"DE-ESCALATION" NELLA TERAPIA SISTEMICA DEL CARCINOMA MAMMARIO: QUALI EVIDENZE?

Trastuzumab adiuvante nell'EBC HER2-positivo

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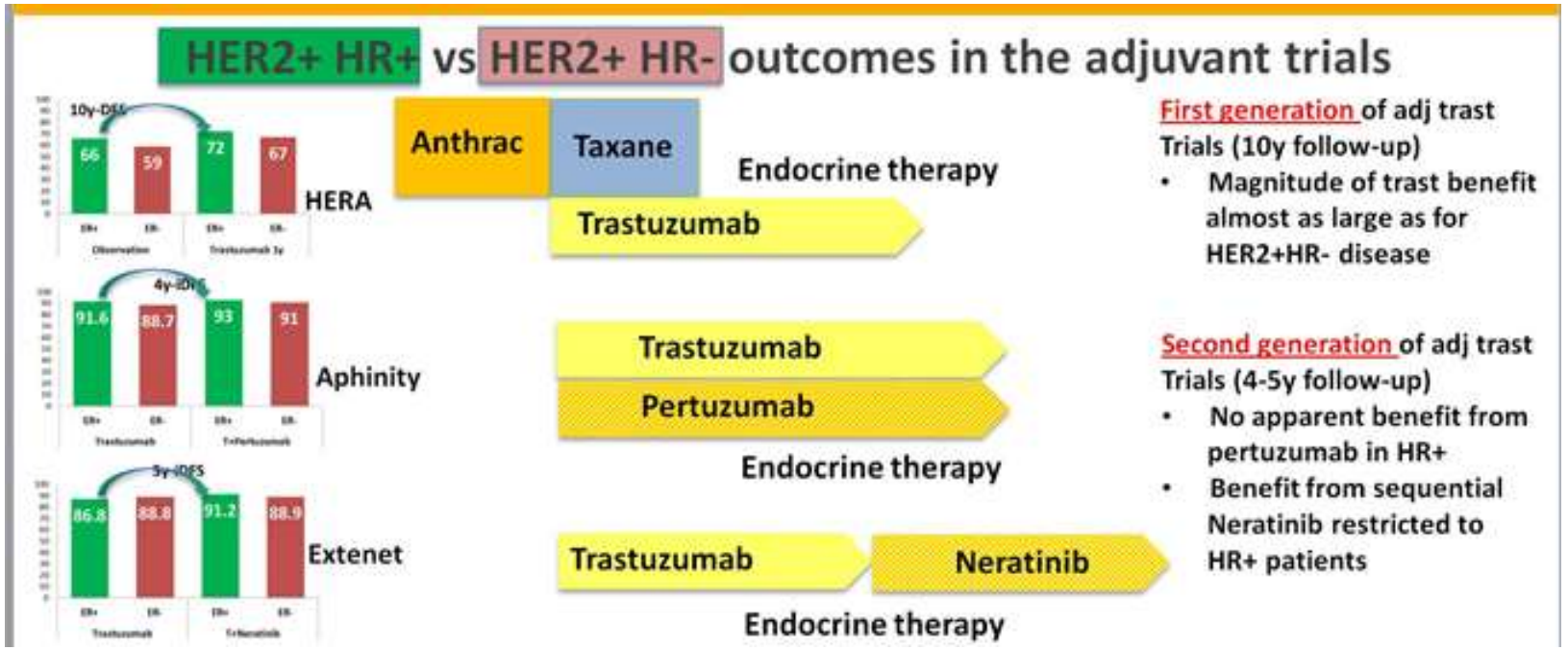
Adjuvant Trastuzumab Improves DFS and OS

Study	Follow-Up, Y	N	DFS HR	DFS *P* Value	OS HR	OS *P* Value
HERA[a-e] CT ± RT→H vs CT ± RT	1	3387	0.54	<.0001	0.76	.26
	2	3401	0.64	<.0001	0.66	.0115
	4	3401	0.76	<.0001	0.85	.1087
	8	3401	0.76	<.0001	0.76	.0005
	11	3401	0.76 Δ 6.8%	.0001	0.74 Δ 6.5%	<.0001
NCCTG N9831/ NSABP B-31[f-h] AC→TH→H vs AC→T	2	3351	0.48	<.0001	–	–
	4	4045	0.52	<.001	0.61	<.001
	8.4	4046	0.60 Δ 11%	<.0001	0.63 Δ 9%	<.0001
BCIRG 006[i,j] AC→TH→H vs AC→T	10	3222	0.72 Δ 6.7	<.0001	0.63 Δ 7.2	<.0001
TCH vs AC→T			0.77 Δ 5.1	.0011	0.76 Δ 4.6	.075

Standard of care: one year of treatment in setting (neo)adjuvant

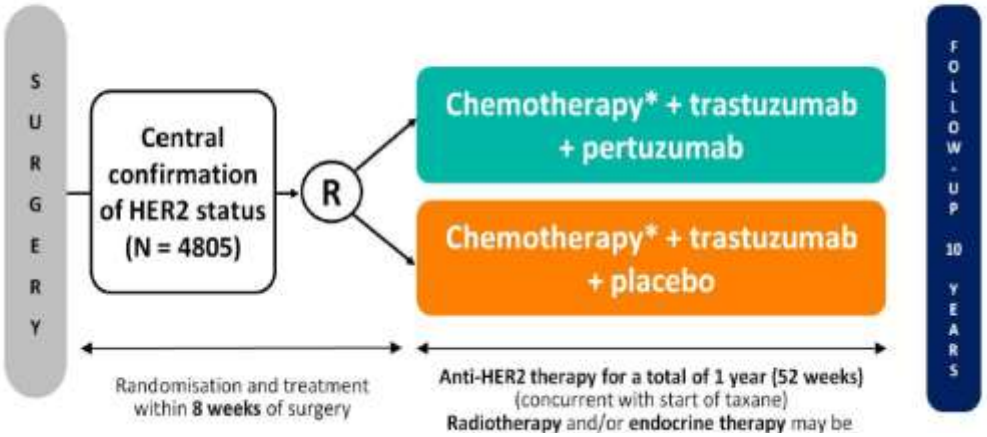
a. Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353(16):1659-1672; b. Smith I, et al. *Lancet.*2007;369(9555):29-36; c. Gianni L, et al. *Lancet Oncol.* 2011;12(3):236-244; d. Goldhirsch A, et al. *Lancet.*2013;382(9897):1021-1028; e. Cameron D, et al. *Lancet.* 2017;389(10075):1195-1205; f. Romond EH, et al. *N Engl J Med.* 2005;353(16):1673-1684; g. Perez EA, et al. *J Clin Oncol.* 2011;29(25):3366-3373; h. Romond EH, et al. Cancer Res. 2012;72(24 suppl): Abstract S5-5; i. Slamon D, et al. *N Engl J Med.* 2011;365(14):1273-1283; j. Slamon DJ, et al. *Cancer Res.* 2016;76(4 suppl): Abstract S5-04.

