HER2 POSITIVE BREAST CANCER: PAST, PRESENT AND FUTURE

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Disclosures

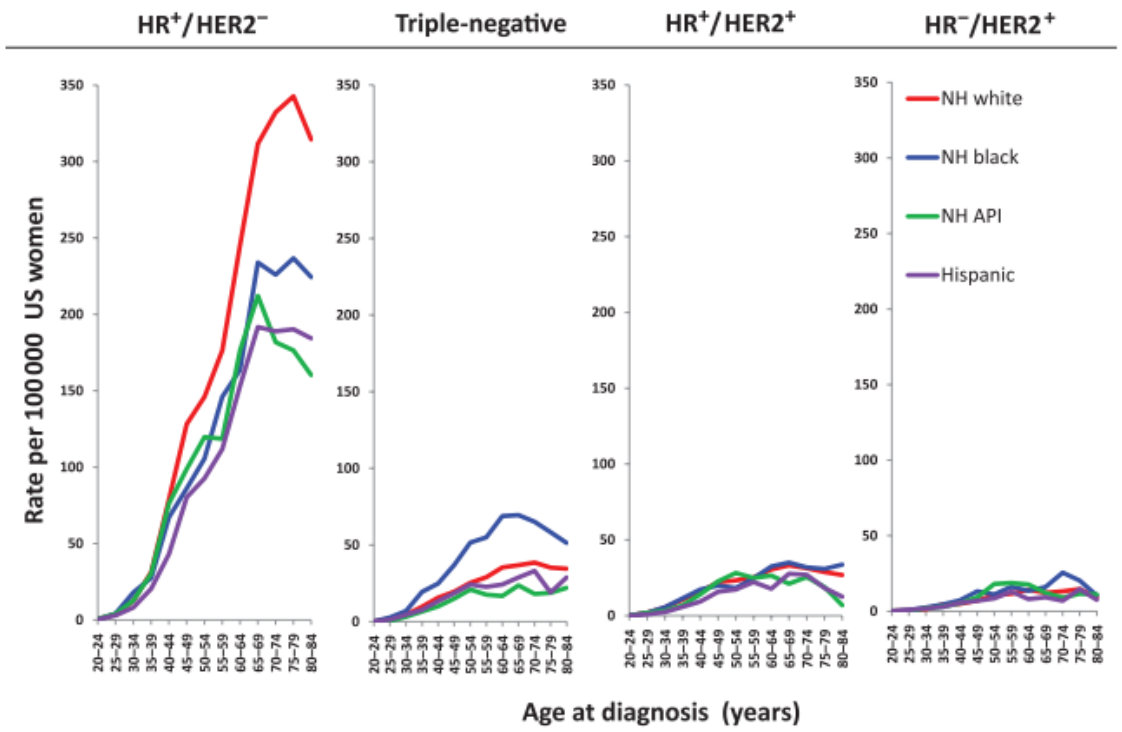
- Consultant for Puma.
- On the Speakers Bureau for Puma, and Seagen.

Outline

- Early-stage breast cancer
  - Adjuvant
    - Escalation
  - Neoadjuvant
    - De-escalation
    - Immune-related gene signatures
- Metastatic Breast cancer
- Future of HER2 positive breast cancer

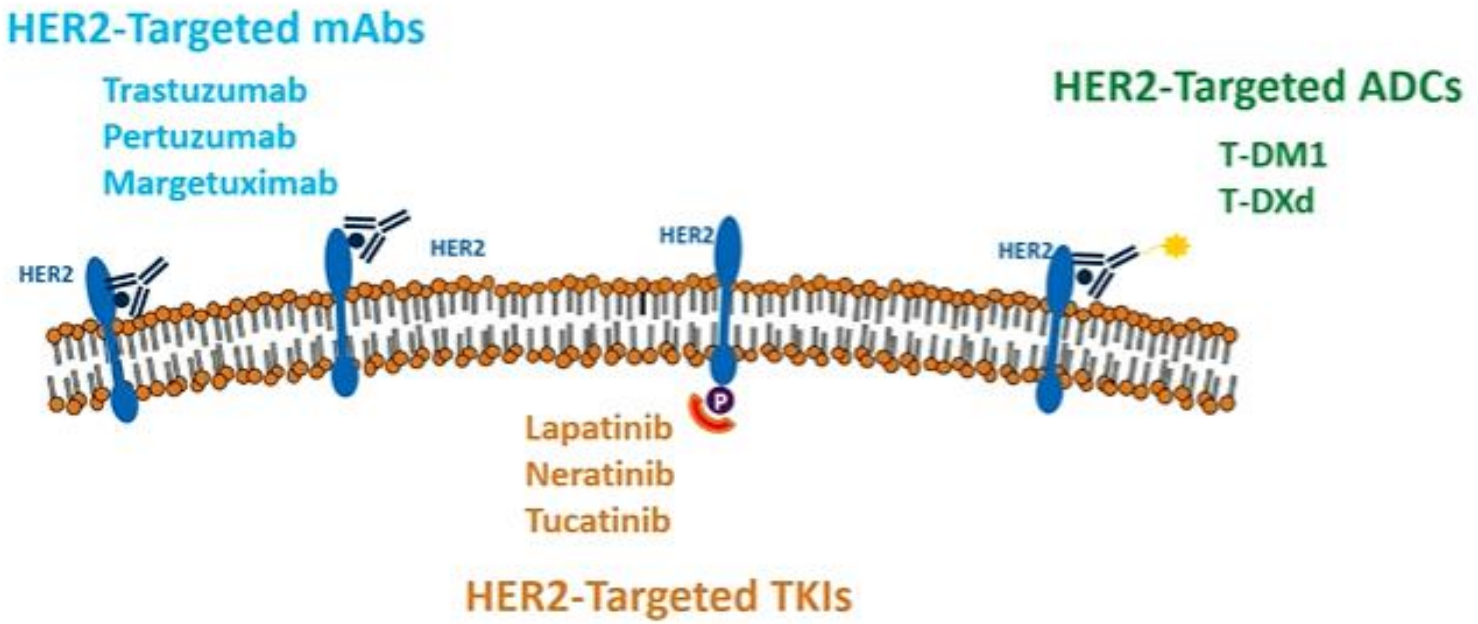
Distribution of Invasive Breast Cancer Subtypes by Age

- 15-20% of breast cancers are HER2+
- HER2 positive BC is more common in younger patients
- HER2 positive BC is associated with poorly differentiated, high-grade tumors



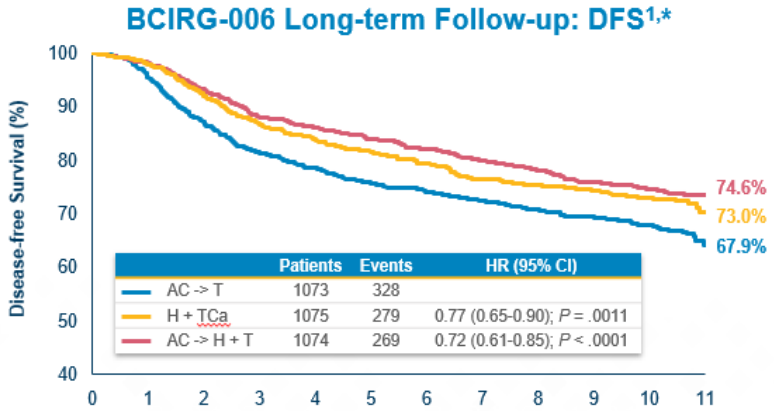
Howlader et al. *JNCI*. 2014; 106(5)
Wolff et al. *JCO*. 2013;31:3997
Burstein. *NEJM*.2005;353:1652

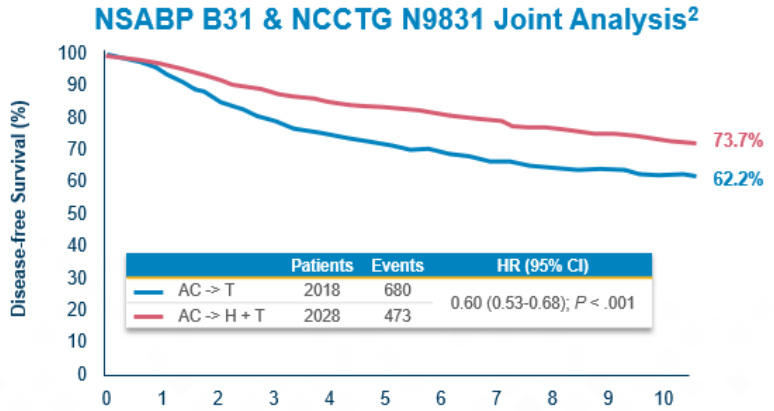
Targeted Therapies for HER2+ Breast Cancer



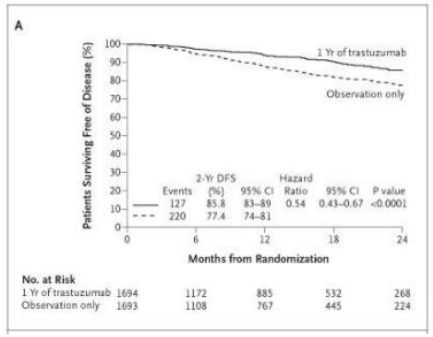
mAbs = monoclonal antibodies; TKIs = tyrosine kinase inhibitors.

Adjuvant Trastuzumab Trials

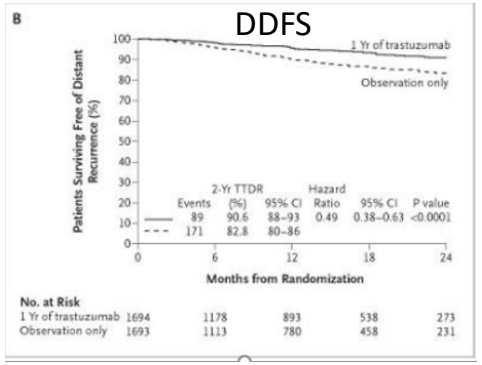




HERA

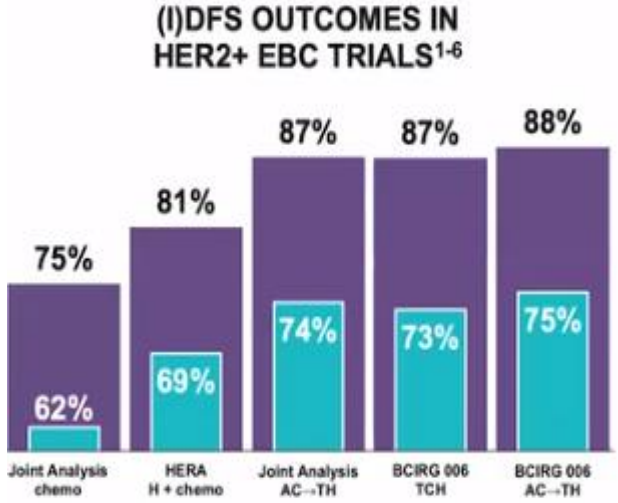


HERA
DDFS



. Slamon et al. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 8-12, 2015; San Antonio, TX. Abstract S5-04;
. Perez et al. *J Clin Oncol*. 2014;32:3744.

Piccart-Gebhart et al. N Engl J Med 2005; 353:1659-1672

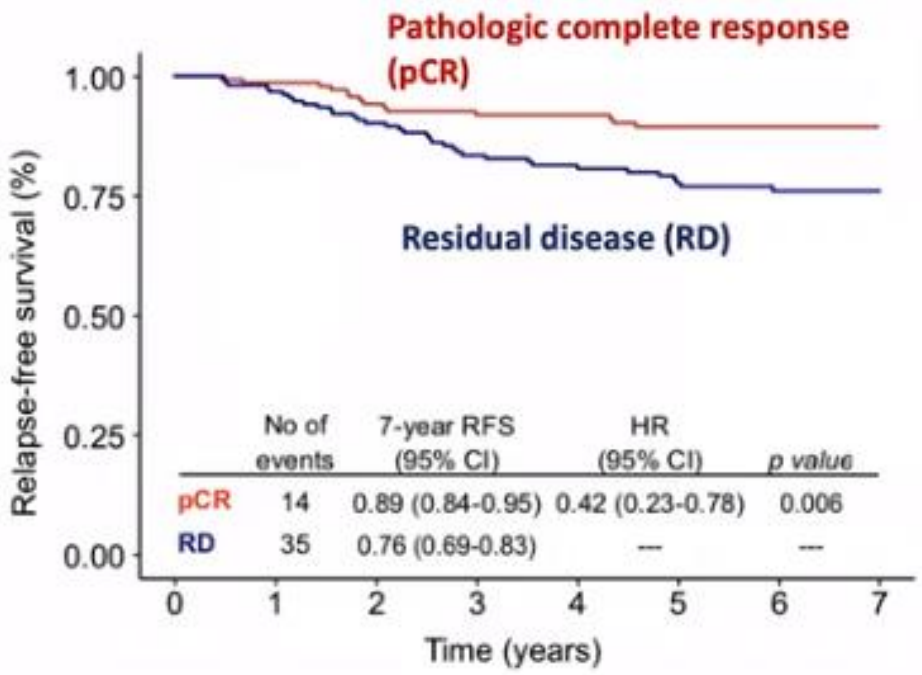


Better outcome of HER2 + early-stage breast cancer compared to HER2-

Study	Median F/U	HER2+/+tras	HER2+/-tras	HER2 –
BCIRG 005[1]/006[2]	10 years	(1841/2149) **86%**	(870/1073) 81%	(2647/3298) **80%**
NOAH[3]	5 years	(87/117) **74%**	(74/118) 63%	(75/99) **76%**
Italian Registry[4]	4.1 years	(52/53) **98%**	(140/161) 87%	(1108/1186) **93%**
GeparQuattro[5]	5.4 years	(392/446) **88%**		(889/1049) **85%**
FinHer[6]	5 years	(12/115) **90%**	(21/116) 82%	(61/778) **92%**

1. Mackey J et al. Annals Oncol. 2016;27:1041-47. 2. Slamon DJ et al. Cancer Res. 2015;76(4 Suppl):Abstract nr S5-04. 3. Gianni L et al. Lancet Oncol. 2014;15:640-47. 4. Musolino A et al. Cancer. 2011;117:1837-46. 5. Von Minckwitz G et al. Ann Oncol. 2013;25(1):81-89.

Neoadjuvant Therapy pCR has prognostic value



#1 Response allows surgical minimization - >50% of N+ converted to N-

= facilitates omission of ALND

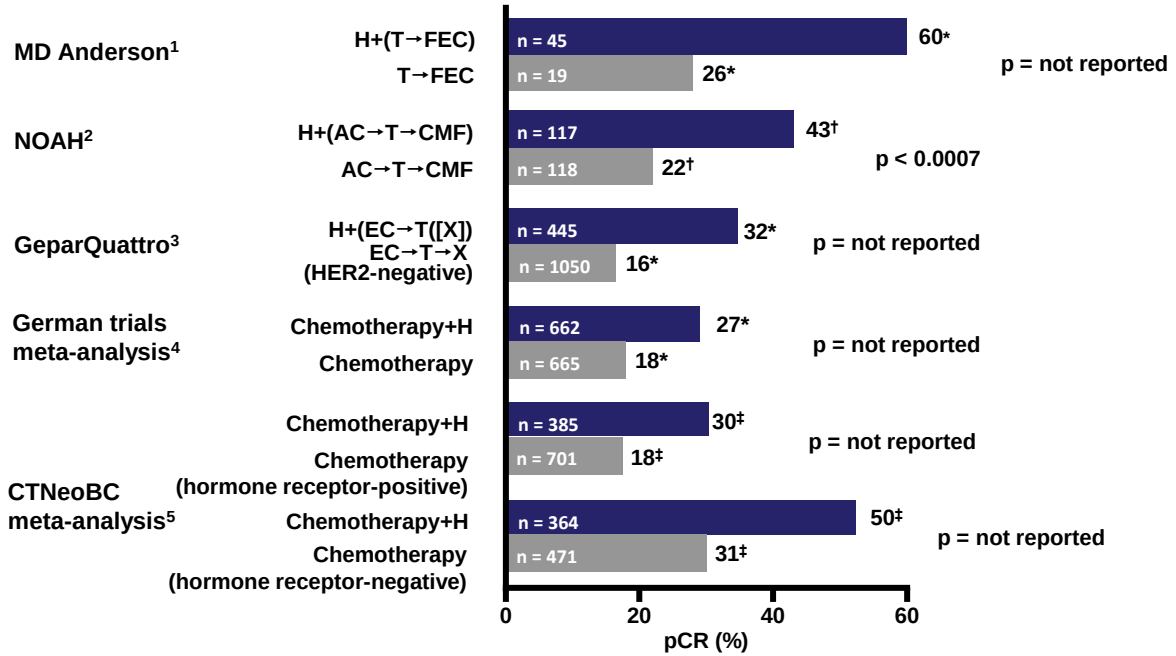
#2 Strong relationship between pCR and relapse/survival in multiple trials

= risk stratification for systemic Rx

ASCO recommends NAT for ≥T2 and or ≥N1

Korde L et al, JCO 2021

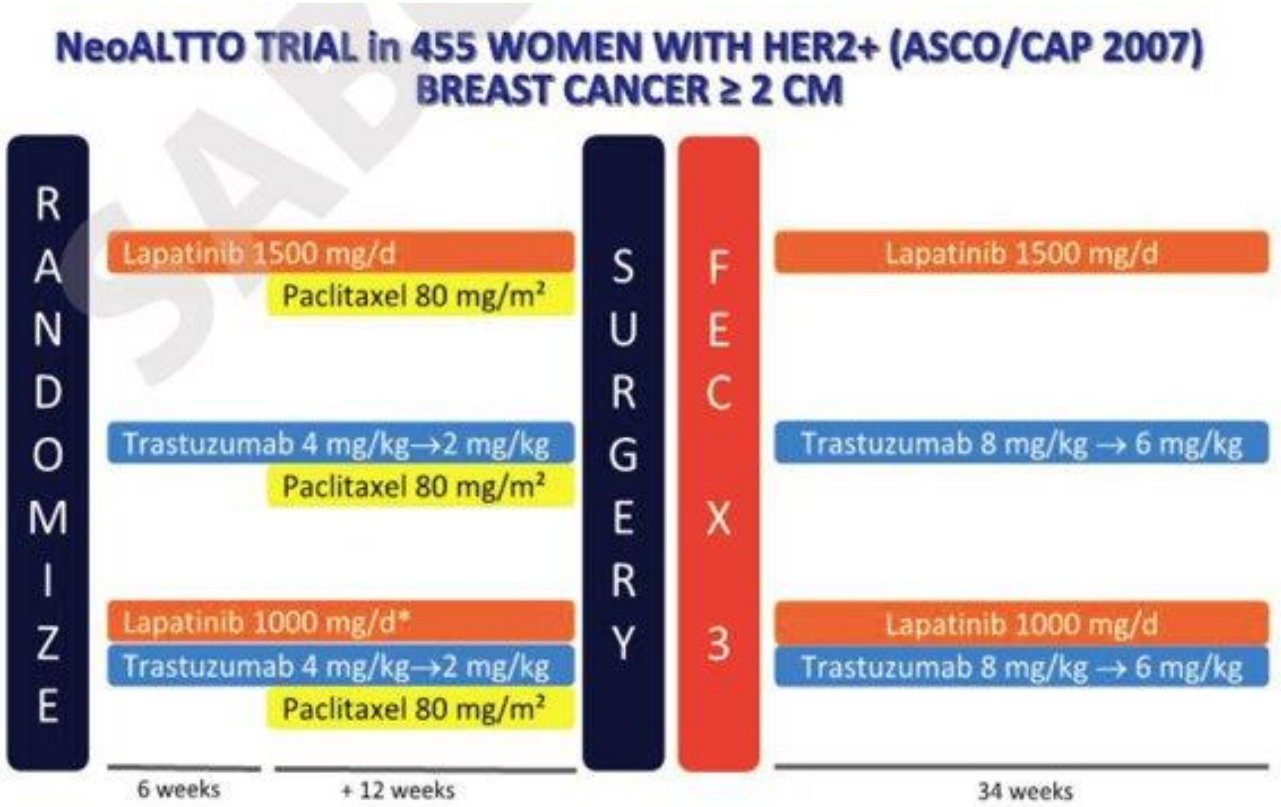
Impact on pCR rates from the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER2-positive EBC



- * No evidence of residual invasive cancer, in breast or axilla
- † No evidence of residual disease in breast tissue
- ‡ Absence of invasive cancer in the breast and axillary nodes; absence of DCIS/
absence of invasive cancer in the breast and axillary nodes;
- DCIS allowed/absence of invasive cancer in the breast and DCIS allowed;
regardless of nodal involvement
- DCIS, ductal carcinoma *in situ*; FEC, 5-fluorouracil+epirubicin+cyclophosphamide;
EC, epirubicin+cyclophosphamide; X, capecitabine.

