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UNC CANCER CARE

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer

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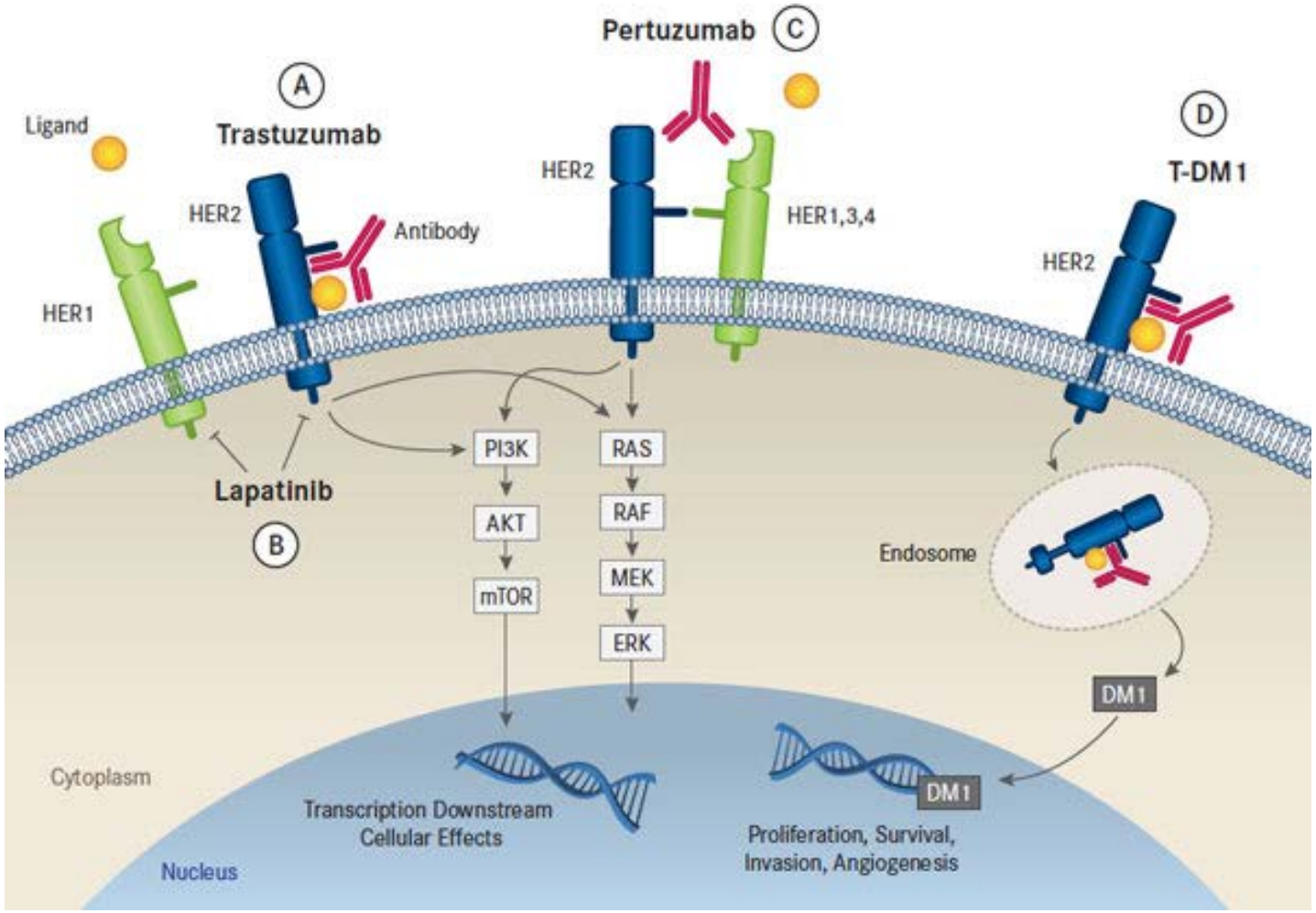
Targeting HER2: a Plethora of Riches!



Monoclonal antibodies

Antibody-drug conjugates

Kinase inhibitors

Early HER2+ Breast Cancer

Trastuzumab (H)	Pertuzumab (added to H)	Neratinib (after H)	TDM1 (in RD)	TH/TDM1 in stage 1	Tailoring to risk…
2005	2013-18	2018	2019	2017-19	2020+

- **Modern therapeutic regimens have augmented effectiveness**
- **There are substantial surgical and medical advantages to neoadjuvant therapy**
- **How best to tailor treatment in early HER2+ disease?**

Systemic Regimens for HER2+ Early Breast Cancer

Adapted from NCCN Guidelines:

Regimens for HER2-positive disease

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab
- Docetaxel + cyclophosphamide + trastuzumab
- FEC followed by docetaxel + trastuzumab + pertuzumab
- FEC followed by paclitaxel + trastuzumab + pertuzumab
- Paclitaxel + trastuzumab
- Pertuzumab + trastuzumab + docetaxel followed by FEC
- Pertuzumab + trastuzumab + paclitaxel followed by FEC
- Paclitaxel + trastuzumab (stage I)
- Above alone (pCR) or followed by TDM1 (RD)

