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Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer Receiving Neoadjuvant Systemic Therapy

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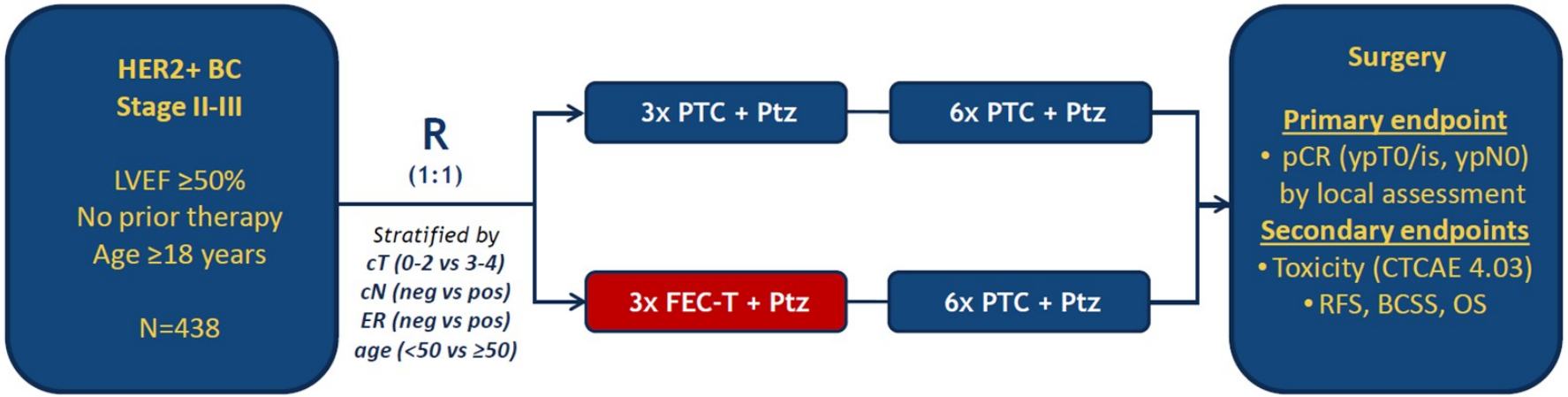
Rationale for neoadjuvant therapy in breast cancer

- Early introduction of therapy for distant micro-metastatic disease
- Converting inoperable to operable breast cancer
- Facilitation of breast conserving surgery
- Down-staging of the axilla
- Assessment of clinical and pathologic response to systemic therapeutics
  - To tailor systemic adjuvant therapy based on pCR
- Opportunity for assessment of molecular, pharmacodynamic and intra-tumoral pharmacokinetic measures

Courtesy of Mark D Pegram, MD

Three year follow-up of neoadjuvant chemotherapy with or without anthracyclines with dual HER2 antibody blockade

TRAIN-2: study design



- PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m^2; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg·min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)
- FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m^2; E = epirubicin 90mg/m^2; C = cyclophosphamide 500mg/m^2;T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)
- Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

van Ramshorst et al, *Lancet Oncol* 2018; van Ramshorst et al, *Eur J Cancer* 2017

ClinicalTrials.gov identifier: NCT01996267

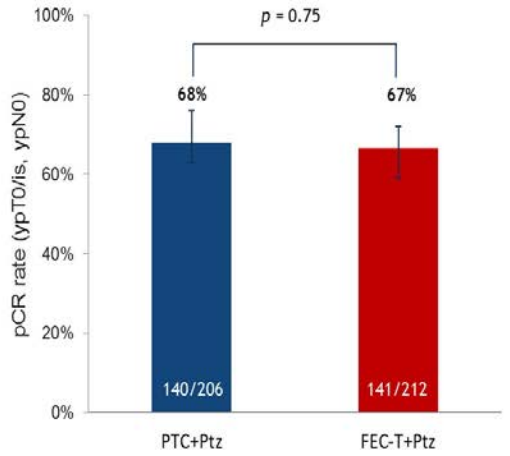
Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

TRAIN-2: primary endpoint pCR
ASCO 2020 Update time-to-event analysis (EFS)

TRAIN-2: primary endpoint pCR

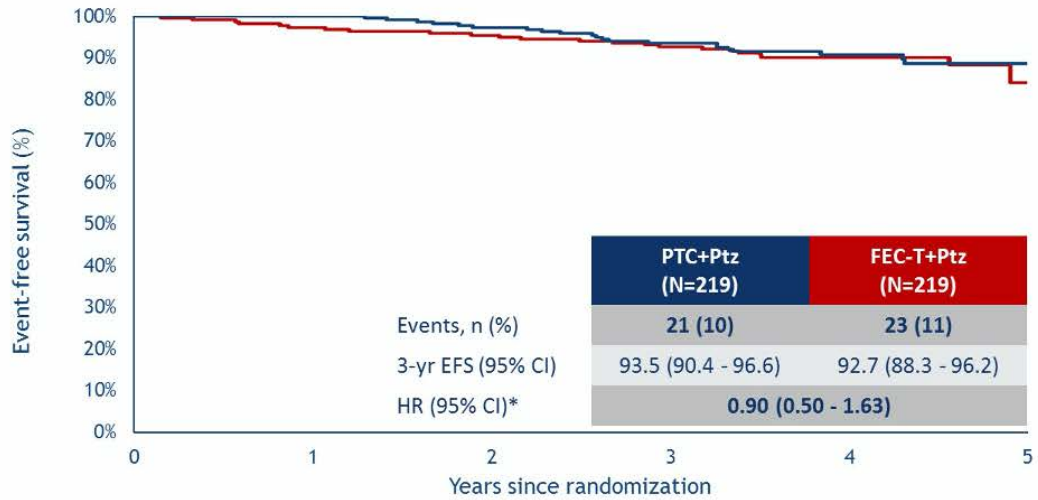
- High pathological complete response rates with and without anthracyclines
- Main outcome was consistent across levels of prespecified subgroups
  - cT (0-2 vs 3-4)
  - cN (negative vs positive)
  - HR (negative vs positive)
  - age (<50 vs ≥50)



van Ramshorst et al, *Lancet Oncol* 2018

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Anna van der Voort

Event-free survival



	PTC+Ptz (N=219)	FEC-T+Ptz (N=219)
Events, n (%)	21 (10)	23 (11)
3-yr EFS (95% CI)	93.5 (90.4 - 96.6)	92.7 (88.3 - 96.2)
HR (95% CI)*	0.90 (0.50 - 1.63)	

No. at risk						
PTC+Ptz	219	219	212	203	106	19
FEC-T+Ptz	219	213	209	200	103	17

*HR <1 favors PTC+Ptz

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Anna van der Voort

EFS by nodal status – no hint of advantage of anthracyclines even in high risk subgroups (cN2/3; HR=0.75 w/ trend favoring non-anthracycline)

Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

Safety: cardiotoxicity and new malignancies

Safety: cardiotoxicity

	PTC+Ptz (n=218) n (%)	FEC-T+Ptz (n=220*) n (%)	p-value
LVEF decrease ≥10% or LVEF <50%	49# (22%)	80 (36%)	0.0016
LVEF decrease ≥10% and LVEF <50%	7 (3%)	17 (8%)	0.044

LVEF was measured every 3 months for 1 year
* one patient was allocated to PTC+Ptz but received neoadjuvant FEC-T+PTZ
# one patient developed grade 2 LVEF decline during adjuvant treatment with anthracyclines

LVEF decline did not recover to normal during follow-up in about one third of the patients

Safety: new malignancies

	PTC+Ptz (n=218*) n (%)	FEC-T+Ptz (n=220#) n (%)
Acute leukemia†	0	2 (1%)
Female genital cancer	0	2 (1%)
Lung carcinoma	1 (<1%)	0
Melanoma	1 (<1%)	0
Papillary thyroid carcinoma	0	2 (1%)
Tongue carcinoma	1 (<1%)	0
Non-melanoma skin cancer	2 (1%)	5 (2%)
Total	**5 (2%)**	**11 (5%)**

* two patients in the PTC+Ptz arm received adjuvant adjuvant anthracyclines
# one patient was allocated to PTC+Ptz but received FEC-T+Ptz
† acute leukemia was chemotherapy associated in both patients

Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

Is the anthracycline TRAIN(-2) finally derailed?

Conclusions

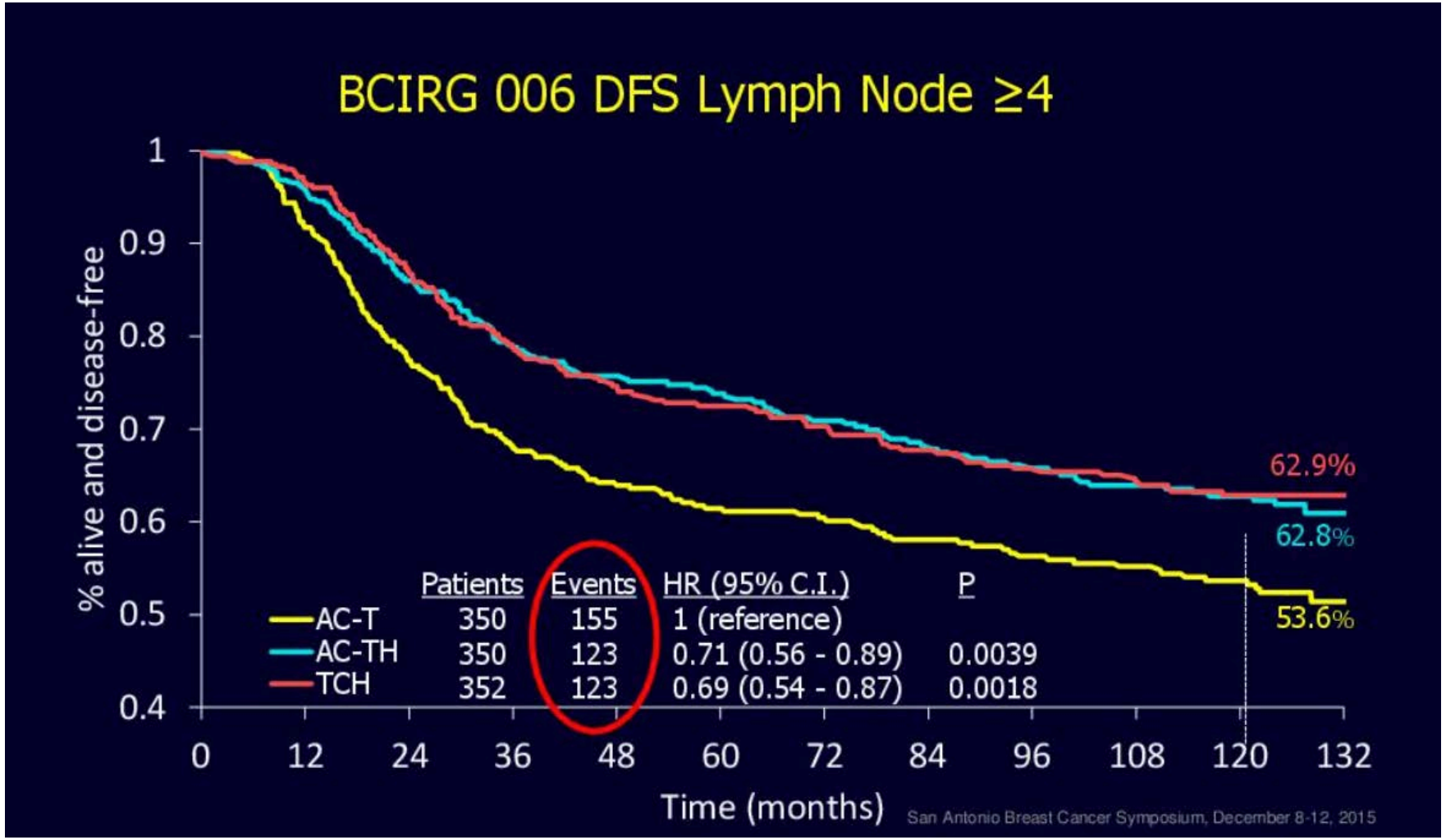
- Three-year follow-up of the TRAIN-2 study shows no EFS and OS benefit for an anthracycline-containing regimen in stage II and III HER2-positive breast cancer
- There is no evidence that higher risk HER2-positive breast cancer patients require anthracyclines
- The addition of anthracyclines increases the risk of febrile neutropenia and cardiac toxicity
- Next step: further de-escalate chemotherapy

Naysayers will say "only" 438 patients, only 3 cycles of FEC, epirubicin dose only 90mg/m^2

Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

TEN YEAR FOLLOW-UP OF THE BCIRG-006 TRIAL COMPARING DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL (ACT) WITH DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL AND TRASTUZUMAB (ACTH) WITH DOCETAXEL, CARBOPLATIN AND TRASTUZUMAB (TCH) IN HER2+ EARLY BREAST CANCER PATIENTS

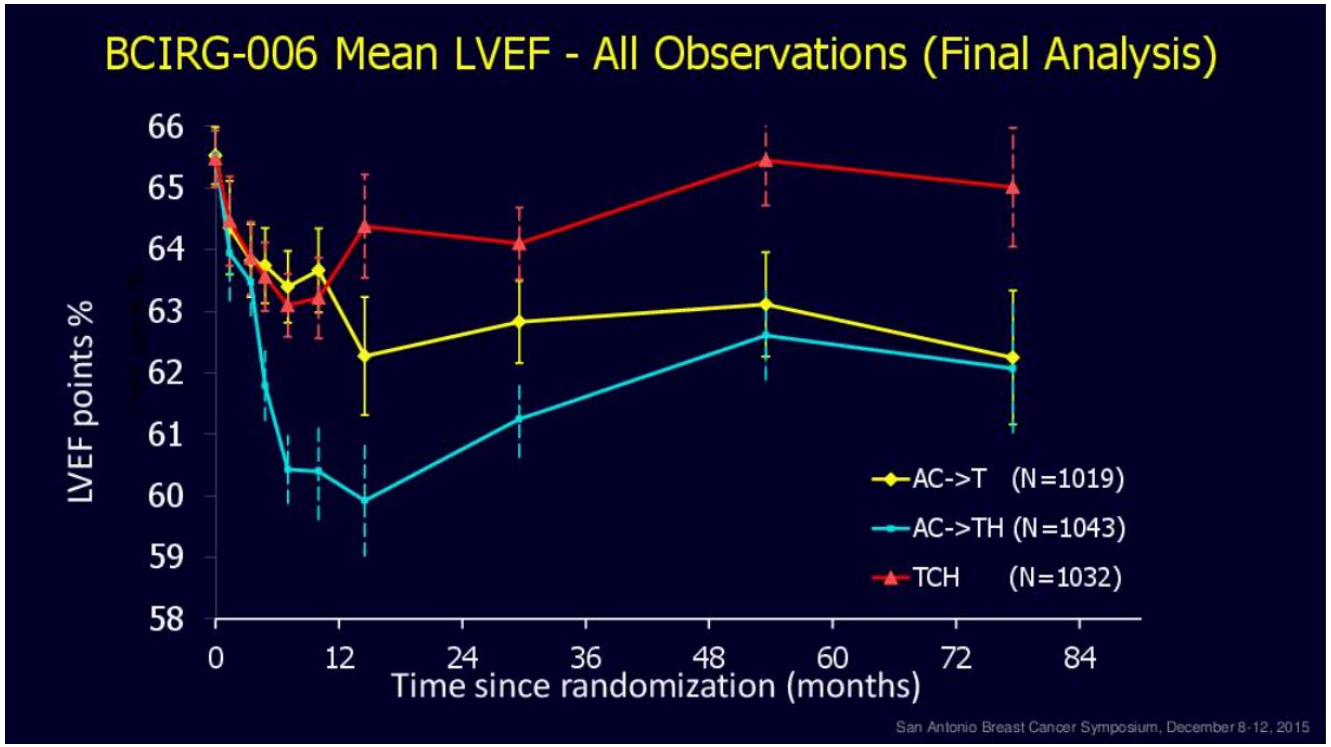


- **Projected DFS in ITT population at year 10 (N=3,222) is 73% (TCH arm) and 74.6% (AC-TH arm, P = N.S.)**
- **Only 10 events (of 876 in the ITT population) now separate the 2 trastuzumab arms**
- **No difference in OS**

Slamon DJ, et al. Cancer Research 76(4 Supplement):S5-04-S5-04 (2016).

Courtesy of Mark D Pegram, MD

BCIRG 006 Cardiac Safety Data -- 10.3 year follow-up



BCIRG 006
Patients with >10% relative LVEF decline

	AC→T n = 1,018	AC→TH n = 1,042	TCH n = 1,031
Number of Patients	120	200	97

p<0.0001

San Antonio Breast Cancer Symposium, December 8-12, 2015

BCIRG 006 Cardiac Deaths and CHF

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
Cardiac related death	0	0	0
Cardiac left ventricular function (CHF) Grade 3 / 4	8	21	4

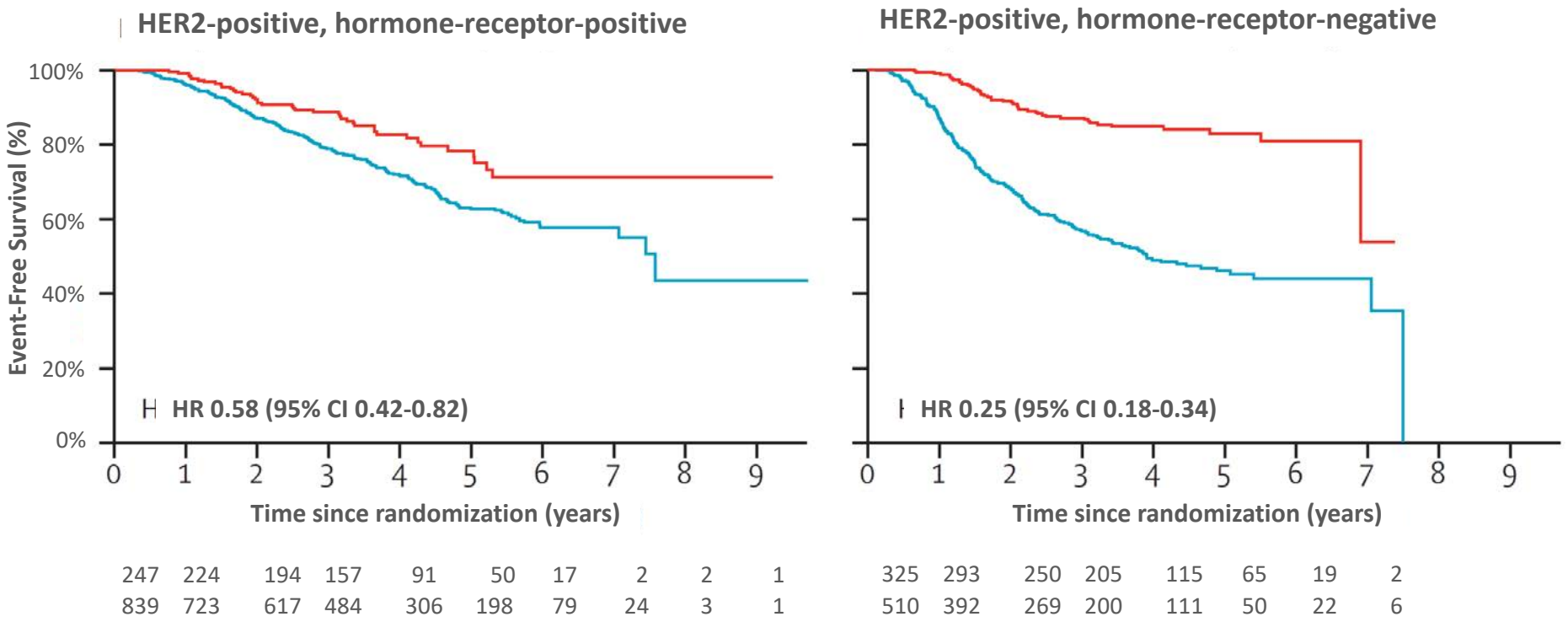
p=0.0005

San Antonio Breast Cancer Symposium, December 8-12, 2015

Slamon DJ, et al. Cancer Research 76(4 Supplement):S5-04-S5-04 (2016).

Courtesy of Mark D Pegram, MD

Among neoadjuvant-treated HER2+ patients, even though pCR portends a more favorable prognosis, risk of relapse still exists



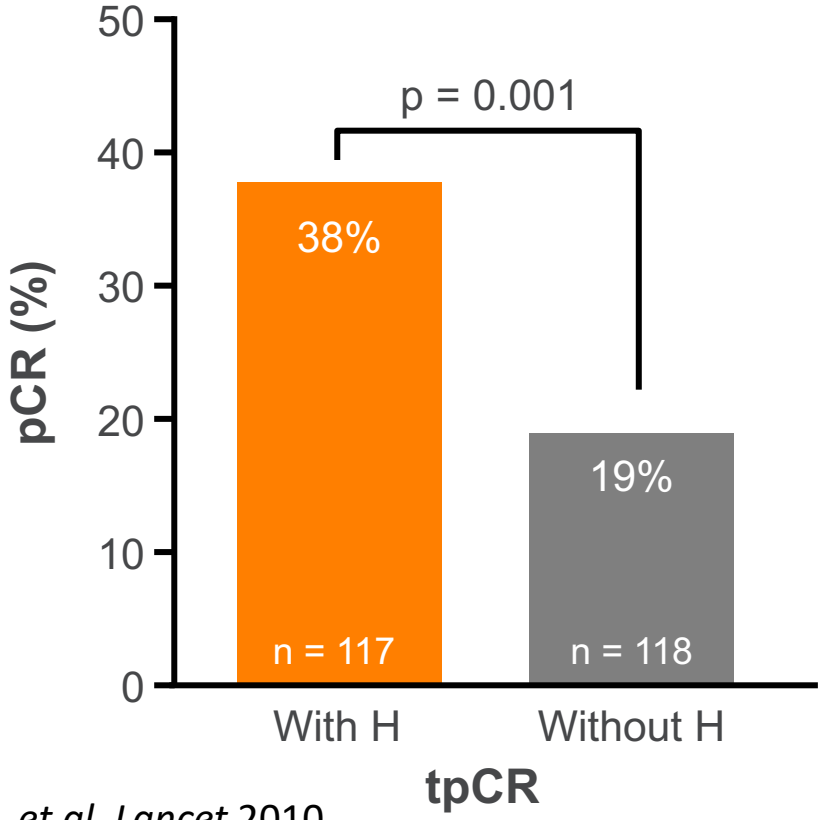
Red line: pCR
Blue line: non-pCR

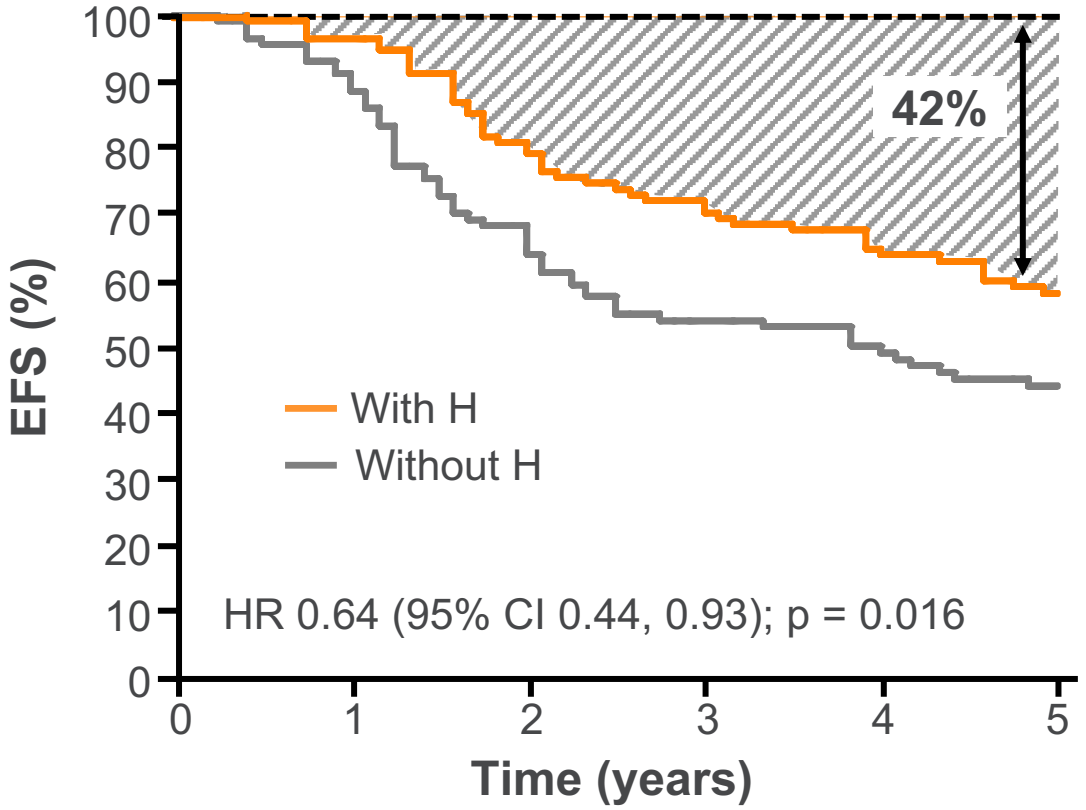
Cortazar, et al., FDA Meta-analysis. *Lancet* 2014

Courtesy of Mark D Pegram, MD

NOAH: Trastuzumab increased both pCR and EFS, but many patients still experienced recurrence

Increased pCR rates with trastuzumab added to chemotherapy resulted in improved EFS, but 42% of patients experienced disease recurrence at 5 years



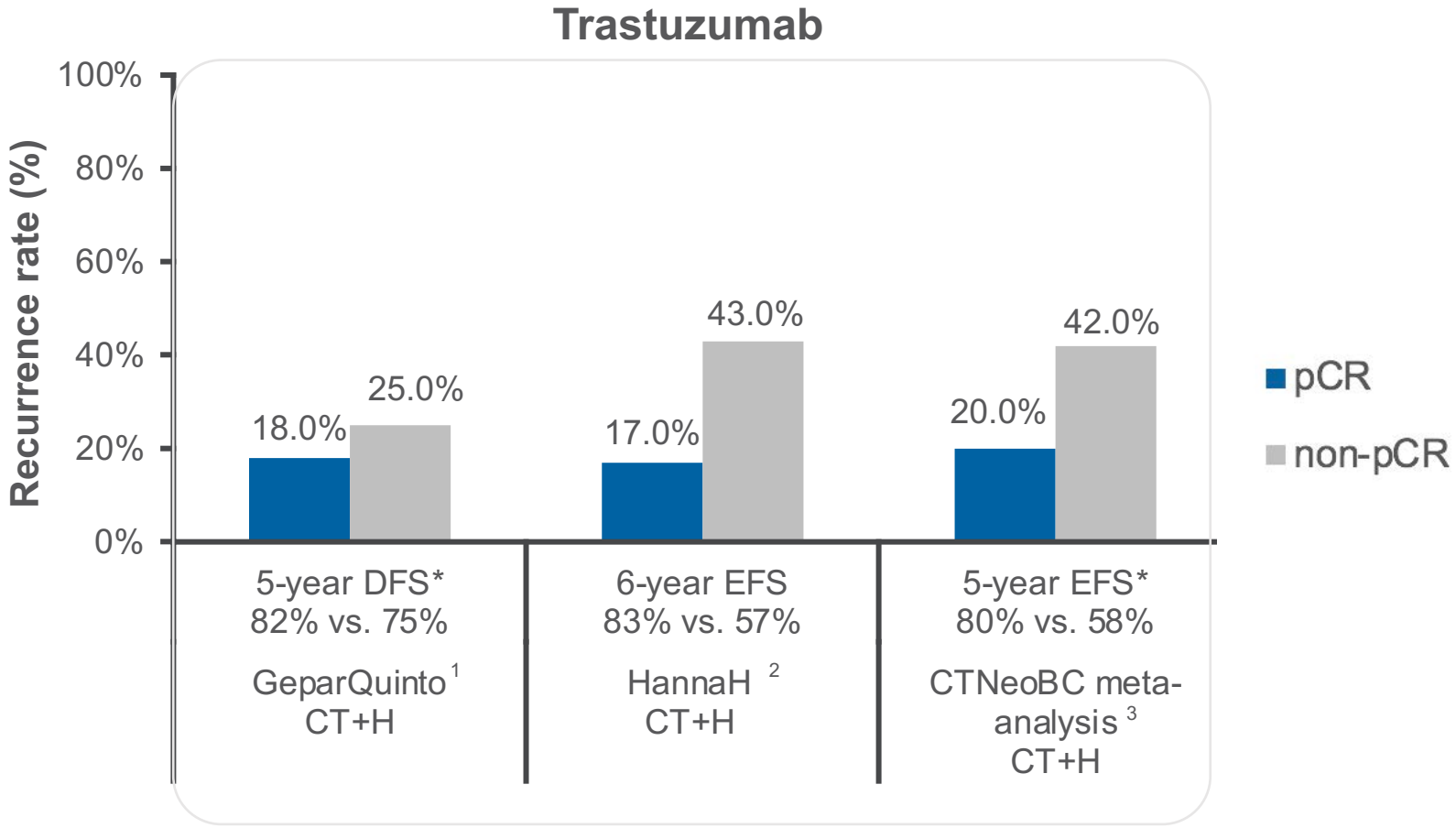


Gianni L, *et al. Lancet* 2010.

bpCR, pathological complete response in the breast; H, trastuzumab; tpCR, total pathological complete response.

