel. The triplet extended median OS to 56.5 months versus 40.8 months with the standard therapy (HR, 0.68; *P*= .0002).

Guideline-Recommended Regimens for HER2-Positive Recurrent or Stage IV Breast Cancer

Preferred regimens*

- Pertuzumab + trastuzumab + taxane[†]

Other Recommended Regimens*

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab deruxtecan (T-DXd)
- Trastuzumab + chemotherapy[‡§]
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[§]
- Lapatinib + capecitabine
- Neratinib + capecitabine

*An FDA-approved biosimilar is an acceptable substitute for trastuzumab. [†]Docetaxel or paclitaxel. [‡]Paclitaxel ± carboplatin, docetaxel, vinorelbine, capecitabine. [§]Anthracycline CT should be avoided due to significant cardiotoxicity.

Wang. Signal Transduct Target Ther. 2019;4:34. Pernas. Ther Adv Med Oncol. 2019:11:1758835919833519.

HER2CLIMB: Tucatinib + Trastuzumab + Capecitabine in Previously Treated HER2-Positive MBC

- Randomized, double-blind, placebo-controlled, active comparator phase II trial

21-day cycles

Patients with HER2+ MBC; prior trastuzumab, pertuzumab, and T-DM1; ECOG PS 0/1; brain mets allowed* (N = 612)

*Including previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 202)

- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients
- Secondary endpoints (total population): OS, PFS in patients with brain mets, ORR in patients with measurable disease, safety in patients who received ≥ 1 dose of study tx

Murthy. NEJM. 2020;382:597.

HER2CLIMB: Primary Analysis Results

- The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.
- Importantly, the secondary endpoint of PFS in patients with brain metastases was met.
- Progression-free survival at 1 year: 33.1 vs 12.3% in the placebo-combination group (P<0.001)

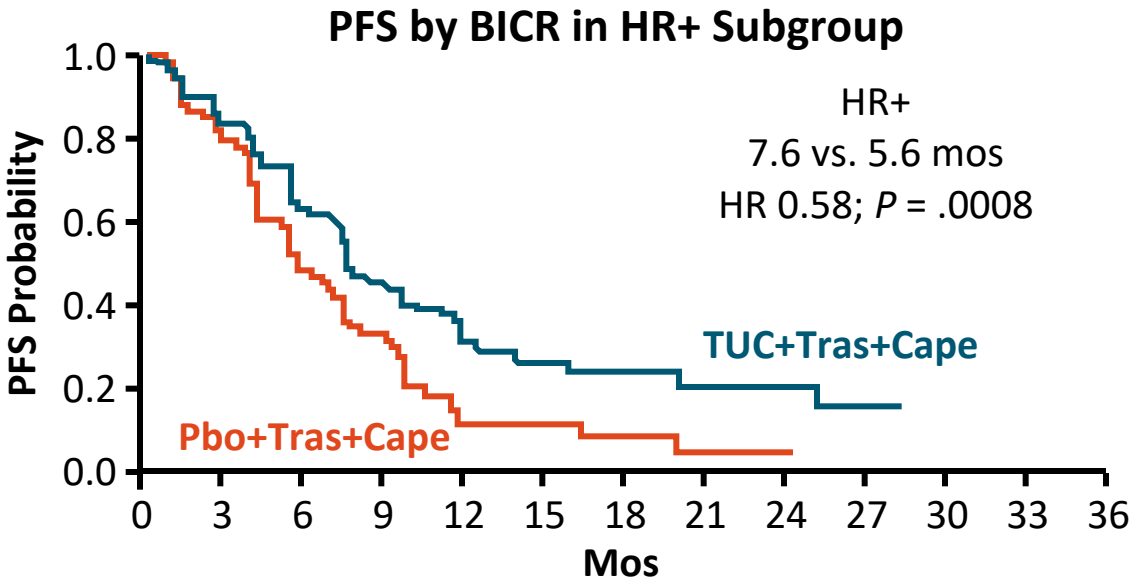
PFS by BICR n = 480*	**OS** N = 612	**PFS by BICR in patients with brain metastases** n = 291
Risk of progression or death was reduced by **46% (HR: 0.54)** 95% CI: 0.42-0.71, *P* < .001 PFS 5.6 to 7.8 mos	**Risk of death was reduced by** **34% (HR: 0.66)** 95% CI, 0.50-0.88, *P* = .005 OS 17.4 to 21.9 mos	**Risk of progression or death was reduced by** **52% (HR: 0.48)** 95% CI, 0.34-0.69, *P* < .001 PFS 5.4 to 7.6 mos

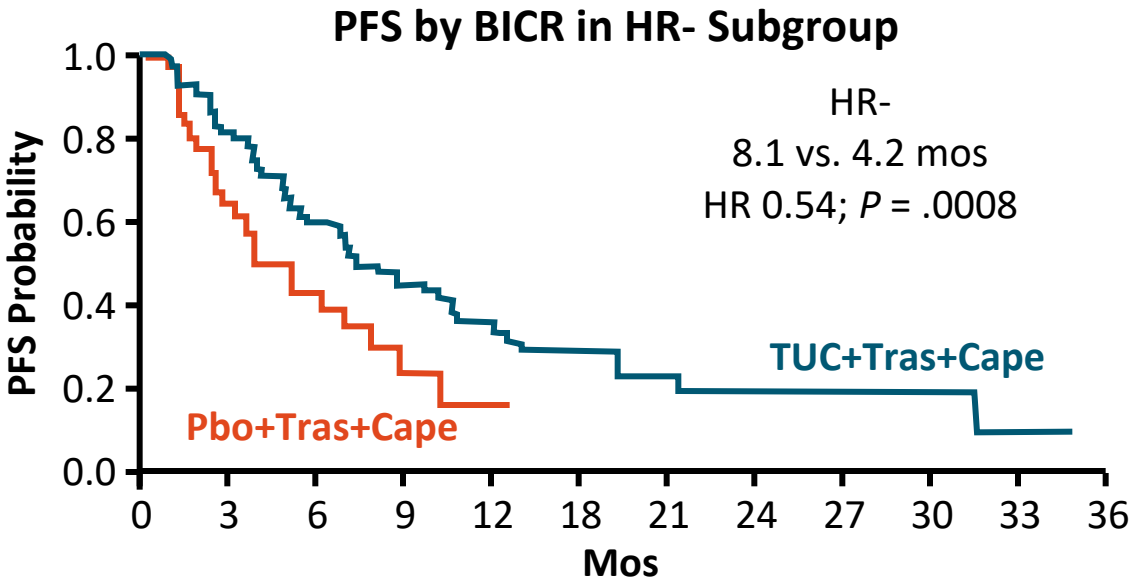
*Primary endpoint of PFS was assessed in the first 480 patients enrolled.

Murthy. NEJM. 2020;382:597.

Slide credit: clinicaloptions.com

HER2CLIMB: PFS by HR Status





Risk of progression or death was reduced 42% in all HR+ patients in the TUC arm

	Events/total	HR (95% CI)	*P*- value	One-year PFS (95% CI)	Median (95% CI)
TUC+TRAS+Cape	106/190	0.58 (0.42, 0.80)	.0008	31.3% (23.1, 39.9)	7.6 mo (7.4, 9.5)
Pbo+Tras+Cape	66/99			11.3% (4.6, 21.2)	5.6 mo (4.3, 7.4)

Risk of progression or death was reduced 46% in all HR- patients in the TUC arm

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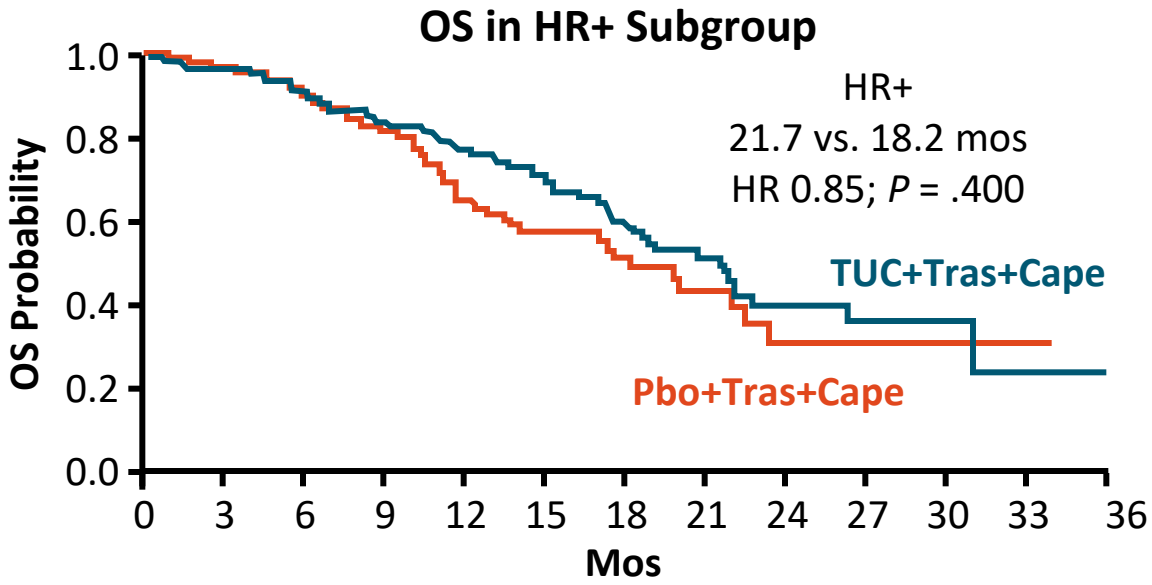
Pbo+Tras+Cape	31/61			15.8% (3.7, 35.5)	4.2 mo (3.1, 8.6)

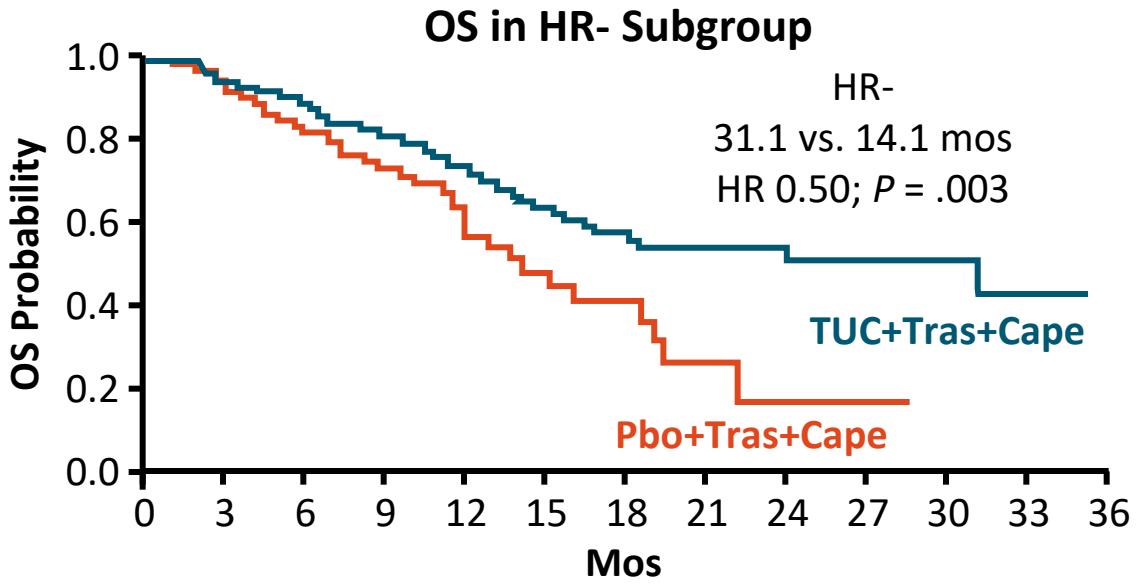
- PFS benefit was observed in patients in the tucatinib arm of the primary endpoint population regardless of hormone receptor status
- Demographics and disease characteristics in HR+/HR- subgroups were generally balanced between treatment arms

Hamilton. SABCS 2020. Abstr 117.

Slide credit: clinicaloptions.com

HER2CLIMB: OS by HR Status





Risk of progression or death was reduced 42% in all HR+ patients in the TUC arm

	Events/total	HR (95% CI)	*P*- value	Two-year OS (95% CI)	Median (95% CI)
TUC+TRAS+Cape	78/243	0.85 (0.59, 1.23)	.4	40.2% (29.1, 50.9)	21.7 mo (18.1, 26.4)
Pbo+Tras+Cape	51/127			30.7% (16.5, 46.1)	18.2 mo (13.6, 22.5)

Risk of progression or death was reduced 46% in all HR- patients in the TUC arm

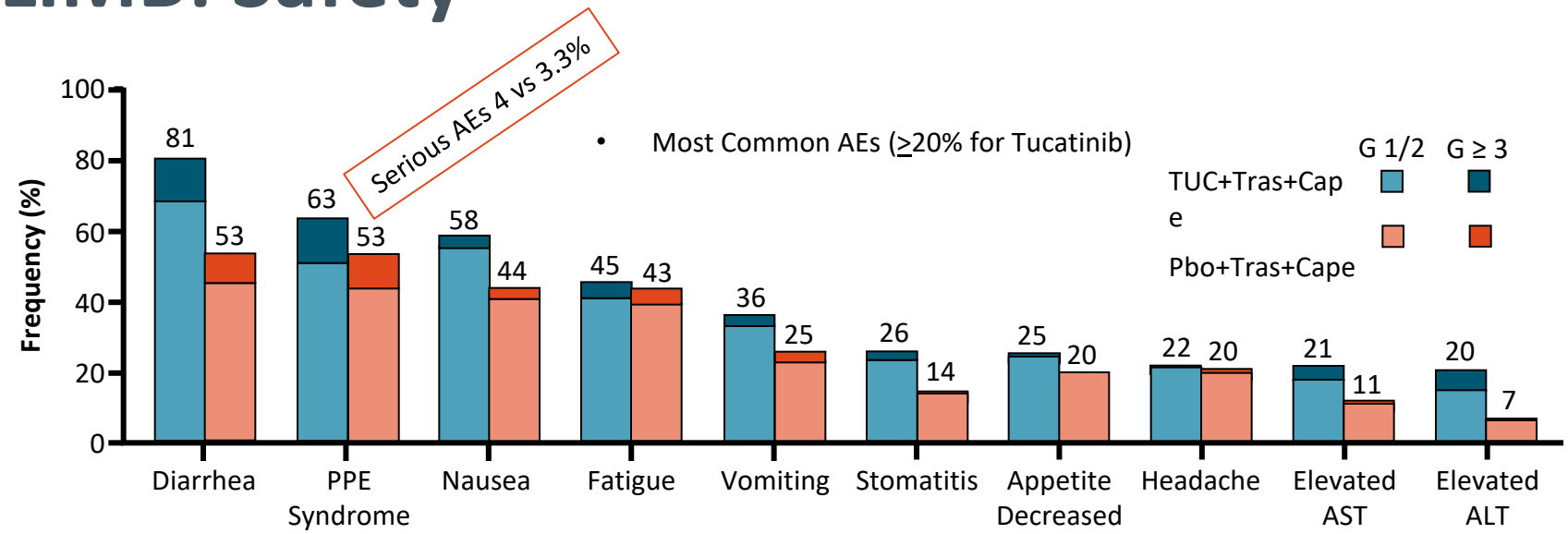
	Events/total	HR (95% CI)	*P*- value	One-year PFS (95% CI)	Median (95% CI)
TUC+TRAS+Cape	52/167	0.50 (0.31, 0.80)	.003	51.3% (39.3, 62.1)	31.1 mo (16.5, NR)
Pbo+Tras+Cape	35/75			17.3% (4.3, 37.6)	14.1 mo (11.5, 19.0)