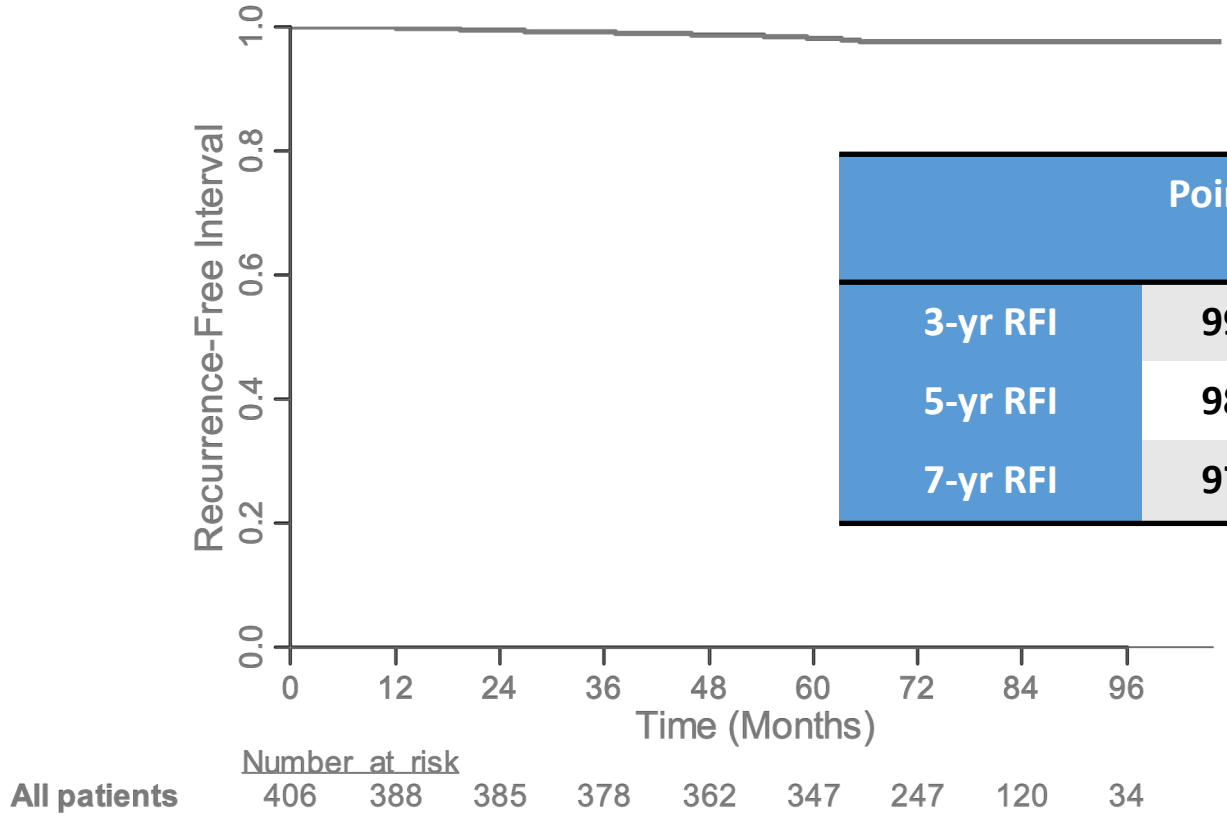
± neratinib

= Polychemotherapy + 1-3 HER2-targeted drugs for 1-2 years

Can we be more rational?

Small Node-Negative HER2+ Tumors

APT Trial: T1N0 excellent outcomes with TH (12 weeks paclitaxel + 1 year trastuzumab)



	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

Less mature data suggest similar excellent outcomes with T-DM1 alone (ATEMPT trial)

Tolaney SM et al, JCO 2019; Tolaney SM et al, JCO 2021

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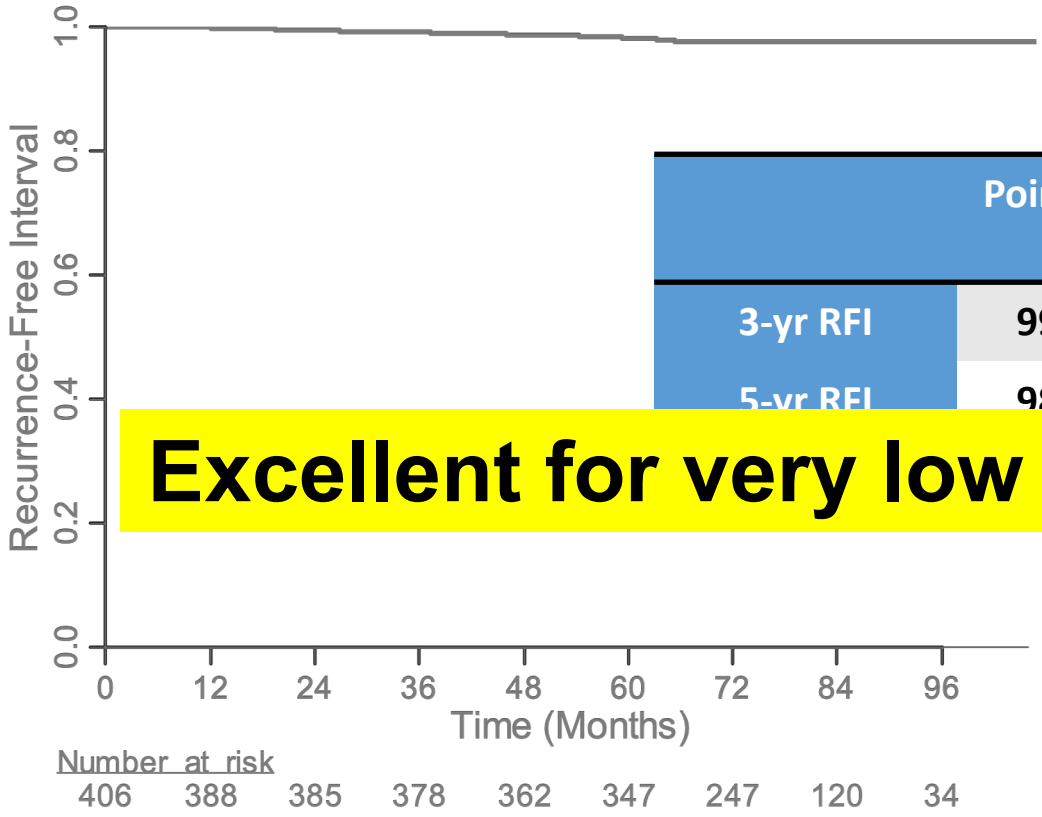

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Excellent for very low clinical risk HER2+

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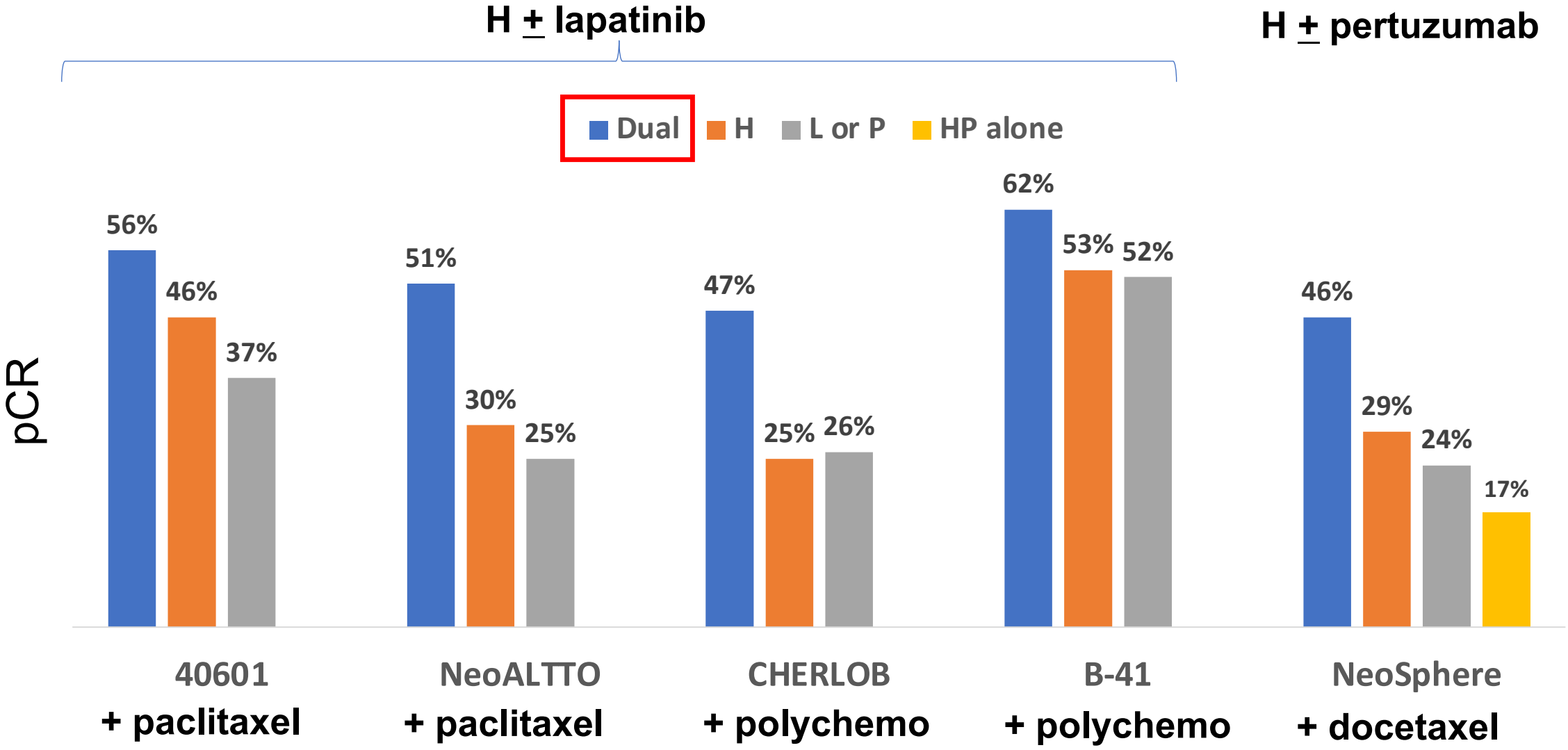
Tolaney SM et al, JCO 2019; Tolaney SM et al, JCO 2021

