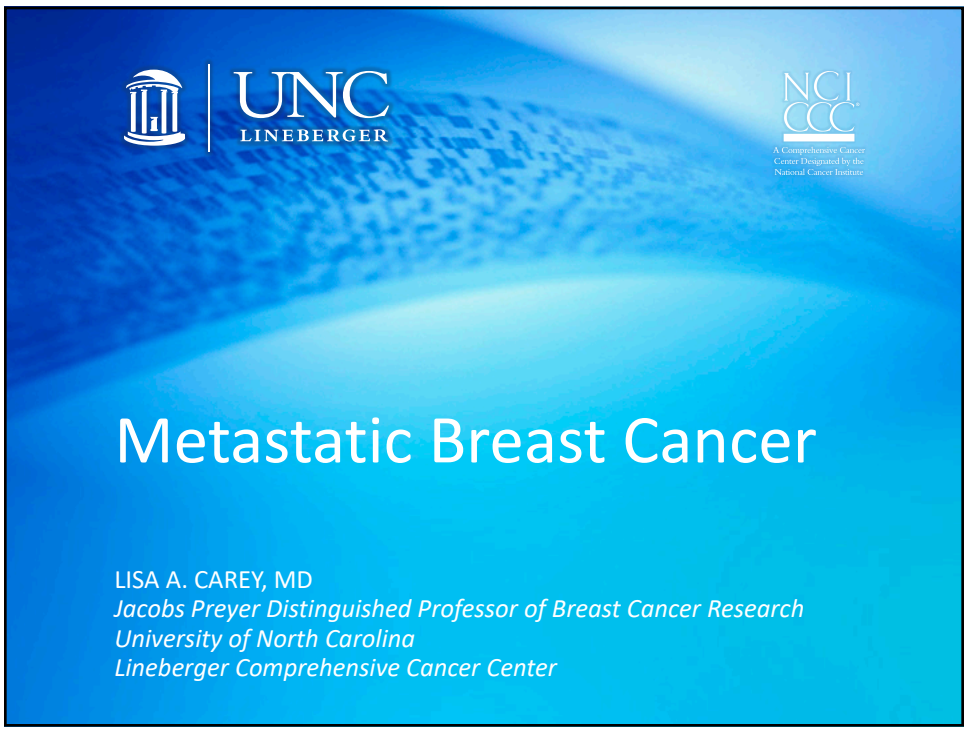


Disclosures

Research funding: GSK, Novartis, Genentech/Roche

Epidemiology of Metastatic Breast Cancer

Approximately 40,000 deaths per year from breast cancer, but declining because of advances in HER2+ disease

Median survival 2-3 years, but highly variable

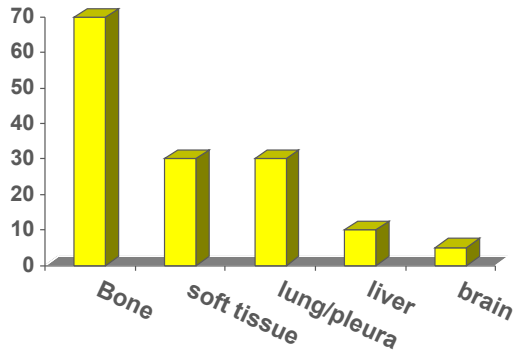
Prevalent population in U.S. ≈200,000 women

Any general oncologist by necessity is also a breast cancer specialist

New Patients With Metastatic Breast Cancer in U.S.

Subtype	Percentage
HER2+	~15-20% (↓ing)
Triple Neg	~ 15-20%
ER/PR+ and HER2-	~ 60-70%

Metastatic Sites



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

Heterogeneity of Metastatic Breast Cancer

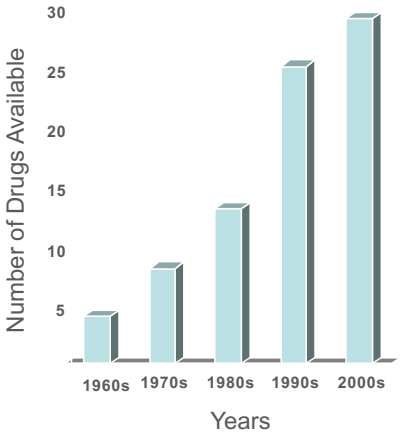
Disease Characteristics

- Disease-free interval
- Sites and volume of disease
- Tempo of disease
- Prior therapy
- ER and PR status
- HER-2 status

Patient Characteristics

- Performance status
- Comorbidity
- Host factors
  - ? Immune response
  - ? Drug metabolism

Growing Number of 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, ixabepilone, eribulin, denosumab, everolimus, palbociclib, fulvestrant, T-DM1, pertuzumab, ribociclib…

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Metastatic Breast Cancer 2018

All therapy is palliative

Survival has increased

Survival depends mostly on tempo

- Biology of tumor is key

Goals of treatment

- Control of disease and symptoms
- Maximizing quality of life
- Minimize treatment toxicity

You can't improve on being asymptomatic!

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Systemic Therapy for Metastatic Breast Cancer

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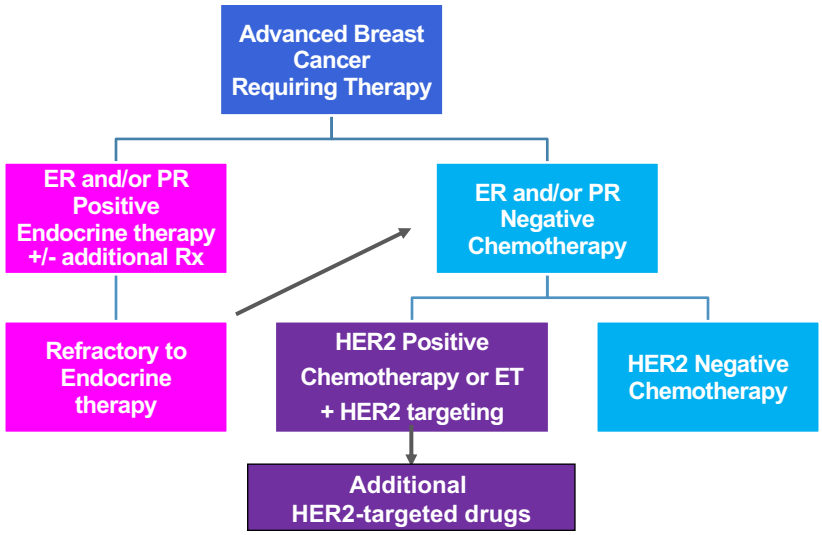
Treatment Based on Tumor Phenotype



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ASCO/ESMO Clinical Practice Guidelines

Chemotherapy and Targeted Therapy for Women With HER2–Negative (or unknown) ABC.

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer.

Endocrine Therapy for Hormone Receptor Positive Metastatic Breast Cancer.

ESO-ESMO Consensus Conference Advanced Breast Cancer (ABC3)

ABC4 coming this fall!

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Partridge A et al, JCO 2014; Giordano S et al, JCO 2014; Rugo H et al, JCO 2016; Cardoso F et al, Ann Oncol 2017

ASCO Guidelines: General Principles

HR+ HER2-
- **Endocrine (usually) preferable to chemotherapy in 1st line**
- **Targeted agents added to ET (CDK4/6, mTOR, PI3K 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**
  - **Factors: prior Rx, toxicity, performance status, comorbidity, patient preference.**

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-, abema- or ribociclib
  - Fulvestrant
  - Fulvestrant + palbo/abema/ribociclib
  - Fulvestrant + alpelisib (PIK3CAmt)
  - Steroidal AI
  - Steroidal AI + everolimus
  - Tamoxifen
  - Estradiol

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

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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.

