2014 San Antonio Breast Cancer Symposium Review

HER2-Positive Disease

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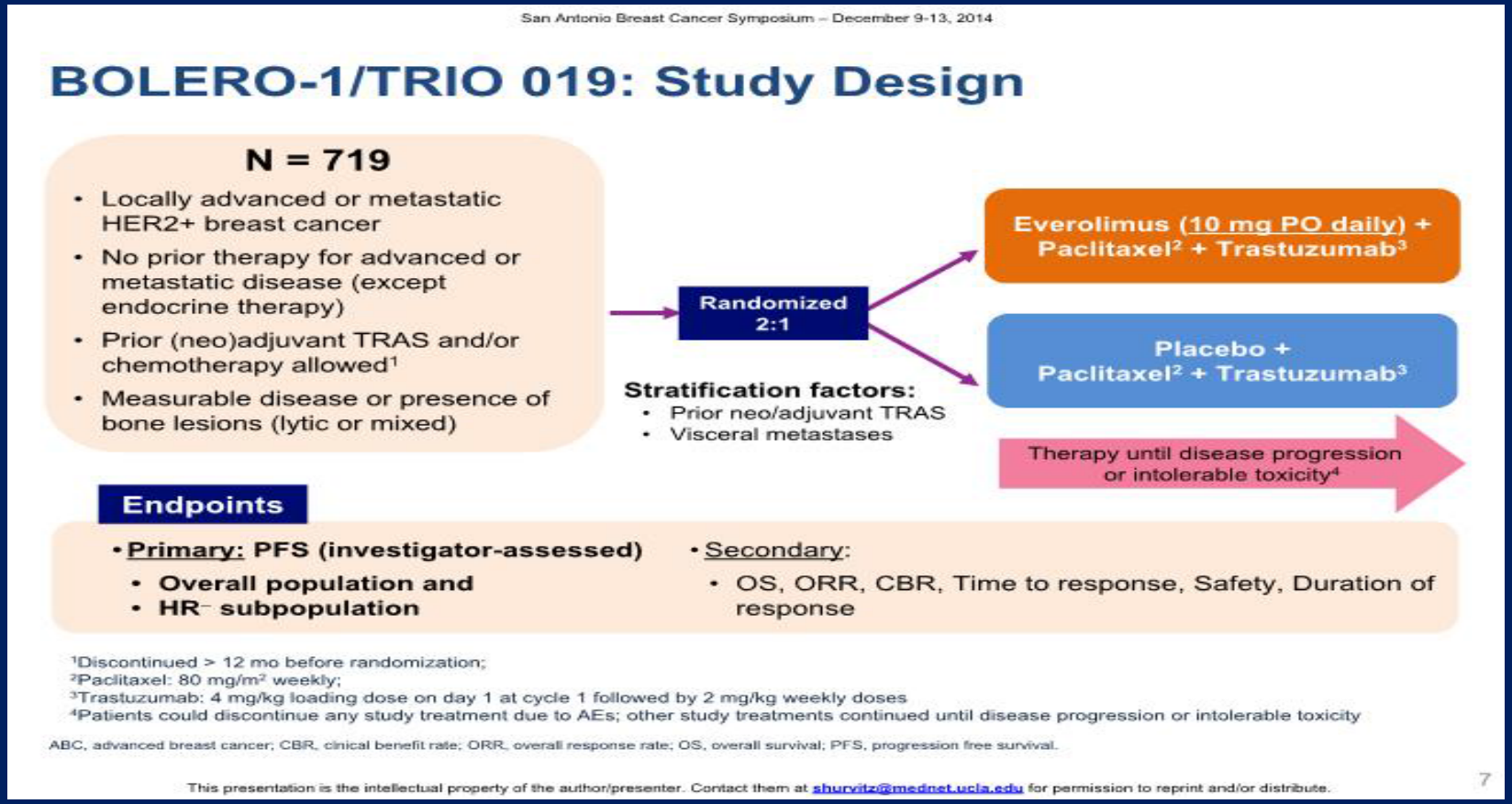
S6-01 Phase 3, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and paclitaxel as first-line therapy in women with HER2+ advanced breast cancer: BOLERO-1

S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

- Clinical rationale
  - Hyperactivation of the PI3K/AKT/mTOR pathway can lead to resistance to HER2-targeted therapies
  - Everolimus, an mTOR inhibitor, has activity in HER2+ advanced BC in preclinical and clinical studies

Hurvitz, et al. SABCS 2014

S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1



To prospectively validate hypothesis of differential efficacy of everolimus in ER-negative ds, study amended 3/2014 to include PFS in ER-negative subpopulation as 2nd primary objective

S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Patient Disposition

Disposition/Reason	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 480) %	PBO + TRAS + PAC (N = 239) %	EVE + TRAS + PAC (N = 208) %	PBO + TRAS + PAC (N = 103) %
Randomized	100	100	100	100
Treated	98	100	99	100
Protocol therapy ongoing	10	11	14	13
Study discontinued due to				
Disease progression	51	65	43	65
Consent withdrawal	13	13	16	14
Adverse event(s)	12	4	14	4
New cancer therapy	5	3	5	3
Administrative problems	3	3	5	2
Death	3	0	1	0
Protocol deviation	1	1	1	0
Lost to follow-up	<1	0	0	0
Abnormal test results	<1	0	0	0

EVE, Everolimus; HR, hormone receptor; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

Hurvitz, et al. SABCS 2014

S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Baseline Characteristics

Characteristic	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 480) %	PBO + TRAS + PAC (N = 239) %	EVE + TRAS + PAC (N = 208) %	PBO + TRAS + PAC (N = 103) %
Median age, years (range)	54 (23 - 86)	52 (19 - 82)	56 (29 - 85)	53 (24 - 82)
Race				
Caucasian	45	41	46	38
Asian	41	44	41	46
Black	5	5	5	6
Native American	1	0	1	0
Other	8	11	7	11
ECOG performance status				
0	58	62	61	63
1	42	38	39	37
Extent of disease at study entry				
Locally advanced disease	7	7	8	8
Metastatic disease	93	93	92	92
Hormone receptor status				
HR+ (ER+ and/or PgR+)	57	57	0	0
HR– (ER- and PgR-)	43	43	100	100
Visceral involvement	70	71	65	70
Lung	45	43	43	41
Liver	37	46	33	49
Lung and liver	15	21	14	20
Bone involvement	44	49	33	45

EVE, Everolimus; HR, hormone receptor; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

Hurvitz, et al. SABCS 2014

S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Prior Antineoplastic Therapy

Characteristic	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 480) %	PBO + TRAS + PAC (N = 239) %	EVE + TRAS + PAC (N = 208) %	PBO + TRAS + PAC (N = 103) %
(Neo)adjuvant trastuzumab	11	10	11	13
(Neo)adjuvant chemotherapy	45	52	39	52
Any taxane	24	27	25	25
Anthracyclines	39	47	34	50
Other chemotherapy	40	46	36	50
Hormonal therapy for HR+ disease	25	23	N/A	N/A
(Neo)adjuvant	19	20		
Metastatic only	1	<1		
Both (Neo)adjuvant and metastatic	5	3		
Radiotherapy	36	41	26	39
Surgery	100	100	100	100

EVE, Everolimus; HR, hormone receptor; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

Hurvitz, et al. SABCS 2014

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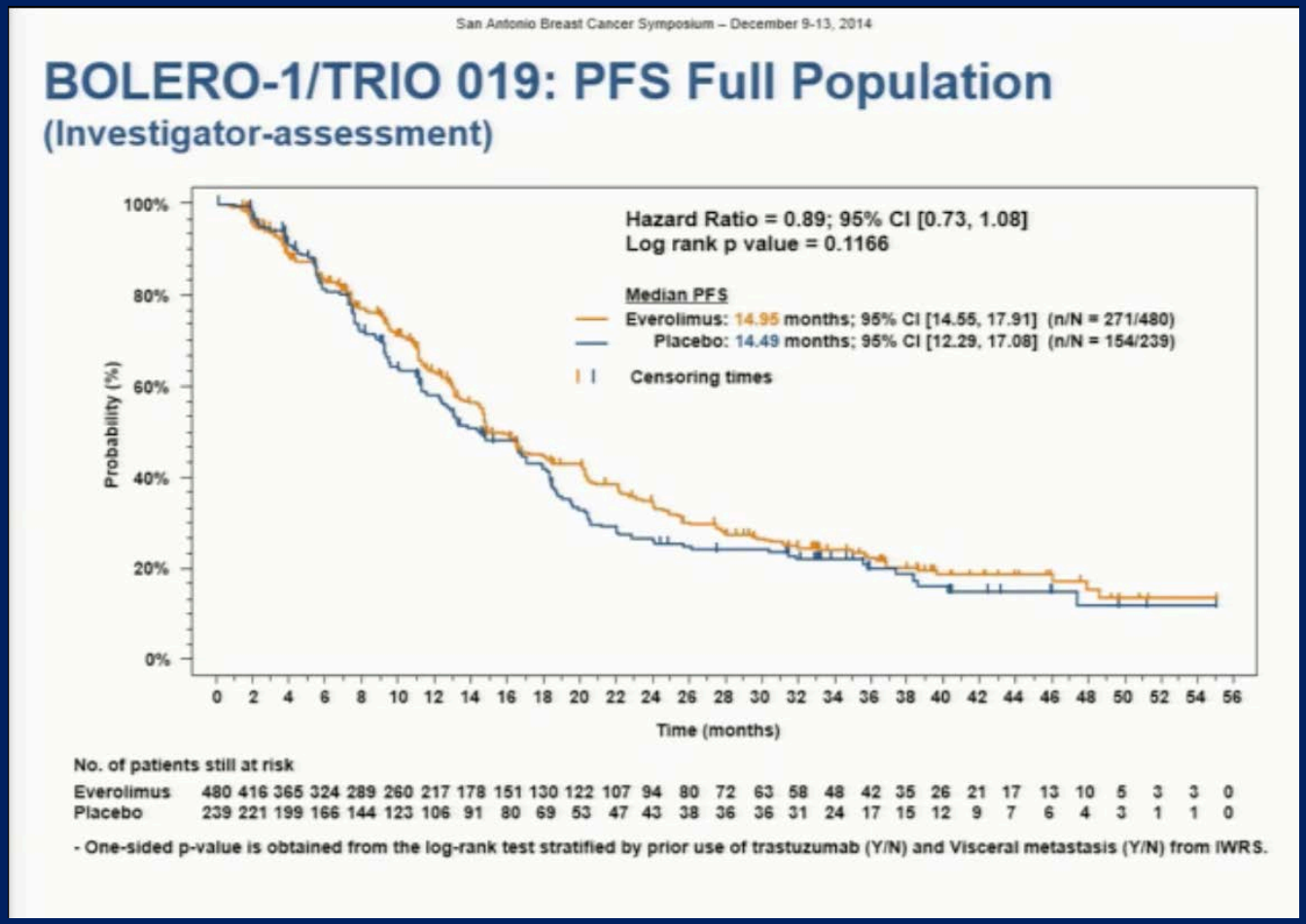

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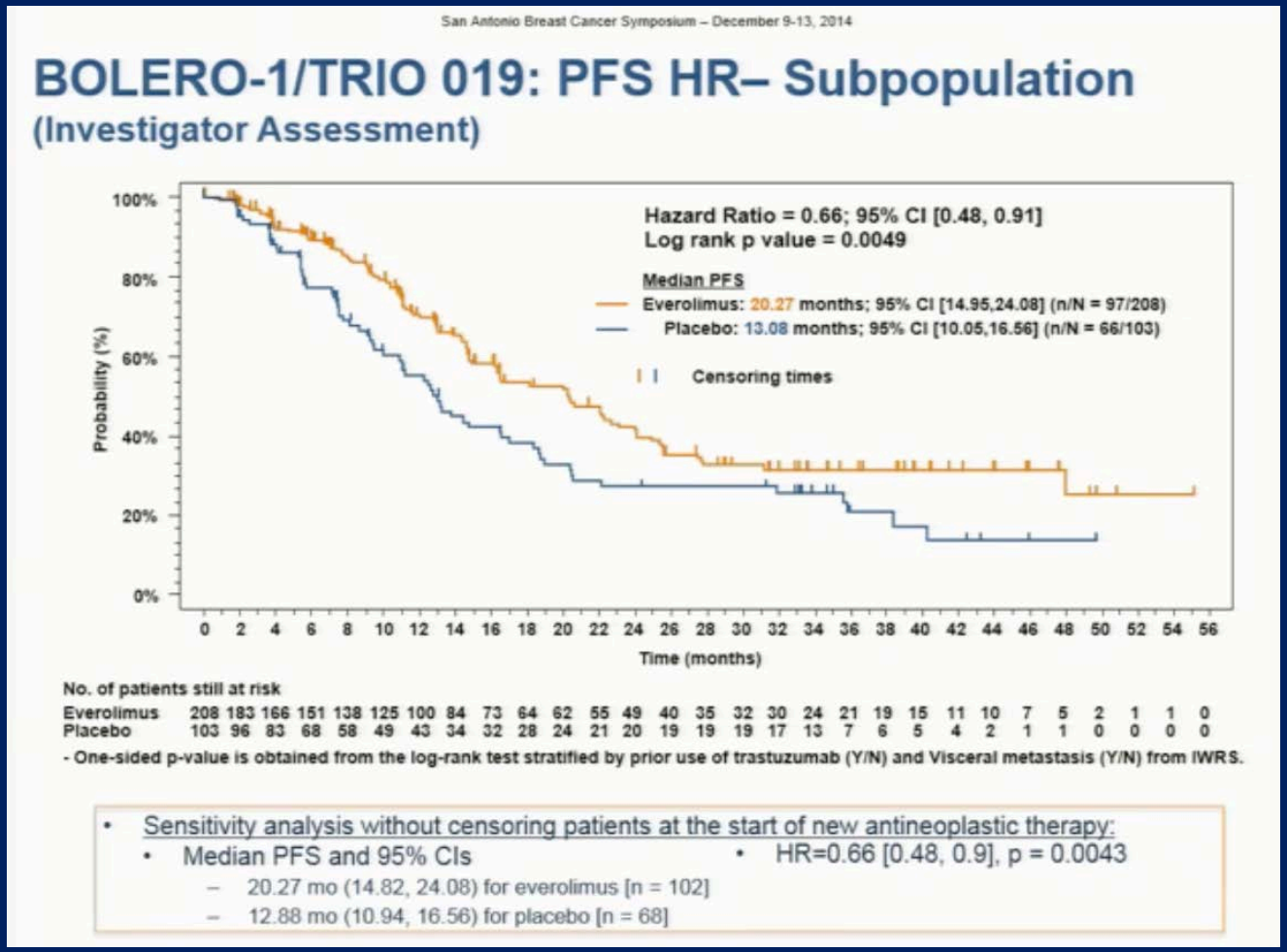

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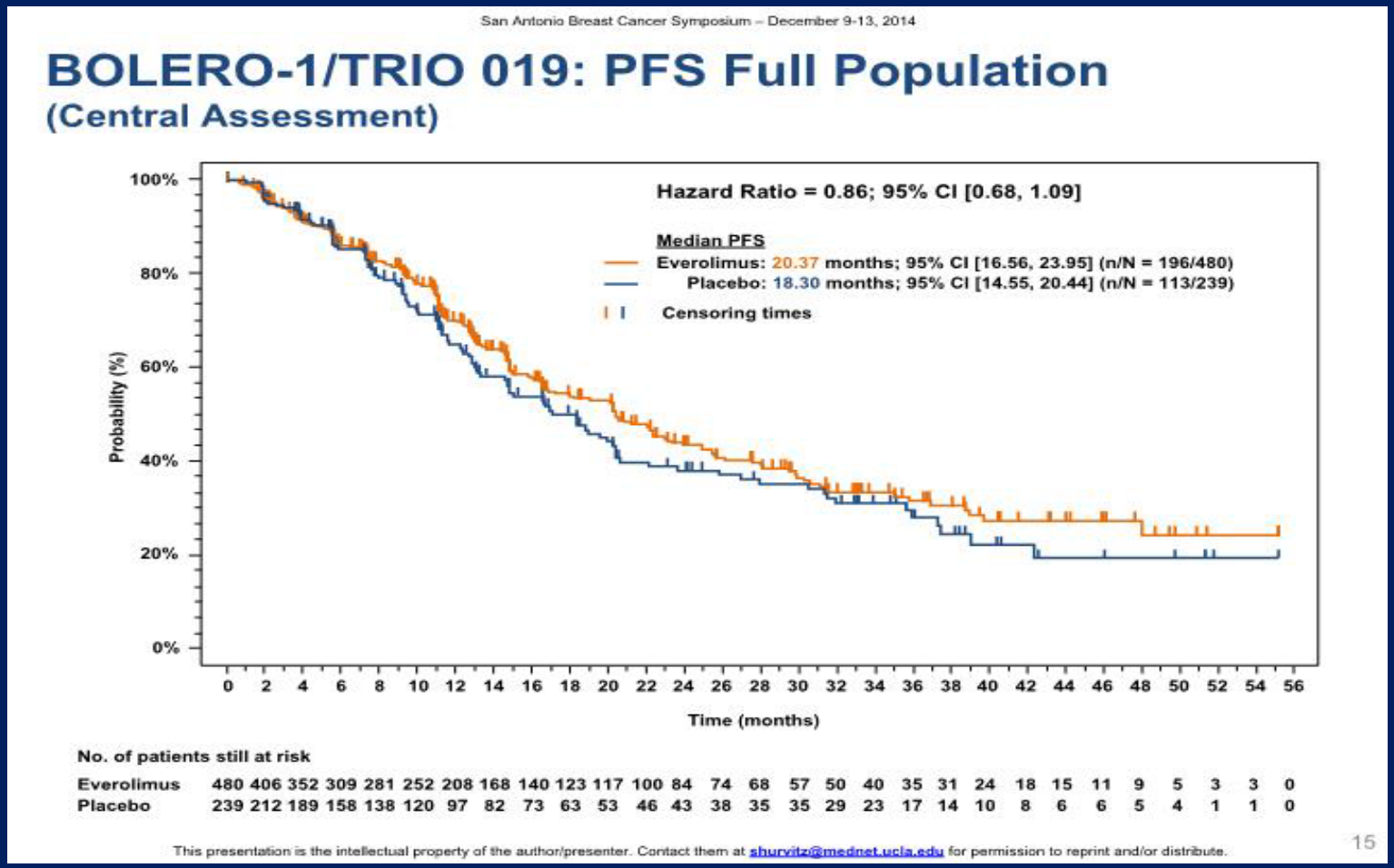

