The HER2+ Continuum:
Risk Stratification as the Foundation for Survival

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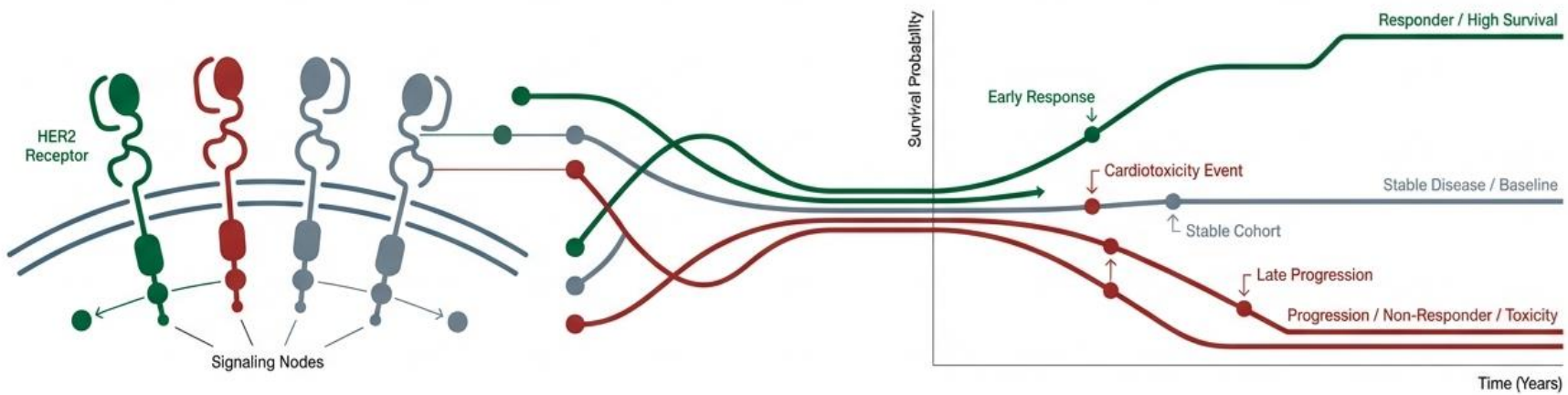
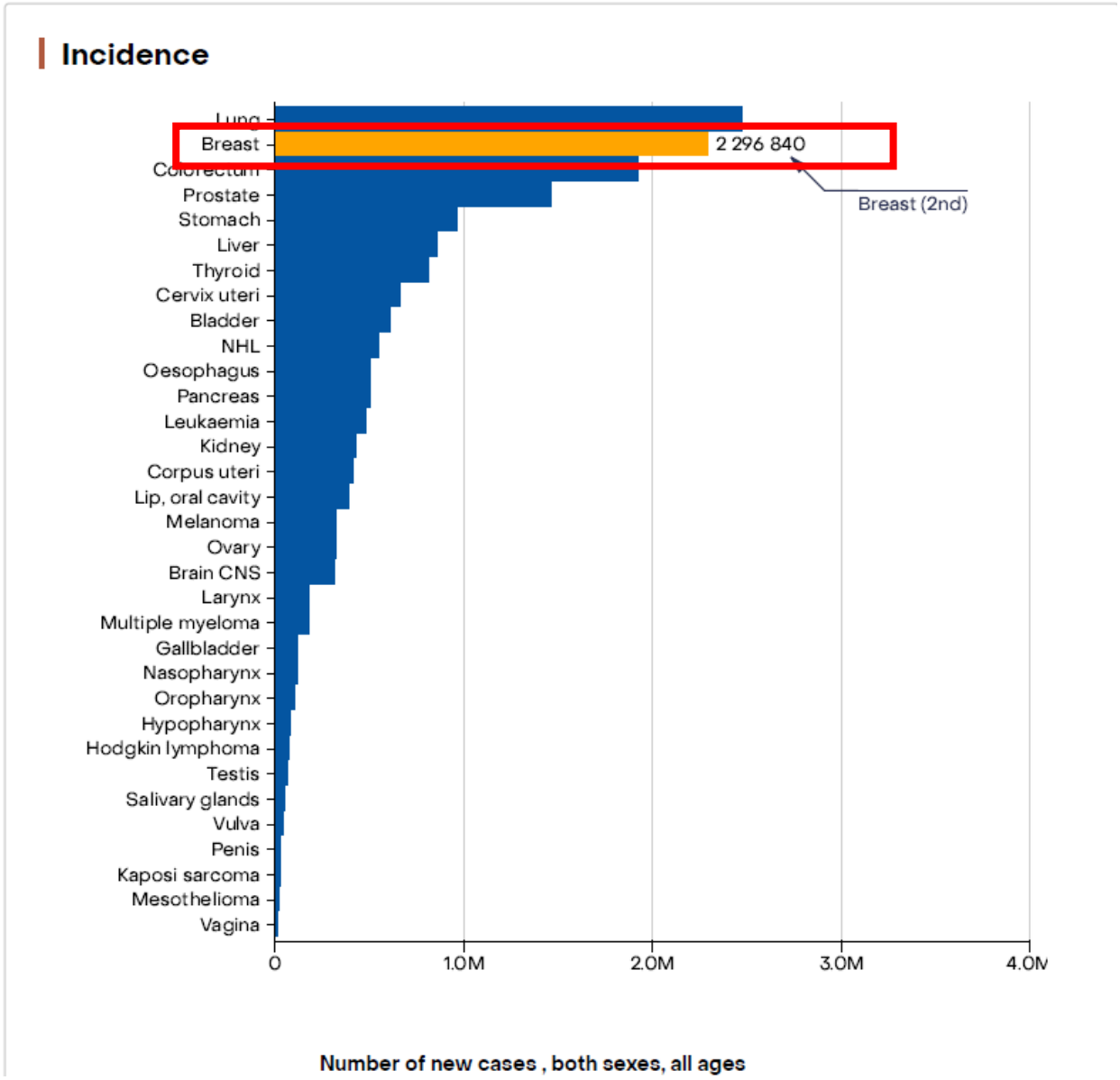
The HER2+ Continuum: Risk Stratification as the Foundation for Survival

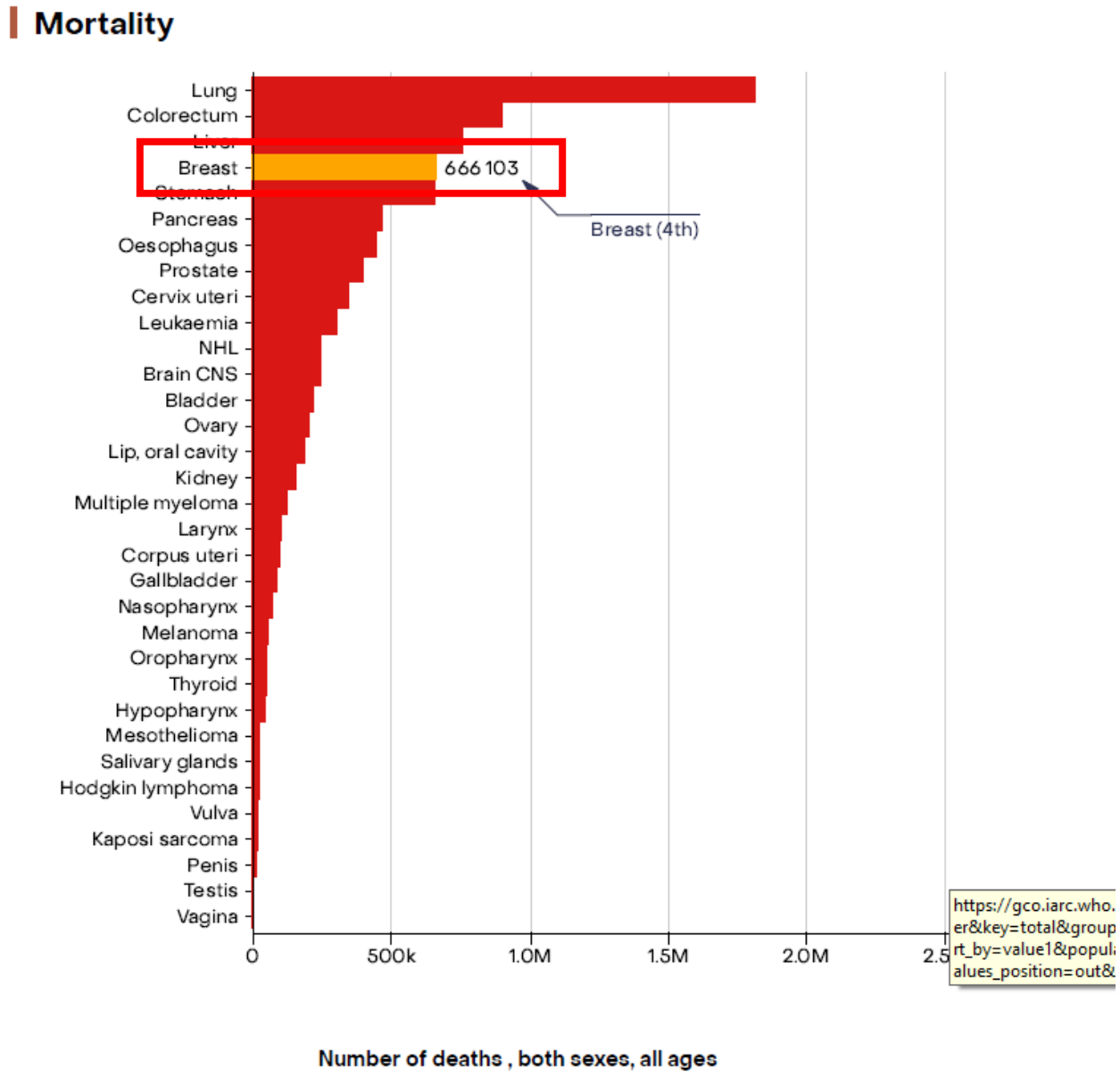
Biology, Patient Journey, and the Balance of Efficacy and Cardiotoxicity



Breast Cancer Epidemiolog Globocan, 2022

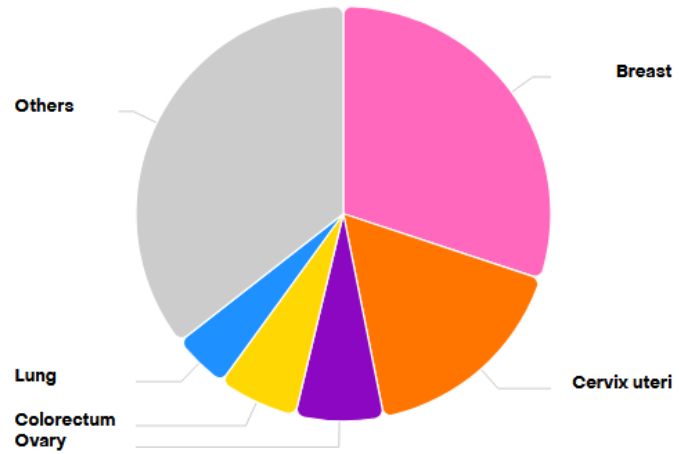


Breast Cancer Epidemiology Globocan, 2022



Breast Cancer Epidemiology in Indonesia Globocan, 2022

Females

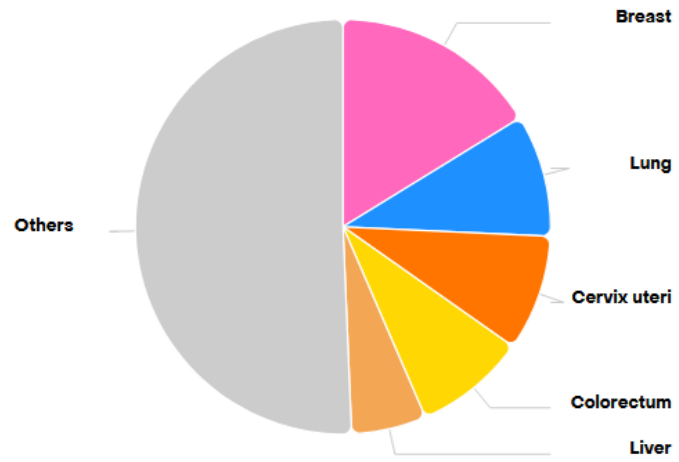


Total: 220 266

Rank	Cancer site	Number of cases	Percent
1st	Breast	66 271	30.1%
2nd	Cervix uteri	36 964	16.8%
3rd	Ovary	15 130	6.9%
4th	Colorectum	13 773	6.3%
5th	Lung	9 797	4.4%
-	Others	78 331	35.6%