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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

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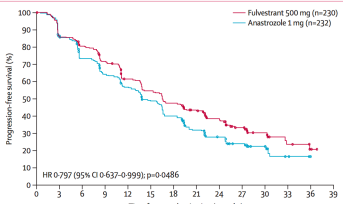
Nabholtz JM et al, JCO 2000; Mouridsen H et al, JCO 2003; Paridaens RJ et al, JCO 2008

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 trials usually AI 1st line, fulvestrant later**

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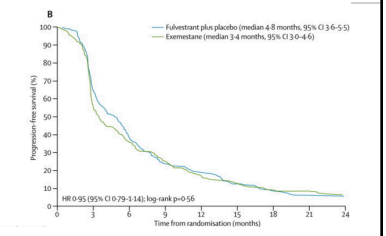
2nd Line Endocrine Rx (after NSAI)

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

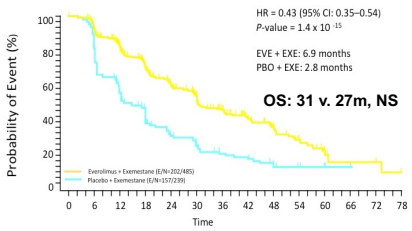
If NSAI/CDK4/6i used 1st, either fulvestrant or exemestane next is ok



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)



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

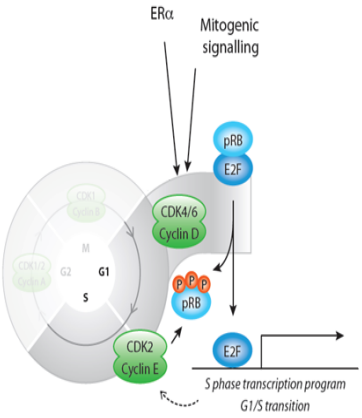
Cyclin Dependent Kinase 4/6 Inhibitors

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**

3 drugs approved for HR+ HER2- MBC with similar efficacy.

- **Palbociclib (ANC major toxicity)**
- **Abemaciclib (GI major toxicity)**
- **Ribociclib (QTc = EKG monitoring)**



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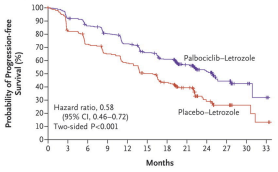
Palbociclib Trials in HR+ Disease

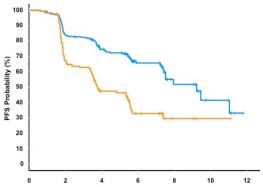
PALOMA-2: Phase III letrozole ± palbo in 1st line HR+/HER2-



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)

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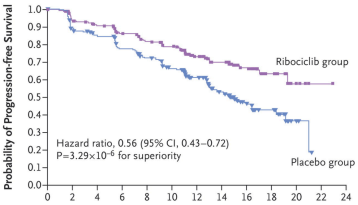
Finn R et al, NEJM 2016; Finn R et al ASCO 2017; Turner N et al, NEJM 2016

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

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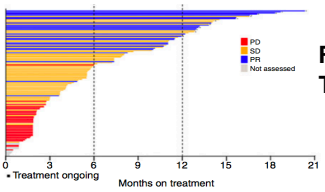
Hortobagyi G et al, NEJM 2016

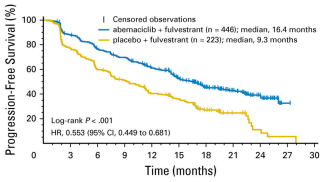
Abemaciclib Trials in HR+ HER2- Disease

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 1st line – PFS HR 0.54
(81% diarrhea, 41% neutropenia)

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

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Dickler M et al, Clin Cancer Res 2017; Sledge G et al, JCO 2017; di Leo A et al, ESMO 2017

Alpelisib Added to Fulvestrant in PreRx

Men or postmenopausal women, with HR+, HER2– ABC
- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

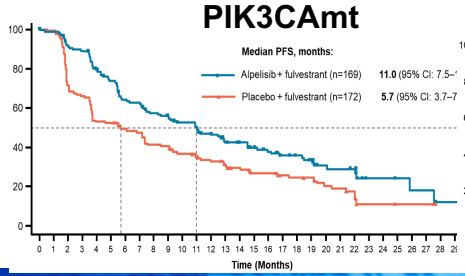
(N=572)

PIK3CA-mutant cohort (n=341) — R
- **ALP** 300 mg QD PO + **FUL** 500 mg IM* n=169
- **PBO** + **FUL** 500 mg IM* n=172

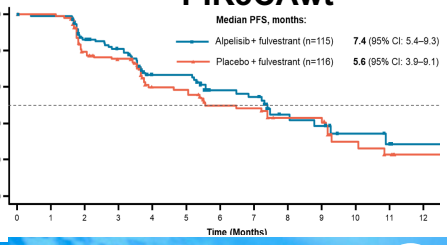
1:1, stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

PIK3CA-non-mutant cohort (n=231) — R
- **ALP** 300 mg QD PO + **FUL** 500 mg IM* n=115
- **PBO** + **FUL** 500 mg IM* n=116

PIK3CAmt



PIK3CAwt



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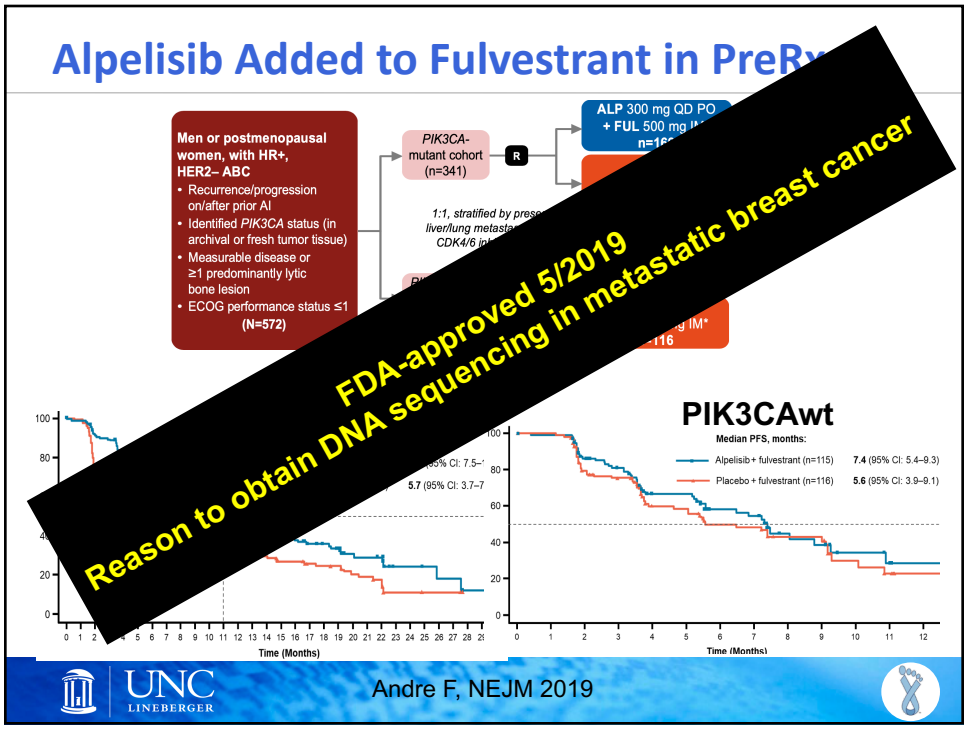
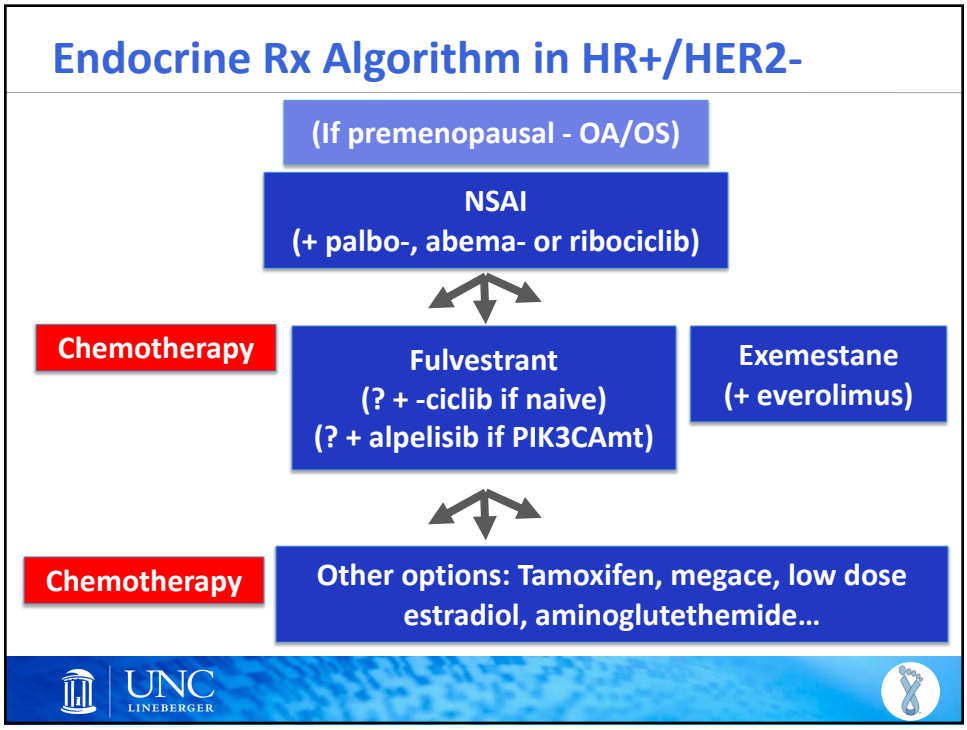
Andre F, NEJM 2019