- 1. Buzdar AU, *et al. Clin Cancer Res* 2007; **13:**228–233;
2. Gianni L, *et al. Lancet* 2010; **375:**377–384;
3. Untch M, *et al. J Clin Oncol* 2010; **28:**2024–2031;
- 4. Loibl S, *et al*. SABCS 2011 (Abstract S5-4; oral presentation);
- 5. Cortazar P, et al. SABCS 2012 (Abstract S1-11; oral presentation.

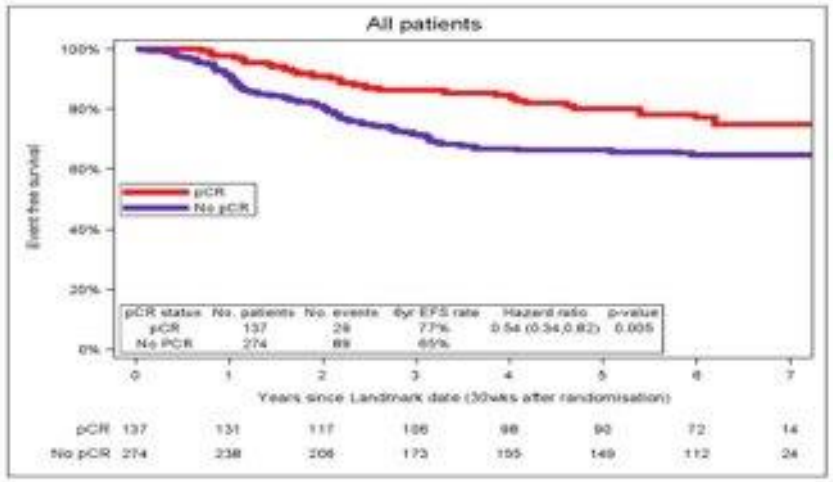
Does pCR translate into improvement in EFS and OS?

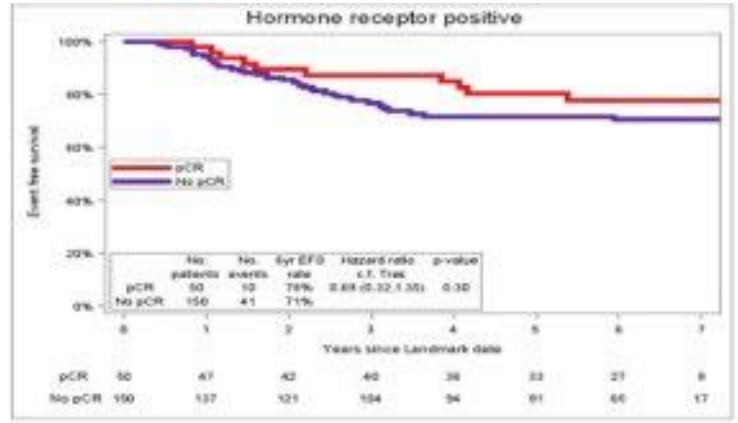


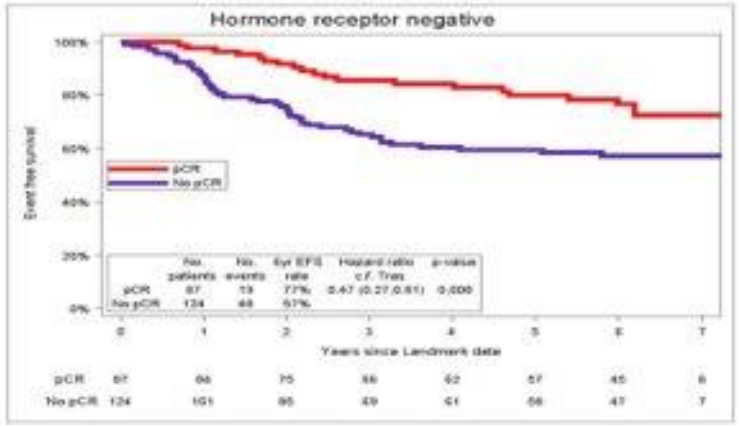
*Amendment-2 October 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel
54/152 had protocol-driven reduction

Baselga J et al; SABCS 2010; Lancet 2012

Does pCR translate into improvement in EFS? Long-term F/U NeoALTTO





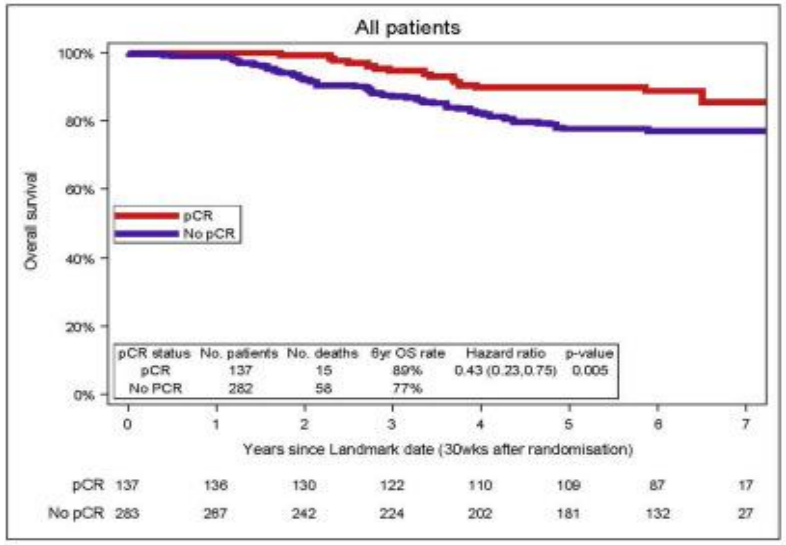


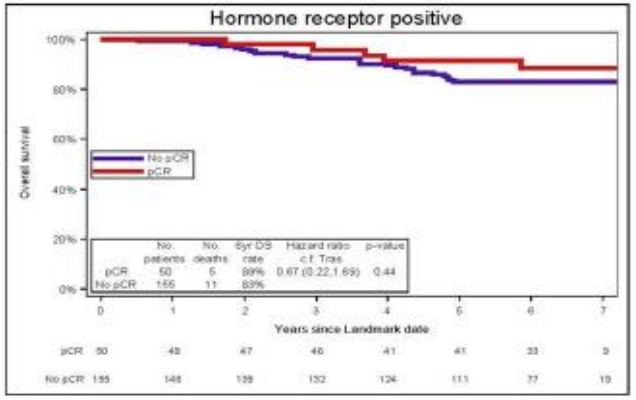
Test for interaction: pCR x hormone receptor status p = 0.29

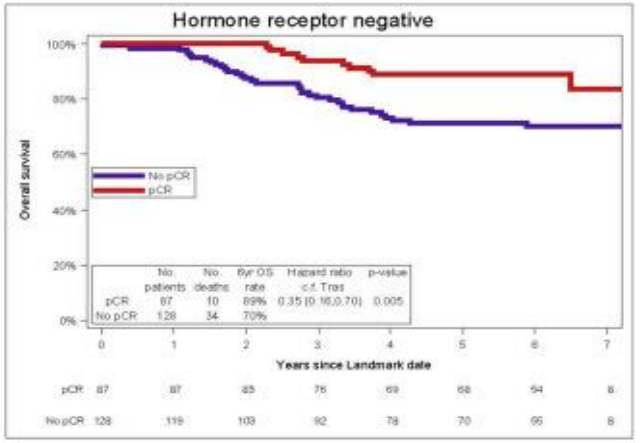
Kaplan–Meier plots showing event-free survival (EFS) for the pCR and no pCR groups by the hormone receptor status.

Huober J. et al. European Journal of Cancer 2019; 118: 169-177

Survival Outcomes of NeoALTTO BIG 1-06







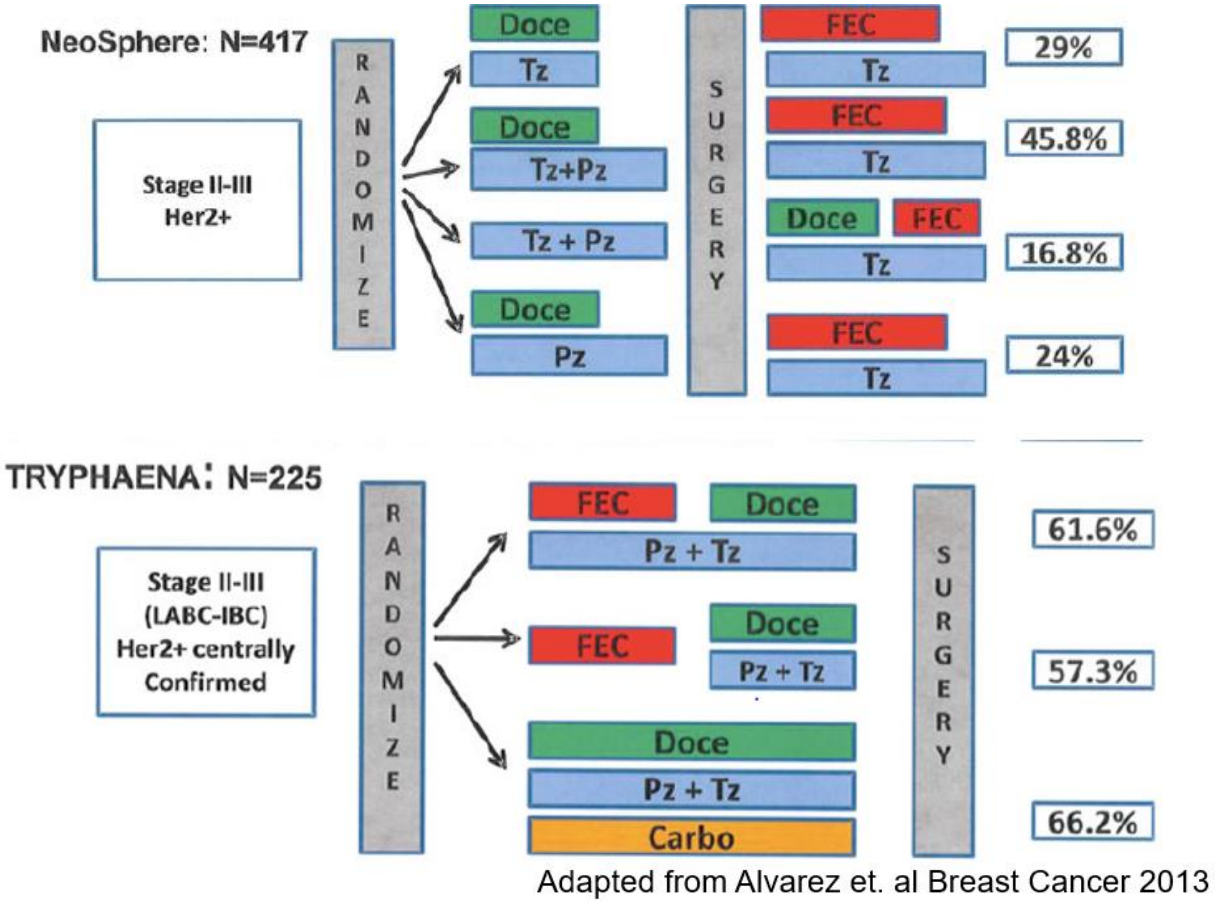
Test for interaction:
pCR x hormone receptor status p=0.33

Kaplan–Meier plots showing overall survival (OS) for the pCR and no pcR groups by the hormone receptor status

Achieving a pathologic complete remission translates into a better long-term outcome with regard to event-free survival (EFS) and overall survival (OS)

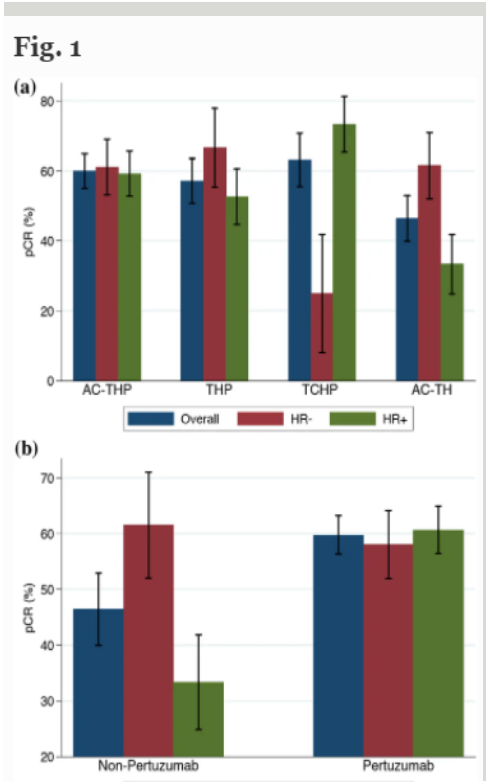
Huober J. et al. European Journal of Cancer 2019; 118: 169-177

Neoadjuvant Trials of Pertuzumab



Adapted from Alvarez et. al Breast Cancer 2013

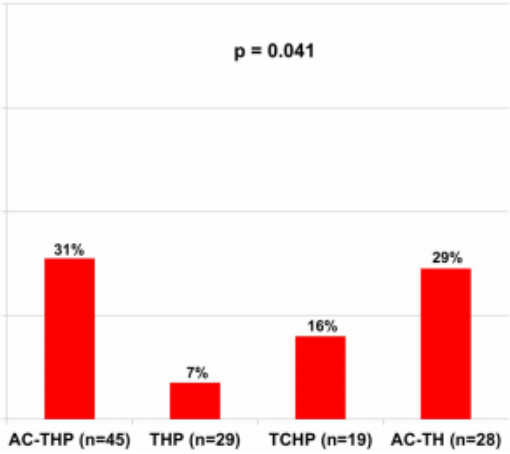
Lancet Oncol. **2012 Jan;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9.**



Predictors of pCR

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age at diagnosis	0.97	0.94–1.00	0.09	0.98	0.94–1.02	0.34
Clinical stage III versus II	0.79	0.33–1.91	0.60	0.73	0.24–2.20	0.57
Grade 3 versus less than grade 3	0.99	0.47–2.10	0.98	0.97	0.37–2.52	0.94
HR+ versus HR−	0.86	0.40–1.81	0.68	0.77	0.28–2.10	0.60
HER2 FISH ratio > 8 versus < 8	2.06	0.84–5.06	0.11	1.47	0.50–4.33	0.48
HER2 IHC 3+ versus less than 3+	3.56	1.37–9.24	0.01	3.71	1.13–12.22	0.03
Pertuzumab-containing regimen versus not	1.72	0.73–4.02	0.21	2.75	0.85–8.88	0.09
Anthracycline-containing regimen versus not	0.82	0.39–1.73	0.61	0.98	0.32–2.93	0.97

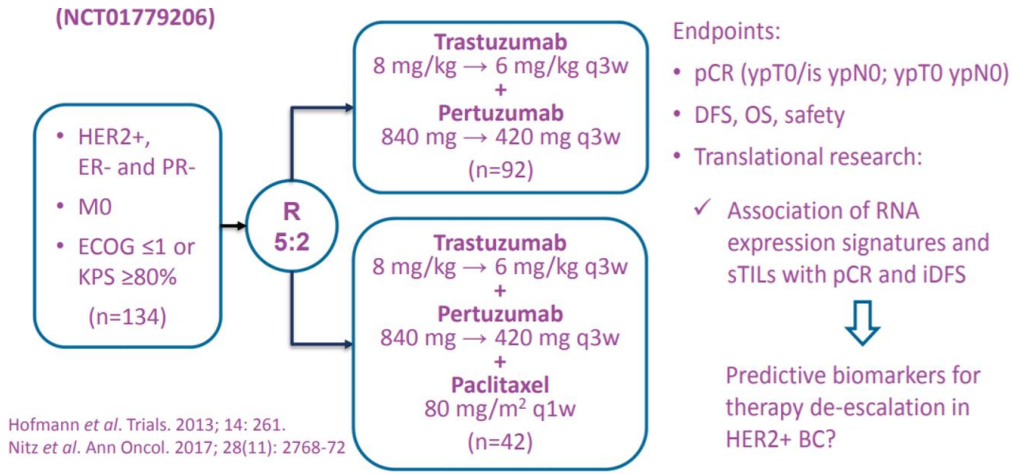
Frequency of cycle delay

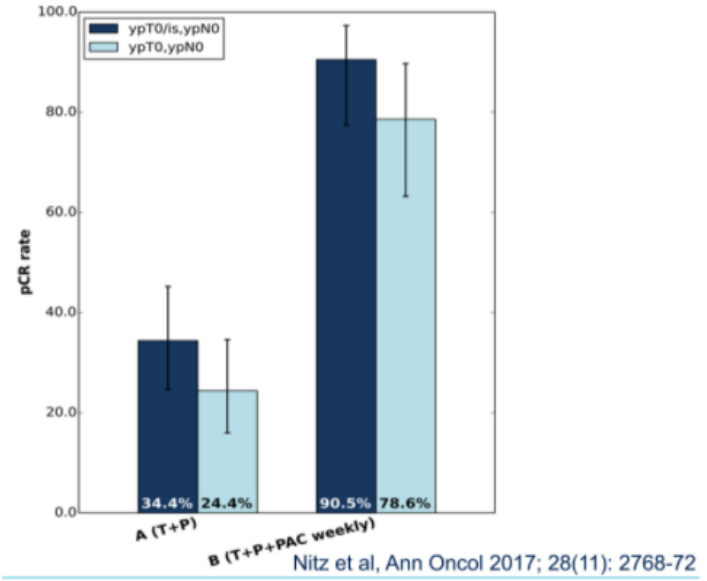


Breast Cancer Research and Treatment (2018) 172:733–740

Escalating and de-escalating treatment of early-stage HER2+

De-Escalation strategies in HER2+ early-stage BC - Neoadjuvant HP +/- weekly Paclitaxel in HER2+/HR-; efficacy, safety and predictive markers: ADAPT (West German Study Group)



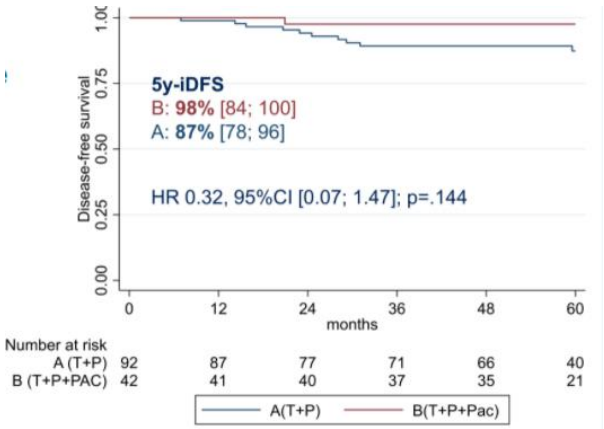


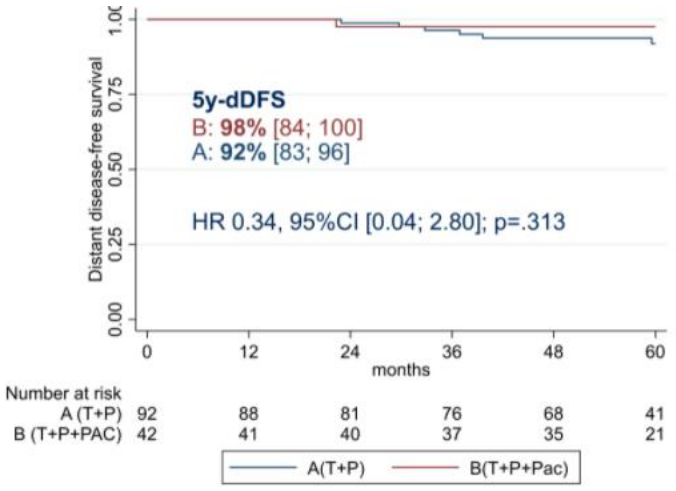
- De-escalation with Neoadjuvant therapy with 12 weeks of paclitaxel + HP had pCR of 57% in HER2+ HR+
- Improved pCR translated to improved outcomes

