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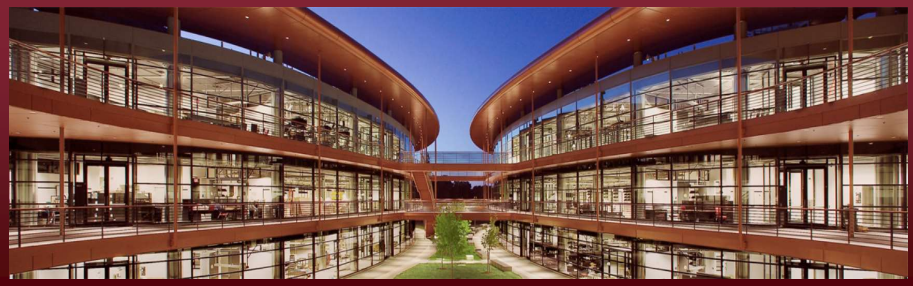
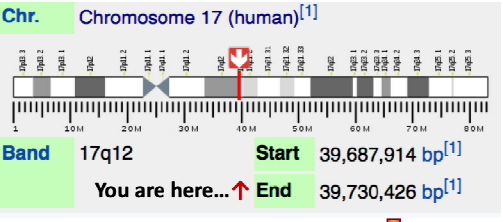
HER2+, ER+ 2019 SABCS Update



February 2020

Mark D. Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford University School of Medicine
Disclosures: Roche/GNE, Seattle Genetics
Macrogenics, Pfizer, Daichi Sankyo/AZ, Novartis



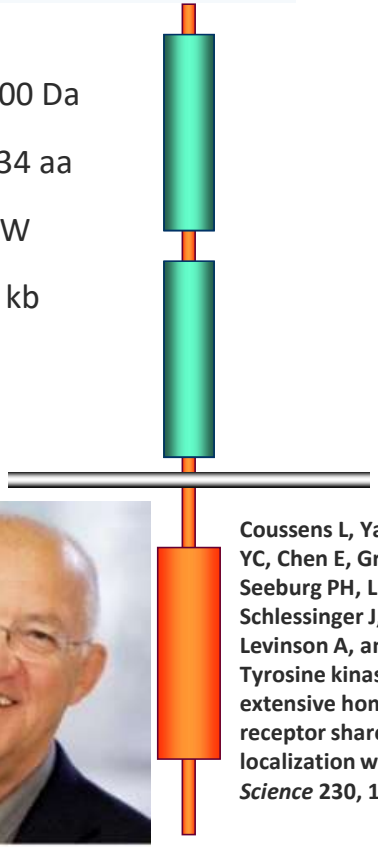
Human EGF Receptor-Related Receptor
HER2 / neu / c-erbB2 – Amplified in Breast CA

Size: 185,000 Da

Length: 1234 aa

136,000 MW

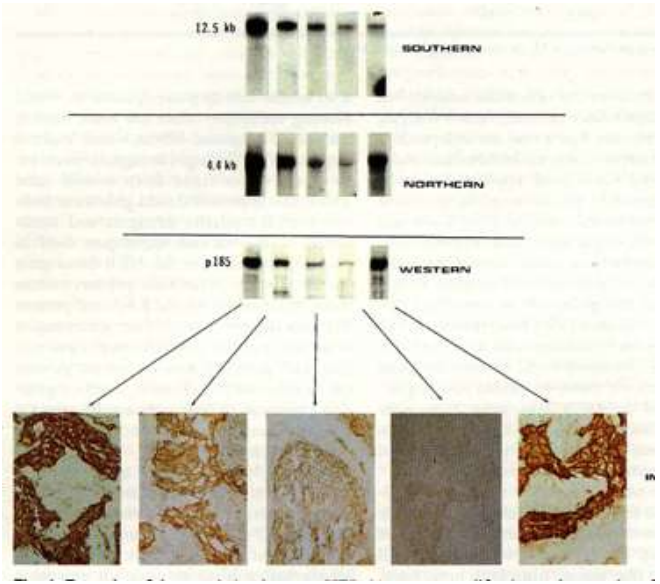
mRNA: 4.8 kb



Axel Ullrich

Max Planck Institute of Biochemistry

Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, Seeburg PH, Libermann TA, Schlessinger J, Francke U, Levinson A, and Ullrich A. (1985) Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal localization with neu oncogene. *Science* 230, 1132-1139

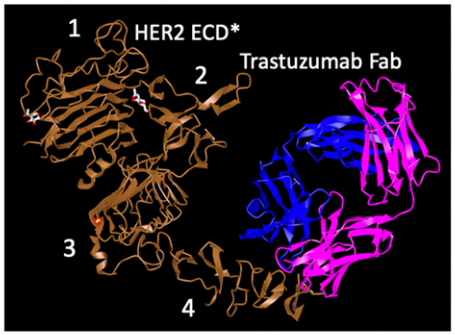


Dennis J. Slamon

University of California, Los Angeles

Slamon *et al*. Science 1987 & 1989

Structure of the extracellular region of HER2 in complex with the trastuzumab Fab



Cho HS1, Mason K, Ramyar KX, Stanley AM, Gabelli SB, Denney DW Jr, Leahy DJ.
Nature. 2003 Feb 13;421(6924):756-60.

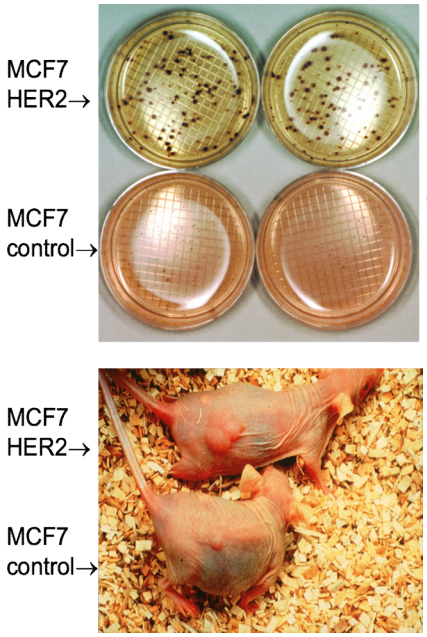
ECD* = Extracellular Domain

H. Michael Shepard

Genentech

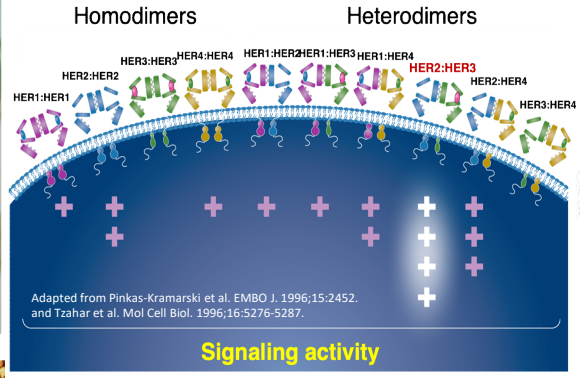
Effects of HER2 overexpression on anchorage-independent growth and tumorigenicity (A) Trastuzumab Blocks Ligand-*independent* HER2|HER3 Association (B), Reducing S-phase Fraction, and synergizing with chemotherapy (C)

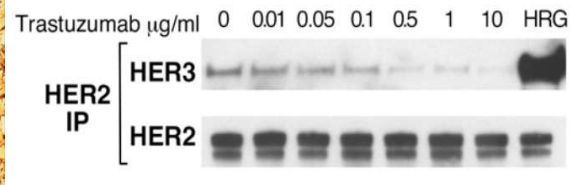
A.



Pegram M, Slamon D.
Semin Oncol 2000; 27(5 suppl 9): 13-19.

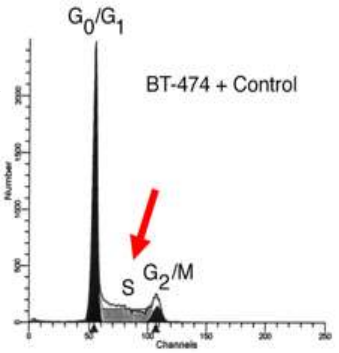
B.

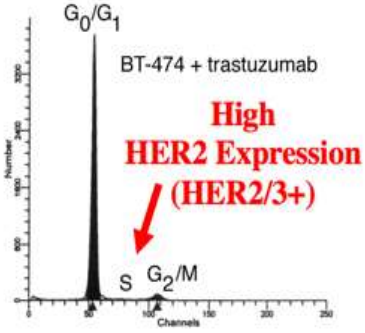


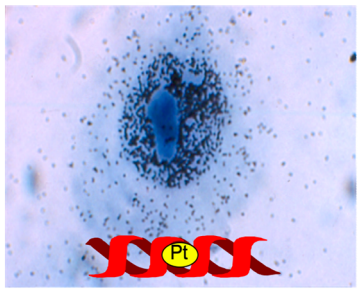


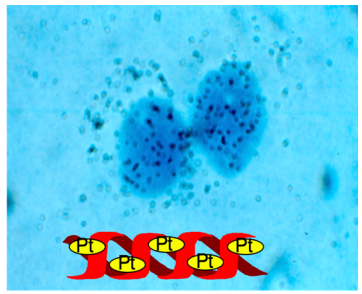
Junttila TT, et al. Cancer Cell. 2009 May 5;15(5):429-40.

C.





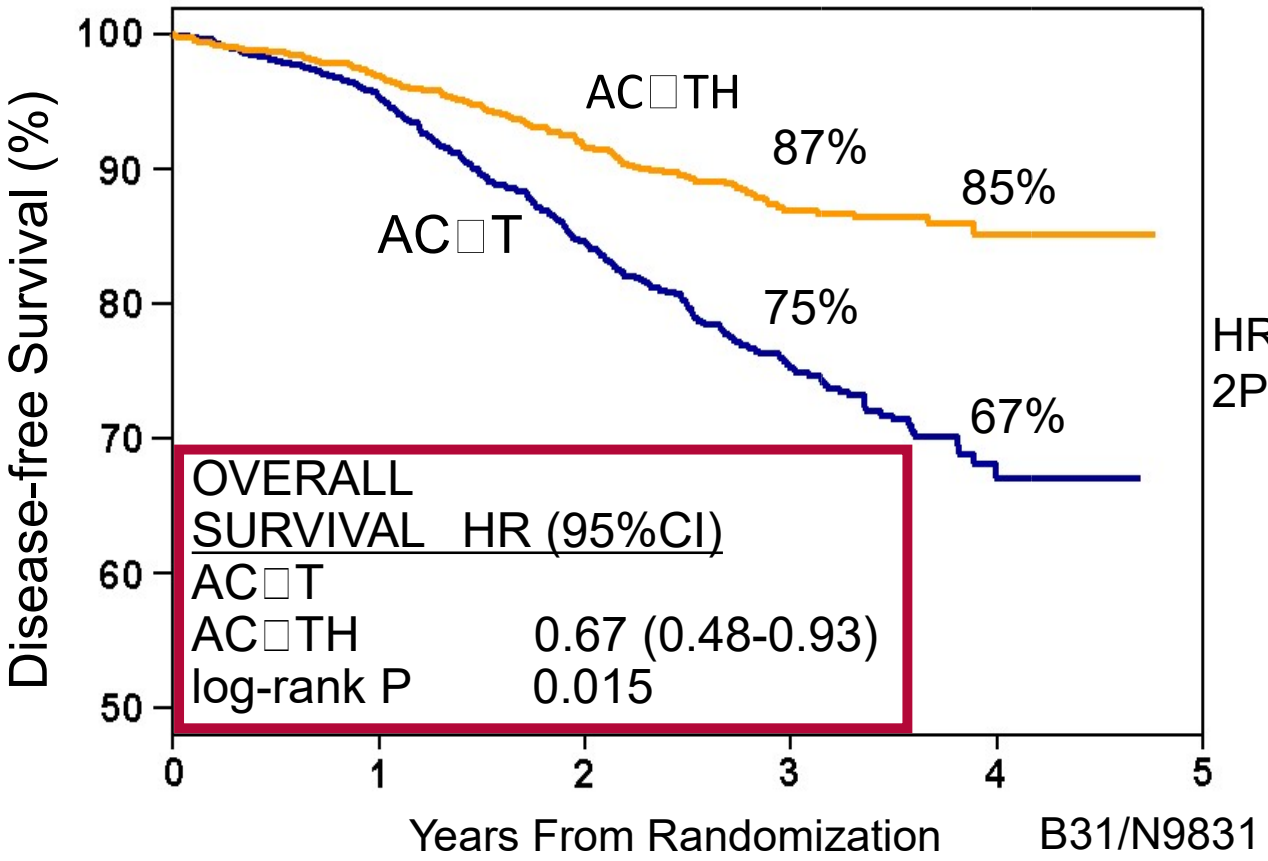




Cell cycle arrest (BrDU) ⇒ Cisplatin ⇒ tritiated thymidine ⇒ autoradiography

Pegram, et al. Oncogene, 13:2241 (1997).
Pietras RJ, Fendly BM, Chazin VR, Pegram MD, Howell SB, and Slamon DJ. Oncogene 9: 1829-1838, (1994).