Alpelisib Added to Fulvestrant in PreRx
Men or postmenopausal women, with HR+, HER2– ABC
• Recurrence/progression on/after prior AI
• Identified PIK3CA status (in archival or fresh tumor tissue)
• Measurable disease or ≥1 predominantly lytic bone lesion
• ECOG performance status ≤1
(N=572)
PIK3CA-mutant cohort (n=341)
R
ALP 300 mg QD PO + FUL 500 mg
FDA-approved 5/2019
Reason to obtain DNA sequencing in metastatic breast cancer
PIK3CAwt
Median PFS, months:
Alpelisib + fulvestrant (n=115) 7.4 (95% CI: 5.4–9.3)
Placebo + fulvestrant (n=116) 5.6 (95% CI: 3.9–9.1)
Time (Months)
Andre F, NEJM 2019


Endocrine Rx Algorithm in HR+/HER2-
(If premenopausal - OA/OS)
NSAI
(+ palbo-, abema- or ribociclib)
Chemotherapy
Fulvestrant
(? + -ciclib if naive)
(? + alpelisib if PIK3CAmt)
Exemestane
(+ everolimus)
Chemotherapy
Other options: Tamoxifen, megace, low dose estradiol, aminoglutethemide…

PARP Inhibition in Germline BRCA1/2 Carriers

OlympiAD

HER2- MBC g*BRCA*mt
≤2 chemo for MBC
(prior A, T. No plat-R)

2:1
N~300

- Olaparib 300 mg po bid
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine

Treat until progression

Primary endpoint PFS

EMBRACA

HER2- MBC g*BRCA*mt
≤2 chemo for MBC
(prior A, T. No plat-R)

2:1
N~300

- Talazoparib 1mg po qd
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine
  - Gemcitabine

Treat until progression

Primary endpoint PFS

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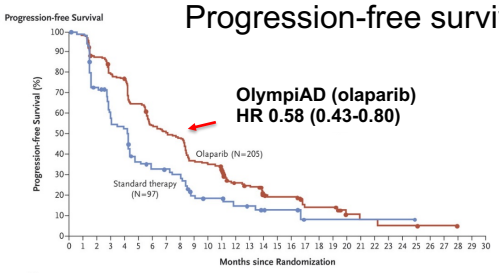
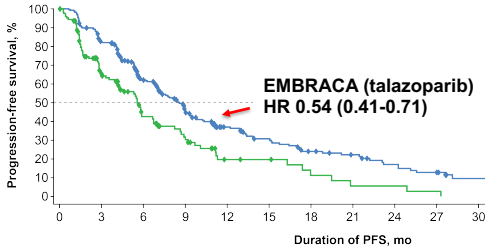
Robson et al, NEJM 2017; Litton et al, NEJM 2018

PARP Inhibition in PreRx Germline BRCA+

Progression-free survival





- **Both drugs are better and more tolerable than 2nd line chemo.**
- **Neither has much of an OS advantage.**
- **Comparison to 1st line Rx especially platinums unknown.**

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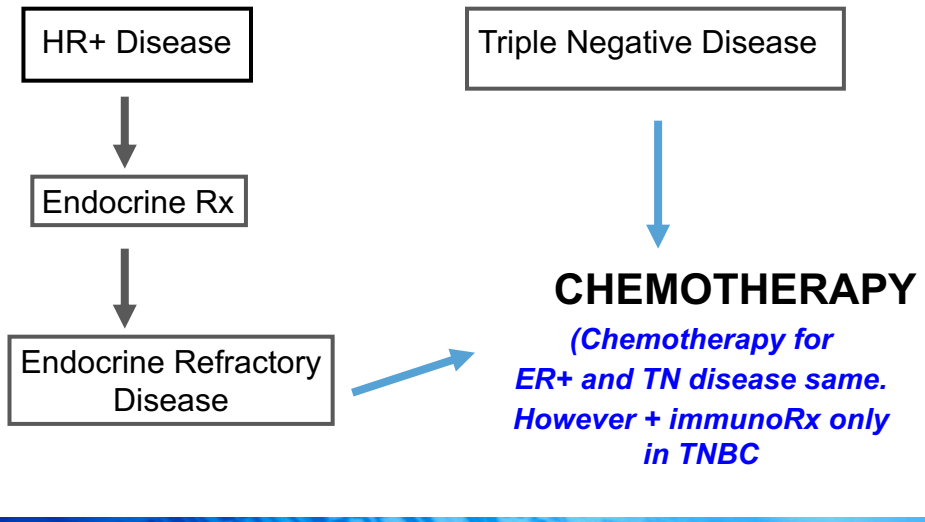
Robson et al, NEJM 2017; Litton et al, NEJM 2018

Chemotherapy in HER2- Breast Cancer



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MBC Chemotherapy: Wide Options

Anthracycline
- Doxorubicin
- Epirubicin
- Liposomal doxorubicin

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

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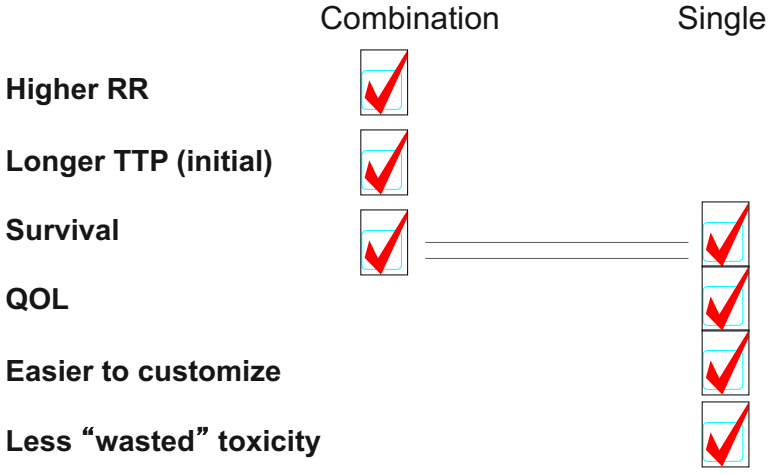
Combination vs Single Agent Chemotherapy



Single agent preferred unless response is important

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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**