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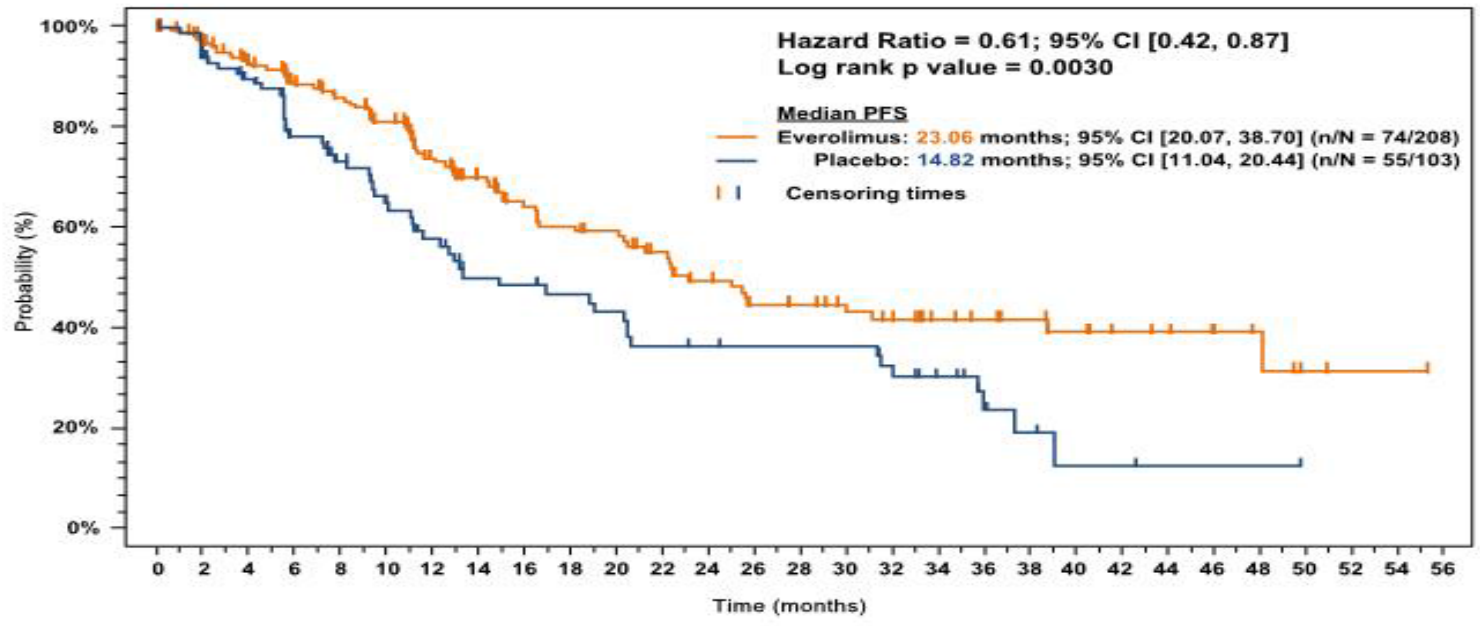
S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: PFS HR– Subpopulation (Central Assessment)



No. of patients still at risk

Everolimus	208	174	156	139	131	118	96	78	65	60	57	49	42	36	34	30	28	22	20	18	15	10	9	6	5	2	1	1	0
Placebo	103	93	81	63	55	46	39	31	30	27	25	21	20	19	19	19	15	12	6	4	2	2	1	1	1	0	0	0	0

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S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Response Rates

Response rates, % [95% CI]	Full Population			HR⁻ subpopulation		
	EVE + TRAS + PAC (N = 480)	PBO + TRAS + PAC (N = 239)	P-value	EVE + TRAS + PAC (N = 208)	PBO + TRAS + PAC (N = 103)	P-value
ORR	67.1 [62.7 - 71.3]	69.0 [62.8 - 74.8]	0.7276	73.1 [66.5 - 79.0]	70.9 [61.1 - 79.4]	0.4085
CBR	75.8 [71.7 - 79.6]	81.2 [75.6 - 85.9]	0.9573	78.8 [72.7 – 84.2]	79.6 [70.5 – 86.9]	0.6382

CBR, clinical benefit rate; EVE, Everolimus; HR, hormone receptor; ORR, objective response rate; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

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S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Most Frequent Adverse Events

(Safety set) [> 25% in everolimus arm]

AE/Grade	EVE + TRAS + PAC (N = 472) %			PBO + TRAS + PAC (N = 238) %		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Non-hematologic						
Stomatitis	67	13	0	32	1	0
Diarrhea	57	9	0	47	4	0
Alopecia	47	<1	0	53	0	0
Rash	40	1	0	21	<1	0
Cough	40	<1	0	33	1	0
Pyrexia	39	2	0	27	1	0
Fatigue	35	5	0	36	3	0
Epistaxis	33	0	0	18	0	0
Peripheral edema	33	1	0	24	<1	0
Nausea	33	1	0	35	1	0
Peripheral neuropathy	29	4	0	24	5	0
Headache	28	1	0	29	1	0
Vomiting	26	1	0	23	3	0
Pneumonitis*	16	4	1	4	<1	0
Hematologic						
Neutropenia	38	21	4	25	11	4
Anemia	31	9	1	16	3	0

*AE of clinical importance

EVE, Everolimus; HR, hormone receptor; PAC, Paclitaxel; PBO, Placebo; TRAS, Trastuzumab.

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S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Fatal Events (Safety Set)

At cutoff, 263 deaths in full population (~60% of 438 events for final analysis)

Characteristic	Full Population	
	EVE + TRAS + PAC (N = 472) %	PBO + TRAS + PAC (N = 238) %
All deaths	37.7	35.3
On-treatment deaths	4.7	0.8
Due to disease progression	1.1	0.8
Due to AE	**3.6**	0
Pneumonitis	0.6	0
Pulmonary embolism	0.4	0
Respiratory failure	0.4	0
Pulmonary edema	0.2	0
Pneumonia	0.4	0
Cardio-respiratory arrest	0.2	0
Sepsis	0.6	0
Fall	0.2	0
Diabetes	0.2	0
Cerebrovascular accident	0.2	0

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S6-01 Everolimus + trastuzumab + paclitaxel as 1st-line tx in HER2+ MBC: BOLERO-1

BOLERO-1/TRIO 019: Fatal Events (Safety Set)

- All but one on-treatment deaths due to AEs occurred within 15 mo from recruitment start
  - May be associated with lack of experience in managing AEs of everolimus when combined with chemotherapy
    - Higher rate of on-treatment deaths in regions with limited experience with everolimus
  - Some cases, protocol defined AE management guidelines not followed
  - IDMC sent communication to investigators regarding management of AEs
    - Only one additional on-treatment death due to AE was reported subsequently

Proactive monitoring and early management of AEs is necessary in patients receiving everolimus in combination with chemotherapy

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Conclusions BOLERO-1

- Primary objective of PFS was not met
  - P=0.0049 however this did not meet prespecified significance threshold of 0.0044
- Safety profile c/w previously reported results
- Higher rate of AE-related on-treatment deaths (3.6% vs 0% with placebo)
  - All but one AE-related on-treatment death occurred within 15 mos of study start
  - Proactive monitoring and early management of AEs is critical

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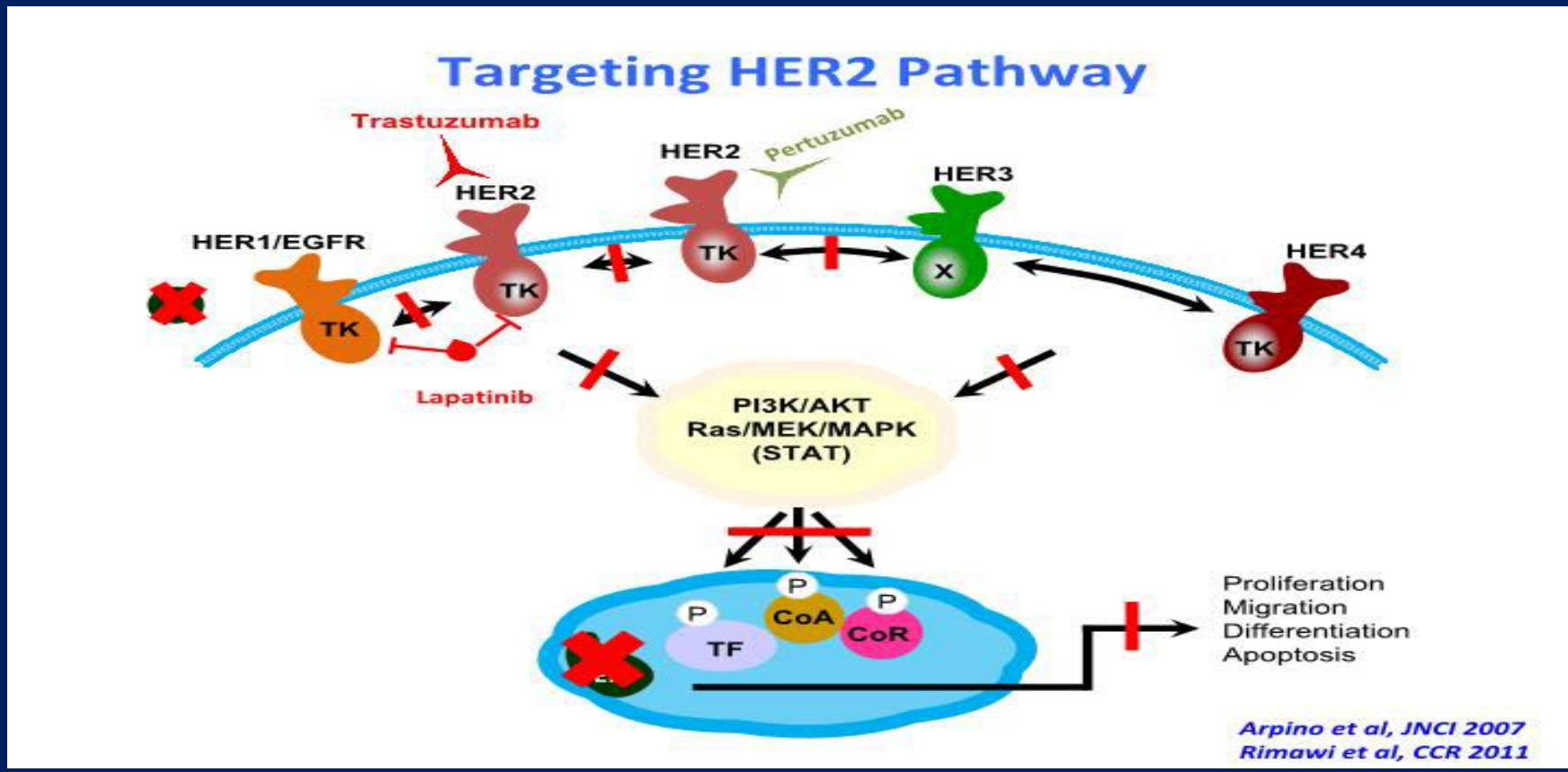
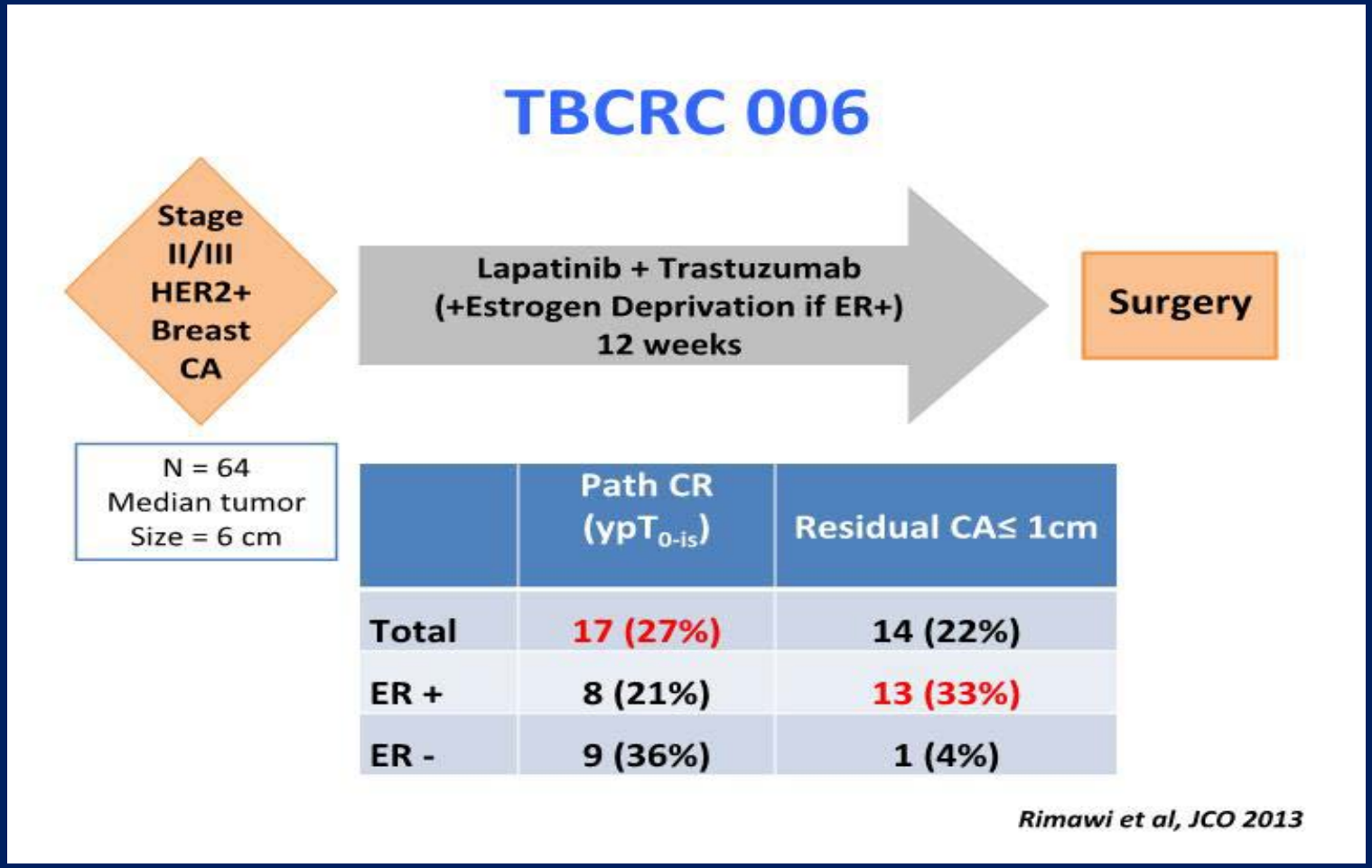
S6-02 TBCRC023: A randomized multicenter phase II neoadjuvant trial of lapatinib plus trastuzumab, with endocrine therapy and without chemotherapy, for 12 vs. 24 weeks in patients with HER2 overexpressing breast cancer