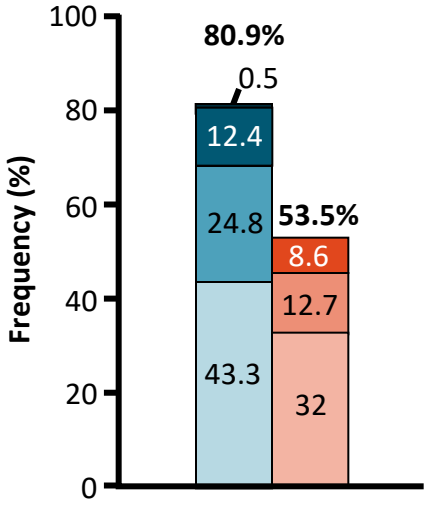
- Clinically meaningful improvement of OS was observed in patients on the tucatinib arm regardless of hormone receptor status
- Demographics and disease characteristics in HR+/HR- subgroups were generally balanced between treatment arms

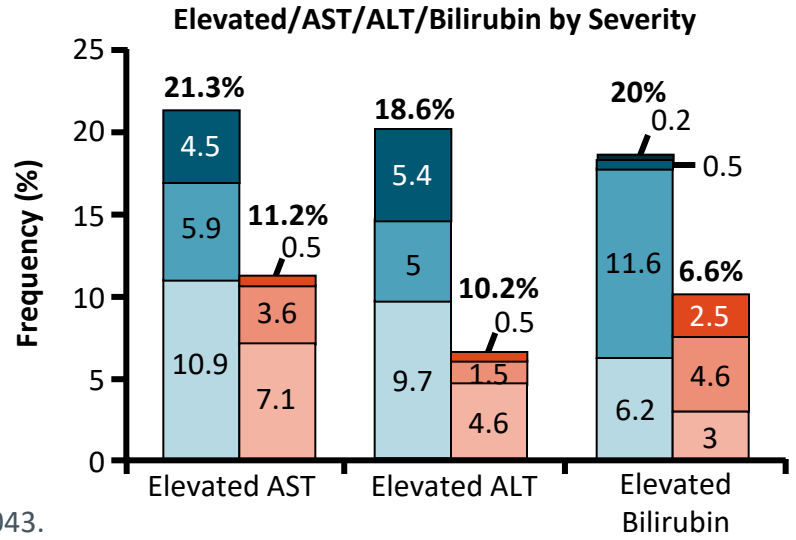
Hamilton. SABCS 2020. Abstr 117.

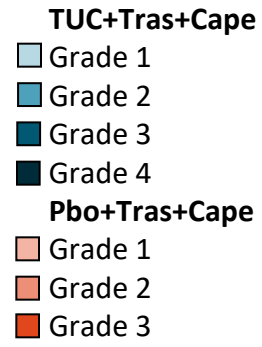
Slide credit: clinicaloptions.com

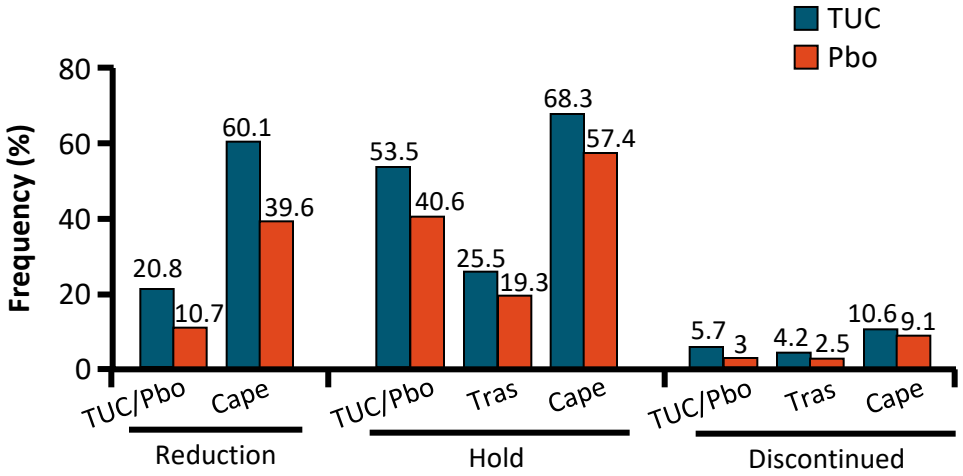
HER2CLIMB: Safety











Capecitabine most commonly reduced, withheld, & discontinued drug due to AEs on both arms

Okines. ASCO 2020. Abstr 1043.

Slide credit: clinicaloptions.com

Code 2

1. Antibody drug conjugates (HER2 antibody+ chemotherapy) always alone (TDM-1, TDXd)

2.TDM1 is better than lapatinib (Tykerb) plus capecitabine

Antibody drug conjugates (HER2 antibody+ chemotherapy)

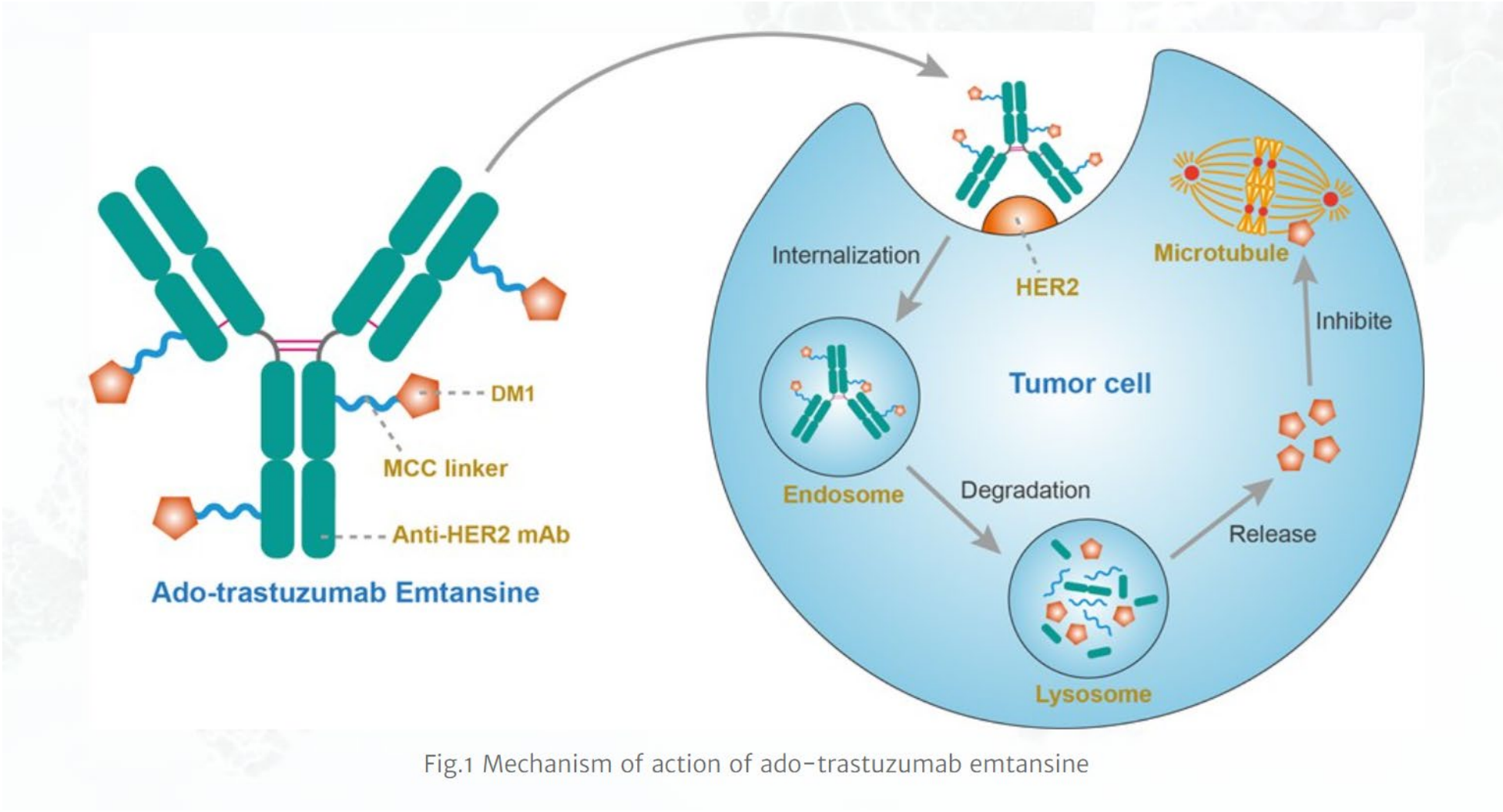
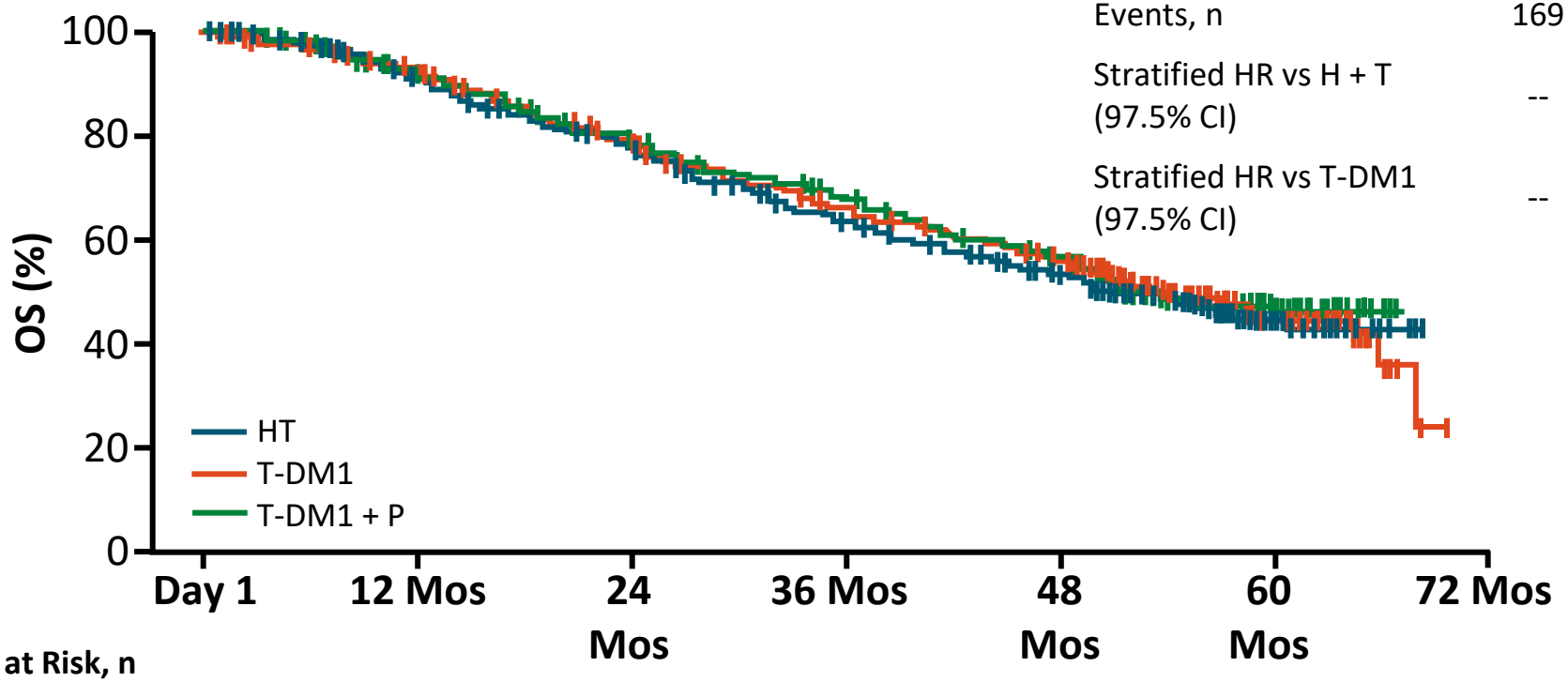


Fig.1 Mechanism of action of ado-trastuzumab emtansine

MARIANNE: First-line T-DM1 in HER2+ MBC

H, trastuzumab; MBC, metastatic breast cancer; P, pertuzumab; T, taxane; T-DM1, trastuzumab emtansine.

	H + T (n = 365)	T-DM1 (n = 367)	T-DM1 + P (n = 363)
Median OS, mos	50.9	53.7	51.8
Events, n	169	175	168
Stratified HR vs H + T (97.5% CI)	--	0.93 (0.73-1.20)	0.86 (0.67-1.11)
Stratified HR vs T-DM1 (97.5% CI)	--	--	1.00 (0.78-1.28)



Patients at Risk, n

H + T	365	303	251	197	155	28
T-DM1	367	322	264	216	176	37
T-DM1 + P	363	309	257	217	172	41

Perez. Cancer. 2019;125:3974.

