Breast Health Global Initiative

Global Summit on International Breast Health and Cancer Control:

Improving Breast Health Care through Resource-Stratified Phased Implementation

Metastatic Disease – Treatment and Palliative Care

Alexandru Eniu, MD
Cancer Institute "Ion Chiricuta" (Romania)

BHGIatFredHutch BreastHealthGlobalInitiative

FRED HUTCH CURES START HERE® susan g. komen® BREAST CANCER INITIATIVE 25 NCCN National Comprehensive Cancer Network®

Metastatic Disease Treatment and Palliative Care

Alexandru Eniu, MD, PhD
Department of Breast Tumors
Cancer Institute Ion Chiricuţă
Cluj-Napoca, Romania

BHGI Veteran (2002- ongoing)
Past Chair, ASCO International Affairs Committee
Chair, ESMO Global Policy Committee

Fatima Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

ESMO Board of Directors & NR Committee Chair
ESO Breast Cancer Program Coordinator & ABC Global Alliance Chair
EORTC Breast Group Past-Chair

THE GLOBAL BURDEN OF BREAST CANCER

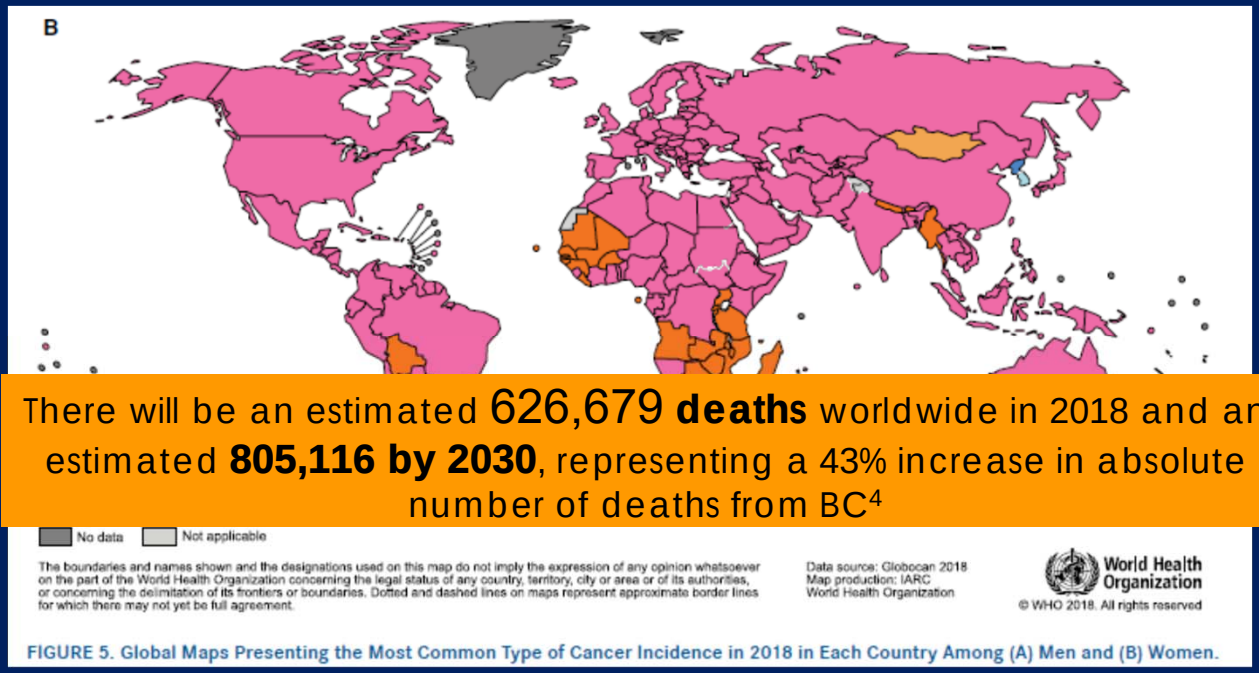


FIGURE 5. Global Maps Presenting the Most Common Type of Cancer Incidence in 2018 in Each Country Among (A) Men and (B) Women.

There will be an estimated 626,679 **deaths** worldwide in 2018 and an estimated **805,116 by 2030**, representing a 43% increase in absolute number of deaths from BC[4]

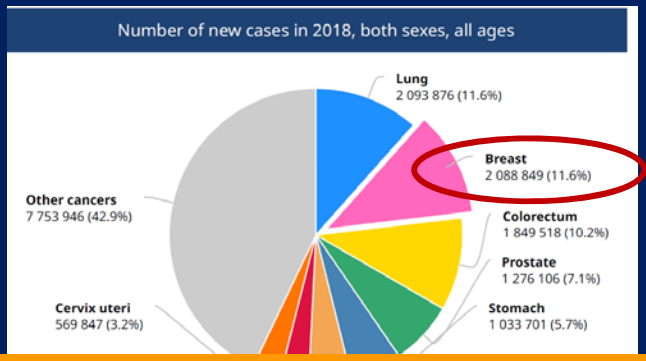
1 out of 8 to 10 women
will have BC during their lifespan
About 1/3 EBC will relapse
MBC at diagnosis: 10-15% developed to
50-60% developing countries

In Europe :
1 diagnosis every 2,5 minutes
1 death every 6,5 minutes
More than half a million deaths
worldwide every year

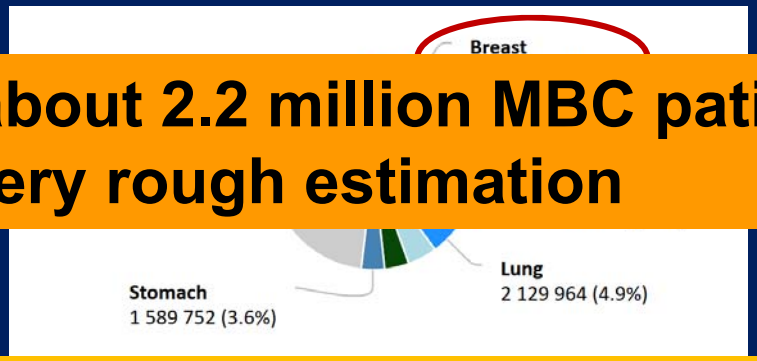
HOW MANY MBC PATIENTS EXIST?