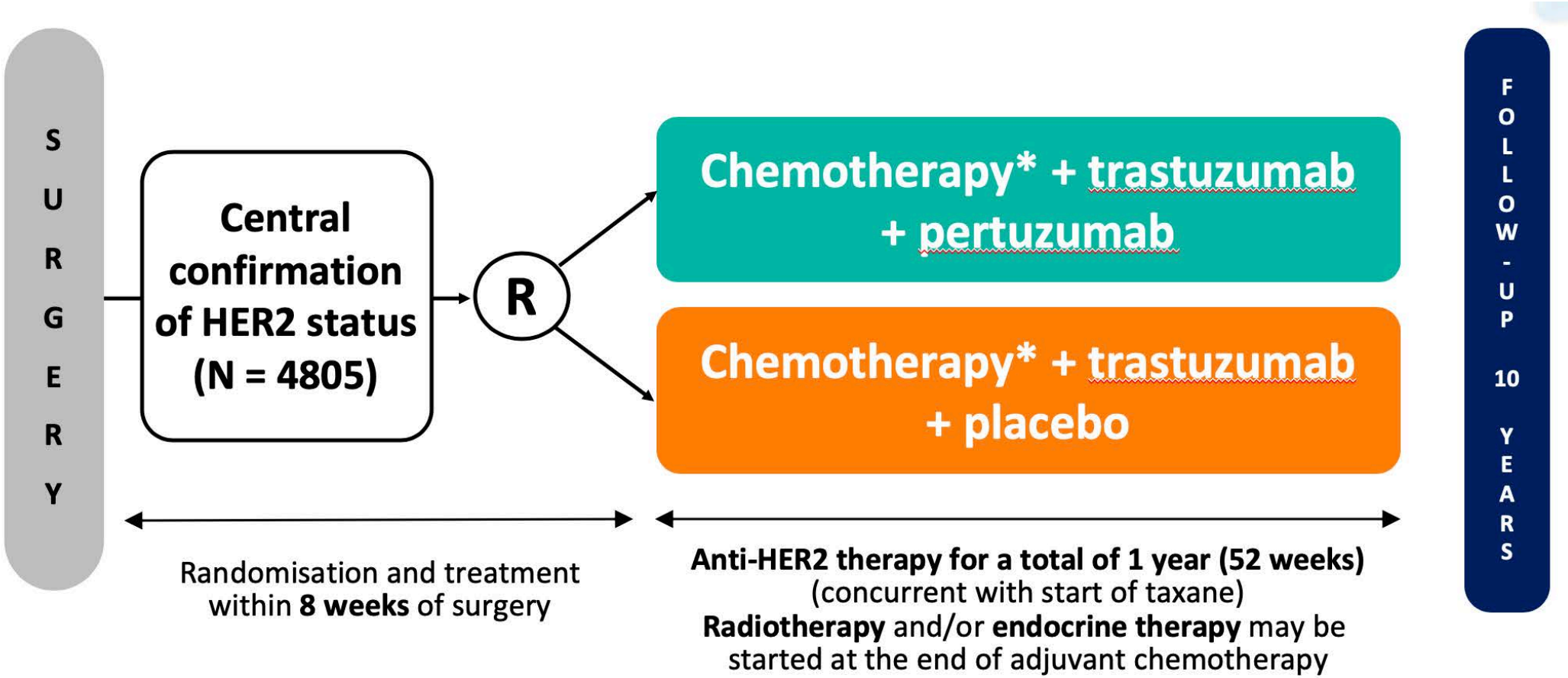
Improving Outcomes Through Dual HER2-Targeted Therapy



Carey LA et al, JCO 2016; Baselga, Lancet Oncol 2012; Guarnieri V et al, JCO 2012; Robidoux A et al, Lancet Oncol 2013

↑ Effectiveness by Dual Anti-HER2 Therapy

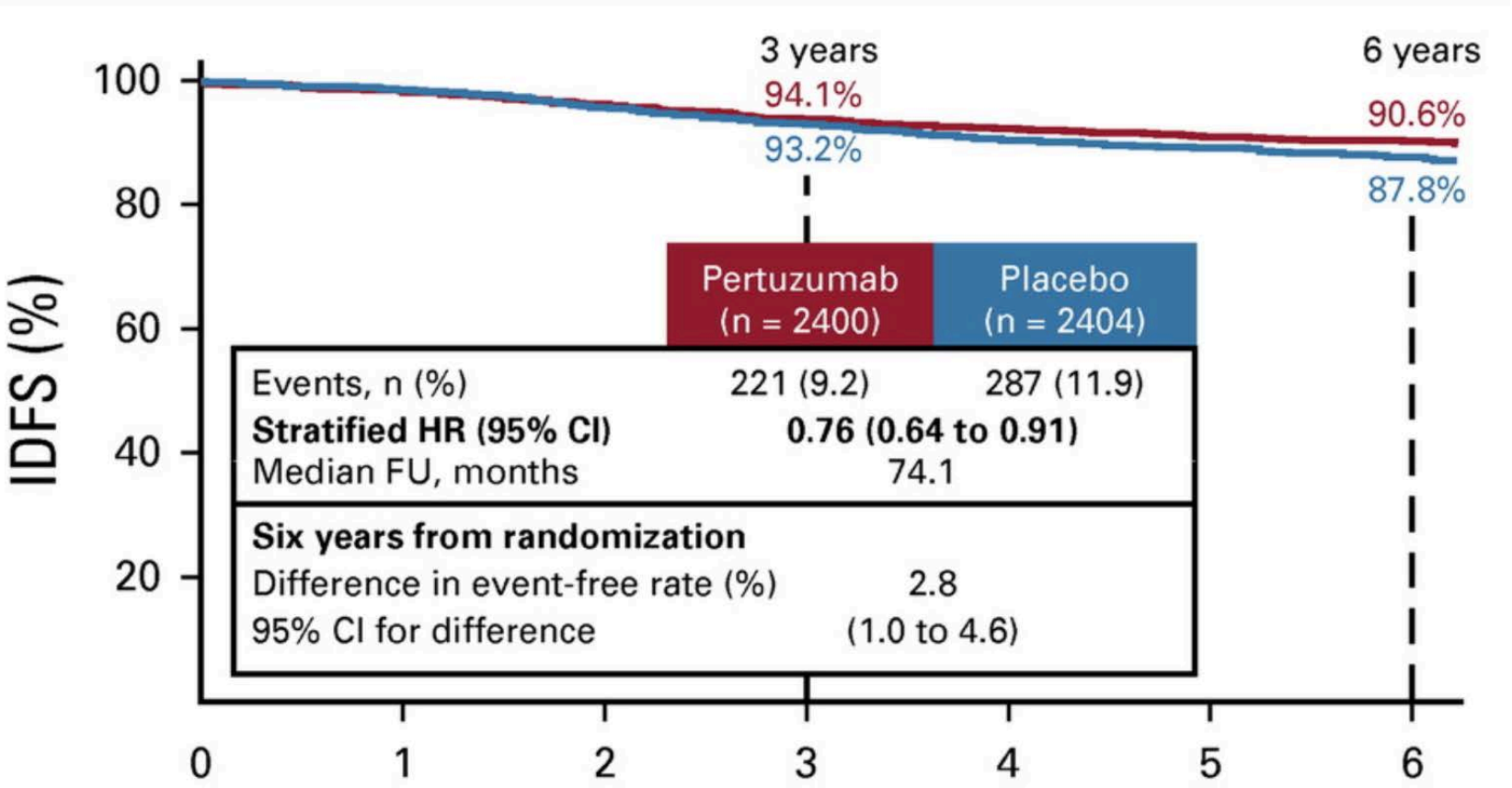
APHINITY – pertuzumab added to chemotherapy + trastuzumab