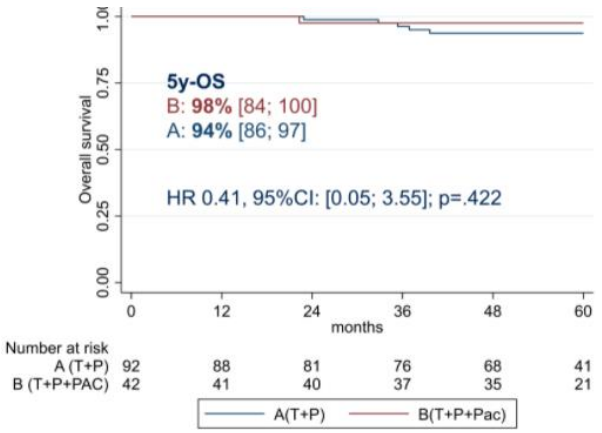
Harbeck N. et al, Presented at: ASCO, 2021

Nitz et al, Ann Oncol 2017; 28(11): 2768-72; Piccart et al, JCO 2020

WSG-ADAPT HER2+/HR-







pCR vs no pCR

Harbeck N. et al, Presented at: ASCO, 2021

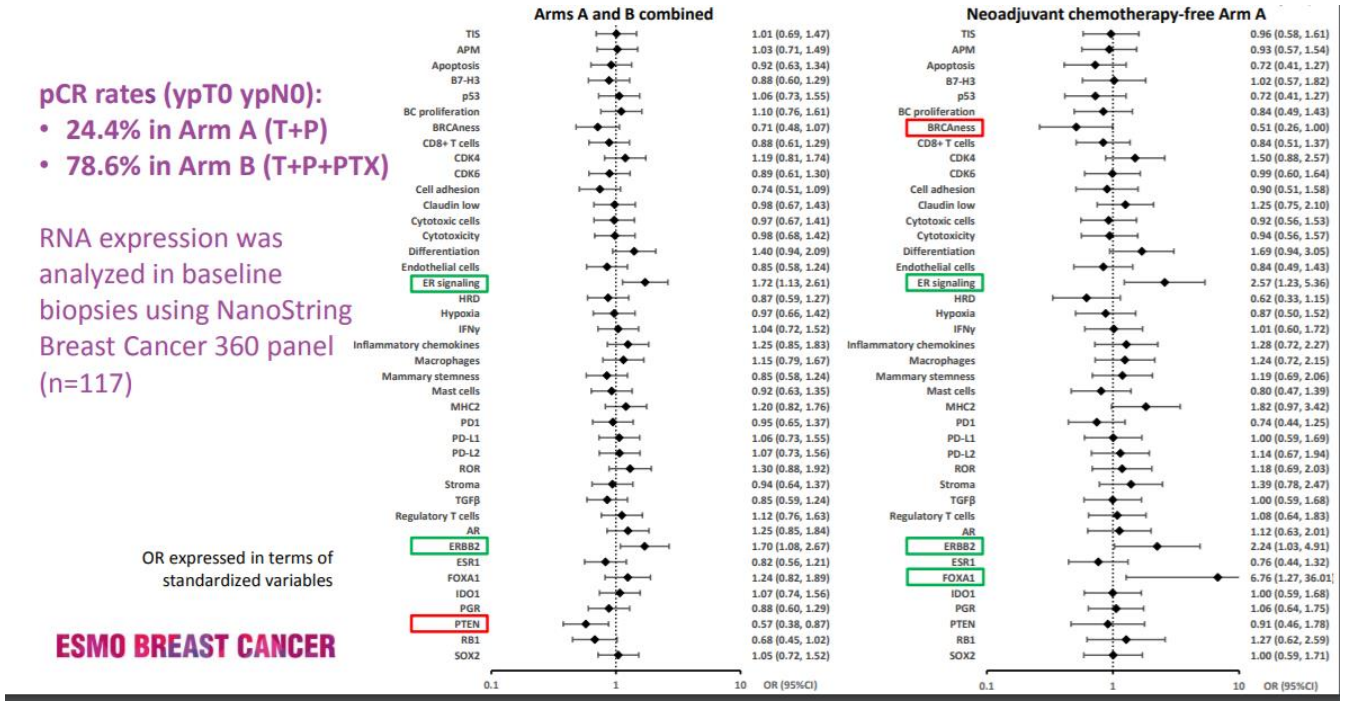
Association between RNA expression signatures and pCR

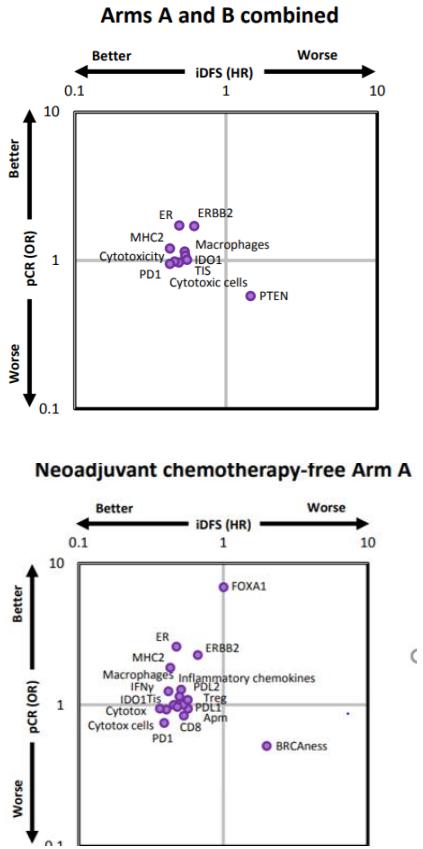
pCR rates (ypT0 ypN0):
- **24.4% in Arm A (T+P)**
- **78.6% in Arm B (T+P+PTX)**

RNA expression was analyzed in baseline biopsies using NanoString Breast Cancer 360 panel (n=117)

OR expressed in terms of standardized variables

ESMO BREAST CANCER





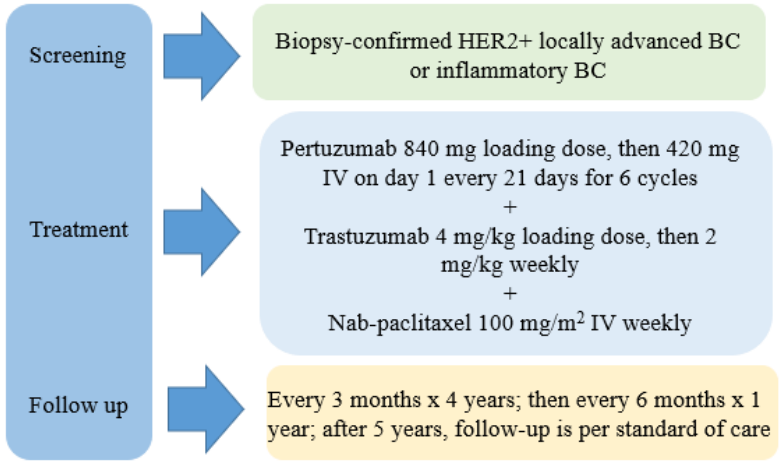
Using Gene signatures to guide de-escalation in HER2

Graeser M. et al, ESMO Breast 2021, *Ann Oncol*. 2021;(suppl 2):S48.

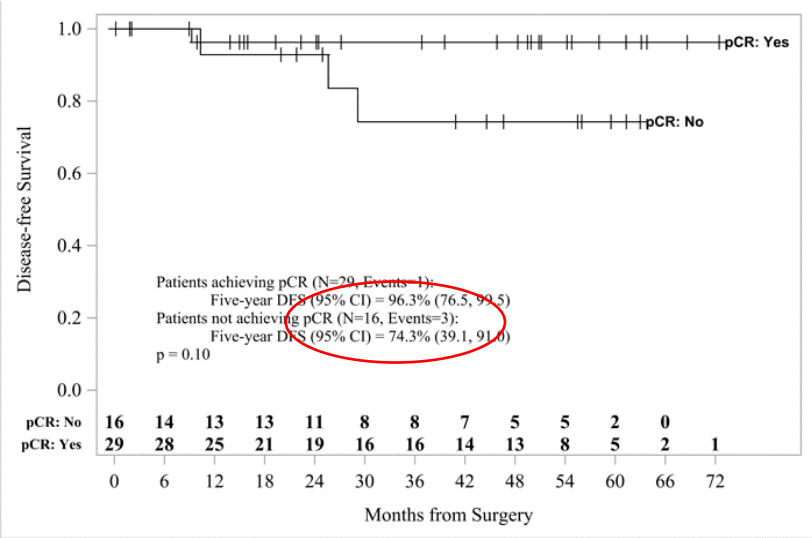
Phase II prospective open label study of neoadjuvant pertuzumab, trastuzumab, and nab-paclitaxel in patients with HER2 + Locally Advanced Breast Cancer

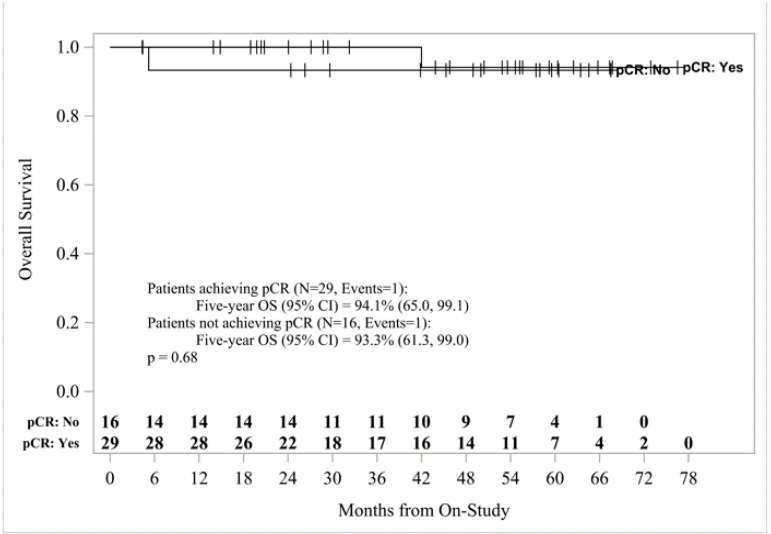
Sayeh Lavasani, Susan E. Yost, Paul H. Frankel, Christopher Ruel, Mireya Murga, George Somlo, Aileen Tang, Norma Martinez, Laura Kruper, Lusine Tumyan, Daniel Schmolze, Christina Yeon, Yuan Yuan, James Waisman, Joanne Mortimer

Lavasani S, et al. Presented at: ASCO; 2021.



Treatment	LABC (N=45)
Median follow-up (95% CI) months	36.5 (28.7, 42.5)
Median treatment cycles completed (range)	6 (1 – 6)
Median treatment cycles delayed (range) Patients with ≥ 1 cycle delayed	0 (0 – 2) 4 (9%)
Median treatment cycles modified (range) Patients with ≥ 1 cycle modified	3 (0 – 7) 32 (71%)
pCR	29 (64%)

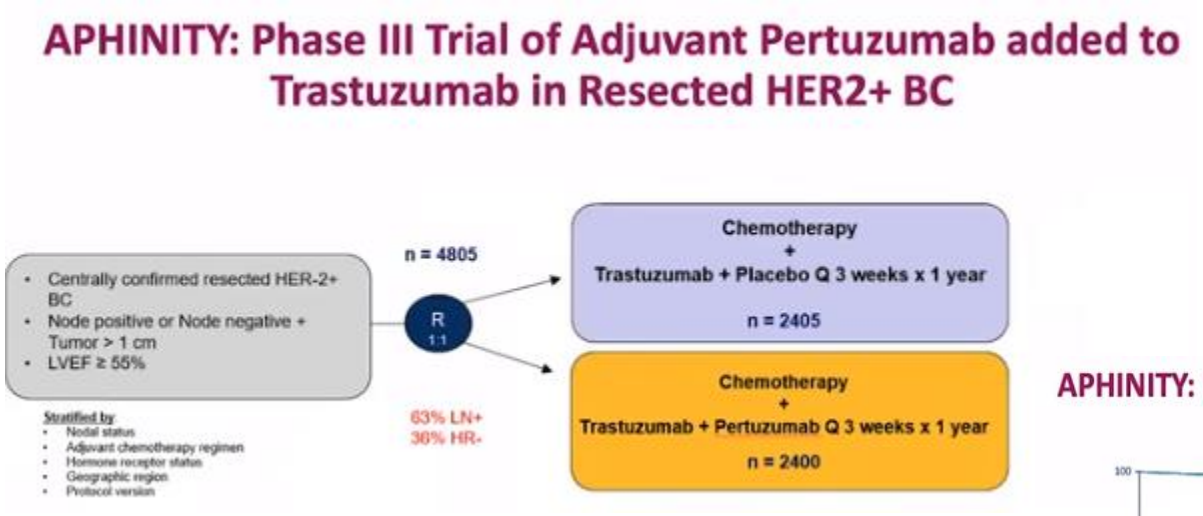


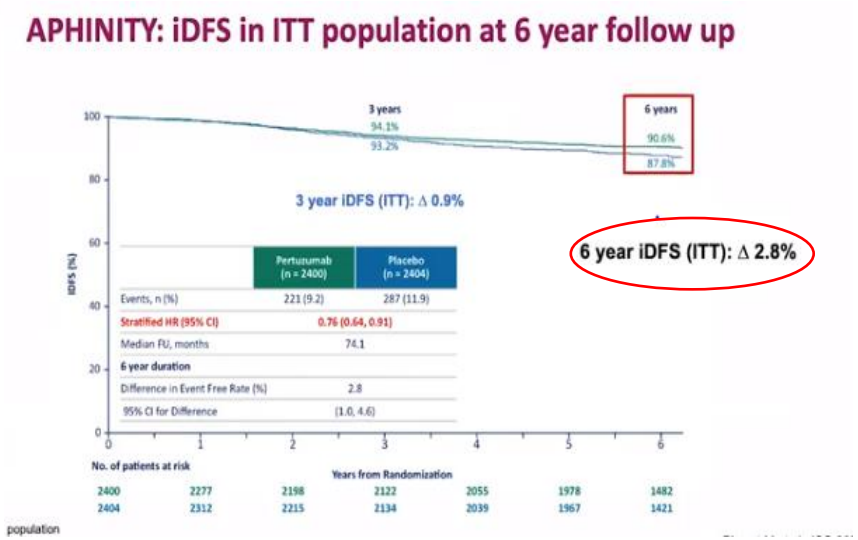


This treatment combination doesn't require any steroid premedication and make it an excellent choice in patients who cannot tolerate steroid

Lavasani S, et al. Presented at: ASCO; 2021.

Adding Pertuzumab to Trastuzumab in Adjuvant setting

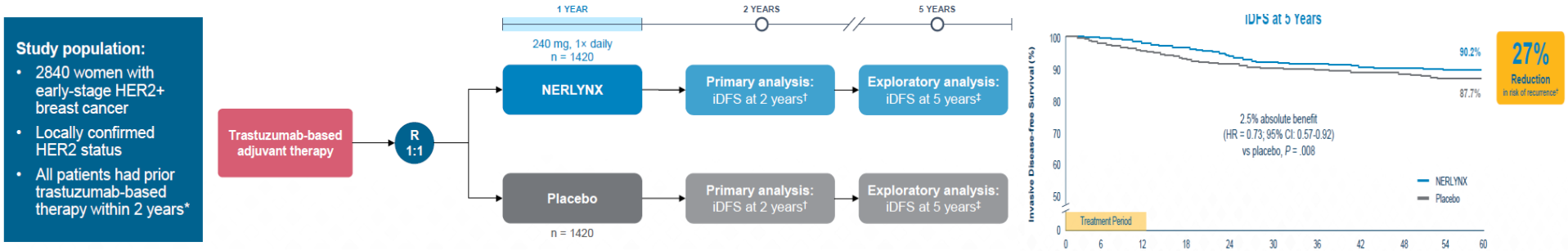


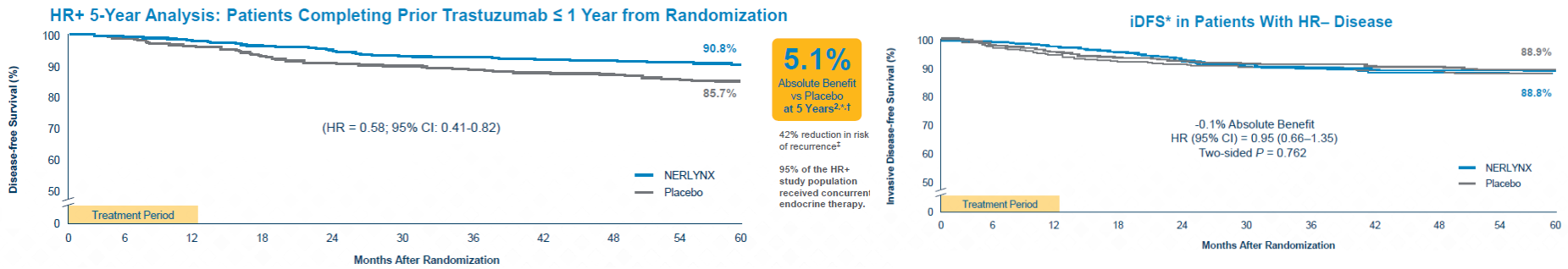


- 6-year F/U showed benefit in both HR- and HR+
- Only node positive patients benefited from adjuvant Pertuzumab

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

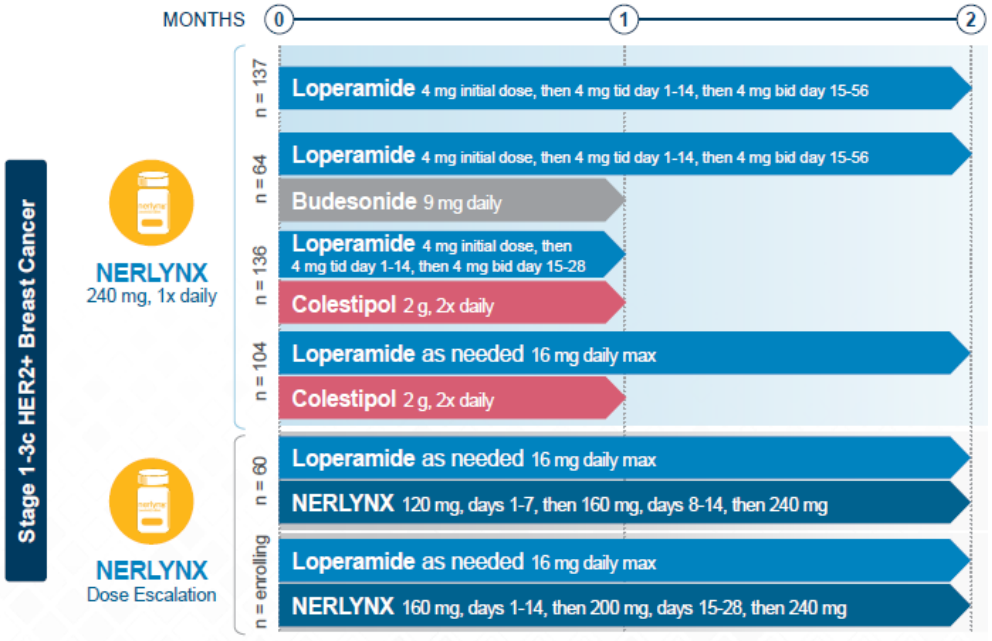
ExteNET Extending adjuvant HER2-targeted therapy





Martin et al. Lancet Oncology 2017; 18:1688,
Grant M. et al. SABCS 2018

CONTROL Trial - Phase II open label



Diarrhea with NERLYNX:
Early Onset, Short Duration

Prophylaxis Can Help Reduce Diarrhea

- Compared to ExteNET (with no antidiarrheal prophylaxis), budesonide and colestipol reduced dose holds/reductions and discontinuation due to diarrhea

Dose Escalate to Minimize Diarrhea

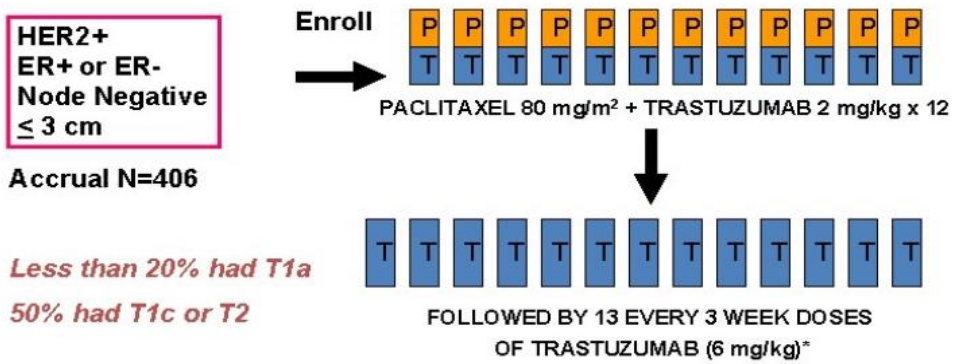
- Early data on neratinib dose escalation are encouraging
  - Enrollment into the dose escalation cohort is ongoing and data are preliminary