Slide credit: clinicaloptions.com

EMILIA: T-DM1: Standard 2nd Line Therapy

HER2+ LABC or MBC (N=980)

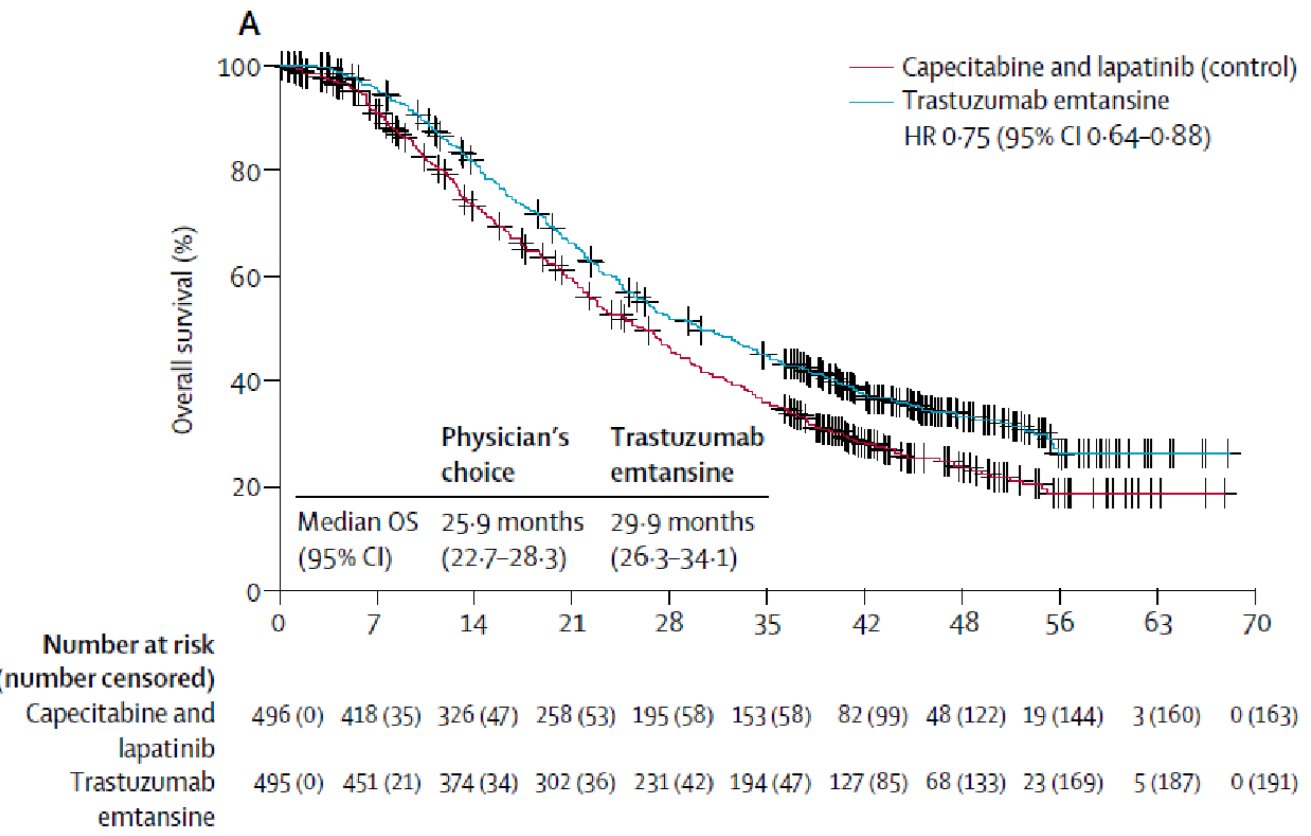
- **Prior taxane and trastuzumab**
- **Progression on metastatic tx or within 6 mos of adjuvant tx**

1:1

- **T-DM1**
- **Capecitabine + Lapatinib**

TDM-1 vs lapatinib (Tykerb) plus capecitabine, T-DM1 extended median OS by 5.8 months (30.9 months vs 25.1 months, respectively). The HR for death from any cause was 0.68. lapatinib-based therapies continue to be used after T-DM1.

OS

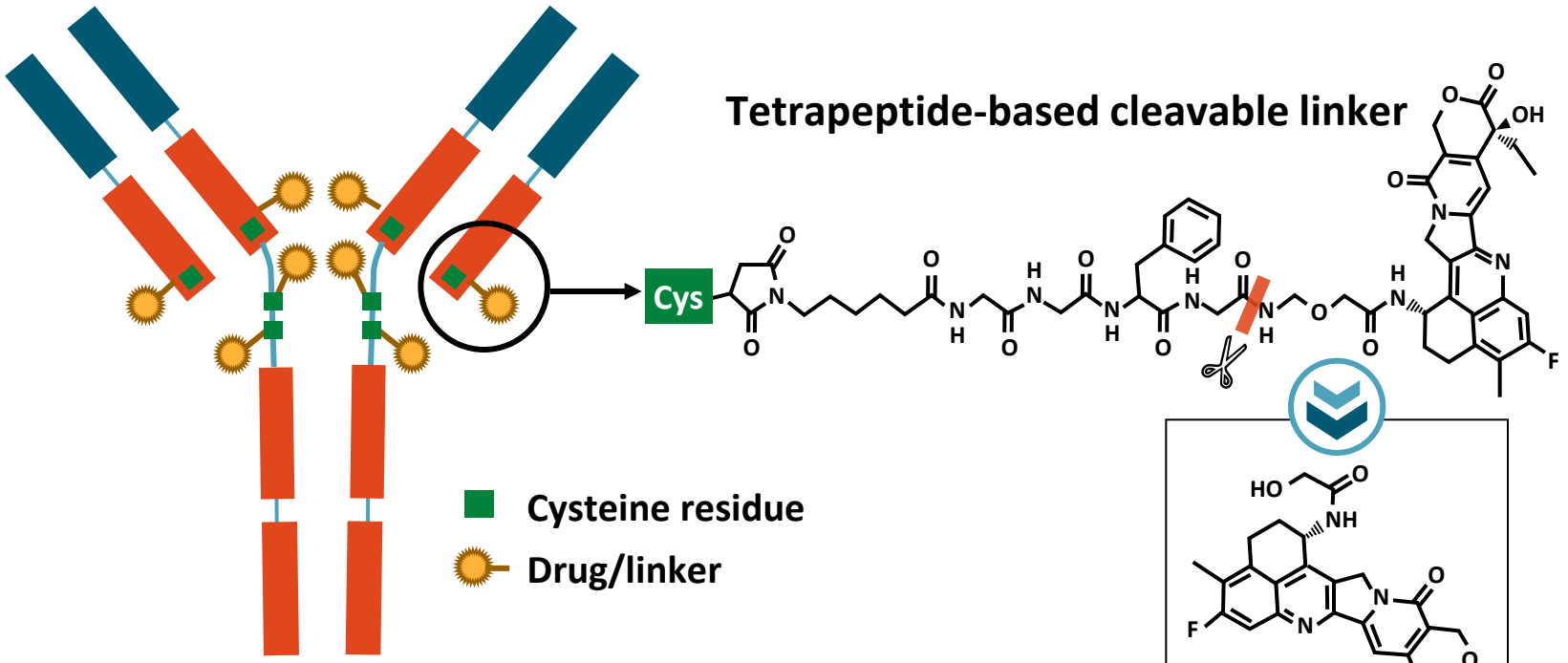


Dieras. Lancet Oncol. 2017;18:732.

Slide credit: clinicaloptions.com

HER2-Targeted ADC: Trastuzumab Deruxtecan (DS-8201)

Humanized anti-HER2 IgG1 mAb with same AA sequence as trastuzumab



Tetrapeptide-based cleavable linker

Topoisomerase I inhibitor (DXd) payload (exatecan derivative)

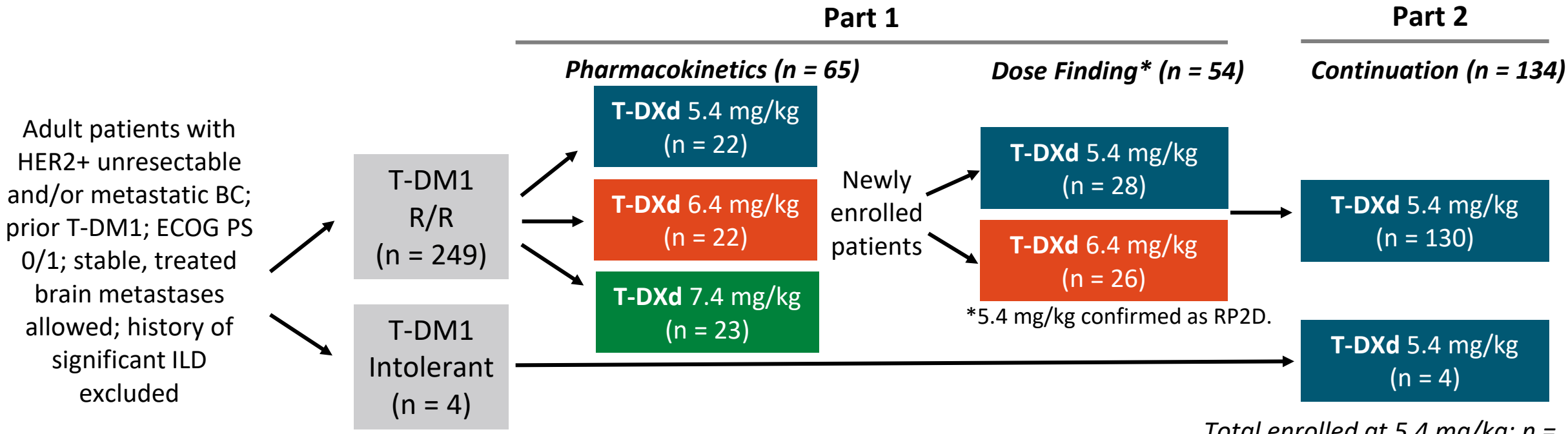
- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Slide credit: clinicaloptions.com

DESTINY-Breast01: Trastuzumab Deruxtecan (T-DXd) in Advanced HER2-Positive Breast Cancer

- Open-label, multicenter, randomized, 2-part phase II study

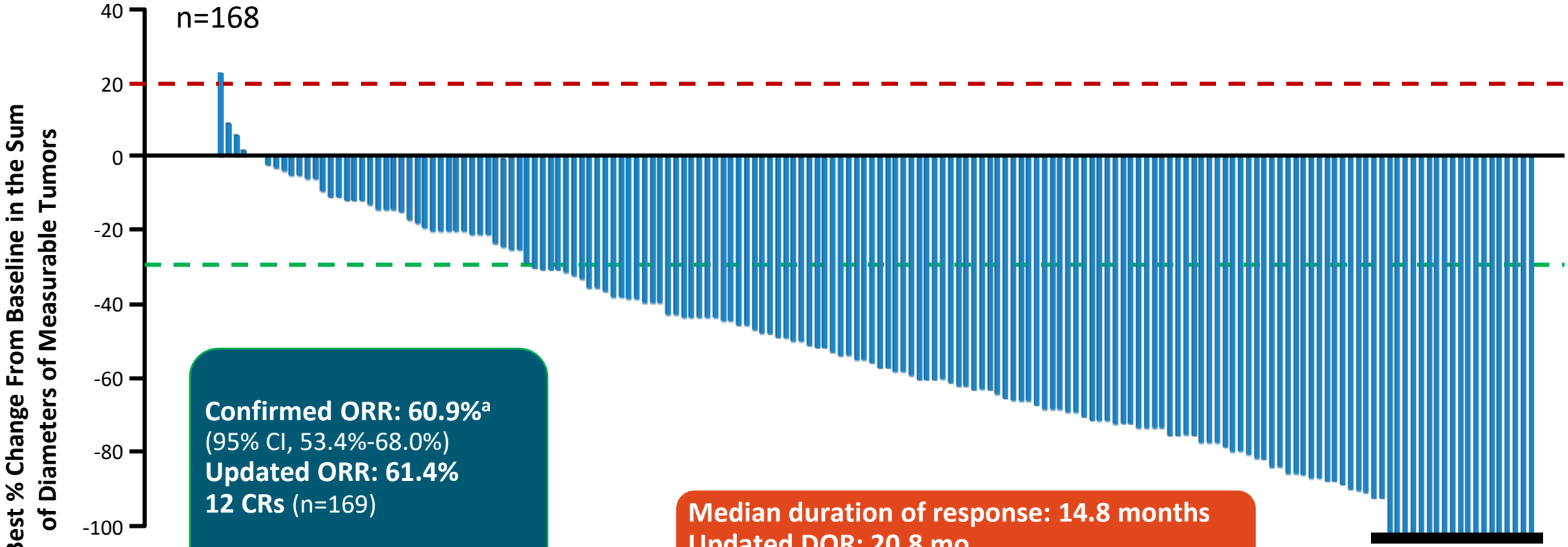


- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: investigator-assessed ORR, DCR, DoR, CBR, PFS, OS, PK, safety
- Data cutoff: August 1, 2019
  - 79 (42%) continuing treatment
  - 105 (57.1%) d/c (mostly for PD, 28.8%)

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

Slide credit: clinicaloptions.com

DESTINY-Breast01: Updated Best Change in Tumor Size



By independent central review.

