

From Bench to Bedside in the Era of Personalized Medicine: Breast Cancer Breakthroughs & Future Research

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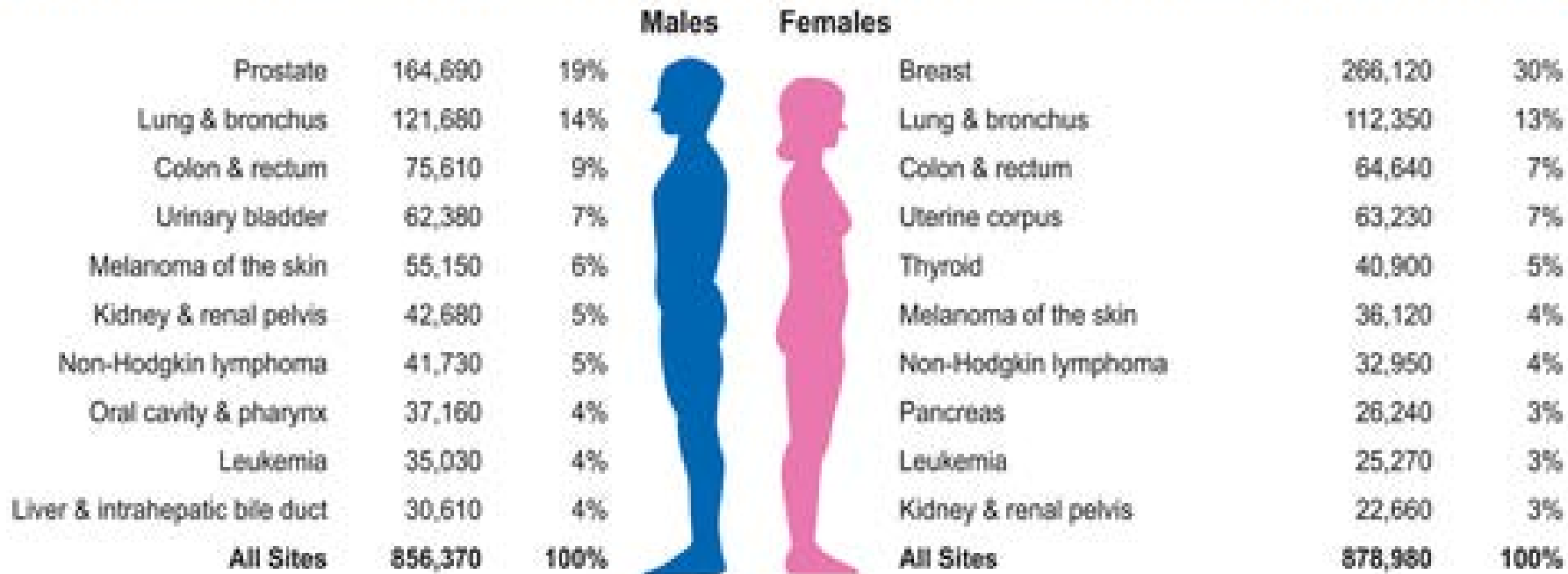


Outline

- **Review modern classification of breast cancer and emergence of targeted therapies**
- **Understand structure and goals of TRIO-US network**
- **Explore benefits of targeted therapies for breast cancer**
- **Gain exposure to cutting edge treatments for ER+ and HER2+ disease**

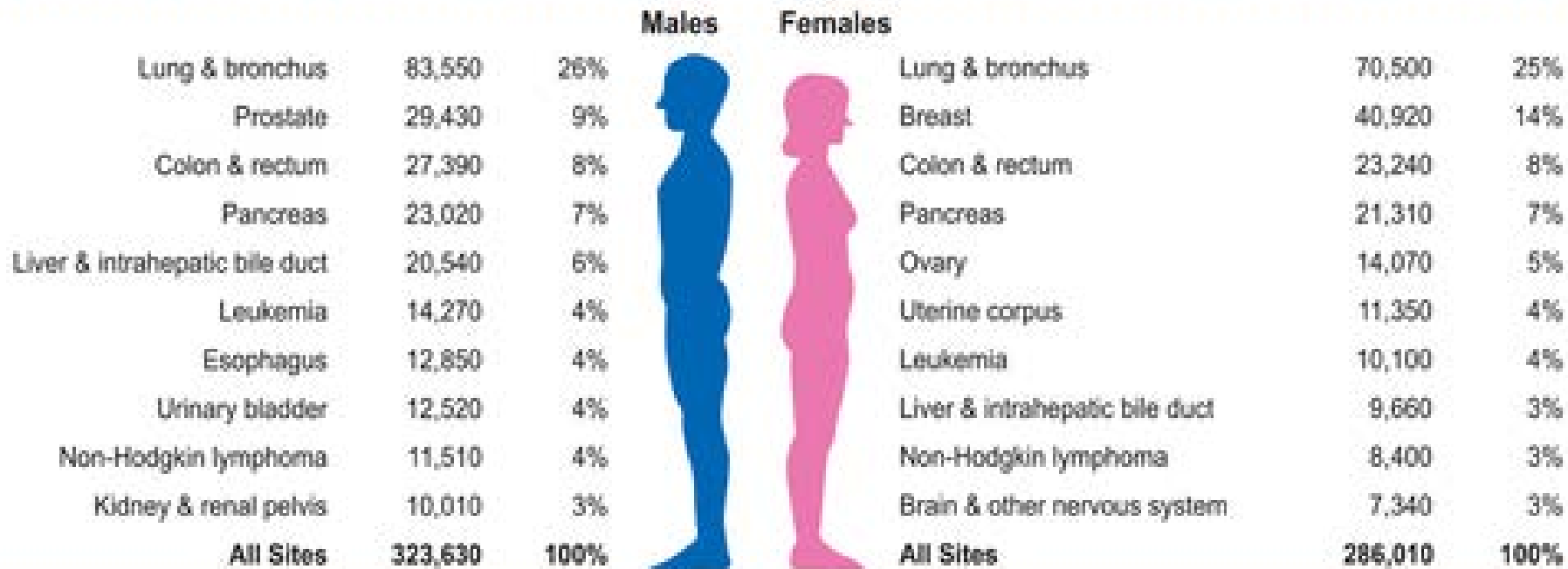
Incidence Cancers, 2018

Estimated New Cases



- Incidence and prevalence of stage IV breast cancer are not formally collected but estimated that >160,000 are living with MBC in the US

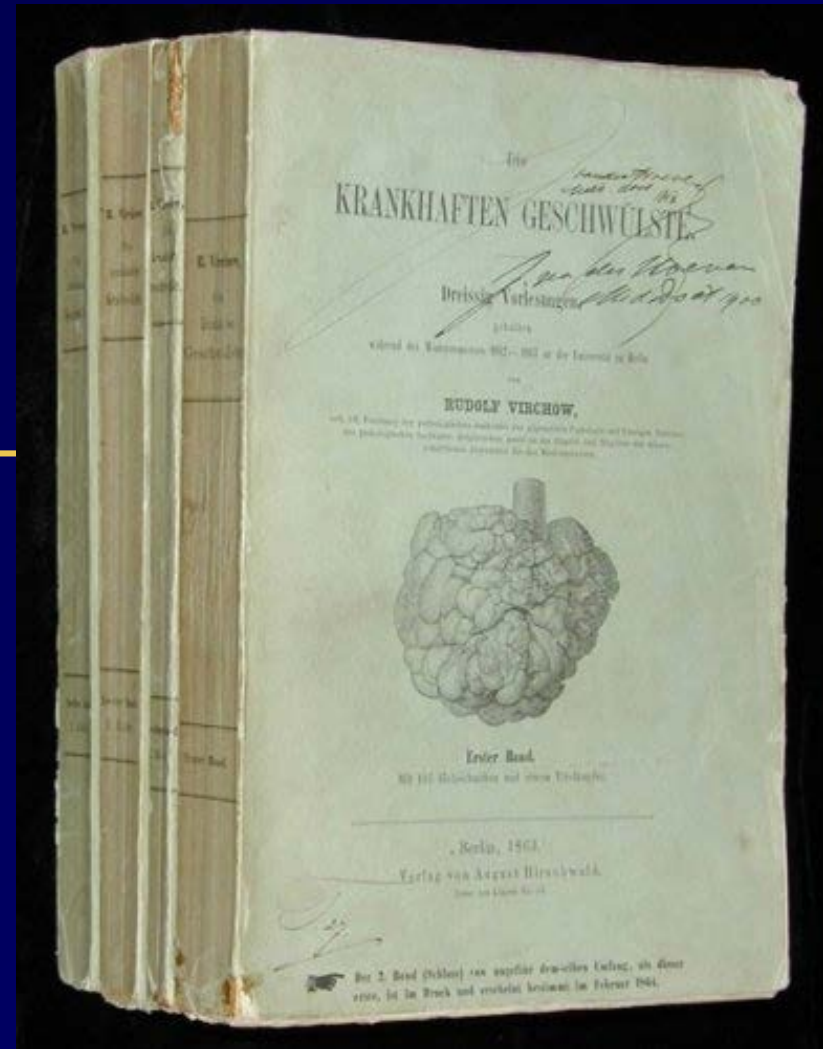
Mortality Cancers, 2018



Classification: Histologic vs. Biologic Subtypes



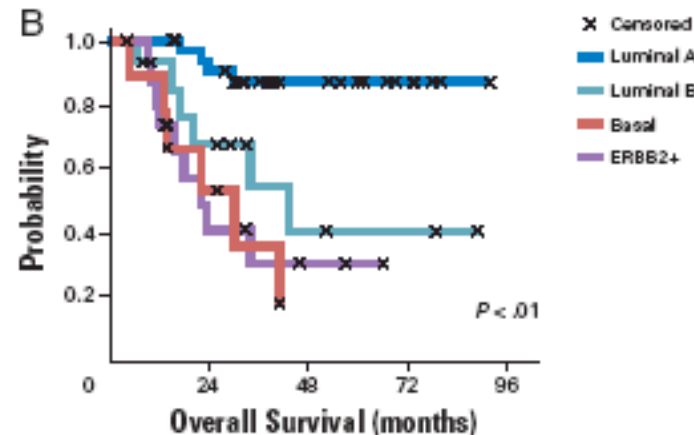
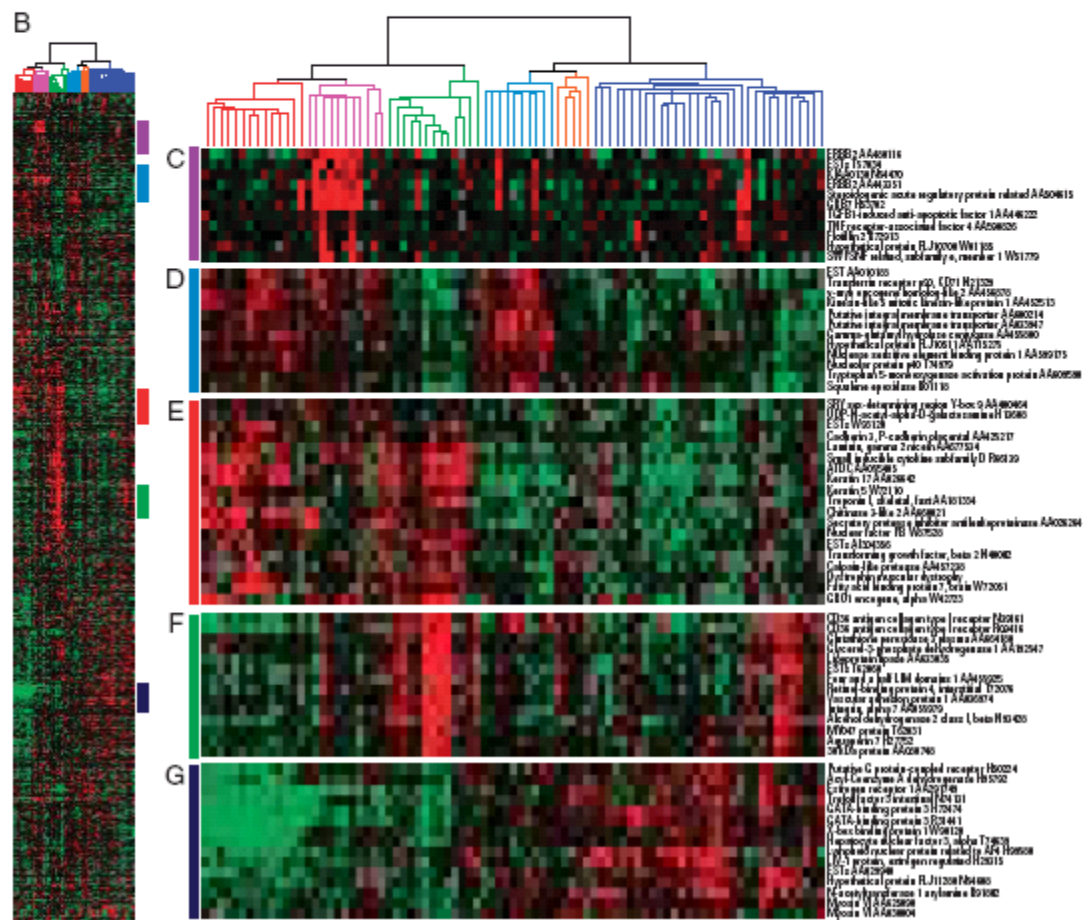
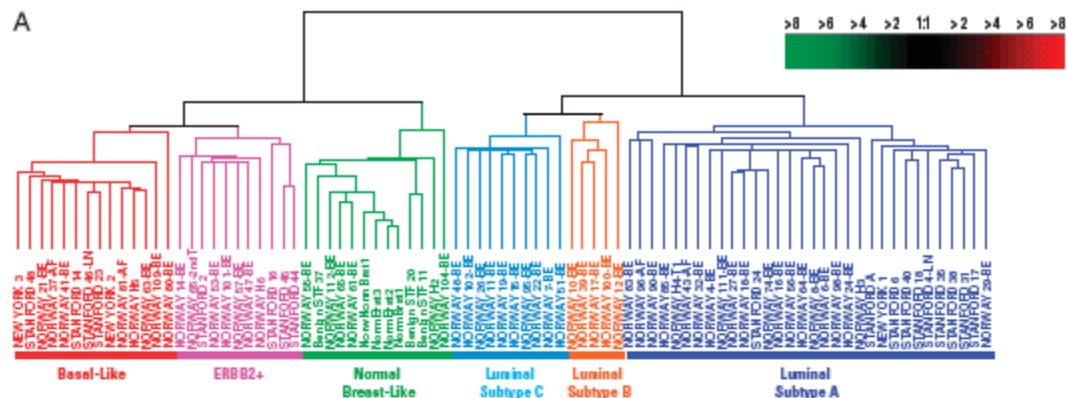
Rudolf Ludwig Karl Virchow (1821-1902)



Die Krankhaften Geschwülste 1863

Pathology of Invasive Breast Carcinomas

Type of Cancer	Frequency	Associated features
Infiltrating Ductal	70-80%	When DCIS is associated, goal is to obtain surgical margins clear of both invasive tumor and DCIS to reduce risk of recurrence
Invasive Lobular	5-10%	LCIS or DCIS; higher freq bilateral & multicentric, spread to unusual locations (meninges, peritoneum, GI)
Mucinous/Colloid	2.4%	Well circumscribed, tumor cells dispersed in large pools of extracellular mucus; uniform, low grade nuclei, prognostically favorable variant of invasive breast carcinoma.
Metaplastic	<5%	Poorly differentiated ductal carcinoma combined with squamous cell carcinoma and/or various forms of sarcomatous differentiation; tends to be resistant to chemotherapy
Tubular	<5%	Well differentiated, low-grade, unusual pre-mmng era, now more common, indolent and rarely metastasizes
Medullary	<5%	Poorly differentiated, lymphoplasmacytic infiltrate, prognosis more favorable despite aggressive histologic features, associated with BRCA1, usually ER-PR-
Micropapillary	<5%	Aggressive with lymph node metastases even when small
Adenoid cystic	<5%	Rare, morphologically identical to that of salivary glands, tends to be favorable prognosis,



Breast Cancer is Not All One Disease



A major shift in how we classify and treat cancers

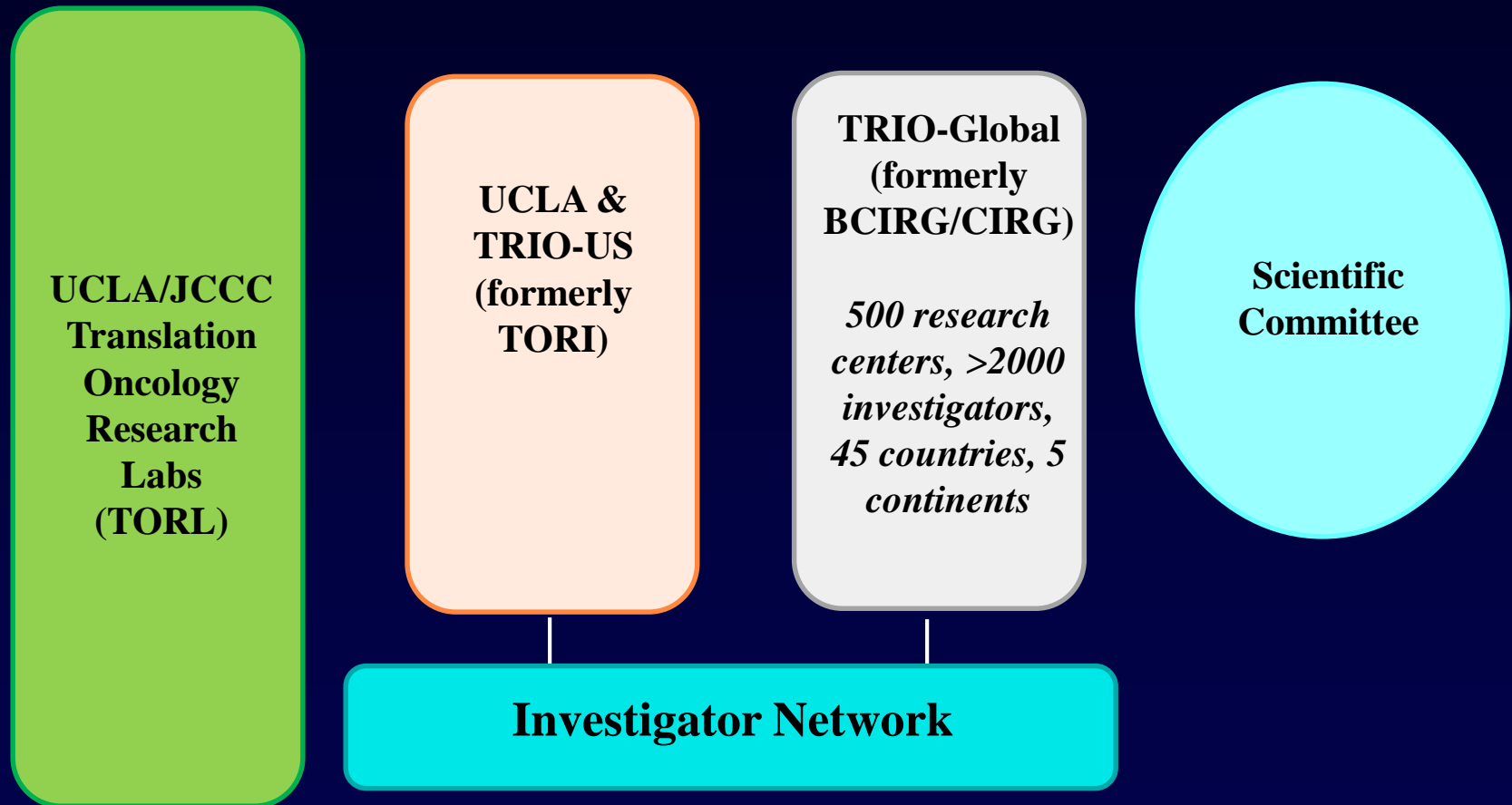
	Classification	Treatment
Traditional	Tumors classified by how they look under the microscope and their organ of origin	Tumors treated with chemotherapy that kills all rapidly dividing cells
Present & Future	Tumors classified by the molecular problems that cause them to behave like cancer	Tumors treated with therapy that is rationally targeted toward the molecular defect in tumor cells, thus leaving normal cells alone

TRIO

Translation of Scientific Discoveries into Clinical Practice

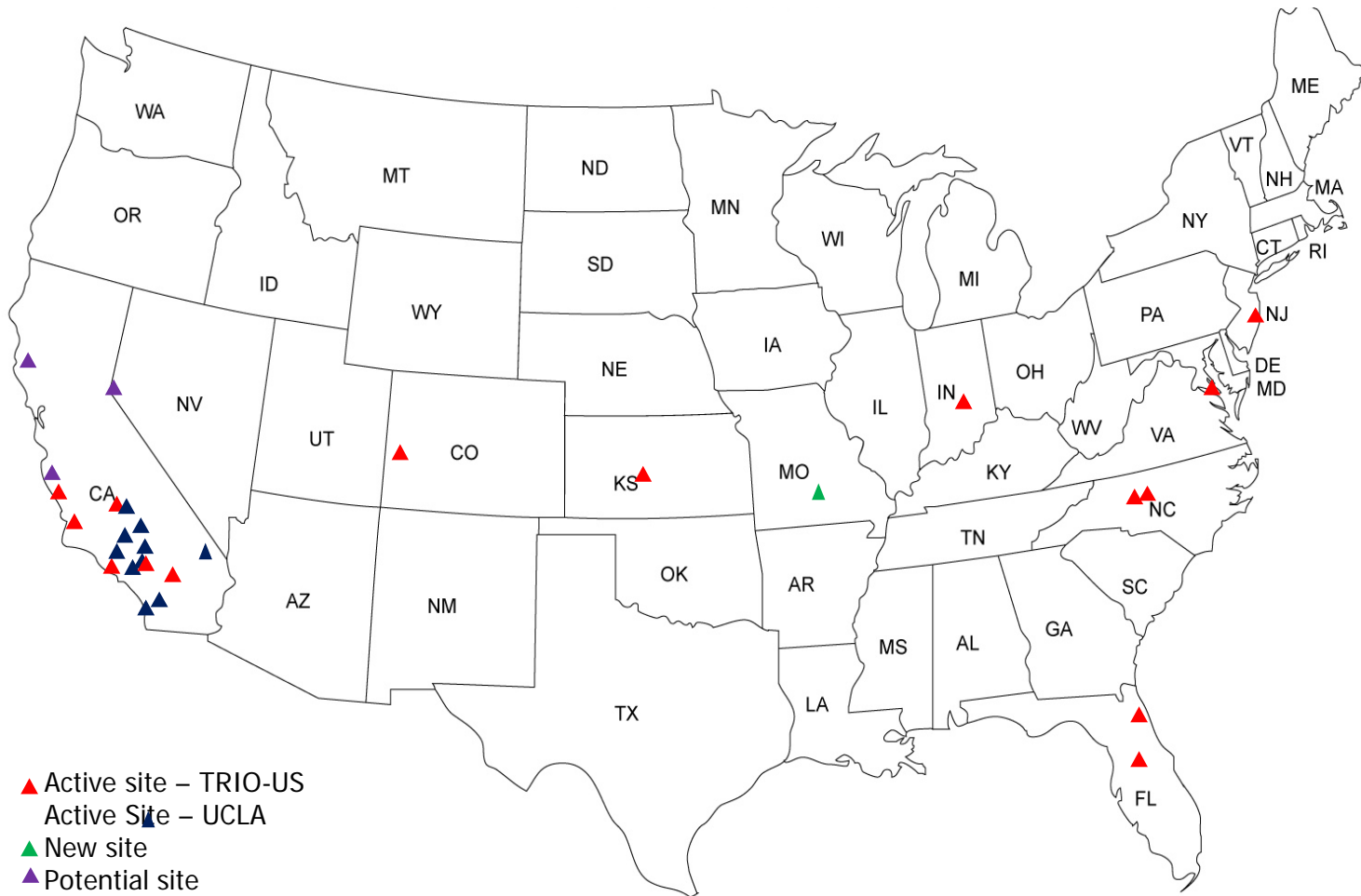


Translational Research In Oncology (TRIO)