From here on: tryumph of incrementalism

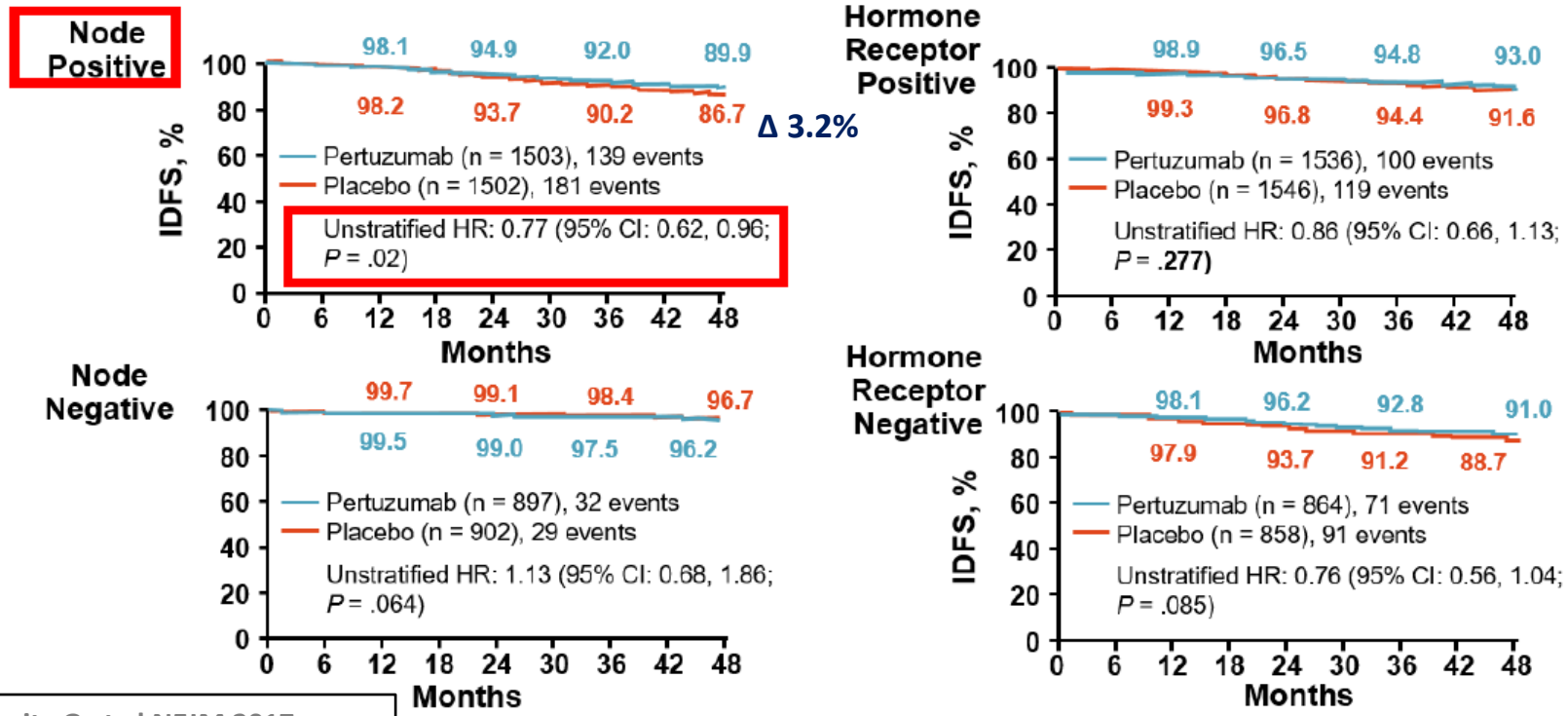


Not to mention Lapatinib, everolimus etc.

APHINITY: Trial Design



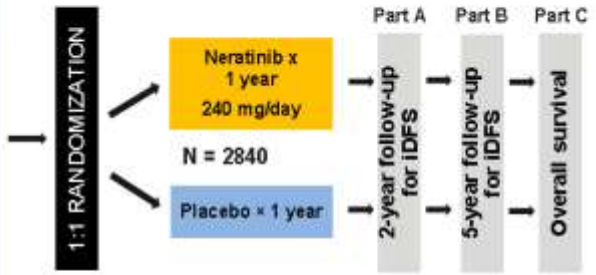
APHINITY: IDFS by Patient Subgroups



Von Minckwitz G et al NEJM 2017

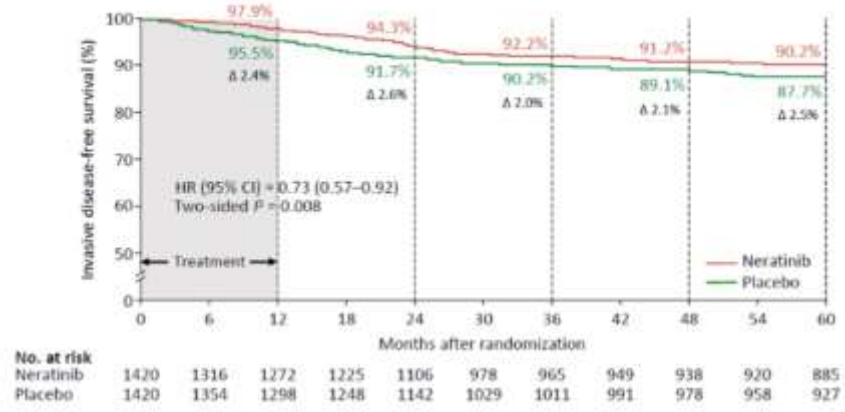
ExteNET: Study Design

- HER2+ breast cancer (local)
  - IHC 3+ or ISH amplification
- Prior adjuvant trastuzumab and chemotherapy
- Lymph node ± or residual invasive disease after neoadjuvant therapy
- ER/PR±

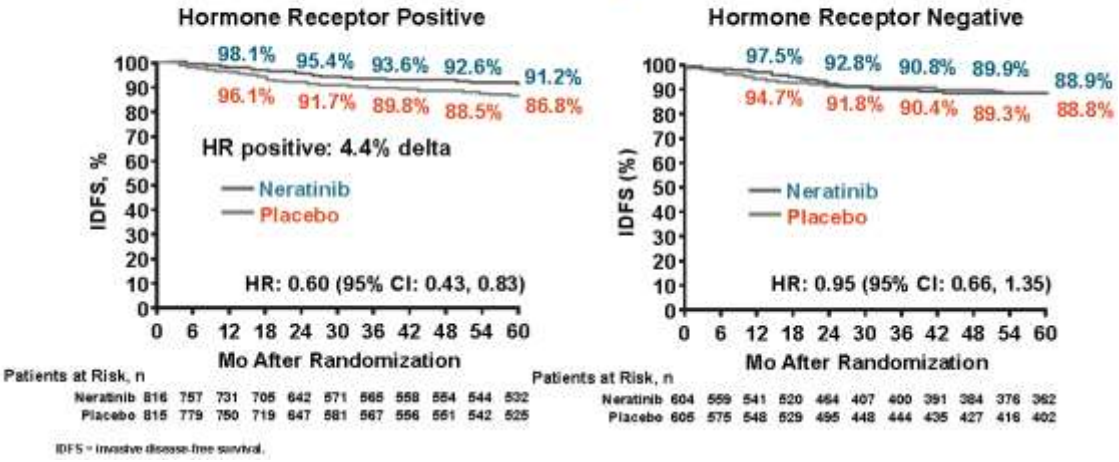


- **Primary endpoint:** iDFS
- **Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- **Other analyses:** biomarkers, health outcome assessment (FACT-B, EQ-5D)
- **Stratified by:** nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

5-year analysis: iDFS : ExteNET Trial

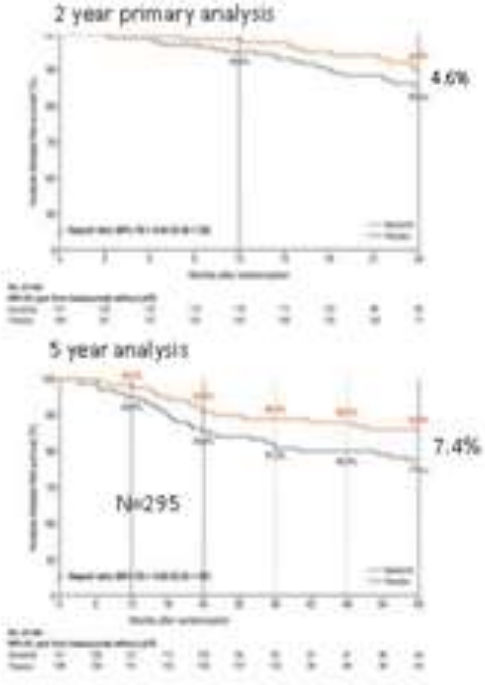


ExteNET: 5-Year IDFS Analysis by Hormone Receptor Status



IDFS = invasive disease-free survival.