Number of new cases in 2022, females, all ages

Both sexes

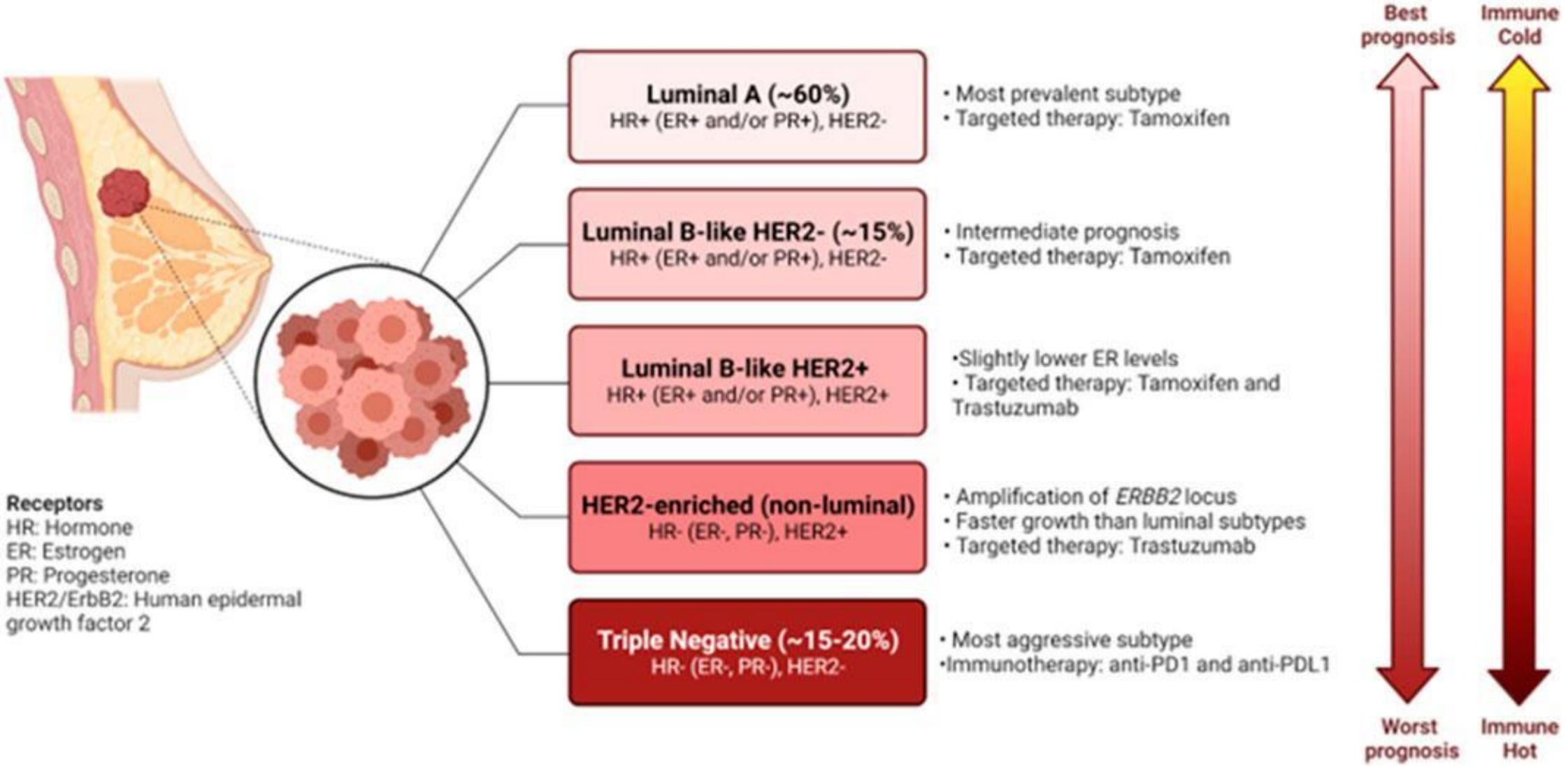


Total: 408 661

Rank	Cancer site	Number of cases	Percent
1st	Breast	66 271	16.2%
2nd	Lung	38 904	9.5%
3rd	Cervix uteri	36 964	9.0%
4th	Colorectum	35 676	8.7%
5th	Liver	23 805	5.8%
-	Others	207 041	50.7%

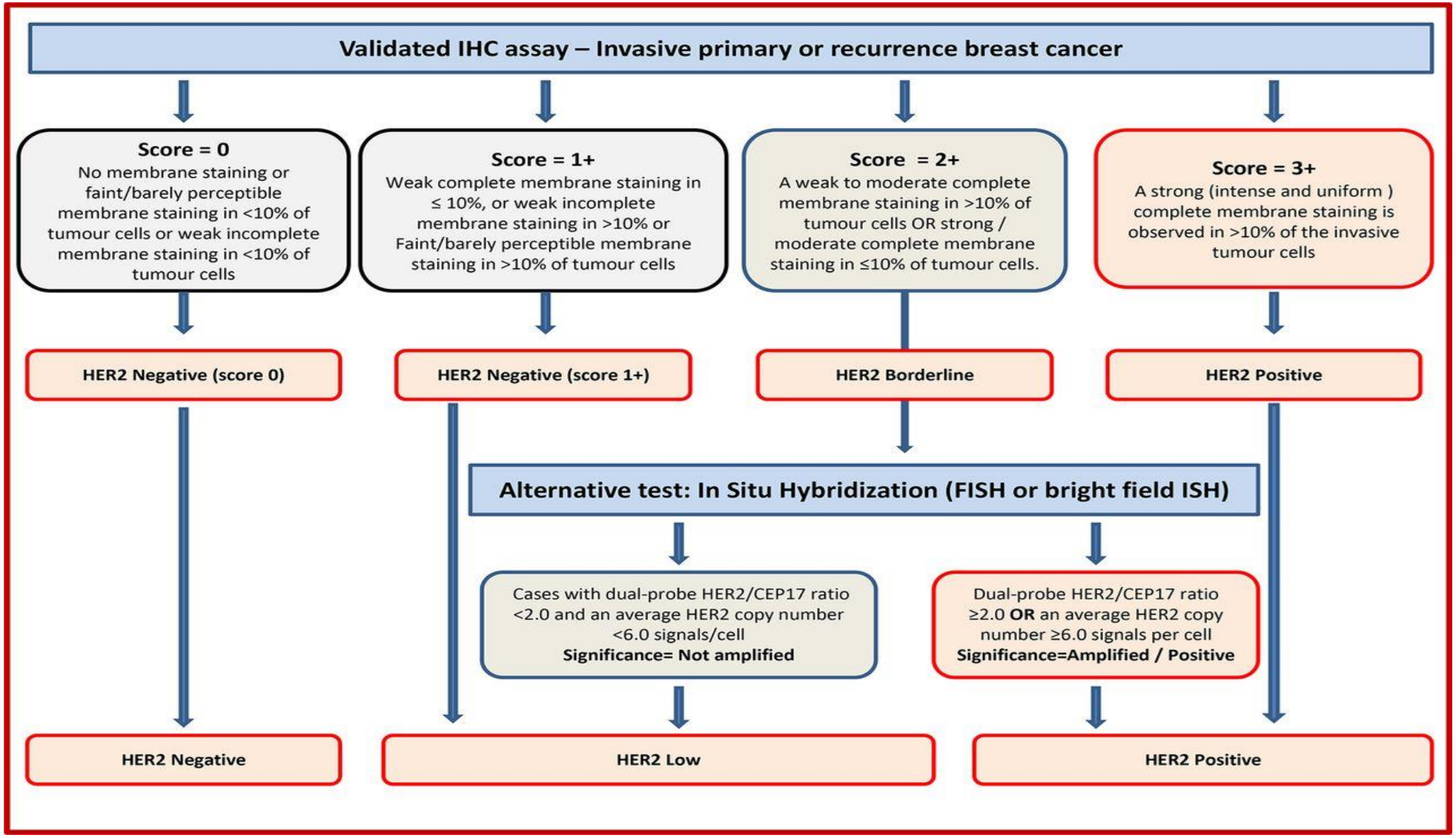
Number of new cases in 2022, both sexes, all ages

Molecular Subtype of Breast Cancer



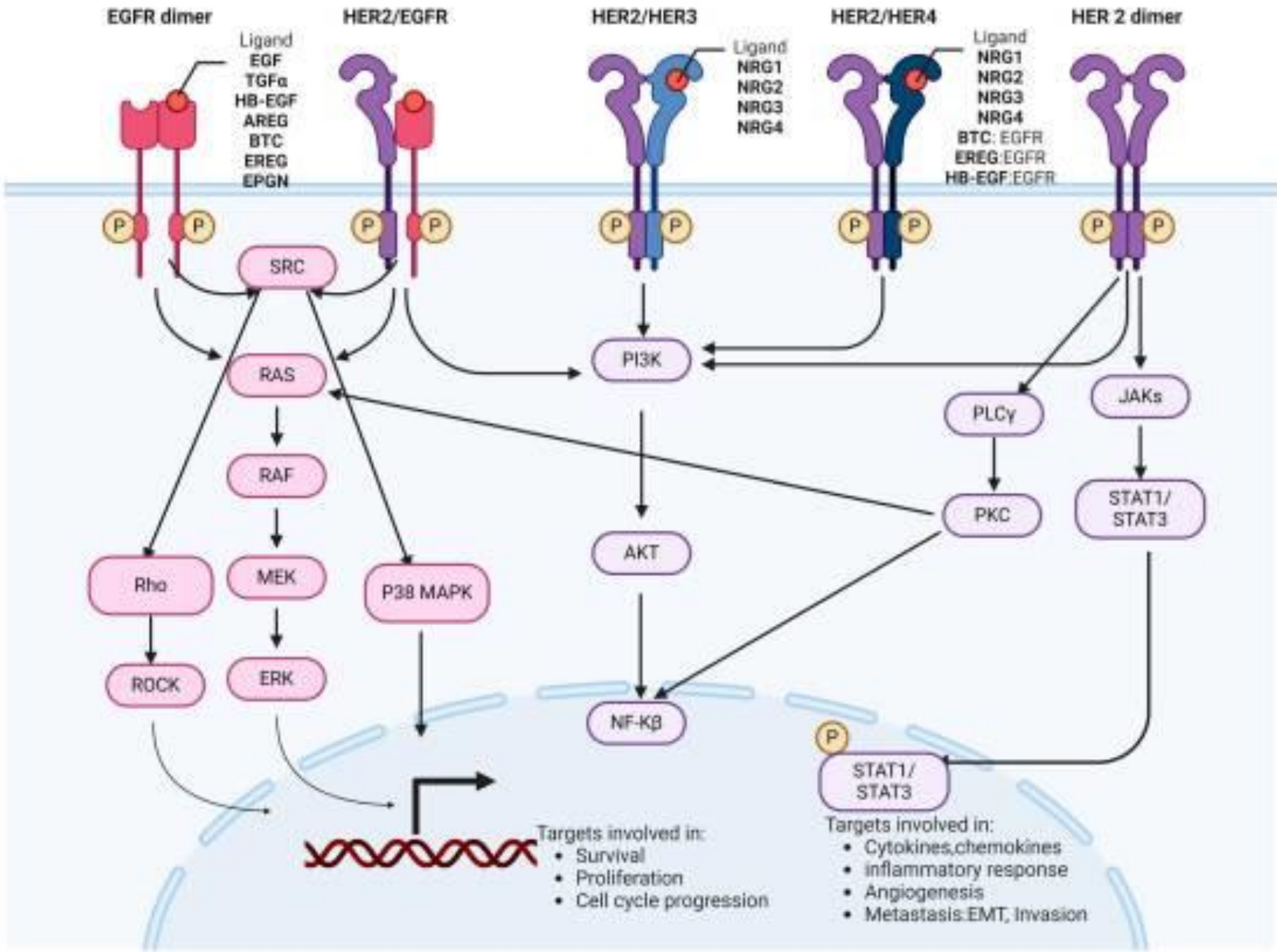
Front. Cell Dev. Biol., 22 February 2023

Algorithms to Determine HER2 Status

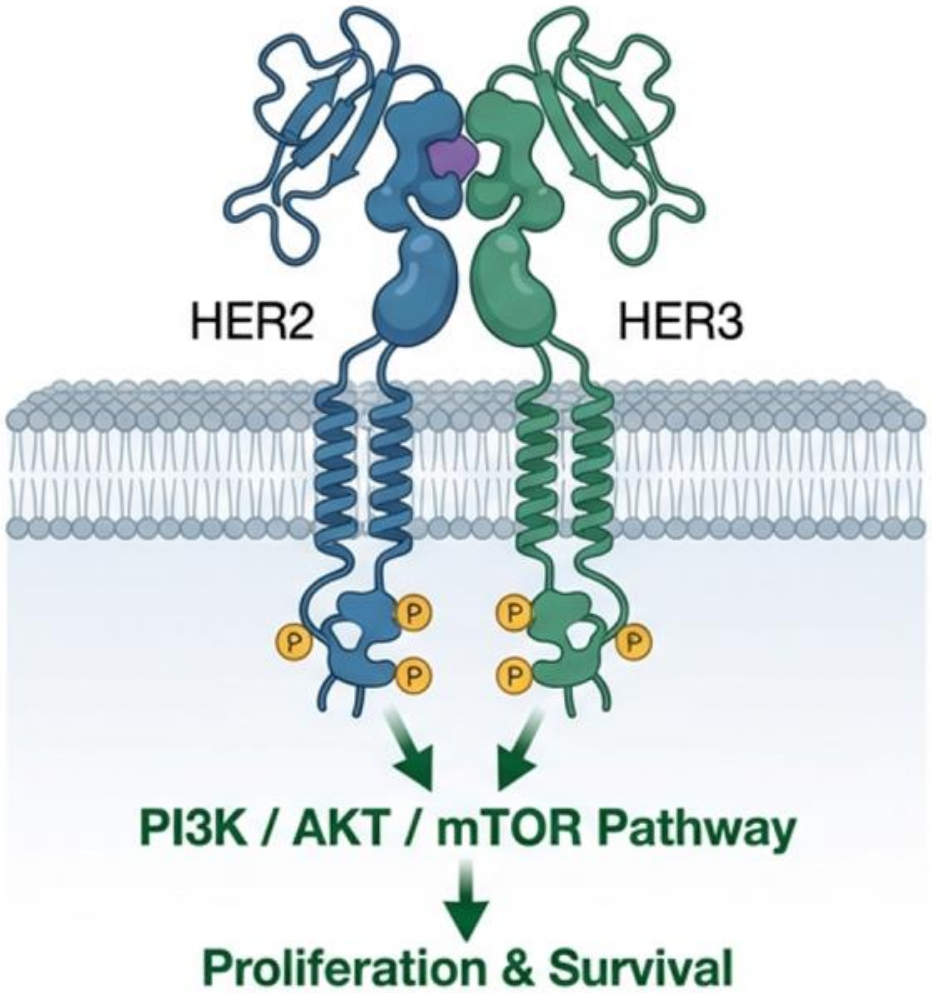


UK recommendations for HER2 assessment in breast cancer: an update. https://doi.org/10.1136/jcp-2022-208632

HER2 Signaling Pathway



The Biological Driver: HER2 Amplification and Signaling Heterogeneity



Mechanism of Aggression:
HER2 amplification drives tumor biology through enhanced cell proliferation and survival signaling pathways. It acts as a potent prognostic marker for aggressive disease outcomes.