Courtesy of Mark D Pegram, MD

Both pCR and non-pCR patients are at risk of relapse



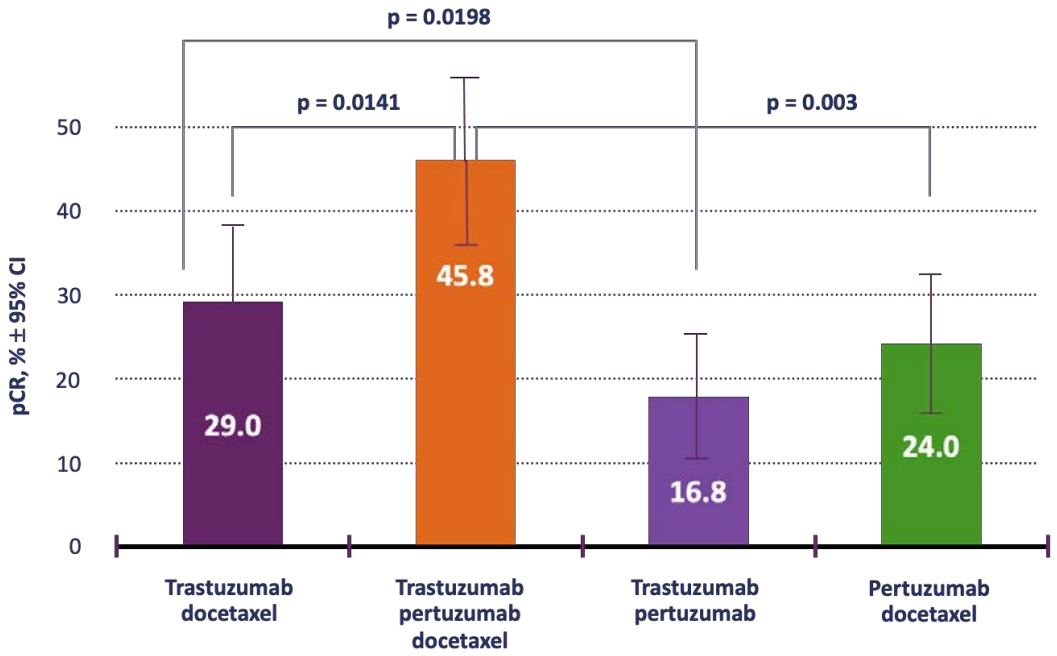
Despite achieving a pCR after trastuzumab therapy plus chemotherapy,
around 20% of patients with a pCR will experience disease recurrence or death within 5 years

1. Untch M, *et al.* ECC 2015; abstract 1801; 2. Jackisch C, *et al*. SABCS 2017; abstract. PD3-11;
3. Cortazar *et al. Lancet* 2014; 4. Gianni L, *et al. Lancet Oncol* 2016 (suppl info); 5. Schneeweiss A, *et al. European J of Cancer* 2018.
* Estimated from Kaplan–Meier curve.

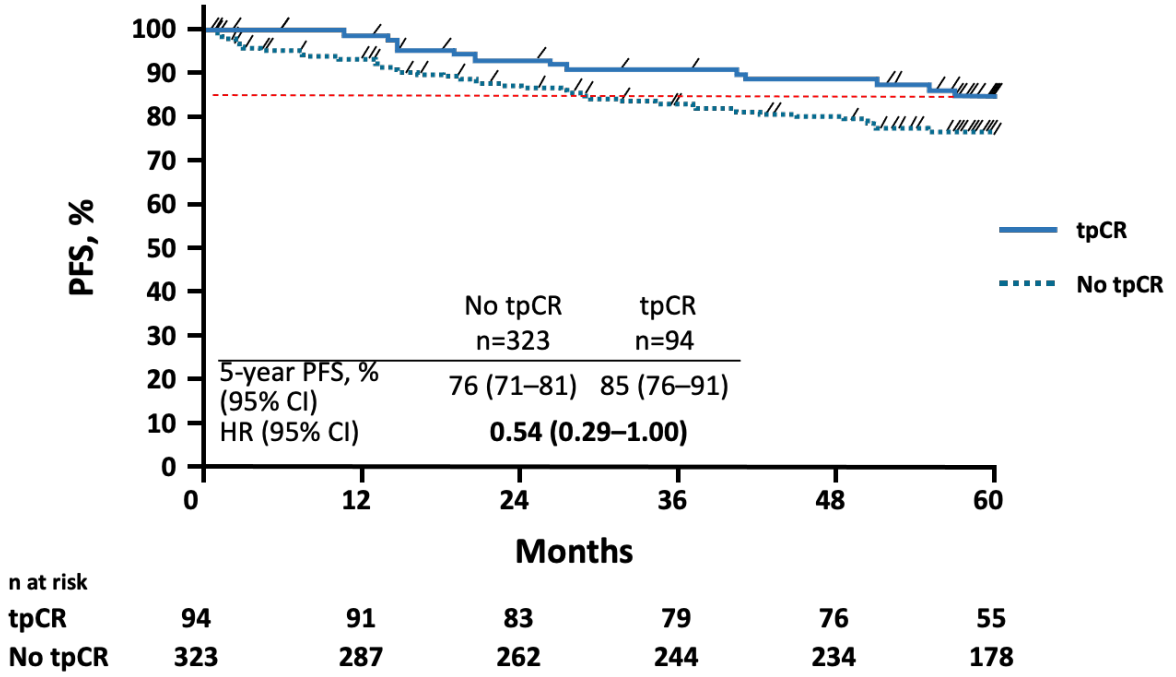
Courtesy of Mark D Pegram, MD

Five-year analysis of the phase II NeoSphere trial

pCR Rate, n=417 patients



PFS by tpCR: all treatment arms combined, ITT population



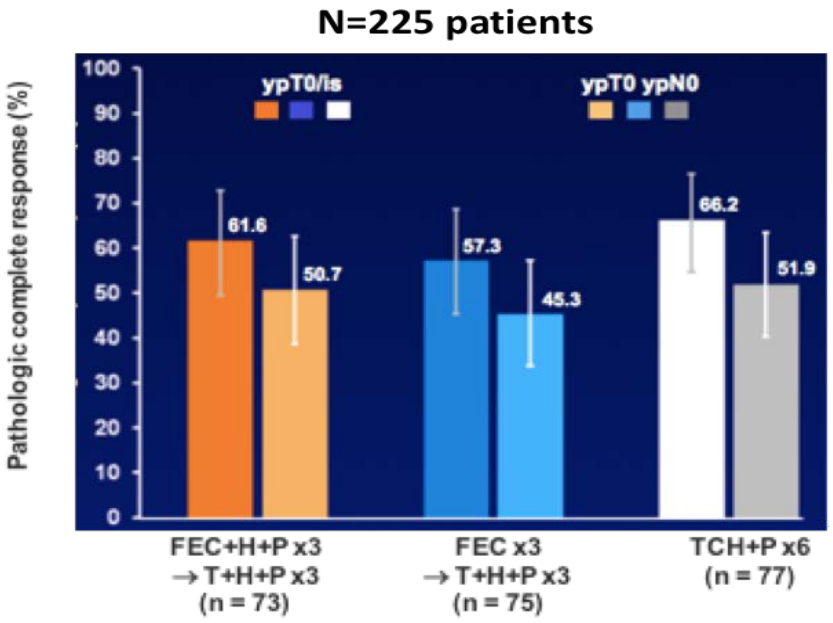
Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. One late event occurred in the no tpCR group due to PD at 71 months; one late event occurred in the tpCR group, a death due to an unrelated cerebrovascular accident without PD at 76 months.

Courtesy of Mark D Pegram, MD

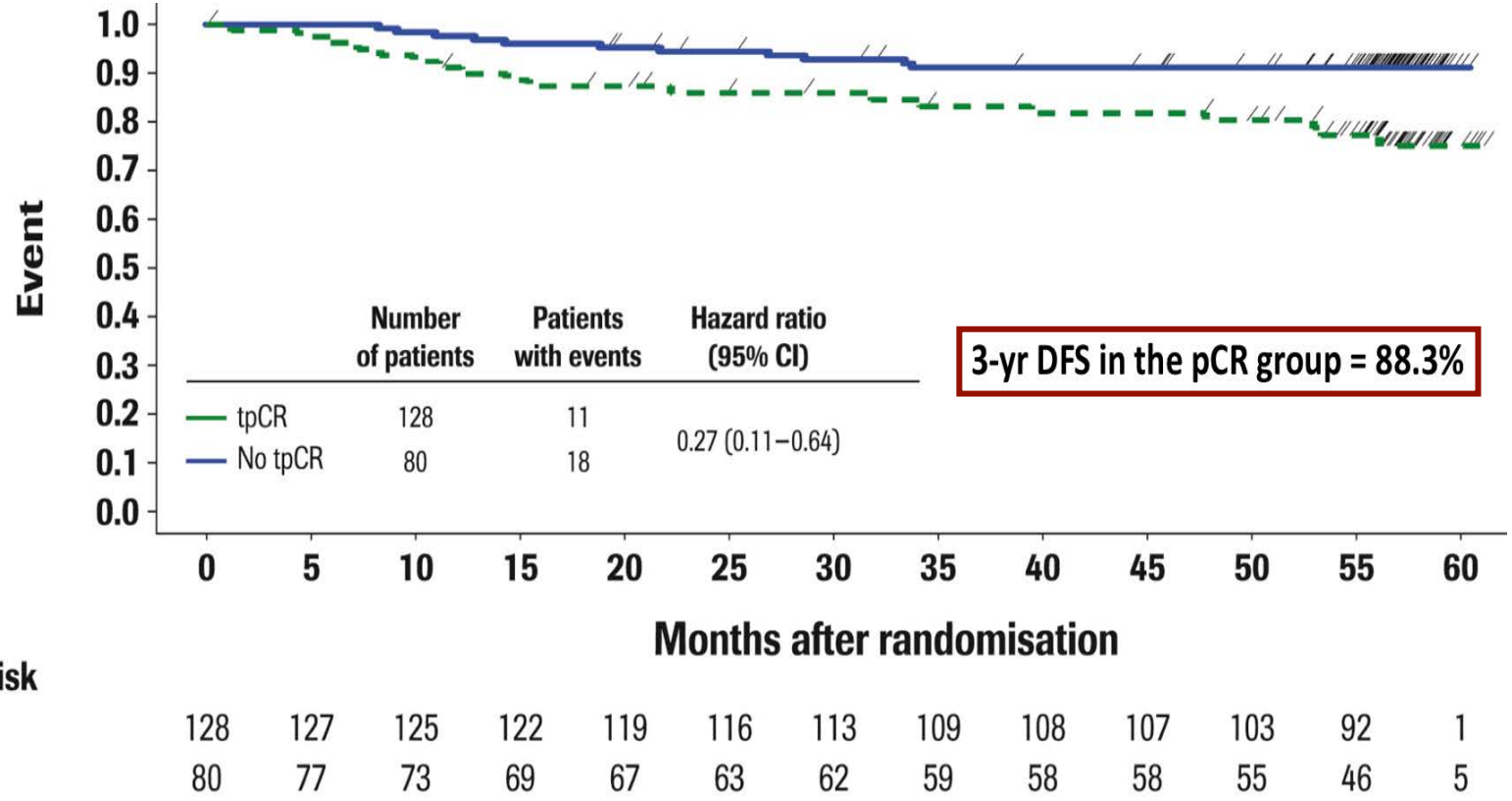
Gianni L, et al., Lancet Oncol. 2012 Jan;13(1):25-32;
L Gianni, et al., ASCO 2015

Long-term efficacy analysis of the randomised, phase II TRYPHAENA study

Disease-free survival in patients with and without tpCR (FECHP-THP, FEC-THP, TCHP)



FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab



Schneeweiss A, *et al*., Eur J Cancer. 2018 Jan;89:27-35.

Courtesy of Mark D Pegram, MD

Based on APHINITY, the FDA and EMA support the use of adjuvant pertuzumab–trastuzumab for 18 cycles in high-risk HER2-positive eBC

Pertuzumab Prescribing Information[1]

Indicated for use in combination with trastuzumab and chemotherapy as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer and the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. Following surgery, **patients should continue to receive pertuzumab and trastuzumab to complete 1 year of treatment (up to 18 cycles).**

Pertuzumab Summary of Product Characteristics[2]

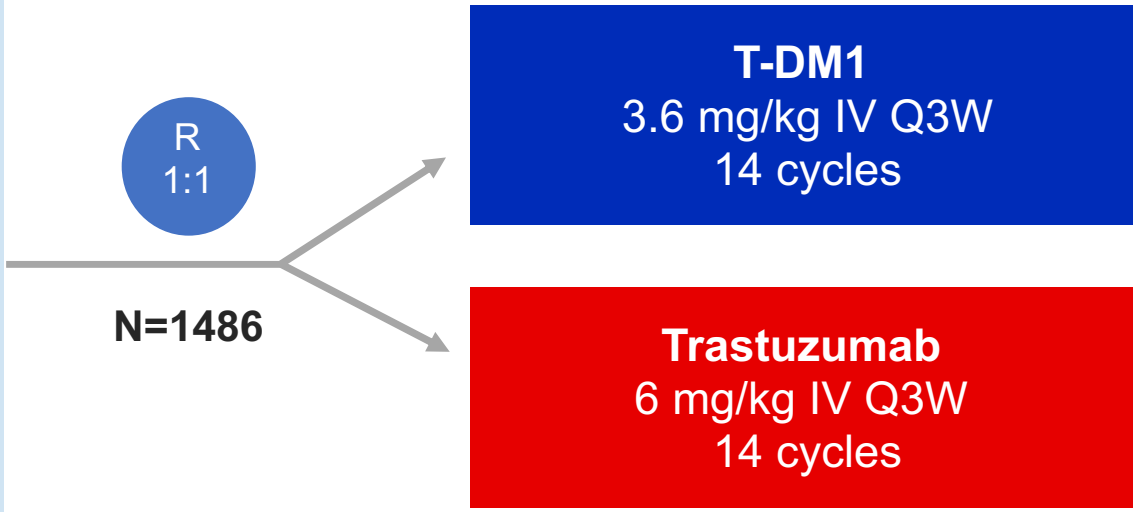
Pertuzumab is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.
Pertuzumab should be administered in combination with trastuzumab for a total of 1 year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery.

1. Pertuzumab US prescribing information, 2017 (Accessed Aug 2018); 2. Pertuzumab SmPC 2018 (Accessed Aug 2018).

Courtesy of Mark D Pegram, MD

KATHERINE Study Design

- **cT1-4/N0-3/M0 at presentation** (cT1a-b/N0 excluded)
- **Centrally confirmed HER2-positive breast cancer**
- Neoadjuvant therapy must have consisted of
  - **Minimum of 6 cycles of chemotherapy**
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - **Minimum of 9 weeks of trastuzumab**
    - Second HER2-targeted agent allowed
- **Residual invasive tumor in breast or axillary nodes**
- Randomization within 12 weeks of surgery



Radiation and endocrine therapy per protocol and local guidelines

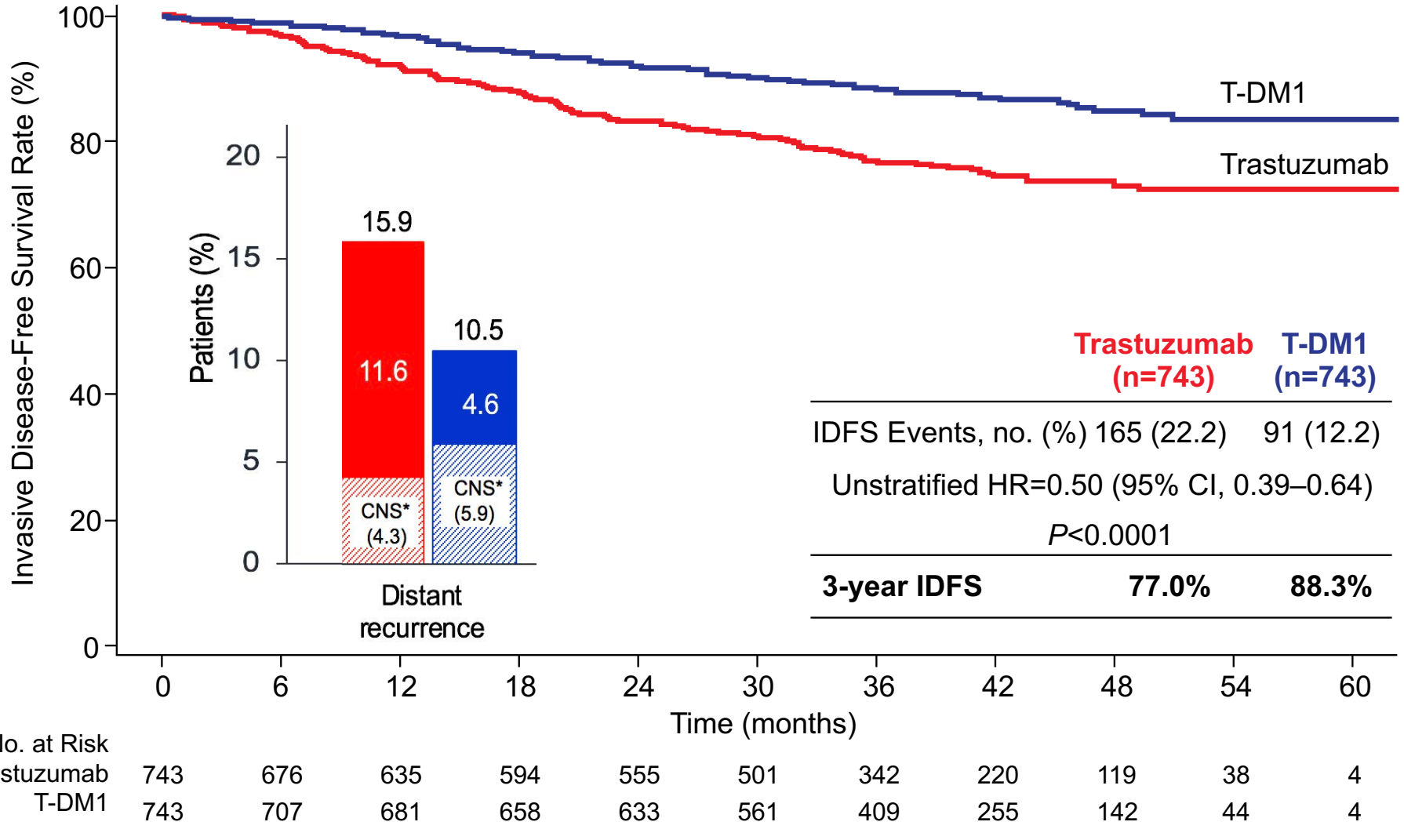
Stratification factors:

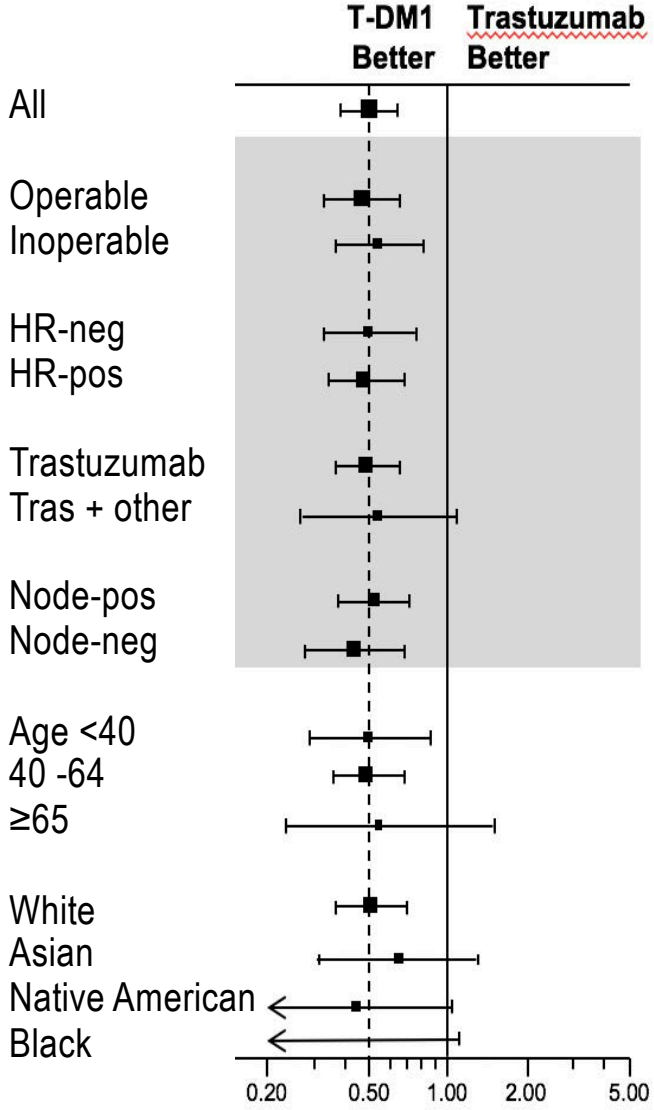
- Clinical presentation: **Inoperable (stage cT4 or cN2–3) vs operable** (stages cT1-3N0-1)
- **Hormone receptor**: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: **Trastuzumab vs trastuzumab plus other** HER2-targeted therapy
- **Pathological nodal status** after neoadjuvant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

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

Invasive Disease-Free Survival





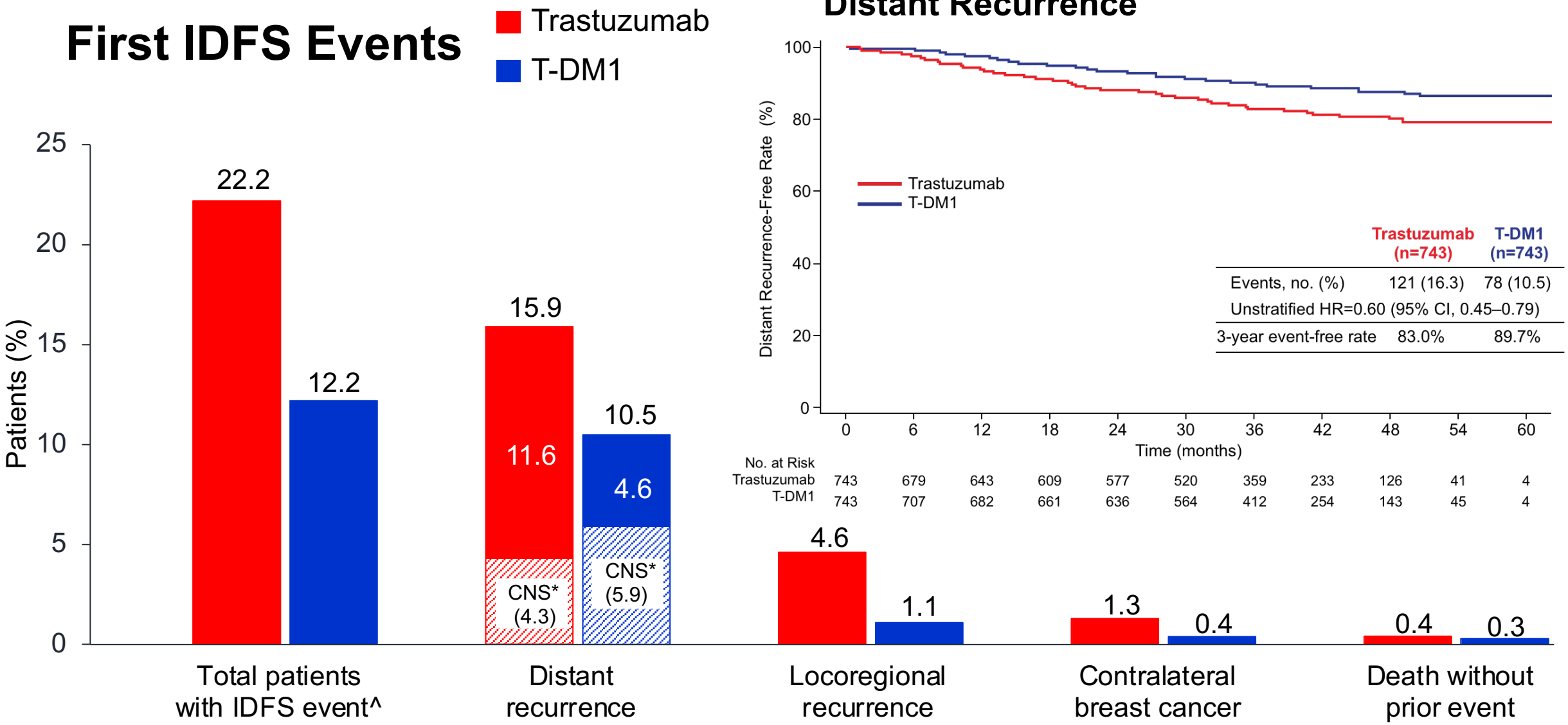
By comparison, 3 year DFS, B31/N9831 Joint Analysis: 87% vs. 75%

Echoes of "The results are simply stunning"? -- Gabriel N. Hortobagyi, N Engl J Med 2005; 353:1734-1736