Von Minckwitz et al, NEJM 2017; Piccart M et al, JCO 2021

APHINITY: When to Add Pertuzumab

2nd interim analysis @ 6 Years' Followup



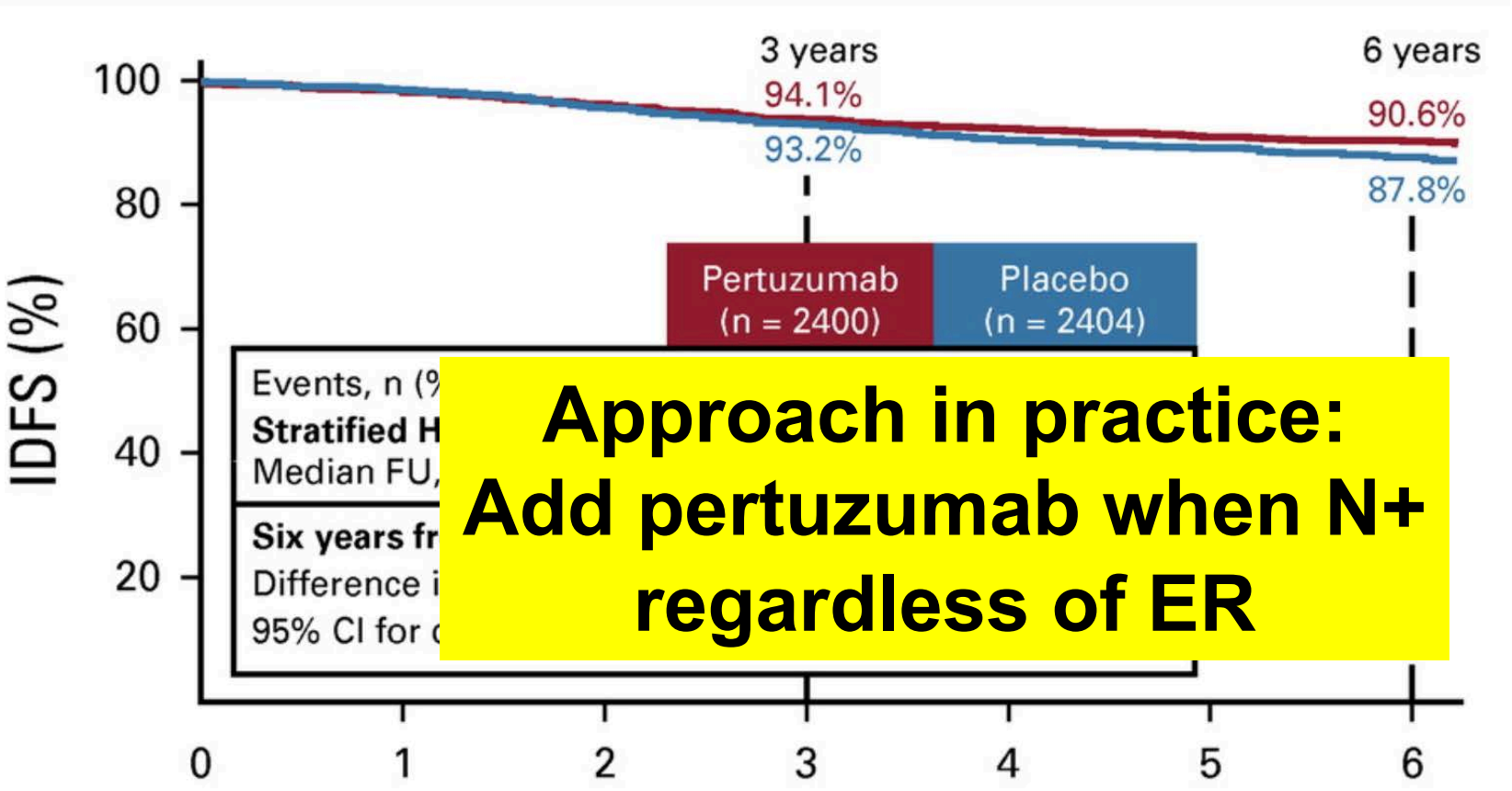
No effect in N-
4.5% absolute △ in N+

Benefit in <u>both</u> ER+ and ER-

Piccart M et al, JCO 2021

APHINITY: When to Add Pertuzumab

2nd interim analysis @ 6 Years' Followup



Approach in practice:
Add pertuzumab when N+ regardless of ER

No effect in N-
4.5% absolute △ in N+

Benefit in <u>both</u> ER+ and ER-

Piccart M et al, JCO 2021

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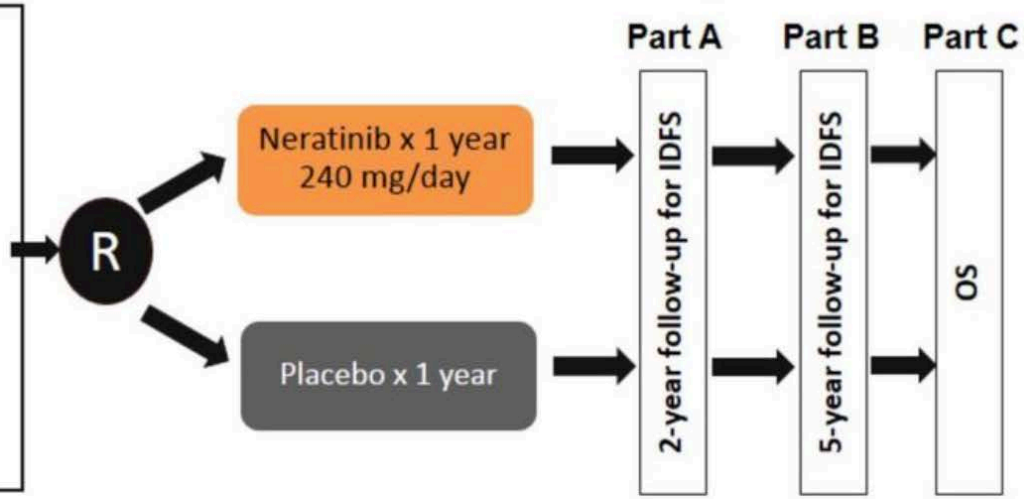
↑ Effectiveness by Extended Adjuvant Therapy

