

Breast Targeted Therapy

HER2, CDK 4/6, PIK3CA

John T. Cole MD, FACP

Ochsner Medical Center New Orleans

Disclosures

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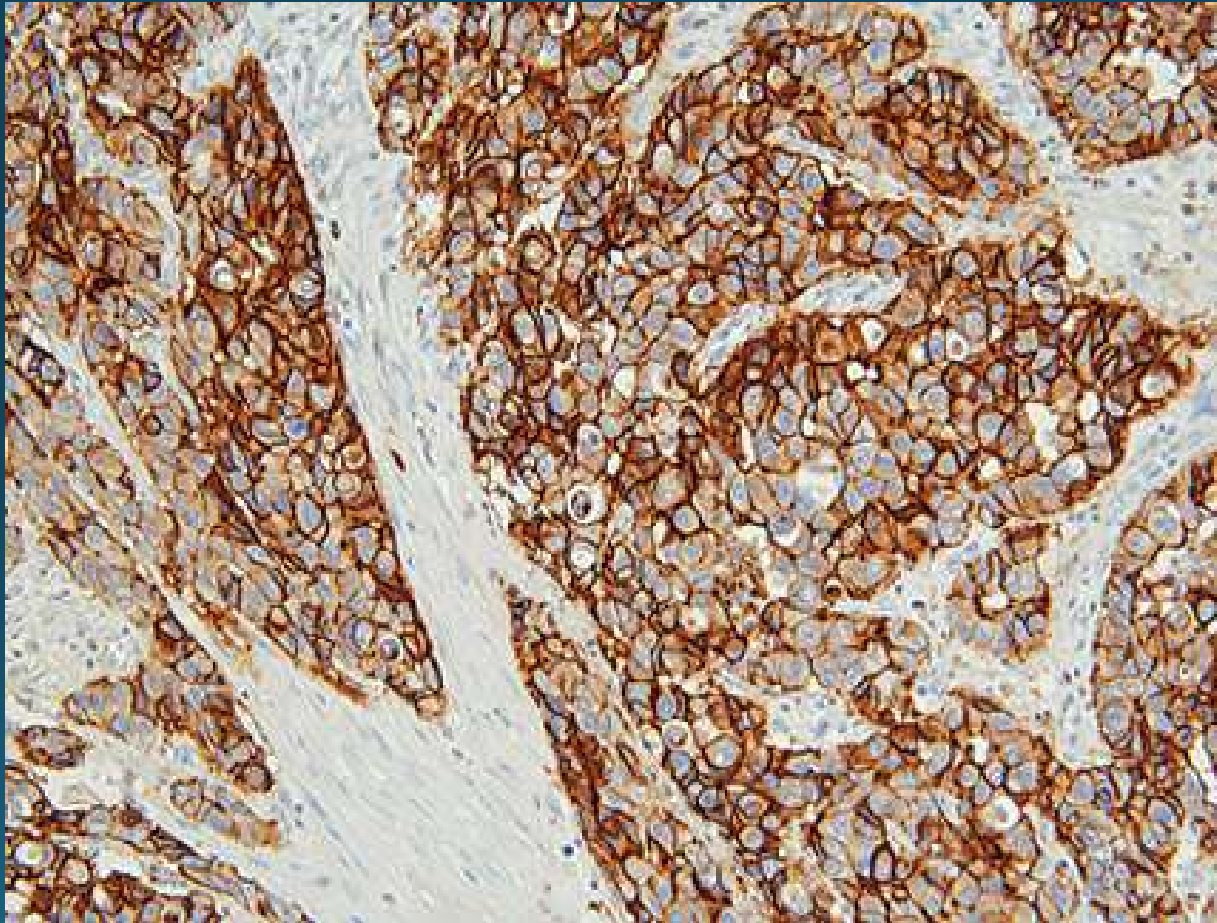
Targeted Therapies

- HER2 Therapies – multiple settings
- CDK 4/6 inhibitors
- PIK3CA inhibitors

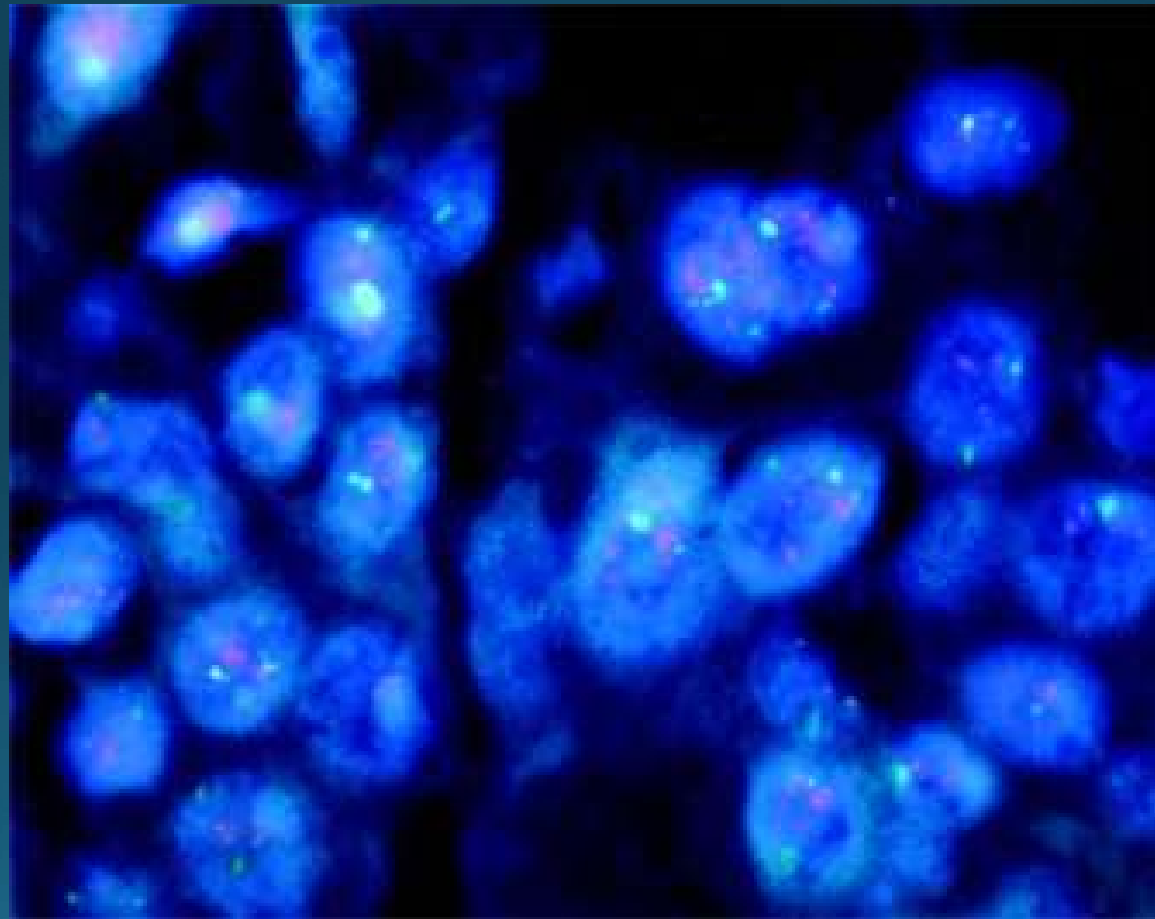
Targeted Therapy:HER 2 Directed Therapies

- Adjuvant
- Neo-adjuvant
- Post Neo-Adjuvant
- Advanced

HER 2 - Immunohistochemistry



HER 2 - FISH



Targeted Therapy :HER 2 Directed Therapies

- Monoclonal Antibodies
- Small Molecule inhibitors -TKIs
- Anti-body drug conjugates