The Continuum of Biology:
HER2 status is dynamic. Heterogeneity exists in expression levels and crosstalk with ER signaling pathways (HR+/HER2+ vs. HR-/HER2+), influencing the continuum from early breast cancer (EBC) to metastatic recurrence.

Predictive Utility:
Overexpression serves as the primary predictive marker for response to targeted monoclonal antibodies (trastuzumab, pertuzumab) and tyrosine kinase inhibitors.

[1] Gianni L, et al. *Lancet*. 2010;375:377-84. [2] Zhou J, et al. *Ann Transl Med*. 2022;10(24):1387.

The Paradigm Shift: From Operability to Biological Intelligence

Historical Paradigm

Goal: Shrinkage for Operability

Focus: Local Control

Neoadjuvant Therapy reserved for inoperable/advanced cases.

Current Standard: Pan-Asian ESMO 2024

Goal: Biological Risk Stratification

Focus: Long-term Survival

Neoadjuvant Therapy is an **ethical obligation** for high-risk patients (T>2cm or Node+).

> Patients with intermediate to high-risk HER2-positive disease (≥T2 and/or lymph-node positive) **must** receive neoadjuvant treatment to stratify long-term survival.
>
> — *Adapted from Pan-Asian ESMO Consensus Guidelines.*

Neoadjuvant Therapy as an In Vivo Stratification Tool

Diagnosis → **Neoadjuvant Systemic Therapy (NST)** → **Surgery** → **Adjuvant Stratification**

Biopsy & Staging
(≥T2 or ≥N1)

In Vivo
Sensitivity Test

Response
Assessment

pCR vs.
Residual Disease

Paradigm Shift:

The neoadjuvant setting has evolved from a method to achieve operability to a critical in vivo test of chemosensitivity and biological response.

The Primary Endpoint:

Pathological complete response (pCR), defined as ypT0/is ypN0, serves as a validated surrogate for long-term survival in HER2+ disease.

Guideline Recommendations:

Preoperative systemic chemotherapy combined with trastuzumab-based therapy is the standard of care for HER2+ tumors ≥T2 or ≥N1.

Assessment Difficulty:

Accurate assessment requires tracking abnormal findings from diagnosis; MRI is superior to mammography for response monitoring.

[3] Eckert JC, et al. *Ann Surg Oncol*. 2023;31:63-69. [4] Jackisch C, et al. *Eur J Cancer*. 2016;62:62-75. [5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2

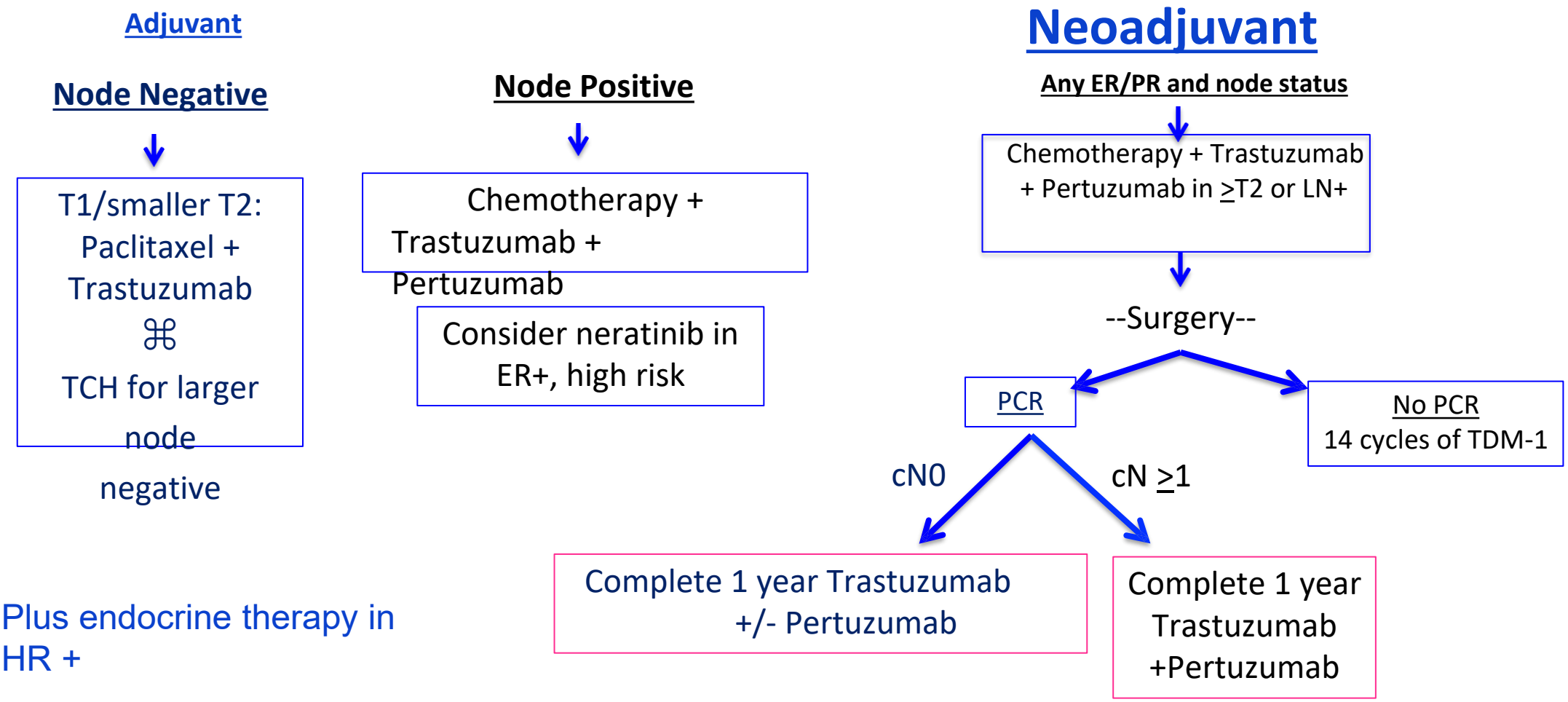
HER2 RISK STRATIFICATION AND THERAPY

HER2 Risk Stratification and Therapy (2026 Guidelines)

Risk Category	Clinical Profile	Primary Therapy Strategy
Low Risk	Small tumors (<2 cm), Node-negative (T1a-b N0)	**De-escalation:** Upfront surgery followed by less-intensive chemotherapy (e.g., paclitaxel) and trastuzumab.
Intermediate Risk	T2 (>2 cm) or Node-positive (N1)	**Neoadjuvant-First:** Preferred to assess pathologic response and tailor subsequent adjuvant therapy.
High Risk	Large tumors (>5 cm), N2/N3 (4+ nodes), or residual disease after neoadjuvant therapy	**Escalation:** Dual HER2 blockade (trastuzumab + pertuzumab) and consideration of adjuvant T-DM1 if residual disease exists.

Tailoring Treatment to Cancer Risk and Patient Preference: The 2025 St Gallen International Breast Cancer Consensus Statement on Individualizing Therapy for Patients With Early Breast Cancer. October 2025. Annals of Oncology; 36(12)

Escalation and De-escalation in HER2+ Early Stage Breast Cancer: Neoadjuvant Therapy for all But Very Small Cancers

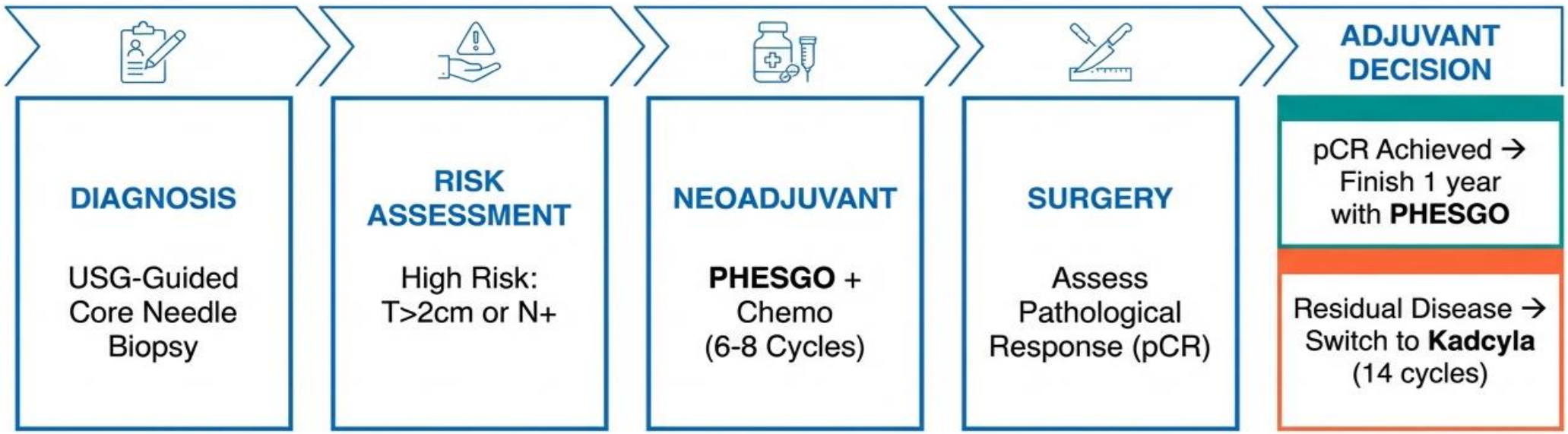


Plus endocrine therapy in HR +

H. Rugo, 07/24

The 2026 Integrated HER2+ Algorithm

Roche Indonesia Protocol



Adapted from Pan-Asian ESMO 2024 Guidelines & NCCN v5.2025.

Pertuzumab-trastuzumab across neoadjuvant and adjuvant settings improves EFS[1]

- A pooled analysis* from 5 neoadjuvant studies (n=1763) evaluated outcomes with respect to single versus dual HER2 targeting in neoadjuvant and adjuvant settings.
- Amongst those who achieved pCR, patients treated with pertuzumab-trastuzumab in both settings had the highest 4-year EFS rate compared with those who switched from pertuzumab-trastuzumab to receive adjuvant trastuzumab therapy alone (95% vs 90%).[1]

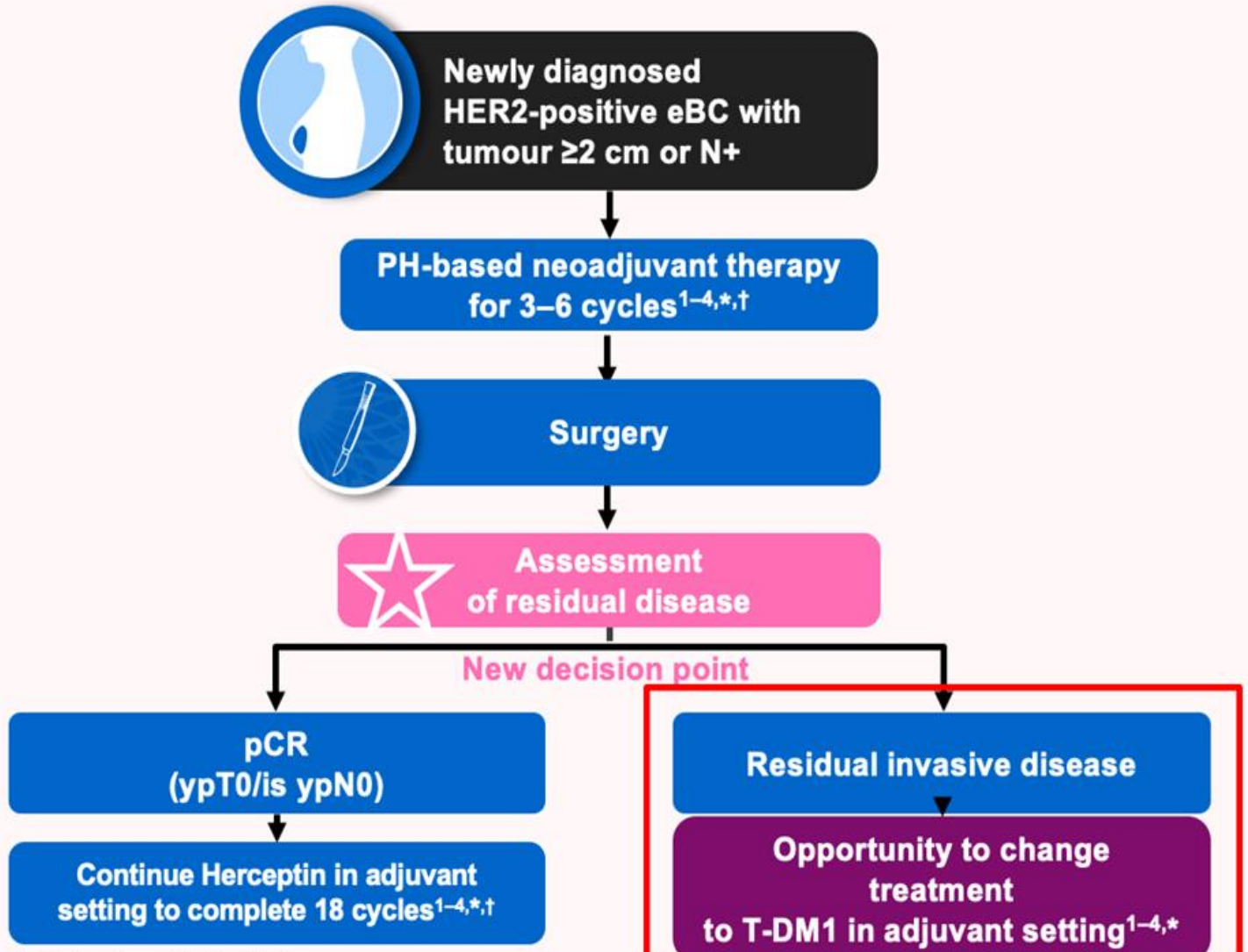
4-year EFS in patients with pCR[1]

	Trastuzumab -> Trastuzumab (n=236)	Pertuzumab-trastuzumab -> Trastuzumab (n=185)	Pertuzumab-trastuzumab -> Pertuzumab-trastuzumab (n=352)
Patients remaining at risk, n	179	155	219
4-year event-free survival rate, % (95% CI)	**86** (81–89)	**90** (85–94)	**95** (92–97)

Adapted from Swain SM, Macharia H, Cortes J, et al. *Cancers (Basel)* 2022.[1]

*Refer to the appendix for further details of this pooled analysis.
Abbreviations: CI, confidence interval; EFS, event-free survival; H, trastuzumab; pCR, pathological complete response; PH, pertuzumab-trastuzumab.
Reference: 1. Swain SM, Macharia H, Cortes J, et al. Event-Free Survival in Patients with Early HER2-Positive Breast Cancer with a Pathological Complete Response after HER2-Targeted Therapy: A Pooled Analysis. *Cancers (Basel)* 2022;14(20):5051.