*GLOBOCAN 2018 data**

Incidence

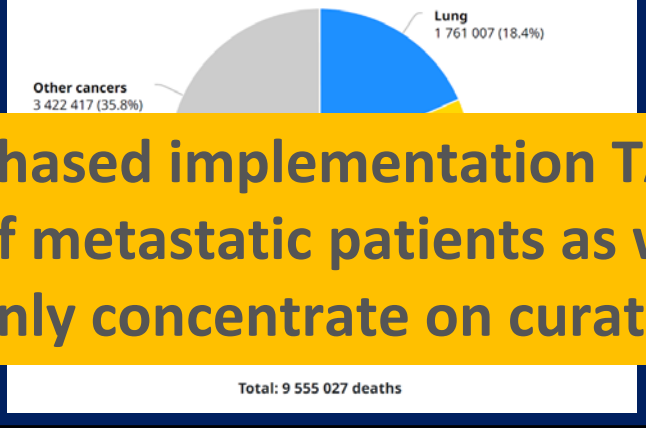


5-year Prevalence



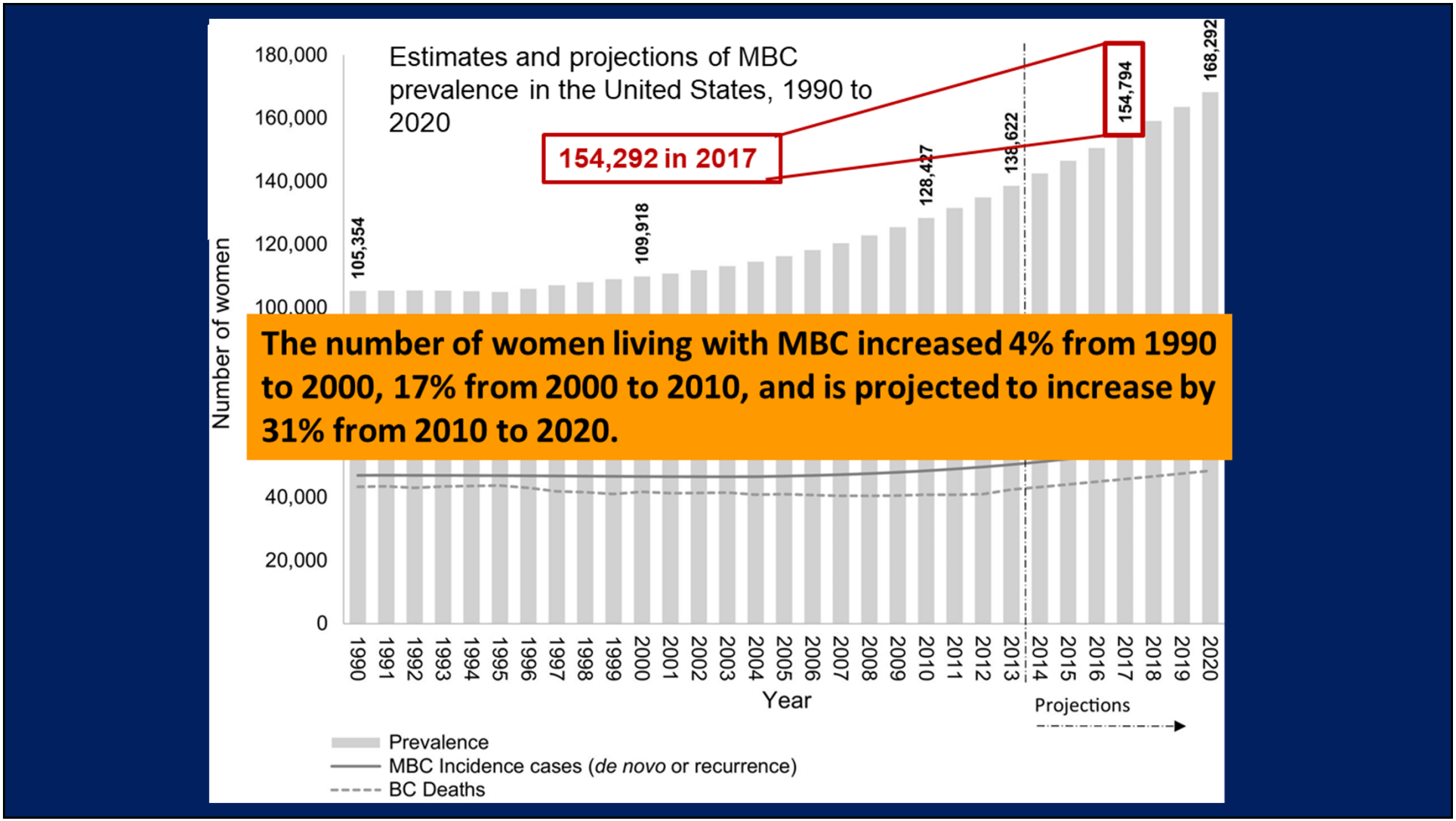
If 1 third would be MBC: about 2.2 million MBC patients
BUT it is just a very rough estimation

Mort



- **Phased implementation TARGET: prioritise management of metastatic patients as we can not ignore them and only concentrate on curative cases**

estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018.



OVERALL SURVIVAL AND SEQUENTIAL TREATMENT OF PATIENTS WITH MBC

- 134 sites, 298 oncologists, all over Germany
- > 3,700 pts/1409 MBC pts
- (goal: 4,500 BC pts/2250 MBC pts by end 2015)

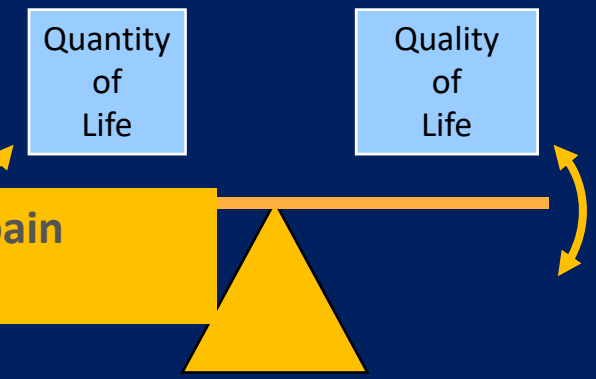
- **Luminal is the most frequent subtype in MBC as well.**
- **If a drug/class of drugs improves OS, it will change substantially the median OS of MBC**

■ **Phased implementation TARGET: ensure proper diagnosis and treatment for luminal cancers**

Oral Presentation, ABC 2
Marschner, N, et al, TMK Registry Group

GOALS OF THE TREATMENT IN MBC

- **Balancing treatment efficacy and toxicity is the main objective**
- **Goals of treatment:**
  - **Improve survival** *(very few agents achieve it!)*
  - **Delay disease progression**
  - **Prolong duration of response**
  - **Palliate symptoms**
  - **Improve or maintain quality of life**
  - **Transform into a chronic disease**



- **Phased implementation TARGET: ensure palliation and pain control, focus on QOL**

