Memorial Sloan Kettering Cancer Center

Stage IA HER2 + Breast Cancer: De-escalation vs Escalation

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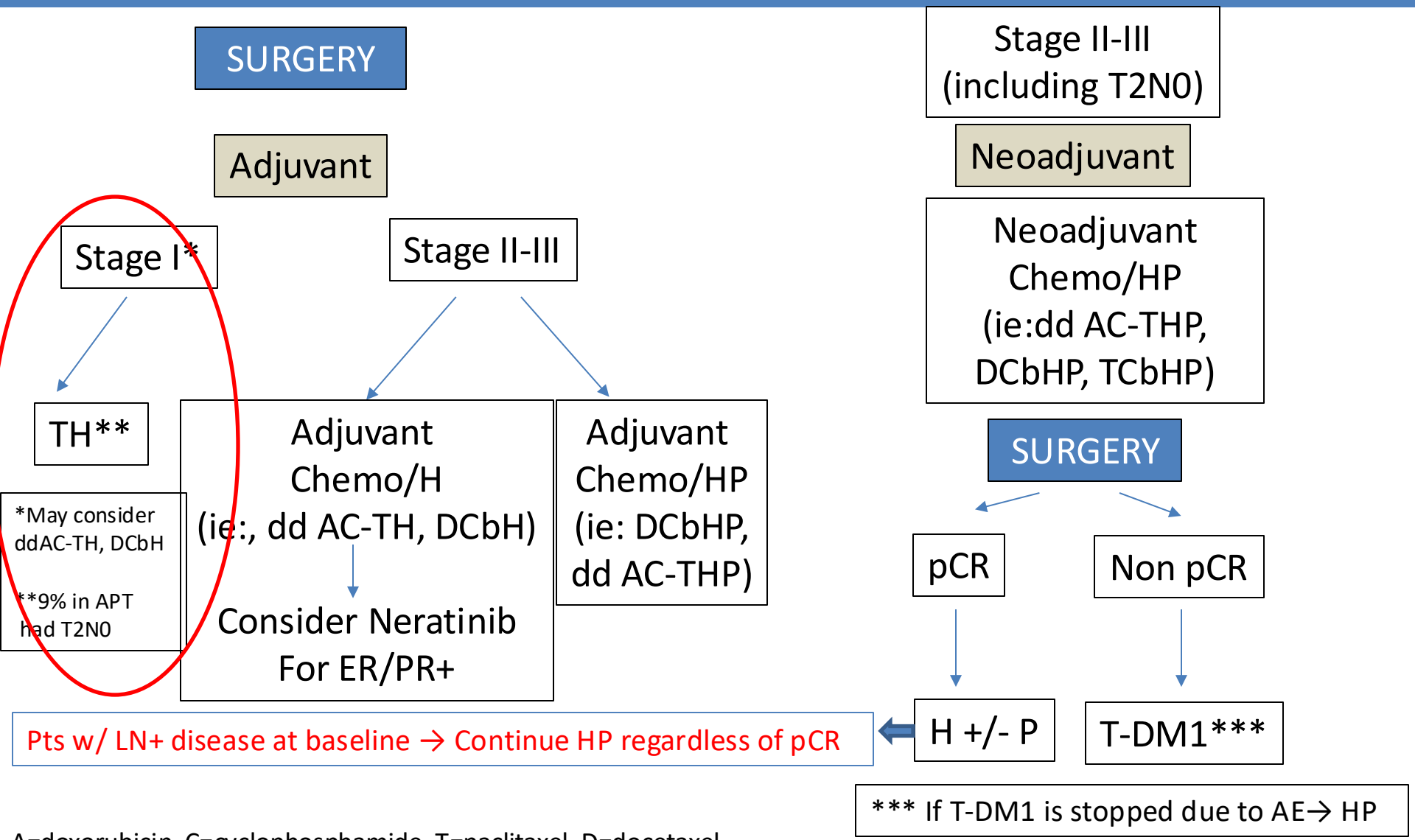
Objectives

- Current treatment algorithm for early stage HER2+ breast cancer
- Limited literature review of outcomes of patients with stage IA HER2+ breast cancer
  - Stage IA = T1N0
- Genomic Tool
- De-escalation and escalation trials

Approach to Early Stage HER2+ Breast Cancer 2024

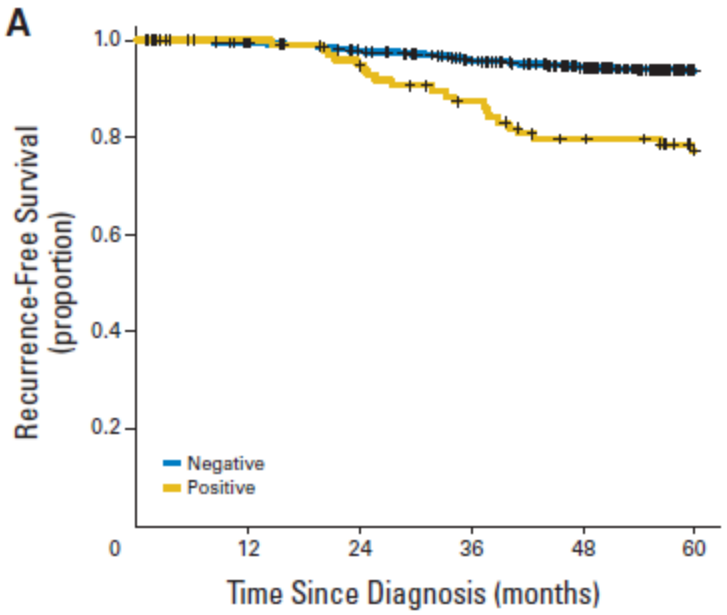


A=doxorubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel,
Cb=carboplatin, H=trastuzumab, P=pertuzumab, dd=dose-dense; pCR=pathologic complete response

Outcomes for T1a/bN0 HER2+ Tumors

MDACC Series (N=98)

HER2 status	N	5 yr RFS
HER2+	98	77.1%
HER2-	867	93.7%



Gonzalez-Angulo et al. JCO 2009

NCCN Series (N=520)