Targeted Therapy :HER 2 Directed Therapies



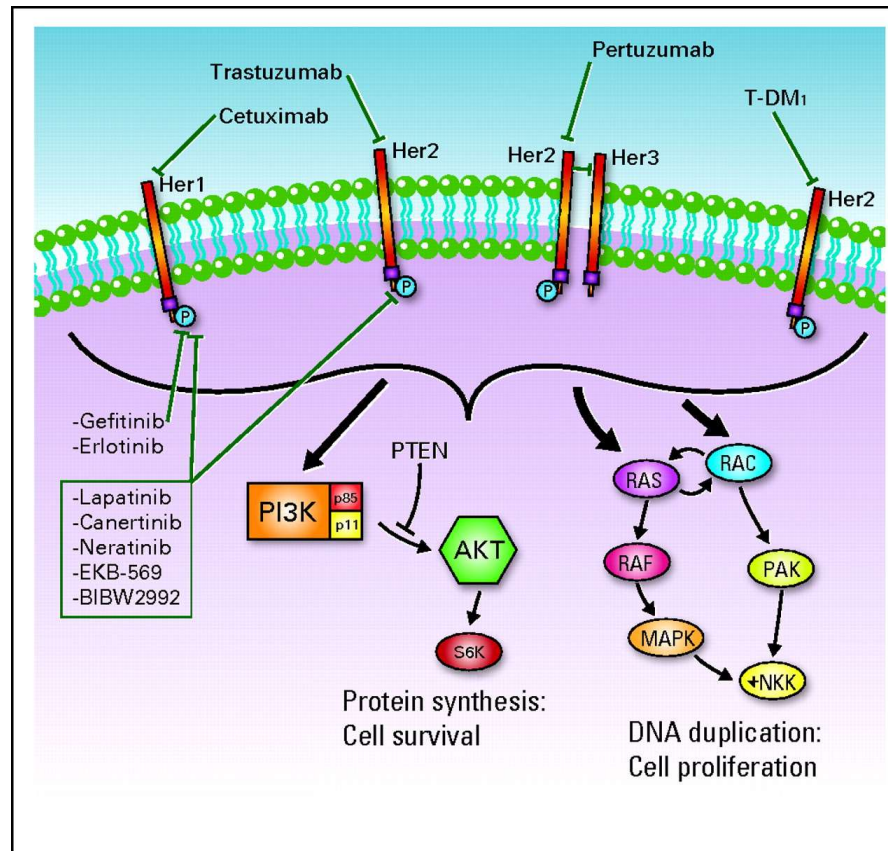
Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene

DJ Slamon, GM Clark, SG Wong, WJ Levin, A Ullrich, WL McGuire

+ See all authors and affiliations

Science 09 Jan 1987:
Vol. 235, Issue 4785, pp. 177-182
DOI: 10.1126/science.3798106

Epidermal growth factor receptor (EGFR) family.



Alvarez R H et al. JCO 2010;28:3366-3379

Targeted Therapy HER2 : Trastuzumab

Herceptin

- A humanized mouse antibody to HER-2 protein
- Modest activity as a single agent
- Greatly enhances the effectiveness of chemotherapy

HER 2 Directed Therapies - Adjuvant

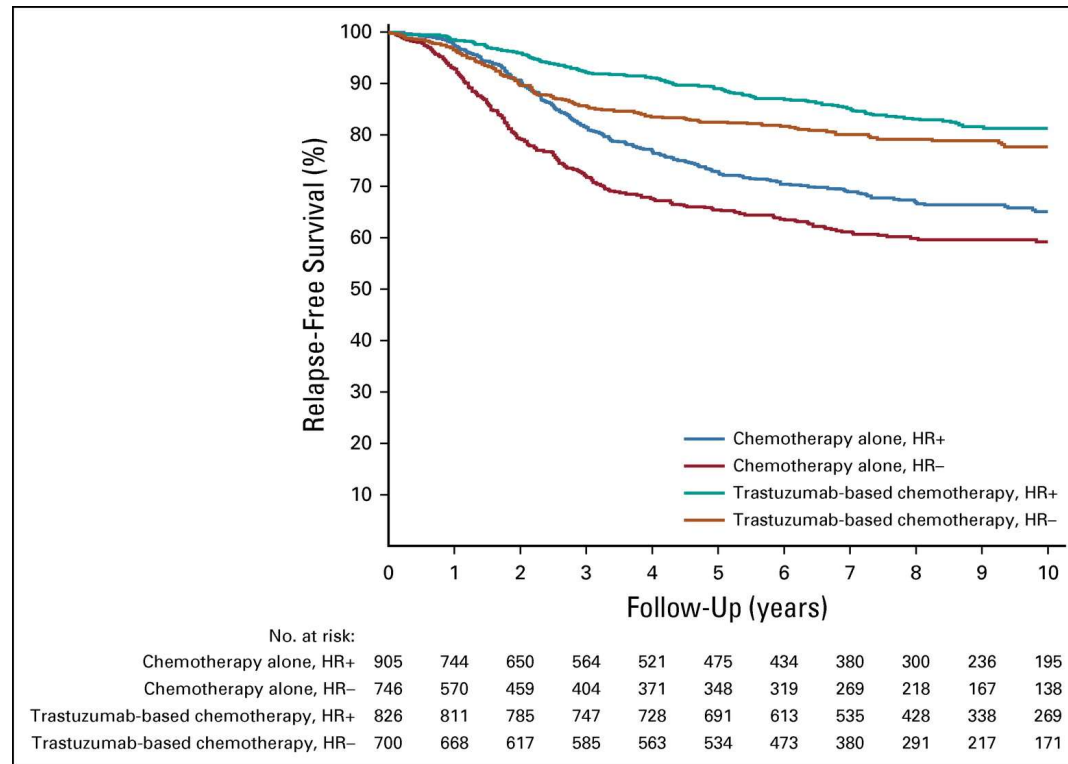
- NSABP B-31/NCCTG 9831 – AC + T vs AC + TH
- HERA – “standard chemotherapy” then control or Trastuzumab X 1 year or 2 years
- BCIRG 06 – AC + T vs AC +TH vs TCH X 6

HER 2 Directed Therapies: Adjuvant Trastuzumab

STUDY	DFS +Trastuzumab	DFS control	OS +Trastuzumab	OS control
NSABP/ NCCTG @4y N=3451	85%	67%	91.4%	86.6%
BCIRG 06 @5y N = 3174	84% ACTH 81% TCHP	75%	92%ACTH 91%TCHP	87%
HERA @2y N = 3387	88%	77%		

HER 2 Directed Therapies - Adjuvant

Long Term Results
NSABP B-31 /NCCTG
9831 – 10 y DFS



RFS @ 10 Y

ER+
81% + T
65% control

ER neg
78% + T
59% control



Churmsi et al J Clin Oncol 2019;37,3425-3435

HER 2 Directed Therapies - Adjuvant

APHINITY Trial

- Chemotherapy with trastuzumab ± pertuzumab
- N=4800 , 63% Node +, 36% HR negative

	IDFS (3y)	DDFS	DFS Node-	DFS Node+	DFS @74M	OS @74M	OS Node neg
T+P	94.1%	95.3%	96.4%	91.8%	90.6%	94%	95%
T + placebo	93.2 %	94.2%	96.8%	87.9%	87.8%	93%	95%

Cardiac events 0.7 vs 0.3%, diarrhea 9.8 vs 3.7%

HER 2 Directed Therapies - Adjuvant

Tolaney et al

- Weekly Paclitaxel and trastuzumab X 12 then trastuzumab to complete 1 Y
- N = 406, age – 55, 64% ER+
- 30% T1b, 41% T1c, 9% T2

	DFS -invasive	Distant DFS
3 year	98.7%	99.2%
7 year	97%	

Tolaney et al , N Engl J Med 2015;372, 134-41
Tolaney SABCS 2019

HER 2 Directed Therapies – Adjuvant

TBRC 033 - ATTEMPT Trial

- TDM-1 vs Paclitaxel + trastuzumab in Node negative HER2 +
- N=497 , median age 56, 43% T1b, 75% HR +
- TDM-1 X 17
- Paclitaxel + trastuzumab weekly X 12 then trastuzumab to complete 1 Y

- 3 year DFS 97.7% for TDM-1 vs 92.8% for paclitaxel/trastuzumab

Tolaney SABCS 2019

Targeted Therapy HER2 : Neoadjuvant

GeparQuattro Trial

- Anthracycline followed by taxane therapy – both with trastuzumab
- N= 445, median age – 50, 85% \geq T2, 53% N+
- pCR 37 %, 40% (only DCIS), 70% N0

HER 2 Directed Therapies – Neo-adjuvant

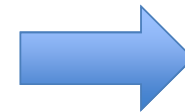
NEOSPHERE

Group A – Docetaxel + Trastuzumab X 4

Group B – Docetaxel + Trastuzumab + Pertuzumab X 4

Group C – Trastuzumab + Pertuzumab X 4

Group D – Docetaxel + Pertuzumab X 4



Surgery

FEC X 3 following surgery

HER 2 Directed Therapies – Neo-Adjuvant

NEOSPHERE

Results:

	pCR (%)	PFS – 5Y (%)	DFS – 5Y (%)
Group A (107) D+T	29	81	81
Group B (107) +P	45.8	86	84
Group C (107) T+P	24	73	80
Group D (96) D+P	16.8	73	75

Gianni Lancet Oncol 2012;13,25-32

Gianni Lancet Oncol 2016: 17, 791-800

HER 2 Directed Therapies – Neo-adjuvant

TRYPHENA Trial

Arm A – FEC + trastuzumab + pertuzumab X 3 then docetaxel + trastuzumab + pertuzumab X3