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

First IDFS Events



Distant Recurrence

	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

No. at Risk											
Trastuzumab	743	679	643	609	577	520	359	233	126	41	4
T-DM1	743	707	682	661	636	564	412	254	143	45	4

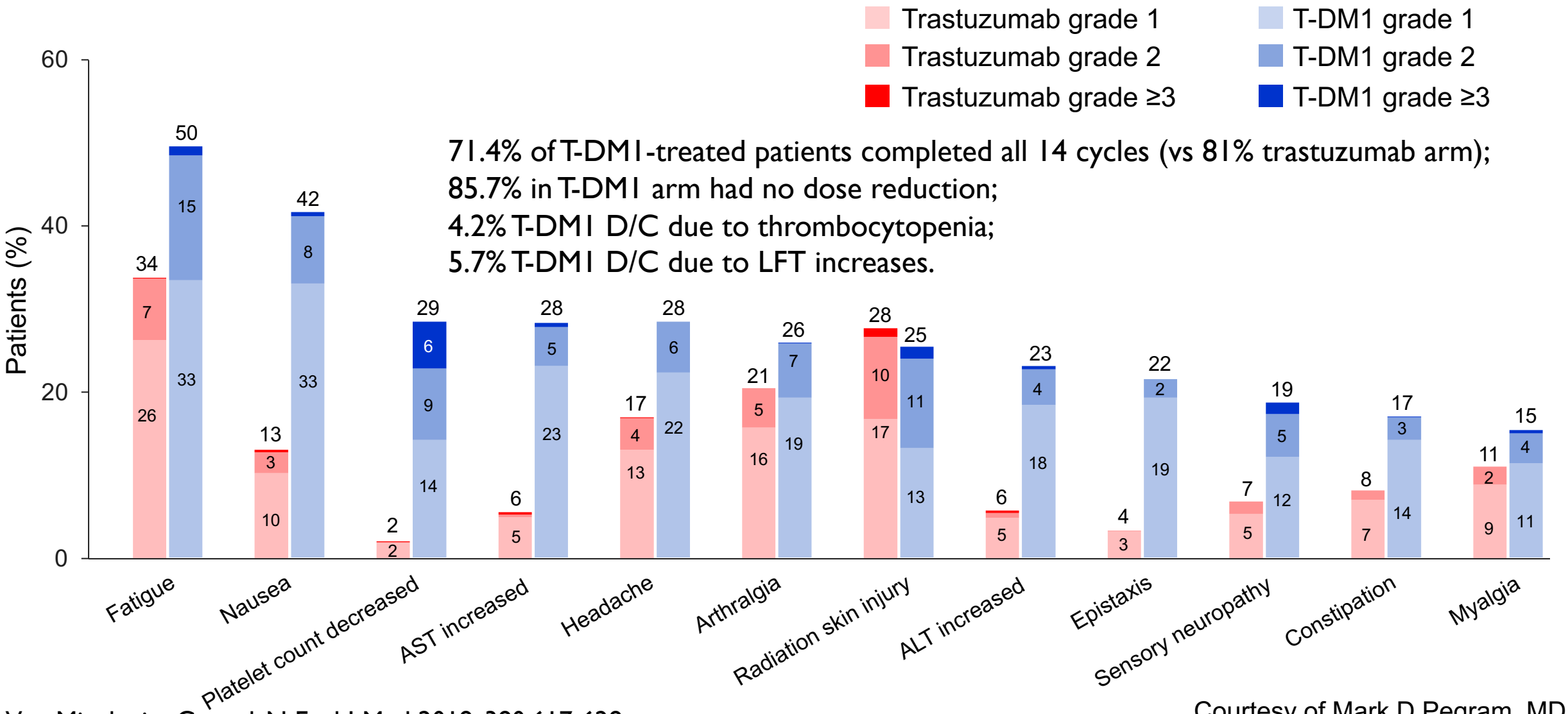
^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

***CNS metastases as component of distant recurrence (isolated or with other sites).** Trastuzumab T-DM1

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

All Grade AEs ≥15% Incidence in Either Arm



Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

CompassHER2 Trials

COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer

EA1181 *(approved by BCSC & CTEP in May 2019)*

Eligibility
HER2+ breast ca
Stage 2 or 3a
(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

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

ECOG-ACRIN cancer research group
Reshaping the future of patient care

→ No pCR → A011801 Alliance Part 2 if RD (60%)

Alliance for Clinical Trials in Oncology

Rationale: Potential overtreatment of some patients w/ HER2+ breast ca w/ polychemo plus poly-HER2 Rx; Use of path response as a functional biomarker for escalation if non-pCR (e.g. T-DM1) and de-escalation if pCR

Primary Objective: 3y RFS HER2+ (patients w/ pCR)
n=1250 (3y RFS H_0=92%, H_1≥95%
Secondary Objectives: 3y RFS and pCR by intrinsic subtype

Courtesy of Mark D Pegram, MD

CONCLUSIONS

- We've reviewed indications for neoadjuvant systemic therapy in patients with HER2-positive localized BC
- Reviewed long-term efficacy outcomes with the use of anthracycline- and non-anthracycline-based neoadjuvant systemic therapy platforms; prognosis of patients who experience a pathologic complete response compared to those who do not
- Considered key efficacy and safety results from the Phase III KATHERINE trial
- Safety profile of pertuzumab–trastuzumab was consistent with previous trials, with no new or unexpected safety signals
- The FDA and EMA labels and international guidelines support the use of pertuzumab–trastuzumab in the adjuvant setting[1-4]
- Discussed design of and rationale for other planned clinical trials seeking to use pathologic response assessment to optimize therapy for localized HER2-positive BC (eg, CompassHER2)

James H. Clark Center
Stanford University

Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering

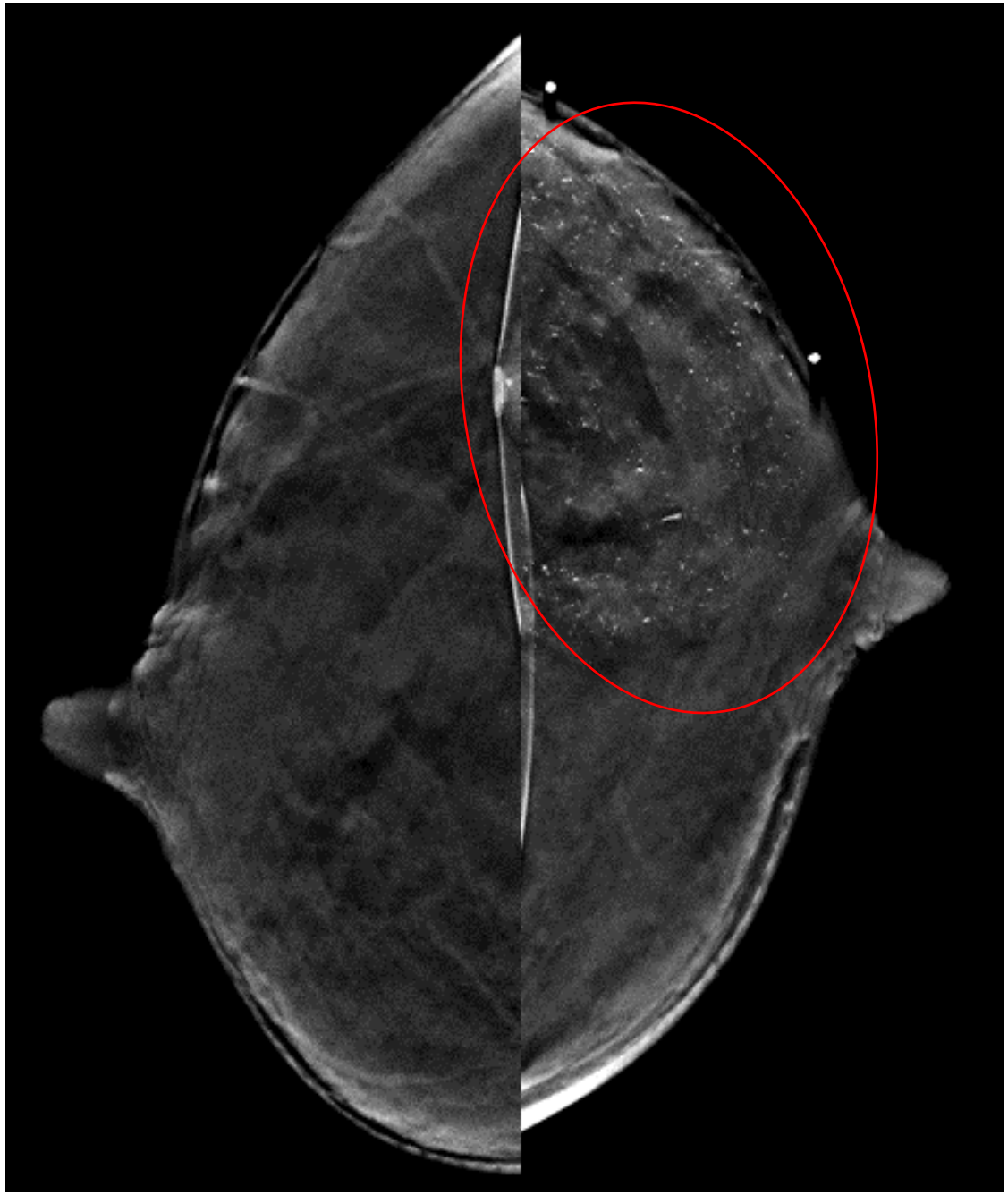
Courtesy of Mark D Pegram, MD

1. Pertuzumab US PI 2017 (accessed Aug 2018);
2. Pertuzumab SmPC 2018 (accessed Aug 2018);
3. NCCN Breast Cancer Guidelines. Version 1, 2018 – March 20, 2018;
4. AGO Guidelines March 2018 (accessed Aug 2018).

Case 1

- 42-year-old female noticed diffuse palpable abnormalities in lateral left breast and left axilla over 6 month period while breastfeeding

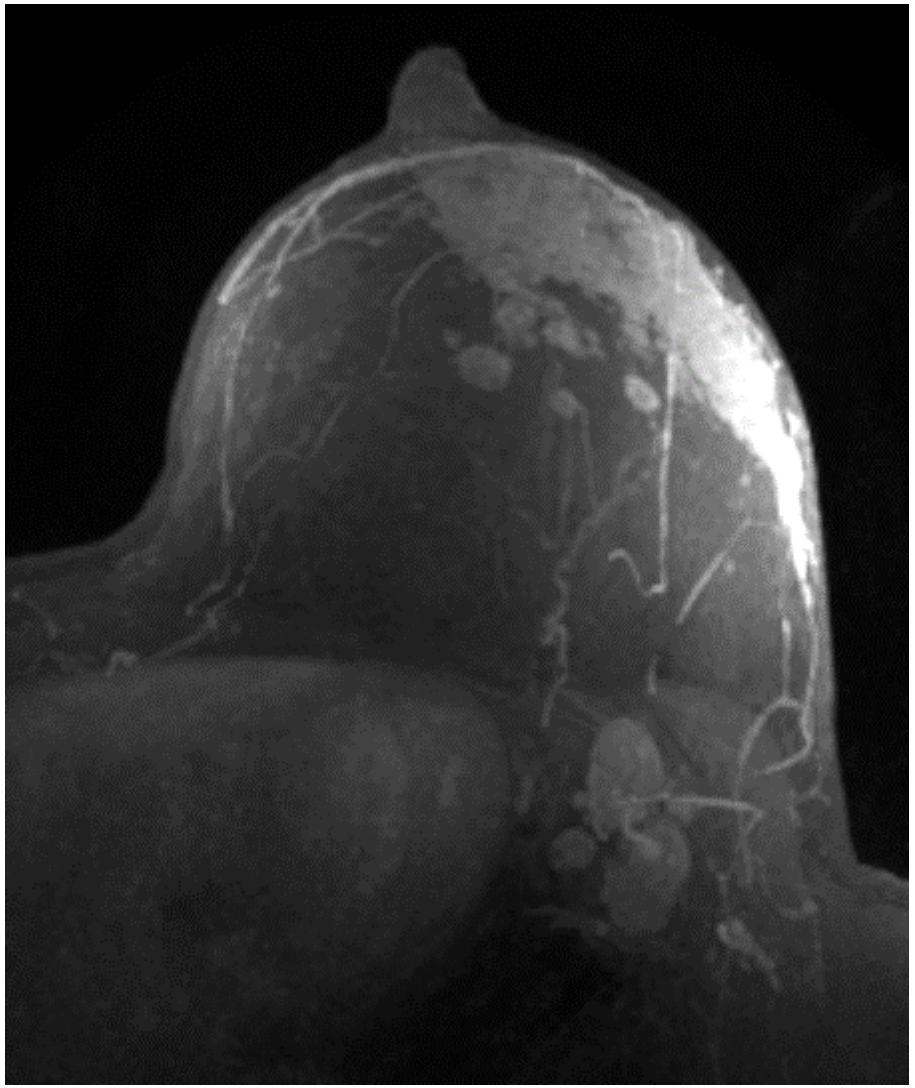
Courtesy of Mark D Pegram, MD



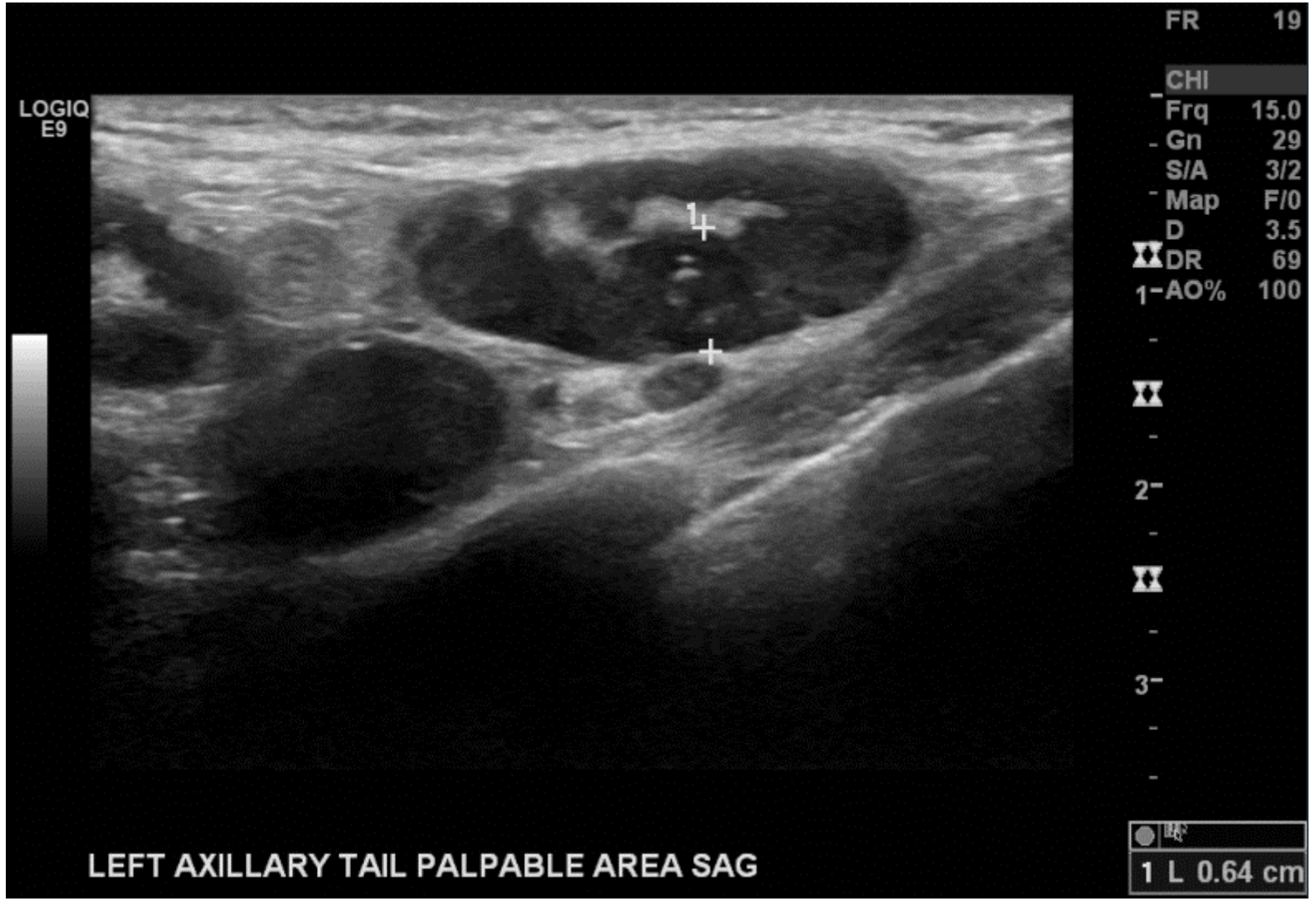
Courtesy of Mark D Pegram, MD

MRI shows abnormal clumped NME spanning the upper outer and entire lower outer quadrant, abnormal lymph nodes

5/25/18 MRI

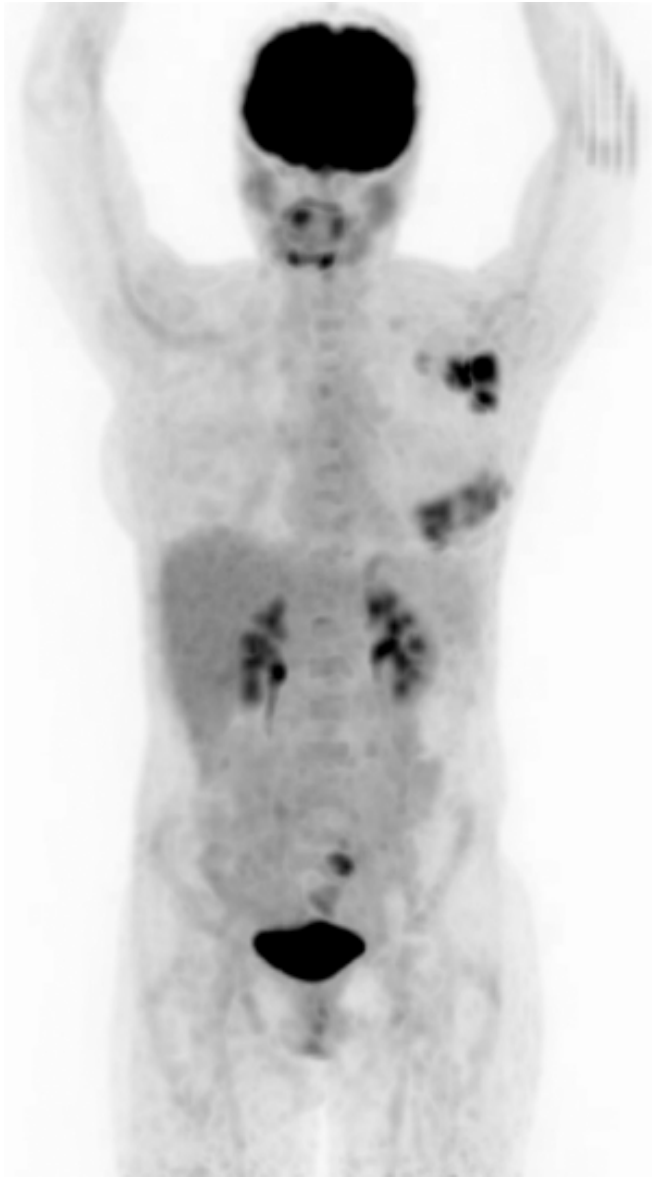


Courtesy of Mark D Pegram, MD



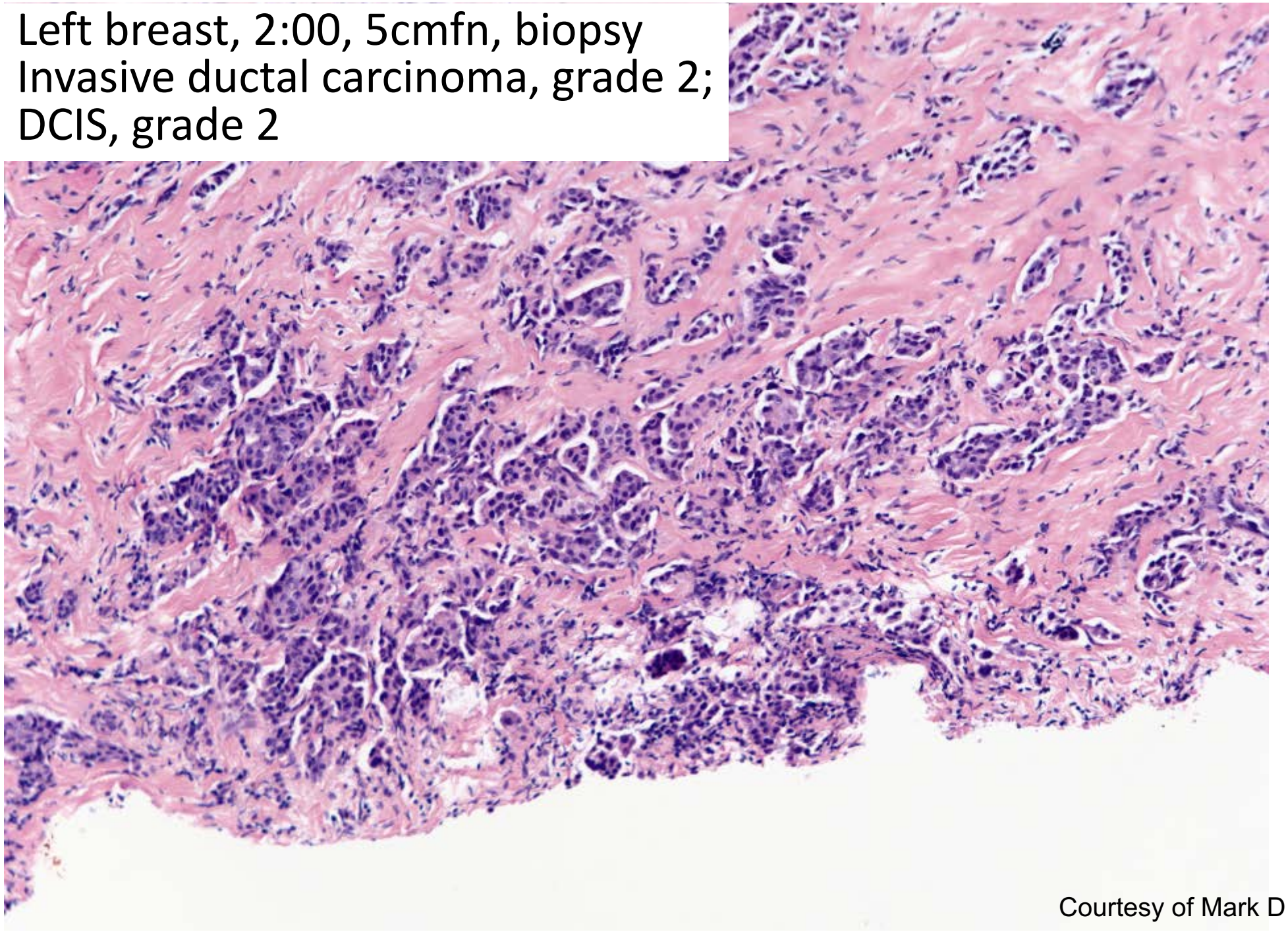
Courtesy of Mark D Pegram, MD

FDG PET/CT shows axillary nodal and breast disease, no distant disease



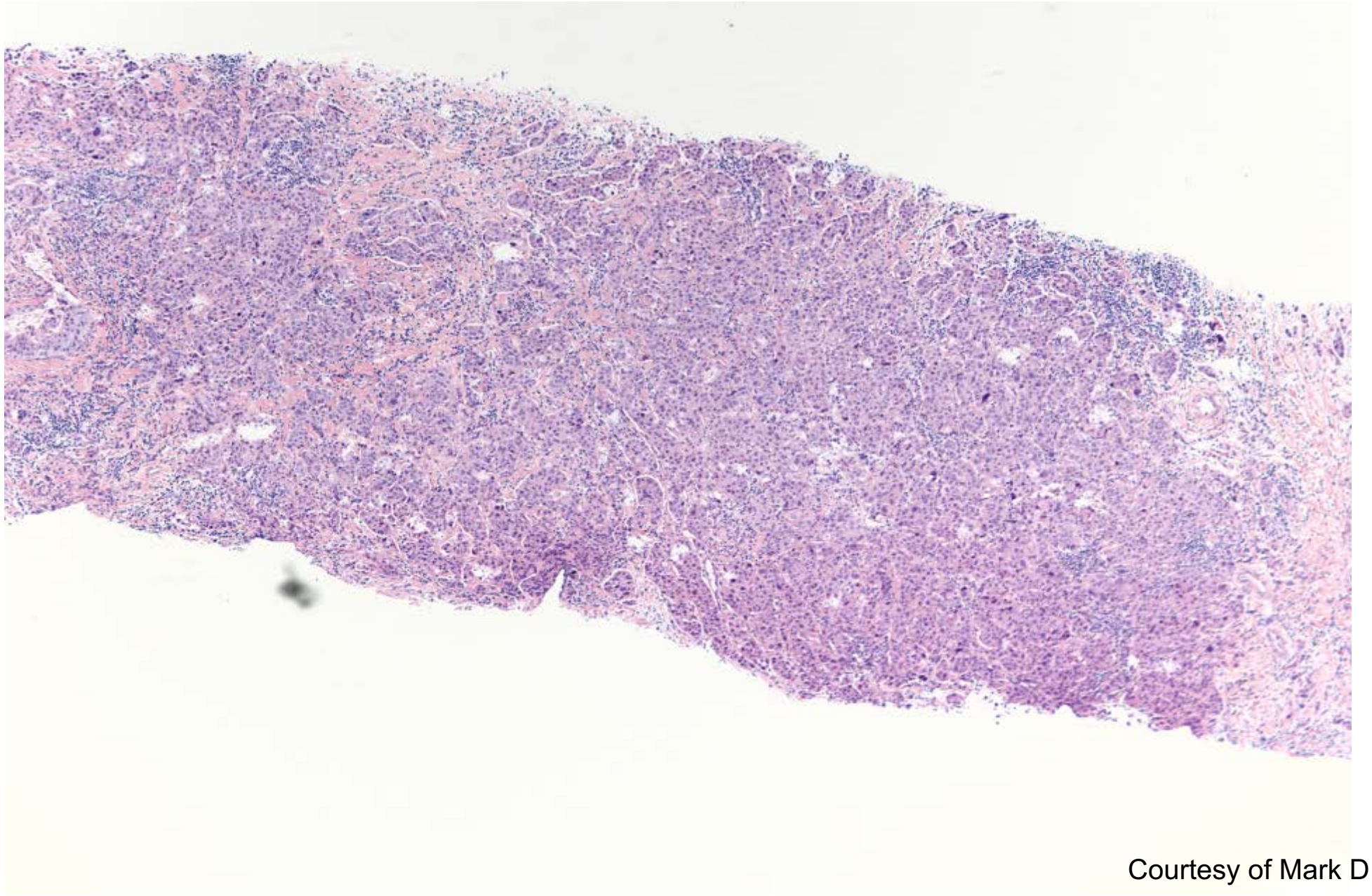
Courtesy of Mark D Pegram, MD

Left breast, 2:00, 5cmfn, biopsy
Invasive ductal carcinoma, grade 2;
DCIS, grade 2