Proactive Management Improves Tolerability

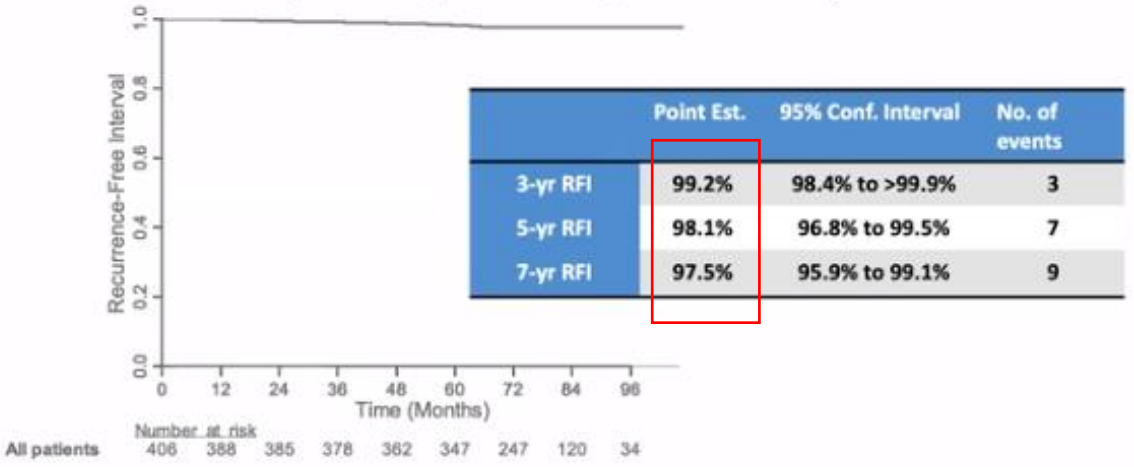
- Patients need a written plan to manage diarrhea after prophylaxis

Barcenas CH. et al. Ann Oncol 2020

APT trial



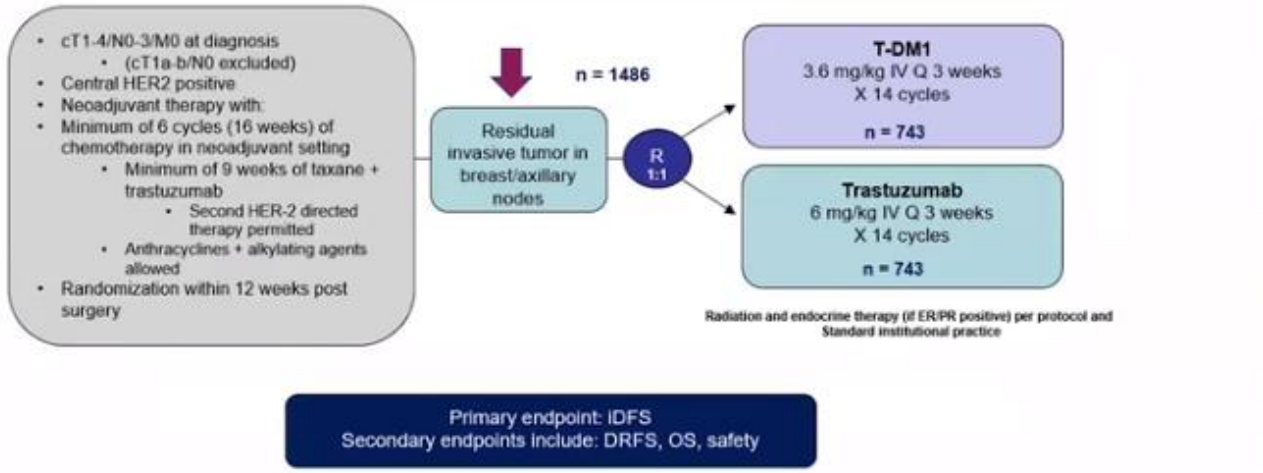
APT Trial: T1N0 excellent outcomes with TH
(12 weeks paclitaxel + 1 year trastuzumab)



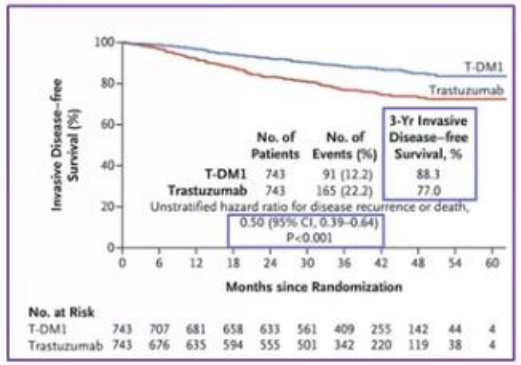
	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

Tolaney SM et al, NEJM 2015; JCO 2019

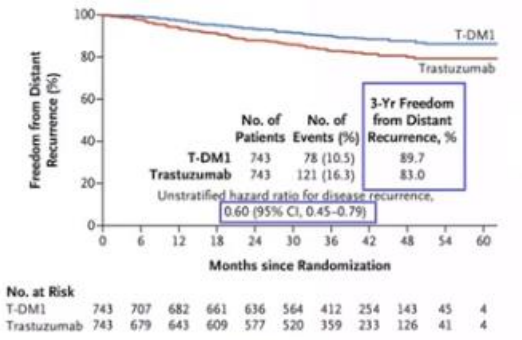
KATHERINE Study



At 41m followup risk of recurrence or death was 50% lower with adjuvant T-DM than trastuzumab



Invasive disease events 12.2% T-DM1 (n=91) vs 22.2% Trastuzumab (n=165)



Distant recurrence as first event 10.5% T-DM1 (n=78) vs 15.9% Trastuzumab (n=118)

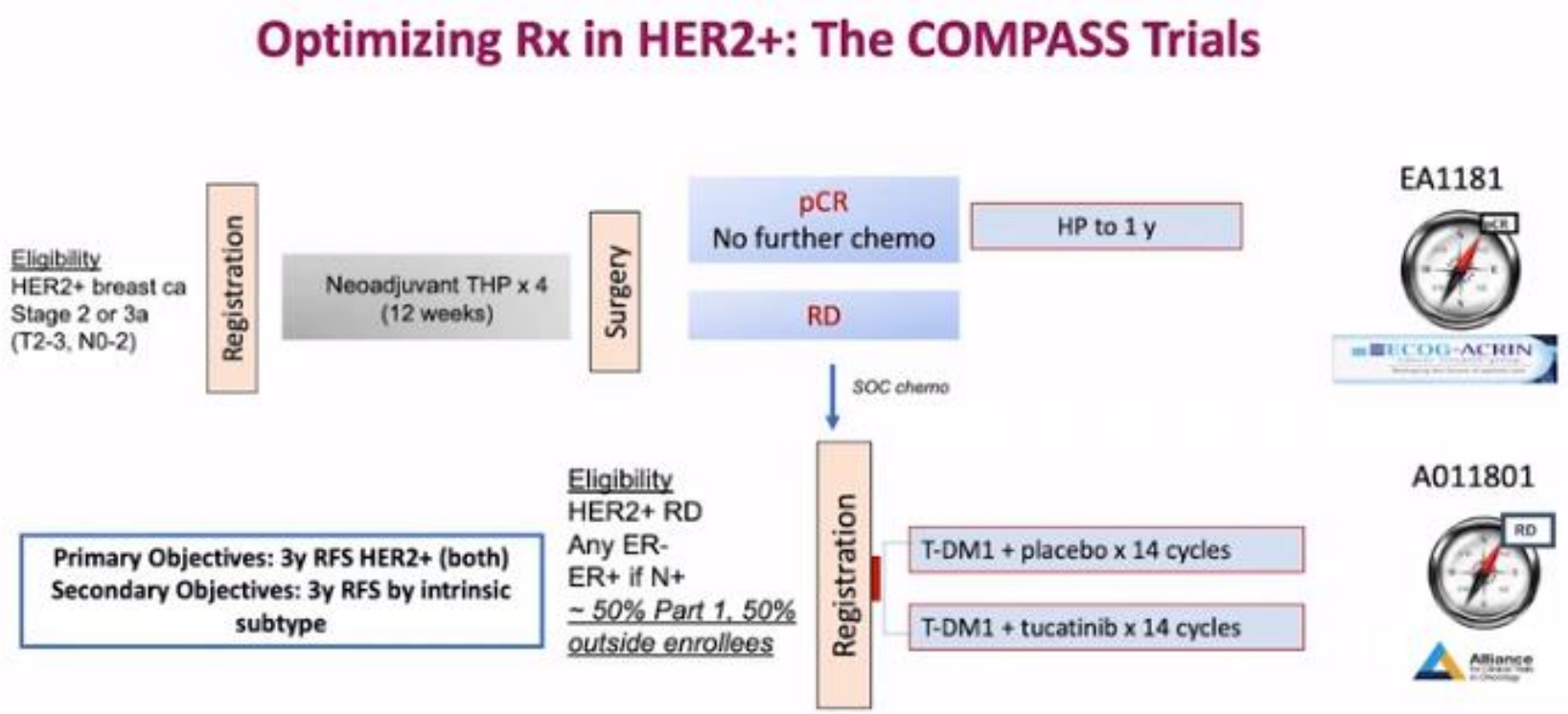
No difference in CNS mets with T-DM1

CNS Recurrence	T-DM1 (n=743)	H (n=743)
Patients with CNS Recurrence, n (%)	45 (6.1)	40 (5.4)
As First IDFS Event[a]	44 (5.9)	32 (4.3)
After First IDFS Event[b]	1 (0.1)	8 (1.1)
Patients with CNS as Only Event[c]	36 (4.8)	21 (2.8)
Median Time to CNS Recurrence, mo	17.5	11.9

Note: CNS recurrence within[a] or after[b] 61 days of first IDFS event, or any time[c].

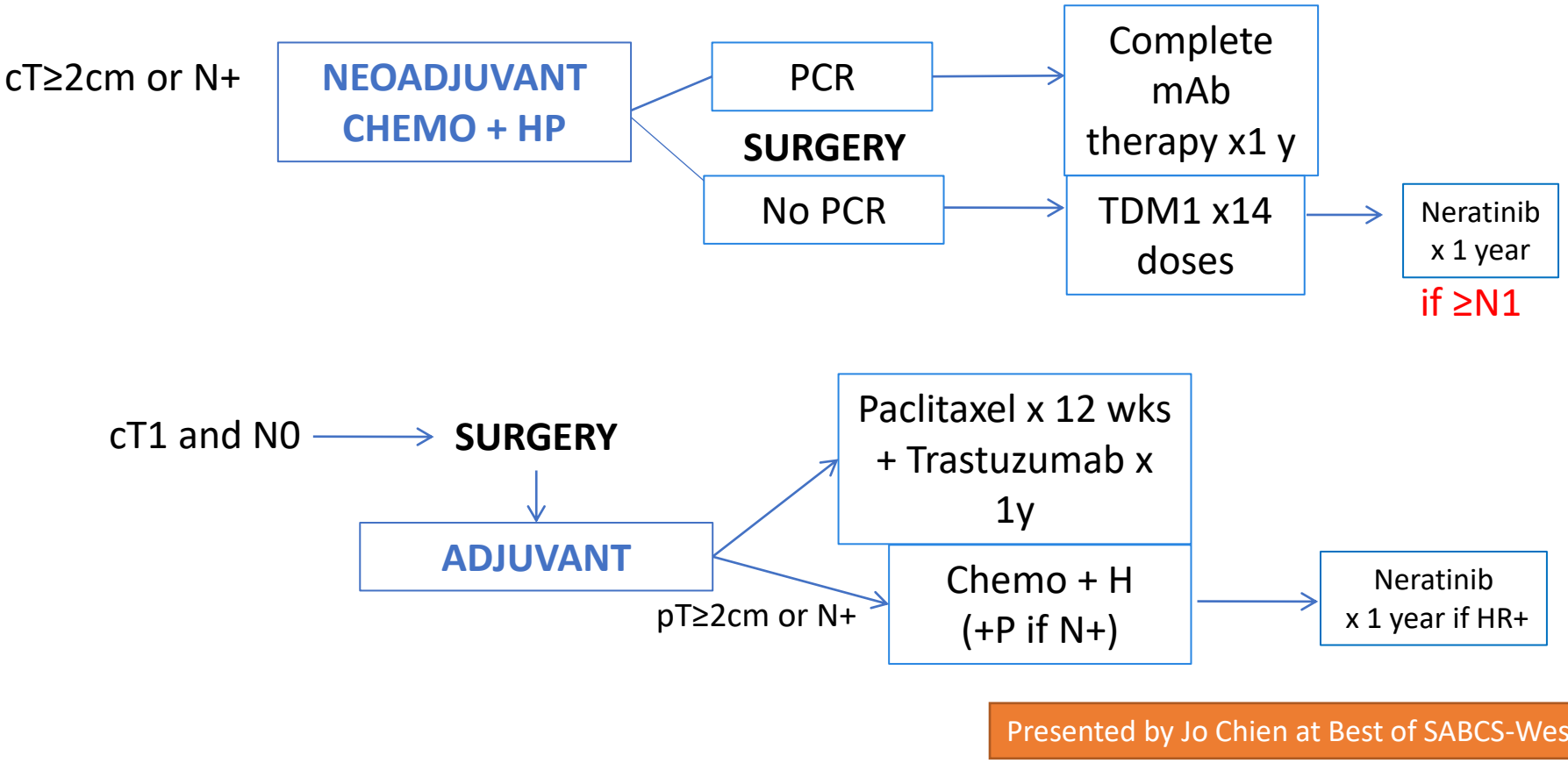
Von Minckwitz et al, NEJM 2019,
Untch et al, ESMO 2019

Study Open at City of Hope



COMPASSHER2 study – IRB 21225 at COH

Early Stage HER2+ Breast Cancer

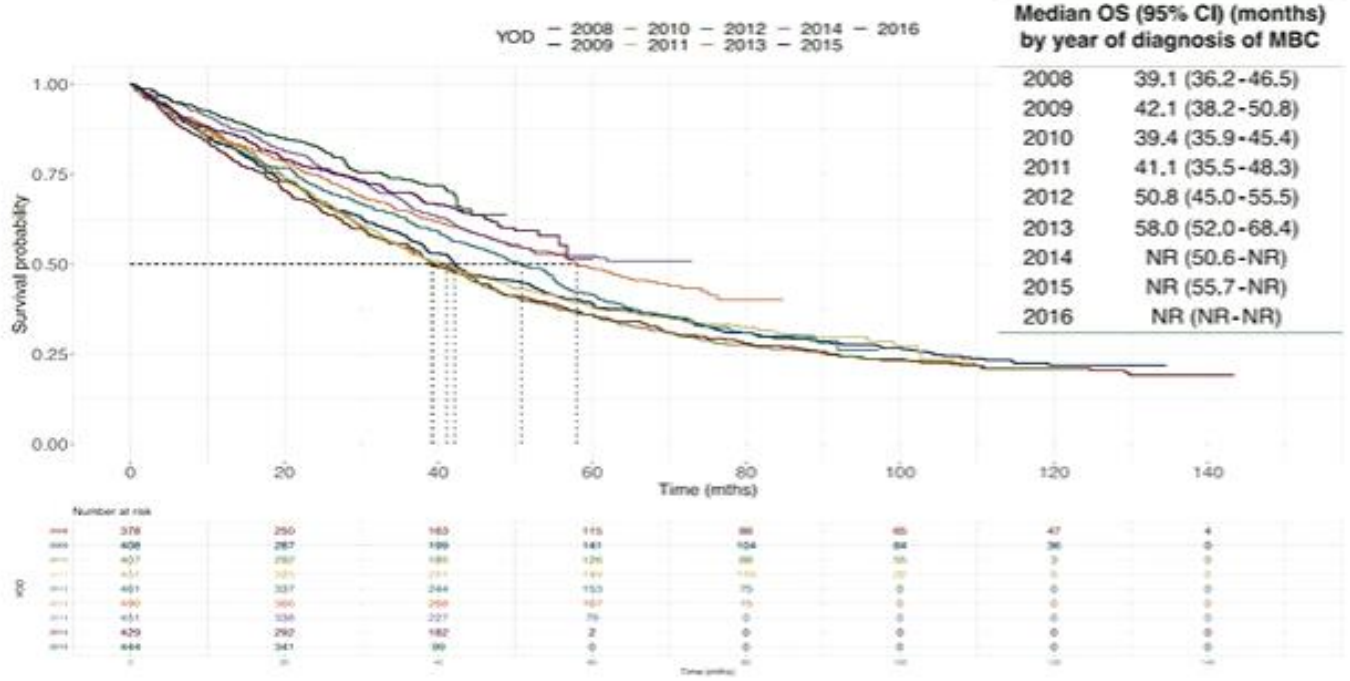


Presented by Jo Chien at Best of SABCS-West 2021

HER2-Positive MBC

Overall Survival in HER2+ MBC by Year of Diagnosis

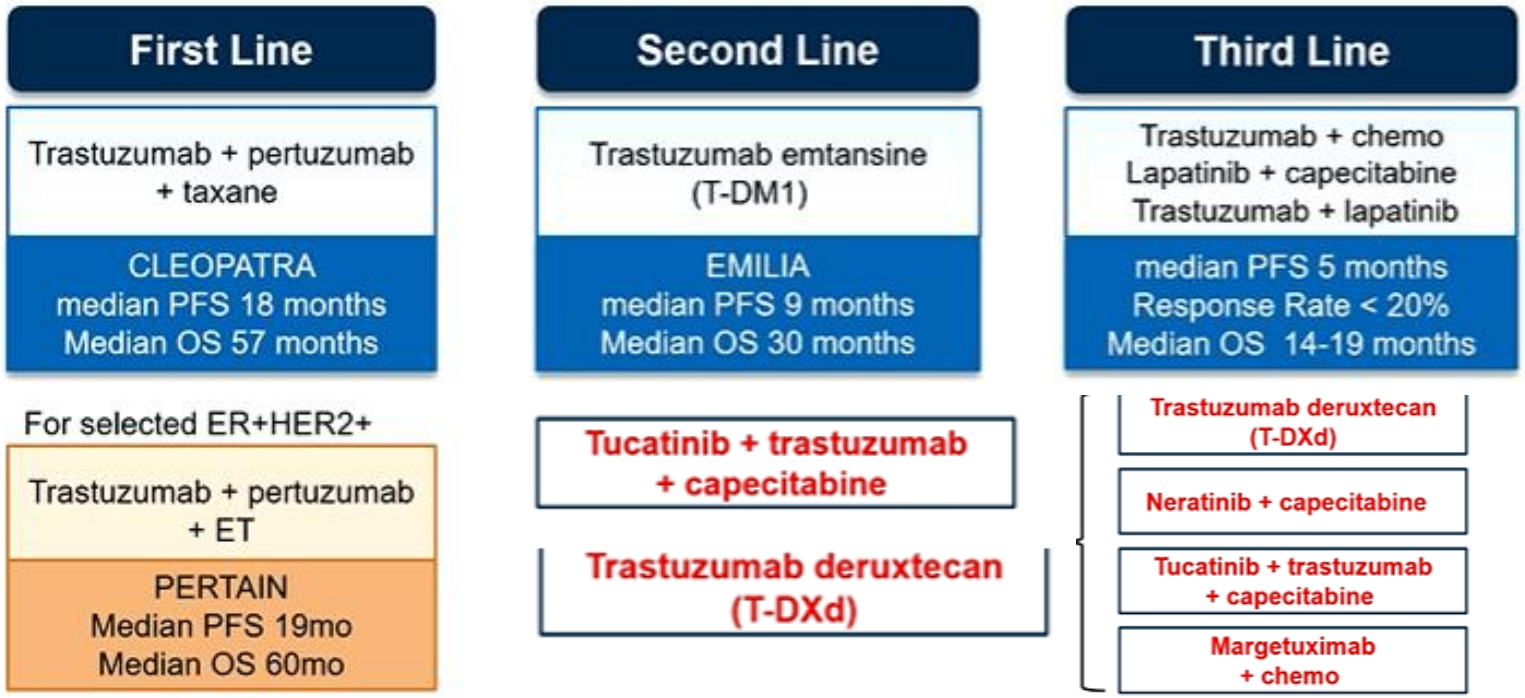
ESME-MBC Registry



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T, et al. *ESMO Open*. 2021;6(3):100114.