Subset Analysis of the ExteNET Study: DFS in Patients With ER+ Disease who did not Achieve PCR[b]

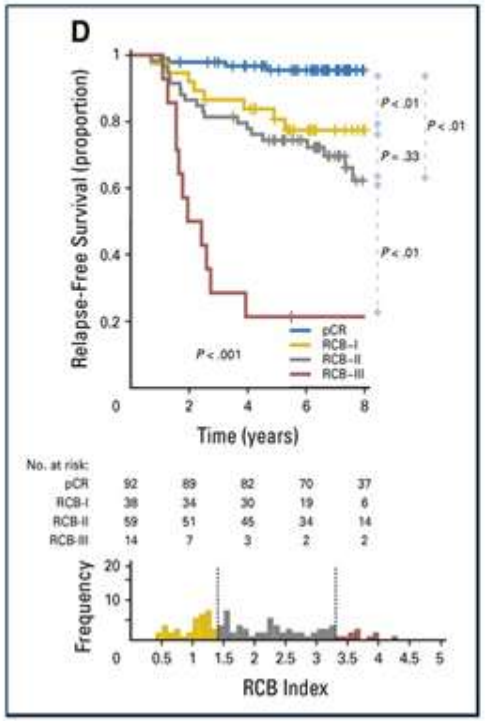


Effect due to treatment extension, or to effective HR and HER2 signaling co-targeting?

Martin M, et al. *Lancet Oncol*. 2017;18:1688-1700.

Risk stratification based on pCR after NAC

Outcomes for HER2+ BC treated with trastuzumab-based therapy



Symmans et al. JCO 2017

KATHERINE (NSABP B50, GBG 77)

- Centrally confirmed HER2-positive breast cancer
- Pathologic residual invasive tumor in breast or axilla

R 1:1

N=1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

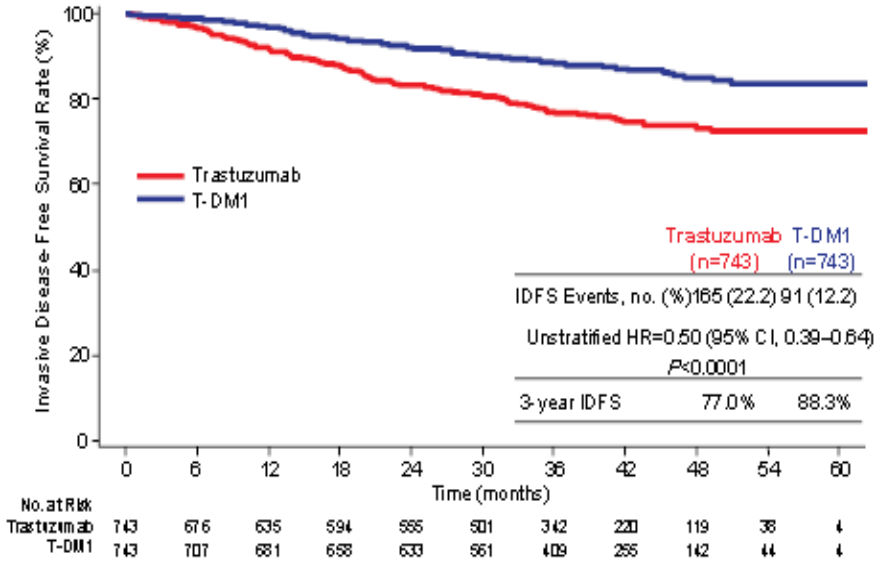
- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

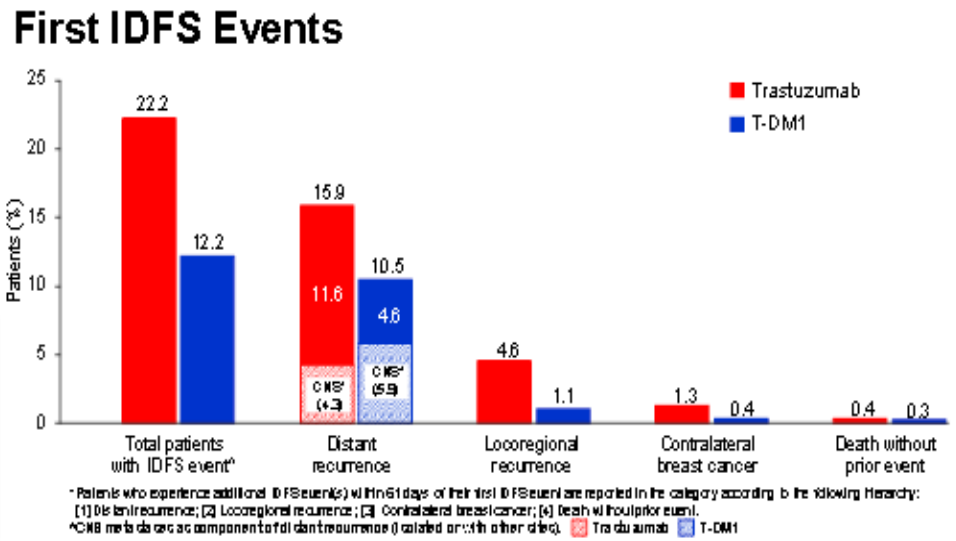
Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Risk stratification based on pCR after NAC

KATHERINE (NSABP B50, GBG 77)





The Standard of Care Has Changed!
T-DM1 should be recommended to the majority of patients with residual disease after a taxane-based neoadjuvant regimen

Geyer CE, et al. *Cancer Res.* 2018;79(10 Suppl): Abstract GS1-10; von Minckwitz G, et al. *N Engl J Med.* 2019;380(7):617-628.

We know How to Escalate
What about De-Escating?

- **The favorable outcomes of HER2 BC increases the importance of:**
  - **Risk stratification strategies to minimize over and under treatment**
  - **De-escalation strategies to potentially further reduce the toxicities of treatment**

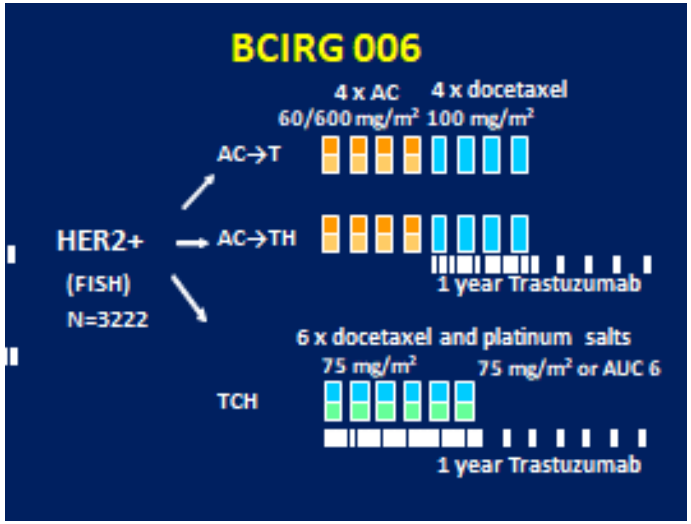
WHO?

- What risk stratification do we have?
  - Anatomic features
    - T, N
  - Molecular features
    - HR
    - HER2 levels
    - TILs
    - Intrinsic subtype

HOW?

- How can we de-escalating?
  - No anthra
  - Shorter duration Trastuzumab?
  - Minimizing chemotherapy?
  - Omission chemotherapy?
    - Treatment decision by Neoadjuvant results
- Biological considerations for de-escalation
  - HER2 enriched
  - TILs