	No Rx	Chemo +/- tras
For HR+ HER2+	↓	↓
5-yr DRFS		
T1a	96%	vs 100%
T1b	94%	vs 96%
5-yr OS		
T1a	95%	vs 100%
T1b	95%	vs 99%
For HR-HER2+		
5-yr DRFS		
T1a	93%	vs 100%
T1b	94%	vs 94%
5-yr OS		
T1a	93%	vs 100%
T1b	100%	vs 95%

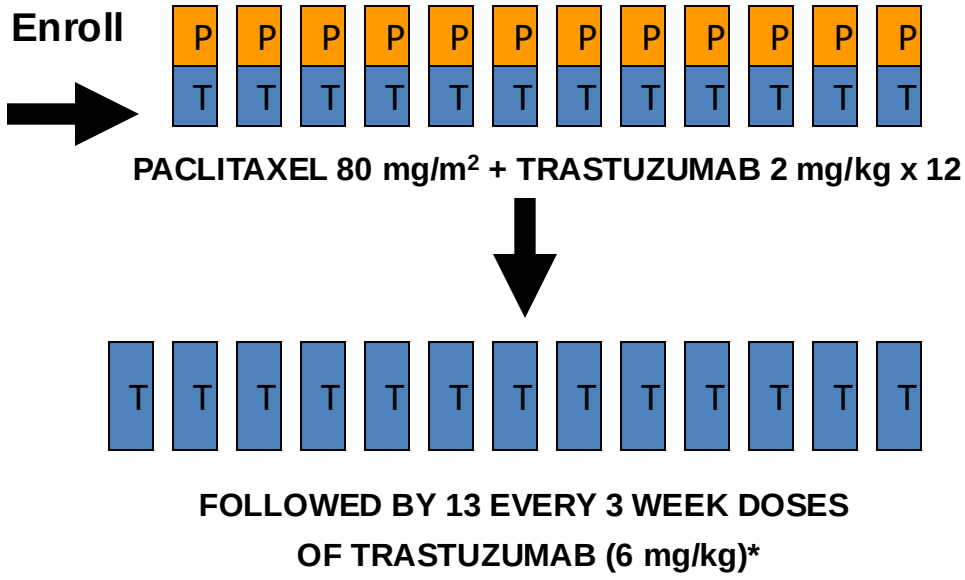
Vaz-Luiz et al. JCO 2014

APT TRIAL: STUDY DESIGN
10-YEAR FU

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

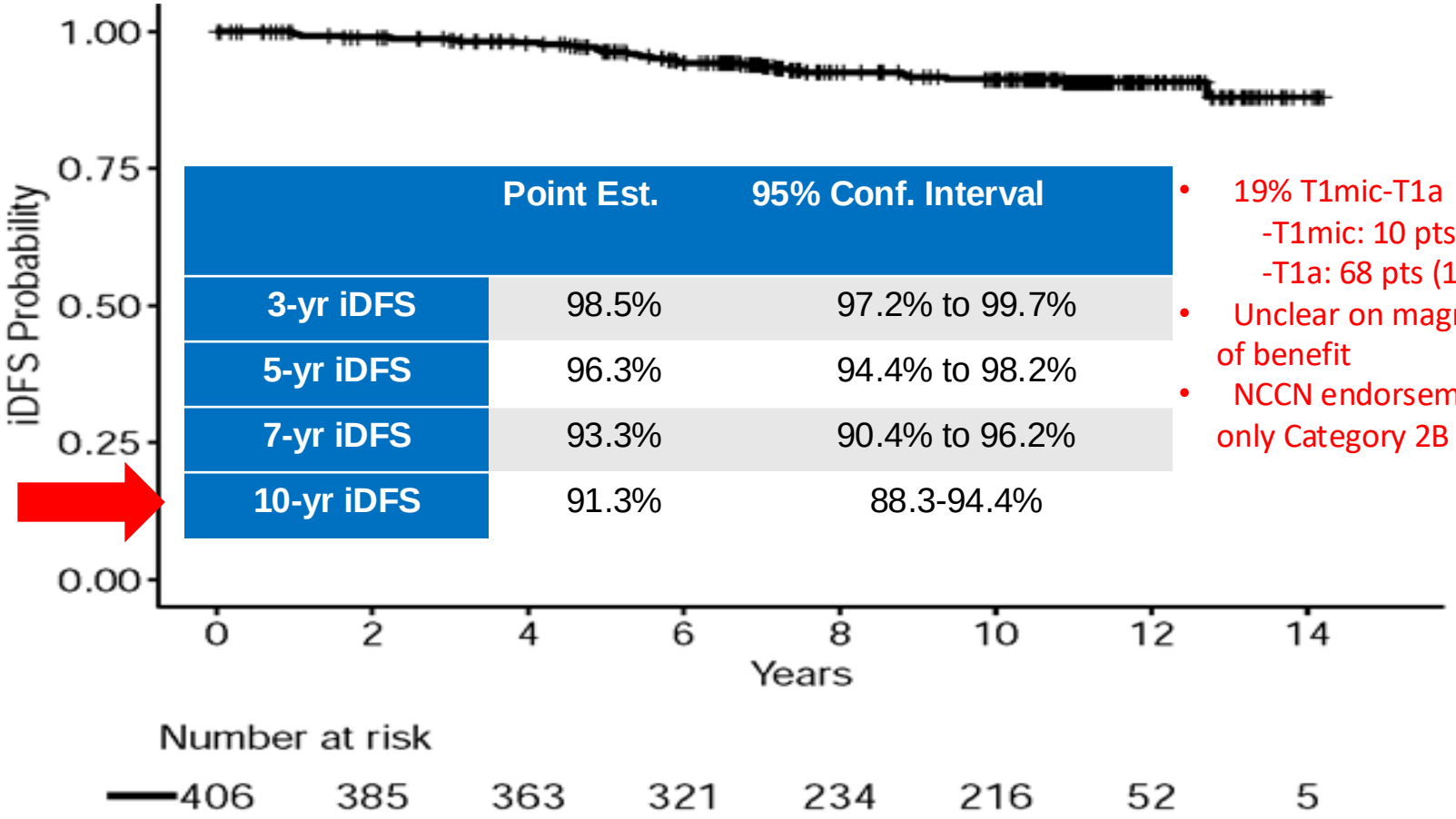
Planned N=400

T1a-19%
1b-31%
1c-42%
T2 - 9%



Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019
Tolaney et al. SABC 2022