S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy



Rimawi, et al on behalf of TBCRC

S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy



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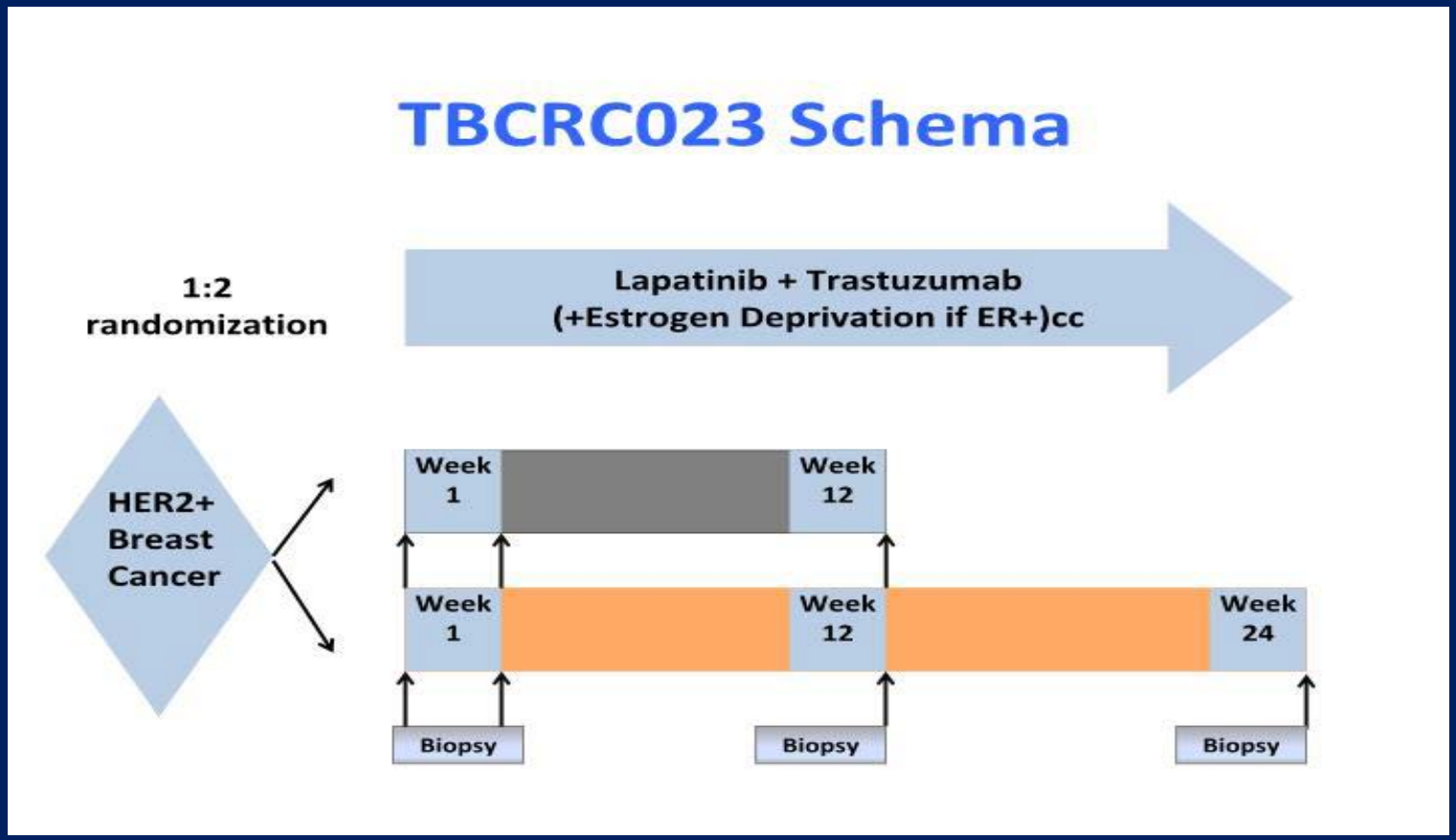


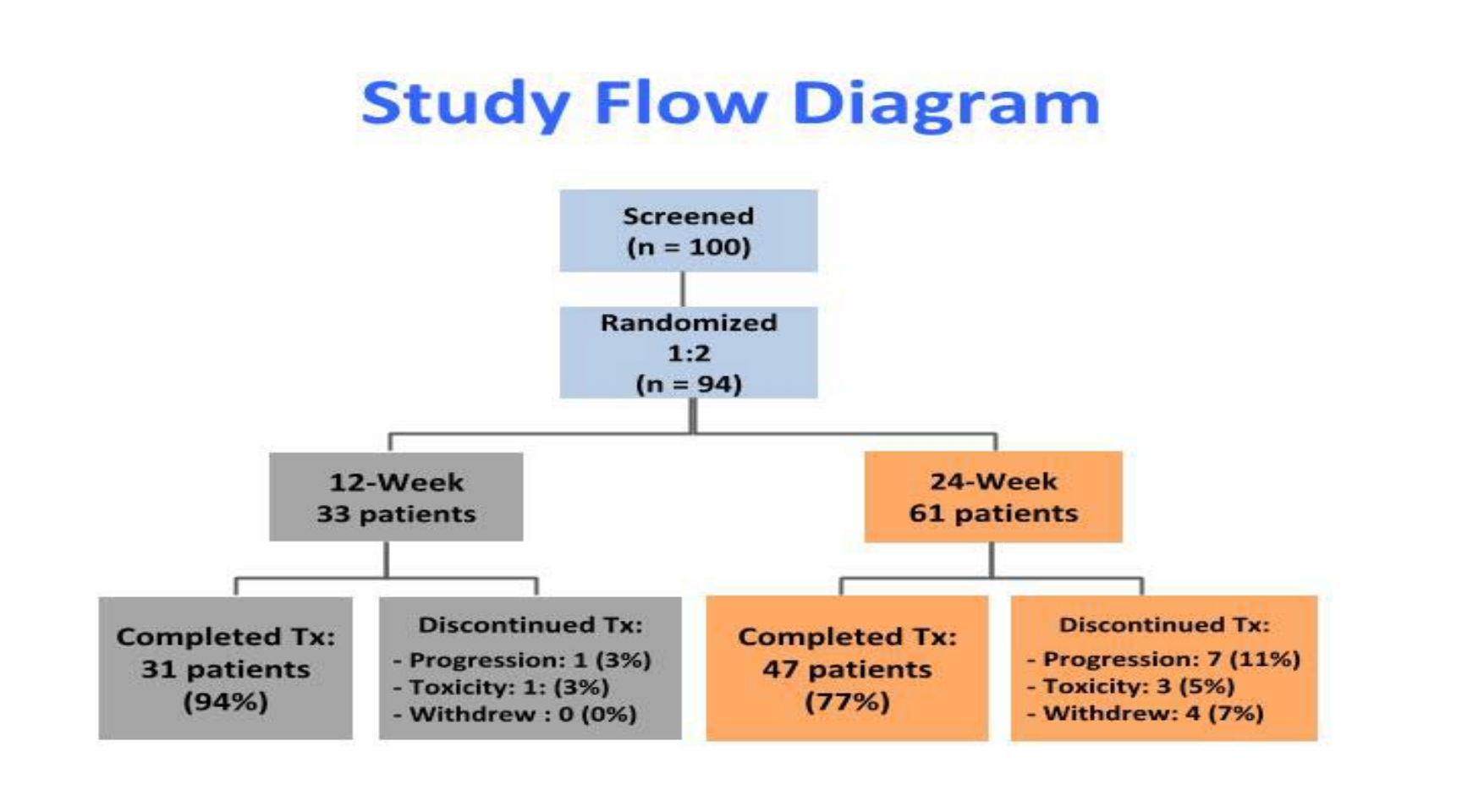
Hypothesis: Longer treatment with anti-HER2 therapy and endocrine therapy in ER+ HER2+ breast cancer would result in higher pCR rate

S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy

- Primary endpoint: pCR in breast ($yoT_{0-is}yoN_x$)
  - 88-96 patients needed to detect increase in pCR from 27% to 45%, with power of 85% and type I error of 10%
- Secondary endpoints:
  - Safety/tolerability
  - Time to 1st recurrence
  - OS
- Study arms not powered to be directly comparable
- Eligibility:
- HER2-positive breast cancer with primary tumor $\geq$ 2cm

Rimawi, et al on behalf of TBCRC

S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy



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S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy

- Demographics:
  - Median age 51 (23-80); 55% postmenopausal
  - Median tumor size 5 cm; 70% Stage II; 29% Stage III
  - 66% ER-positive; 32% ER-negative
- Toxicity:
  - 12 week:
    - 3% anemia
    - 3% renal calculi
  - 24 week:
    - 9% elevated LFTs
    - 2% diarrhea
    - 2% mucositis

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S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy

Pathologic Response

Path CR (ypT_{0-is})	12 weeks (n=33)	24 weeks (n=61)
Overall	4 (12%)	17 (28%)
ER-positive	2 (9%)	13 (33%)
ER-negative	2 (20%)	4 (18%)

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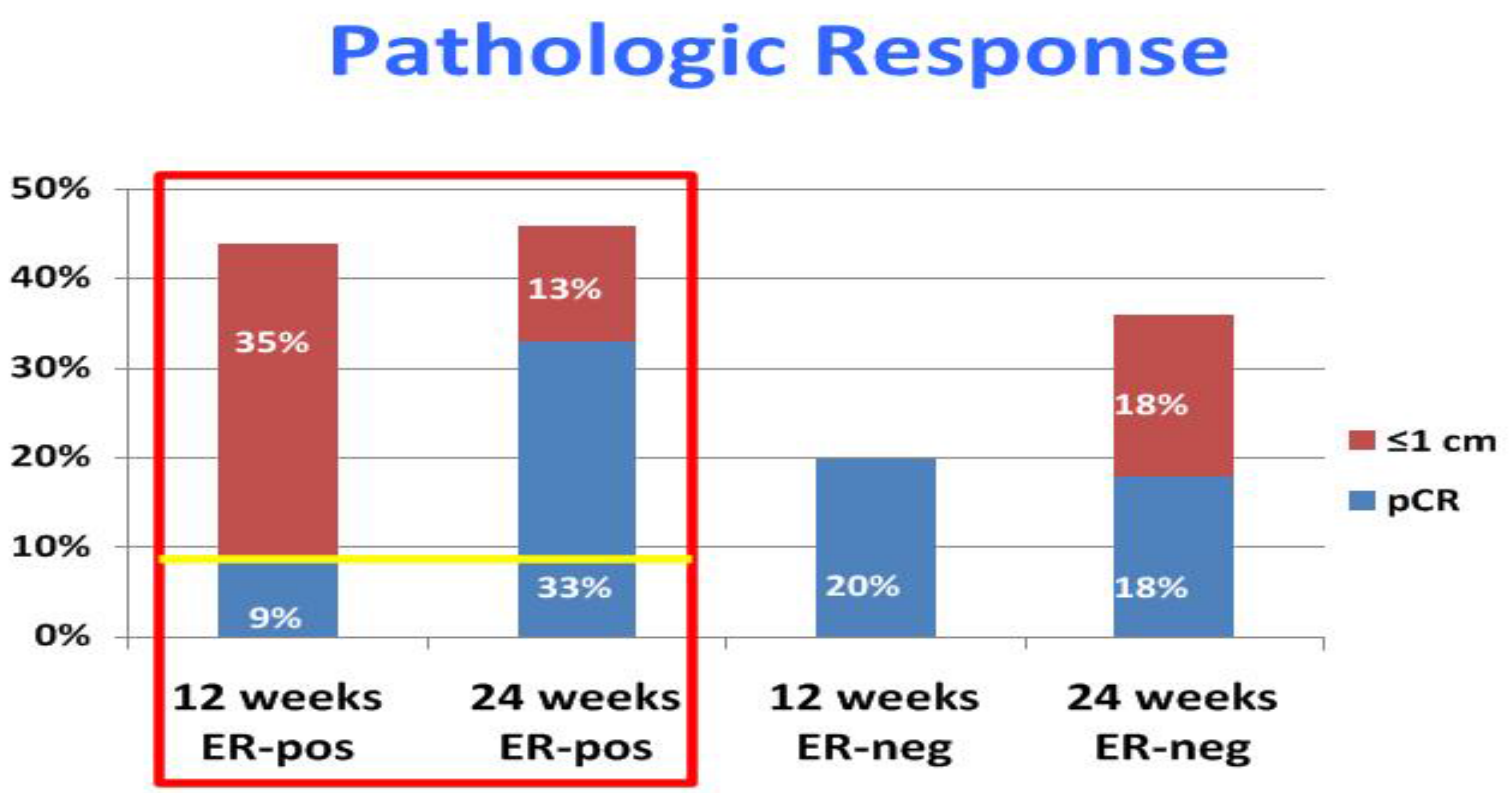
S6-02 Lapatinib + trastuzumab + endocrine therapy and no chemotherapy



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Conclusions

- The trial did not meet its primary endpoint due to lower than anticipated pCR in both arms
- Twofold numeric increase in pCR for 24 weeks; threefold if ER-positive
  - First trial to show that longer treatment with dual anti-HER therapy in combination with endocrine therapy leads to increase in pCR rate in ER+/HER2+ breast cancer

Rimawi, et al on behalf of TBCRC

S3-05 Intrinsic subtypes, PIK3CA mutation, and the degree of benefit from adjuvant trastuzumab in NSABP trial B-31

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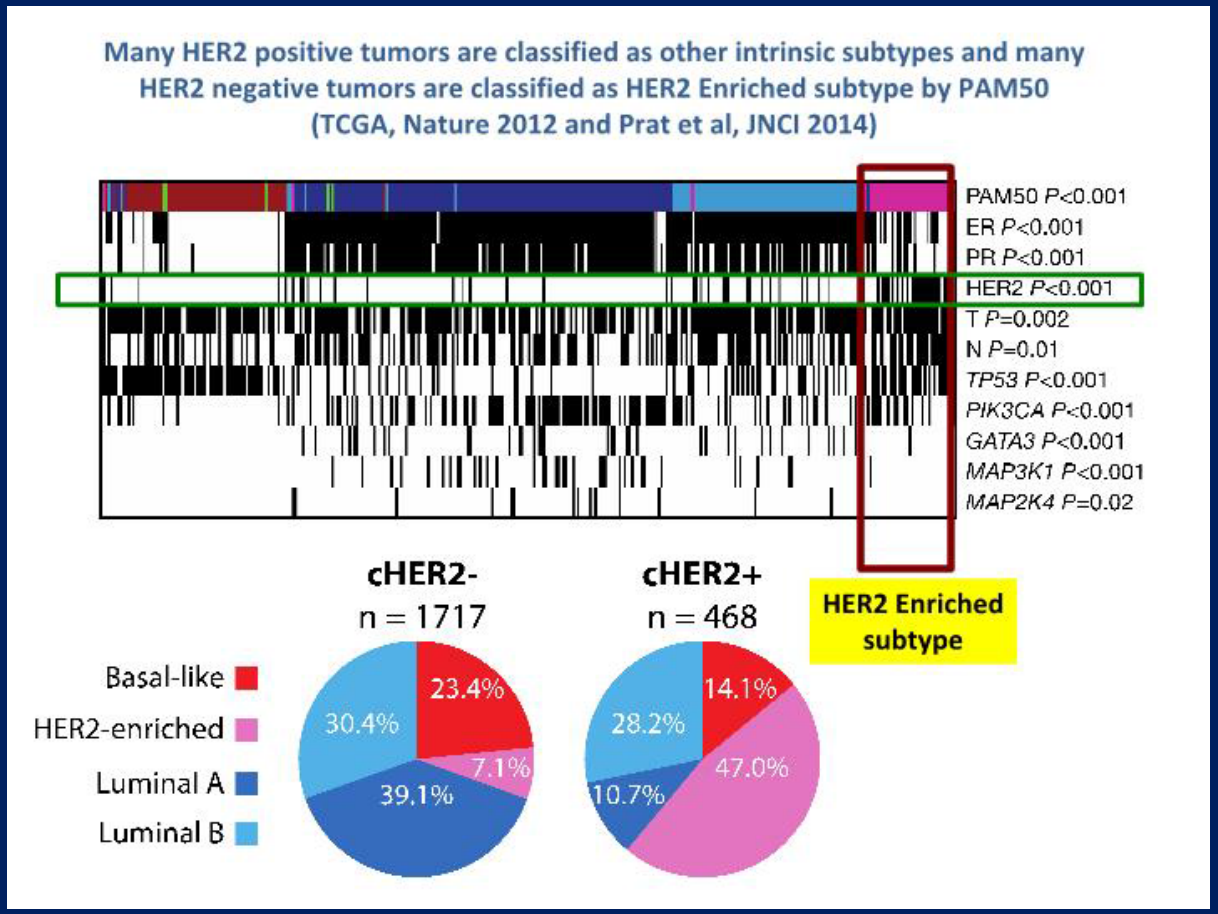
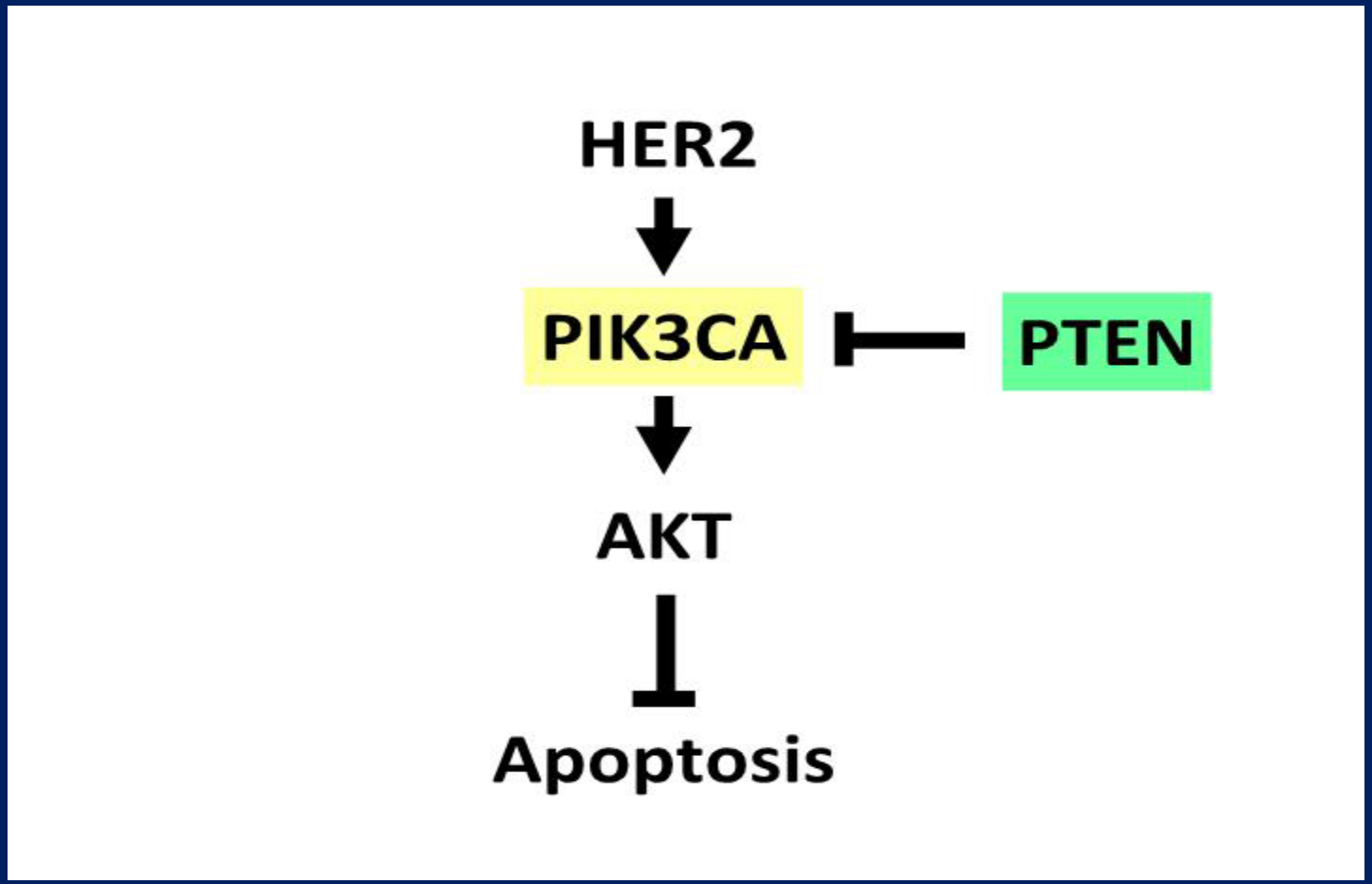