Analysis of Trastuzumab Efficacy
Joint (B31/N9831) Analysis (N = 3,351)



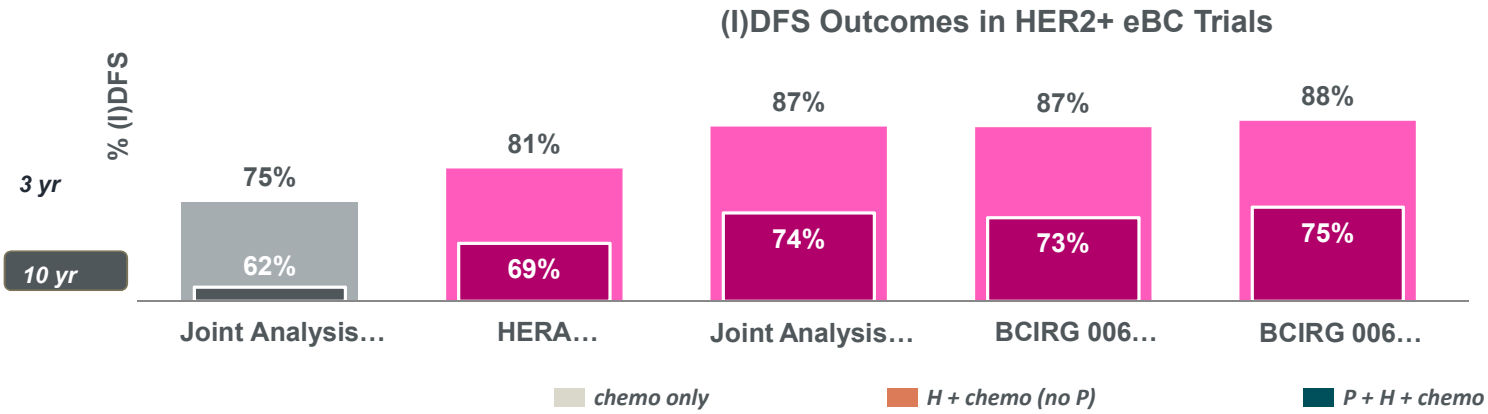
HR=0.48,
2P=3x10^{-12}

2019 Lasker DeBakey Clinical Medical Research Award:

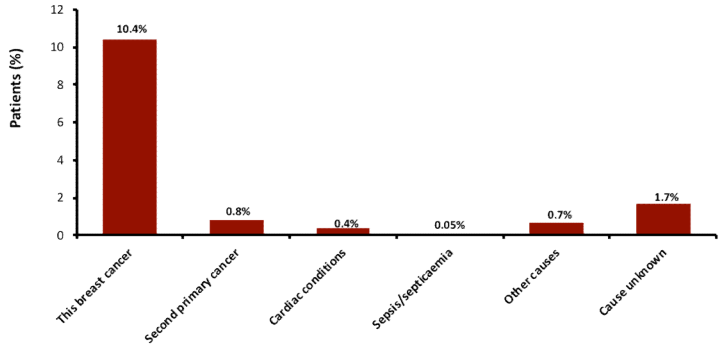
- **Axel Ullrich, Dennis Slamon, and Mike Shepard: "For invention of a targeted antibody therapy for breast cancer"**
- **Over 2.3 million women treated with trastuzumab globally…**
- **Trastuzumab is on the WHO List of Essential Medicines**
- **Four pivotal trials (N>13,000) established trastuzumab as *the* standard of care for HER2-positive early breast cancer**

Romond, et al., New England Journal of Medicine (2005).

HER2+ Breast Cancer – Remains a High Unmet Need



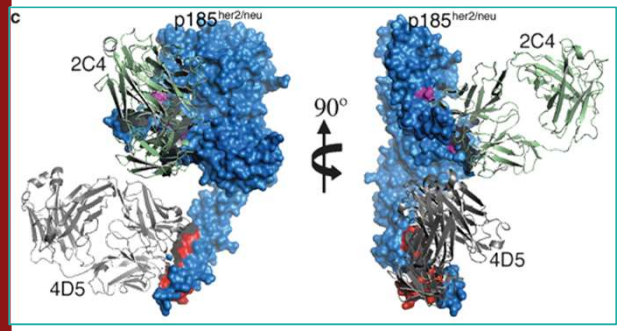
B-31/N9831: 10-year overall survival events and causes of death in patients treated with trastuzumab



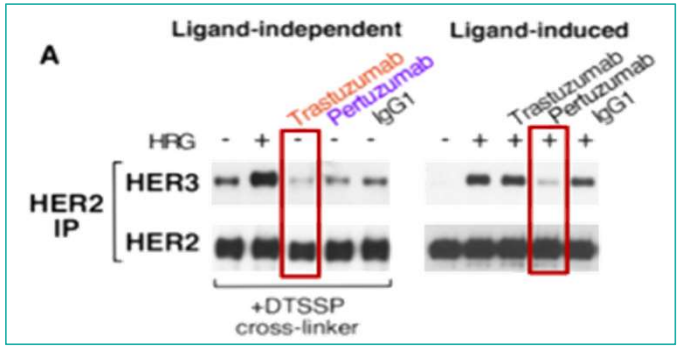
BC was the cause of death for the majority of the ~14% of patients who died

Perez EA, *et al. J Clin Oncol* 2014; 32:3744–3752.

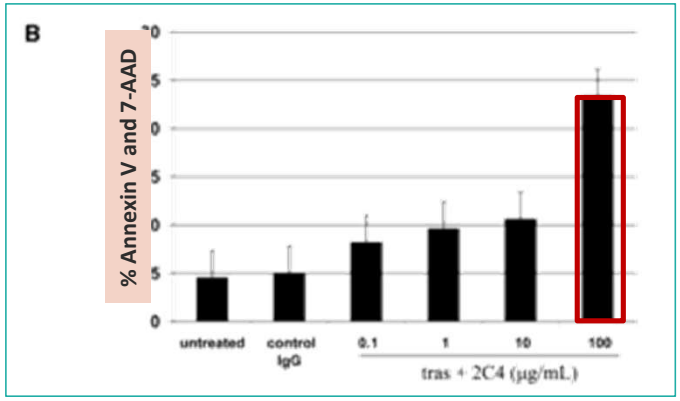
Pertuzumab Binds Subdomain II and Disrupts Ligand-*Dependent* HER2:HER3 Interaction; Pertuzumab + Trastuzumab Induces Apoptosis



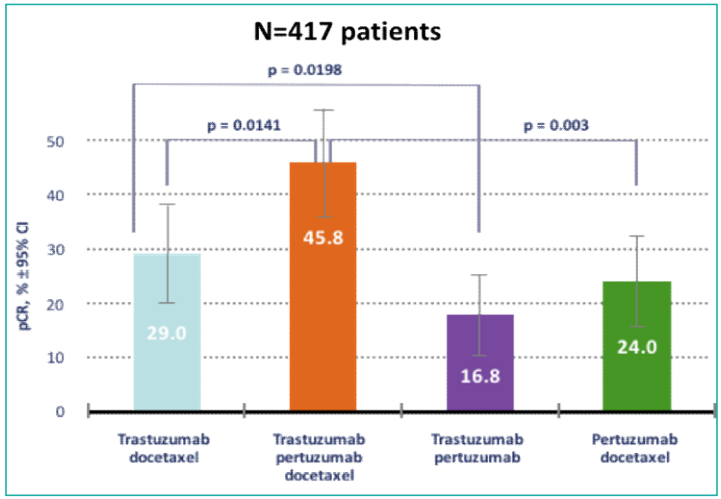
Z Cai, et al., Oncogene (2008) 27, 3870–3874



Junttila TT, et al., Cancer Cell. 2009 May 5;15(5):429-40.

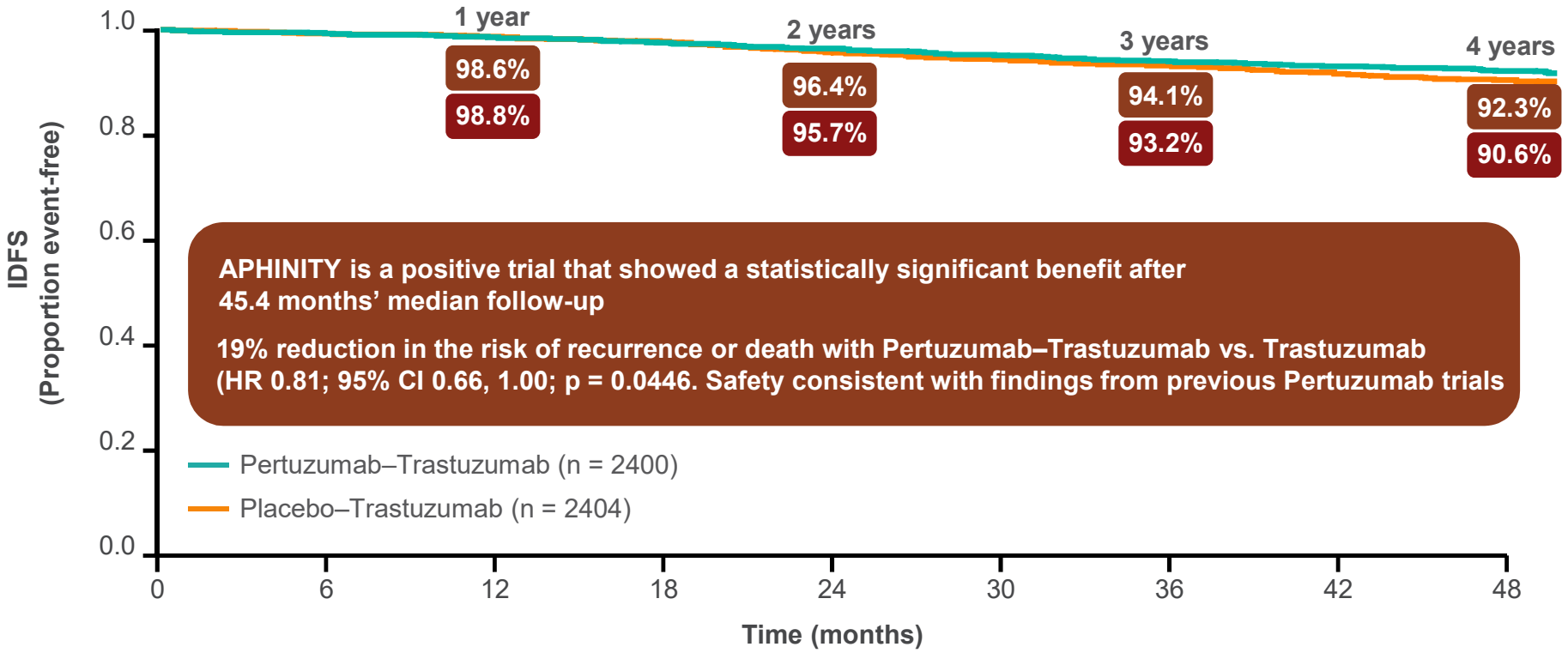


Rita Nahta, *et al*. Cancer Res 2004;64:2343-2346.



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

APHINITY Primary Analysis: Pertuzumab–Trastuzumab plus chemotherapy statistically significantly increased IDFS for HER2-positive eBC in the adjuvant setting



von Minckwitz G, *et al*. *N Engl J Med* 2017.
Stratification factors are: nodal status and protocol version, intended adjuvant chemotherapy and central hormone receptor status.
Hazard ratio was estimated by Cox regression.
IDFS, invasive disease-free survival

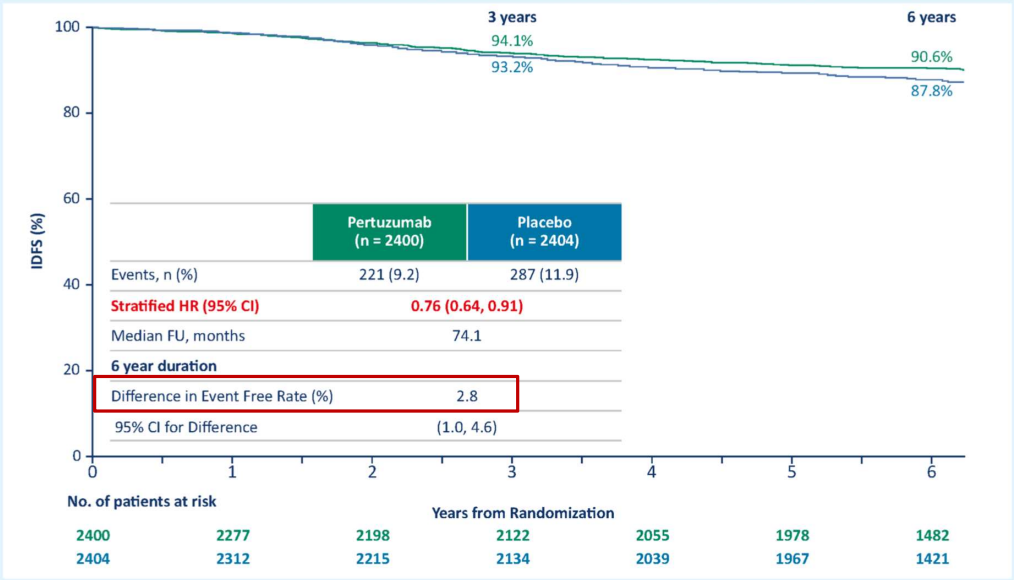
Methods

- **2nd interim analysis of OS** - pre-planned, time-driven, 2.5 years from primary analysis (PA), when 50% of the target events were anticipated.
  - Median follow-up time is 74.1 months, 28.7 months longer than at the PA.
  - P-value of 0.0012 is required for statistical significance for this interim OS analysis.
  - There are now 272 deaths (103 more than at the PA).
  - This is 42.5% of the 640 deaths needed for definitive OS analysis.
- Updated **descriptive analyses** of iDFS and cardiac safety were also performed.
  - There are now 508 patients with an IDFS event (127 more than at the PA).

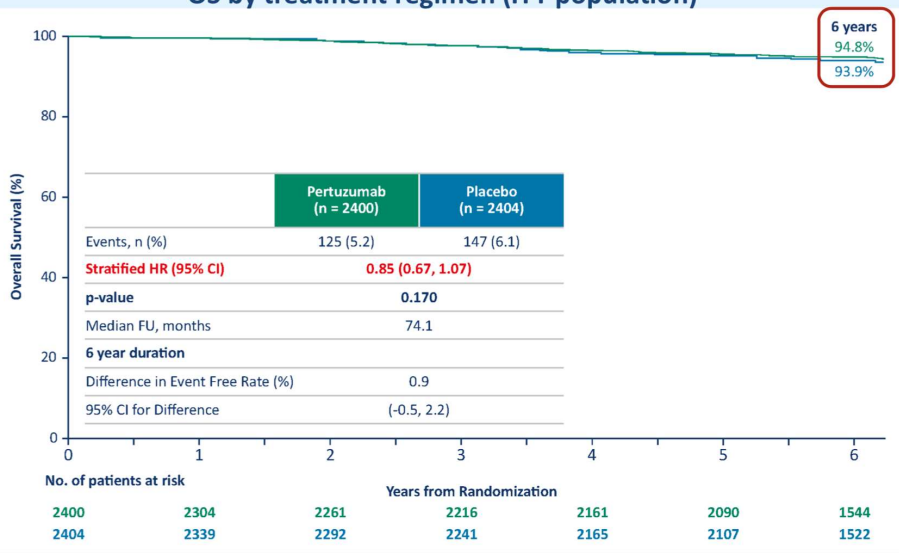
Piccart M, et al. 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS1-04.