APT: 10-year RESULTS (iDFS)



	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%

- 19% T1mic-T1a
  - -T1mic: 10 pts (2.2%)
  - -T1a: 68 pts (16.7%)
- Unclear on magnitude of benefit
- NCCN endorsement only Category 2B

Tolaney et al. Lancet Oncol 2023

6 IBTR, 9 Contralateral BC, 6 distant events (2 leading to deaths)

Tolaney et al. SABC 2022
Tolaney et al. Lancet Onol 2023

ATEMPT Trial
N= 497

Co-1◦ EPs: 3 y DFS w/ T-DM1
Eval Clin Relevant Tox (CRT)
b/t TH vs T-DM1

3 y DFS w/ T-DM1 → 97.8%
CRT → No difference

T1mic = 11 pts (2%)
T1a = 70 pts (14%)

Key Eligibility Criteria
- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1
3.6 mg/kg IV q3 wks x 17

N = 114

TH
Paclitaxel 80 mg/m^2 IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

***Radiation and endocrine therapy could be initiated after 12 weeks on study therapy**

Discontinuation rates 17% (TDM) vs 6%, (TH)
ATEMPT Version 2.0 ongoing

Tolaney et al. SABC 2019
Tolaney et al. JCO 2021

npj | breast cancer
Published in partnership with the Breast Cancer Research Foundation
Article
https://doi.org/10.1038/s41523-024-00652-4

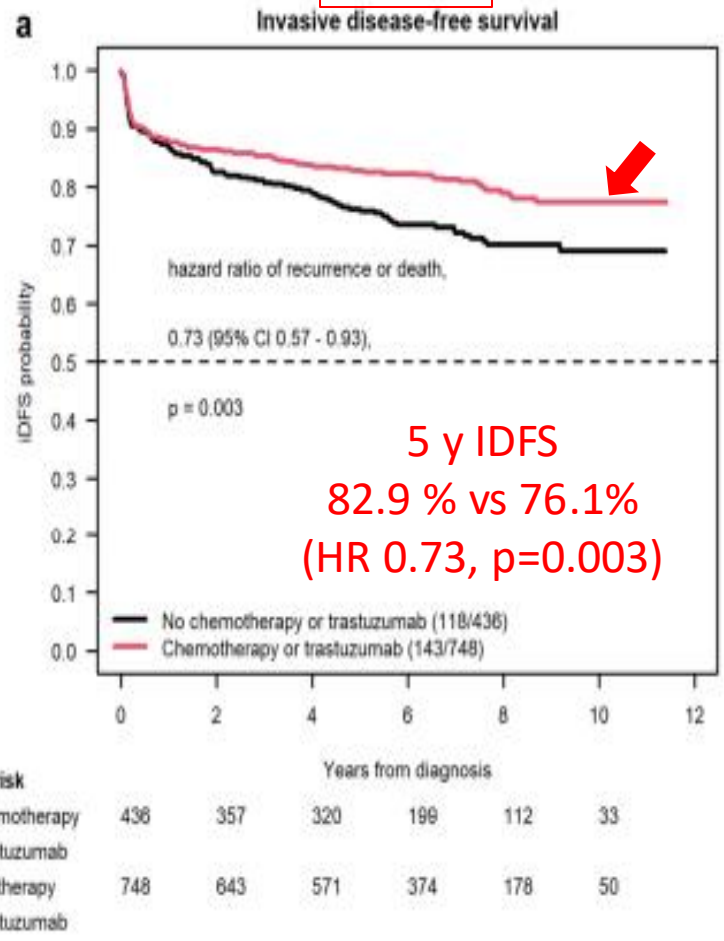
The survival benefit of adjuvant trastuzumab with or without chemotherapy in the management of small (T1mic, T1a, T1b, T1c), node negative HER2+ breast cancer

- Retrospective analysis of outcomes of pts with T1a-c HER2+ breast ca using ASCO CancerLinQ database (2010-2021).
- N = 1184
  - Local Rx alone (N of 436)
  - Tras +/- chemo (N of 748)
    - Tras (N of 169)
    - Tras + chemo (N of 579)
- Demographic
  - T1mic = 14 (1.2%)
  - T1a = 202 (17.1%)
  - T1b = 325 (27.4%)
  - T1c = 615 (51.9%)

Johnson et al. NPJ Beast 2024

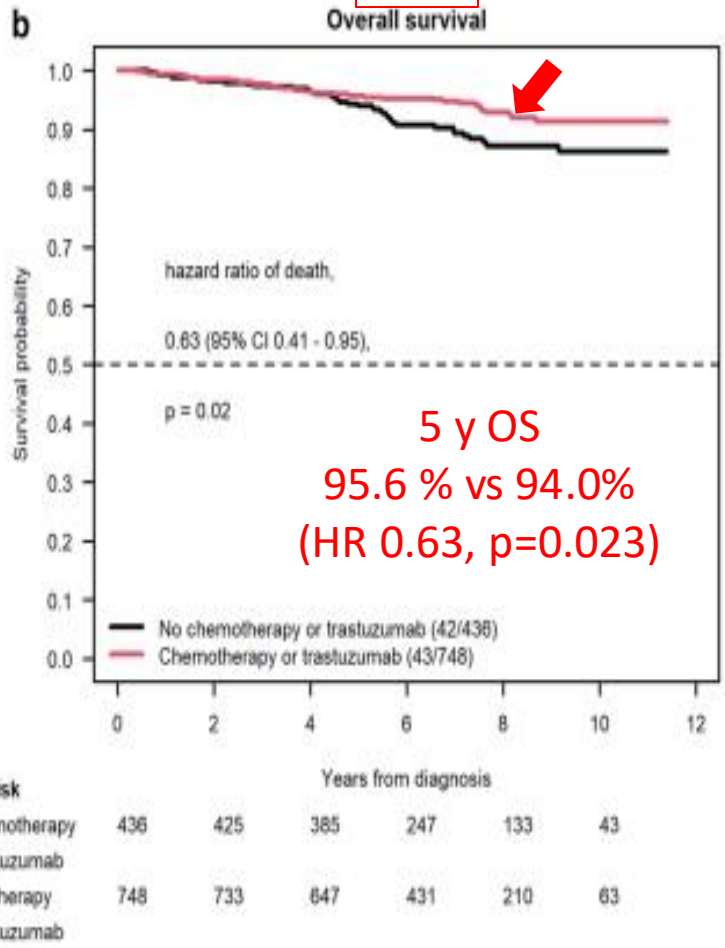
IDFS and OS (Treated vs Untreated)