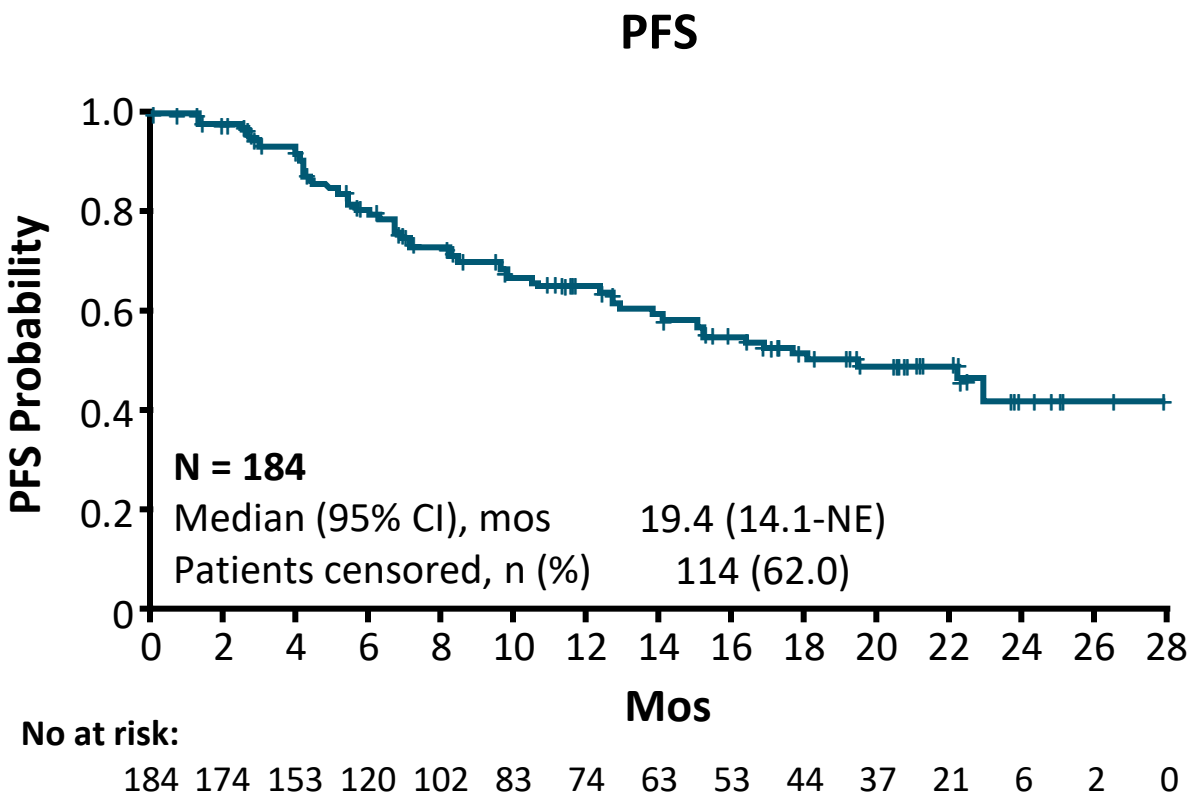
The line at 20% indicates progressive disease; the line at −30% indicates partial response.

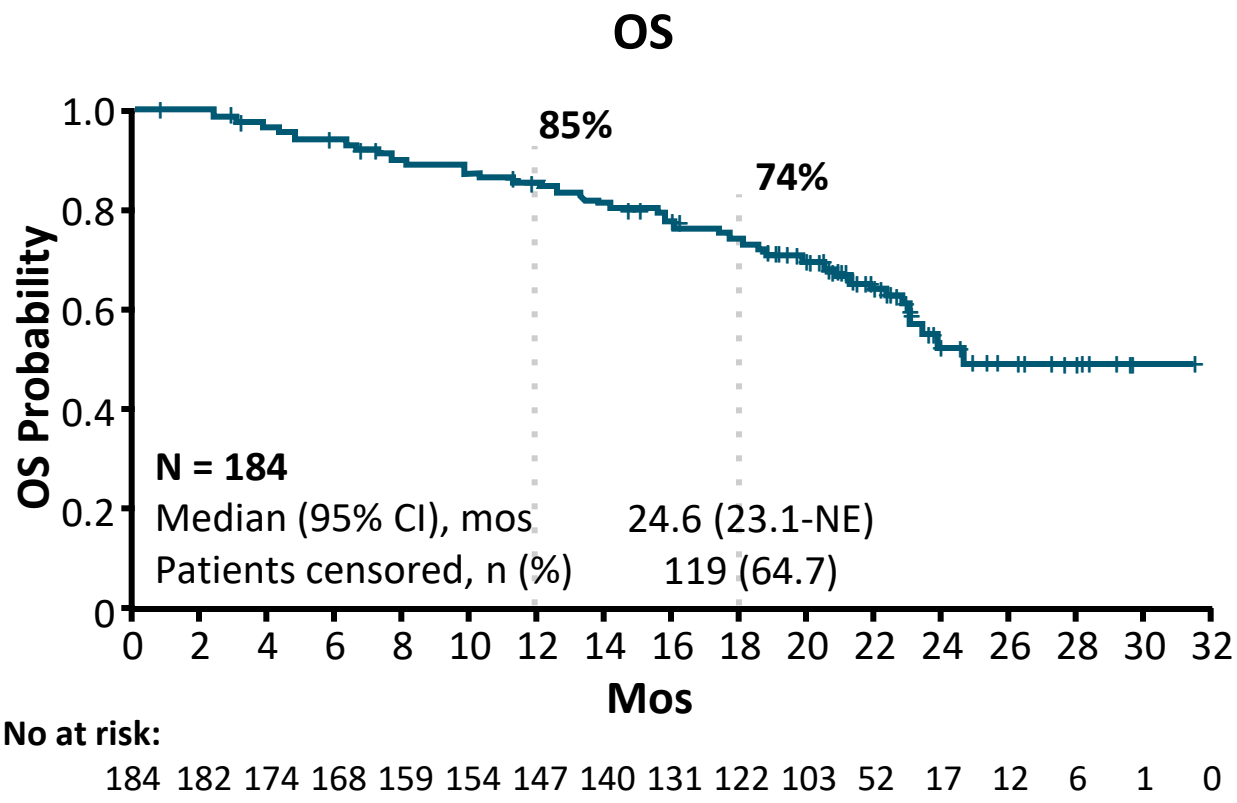
[a]Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Modi. NEJM. 2020;382:610. Modi. SABCS 2020. Abstr. PD3-06.

Slide credit: clinicaloptions.com

DESTINY-Breast01: Updated PFS and OS



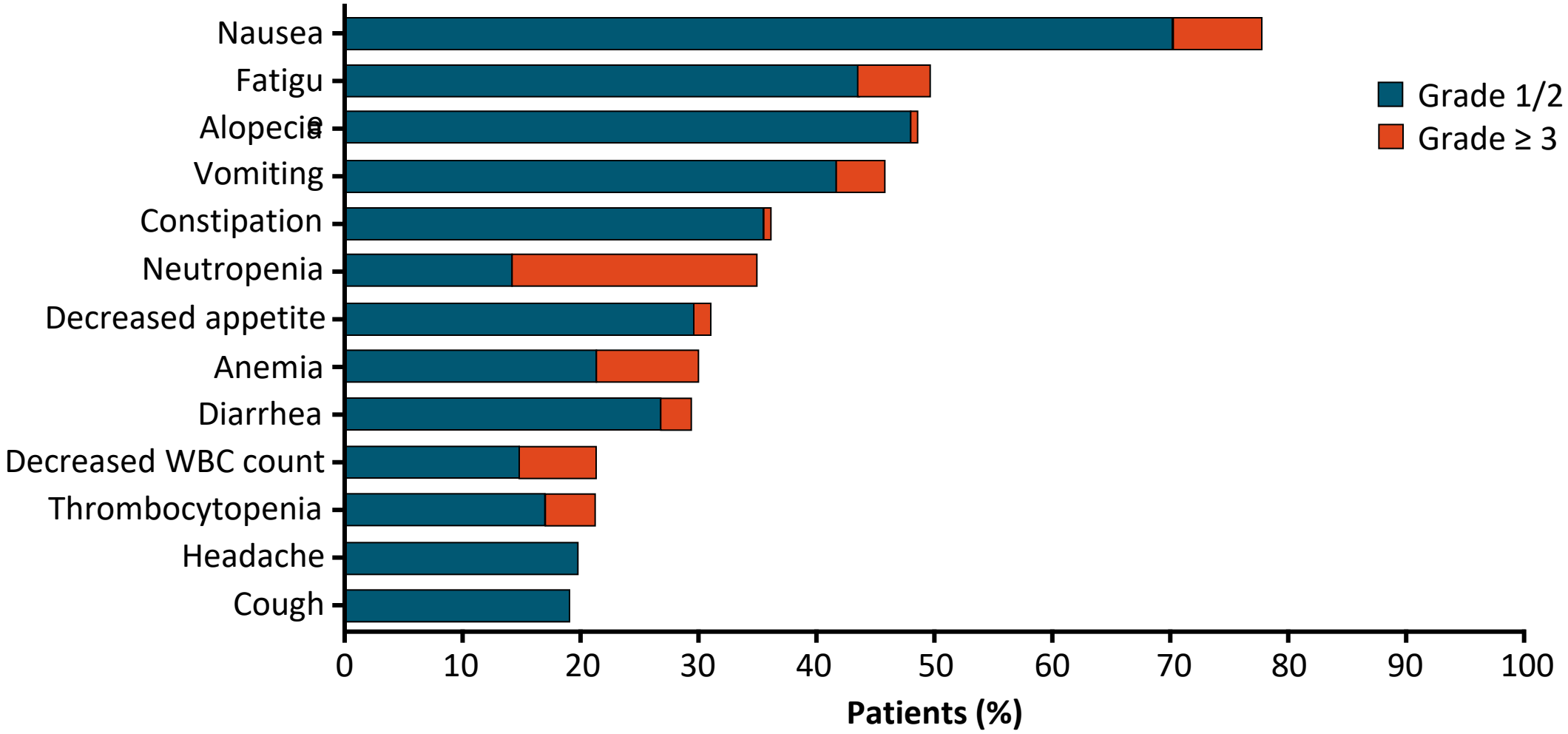


- 20.5 month median follow up (11.1 month at initial reporting)

Modi. NEJM. 2020;382:610. Modi. SABCS 2020. Abstr. PD3-06.

Slide credit: clinicaloptions.com

DESTINY-Breast01: AEs in Overall Population



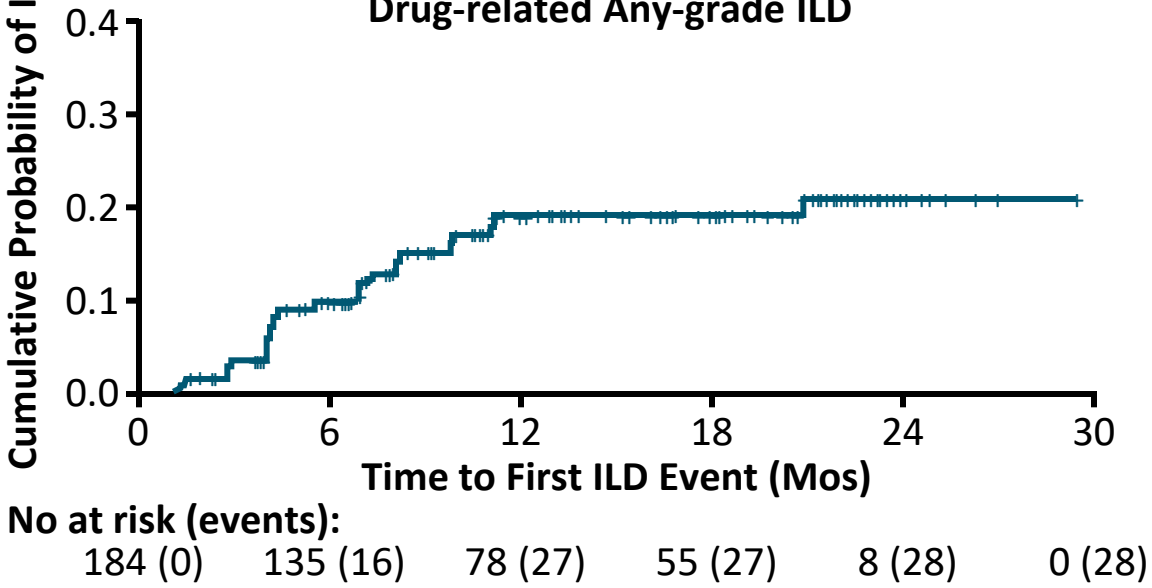
Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

Slide credit: clinicaloptions.com

Warnings and Precautions: ILD/Pneumonitis Monitoring and Management

Interstitial lung disease, n (%)	T-Dxd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

Cumulative Probability of Adjudicated Drug-related Any-grade ILD



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Fam-trastuzumab deruxtecan-nxki PI. 2021.