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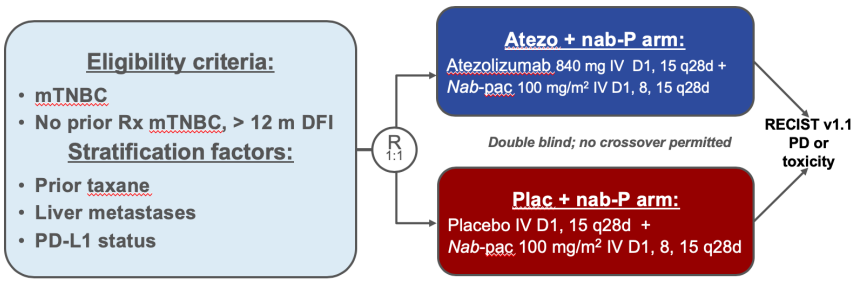
Immunotherapy in TNBC



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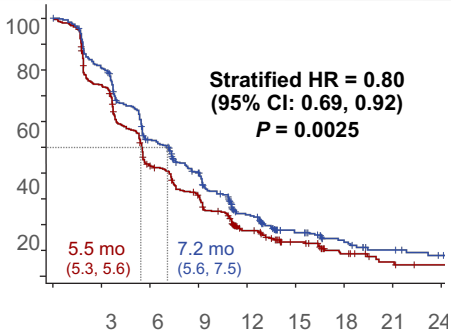
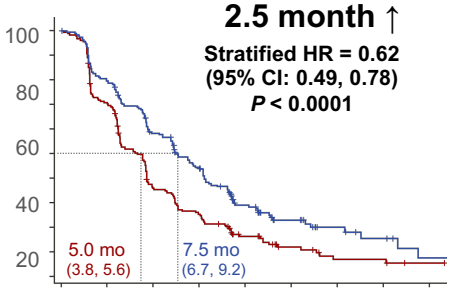
IMpassion 130: Progression-Free Survival (ITT)



Overall population
1.7 month ↑



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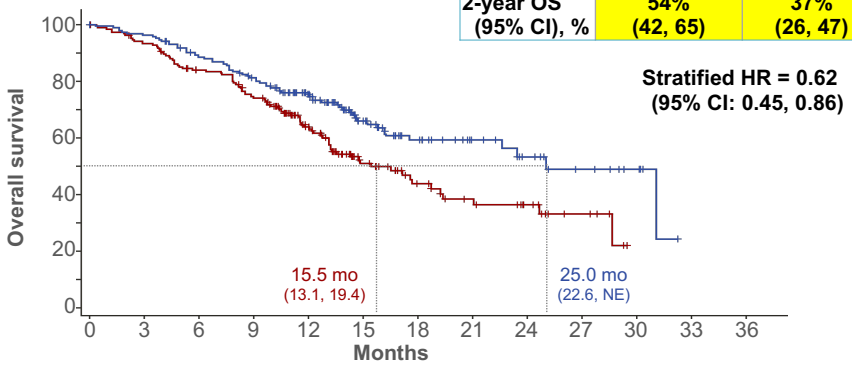
Schmid et al, NEJM 2019

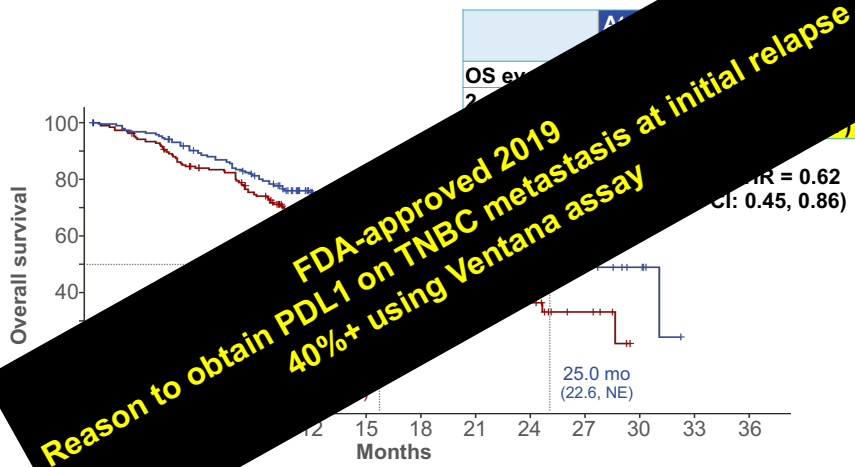
IMpassion 130 Interim Overall Survival: PD-L1+

	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)



Schmid et al, NEJM 2019

IMpassion 130 Interim Overall Survival: PD

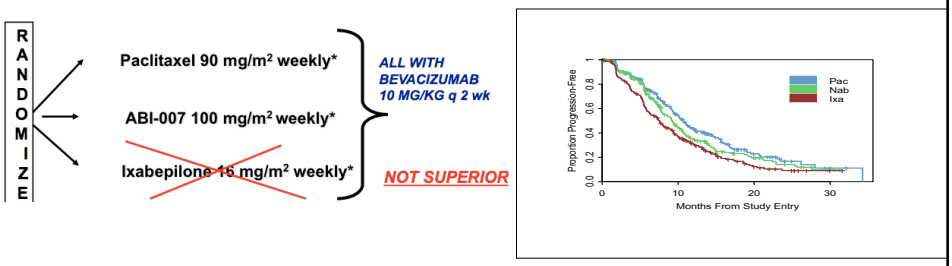


FDA-approved 2019
Reason to obtain PDL1 on TNBC metastasis at initial relapse
40%+ using Ventana assay

Schmid et al, NEJM 2019

1st Line Chemotherapy Otherwise

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

REASONABLE: single agent weekly taxane (paclitaxel, nab-paclitaxel, docetaxel) unless recent adjuvant taxane. Platinums ok 1st line in triple negative.

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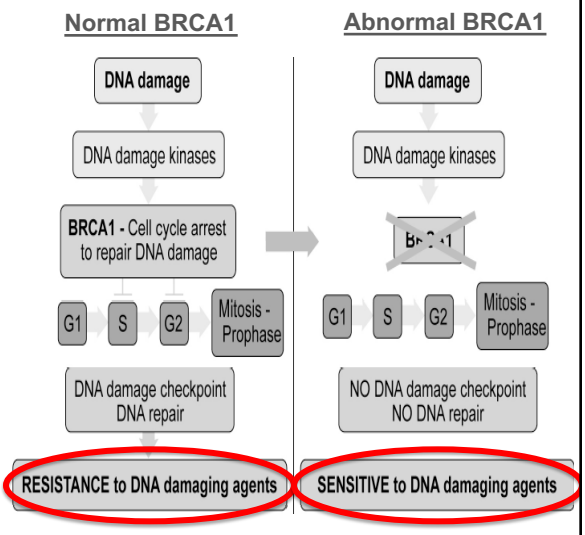
Rugo H et al, JCO 2015; Piccart-Gebhart MJ et al, JCO 2008

Direct DNA Damaging Agents in TNBC

BRCA-associated cancer is usually TNBC (basal-like)

BRCA + and BRCA – TNBC have many shared characteristics.

Is this therapeutically meaningful?



Classic DNA-damaging agents = platinums, ionizing radiation

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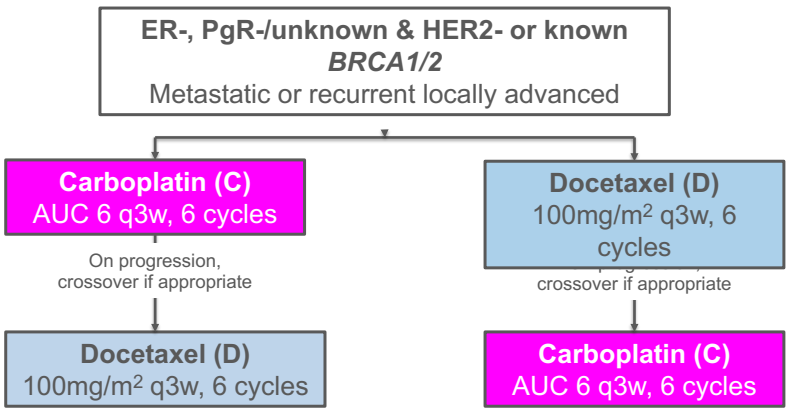
Platinums 1st Line in TNBC: TNT Trial