Assessment of residual disease after surgery is a new decision point for adapting adjuvant therapy

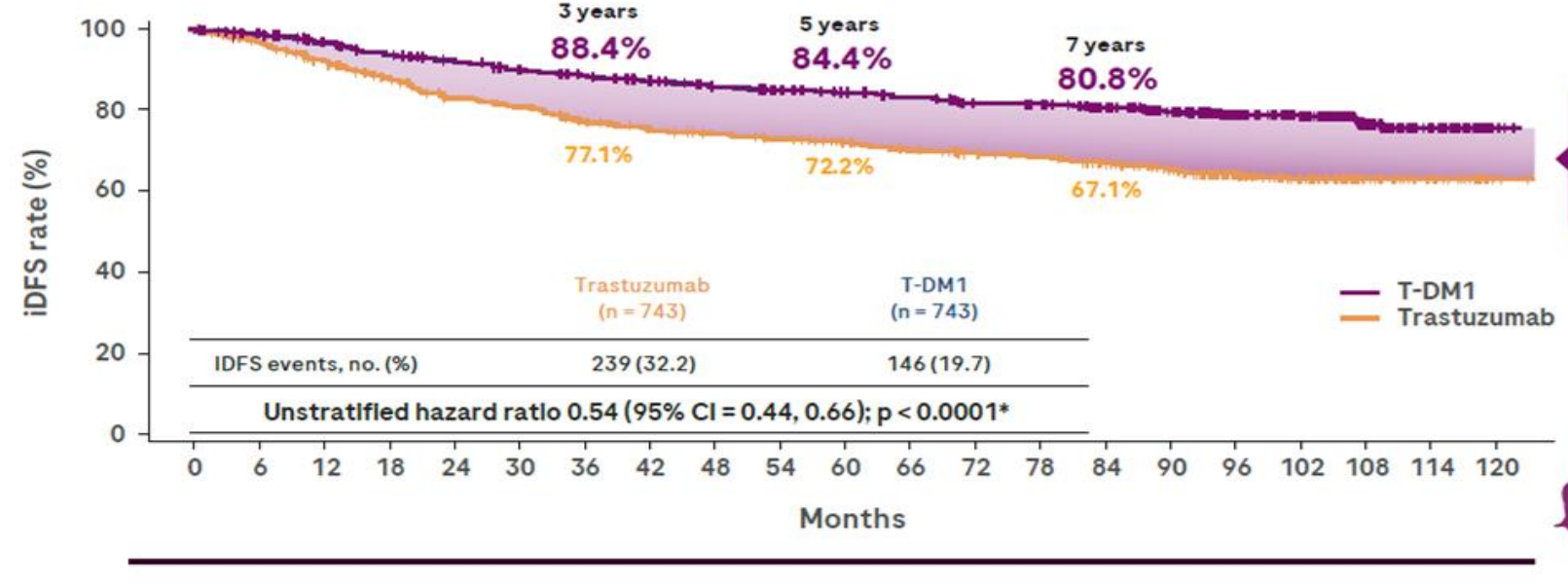


* Including loco-regional radiotherapy and adjuvant endocrine treatment according to guidelines.
† AGO and ESMO guidelines: (neo)adjuvant PH is only recommended for the treatment of patients with node-positive disease.
eBC, early breast cancer; N+, node-positive; pCR, pathological complete response; PH, pertuzumab–trastuzumab.

1. NCCN Breast Cancer Guidelines. Version 4. 2025; 2. AGO Breast Cancer Guidelines. 2022; 3. Cardoso F, *et al. Ann Oncol* 2019; 4. Burstein HJ, *et al. Ann Oncol* 2021.

KATHERINE IDFS FINAL ANALYSIS:
KADCYLA reduced the risk of recurrence by 46% compared with Herceptin [1,2]

Final IDFS in the intention to treat (ITT) population at median follow up 8.4 years



Δ 7 years IDFS
13.7%

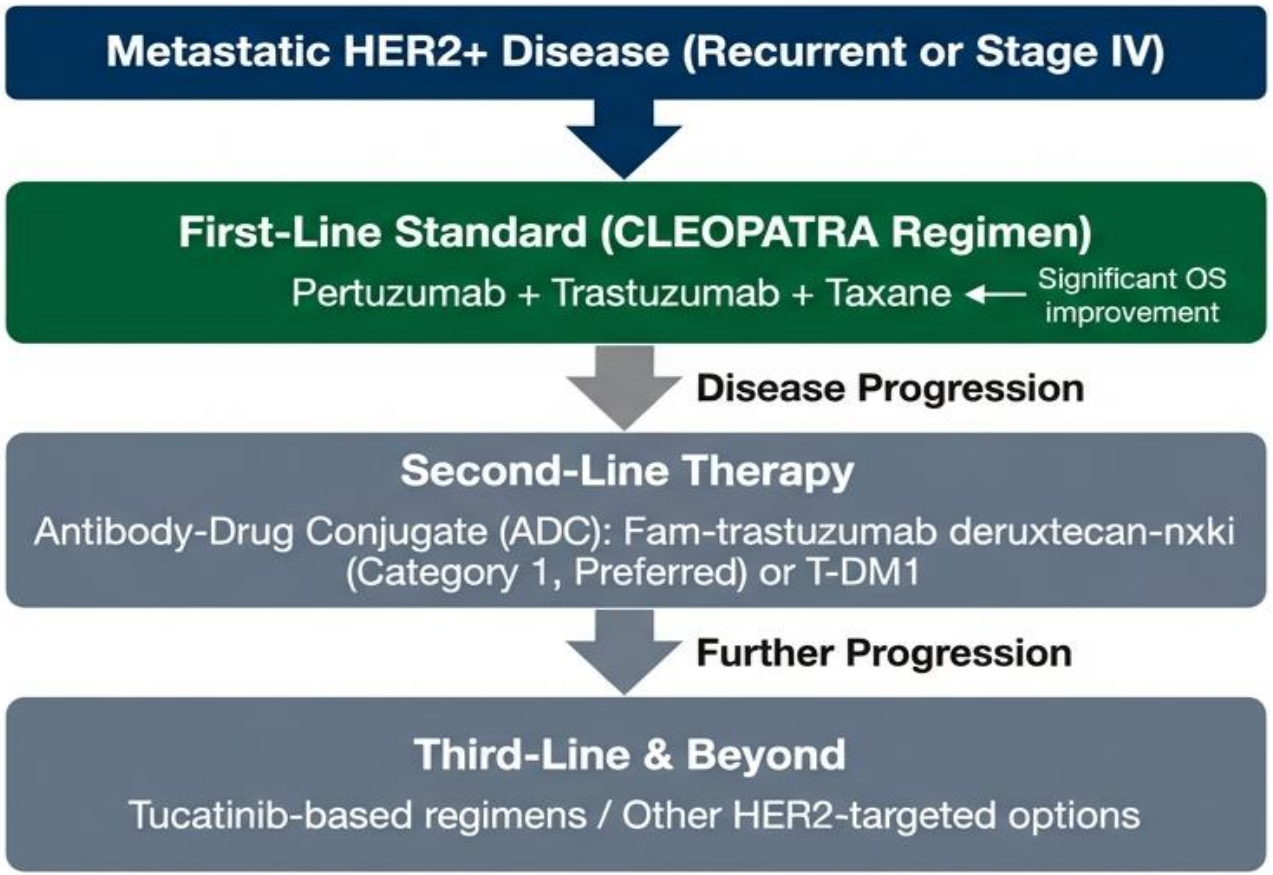
reduction in the risk of recurrence

HR=0.54; 95% CI: 0.44-0.66;
P<0.0001

* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

1. von Minckwitz G, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017 ; 2. Loibl S, et al. Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis. SABCS 2023. (Abstract GS03-12; oral presentation

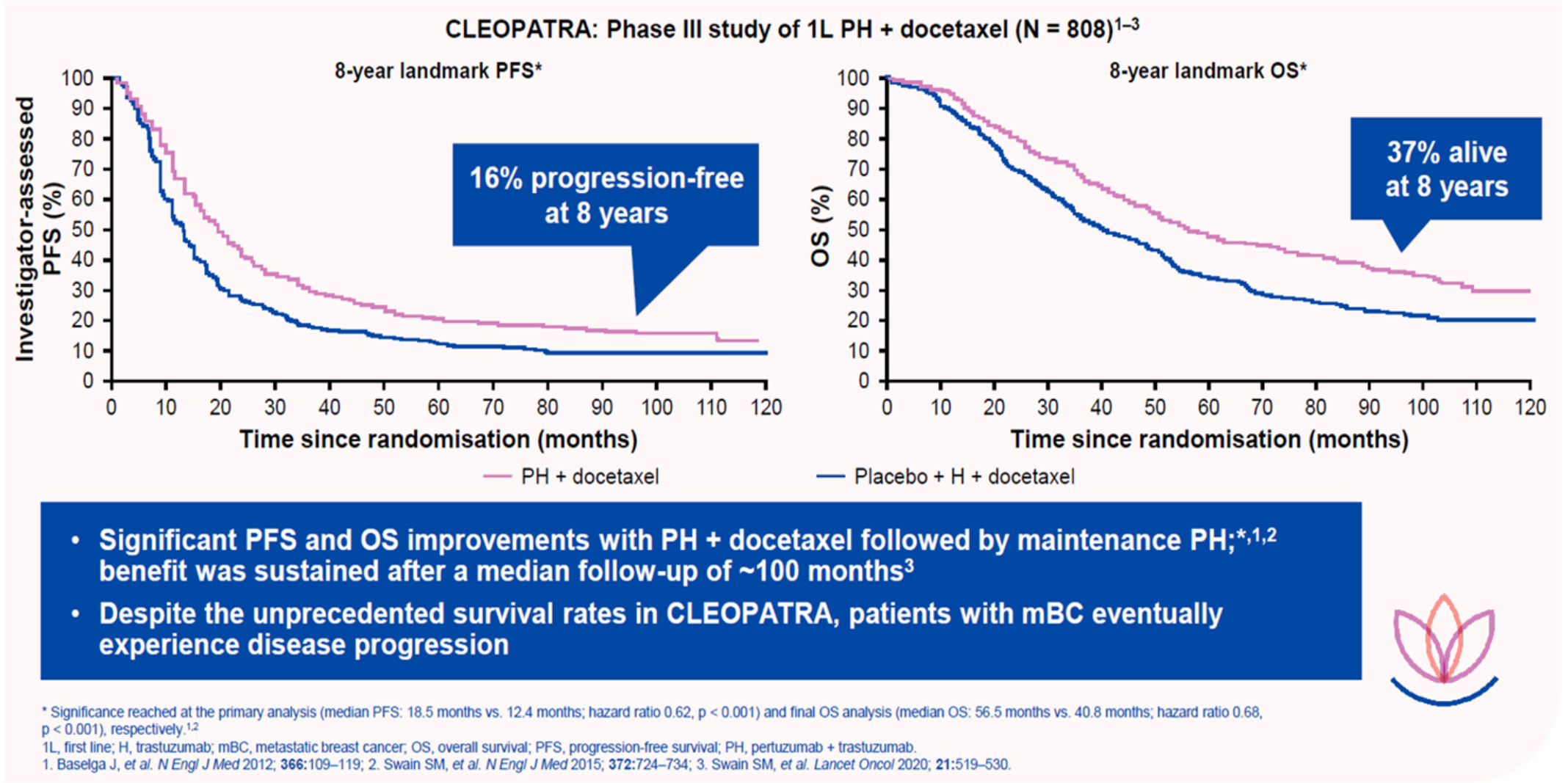
The Continuum to Metastatic Disease: Standards of Suppression



- **Continuum of Suppression:** Continued suppression of the HER2 pathway is beneficial even after disease progression; therapy should be maintained until unacceptable toxicity.
- **CNS Involvement:** Local therapy is prioritized for brain metastases, integrated with systemic HER2-targeted options like tucatinib.

[5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2024.