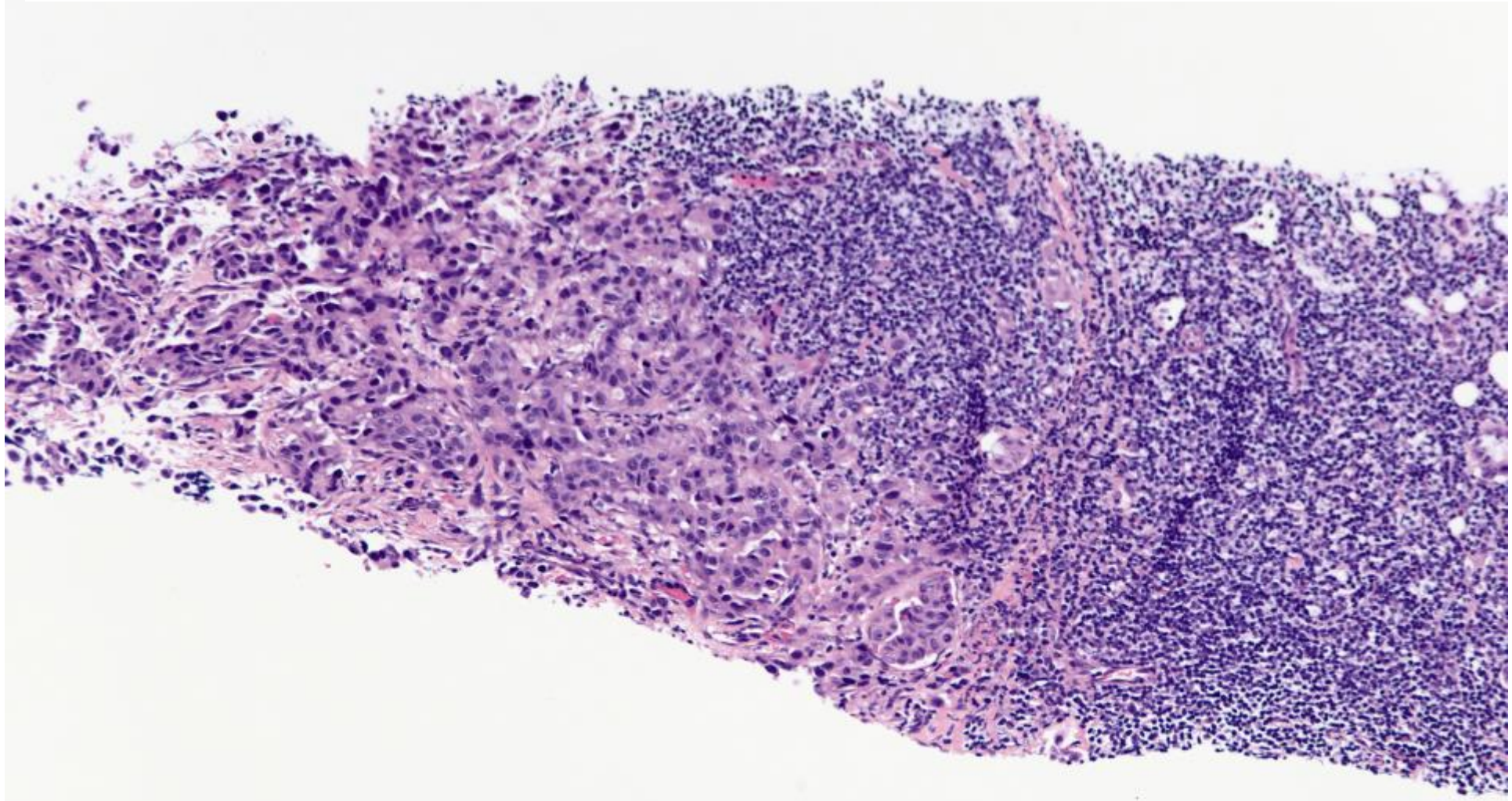
Courtesy of Mark D Pegram, MD

Left breast, 6:00, biopsy -- Invasive ductal carcinoma, grade 2-3; DCIS, grade 3

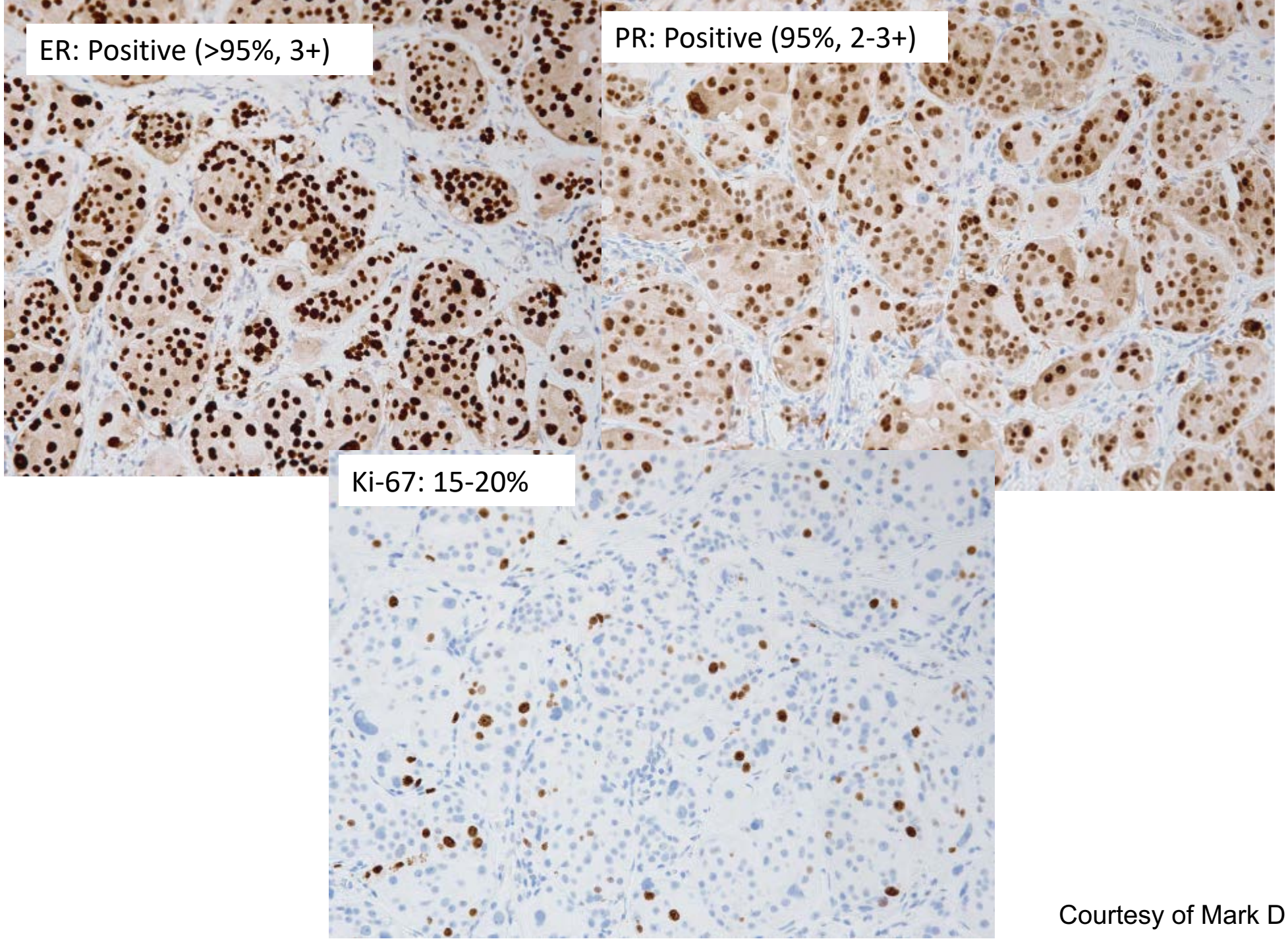


Courtesy of Mark D Pegram, MD

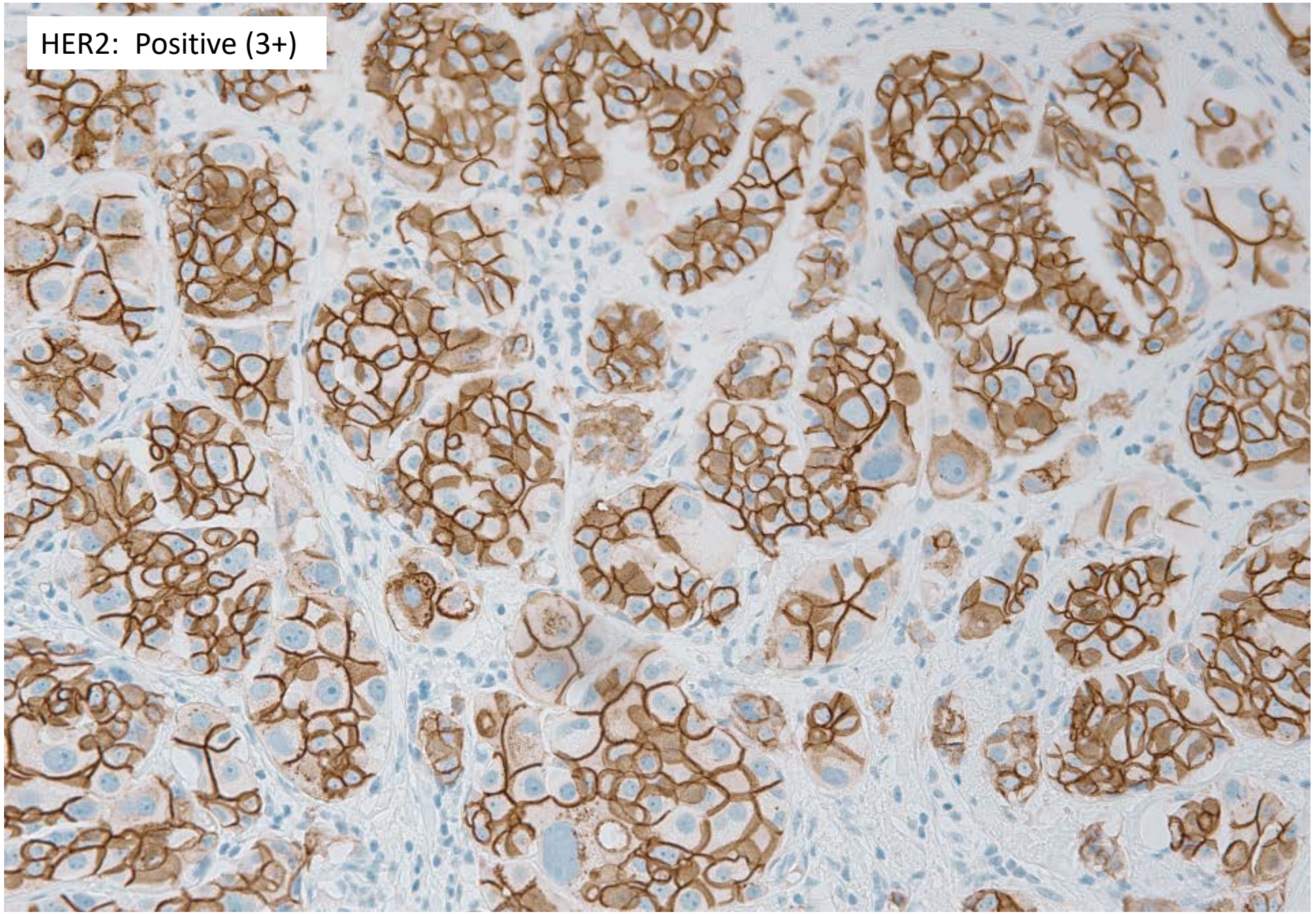
Left axilla, biopsy -- Metastatic ductal carcinoma (0.8 cm)



Courtesy of Mark D Pegram, MD



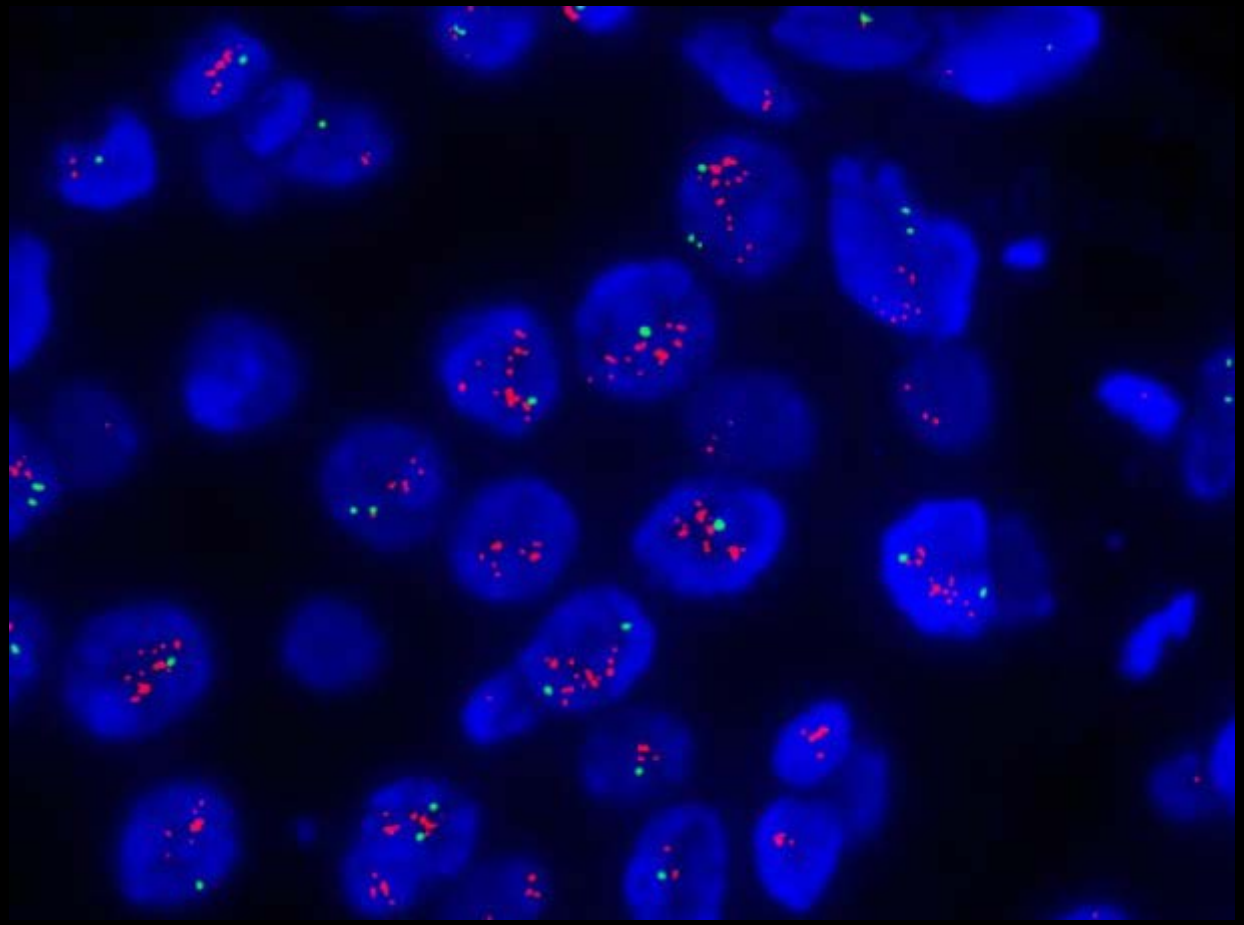
Courtesy of Mark D Pegram, MD



Courtesy of Mark D Pegram, MD

HER2 FISH

HER2 Gene Status by FISH:	**HER2 POSITIVE**
Average HER2 copies/cell:	10.00
Average centromere 17 signals/cell:	1.80
Ratio of HER2:CEP17 signals:	5.55
Total Number of Cells Counted:	25



Courtesy of Mark D Pegram, MD

Case 1

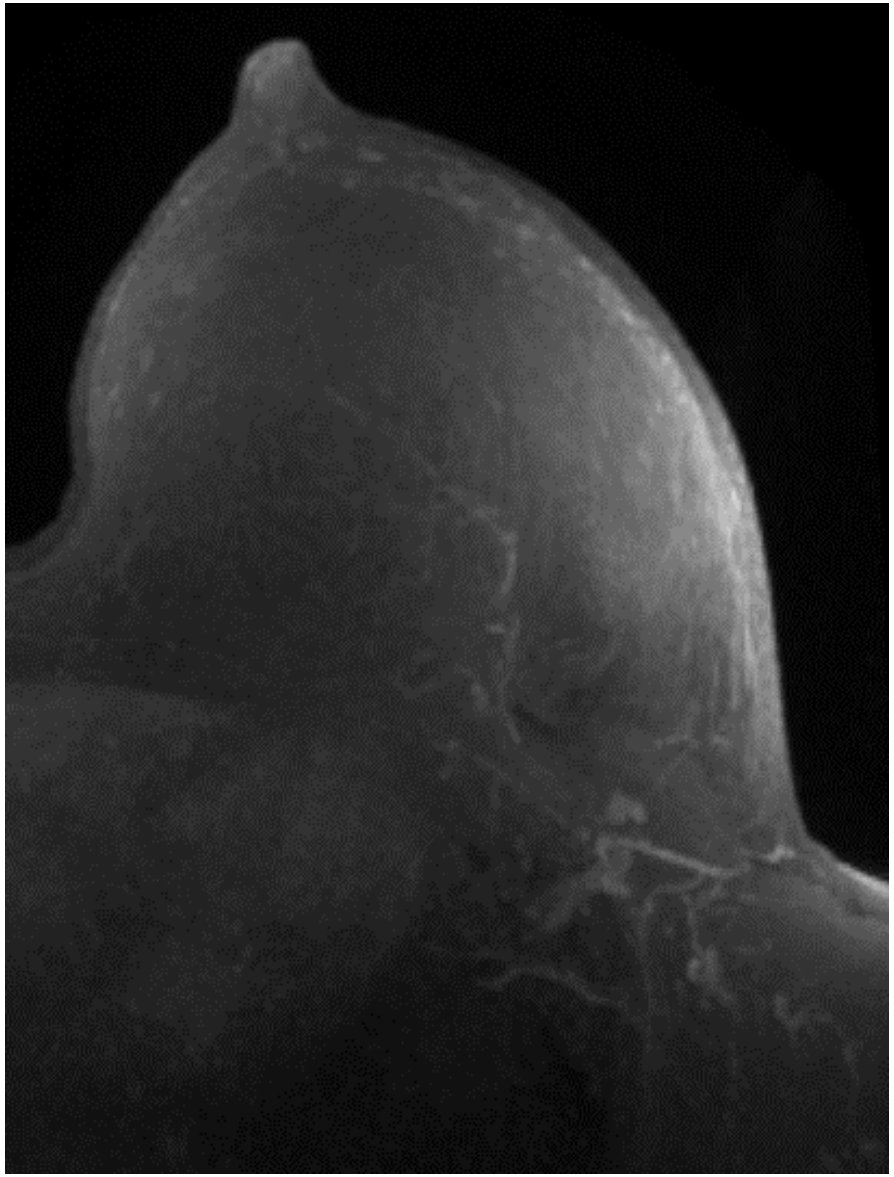
9/11/18 to 12/26/18: Completed neoadjuvant TCHP x 6 cycles