Resource-stratified guidelines: BHGI Incremental allocation & implementation

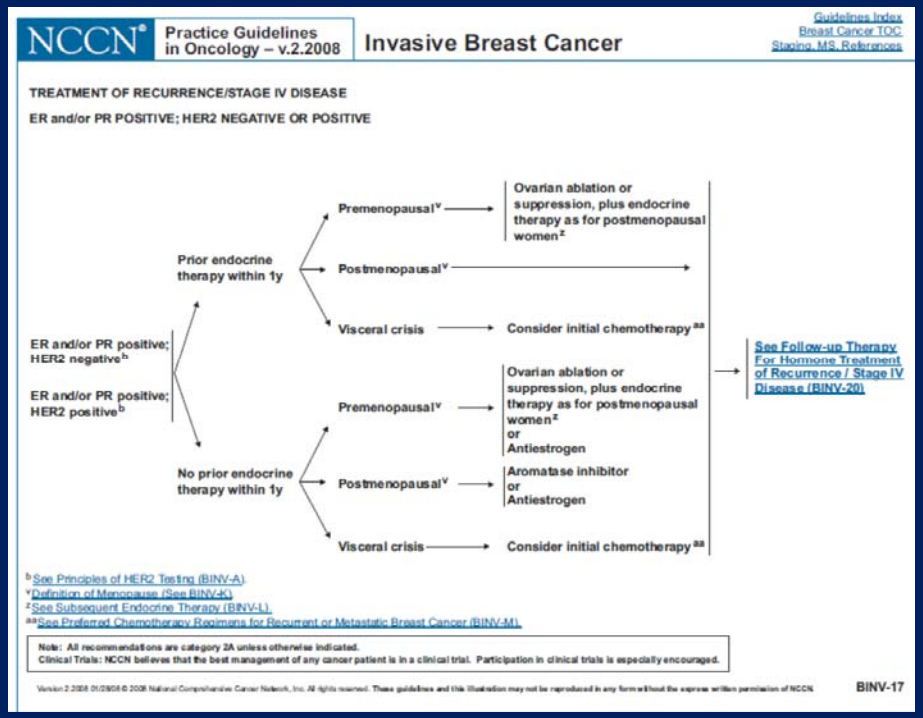
- Basic level: Core resources or fundamental services necessary for any breast health care system to function.
- Limited level: Second-tier resources or services that produce major improvements in outcome such as survival.
- Enhanced level: Third-tier resources or services that are optional but important, because they increase the number and quality of therapeutic options and patient choice.
- Maximal level: Highest-level resources or services used in some high resource countries with *lower priority* on the basis of extreme cost

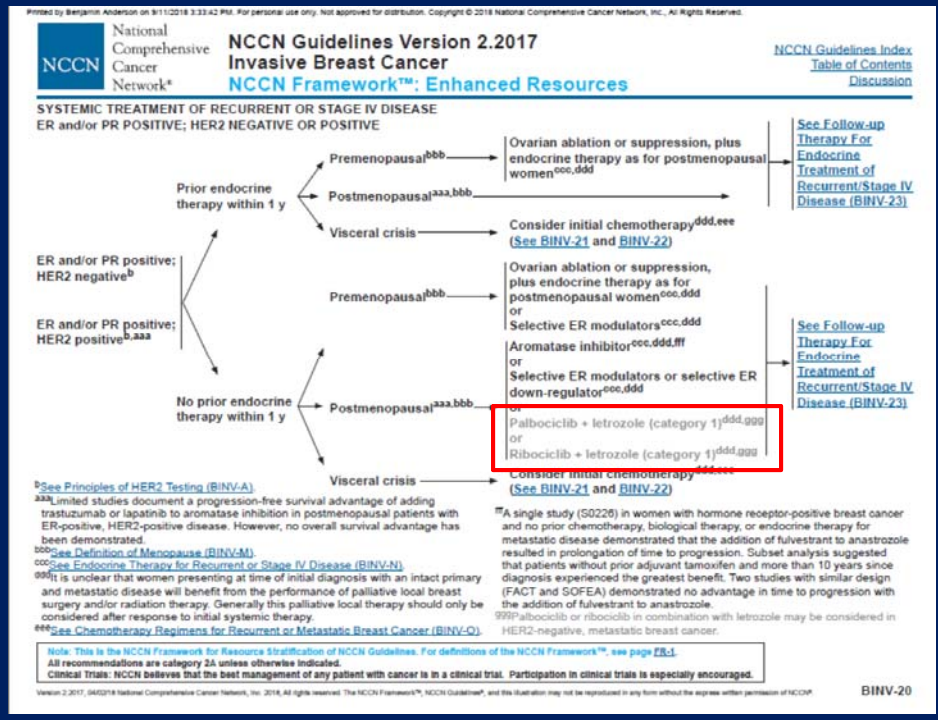
Anderson et al, The Breast J: 12 (1), 2006

Level of resources	Local-Regional Treatment		Systemic Treatment (Palliative)			Process Metrics
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Supportive Therapy	
Basic	Total mastectomy for ipsilateral breast tumor recurrence after breast conserving surgery			Oophorectomy in premenopausal women Tamoxifen*	Nonopioid and opioid analgesics and symptom management	Pain control provided (min 80%, target 95%) Hormone tx for all patients with ER+ ca 120d of diagnosis (min 80%, target 90%)
Limited		Palliative radiation therapy	Classical CMF† Anthracycline monotherapy or in combination†			Palliative XRT for CNS mets (min 70%, target 80%) First line palliative chemo if ER- ca (min 80%, target 90%)
Enhanced			Sequential single agent or combination chemotherapy Trastuzumab Lapatinib	Aromatase inhibitors	Bisphosphonates	Second line chemo, if visceral metastasis and good performance status (min 90%, target 95%) Bisphosphonates for lytic/symptomatic bone disease (min 90%, target 95%)
Maximal			Bevacizumab	Fulvestrant	Growth factors	Maximal category process metrics determined based upon standards of care in high-income countries

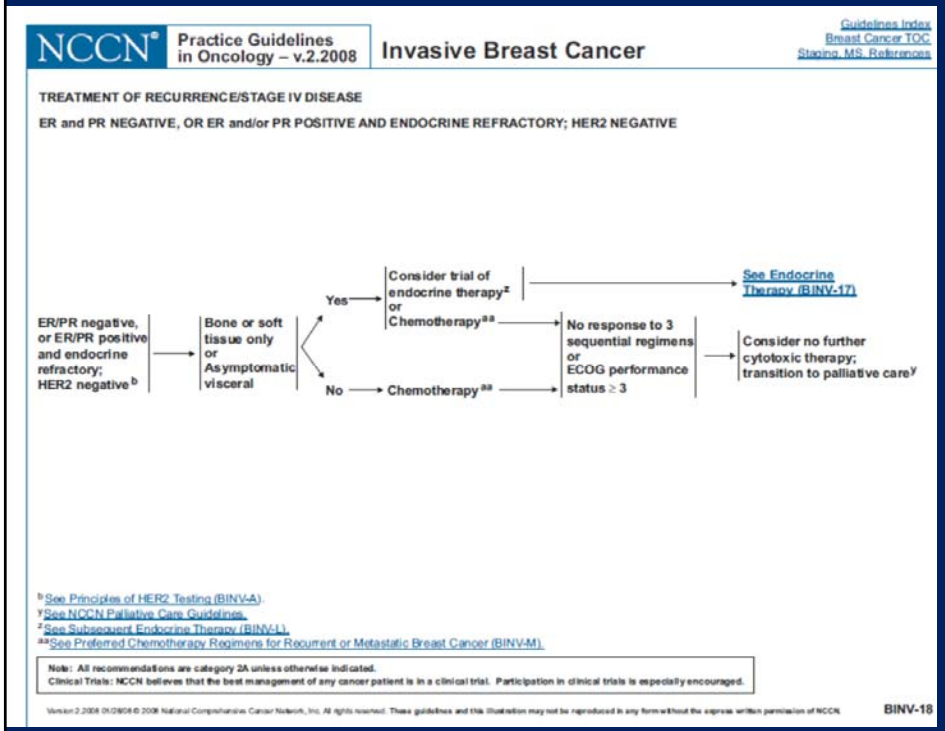
Eniu A et al, Cancer: 113 (8 suppl), 2008