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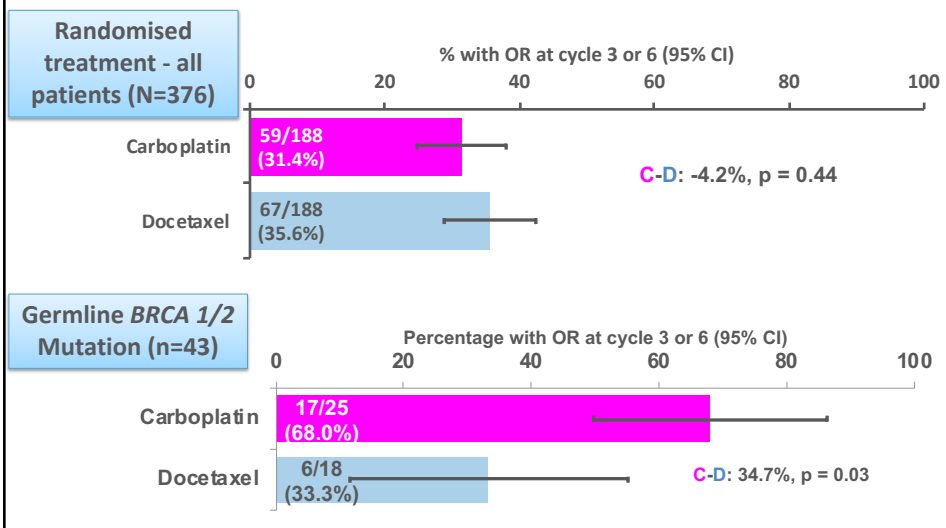
Tutt et al, AACR-SABCS 2014

TNT: Objective response



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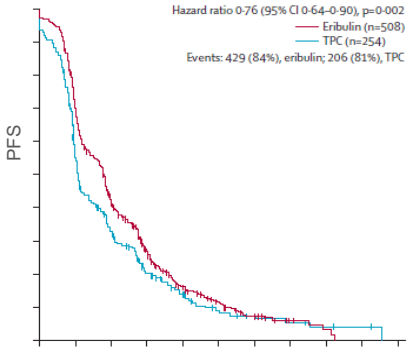
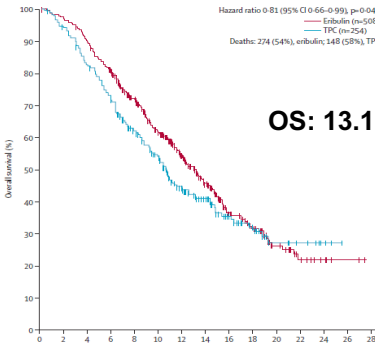
Tutt et al, AACR-SABCS 2014

2nd+ Chemotherapy Lines: Eribulin vs TPC



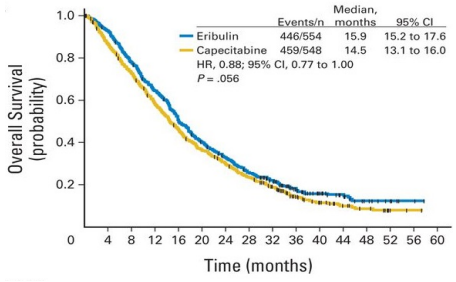
Eribulin novel antitubule drug (halichondrin A analog from sea sponge)



OS: 13.1 vs 10.6m

Cortes J et al, Lancet 2011

2nd+ Chemotherapy Lines

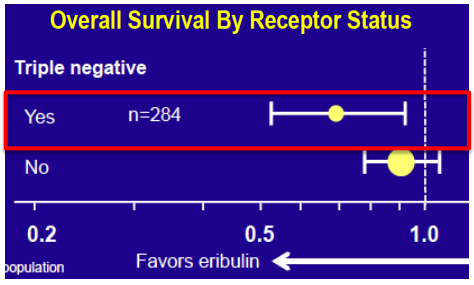


Capecitabine (older oral antimetabolite)= eribulin (novel antimetabolite)

OS 14.5m vs 15.9m

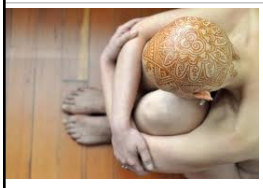
Eribulin <u>may be</u> better in TNBC

Very different toxicity profiles:
- **Eribulin: neutropenia, alopecia, neuropathy**
- **Capecitabine: HFS, diarrhea**



Kaufman P et al, JCO 2015

Toxicity is a Key Feature to Consider



- alopecia
  - Capecitabine
  - Vinorelbine
  - Carboplatin

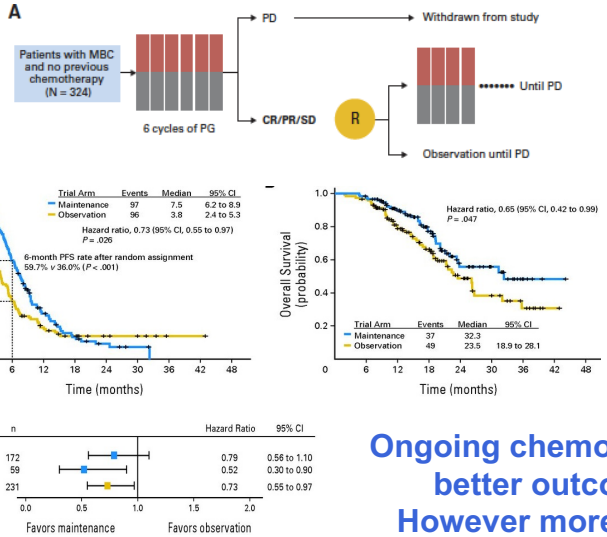
- GI symptoms
  - Taxanes
  - Gemcitabine

- neuropathy
  - Capecitabine
  - Anthracyclines
  - Gemcitabine

- myelosuppression
  - Taxanes
  - Capecitabine

- IVs
  - Capecitabine

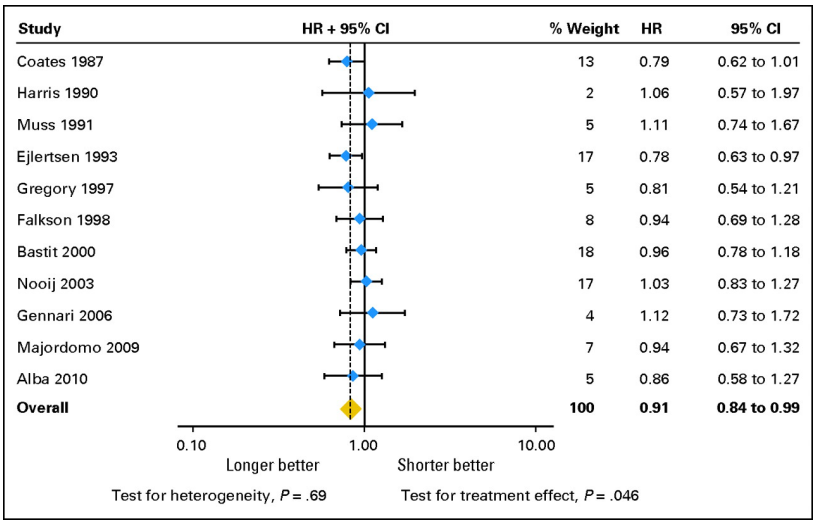
Continued versus Interrupted Chemotherapy



Ongoing chemotherapy better outcome
However more toxic

Park YH et al, JCO 2013

Meta-Analysis Chemotherapy Duration: Survival



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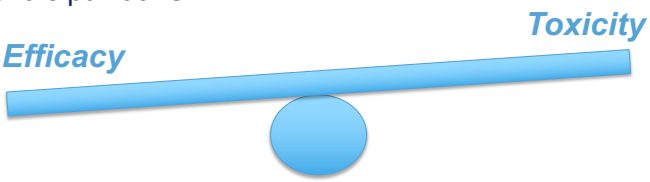
Gennari A et al, JCO 2011

