

**UNC LINEBERGER**

**Metastatic Breast Cancer**

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UNIVERSITY OF NORTH CAROLINA

**UNC N.C. CANCER HOSPITAL LINEBERGER COMPREHENSIVE CANCER CENTER**

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### Cancer Top Ten

**Estimated New Cases**

	Male	Female	All Sites
Prostate	182,890	21%	246,890
Lung & bronchus	133,000	14%	186,070
Colon & rectum	70,800	8%	63,070
Urinary bladder	58,000	7%	60,000
Melanoma of the skin	48,970	6%	49,300
Non-Hodgkin lymphoma	45,170	5%	32,410
Kidney & renal pelvis	38,000	5%	29,010
Oral cavity & pharynx	34,760	4%	26,000
Leukemia	34,000	4%	25,400
Liver & intrapleural bile duct	28,410	3%	23,000
<b>All Sites</b>	<b>841,388</b>	<b>100%</b>	<b>843,838</b>

**Estimated Deaths**

	Male	Female	All Sites
Lung & bronchus	85,000	27%	72,960
Prostate	28,100	8%	40,400
Colon & rectum	26,000	8%	23,170
Pancreas	21,400	7%	20,300
Liver & intrapleural bile duct	18,300	6%	16,340
Leukemia	14,130	4%	16,470
Esophagus	12,700	4%	10,270
Urinary bladder	11,600	4%	8,900
Non-Hodgkin lymphoma	11,000	4%	8,830
Brain & other nervous system	5,440	3%	6,610
<b>All Sites</b>	<b>314,288</b>	<b>100%</b>	<b>281,488</b>

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/abstract/1332-fg10001>

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### 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

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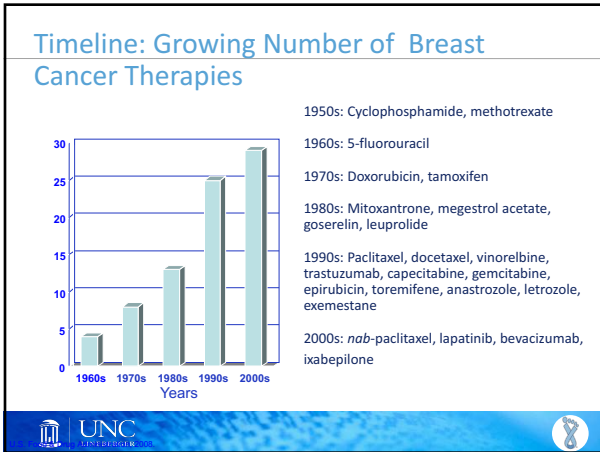
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### Choice of therapy

Goal is control of disease and symptoms  
Maximize quality of life

Biology is Key

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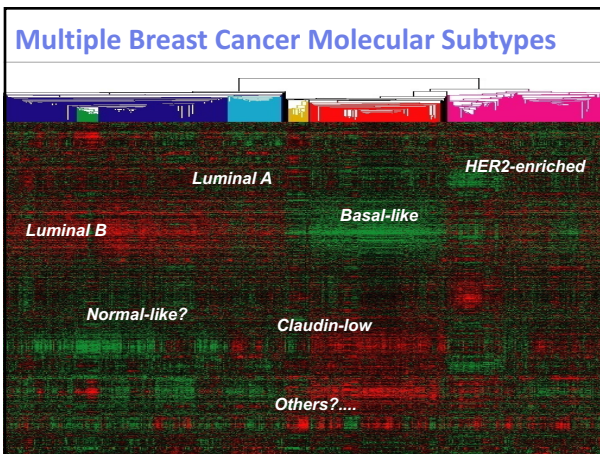
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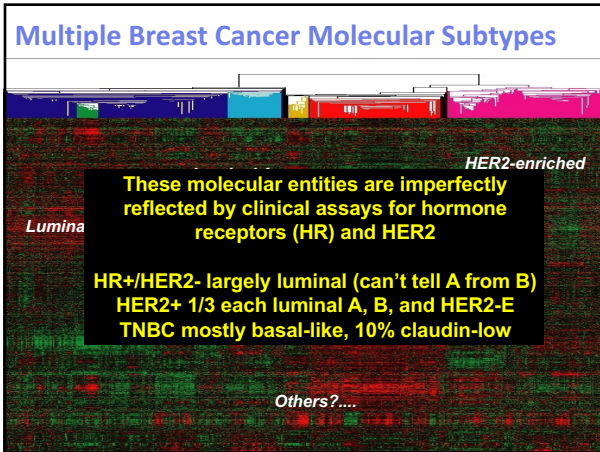
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### Clinical Subtypes