Slide credit: clinicaloptions.com

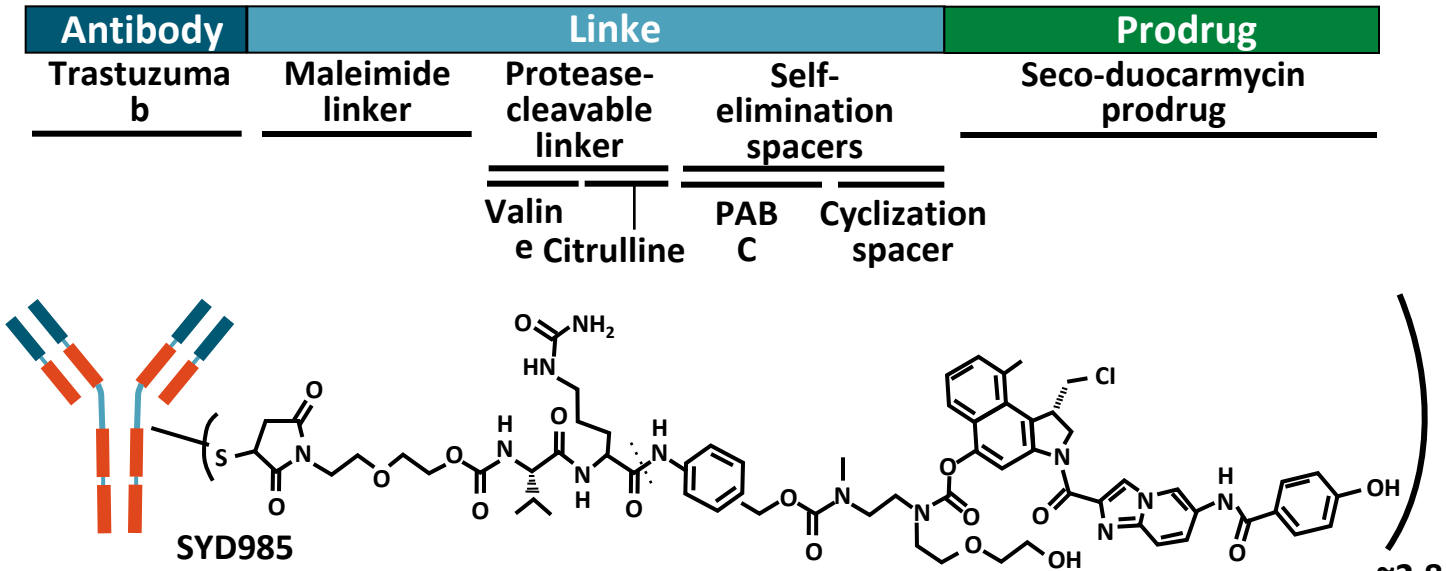
On December 20, 2019
Food and Drug Administration (FDA)

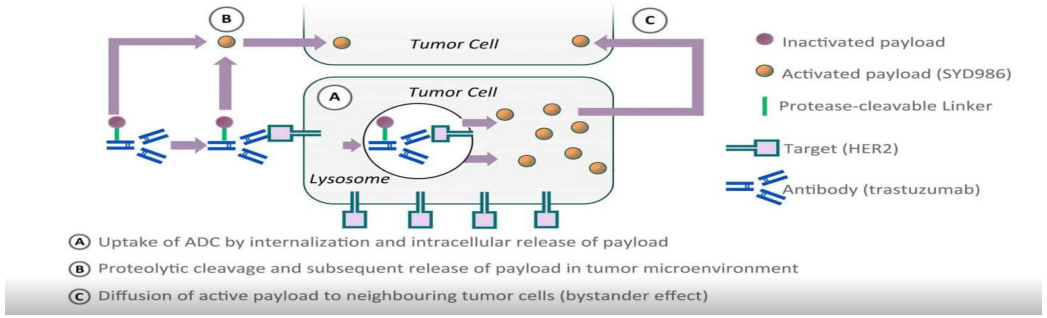
- approved the use of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive breast cancer who have undergone at least two anti-HER2 regimens.

HER2-Targeted ADC: Trastuzumab Duocarmazine (SYD985)

- HER2 antibody with same amino acid sequence as trastuzumab
- Proteolytic cleavage of linker in tumor microenvironment leads to activation of prodrug payload
- Active toxin (DUBA) alkylates DNA, kills dividing and nondividing cells
- Bystander killing effect

Trastuzumab-vc-seco-duocarmycin-hydroxybenzamide-azaindole

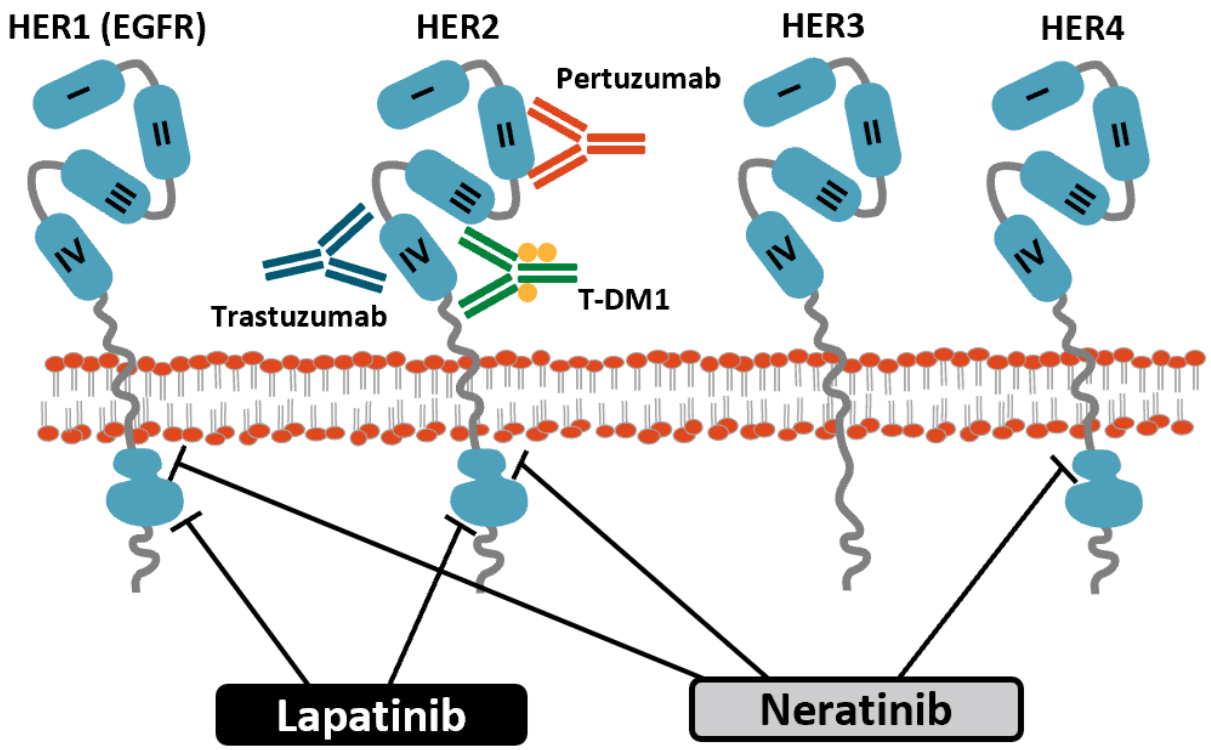




Dokter. Mol Cancer Ther. 2014;13:2618. Elgersma. Mol Pharm. 2015;12:1813.

Code3 : HER2-targeted tyrosine kinase inhibitors (TKIs)/capecitabine

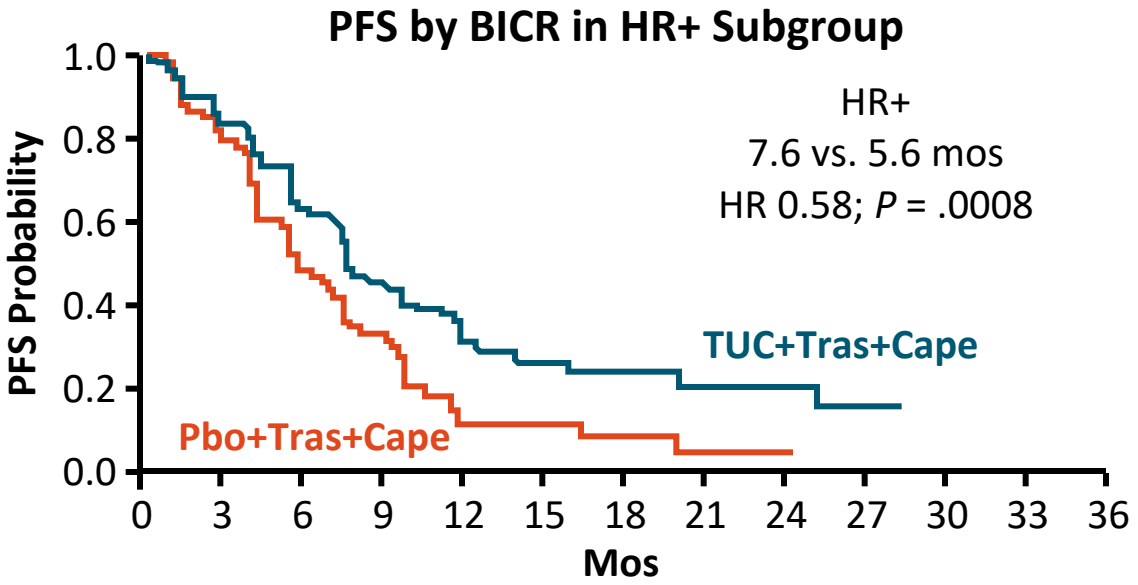
- New agent is better or less side effect
- Better choice in brain metastases

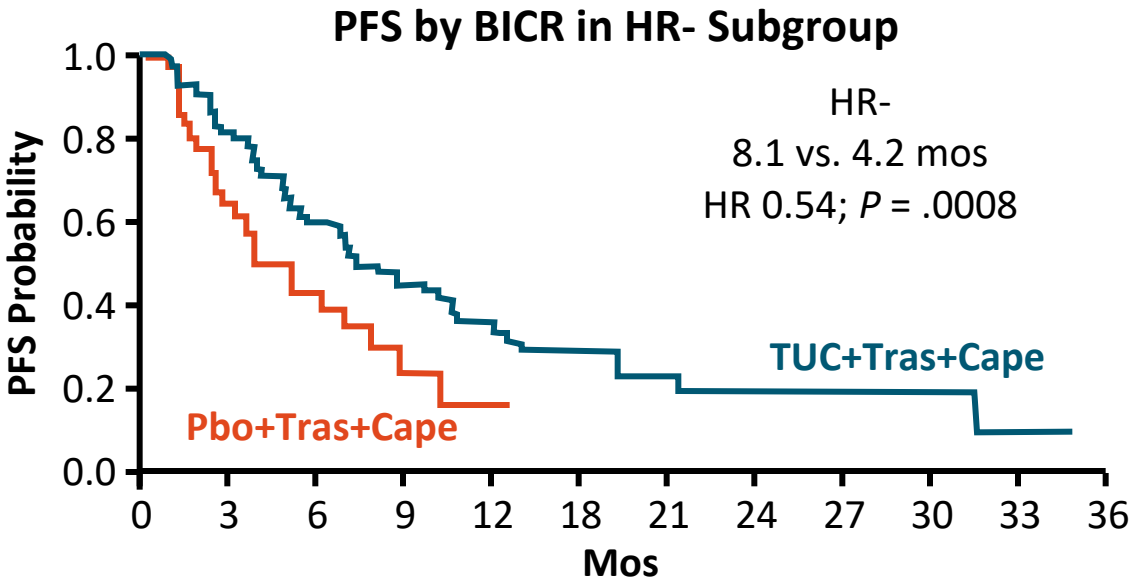


Lapatinib , Tucatinib, Neratinib

- An orally HER1 and HER2 tyrosine kinases inhibitor is superior in (lapatinib+capecitabine vs capecitabine alone in the treatment of metastatic breast cancer (MBC) that had progressed after trastuzumab-based therapy
- Tucatinib : oral HER2 tyrosine kinase inhibitor that is highly selective for the kinase domain and, unlike other HER2 tyrosine kinase inhibitors, has minimal inhibition of epidermal growth factor receptor, which may lead to a more favorable safety profile.

HER2CLIMB: PFS by HR Status





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Hamilton. SABCS 2020. Abstr 117.

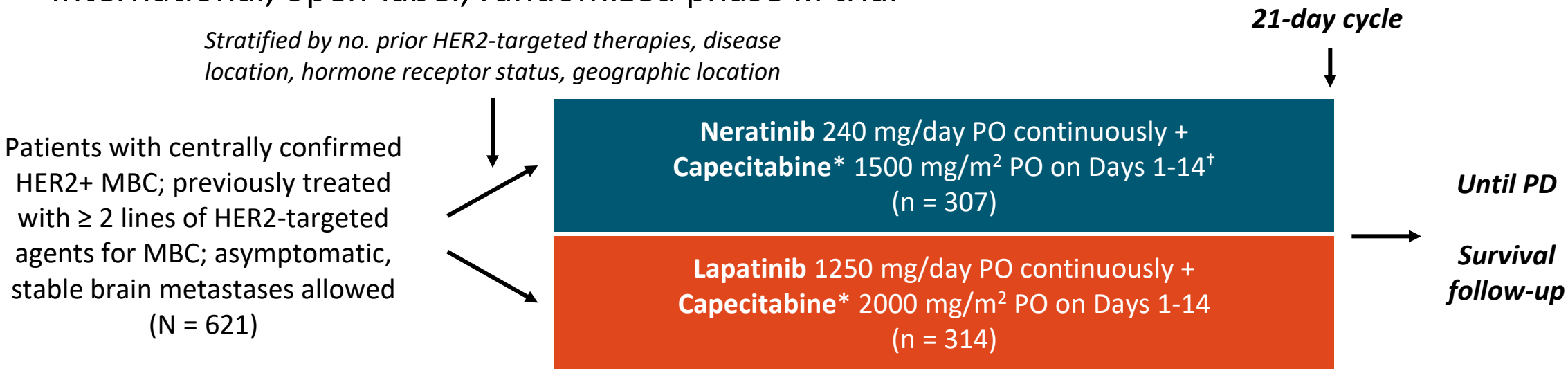
Slide credit: clinicaloptions.com

ExteNET trial (Neratinib)

- Invasive disease-free survival (iDFS) at 24 months was 94.2% in patients treated with neratinib vs 91.9% (placebo) (HR, 0.66; 95% CI, 0.49-0.90;*P*= .008).
- In terms of lymph nodes, patients with ≥4 positive nodes experienced a higher rate of iDFS benefit with neratinib versus placebo (91.4% vs 87.3%, respectively) than did those with negative nodes or 1 to 3 positive nodes.
- The phase III NALA trial
  - Neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer who failed 2 or more prior lines of HER2-directed therapy.
  - The neratinib combination also improved overall survival, but no significant (*P*= .21)

NALA: Neratinib/Cape vs Lapatinib/Cape in HER2+ MBC With ≥ 2 Prior Lines of HER2-Targeted Agents

- International, open-label, randomized phase III trial



*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hrs through end of cycle 1; as needed thereafter.

