Metastatic Breast Cancer

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Cancer Top Ten

Estimated New Cases	Males		Females		
Prostate	180,890	21%	Breast	246,660	29%
Lung & bronchus	117,920	14%	Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%	Colon & rectum	63,670	8%
Urinary bladder	58,950	7%	Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%	Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%	Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%	Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%	Leukemia	26,050	3%
Leukemia	34,090	4%	Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%	Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**	**All Sites**	**843,820**	**100%**

Estimated Deaths	Males		Females		
Lung & bronchus	85,920	27%	Lung & bronchus	72,160	26%
Prostate	28,120	8%	Breast	40,450	14%
Colon & rectum	26,020	8%	Colon & rectum	23,170	8%
Pancreas	21,450	7%	Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%	Ovary	14,240	5%
Leukemia	14,130	4%	Uterine corpus	10,470	4%
Esophagus	12,720	4%	Leukemia	10,270	4%
Urinary bladder	11,820	4%	Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%	Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%	Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**	**All Sites**	**281,480**	**100%**

CA: A Cancer Journal for Clinicians
Volume 66, Issue 1, pages 7-30, 7 JAN 2016 DOI: 10.3322/caac.21332
http://onlinelibrary.wiley.com/doi/10.3322/caac.21332/full#caac21332-fig-0001

Breast Cancer: Metastatic Sites at Recurrence

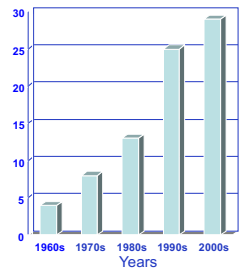
• Bone	50-70%
• Soft Tissues	20-30%
• Lung or Pleura	20-30%
• Liver	5-10%
• Brain	<5%

Breast cancer tropisms differ by subtype
Bone more dominant in hormone receptor positive
Visceral and CNS in hormone receptor negative

Goals of Therapy

- "to keep you feeling as well as possible for as long as possible"
- In 2017 there is not a cure for metastatic breast cancer,
- However, long term NED does happen (2-5%)
- Median life expectancy = 28-36 months?
  - Higher in some subsets
- 22% 5 yr survival, 10% 10 yr survival
- New drugs are needed

Timeline: Growing Number of Breast Cancer Therapies



1950s: Cyclophosphamide, methotrexate

1960s: 5-fluorouracil

1970s: Doxorubicin, tamoxifen

1980s: Mitoxantrone, megestrol acetate, goserelin, leuprolide

1990s: Paclitaxel, docetaxel, vinorelbine, trastuzumab, capecitabine, gemcitabine, epirubicin, toremifene, anastrozole, letrozole, exemestane

2000s: *nab*-paclitaxel, lapatinib, bevacizumab, ixabepilone

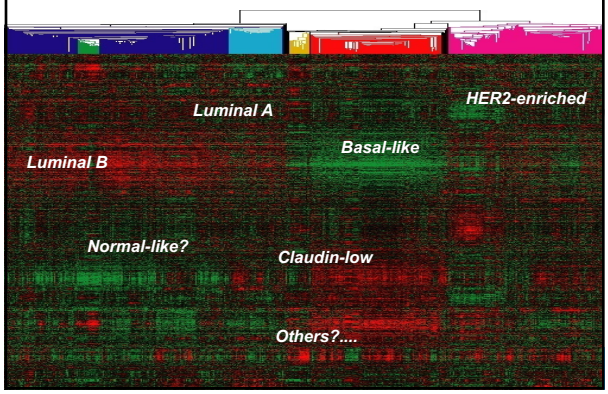
Choice of Therapy

- Biology is Key
- Goal is control of disease and symptoms
- Maximize quality of life

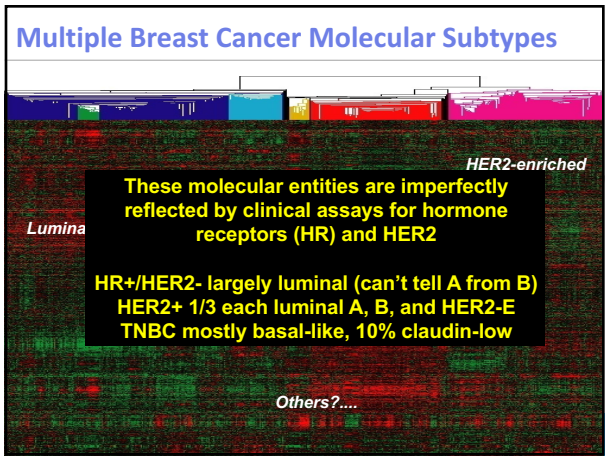
- New Drug development is needed
- THINK – clinical trial

One organ, but not one disease.