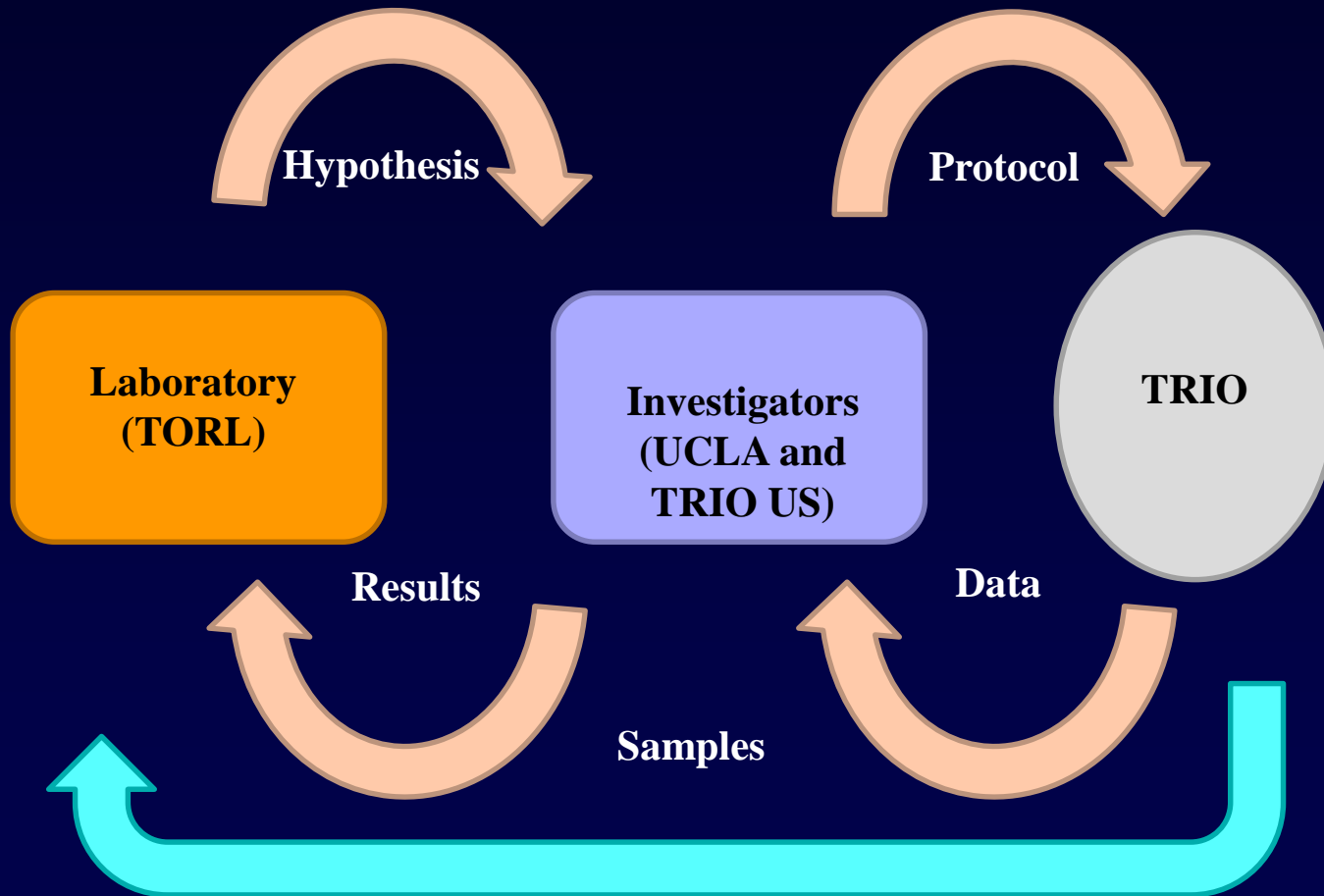


TRIO-US/UCLA Locations

1. Alhambra CA
2. Burbank CA
3. Ashville NC (x2)
4. Bakersfield CA
5. Bethesda MA
6. Fort Wayne, IN
7. Fullerton CA
8. Grand Junction CO
9. Hollywood FL
10. Irvine CA
11. Laguna Hills CA
12. Livingston NJ
13. Paducah, KY
14. Pasadena CA
15. Porter Ranch CA
16. Orlando FL
17. Redondo Beach CA
18. San Luis Obispo CA
19. Santa Barbara CA
20. Santa Maria CA
21. Torrance CA
22. Valencia CA
23. Ventura, CA
24. Westlake Village CA
25. Wichita, KS

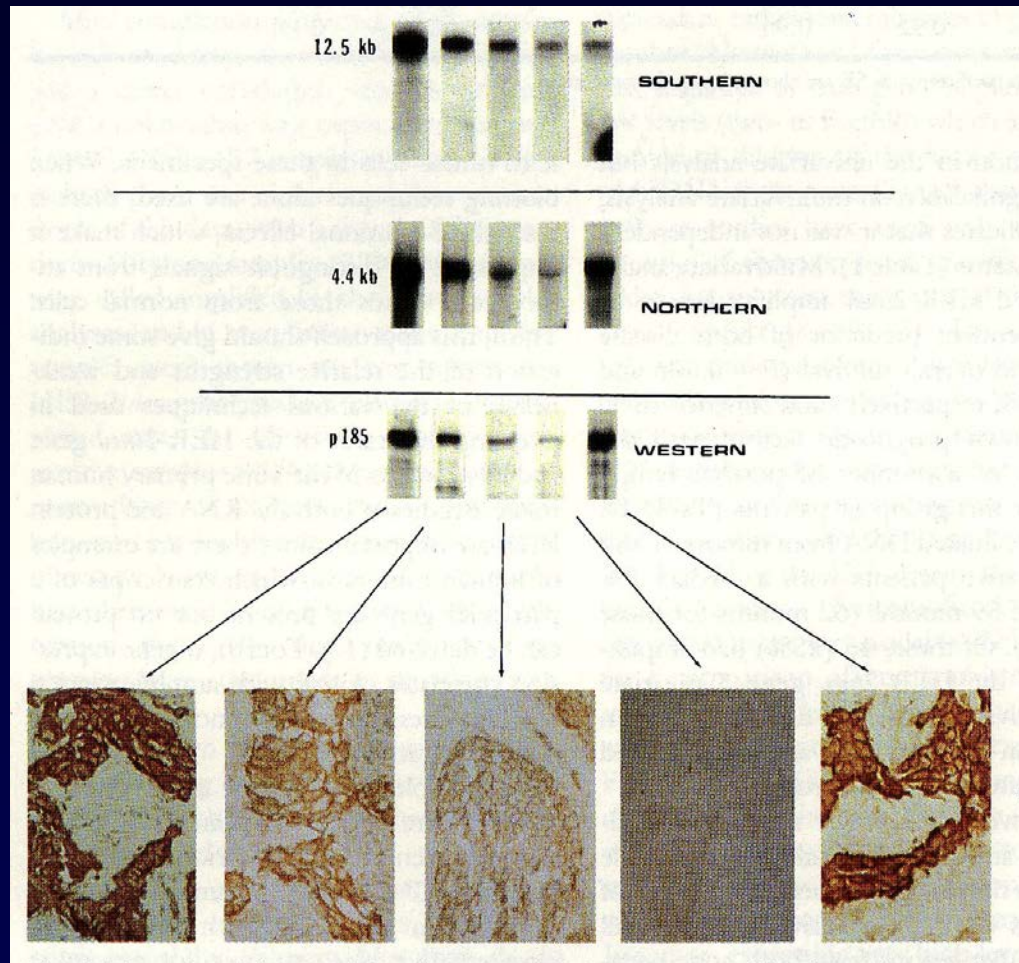


TRIO: Iterative Process



The HER2 discovery & trastuzumab

The HER-2/*neu* Alteration



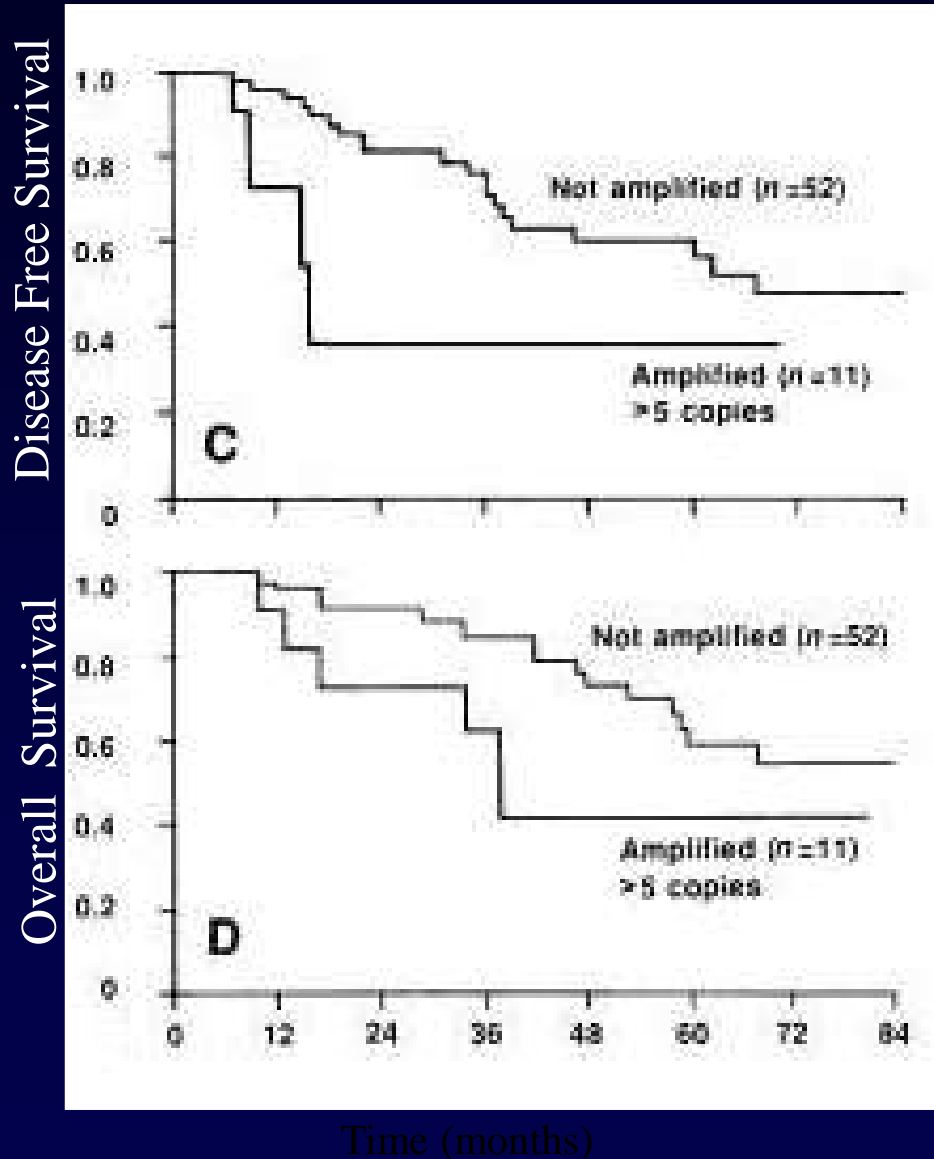
Southern (DNA)

Northern (RNA)

Western (protein)

IHC

Significance of HER-2/*neu*

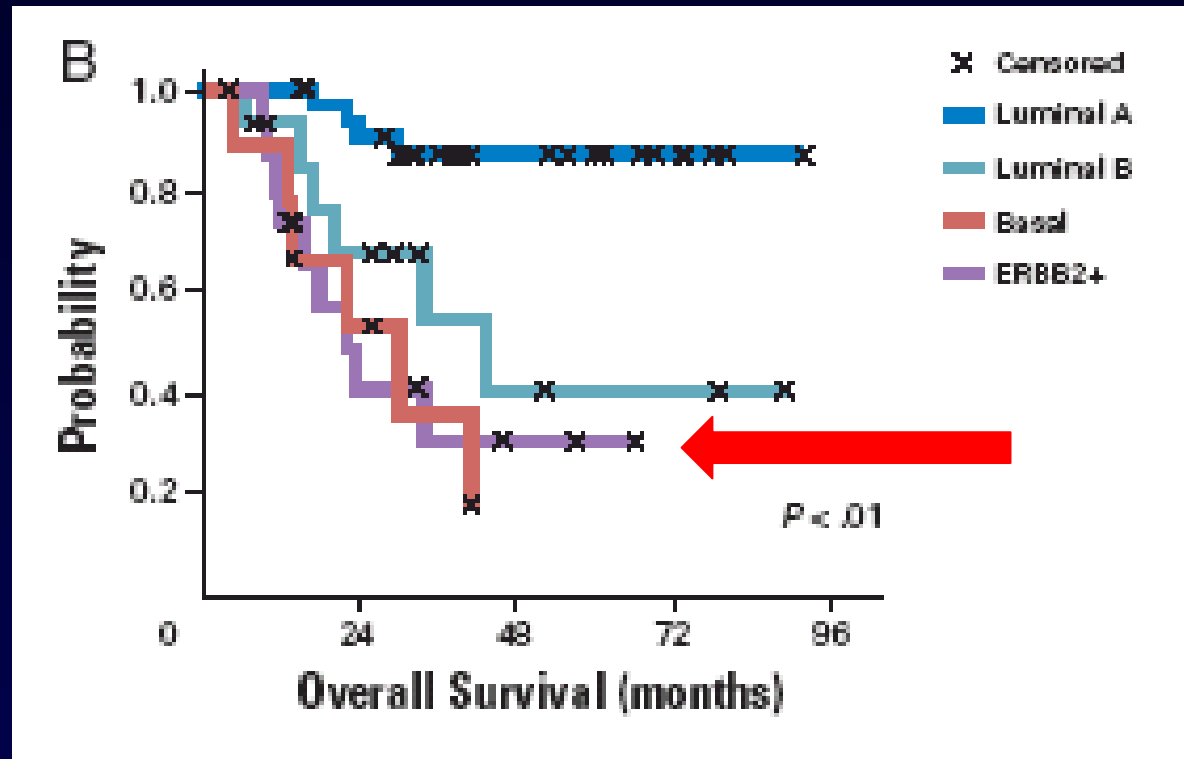


Median Survival:

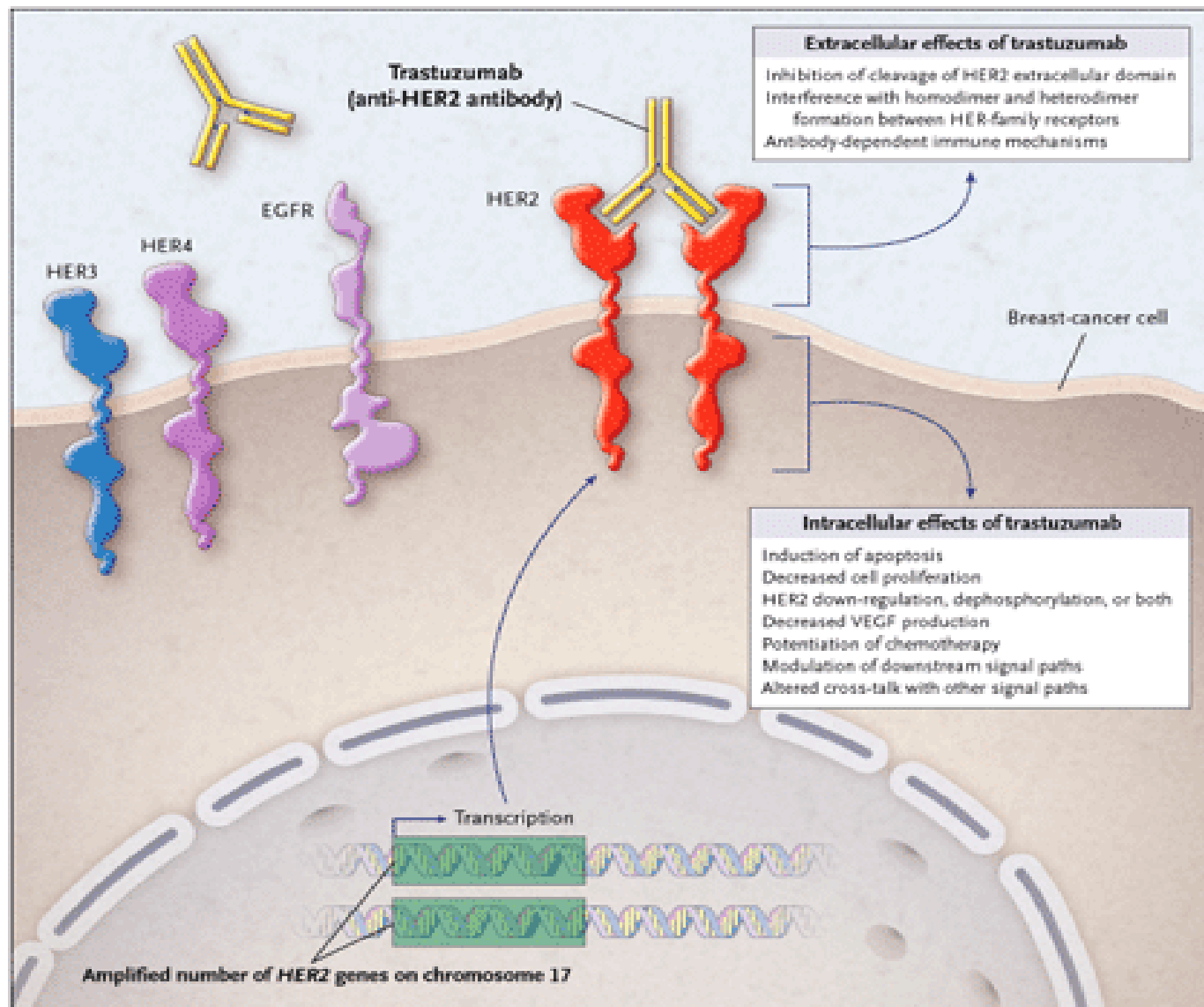
Her2/neu Negative: 6-7 yrs

Her2/neu Positive: 3 yrs

Poor Prognosis HER2+ Disease

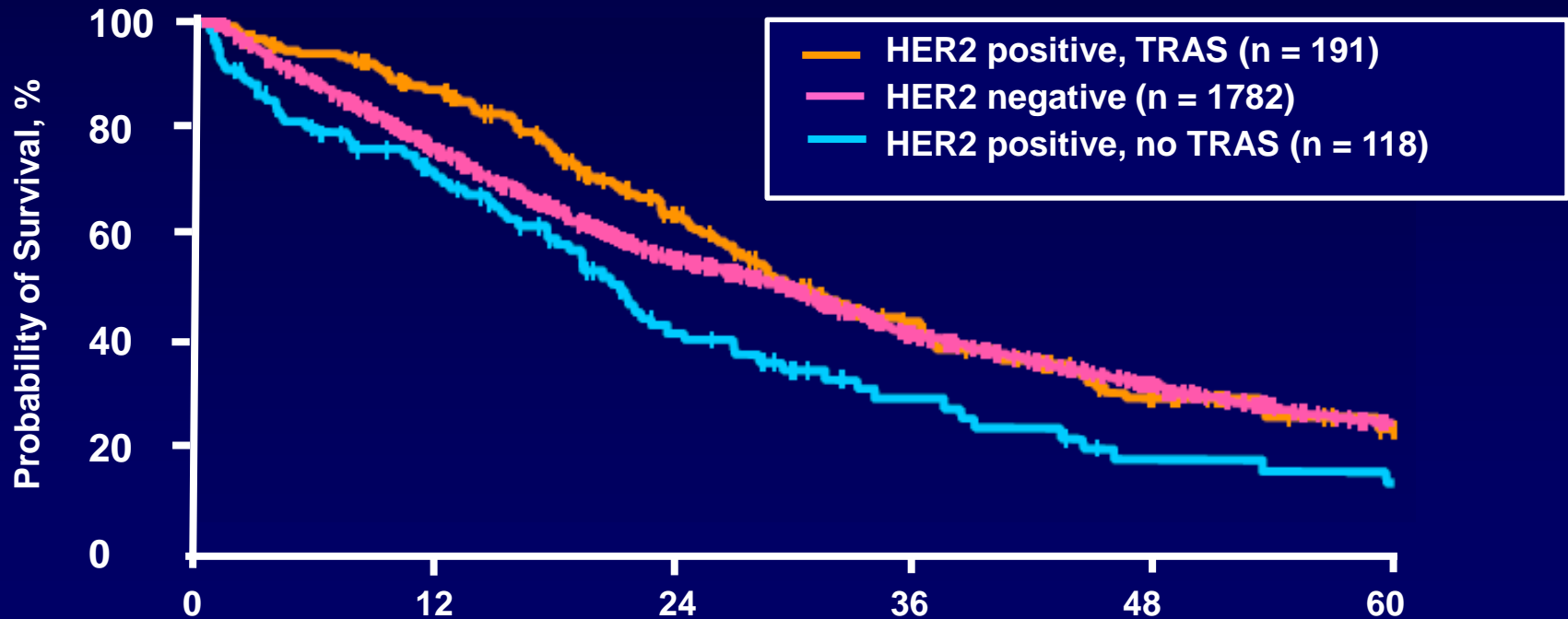


Trastuzumab (Herceptin)



Trastuzumab Has Changed the Natural History of HER2-Positive Breast Cancer

- Patients with HER2-positive metastatic breast cancer (MBC) now have comparable outcomes with HER2-negative MBC



TRAS, trastuzumab

Dawood S, et al. *J Clin Oncol*. 2010;28(1):92-98.