APHINITY: 2nd Interim

APHINITY Updated descriptive analysis, 74.1 months median FU
Time to first IDFS event by treatment regimen (ITT population)



APHINITY Interim Overall Survival Analysis 74.1 months median FU,
OS by treatment regimen (ITT population)

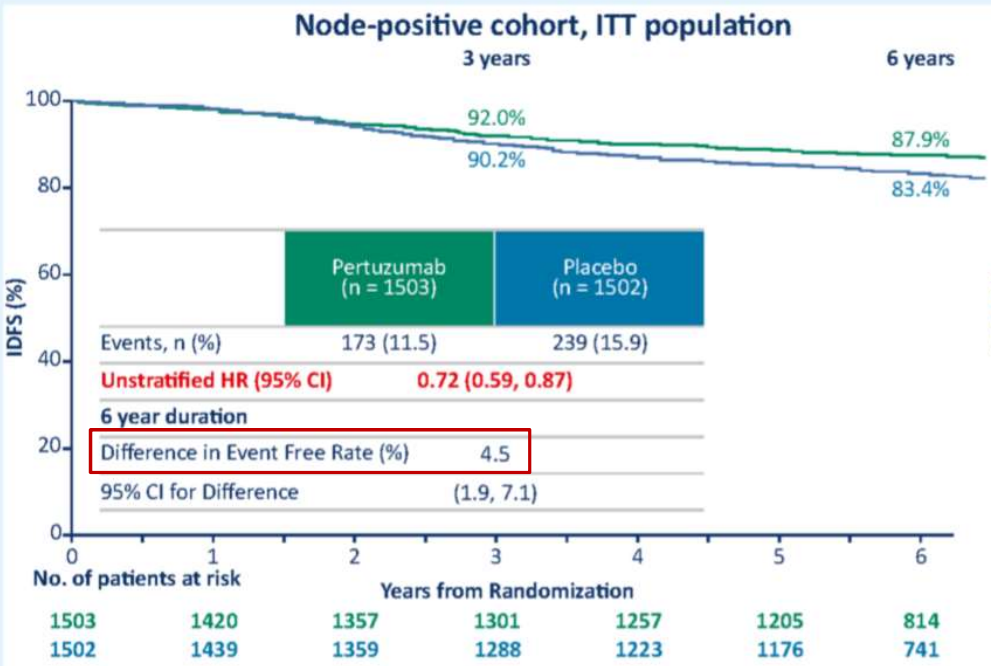


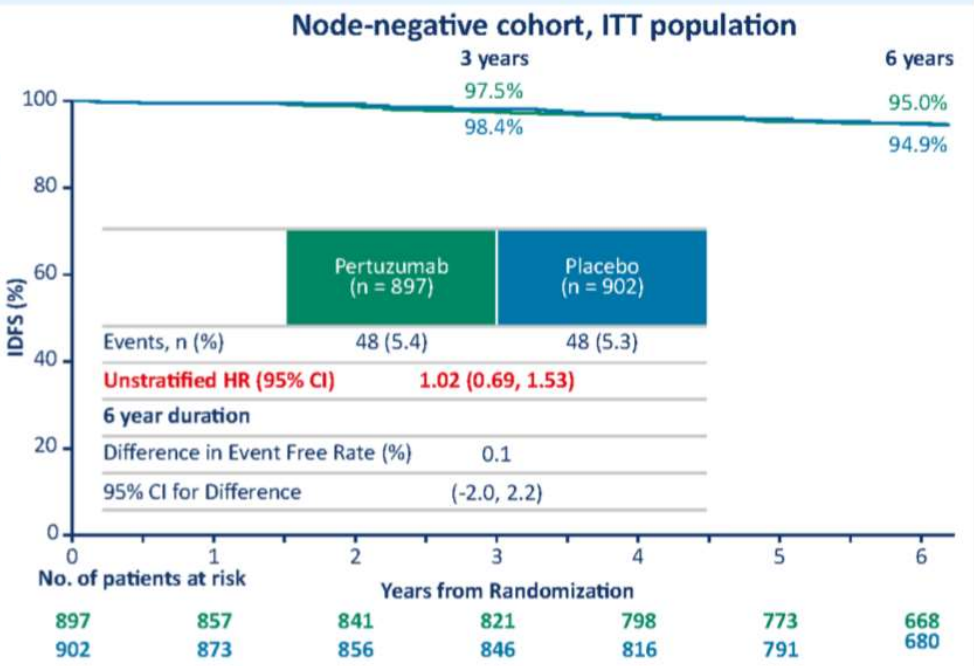
P-value of 0.0012 is required for statistical significance for OS. Survival data remain immature at this time.

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

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.

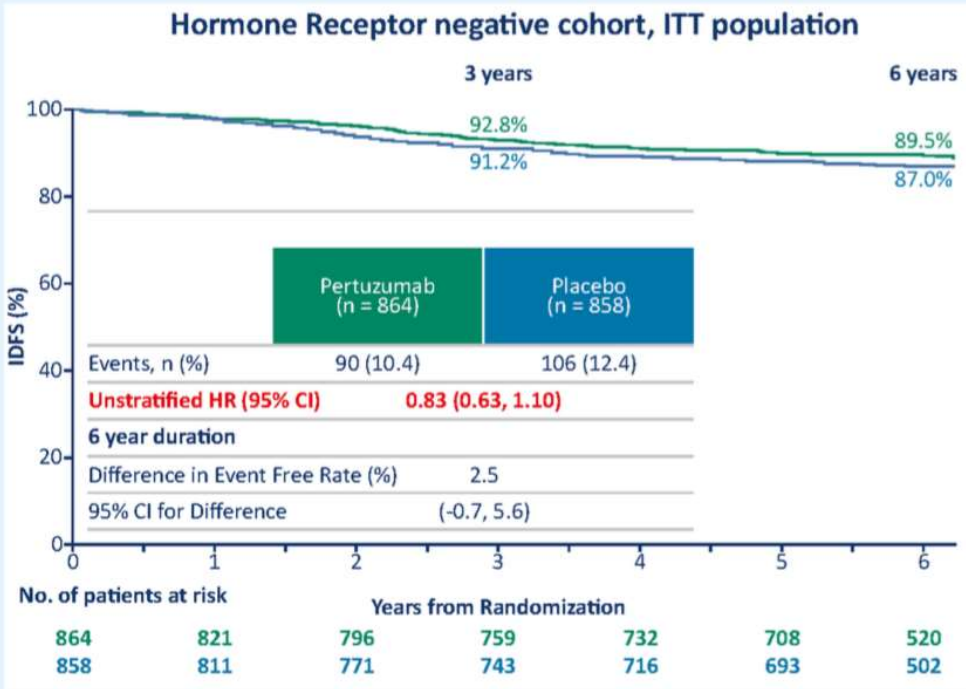


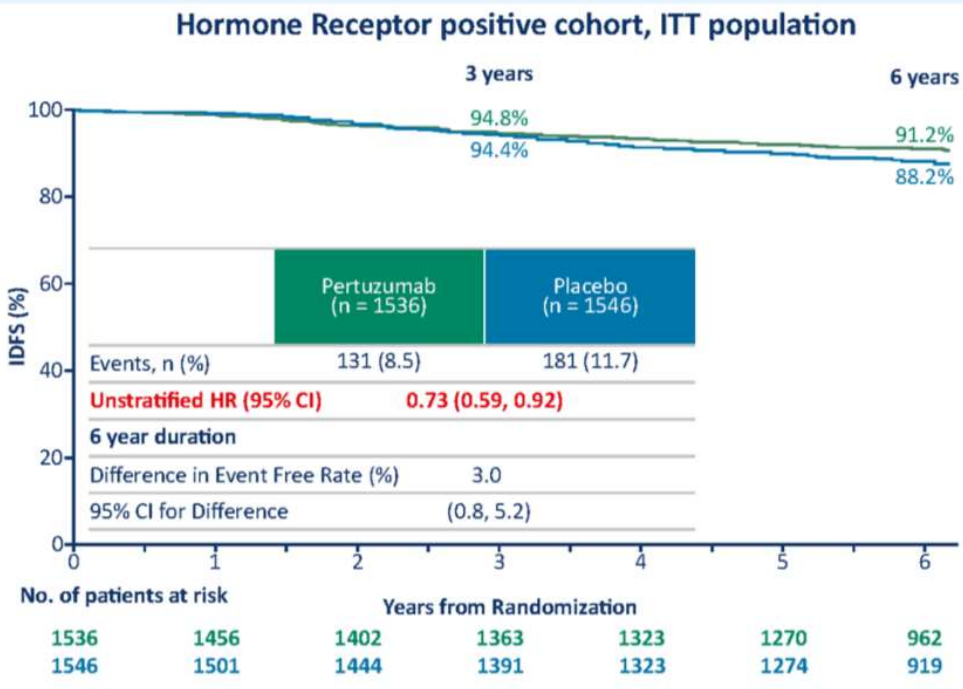


Piccart M, et al. 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS1-04.

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

Treatment benefit of pertuzumab is also seen in the hormone positive cohort.

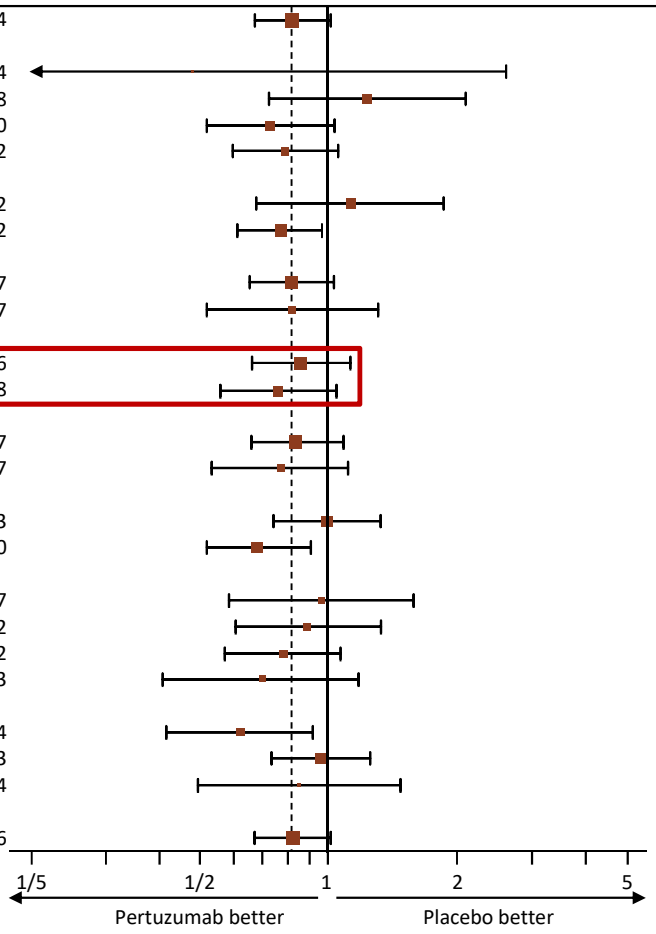




Piccart M, et al. 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS1-04.

APHINITY: IDFS Forest Plot by Subgroups

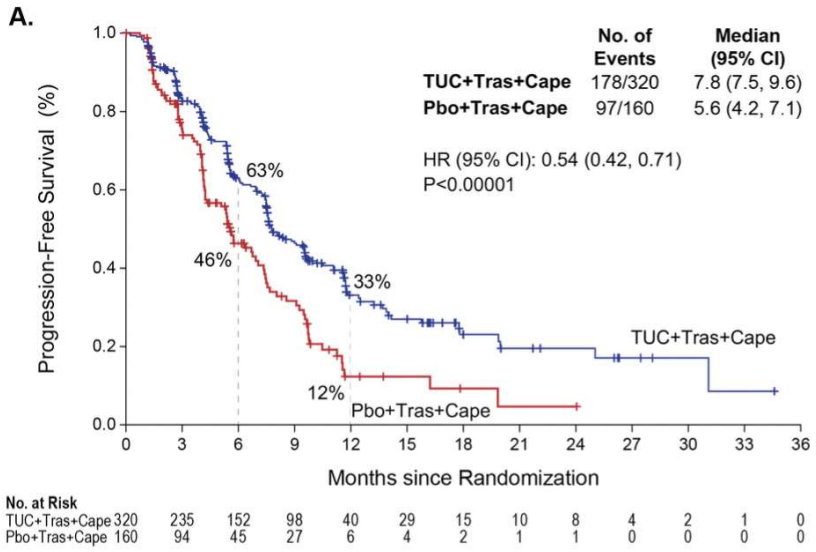
Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive 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

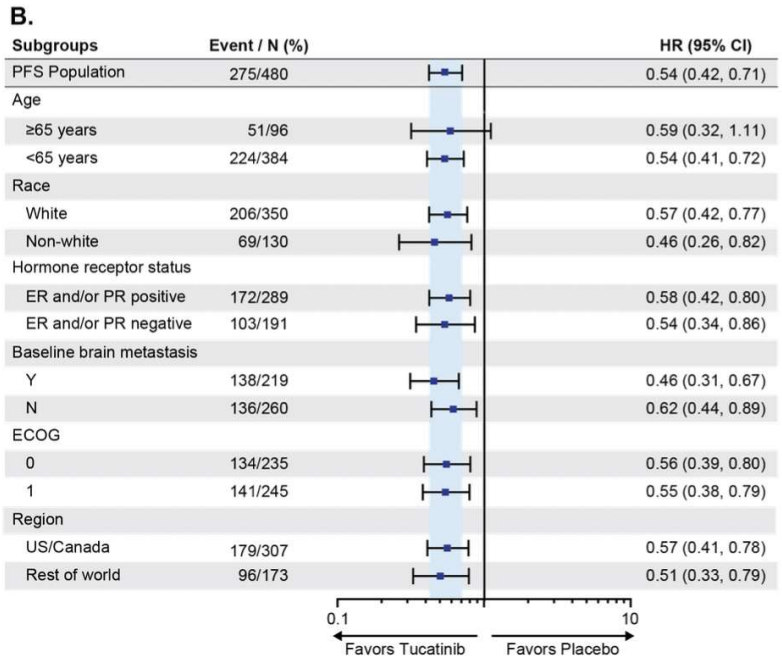


von Minckwitz, G et al. *N Engl J Med.* 2017;377:122-131

Tucatinib, Trastuzumab and Capecitabine for Previously Treated HER2+ Metastatic Breast Cancer: The HER2CLIMB Trial

Figure 1. Kaplan-Meier Estimate of Progression-Free Survival in the Primary Endpoint Population and Prespecified Subgroups

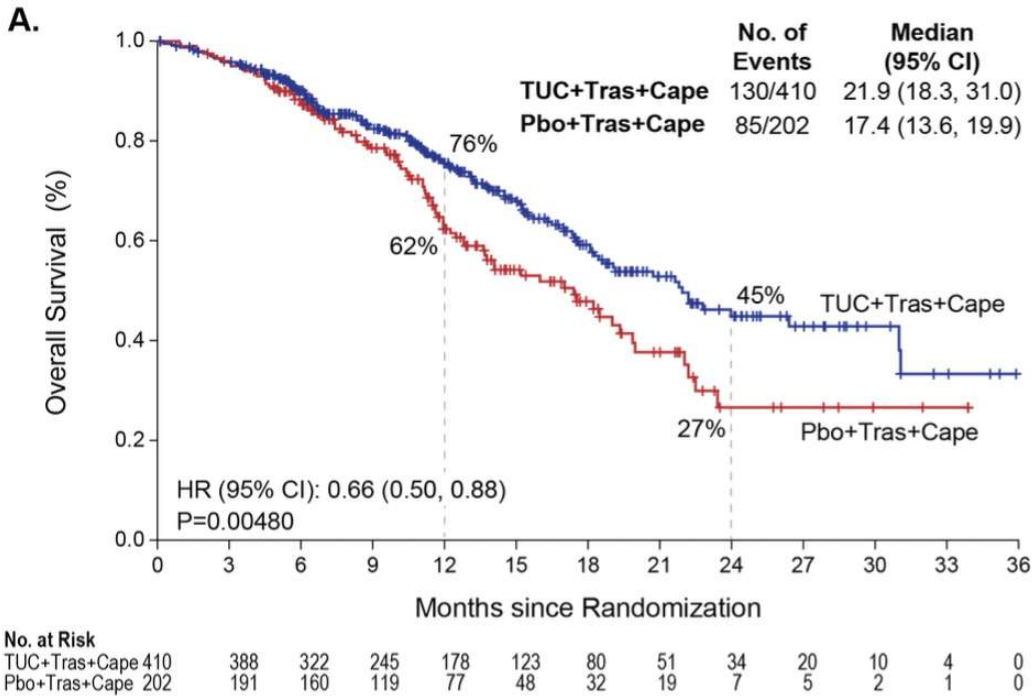




Murthy, et al. December 27, 2019. DOI: 10.1056/NEJMx190039

Tucatinib, Trastuzumab and Capecitabine for Previously Treated HER2+ Metastatic Breast Cancer: The HER2CLIMB Trial

Figure 2. Kaplan-Meier Estimate of Overall Survival in the Total Population and Prespecified Subgroups



Murthy, et al. December 27, 2019. DOI: 10.1056/NEJMx190039

DESTINY-Breast01: [Fam-]trastuzumab deruxtecan (T-DXd) in HER2+ mBC

General Session 1 [Abstract GS1-03]: Dr Ian Krop (Dana-Farber Cancer Institute, Boston, MA, USA)

Trial: DESTINY-Breast01 (NCT03248492)

Population: Patients with HER2+ mBC previously treated with T-DM1 (trastuzumab emtansine).