Multiple Breast Cancer Molecular Subtypes



Multiple Breast Cancer Molecular Subtypes

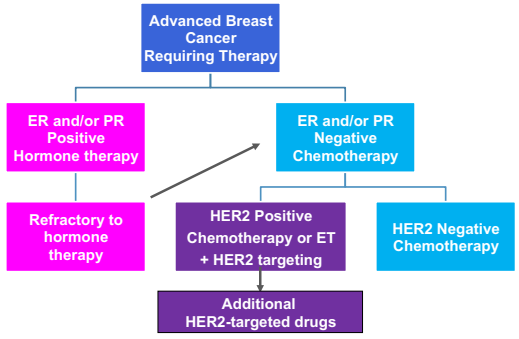


Clinical Subtypes

Hormone Receptor Positive **HER-2 Negative** **Most (50-60%)**	**Hormone Receptor Negative** **HER-2 Positive** **(~10%)**
Hormone Receptor Positive HER-2 Positive (~10%)	Hormone Receptor Negative HER-2 negative "Triple Negative" (~20%)

Systemic Therapy for Metastatic Breast Cancer

Treatment Based on Tumor Phenotype



ASCO Guidelines: General Principles

HR+ HER2-
- Endocrine (usually) preferable to chemotherapy in 1st line
- Evolving use of targeted agents in addition to ET (CDK4/6 or mTOR inhibitors)

Any HER2- receiving chemotherapy
- Single agent chemotherapy preferable to combination
  - Exception: symptomatic, immediately life-threatening
- Longer duration ↑ outcome but must be balanced against ↑ toxicity.
- No single optimal 1st or later chemotherapy
  - Relevant factors: prior Rx, toxicity, performance status, comorbidity, patient preference.
- Additional therapies not yet proven in HER2- (bevacizumab controversial).

HER2+
- HER2-directed Rx is mainstay
- First-line taxane + trastuzumab + pertuzumab, 2nd line T-DM1
- HR+ HER2+ may consider ET + HER2-Rx or ET alone in selected cases

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Partridge A et al, JCO 2014; Rugo H et al, JCO 2016

Endocrine Therapy Options

- Premenopausal
  - Tamoxifen
  - Oophorectomy (OA)/LHRH agonist (OS)
  - OA/OS + the postmenopausal options
- Postmenopausal
  - Nonsteroidal aromatase inhibitor (AI*)
  - AI plus palbo- or ribociclib
  - Steroidal AI
  - Steroidal AI + everolimus
  - Tamoxifen
  - Fulvestrant
  - Fulvestrant + palbociclib
  - Estradiol

**Nonsteroidal AI = letrozole, anastrozole; Steroidal AI = exemestane*

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Endocrine Therapy

Can see response in all sites
ER+ and PR+ do best
↑ % of ER and PR+ cells do best
All SERMs are probably the same
All aromatase inhibitors are the same
- (At least for metastases, I think so)

"You can't improve on being asymptomatic"

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Ovarian Suppression (or Ablation) in MBC

161 pts. with ER+ and MBC
- Tamoxifen
- Buserelin
- Combination

Median f/u 7.3 years
76% of patients DOD

	RR	PFS	OS	5-yr OS
Tamoxifen	28%	5.6m	2.9y	18%
Buserelin	34%	6.3m	2.5y	14%
Combination	48%	9.7m	3.7y	34%
P-value	0.11	0.03	0.01	

Klijn JGM et al, JNCI 2000

OS/OA is itself therapeutic, and opens door for highly effective postmenopausal drugs. Standard of care.