ExteNET

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab and chemotherapy
- Completed trastuzumab ≤ 1 year prior to study entry
- Lymph node positive or non-pCR after adjuvant therapy
- ER/PR status unknown



iDFS @ 5y:
87.7% vs 90.2% (△2.5%)
Esp in Asia, HR+, 4+ LN

Study population received chemo+H.

Behavior post HP or TDM1?

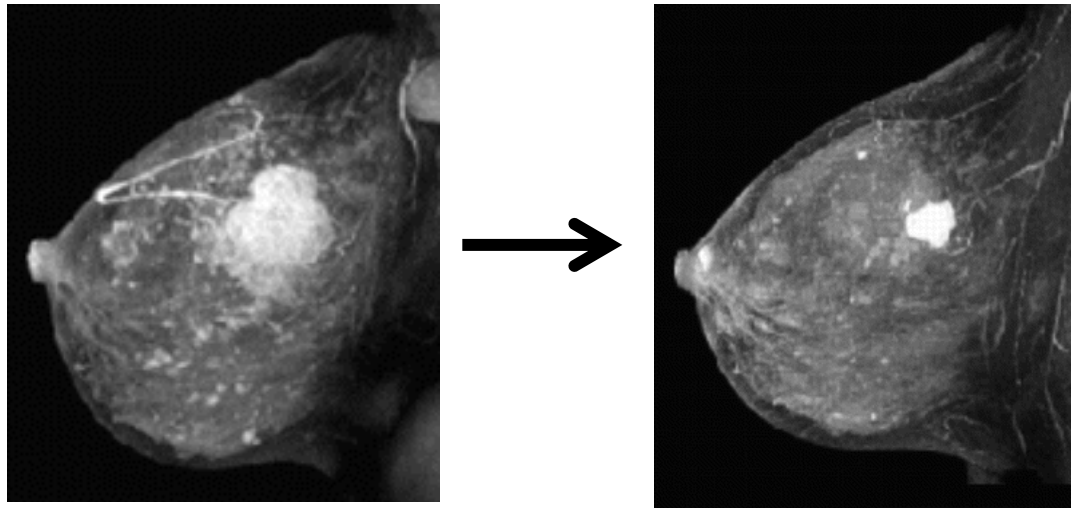
Gr3+ Diarrhea 40% despite prophylaxis
CONTROL Trial: additional maneuvers may help (budesonide, colestipol,) dose escalation

Martin M et al, Lancet Oncol 2017; Barcenas CH et al, Ann Oncol 2020

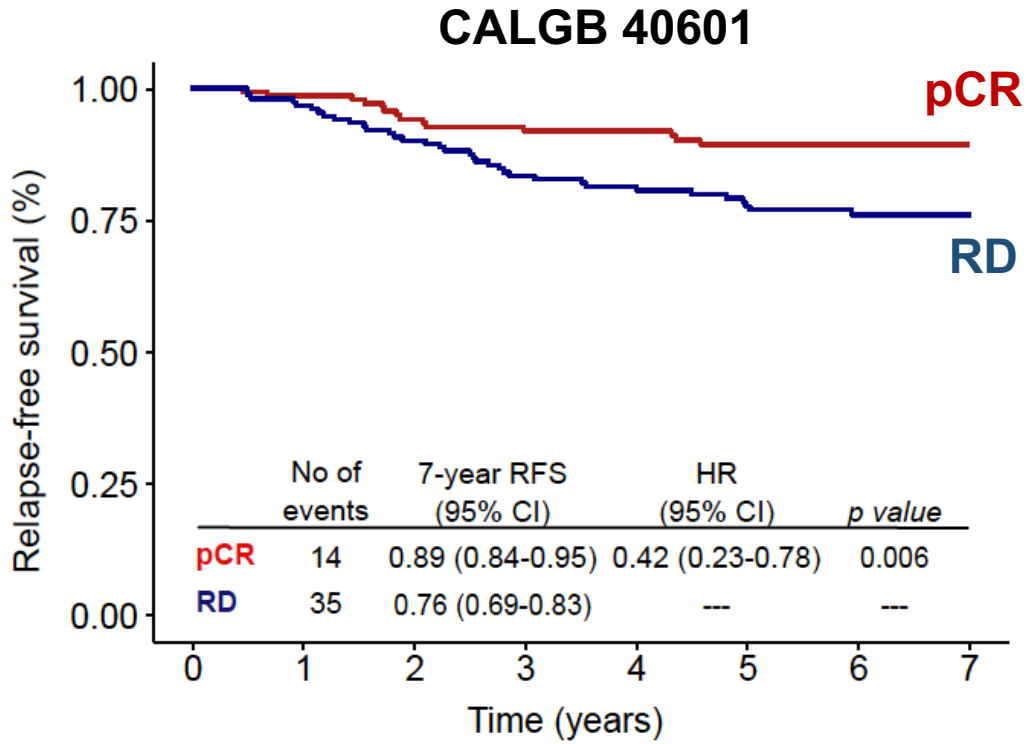
Neoadjuvant Therapy: Allows Tailoring (Surgical and Medical)

Clear surgical benefits

(smaller surgeries, more lumpectomies, fewer ALND)