Arm B – FEC X 3 then Docetaxel + trastuzumab + pertuzumab X 3

Arm C – Docetaxel + carboplatin + trastuzumab + pertuzumab X 6

HER 2 Directed Therapies – Neo-adjuvant

TRYPHENA Results:

	pCR Breast %	pCR – breast/AX	DFS 3Y % *
Arm A (73)	61.1	50.7	87
Arm B (75)	57.3	45.3	88
Arm C (77)	66.2	51.9	90

Schneeweiss, Ann Oncol 2013;24, 2278-2284

Schneeweiss Eur J Cancer 2018;89, 27-35 *

HER 2 Directed Therapies – Neo-adjuvant

KRISTINE Trial

- Chemotherapy + trastuzumab and pertuzumab vs TDM-1 + pertuzumab
- 6 cycles for each arm
- FU -36 M
- Post op therapy – 12 cycles of trastuzumab (control) or 12 cycles TDM-1
- 50 TDM-1 patients got additional chemotherapy

	pCR	EFS
Standard chemo +TP(n=214)	56%	94.2
TDM-1 (n=204)	44%	85.3

Targeted Therapy : HER 2 - Adjuvant

- EXENET Trial : Neratinib – small molecule HER 2 TKI
- Neratinib (240 mg/d) or placebo for 1 year after completion of neo-adjuvant or adjuvant chemotherapy with trastuzumab.
- 2840 patients enrolled
- Median follow-up 5.2Y

- Results: 5 year invasive disease free survival – 90.2% for Neratinib vs 87.7% for placebo
- 40% grade 3 diarrhea with Neratinib

Martin et al Lancet Oncol 2017;18, 1688-1700

Targeted Therapy : HER 2 – Post Neo-Adjuvant

KATHERINE TRIAL

Trastuzumab emtansine (TDM1) or Trastuzumab after neoadjuvant therapy with residual disease in breast and / or axilla

FU- 41.4M

N=743 pts/group

TDM-1 -More neuropathy
and thrombocytopenia

	Invasive DFS	Distant recurrence
TDM1	88.3%	10.5%
Trastuzumab	77%	15.9%
	HR 0.5, p<0.001	HR 0.60

Targeted Therapy : HER 2 - Metastatic

Results of Studies of Trastuzumab as Monotherapy for Metastatic Breast Cancer

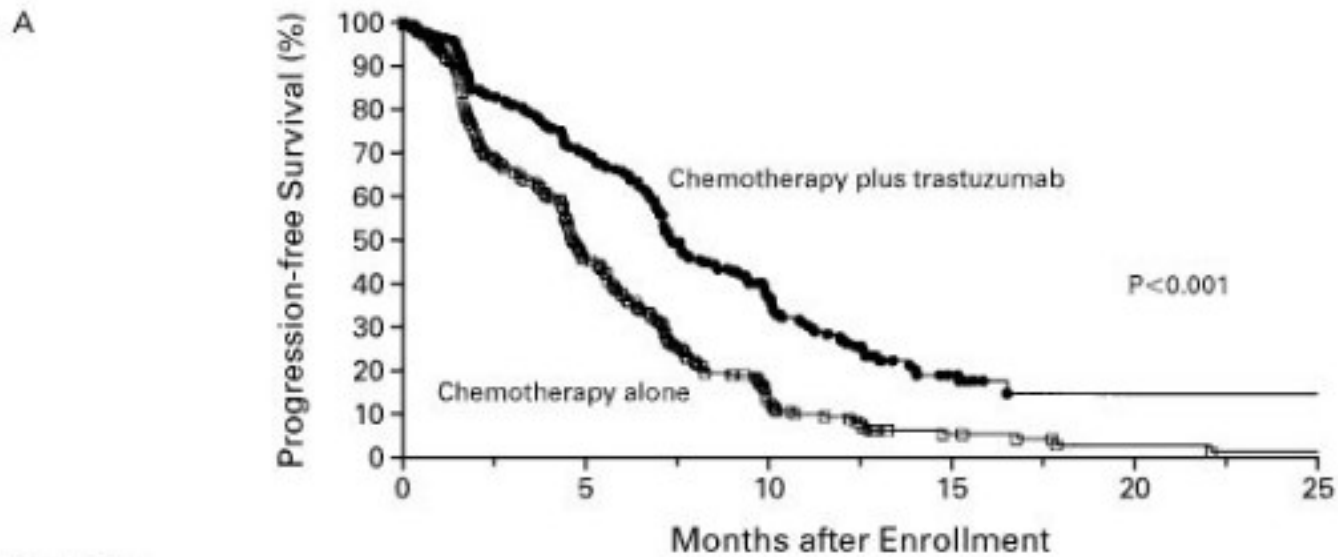
Table 1. Results of Studies of Trastuzumab as Monotherapy for Metastatic Breast Cancer.

Study	No. of Patients	Immunohistochemical Staining Grade (Assay)	Dose		No. of Previous Chemotherapy Regimens	Overall Response Rate	Median Treatment Duration (range)
			Loading	Maintenance			
						%	wk
Baselga et al. ⁴¹	46	2–3+ (4D5)	250 mg	100 mg weekly	0 to 5	11	20 (4–240)
Cobleigh et al. ⁴²	222	2–3+ (4D5 or CB11)	4 mg/kg	2 mg/kg weekly	1 or 2	15	12 (0–118)
Vogel et al. ⁴³	114	2–3+ (4D5 or CB11)	4 mg/kg or 8 mg/kg	2 mg/kg weekly or 4 mg/kg weekly	0	26	15 (13–21)

Hudis C. N Engl J Med 2007;357:39-51

HER 2 Directed Therapies - Metastatic

- Slamon et al - Chemotherapy with or without Trastuzumab
- OS 25.1 for C+T vs 20.3 M for chemo alone



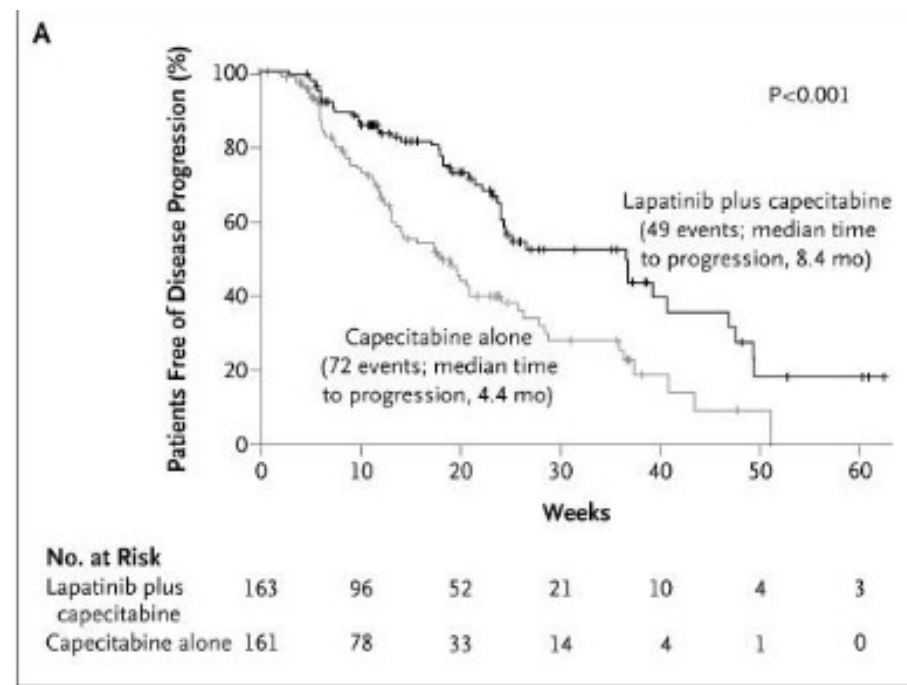
Targeted Therapy HER 2 – Metastatic

Table 2. Randomized Trials Comparing Chemotherapy Alone with Chemotherapy plus Trastuzumab for Metastatic Disease.