AI vs Tamoxifen: 1st Line Postmenopausal

	Anastrozole	Letrozole	Exemestane
N	353	907	371
CR+PR	21% vs 17%	30% vs 20%	45% vs 30%
CR+PR+SD	59% vs 46%	49% vs 38%	--
TTP (mo)	11.1 vs 5.6	9.4 vs 6.0	9.9 vs 5.8

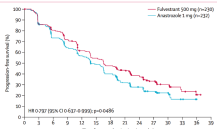
AI at least as good as tamoxifen
Anastrozole = Letrozole = Exemestane
Limited data including CDK4/6i or mTORi

Nabholtz JM et al, JCO 2000; Mouridsen H et al, JCO 2003; Paridaens RJ et al, JCO 2008

Fulvestrant vs AI: 1st Line

FALCON study: Phase III trial

	Fulvestrant	Anastrozole	P-value
CR+ PR	46%	45%	NS
CBR	78%	74%	NS
PFS*	17m	14m	0.049



ET-naïve!
OS 5.5m improvement in phase II FIRST trial

Robertson JFR et al, Lancet 2016

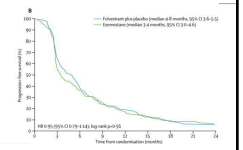
Fulvestrant as single agent =/> AI in 1st line endocrine Rx

Considerations:
1. **Prior adjuvant AI if anything should augment difference**
2. **CDK 4/6i now standard have used AI 1st line, fulvestrant later**

2nd Line Endocrine Rx (after NSAI)

SoFEA: Phase III trial fulvestrant vs exemestane (**no difference**)

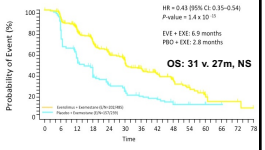
If NSAI used 1st, either fulvestrant or exemestane next is ok



However, if you're going to use exemestane…

BOLERO-2: Phase III trial exemestane + everolimus (mTOR inhibitor) in 2nd line

Everolimus added to exemestane improves PFS but not OS
(AE- stomatitis, anemia, ↑ glc, pneumonitis)



Johnston S et al, Lancet Oncol 2013; Baselga J et al, NEJM 2011; Piccart M et al, Ann Oncol 2014

What about dual endocrine therapy?

For post menopausal women--Conflicting recent results.

SWOG 0226.

- 707 ER+ patients FIRST LINE
- Fulvestrant 500/250/250 + Anastrazole vs Anastrazole alone
- Combination has better PFS by 2.5 months and better OS by 6 months
- Mehta et al. NEJM 2012

FACT .

- 514 ER + patients also FIRST LINE
- Fulvestrant 500/250/250 + Anastrazole vs Anastrazole alone
- No difference in TTP or OS

For premenopausal women – SOFT/ TEXT **adjuvant data.**

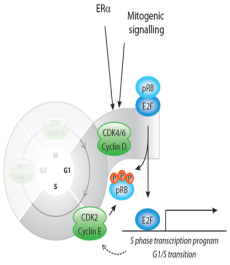
Cyclin Dependent Kinase 4/6 Inhibitors

Role in HR+ breast cancer

- **Growth of HR+ BC depends on cyclin D1, a transcriptional target of ER**
- **Cyclin D1 activates CDK 4/6 causing G1-S phase transition and cell cycle entry**

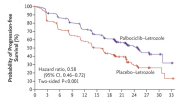
Major area drug development

- **Palbociclib**
- **Abemaciclib**
- **Ribociclib**



Palbociclib Trials in HR+ Disease

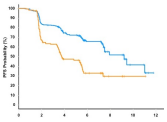
PALOMA-2: Phase III letrozole ± palbo in 1st line HR+/HER2-



PFS: 25m vs 14m, p<0.001
(OS in PALOMA1 phase II: 37m vs 33m, ns)
AE: ANC (66% grade 3+, febrile 2%)*
FDA approved 2015:
Letrozole + palbo in 1st line

WBC monitoring with these drugs

PALOMA-3: Phase III fulvestrant ± palbo in 2nd+ line HR+/HER2-



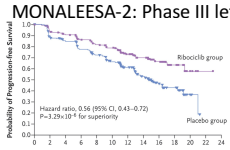
PFS: 9m vs 4m, p<0.0001
(OS immature)
Accelerated FDA approval 2016:
Fulvestrant + palbo in pretreated (no prior palbo)

Key AE: neutropenia, infections, anemia (needs monitoring ET doesn't)

Finn R et al, NEJM 2016; Finn R et al ASCO 2017; Turner N et al, NEJM 2016

Ribociclib Trials in HR+ Disease

MONALEESA-2: Phase III letrozole ± ribo in 1st line



PFS: NR vs 15m, p<0.001
Grade 3+ AE: ANC (63%, febrile 2%), LFT 11%. QTc ↑ 3%*
FDA approved 2016:
Letrozole + ribo in 1st line