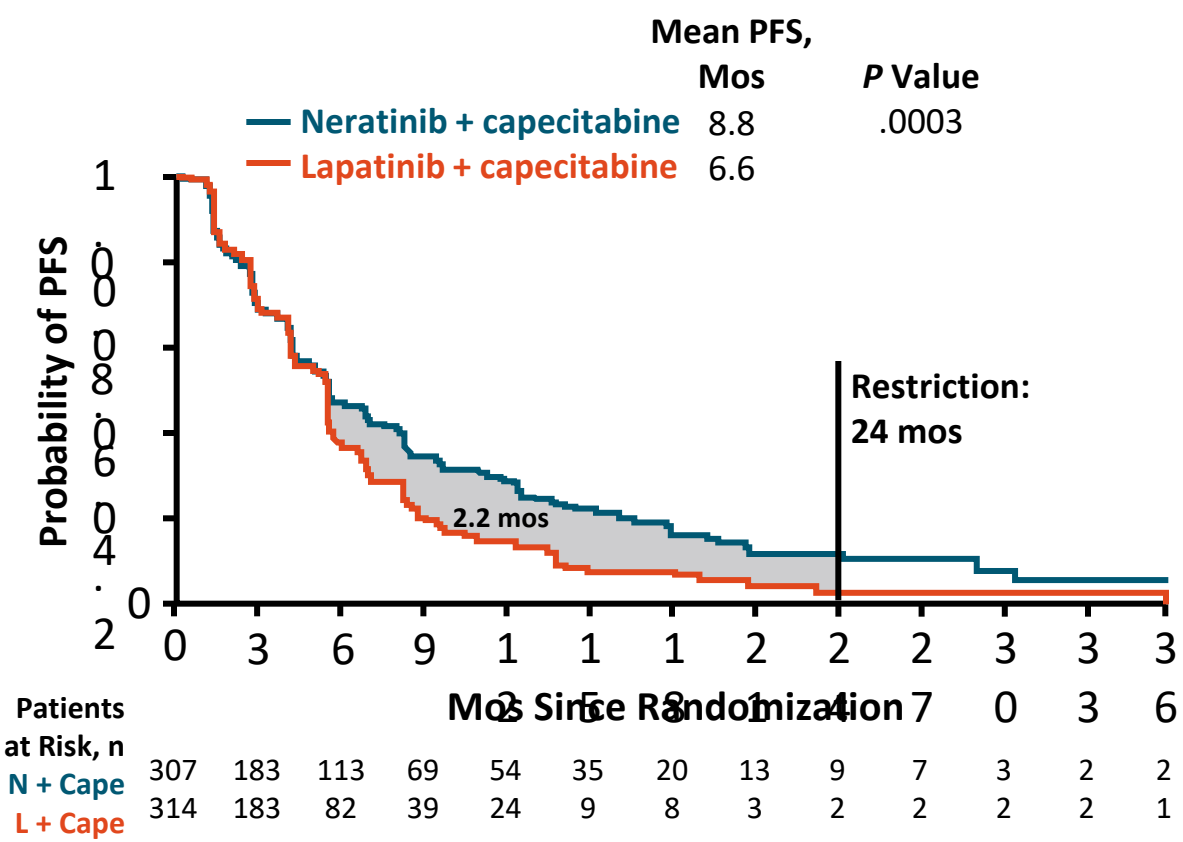
- Coprimary endpoints: OS, PFS (centrally confirmed)
  - Study positive if either endpoint statistically significant (OS, $P < .04$; PFS, $P < .01$)
- Secondary endpoints: PFS (locally determined), ORR, DoR, CBR, intervention for CNS metastases, safety, PRO
- No endocrine therapy permitted

Saura. J Clin Oncol. 2020; 38:3138.

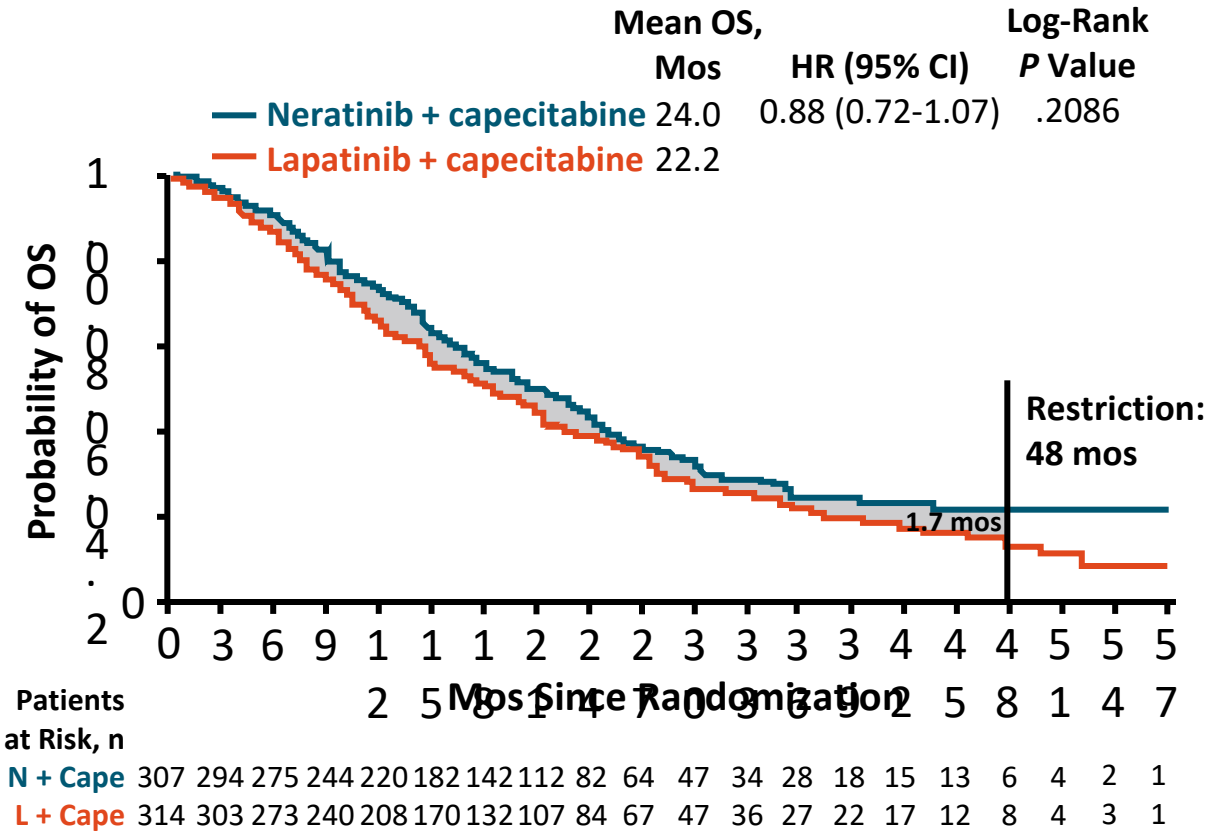
Slide credit: clinicaloptions.com

NALA: Survival

PFS (Prespecified Means Analysis)



OS (Coprimary Endpoint)



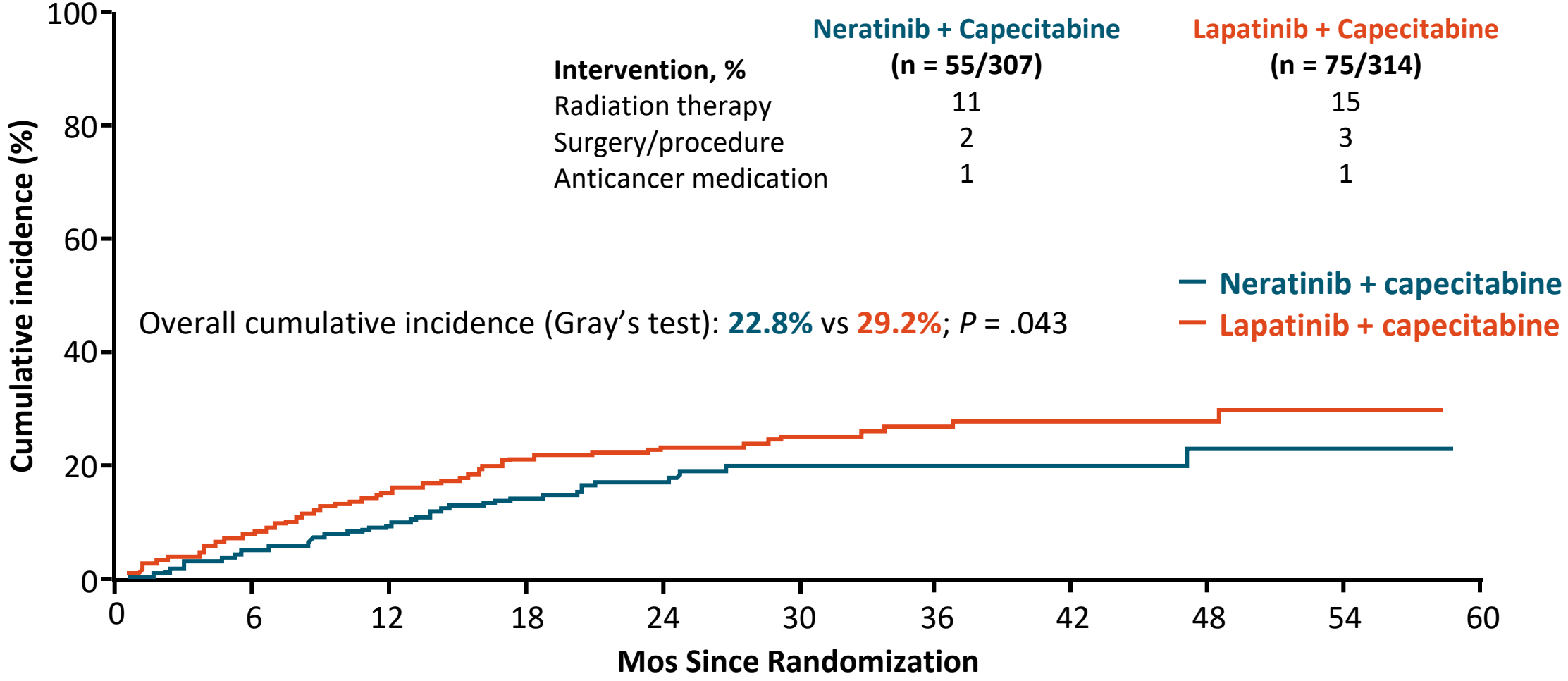
Saura. J Clin Oncol. 2020;38:3138.

Slide credit: clinicaloptions.com

NALA: Time to Intervention for CNS Metastases

Intervention, %	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11	15
Surgery/procedure	2	3
Anticancer medication	1	1

Overall cumulative incidence (Gray's test): **22.8%** vs **29.2%**; *P* = .043

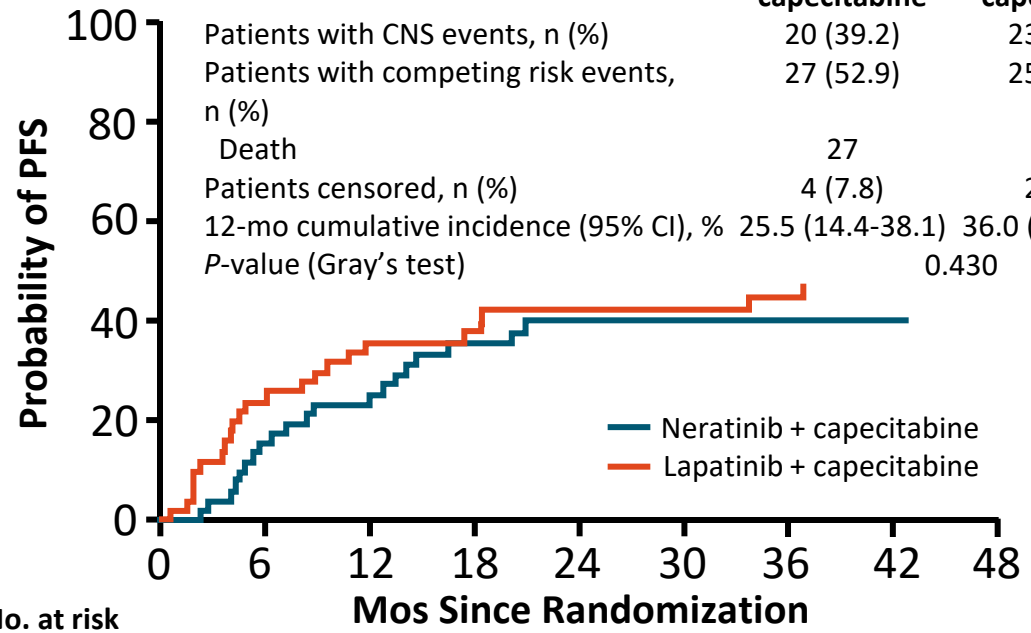


Saura. J Clin Oncol. 2020;38:3138.

Slide credit: clinicaloptions.com

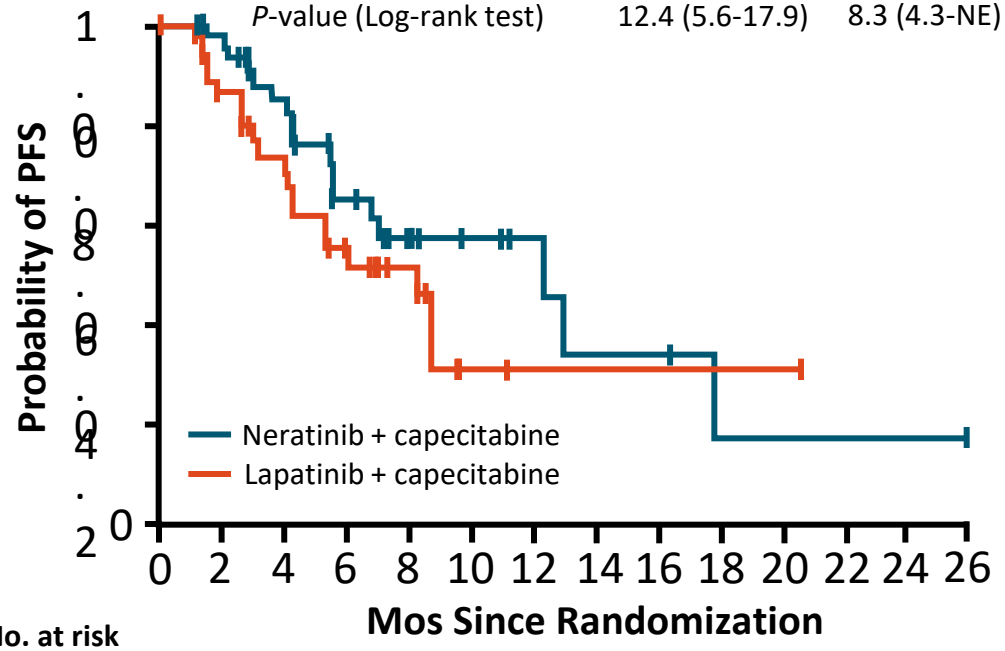
NALA: CNS-Specific Outcomes in Patients with CNS Metastases at Baseline

	Neratinib + capecitabine	Lapatinib + capecitabine
Patients with CNS events, n (%)	20 (39.2)	23 (46.0)
Patients with competing risk events, n (%)	27 (52.9)	25 (50.0)
Death	27	25
Patients censored, n (%)	4 (7.8)	2 (4.0)
12-mo cumulative incidence (95% CI), %	25.5 (14.4-38.1)	36.0 (22.9-49.3)
P-value (Gray's test)	0.430	



No. at risk									
Neratinib + capecitabine	51	39	21	10	3	2	1	1	0
Lapatinib + capecitabine	50	34	17	10	4	2	1	0	0

Patients with events, n (%)	Neratinib + capecitabine	Lapatinib + capecitabine
Median (95% CI), mos	17 (33.3)	21 (42.0)
HR (95% CI)	12.4 (5.6-17.9)	8.3 (4.3-NE)
P-value (Log-rank test)		



No. at risk														
Neratinib + capecitabine	51	46	30	17	12	8	5	3	3	1	1	1	1	1
Lapatinib + capecitabine	50	36	25	15	10	2	1	1	1	1	1	0	0	0

Leptomeningeal disease (LMD): pts with LMD at enrollment (n=3):

- 2 pts received N+C; disease progression:5.6 & 9.8 mos; OS 17.4 &19.8 mos
- 1 pt received L+C; disease progression: 4.3 mos; OS 6.5 mos.