Trial and End Result	Chemotherapy	Chemotherapy plus Trastuzumab	P Value
Slamon et al. ⁴⁶			
No. of patients	234 (doxorubicin and cyclophosphamide or paclitaxel)	235 (doxorubicin and cyclophosphamide or paclitaxel)	
Time to disease progression (mo)	4.6	7.4	<0.001
Response rate (%)	32	50	<0.001
Median overall survival (mo)	20	25	0.046
Marty et al. ⁴⁷			
No. of patients	94 (docetaxel)	92 (docetaxel)	
Time to disease progression (mo)	6.1	10.7	0.001
Response rate (%)	34	61	0.001
Median overall survival (mo)	23	31	0.032

HER 2 Directed Therapies - Metastatic

Lapatinib + Capecitabine vs Capecitabine



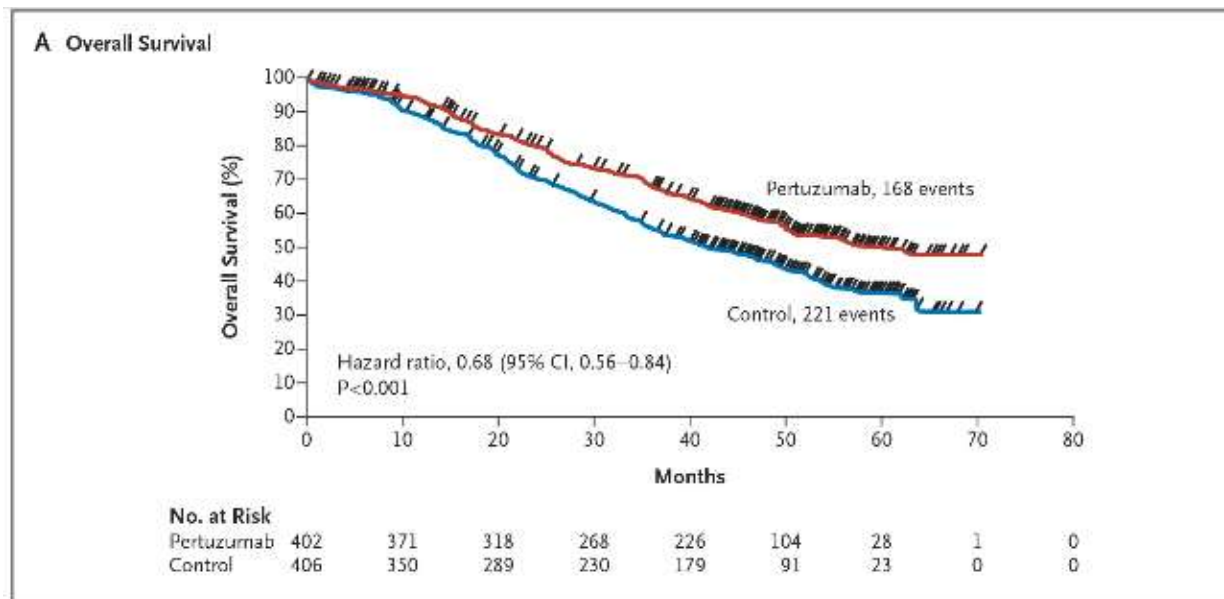
HER 2 Directed Therapies - Metastatic

CLEOPATRA Trial

- Randomization between Docetaxel + Trastuzumab and Docetaxel + Trastuzumab + Pertuzumab
- 6 cycles of chemo + antibody then antibody therapy alone
- Median age 54
- 48% ER +
- 53% no prior adjuvant or neo-adjuvant treatment

Baselga et al N Engl J Med 2012; 366:109-119

Targeted Therapy HER 2 – Metastatic - pertuzumab



CLEOPATRA Trial – N=808
Follow-up 49.5 M

OS – 56.5 M – T+P vs 40.8 M - T

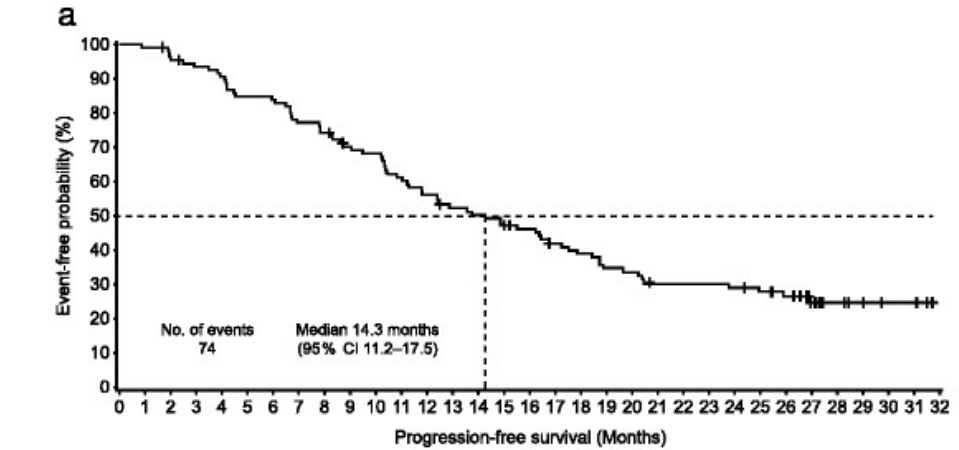
37% 8 Y survival for pertuzumab +
trastuzumab vs 23% for trastuzumab
(ASCO-2019)

HER 2 Directed Therapies - Metastatic

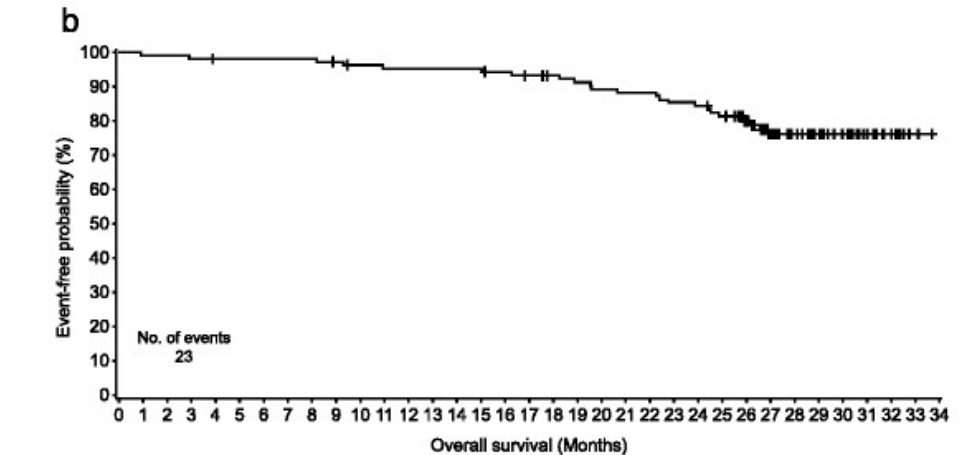
VELVET Study -First Line

- Trastuzumab + Pertuzumab Day 1 with Vinorelbine D1,8
- N = 102, median age 56
- 66% ER +
- 41% prior trastuzumab

- ORR – 74%



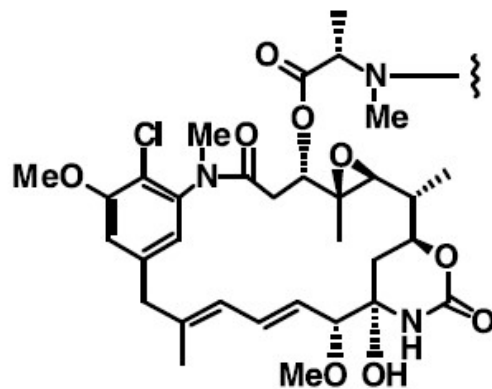
Number at risk 106 105 103 97 94 88 87 80 77 71 69 62 57 52 50 47 44 39 36 32 31 27 27 27 26 24 20 13 7 5 3 3 0



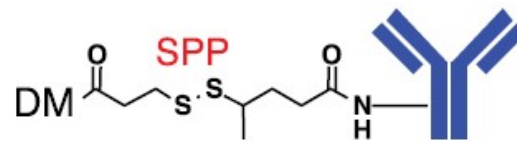
Number at risk 106 105 105 104 103 103 103 103 101 99 98 98 98 98 96 94 92 90 88 87 87 84 83 79 69 56 38 28 18 13 7 2 0

Targeted Therapy HER 2 – TDM-1

- TDM-1 = Trastuzumab emtansine



Drug Maytansinoid
(DM)