IDFS



5 y IDFS
82.9 % vs 76.1%
(HR 0.73, p=0.003)

OS

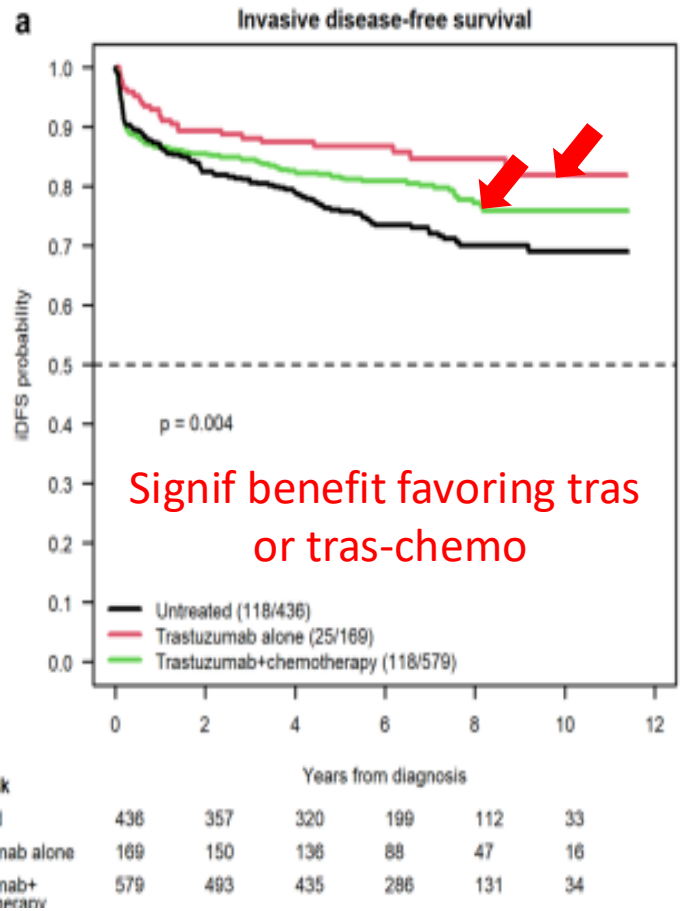


5 y OS
95.6 % vs 94.0%
(HR 0.63, p=0.023)

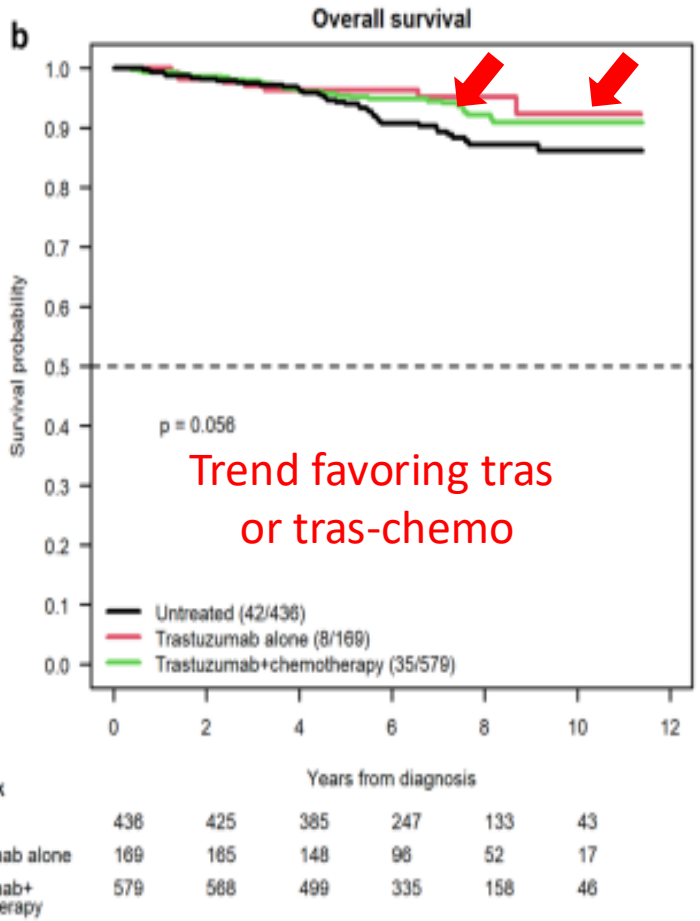
Johnson et al. NPJ Beast 2024

IDFS and OS (Tras or Tras/Chemo vs Untreated)