Saura. J Clin Oncol. 2020; 38:3138. Saura. SABCS 2020. Abstr. PD-13-09.

Slide credit: clinicaloptions.com

NALA: Safety

- Median duration of treatment numerically longer with neratinib vs lapatinib (5.7 vs 4.4 mos)
- D/c due to treatment-emergent AEs: neratinib arm, 10.9%; lapatinib arm, 14.5%

Treatment-Emergent AE, %	Neratinib + Capecitabine (n = 303)		Lapatinib + Capecitabine (n = 311)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Overall	100	61	99	60
Diarrhea	**83**	**24***	66	13*
Hand–foot syndrome	46	10	**56**	11
Hypokalemia	12	5	14	6
Nausea	**53**	4	42	3
Vomiting	**46**	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	**35**	3	22	2
Dehydration	6	2	6	2

*No grade 4 diarrhea observed

Saura. J Clin Oncol. 2020; 38:3138. Saura. SABCS 2020. Abstr. PD-13-09.

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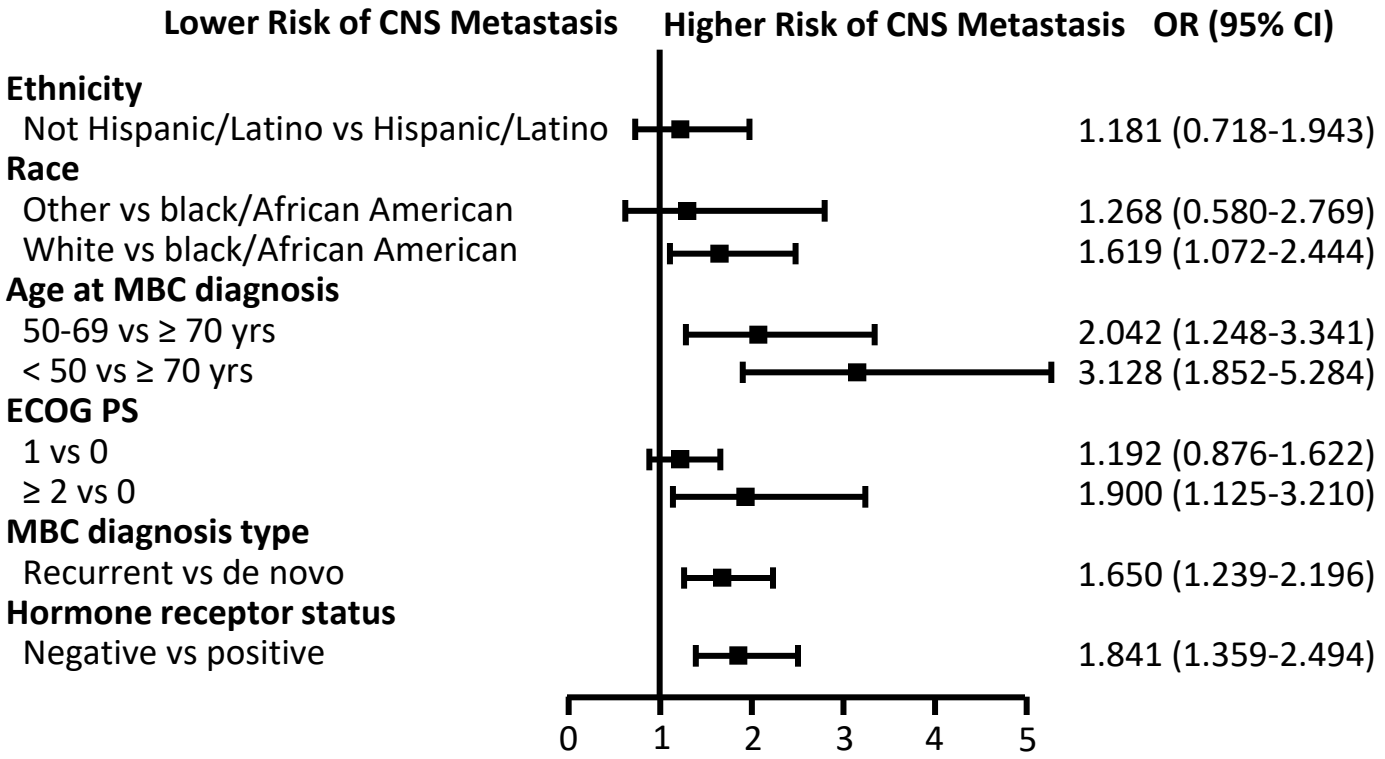
In HER2+ MBC, CNS Disease Remains Incurable Despite Current Treatment Options

- ≥ 50% of patients with HER2+ MBC will develop brain metastases[1]
- Lapatinib + capecitabine is approved option in the setting but few patients respond[2]
  - In a pooled analysis, achieved a CNS ORR of 21.4%, median PFS of 4.1 mos, and median OS of 11.2 mos[1]
- Neratinib + capecitabine also approved for this setting with CNS ORR of 33%[3,4]
- T-DM1, trastuzumab, and pertuzumab do not penetrate the CNS under normal conditions

Risk of CNS Metastasis in HER2+ MBC by Subgroup[5]



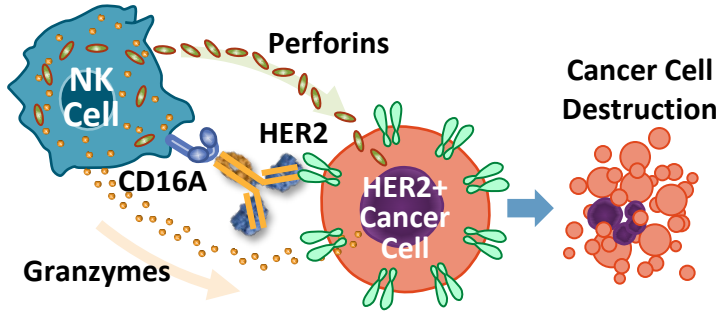
1. Petrelli. Eur J Cancer. 2017;84:141. 2. Lapatinib PI. 3. Freedman. JCO. 2019;13:1081. 4. Neratinib PI.
5. Hurvitz. Clin Cancer Res. 2019;25:2433.

Slide credit: clinicaloptions.com

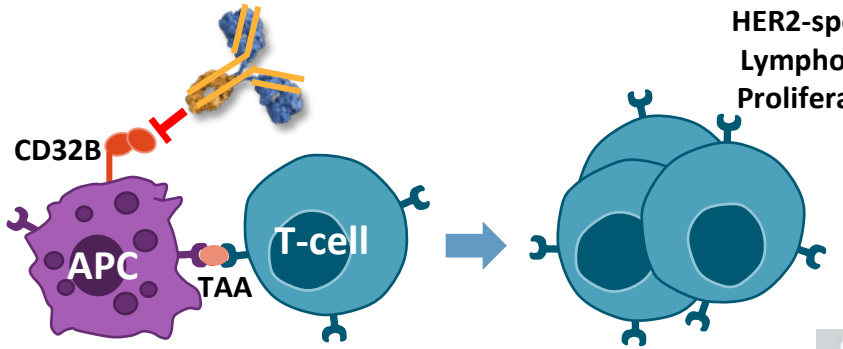
Margetuximab: Fc Engineering Alters Fc Receptor Affinities and Activates the Immune Response

- Margetuximab has the same specificity, affinity to HER2 as trastuzumab with similar ability to disrupt signaling
- However, via Fc engineering with intent to activate immune responses, margetuximab has altered Fc receptor affinity
  - Trastuzumab: WT IgG1 effector domains; binds and activates immune cells
  - Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)

Increased CD16A Affinity:
Enhance Innate Immunity/More Potent ADCC Stimulation



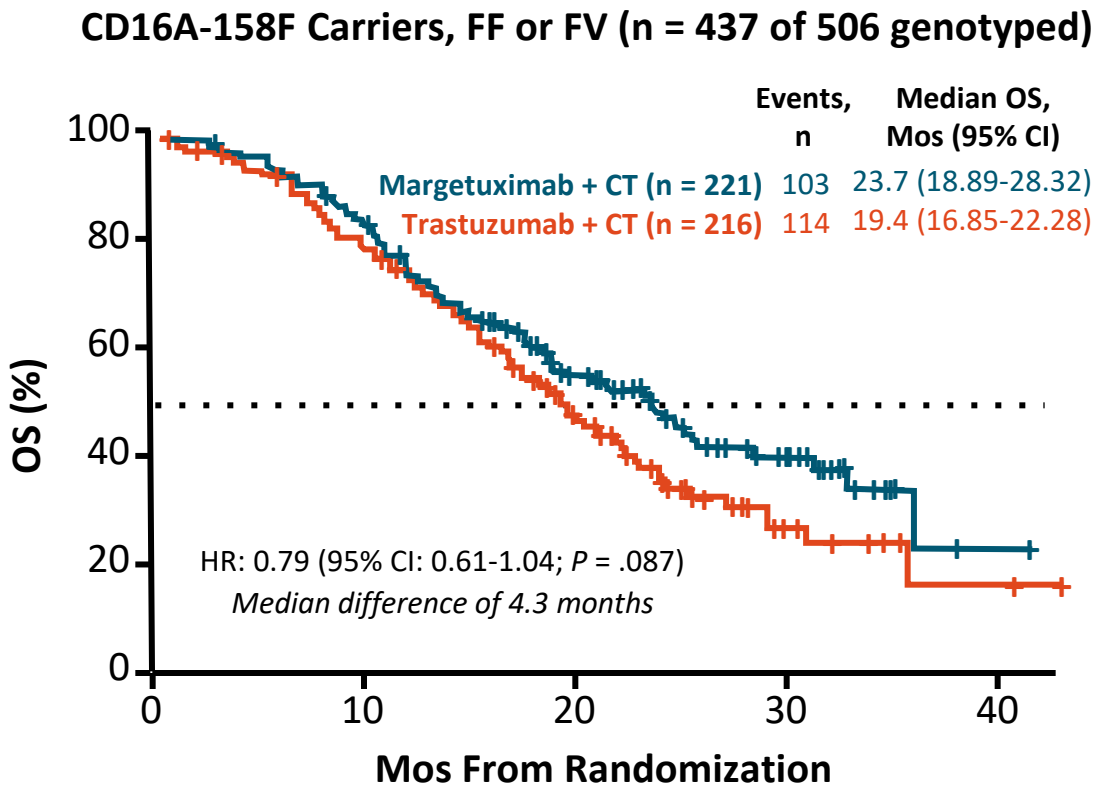
Decreased CD32B Affinity:
Enhance Adaptive Immunity/Increase Immune Activation

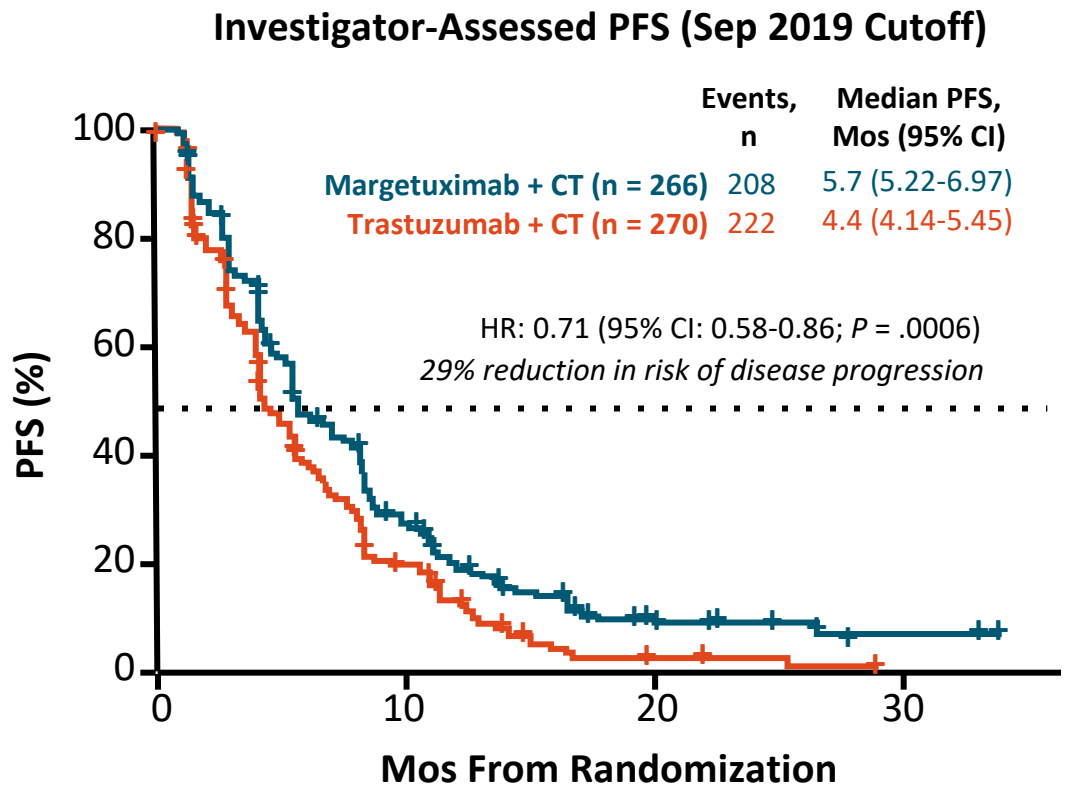


Nordstrom. Breast Cancer Res. 2011;13:R123. Nordstrom. ASCO 2019. Abstr 1030. Stavenhagen. Cancer Res. 2007;67:8882.