Four large initial adjuvant trastuzumab trials

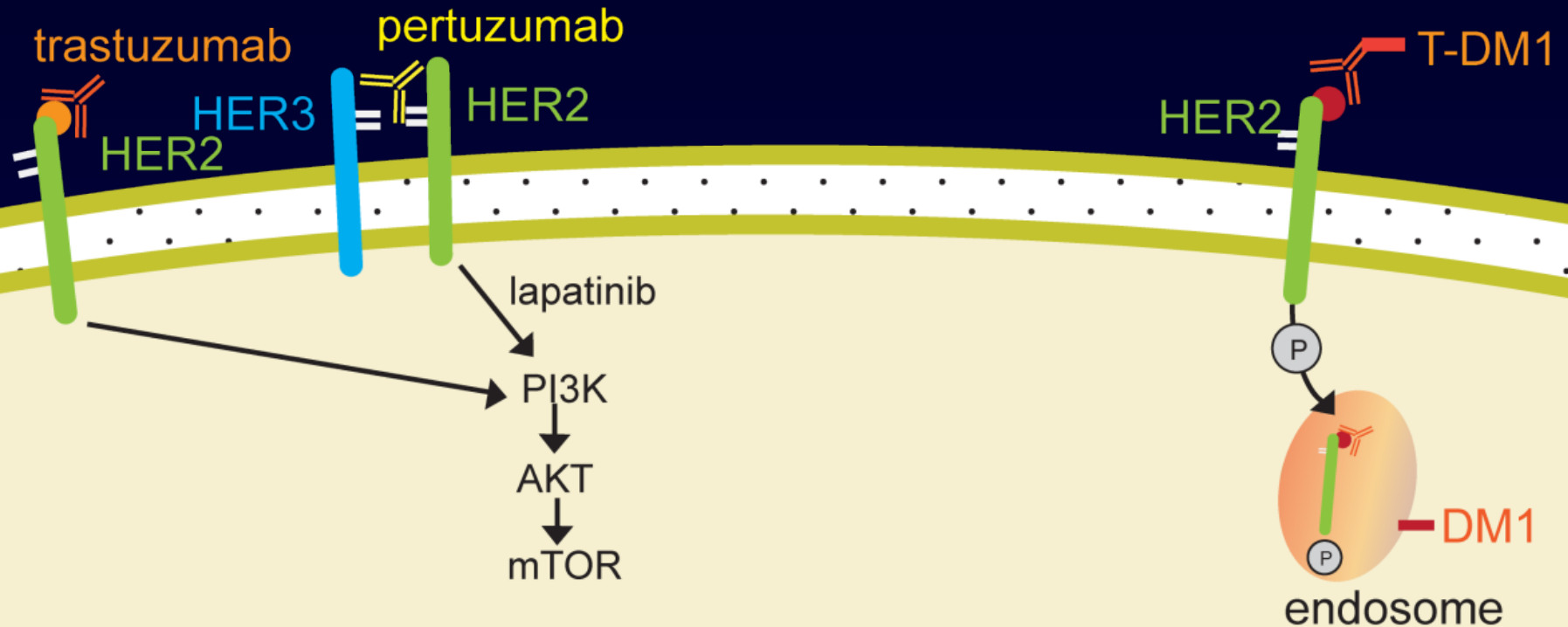
TRIAL	ARMS	N	DFS	OS	Median F/U	Cross-over
NCCTG N9831 NSABP B-31 Perez J Clin Oncol 2014	<u>N9831</u> AC→wP (Arm A) AC→wP→wH (Arm B) AC→wPwH (Arm C) <u>B-31²</u> AC→P (Group 1) AC→PwH (Group 2)	3351	10-year Groups C/2 vs A/1 73% AC-PH 62% AC-P HR 0.60	10-year Groups C/2 vs A/1 84% AC-PH 75% AC-P HR 0.63	8 yr	20%
HERA Goldhirsch Lancet Oncol 2013;82:1021	<u>Std chemo then</u> Observ vs. H x 1 yr vs. H x 2 yr	5090	72% H 1 yr 66% obs HR 0.76	84% H 1 yr 79% obs HR 0.76	8 yr	52%
BCIRG-006 Slamon Cancer Res 2016;76(4 Suppl) Abs PD5-01	AC→T AC→TH TCH	3222	75% AC-TH 73% TCH 68% AC-T HR: 0.72 ACTH 0.77 TCH	86% AC-TH 83% TCH 79% AC-T HR: 0.63 ACTH 0.76 TCH	10.3 yr	3.1%

Overall Survival for HER2+ trastuzumab-treated early disease similar to or better than HER2-normal

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

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

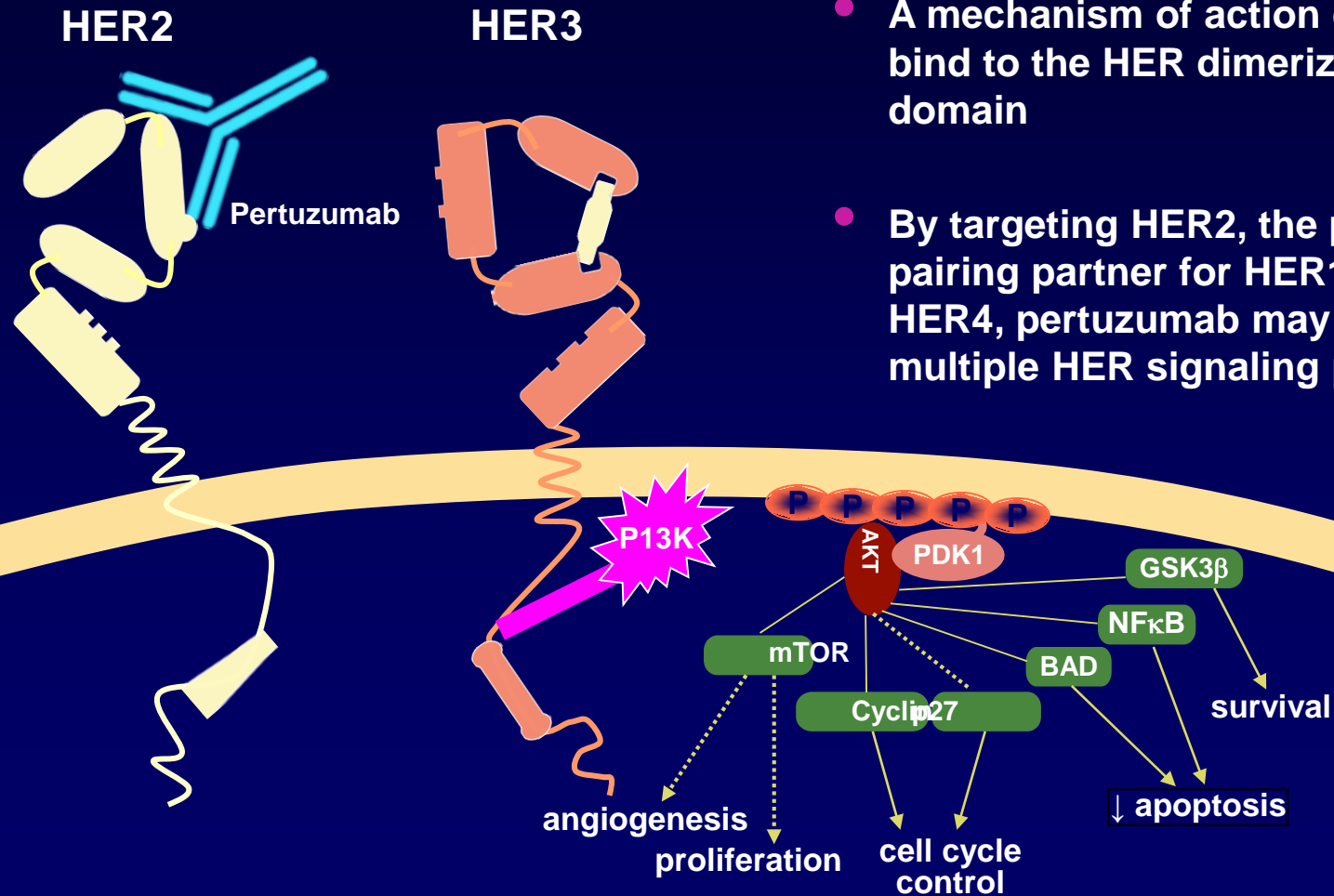
Anti-HER2 Therapy: Mechanisms of Action



T-DM1 = trastuzumab emtansine

Gajria D, et al. *Expert Rev Anticancer Ther.* 2011;11:263-275.

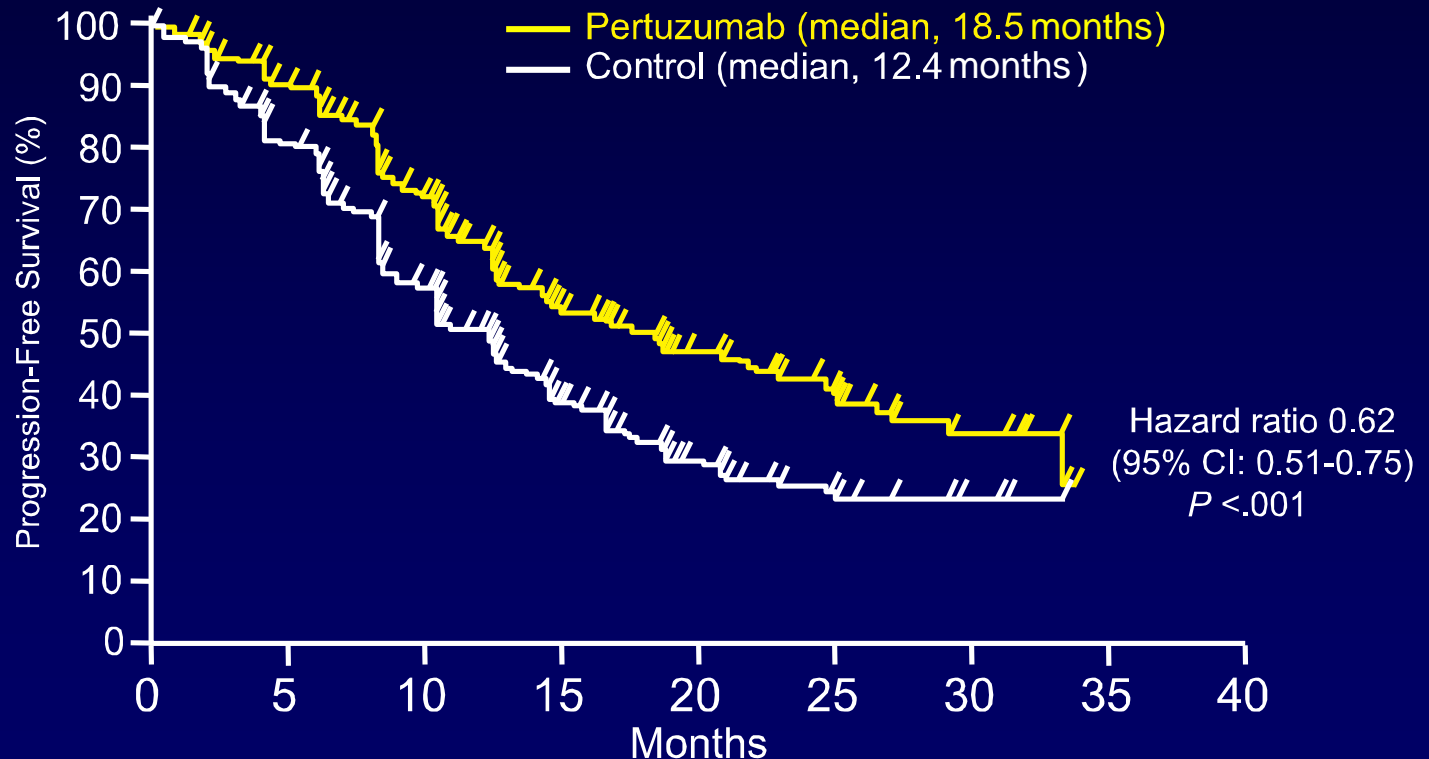
Pertuzumab: a HER dimerization inhibitor



- A mechanism of action designed to bind to the HER dimerization domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways

CLEOPATRA: PFS

Independent Assessment



No. at risk

Pertuzumab

Control

402

345

267

139

83

32

10

0

0

406

311

209

93

42

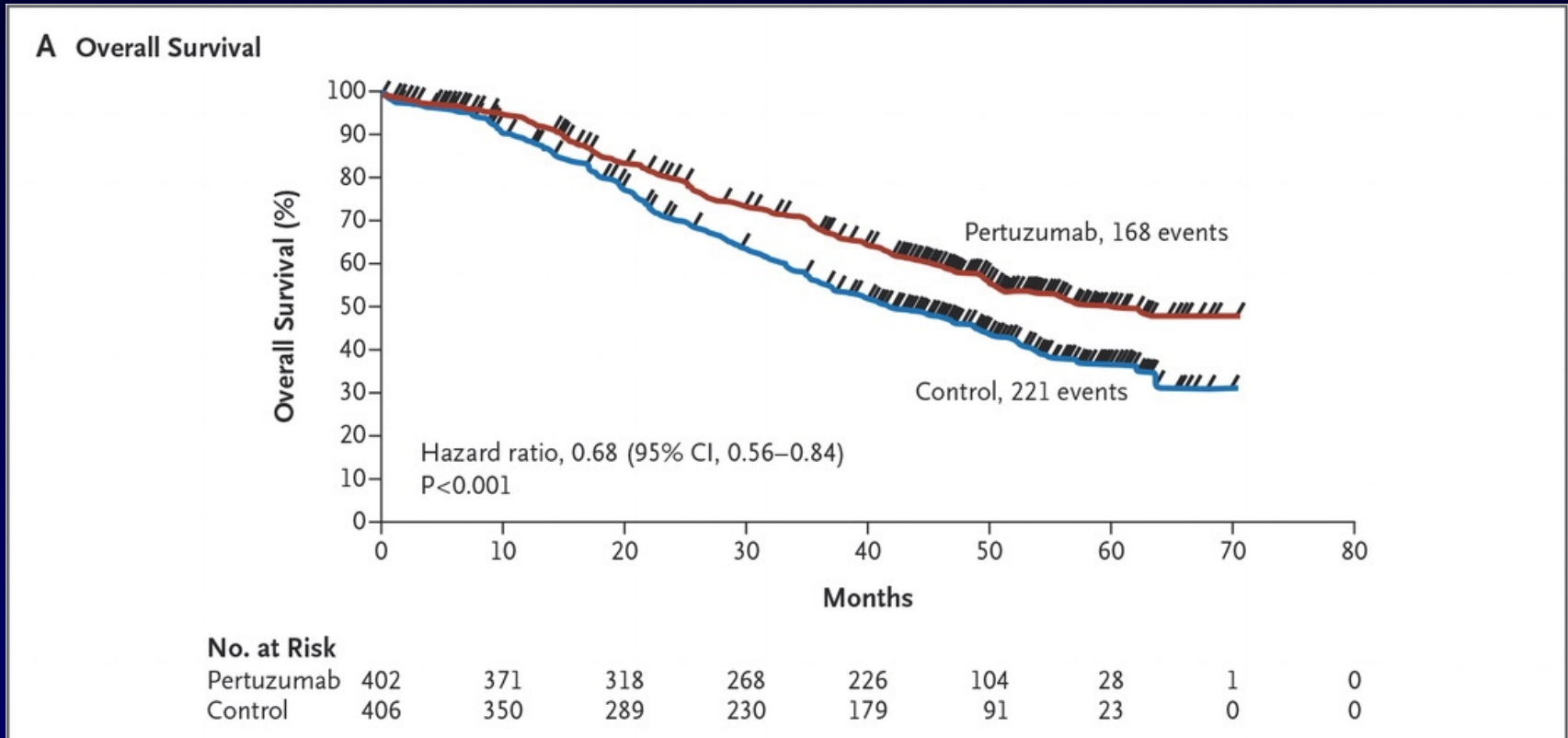
17

7

0

0

CLEOPATRA Overall Survival



PTZ + TRAS + DOC

56.5 months

Placebo + TRAS + DOC

40.8 months

HR = 0.68, $P = .0002$

Summary: Optimal Choice First-Line Setting 2017

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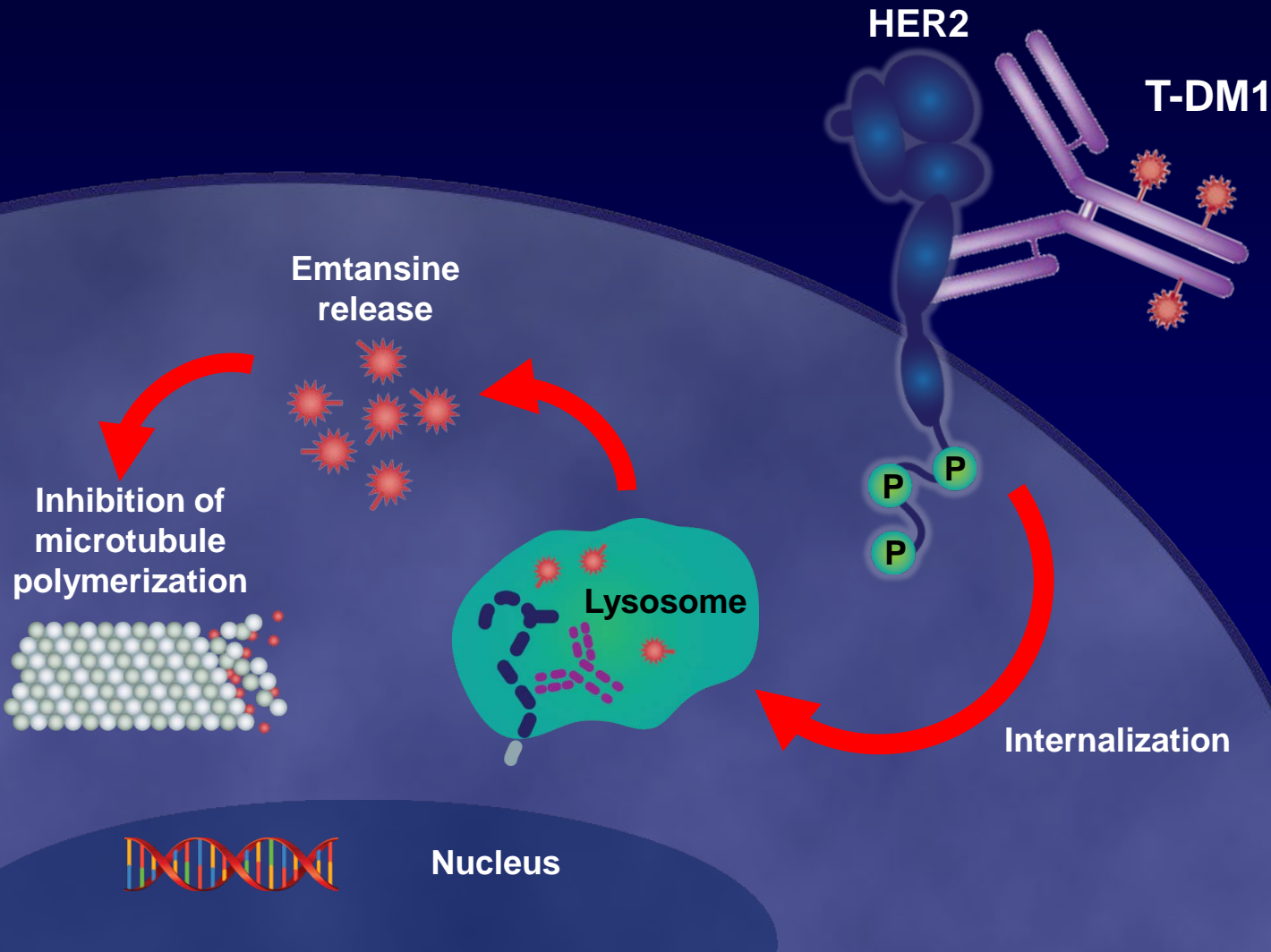
ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

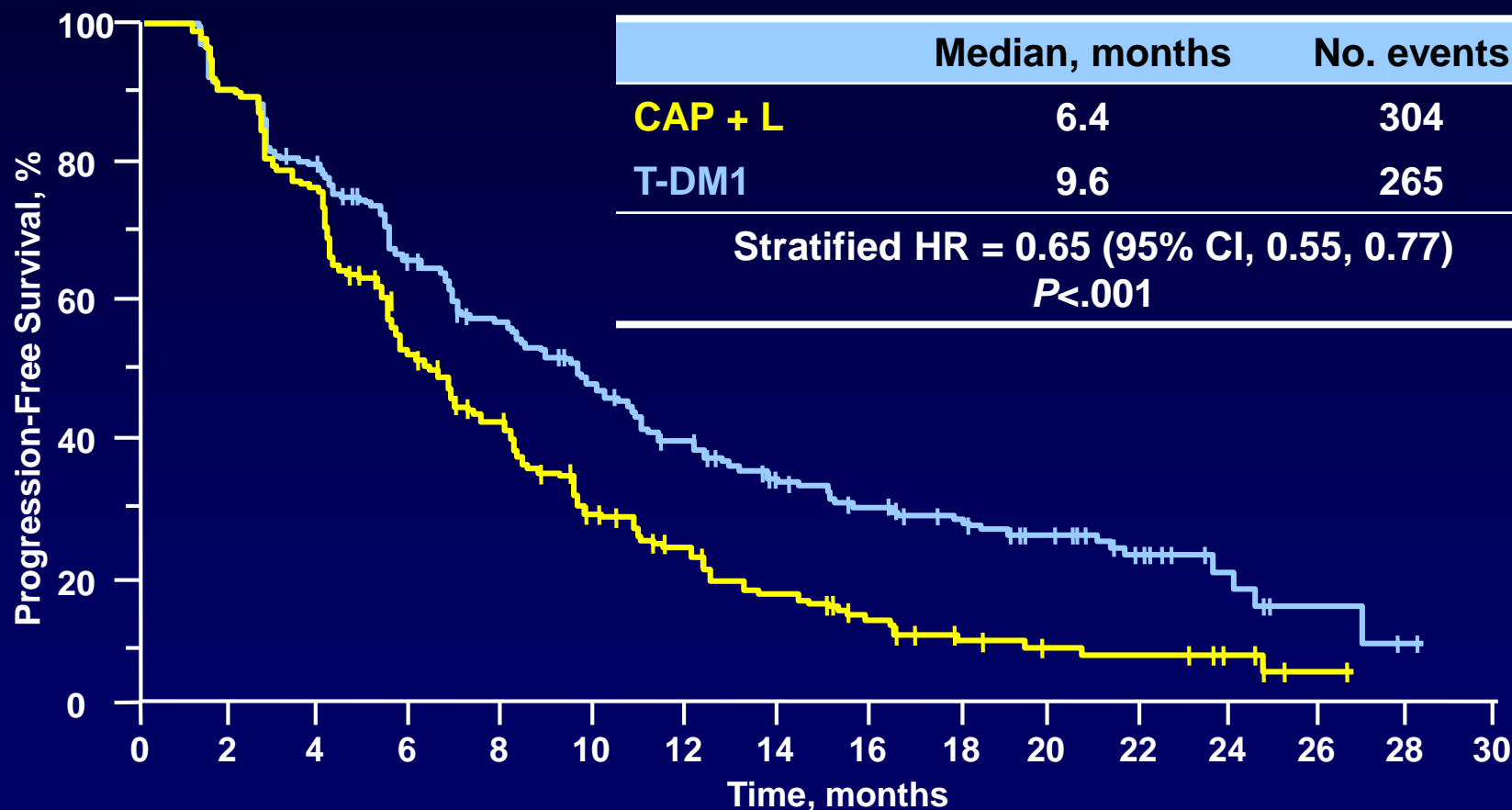
- **Clinicians should recommend combination of trastuzumab, pertuzumab and a taxane for first-line treatment, unless contraindication to taxane use**
- **If ER+, can consider endocrine therapy + trastuzumab or lapatinib in selected cases**

T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res.* 2011;17(20):6437-6447.