Can we omit anthracyclines: the BCIRG 006 case



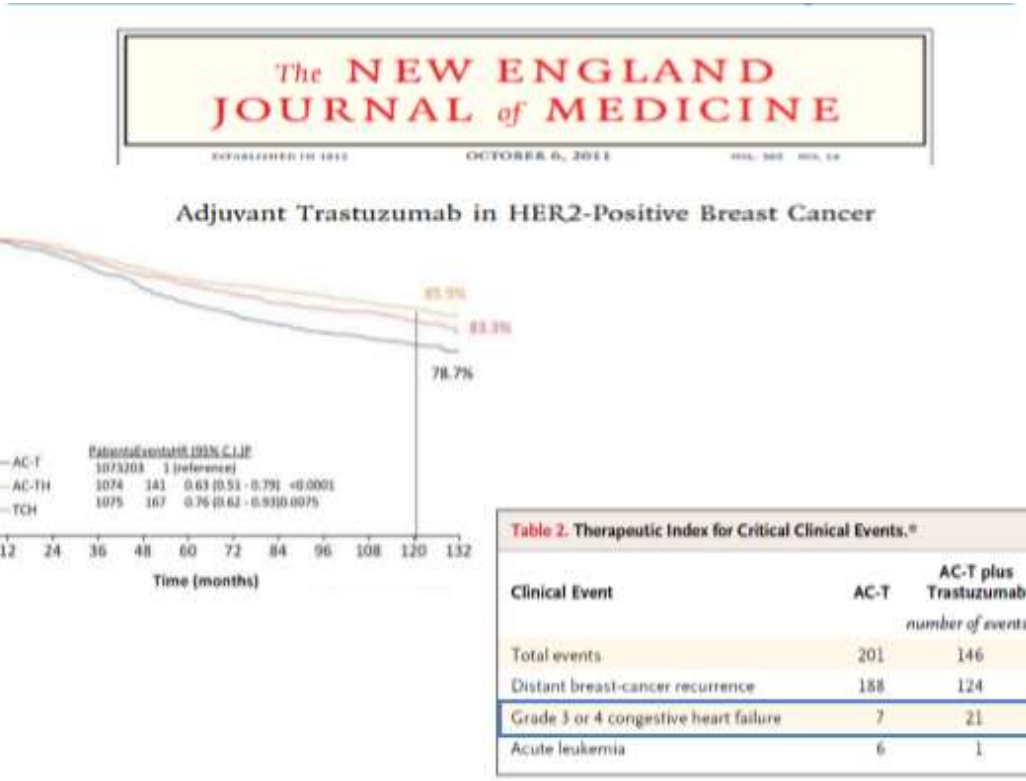


Table 2. Therapeutic Index for Critical Clinical Events.*

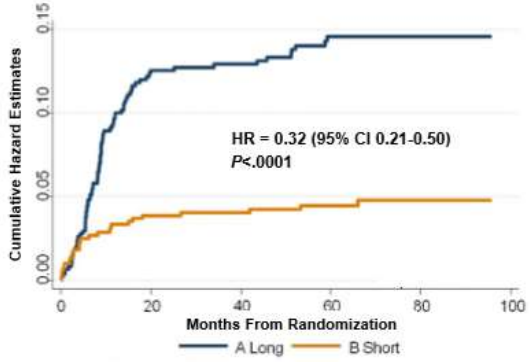
Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
	number of events		
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

Slamon et al , NEJM 2011&SABCS 2015

Shorter duration trastuzumab

Trials of Shorter Durations of Adjuvant Trastuzumab

Trial	Sample	Recruitment Time	Timing of randomization	Patient characteristics	Chemotherapy		Prespecified non inferiority margin	Results
					% A and T	% concomitant trastuzumab		
6 months vs 12 months								
PHARE (1)	3380	6 y	at 6 m	N- 55% ER+ 58%	74%	56%	1.15	DFS events at 2 y 8.9% vs 6.2% HR 1.28 (1.05-1.56)
HORG (2)	481	8 y	upfront	N- 21% ER+ 67%	100%	100%	1.53	DFS events at 3 y 6.7% vs 4.3% HR 1.57 (0.86-2.10)
PERSEPHONE (3)	4089	8 y	within first 6 m	N- 59% ER+ 69%	48%	47%	1.29	DFS events at 4 y 11.6% vs 11.2% HR 1.07 (0.93-1.24)
9 weeks vs 12 months								
SHORT-HER (4)	1253	9 y	upfront	N- 53% ER+ 68%	100%	100%	1.29	DFS events at 5 y 14.6% vs 12.5% HR= 1.15 (90% CI 0.91-1.46)
SOLD (5)	2176	9 y	upfront	N- 60% ER+ 66%	100%	100%	1.3	DFS events at 5 y 12% vs 9.5% HR 1,39 (90% CI 1.12-1.72)



Ok to use shorter duration trastuzumab if cardiac RF, in frail pts, in case of intollerance

1.Earl HM, et al. J ClinOncol. 2018;36(suppl): Abstract 506. 2. Pivot X, et al. Lancet Oncol.2013;14(8):741-748. 3. Pivot X, et al. Eur J Cancer. 2015;51(13):16601666.4. Joensuu H, et al. JAMA Oncol. 2018 [Epubahead of print]. 5. Conte PF, et al. Ann Oncol. 2018 Sep 13. [Epubahead of print]. 6. MavroudisD, et al. Ann Oncol. 2015;26(7):1333-1340.

Minimizing chemotherapy

Docetaxel/Cyclophosphamide/Trastuzumab

Stage I-II Breast Cancer HER2+ → Docetaxel Cyclophosphamide Trastuzumab → x 4 → Trastuzumab

	Patients (N=493)
Age (years)	55 (24-75)
ECOG performance status	
0	431 (87·4%)
1	62 (12·6%)
Stage at diagnosis	
I	284 (57·6%)
II	203 (41·2%)
III	6 (1·2%)
Positive nodes	
None	391 (79·3%)
1–3	96 (19·5%)
≥4	6 (1·2%)
Tumour size (cm)	
≤0·5	17 (3·4%)
0·5–1·0	90 (18·3%)
1·1–2·0	224 (45·4%)
2·1–5·0	162 (32·9%)
Oestrogen receptor status	
Negative	173 (35·1%)
Positive	320 (64·9%)
Progesterone receptor status	
Negative	260 (52·7%)
Positive	233 (47·3%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.

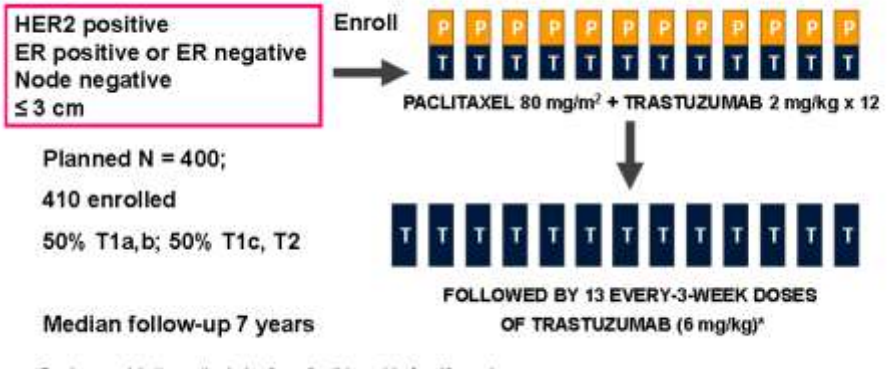
Table 1: Baseline characteristics

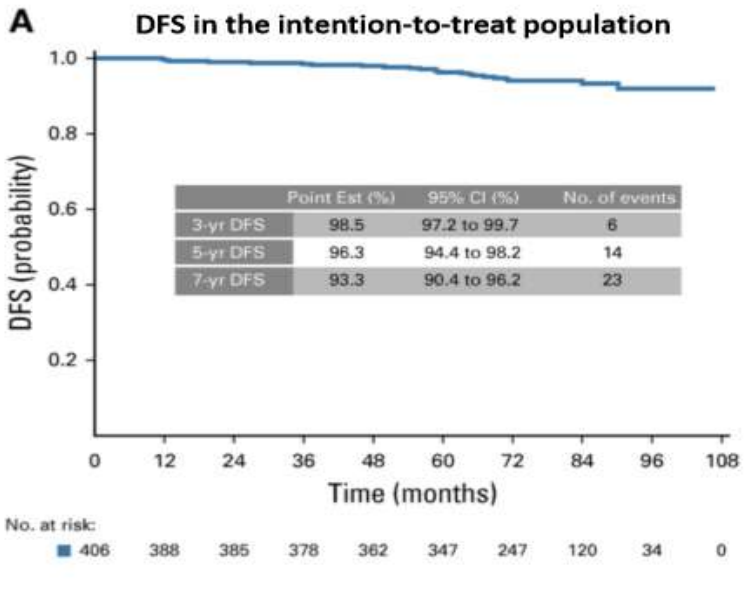
	2-year DFS	3-year DFS
All patients (n=493)	97·8% (96·0–98·8)	96·9% (94·8–98·1)
Node status		
Node positive (n=102)	96·9% (90·7–99·0)	93·5% (86·2–97·1)
Node negative (n=391)	98·1% (96·0–99·1)	97·8% (95·6–98·9)
≤1·0 cm node negative (n=95)	100%	100%
Tumour size		
≤1·0 cm (n=107)	100%	100%
1·1–2·0 cm (n=224)	98·1% (95·0–99·3)	96·5% (92·8–98·3)
>2·0 cm (n=162)	96·0% (91·3–98·2)	95·2% (90·2–97·7)