Pogue-Gelle, et al. SABCS 2014

S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31



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S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31

- Hypothesis:
  - Patients with HER2-positive breast cancer that are non-HER2E intrinsic subtype or PIK3CA hotspot mutation did not benefit from trastuzumab added to adjuvant chemotherapy

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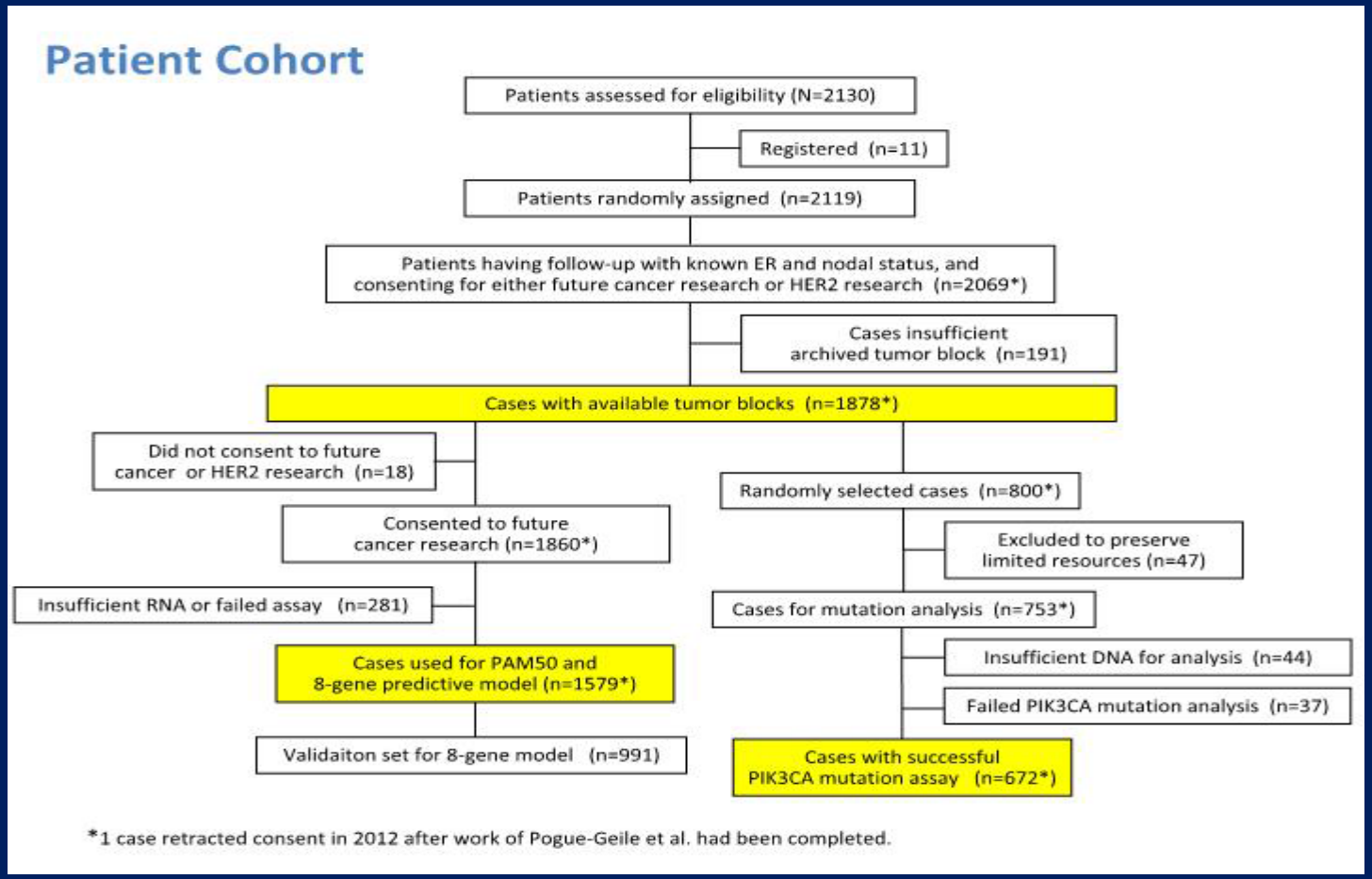
S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31



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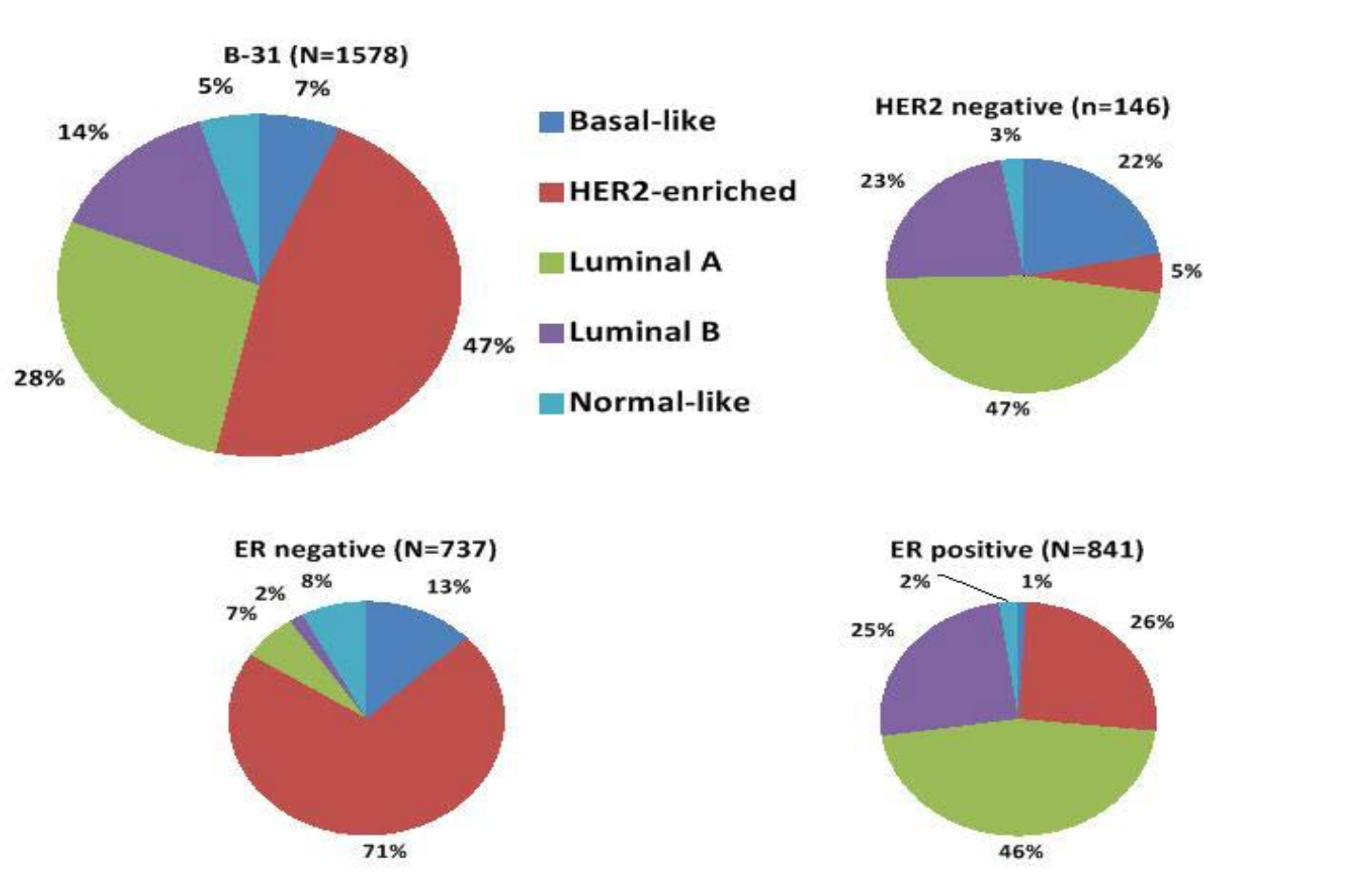

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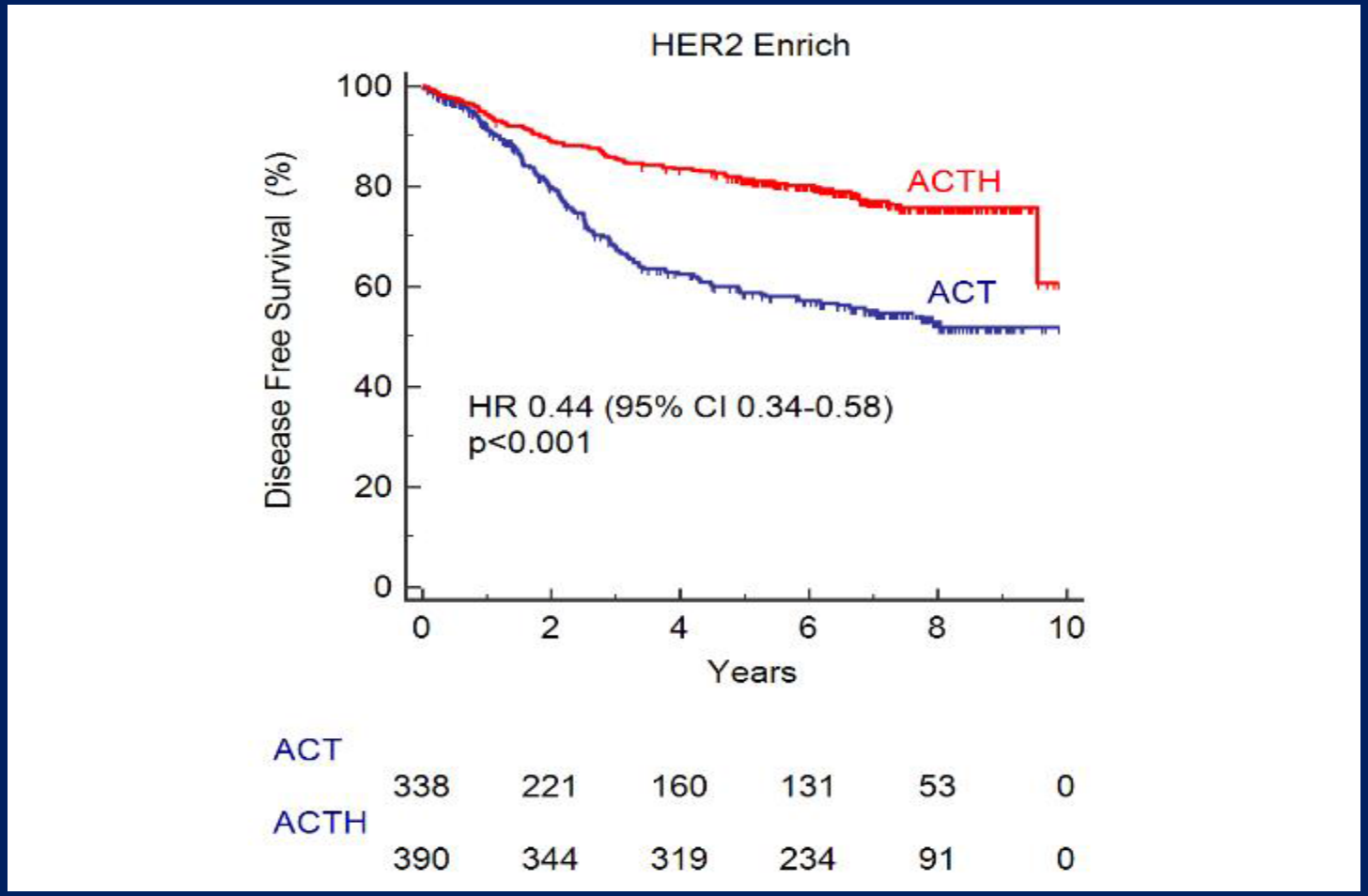
Trastuzumab Benefit based on PAM50 intrinsic subtypes



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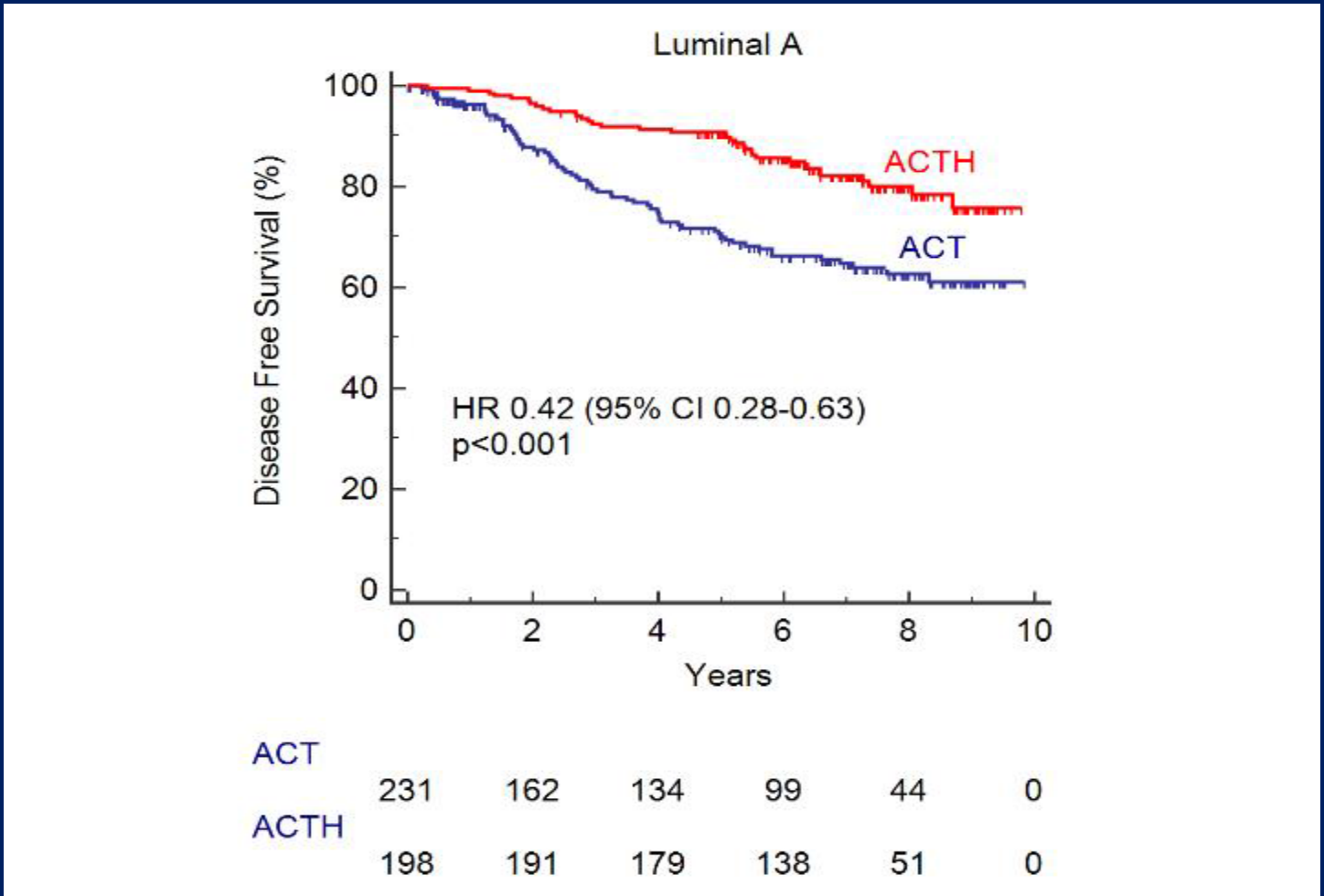
Trastuzumab Benefit based on PAM50 intrinsic subtypes (cont)