EMILIA: PFS by Independent Review



No. at risk by independent review:

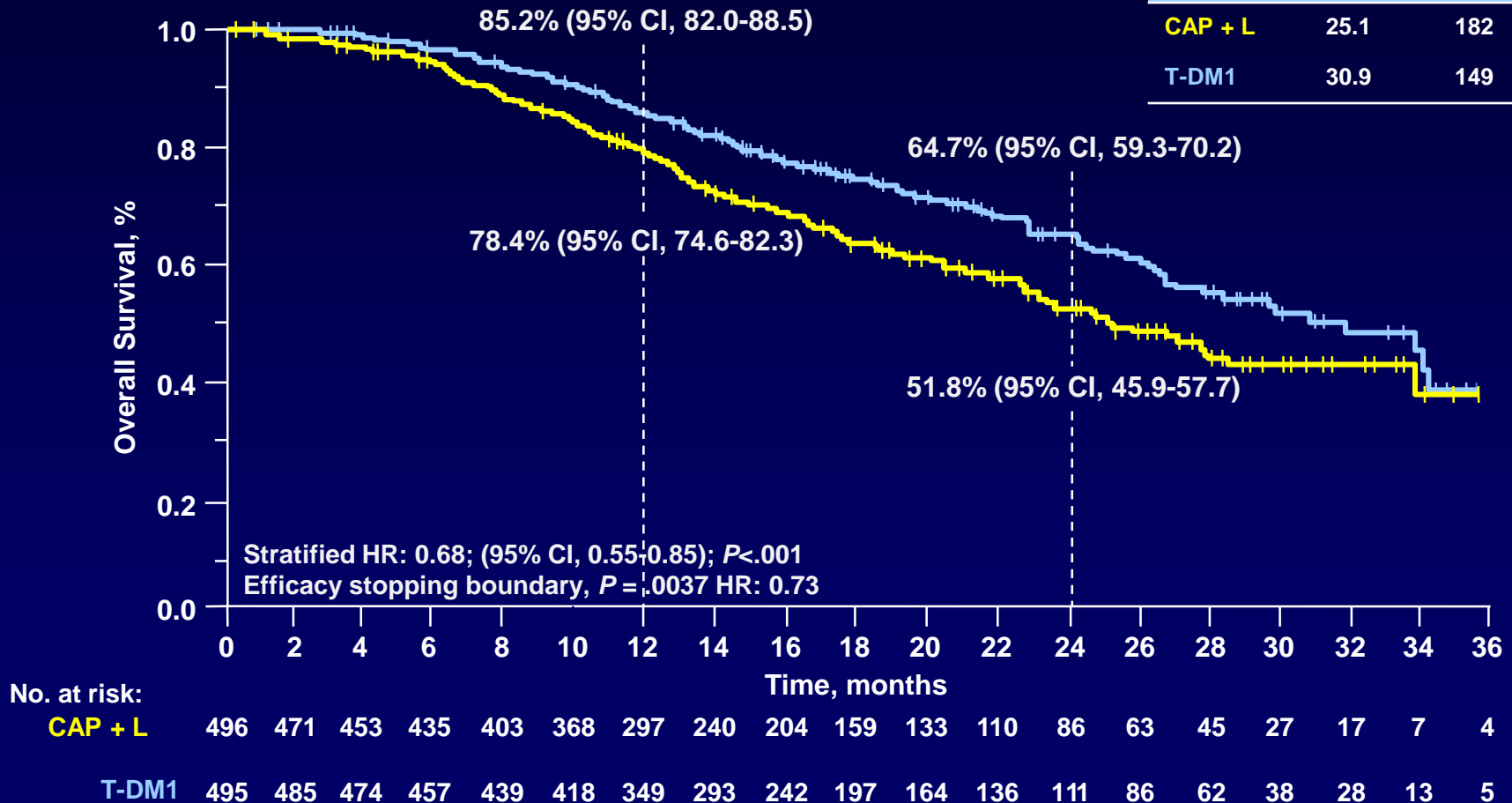
CAP + L	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

CAP, capecitabine; L, lapatinib

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

EMILIA: OS

	Median, months	No. events
CAP + L	25.1	182
T-DM1	30.9	149



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

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

- **If a patient's HER2+ ABC has progressed during or after first-line HER2-targeted therapy, T-DM1 as second-line therapy should be recommended**
- **If a patient finished trastuzumab based adjuvant treatment in ≤ 12 months before recurrence, second-line HER2-targeted therapy should be recommended**

**Can we de-escalate treatment
in the curative setting?**

Why Neoadjuvant Systemic Therapy?

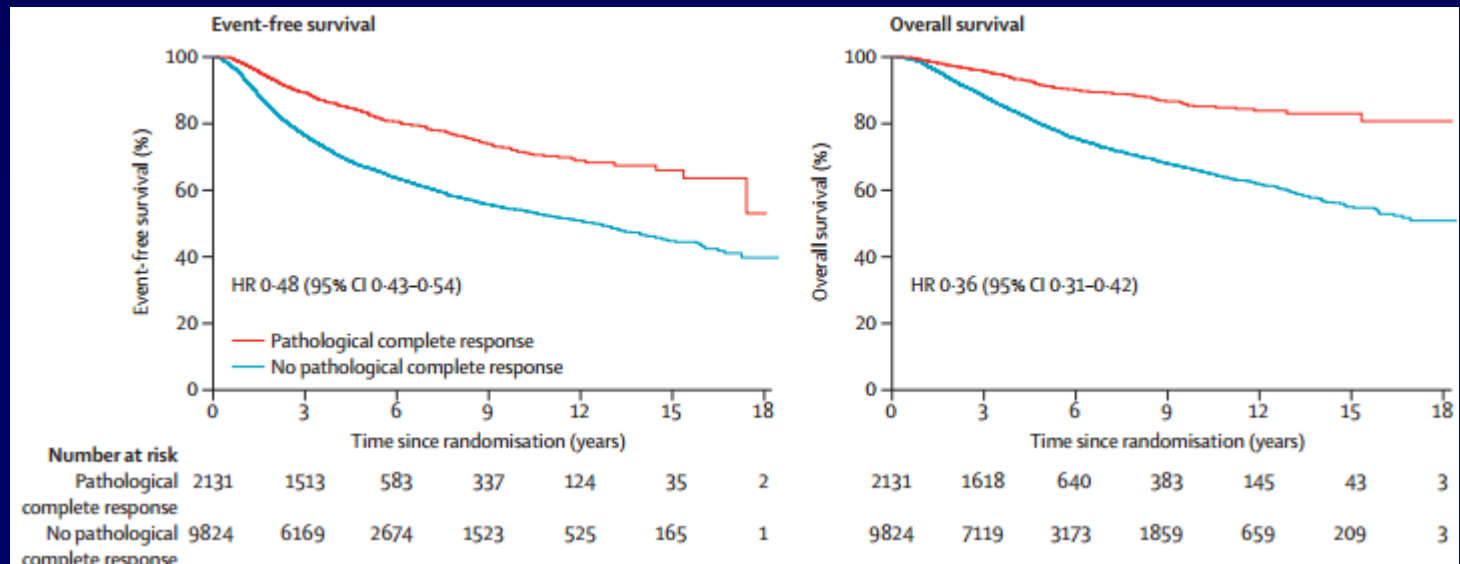
- **Similar to adjuvant therapy, can improve disease-free and overall survival**
- **Increases breast-conserving surgery rates with operable locally advanced BC^[1,2]**
- **Neoadjuvant trial design allows *in vivo* analyses**
- **Monitor response and adjust systemic therapy**
- **Residual cancer after neoadjuvant systemic therapy: prognostic?^[3,4]**

1. Kaufmann M, et al. *J Clin Oncol*. 2006;24:1940-1949. 2. Caudle AS, et al. *Curr Opin Obstet Gynecol*. 2011;23:31-36. 3. Von Minckwitz G, et al. *J Clin Oncol*. 2011;29:1028. 4. Montagna E, et al. *Breast Cancer Res Treat*. 2010;124:689-699.

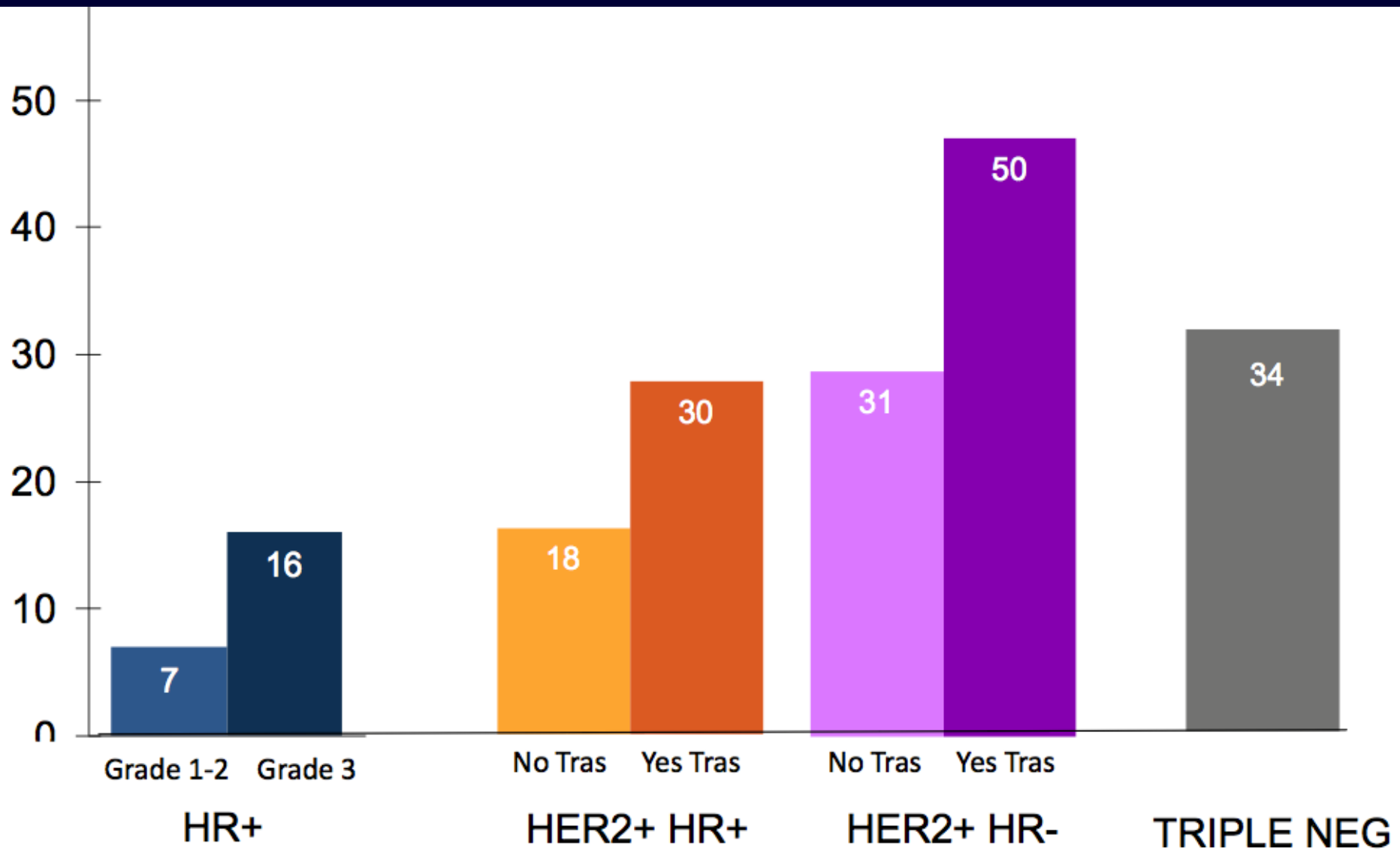
CTNeoBC Pooled Analysis: pCR and Long-Term Clinical Benefit

- N = 11,955 patients in 12 neoadjuvant trials
 - Primary breast cancer; chemo before surgery; ≥ 3 yrs follow-up
- pCR associated with improved survival

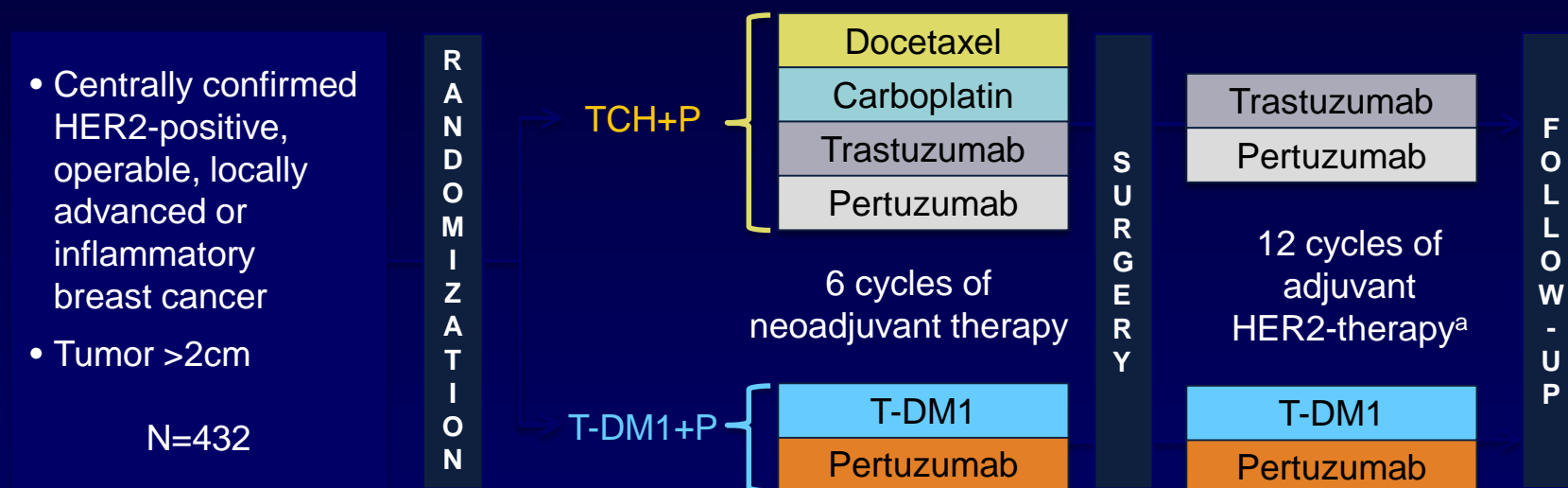
pCR defined as:
ypT0 ypN0 or
ypT0/is ypN0



pCR rates by tumor subtypes



KRISTINE Study Design



Primary endpoint: pCR by local assessment (ypT0/is, ypN0)

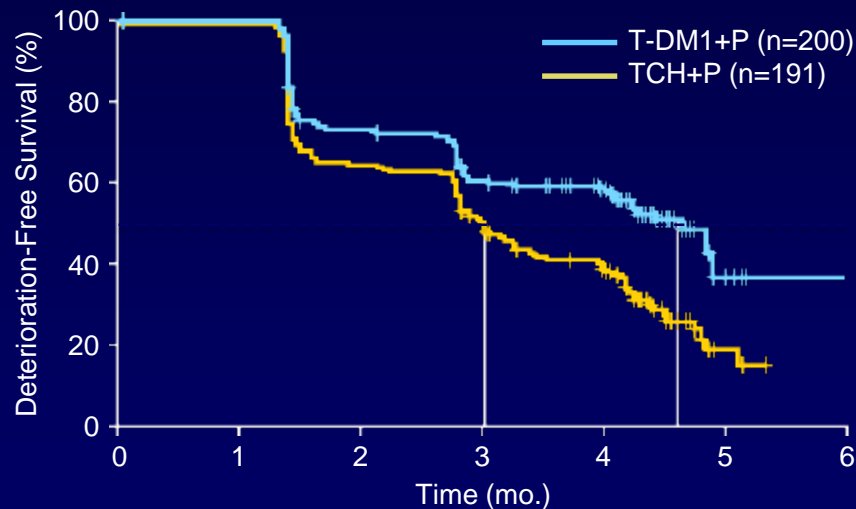
- Stratification factors:** local HR status, geographic location, and clinical stage at presentation

^aAdjuvant chemotherapy was recommended for patients in the T-DM1+P arm who had residual disease in lymph node(s) or in the breast (>1cm).

Maintenance of HRQoL and Physical Function

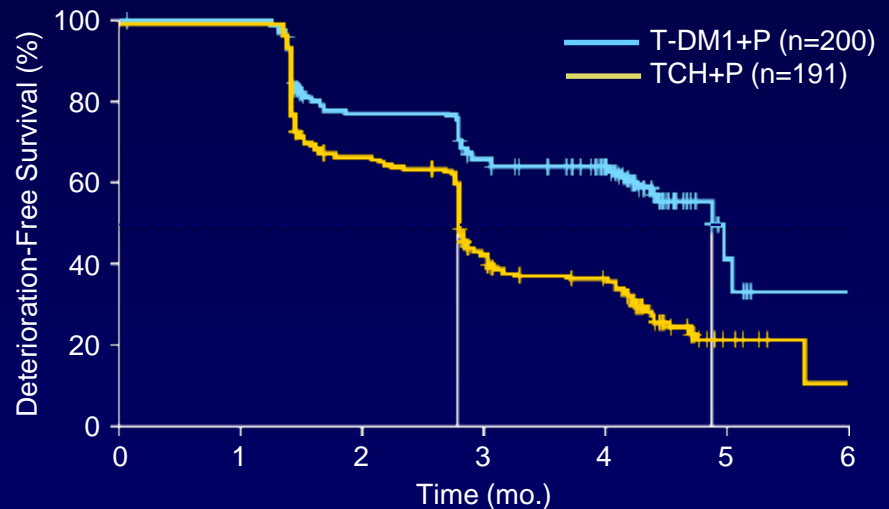
Maintenance of HRQoL^a

HR (95% CI): 0.60 (0.46–0.78)



Maintenance of physical function^a

HR (95% CI): 0.47 (0.36–0.62)



^aData are based on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and QLQ-modified breast cancer module (BR23). Maintenance of health-related quality of life (HRQoL) and physical function were assessed as the time to deterioration defined as the time from baseline to first 10-point (or greater) decrease.

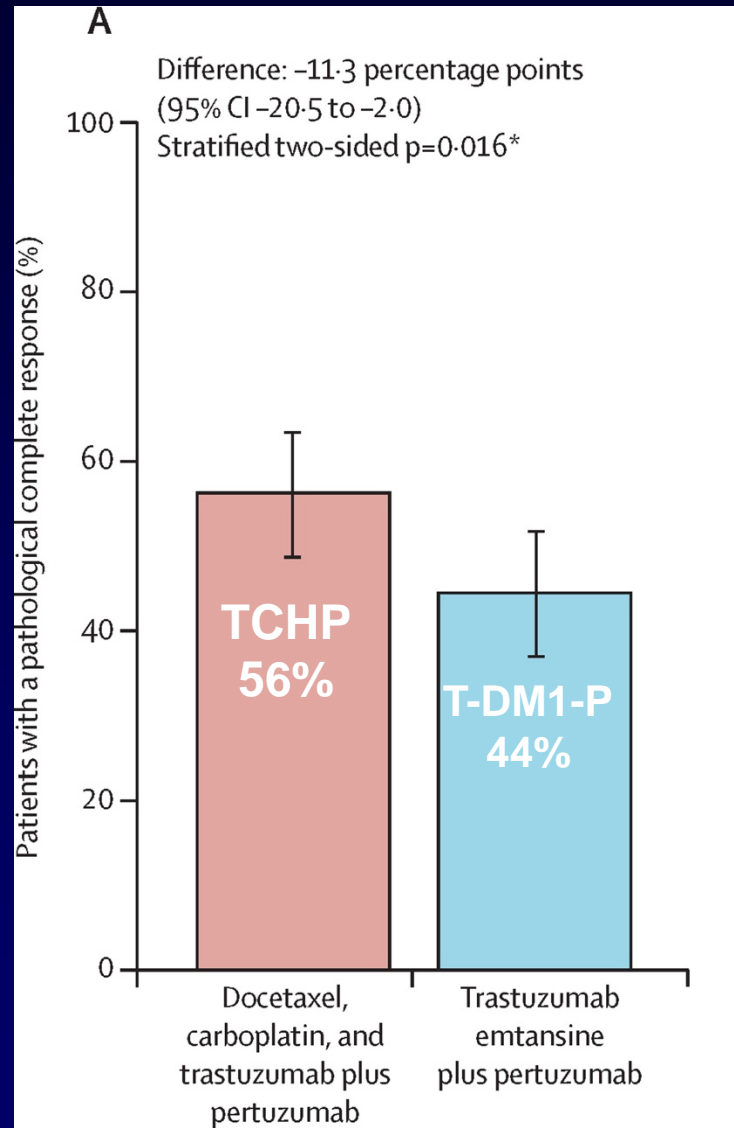
Only data from the neoadjuvant treatment phase including pre-surgery visit are used. Patients of the ITT population with a baseline assessment and at least 1 post-treatment assessment are included in this analysis.

Treatment Exposure and Overview of Adverse Events: Neoadjuvant Phase

	TCH+P (n=219) ^a	T-DM1+P (n=223) ^a
Median number of cycles (min–max)	6 (1–6)	6 (2–6)
Any adverse event, %	98.6	88.3
Serious adverse event, %	28.8	4.9
Grade ≥3 adverse event, %	64.4	13.0
Adverse event leading to treatment discontinuation of any component, %	8.7	3.1
LVEF <50% and ≥10% points decrease from baseline, %	0.5	0.4

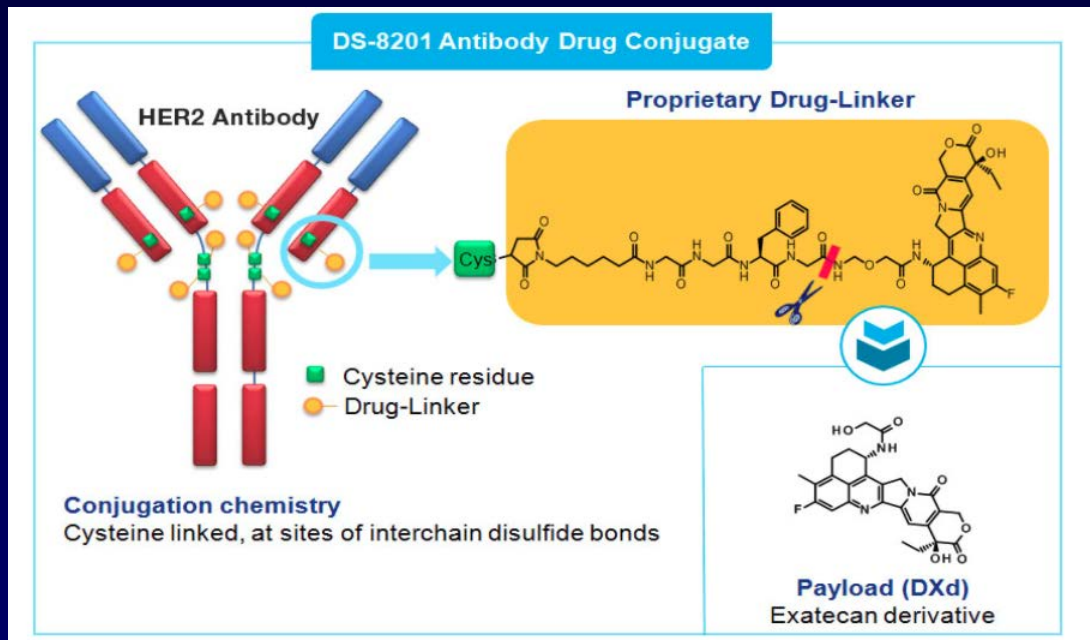
- Serious adverse events occurring in ≥1% of patients in the TCH+P arm: febrile neutropenia (12%), neutropenia (3%), diarrhea (4%), vomiting (1.8%), colitis (1%), and neutrophil count decreased (1%).
- No single serious adverse event occurred in ≥1% of patients in the T-DM1+P arm.

TRIO-021 (“KRISTINE”)



Highlighting The Next Generation in HER2-targeted therapy

Trastuzumab Deruxtecan (DS-8201)



- Highly potent: Drug-to-antibody ratio = 7.8 vs 3.5 for T-DM1
- Topoisomerase I inhibitor vs tubulin inhibitor (T-DM1)
- Preclinically, DS-8201a has a potent bystander effect due to highly membrane-permeable payload

Characteristics by HER2 receptor expression

Characteristics	HER2-positive (n = 96)	HER2-low (n = 34)
Age, median (range)	55.5 (33–77)	54.5 (33–75)
ECOG performance status, n (%)		
0	50 (52.1)	20 (58.8)
1	31 (32.3)	14 (41.2)
Missing	15 (15.6)	0 (0.0)
Hormone receptor, n (%)		
Positive	58 (60.4)	27 (79.4)
Negative	25 (26.0)	5 (14.7)
Unknown	13 (13.5)	2 (5.9)
HER2 expression (IHC), n (%)[*]		
3+	68 (70.8)	0 (0.0)
2+	24 (25.0)	19 (55.9)
ISH positive	24 (25.0)	0 (0.0)
ISH negative	0 (0.0)	17 (50.0)
ISH equivocal	0 (0.0)	1 (2.9)
ISH missing	0 (0.0)	1 (2.9)
1+	1 (1.0) [†]	14 (41.2)
Missing	3 (3.1)	1 (2.9)
Number of prior cancer regimens, n (%)		
1	0 (0.0)	0 (0.0)
2	2 (2.1)	0 (0.0)
3	5 (5.2)	2 (5.9)
4	11 (11.5)	4 (11.8)
5 or more	70 (72.9)	28 (82.4)
Missing	8 (8.3)	0 (0.0)
Prior therapy, n (%)		
T-DM1 [‡]	96 (100)	4 (11.8)
Pertuzumab	72 (75.0)	6 (17.6)

Efficacy: Confirmed ORR, DCR, and PFS

Population	ORR, n/N (%) [*]	DCR, n/N (%) [*]	PFS (months), median (range) [†]
HER2-positive			
All	35/57 (61.4)	54/57 (94.7)	10.4 (1.2+, 16.8+)
HR-positive	22/39 (56.4)	36/39 (92.3)	NR (1.2+, 16.8+)
HR-negative	12/16 (75.0)	16/16 (100.0)	10.4 (1.2+, 14.1+)
Prior pertuzumab-treated	31/50 (62.0)	47/50 (94.0)	10.3 (1.2+, 16.8+)
HER2-low			
All	6/19 (31.6)	16/19 (84.2)	NR (0.5, 12.2+)
HR-positive	5/16 (31.3)	14/16 (87.5)	NR (1.2+, 12.2+)
HR-negative	0/2 (0.0)	1/2 (50.0)	7.6 (0.5, 7.6)

^{*}Analysis set for ORR (CR+PR) and DCR (CR+PR+SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.