<p>Hormone Receptor Positive</p> <p>HER-2 Negative</p> <p>Most (50-60%)</p>	<p>Hormone Receptor Negative</p> <p>HER-2 Positive</p> <p>(~10%)</p>
<p>Hormone Receptor Positive</p> <p>HER-2 Positive (~10%)</p>	<p>Hormone Receptor Negative</p> <p>HER-2 negative</p> <p>"Triple Negative" (~20%)</p>

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### Systemic Therapy for Metastatic Breast Cancer

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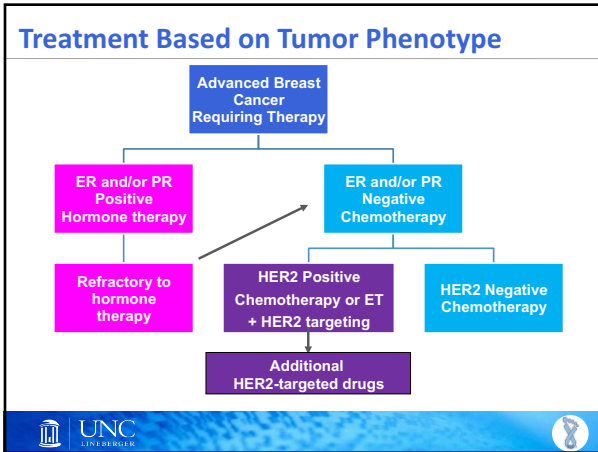
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- ### Endocrine Therapy Options
- Premenopausal
    - Tamoxifen
    - Oophorectomy (OA)/LHRH agonist (OS)
    - OA/OS + the postmenopausal options
  - Postmenopausal
    - Nonsteroidal aromatase inhibitor (AI\*)
    - AI plus palbo- or ribociclib
    - 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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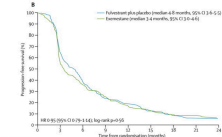
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### 2<sup>nd</sup> Line Endocrine Rx (after NSAI)

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

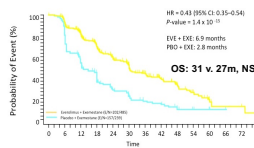
If NSAI used 1<sup>st</sup>, either fulvestrant or exemestane next is ok



However, if you're going to use exemestane...

BOLERO-2: Phase III trial exemestane + everolimus (mTOR inhibitor) in 2<sup>nd</sup> 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; Piceart M et al, Ann Oncol 2014

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### What about dual endocrine therapy?

For post menopausal women--Conflicting recent results. SWOG 0226.

- 707 ER+ patients FIRST LINE
- Fulvestrant 500/250/250 + Anastrozole vs Anastrozole 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 + Anastrozole vs Anastrozole alone
- No difference in TTP or OS

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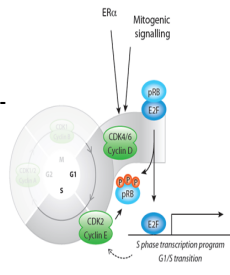
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### Cyclin Dependent Kinase 4/6 Inhibitors