Tmab-SPP-DM1

Targeted Therapy HER 2 - TDM-1 - Metastatic

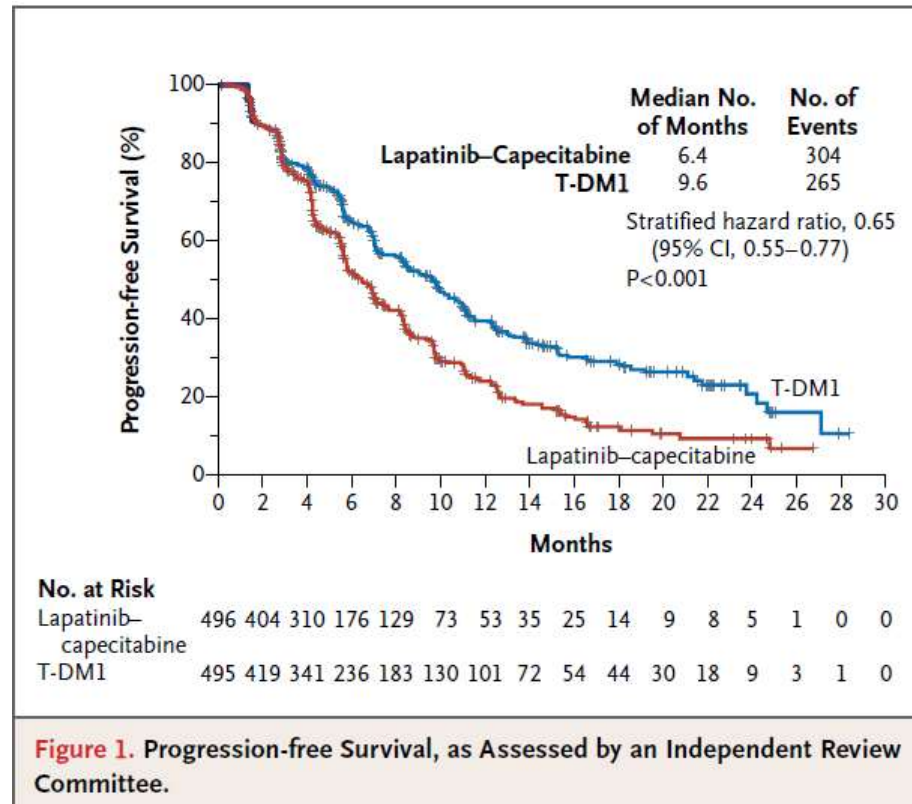
N = 991

Avg Age 53

55% ER +

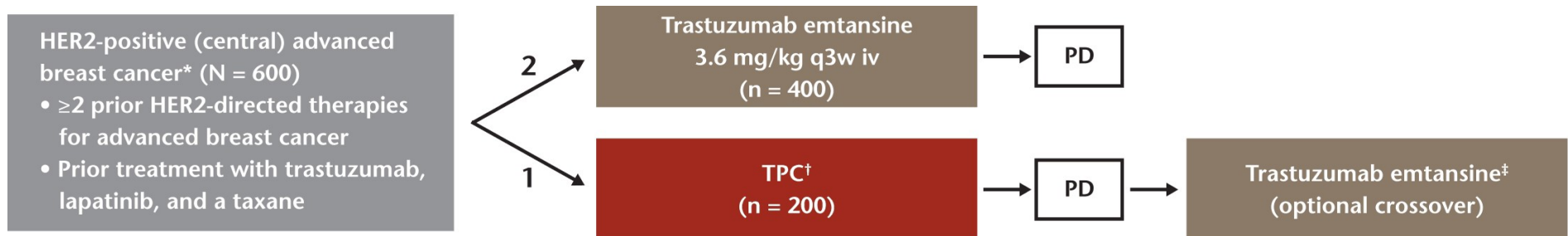
82% prior
Trastuzumab

PFS 9.6 vs 6.4 M



Verma et al N Engl J Med
2012;367, 1783-91 2012;

HER 2 Directed Therapies - TDM-1 Metastatic



- Stratification factors: world region, number of prior regimens for advanced breast cancer,[§] presence of visceral disease
- Coprimary end points: PFS by investigator and OS
- Key secondary end points: ORR by investigator and safety

HER2 = human epidermal growth factor receptor 2; iv = intravenous; MBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; q3w = every 3 weeks; TPC = treatment of physician's choice

*Advanced breast cancer includes MBC and unresectable locally advanced/recurrent breast cancer.

†TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.

‡First patient in: September 2011. The study was amended September 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive trastuzumab emtansine after documented PD.

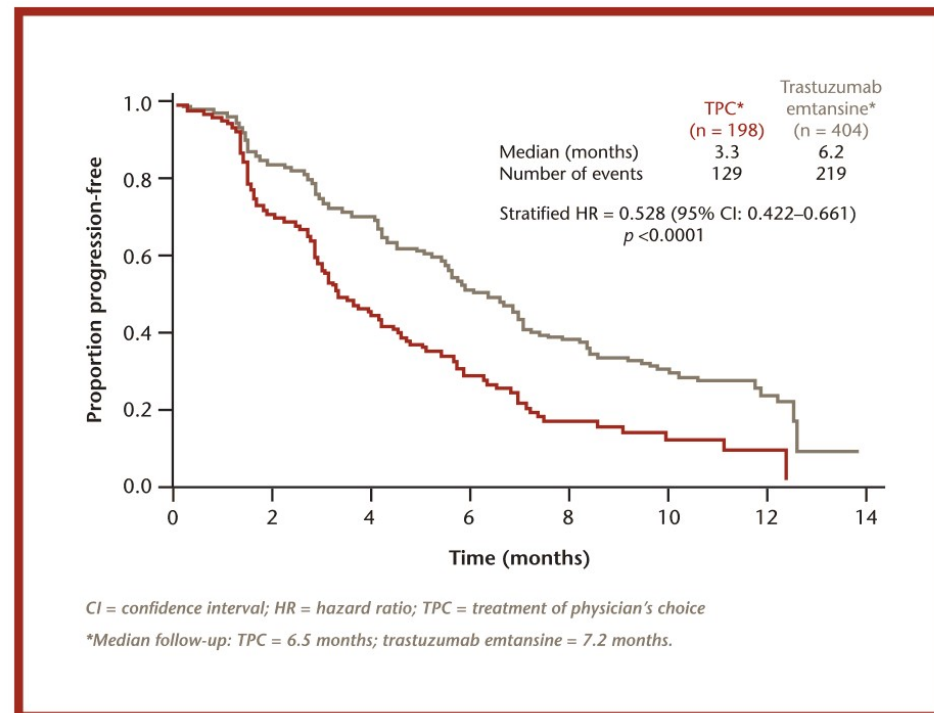
§Excluding single-agent hormonal therapy.

Targeted Therapy : HER 2 - TDM-1 Metastatic

Figure 1. Progression-free survival by investigator assessment

PFS 6.2 vs 3.3
months

OS – 22.7 vs
15.8 months



HER 2 Directed Therapies - Metastatic

- MARIANNE Study - TDM-1 \pm Pertuzumab vs Trastuzumab + Taxane
- N=1095, Median age 52, 55% ER+, 68% visceral disease
- 31% with prior HER 2 therapy