Study Design: Open-label, international Phase 2 registration study consisting of a PK and dose finding stage (T-DXd 5.4, 6.4, 7.4 mg/kg) followed by second stage at the recommended part 2 dose (5.4 mg/kg).

Primary Outcome: ORR (complete response [CR] + partial response [PR]) per independent central review (ICR).

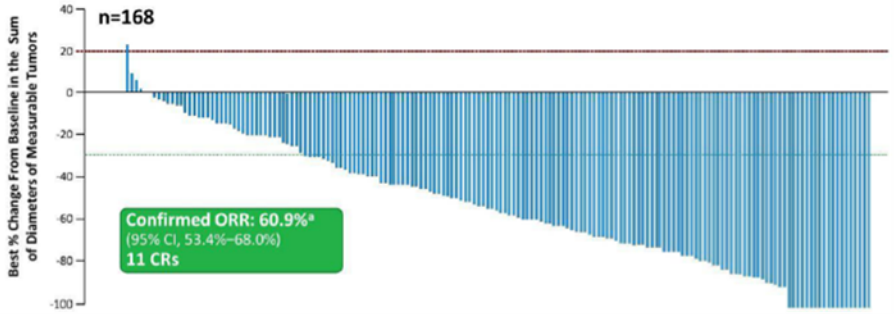
Secondary Outcomes: Investigator-assessed ORR, disease control rate (DCR; CR + PR + stable disease), DOR, CBR, PFS, OS, PK and safety.

Authors' Conclusions: Clinically meaningful and durable activity, with a generally manageable safety profile, was observed for T-DXd in a heavily pretreated patient population. ILD was identified as an important risk requiring careful monitoring and prompt intervention.

Results:

- 184 patients were enrolled in Stage 2 at a dose of 5.4 mg/kg, with a median of 6 lines of previous treatment.
- Confirmed ORR by ICR was 60.9% (n=112), with CR of 6.0% (n=11) and PR of 54.9% (n=101). Best change in tumour size is presented in Figure 3. Median DOR was 14.8 months, with median PFS of 16.4 months.
- TEAEs occurred in 99.5% of subjects (Grade ≥3, 57.1%). Interstitial lung disease was identified as an important risk, occurring in 13.6% of patients (n=25) with four fatal cases.

Figure 3: Best change from baseline in tumour size (sum of diameters of measurable tumours) by ICR



ITT population, n=184. The line at 20% indicates progressive disease, the line at -30% indicates PR

Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor-2; ICR, independent central review; mBC, metastatic breast cancer; ORR, objective response rate; OS: overall survival; PFS, progression free survival; PK, pharmacokinetics; PR, partial response; TEAE, treatment emergent adverse events; T-DXd, [Fam-]trastuzumab deruxtecan.

SOPHIA: Margetuximab (M) in Pre-Treated Patients with HER2+ mBC

General Session 1 [Abstract GS1-02]: Prof Hope Rugo (University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, USA)

Trial: SOPHIA (NCT02492711)

Population: Patients with HER2+ mBC and disease progression after 1–3 lines of therapy for HER2+ mBC and ≥2 lines of anti-HER2 therapy including pertuzumab.

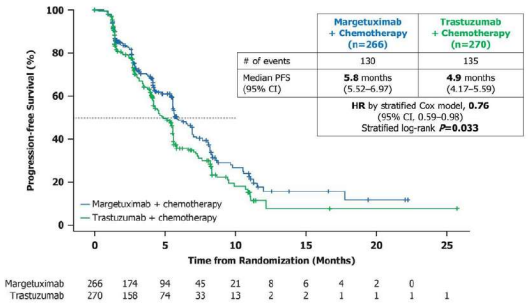
Study Design: Patients were randomised 1:1 to investigator's choice of chemotherapy with either M or trastuzumab (T).

Co-Primary Outcomes: Centrally-blinded PFS and OS.

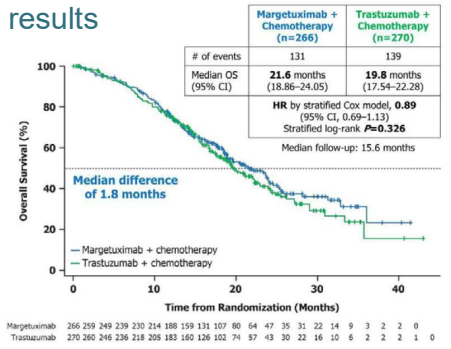
Secondary outcomes: Investigator-assessed PFS, centrally-blinded ORR.

Results: In the ITT population (N=536), M + chemotherapy prolonged PFS (centally-blinded) vs T + chemotherapy (median PFS 5.8 vs 4.9 months; Figure 2). The second interim OS analysis (data cut-off Sept 2019) favoured M (Figure 2). Safety results, as measured at the April 2019 cut-off, were consistent between the two treatment arms as shown in Table 1.

Figure 2: Centrally-blinded PFS and OS results



Data cut-off October 2018



Data cut-off September 2019

Table 1: Summary of safety data

	M + chemotherapy	T + chemotherapy
Any grade AE, n (%)	260 (98.5)	261 (98.1)
Grade ≥3, n (%)	142 (53.8)	140 (52.6)
Any SAE, n (%)	43 (16.3)	49 (18.4)
AE leading to treatment discontinuation, n (%)	8 (3.0)	7 (2.6)

Authors' Conclusion: M + chemotherapy demonstrated superiority in terms of PFS vs trastuzumab in patients with pre-treated HER2+ mBC, with comparable safety results.

Abbreviations: AE, adverse event; CI, confidence interval; HER2, human epidermal growth factor receptor-2; ITT, intention-to-treat; M, margetuximab; mBC, metastatic breast cancer; ORR, objective response rate; OS: overall survival; PFS, progression free survival; SAE, serious adverse event; T, trastuzumab.

SOLTI-1402/CORALLEEN: Neoadjuvant ribociclib (RIB) + LET

General Session 2 [GS2-06]: Dr Joaquín Gavilá (Instituto Valenciano de Oncología, Valencia, Spain)

Different approaches for treatment de-escalation are being investigated; however, the current ongoing Phase 3 adjuvant trials with CDK4/6is are not addressing the question of whether these drugs can replace multi-agent chemotherapy (CT) in patients with high-risk eBC. **Dr Joaquín Gavilá** presented the primary results of the Phase 2 **SOLTI-1402/ CORALLEEN** trial, evaluating the efficacy of RIB + ET as neoadjuvant treatment in patients with high-risk Luminal B disease.

Population: **Postmenopausal women with stage I-IIIA operable HR+/HER2- BC, Luminal B by Prosigna® and ECOG 0-1.**
Study Design: A parallel, multicentre, two-arm, exploratory study. **Patients were randomised 1:1 to receive either six 28-days cycles of RIB (600 mg; 3-weeks on/1-week-off) + daily LET (2.5 mg) or CT: 4 cycles of AC (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 21 days) followed by 12 weeks of weekly paclitaxel (80 mg/m^2).**
Primary Outcome: **Rate of PAM50/Prosigna® Risk of Relapse (ROR)-low disease at surgery.** PAM50 ROR score integrates gene expression data, tumour size and nodal status to define a low-risk group in the adjuvant setting (i.e. >90% distant relapse-free survival at 10 years).
Secondary Outcomes: Included safety, intrinsic subtype at surgery, RCB and Preoperative Endocrine Prognostic Index (PEPI).

Results: 52 patients were randomised to treatment with RIB+LET and 54 patients to treatment with CT. ROR rates as surgery are presented in Table 4. Intrinsic subtype conversion to Luminal A at surgery occurred in 87.8% of patients in the RIB+ET arm and in 82.7% in the CT arm.

Table 4: Primary endpoint (ROR-low) at the time of surgery

	CT (n=52)		RIB + LET (n=49)	
	n (%)	95% CI	n (%)	95% CI
ROR-low	**24 (46.1%)**	**32.9-61.5**	**23 (46.9%)**	**32.5-61.7**
ROR-intermediate	16 (30.8%)	19.1-45.9	15 (30.6%)	18.2-45.4
ROR-high	11 (21.2%)	11.2-35.2	11 (22.5%)	11.8-36.7
Missing	1 (1.9%)	NA	NA	NA

Grade ≥3 toxicities were observed in 56.9% of patients in the RIB+LET arm and 69.2% of patients in the chemotherapy arm.

Authors' Conclusion: Neoadjuvant RIB+LET in high-risk Luminal B breast cancer achieves similar rates of ROR-low disease at surgery as multi-agent chemotherapy.

Abbreviations: AC, doxorubicin + cyclophosphamide; CT, chemotherapy; eBC, early breast cancer; ET, endocrine therapy; LET, letrozole; RIB, ribociclib; ROR, risk of relapse.

SOLTI-1402/CORALLEEN: Neoadjuvant ribociclib (RIB) + LET

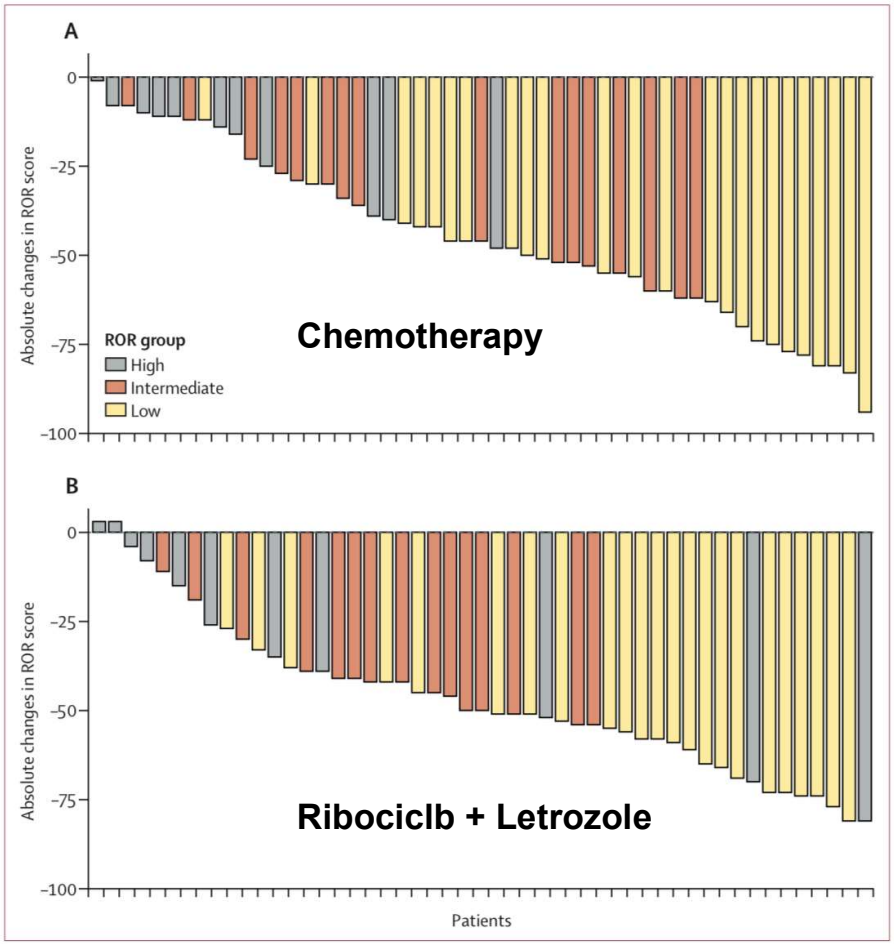


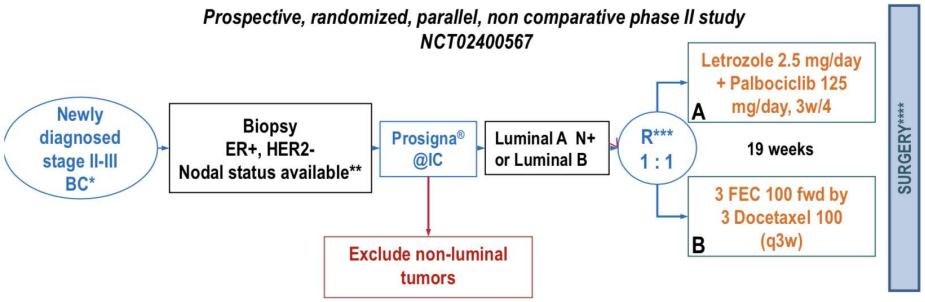
Figure 2: **Absolute changes in ROR score between baseline and surgery**
(A) Chemotherapy group; (B) ribociclib and letrozole group. The ROR risk group was determined at surgery. ROR=risk of relapse.