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

And 3 new approvals in past 2 years

- Palbociclib
- Abemaciclib
- Ribociclib

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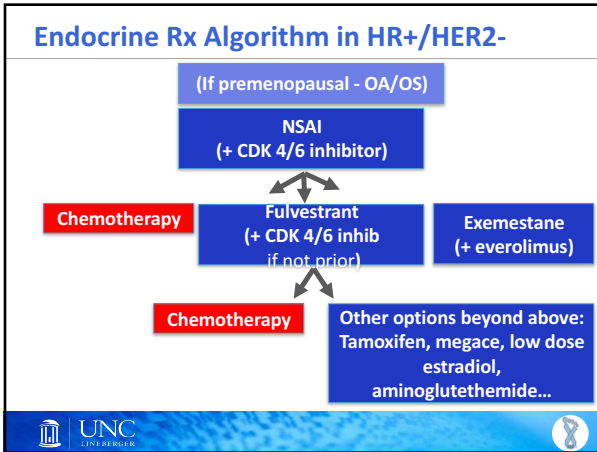
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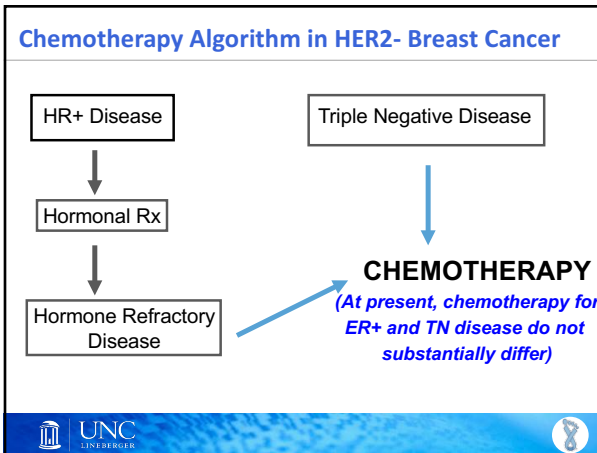
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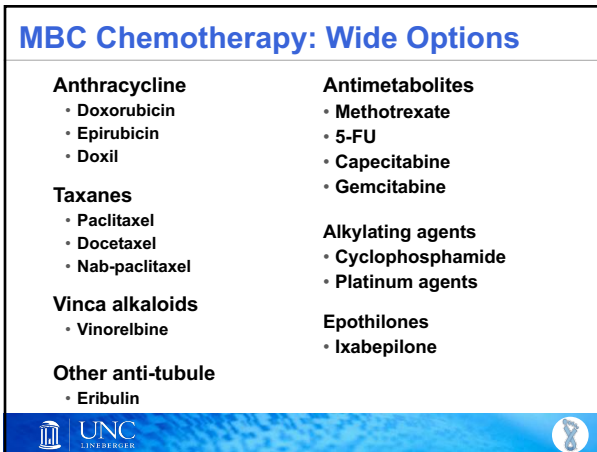
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### Combination regimens with activity in metastatic breast cancer

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


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### Combination vs Single Agent Chemotherapy

	Combination	Single Agent
Higher RR	<input checked="" type="checkbox"/>	
Longer TTP (initial)	<input checked="" type="checkbox"/>	
Survival	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
QOL		<input checked="" type="checkbox"/>
Easier to customize		<input checked="" type="checkbox"/>
Less "wasted" toxicity		<input checked="" type="checkbox"/>

**Single agent preferred unless response is important**


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### 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.


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### 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




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### Is There a Standard 1<sup>st</sup> Line Agent?

**Anthracyclines and taxanes 1<sup>st</sup> 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**




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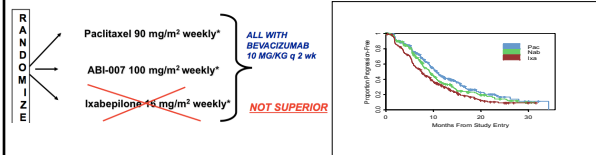
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### 1<sup>st</sup> Line Chemotherapy

CALGB 40502: Phase III trial of 3 antitubule drugs in 1<sup>st</sup> 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 1<sup>st</sup> line in triple negative.**




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### Eribulin pivotal trial: EMBRACE Study

**Eligibility (N = 762)**

Locally recurrent or mBC

2-5 prior chemotherapies  
–  $\geq 2$  for advanced disease

– Prior anthracyclines and taxanes

Progression  $\leq 6$  months of last chemotherapy

Neuropathy  $\leq$  Grade 2

ECOG  $\leq 2$

**R**

**2:1**

**Eribulin mesylate** 13 m OS

1.4 mg/m<sup>2</sup>, 2-5 min IV D1, 8 q21 days

**Treatment of Physician's Choice (TPC)** 10 m OS

Any monotherapy (chemotherapy, hormonal, biological)\* or supportive care only\*\*

\* Approved for cancer treatment  
\*\* Or palliative treatment or radiotherapy according to local practice

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

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### Grade 3 and 4 Adverse Events

	Grade 3		Grade 4	
	Eribulin (n = 503)	TPC (n = 247)	Eribulin (n = 503)	TPC (n = 247)
<b>Hematologic events</b>				
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%
<b>Non-hematologic events</b>				
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.

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### Toxicity is a Key Feature to Consider

↓ alopecia

- Capecitabine
- Vinorelbine
- Carboplatin

↓ GI symptoms

- Taxanes
- Gemcitabine

↓ neuropathy

- Capecitabine
- Anthracyclines
- Gemcitabine

↓ myelosuppression

- Taxanes
- Capecitabine

↓ IVs

- Capecitabine

Credit: Lisa Carey, MD

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Remember, biology is key...