IDFS



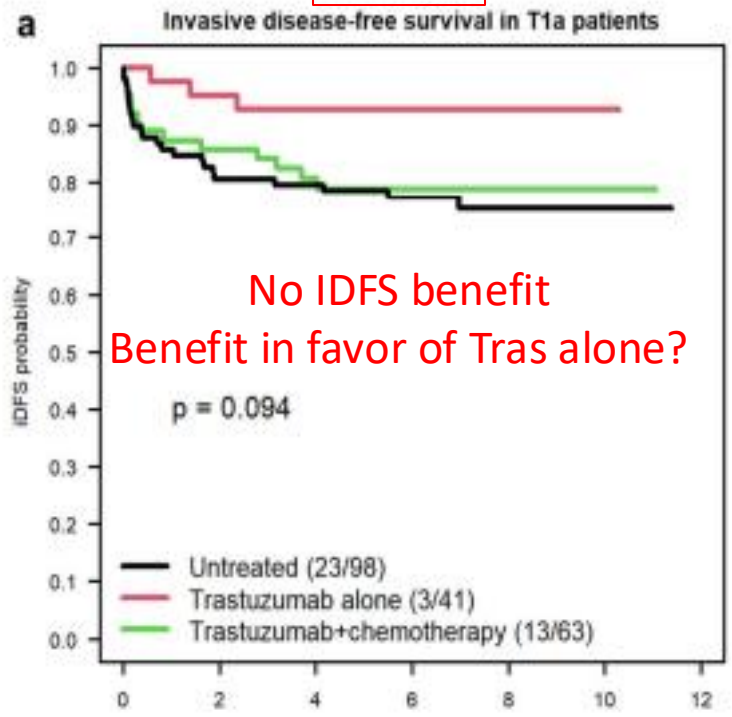
OS



Johnson et al. NPJ Beast 2024

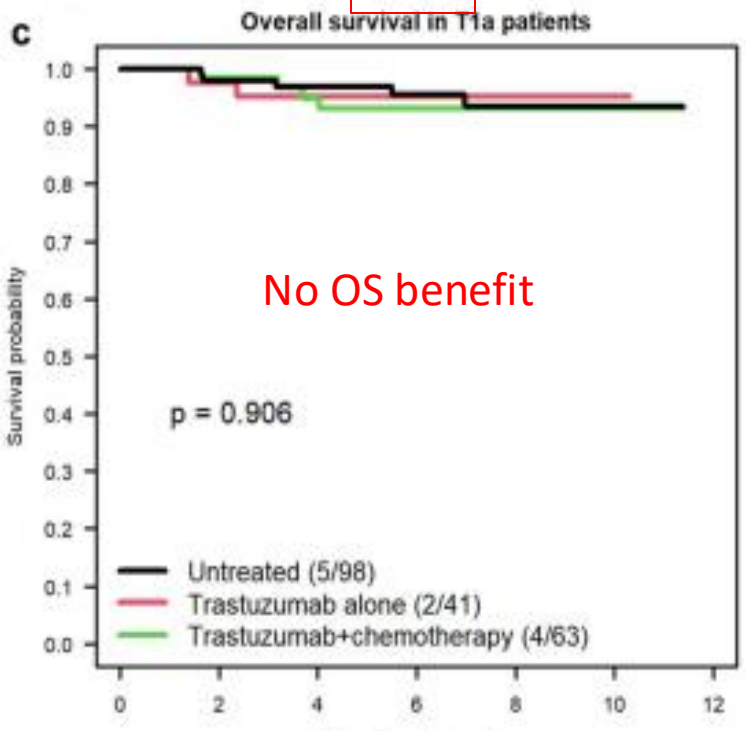
IDFS and OS for T1a (Tras or Tras/Chemo vs Untreated)

IDFS



No. at risk						
Untreated	313	257	228	137	75	25
Trastuzumab alone	120	104	95	64	35	12
Trastuzumab+ chemotherapy	507	431	383	254	114	30

OS

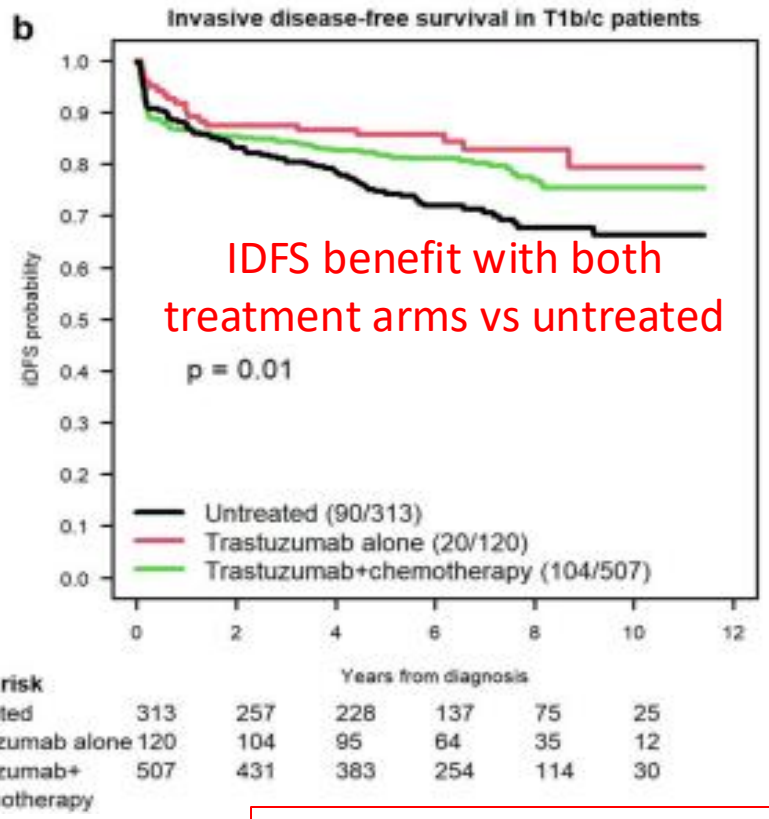


No. at risk						
Untreated	98	96	89	62	32	8
Trastuzumab alone	41	40	35	20	8	3
Trastuzumab+ chemotherapy	63	62	52	32	16	6