Allows tailoring medical therapy because outcome dependent on drug response



Fernandez-Martinez A et al, JCO 2020

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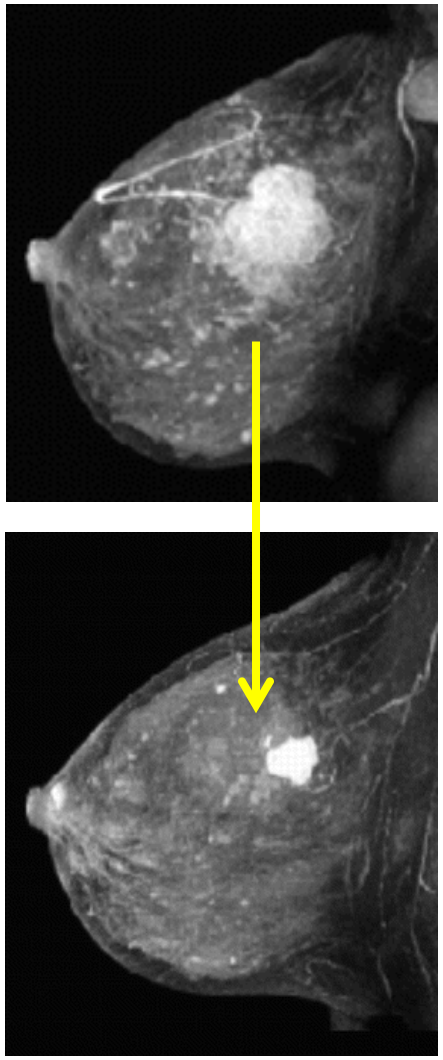
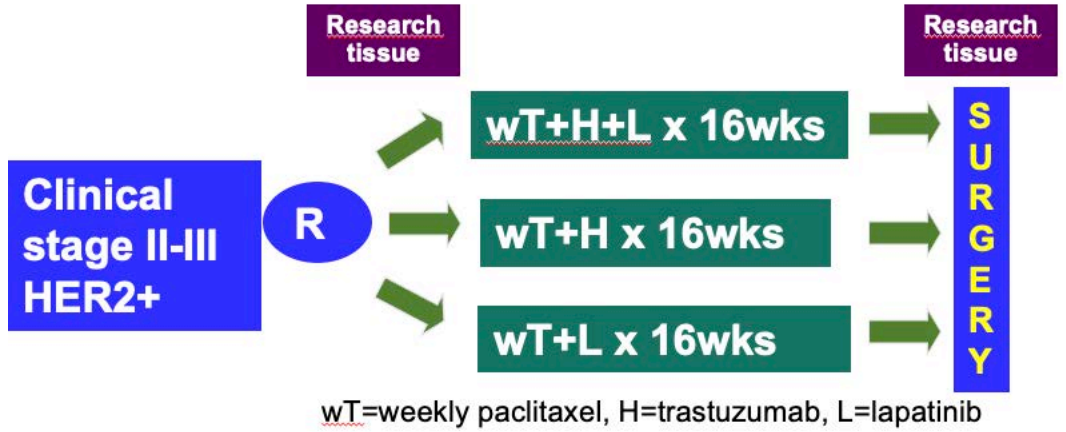
CALGB 40601: Improved TNBC In-Breast Operability





Surgical Substudy: Breast conservation

171 (59%) not BCT candidate at diagnosis

↓

73 (43%) of these converted to BCT after chemotherapy+HER2-targeted Rx

(80% BCT success rate)

Golshan M et al, Breast Cancer Res Treat 2016

Reduced Need for Axillary Dissection

Post-Rx positive axillary LN → axillary dissection (ALND)

Lymphedema: 10-20% with ALND

ACOSOG Z1071

Post-chemo SN is accurate (< 10% false negative)

If: Dual tracer, > 2 retrieved SN (maybe LN clipping)

CALGB 40601 Surgical Substudy: Axillary clearance

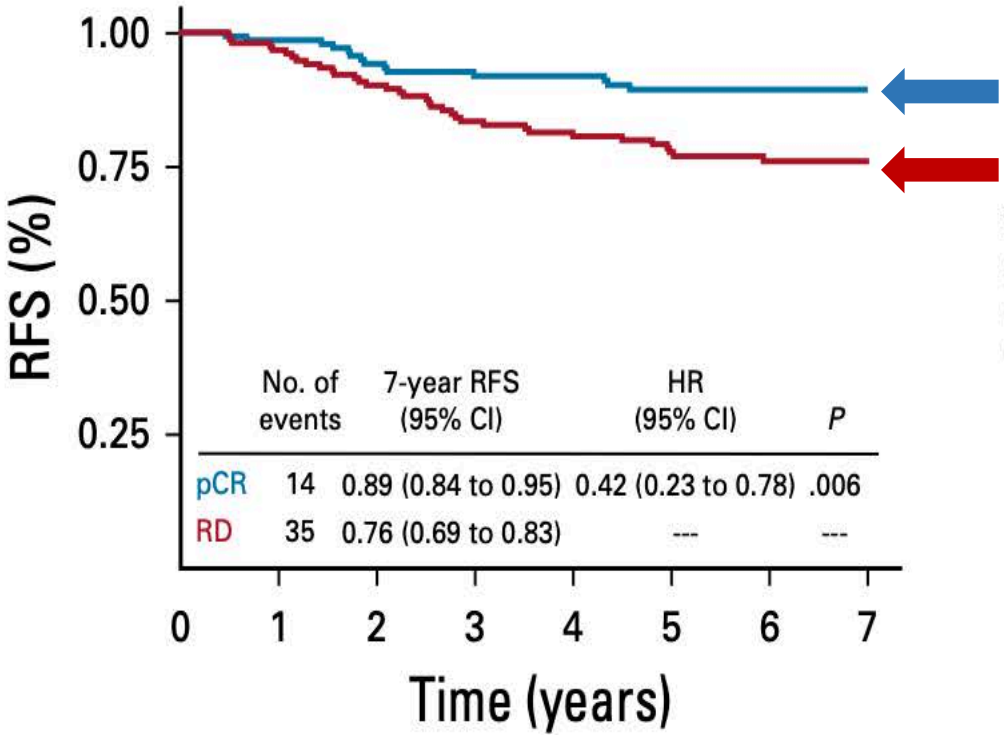
136 cN+ HER2+ → *All arms* → **90 ypN0 (66%)**

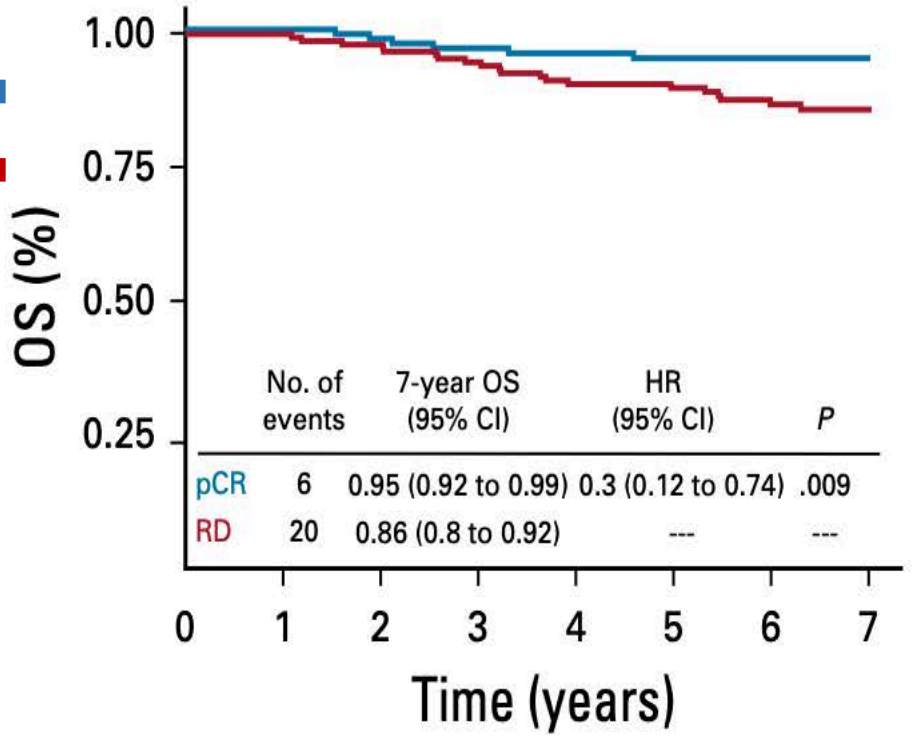
Axillary clearance is highly clinically relevant