Standard of Care for HER2+ Advanced Breast Cancer



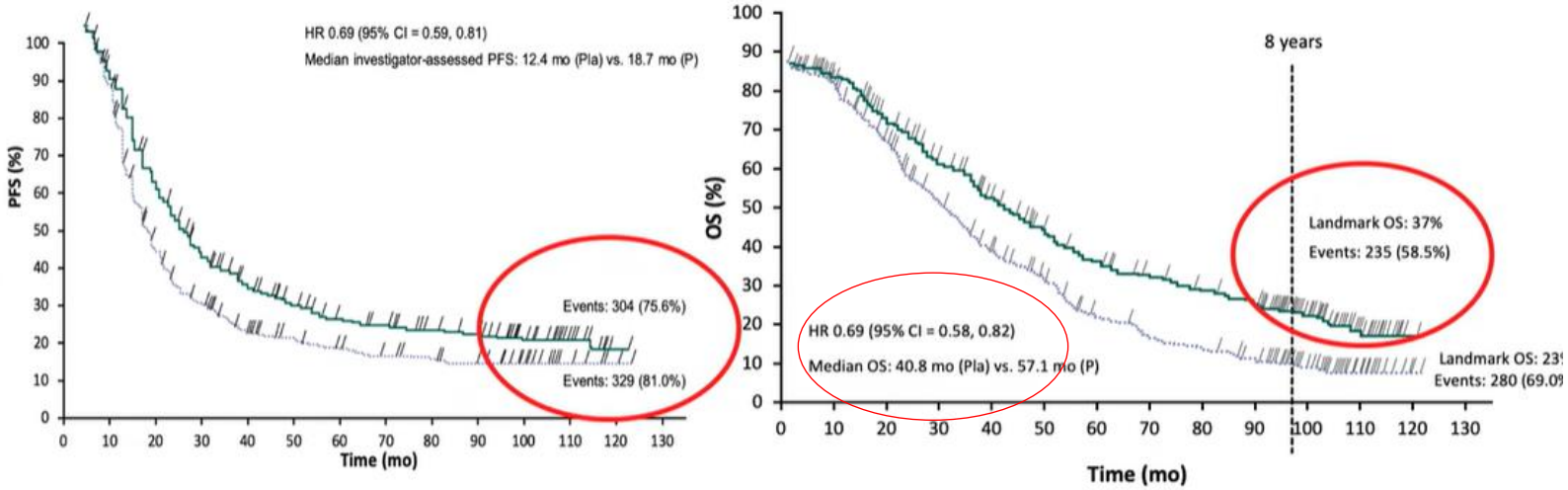
Rimawi M, et al. Presented at: SABCS; 2020. Swain SM, et al. *N Engl J Med*. 2015;372(8):724-734. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743. Blackwell KL, et al. *J Clin Oncol*. 2010;28(7):1124-1130.

ESMO 2021

HER2 + MBC (CLEOPATRA)

Docetaxel/Trast +/- Pertuzumab in 1L HER2+ MBC



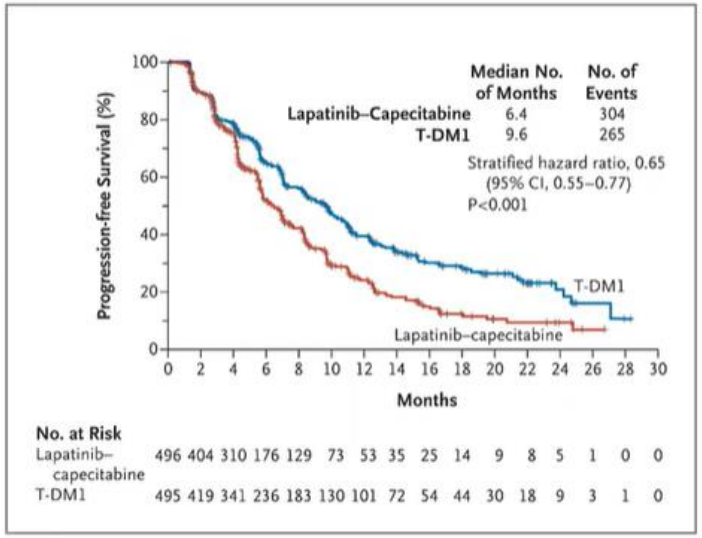
Patients were enrolled from **February 2008 - July 2010**.

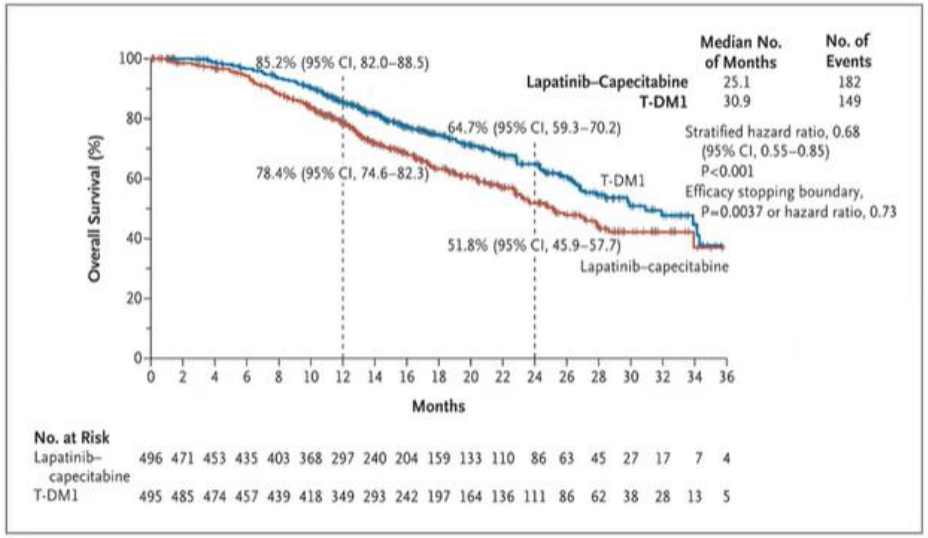
8-year landmark OS of 37%

Swain S, et al. Presented at: ASCO Annual Meeting; 2019. Swain S, et al. *Lancet Oncol*. 2020;21(4):519-530.

EMILIA Study

TDM1 vs Lapatinib-Capecitabine in 2L HER2+ MBC





Patients were enrolled from **February 2009 - October 2011**

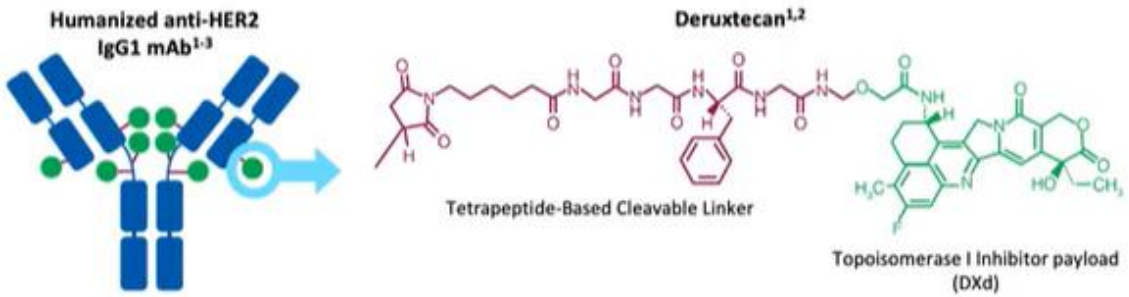
Median OS: 25.1 vs 30.9 mo

T-DM1 = trastuzumab emtansine.
Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

Trastuzumab Deruxtecan

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload: topoisomerase I inhibitor (10 times more potent than SN38)

High drug to antibody ratio ≈ 8

Membrane-permeable payload

Half-life of intact ADC is 6 days

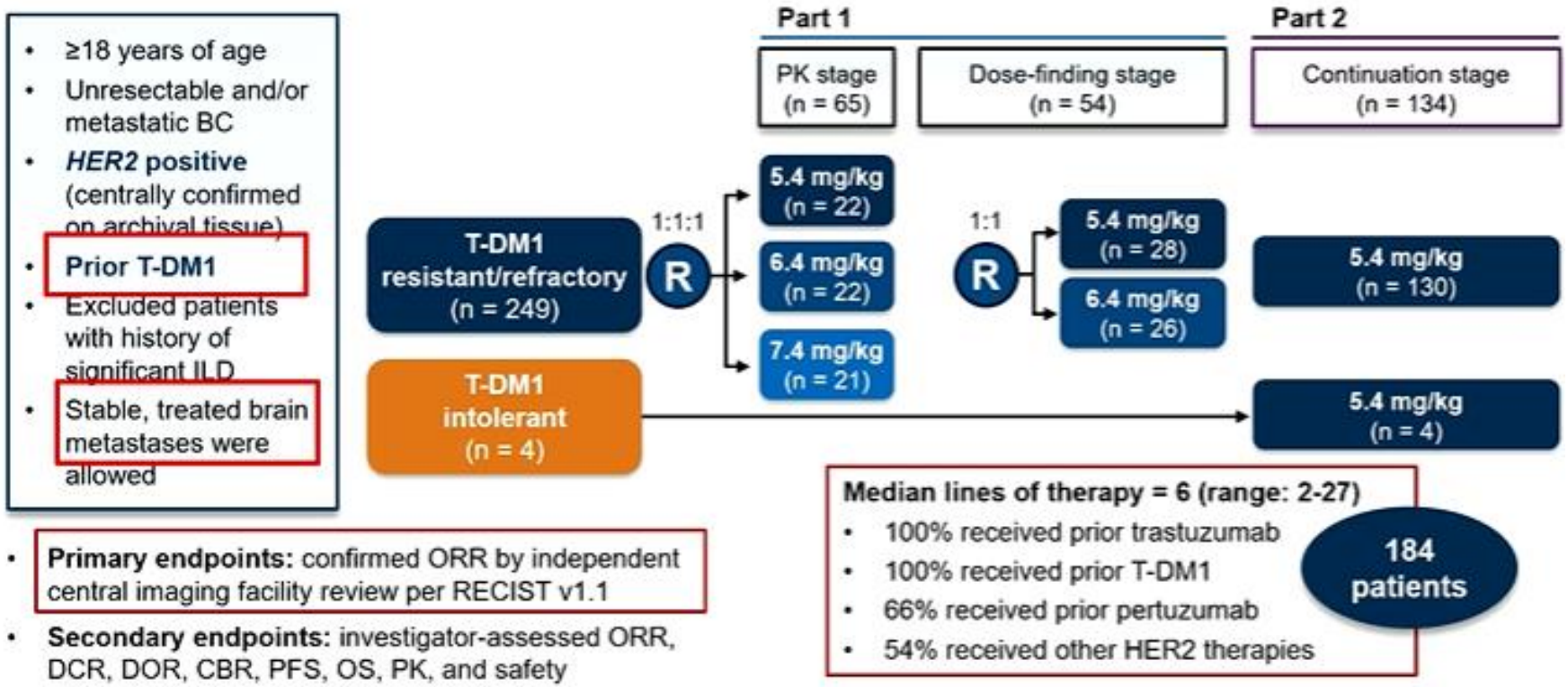
Stable linker-payload

Tumor-selective cleavable linker

The clinical relevance of these features is under investigation.

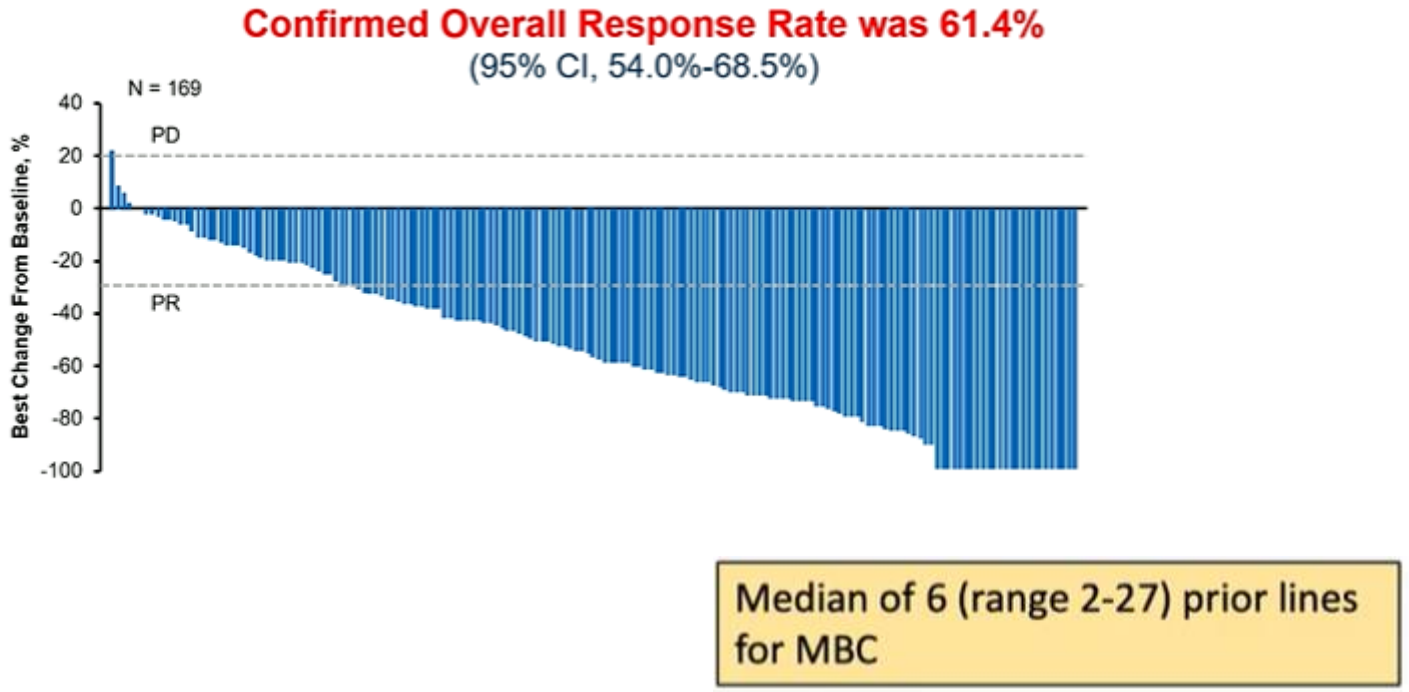
Nakada T, et al. *Chem Pham Bull* (Tokyo). 2019;67(3):173-185. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

DESTINY-Breast01:
Phase 2 Study of T-DXd in HER2-Positive MBC



ILD = interstitial lung disease; CBR = clinical-benefit rate; PK = pharmacokinetics.
Modi S, et al. *N Engl J Med*. 2020;382(7):610-621.

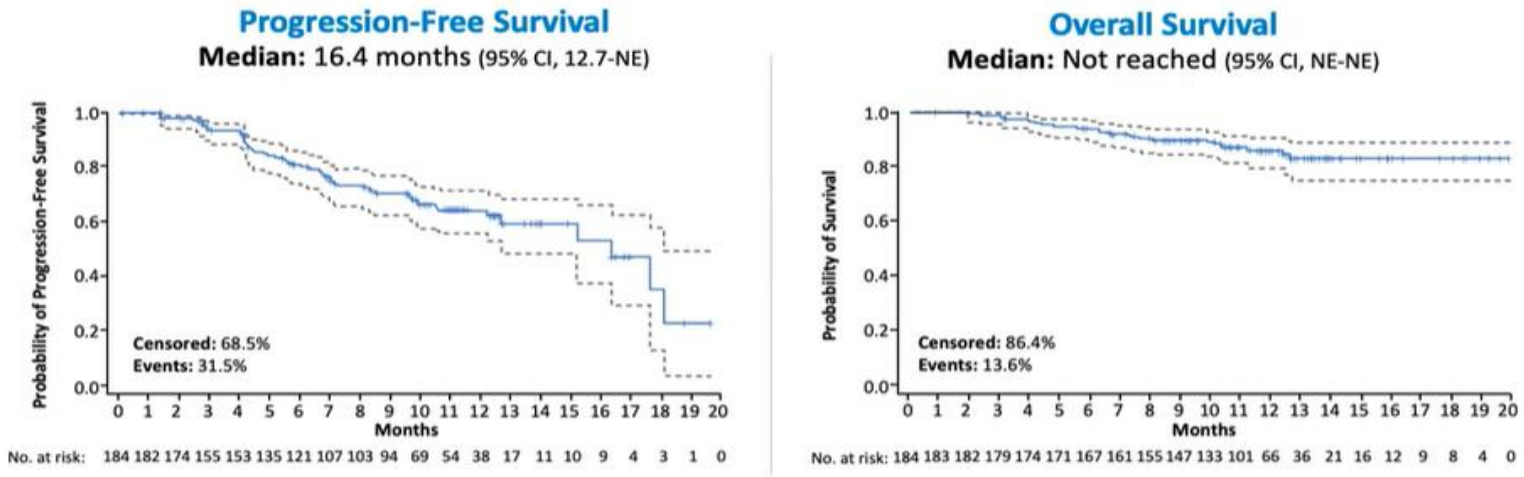
DESTINY-Breast01: Phase 2 Study of T-DXd (Updated ORR Results with 20.5 Months Follow-Up)



Median of 6 (range 2-27) prior lines for MBC

Modi S, et al. Presented at: SABCS; 2020. Presented at: ESMO Congress; 2021.

DESTINY-Breast01:
Trastuzumab Deruxtecan for 3L+ HER2+ MBC



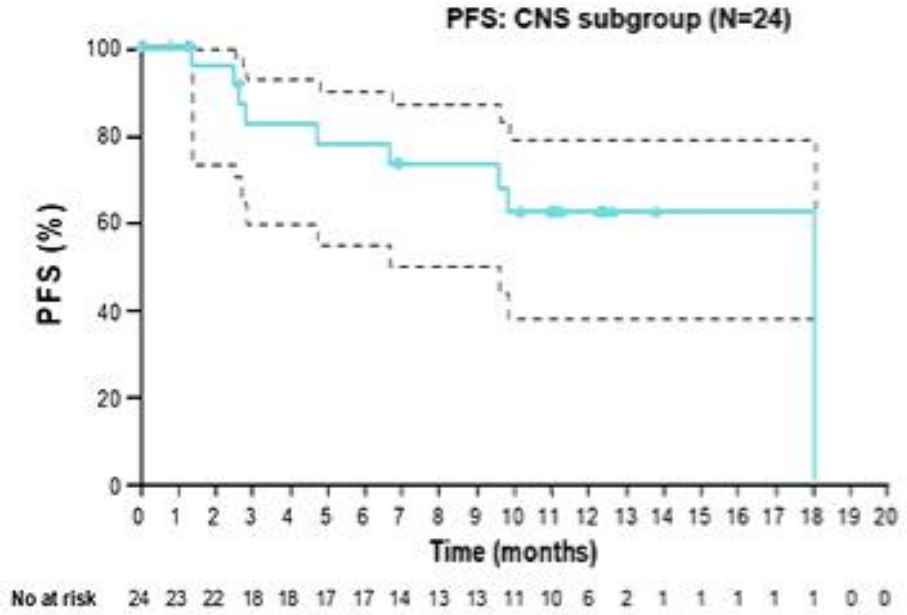
- Median follow-up, 11.1 months (range, 0.7-19.9 months)
- Median PFS in the 24 patients with brain metastases was 18.1 months (95% CI, 6.7-18.1 months)

Patients who received T-DXd 5.4 mg/kg.
CI, confidence interval; NE, not estimable.

Patients were enrolled from **October 2017 – September 2018**

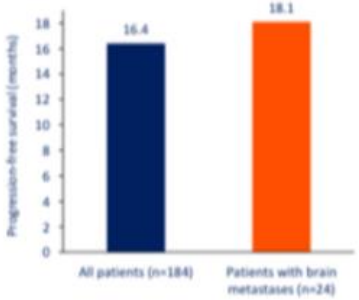
Median OS update at ESMO 2021: 29.1 months in exploratory analysis with 31.1 months of F/U.
Modi S, et al. *N Engl J Med*. 2020;382(7):610-621.

T-DXd Showed Similar Efficacy in Patients with a History of CNS Metastases at Baseline to the Overall Population



	CNS subgroup (N=24)	All patients (N=184)
Confirmed ORR by ICR, n (%) (95% CI)	**14 (58.3)** (36.6–77.9)	**112 (60.9)** (53.4–68.0)
DCR, n (%)	22 (91.7)	179 (97.3)
TTR, median, months (95% CI)	2.8 (1.3–4.1)	1.6 (1.4–2.6)
DOR (CR or PR), median, months (95% CI)	16.9 (5.7–16.9)	14.8 (13.8–16.9)
PFS, median, months (95% CI)	**18.1** (6.7–18.1)	**16.4** (12.7–NE)

- Median PFS in the CNS subgroup was 18.1 months (95% CI, 6.7–18.1) vs 16.4 months (95% CI, 12.7–n reached) in the overall population[1]



CNS = central nervous system.
Jerusalem G, et al. Presented at: ESMO Breast Cancer Virtual Meeting; 2020.