Johnson et al. NPJ Beast 2024

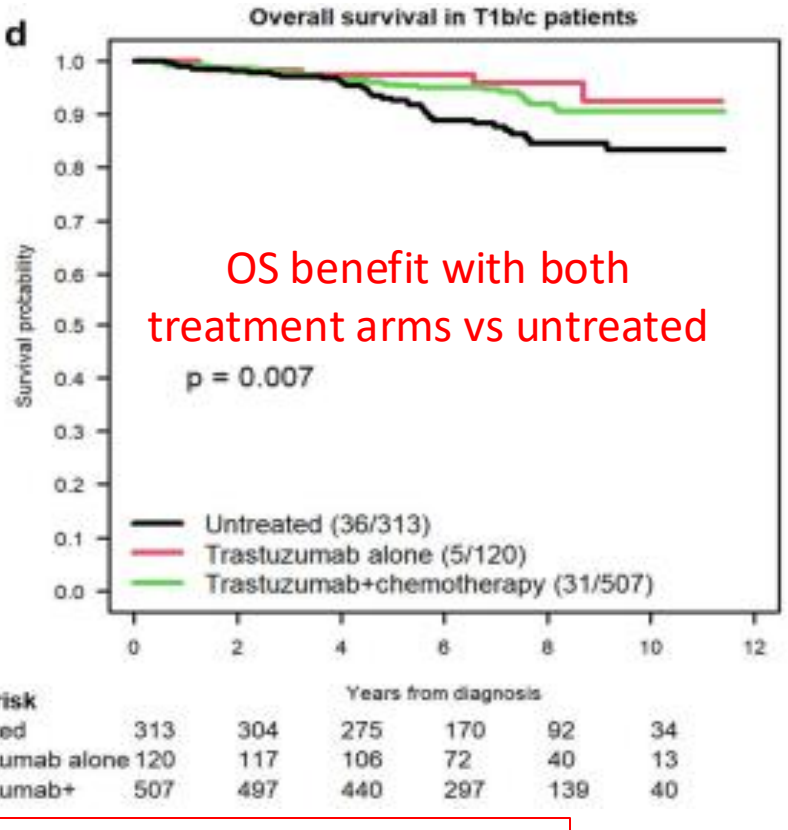
IDFS and OS for T1 b/c (Tras or Tras/Chemo vs Untreated)

IDFS



No. at risk						
Untreated	313	257	228	137	75	25
Trastuzumab alone	120	104	95	64	35	12
Trastuzumab+ chemotherapy	507	431	383	254	114	30

OS



No. at risk						
Untreated	313	304	275	170	92	34
Trastuzumab alone	120	117	106	72	40	13
Trastuzumab+	507	497	440	297	139	40

Overall, subgroup data suggest that T1b/c tumors derived greatest benefit from Tras or Tras-chemo

Johnson et al. NPJ Beast 2024

A US Registry–Based Assessment of Use and Impact of Chemotherapy in Stage I HER2-Positive Breast Cancer

Benjamin M. Parsons, DO[a]; Dipesh Uprety, MD[a]; Angela L. Smith, MA[b]; Andrew J. Borgert, PhD[b]; and Leah L. Dietrich, MD[a]

- Retrospective analysis using propensity matched cohort model
- 1 EP: OS
- N = 8222
- Effect of adjuvant chemo on 5-y OS
  - T1mic (N = 626) (worse effect, 89.1% vs 99.1%)
  - T1a (N = 2901) (no effect, 95.4% vs 96.9%)
  - T1b (N = 2340) (better, 97.1% vs 92.3%)
  - T1c (N = 2355) (better, 95.9% vs 91.5%)

Unclear that systemic tras or tras-chemo is beneficial in pts with T1mic or T1a

Parsons et al. JNNC 2018

Can Genomic Tool Help to Refine Treatment?

HER2DX Genomic Test

- First genomic tool - predictive of likelihood of pCR and long-term prognosis in pts with early stage HER2+ breast Ca

- Based on
  - 4 gene signatures (comprised of 27 genes)
    - 14 gene immunoglobulin module
    - 4 gene tumor cell proliferation signature
    - 5 gene luminal differentiation signature
    - 4 gene HER2 amplicon signature
  - Clinical features (size, nodal status)

- Villacampa et al eval assoc of HER2DX score in 7 neoadj cohorts (DAPHNE, GOM-HGUGM-2018-05, CALGB 40601, ISPY-2, BiOnHER, NEOHER, PAMELA) [1]
  - pCR according to HR status and Rx type
  - Survival outcomes according to pCR

Villacampa, Tung, Prat, Tolaney et al. Ann Oncol 2023

HER2DX Genomic Test

- pCR high, pCR medium, and pCR low tumors
  - pCR high tumors: high pCR w/ single taxane/HP
    - Highly HER2 addicted, proliferative, immune infiltrated
  - pCR low tumor: low pCR (regardless of dual anti-HER2 or multi-chemo Rxs given)
    - Highest expression luminal features
  - pCR medium tumors: benefitted from multi-chemo Rxs w/ anti-HER2
    - Intermediate
- HER2DX low-risk and high-risk
  - Low-risk group assoc w/ high EFS and OS regardless of pCR status
- Validation studies ongoing
- Can we use HER2DX genomic test to identify pts who need less vs more Rx?