Monitor serial ECG and drugs

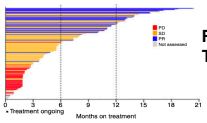
MONALEESA-3: Phase III fulvestrant ± ribo in 1-2nd+ line
Not yet reported

FDA approval 2016: Letrozole + ribo in 1st line
How much will QTc matter?
HR 0.56 ribo, HR 0.55 palbo vs letrozole alone

Hortobagyi G et al, NEJM 2016

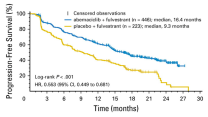
Abemaciclib Trials in HR+ HER2- Disease

MONARCH-1: Single agent abemaciclib in 2nd+ line



RR 15-20% (unusual in single agent CDK4/6i)
Toxicity differs: diarrhea grade 3+ 20% > ANC ↓

MONARCH-2: Phase III fulvestrant ± abema in 2st line



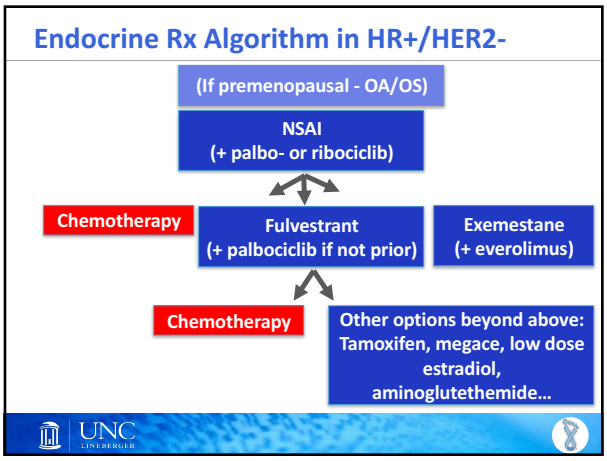
PFS: 16m vs 9m, HR 0.55, p<0.001

MONARCH-3: Phase III NSAI ± abema in 1st line – PFS advantage in press report

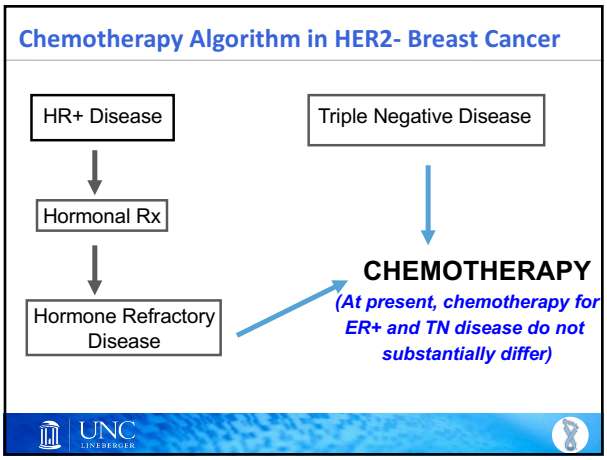
Not yet approved.
FDA review likely in 2018 alone and combined with fulvestrant

Dickler M et al, Clin Cancer Res 2017; Sledge G et al, JCO 2017

Endocrine Rx Algorithm in HR+/HER2-



Chemotherapy Algorithm in HER2- Breast Cancer



MBC Chemotherapy: Wide Options

Anthracycline
- Doxorubicin
- Epirubicin
- Doxil

Taxanes
- Paclitaxel
- Docetaxel
- Nab-paclitaxel

Vinca alkaloids
- Vinorelbine

Other anti-tubule
- Eribulin

Antimetabolites
- Methotrexate
- 5-FU
- Capecitabine
- Gemcitabine

Alkylating agents
- Cyclophosphamide
- Platinum agents

Epothilones
- Ixabepilone

Combination regimens with activity in metastatic breast cancer

cyclophosphamide and doxorubicin
Docetaxel and doxorubicin
cyclophosphamide, doxorubicin, 5-fluorouracil
cyclophosphamide, methotrexate, 5-fluorouracil
Doxorubicin and paclitaxel.
Docetaxel and capecitabine.
Weekly paclitaxel + capecitabine
Gemcitabine + paclitaxel
Vinorelbine and epirubicin.
Capecitabine and ixabepilone

Cochrane 2006. OR=1.2 for RR but no impact on TTP or OS

Combination vs Single Agent Chemotherapy

	Combination	Single Agent
Higher RR	✓	
Longer TTP (initial)	✓	
Survival	✓	✓
QOL		✓
Easier to customize		✓
Less "wasted" toxicity		✓

Single agent preferred unless response is important

ASCO Choosing Wisely:

#7. Don't use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.