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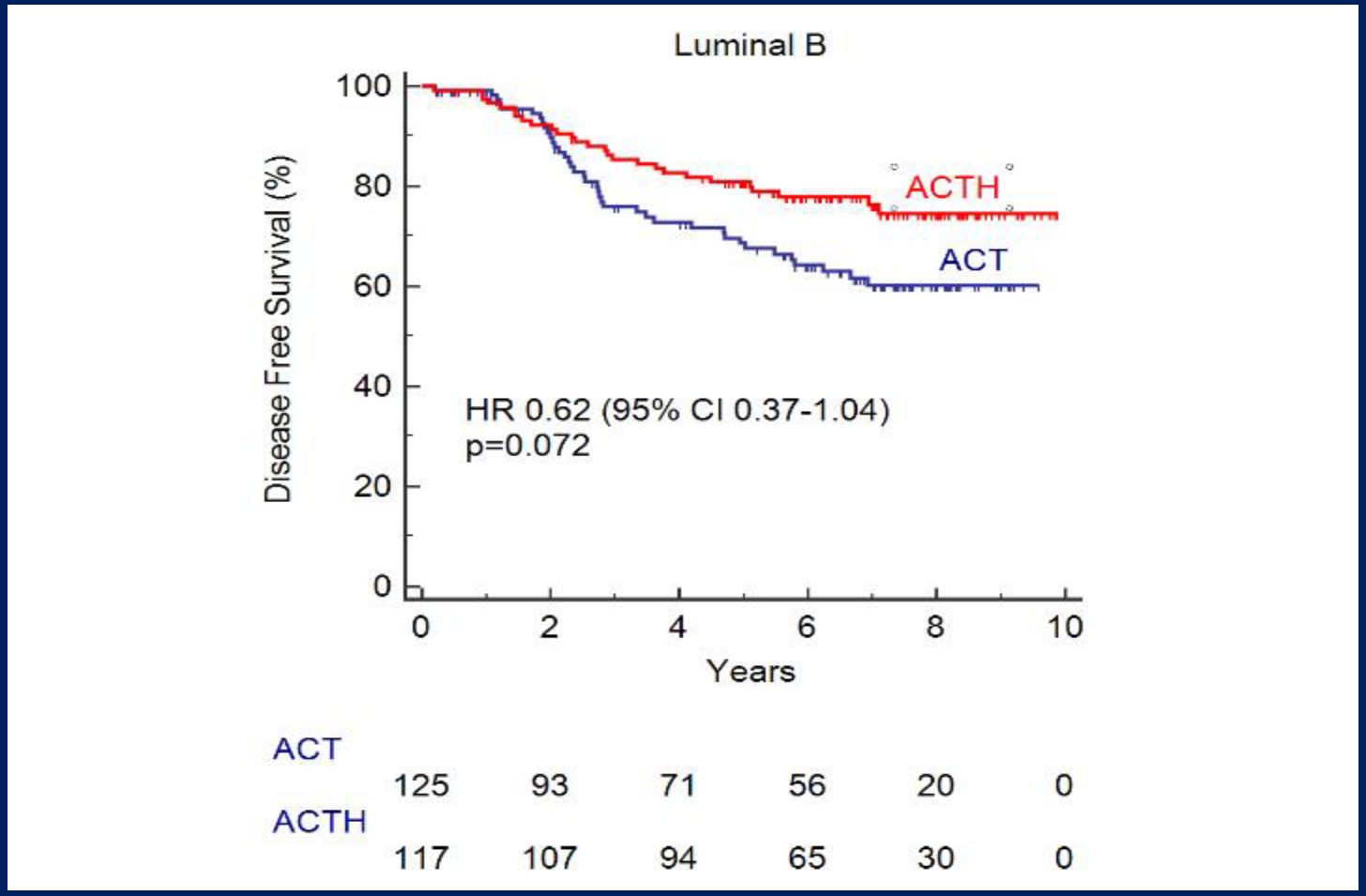
Trastuzumab Benefit based on PAM50 intrinsic subtypes (cont)



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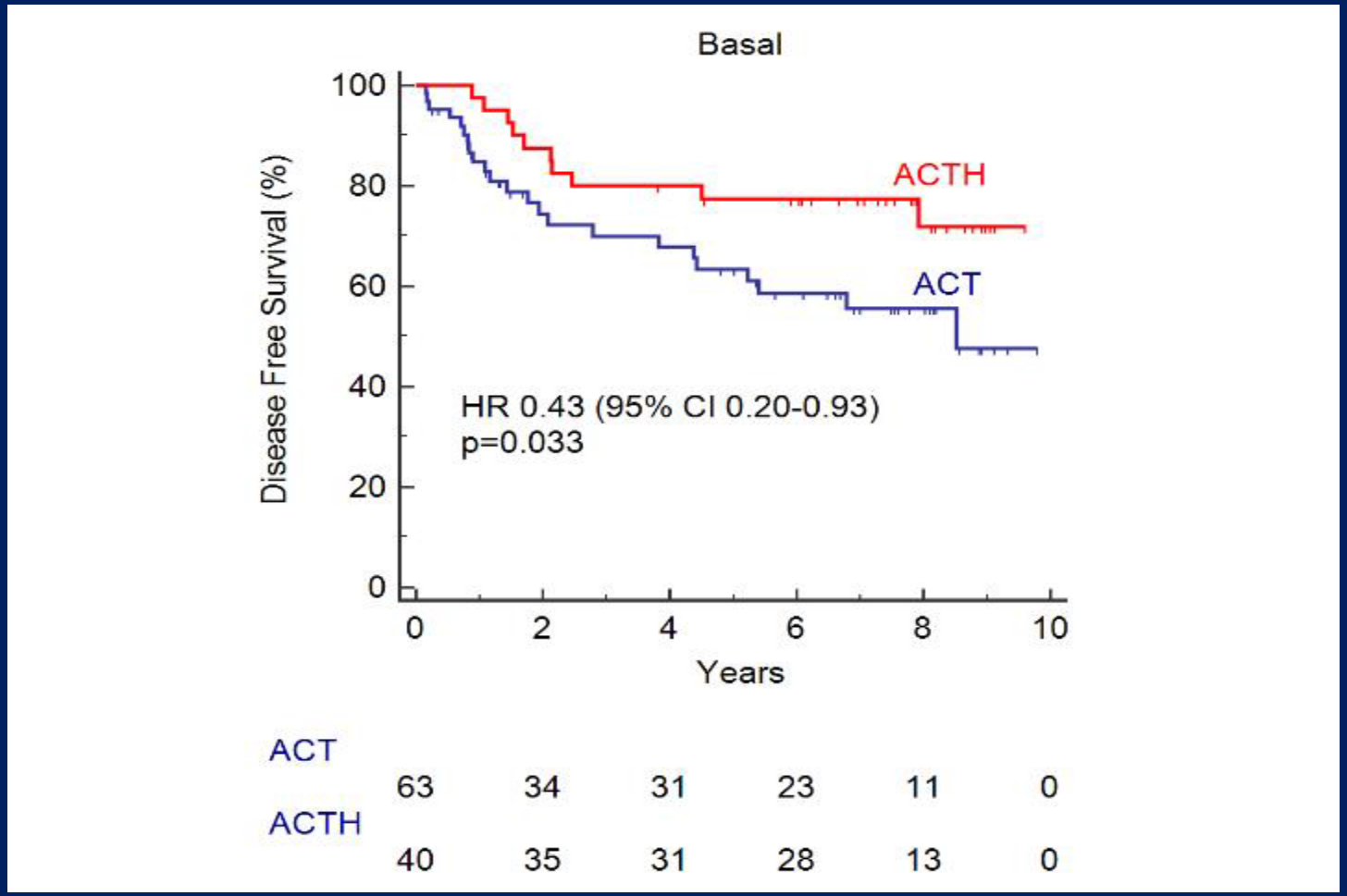
Trastuzumab Benefit based on PAM50 intrinsic subtypes (cont)



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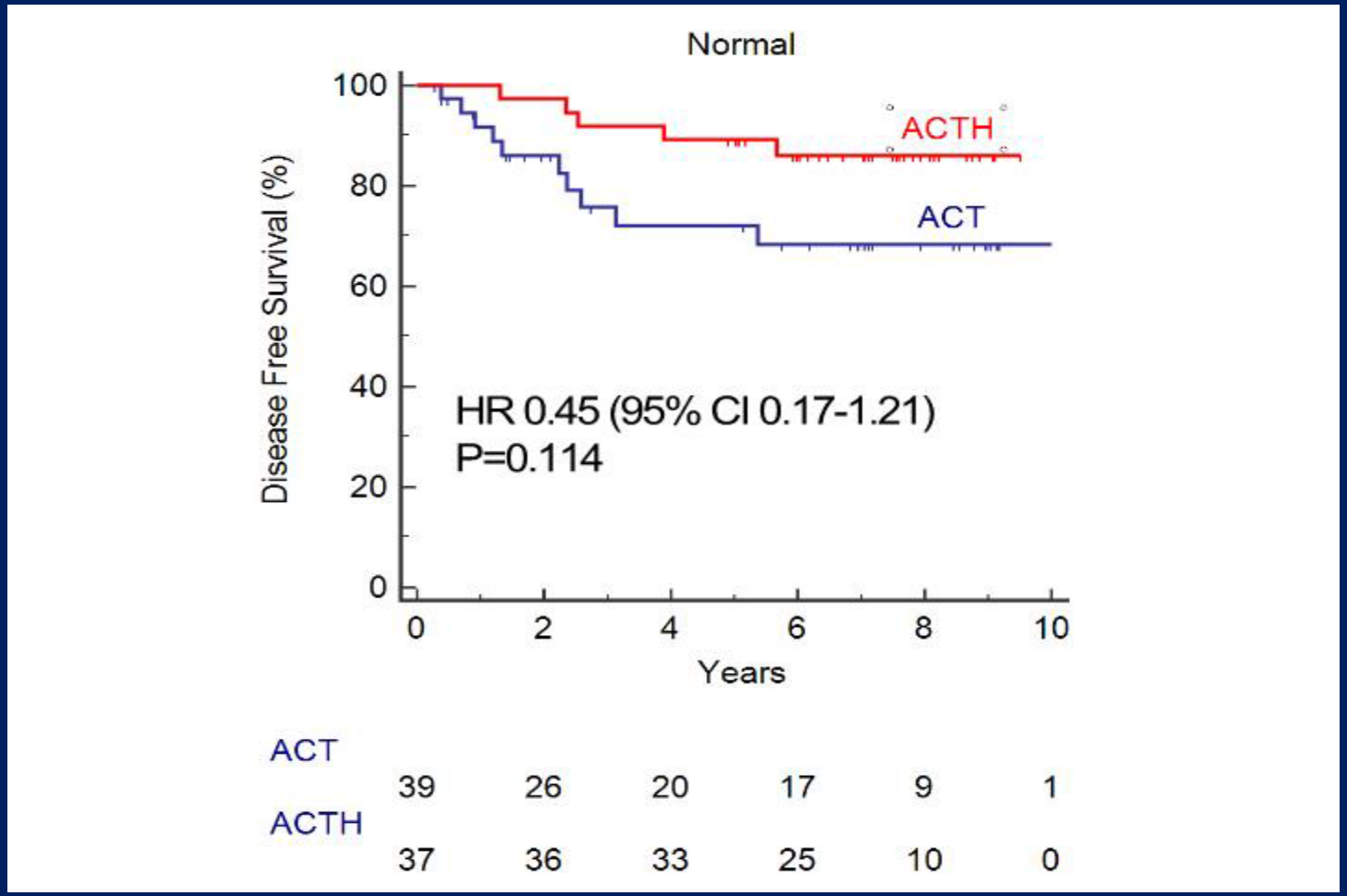
Trastuzumab Benefit based on PAM50 intrinsic subtypes (cont)



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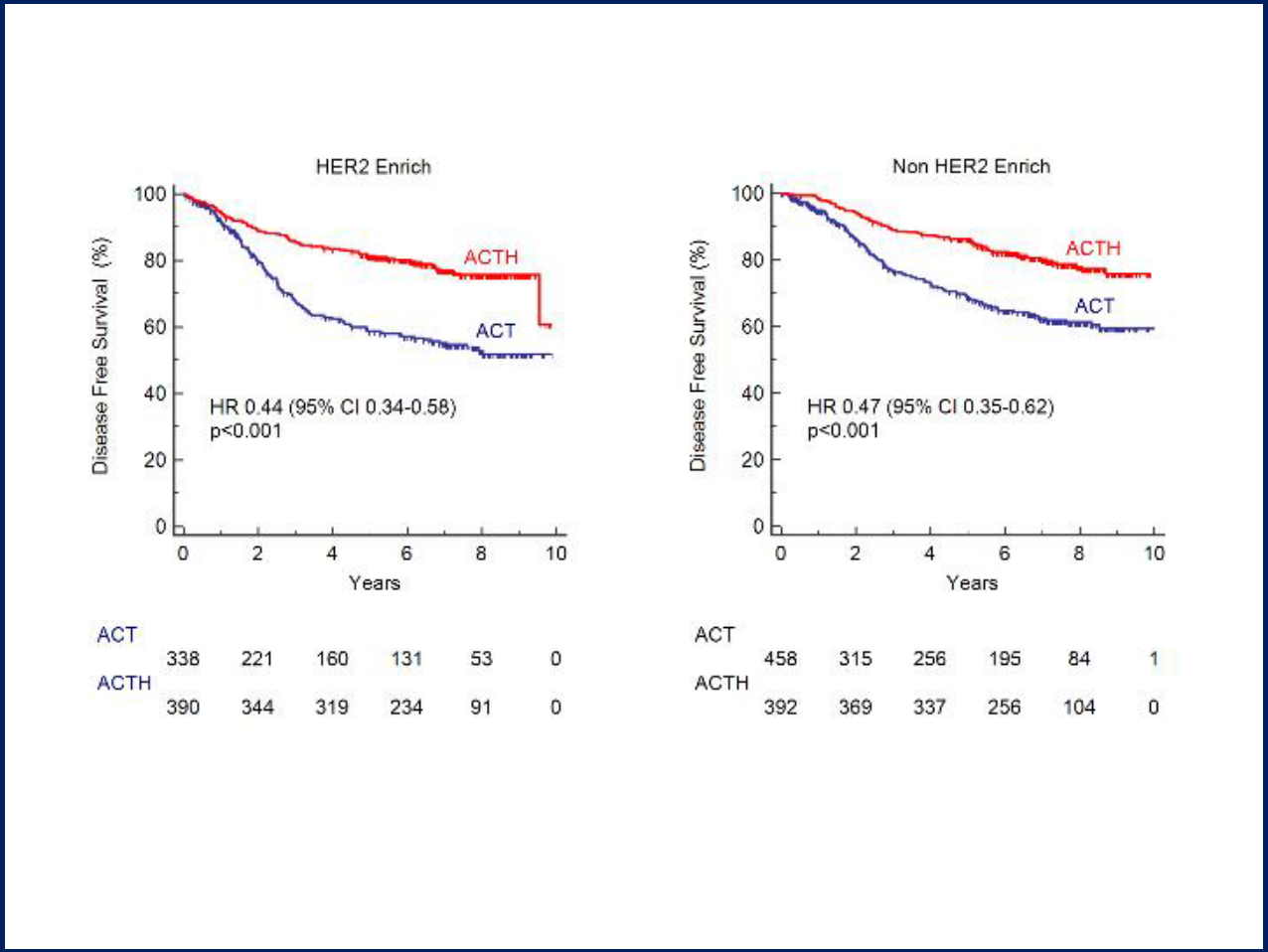
Trastuzumab Benefit based on PAM50 intrinsic subtypes (cont)