General Principles of Chemotherapy

All treatment is palliative



- **TNBC and endocrine-resistant HR+**
  - **HER2 different principles**
  - **TNBC – initial Rx nab-paclitaxel if PDL1+ and giving immunotherapy**
- **Single agent > polychemotherapy**
  - **(unless symptomatic or rapidly progressive)**
- **First-line: Taxane (unless recently Rx adjuvantly)**
  - **Platinum in TNBC**
- **Later-line: Many choices**
  - **Eribulin, capecitabine, platinums**
  - **Anthracyclines (if did not receive adjuvantly – cannot give twice)**

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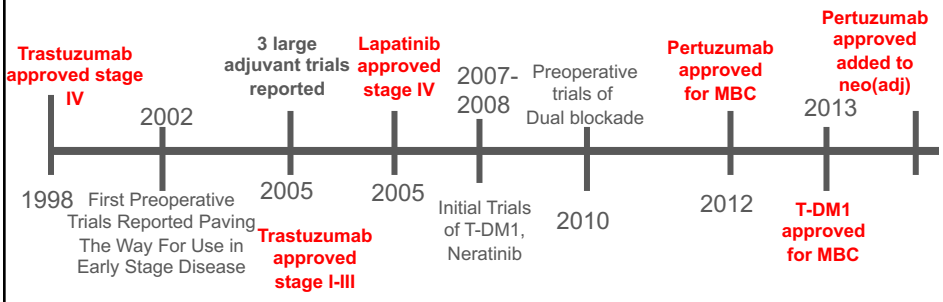
HER2+ Disease: Major Clinical Advances

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, Duane E. Keith, Wendy J. Levin, Susan G. Stuart, Judy Udove, Axel Ullrich, Michael F. Press

1989



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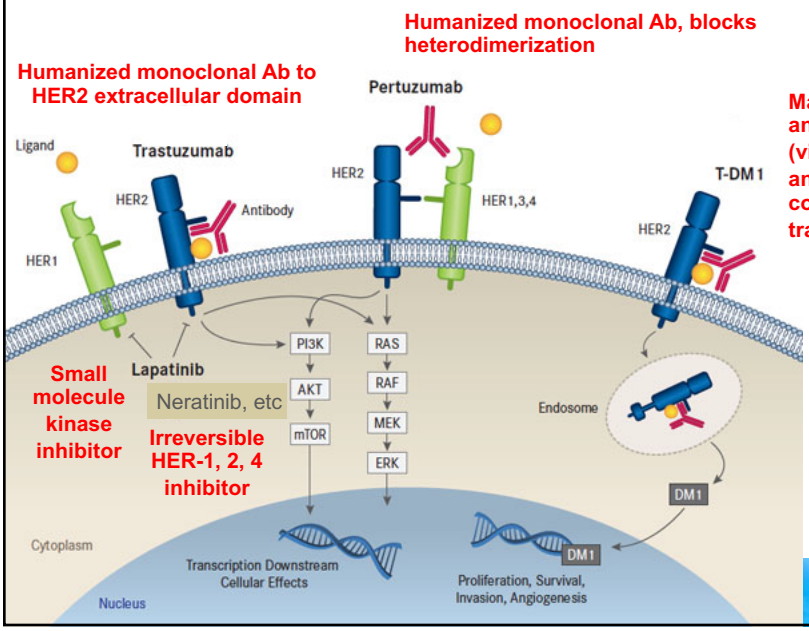
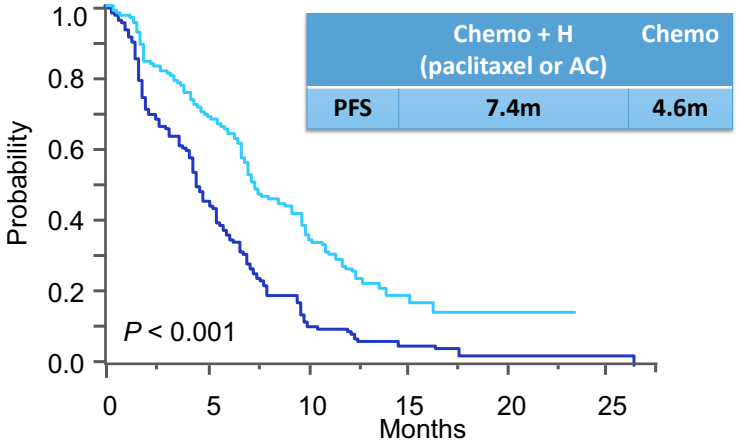
Targeting HER2



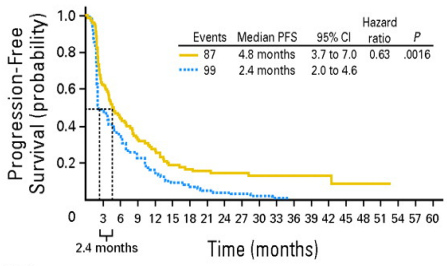
Trastuzumab Added To Chemotherapy



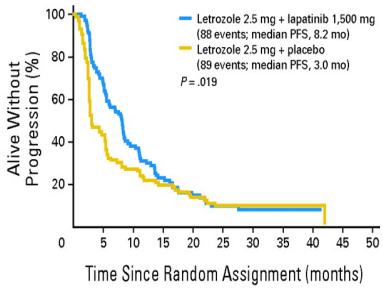
	Chemo + H (paclitaxel or AC)	Chemo
PFS	7.4m	4.6m

Slamon DJ, et al. NEJM 2001

HER2-Targeting Added To Endocrine Therapy



anastrozole vs anastrozole + trastuzumab
Kaufman B et al, JCO 2009



letrozole vs letrozole + lapatinib
Johnston S 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-trastuzumab 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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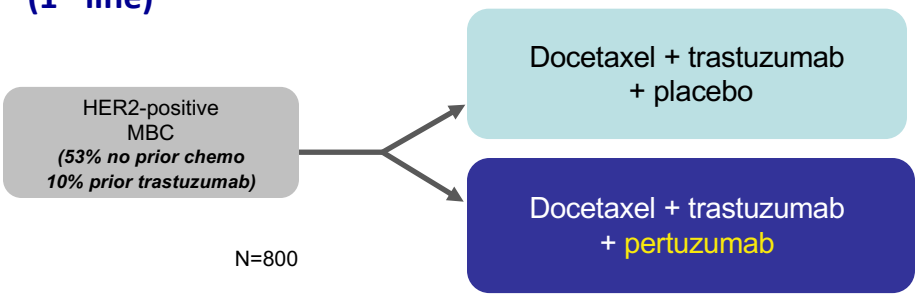
Pertuzumab

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



End points

- PFS and OS
- quality of life
- biomarker analysis

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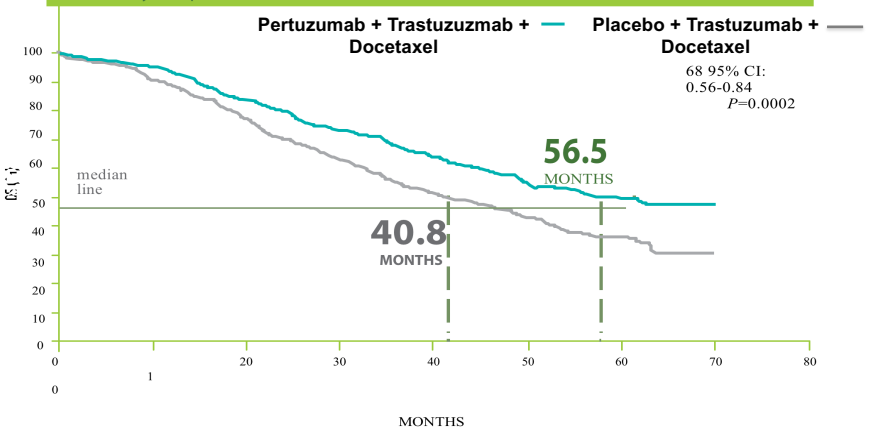
Baselga J et al. NEJM 2012

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]