[†]Minimum and maximum of PFS include "+" after value indicates censoring.

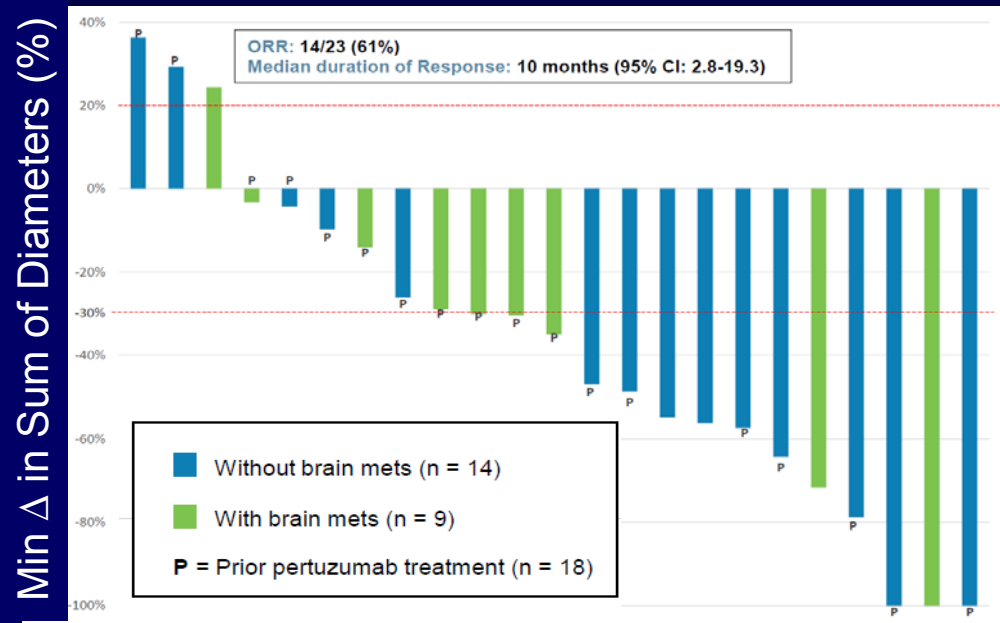
CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

Trastuzumab Deruxtecan

- Significant activity in subjects with HER2+ advanced breast cancer who have received T-DM1, as well as trastuzumab with or without pertuzumab, and in heavily pretreated subjects with HER2-low breast cancer demonstrating durable responses regardless of hormone receptor status
- FDA granted breakthrough therapy designation 8/2017
- Upcoming/ongoing studies:
 - Pivotal phase 2 DESTINY-Breast01 study (NCT03248492)
 - *Phase 1 study evaluating DS-8201 + nivolumab*
 - Phase 3 studies planned

Phase 1b Study: Tucatinib With Capecitabine and/or Trastuzumab in HER2+, Metastatic Breast Cancer

N=23



- 300mg BID
- Encouraging antitumor activity seen with triplet combination, in a heavily pretreated population including those with brain mets
- ORR = 14/23 (61%);
- mPFS = 7.8 mo
- Median DOR = 10 mo (95% CI, 2.8-19.3)
- CNS ORR: 5/12 (42%)

FDA granted tucatinib orphan drug status for HER2+ brain metastases in June 2017

Phase 2 Study of Tucatinib vs Placebo in Combination With Capecitabine & Trastuzumab in HER2+ Breast Cancer

San Antonio Breast Cancer Symposium, December 7, 2017

N=480



Eligibility Criteria

- HER2+ metastatic breast cancer
- Stable or progressive brain metastases, or no evidence of CNS lesions
- Prior treatment with a taxane, trastuzumab, pertuzumab, or T-DM1 allowed
- ECOG performance status of 0 or 1

Randomized 2:1
n = 480

Capecitabine + trastuzumab
+ tucatinib

Capecitabine + trastuzumab
+ placebo

Endpoints

Primary endpoints

- PFS

Secondary endpoints

- ORR, DOR, CBR, safety and tolerability

Therapies Administered on 21-day Cycle

- Tucatinib at 300 mg twice daily
- Capecitabine at 1000 mg/m² twice a day on days 1 through 14 of each cycle
- Trastuzumab as a loading dose of 8 mg/kg, followed by 6 mg/kg once every 21 days; can be given weekly if needed to compensate for treatment modifications

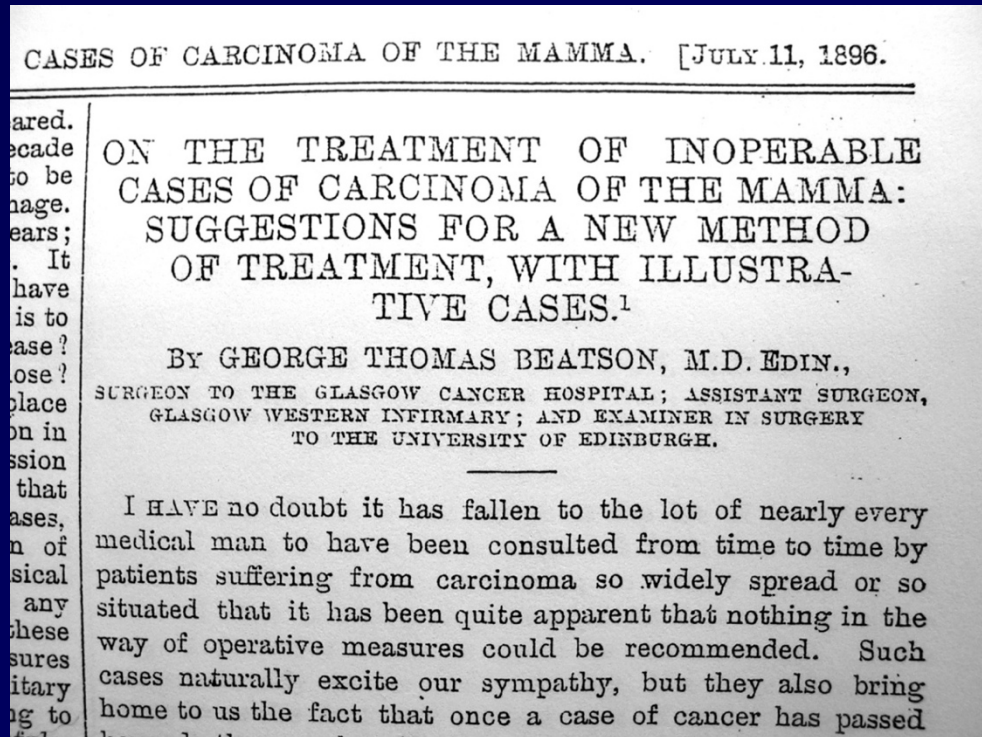
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Current Approach to HER2+ MBC

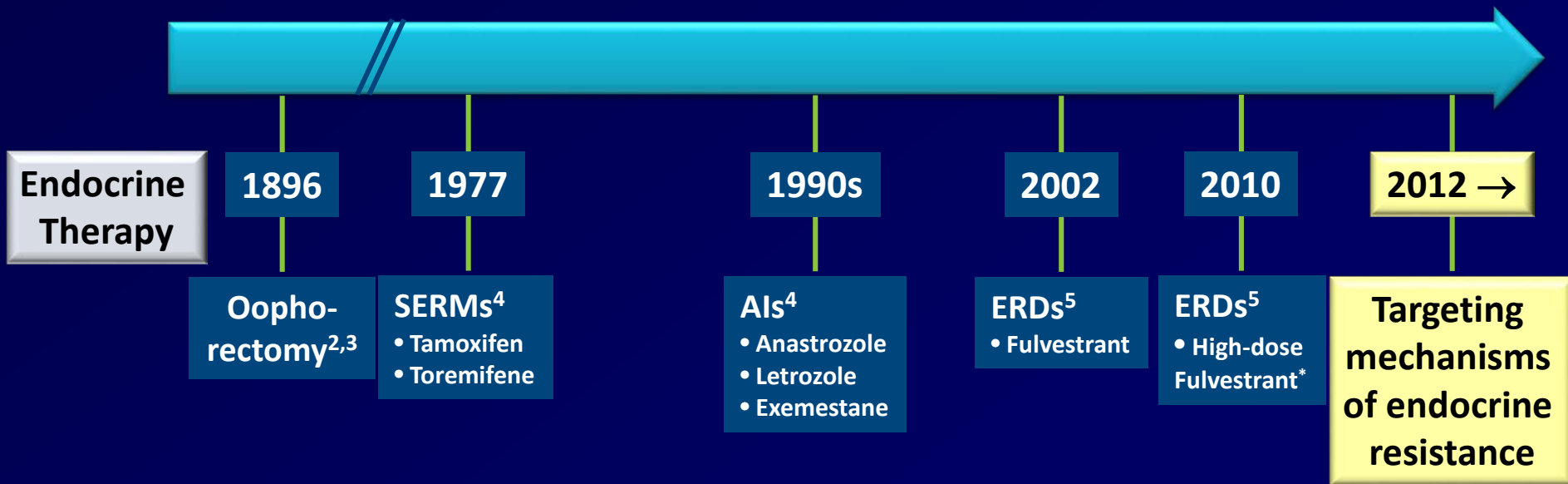
- **First line: Pertuzumab-Trastuzumab-Taxane**
 - Hormonal inhibition: cross-trial comparison indicates THP is preferred in most patients; consider adding hormonal blockade during maintenance HP
 - No data to support continued use of pertuzumab beyond PD
- **Second line: T-DM1**
- **Third line: Many options...optimal timing unknown**
- **Optimizing treatment of HER2+ CNS metastases remains unmet clinical need. Early clinical data of activity of newer agents that penetrate BBB.**
- **Multiple other targeted therapies being explored: Refer for clinical trials!**

Endocrine Therapy

- (Anti)Hormonal Therapy -first kind of targeted therapy
- First recognized in the 1890, by a Scottish surgeon George Beatson. Learned from Scottish farmers that the removal of ovaries from cows alters their ability to lactate.
- Removed ovaries from 3 women with breast cancer-the breast tumors shrank dramatically, however when repeated on a larger scale in London-only 2/3 of the patients responded.
- Estrogen discovered by Doisy in 1920
- Estrogen receptor discovered by Elwood Jensen in 1968



Historical Timeline of Therapies for HR⁺ Advanced Breast Cancer



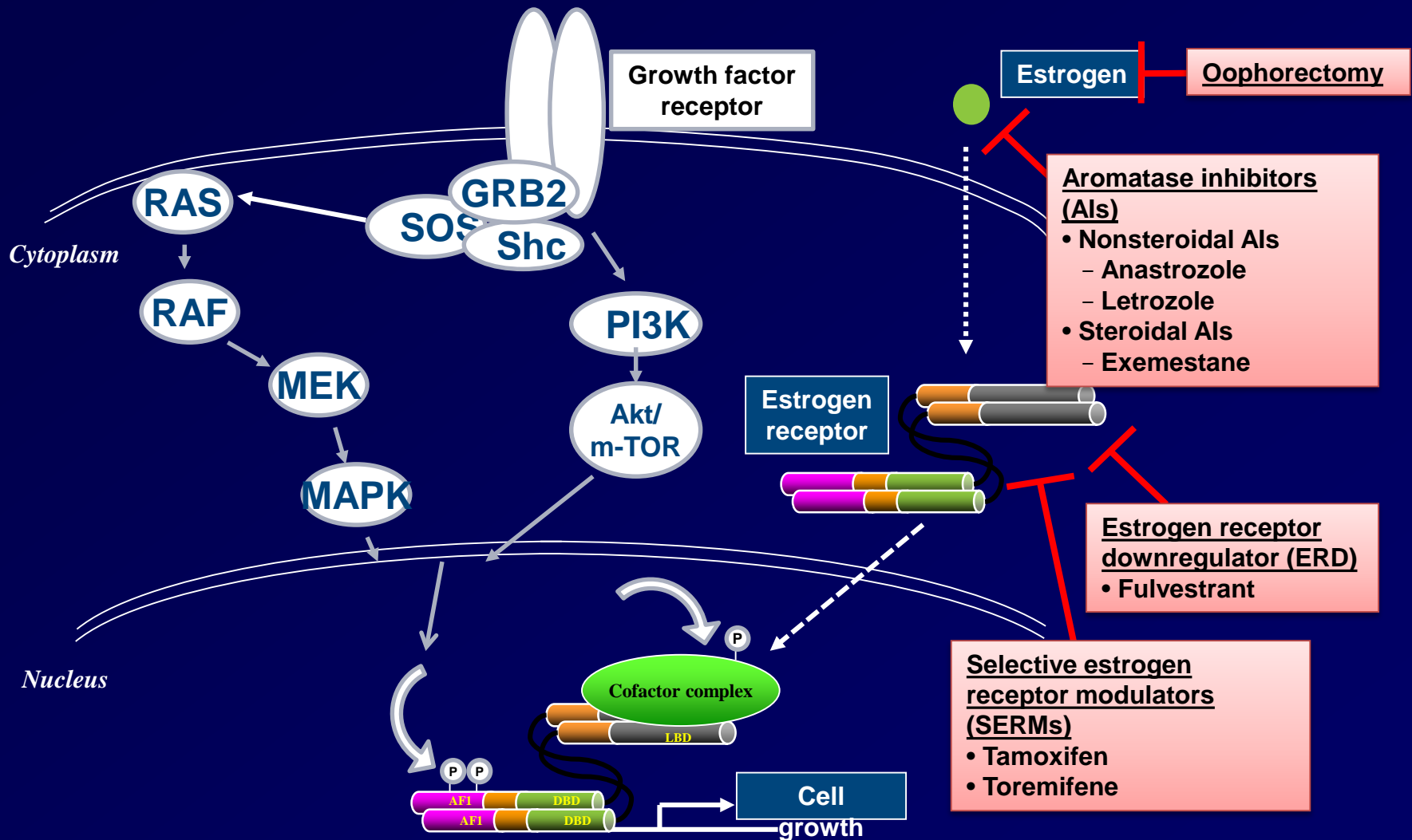
Abbreviations: AI, aromatase inhibitor; ERDs, estrogen receptor downregulator; HR⁺; hormone receptor positive; SERMs, selective estrogen receptor modulators.

* Marginal improvement over lower dose fulvestrant.

1. <http://www.advancedbreastcancercommunity.org/treatment/drugs.htm>; 2. Beatson CT. *Lancet*. 1896;2:104-107; 3. Beatson CT. *Lancet*. 1896;2:162-165;

4. Cohen MH, et al. *Oncologist*. 2001;6:4-11; 5. Faslodex [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2011.

Endocrine Therapy for HR⁺ Advanced Breast Cancer



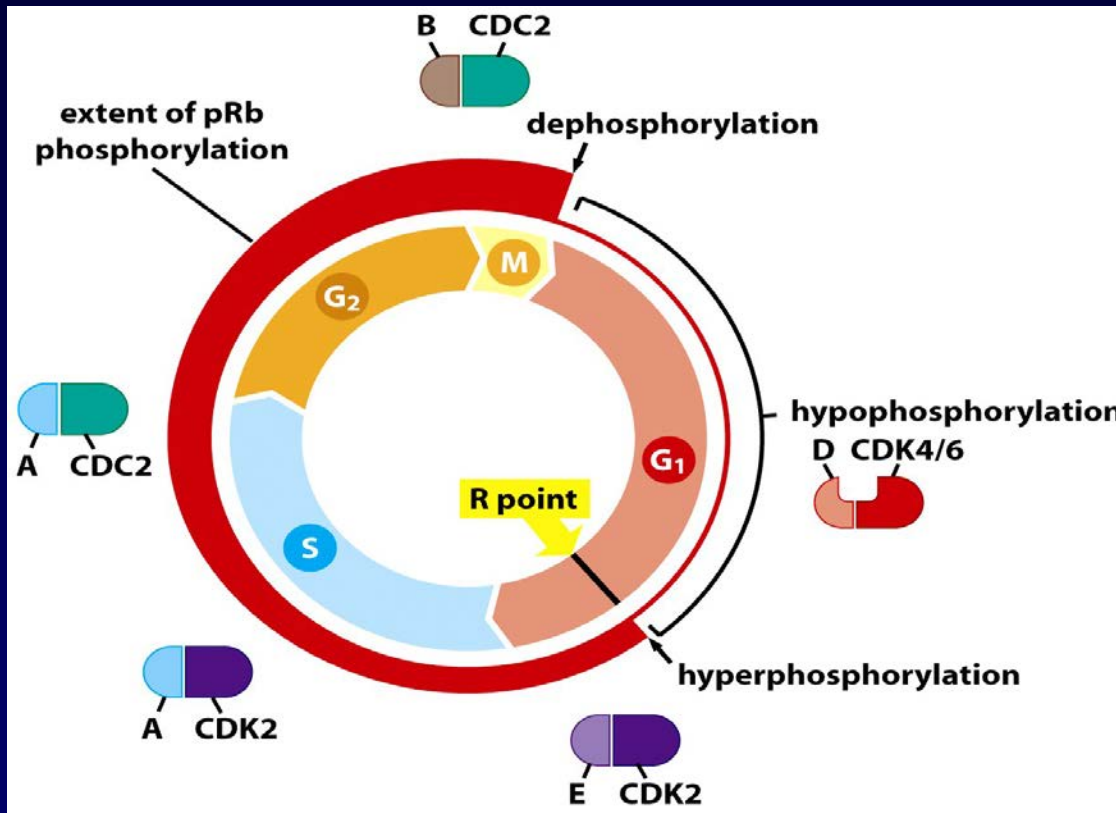
Endocrine Trials in 1st-Line MBC

	Trial	Treatment	# Patients	TTP/PFS, months	ORR, %	CBR, %
AI vs Tamoxifen	Bonnetterre et al ¹	Anastrozole vs	340	8.2	32.9	56.2
		Tamoxifen	328	8.3	32.6	55.5
	Nabholtz et al ¹	Anastrozole vs	171	11.1	21.1	59.1
		Tamoxifen	182	5.6	17.0	45.6
	Mouridsen et al ¹	Letrozole vs	453	9.4	32	50
		Tamoxifen	454	6.0	21	38
AI vs AI + fulvest	Paridaens et al ¹	Exemestane vs	182	9.9	46	NR
		Tamoxifen	189	5.8	31	NR
	Chernozemsky et al ¹	Exemestane vs	83	12	37.4	79.5
		Tamoxifen	84	8.3	29.8	78.6
	Mehta et al ²	Anastrozole vs	345	13.5	NR	70
		Anastrozole + Fulvestrant (250 mg)	349	15.0	NR	73
AI vs fulvest	Bergh et al ³	Anastrozole vs	256	10.2	33.6	55.1
		Anastrozole + Fulvestrant (250 mg)	258	10.8	31.8	55.0
AI vs fulvest	Robertson J et al ⁴	Anastrozole vs	232	13.8	44.9	74
		Fulvestrant (500 mg)	230	16.6	46.1	78

1. Cardoso F, et al. *Cancer Treat Rev.* 2013;39:457-65; 2. Bergh J, et al. *J Clin Oncol.* 2012;30(16):1919-1925; 3. Mehta RS, et al. *N Engl J Med.* 2012;367(5):435-444; 4. Roberston J, et al. *Lancet Oncol* 2016

Cyclin dependent kinases and the cell cycle

Rationale: Rb as Master-Regulator of the G1/S-Cell Cycle Checkpoint



- Protein kinases control cell cycle progression
- Depend on associating regulatory subunits: Cyclins
- CDK 4/6 associate with D-cyclin
- P16 inhibits CDK4/6-D
- CDK4/6-D complex → hyperP04 of Rb
- HyperP04 of Rb inactivates Rb and allows the cell to progress from G₁ to S...G₂...M

Can inhibiting CDK4/6-D prevent Rb hyperP04 & cell cycle progression?