Over the past few decades, much progress has been made with dual HER-2 targeted therapy in the 1L setting for patients with HER 2+ mBC

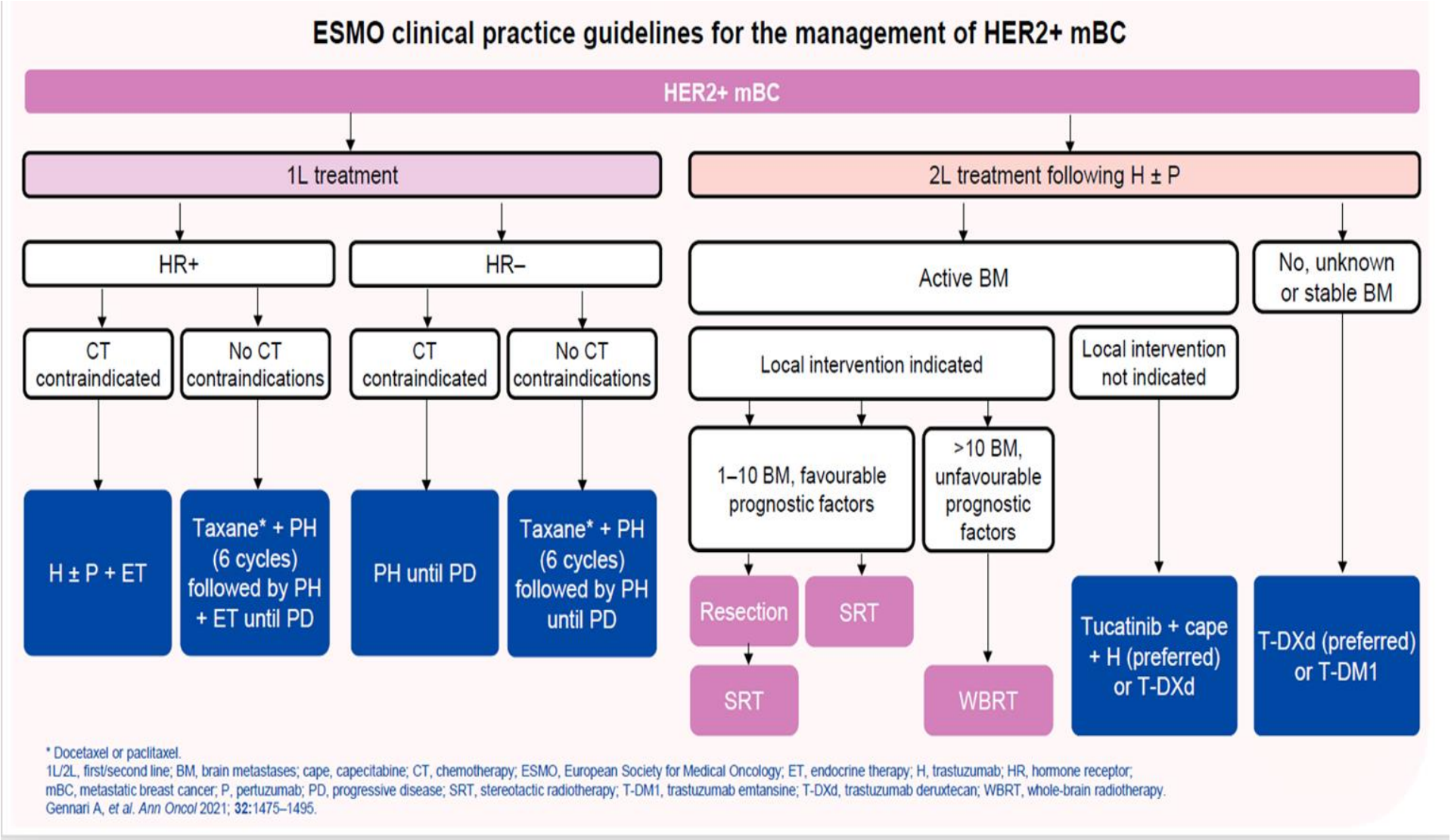


* Significance reached at the primary analysis (median PFS: 18.5 months vs. 12.4 months; hazard ratio 0.62, $p < 0.001$) and final OS analysis (median OS: 56.5 months vs. 40.8 months; hazard ratio 0.68, $p < 0.001$), respectively.[1,2]

1L, first line; H, trastuzumab; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PH, pertuzumab + trastuzumab.

1. Baselga J, *et al. N Engl J Med* 2012; **366**:109–119; 2. Swain SM, *et al. N Engl J Med* 2015; **372**:724–734; 3. Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530.

Current guidelines consider clinical risk factors and HR status for treatment decision-making in HER2+ mBC

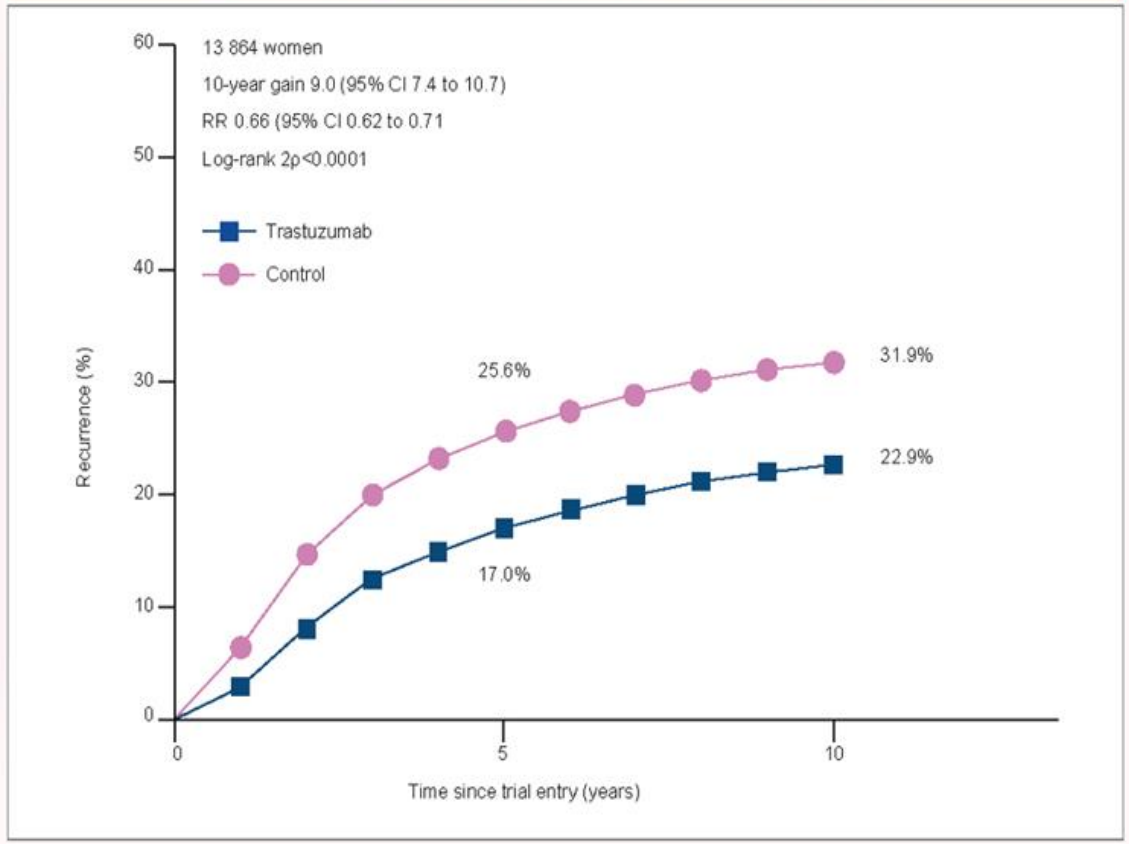


1 in 4 patients with eBC continue to grapple with unmet needs[1,2]

- Recurrence-free survival is the goal of treatment in eBC.[1]
- **However, 1 in 4 patients** with HER2+ eBC experience **recurrence or death within 10 years** despite trastuzumab-based adjuvant therapy.[2]

67% of first-line HER2+ mBC are recurrent patients after prior treatment in eBC[3]

Effect of trastuzumab versus control on disease recurrence[2]

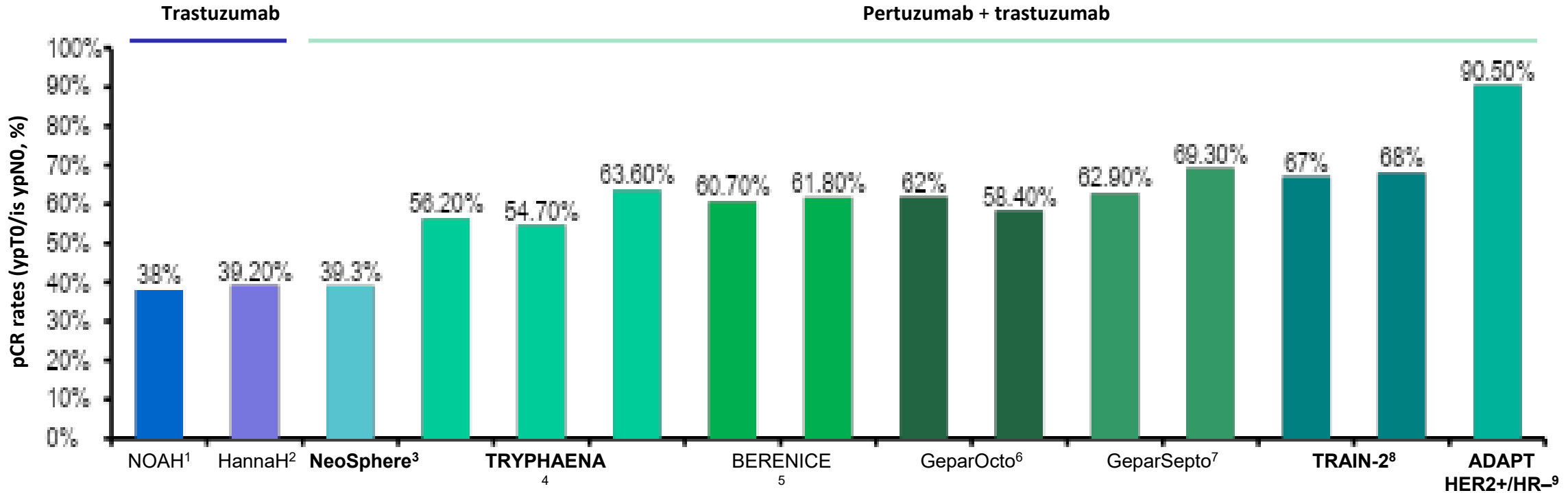


Adapted from Early Breast Cancer Trialists' Collaborative Group. *Lancet Oncol*. 2021.[2]

Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor-2 positive; RR, rate ratio; SoC, standard of care.

References: 1. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer (Review). *Cochrane Database Syst Rev*. 2012;2012:CD006243. 2. Early Breast Cancer Trialists' Collaborative group. Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. *Lancet Oncol*. 2021;22(8):1139-1150. 3. Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat*. 2014;145(3):725-734.

Studies of neoadjuvant PHESGO + chemotherapy showed consistently higher pCR rates compared to trastuzumab + chemotherapy



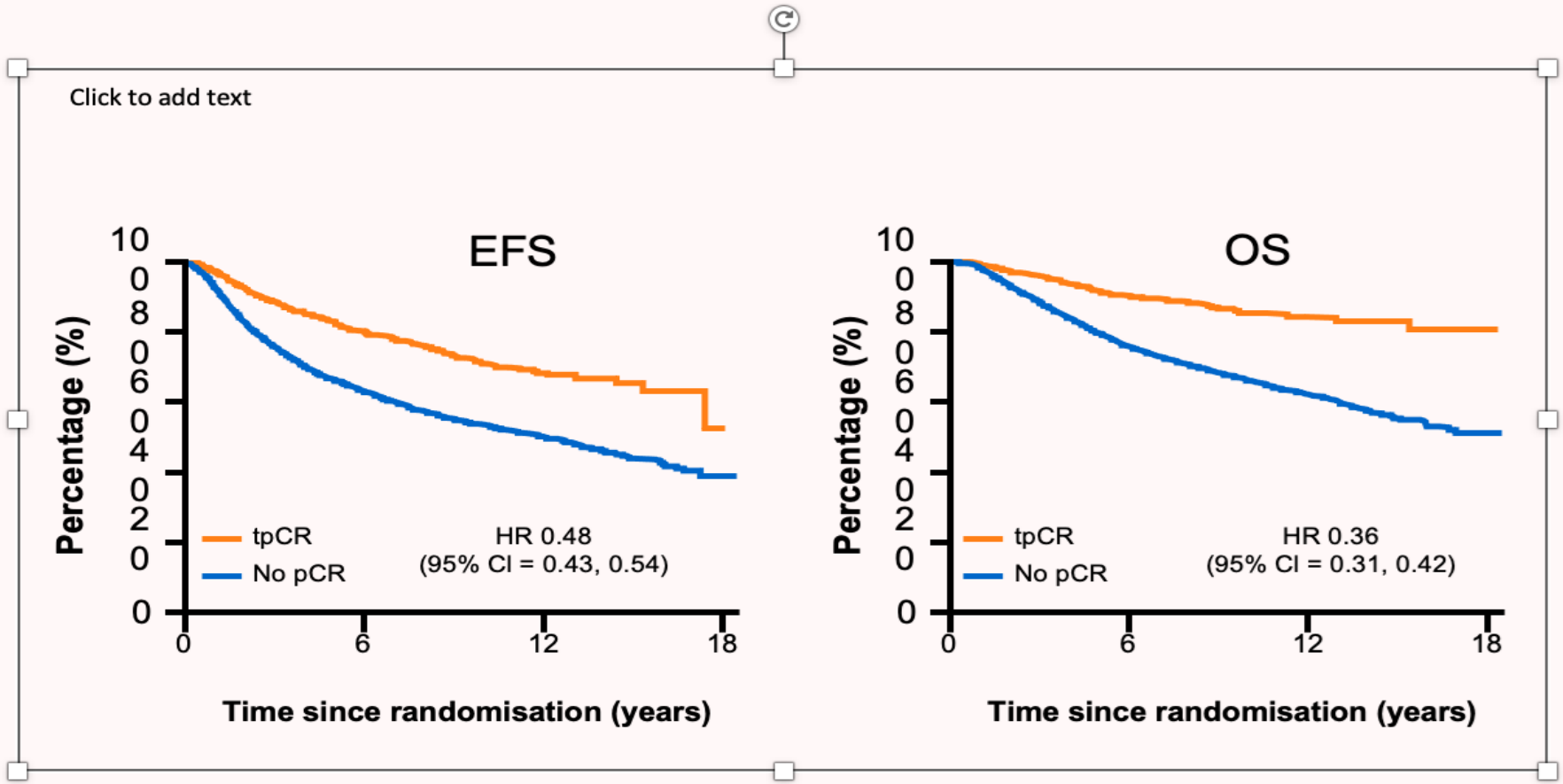
Phase	III[1]	III[2]	II[3]	II[4]			II[5]		III[6]		III[7]		III[8]		II[9]
n*	117	260	107	73	75	77	201	199	192	190	197	199	212	206	42
Regimen	AT+H – T+H – CMF+H	Doc+H – FEC+H	Doc/PH	FEC-Doc/PH	FEC-Doc/PH	Cb/Doc/PH	FEC-Doc/PH	ddAC-Pac/PH	E-TC/PH	Pac/NPLD/Cb/PH	Pac-EC/PH	nabPac-EC/PH	FEC-Pac/Cb/PH	Pac/Cb/PH	Pac weekly/ PH
Duration of anti-HER2 therapy	33 weeks	24 weeks	12 weeks	18 weeks	9 weeks	18 weeks	18 weeks	20 weeks	12 weeks	18 weeks	24 weeks		27 weeks		12 weeks

1. Gianni L, et al. Lancet 2010; 2. Ismael G, et al. Lancet Oncol 2012; 3. Gianni L, et al. Lancet Oncol 2012;
4. Schneeweiss A, et al. Ann Oncol 2013; 5. Swain SM, et al. Ann Oncol 2018; 6. Schneeweiss A, et al. Eur J Cancer 2018 (incl. suppl. info.);
7. Loibl S, et al. Ann Oncol 2017; 8. van Ramshorst MS, et al. Lancet Oncol 2018; 9. Nitz UA, et al. Ann Oncol 2017.