T-DXd AE of Special Interest

Drug-Related ILD/Pneumonitis

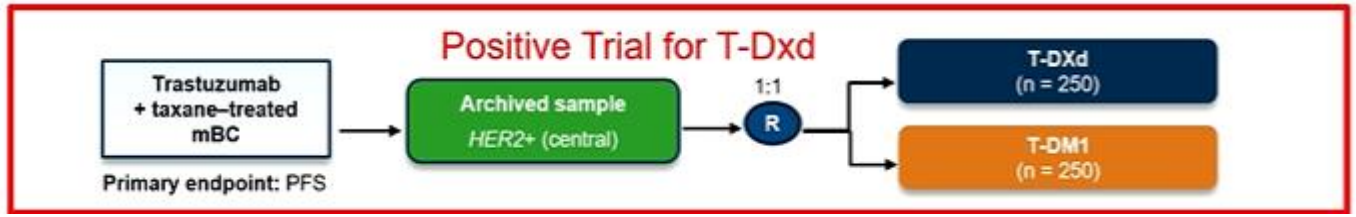
Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184) (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)

[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

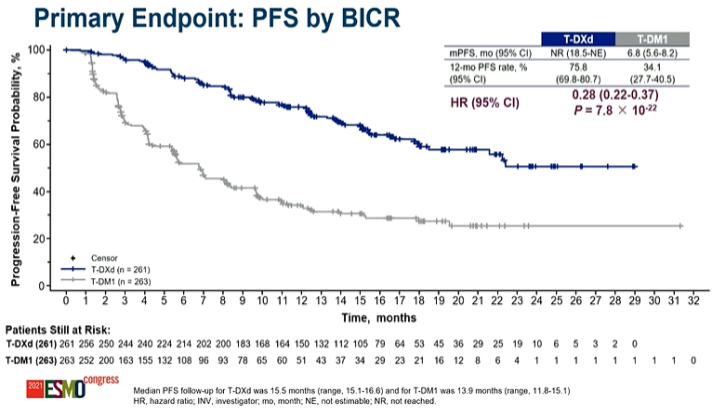
- Median time to onset of ILD was 27.6 weeks (range, 6-76 weeks)
- Requires awareness via monitoring, dose interruptions/modification, and early institution of steroids
- Majority of cases occur within 12-14 months of therapy; no cumulative risk

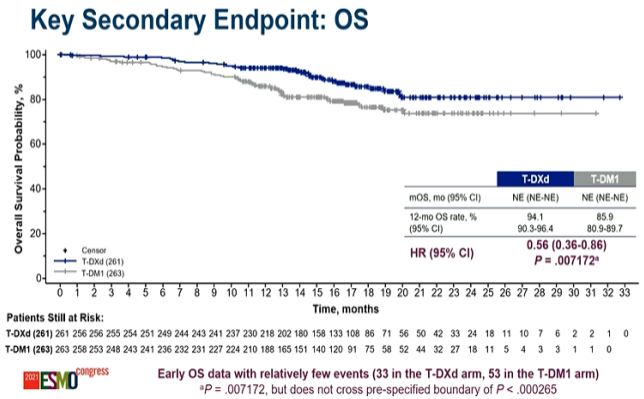
Modi S, et al. Presented at: SABCS; 2020.

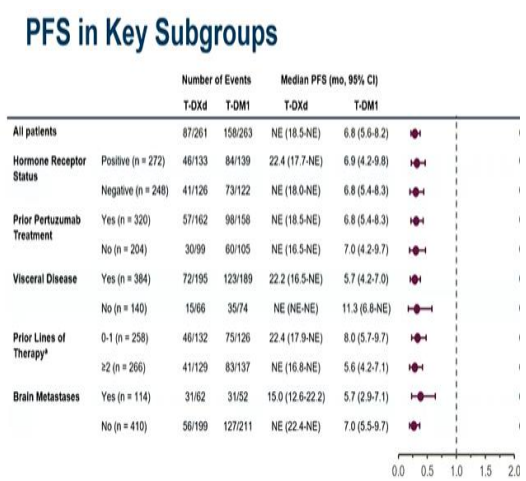
DESTINY-Breast03



Presidential presentation on 9/18 at ESMO 2021 by Dr. Cortes: PFS HR: 0.28 for T-DXd





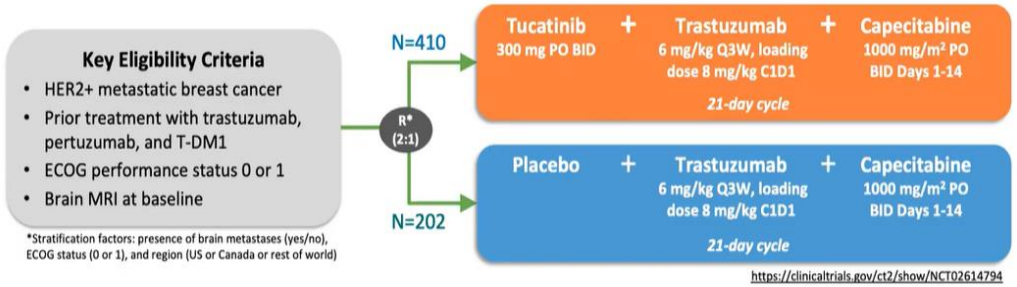


- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1**
- The most common TEAE associated with treatment discontinuation for T-DXd was ILD/pneumonitis[a] (8.2%) and for T-DM1 was thrombocytopenia[b] (2.7%)

TEAE = treatment-emergent AE.

Cortes J, et al. Presented at: ESMO Congress; 2021

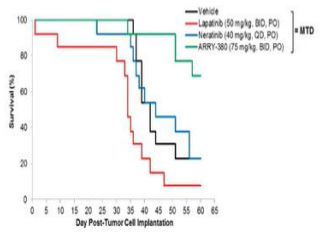
Tucatinib – HER2CLIMB



- Oral, HER2-selective, tyrosine kinase inhibitor[1]
- Preclinical activity in HER2+ breast cancer models, including intracranial models
- Extracranial and intracranial activity observed in phase 1 program[2-4]

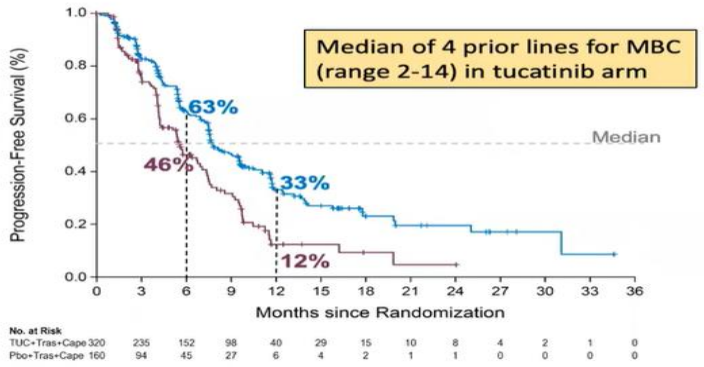
Cellular Selectivity Data

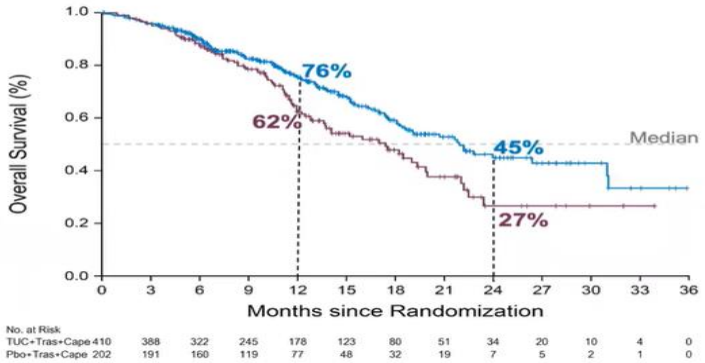
Compound	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)	HER2 IC_{50} (nM) 50% Human Serum
ARRY-380	8	4000	67
Neratinib	7	8	39
Lapatinib	49	31	810



Patients with or without brain mets
PFS HR 0.54; medians 5.6 vs 7.8 months; p <0.001
OS HR 0.66; medians 17.4 months vs 21.9 months; p=0.005

[1]Pheneger et al, Cancer Res 2009
[2]Moulder et al, Clin Cancer Res 2017
[3]Murthy et al, JAMA Oncol 2018
[4]Metzger et al, Ann Oncol 2020





Patients were enrolled from **February 2016 – May 2019**

Murthy et al, NEJM 2019

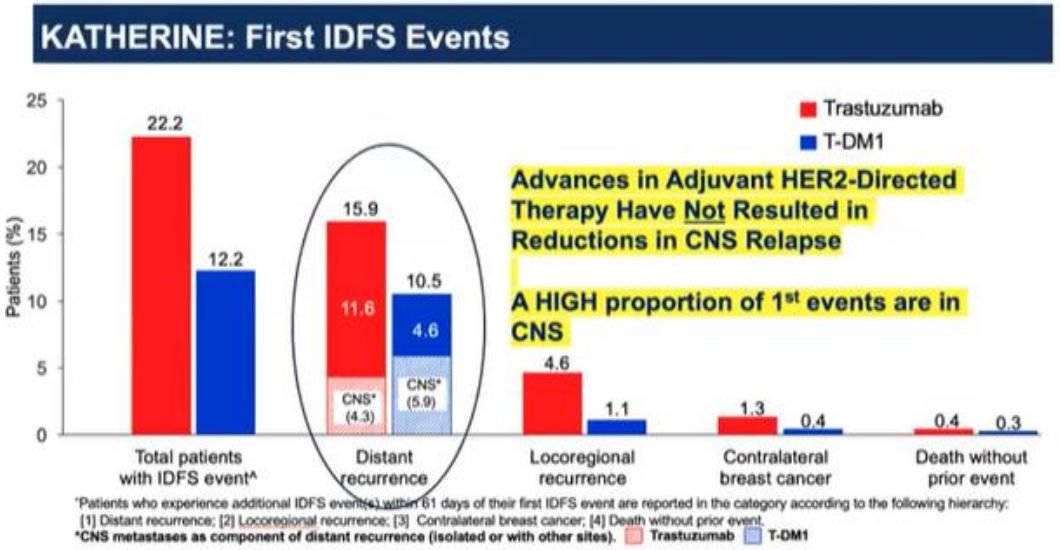
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

EGFR = estimated glomerular filtration rate.

ClinicalTrials.gov. Accessed September 21, 2021. https://clinicaltrials.gov/ct2/show/NCT02614794. Pheneger T, et al. Presented at: AACR Annual Meeting; 2009. Moulder SL, et al. *Clin Cancer Res*. 2017;23(14):3529-3536. Murthy R, et al. *Lancet Oncol*. 2018;19(7):880-888. Metzger Filho O, et al. *Ann Oncol*. 2020;31(9):1231-1239. Murthy RK, et al. *N Engl J Med*. 2020;382(7):597-609.

CNS metastasis remains a challenge

Up to 50% of HER2+ MBC patients develop brain metastases



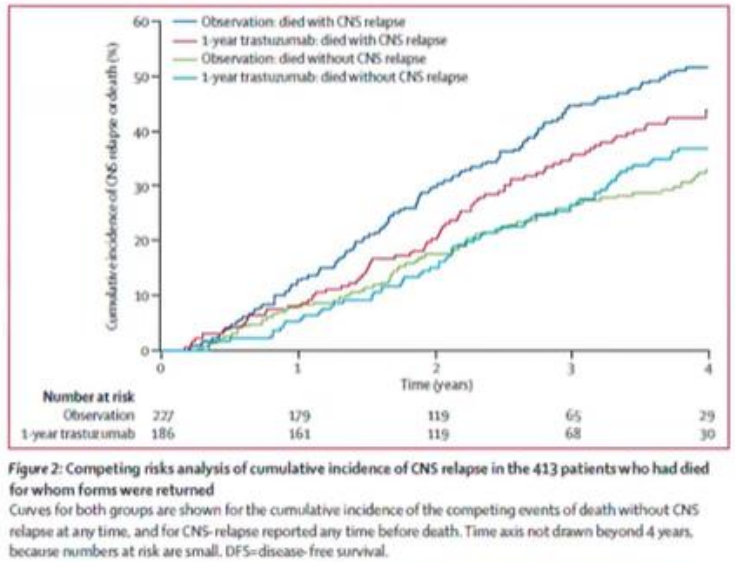
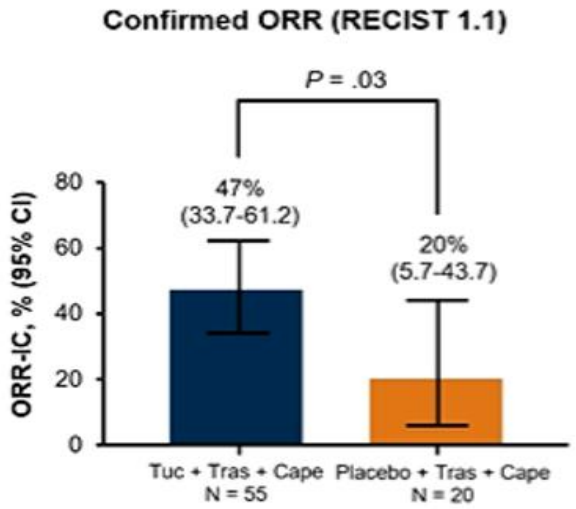


Figure 2: **Competing risks analysis of cumulative incidence of CNS relapse in the 413 patients who had died for whom forms were returned**
Curves for both groups are shown for the cumulative incidence of the competing events of death without CNS relapse at any time, and for CNS-relapse reported any time before death. Time axis not drawn beyond 4 years, because numbers at risk are small. DFS=disease-free survival.

Once patients develop MBC, continuous and unabated risk of CNS involvement over time

Von Minckwitz et al, NEJM 2010
Pestalozzi et al, Lancet Oncol 2013

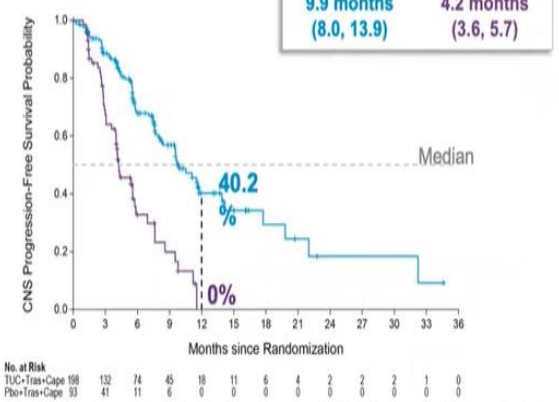
CNS Metastasis – HER2CLIMB Improves ORR, CNS PFS, and OS



CNS-PFS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

Median CNS-PFS (95% CI):	
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

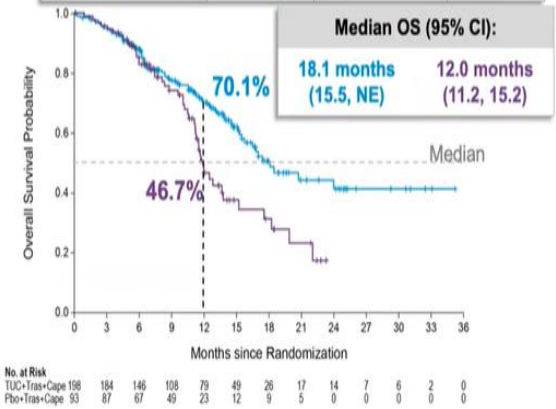


CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.

OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		

Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)



TUC = tucatinib.

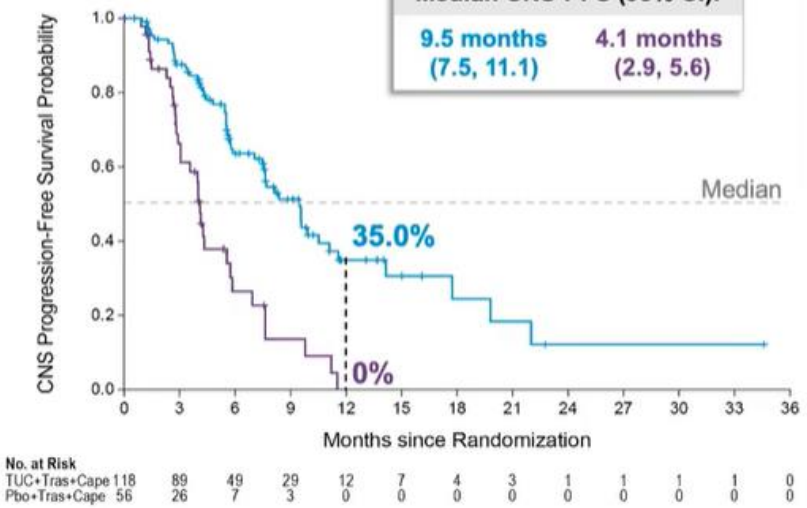
Von Minckwitz G, et al. *N Engl J Med*. 2019;380(7):617-628. Pestalozzi BC, et al. *Lancet Oncol*. 2013;14(3):244-248. Lin NU, et al. *J Clin Oncol*. 2020;38(23):2610-2619.

HER2CLIMB: Active Brain Mets

CNS-PFS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	54/118	0.36 (0.22, 0.57)	<0.0001
Pbo+Tras+Cape	33/56		

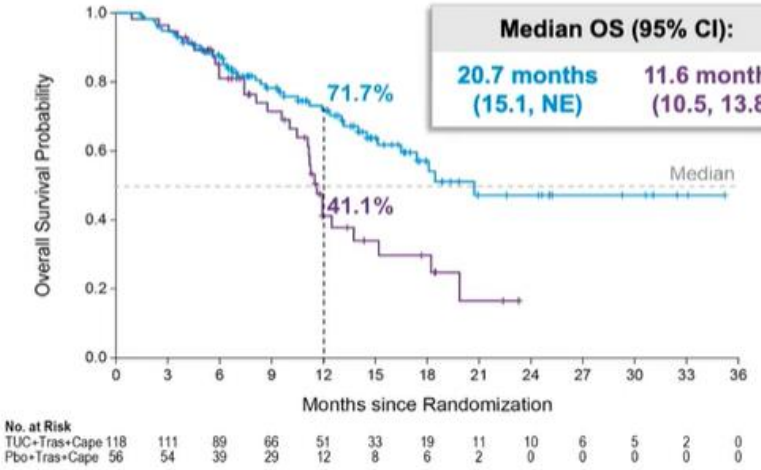
Median CNS-PFS (95% CI):	
9.5 months (7.5, 11.1)	4.1 months (2.9, 5.6)



OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		

Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

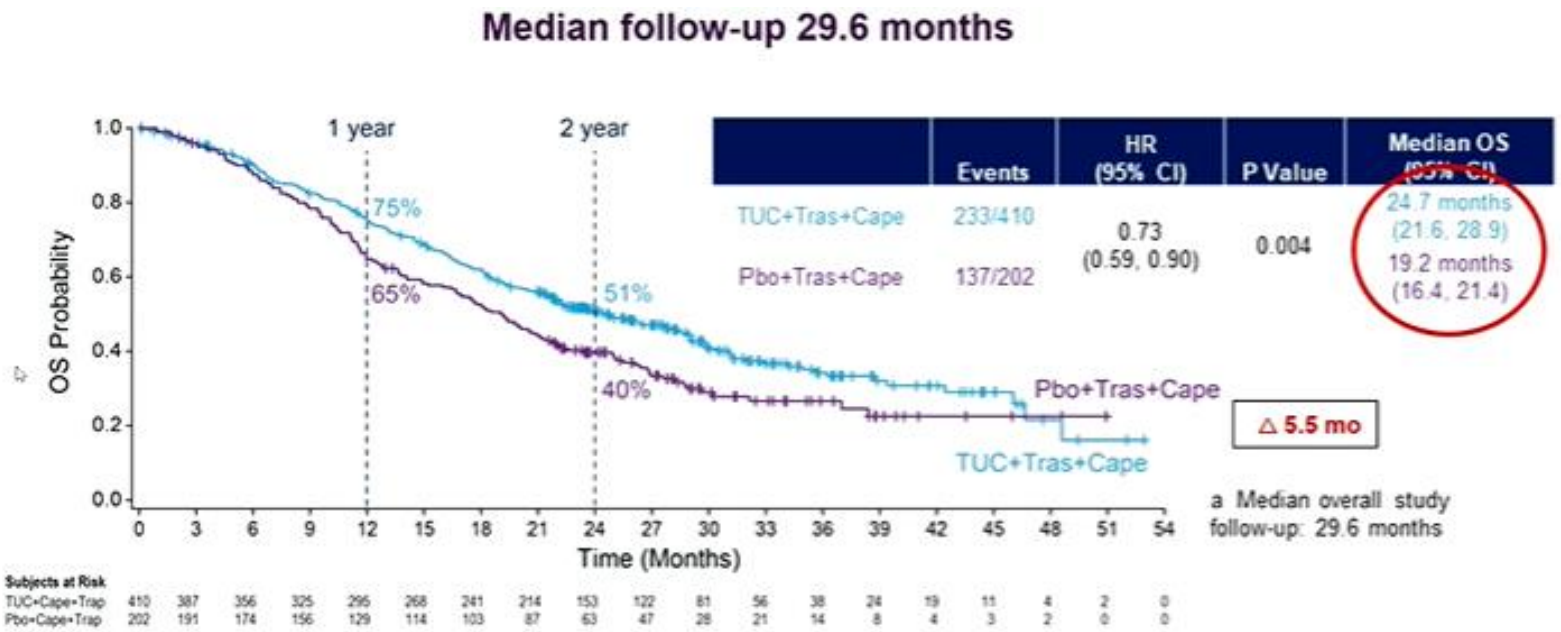


CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

Lin et al, J Clin Oncol 2020

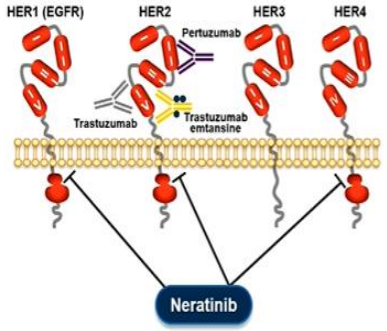
HER2CLIMB: Updated Overall Survival



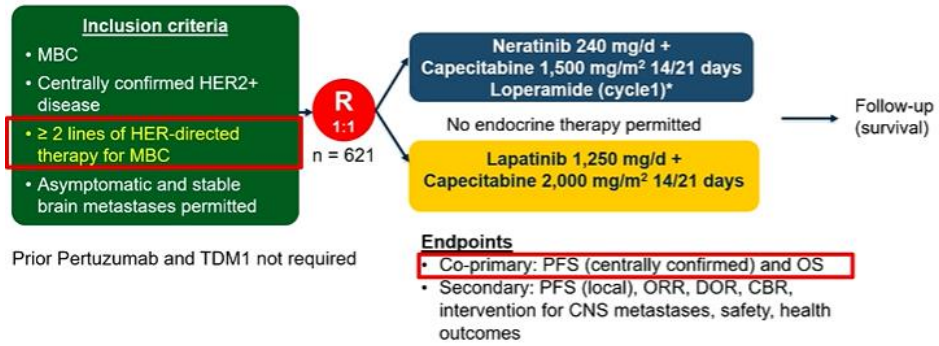
- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5 month improvement in median OS in the tucatinib arm compared to the placebo arm.
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis.