51 Human Breast Cell Lines

```
graph TD; Root[51 Human Breast Cell Lines] --> Luminal[25 Luminal]; Root --> NonLuminal[26 Non-luminal]; Luminal --> ERPosNormal[10 ER positive Normal HER-2]; Luminal --> ERPosAmplified[9 ER positive HER-2 amplified]; Luminal --> ERNegAmplified[6 ER negative HER-2 amplified]; NonLuminal --> NonMalignant[4 Non-malignant]; NonLuminal --> BasalProgenitor[13 Basal/Progenitor]; NonLuminal --> Mesenchymal[9 Mesenchymal]; BasalProgenitor --> HER2Amplified1[1 HER-2 Amplified]; BasalProgenitor --> BasalProgenitor12[12 Basal/Progenitor]; Mesenchymal --> HER2Amplified2[1 HER-2 Amplified]; Mesenchymal --> Mesenchymal8[8 Mesenchymal];
```

25

Luminal

26

Non-luminal

10

**ER positive
Normal HER-2**

9

**ER positive
HER-2 amplified**

6

**ER negative
HER-2 amplified**

4

Non-malignant

13

Basal/Progenitor

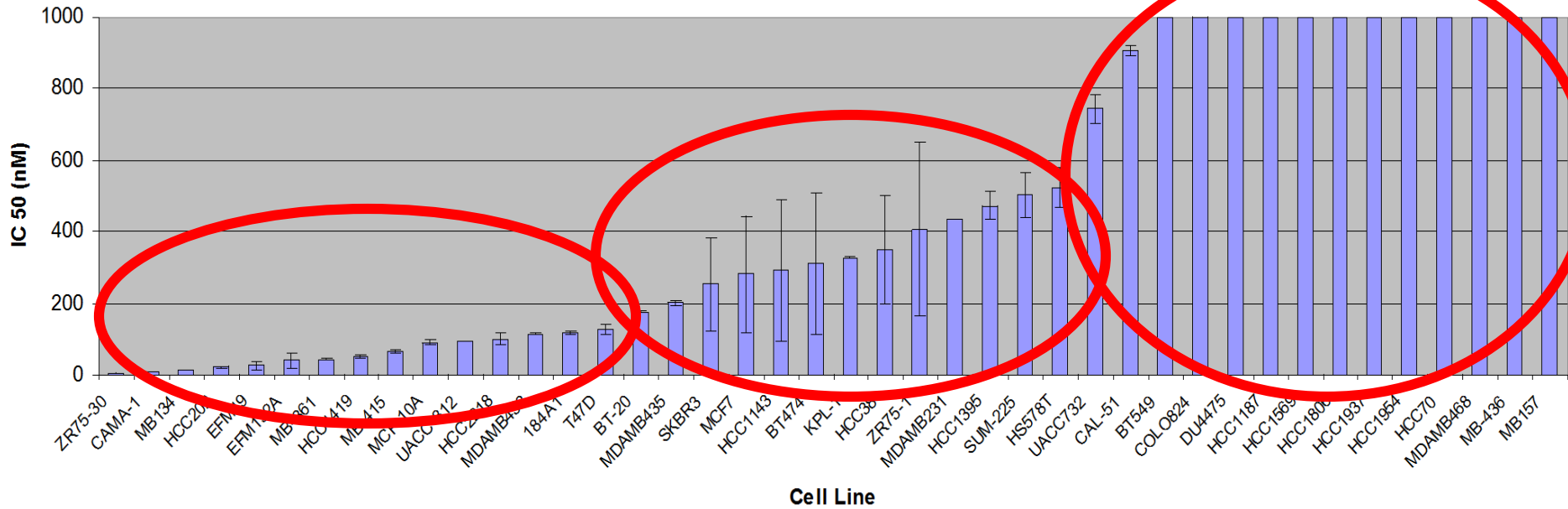
9

Mesenchymal

**1 HER-2
Amplified**

**1 HER-2
Amplified**

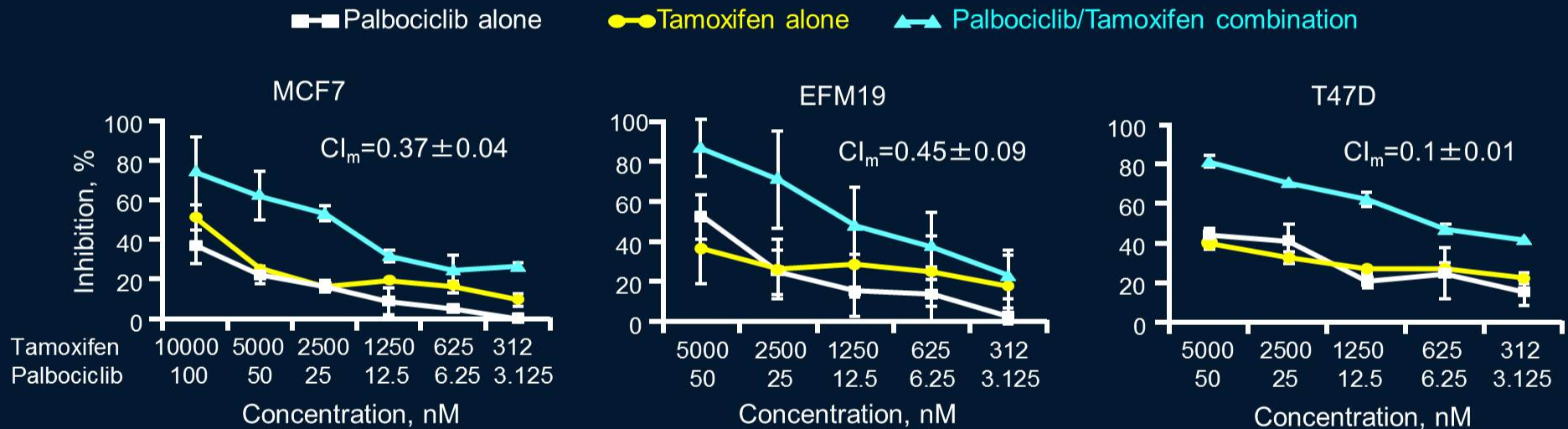
UCLA Breast panel- Pfizer CDK 4/6 Inhibitor IC50s (nM)



UCLA BREAST Cell Lines: IC50s in nM, palbociclib

Rank	Sample Name	IC50 nM	IC50g SE	Response	Classification	Subtype
1	ZR-75-30	4.7	0.15	S	Luminal	Luminal ER+
2	CAMA-1	8.0	0.38	S	Luminal	Luminal ER+
3	MDA-MB-134	12.6	0.42	S	Luminal	Luminal ER+
4	HCC202	21.2	2.32	S	Luminal	Luminal ER+
5	EFM-19	26.9	12.33	S	Luminal	Luminal ER+
6	EFM-192A	41.6	21.20	S	Luminal	Luminal ER+
7	MDA-MB-361	43.7	1.28	S	Luminal	Luminal ER+
8	HCC1419	50.8	3.69	S	Luminal	Luminal ER+
9	MDA-MB-415	64.5	4.10	S	Luminal	Luminal ER+
10	MCF-10A	91.5	6.62	S	Nonluminal	Immortalized
11	UACC-812	95.6	0.11	S	Luminal	Luminal ER+
12	HCC2218	99.9	16.96	S	Luminal	Luminal ER-
13	MDA-MB-453	115.2	1.39	S	Luminal	Luminal ER-
14	T-47D	127.4	15.00	S	Luminal	Luminal ER+
15	BT-20	176.6	2.02	I	Nonluminal	Basal
16	MDA-MB-435	201.1	7.50	I	Nonluminal	Mesenchymal
17	SK-BR-3	253.1	130.78	I	Luminal	Luminal ER-
18	MCF-7	281.8	163.19	I	Luminal	Luminal ER+
19	HCC1143	292.5	198.07	I	Nonluminal	Basal
20	BT-474	312.5	197.25	I	Luminal	Luminal ER+
21	KPL-1	326.7	3.07	I	Luminal	Luminal ER+
22	HCC38	347.4	151.16	I	Nonluminal	Basal
23	ZR-75-1	406.9	243.28	I	Luminal	Luminal ER+
24	MDA-MB-231	432.3		I	Nonluminal	Mesenchymal
25	HCC1395	472.1	39.80	I	Nonluminal	Mesenchymal
26	SUM-225	503.1	64.26	I	Luminal	Luminal ER-
27	Hs578T	523.8	55.68	I	Nonluminal	Mesenchymal
28	UACC-732	744.2	41.11	I	Luminal	Luminal ER+
29	CAL-51	905.5	14.95	I	Nonluminal	Mesenchymal
30	BT-549	1000.0		R	Nonluminal	Mesenchymal
31	COLO-824	1000.0		R	Nonluminal	Basal
32	DU4475	1000.0		R	Nonluminal	Basal
33	HCC1187	1000.0		R	Nonluminal	Basal
34	HCC1569	1000.0		R	Nonluminal	Basal
35	HCC1806	1000.0		R	Nonluminal	Basal
36	HCC1937	1000.0		R	Nonluminal	Basal
37	HCC1954	1000.0		R	Nonluminal	Basal
38	HCC70	1000.0		R	Nonluminal	Basal
39	MDA-MB-157	1000.0		R	Nonluminal	Mesenchymal
40	MDA-MB-436	1000.0		R	Nonluminal	Mesenchymal
41	MDA-MB-468	1000.0		R	Nonluminal	Basal

Palbociclib Synergy With Tamoxifen in ER+ Breast Cancer Cell Lines

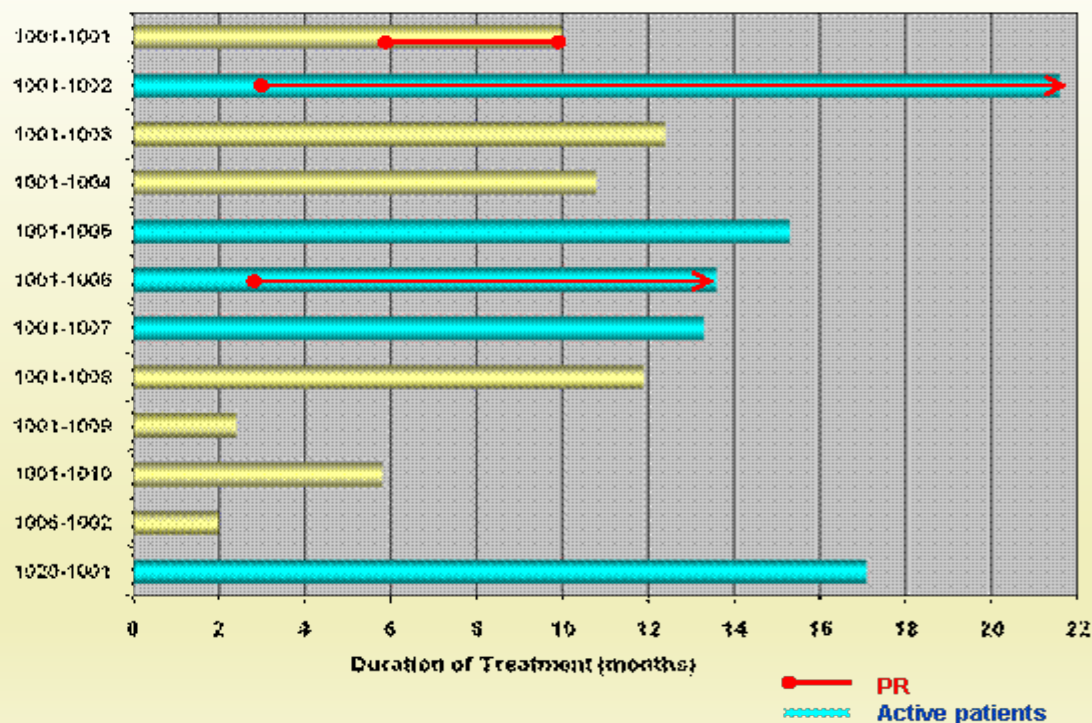


- Mean combination index (CI_m) <1 indicates synergy for the combinations

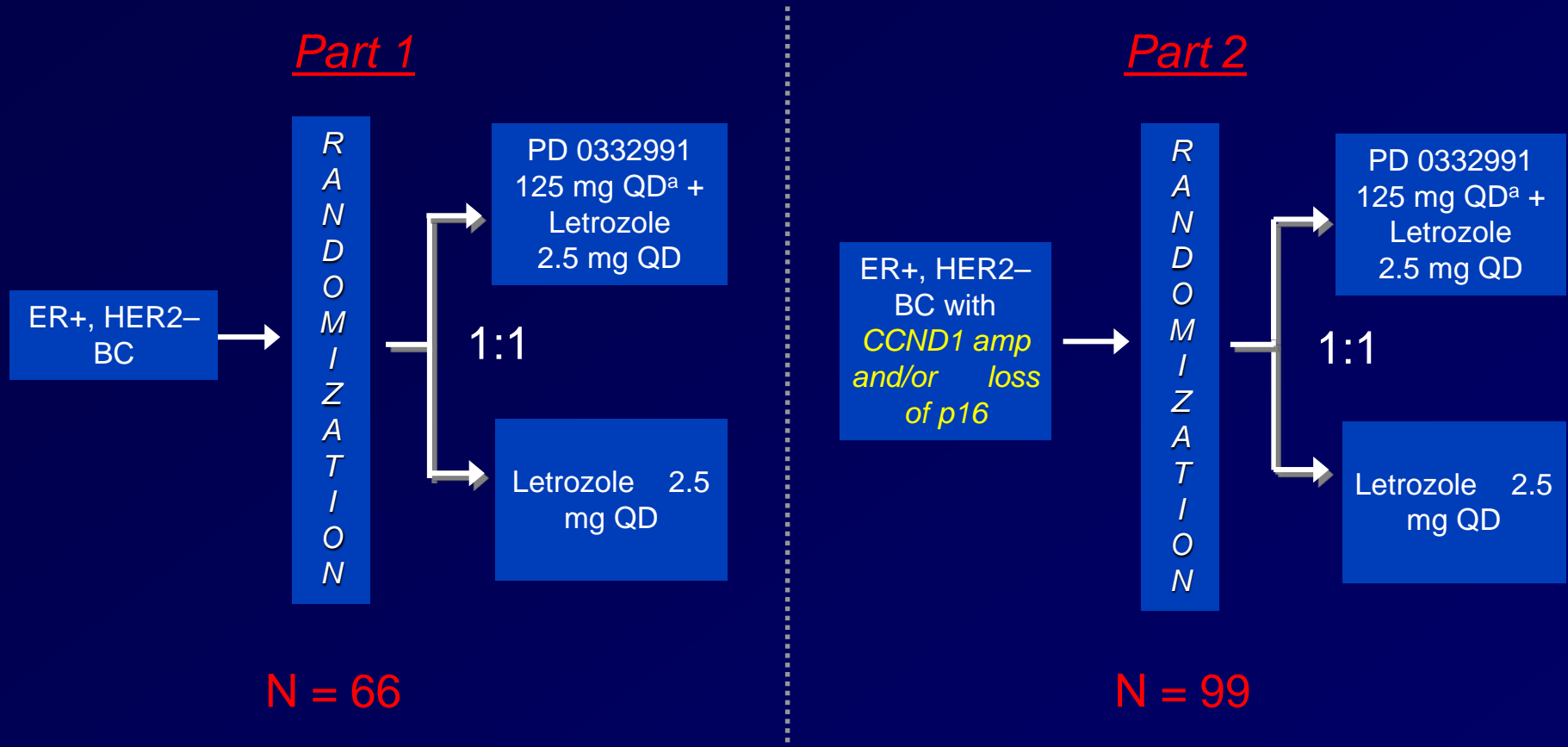
Finn,Slamon et al. *Breast Cancer Res.* 2009.

TRIO 18: Phase 1 Patient Summary

Pt. ID	Age	Prior Systemic Tx	Prior XRT	DLT	Best Response
1001-1001	62	AC → T (2005)	2005	-	PR
1001-1002	68	TC (2005); Anastrozole (2005-8)	None	-	PR
1001-1003	43	FEC → T (2005); Tamoxifen (2005-8)	2006	-	SD (bone only)
1001-1004	59	AC → T (2004); Anastrozole (2004)	2004	-	SD
1001-1005	53	Tamoxifen (2005-9)	None	-	SD
1001-1006	57	None	None	Yes	PR
1001-1007	74	Fluoxymesterone (1997); Anastrozole (1997-2001)	None	-	SD
1001-1008	63	AC → T (2003); Anastrozole (2003-8)	2003	-	SD
1001-1009	74	AC (2001); Tamoxifen (2001-6); Letrozole (2006-9)	2009	Yes	SD (bone only)
1001-1010	71	None	2009	-	SD
1006-1002	59	AC → Pac (2002)	2002	Yes	SD (bone only)
1020-1001	53	CMF (1988)	None	-	SD



Phase 2 Design



Primary Endpoint PFS

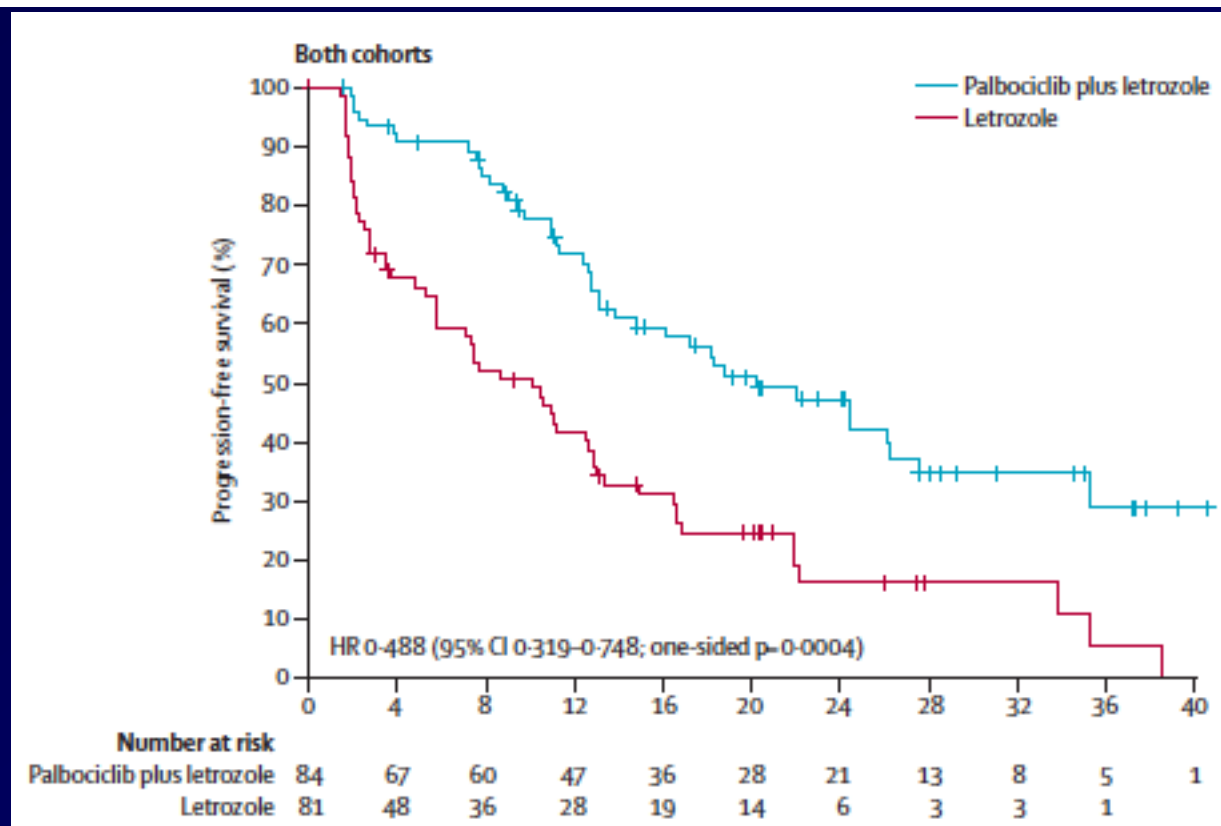
Stratification Factors

- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

^a Schedule 3/1.

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

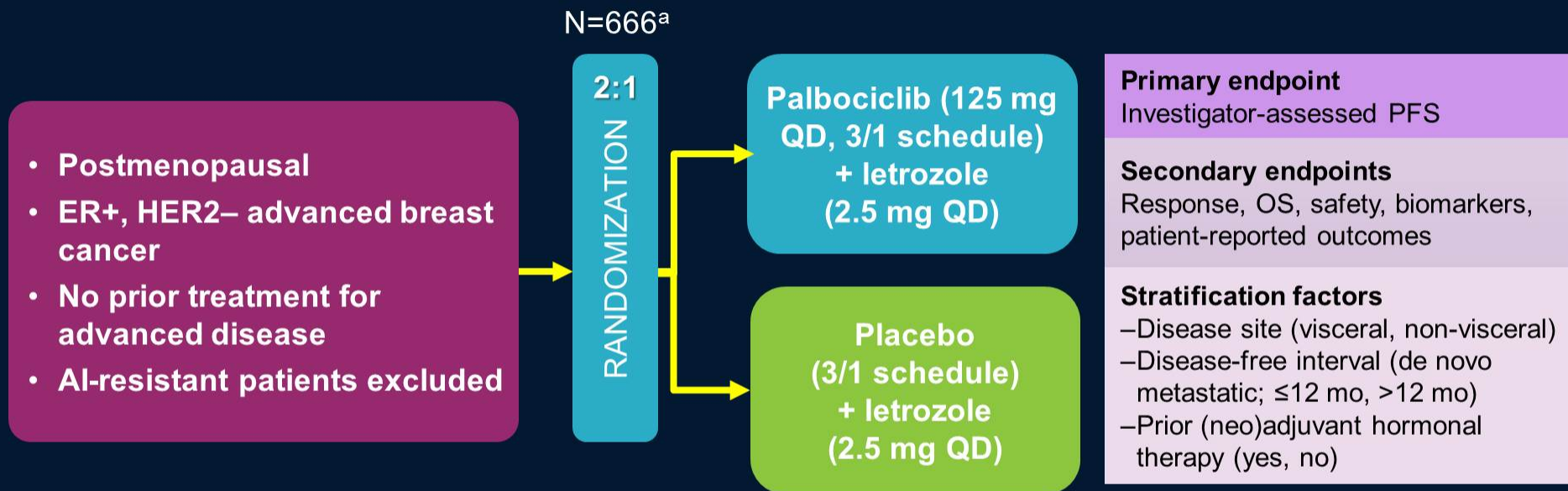
Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Cindy T Kim, Sophia Randolph, Dennis J Slamon



Based on these phase II data...

- **Palbociclib received the first designation as breakthrough therapy by the FDA**
- **Prior to the phase III study results being presented, palbociclib granted accelerated FDA approval February 2015 for patients with metastatic ER+ breast cancer**

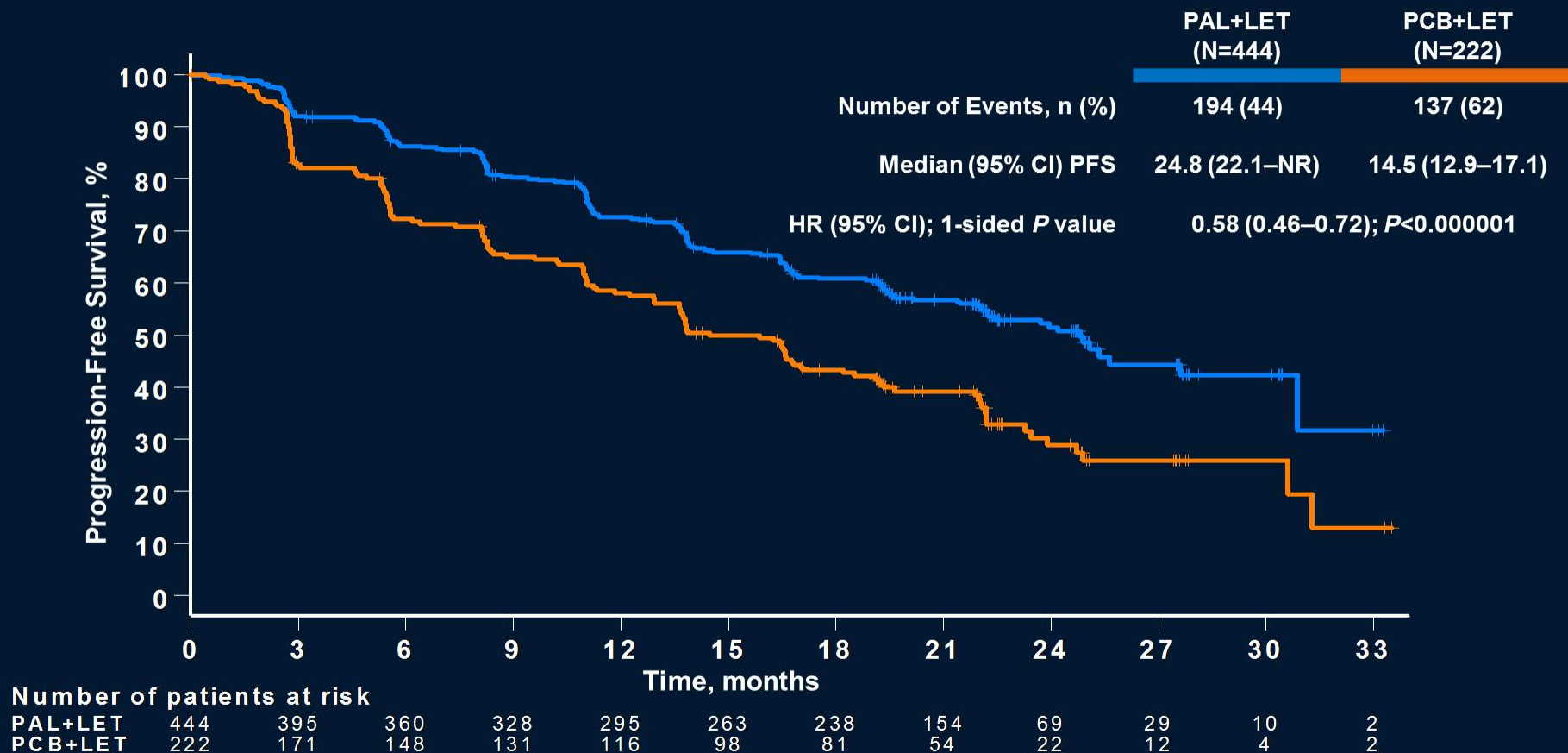
PALOMA-2: Study Design (1008)¹



- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided $\alpha=0.025$
 Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
- Blinded independent central review of efficacy endpoints performed as supportive analysis

¹[clinicaltrials.gov
NCT01740427](https://clinicaltrials.gov/NCT01740427)

PFS: Investigator-Assessed - (ITT Population)



ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Hematologic AEs –All Causality

	Palbociclib + Letrozole (N=444)			Placebo + Letrozole (N=222)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE, %	99	62	14	95	22	2
Neutropenia ^a	80	56	10	6	1	<1
Leukopenia ^a	39	24	1	2	0	0
Anemia ^a	24	5	<1	9	2	0
Thrombocytopenia ^a	16	1	<1	1	0	0

AE=adverse event. ^aIncludes clustered Medical Dictionary for Regulatory Activity (MedDRA) preferred terms.