* n-values represent number of patients in particular treatment arm.

Achieving pCR improves long-term efficacy

Patients who achieved tpCR had longer EFS and OS than patients with residual cancer



tpCR: total pathological complete response

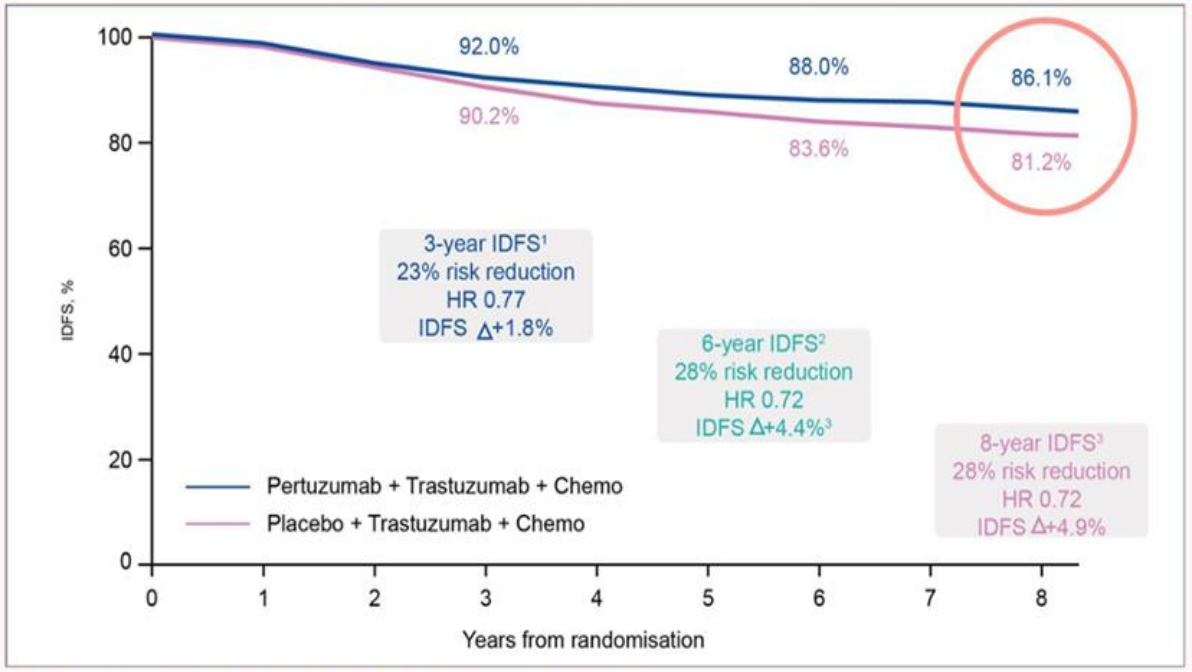
Cortazar, *et al. Lancet* 2014

Patients with node-positive eBC are the ideal candidates for pertuzumab-trastuzumab[1-4]

- Subgroup analysis from the 8.4-year follow-up of the APHINITY trial* demonstrated:

Patients with node-positive eBC continued to derive benefit, with a 28% reduction in the risk of recurrence or death with pertuzumab + trastuzumab + chemo compared to placebo + trastuzumab + chemo.[3,4]

APHINITY: IDFS rate in patient with node-positive disease[1-4]



Adapted from Loibl S, et al. ESMO Virtual Plenary. July 2022.[3]

*Refer to the appendix for the APHINITY trial design.

Abbreviations: chemo, chemotherapy; eBC, early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival

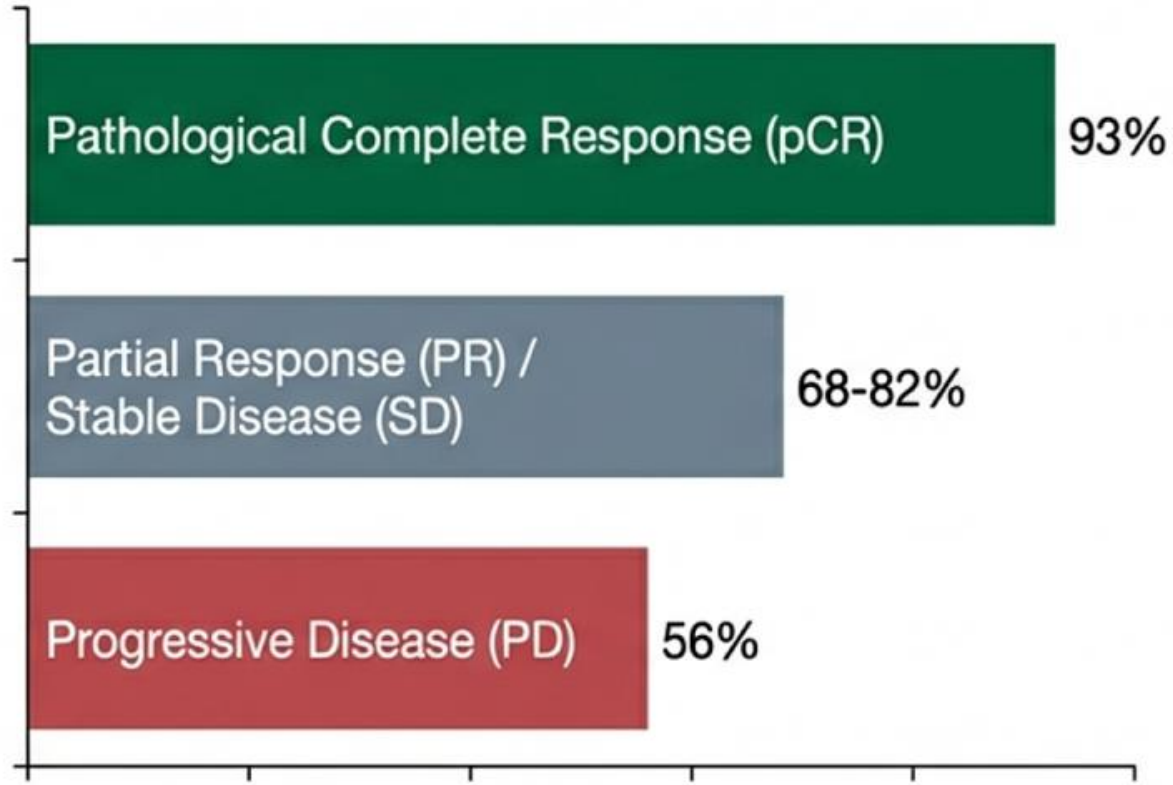
References: 1. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017;377(2):122-131. 2. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021;39(13):1448-1457. 3. Loibl S, Jassem J, Sonnenblick A, et al. Updated results of APHINITY at 8.4 years median follow up. Presented at ESMO Virtual Plenary. July 14–15, 2022. 4. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;33(9):P986-987.

The High-Risk Inflection Point: In-Breast Disease Progression (PD)

Incidence & Impact: In-breast PD occurs in 1.6% to 5% of patients during NST. It is a potent predictor of poor outcomes.

Biological Predisposition: While TNBC carries the highest risk, HER2+ patients with PD face high risks of distant recurrence. Post-NST grade and ypT3-4 status are strong predictors of poor DRFS.

Immediate Action Required: Direct surgery surgery is statistically associated with better outcomes for operable PD patients compared to switching systemic regimens.

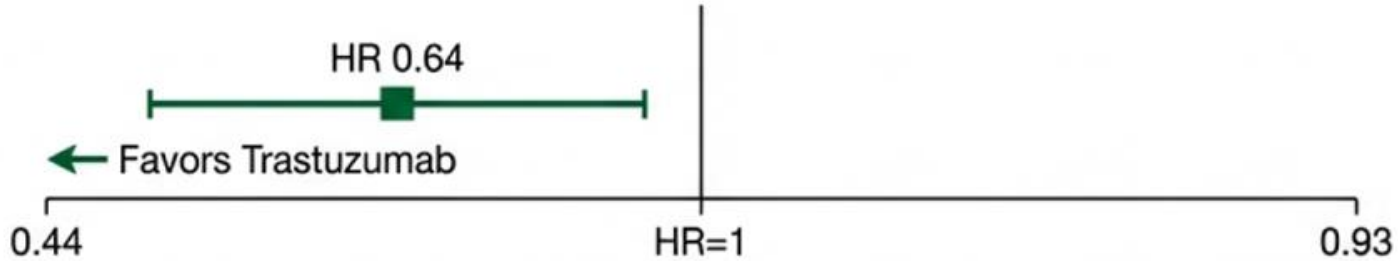


Median DDFS for PD: 23.2 months (Surgery) vs. 12.5 months (No Surgery)

[3] Eckert JC, et al. *Ann Surg Oncol.* 2023;31:63-69. [6] Ling Y, et al. *Breast.* 2023;70:63-69.

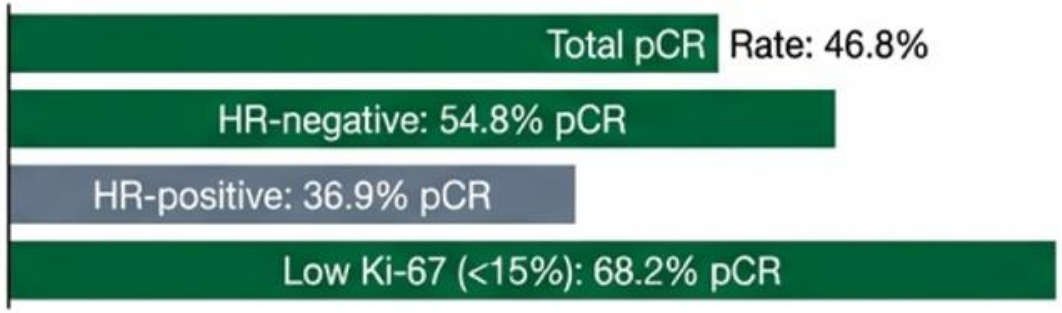
Maximizing Response: Evidence for Dual Blockade

NOAH Trial (Chemo + Trastuzumab vs. Chemo Alone)



- **NOAH Efficacy:** Neoadjuvant chemotherapy with trastuzumab significantly improves event-free survival (EFS) compared to chemotherapy alone.

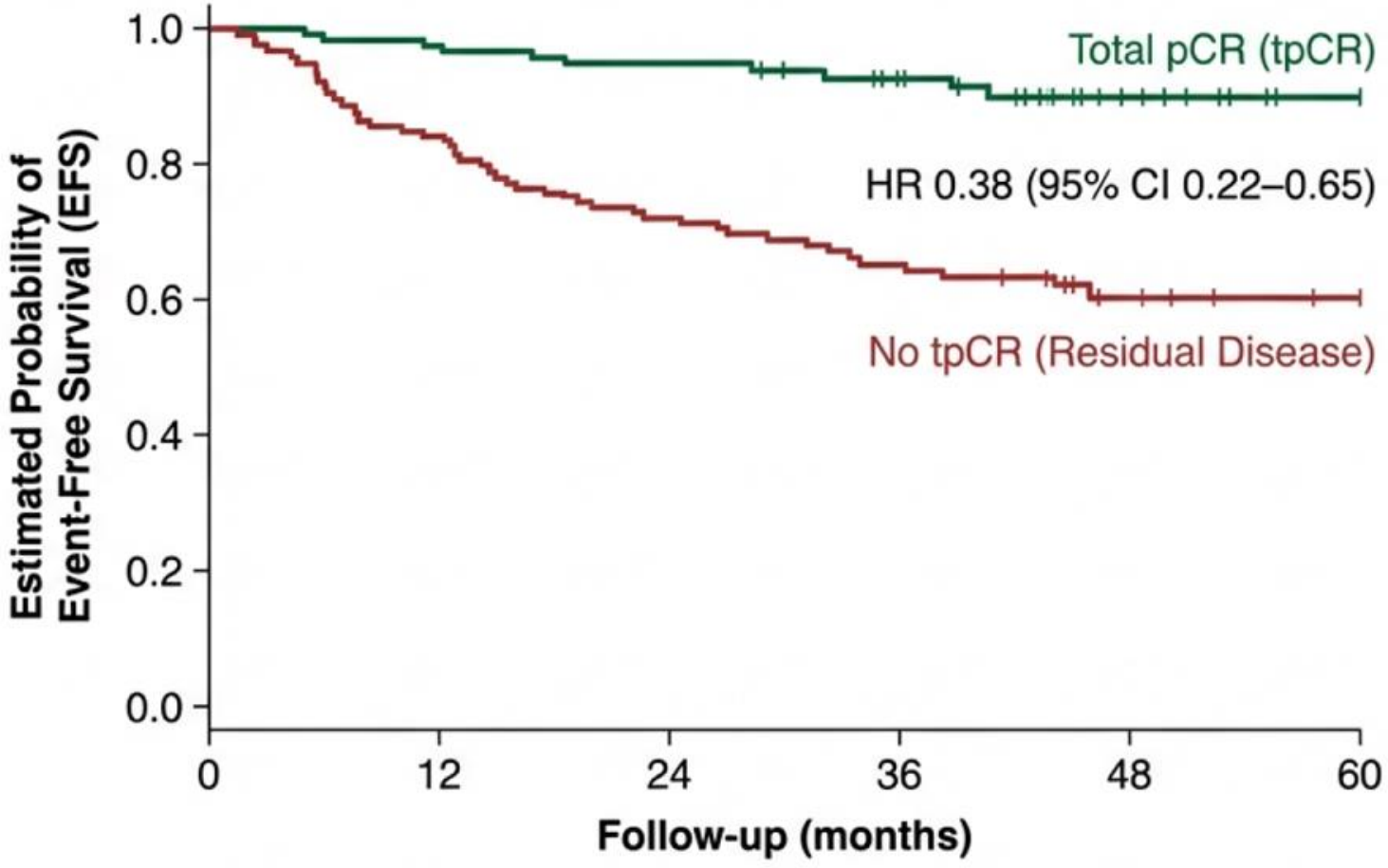
PEONY Real-World Study (Dual Blockade + Chemo)



- **Real-World Dual Blockade:** Addition of pertuzumab to trastuzumab and chemotherapy validated in routine practice (PEONY study).
- **Predictive Factors:** HR-negative status and Low Ki-67 (<15%) are independent predictors of achieving pCR.