3/25/19: Left breast nipple sparing mastectomy, left SLN, TE/ADM reconstruction

Courtesy of Mark D Pegram, MD

post NACT MRI shows resolution of disease

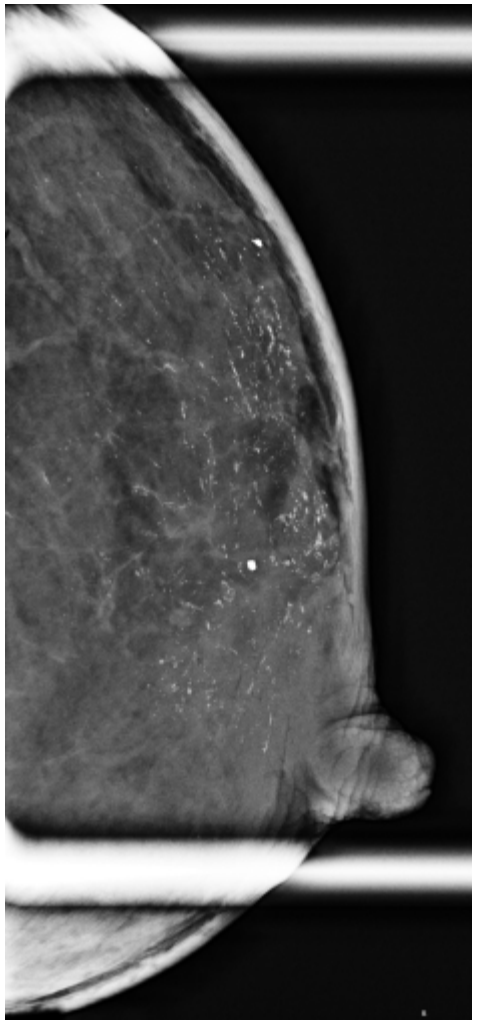
1/4/19 post NACT MRI

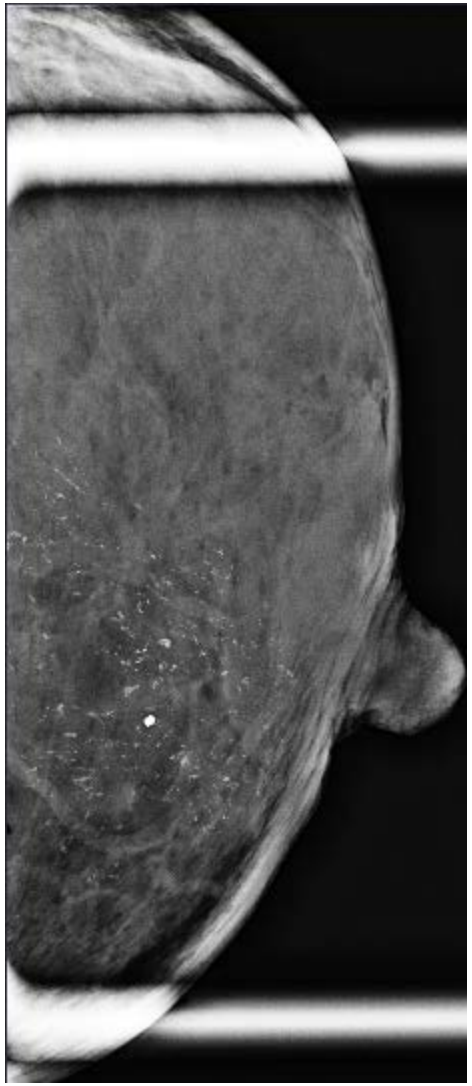


Courtesy of Mark D Pegram, MD

2/14/19 diagnostic mammogram shows stable distribution and extent of calcs

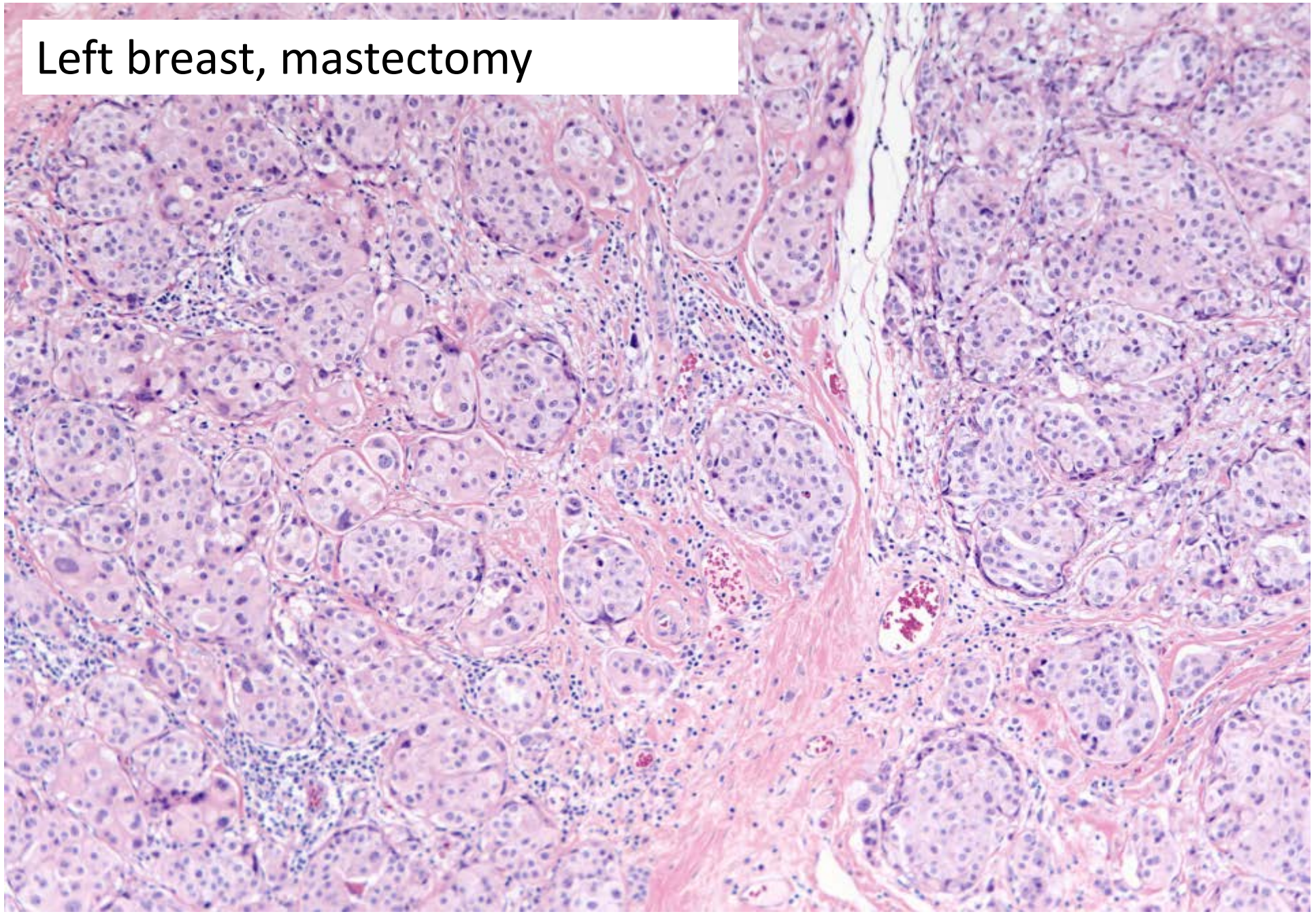
2/14/19 diagnostic mammogram





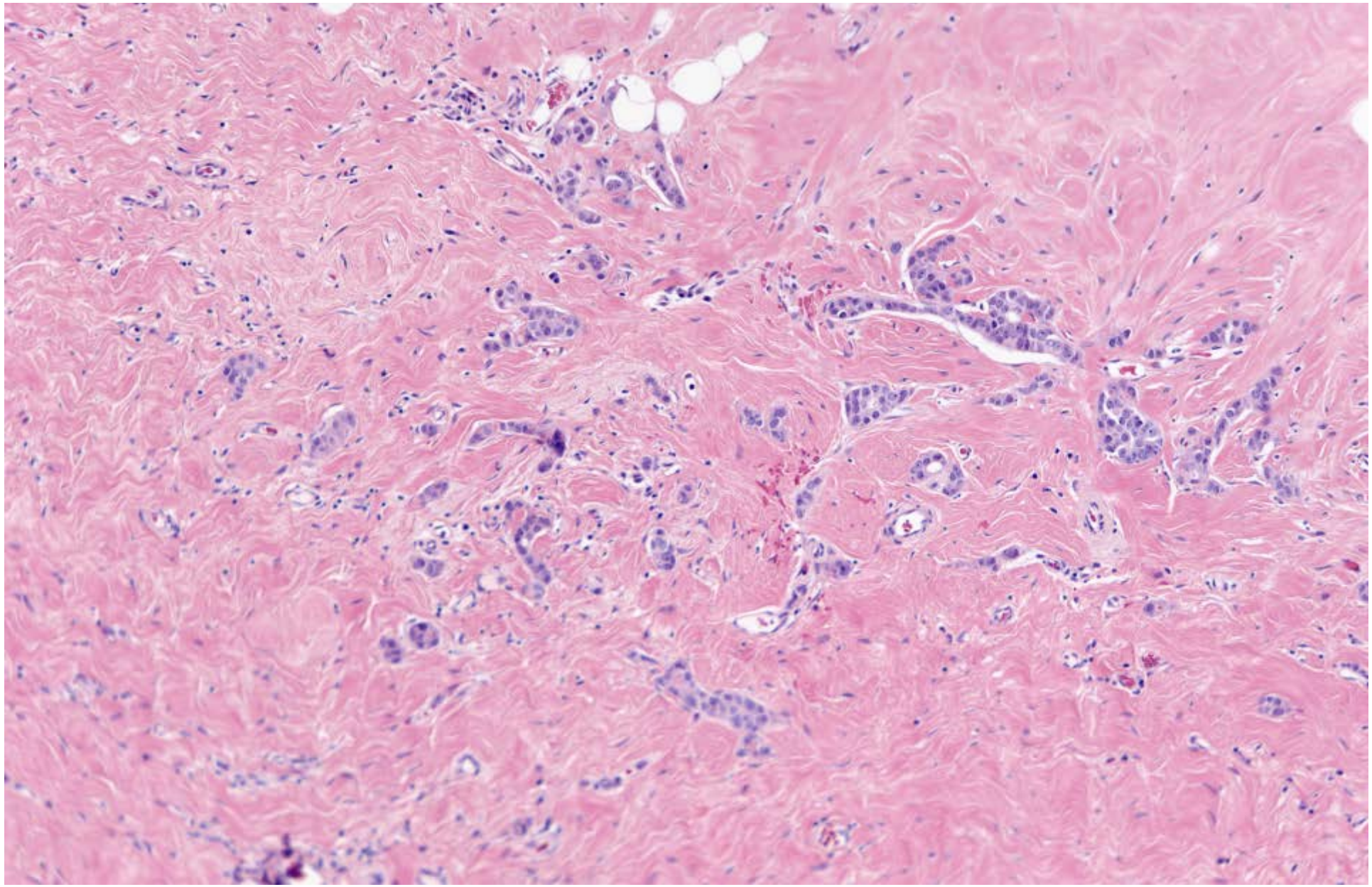
Courtesy of Mark D Pegram, MD

Left breast, mastectomy



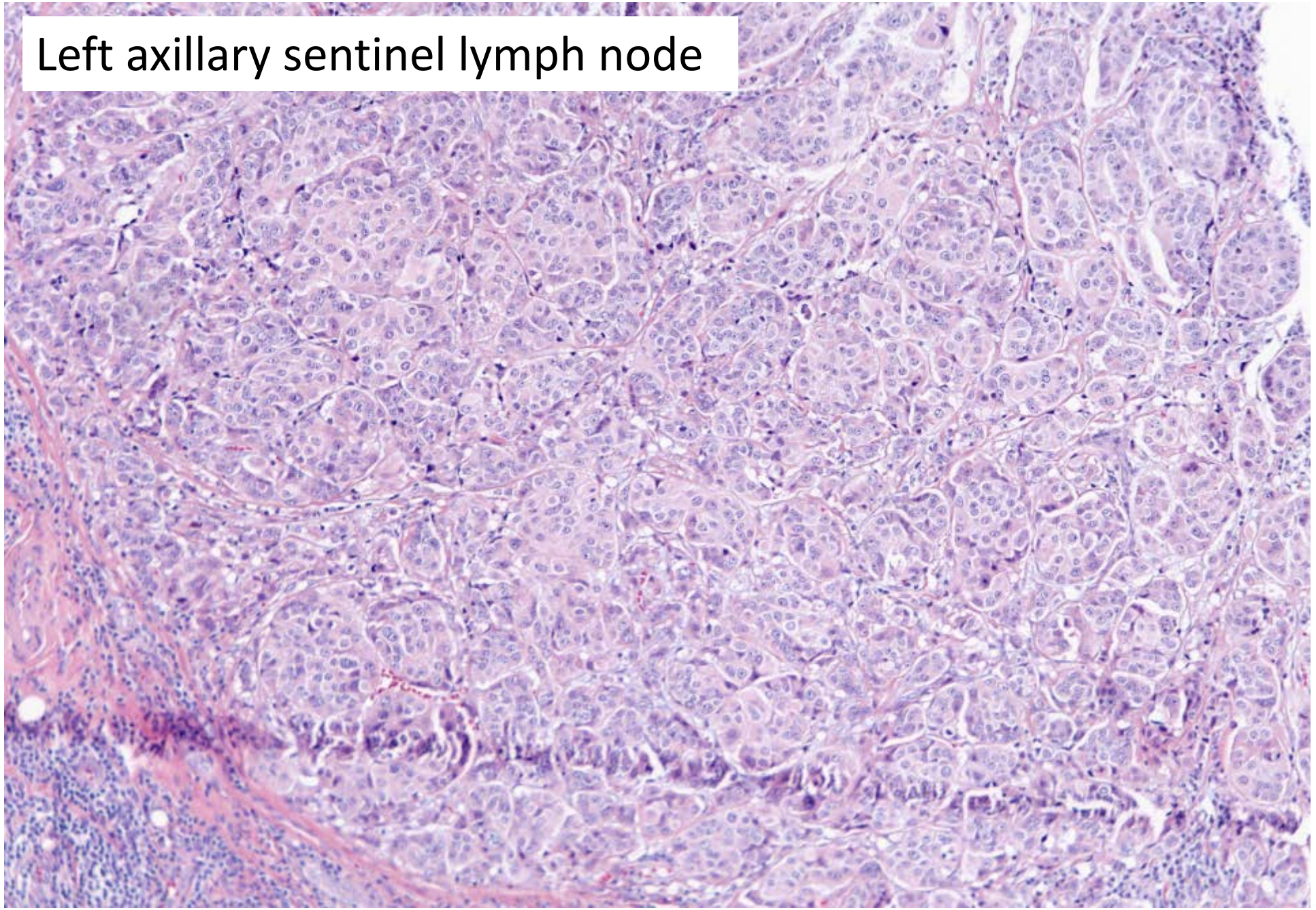
Courtesy of Mark D Pegram, MD

Left breast, mastectomy -- Overall spans 7.8 cm, with 5% cellularity



Courtesy of Mark D Pegram, MD

Left axillary sentinel lymph node



Courtesy of Mark D Pegram, MD

Case 1: Final Pathology

Left breast, mastectomy

- Residual invasive ductal carcinoma with treatment effect, 7.8 cm, 5% tumor cellularity
- Residual DCIS
- Extensive lymphovascular invasion
- Invasive carcinoma present at posterior margins, other close margins

Left axillary sentinel lymph nodes

- Metastatic carcinoma in two of three lymph nodes (2/3)

Left axillary lymph nodes

- Metastatic carcinoma in three of eleven lymph nodes (3/11)

Pathologic Stage: ypT3 N2a

Courtesy of Mark D Pegram, MD

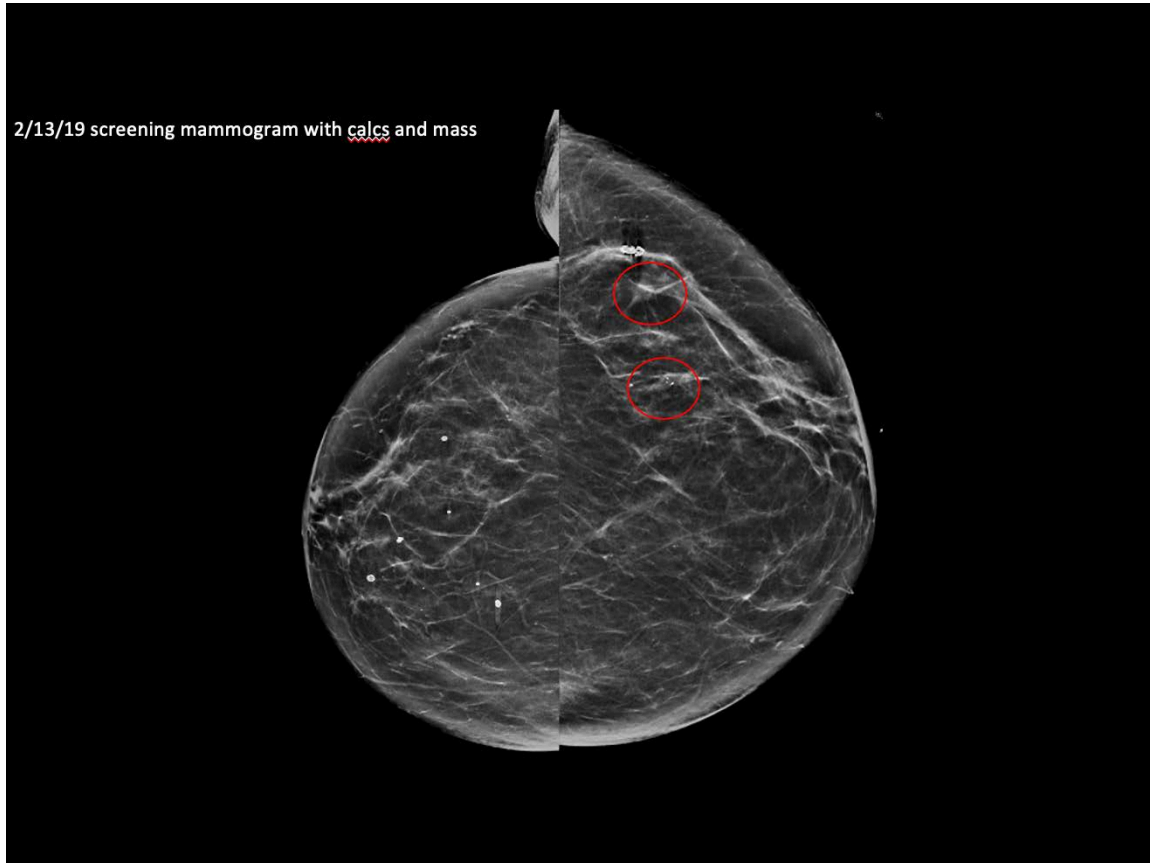
Case 1

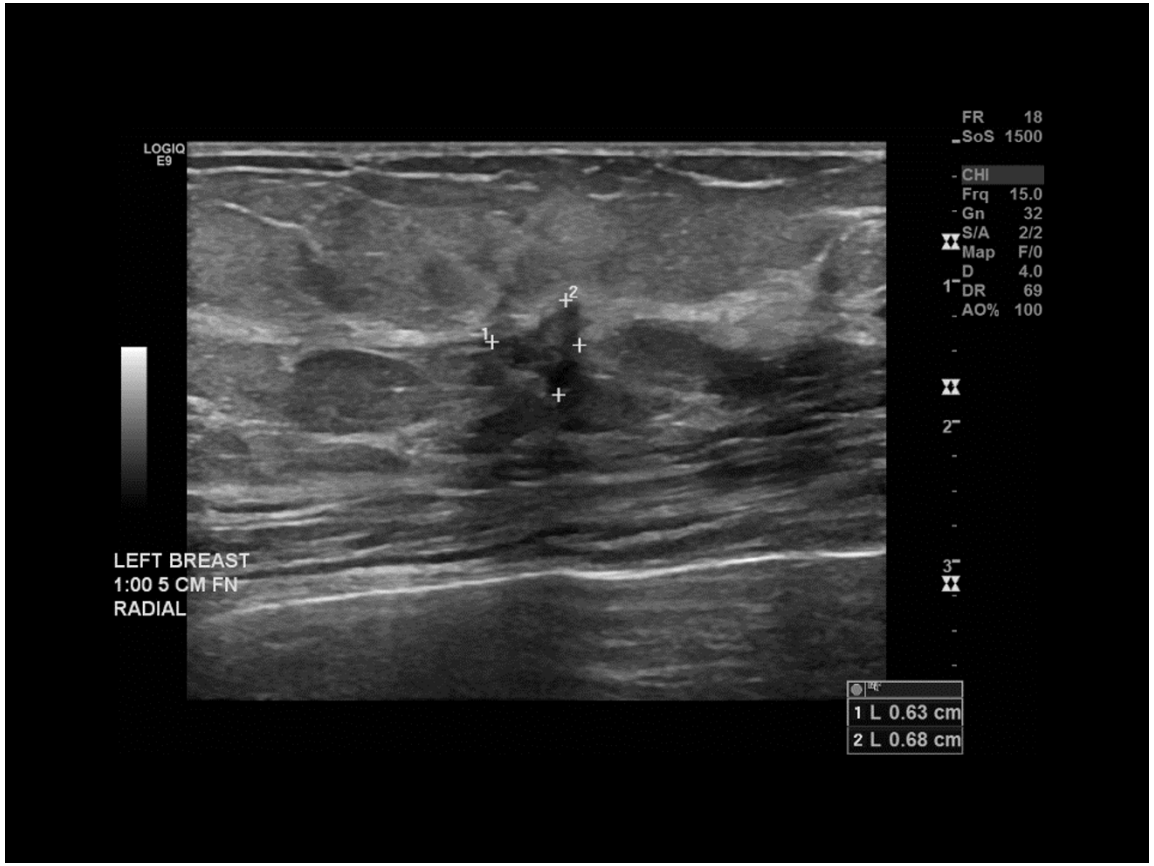
- 5/6/19: Revision of left mastectomy flap
- Received T-DM1 X 14 cycles post-op
- Final reconstruction planned 12/2019

Courtesy of Mark D Pegram, MD

Case 2

75-year-old female presented with abnormal screening mammogram

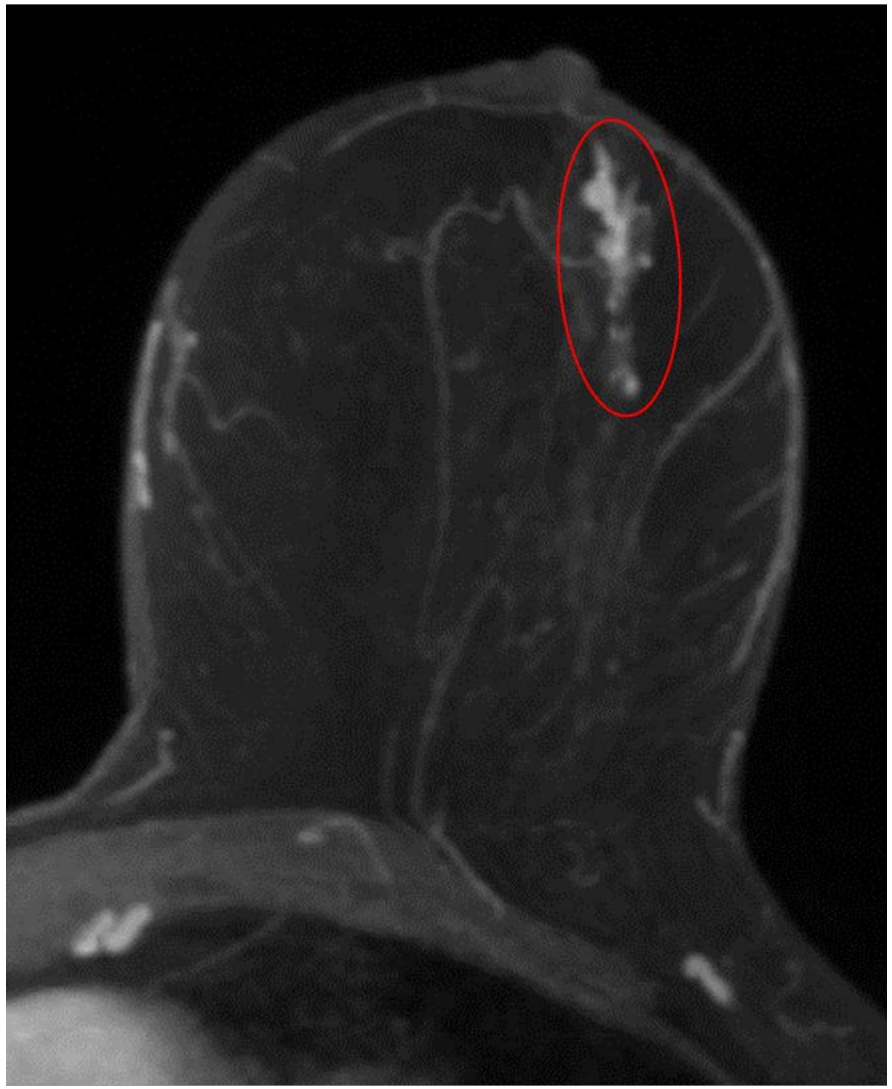


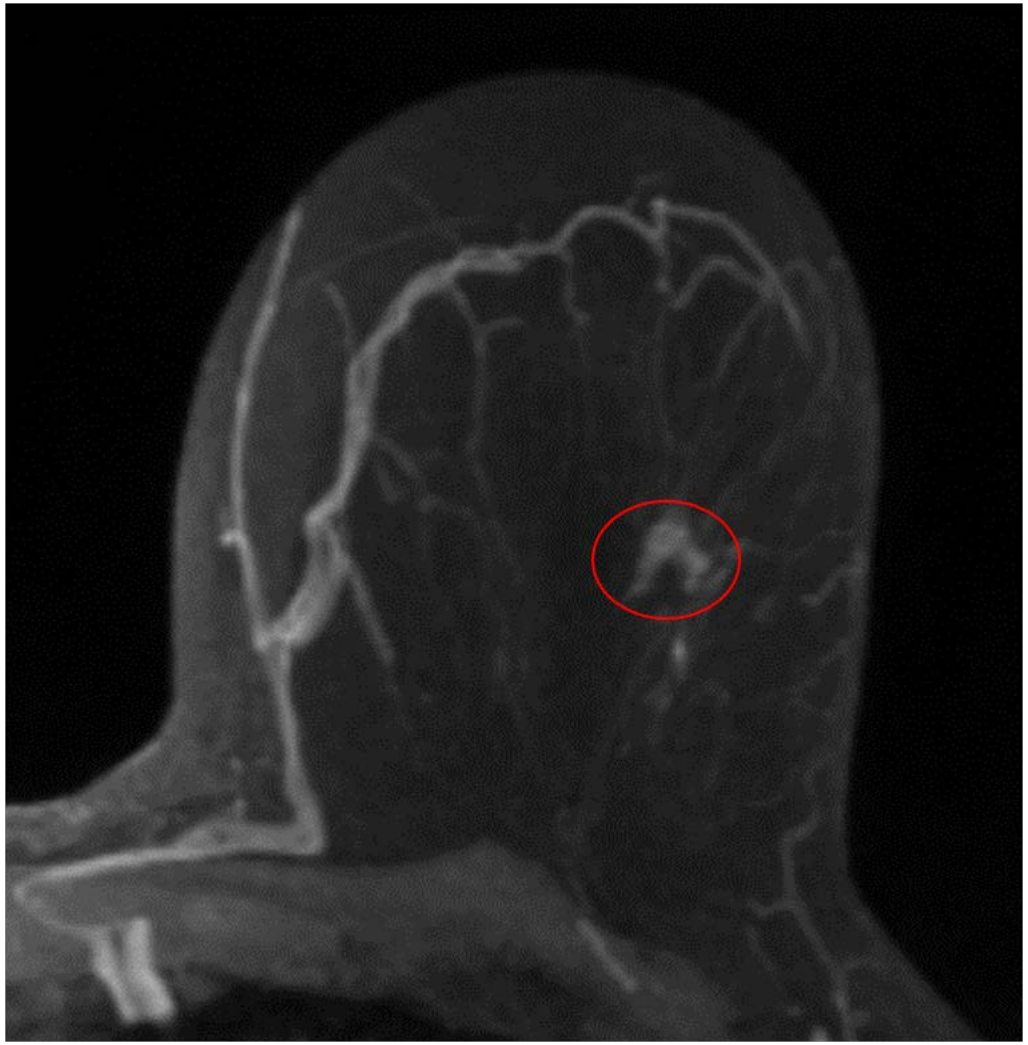


L1: Targeted ultrasound was performed at the site of the mammogram findings at 1:00 5 cm from the nipple and demonstrates a hypoechoic irregular mass with angular margins measuring 0.6 x 0.6 x 0.7 cm.

Courtesy of Mark D Pegram, MD

Case 2: MR Imaging showing L1 mass and L2 NME + marker



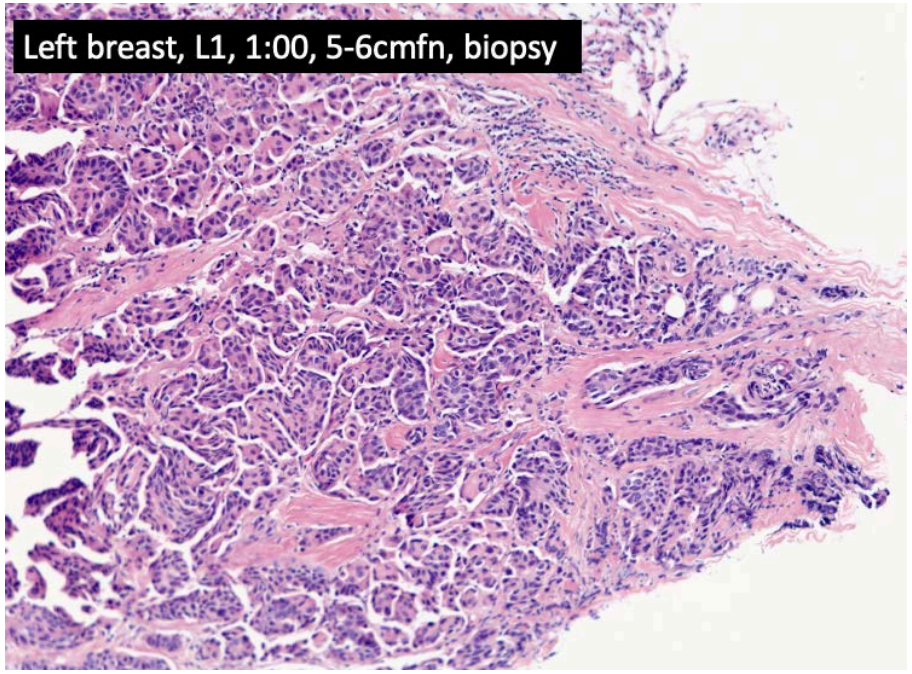


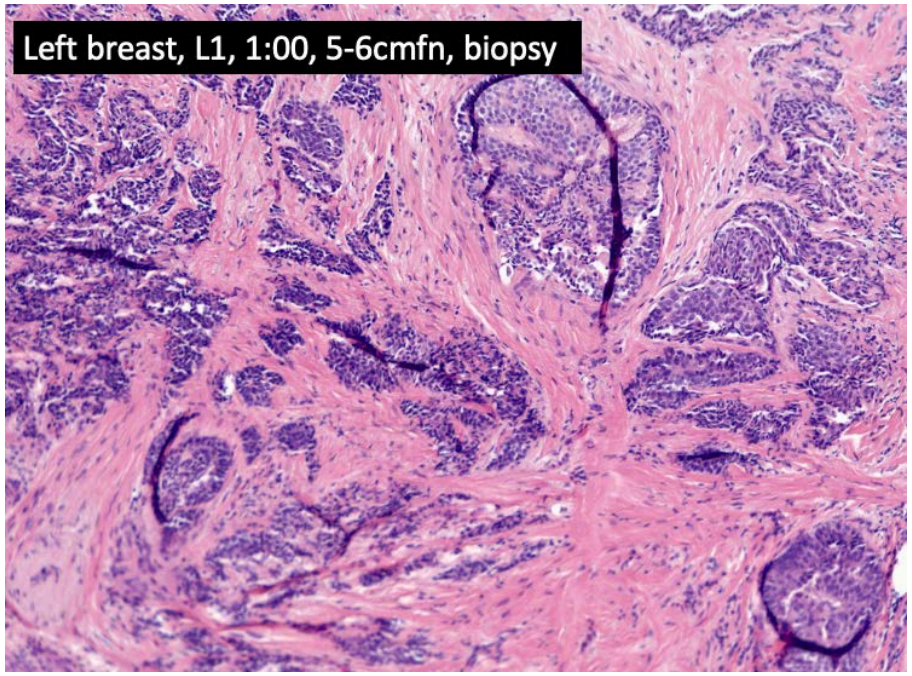
Courtesy of Mark D Pegram, MD

Case 2: Pathology

A. Left breast, L1, 1:00, 5-6 cmfn, core biopsy:

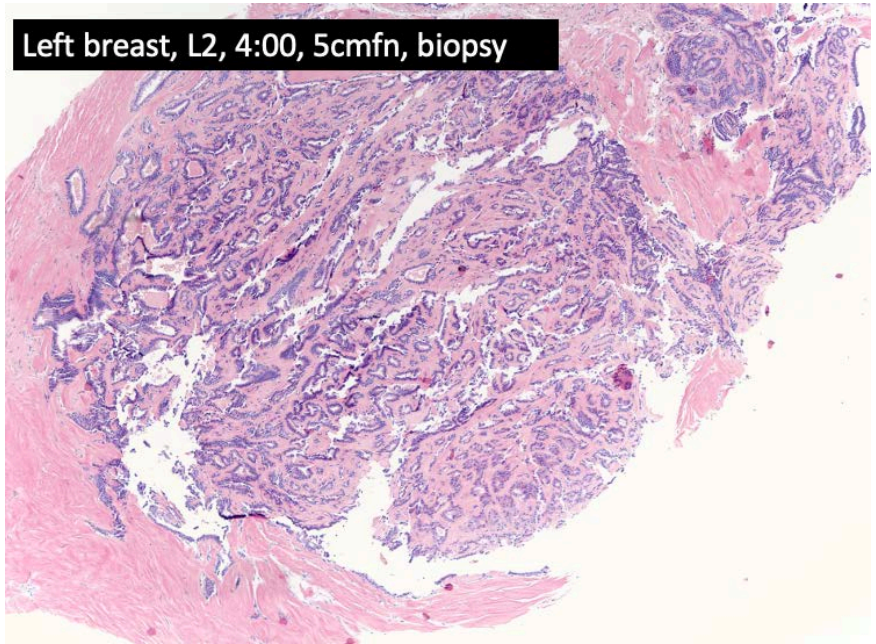
- Invasive ductal carcinoma with micropapillary features, grade 2, with calcifications
- DCIS, grade 2 (no calcifications)