Although chemotherapy with multiple drugs, or combination chemotherapy, for metastatic breast cancer may slow tumor growth for a somewhat longer time than occurs when treating with a single agent, use of combination chemotherapy has not been shown to increase overall survival. In fact, the trade-offs of more frequent and severe side effects may have a net effect of worsening a patient's quality of life, necessitating a reduction in the dose of chemotherapy.

Combination chemotherapy may be useful and worth the risk of more side effects in situations in which the cancer burden must be reduced quickly because it is causing significant symptoms or is life threatening. As a general rule, however, giving effective drugs one at a time lowers the risk of side effects, may improve a patient's quality of life, and does not typically compromise overall survival.

So how do we pick?

- Most oncologists would agree that sequential single agents is the way to go (except in visceral crisis)
- Think about your goals of therapy – do no harm
- Mark Graham's Fab 5: Doxil, Xeloda, Gem, Navelbine, CMF
- There is no ONE right order
- Think about co-morbidities and organ function

Is There a Standard 1st Line Agent?

Anthracyclines and taxanes 1st line agents; may be less appealing in relapse soon post adjuvant Rx

No evidence that sequence of therapies affects OS or QOL

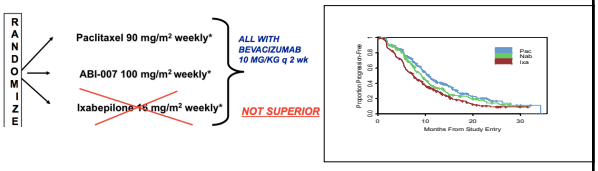
Response more influenced by line of therapy than specific agent

Treatment decisions often individualized to patient

NCCN/ASCO guidelines generally avoid specific recommendations first-line agents

1st Line Chemotherapy

CALGB 40502: Phase III trial of 3 antitubule drugs in 1st line



Results of 40502:
- Paclitaxel > ixabepilone
- Paclitaxel least toxic

Meta-analysis first-line trials
- Taxane > anthracycline

Most start with single agent weekly taxane (paclitaxel, nab-paclitaxel, docetaxel) unless recently had taxane adjuvantly.
Platinums ok 1st line in triple negative.

Rugo H et al, JCO 2015; Piccart-Gebhart MJ et al, JCO 2008

Eribulin pivotal trial: EMBRACE Study

Eligibility (N = 762)

- **Locally recurrent or mBC**
- **2-5 prior chemotherapies**
  - **≥2 for advanced disease**
  - **Prior anthracyclines and taxanes**
- **Progression ≤6 months of last chemotherapy**
- **Neuropathy ≤ Grade 2**
- **ECOG ≤ 2**

R

2:1

Eribulin mesylate
1.4 mg/m^2, 2-5 min IV
D1, 8 q21 days
13 m OS

Treatment of Physician's Choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological)* or supportive care only**
10 m OS

* Approved for cancer treatment

** Or palliative treatment or radiotherapy according to local practice

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Grade 3 and 4 Adverse Events

	Grade 3		Grade 4	
	Eribulin (n = 503)	TPC (n = 247)	Eribulin (n = 503)	TPC (n = 247)
Hematologic events				
Neutropenia	21.1%	14.2%	24.1%	6.9%
Leukopenia	11.7%	4.9%	2.2%	0.8%
Anemia	1.8%	3.2%	0.2%	0.4%
Febrile neutropenia	3.0%	0.8%	1.2%	0.4%
Non-hematologic events				
Asthenia/fatigue	8.2%	10.1%	0.6%	0
Peripheral neuropathy	7.8%	2.0%	0.4%	0
Nausea	1.2%	2.4%	0	0
Dyspnea	3.6%	2.4%	0	0.4%
Mucosal inflammation	1.4%	2.0%	0	0
Hand-foot syndrome	0.4%	3.6%	0	0