[1] Gianni L, et al. Lancet. 2010;375:377-84. [2] Zhou J, et al. Ann Transl Med. 2022;10(24):1387.

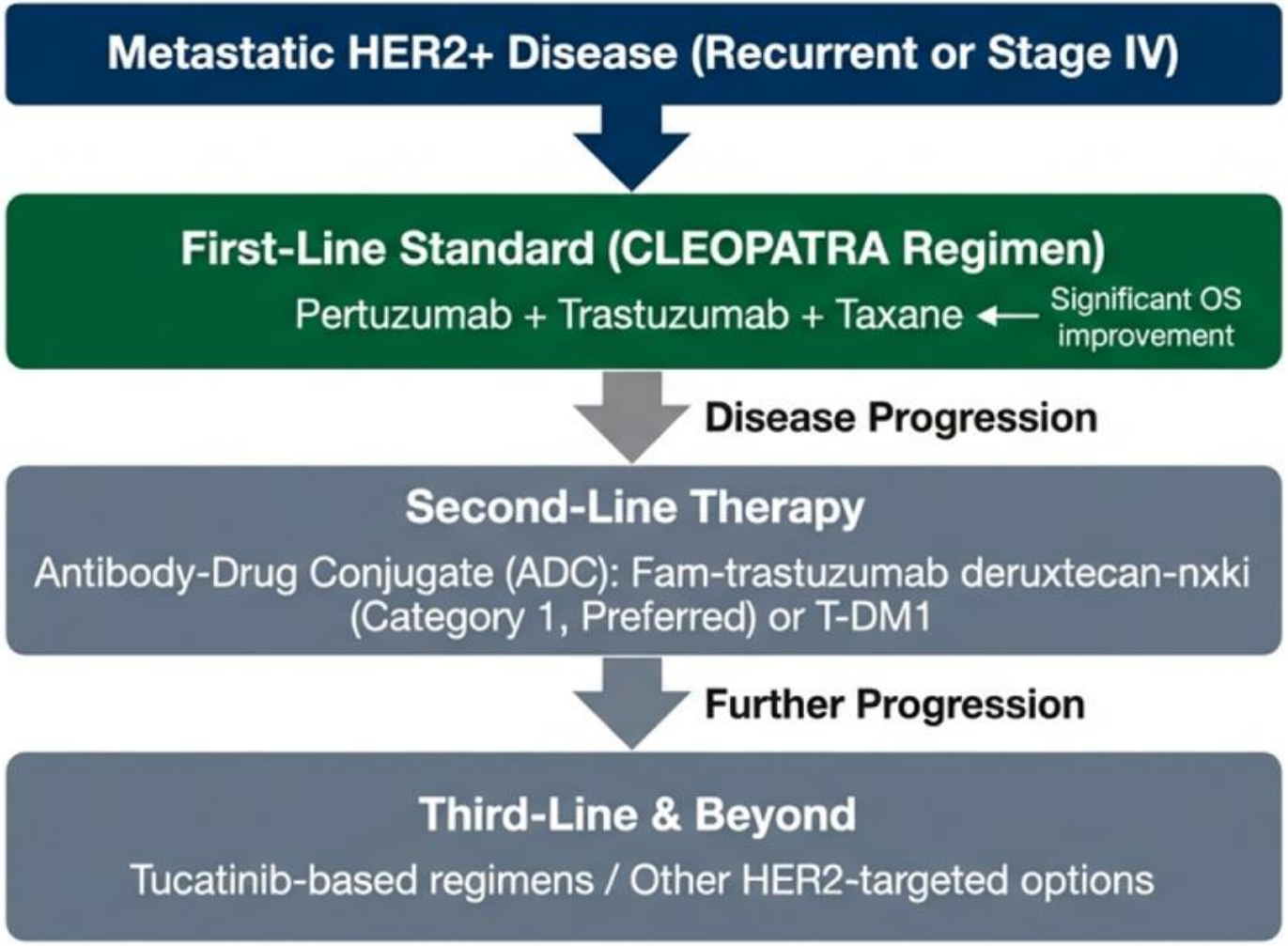
Validating the Surrogate: pCR as a Predictor of Long-Term Survival



- **HannaH Phase III Data:** Achieving tpCR is associated with a >60% reduction in the risk of an EFS event compared to patients with residual disease.
- **Administration Consistency:** The survival benefit is consistent regardless of administration route (Intravenous vs. Subcutaneous).
- **Long-Term Impact:** 3-year EFS rates are significantly higher in patients achieving tpCR, reinforcing pCR as a robust early surrogate for survival.

[4] Jackisch C, et al. *Eur J Cancer*. 2016;62:62-75.

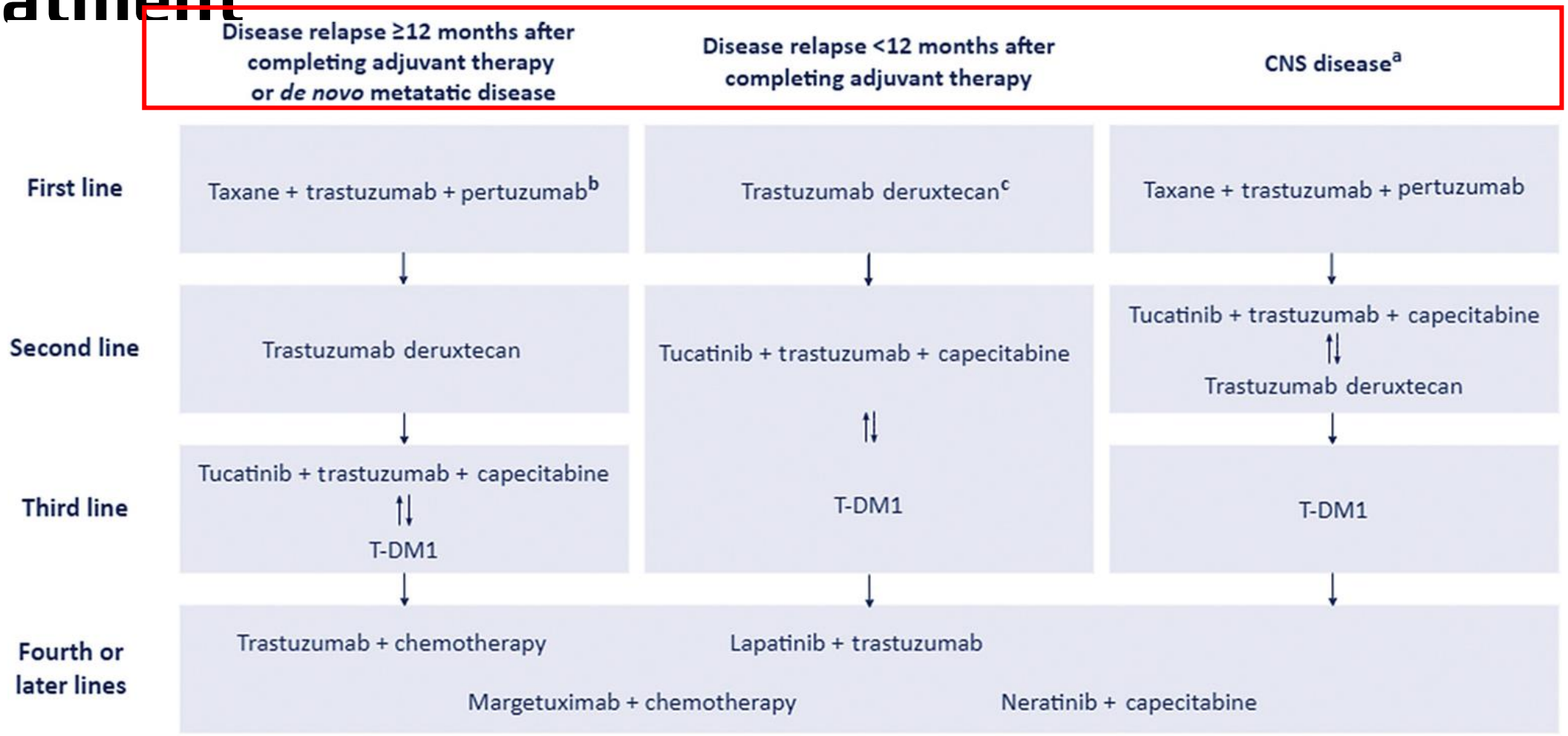
The Continuum to Metastatic Disease: Standards of Suppression



- **Continuum of Suppression:** Continued suppression of the HER2 pathway is beneficial even after disease progression; therapy should be maintained until unacceptable toxicity.
- **CNS Involvement:** Local therapy is prioritized for brain metastases, integrated with systemic HER2-targeted options like tucatinib.

[5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2024.

Metastatic HER2-Positive Breast Cancer Treatment



a. Proposed sequence of systemic therapies. Combination with local therapy might be necessary.
b. Trastuzumab ± Pertuzumab (+ endocrine therapy if HR-positive) may be considered in patients with contraindications to chemotherapy.
c. For patients with treatment-free interval between 6 and 12 months after exposure to pertuzumab-free adjuvant regimens THP can be considered as first-line option.

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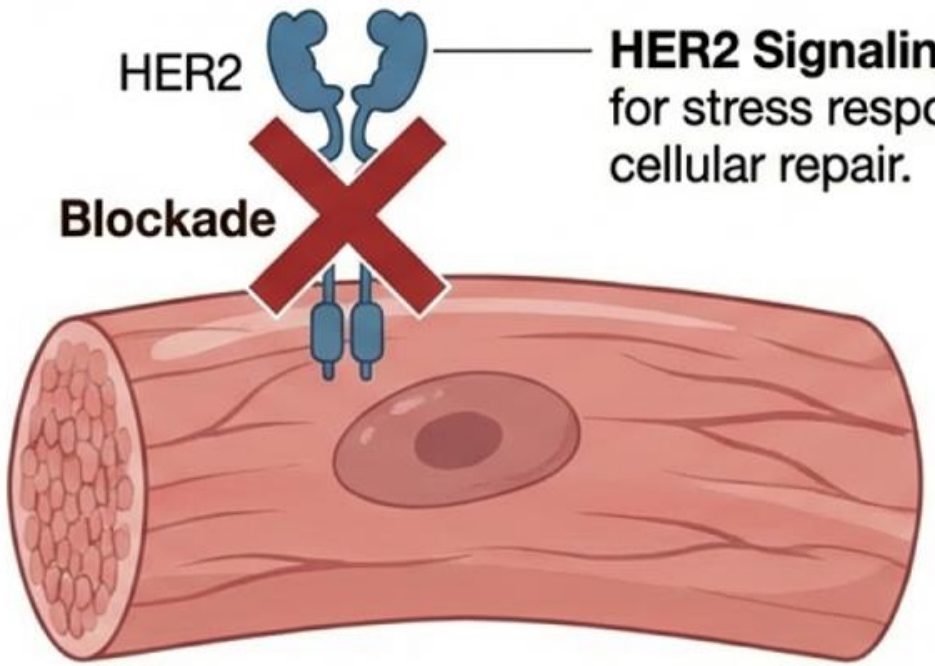
Cardiotoxicity: The Competing Risk in HER2 Blockade

Mechanism of Interference



HER2 Signaling: Essential for stress response and cellular repair.

Inhibition prevents repair, leading to Type II Cardiotoxicity (Reversible).

NOAH Trial Safety Profile

- **LVEF Declines:** Observed in subset of patients.
- **Incidence:** Symptomatic heart failure is relatively low.
- **Reversibility:** Unlike anthracycline-induced damage (Type I, permanent), trastuzumab toxicity is often reversible upon discontinuation.
- **Monitoring Baseline:** Patients with baseline LVEF <55% generally excluded from pivotal trials.

[1] Gianni L, et al. *Lancet*. 2010;375:377-84.

Stratifying Cardiac Risk: Patient and Treatment Factors

Body Weight

Body Weight

Higher frequency of cardiac adverse events in patients within the highest body weight quartiles (>79 kg), seen in both SC and IV administration (HannaH study).

Anthracycline Exposure

Anthracycline Exposure

Regimens containing anthracyclines carry higher baseline risk. Must NEVER be administered concurrently with trastuzumab; sequential administration is mandatory.

Formulation Safety

Formulation Safety

Subcutaneous trastuzumab shows a consistent cardiac safety profile to intravenous formulation. No new safety signals in long-term follow-up.

[4] Jackisch C, et al. *Eur J Cancer*. 2016;62:62-75.
[5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2024.