HER 2 positive MBC

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


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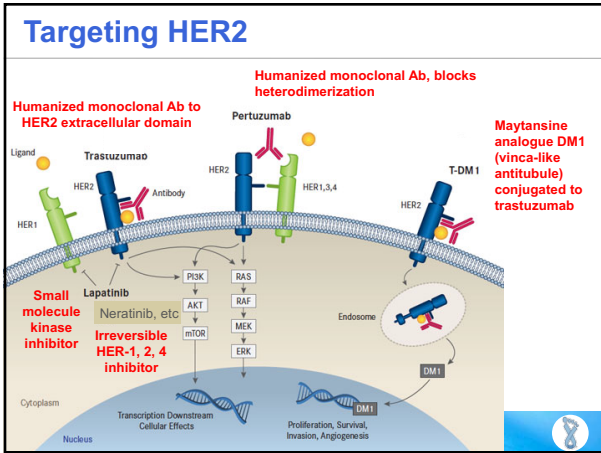
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### HER2+ Disease: Major Clinical Advances

**Science** Studies of the HER-2/*neu* Proto-oncogene in Human Breast and Ovarian Cancer  
 DENISE J. SLAMON,\* WILLIAM GODOLPHIN, LOWELL A. JONES, JOHN A. HOLT, STEVEN G. WONG, DONNE E. KEITH, WENDY J. LEVIN, SUSAN G. STUART, JUDY UDOWE, AXEL ULLRICH, MICHAEL F. PRESS  
 1989

1989: Studies of the HER-2/*neu* Proto-oncogene in Human Breast and Ovarian Cancer (Science)

1998: First Preoperative Trials Reported Paving The Way For Use in Early Stage Disease

2002: Trastuzumab approved stage IV

2005: 3 large adjuvant trials reported

2005: Trastuzumab approved stage I-III

2005: Lapatinib approved stage IV



2007-2008: Initial Trials of T-DM1, Neratinib

2007-2008: Preoperative trials of Dual blockade

2012: T-DM1 approved for MBC

2012: Pertuzumab approved for MBC

2013: Pertuzumab approved added to neo(adj)


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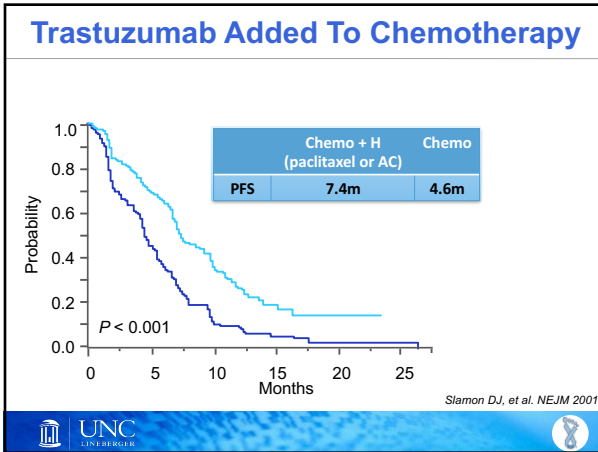
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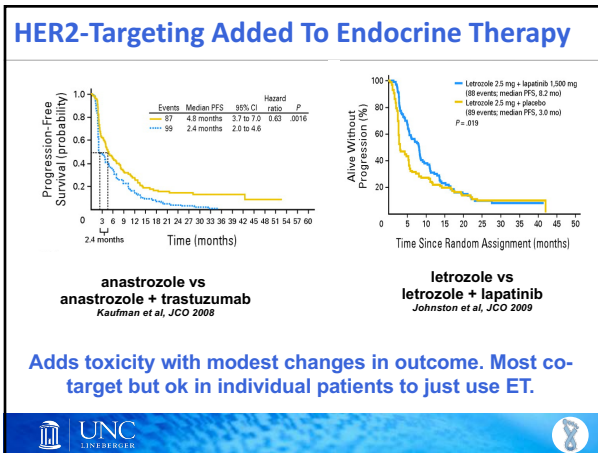
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### HER2-Targeting: The First Generation

**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.

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### Newer Anti-HER2 Drugs

**CLEOPATRA: Phase III trial testing addition of pertuzumab (1<sup>st</sup> 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