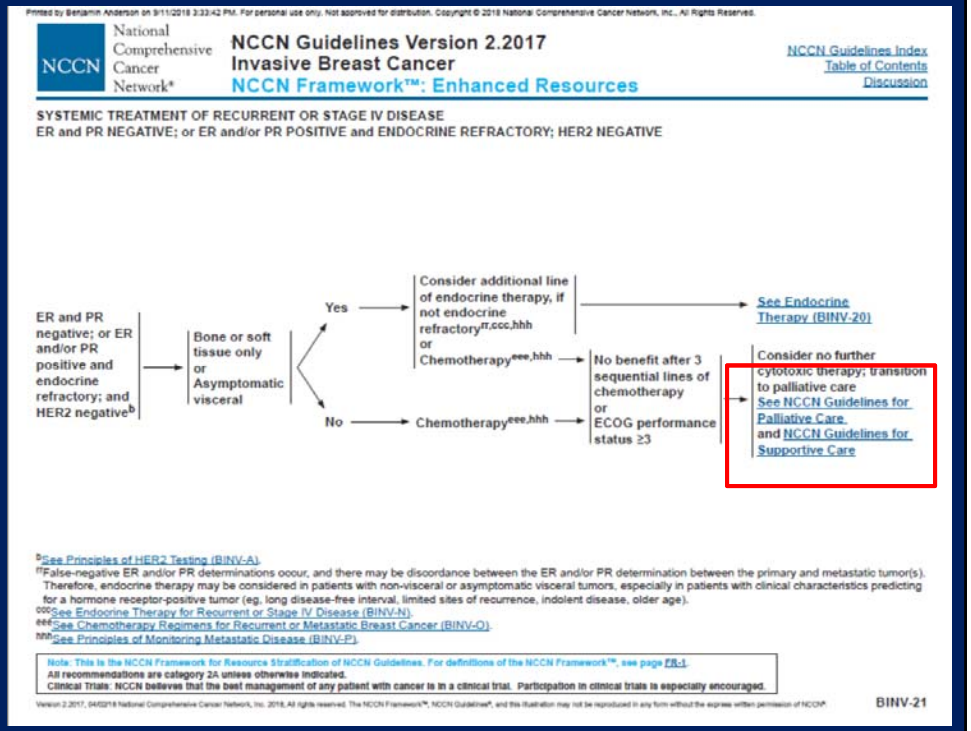
What has changed in 10 years?
…addition of CDK4/6 inhibitors



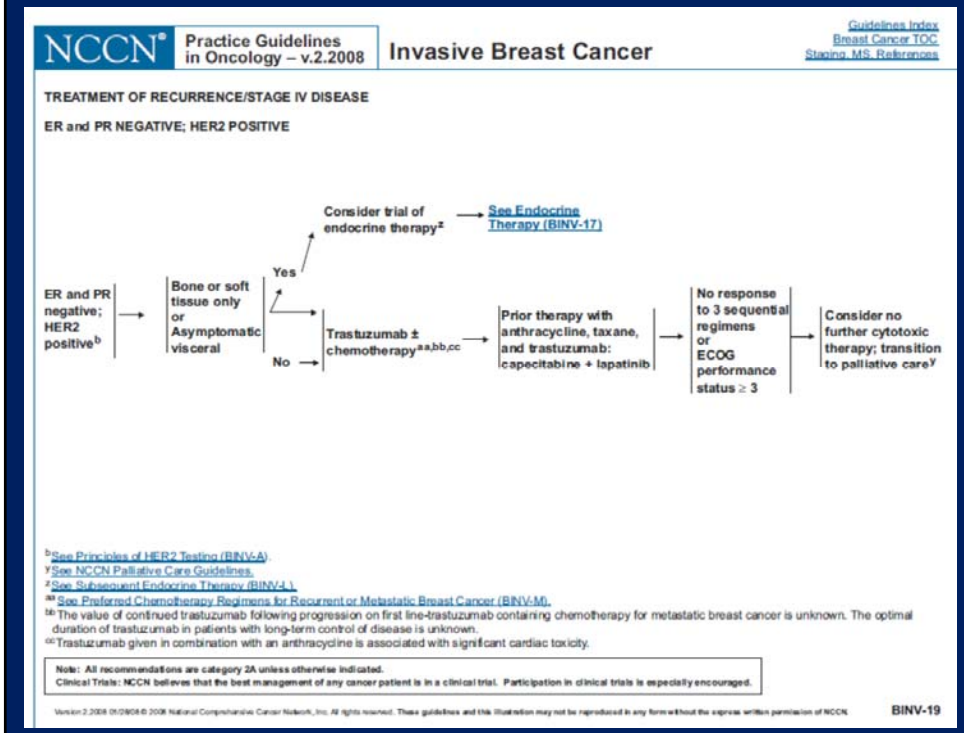


What has changed in 10 years?
…palliative & supportive care more structured





What has changed in 10 years?
…addition of new anti-HER2 therapies



NCCN Practice Guidelines in Oncology – v.2.2008 — Invasive Breast Cancer

Guidelines Index | Breast Cancer TOC | Staging, MS, References

TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and PR NEGATIVE; HER2 POSITIVE

ER and PR negative; HER2 positive[b] → Bone or soft tissue only or Asymptomatic visceral

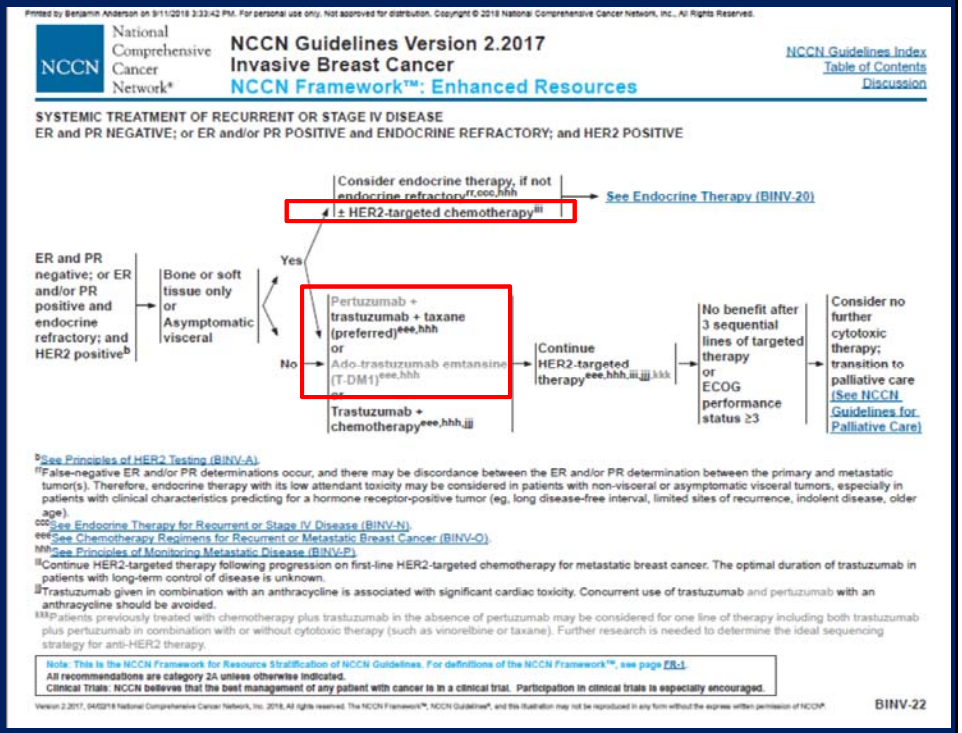
Yes → Consider trial of endocrine therapy[z] → See Endocrine Therapy (BINV-17)