	PFS - Months
TDM-1	14.1
TDM-1 + P	15.2 (NS difference)
Trastuzumab + Taxane	13.7

Perez et al J Clin Oncol 2016;67, 141-148

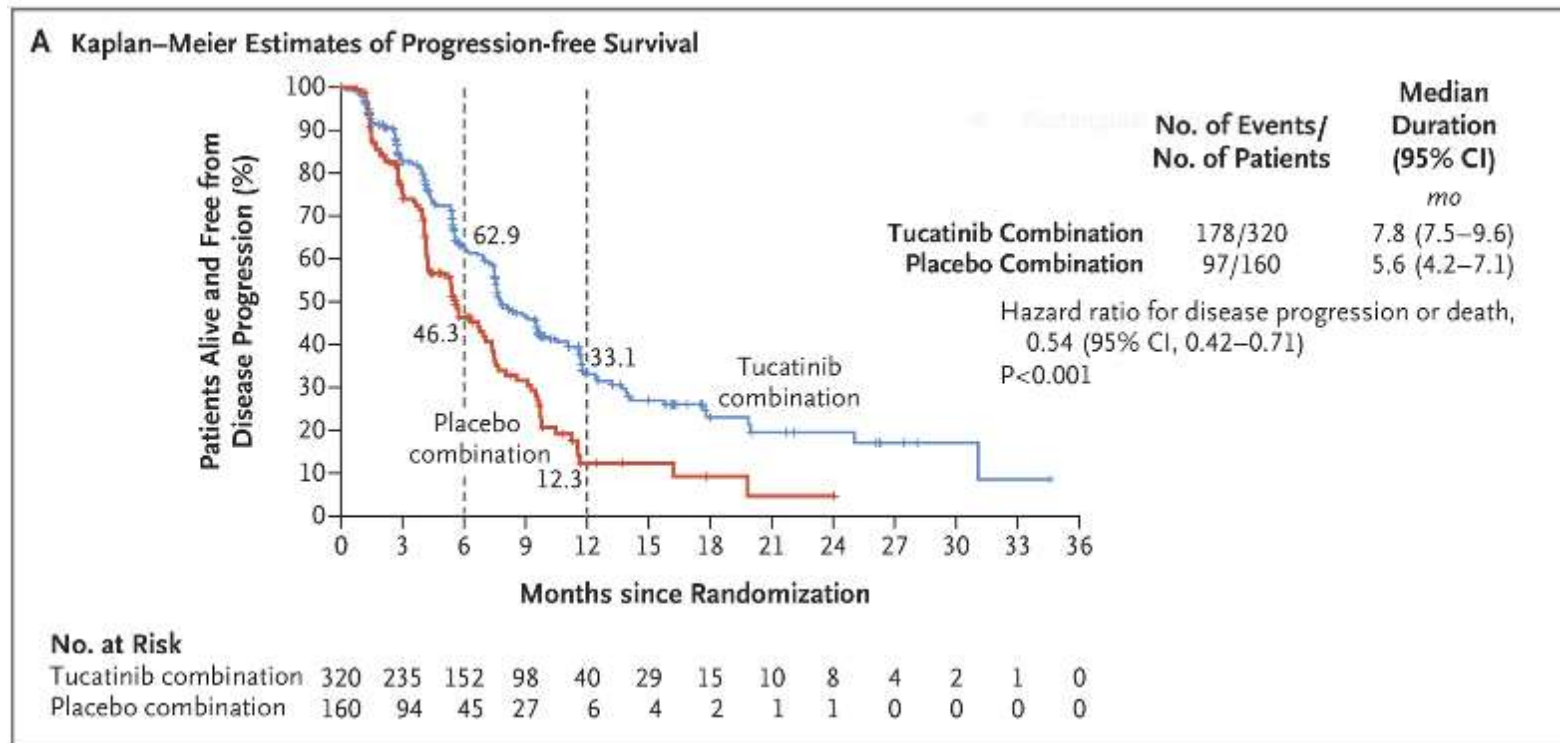
Targeted Therapy : HER 2 - Metastatic

Tucatinib - HERCLIMB Trial

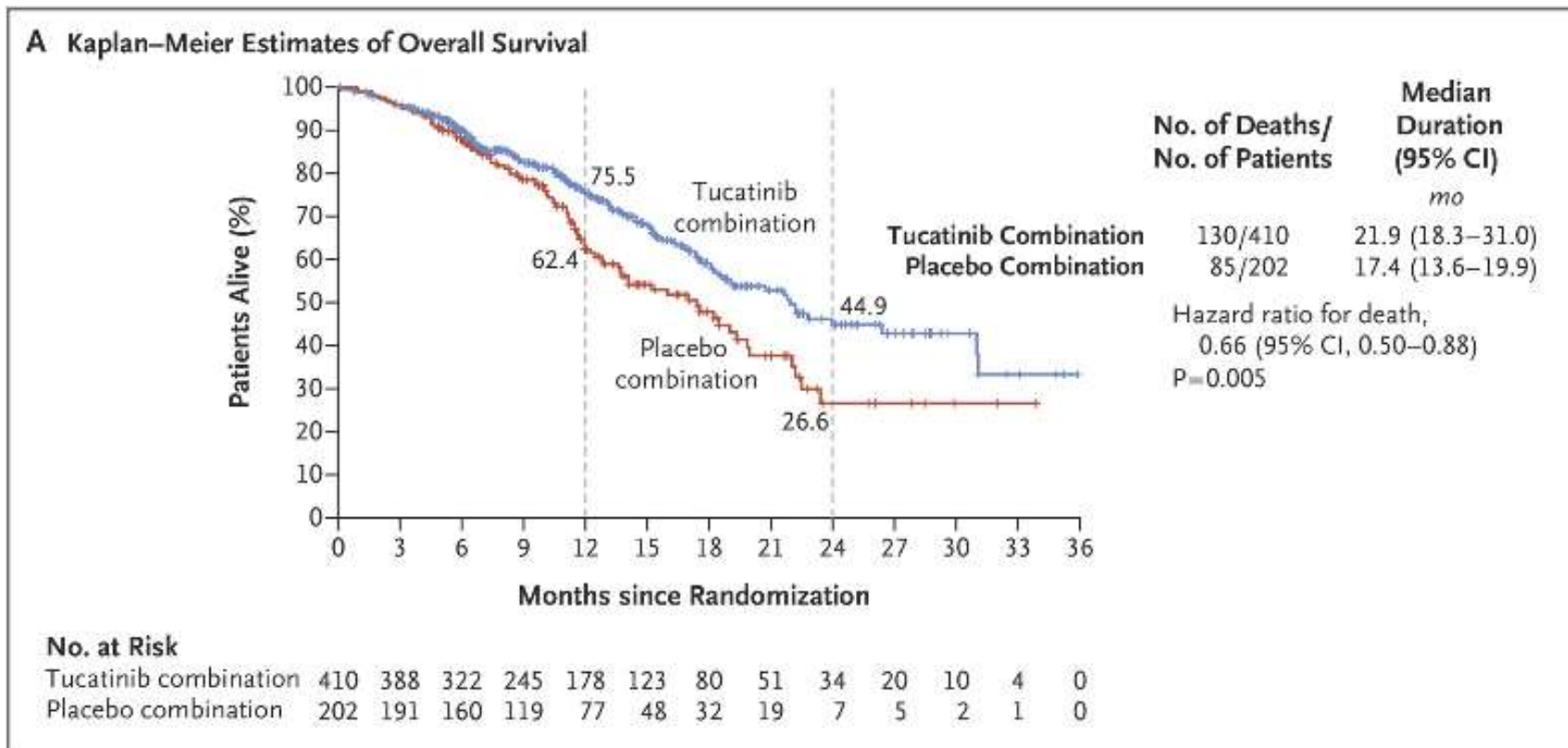
- Small molecule inhibitor, highly selective for HER2 with minimal EGFR inhibition
- patients with prior Trastuzumab + Pertuzumab and TDM-1 therapy, also included pts with untreated brain metastasis
- Randomized to Trastuzumab + Capecitabine \pm Tucatinib (1:2)
- N = 612, median age 54, 60% ER+
- 47% had brain metastasis

Murthy et al N Engl J Med Dec 11,2019

Targeted Therapy HER 2 - Tucatinib

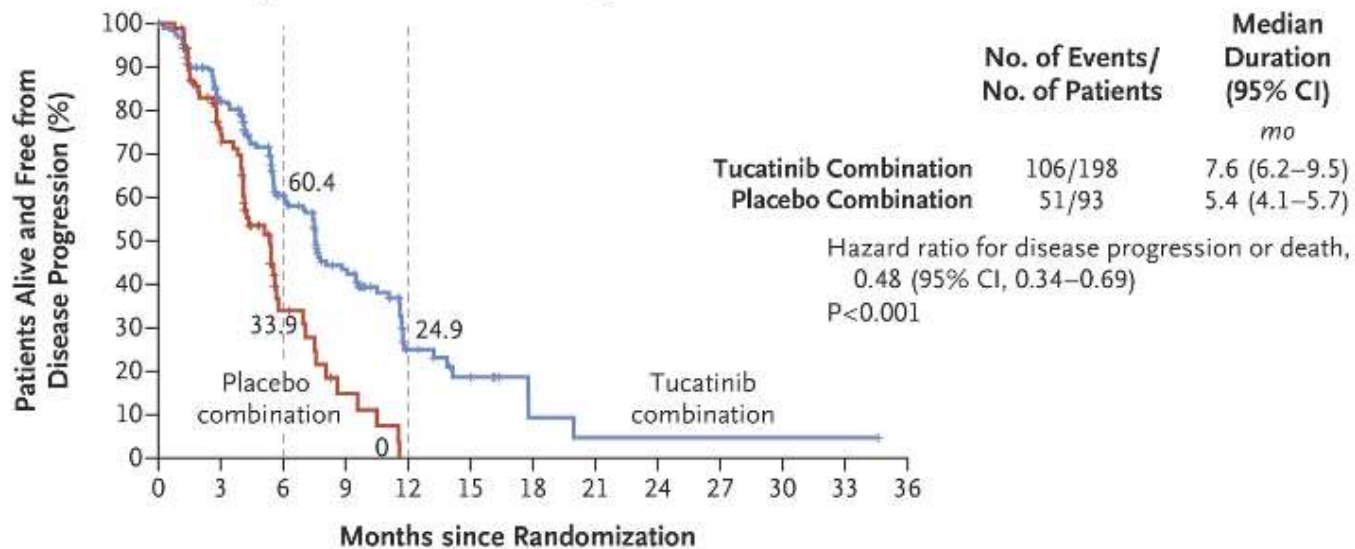


Targeted Therapy: HER 2 - Tucatinib



Targeted Therapy : HER 2 - Tucatinib

A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



No. at Risk

Tucatinib combination	198	144	78	45	14	8	2	1	1	1	1	1	0
Placebo combination	93	49	12	4	0	0	0	0	0	0	0	0	0