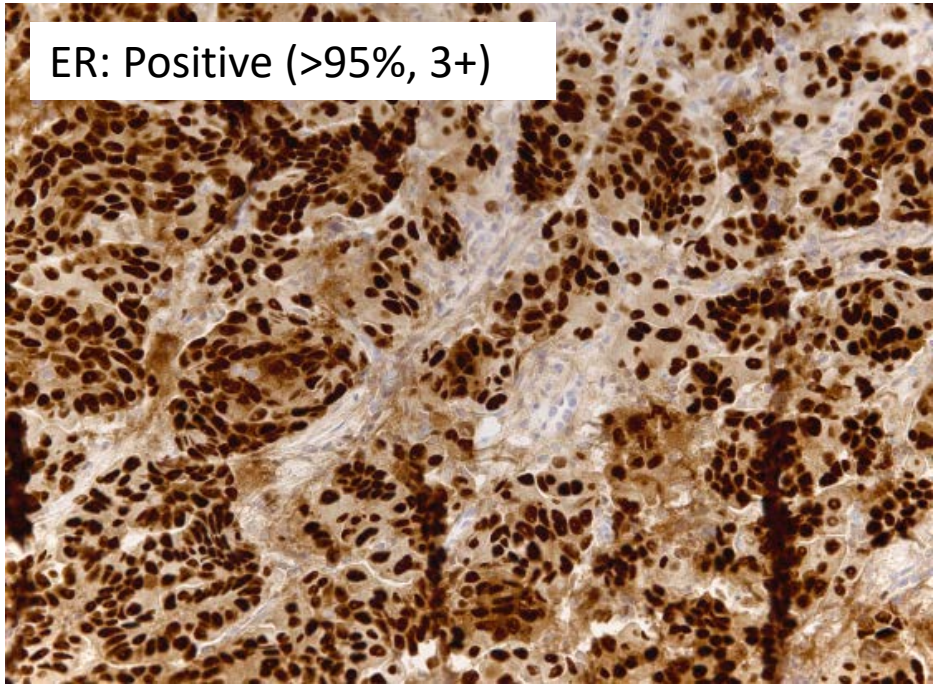


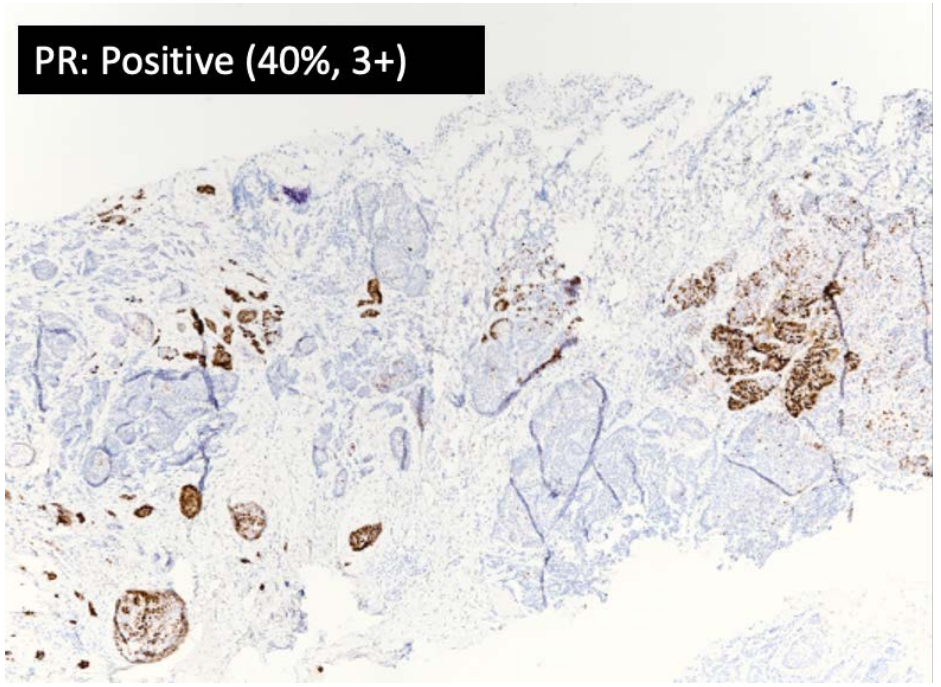
Left breast, L2, 4:00, 5 cmfn, core biopsy

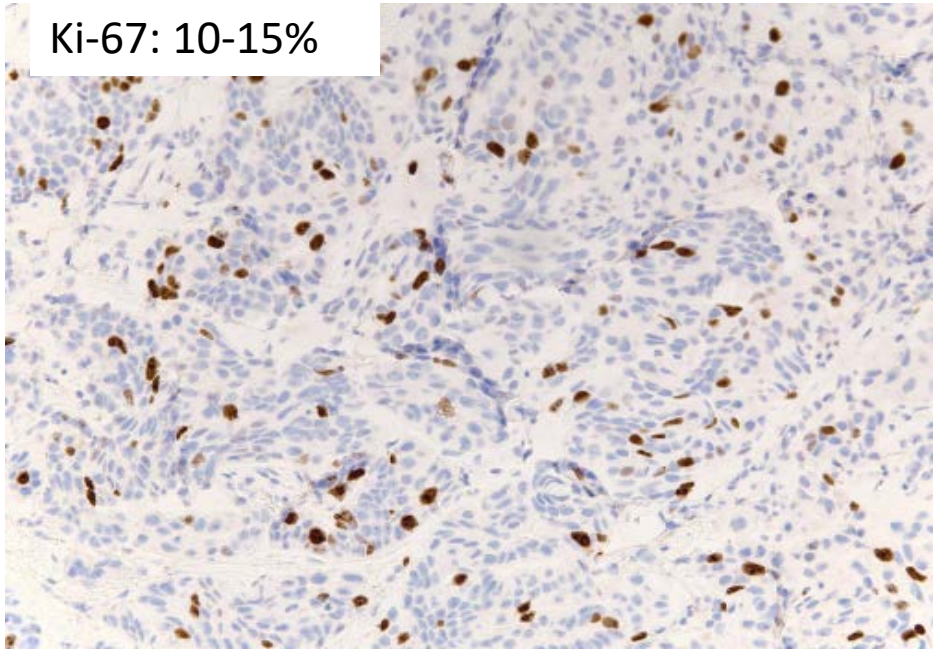
- Intraductal papilloma with sclerosis and calcifications

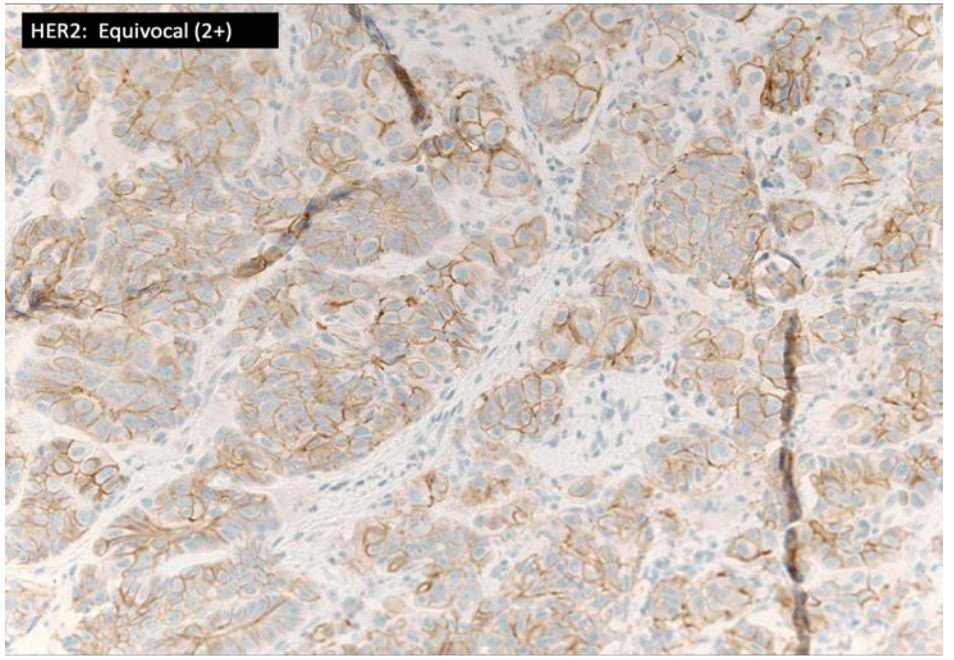


Courtesy of Mark D Pegram, MD





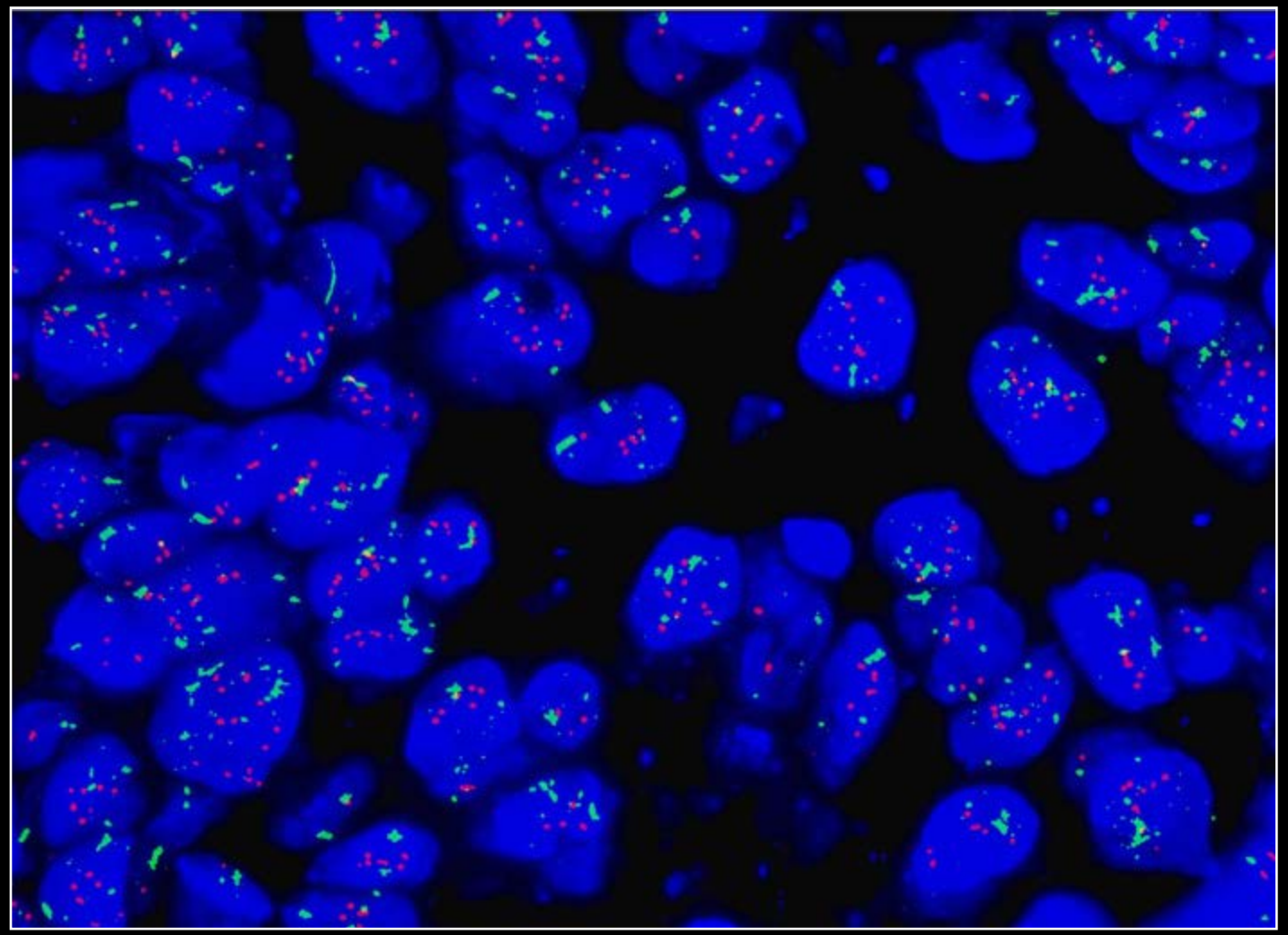




Courtesy of Mark D Pegram, MD

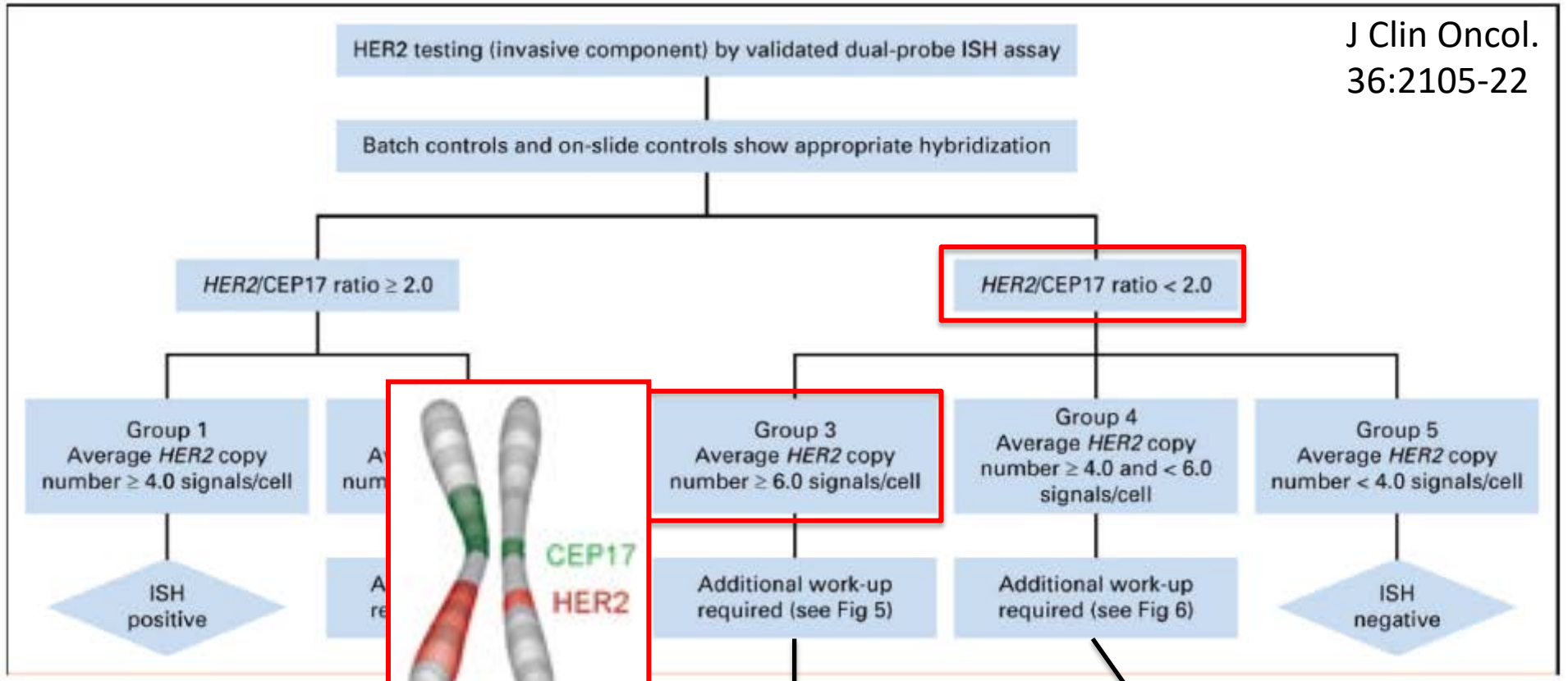
HER2 FISH

Average HER2 copies/cell:	7.04
Average centromere 17 signals/cell:	10.00
Ratio of HER2:CEP17 signals:	0.70



Courtesy of Mark D Pegram, MD

2018 ASCO/CAP HER2 FISH simplified



J Clin Oncol. 36:2105-22

Require comments:

Group 2: Negative unless IHC 3+ "monosomy"

Group 3: POSITIVE unless IHC 0, 1+ "Co-amplified"

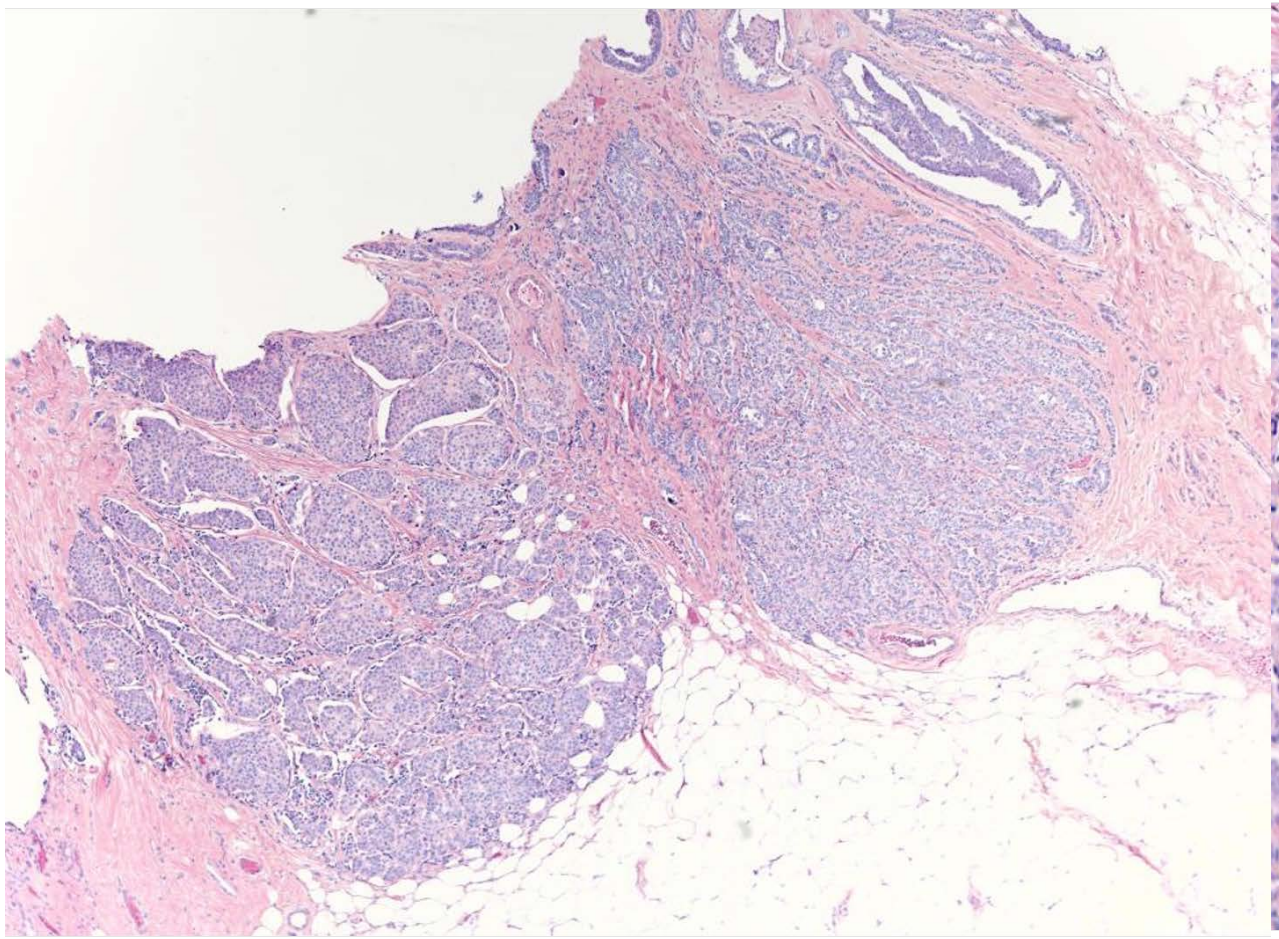
Group 4: Negative unless IHC 3+ "Equivocal"

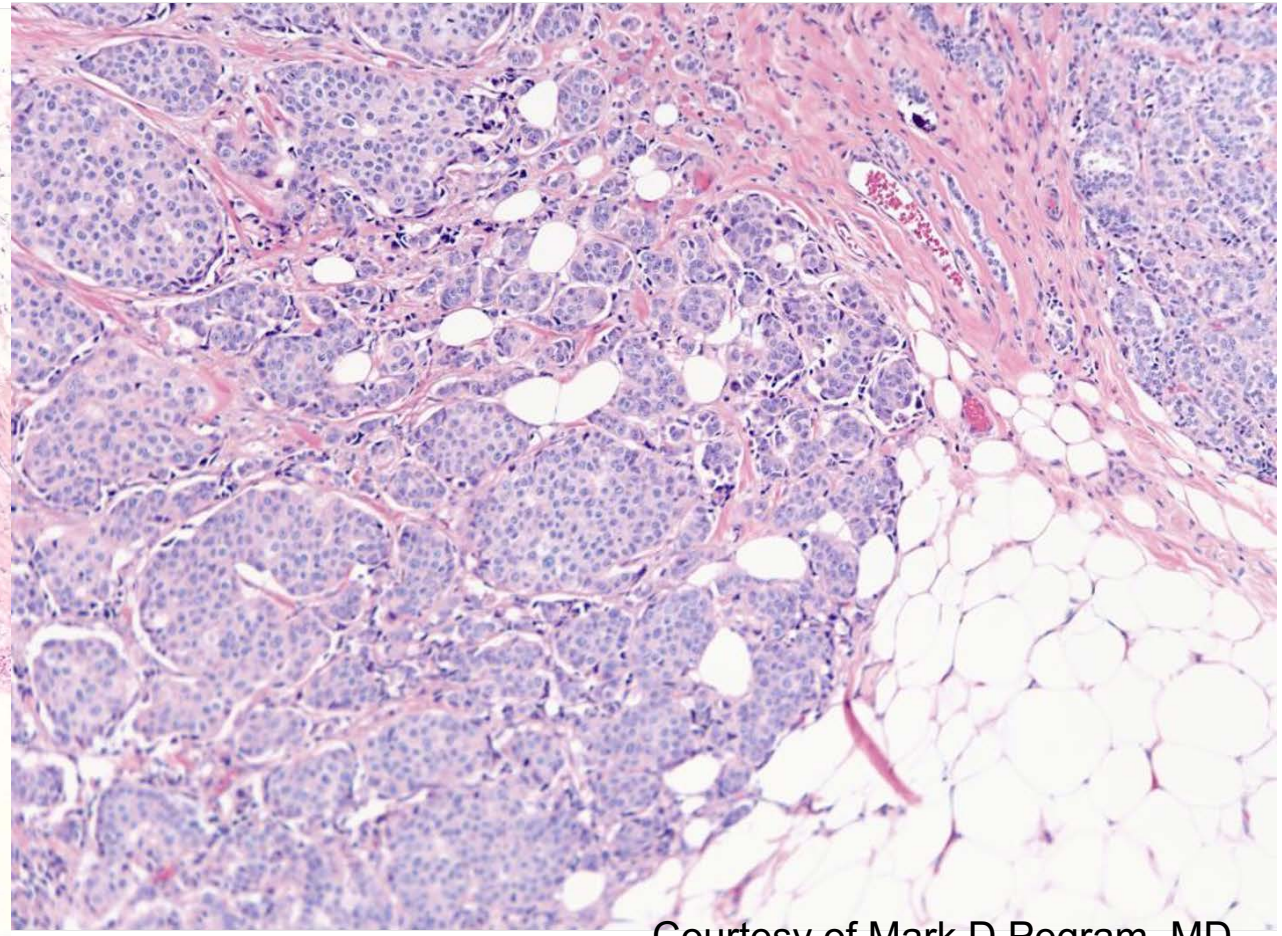
Courtesy of Mark D Pegram, MD

Case 2

- 5/31/19: left lumpectomy, SLN

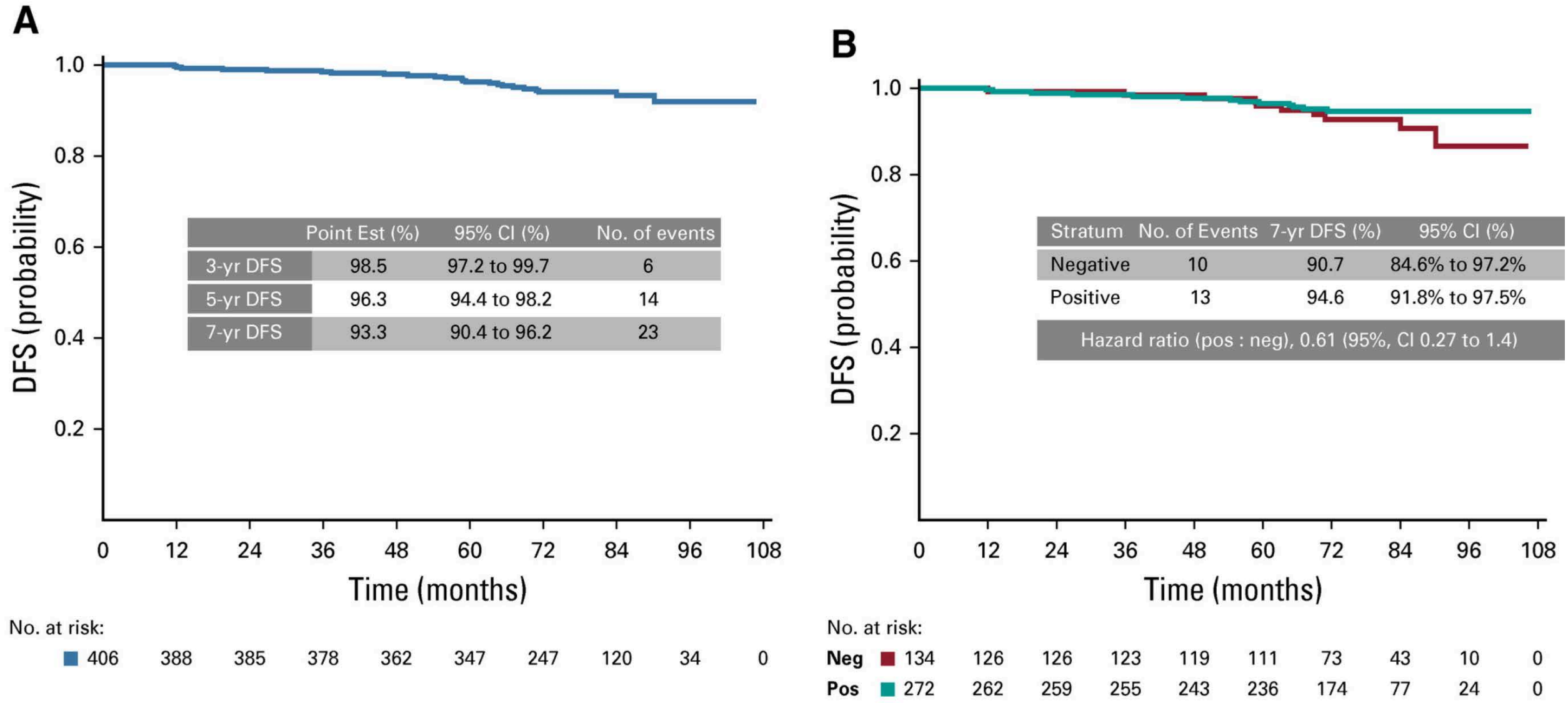
Invasive ductal carcinoma, grade 2, 0.8 cm, negative margins; DCIS, grade 2, negative margins
Left axillary sentinel lymph nodes:
No carcinoma in two lymph nodes (0/2)
Separately submitted margins (lateral posterior; inferior; posterior): Negative for carcinoma
Pathologic Staging: pT1b N0(sn)





Courtesy of Mark D Pegram, MD

Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab (APT) Trial for Node-Negative, HER2+ Breast Cancer



(A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status.