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Toxicity is a Key Feature to Consider

↓ alopecia
- Capecitabine
- Vinorelbine
- Carboplatin

↓ GI symptoms
- Taxanes
- Gemcitabine

↓ neuropathy
- Capecitabine
- Anthracyclines
- Gemcitabine

↓ myelosuppression
- Taxanes
- Capecitabine

↓ IVs
- Capecitabine

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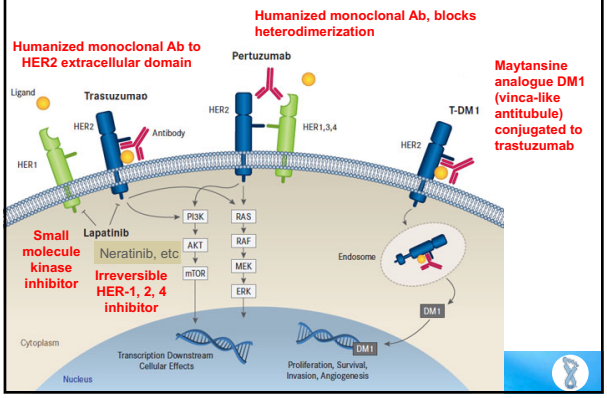
Credit: Lisa Carey, MD

Remember, biology is key…

HER 2 positive MBC

FOUR targeted therapies approved in past decade for treatment of met breast cancer

Targeting HER2

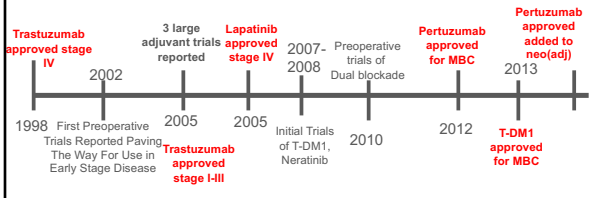


HER2+ Disease: Major Clinical Advances

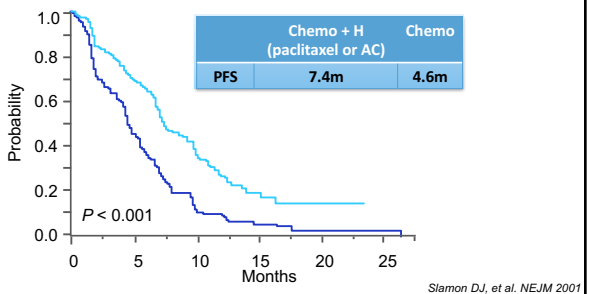
Studies of the HER-2/*neu* Proto-oncogene in Human Breast and Ovarian Cancer

Dennis J. Slamon,* William Godolphin, Lovell A. Jones, John A. Holt, Steven G. Wong, Diane E. Keith, Wendy J. Levin, Susan G. Stuart, Judy Udove, Axel Ullrich, Michael F. Press

1989



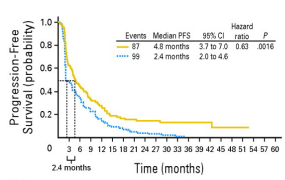
Trastuzumab Added To Chemotherapy



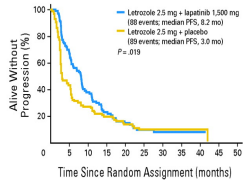
	Chemo + H (paclitaxel or AC)	Chemo
PFS	7.4m	4.6m

Slamon DJ, et al. NEJM 2001

HER2-Targeting Added To Endocrine Therapy



anastrozole vs anastrozole + trastuzumab
Kaufman et al, JCO 2008



letrozole vs letrozole + lapatinib
Johnston et al, JCO 2009

Adds toxicity with modest changes in outcome. Most co-target but ok in individual patients to just use ET.

HER2-Targeting: The First Generation

Post-H progression ongoing HER2-targeting works
- Lapatinib
- TDM1
- Trastuzumab!

Multiple chemotherapy partners for HER2-targeting
- Platinums, vinorelbine, gemcitabine, capecitabine
- What is optimal?

ER+ HER2+ disease benefits from dual targeting
- AI + either trastuzumab or lapatinib
- Ok to omit HER2-targeting in strongly ER+, indolent, asymptomatic.