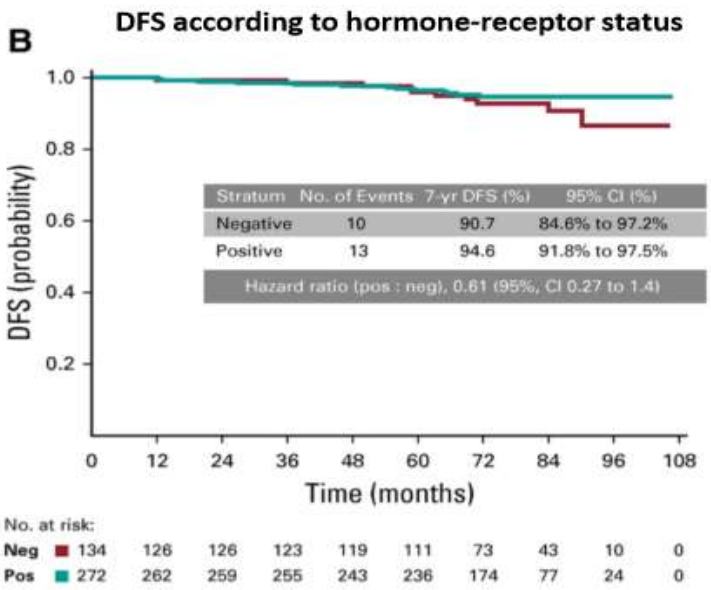
Jones et al Lancet Oncol 2013

Minimizing chemotherapy

Adjuvant Paclitaxel and Trastuzumab (APT)







Tolaney SM, et al. N Engl J Med. 2015;372(2):134-141

Tolaney SM et al Journal of Clinical Oncology April 2, 2019

Minimizing chemotherapy

Adjuvant Paclitaxel and Trastuzumab (APT)

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nelle donne con carcinoma mammario operato HER2 positivo, diametro tumorale <3 cm, con linfonodi ascellari negativi o con al massimo un linfonodo ascellare micrometastatico confermato dopo dissezione ascellare completa, può essere considerato uno schema con paclitaxel 80 mg/mq/settimana con trastuzumab concomitante, proseguito poi fino al completamento di un anno di trattamento	Positiva debole

DFS Event: 7 Years	N (%)	Time to Event, Months
Any recurrence or death	23 (5.7)	
Local/regional recurrence*	5 (1.2)	
Ipsilateral axilla (HER2 positive)		12, 20, 54
Ipsilateral breast (HER2 positive)		37, 65
New contralateral primary breast cancer	6 (1.5)	
HER2 positive		56
HER2 negative		12, 37, 59
Unknown HER2		84, 90
Distant recurrence*	4 (1.0)	27, 46, 59, 63
Death		
Non–breast cancer related	8 (2.0)	13, 50, 59, 65, 67, 69, 71, 71

Characteristic	All Treated Patients (N = 406)
Age group, years	
< 50	132 (33)
50-59	137 (34)
60-69	96 (24)
≥ 70	41 (10)

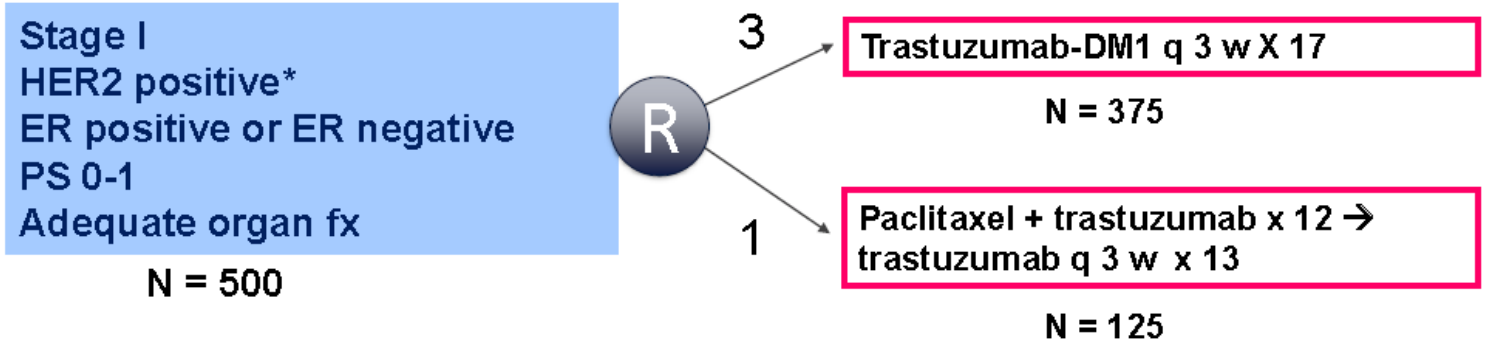
Size of primary tumor, cm	
T1mi (≤ 0.1)	9 (2)
T1a (0.1 to ≤ 0.5)	68 (17)
T1b (> 0.5 to ≤ 1.0)	124 (31)
T1c (> 1.0 to ≤ 2.0)	169 (42)
T2 (> 2.0 to ≤ 3.0)	36 (9)

Histologic grade	
I: Well differentiated	44 (11)
II: Moderately differentiated	131 (32)
III: Poorly differentiated	228 (56)
Unknown	3 (1)

Unknown	1 (< 1)
HR status	
Positive	272 (67)
Negative	134 (33)

TolaneySM, et al. *N Engl J Med.*2015;372(2):134-141;
TolaneySM, et al. *J Clin Oncol.* 2019 Apr 2.

ATEMPT Trial Schema



Results anticipated later this year

PI: Sara Tolaney, MD, MPH

Omitting chemotherapy

RESPECT TRIAL: HER2-positive elderly patient
Age: 70 - 80 years old
Stage: I (pT>0.5cm), IIA, IIB, IIIA / M0

Stratification Factors for Randomization
1. Age at registration: 70-75/76-80
2. PS: 0/1
3. Hormone receptor status*: +/
4. Pathological nodal status: +/-
5. Institution

*>10% positive by IHC method

Randomization

Trastuzumab monotherapy
Trastuzumab (1 year)

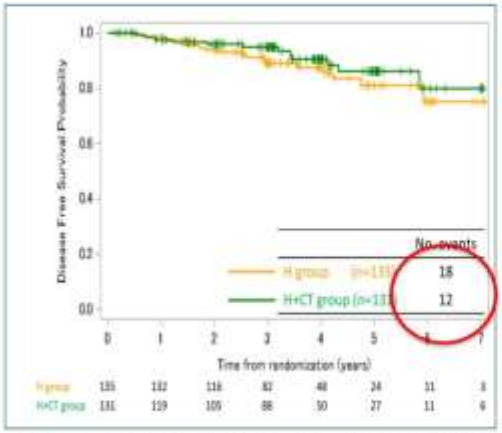
Trastuzumab + Chemotherapy
Trastuzumab (1 year) + Chemotherapy
(Investigator's choice from
PTX/DTX/AC/EC/FEC/CMF/TC/TCbH)

Primary endpoint: Disease-free Survival
Secondary endpoints: OS, RFS, AEs, HRQOL, comprehensive geriatric assessment (CGA), cost-effectiveness (utility)

Sawaki et al, ASCO 2018

In cases of contraindications for ChT or patient refusal, it is acceptable to offer the combination of targeted agents(ET and trastuzumab)

Primary Endpoint of DFS: Not Achieved



DFS at 3 years was 94.8% in H+CT group vs 89.2% in H group (HR=1.42; 95% CI, 0.68 to 2.95, P=0.35)
The difference in RMST between arms at 3 years was -0.45 months (95% CI, -1.71 to 0.80)

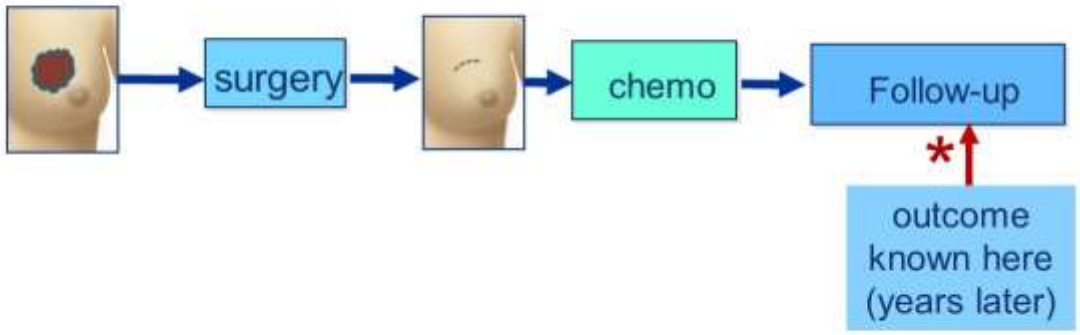
STATISTICS:
required numbers of events =120
No pts= 260
power of 80% for a 95% (CI) with a HR of H to H+CT not to exceed 1.69