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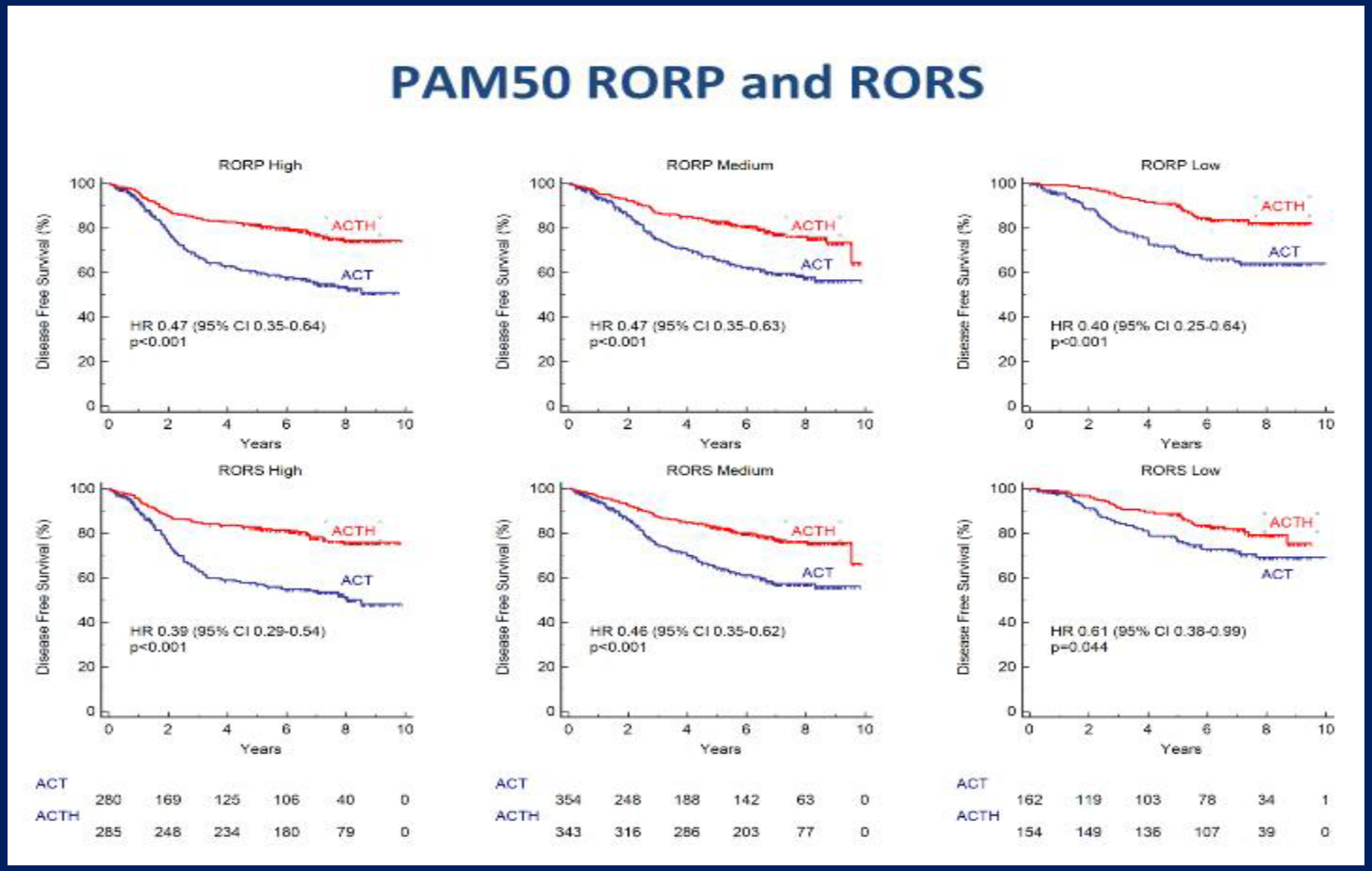
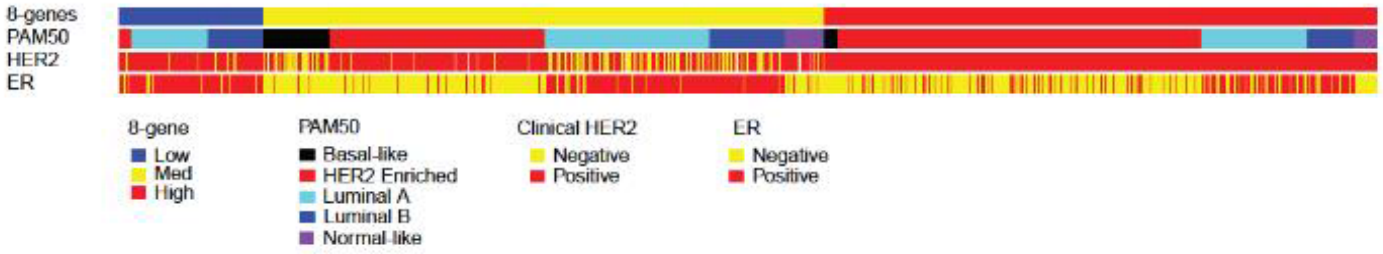
S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31

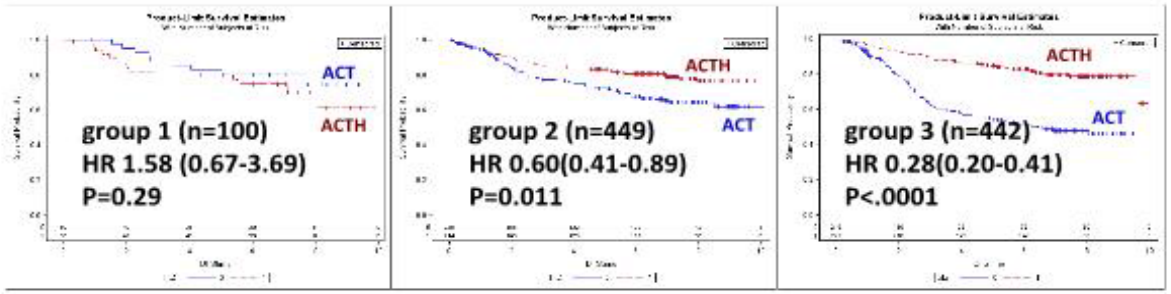


S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31

Association between Intrinsic Subtypes and HER2, ER, and 8-gene predictive signature

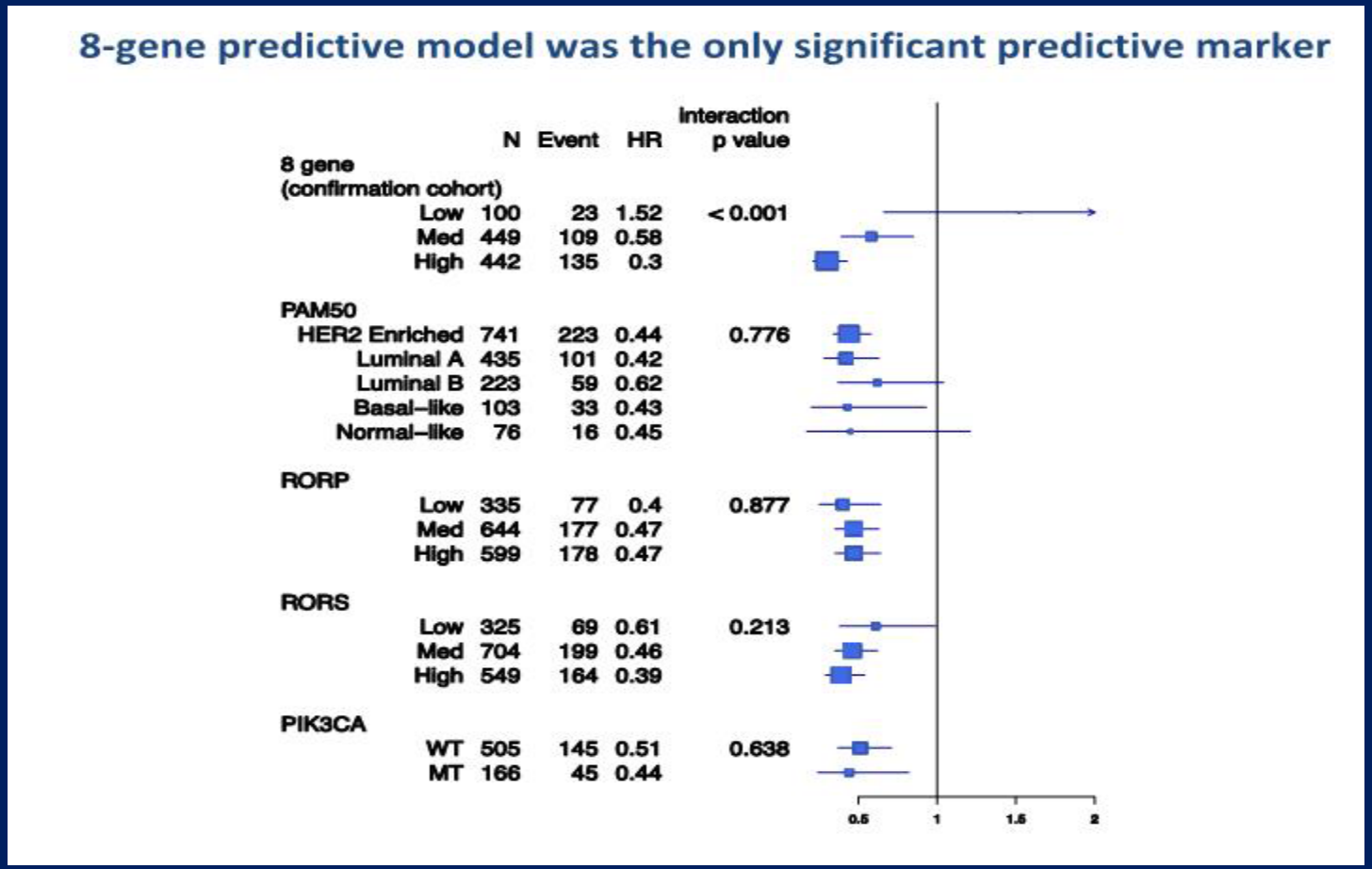


8-gene predictive model validation set (Pogue-Geile et al, JNCI 2013)



Interaction p=0.0002

S3-05 Intrinsic Subtypes, PIK3CA mutation and degree of benefit from adjuvant trastuzumab in NSABP B-31



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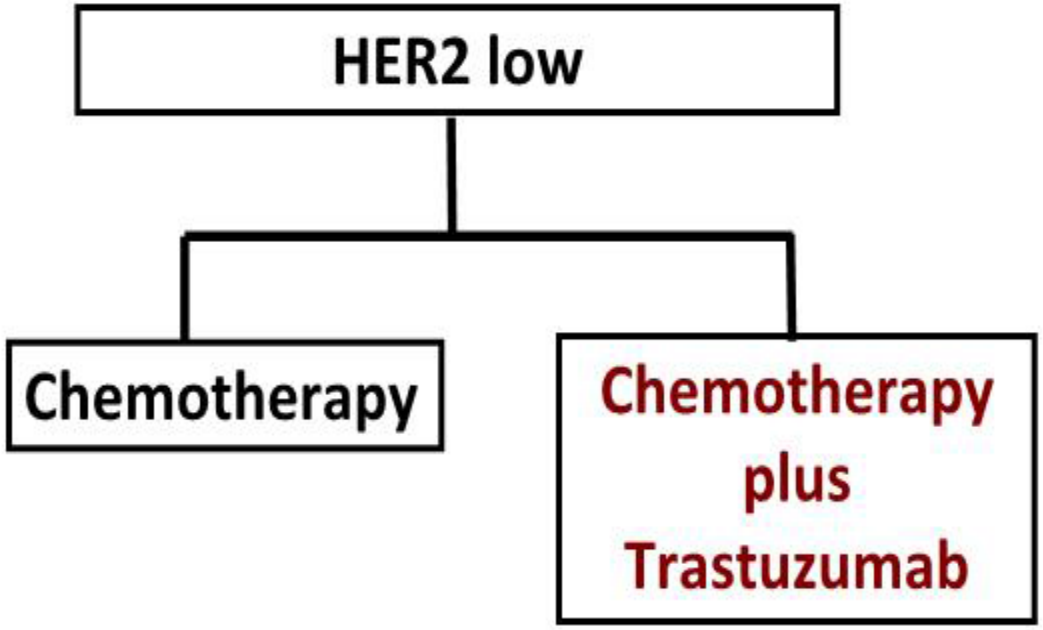
NSABP B-47

Testing of trastuzumab as a cancer stem cell therapy



Conclusions

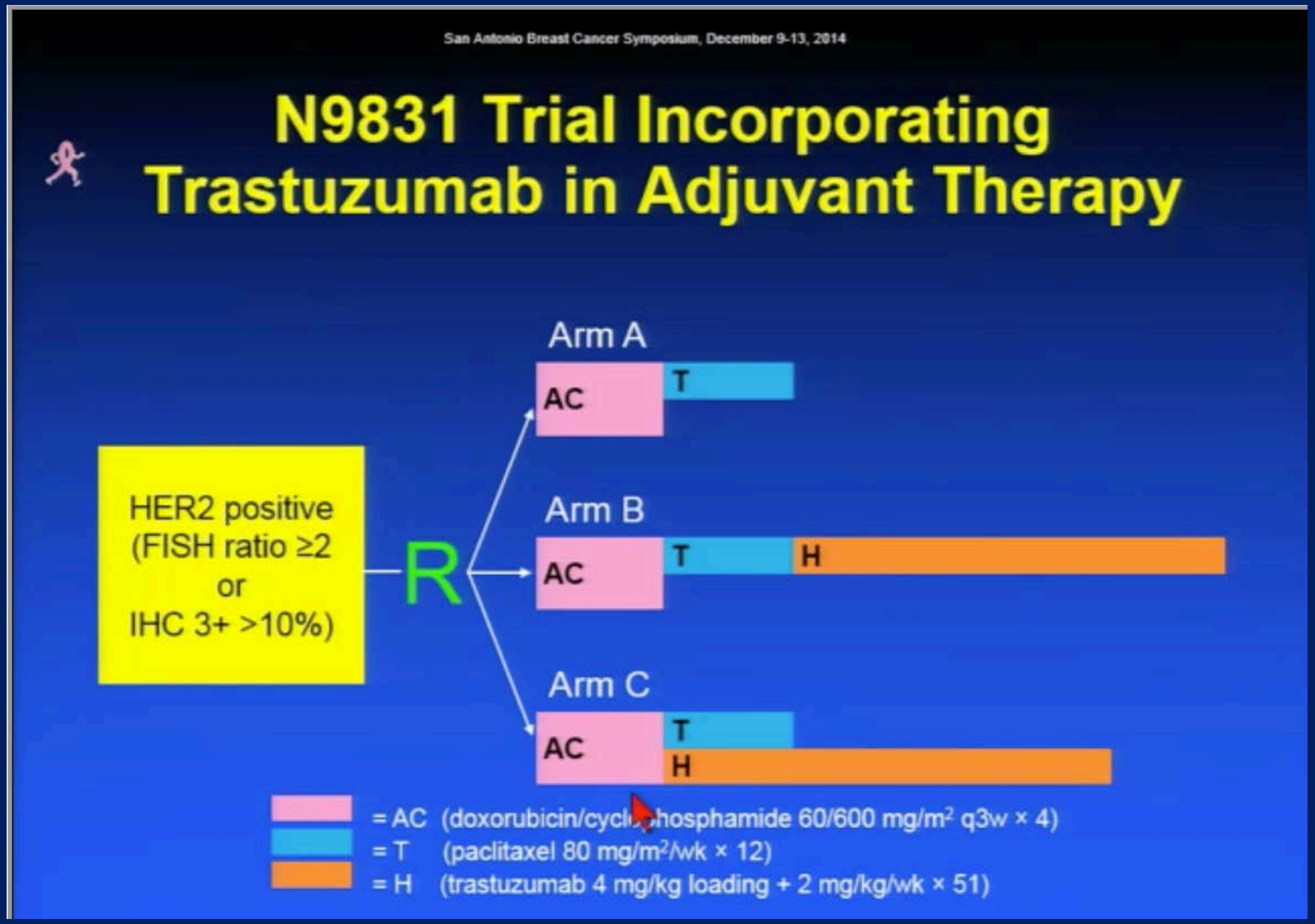
- PAM50 intrinsic subtype or PIK3CA mutation failed to identify subgroups that did not benefit from trastuzumab
- Support the on-going clinical trial to test efficacy of trastuzumab in HER2-negative patients (B-47)

S1-06 Stromal tumor-infiltrating lymphocytes(S-TILs): In the alliance N9831 trial S-TILs are associated with chemotherapy benefit but not associated with trastuzumab benefit

Background

- Str-TILs have been reported to be prognostic in TNBC
- FinHer trial concluded that higher levels of Str-TILs are associated with higher trastuzumab benefit