Prat A, et al. The Lancet 21(1): 2020, 33-4

Biological Endpoints

NEOPAL STUDY DESIGN

Prospective, randomized, parallel, non comparative phase II study
NCT02400567



Primary Objective :

- To evaluate the ability of each treatment strategy to provide RCB 0-I pathological response at surgery

A **two-step Fleming statistical design was used in the LET PALBO arm:**

- **Null hypothesis (p0) : RCB 0-I is observed in at least 20% of the cases (p0 = 0.20)**
- Alternative hypothesis: p1 = 40% (0.40)
- Type I error of 0.045 - type II error of 0.042 (power = 95.8%)
- 60 evaluable patients per arm

Final RCB 0 (pCR) and RCB III rates are strikingly similar between arms

		LET PALBO (n=52)	CHEMO (n=51)
RCB class	0	2 (3.8%)	3 (5.9%)
	I	2 (3.8%)	5 (9.8%)
	II	27 (51.9%)	19 (37.3%)
	III	21 (40.4%)	24 (47.1%)

Sharp decrease of Ki67 in both arms
(exploratory p values)

	LETROZOLE PALBOCICLIB	CHEMO	
Baseline geometric mean[1]	24.1%	27.7%	p=0.405
Final geometric mean	**1.17%**	**3.7%**	p=0.0418
Decrease	-0.95 $p<10^{-12}$	-0.86 $p<10^{-8}$	

Moving CDK4/6 Inhibitors Into Earlier Settings: Current Data and Ongoing Phase III Trials

- BC recurrence risk remains high among women with early-stage ER+ BC who were disease free after 5 yrs of ET[1,2]
  - 17% to 26% through 20 yrs
  - Motivating evaluation of CDK4/6i in EBC
- In phase II trials, CDK4/6 inhibitors showed enhanced antiproliferative activity in ER+ EBC
  - NeoPalAna: 87% complete cell cycle arrest with palbociclib + anastrozole vs 26% with anastrozole only; $P < .001$[3]
  - MONALEESA-1: 92% mean decrease in Ki67+ cells with ribociclib + letrozole vs 69% with letrozole only[4]

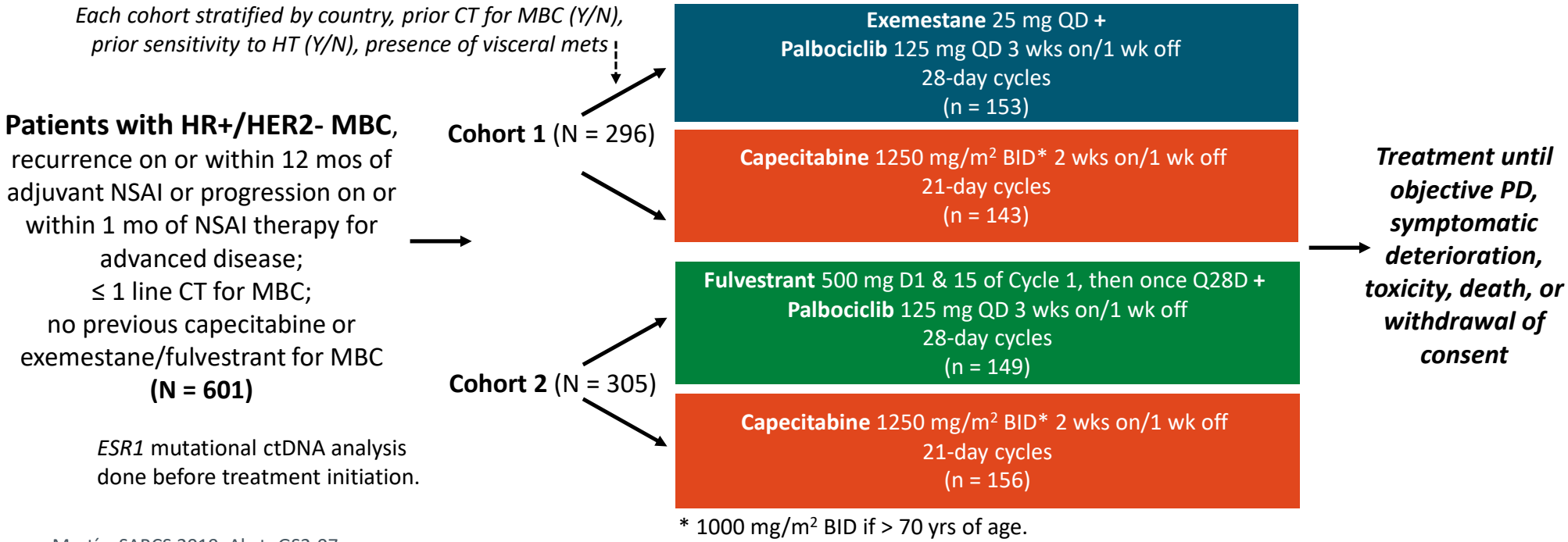
1. Pan. NEJM. 2017;377:1836. 2. Pernas. Ther Adv Med Oncol. 2018;10:1. 3. Ma. Clin Cancer Res. 2017;23:4055.
4. Curigliano. Breast. 2016;28:191. 5. NCT02513394. 6. NCT01864746. 7. NCT03701334. 8. NCT03155997.

Ongoing Phase III Trials in Early-Stage ER+/HER2- BC

Trial	Study Population	Study Tx
PALLAS*[5]	Stage II-III invasive BC	SoC adjuvant ET ± palbociclib
PENELOPE-B*[6]	Residual disease post neoadj CT, high relapse risk	SoC adjuvant ET ± palbociclib
NATALEE†[7]	Stage II-III invasive BC	SoC adjuvant ET ± ribociclib
MonarchE*[8]	High-risk, N+ BC post-surgery	SoC adjuvant ET ± abemaciclib

PEARL: Study Design

- Phase III, international, randomized study with 2 cohorts; 4 countries, 37 sites (GEICAM, CECOG)
  - Cohort 1 recruited March 2014 to September 2016; Cohort 2 from May 2016 to July 2018



* 1000 mg/m² BID if > 70 yrs of age.

Martín. SABCS 2019. Abstr GS2-07.

PEARL: Palbociclib (PAL) + ET vs CAP in Patients with HR+/HER2- mBC Whose Disease Progressed on AIs

General Session 2 [GS2-07]: Prof Miguel Martín (Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain)

Trial: PEARL, a multinational, open-label, Phase 3 RCT comparing the efficacy and safety of PAL+ET (EXE or FUL) vs CAP.

Population: Postmenopausal women with HR+/HER2- mBC whose disease progressed on AIs.

Study Design:

- Cohort 1 (C1): patients were randomised 1:1 to PAL+EXE vs CAP.
- Cohort 2 (C2): in 2016, after data showing that *ESR1* mutations may induce resistance to AIs but not to FUL, a second cohort with FUL+PAL vs CAP was added to the trial.

Co-Primary Objectives: To demonstrate:

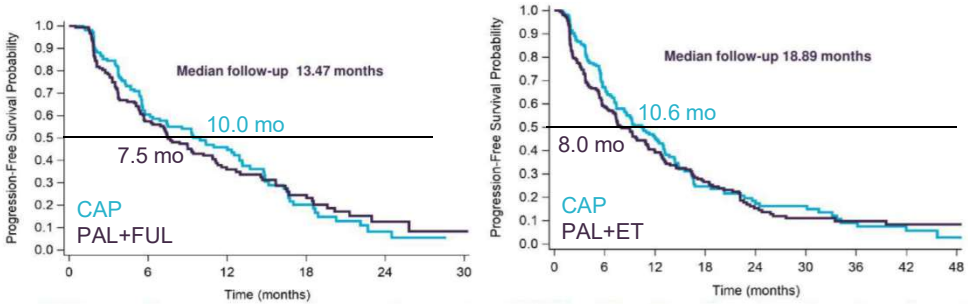
1) Superiority of PAL+FUL over CAP in terms of PFS (regardless of *ESR1*).
2) Superiority of PAL+ET (EXE or FUL) over CAP in PFS in patients with *ESR1* wild type (wt).

Authors' Conclusions: The study did not show statistical superiority in terms of PFS for PAL+ET vs CAP in patients with mBC who progressed on AIs, and superiority of PAL+ET was not observed in the luminal subgroup either. Treatment with PAL+ET was generally better tolerated than CAP.

Results: 601 patients were recruited: 296 in C1 and 305 in C2. In C1 and C2 respectively, 26.4% and 28.2% had *ESR1* mutations and 79.4% and 73.1% had received ≥1 prior hormone therapy for mBC.

The results of the co-primary analyses are presented in Figure 7.

Figure 7: PFS in C2 (n=305) and PFS in the *ESR1* wt population (n=393)



The most frequent grade 3–4 toxicities with EXE+PAL, FUL+PAL and CAP respectively were neutropenia (57.3%, 55.7% and 5.5%), followed by febrile neutropenia (1.3%, 0.7% and 1.4%), hand/foot syndrome (0%, 0% and 23.5%) and diarrhoea (1.3%, 1.3% and 7.6%).

Abbreviations: AI, aromatase inhibitor; BC, breast cancer, C1/2, cohort 1/2; CAP, capecitabine; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; mBC, metastatic breast cancer; mo, months; PAL, palbociclib; PFS, progression-free survival; RCT, randomised controlled trial; wt, wild type.

Young-PEARL: Study Design

- Prospective, multicenter, open-label phase II study by the Korean Cancer Study Group

Premenopausal MBC pts, HR+*/HER2- who received treatment with tamoxifen and ≤ 1 line of chemo for MBC; no previous treatment with AI, CDK4/6 inhibitor or capecitabine (N = 184)

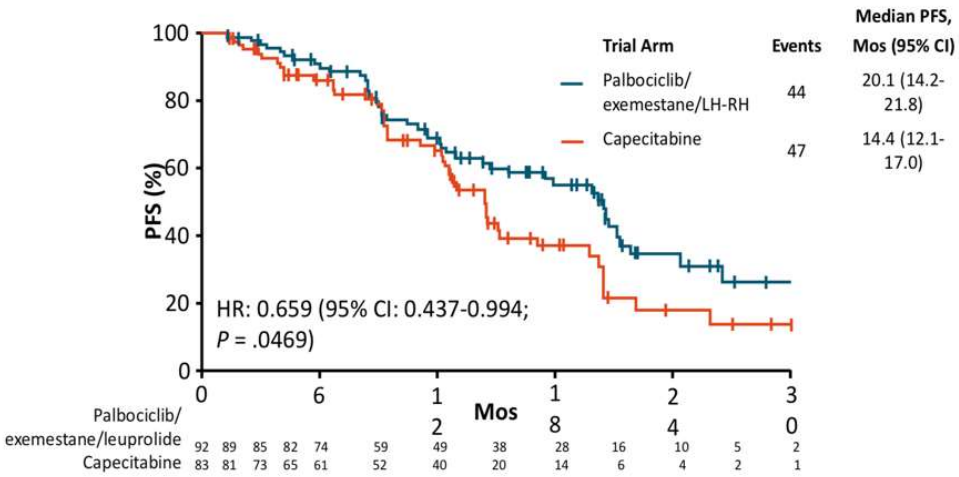
→ **Palbociclib** 125 mg QD x 3 wks
Exemestane 25 mg QD x 4 wks
LH-RH 3.75 mg SC D1 every 4 wks
for 28-day cycles
(n = 92)

→ **Capecitabine**
1250 mg/m^2 BID x 2 wks
for 21-day cycles
(n = 86†)

- Primary endpoint: PFS (investigator assessed)
- Secondary endpoint: DCR, OS, safety, QoL, biomarkers

Park. ASCO 2019. Abstr 1007.

Young-PEARL: PFS (Investigator Assessed)



- Median follow-up: 17 mos
- Treatment ongoing in 47.8% of patients receiving palbociclib/exemestane/leuprolide, 39.5% of patients receiving capecitabine

Park. ASCO 2019. Abstr 1007. Reproduced with permission.

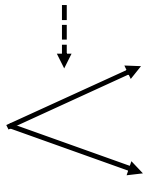
Investigator's conclusion: palbociclib plus exemestane/OFS is active in tamoxifen pre-treated, premenopausal patients with

NSABP B-42 10-Yr Follow-up: Study Design

- Multicenter, randomized, placebo-controlled phase III trial[1,2]

Stratification for pathologic nodal status (negative vs positive); prior adjuvant TAM (yes vs no); lowest BMD T-score in spine, hip, or femur (> -2.0 to ≤ - 2.0 SD)

Postmenopausal pts with stage I-IIIA ER+ or PgR+ BC at diagnosis who were disease free after 5 yrs of endocrine therapy* (N = 3966)



Letrozole 2.5 mg PO QD x 5 yrs (n = 1983)

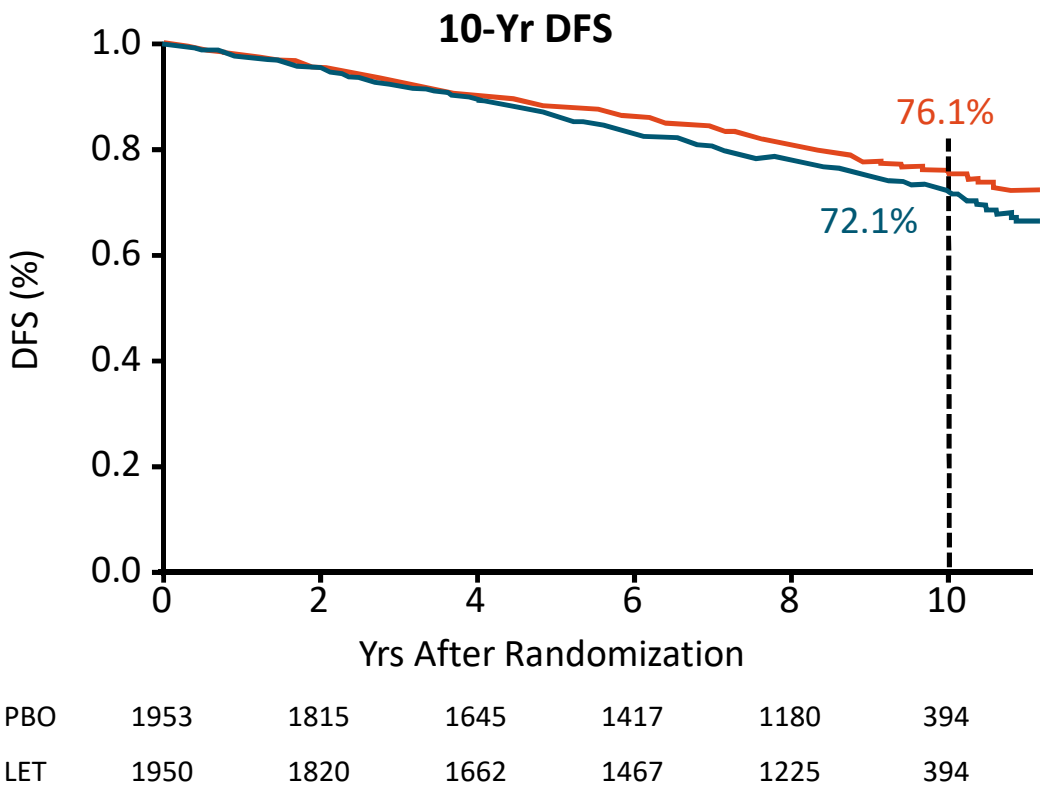
Placebo x 5 yrs (n = 1983)

*Endocrine therapy defined as treatment with an AI or tamoxifen for ≤ 3 yrs followed by an AI to complete 5 yrs.