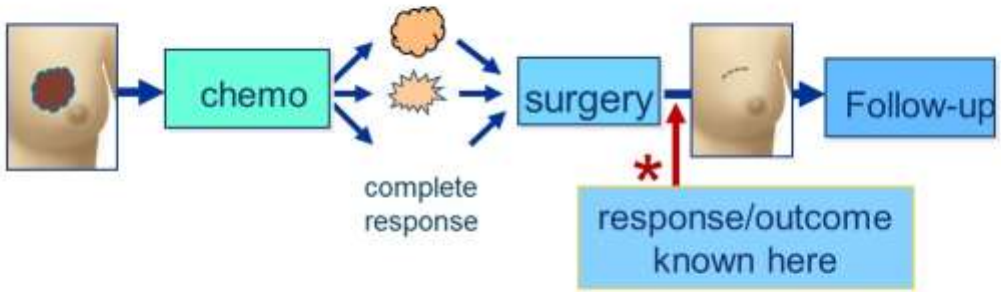
RESULTS:
A blinded interim analysis showed that the number of events was much fewer than expected, and the statistical power of the non-inferiority test based on HR was not assured.
Hence, restricted mean survival time (RMST) was calculated as a supplementary endpoint for interpreting the relative benefit of H

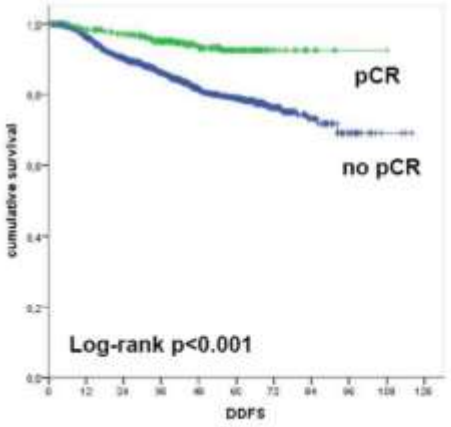
Sawaki et al, ASCO 2018

The «Neoadjuvant approch» to chemotherapy de-escalation: Leveraging pCR to decision making

Paradigm Shift: Moving to the Neoadjuvant setting







Von Minckwitz et al, JCO 2012

Presented By Matthew Goetz at 2019 ASCO Annual Meeting

Leveraging pCR

CompassHER2-pCR: De-escalation if pCR after preoperative THP (EA1181)
CompassHER2-RD: Optimizing treatment in residual HER2+ disease (A011801)

CompassHER2 *Schemas*

CompassHER2-pCR (preop and postop pCR)

Eligibility
.HER2+ breast ca
.Stage II/III3a
(T2-3, N0-2)
Newly diagnosed, no prior therapy

Registration

EA1181 preop
THP x 4 (12 weeks)
pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

Research biopsy

Surgery

EA1181 if pCR (~40%)
Complete 1y of HP
with no further chemo

CompassHER2-RD (postop non-pCR)

A011801 if RD (~60%)

Group 1: if preop THP -> AC, Cb/HP x 4
Group 2: if preop TCHP or AC-THP -> no further chemo

Eligibility
.HER2+ RD
.Any ER-
.if ER+ must be N+
(~30% of A011801 patients expected to come from EA1181)

Registration

R

T-DM1 x 14 doses

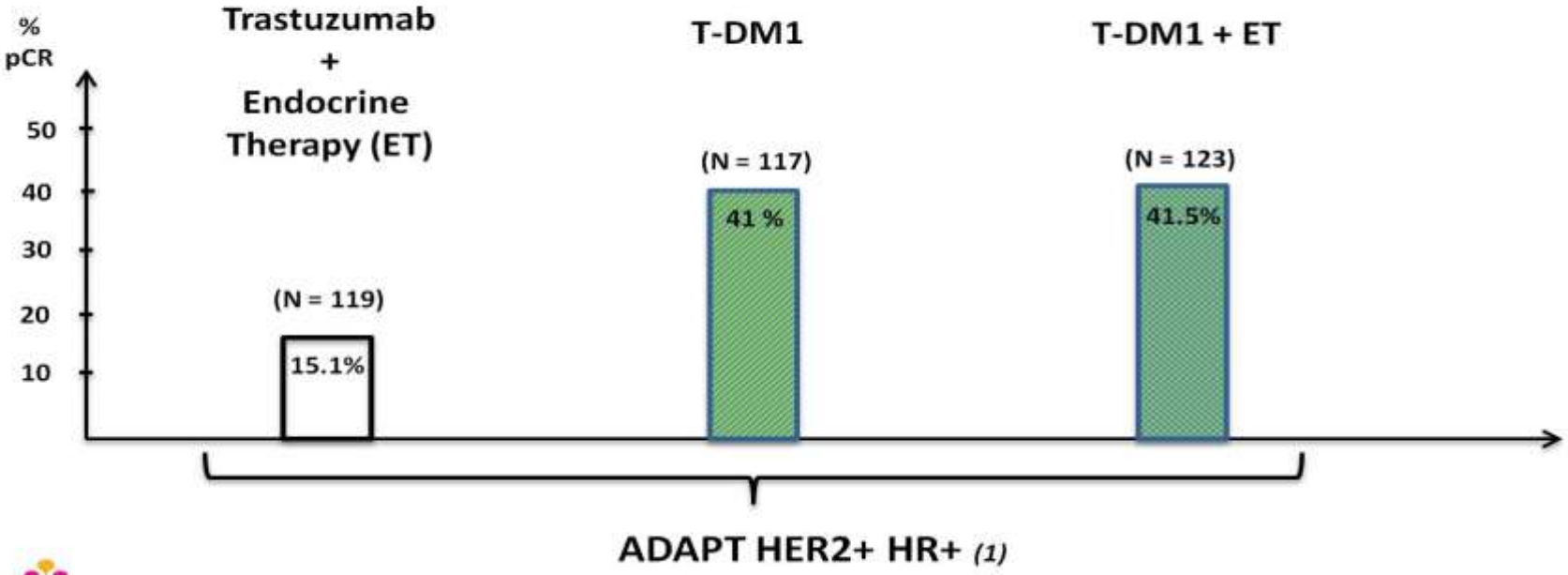
T-DM1/tucatinib x 14 doses

CompassHER2-pCR: (EA1181) (PI N. Tung)
CompassHER2-RD: (A011801) (PI: C. O'Sullivan

Presented By Matthew Goetz at 2019 ASCO Annual Meeting

Omitting chemotherapy

Neoadjuvant trial comparing single HER2 blockade + endocrine therapy to TDM1 (± endocrine therapy) in HER2+ HR+ disease



(1) Harbeck N. et al, JCO 2017

Omitting chemotherapy

Neoadjuvant Dual HER2-Targeted Therapy without Chemotherapy

Study	Phase	PTS	HER2-Targeted therapy	Concomitant Endocrine therapy	Duration (weeks)	pCR	pCR ER positive	pCR ER negative
NeoSphere	II	107	T+P	No	16	17%	6%	29%
TBCRC006	II	64	T+L	Yes	12	27%	21%	36%
TBCRC023	II	33	T+L	Yes	12	12%	9%	20%
		61	T+L	Yes	24	28%	33%	18%
PAMELA	II	150	T+L	Yes	18	31%	18%	43%
TBCRC026	II	88	T+P	No	12	34%	NA	34%