Curigliano G, et al. Presented at: ASCO Annual Meeting; 2021.

Neratinib: A Pan-HER Kinase Inhibitor

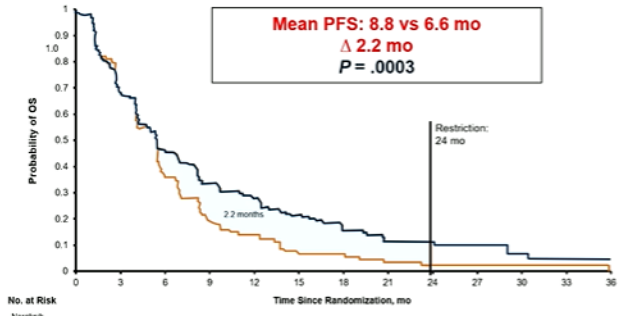


NALA: Phase 3 Trial of Neratinib for HER2+ MBC



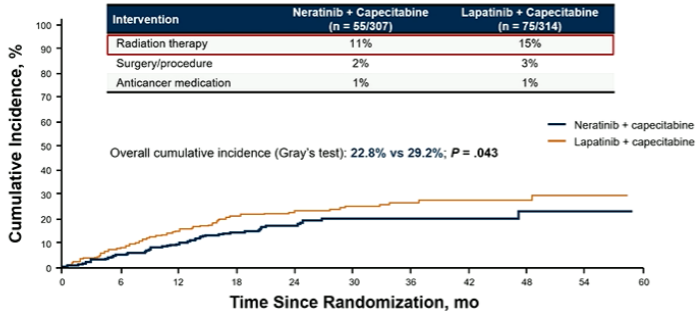
NALA Trial: Centrally Confirmed Mean PFS

Primary Endpoint



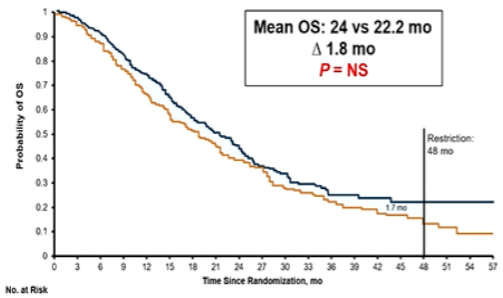
NALA Trial: CNS Benefits in favor of Neratinib

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



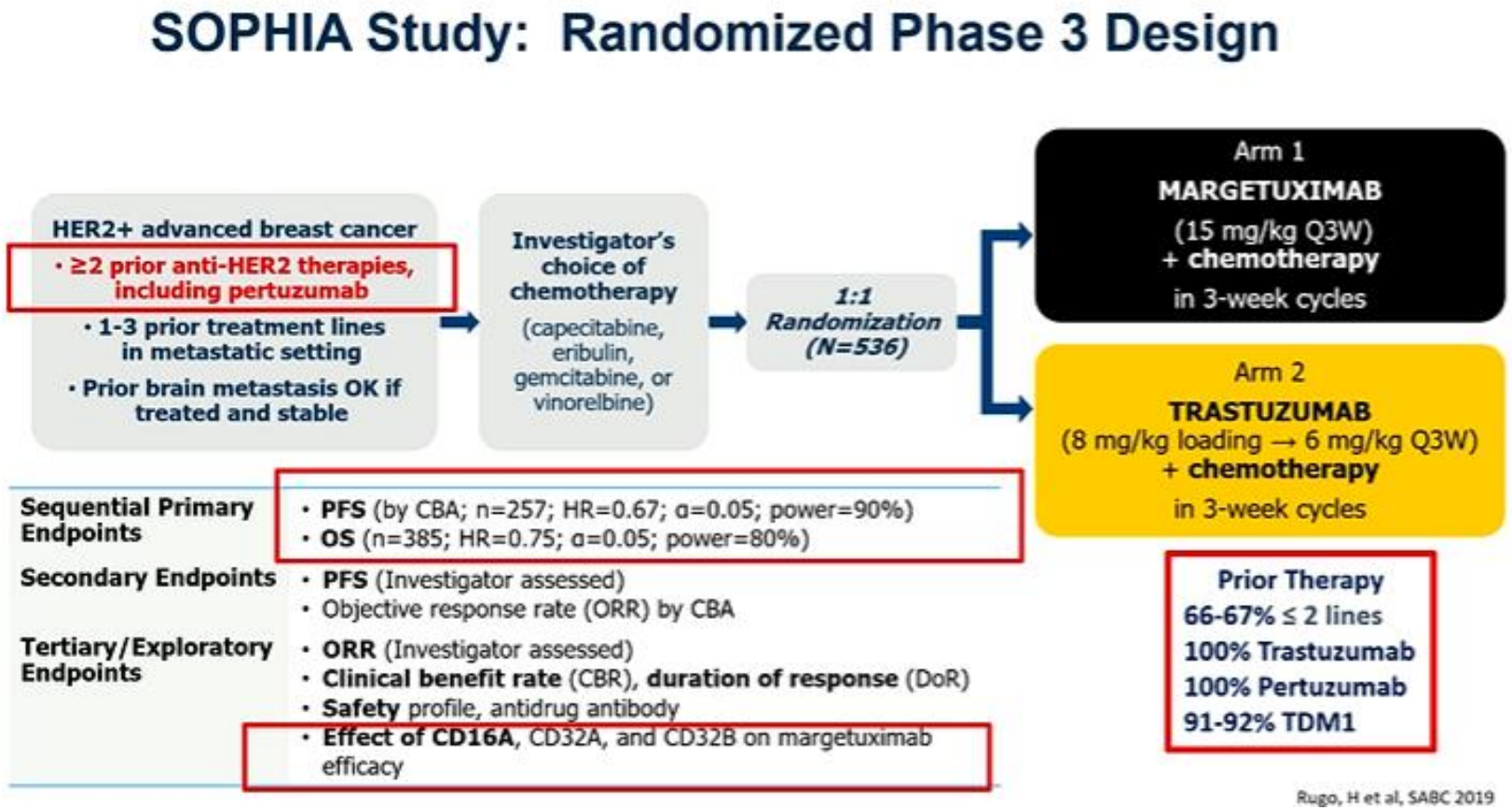
NALA Trial: No Difference in OS

Primary Endpoint



Baselga J, et al. *Crit Rev Oncol Hematol*. 2017;119:113-122. Kim JY, et al. *Int J Cancer*. 2019;145(6):1669-1678. Kunte S, et al. *Cancer*. 2020;126(19):4278-4288. Xuhong JC, et al. *Am J Cancer Res*. 2019;9(10):2103-2119. Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149.

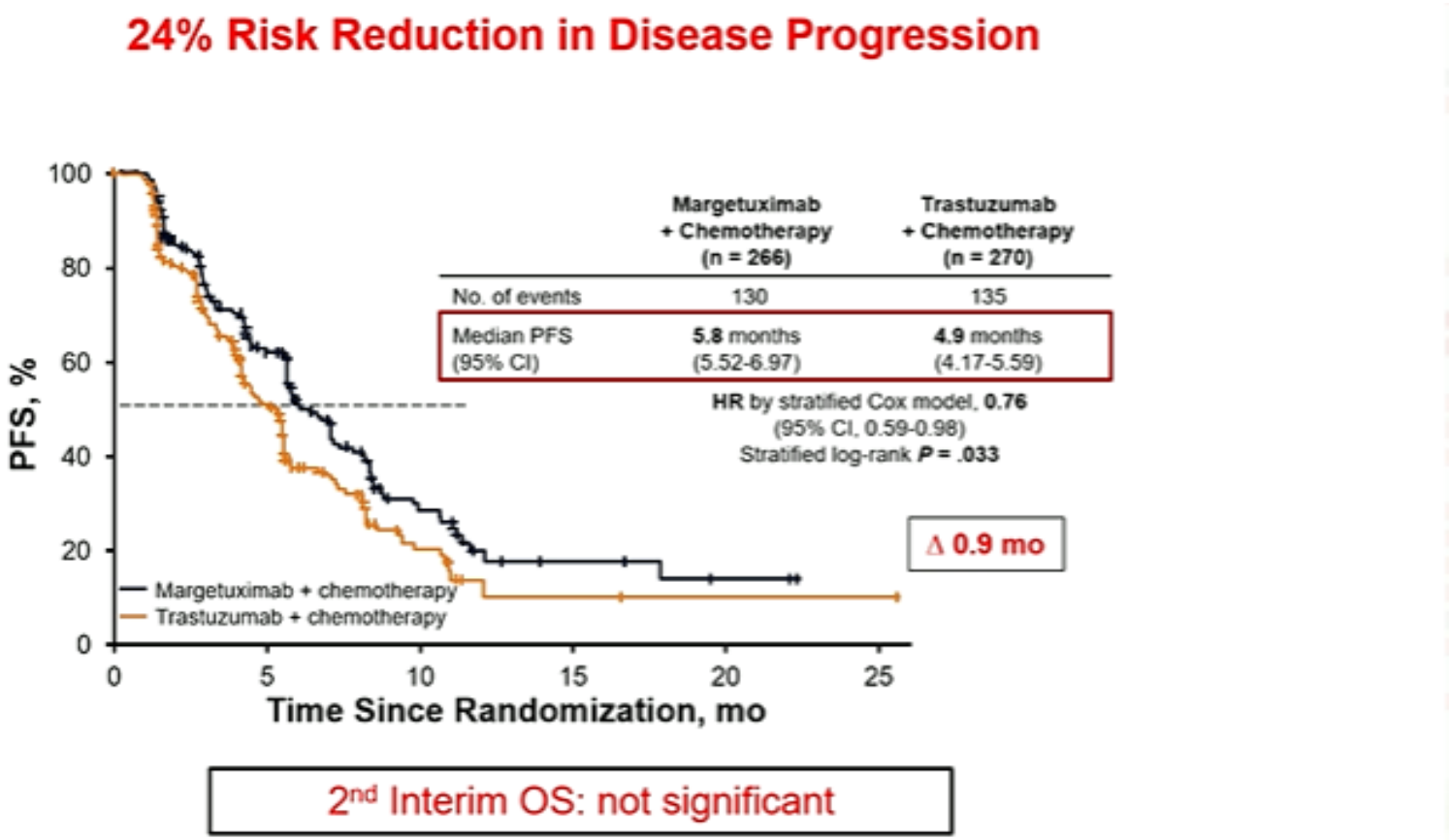
Margetuximab: A Novel HER2 mAB with a Modified Fc Domain



CBA = central blinded analysis.

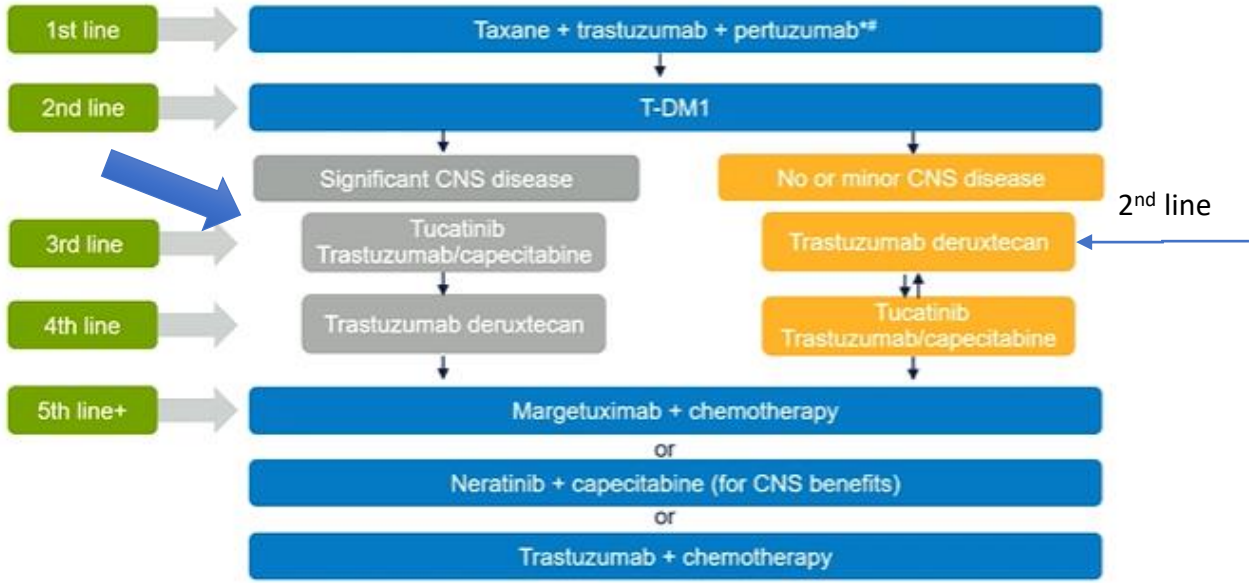
Rugo H, et al. Presented at: SABCS; 2019.

Phase 3 SOPHIA Trial: Primary PFS Endpoint



Rugo H, et al. Presented at: ASCO Annual Meeting; 2019. Rugo H, et al. Presented at: SABCS; 2019.

2021 Approach to Therapy for Metastatic HER2+ BC



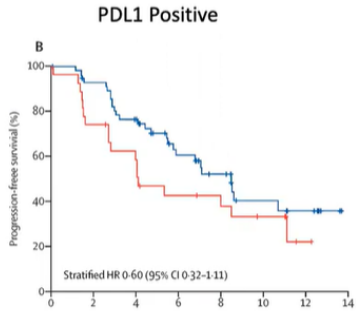
*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

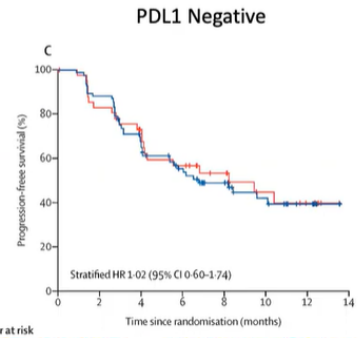
Tucatinib + Trastuzumab + Capecitabine	Trastuzumab deruxtecan	Neratinib + Capecitabine	Margetuximab + chemotherapy
+ OS Advantage + CNS activity + Effective post-TDM1 - diarrhea	+ High probability of tumor response + Durable tumor control + Active in HER2 heterogeneity - Requires Pulmonary Monitoring	+ All oral regimen + CNS activity - GI Toxicity - No OS - Activity post Tucatinib & cape?	+ Novel immune mechanism + Favorable safety - Modest activity - No OS yet - Patient selection?

GI = gastrointestinal.
Modi S, et al. Presented at: ESMO; 2021.

Immunotherapy in HER2+

KATE-2: Ph 2 T-DM1 +/- Atezolizumab





HER2 + 1st line MBC-
Immunotherapy
IRB#19339

NRG BR-004 Schema

HER2-Positive, First-line Metastatic Breast Cancer

STRATIFICATION
- Prior adjuvant or neoadjuvant trastuzumab (yes; no)
- Prior pertuzumab or neratinib in adjuvant or neoadjuvant setting (yes; no)
- Estrogen receptor status (positive; negative)
- PD-L1 status (positive; negative)

RANDOMIZATION

Arm 1
Weekly Paclitaxel
+
Trastuzumab + Pertuzumab‡
every 3 weeks until progression
+
Placebo every 3 weeks until progression or 2 years

Arm 2
Weekly Paclitaxel
+
Trastuzumab + Pertuzumab‡
every 3 weeks until progression
+
Atezolizumab 1200 mg every 3 weeks until progression or 2 years

Weekly Paclitaxel (WP): 80 mg/m2 IV Days 1, 8, 15, 22, 29, and 36 every 6 weeks for 4 cycles

Emens et al, Lancet Oncol 2020

TBCRC 045: AVIATOR

- Advanced HER2+ cancer
- Prior T-DM1, Trastuzumab, Pertuzumab
- No prior immunotherapy
- PD-L1 unselected

N=40 → Vinorelbine +trastuzumab+ avelumab

Vinorelbine +trastuzumab N=20 → Trastuzumab + avelumab + Utomilumab

Vinorelbine +trastuzumab+ avelumab + Utomilumab N=40

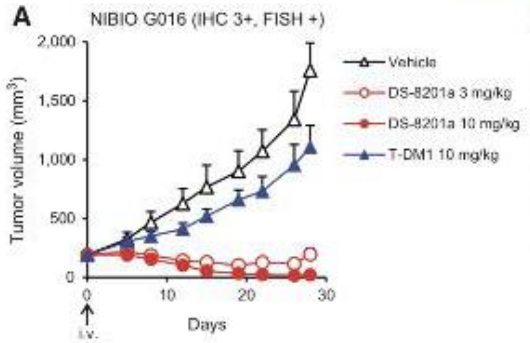
Tumor tissue | Tumor Tissue | Tumor Tissue