Criteria for Minimizing Cardiotoxicity: Selection and Surveillance

Baseline Assessment

Surveillance During Therapy

✓ **Green Light:** Stable LVEF.

Yellow Light: Asymptomatic dysfunction -> Increase monitoring to every 4 weeks.

Real-World Evidence

Baseline Assessment

Mandatory LVEF assessment (Echo/MUGA).

Eligibility: LVEF ≥50-55%.

Exclusion: History of significant cardiac disease/CHF.

Assess LVEF every 3 months.

Real-World Evidence

PEONY Study Data:

Only 7.8% experienced cardiac function decrease.

No cases of LVEF decline >10%.

[1] Gianni L, et al. Lancet. 2010. [2] Zhou J, et al. Ann Transl Med. 2022. [5] NCCN Clinical Practice Guidelines v2.2024.

Monitoring after Cardiotoxic Therapy (e.g. Anthracyclines, anti-HER2, Immuno-oncology)

<u>After anthracyclines / Trastuzumab:</u>

- **ECG and echocardiography:**
  - **6, 12, 24 months and yearly up to 5 years after therapy**
  - **after 5th year, every 5 years and if patient is symptomatic**
- **If cardiovascular risk factors:**
  - **blood pressure at least yearly**
  - **lipids and HbA1c in serum yearly**
- **Modify risk factors if possible:**
  - **nicotine, body weight, bmi**
- **Education about individual risk profile and lifestyle**

<u>Risk factors:</u>

radiotherapy of left breast, nicotine, hypertonus, diabetes mell., dyslipidaemia, adiposity, age > 60, cardiac diseases: reduced ejection fraction, post- myocardial infarction status , ≥ moderate heart defects

Side Effects According to Organ Systems
Cardiotoxicity as Long-term Side Effect

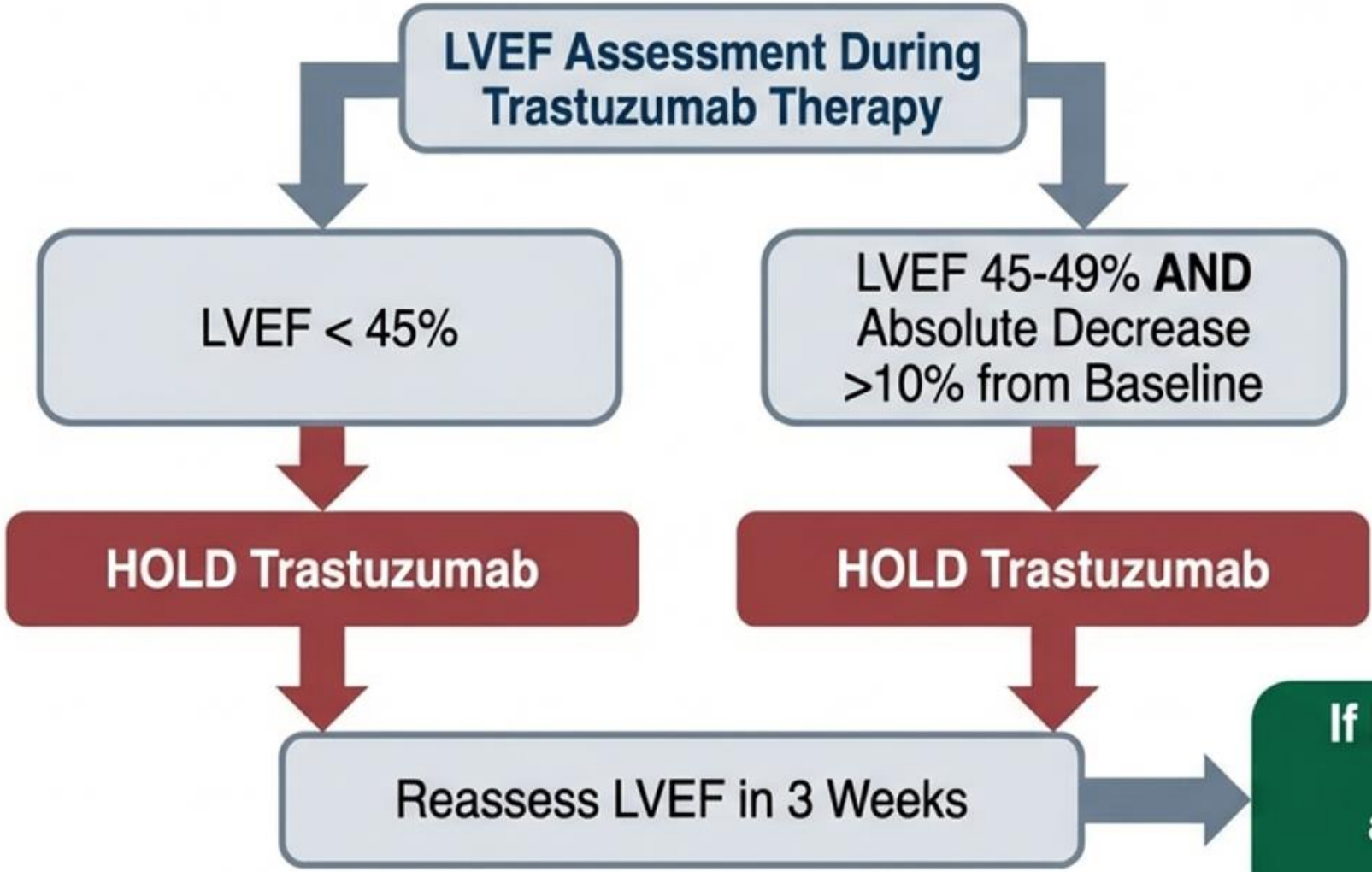
	Oxford		
	LoE	GR	AGO
▪ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)	2b	B	
▪ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
▪ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
▪ Elderly patients, obesity, hypertension, hypercholesterinemia, üre-existing cardiac disease (incl. borderline LVEF), diabetes mellitus			
▪ Monitoring of cardiac function:			
▪ Standardized echocardiography (LVEF or SF in %)	3b	C	+
▪ ECG (QT-interval)	1a	A	+
▪ Troponin I as marker of cardiac toxicicty	2b	B	+/-
▪ Betablocker-prohylaxis during anthracycline therapy	2a	B	+/-

Regimen Selection: Balancing Efficacy and Cardiac Safety

Non-Anthracycline Regimens (Preferred)	Anthracycline-Containing Regimens
Example: TCHP (Docetaxel / Carboplatin / Trastuzumab / Pertuzumab)	**Example:** AC followed by T + Trastuzumab
• **NCCN** Preferred for neoadjuvant/adjuvant setting. • Minimizes cardiac risk while maintaining dual blockade efficacy. • **PEONY** Study: **Low rates of Grade 3-4 cardiac events**. • Ideal for patients with lower baseline LVEF or cardiac risk factors.	• **Higher baseline risk** of **cardiotoxicity**. • Risk of leukemia and **permanent heart damage** (**Type I toxicity**). • Strict requirement for **SEQUENTIAL** administration (**never concurrent**).

[2] Zhou J, et al. Ann Transl Med. 2022;10(24):1387.
[5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2024.

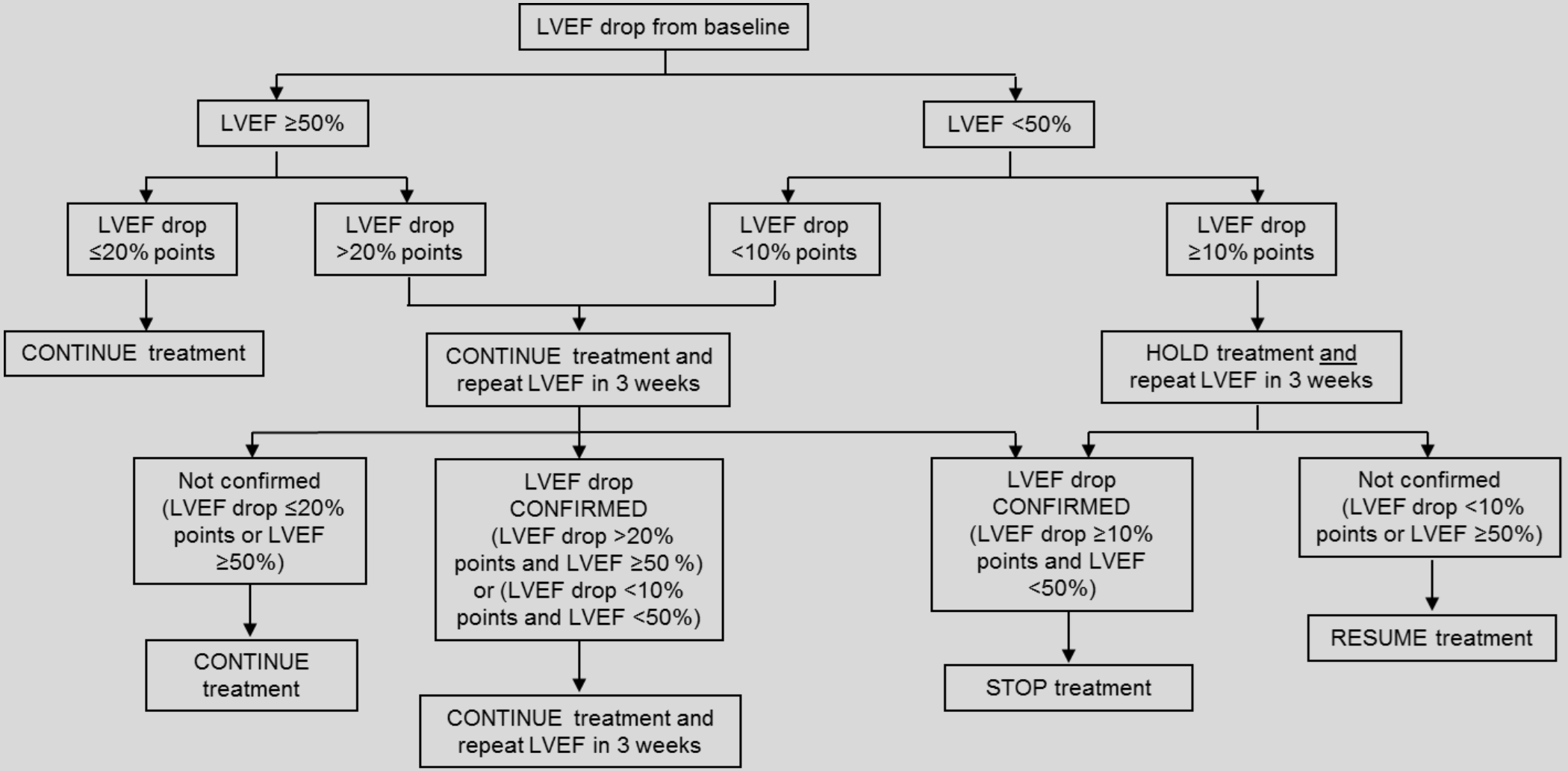
Management Algorithm for LVEF Decline



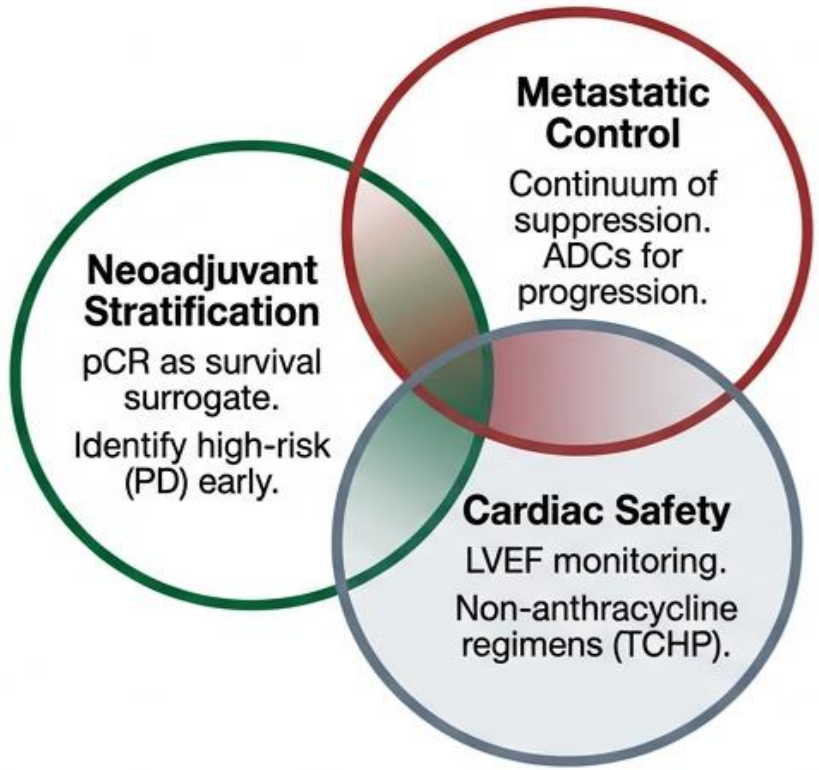
Metastatic Context: In metastatic settings, the decision to continue therapy in asymptomatic cardiac dysfunction is a risk-benefit analysis, weighing the cardiac risk against the survival benefit of continued HER2 suppression.

[1] Gianni L, et al. Lancet. 2010;375:377-84.
[5] NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2024.

Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity



Summary: Integrating Biology, Risk, and Survival



- **The Continuum:** HER2+ management is dynamic; **neoadjuvant response** dictates adjuvant strategy.
- **Risk Stratification:** Early identification of **non-responders** allows for escalation (surgery/ADCs) to improve DDFS.
- **Safety Foundation:** Strict protocols ensure survival benefits of **dual blockade** are not compromised by **cardiotoxicity**.

[2] Zhou J, et al. *Ann Transl Med*. 2022; [3] Eckert JC, et al. *Ann Surg Oncol*. 2023; [4] Jackisch C, et al. *Eur J Cancer*. 2016; [5] NCCN Guidelines v2.2024; [6] Ling Y, et al. *Brea*


TERIMA
KASIH
thank
you