Boughey JC et al, JAMA 2014; Weiss A et al, SSO 2021

Medical Tailoring: Outcome Dependent on Drug Response

CALGB 40601 @ 7y





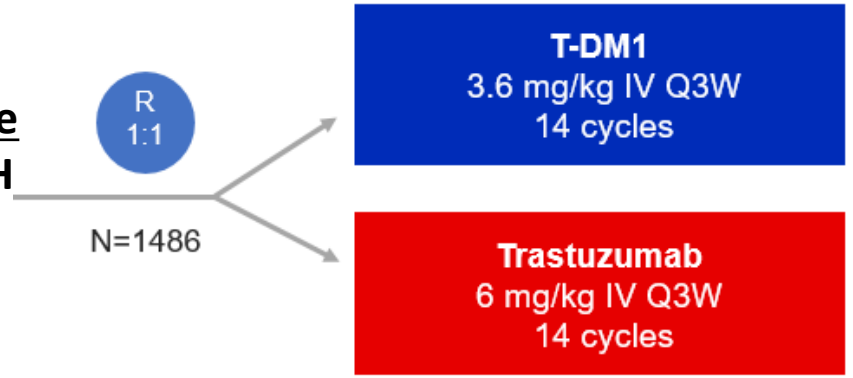
pCR

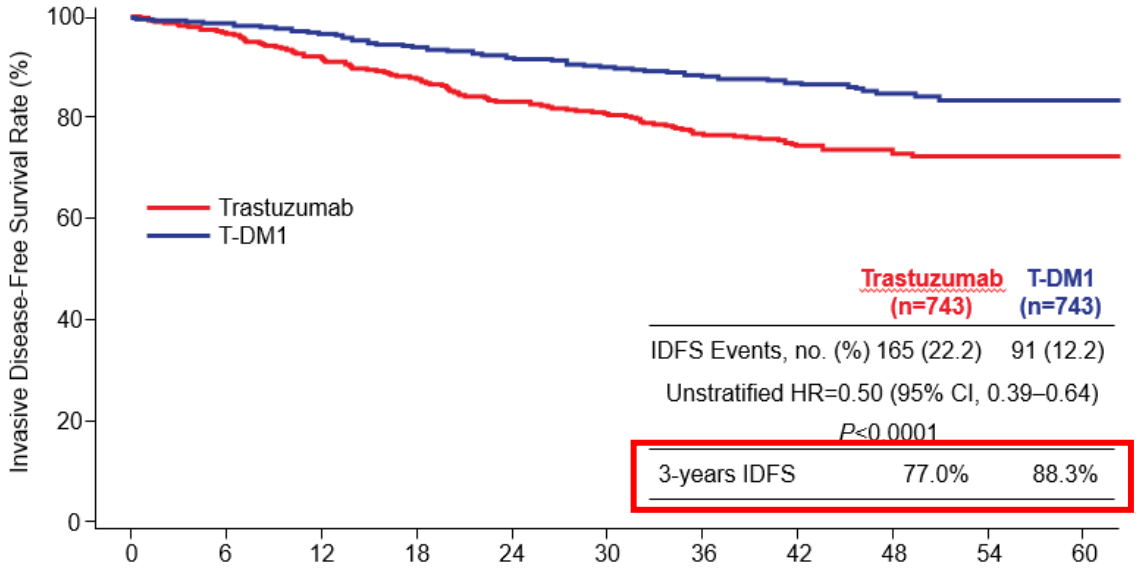
Residual disease

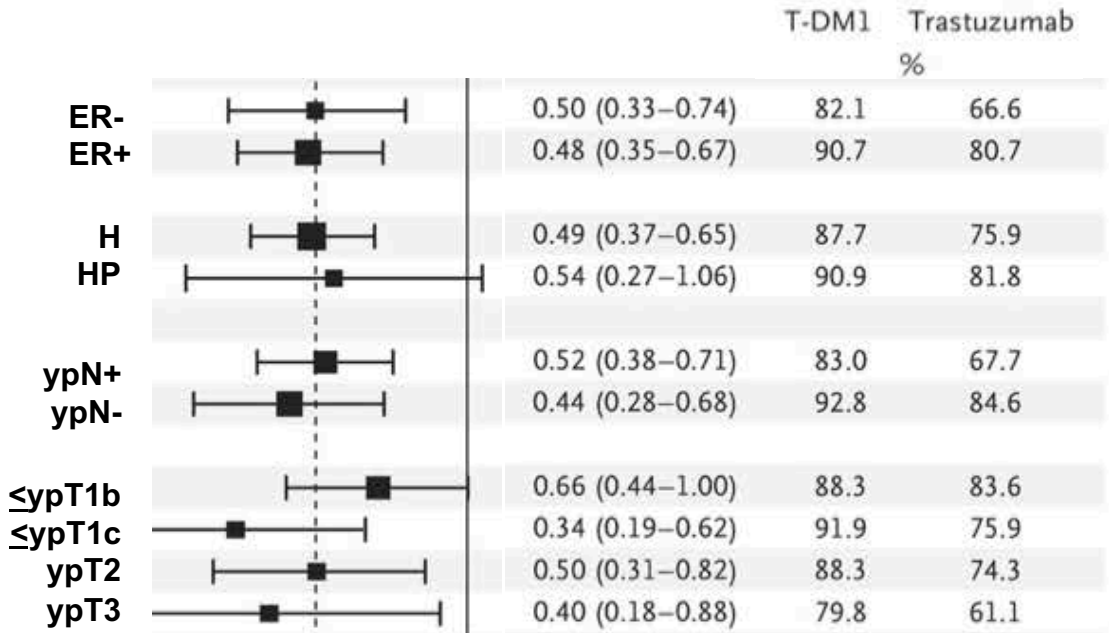
Fernandez Martinez et al, JCO 2020

Tailoring by Pathologic Response to Neoadjuvant: KATHERINE

Residual disease after chemo + H







- **ER-, LN+ still 82-83%**
- **CNS relapse unaffected**
- **T-DM1 toxicity – 18% d/c early (LFT, PN, plt)**