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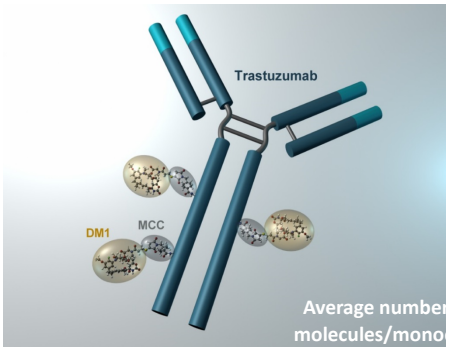
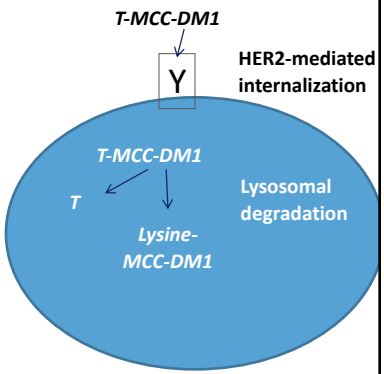
Baselga J et al, NEJM 2012; Swain S et al, NEJM 2015

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)

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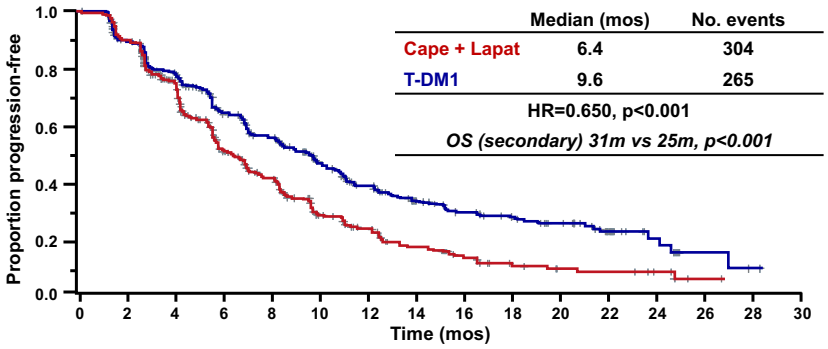
EMILIA: Phase III Trial T-DM1 versus XL

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

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

Win-Win

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Verma S et al, NEJM 2012

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

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Baselga J et al, NEJM'12; Swain S et al, NEJM'15; Hurvitz S et al, Lancet Oncol'15; Verma S et al, NEJM'12; Andre F et al, Lancet Oncol'14; Krop IE et al, Lancet Oncol'14

Next Generation of HER2-Targeting

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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	?fewer CNS with TN?
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

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Baselga J et al, NEJM'12; Swain S et al, NEJM'15; Hurvitz S et al, Lancet Oncol'15; Verma S et al, NEJM'12; Andre F et al, Lancet Oncol'14; Krop IE et al, Lancet Oncol'14

Oncogene Addiction:

HER2 is Still a Relevant Target After Progression on Trastuzumab

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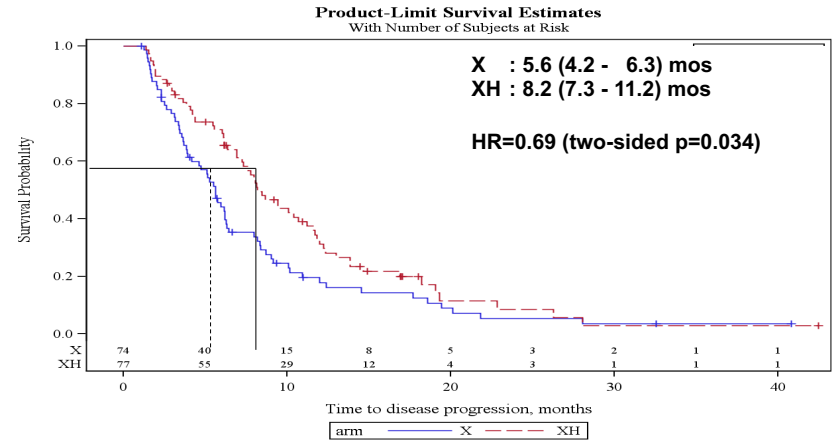
Capecitabine ± Trastuzumab: Time To Progression (after prior trastuzumab)



ORR 48% vs 27%, p=0.0011

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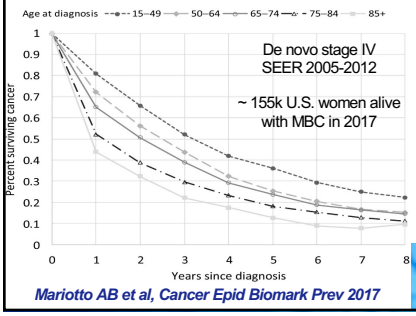
von Minckwitz G et al, JCO 2009

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	



Mariotto AB et al, Cancer Epid Biomark Prev 2017

Median survival increasing
Multiple drug choices

How do we treat most thoughtfully?

Treatment Approach HER2+ MBC in 2018

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

Who Should Receive Endocrine Therapy Upfront?

ET + HER2-targeting
ET alone

Second Line: **TDM-1**

Third, Fourth, Fifth, Sixth Line:

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

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Local Therapy for Metastatic / Recurrent Breast Cancer

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Local Therapy of Metastatic Breast Cancer

Role of surgery or radiation

- Regional recurrence – e.g. chest wall lesion, regional LN – curative intent R
- Distant disease – e.g. isolated pulmonary nodule, hepatic met – not standard, used for symptomatic relief
- Local Rx of oligometastatic disease – controversial – not standard

Exception #1: symptomatic or locally threatening disease

Exception #2: brain metastases

- Survival advantage associated with local therapy
  - Surgery
  - Radiosurgery
  - Coordinated multidisciplinary management is key

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When Else to Consider Local Therapy

Disease is truly localized

Local symptoms are present and low chance of palliation with systemic rx

Impending localized complication (spinal cord compression, fracture)

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Breast Surgery in Metastatic Disease

Multiple retrospective, a few prospective studies – remains controversial

Patients who undergo breast surgery typically live longer than those who do not – but many uncontrolled variables

Underlying hypothesis is the breast serves as a site of ongoing tumor cell dissemination

Recently completed randomized trial in U.S.

RECOMMENDATION: option but not standard. Consider if local complications exist or oligometastatic.

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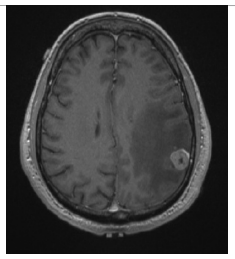
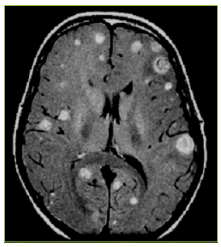
Diagnosis of Brain Metastases





Presentation
- Headaches, seizures, neurologic deficit
- More found incidentally
- Routine screening not recommended
- 4x more common in HER2+ (often isolated) and TNBC (usually with progression elsewhere)

MRI best diagnostic test, CT next choice
- 50% multiple, 50% 1-3 lesions

11% false + if single lesion *(Patchell RA et al, NEJM 1990)*
- DDx: Primary brain tumors, infections, infarcts, MS, hemorrhage

Rx:
- 1-3 metastases: SRS or surgery then consideration of whole brain RT (may defer in good prognosis patients)
- multiple intraparenchymal = WBRT, then systemic Rx
- Leptomeningeal – poor px = consider craniospinal RT, IT Rx

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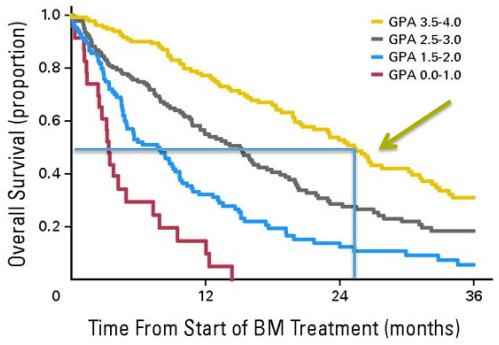
Brain Metastasis: Heterogeneous Prognosis

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____



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Sperduto PW et al, JCO 2012

Drugs with Reported CNS Activity

CMF
CAF
Cisplatin
Carboplatin
Capecitabine
Temozolomide
Irinotecan
High dose methotrexate

In HER2+: lapatinib (and newer small molecule TKI) maybe trastuzumab.