No → Trastuzumab ± chemotherapy[aa,bb,cc] → Prior therapy with anthracycline, taxane, and trastuzumab: capecitabine + lapatinib → No response to 3 sequential regimens or ECOG performance status ≥ 3 → Consider no further cytotoxic therapy; transition to palliative care[y]

[b] See Principles of HER2 Testing (BINV-A)
[y] See NCCN Palliative Care Guidelines.
[z] See Subsequent Endocrine Therapy (BINV-L).
[aa] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).
[bb] The value of continued trastuzumab following progression on first line-trastuzumab containing chemotherapy for metastatic breast cancer is unknown. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[cc] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-19



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Invasive Breast Cancer
NCCN Framework™: Enhanced Resources

NCCN Guidelines Index | Table of Contents | Discussion

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; and HER2 POSITIVE

ER and PR negative; or ER and/or PR positive and endocrine refractory; and HER2 positive[b] → Bone or soft tissue only or Asymptomatic visceral

Yes → Consider endocrine therapy, if not endocrine refractory[rr,ccc,hhh] → See Endocrine Therapy (BINV-20)
± HER2-targeted chemotherapy[iii]

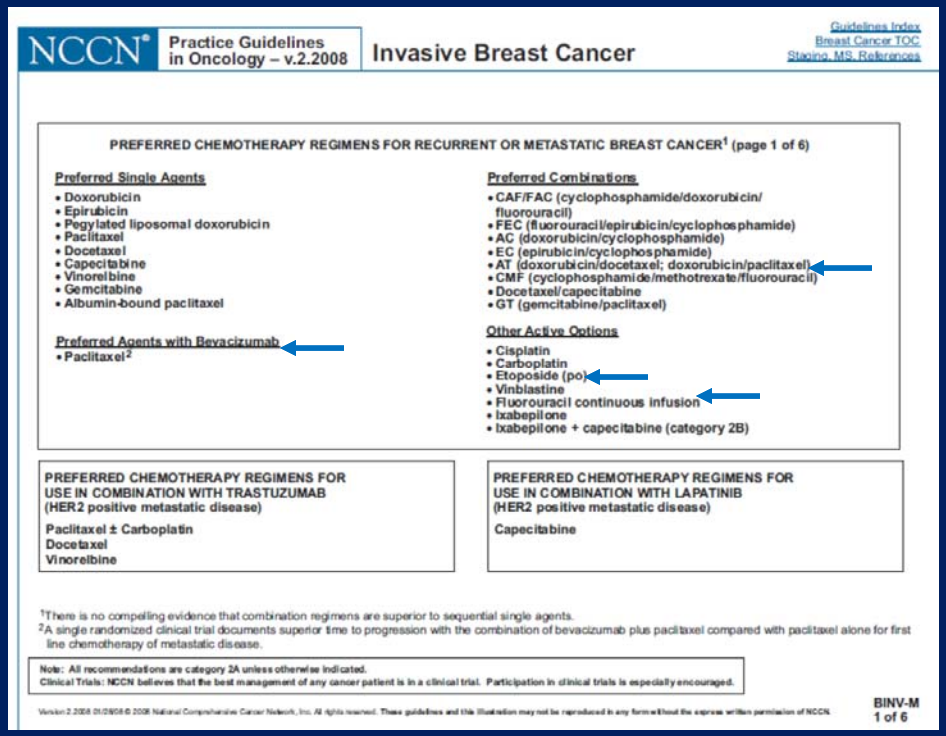
No → Pertuzumab + trastuzumab + taxane (preferred)[eee,hhh] or Ado-trastuzumab emtansine (T-DM1)[eee,hhh] or Trastuzumab + chemotherapy[eee,hhh,jjj] → Continue HER2-targeted therapy[eee,hhh,iii,jjj,kkk] → No benefit after 3 sequential lines of targeted therapy or ECOG performance status ≥3 → Consider no further cytotoxic therapy; transition to palliative care (See NCCN Guidelines for Palliative Care)

[b] See Principles of HER2 Testing (BINV-A).
[rr] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[ccc] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-N).
[eee] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).
[hhh] See Principles of Monitoring Metastatic Disease (BINV-P).
[iii] Continue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[jjj] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[kkk] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™, see page FR-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-22

What has changed in 10 years?
…new preference, new anti-HER2 therapies



NCCN® Practice Guidelines in Oncology – v.2.2008 — Invasive Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1] (page 1 of 6)

Preferred Single Agents
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine
- Albumin-bound paclitaxel

Preferred Agents with Bevacizumab
- Paclitaxel[2]

Preferred Combinations
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

Other Active Options
- Cisplatin
- Carboplatin
- Etoposide (po)
- Vinblastine
- Fluorouracil continuous infusion
- Ixabepilone
- Ixabepilone + capecitabine (category 2B)

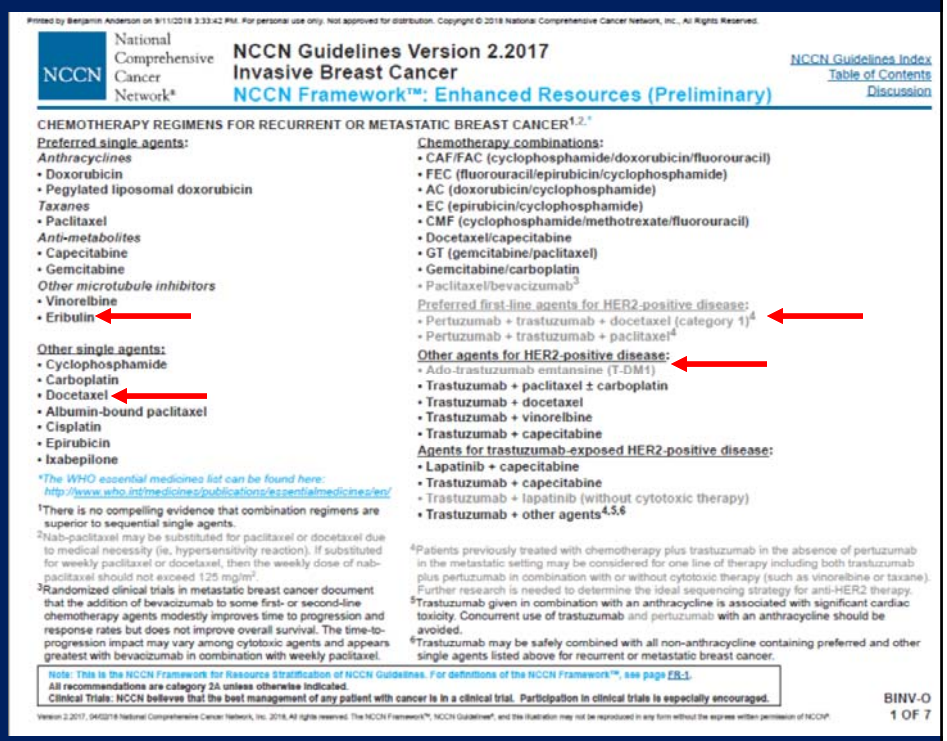
PREFERRED CHEMOTHERAPY REGIMENS FOR USE IN COMBINATION WITH TRASTUZUMAB (HER2 positive metastatic disease)
Paclitaxel ± Carboplatin
Docetaxel
Vinorelbine