Courtesy of Mark D Pegram, MD

Phase II ATEMPT: Study Design

- A randomized (3:1), open-label phase II study

Stratified by age (<55, ≥ 55), planned radiation therapy (Y/N), planned hormonal therapy (Y/N)

Women with stage 1 HER2+ BC with N0 or N1mic disease; LVEF ≥ 50%; no prior invasive BC surgery; ≤ 90 days from last surgery (N = 497)

T-DM1
3.6 mg/kg IV Q3W x 17
(n = 383)

Paclitaxel 80 mg/m2 IV +
Trastuzumab 2 mg/kg IV Q1W x 12
(n = 114)

Trastuzumab
6 mg/kg Q3W x 13

Follow-up for 5 yrs after final dose of T-DM1 or TH

Study not powered to assess efficacy of TH or to compare efficacy of T-DM1 to TH

- Coprimary endpoints: 3-yr DFS in T-DM1; comparison of incidence of clinically relevant toxicities with T-DM1 vs TH, including: grade ≥ 3 non-hematologic AEs, grade ≥ 2 neurotoxicity, grade ≥ 4 hematologic AEs, febrile neutropenia, and any AE requiring dose delay or discontinuation of protocol therapy

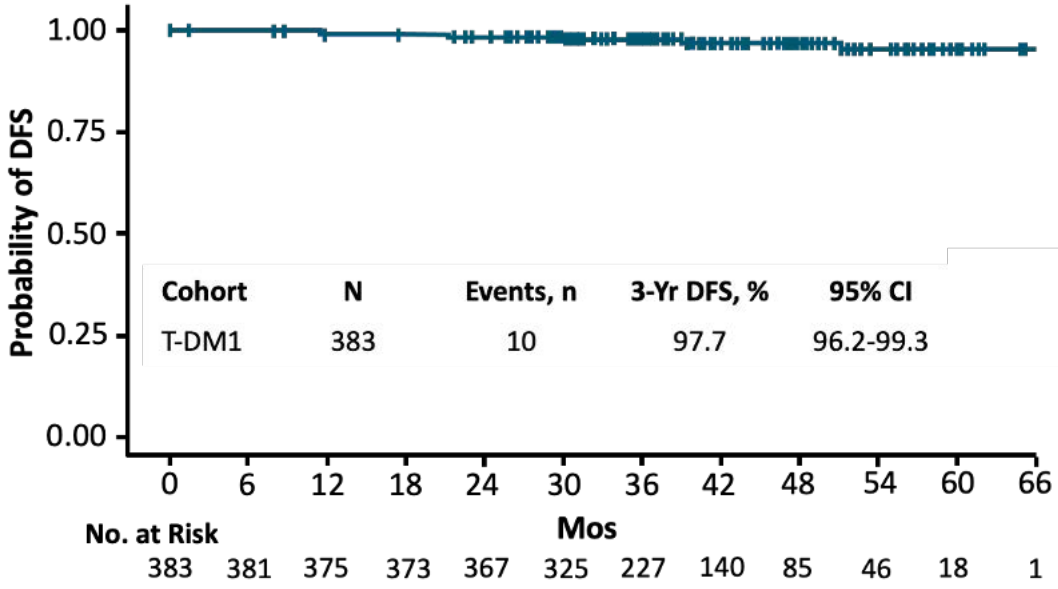
Tolaney. SABCS 2019. Abstr GS1-05.

Courtesy of Mark D Pegram, MD

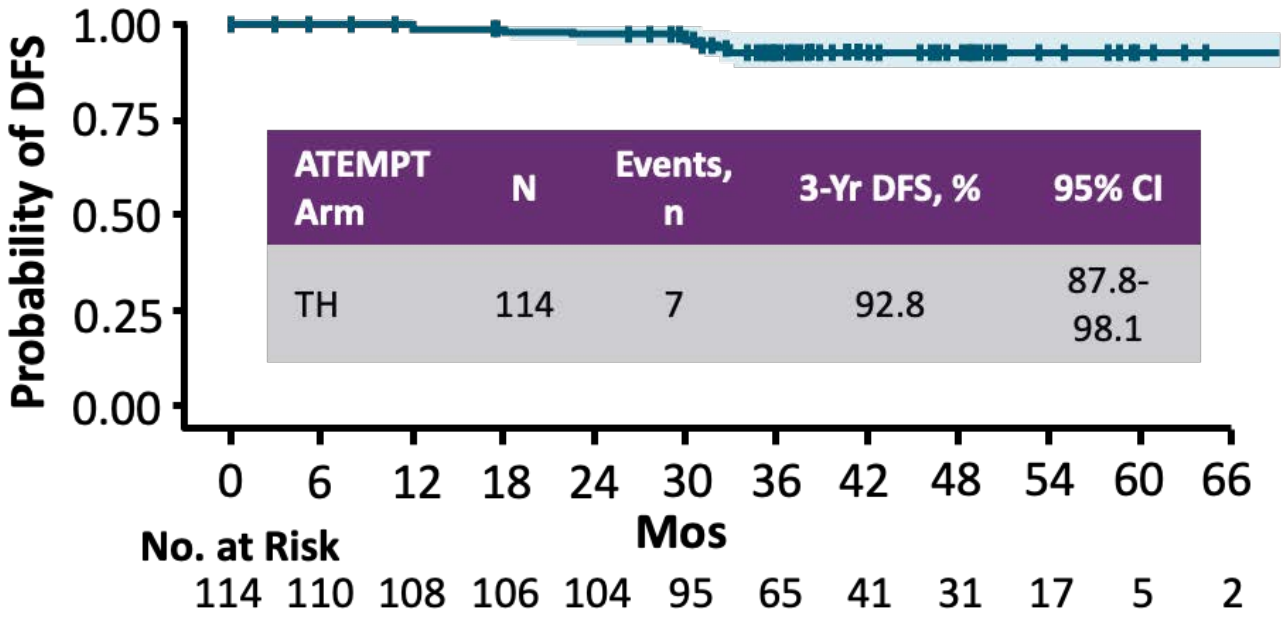
Phase II ATEMPT: A randomized (3:1), open-label phase II study

The majority (73%) had hormone receptor-positive tumors (T1a, 11%; T1b, 31%; T1c, 57%).

Phase II ATEMPT: T-DM1 DFS in ITT



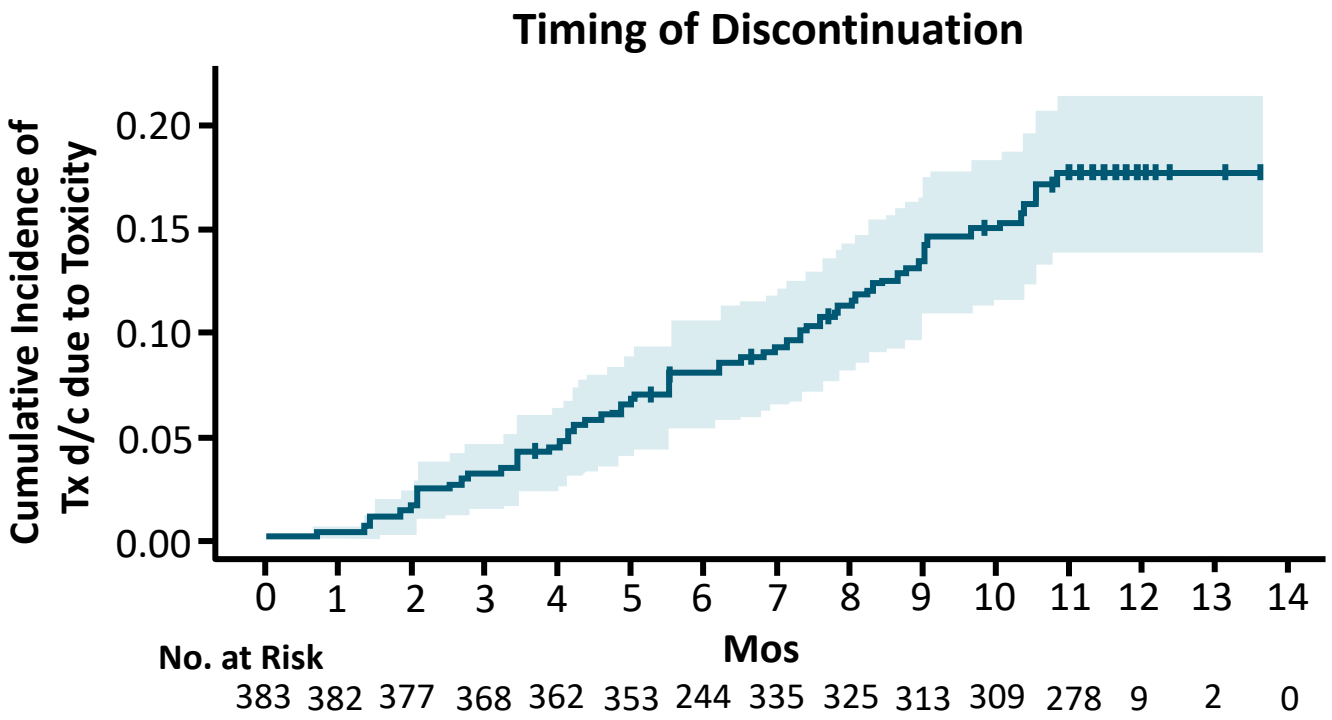
DFS for TH (ATEMPT Trial, n = 114)[1]



Tolaney. SABCS 2019. Abstr GS1-05.

Courtesy of Mark D Pegram, MD

Phase II ATEMPT: T-DM1 Discontinuations



- Probability of d/c therapy in < 6 mos: 8.2%
- Probability of d/c therapy at 6-12 mos: 10.7%

Discontinuations	n (%)
For any reason	90 (23.5)
For toxicity	67 (17.0)
For toxicity, protocol mandated	33 (9.0)

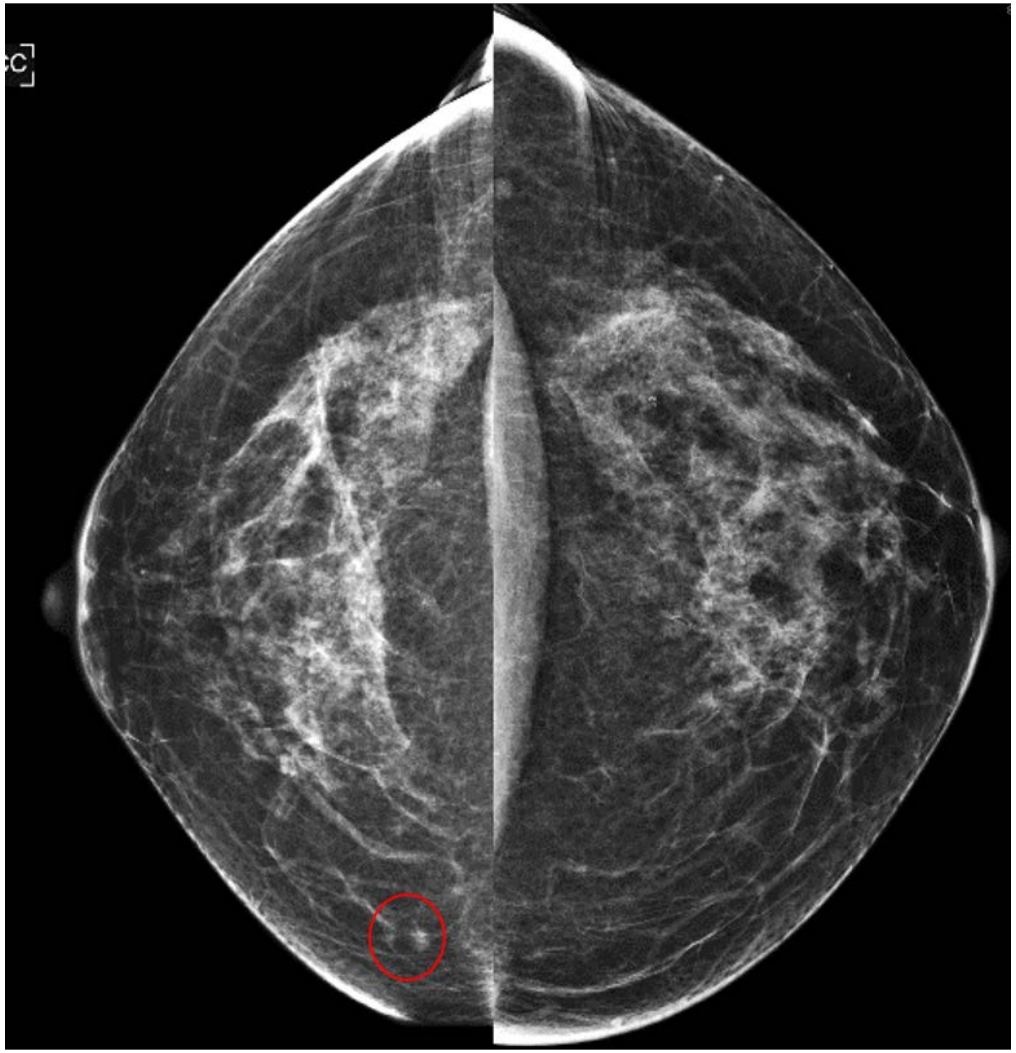
- Most frequent toxicities resulting in d/c include elevated liver enzymes, elevated bilirubin, neuropathy, and thrombocytopenia
- 66% of patients who discontinued T-DM1 due to toxicity had additional trastuzumab therapy

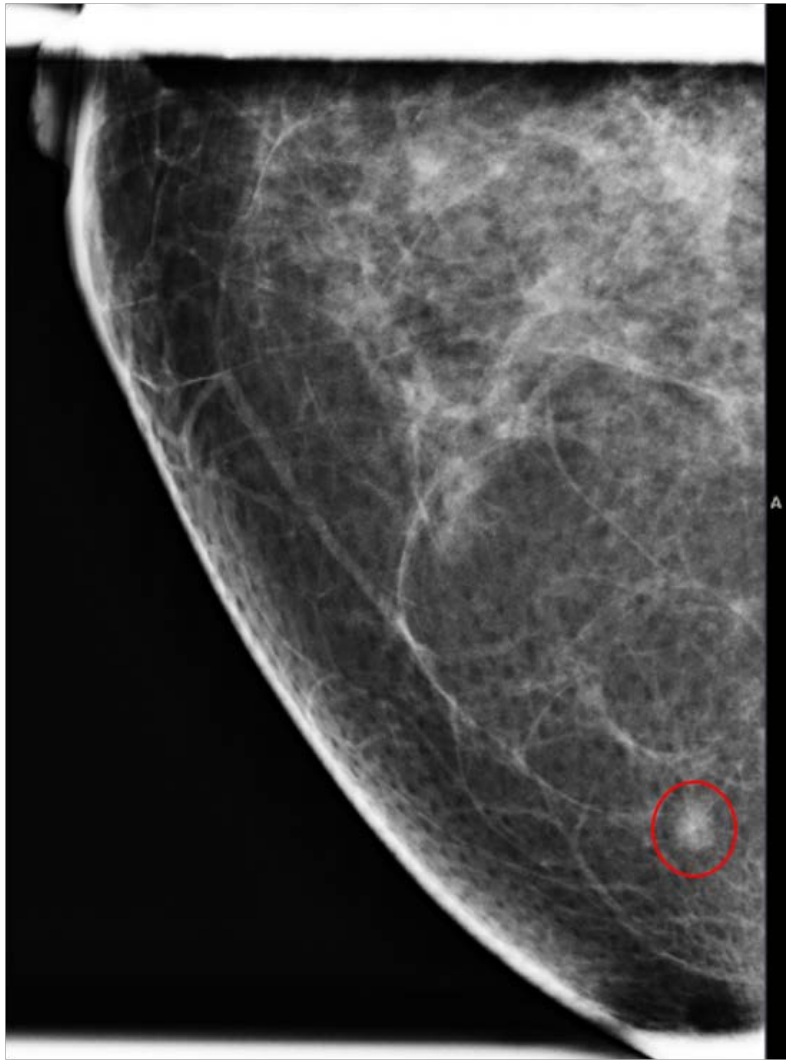
Tolaney. SABCS 2019. Abstr GS1-05.

Courtesy of Mark D Pegram, MD

Case 3

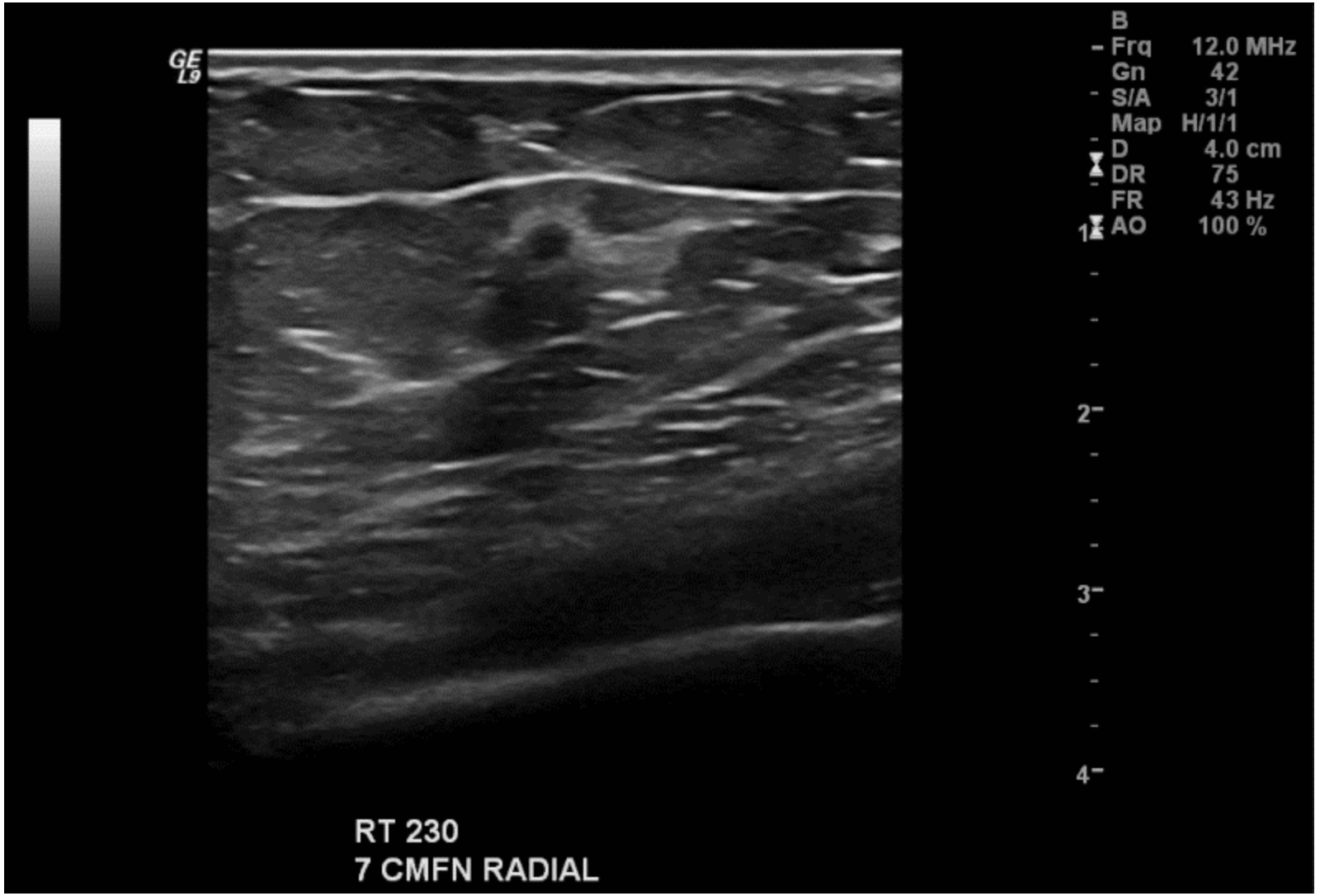
- 50-year-old female with asymmetry on screening mammogram