No systemic standard of care, Rx is individualized.

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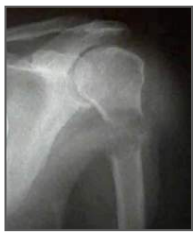
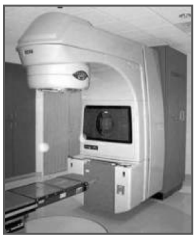
Skeletal Morbidity from Bone Metastases in Advanced Cancer

Skeletal Related Events (SREs)

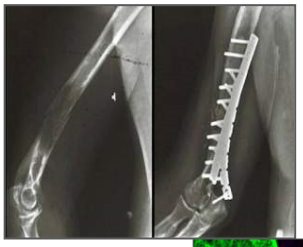
Pathologic Fracture



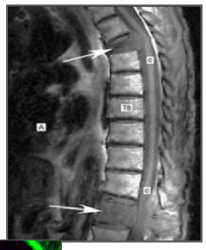
Radiotherapy to Bone



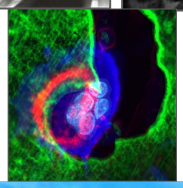
Surgery to Bone



Spinal Cord Compression



Hypercalcemia



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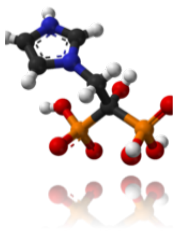
Bone-targeted Agents

Little data, not standard

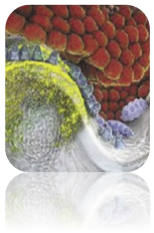


Bisphosphonates

Zoledronic acid
Clodronate
Pamidronate
Ibandronate

RANK Ligand inhibitor

Denosumab



Radiopharmaceuticals

Radium-223
Strontium-89
Samarium-153

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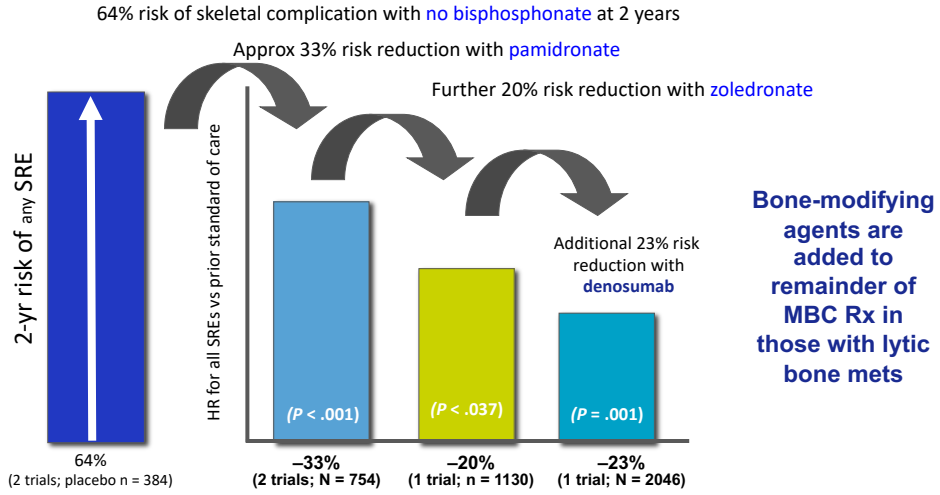
Benefits of Bone Resorption Inhibitors in Advanced Breast Cancer



Bone-modifying agents are added to remainder of MBC Rx in those with lytic bone mets

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Lipton et al, Cancer 2000; Rosen et al, Cancer 2003; Stopeck et al. JCO 2010 (adapted courtesy of Hope Rugo)

Treatment of MBC: Where Now?

Major progress in MBC management:

- **Multiple HR- and HER2-targeted options**
- **Immunotherapy in some TNBC**
- **PARP inhibition mainstay in germline carriers.**

Chemotherapy still primary or key for many – optimize!

- **Consider entire menu of Rx, toxicity, and patient preference.**

Involve Palliative Care / Symptom Management colleagues early.

Goals of therapy in MBC:

1. Disease control

2. Quality of life

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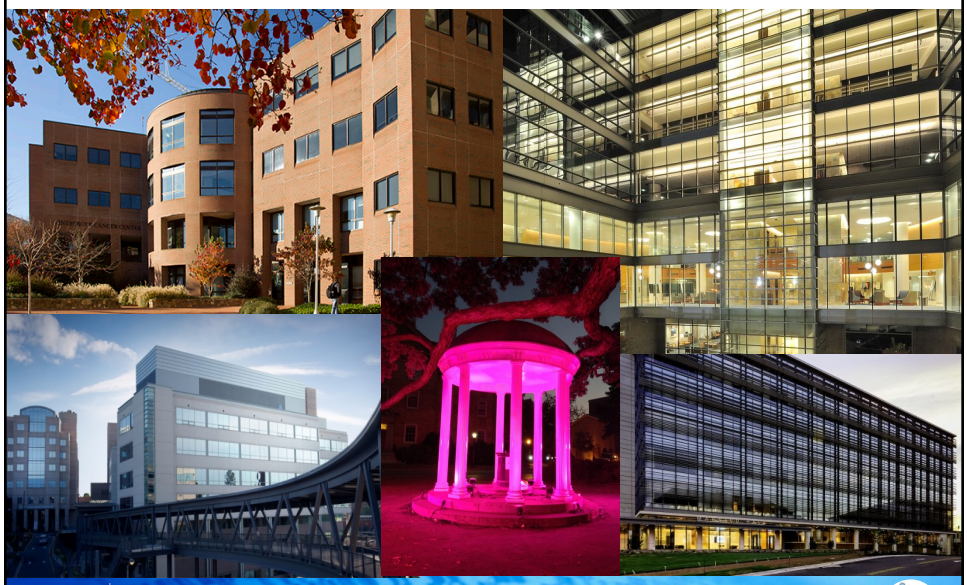
Thank you!



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Questions

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Question 1

Which of the following regimens represent acceptable first-line treatment for a postmenopausal women with hormone receptor positive breast cancer?

A. Letrozole
B. Anastrozole
C. Exemestane
D. Low dose estradiol
E. Megesterol acetate
F. Tamoxifen

Choices

1) A only
2) A, B, and C
3) All of the above
4) A, B, C, F

Question 1: Explanation

Answer = 4

The aromatase inhibitors (letrozole, anastrozole, and exemestane) represent appropriate first-line drugs. A CDK4/6 inhibitor (palbociclib, ribociclib, abemaciclib) can be added in first-line with the nonsteroidal AI (letrozole, anastrozole).

Fulvestrant, an ER downregulator, is at least as effective as AI in the first-line but has only been combined with CDK4/6 inhibitors in pretreated setting.

Tamoxifen is an acceptable alternative, generally in those who have already received AI and fulvestrant.

Neither low dose estradiol nor megesterol acetate are appropriate first-line treatments as each has more toxicity and is likely less effective than the other options.

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Question 2

When chemotherapy is administered in the first- or second-line setting, combination therapy should usually be used.

A. True

B. False

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Question 2: Explanation

False. Although combination chemotherapy is associated with higher response rates and longer time to progression than single agents, combination therapy does not improve survival when cross-over is allowed and has greater toxicity.

Combination therapy is appropriate for symptomatic disease or impending visceral crisis, when higher response rate is desired.

Either combination therapy or single agent treatment represents appropriate clinical care, and the approach can be individualized to the patient's disease status and preferences.

Question 3

In a patient progressing on antiHER2 therapy with trastuzumab, subsequent treatments should also include antiHER2 therapy.

A. True

B. False

Question 3: Explanation

Unlike most cancer treatments, randomized controlled trials suggest benefit from continuing anti-HER2 therapy after disease progression on trastuzumab.

This has been seen in studies with regimens including trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1).