PREFERRED CHEMOTHERAPY REGIMENS FOR USE IN COMBINATION WITH LAPATINIB (HER2 positive metastatic disease)
Capecitabine

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.
[2]A single randomized clinical trial documents superior time to progression with the combination of bevacizumab plus paclitaxel compared with paclitaxel alone for first line chemotherapy of metastatic disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-M
1 of 6



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Invasive Breast Cancer
NCCN Framework™: Enhanced Resources (Preliminary)

NCCN Guidelines Index
Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1,2,*]

Preferred single agents:
Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

*The WHO essential medicines list can be found here: http://www.who.int/medicines/publications/essentialmedicines/en/

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[3]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[4]
- Pertuzumab + trastuzumab + paclitaxel[4]

Other agents for HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

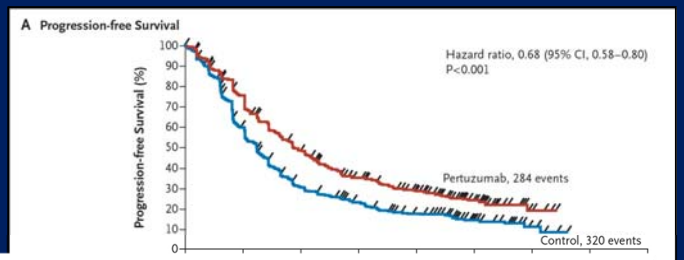
Agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[4,5,6]

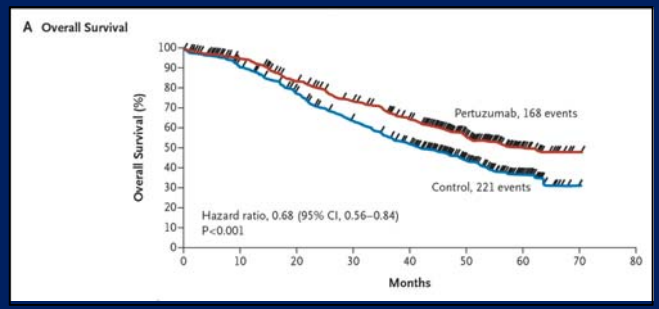
[1]There is no compelling evidence that combination regimens are superior to sequential single agents.
[2]Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².
[3]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.
[4]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[5]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[6]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™, see page FR-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-O
1 OF 7

CLEOPATRA: First-line Trastuzumab + Pertuzumab vs. Trastuzumab (mFU 50 mos)





ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

MCBS SCORE= 4

	Pertuzumab + trastuzumab+docetaxel	Placebo + trastuzumab+docetaxel	Hazard ratio	P-value
ORR[1]	**80.2%**	69.3%		**0.0001**
PFS[2]	**18.7 months**	12.4 months	**0.68**	**<0.0001**
OS[2]	**56.5 months**	40.8 months	**0.66**	**0.0001**

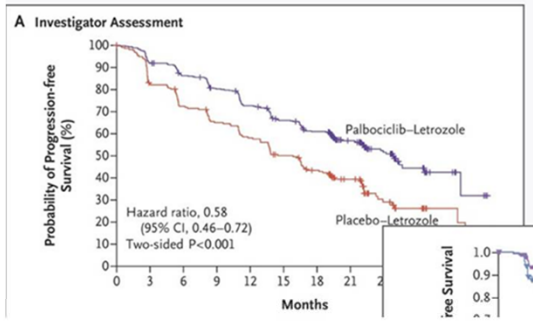
Most common adverse events ≥Grade 3 in the pertuzumab+trastuzumab+docetaxel group:
Neutropenia (48.9%), febrile neutropenia (13.8%), leukopenia (12.3%), and diarrhea (7.9%)
Long term cardiac safety maintained

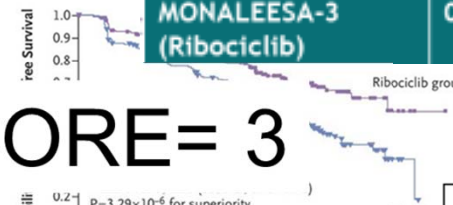
1. Baselga et al, N Eng J Med 2012; 2. Swain S et al, NEJM 2015

34

First-line Metastatic ER+/HER2- Breast Cancer
PALOMA-2, MONALEESA 2, and MONARCH 3

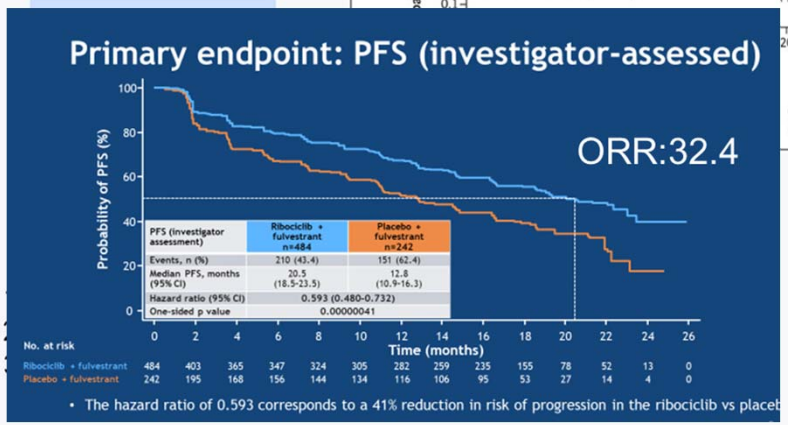
	HR	HT alone	HT+CDK4/6
PALOMA 2 (Palbociclib)	0.58	14.5 m	24.8 m
MONALEESA 2 (Ribociclib)	0.56	14.7 m	Not Reached
MONARCH 3 (Abemaciclib)	0.54	14.7 m	Not Reached
MONALEESA-3 (Ribociclib)	0.57	18.7	Not Reached