Perez, et al. SABCS 2014



Perez, et al. SABCS 2014

Methods

Str-TILS defined as

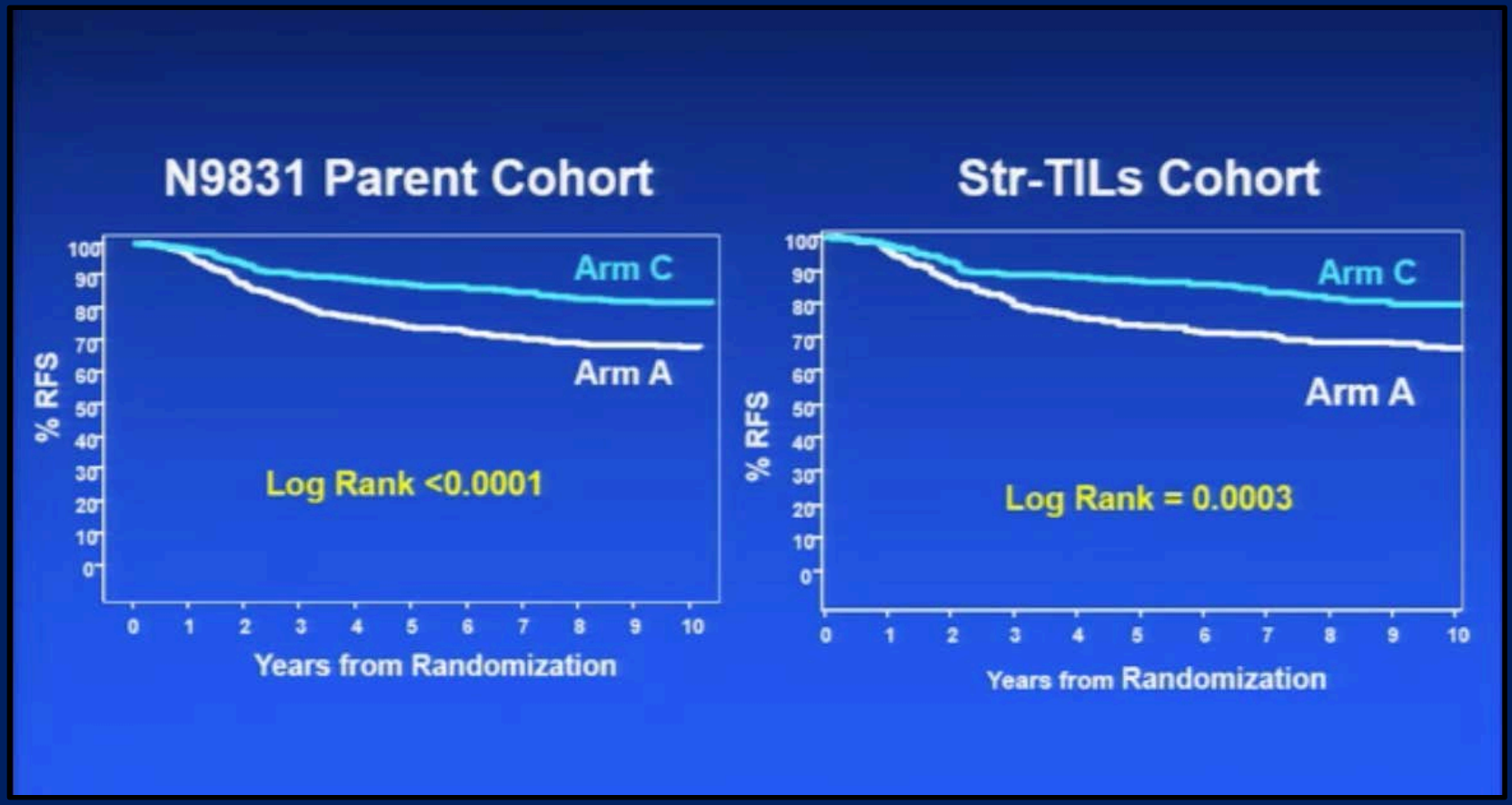
- % tumor stroma that contains lymphocytic infiltrate
- LI around DCIS, biopsy sites, areas of necrosis, and benign lobules were not scored
- ≥ 60% Str-TILs classified as “lymphocyte predominant breast cancer” (LPBC)

Patients assessed

- 489 Arm A chemo and 456 Arm C chemo with trastuzumab
- 54% hormone receptor positive
- 14% node negative disease

Perez, et al. SABCS 2014

Clinical outcome: similar RFS in 2 groups



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Distribution of Str-TILs

	Total (N=945)	Arm A (N=489)	Arm C (N=456)	p-value
Str-TIL decile, n (%)				0.2899
0-9%	318 (33.7%)	171 (35.0%)	147 (32.2%)	
10-19%	236 (25.0%)	126 (25.8%)	110 (24.1%)	
20-29%	139 (14.7%)	65 (13.3%)	74 (16.2%)	
30-39%	69 (7.3%)	27 (5.5%)	42 (9.2%)	
40-49%	45 (4.8%)	28 (5.7%)	17 (3.7%)	
50-59%	44 (4.7%)	24 (4.9%)	20 (4.4%)	
60-69%	39 (4.1%)	17 (3.5%)	22 (4.8%)	
70-79%	29 (3.1%)	17 (3.5%)	12 (2.6%)	
80-89%	17 (1.8%)	10 (2.0%)	7 (1.5%)	
90-100%	9 (1.0%)	4 (0.8)	5 (1.1%)	
LP group, n (%)				0.89
LP: ≥ 60% Str-TIL	94 (9.9%)	48 (9.8%)	46 (10.1%)	
Non-LP: < 60% Str-TIL	851 (90.1%)	441 (90.2%))	410 (89.9%)	

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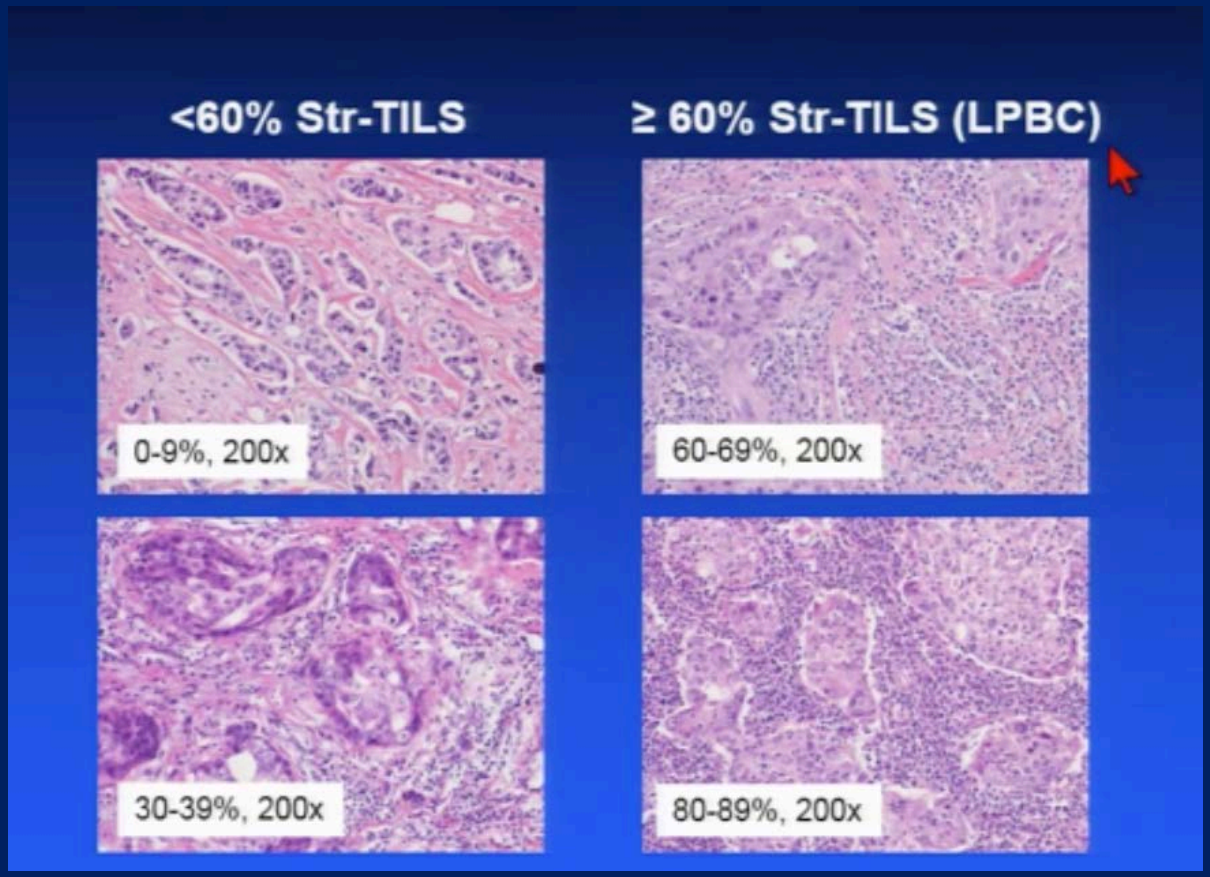
Examples of scoring



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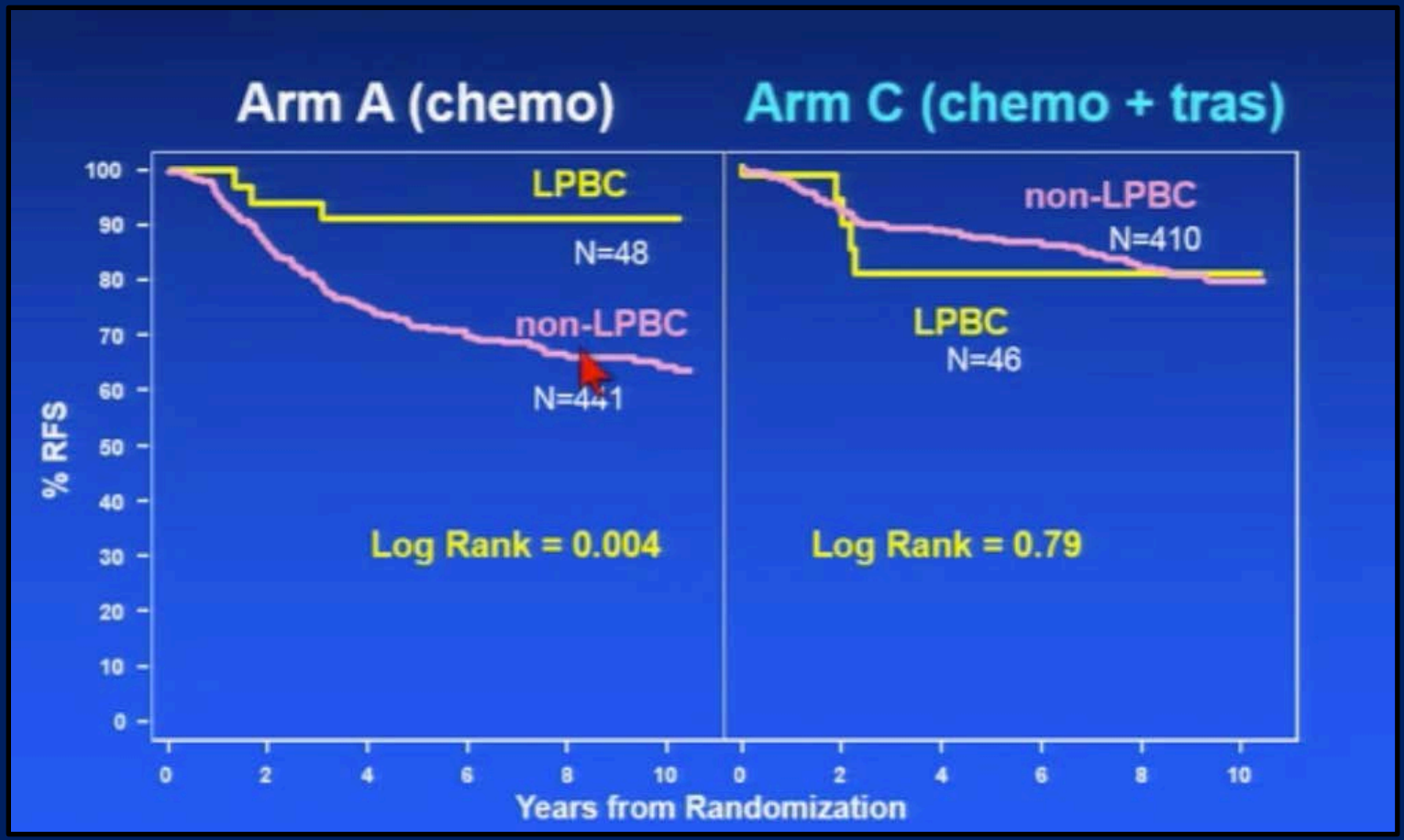
LPBC association with RFS: by treatment arm



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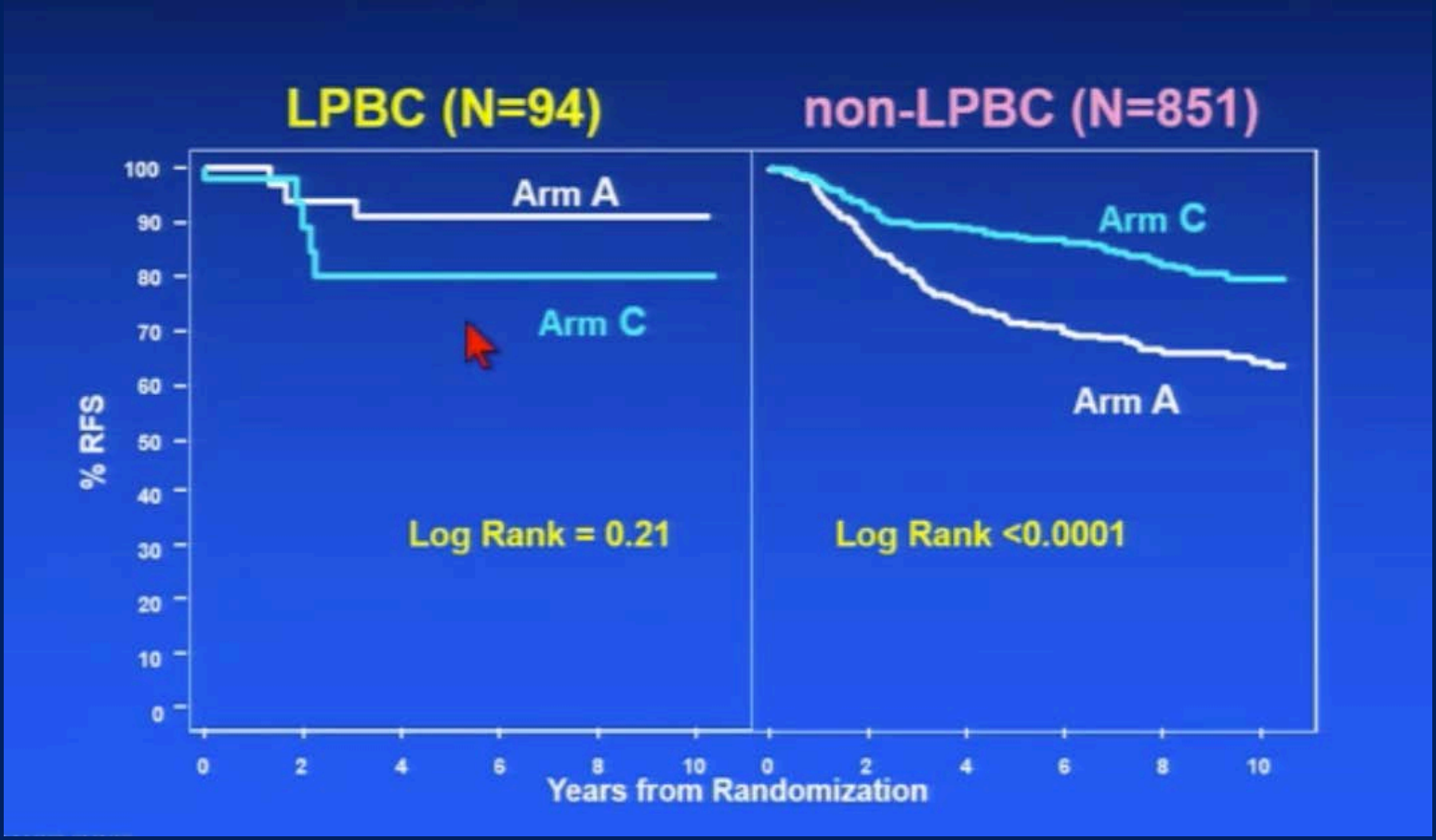
Treatment association with RFS: by LPBC status



Perez, et al. SABCS 2014

Conclusions

- Increasing % of Str-TILs correlate with benefit to chemotherapy while the addition of trastuzumab is not as clear in LPBC

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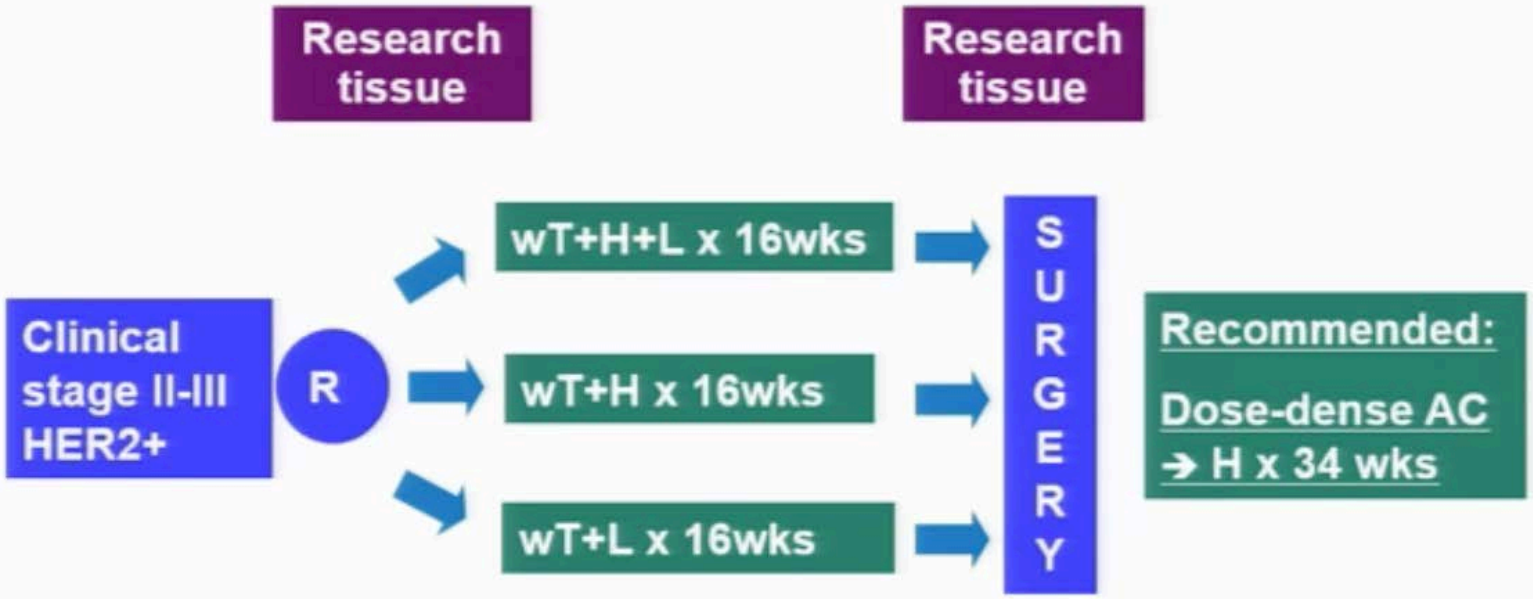
S3-06 Mutational analysis of CALGB 40601 (Alliance), a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with or without lapatinib (L) for HER2-positive breast cancer