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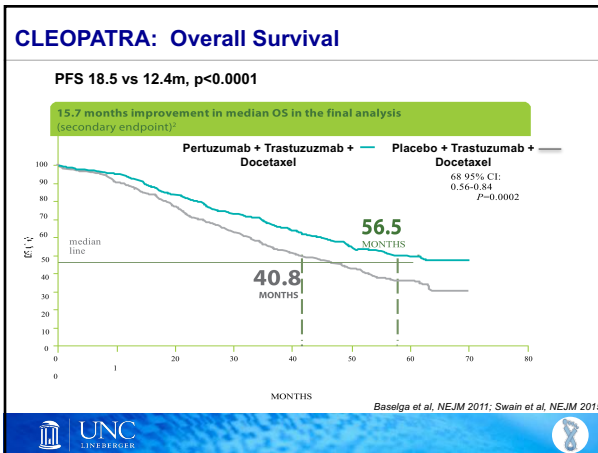
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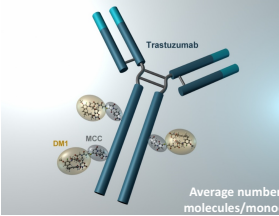
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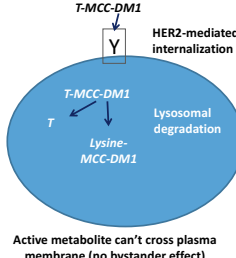
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### Trastuzumab-emtansine (T-DM1), HER2 Antibody-Drug Conjugate

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



Average number molecules/monomer





HER2-mediated internalization

Lysosomal degradation

Lysine-MCC-DM1

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

Beeram et al. J Clin Oncol 2008.


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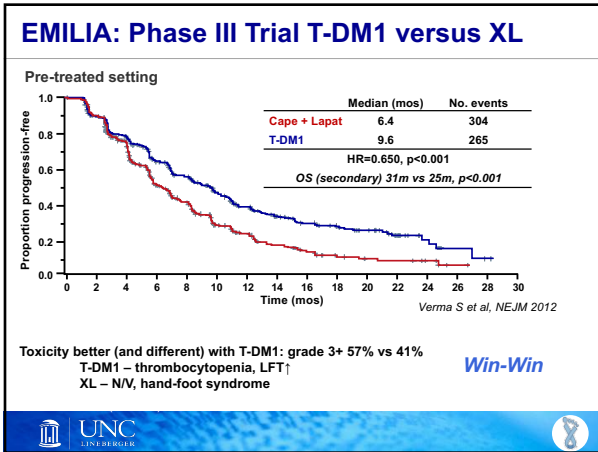
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### Next Generation of HER2-Targeting

Trial	Line	Regimens	PFS	OS
CLEOPATRA	1	TH + Pert	19 v. 12m (HR 0.69*)	56 v. 41m (HR 0.68*)
MARIANNE <sup>&amp;</sup>	1	TH v. TDM1 v. TDM1+P	ns	-
NEFERTT <sup>&amp;</sup>	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 NEJM12; Swain ESMO14; Hurvitz SABCS14; Verma NEJM12; Andre Lancet Oncol14; Krop Lancet Oncol14

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

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**Oncogene Addiction:**

**HER2 is Still a Relevant Target After Progression on Trastuzumab**





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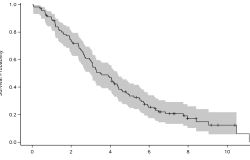
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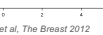

**Summary: Metastatic Options for HER2+**

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



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

How do we treat most thoughtfully?


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**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 + Trastuzumab
- Endocrine Therapy + Trastuzumab


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### Future Rx?

- Olaparib or other PARPi in germline BRCA carriers**
  - OlympiAD trial*
    - 1-3<sup>rd</sup> 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

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

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### 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.

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### ASCO Guidelines: General Principles

**HR+ HER2-**

- Endocrine (usually) preferable to chemotherapy in 1<sup>st</sup> line (and beyond)
- Evolving use of targeted agents in addition to ET (CDK4/6 or mTOR inhibitors)

**Any HER2 negative receiving chemotherapy**

- Single agent chemotherapy preferable to combination
  - Exception: symptomatic, immediately life-threatening
- No single optimal 1<sup>st</sup> 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, 2<sup>nd</sup> line T-DM1
- HR+ HER2+ may consider ET + HER2-Rx or ET alone in selected cases

**For All: QOL and symptom management is key.**  
**For All: A clinical trial may be the best option.**

UNC LINCOLN BERGER  
Partridge A et al, JCO 2014; Rugo H et al, JCO 2016

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