Newer Anti-HER2 Drugs

CLEOPATRA: Phase III trial testing addition of pertuzumab (1st line)

HER2-positive MBC
(53% no prior chemo
10% prior trastuzumab)

N=800

- Docetaxel + trastuzumab + placebo
- Docetaxel + trastuzumab + pertuzumab

End points

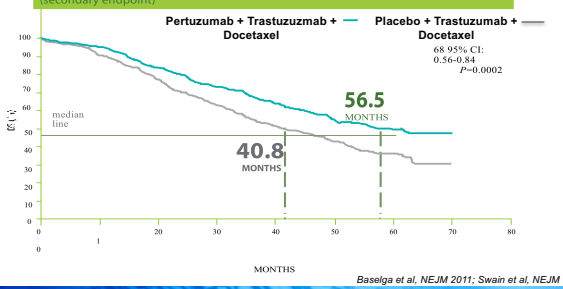
- PFS and OS
- quality of life
- biomarker analysis

Baselga J et al. NEJM 2012

CLEOPATRA: Overall Survival

PFS 18.5 vs 12.4m, p<0.0001

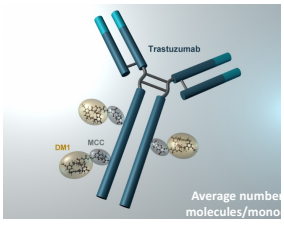
15.7 months improvement in median OS in the final analysis (secondary endpoint)[2]

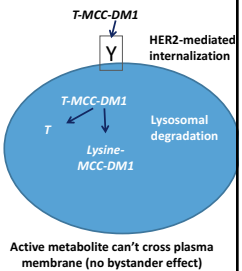


Baselga et al, NEJM 2011; Swain et al, NEJM 2015

Trastuzumab-emtansine (T-DM1), HER2 Antibody-Drug Conjugate

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)
- Will it allow omission of separate cytotoxic?



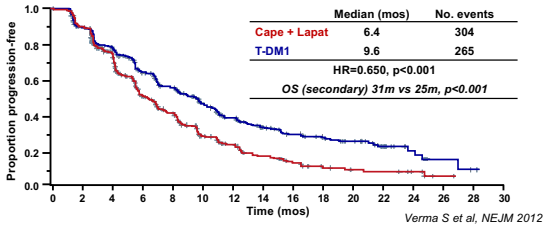


Active metabolite can't cross plasma membrane (no bystander effect)

Beeram et al. J Clin Oncol 2008.

EMILIA: Phase III Trial T-DM1 versus XL

Pre-treated setting



	Median (mos)	No. events
Cape + Lapat	6.4	304
T-DM1	9.6	265

HR=0.650, p<0.001

OS (secondary) 31m vs 25m, p<0.001

Verma S et al, NEJM 2012

Toxicity better (and different) with T-DM1: grade 3+ 57% vs 41%
T-DM1 – thrombocytopenia, LFT↑
XL – N/V, hand-foot syndrome

Win-Win

Next Generation of HER2-Targeting

Trial	Line	Regimens	PFS	OS
CLEOPATRA	**1**	**TH + Pert**	**19 v. 12m (HR 0.69*)**	**56 v. 41m (HR 0.68*)**
MARIANNE[&]	1	TH v. TDM1 v. TDM1+P	ns	-
NEfERTT[&]	1	TH v. TN	17 v. 17m (ns)	?fewer CNS with TN?
BOLERO-1	1	TH + Eve	15 v. 14m	-
EMILIA	**2**	**TDM1 v. XL**	**10 v. 6m (HR 0.65*)**	**31 vs 29m (HR 0.68*)**
BOLERO-3	2	VH + Eve	7 v. 6m (HR 0.78*)	-
TH3RESA	**3+**	**TDM1 v. MD choice**	**6 v. 3m (HR 0.53)**	**HR 0.55 (interim)**

* significant T=taxane; N=neratinib; V=vinorelbine; E=everolimus

Baselga NEJM'12; Swain ESMO'14; Hurvitz SABCS'14; Verma NEJM'12; Andre Lancet Oncol'14; Krop Lancet Oncol'14

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BOLERO-1	1	TH + Eve		-
EMILIA	2		(HR 0.65*)	31 vs 29m (HR 0.68*)
BOLERO-3			7 v. 6m (HR 0.78*)	-
TH3RESA	3+	TDM1 v. MD choice	6 v. 3m (HR 0.53)	HR 0.55 (interim)