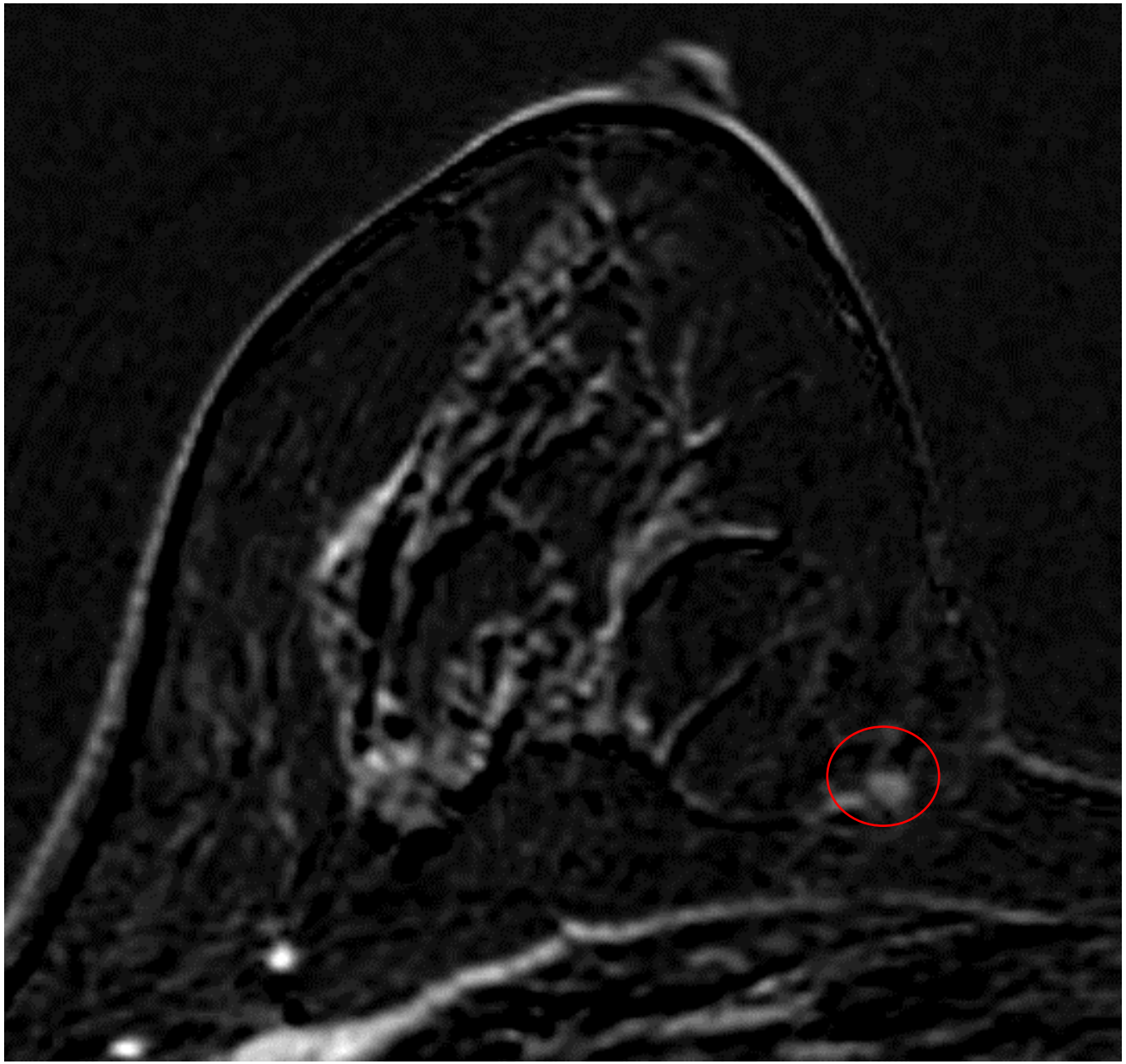


Courtesy of Mark D Pegram, MD

3/1/19– US shows sonographic correlate: Hypoechoic mass with posterior shadowing



Courtesy of Mark D Pegram, MD



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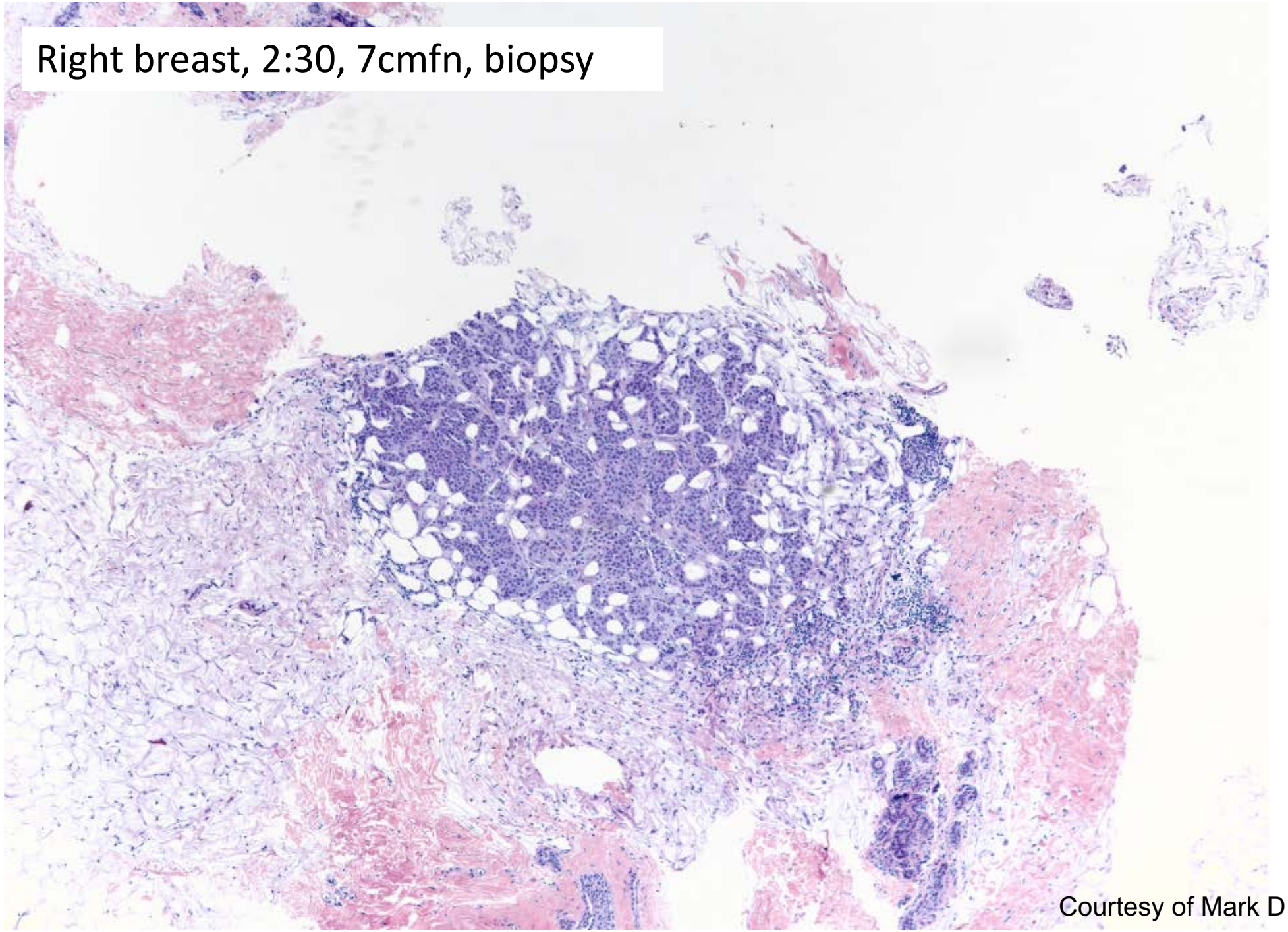
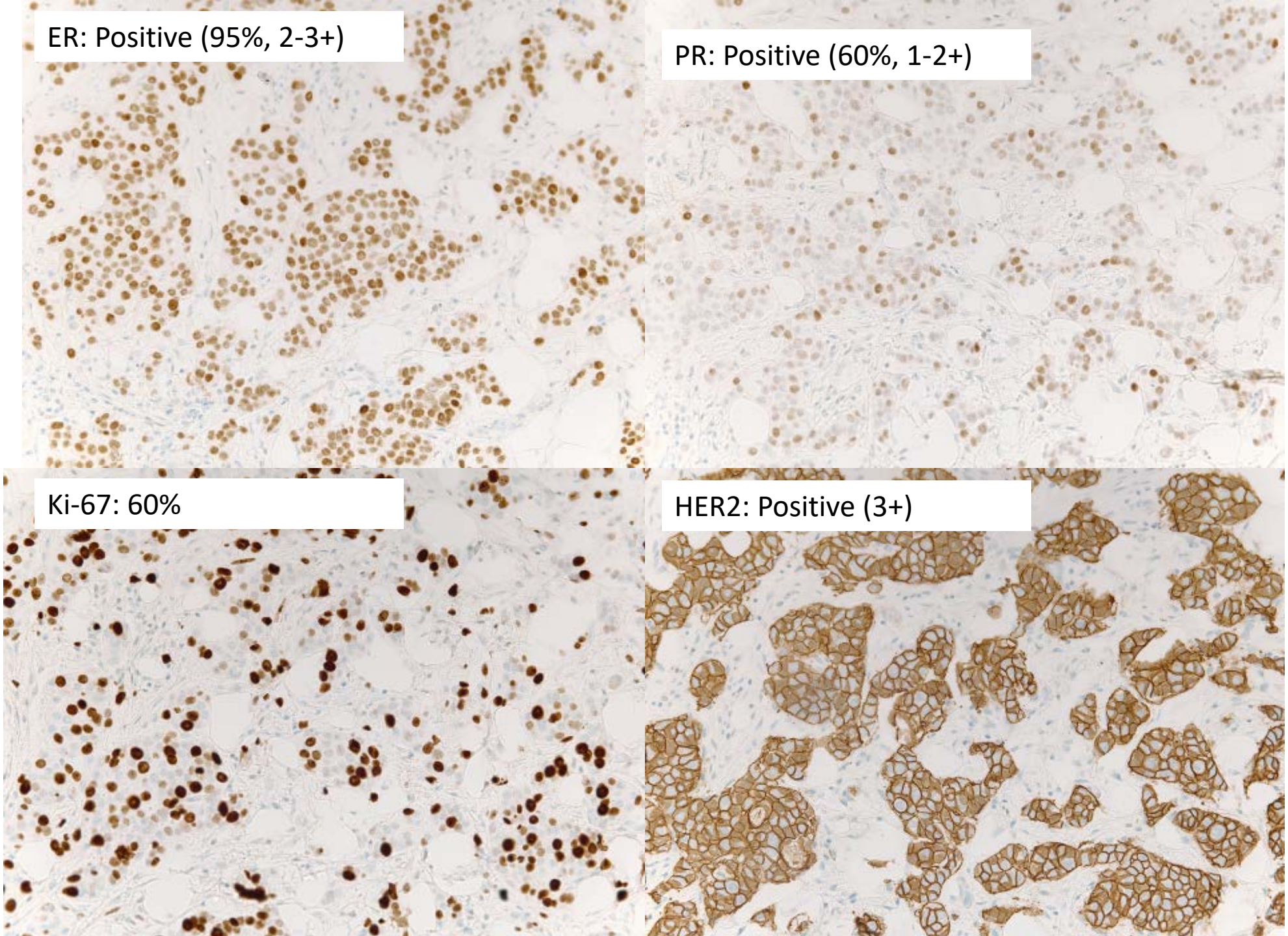


Courtesy of Mark D Pegram, MD



Courtesy of
Mark D Pegram, MD

HER2 FISH

HER2 Gene Status by FISH:	**HER2 POSITIVE**
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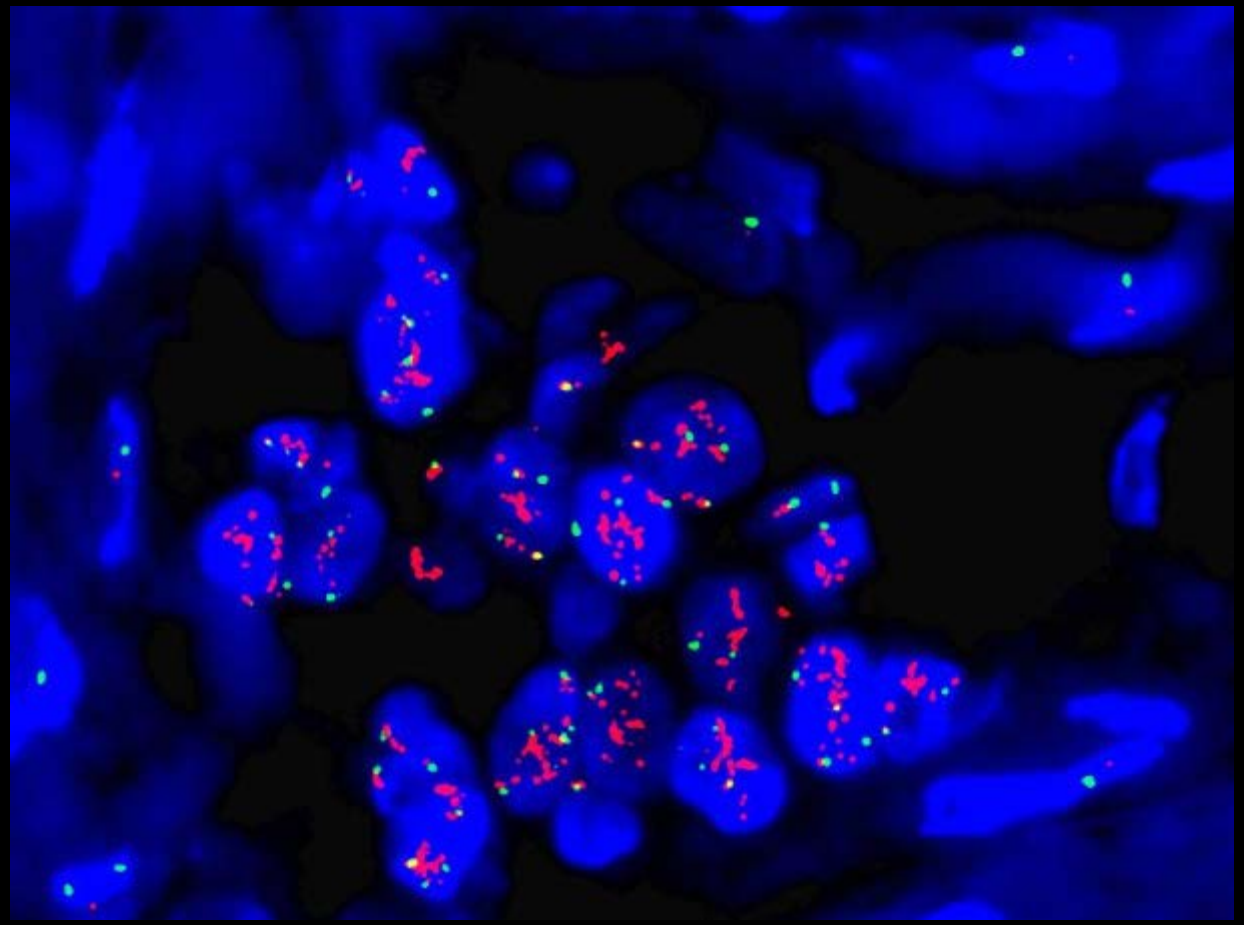
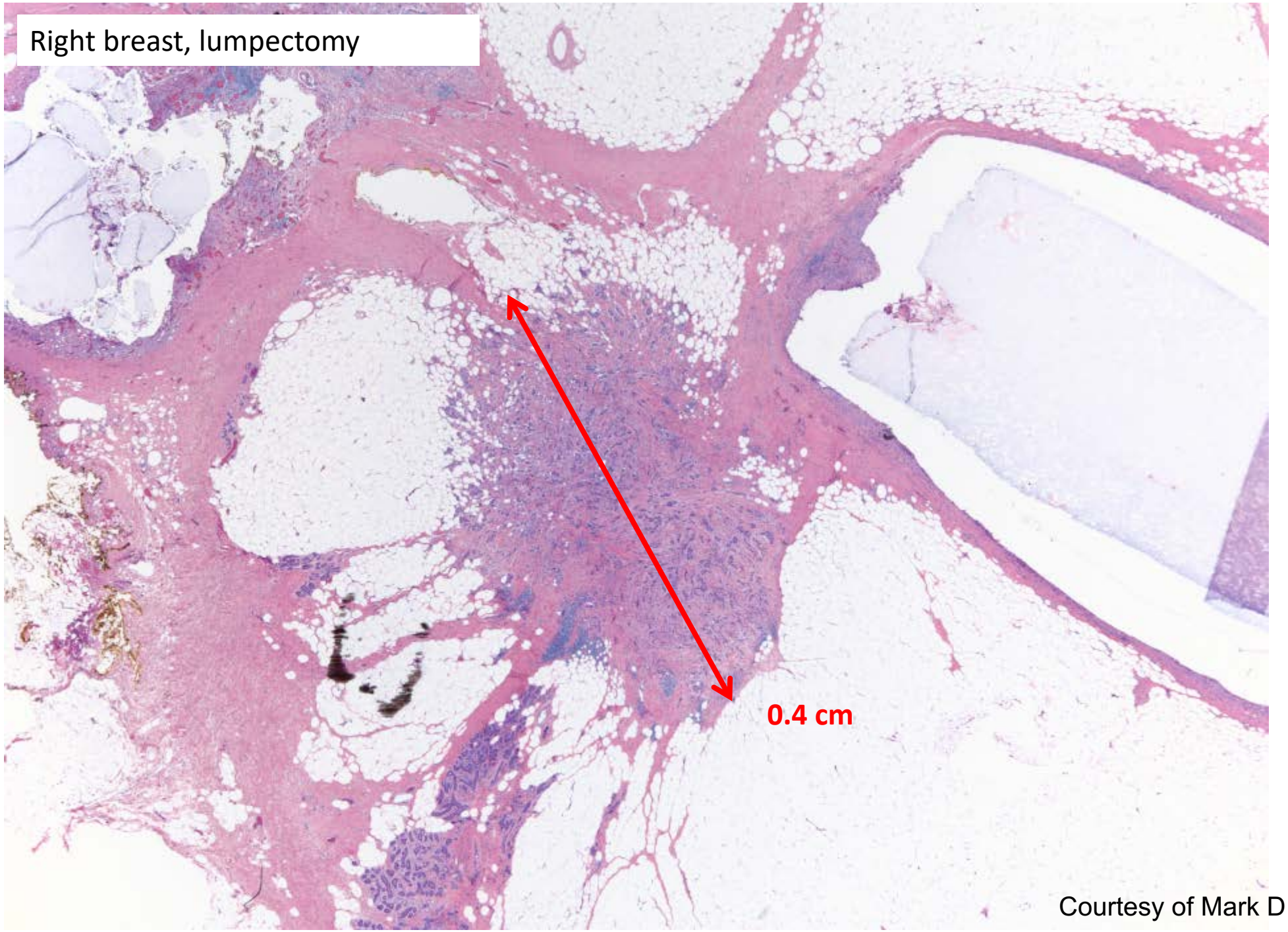
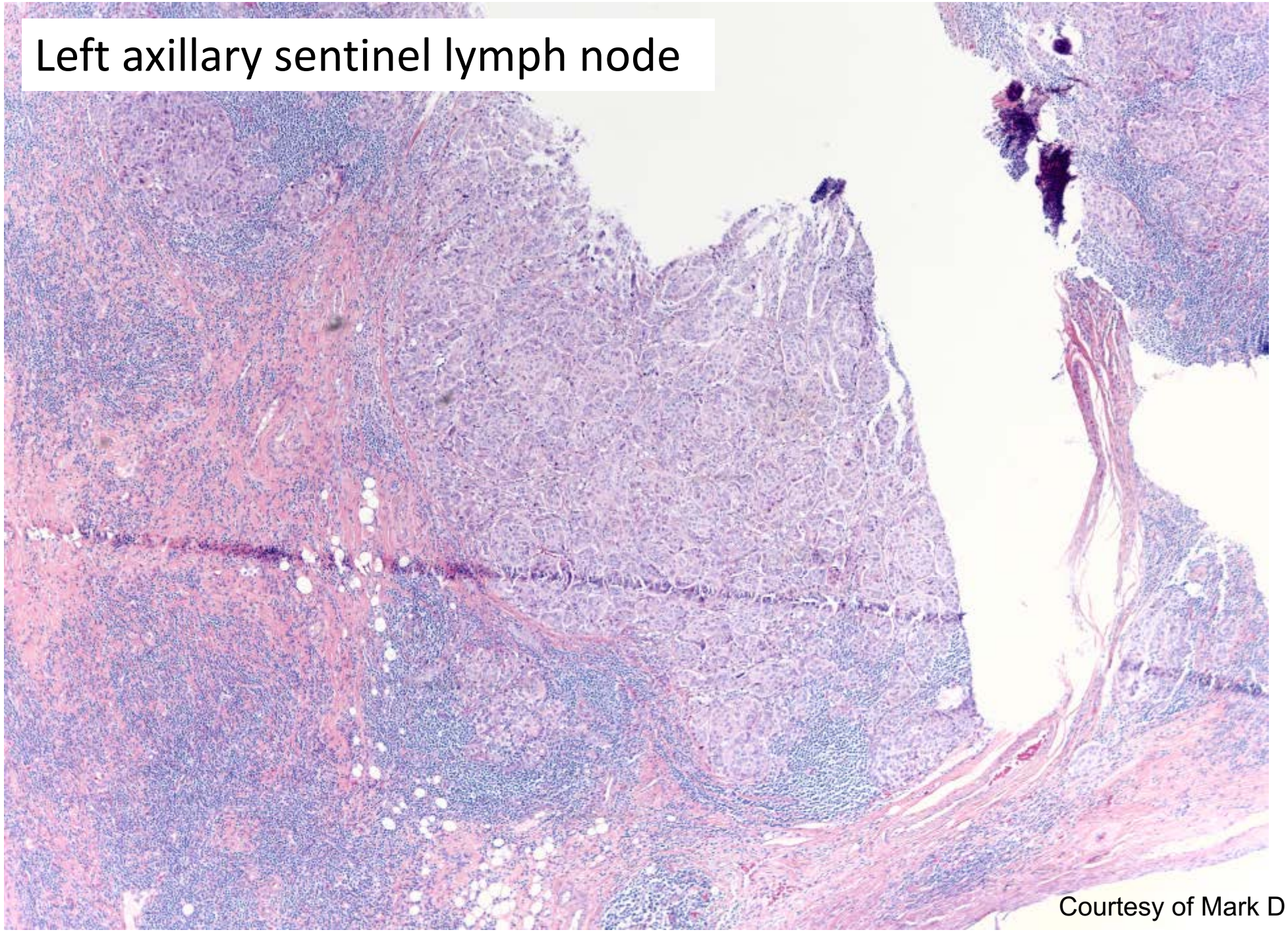


Courtesy of Mark D Pegram, MD



Courtesy of Mark D Pegram, MD

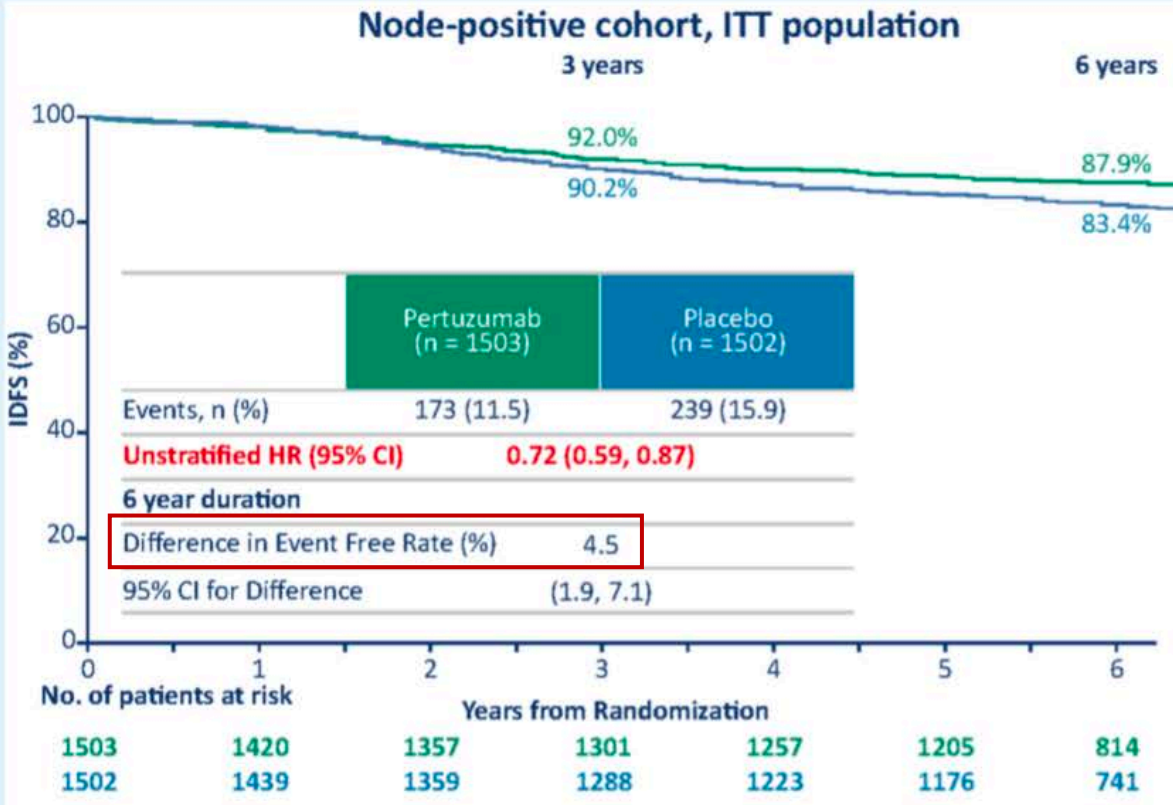
Left axillary sentinel lymph node

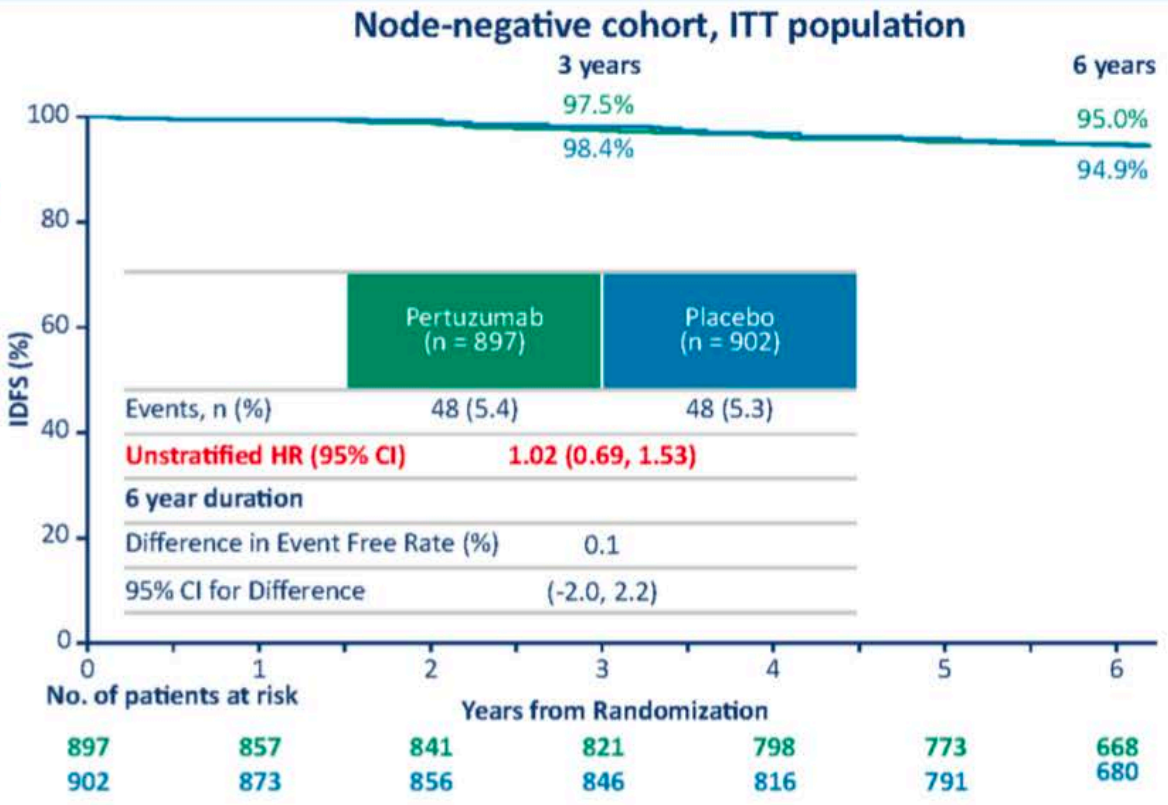


Courtesy of Mark D Pegram, MD

APHINITY Updated descriptive analysis 74.1 months median FU
Time to first IDFS event by treatment regimen and nodal status

The node positive cohort continues to derive clear benefit from addition of pertuzumab.



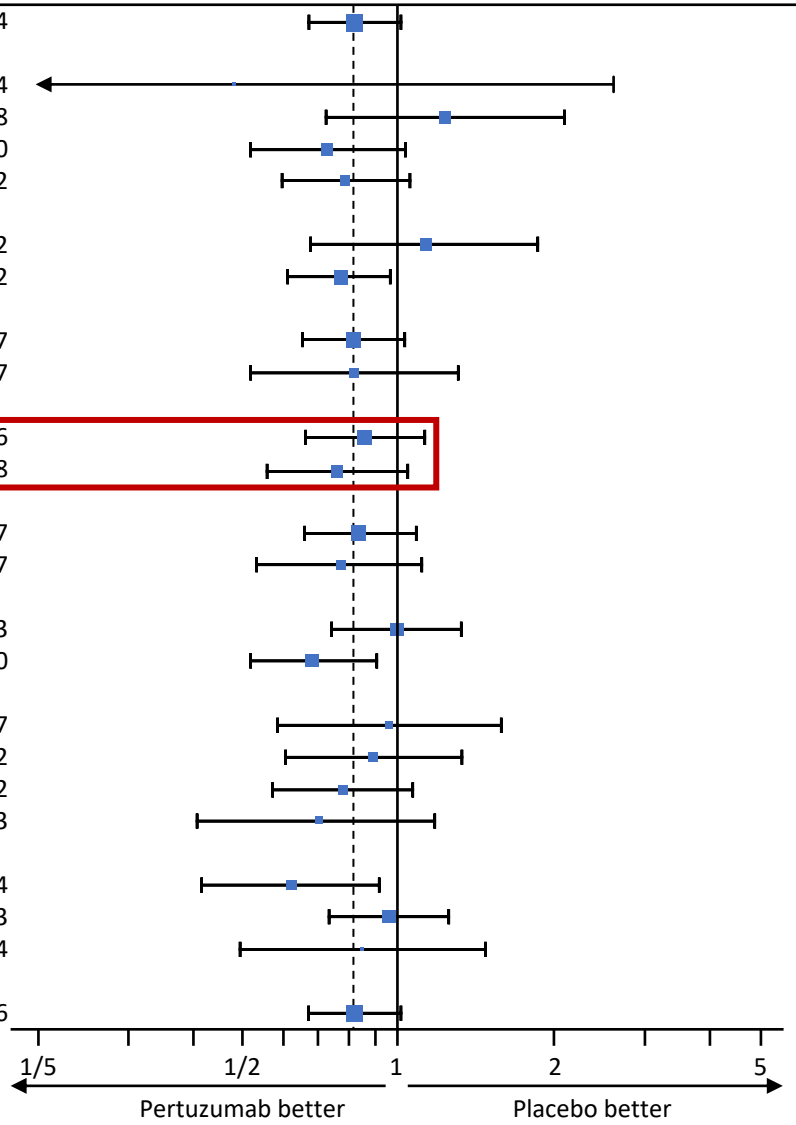


Piccart M, et al. 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS1-04.

Courtesy of Mark D Pegram, MD

APHINITY: IDFS Forest Plot by Subgroups

Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive nodes, tumor ≤1cm	2 / 90	4 / 84	0.48 (0.09–2.60)	97.7	97.5	
0 positive nodes, tumor >1cm	30 / 807	25 / 818	1.23 (0.72–2.10)	97.5	98.5	0.374
1–3 positive nodes	55 / 907	75 / 900	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	84 / 596	106 / 602	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	32 / 897	29 / 902	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	139 / 1503	181 / 1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						
Anthracycline	139 / 1865	171 / 1877	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	32 / 535	39 / 527	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status						
Positive (ER- and/or PgR-positive)	100 / 1536	119 / 1546	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	71 / 864	91 / 858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						
Protocol A	120 / 1828	143 / 1827	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	51 / 572	67 / 577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						
Pre-menopausal	93 / 1152	96 / 1173	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	78 / 1242	113 / 1220	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)						
<40	30 / 326	32 / 327	0.96 (0.59–1.59)	93.4	93.1	
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	0.781
50–64	69 / 1051	91 / 1082	0.78 (0.57–1.07)	94.3	93.3	
≥65	24 / 315	34 / 293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)						
<2	41 / 977	64 / 944	0.62 (0.42–0.92)	97.0	94.6	
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	0.203
≥5	22 / 147	31 / 174	0.85 (0.49–1.47)	87.5	87.5	
Sex						
Female	171 / 2397	209 / 2396	0.82 (0.67–1.01)	94.1	93.2	NA



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Courtesy of Mark D Pegram, MD