- Primary endpoint: DFS, defined as time from randomization to BC recurrence, second non-breast primary malignancy, or death from any cause (ITT)
- Secondary endpoints: OS, BCFI, distant recurrence, osteoporotic fractures, arterial thrombotic events

1. Mamounas. Lancet Oncol. 2019;20(1):88. 2. Mamounas. SABCS 2019. Abstr GS4-01.

NSABP B-42 10-Yr Follow-up: DFS



Mamounas. SABCS 2019. Abstr GS4-01. Reproduced with permission.

Analysis	Events, N		HR (95% CI)	*P* Value*
	LET	PBO		
7 yrs	292	339	0.85 (0.73-0.999)	.048
10 yrs	411	479	0.84 (0.74-0.96)	.011

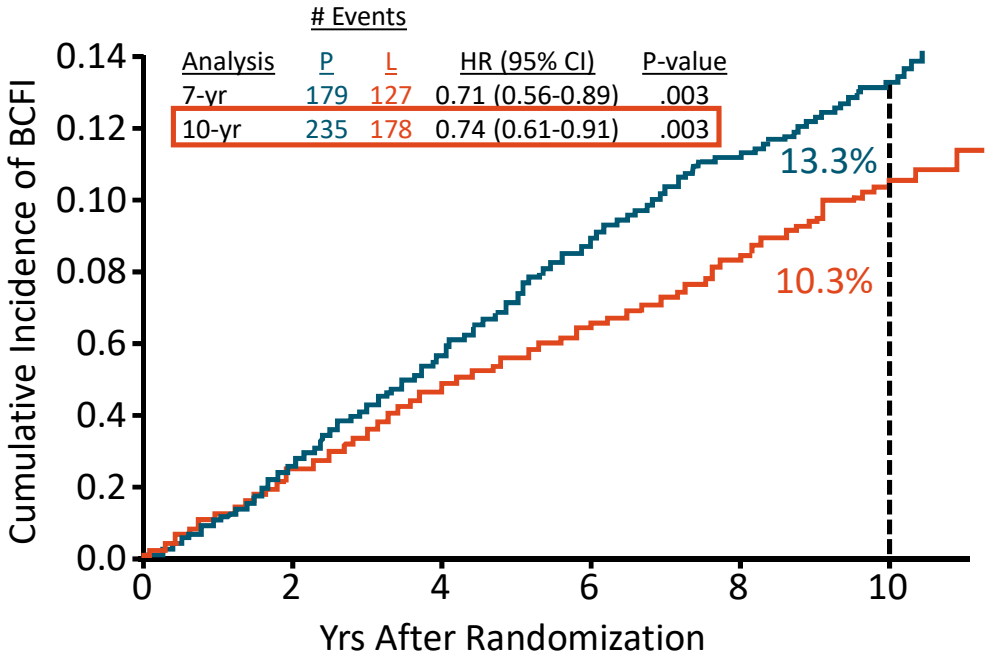
*Statistical significance level for DFS set at .0418.

- Median follow-up:
  - 7-yr analysis: 6.9 yrs
  - 10-yr analysis: 9.3 yrs

No difference in OS: HR = 0.97, p = 0.77.

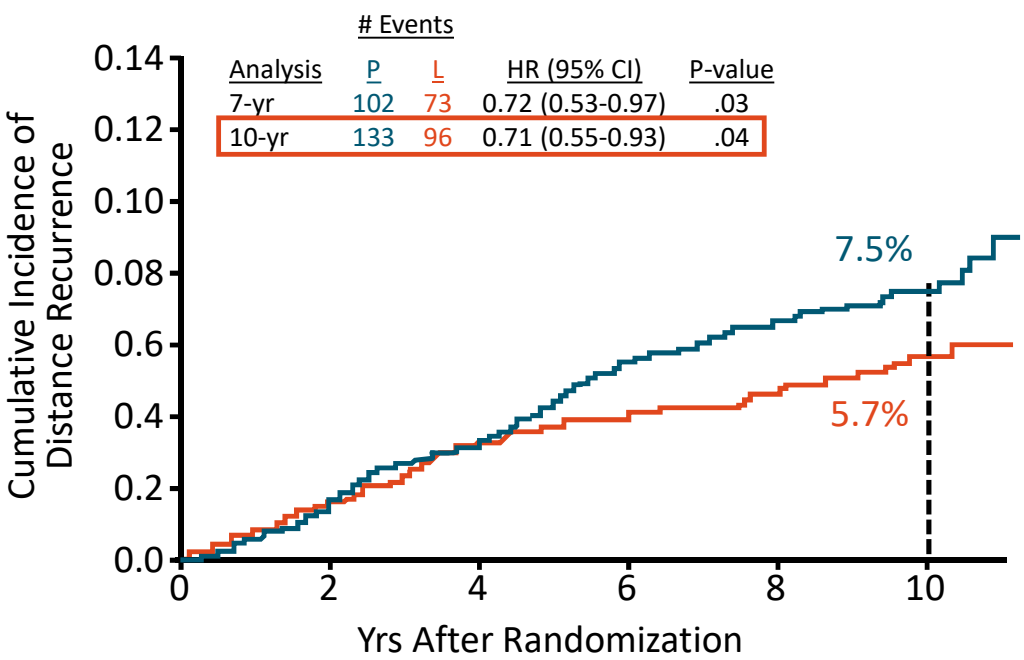
NSABP B-42 10-Yr Follow-up: BCFI and Distant Recurrence

Breast Cancer-Free Interval



PBO	1953	1815	1645	1417	1180	394
LET	1950	1820	1662	1467	1225	394

Distant Recurrence

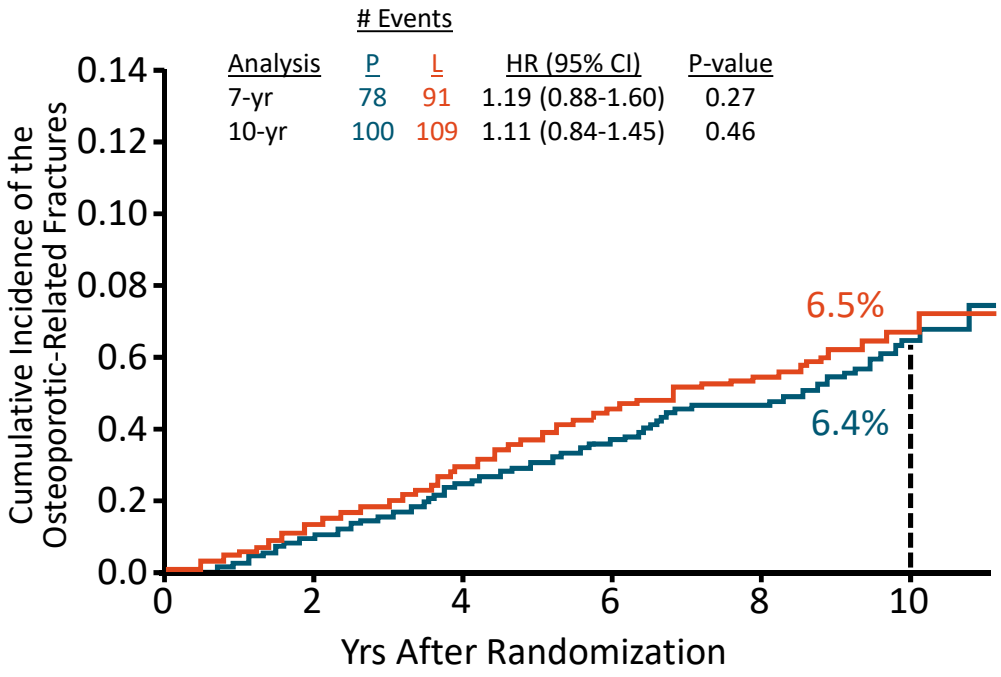


PBO	1953	1861	1733	1540	1312	444
LET	1950	1862	1729	1551	1334	432

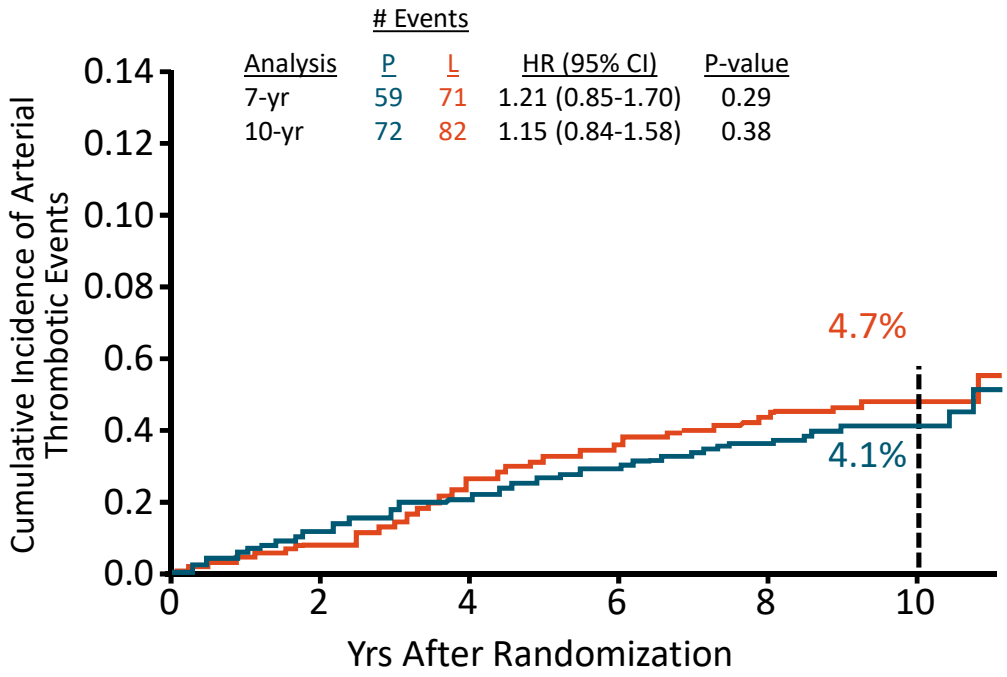
Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)

NSABP B-42 10-Yr Follow-up: Osteoporotic Fractures and Arterial Thrombotic Events

Osteoporotic Fractures



Arterial Thrombotic Events



Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)

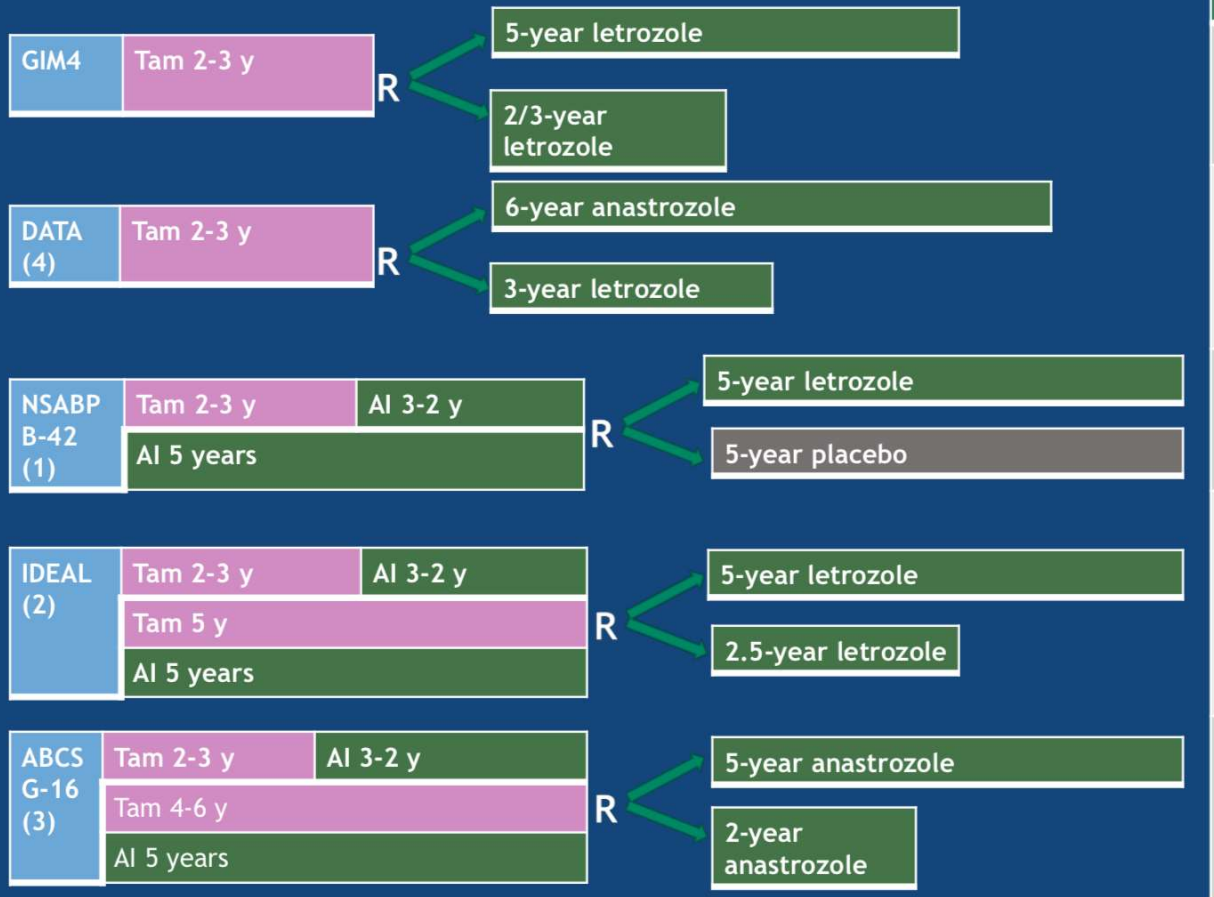
Mamounas. SABCS 2019. Abstr GS4-01. Reproduced with permission.