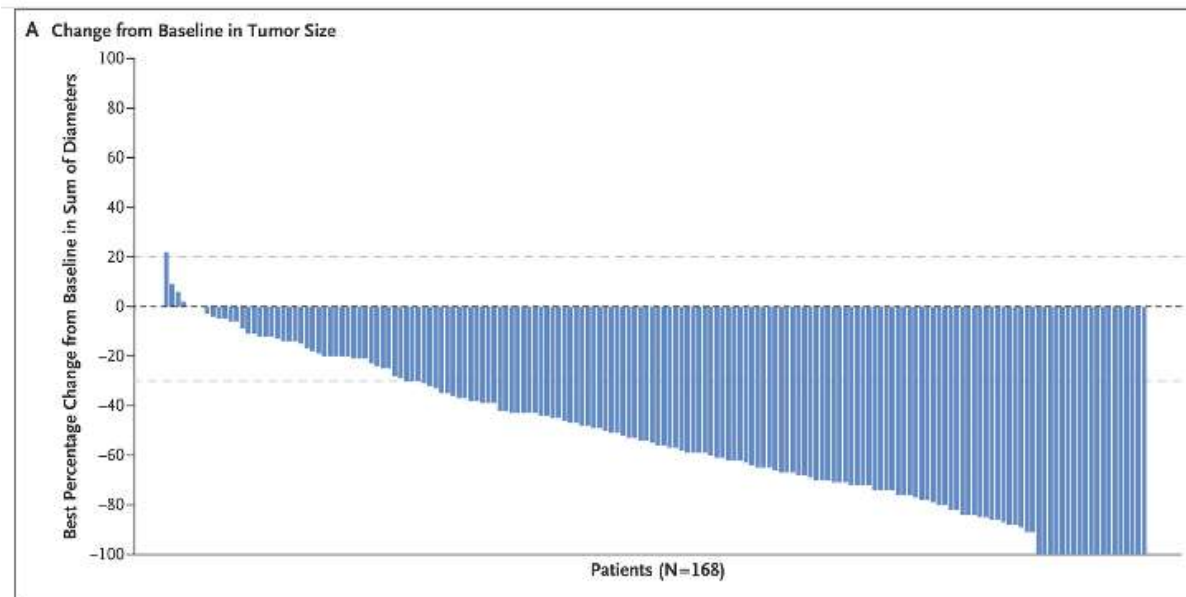
Targeted Therapy : HER 2 - Metastatic

Trastuzumab Deruxtecan - DESTINY – 01 Trial

- Phase 1-2 with dose finding
- N = 184 at the 5.4 mg dose (phase 2 dose)
- Median age 55, 52% ER +
- Prior therapy: 100 % Trastuzumab and 100% prior TDM-1, 65 % Pertuzumab

Targeted Therapy : HER 2 - Metastatic

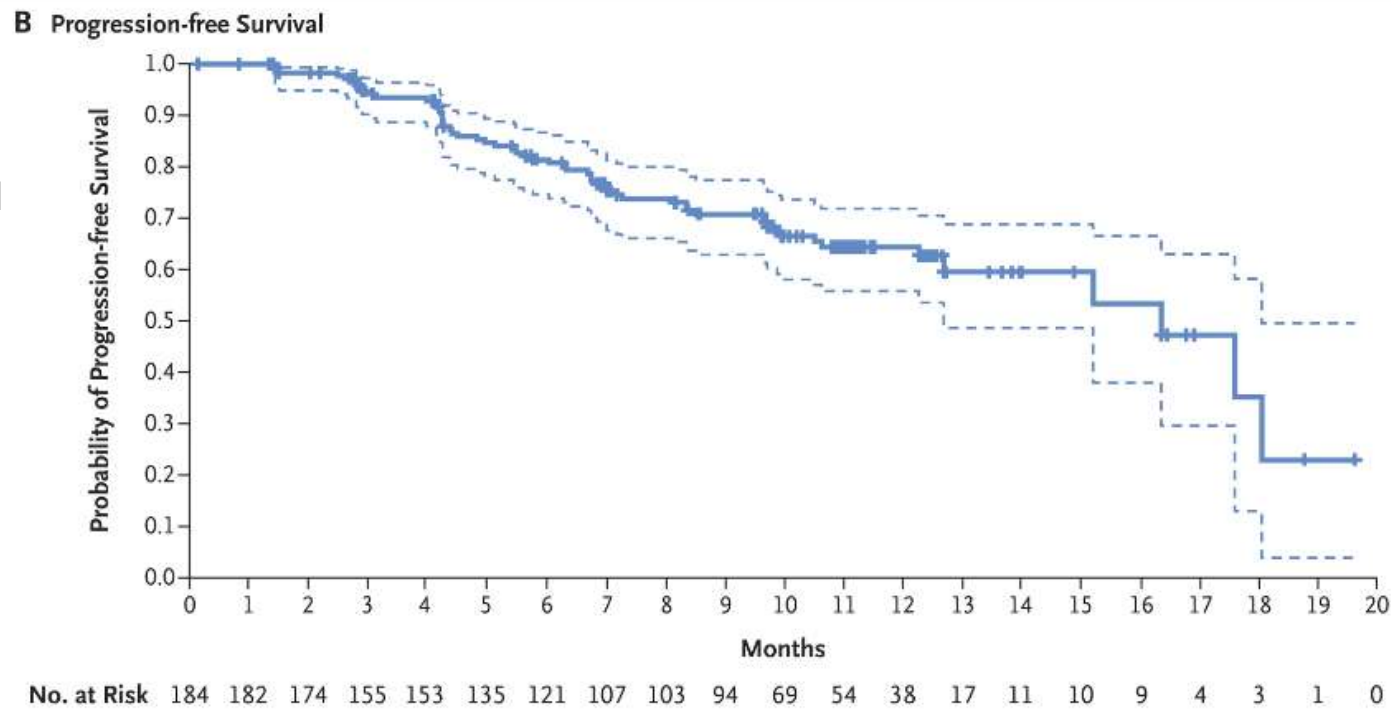
Trastuzumab Deruxtecan – Response Rate – 61%



Targeted Therapy : HER 2 – Deruxtecan

PFS 16.4 M

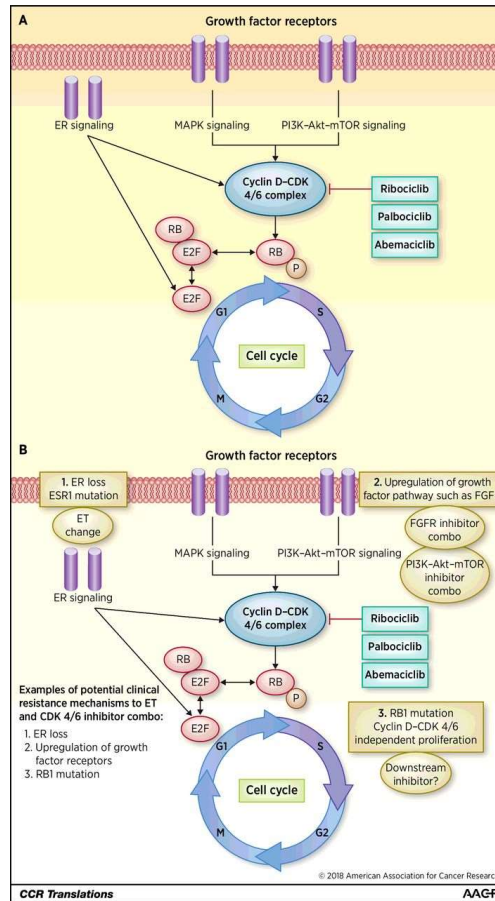
OS – 86%
at 1 year



Targeted Therapy: CDK 4/6 Directed Therapy

- Palbociclib
 - Ribociclib
 - Abemaciclib
-
- Efficacy
 - Toxicity

A, Cyclin D-CDK 4/6 pathway.