Villacampa, Tung, Prat, Tolaney et al. Ann Oncol 2023

Thoughts…

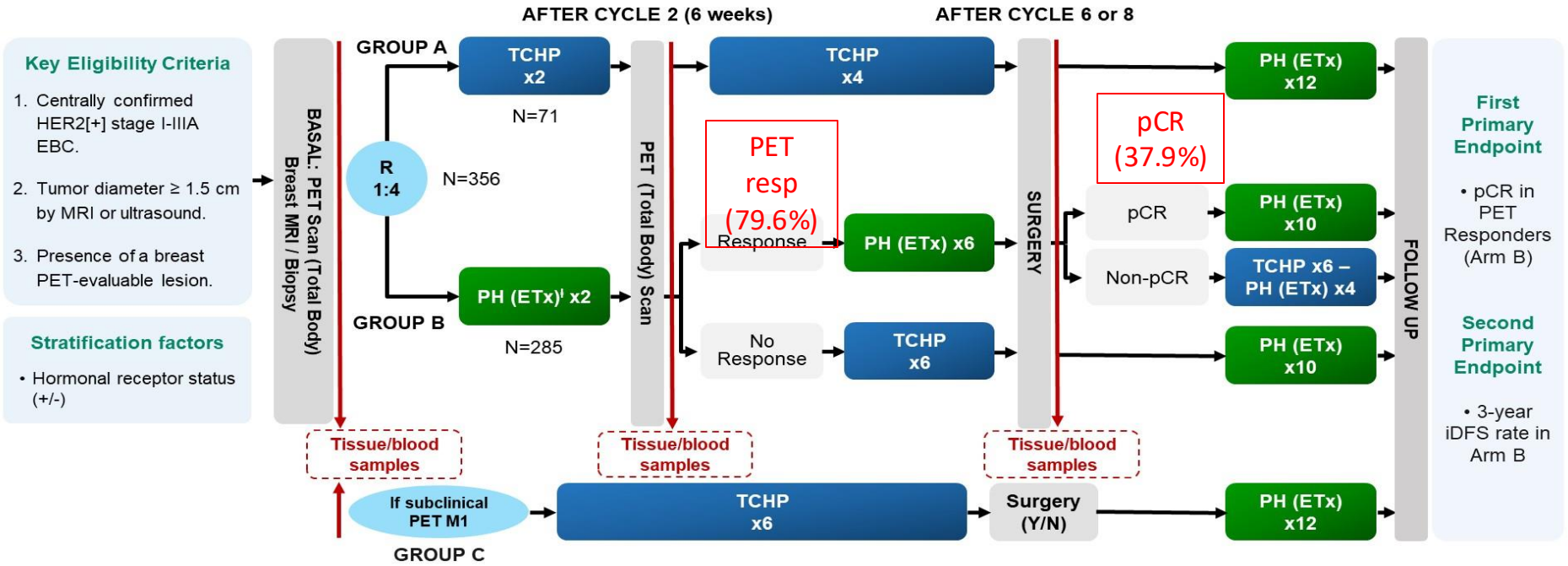
- HER2 DX Genomic Test
  - Predictive of pCR and long-term outcomes (pts with early stage HER2+ breast Ca)
  - Prospective validation studies needed
  - Future prospective trials using HER2 DX
    - T1mic and T1a
      - Need systemic Rx?
    - T1b/c
      - Shorter duration ?
- Other Biomarkers?
  - HER2 Enriched, PIK3CA, TILS/immune activation

De-escalation and Escalation Trials

De-Escalation Trials

1 EP: pCR in PET responders in Group B
3-y iDFS in Group B

PHERGain Study Design



C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. [I] All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0)

De-escalation
Using PET response to de-escalate chemo use

Cortes et al. ASCO 2023
Perez-Garcia et al. Lancet 2024

Efficacy Analysis: Summary of other efficacy endpoints

	Group A (n = 63)	Group B (n = 267)	Group B without CT (n = 86)
3-year iDFS	**98.3%**	**95.4%**	**98.8%**
(95% CI)	(95.1–100%)	(92.8–98.0%)	(96.3–100%)
3-year DDFS	**98.3%**	**96.5%**	**100%**
(95% CI)	(95.1–100%)	(94.3–98.8%)	(100–100%)
	(n = 71)	(n = 285)	(n = 86)
3-year EFS	**98.4%**	**93.5%**	**98.8%**
(95% CI)	(95.3–100%)	(90.7–96.5%)	(96.6–100%)
3-year OS	**98.4%**	**98.5%**	**100%**
(95% CI)	(95.3–100%)	(97.1–100%)	(100–100%)

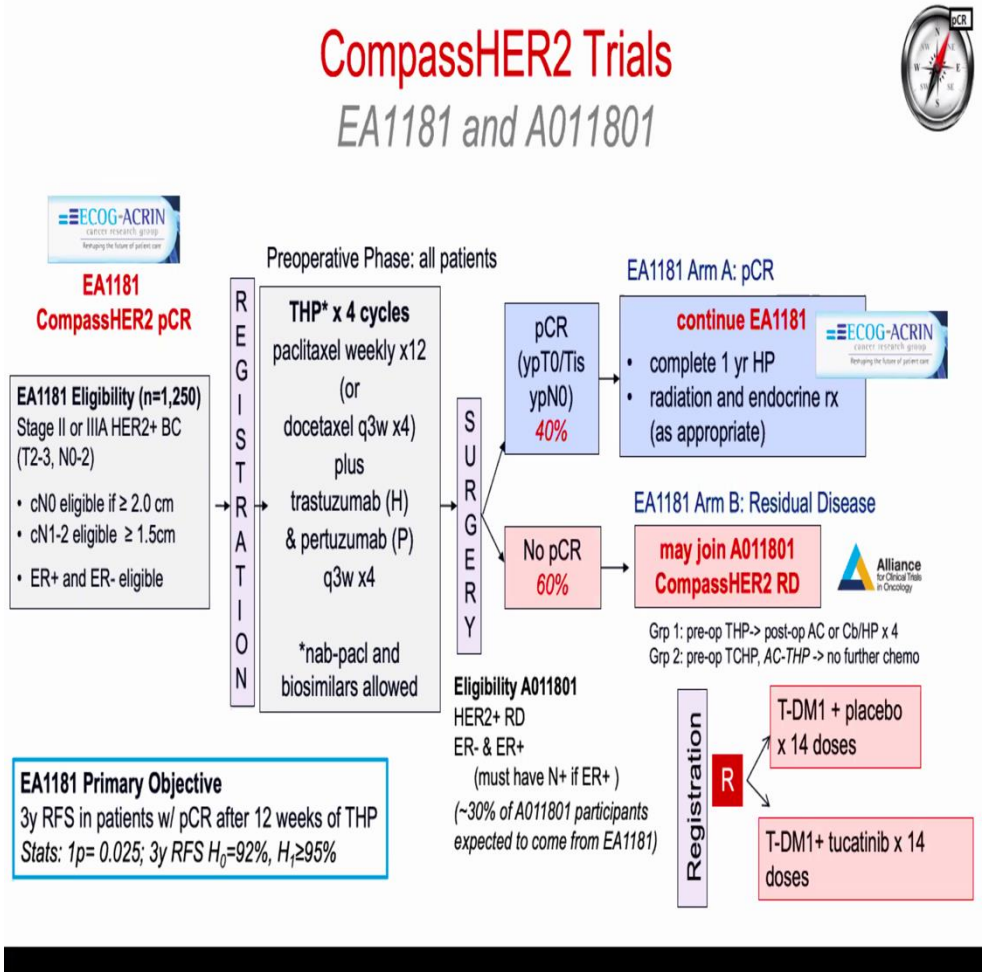
None of these comparisons between the groups reached statistical significance.
iDFS and DDFS are defined from the time of surgery; EFS and OS are defined from randomization.