Von Minkwitz et al, NEJM 2018

Tailoring by Pathologic Response to Neoadjuvant: KATHERINE

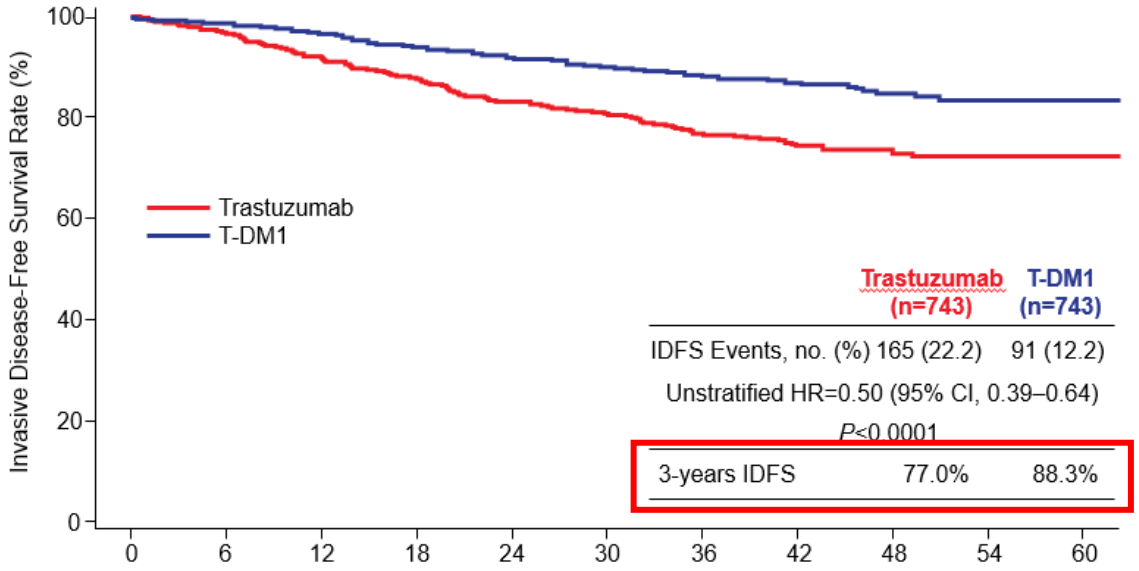
Residual disease after chemo + H

R 1:1

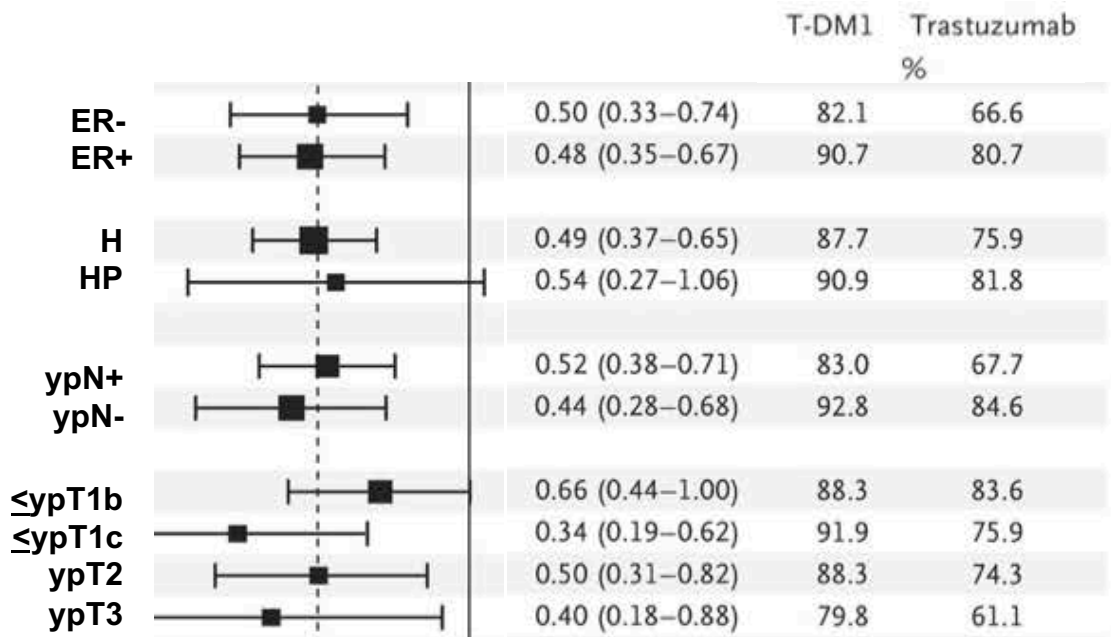
N=1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles



	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-years IDFS	77.0%	88.3%



Approach in practice:
Switch to T-DM1 in any residual disease

Von Minkwitz et al, NEJM 2018

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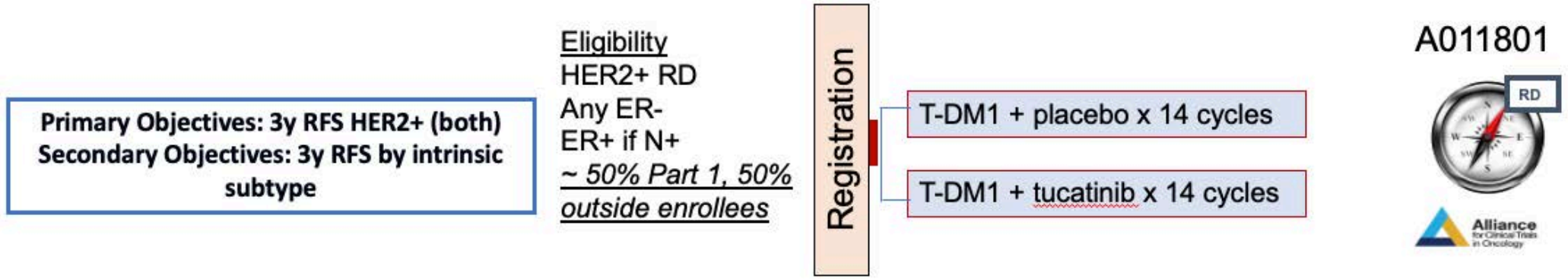
Ongoing Challenge of CNS Metastasis

- **KATHERINE did not see a difference with T-DM1 in incidence of CNS relapse (~ 5% both arms)**
- **Small molecule inhibitors may be key**
  - **Post-hoc subset analysis of ExteNET HR+ suggest 59% reduction in risk of CNS relapse**
  - **Tucatinib added to trastuzumab + capecitabine in MBC found 68% improvement in CNS PFS**
- **Being tested in COMPASS-RD:**



Chan A et al, Clin Breast Cancer 2021; Lin NU et al, JCO 2021

Strategies for Treatment of Early HER2+ Breast Cancer

Clinical stage	Initial Rx	Path stage	Adjuvant phase*
Stage I cT1N0	**Surgery**	pT1aN0	No systemic therapy (ET prn)
		pT1b-c,N0	TH x 12 wk, H to 6-12m
Stage II cT2-3N0 cT0-2N1	**Neoadjuvant Rx** Chemo + H (HP if LN+)	pCR	H or HP to 1y
		Residual disease	T-DM1 x 14 cycles
Stage III cT3N1 cT4N(any) cT(any)N2-3	**Neoadjuvant Rx** Chemo + HP	pCR	H or HP to 1y
		Residual disease	T-DM1 x 14 cycles Consider neratinib x 1y if ER+
Surgery first Stage II-III	Neoadjuvant recommended!	Stage II-III	Chemo + H (HP if LN+) Consider neratinib x 1y if ER+ and 4+ LN

*ET recommended if HR+

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Thank You!