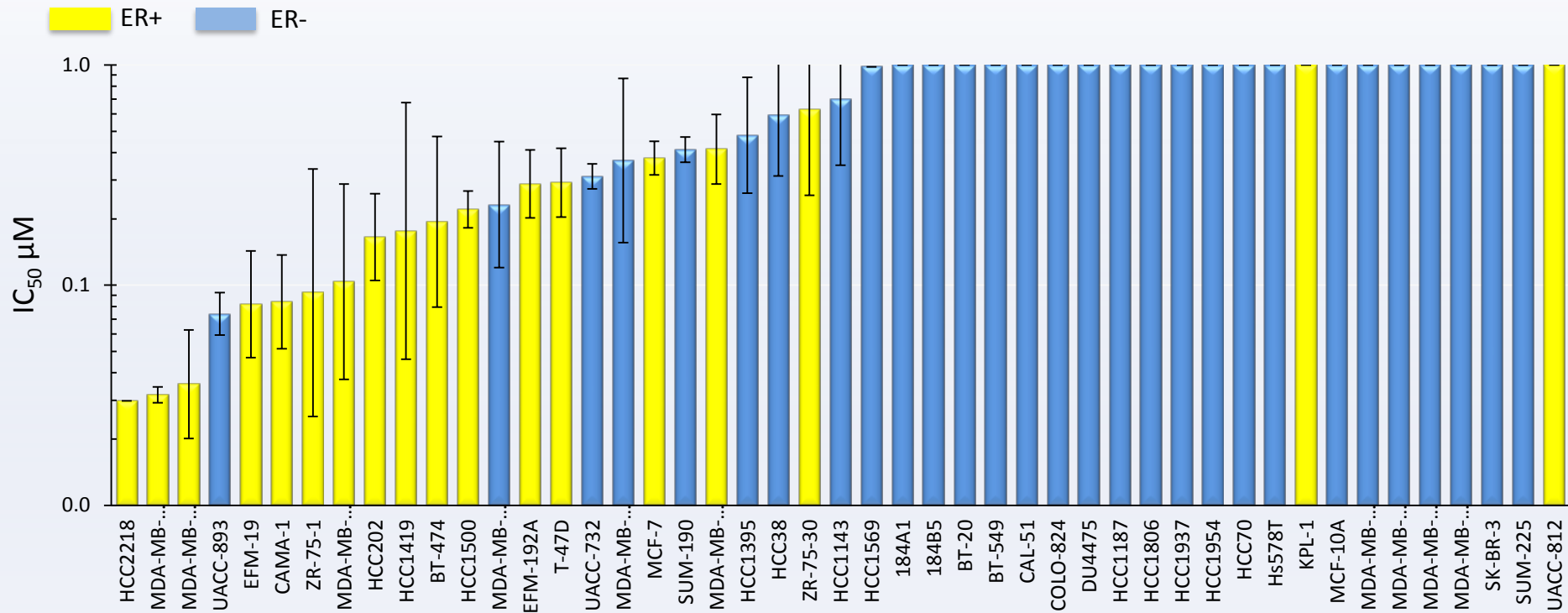
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		Fulvestrant (500 mg)	230	16.6	46.1	78
	Finn et al ⁵	Letrozole vs	222	14.5	35	70
		Letrozole + Palbociclib	444	24.8	42	85

1. Cardoso F, et al. *Cancer Treat Rev.* 2013;39:457-65; 2. Bergh J, et al. *J Clin Oncol.* 2012;30(16):1919-1925; 3. Mehta RS, et al. *N Engl J Med.* 2012;367(5):435-444; 4. Robertson J et al. *Lancet Oncol* 2016 5. Finn RS, Slamon DJ, et al. *NEJM* 2016

Ribociclib

NVP-LEE011: CDK4/6 Inhibitor



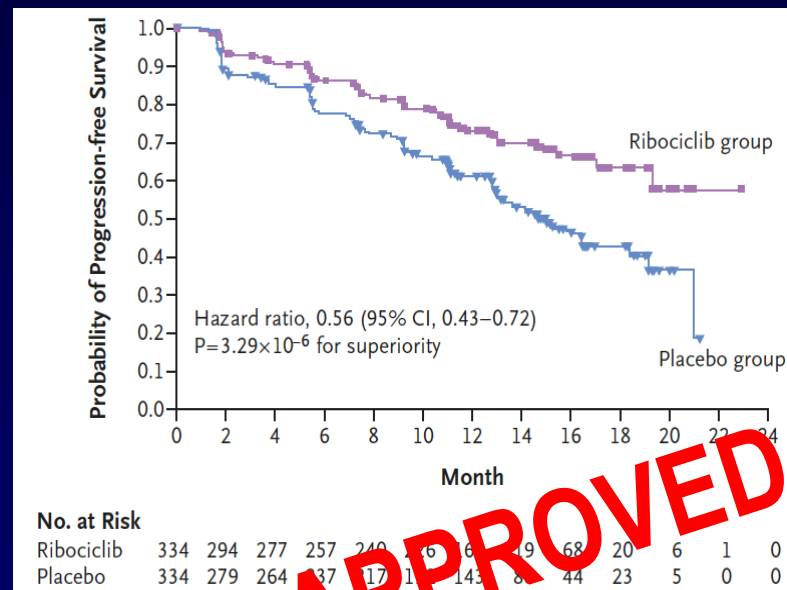
CDK4/6 inhibitor, LEE011 is most active in ER+ breast cancer cell lines

Neil O'Brien, Dennis Slamon AACR 2014



MONALEESA-2: Ribociclib 1st Line

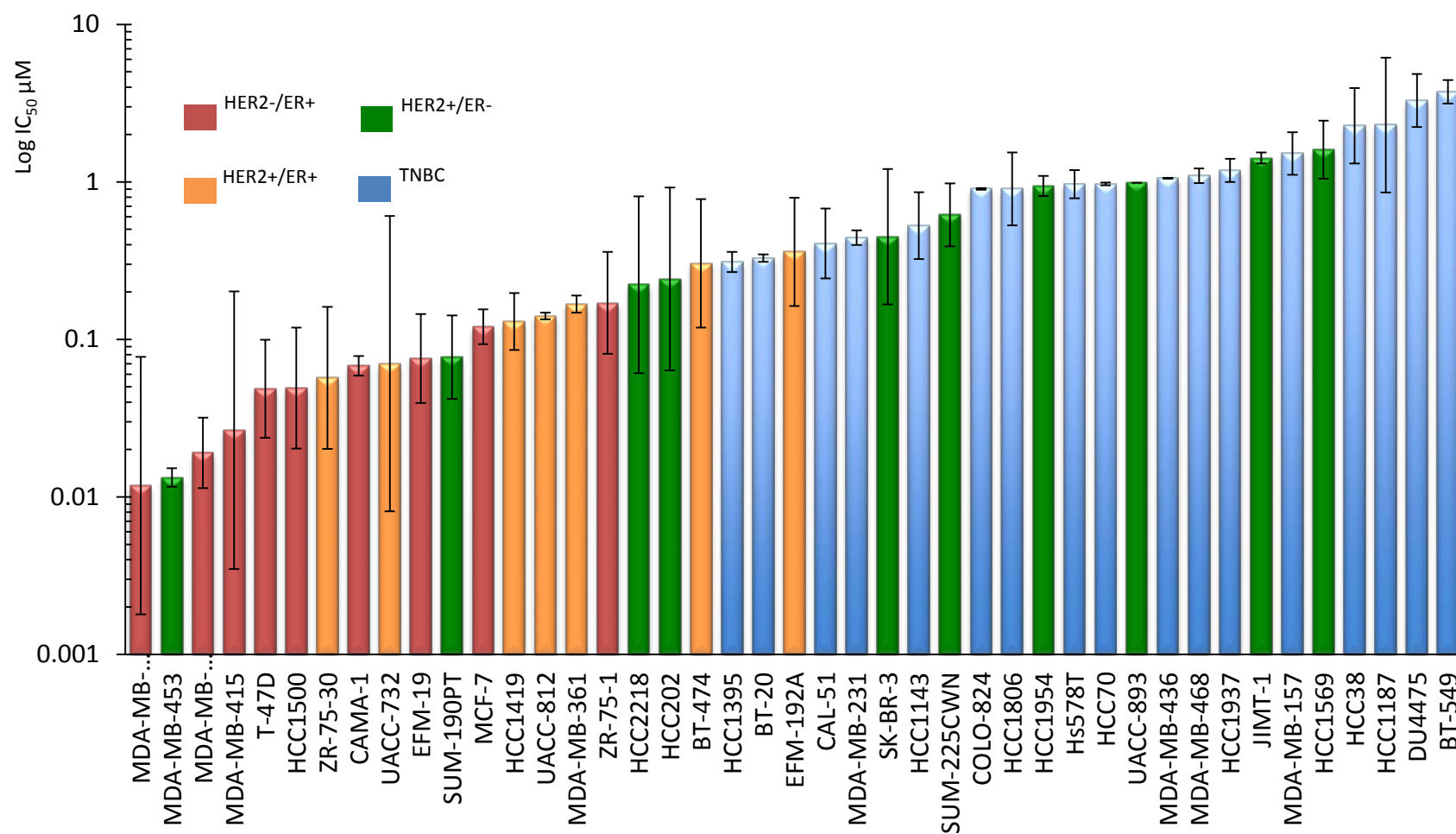
- Phase 3 study of ribociclib+letrozole vs. placebo + letrozole in first-line treatment of recurrent/metastatic breast cancer*
- Duration of PFS significantly greater in ribociclib group (HR, 0.56; 95% CI 0.43-0.72; $P=3.29 \times 10^{-6}$)
- 12 month PFS rate 72.8% in ribociclib group vs 60.9% placebo
- Patients with measurable disease at baseline: ORR 52.7% in ribociclib group vs. 37.1% in placebo group ($P<0.001$)
- Common grade 3/4 AEs (ribo group vs placebo group):
 - Neutropenia (59.3% vs. 0.9%)
 - Leukopenia (21.0% vs. 0.6%)



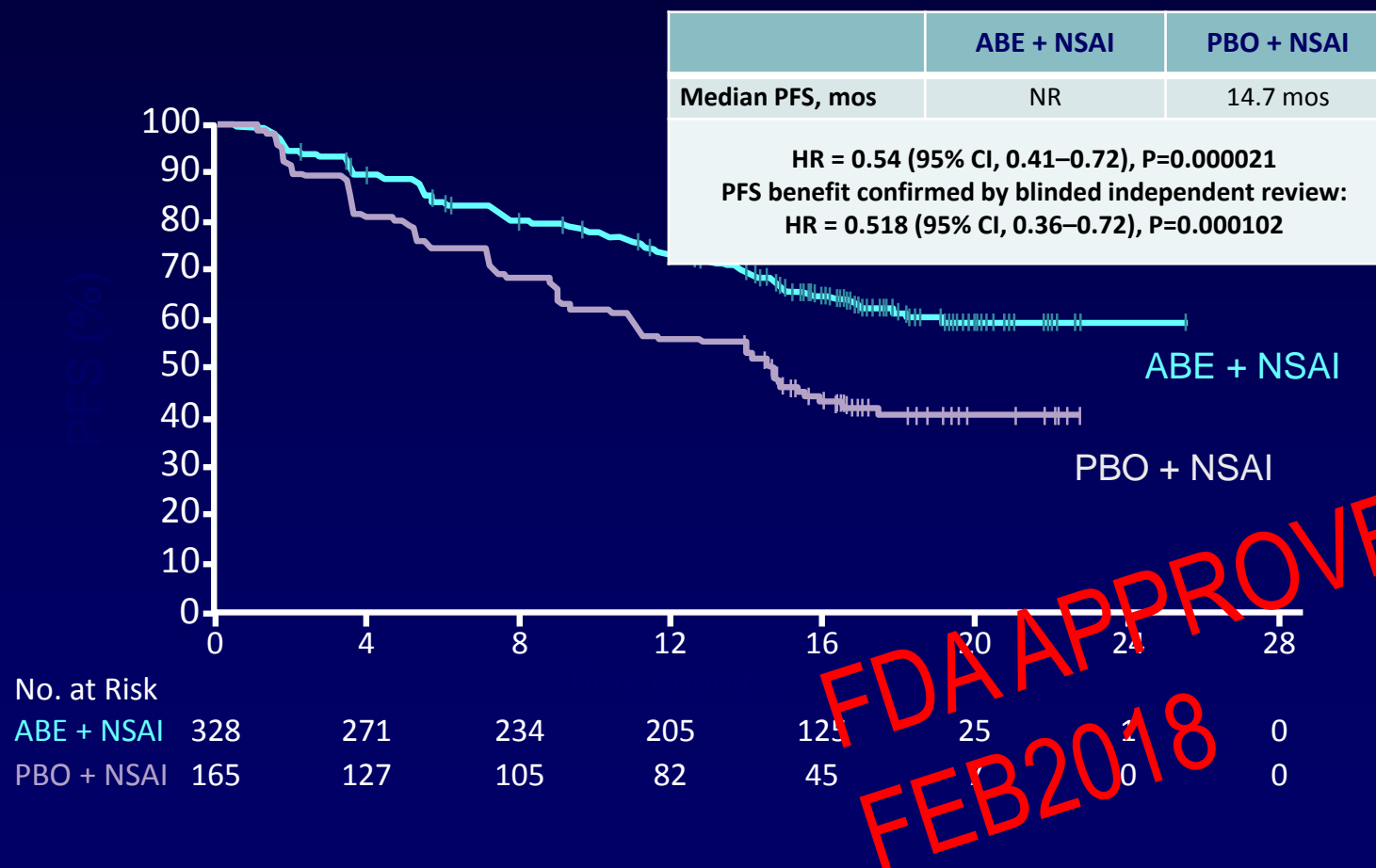
FDA APPROVED
13 MAR 2017

Preclinical Activity of Abemaciclib Alone or in Combination with Antimitotic and Targeted Therapies in Breast Cancer

Neil O'Brien¹, Dylan Conklin¹, Richard Beckmann², Tong Luo¹, Kevin Chau¹, Josh Thomas¹, Ann Mc Nulty², Christophe Marchal², Ondrej Kalous¹, Erika von Euw¹, Sara Hurvitz¹, Colleen Mockbee², and Dennis J. Slamon¹



MONARCH 3: Abemaciclib 1st Line Primary Endpoint (PFS) Met at Interim Analysis



Summary: CDKi Phase III Trials: 1st Line

	Palbociclib ¹	Ribociclib ^{2,3}	Ribociclib ⁴	Abemaciclib ⁵
	PALOMA-2	MONALEESA-2	MONALEESA-7	MONARCH-3
Partner	Letrozole	Letrozole	NSAI or Tam Plus goserelin	Letrozole or anastrozole
Eligibility	No prior met ET	No prior met ET No adj AI <12 mos	No prior met ET 1 line chemo ok (only 14%)	No prior adv ET No adj AI <12 mos
Population	N = 666	N = 668	N=672	N = 493
De novo stage IV, %	31.1	34	40	39.8
Relapse ≤12 mos, %	22	1.2	7	0
Bone only, %	23	25	24	22
PFS	27.6 vs. 14.5	25.3 vs. 16.0	23.8 vs. 13.0	NR vs. 14.7
ORR (%)	55.3 vs 34.7	47 vs 34	51 vs. 36	59 vs 44
CBR	84.9 vs 70.3	83 vs 77	80 vs 67	79 vs 69

1. Finn RS et al. *N Engl J Med.* 2016;375:1925-1936. 2. Hortobagyi GN et al. *N Engl J Med.* 2016;375:1738-1748. 3. O'Shaughnessy J et al. *Breast Cancer Res Treat.* 2017;Nov 21: Epub ahead of print. 4. Di Leo A et al. ESMO 2017: abstract 236O_PR.

Further Exploration of CDK4/6i

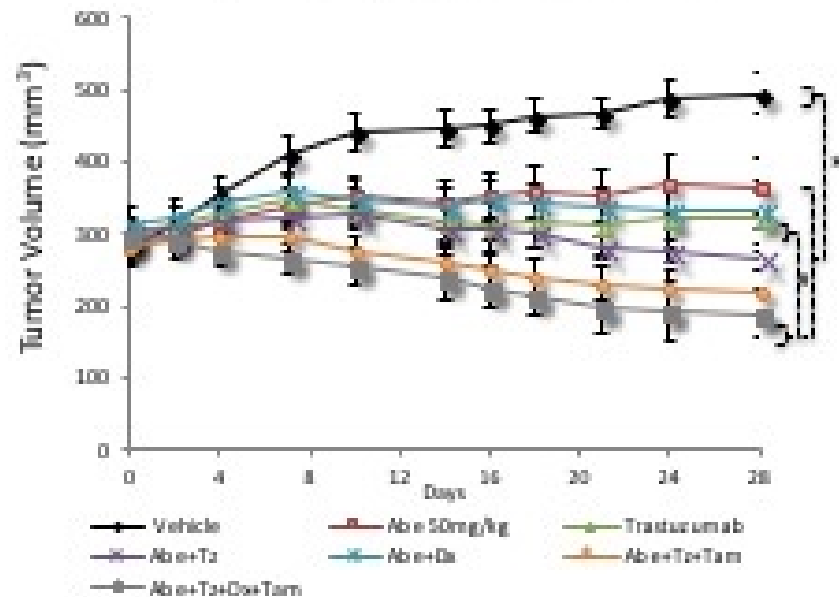
- **Palbociclib and abemaciclib both received FDA approval in the second/third line setting for ER+ breast cancer in combination with fulvestrant**
- **Abemaciclib received FDA approval as single agent (200 mg bid) 9/2017 in pretreated disease**
- **Ongoing studies evaluating CDK4/6 inhibitors in the curative (early stage, adjuvant) setting**
- **What about other types of breast cancer**
 - **HER2+...**
 - **Triple negative...**

Evaluation of Abemaciclib in other Settings

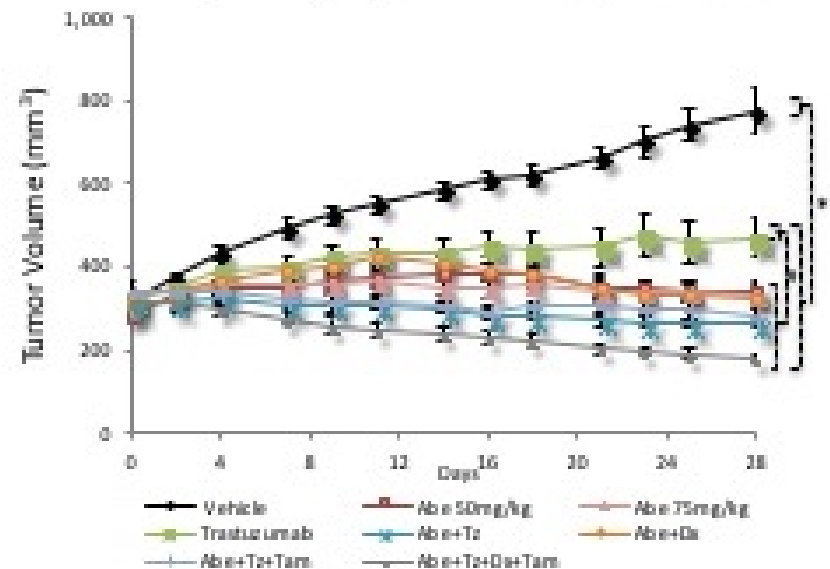
**Preclinical data from the UCLA
Translational Oncology
Research Laboratory (TORL)**

Activity of Abemaciclib + HER2 and HR targeted therapies, and SOC Chemotherapy

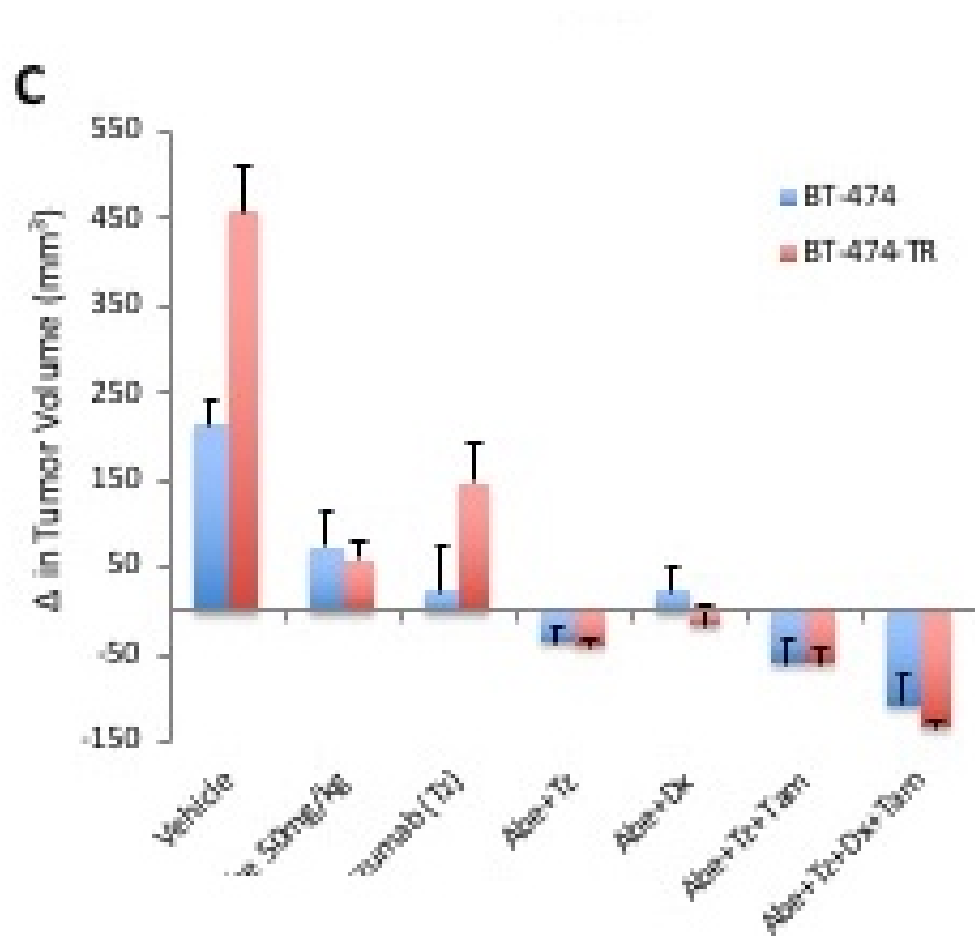
A BT-474, HER2+/ER+, Trastuzumab Sensitive