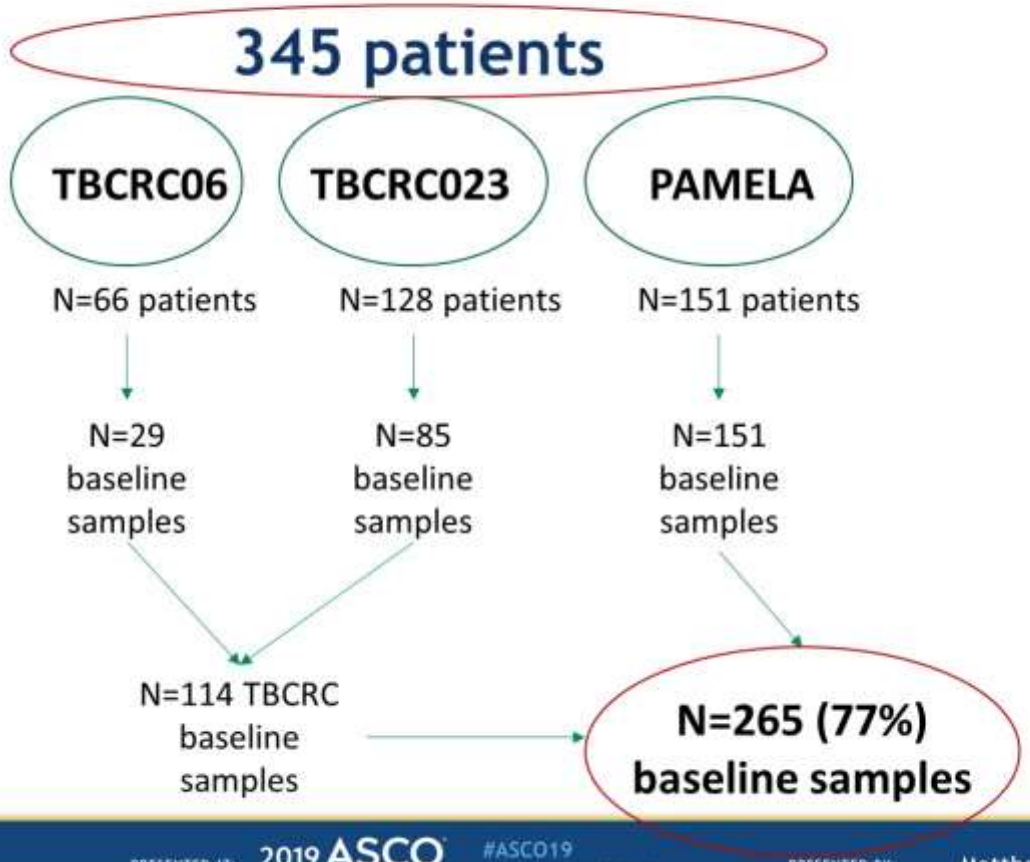
Slide courtesy of Mo Rimawi

L, L; P, P; pCR, pathological complete response; T, T

Presented By Matthew Goetz at 2019 ASCO Annual Meeting

Can we identify «super-sensitive» tumors?

TBCRC06/023/PAMELA COMBINED COHORTS



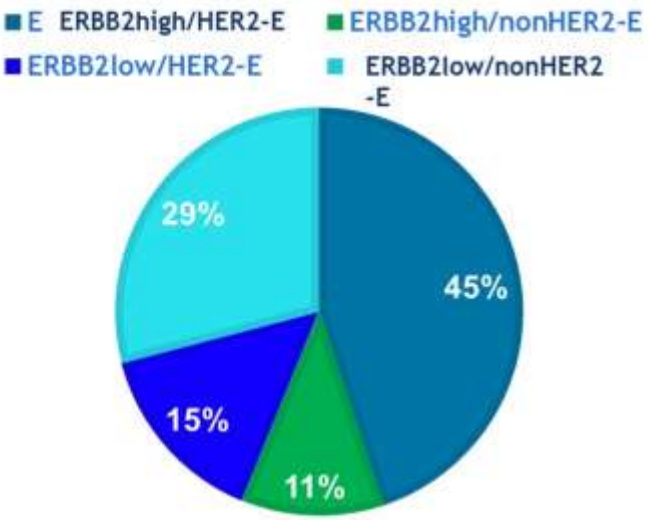
MAIN CLINICAL PATHOLOGICAL FEATURES (N=265)		
Tumor stage		
T1-2	201	76%
T3-T4	64	24%
Clinical Nodal status		
Negative	160	60%
Hormone receptor		
Positive	147	55%
Menopausal status		
Post-menopausal	155	58%
Breast pCR rate	70	26%

Prat et al. JNCI, 2019

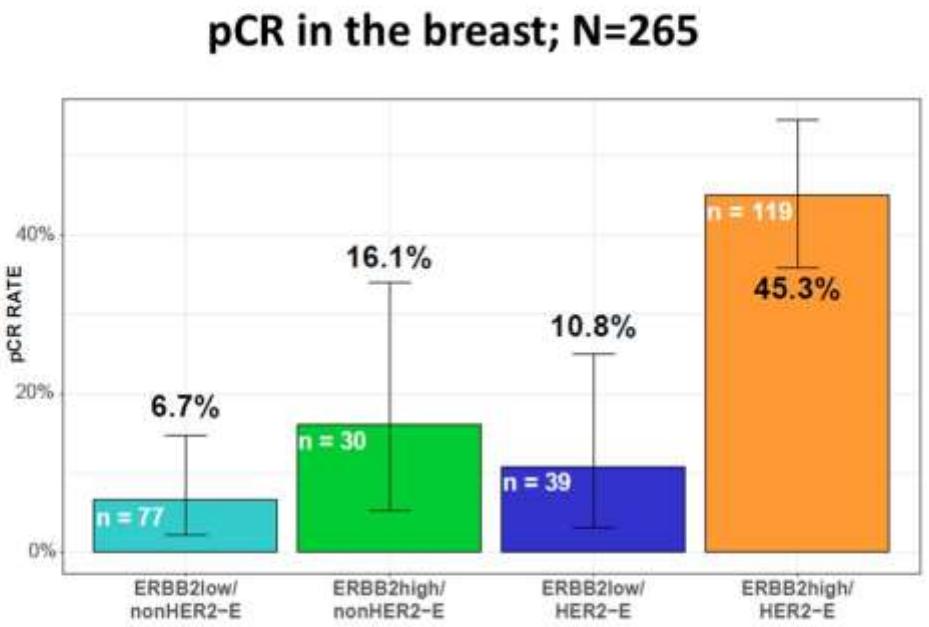
Presented By Matthew Goetz at 2019 ASCO Annual Meeting

Can we identify «super-sensitive» tumors?

HER2-E/ERBB2-high combined biomarker vs pCR



Prat et al. JNCI, 2019

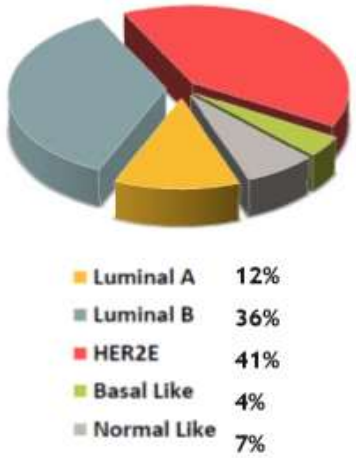


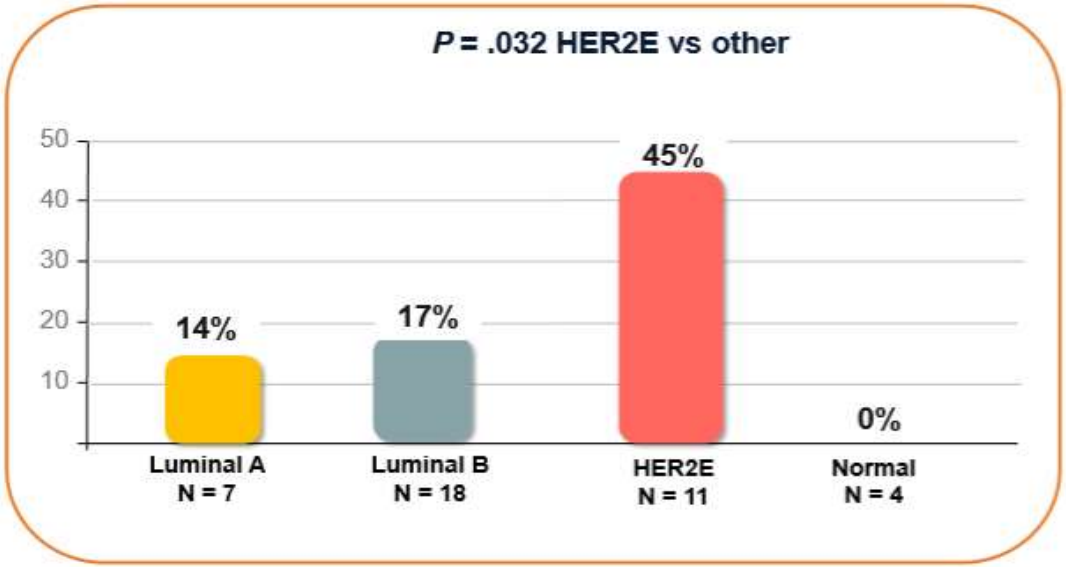
Odds Ratio for HER2-E/ERBB2-high group achieving a pCR (compared to other groups 6.0 (95% CI 3.1-11.8; p<0.001)