CALGB 40601 (Alliance), a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with or without lapatinib (L) for HER2-positive breast cancer

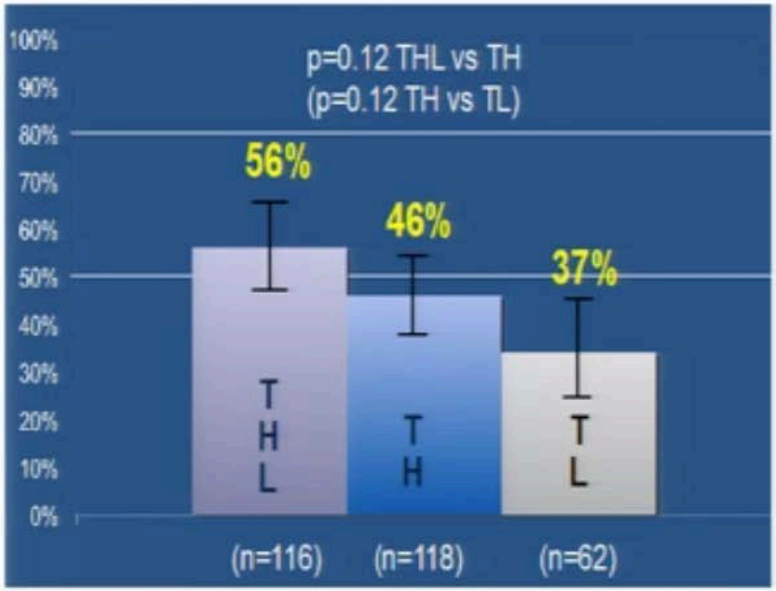


wT= weekly paclitaxel, H= trastuzumab, L= lapatinib

Hoadley et al. SABCS 2014

Primary endopoint ASCO 2013

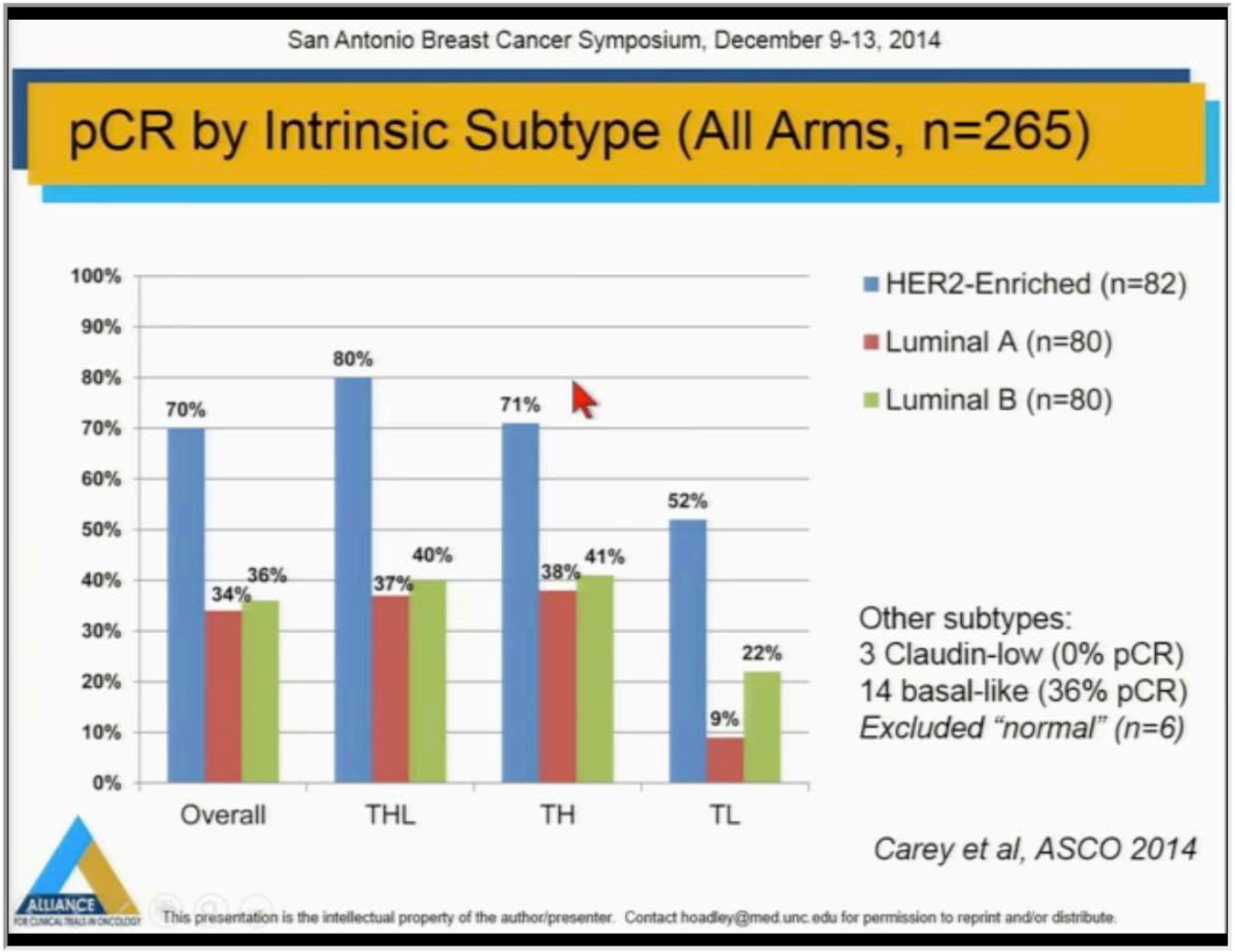
- In-breast pCR to dual therapy (THL) versus single (TH)
  - 56% versus 46% (p=0.12)



Carey et al, ASCO 2013

Hoadley et al. SABCS 2014

pCR by intrinsic subtype All Arms n=265



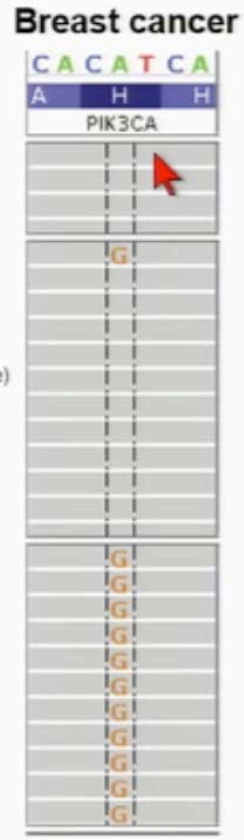
Hoadley et al. SABCS 2014

San Antonio Breast Cancer Symposium, December 9-13, 2014

Somatic mutation detection by integrating DNA and RNA sequencing

RNA, DNA → UNCeqR → Integrated mutations, DNA mutations, RNA mutations

- First-of-its-kind tool
- RNA seq ↑ power to detect mutations
  - Low tumor cellularity
  - Low mutant allele fraction
- Outperforms DNA sequencing methods (greater sensitivity at same specificity)
- http://lbg.med.unc.edu/tools/unceqr/

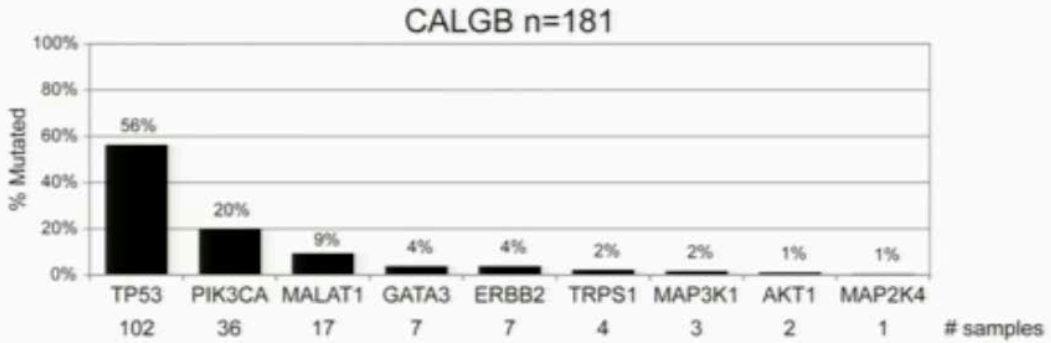


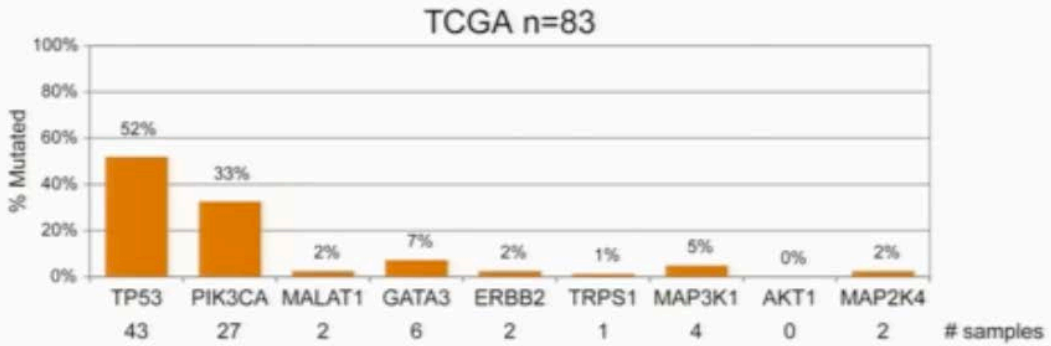
Wilkerson et al, Nucleic Acids Res 2014

Hoadley et al. SABCS 2014

San Antonio Breast Cancer Symposium, December 9-13, 2014

Comparison with TCGA HER2+ subset





TCGA HER2 subset was documented IHC 3+ and/or FISH >2.2

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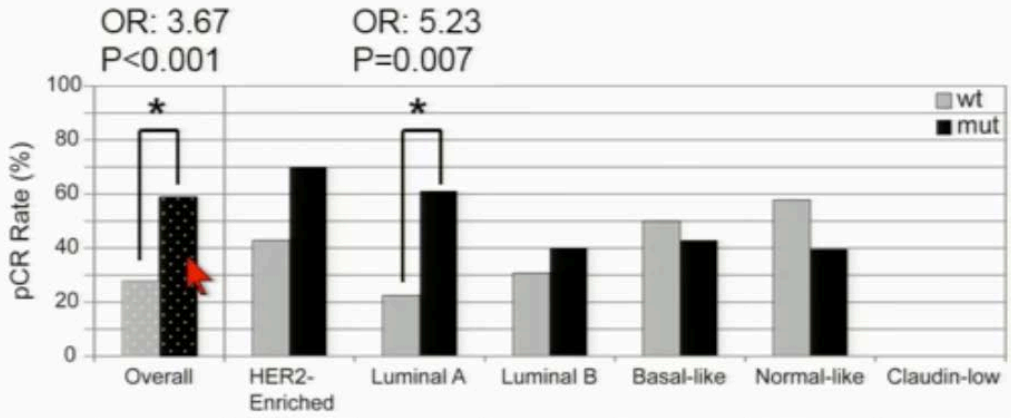
TP53 Mutations by pCR and Subtype



Total (n)	181	57	58	51	9	4	2
# TP53 mutant	102 (56%)	50 (88%)	18 (31%)	25 (49%)	7 (78%)	2 (50%)	0 (0%)

TP53 mutations significantly associated with pCR

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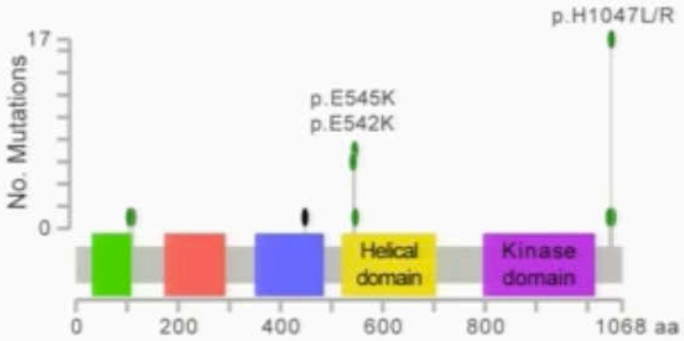
PIK3CA Mutations

Subtype	Wildtype	Mutant
Basal-like	8	1 (11%)
Claudin-low	2	0 (0%)
HER2-E	43	14 (25%)
Luminal A	51	4 (7%)
Luminal B	35	16 (31%)
Normal-like	3	1 (25%)

93% of mutations were in exons 9 and 20



	No pCR	pCR
Wildtype	77 (53%)	68 (47%)
Mutant	22 (61%)	14 (39%)

p-value = 0.5

PIK3CA mutation not correlated with pCR

Hoadley et al. SABCS 2014

Conclusions

- p53 the most mutated gene (56% overall)
- P53 mutations associated with pCR
- PIK3CA mutations and other less common mutations did not correlate with pCR

P4-15-09 Phase 1 study of T-DM1 in HER2-positive patients with MBC and normal or reduced hepatic function

- Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab, a stable linker, and the microtubule inhibitor DM1. In phase 3 studies of HER2-positive MBC, T-DM1 significantly increased PFS (EMILIA and TH3RESA) and OS (EMILIA) vs. control regimens.
- 2-4% of patients treated with T-DM1 - grade ≥3 increases in transaminases. No data on PK of T-DM1 in patients with hepatic impairment.
- International, multicenter, open-label, parallel group, phase 1 PK study (BO25499/NCT01513083) designed to assess PK of T-DM1 in MBC patients with normal hepatic function and mild or moderate hepatic impairment

Li, et al. SABCS 2014

P4-15-09 Phase 1 study of trastuzumab emtansine in HER2-positive patients with MBC and normal or reduced hepatic function

- Up to 10 patients each with HER2-positive MBC and ECOG PS of 0–2 enrolled in 1 of 3 independent cohorts based on hepatic function per Child-Pugh criteria:
  - normal hepatic function
  - mild hepatic impairment (Child-Pugh A)
  - moderate hepatic impairment (Child-Pugh B).
  - Patients with severe hepatic impairment (Child Pugh C) were ineligible.
- Patients received 3 cycles of T-DM1 3.6 mg/kg Q 3 weeks. After 3 cycles, patients could continue to receive T-DM1 until disease progression, unmanageable toxicity, or study termination in present study, or enrollment in extension study (BO25430/TDM4529g).
- PK samples collected during cycles 1, 2 and 3

Li, et al. SABCS 2014

P4-15-09 Phase 1 study of trastuzumab emtansine in HER2-positive patients with MBC and normal or reduced hepatic function

- PK data were fully evaluable for 10 out of 10 patients each in the normal and mild cohorts and for 6 out of 7 patients in the moderate cohort.
- Compared with normal cohort, T-DM1 clearance at cycle 1 was ~1.9- and 3.3-fold faster in the mild and moderate cohorts, respectively.
- Trend of faster clearance less apparent for cycle 3 after repeated dosing, with similar T-DM1 exposures across the 3 cohorts.
- Plasma concentrations of DM1 and DM1-containing catabolites were largely comparable across the 3 cohorts.
- No new safety signals were seen relative to the known safety profile of T-DM1.

Li, et al. SABCS 2014

Conclusions- HER2 positive disease

- Trend for faster clearance of T-DM1 at cycle 1 in patients with mild and moderate hepatic impairment vs. those with normal hepatic function
  - can be partly explained by demographic and pathophysiological covariates such as tumor burden, albumin, and body weight.
  - study's small sample size could also partly explain the variability.
- Work to better understand the mechanisms for the observed differences in clearance is ongoing
- No increase in the systemic concentration of DM1 was observed in patients with mild or moderate hepatic impairment vs. those with normal hepatic function.
- No additional safety concerns were observed.

Li, et al. SABCS 2014

Conclusions

- The BOLERO-1 study failed to reach it primary endpoint of improvement of PFS with everolimus with trastuzumab and chemotherapy in the first line setting
- Data from BOLERO-1 validate the observation seen in BOLERO-3 that treatment effect of EVE differs depending on HR status
- Targeted therapy without chemotherapy may be a promising strategy in patients with HER2 +/ER + BC
- T-DM1 clearance at cycle 1 was faster in the mild and moderate liver dysfunction cohorts
- P53 mutations are associated with pCR rates
- The role of LPBC may be worth investigating