NSABP B-42 10-Yr Follow-up: Investigator Conclusions

- 10-yr follow-up of NSABP B-42 in postmenopausal patients with hormone receptor–positive BC found that 5 yrs of adjuvant letrozole after previous adjuvant AI therapy significantly improved DFS vs placebo
  - HR: 0.84 (95% CI: 0.74-0.96; *P* = .011) with 4% absolute improvement
- Extended adjuvant letrozole had no significant effect on OS, but did reduce BCFI and distant recurrence
- There was no significant increase in risk of osteoporotic fracture or arterial thrombotic events with letrozole vs placebo in this patient population
- Authors conclude that careful assessment of possible risks and benefits is needed when considering extended adjuvant letrozole for patients with early-stage BC, including:
  - Patient and tumor characteristics, comorbidities, BMD, tolerance of adjuvant AI therapy

Mamounas. SABCS 2019. Abstr GS4-01.

Extended adjuvant AI studies



HR DFS
0.81 (0.65-1.00)
0.79 (0.62-1.02)
0.85 (0.62-1.02)
1.007 (0.87-1.16)
0.92 (0.74-1.16)

1. Mamounas; Lancet Oncol. 2019; 20:88-99; 2. Blok; J Natl Cancer Inst 2018; 110:40-48; 3. Gnant; SABCS 2017; 4. Tjan-Heijnen ; Lancet Oncol 2017; 18:1502-11

Women's Health Initiative Hormone Therapy Trials (WHI HT) Long Term Findings: Menopausal Hormone Therapy and Breast Cancer

General Session 5 [GS5-00]: Prof Rowan Chlebowski (Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, USA)

Background: The influence of hormone therapy on BC remains controversial. A recent meta-analysis suggested that both oestrogen alone and oestrogen + progestin significantly increased breast cancer incidence.

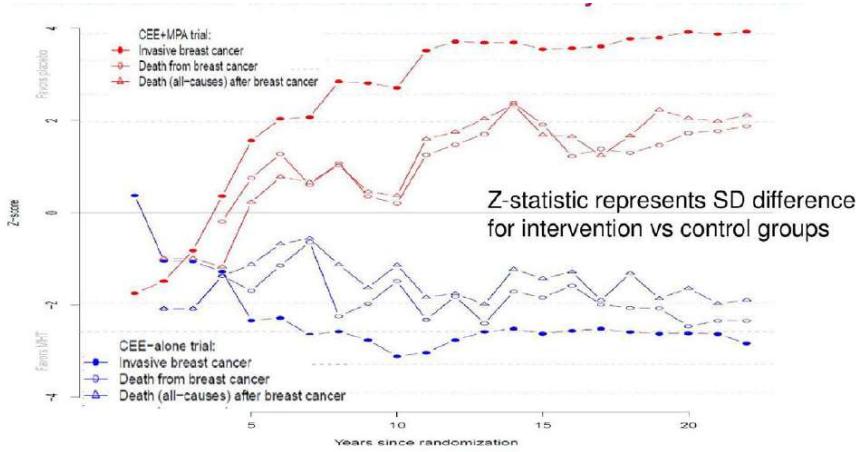
Methods: Two randomised clinical trials at 40 US centres enrolled postmenopausal women aged 50-79 with no prior BC and non-suggestive mammograms between 1993-1998, with follow-up to September 2016. Patients with no prior hysterectomy received conjugated equine oestrogens (CEE) + medroxyprogesterone acetate (MPA) (n=8,506) or PBO (n=8,102) for a median of 5.6 years. Patients with prior hysterectomy received CEE alone (n=5,310) or PBO (n=5,429) for a median of 7.2 years.

Results: CEE alone decreased BC incidence and BC deaths, whereas CEE+MPA significantly increased BC incidence and mortality.

Table 9: Risk of breast cancer and mortality

Treatment regimen	BC incidence HR (95% CI)	Deaths from BC HR (95% CI)	Deaths after BC HR (95% CI)
CEE alone	0.77 (0.65-0.92) p=0.005	0.56 (0.34-0.92) p=0.02	0.75 (0.56-1.01) p=0.06
CEE+MPA	1.29 (1.14-1.47) p<0.001	1.45 (0.98-2015) p=0.06	1.29 (1.02-1.63) p=0.03

Figure 15: Breast cancer incidence and mortality as z-scores



Authors' Conclusion: The results of these trials should inform clinical decision making regarding hormone therapy, bearing in mind the other effects of hormone therapy on clinical outcomes.

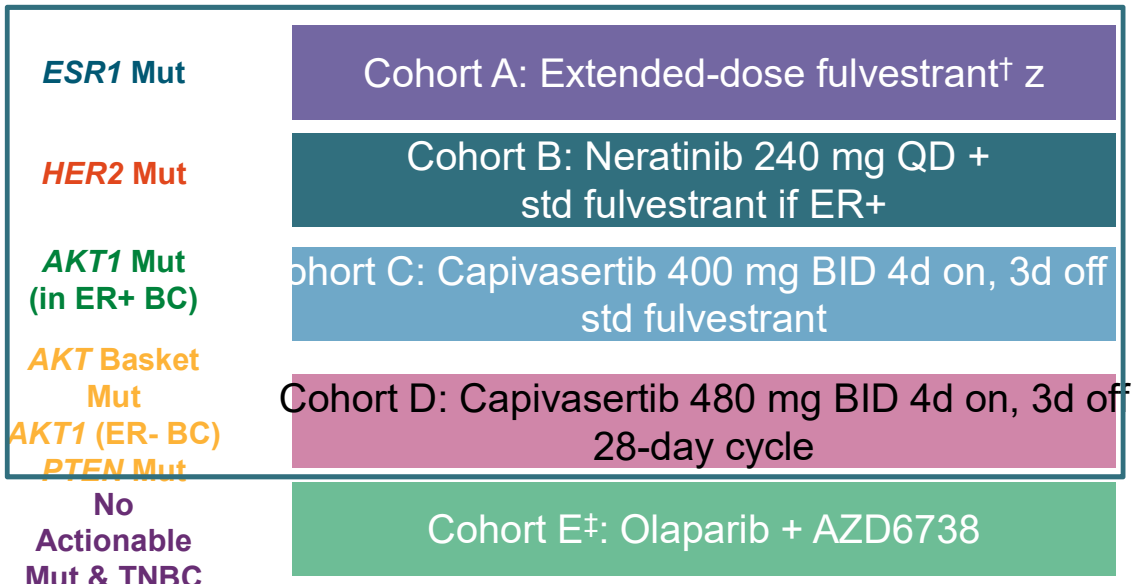
Abbreviations: BC, breast cancer; CEE, conjugated equine oestrogens; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate; PBO, placebo; SD, standard deviation; WHI HT, Women's Health Initiative Hormone Therapy.

plasmaMATCH: Study Design

Open-label, multicenter, multicohort trial with ctDNA testing in ~1000 patients with advanced BC

- n = 364 prospective; n = 438 retrospective

Patients with metastatic or locally recurrent BC, measurable disease, PD on prior tx for advanced disease or relapsed within < 12 mos of adj CT; ≤ 2 prior lines CT; an actionable mutation detected by ctDNA screening*



Tumor assessment every 2 cycles to cycle 9, then every 3 cycles

*ctDNA testing performed via digital droplet PCR and NGS. †Extended dose: 500 mg IM on Days 1, 8, 15 of cycle 1, Day 1, 15 of cycle ≥ 2 until PD (28-day cycle). ‡Cohort E to report separately.

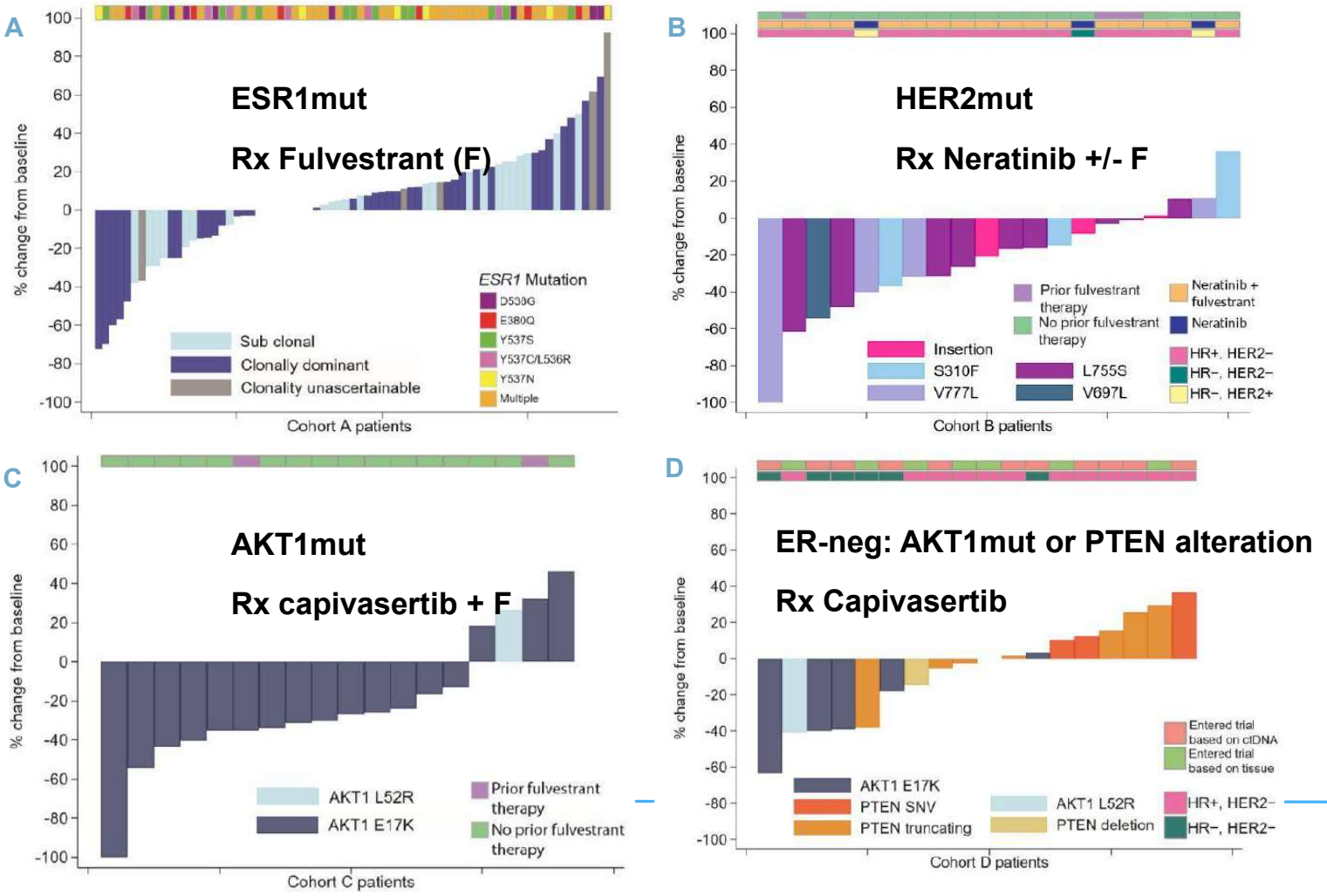
Turner. SABCS 2019. Abstr GS3-06

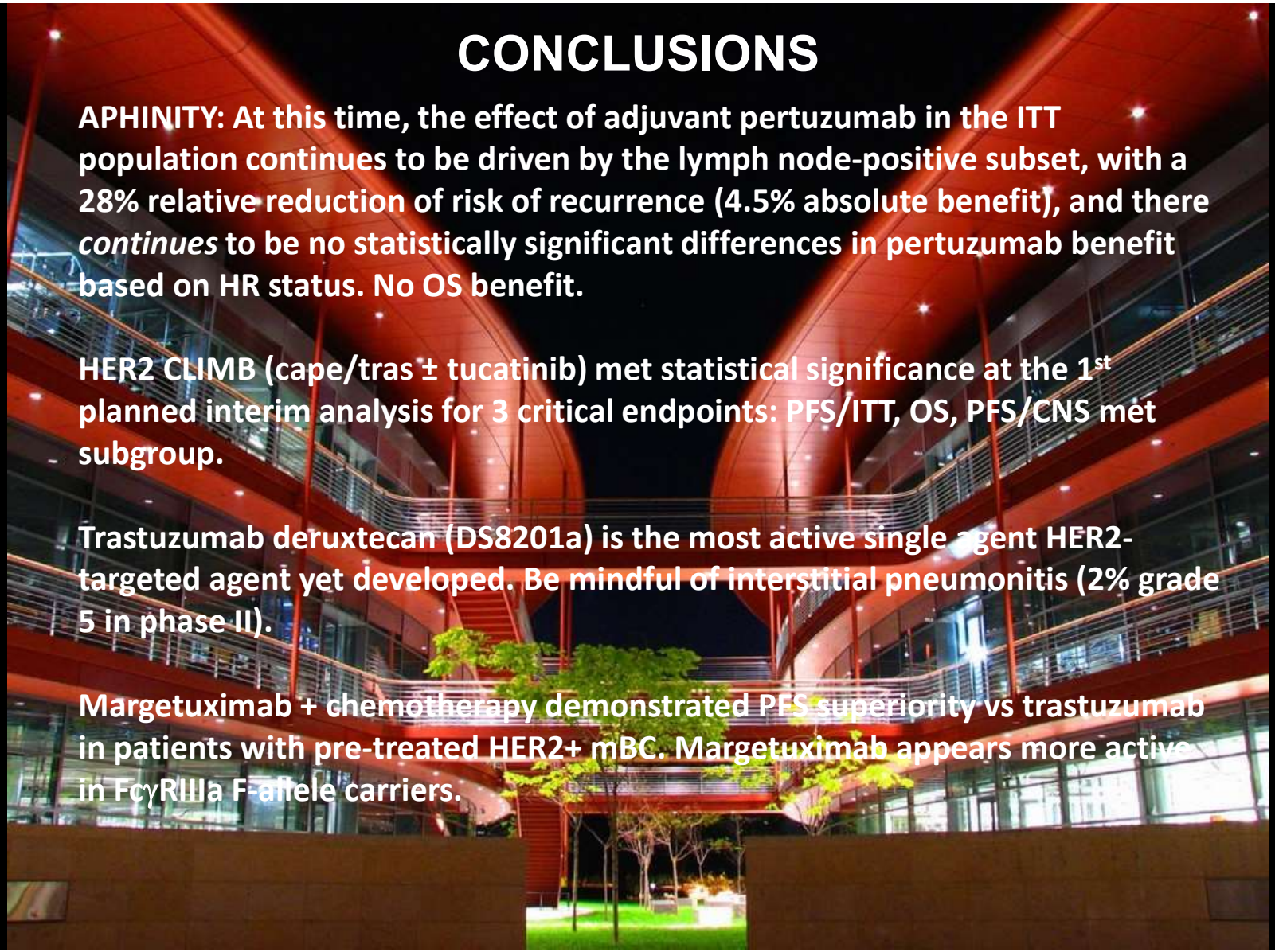
The plasmaMATCH Study: Targeting Treatment Using ctDNA (cont.)