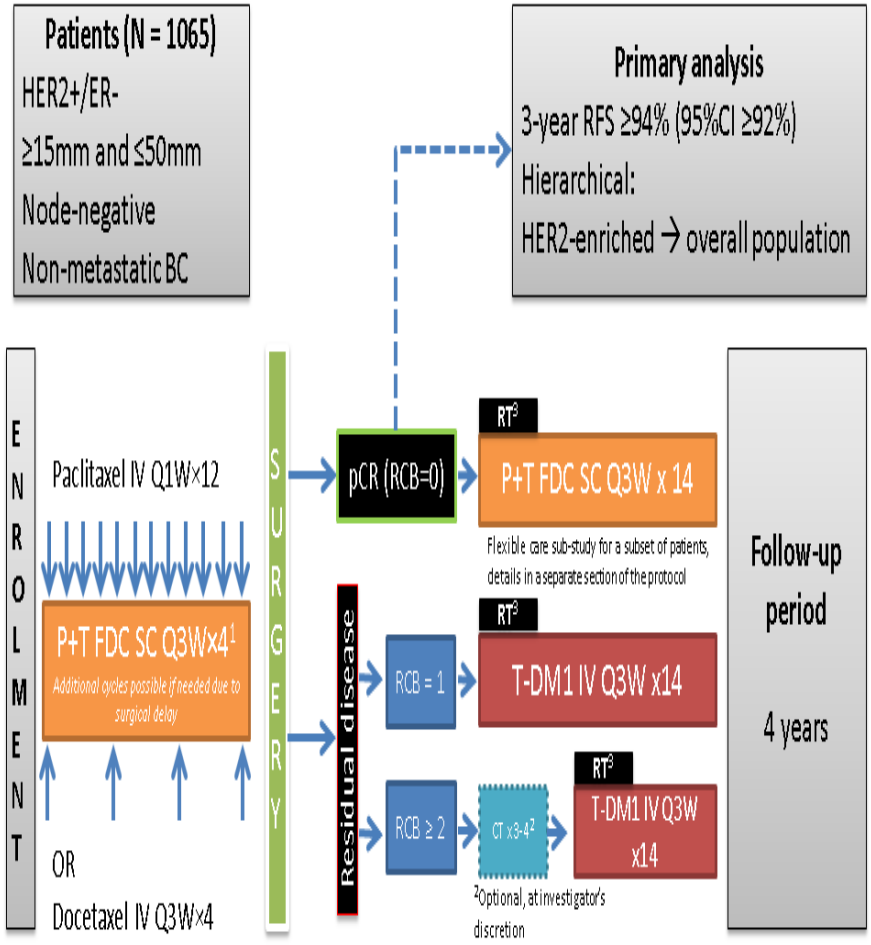
PET-based, pCR-adapted strategy assoc w/ excellent 3 y iDFS !

Can HER2DX identify pts who can avoid chemo upfront (ie: pCR high)?

Cortes et al. ASCO 2023
Perez-Garcia et al. Lancet 2024

De-Escalation Trials DECRESENDO





<u>De-escalation</u>

Omission of neo anthr and multi-chemo Rxs

<u>Risk-Based Strategy</u>

HER2DX pCR score may identify pts who benefit from:

-Neo THP (ie: pCR high)

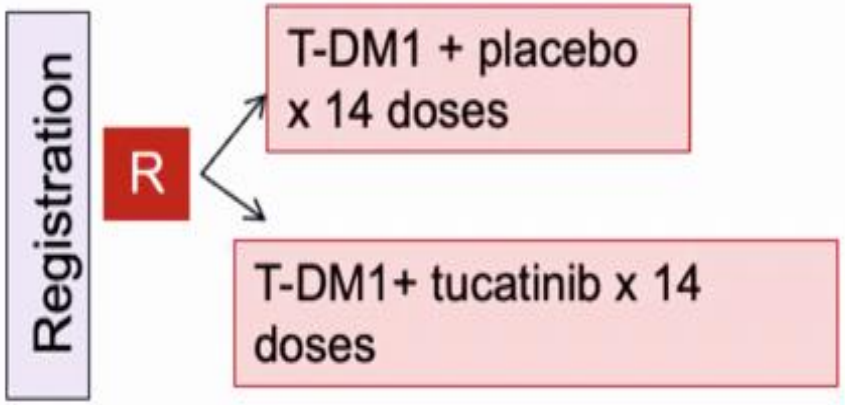
-Multi-chemo Rx (ie: pCR medium)

External validation of HER2DX planned

Escalation Trials

COMPASS HER RD

Eligibility A011801
HER2+ RD
ER- & ER+
(must have N+ if ER+)
(~30% of A011801 participants expected to come from EA1181)



NSABP B-60 / DESTINY Breast 05 ADJUVANT Trial

- Centrally confirmed HER2-positive breast cancer
- High risk EBC:
  - Clinically inoperable at presentation with residual invasive disease in breast or axilla
    or
  - residual disease in axillary nodes
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles of chemotherapy
    - All chemotherapy as neoadjuvant therapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylators allowed
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Randomization within 12 weeks of surgery

R 1:1

N=1600

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab Deruxtecan
5. 4mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if ADCs discontinued due to AEs

Primary Endpoint: IDFS

Can HER2DX risk score identify pts who will not benefit from escalation ?

Summary

- Current strategy is based on burden of disease
  - Stage IA → TH
    - T1a: Unclear benefit of chemo/H
    - T1b/c: Benefit of chemo/H more defined

- Future risk-based Rx strategy – based on biology

- HER2 DX Genomic Test promising
  - Prospective trial needed to refine therapy, especially those with T1mic and T1a disease

- PET based pCR adapted approach is promising

Thank You!