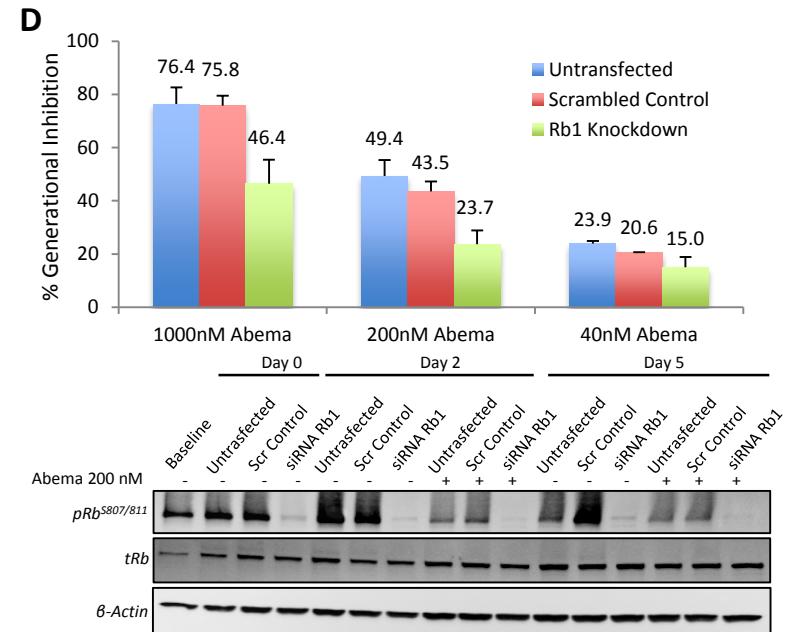
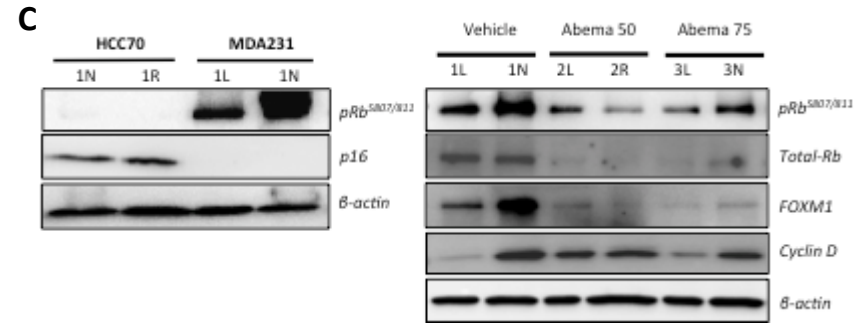
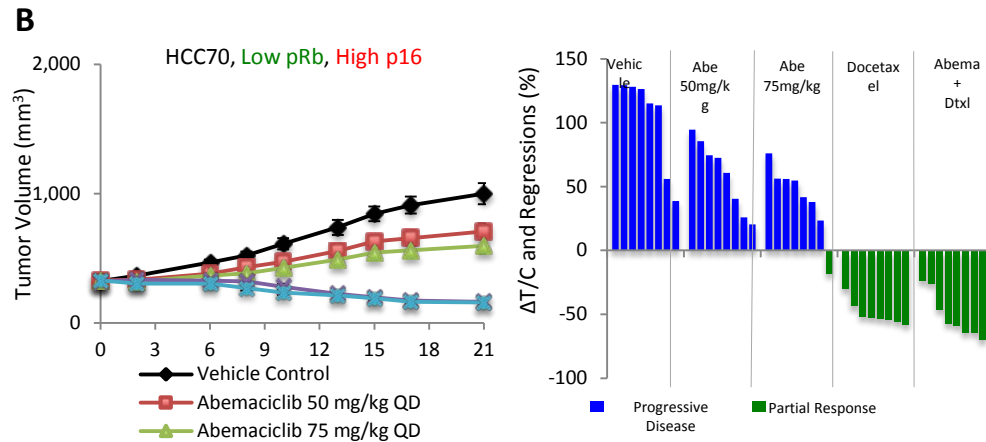
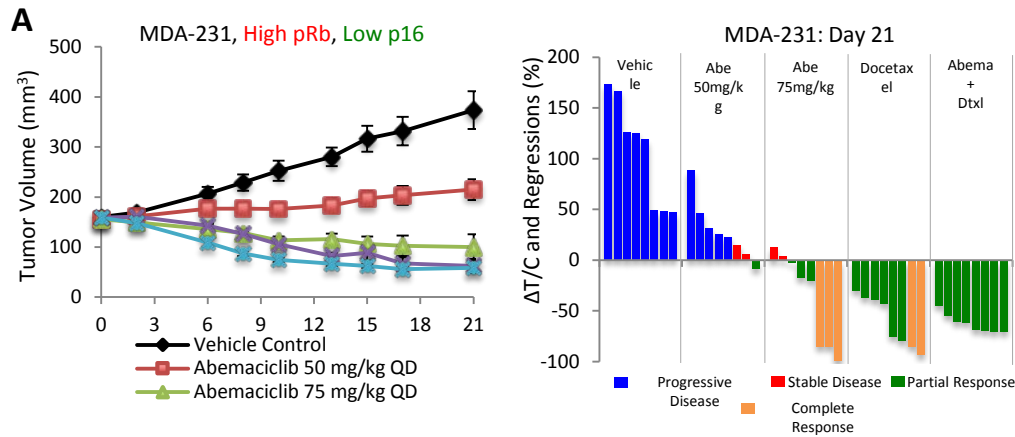
B BT-474-TR, HER2+/ER+, Trastuzumab Acquired Resistant



Activity of Abemaciclib + HER2 and HR targeted therapies, and SOC Chemotherapy



Abemaciclib in Triple Negative Breast Cancer



Evaluating novel therapies using neoadjuvant study design

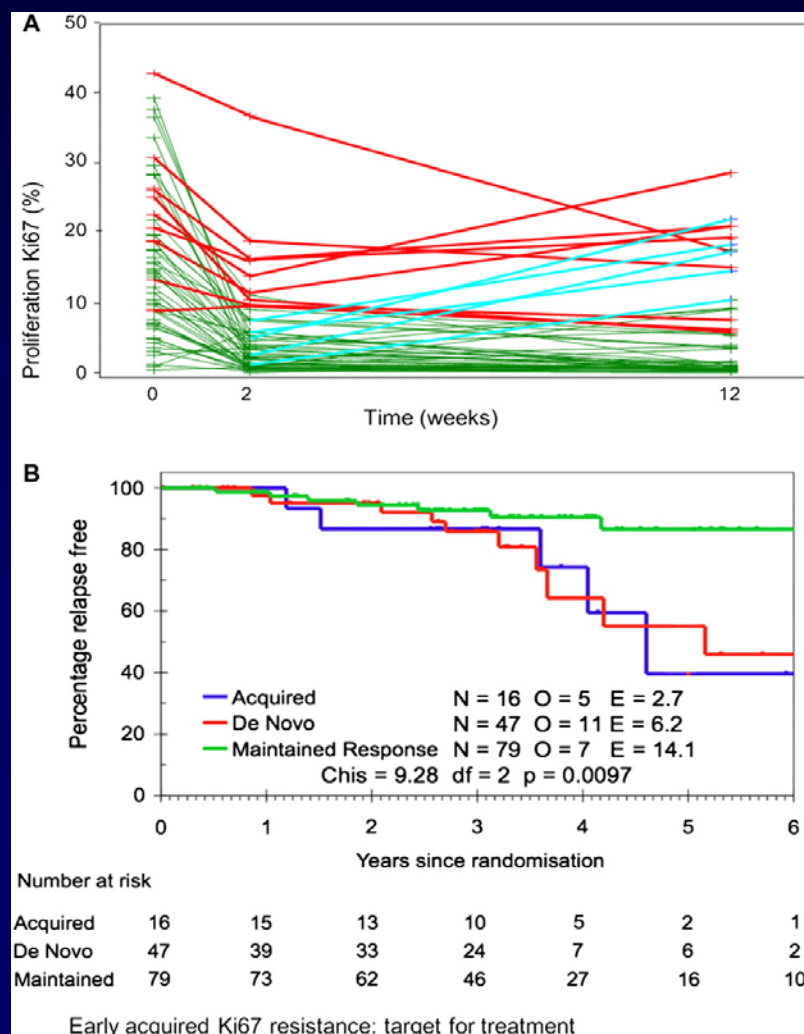
Neoadjuvant Tx in HR+ BC

- Challenging to correlate pCR with prognosis in ER+ breast cancer due to low rate of pCR and effectiveness of adjuvant endocrine therapy
- Is there a better surrogate marker of long term outcome in ER+ breast cancer in the neoadjuvant setting?

Rationale for use of Ki-67 change

- **IMPACT Trial: preoperative tamoxifen, anastrozole or tamoxifen/anastrozole**
- **N=330**
- **Biomarkers at baseline, after 2 weeks and 12 weeks**
- **Decrease in proliferation (Ki67) occurred in 93% anastrozole; 85% tamoxifen; 84% combination**
- **Ki67 response correlated with ER level and PR expression**
- **Confirm value of Ki67 as molecular marker**

A) Ki67 changes in individual patients on anastrozole and B) Recurrence-free survival of patients receiving anastrozole, tamoxifen, or the combination in IMPACT according to their being defined as showing de novo Ki67 resistance (<50% reduction in Ki67 at 2 weeks; red lines), persistent Ki67 response (>50% reduction in Ki67 at 2 weeks followed ≤50% increase from 2 weeks to 12 weeks; green lines), and acquired Ki67 resistance (>50% reduction in Ki67 at 2 weeks followed >50% increase from 2 weeks to 12 weeks; blue lines).



Neoadjuvant Abemaciclib

NeoMONARCH

Phase 2 neoMONARCH Study Design

Rationale:

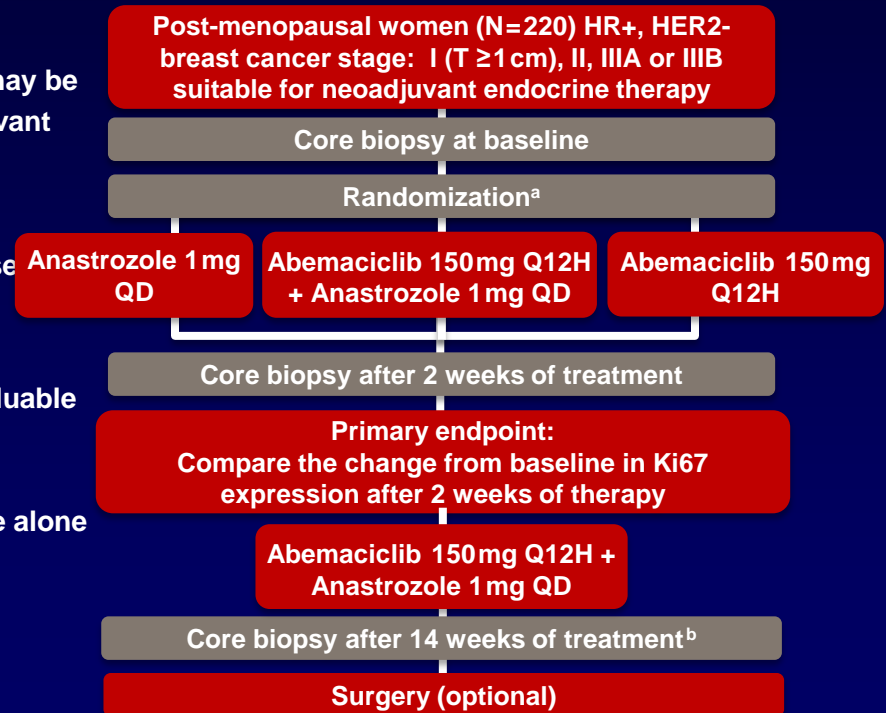
- ◆ Change in Ki67 at 2 weeks in neoadjuvant studies may be predictive of improved disease-free survival in adjuvant studies.^{1,2}

Secondary and exploratory objectives:

- ◆ Safety, clinical, radiologic and pathological response
- ◆ cell cycle associated gene expression.

Statistical design:

- ◆ 220 randomized patients required to achieve 50 evaluable patients in each arm
- ◆ 80% power at one-sided alpha of 0.1, assuming:
 - Assumed mean reduction of 82% for anastrozole alone and 91% for combination
- ◆ 2 mg loperamide was administered prophylactically with each abemaciclib dose for the first 28 days then at discretion of investigator.



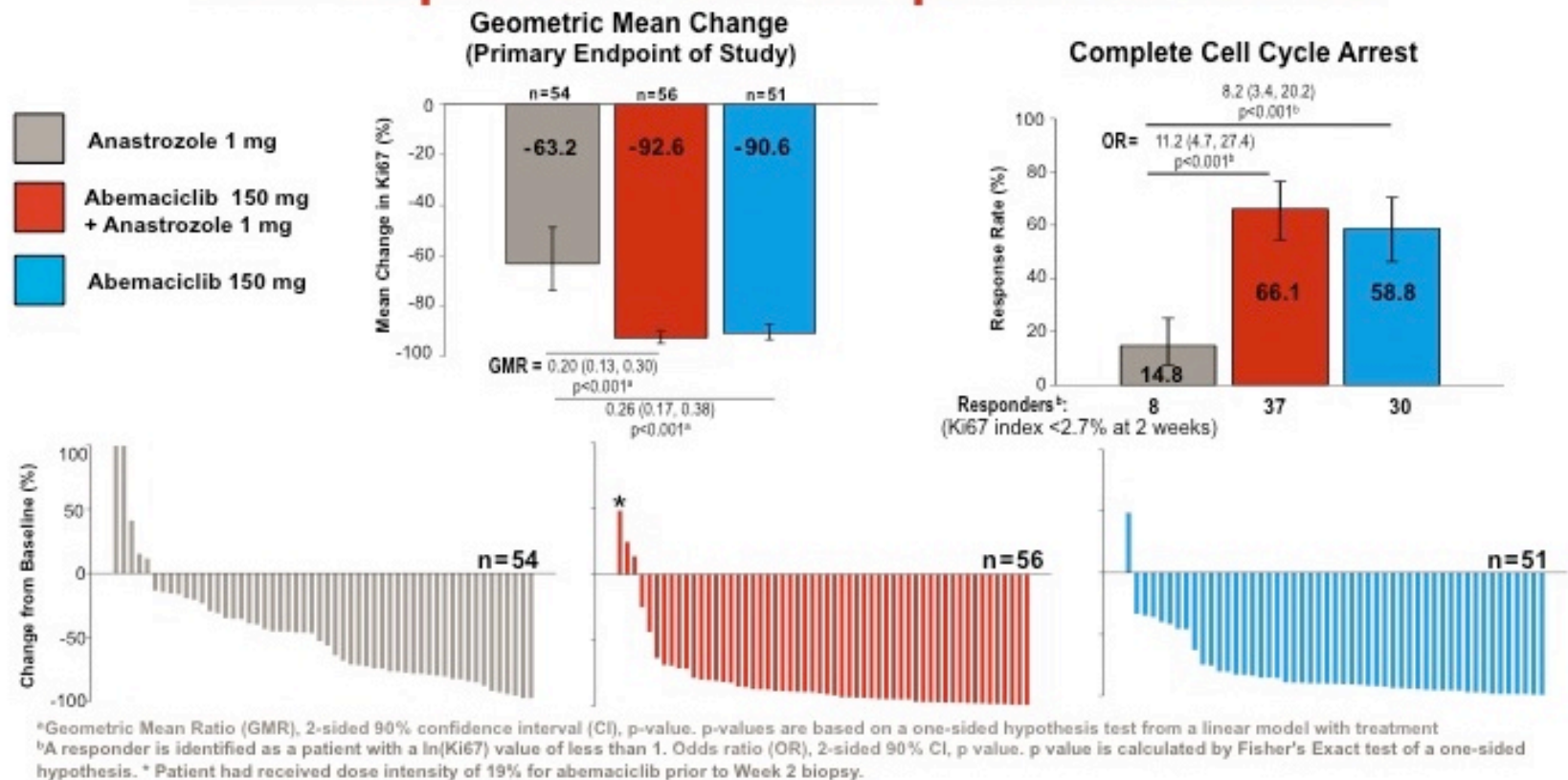
^aStratified for PR status, tumor size

^bParticipants who experience benefit following 14 weeks may remain on neoadjuvant therapy for up to 8 additional weeks

1. Dowsett M et al. *Clin Cancer Res* 2005; 11:951s-958s.
2. Dowsett M et al. *J Natl Cancer Inst*. 2011a;103(22):1656-1664.

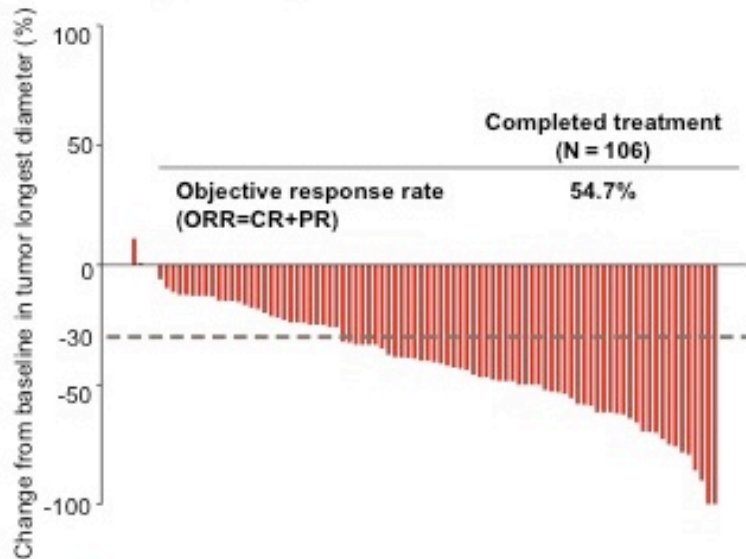
***At time of reporting, 223 pts treated, 161 evaluable for Ki67 at day 14**

Ki67 Response at Week 2

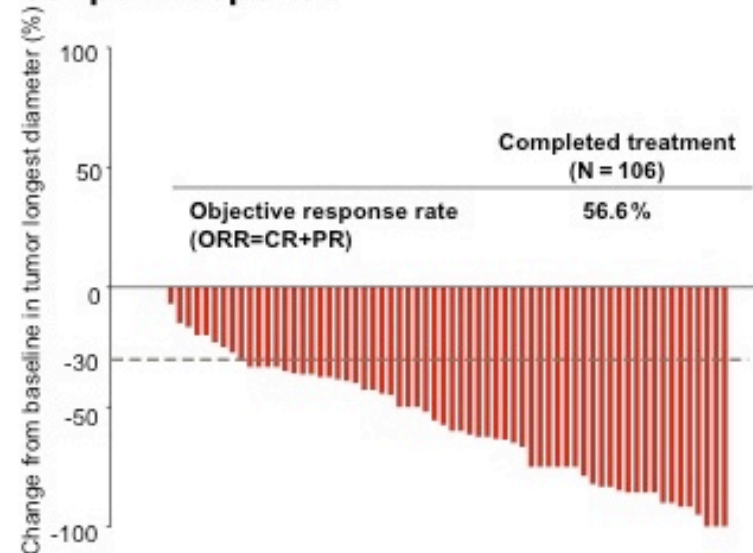


neoMONARCH RECIST Response Data Over Time

Radiologic Response

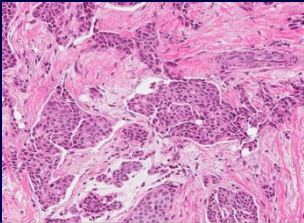
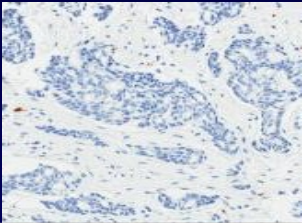
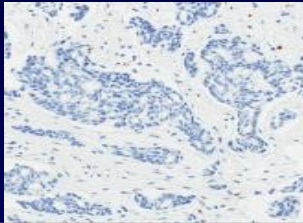
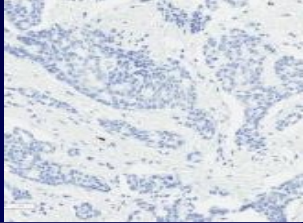
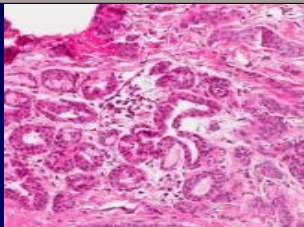
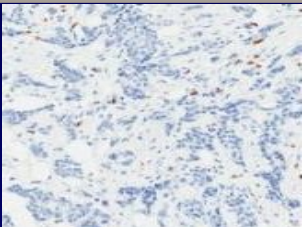
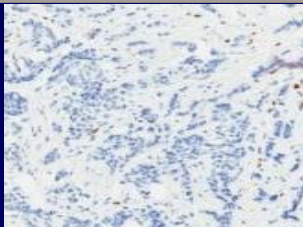
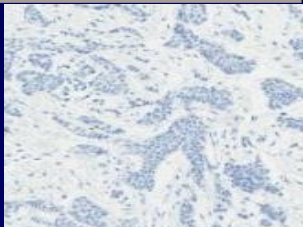
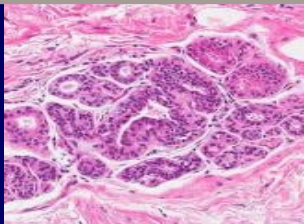
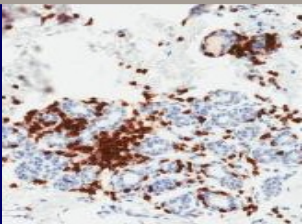
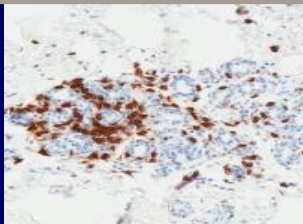
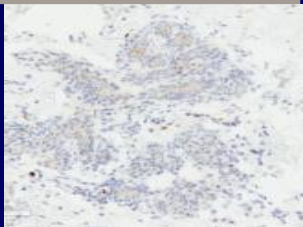


Caliper Response



- ♦ At time of analysis:
 - Complete pathologic response in three (3.2%) of 95 patients that underwent surgery.
 - One patient discontinued therapy for progressive disease (20.7% change from baseline in tumor size at week 12).

Tumor Differentiation & Immune Infiltrates Over Time

	H&E	Total T cells (CD3)	Suppressor/ Cytotoxic T cells (CD8)	T Regulatory cells (FOXP3)
Baseline Moderately Differentiated Ki67: 20%				
C1D15 (Abemaciclib monotherapy) Well Differentiated Ki67: 3.4%				
C5D28 (Abemaciclib & Anastrozole) Well Differentiated Ki67: 0.2%				

Targeting pathways of resistance to CDK4/6: the PI3K pathway

Ongoing

TRIO-B11: Phase Ib/II neoadjuvant trial of copanlisib/palbo/letrozole in ER+

Breast cancer
(ER pos)
Stg I-III
>1.0 cm

Letrozole plus
Palbociclib x 2 weeks then 14
weeks letrozole plus
copanlisib

Surgery (EOS)

Letrozole plus
Copanlisib

Surgery (EOS)

Letrozole plus
Palbociclib plus
Copanlisib

Surgery (EOS)

Research Based Core biopsy
baseline and post cycle 1

Additional biopsy taken at time
of surgery

Primary Endpoint: change in Ki67
Secondary Endpoints: Safety, pCR, Biomarker evaluation

Summary: Individualized Treatment Options Available

- Hormone Receptor positive breast cancer
 - Standard of care personalized therapy:
 - Early disease
 - Tamoxifen and aromatase inhibitors
 - Sometimes chemotherapy used if higher risk
 - Investigational: CDK4/6i, mTOR inhibitors, metformin
 - Stage IV
 - CDK4/6i + AI or fulvestrant
 - Everolimus + exemestane
 - Fulvestrant single agent
 - Under evaluation:
 - » Histone deacetylase inhibitors



Summary: Individualized Treatment Options Available

- HER2-driven breast cancer
 - Early disease
 - Trastuzumab (plus pertuzumab in neoadj) plus chemotherapy
 - Under investigation: T-DM1, pertuzumab full year
 - Stage IV
 - Trastuzumab/taxane/pertuzumab (new standard 2012)
 - T-DM1 (new standard 2nd line 2013)
 - Lapatinib/capecitabine
 - Lapatinib/trastuzumab
 - Trastuzumab or lapatinib + other chemotherapy or endocrine tx
 - Being evaluated: ONT-380, DS-8201, everolimus, neratinib, CDK4/6i...