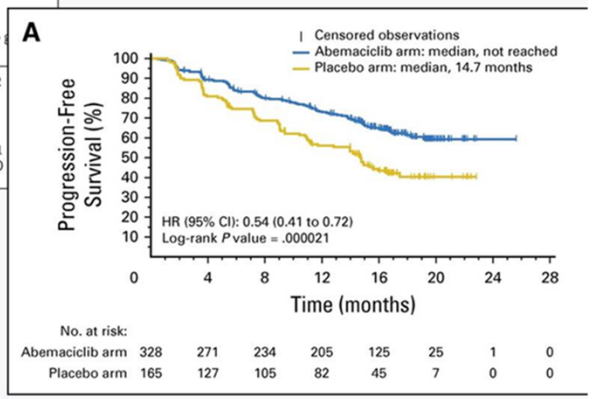




ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

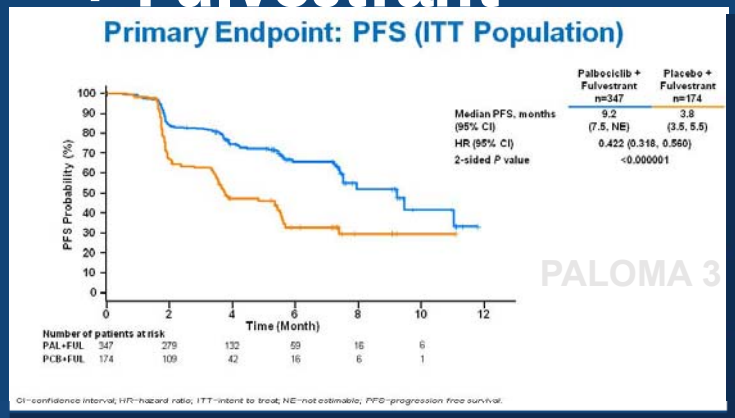
MCBS SCORE= 3

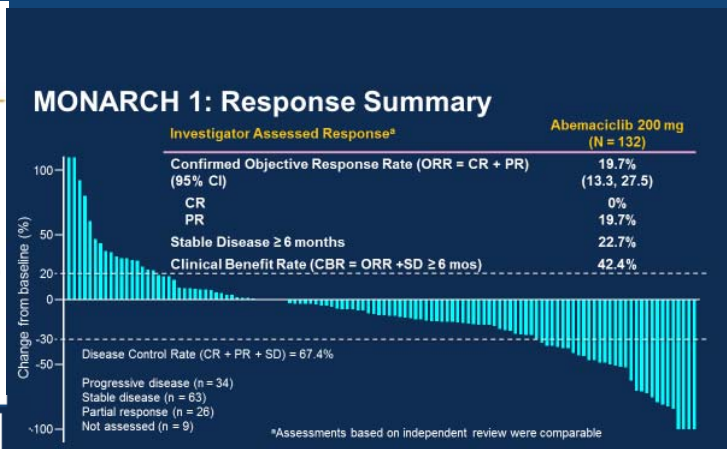




ORR: 59.2%

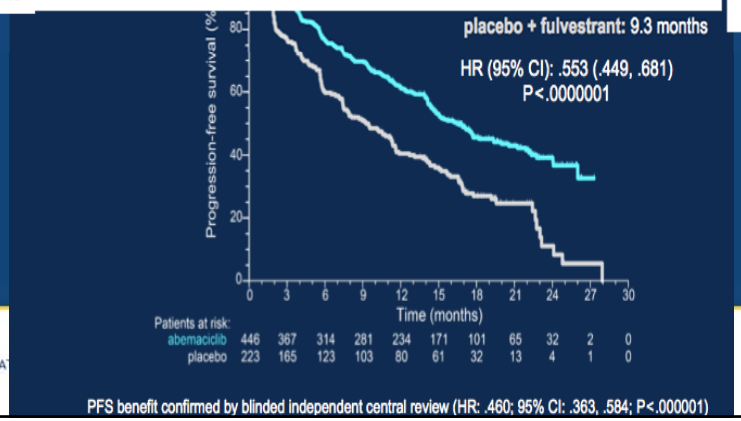
Second line: Fulvestrant vs CDK4/6 inh + Fulvestrant



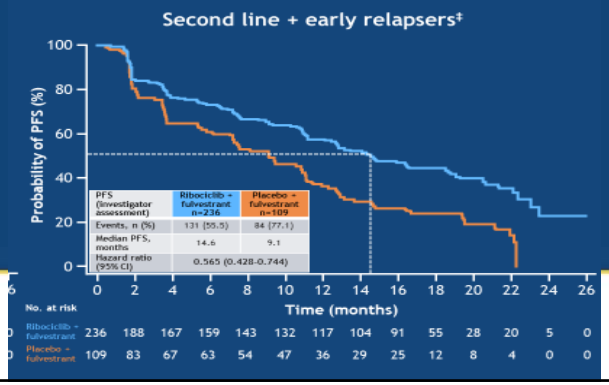


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

MCBS SCORE= 4

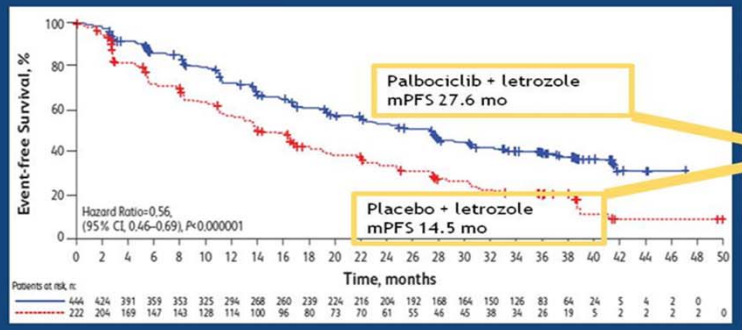


MONALEESA 3- second line

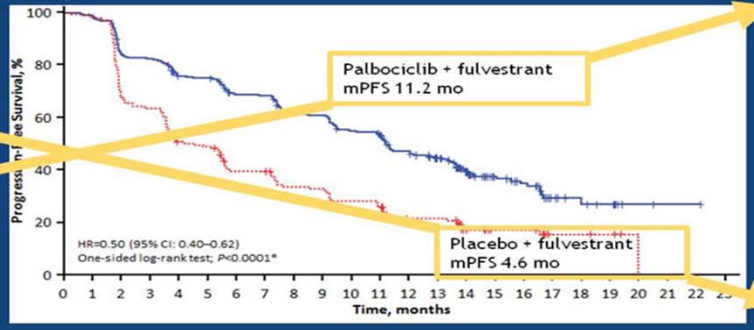


Is Getting CDKi 1st Line Important?

PALOMA-2 Progression-free survival[1]



PALOMA-3 Progression-free survival[2]



PFS over BOTH LINES:

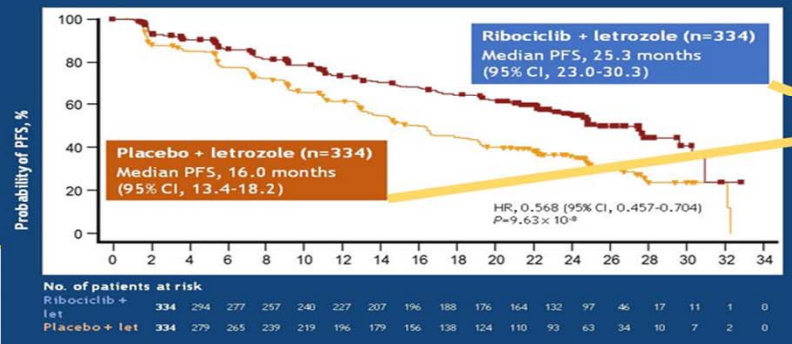
CDKi 2nd line PFS:
25.7 months

Δ 6.5 months -
seems clinically
significant

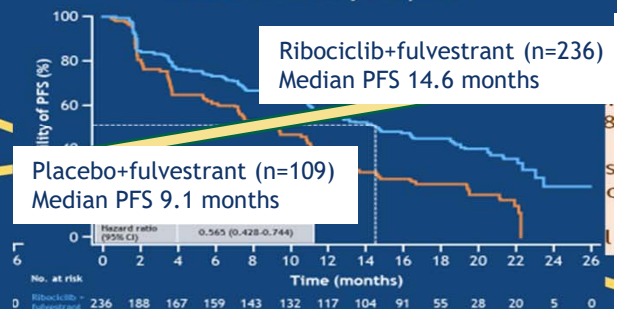
CDKi 1st line PFS:
32.2 months

Is Getting CDKi 1st Line Important: Ribociclib

MONALEESA-2 Progression-free survival[1]