Slide credit: clinicaloptions.com

SOPHIA: Investigator-Assessed PFS, and Exploratory OS in CD16A-158F Carriers



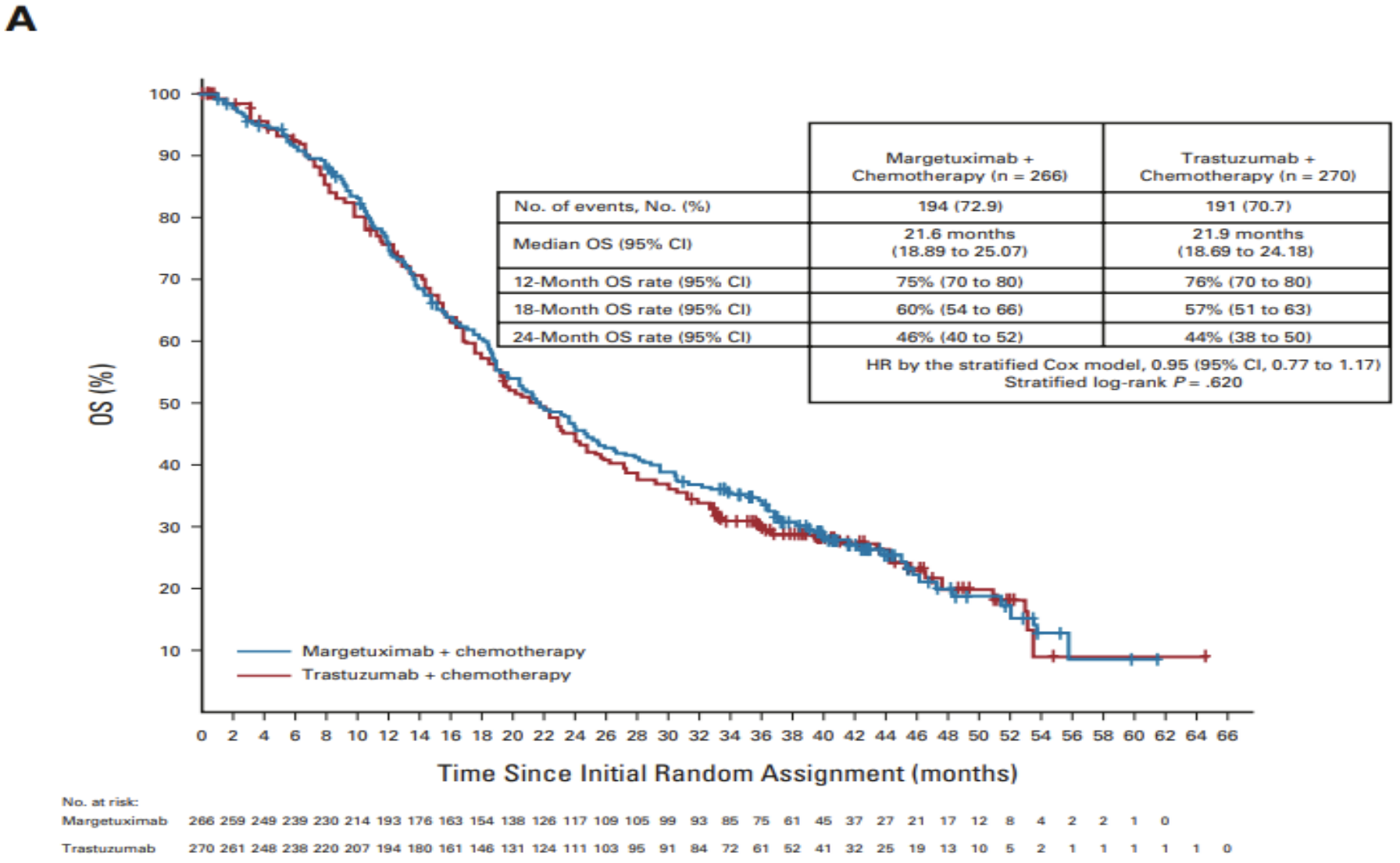


- 12.16.20: Margetuximab was FDA approved in combination with chemotherapy as 3rd or greater line therapy for metastatic HER2+ BC

Rugo. SABCS 2019. Abstr GS1-02.

Slide credit: clinicaloptions.com

Margetuximab + CT resulted in improved PFS and ORR vs trastuzumab + CT in patients with HER2+ MBC after ≥ 2 previous lines of anti-HER2 therapy.

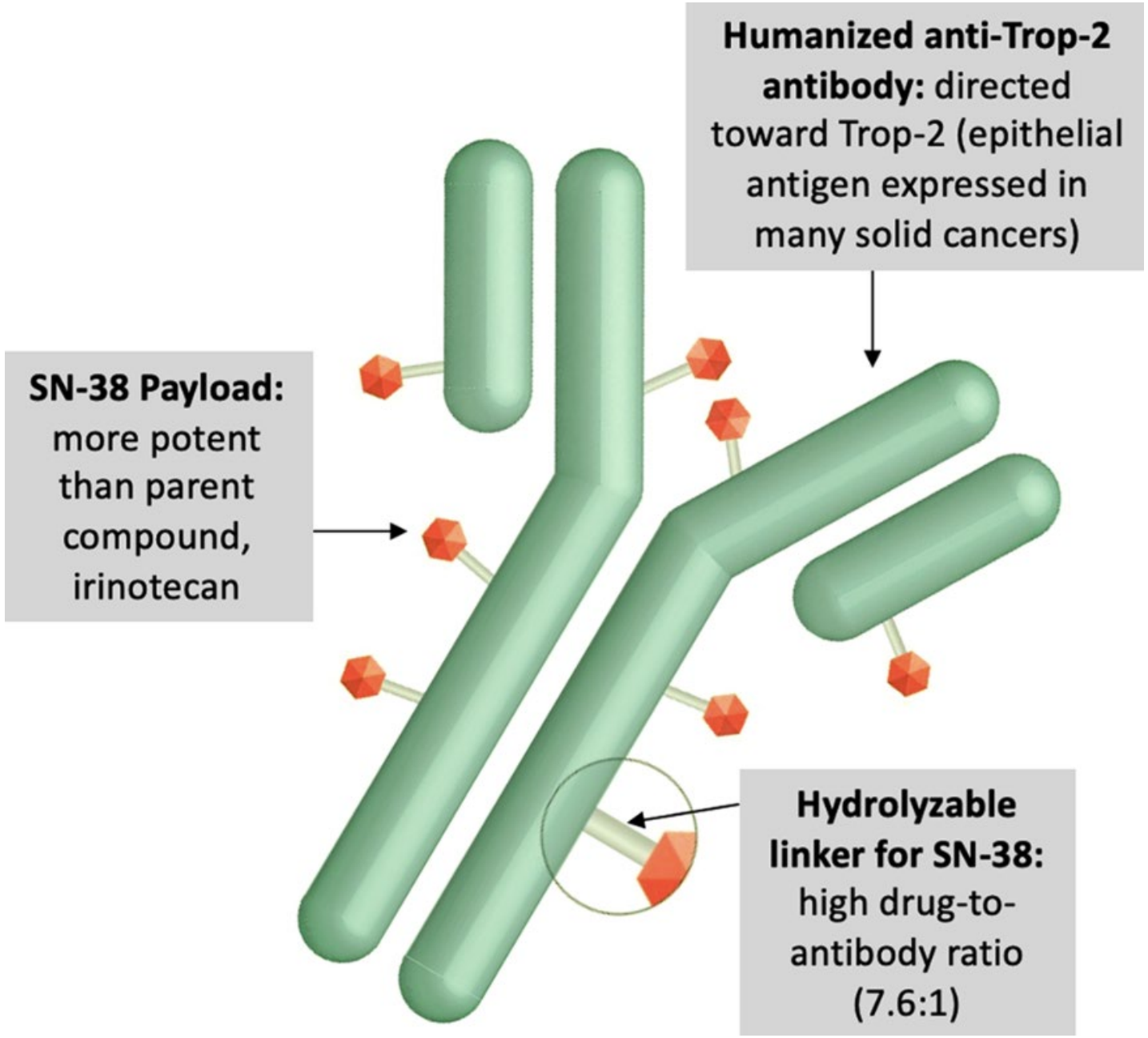


	Margetuximab + Chemotherapy (n = 266)	Trastuzumab + Chemotherapy (n = 270)
No. of events, No. (%)	194 (72.9)	191 (70.7)
Median OS (95% CI)	21.6 months (18.89 to 25.07)	21.9 months (18.69 to 24.18)
12-Month OS rate (95% CI)	75% (70 to 80)	76% (70 to 80)
18-Month OS rate (95% CI)	60% (54 to 66)	57% (51 to 63)
24-Month OS rate (95% CI)	46% (40 to 52)	44% (38 to 50)
HR by the stratified Cox model, 0.95 (95% CI, 0.77 to 1.17) Stratified log-rank *P* = .620		

- The median OS was 21.6 months with margetuximab versus 21.9 months (7 to 1.17; P = .620).
- Exploratory analysis of CD16A genotyping suggested a possible improvement in OS for margetuximab in CD16A-158FF patients versus trastuzumab (median OS, 23.6 v 19.2 months; HR, 0.72) and a possible improvement in OS for trastuzumab in CD16A-158VV patients versus margetuximab (median OS, 31.1 v 22.0 months; HR, 1.77).
- Margetuximab safety was comparable with trastuzumab.
- Final overall OS analysis did not demonstrate margetuximab advantage over trastuzumab.
- Epidermal growth factor receptor 2-positive breast cancer with different CD16A allelic variants are warranted.

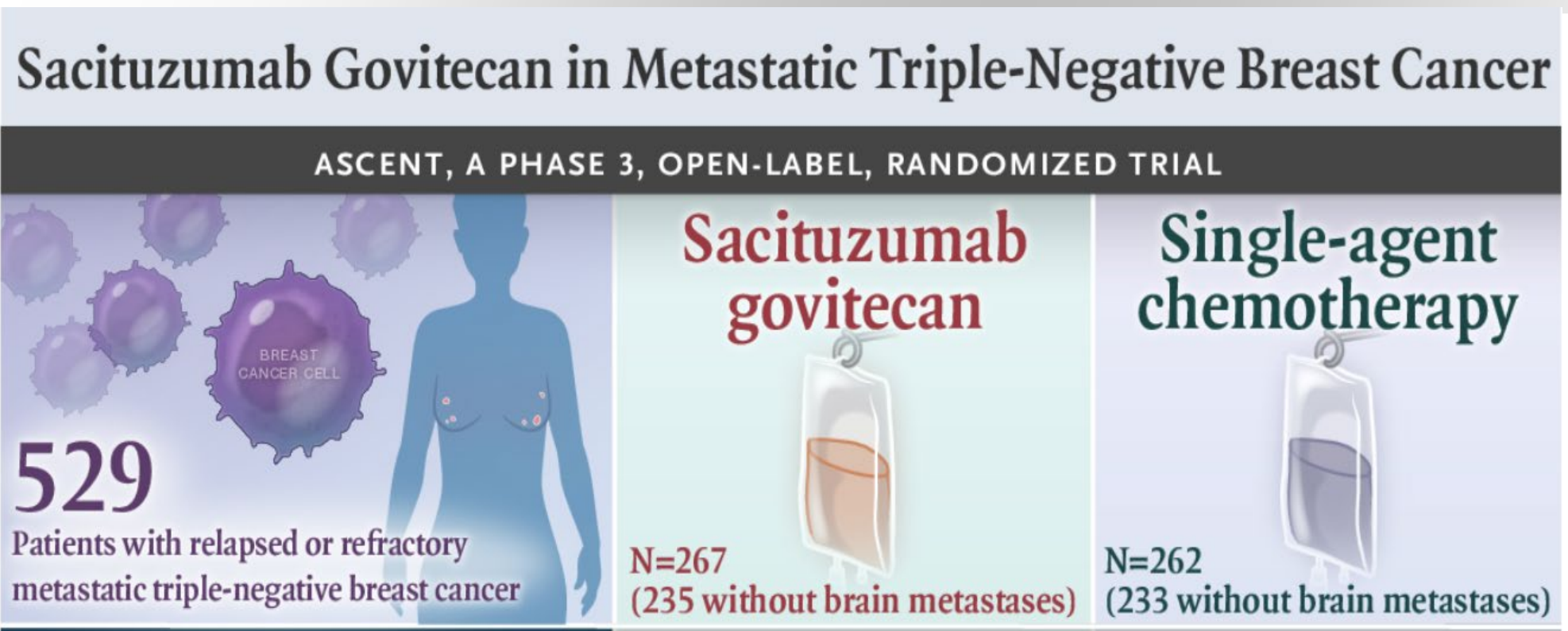
J Clin Oncol. 2023 Jan 10;41(2):198-205.

Sacituzumab govitecan



The Oncologist, Volume: 26, Issue: 10, Pages: 827-834,

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer



A. Bardia et al. 10.1056/NEJMoa2028485

Sacituzumab 10 mg/kg IV on days 1, 8 every 21 day
or single-agent chemotherapy as : eribulin 1.4 mg/m2 on days 1, 8 of a 21-day cycle, vinorelbine 25 mg /m2y on day 1 weekly), capecitabine 1000 to 1250 mg/m2 orally bid on days 1 to 14 of a 21-day cycle), or gemcitabine (800 to 1200 mg /m2 IV on days 1, 8, and 15 of a 28-day cycle).

Thank you for listening

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搜尋結果均以本站制定的格式編寫，提供專業人士及一般民眾更易閱讀的藥物資訊！

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