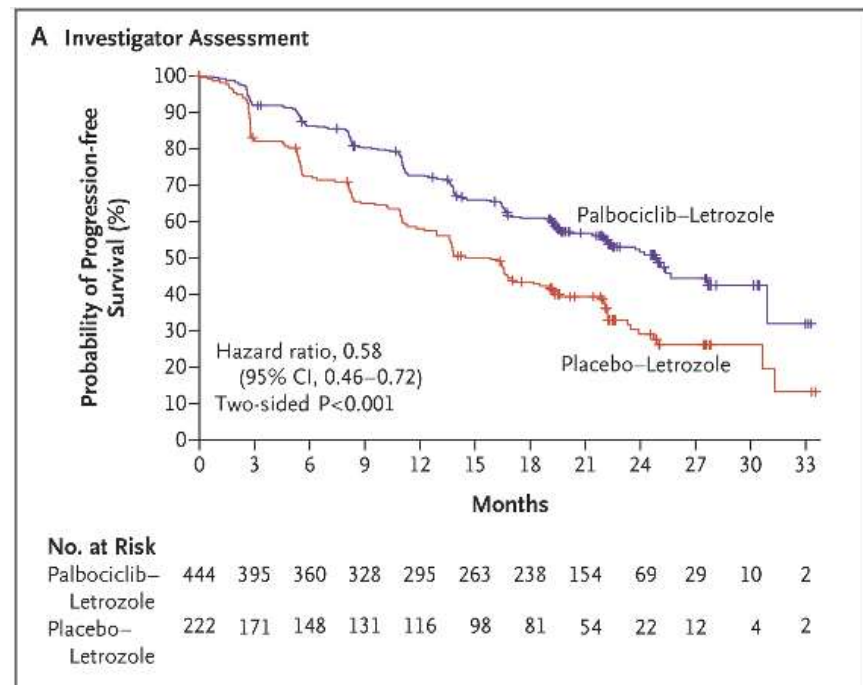


Laura Spring, and Aditya Bardia Clin Cancer Res 2018;24:2981-2983

Targeted Therapy – CDK 4/6 Inhibitors

First Line Palbociclib – PALOMA 2

- Palbociclib + letrozole vs letrozole
- N= 666, median age 62, 48% visceral mets
- PFS 24.8 M - palbociclib vs 14.5 M - control (HR 0.58)



• 66% G 3-4 neutropenia

Ochsner[™]
Health System

Finn et al N Engl J Med 2016;375, 1925-36

Targeted Therapy – CDK 4/6 Inhibitors

First Line : Ribociclib – MONALEESA 3

- 2:1 Randomization Fulvestrant + Ribociclib(N=484) vs Fulvestrant + Placebo(N=242)
- PFS – 33.6 M for Ribociclib vs 19.2 M placebo – HR 0.55
- OS @ 42 M – 66.9 M (R) vs 56.3M (P) HR 0.70
- 57% G3-4 neutropenia

Targeted Therapy – CDK 4/6 Inhibitors

First Line Abemaciclib – MONARCH 3

- Nonsteroidal aromatase inhibitor ± Abemaciclib
- 2:1 randomization , N=493 , FU – 26.7M
- PFS 28.2 M for Abemaciclib vs 14.7M AI alone, HR 0.54
- 73% G1-2 Diarrhea, 22% G3 neutropenia, 6% DVT(0.6% in control)

Johnson et al Nature Breast Cancer 2019

Targeted Therapy – CDK 4/6 Inhibitors

MONALEESA 7 – First Line in pre/peri menopausal

- Goserelin + (anastrozole, letrozole or tamoxifen) ± Ribociclib-
N =672 (1:1)
- PFS at 42 M - 54.6 M(R) vs 37.8 M(P) , HR 0.69
- OS at 42 M – 70.2 M for Ribociclib vs 46 M placebo, HR 0.71
- 63% G3-4 neutropenia, 11% hepatobiliary, 1.8% QT
prolongation

Targeted Therapy – CDK 4/6 Inhibitors

Second Line Palbociclib – PALOMA 3

- Fulvestrant + Palbociclib vs Fulvestrant + Placebo (2:1 randomization)
N=521
- Median Followup 44.8 M
- PFS 11.2M (Palbo) vs 4.6 M (placebo) , HR 0.58
- OS 34.9 M vs 28 M, HR 0.79
- 70% Grade 3-4 neutropenia, 3% hepatobiliary

Targeted Therapy – CDK 4/6 Inhibitors

Second Line – Abemaciclib – MONARCH 2

- Fulvestrant + Abemaciclib or placebo (2:1), N=713
- Median Followup 47.7 M
- PFS 16.9 vs 9.3 M – HR 0.55
- OS 46.7 vs 37.3 M - HR 0.75
- Diarrhea in 86% - 13.4% G3, 24% G3 neutropenia

Targeted Therapy – CDK 4/6 Inhibitors: Summary

- Very active in both the first and second line setting
- Active with a variety of endocrine therapy partners
- Although absolute numbers differ from study to study, the Hazard ratios are quite similar suggesting no major differences between these agents

CDK 4/6 Directed Therapy – Adjuvant Trials

- PALLAS – Palbociclib + endocrine therapy vs standard endocrine therapy, N= 5796 pts, Palbociclib for 2 years
- NATALEE – Ribociclin + letrozole \pm Ovarian suppression(pre-menopausal), N =4000 pts, Ribocilib for 3 years
- NSABP Foundation – Abemaciclib + endocrine therapy vs standard adjuvant ET, N= 4580 pts

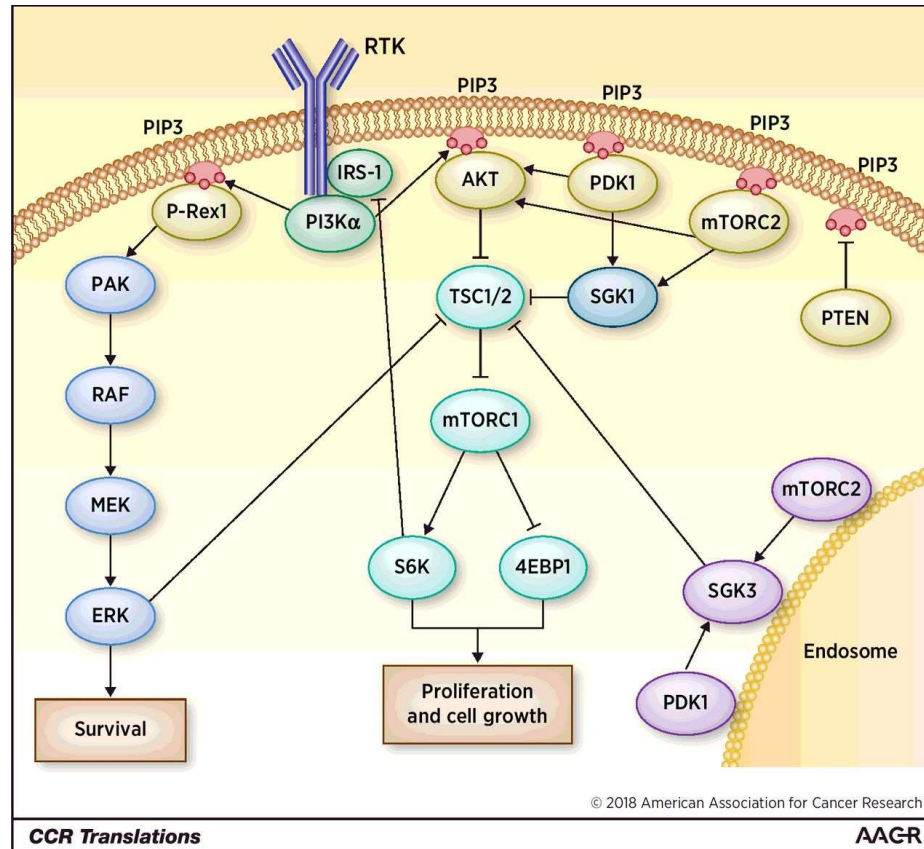
CDK 4/6 Directed Therapy - Unanswered questions:

- Can we recycle CDK inhibitors with different endocrine therapy partners?
- Is there cross resistance between CDK inhibitors? (pre-clinical)
- Does every patient need a CDK inhibitor - \$
- Role in Neo-adjuvant endocrine therapy?

Targeted Therapy : PIK3CA directed therapy

- PIK3CA - activating mutations occur in approximately 40% of ER +, HER2 negative patients
- Alpelisib is an inhibitor of the alpha isoform (p110alpha) of the phosphatidylinositol 3-kinase (PIK3CA)
- Alpelisib is orally available and inhibits the alpha isoform 50 fold compared to the other isoforms

Schematic representation of the PI3K pathway.



Carlotta Costa, and Ana Bosch Clin Cancer Res
2018;24:2029-2031

PIK3CA directed therapy -Alpelisib

- SOLAR-1 Trial - Fulvestrant \pm Alpelisib (300 mg continuous)
- PCR for mutations in exons 7,9,20
- N = 341, median age – 63, prior AI therapy required

	PFS (M)	ORR	CBR
ALPELISIB	11 (HR 0.65)	26.6 %	61.5%
Control	5.7	12.8	45.3%

- Toxicity – 36% G3-4 hyperglycemia, 57% diarrhea(7% G3), nausea, decreased appetite and rash (25% discontinuation rate)

Targeted Therapies: Summary

- Targeted therapies are an integral part of breast cancer therapy
- The use of targeted therapies has extended survival in HER2 positive patients and in ER positive HER2 negative patients
- Additional studies will help define the role of CDK 4/6 inhibitor therapy in the adjuvant and neo-adjuvant space
- PIK3CA inhibition is an important therapeutic opportunity and we should expect additional drugs in this area in the near future

Gayle and Tom Benson Cancer Center