General Session 3 [GS3-06]: Prof Nicholas Turner (Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK)

Figure 13: Waterfall plots from each cohort of the plasmaMATCH study A) *ESR1* mutation treated with extended dose fulvestrant; B) *HER2* mutation treated with neratinib ± fulvestrant; C) *AKT1* mutation treated with capivasertib + fulvestrant; D) *AKT1* mutation in ER- BC or *PTEN* inactivating mutation treated with capivasertib

Authors' Conclusion: ctDNA testing identified patients with rare *AKT1* and HER2 mutations, who had clinically relevant response rates with matched targeted therapies.





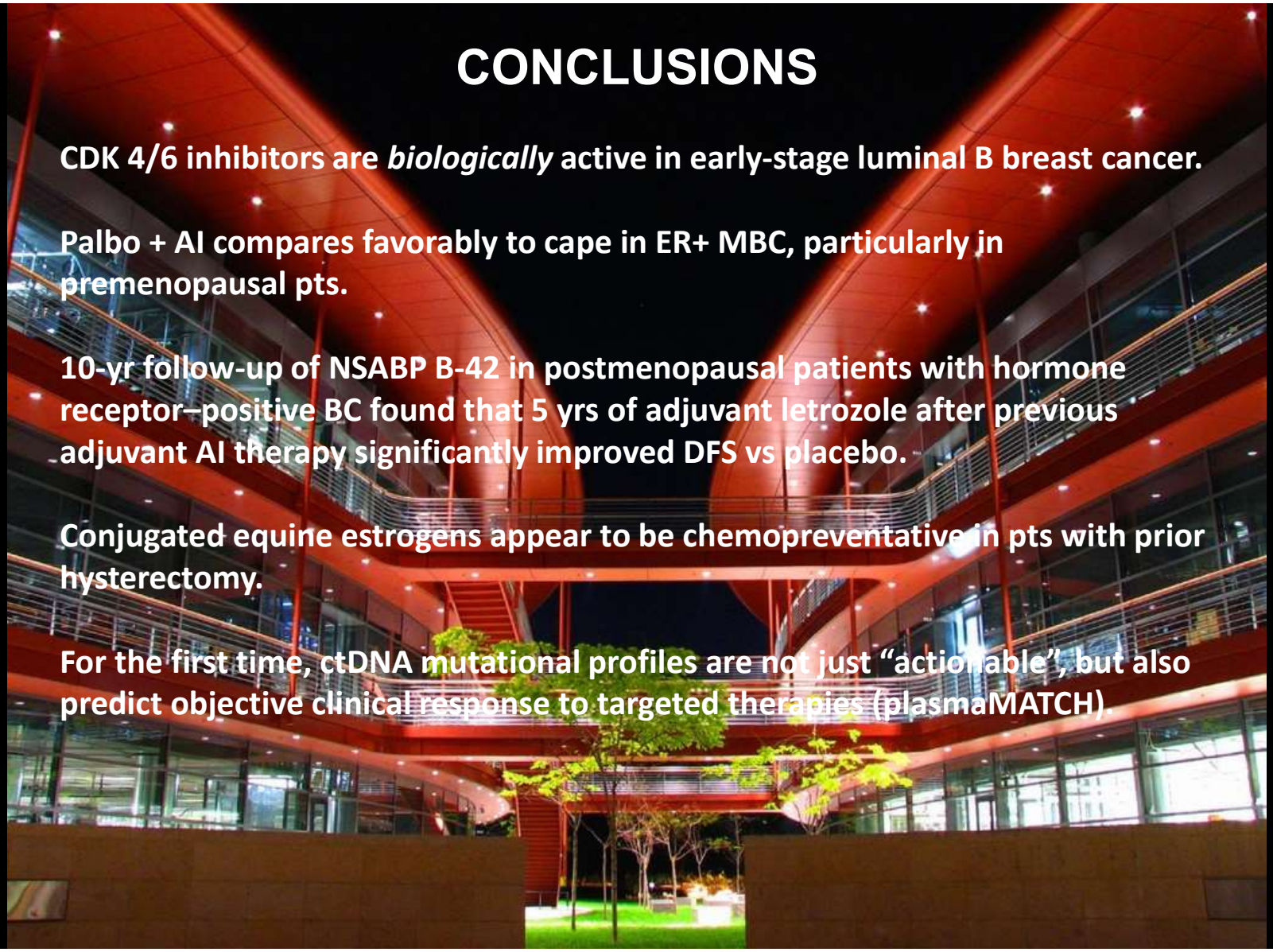
CONCLUSIONS

APHINITY: At this time, the effect of adjuvant pertuzumab in the ITT population continues to be driven by the lymph node-positive subset, with a 28% relative reduction of risk of recurrence (4.5% absolute benefit), and there *continues* to be no statistically significant differences in pertuzumab benefit based on HR status. No OS benefit.

HER2 CLIMB (cape/tras ± tucatinib) met statistical significance at the 1st planned interim analysis for 3 critical endpoints: PFS/ITT, OS, PFS/CNS met subgroup.

Trastuzumab deruxtecan (DS8201a) is the most active single agent HER2-targeted agent yet developed. Be mindful of interstitial pneumonitis (2% grade 5 in phase II).

Margetuximab + chemotherapy demonstrated PFS superiority vs trastuzumab in patients with pre-treated HER2+ mBC. Margetuximab appears more active in FcγRIIIa F-allele carriers.



CONCLUSIONS

CDK 4/6 inhibitors are *biologically* active in early-stage luminal B breast cancer.

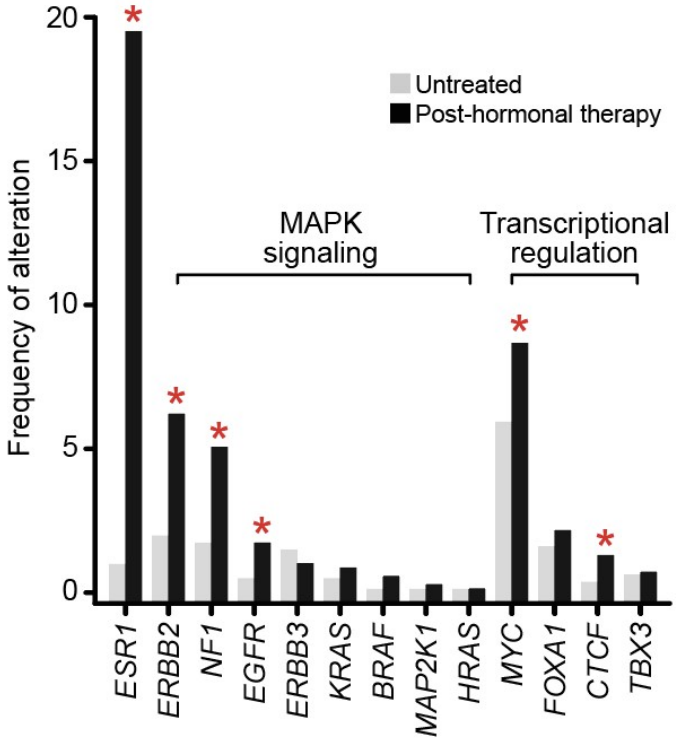
Palbo + AI compares favorably to cape in ER+ MBC, particularly in premenopausal pts.

10-yr follow-up of NSABP B-42 in postmenopausal patients with hormone receptor–positive BC found that 5 yrs of adjuvant letrozole after previous adjuvant AI therapy significantly improved DFS vs placebo.

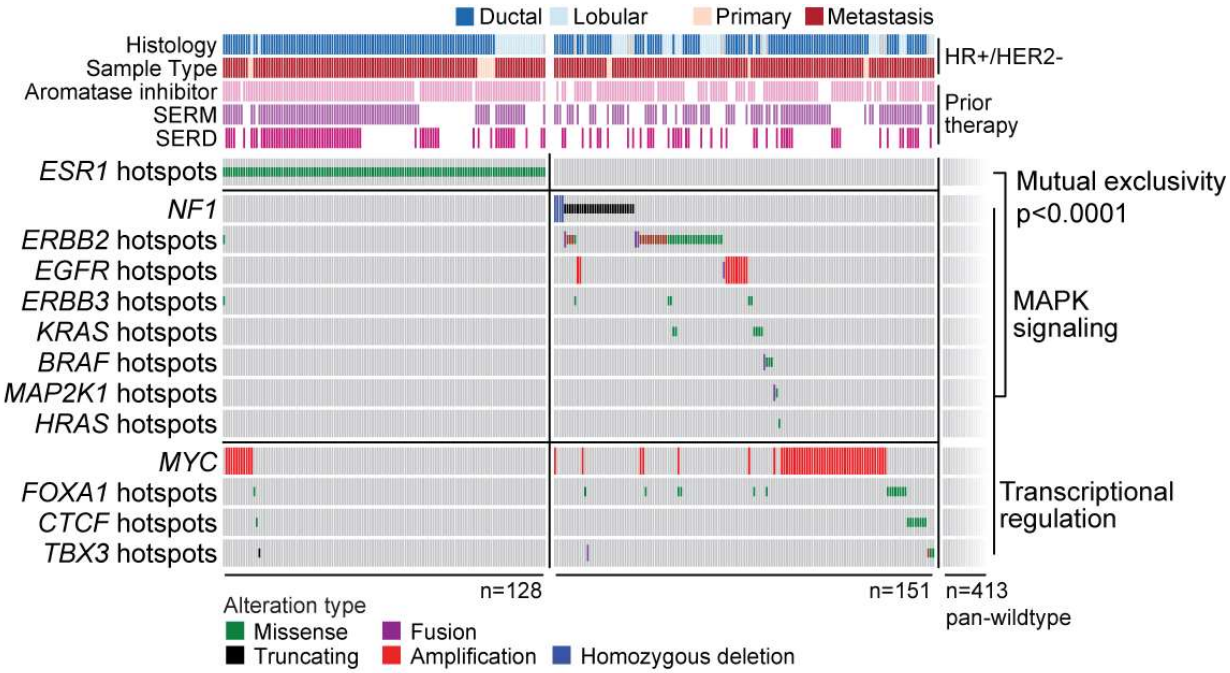
Conjugated equine estrogens appear to be chemopreventative in pts with prior hysterectomy.

For the first time, ctDNA mutational profiles are not just "actionable", but also predict objective clinical response to targeted therapies (plasmaMATCH).

MAPK and transcription factors frequent alterations were significantly more common in endocrine resistant tumors and were *mutually exclusive* with *ESR1* hotspots

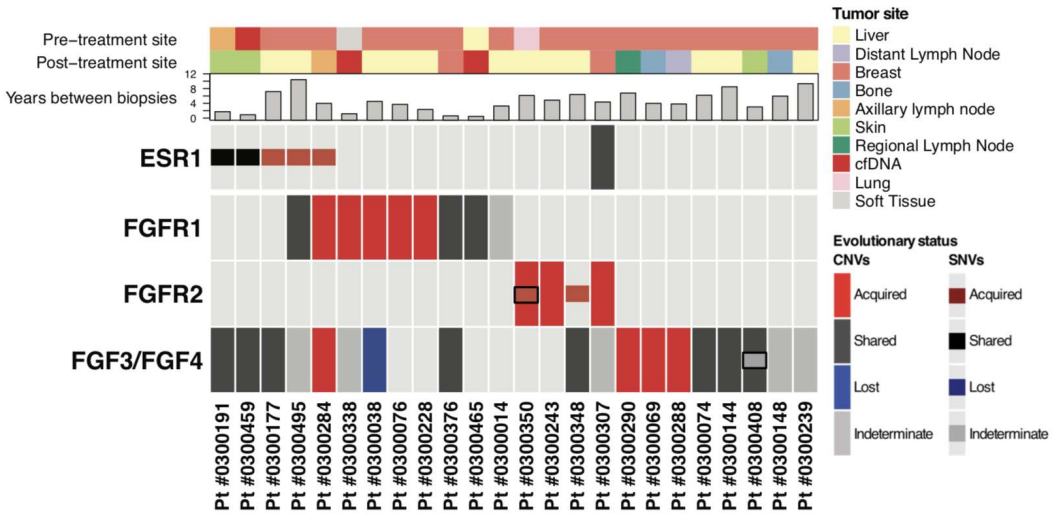


1501 HR+/HER2-
692 post-endocrine therapy tumors

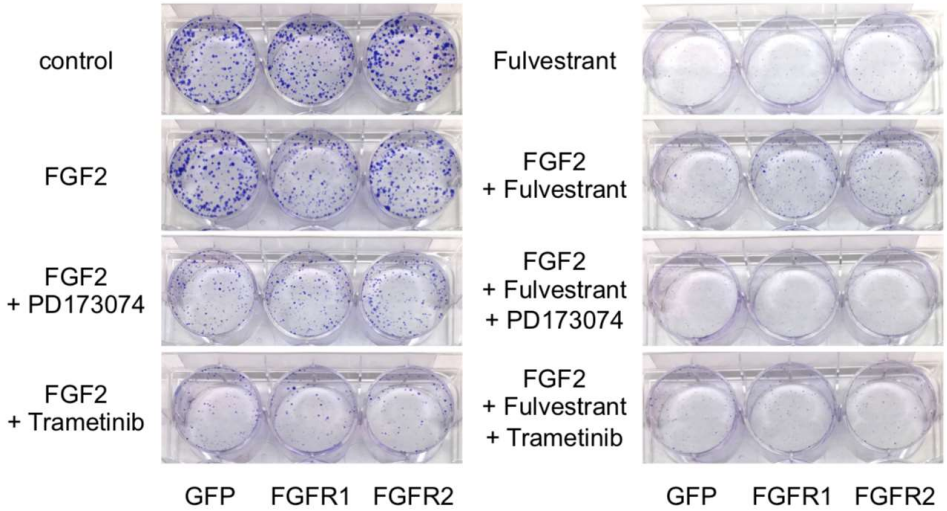


151/564 of *ERS1* WT endocrine resistant tumors harbored alterations in MAPK pathway or TF

Acquired FGFR and FGF alterations confer resistance to estrogen receptor (ER) 2 targeted therapy in ER+ metastatic breast cancer



Identification of acquired FGFR and FGF alterations in metastatic biopsies from patients with resistant ER+ MBC



Active FGFR signaling leads to resistance to SERDs through activation of MAPK pathway