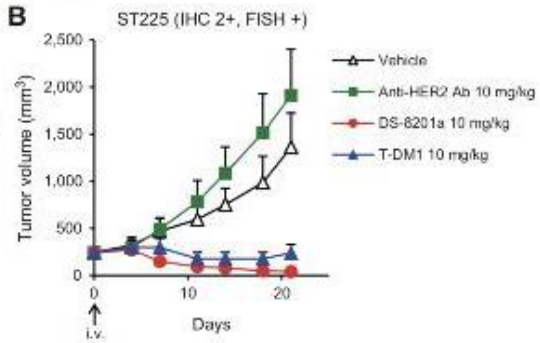
PI: Ian Krop

DS8201 has anti-tumor activity in HER2 LOW Expressing Cancers

PDX models

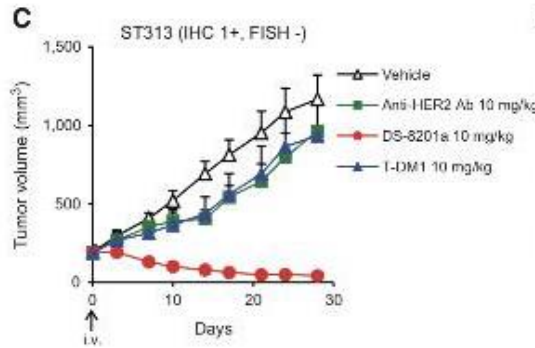
Gastric Cancer
IHC 3+

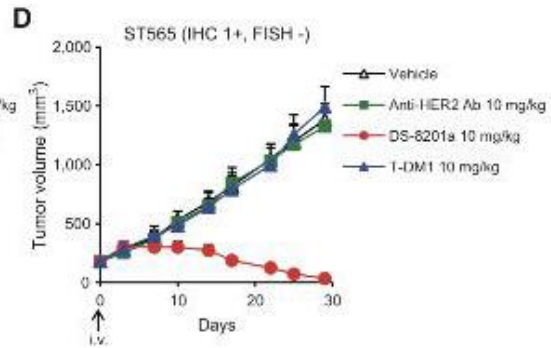




Breast Cancer
IHC 2+
FISH +

Breast Cancer
IHC 1+
FISH -

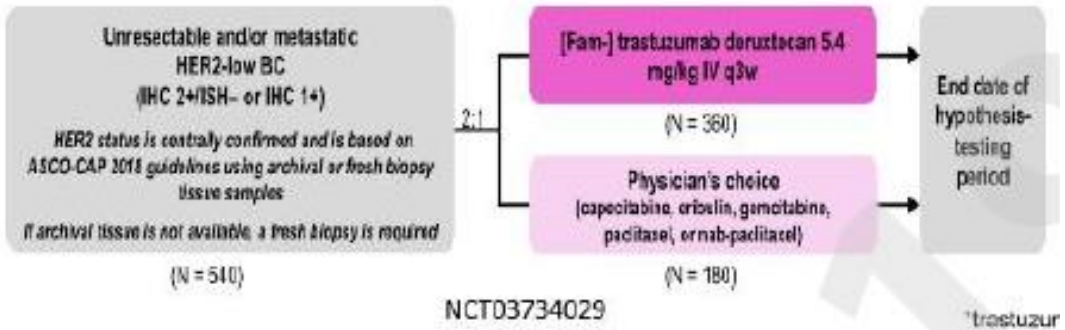




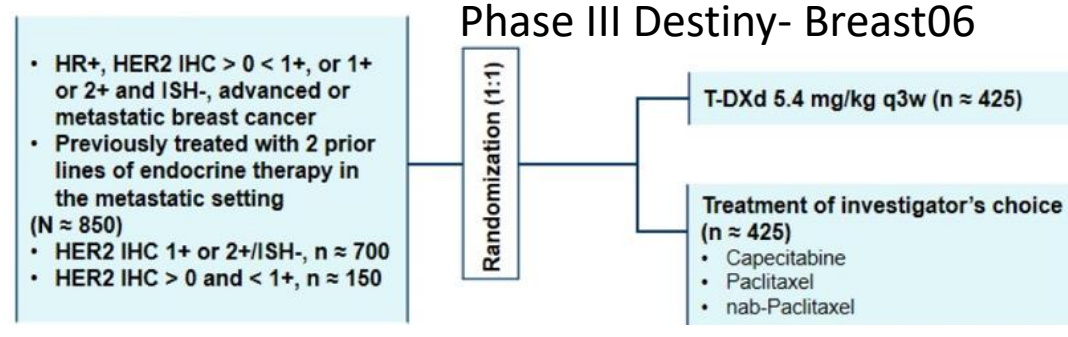
Breast Cancer
IHC 1+
FISH -

Ogitani Y et al, Clin Can Res 2016

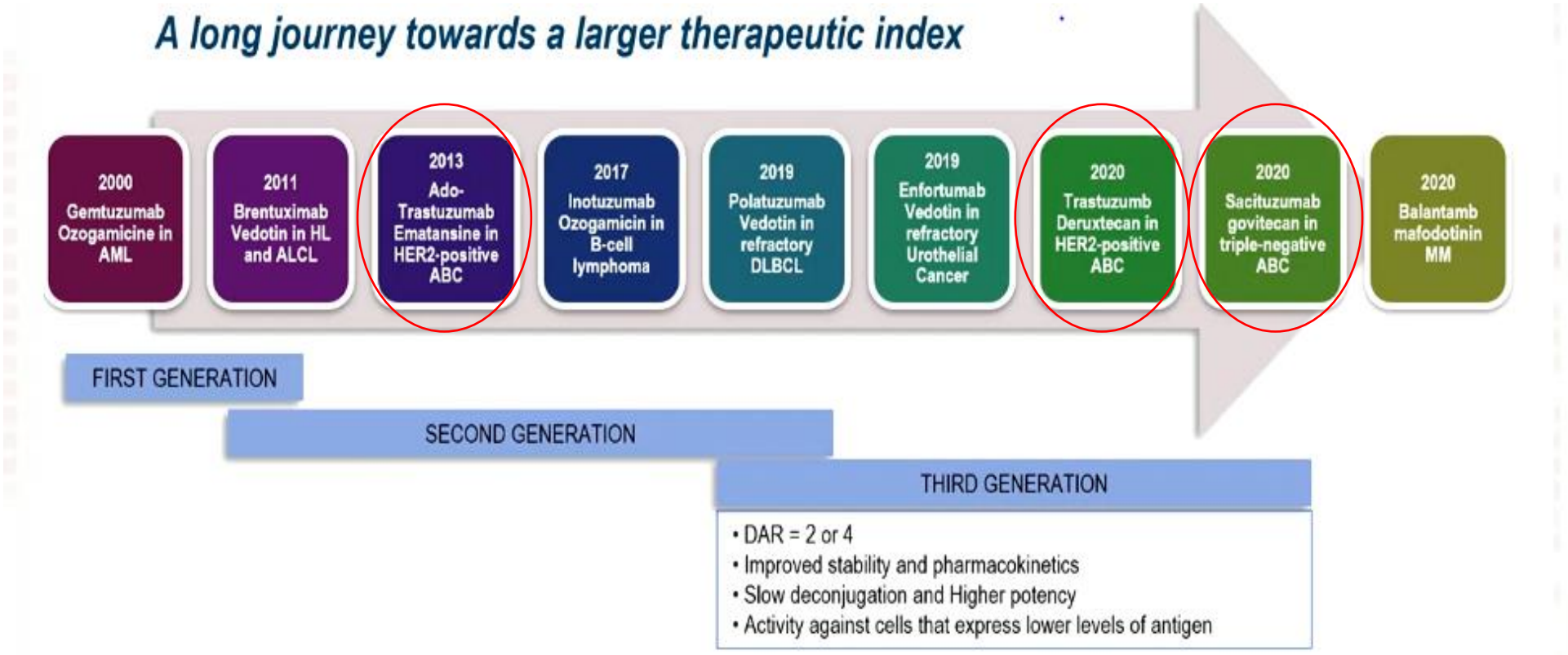
Phase III DESTINY-Breast04 (U303)



Phase III Destiny- Breast06



ADCs approved by FDA



Drago et al, Nat Rev Oncol 2021; Beck et al, Nat Rev Drug Discov 2017; Tolcher et al, ASCO Educational Book 2020

Future…2nd and 3rd generations of ADC
ASCO & ESMO 2021

- Primary or secondary resistance to T-DM1 can develop.
- Second generation ADCs are using a cleavable linker and a more potent payload with a different mechanism of action.
- Fam-trastuzumab-deruxtecan has already been approved by FDA.
- There are at least 4 ADCs for treatment of HER2 positive metastatic breast cancer on the pipeline.

- Abstract 1022 was presented in ASCO 2021 annual meeting.
- The RC48-ADC (disitamab vedotin) is a novel humanized anti-HER2 antibody conjugated with a microtubule inhibitor payload, monomethyl auristatin E (MMAE) via a cleavable linker.
- bystanding effect in killing cancer cells.
- A pooled analysis of 2 phase I/Ib studies was conducted for the safety and efficacy of this compound in HER2 positive or HER2 low expressing subgroups.
- ORR 22.2-40% with
- mPFS 4-6.3 months.
- HER2 low expressing cohort had ORR about 40% and mPFS of 6 mo.
- SE: Liver enzymes and neutropenia

- Abstract #1038 was a phase I study of ARX788 that was presented by Dr. Sara Hurvitz.
- ARX788 is a site-specific ADC , a combination of anti-HER2 and AS269 which is highly stable and has low toxicity and has activity in HER2 positive, HER2 low and T-DM1 resistant tumors.
- It was well tolerated with no reported DLT.
- ORR in breast cancer cohort was 74%.

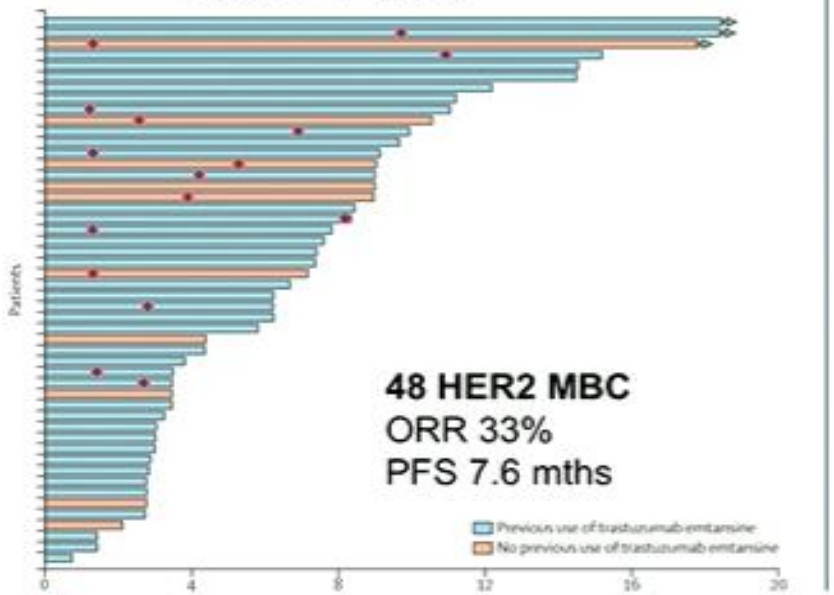
- Abstract #1024: A166 is a 3rd generation ADC that has tubulin inhibitor Duo-5 toxin, cleavable linker, and a site-specific K-Lock conjugation chemistry. The ORR was reported at 60.9% at 5.4 mg/kg dose. Ocular toxicity was reported.

- SYD985 is a 2nd generation ADC consisting of Trastuzumab bound to a potent duocarmazine payload via a cleavable linker (VC-Seco-DUBA).
- It has activity in Her2 positive and HER2 low ow expressing breast cancer.
- Phase I/Ib study evaluating safety of weekly paclitaxel plus SYD985 reported in ESMO 2021.

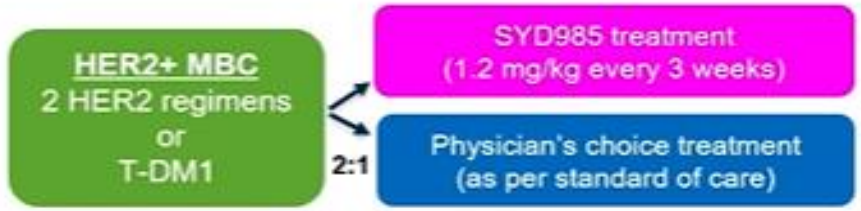
Trastuzumab Duocarmazine (SYD-985): HER2 ADC

Trastuzumab mAb, Cleavable Linker, and a DNA Alkylating Toxin Duocarmycin Payload

Phase 1 Trial



TULIP Trial



Primary endpoint: PFS

Relevant activity in T-DM1-resistant breast cancer

Tano et al. Cancers 2020. Banerji et al. The Lancet 2019,

2021 ESMO congress

Primary outcome of the phase III SYD985.002/TULIP trial comparing [vic-]trastuzumab duocarmazine to physician's choice treatment in patients with pre-treated HER2-positive locally advanced or metastatic breast cancer

Heavily pretreated HER2-pos MBC

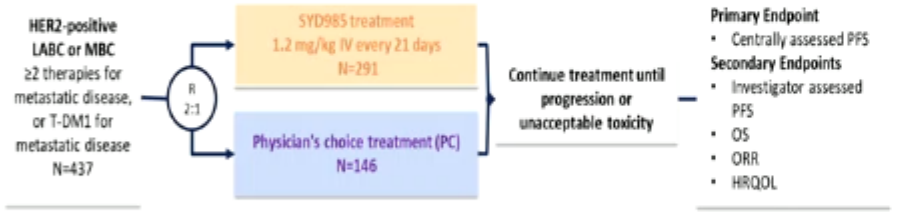
SYD-985 (TULIP)

All TEAEs reported in >= 15% of patients in SYD985 or PC group + ILD/Pneumonitis

Number of patients with By Preferred Term	SYD985 (n=288)		Physician's choice (n=137)	
	All Grades	>=grade 3	All Grades	>=grade 3
At least one TEAE	278 (96.5%)	152 (52.8%)	132 (96.4%)	66 (48.2%)
Conjunctivitis	110 (38.2%)	16 (5.6%)	3 (2.2%)	0
Keratitis	110 (38.2%)	35 (12.2%)	11 (8.0%)	0
Fatigue	96 (33.3%)	9 (3.1%)	41 (29.9%)	2 (1.5%)
Dry eye	87 (30.2%)	12 (4.2%)	14 (10.2%)	0
Nausea	73 (25.3%)	3 (1.0%)	43 (31.4%)	0
Alopecia	62 (21.5%)	1 (0.3%)	16 (11.7%)	0
Decreased appetite	61 (21.2%)	0	15 (10.9%)	0
Diarrhea	60 (20.8%)	3 (1.0%)	49 (35.8%)	3 (2.2%)
Asthenia	58 (20.1%)	5 (1.7%)	23 (16.8%)	1 (0.7%)
Constipation	57 (19.8%)	0	24 (17.5%)	0
Lacrimation increased	53 (18.4%)	0	2 (1.5%)	0
Cough	48 (16.7%)	1 (0.3%)	14 (10.2%)	0
Vomiting	36 (12.5%)	1 (0.3%)	23 (16.8%)	1 (0.7%)
Neutropenia	31 (10.8%)	14 (4.9%)	33 (24.1%)	23 (16.8%)
Pneumonitis	19 (6.6%)	6 (2.1%)	0	0
Interstitial lung disease	3 (1.0%)	1 (0.3%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	2 (0.7%)	1 (0.3%)	32 (23.4%)	5 (3.6%)

Eye toxicity 78.1%

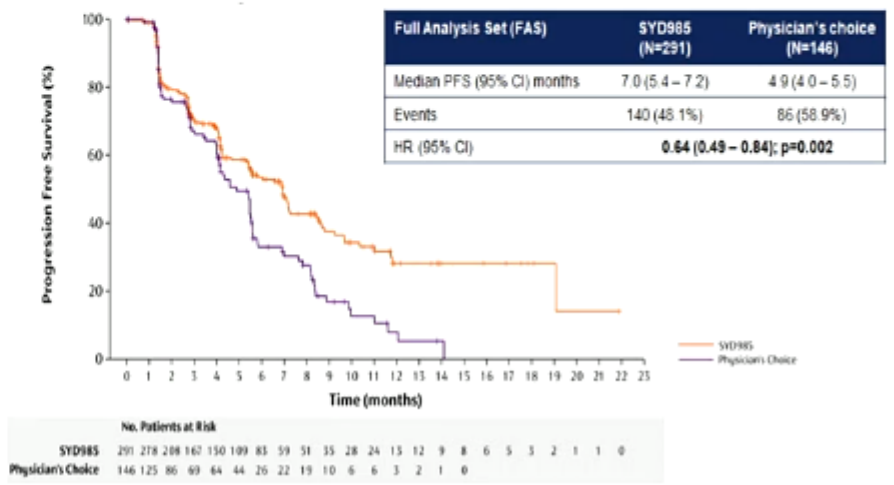
STUDY DESIGN



Stratification - Treatment - Participating Countries

- Stratification factors
  - Region (EU+Singapore vs North America)
  - Number of prior treatment lines for LMBC/MBC (1-2 vs >2)
  - Prior treatment with pertuzumab (yes vs no)
- Physician's choice
  - Lapatinib+Capecitabine
  - Trastuzumab+Capecitabine
  - Trastuzumab+Vinorelbine
  - Trastuzumab+Eribulin
- NCT03262935
- 83 sites
  - USA, Canada, Belgium, Denmark, France, Italy, Netherlands, Spain, Sweden, UK, Singapore

CENTRALLY REVIEWED PFS

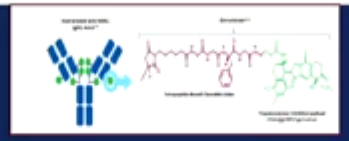
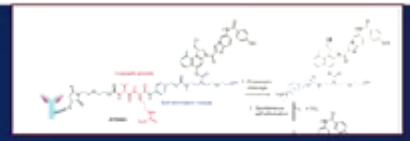


Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

Saura C. et al. ESMO 2021 (LBA 15)

Is there any chance that SYD985 is active after progression on T-DXd ?

Main differences and similarities between T-DXd and SYD985

ADC attributes	T-DXd 	SYD985 
mAb	Trastuzumab	Trastuzumab
Linker	Peptide-cleavable linker (cleaved by cathepsins)	Peptide-cleavable linker (cleaved by cathepsins)
Payload	Camptothecins: DXd (topo-I inhibitor) Induces double-strand DNA breaks and apoptosis in dividing cells	Duocarmycins:Duocarmycin-hydroxybenzamide-azaindole Binds DNA irreversibly Alkylates DNA Kills dividing and non-dividing cells equally
DAR	8	2.4-2.8
BYSTANDER EFFECT	YES	YES

Presented at ESMO 2021: Barbara Pistilli

Sequencing treatments

Is there any chance that SYD985 is active after progression on T-DXd ?

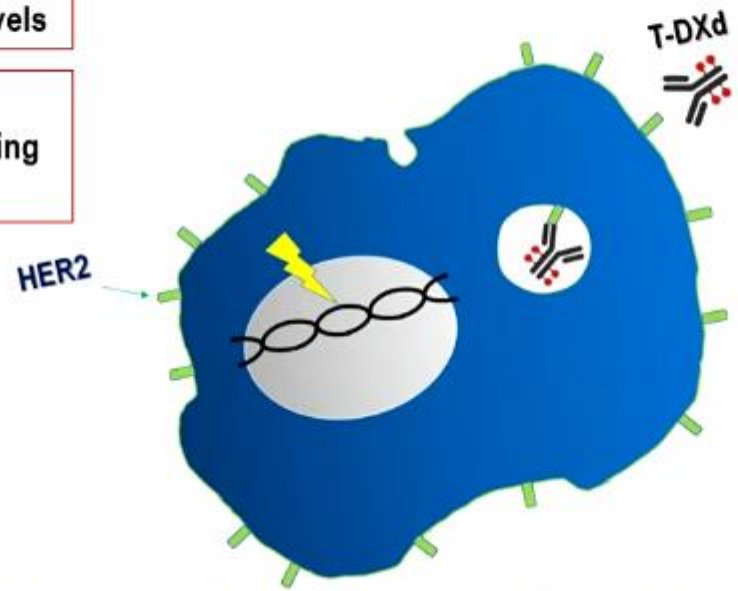
If T-DXd resistance depends on:

reduced membrane HER2 levels

ADCs trafficking: endosome/lysosome-mediating processing

↓

SYD985 activity after T-DXd is less likely but not impossible



Resistance mechanisms to DXd (payload)

Immunogenic properties of T-DXd

↓

possible SYD985 activity after T-DXd

Of course it needs confirmation in clinical trials

Ogitani et al, Clin Cancer Res 2016; Dokter et al, Mol Cancer Ther 2014
Presented at ESMO 2021: Barbara Pistilli

Future…

- To do biomarker studies:
  - to explore the mechanisms of resistance in metastatic HER2 positive patients
  - To identify key biomarkers driving cancer progression
  - To evaluate patients who are exceptional responders
  - To use Gene signatures to guide de-escalation in HER2+ cancers
- Promising new combinations , role of ICI, PI3Ki, CDK4/6i
- New generation of ADC, TKI and mAB
- To prevent brain metastasis and leptomeningeal disease with prophylactic treatments – treatment escalation in adjuvant setting, CAR-T approaches


Questions