PerElisa Study Plan

Investigator-driven, nonprofit study. EUDRACT 2013-002662-40

PAM50 and pCR in Molecular Responders





HER2E, HER2 enriched

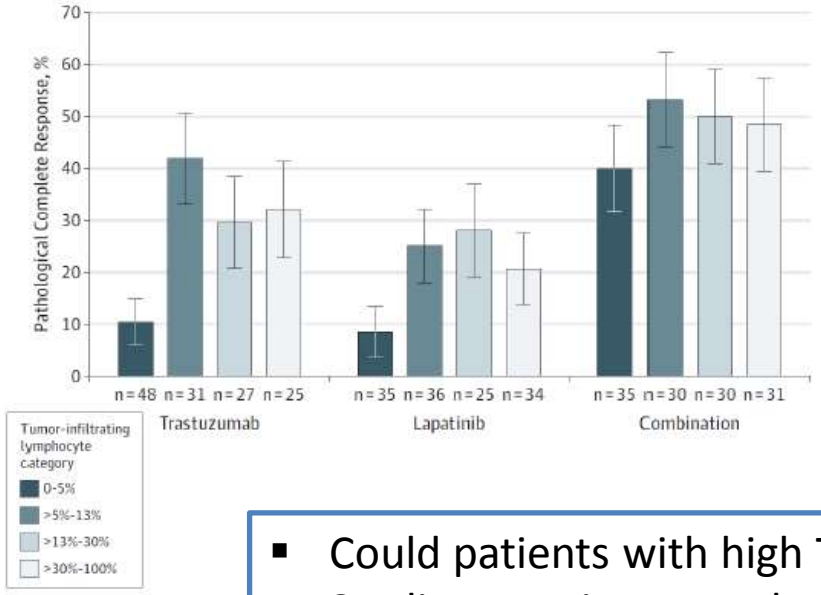
Guarneri V, et al. *J Clin Oncol.* 2018;36(Suppl): Abstract 507.

Can Incorporation of TILs Help De-Escalate Therapy?

Low TILs Associated With Low pCR

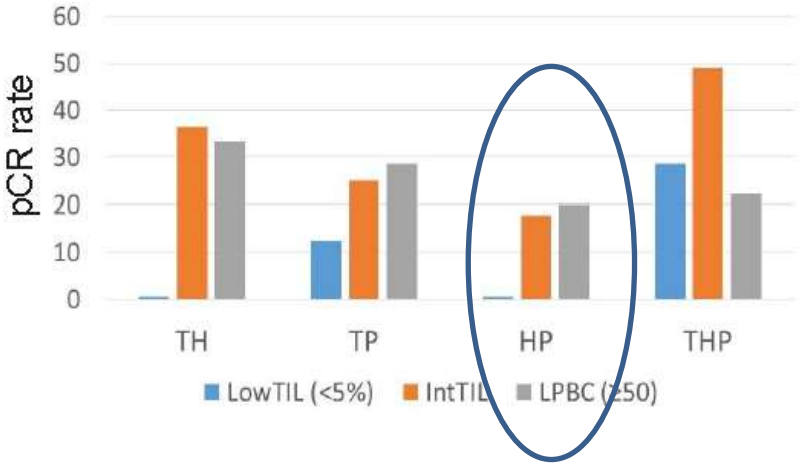
NeoALTTO (n = 387)

Salgado R, et al. *JAMA Oncol*. 2015;1448-1454.



NeoSphere (n = 243)

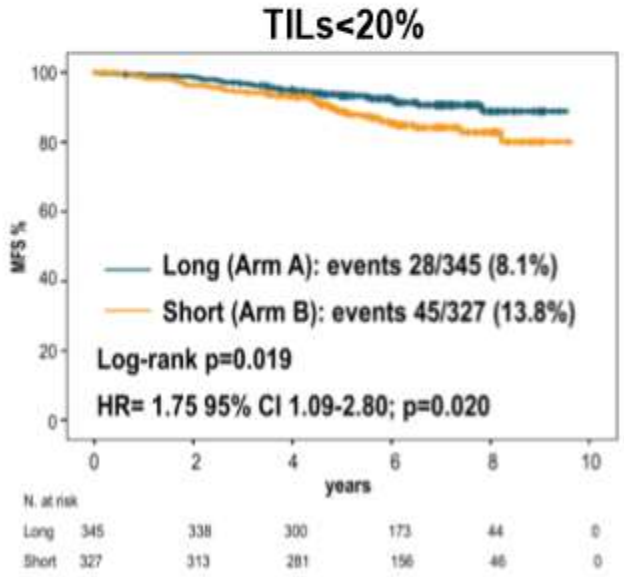
Bianchini G, et al. *Ann Oncol*. 2015;26:2429-2436.

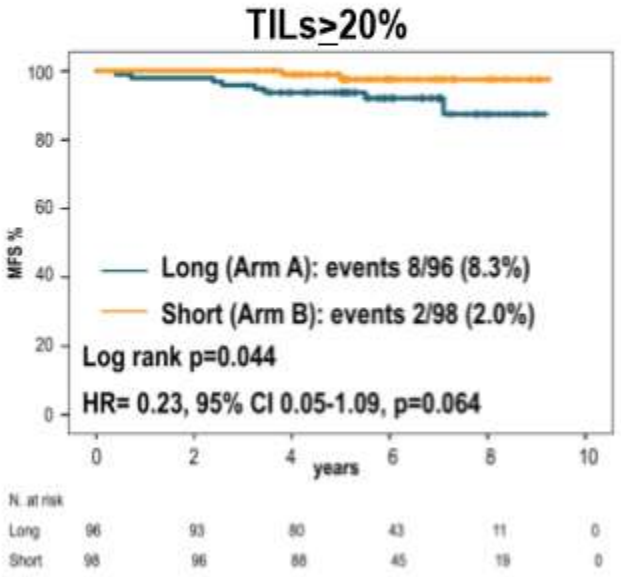


- Could patients with high TILs receive less aggressive therapy?
- Studies ongoing to evaluate immune checkpoint inhibition plus HER2-targeted therapy

TILS Interaction With Treatment ARM in Short-HER2 trial

TILs 10% incr	MFS HR	95% CI	interaction p
Long (Arm A)	0.89	0.71-1.12	
Short (Arm B)	0.60	0.41-0.88	0.088





Interaction p=0.015

Dieci MV ESMO 2018

Final considerations

- A risk-driven approach is the best way for treatment optimization in HER2+ disease
- In patients at higher risk of relapse, the addition of pertuzumab or neratinib should be considered
- 1 yr trastuzumab plus chemotherapy remains standard of care for many patients at low and intermediate risk of relapse
- Treatment de-escalation is of value for a proportion of real-world patients at low risk of relapse
- Is there still a role for anthracycline in regimens of the future?
  - With another active agent in early disease, anthracyclines become less appealing
- Risk stratification based on pCR after NAC allows for a more personalized treatment and a more rational resource allocation

Roadmap for the adjuvant treatment of EBC

Adjuvant

Low Risk:	Intermediate risk:	High risk:
T< 1 cm N0 ER-/ER+ T≤ 2 cm N0 (>ER+)	Larger T ER +/ LN negative or (1-3)	Larger T/N (> 4) and/or ER-
APT wPaclitaxel + Trastuzumab	Longer chemo (anthra) + Trastuzumab	Chemo + Trastuzumab + Pertuzumb*
		Consider neratinib in ER+

*no-refundable in Italy