1st line: T+H+P wins (~$10,000/m)
2nd+ line: TDM1 wins (~$10,000/m)

* significant T=taxane; N=neratinib; V=vinorelbine; E=everolimus

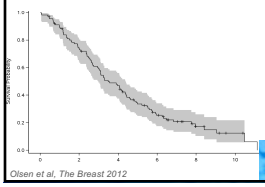
Baselga NEJM'12; Swain ESMO'14; Hurvitz SABCS'14; Verma NEJM'12; Andre Lancet Oncol'14; Krop Lancet Oncol'14

Oncogene Addiction:

HER2 is Still a Relevant Target After Progression on Trastuzumab

Summary: Metastatic Options for HER2+

Line of therapy	Regimen Options	
	Chemotherapy-based	***Endocrine therapy-based***
First	Taxane + trast + pert	AI + lapatinib or trastuzumab
Second	T-DM1	Fulvestrant + lapatinib or trastuzumab
Third	Capecitabine + lapatinib	
Later	Other drugs + trastuzumab	



Olsen et al, The Breast 2012

Median survival > 4 years, likely to rise
Multiple drug choices

How do we treat most thoughtfully?

Treatment Approach HER2+ MBC in 2017

First Line: **Taxane + Trastuzumab + Pertuzumab**

Who Should Receive Endocrine Therapy Upfront?

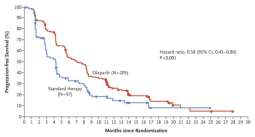
Second Line: **TDM-1**

Third, Fourth, Fifth, Sixth Line:

Capecitabine + Lapatinib
Capecitabine + Trastuzumab
Vinorelbine + Trastuzumab
Lapatinib + Trastuzumab
Other chemotherapy + Trastuzmab
Endocrine Therapy + Trastuzumab

Future Rx?

- **Olaparib or other PARPi in germline BRCA carriers**



OlympiAD trial
- *1-3rd line, no prior progression on platinum*
- *Olaparib vs (capecitabine or eribulin or vinorelbine)*
- *Benefit particularly seen in triple negative*

- **Immune checkpoint inhibitors**
  - **Pembrolizumab**
  - **Avelumab**
  - **Atezolizumab**

RR ~15-20% TNBC
Immune-related AE
Late drug development

Robson M et al, NEJM 2017; Nanda R et al, JCO 2016; Dirix LY et al, AACR-SABCS 2015 (abs S1-07); Schmid P et al, AACR 2017 (abs 2986)

Myth

Because so many agents have modest activity in metastatic breast cancer, there is a common belief that much progress has been made.

Reality

The data suggest only modest progress

Clinical trials of more effective agents are still sorely needed.

New targets/ New compounds

Keep an eye out for….

Angiogenesis
Cell cycle control
Apoptosis
Signal Transduction

Novel HER 2 inhibitors
- _ LJM716 – HER 3
- Neratinib
- ONT

VEGFR inhibitors
- Sorafenib, sunintinib, cediranib, motesanib, vandetinib, pazopanib

CDK 4/6
PD1/ PDL1
Dasatinib
PI3K inhib
AKT or mTOR inhib
Aurora A kinase inhib
IAP inhib
BCL2 inhib
IGF1R antag (25)
PARP
HSP90
Hedgehog

So….

In HR+ endocrine Rx until refractory

In HER-2 +

- trastuzumab and lapatinib
- Pertuzamab
- TDM1

In endocrine refractory HER-2 negative, or triple negative

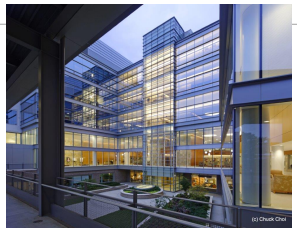
- Sequential single agents for most
- Consider everolimus or palbociclib

THINK about a clinical trial .

For almost QOL and symptoms key

- minimize tests
- Don't forget supportive and palliative care

Thank you



Standing on the shoulders of giants….
I am indebted to Hy Muss, Lisa Carey and others for loaning their slides.
And to Carey Anders Katie Reeder Hayes Rachel Phipps Katie Lansing Camilla Brewer Charlotte Dunn Nicole Whitman and the rest of the UNC breast cancer research team for working to move the bar forward.
And of course to all the patients who participated in trials and their families and support networks.