Second line + early relapsers[‡]



PFS over BOTH LINES:

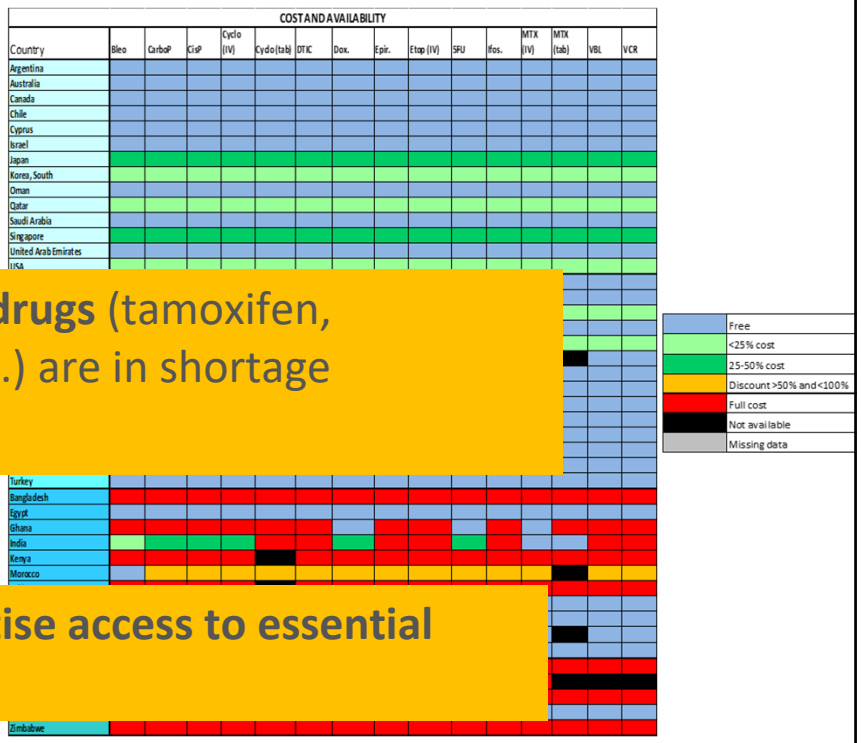
Ribociclib 2nd line
PFS 30.6 months

Δ 3.8 months

Ribociclib 1st line:
PFS 34.4 months

AVAILABILITY OF (WHO) ESSENTIAL MEDICINES

TAMOXIFEN



- **Several essential, old and inexpensive drugs** (tamoxifen, doxorubicin, cisplatin, 5-FU, bleomycin…) are in shortage
- Not always an issue of resources!

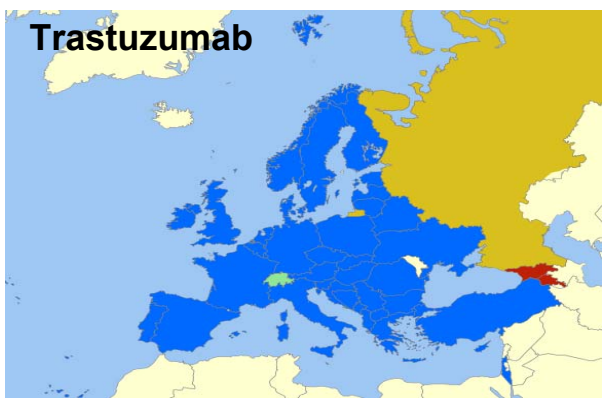
- **Phased implementation TARGET: prioritise access to essential medicines**

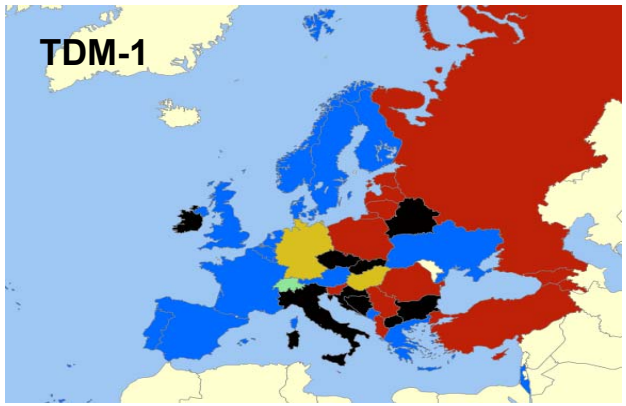
Free | <25% cost | 25-50% cost | Discount >50% and < 100% | Full cost | Not available | Missing data | European Data

Cherny, Sullivan, Torode, Saar, Eniu Ann Oncol. 2017 Nov;28(11):2633–2647

Metastatic breast cancer

(formulary inclusion and cost to patients): Anti-Her2 therapy





- **Phased implementation TARGET: next step is to prioritise access to "valuable" new agents**
- **No "new miraculous" medicine can correct for bad management or unavailability of essential interventions**

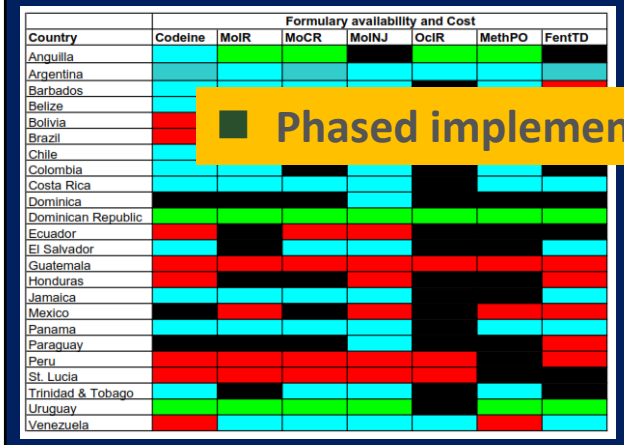
Free | <25% cost | 25-50% cost | Discount >50% and < 100% | Full cost | Not available | Missing data | European Data

Cherny, Sullivan, Torode, Saar, Eniu Ann Oncol. 2017 Nov;28(11):2633–2647

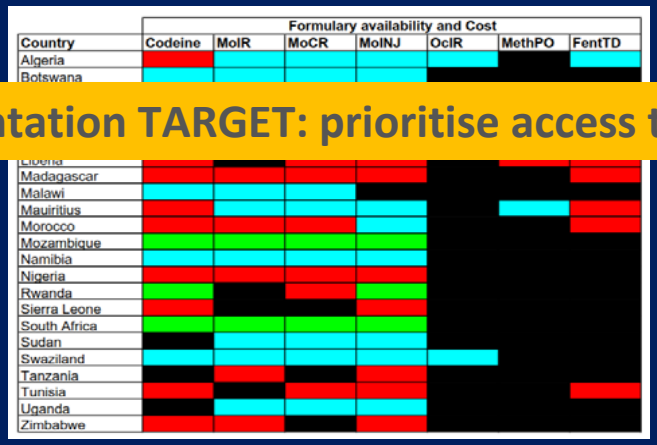
Palliation: availability of opioids

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

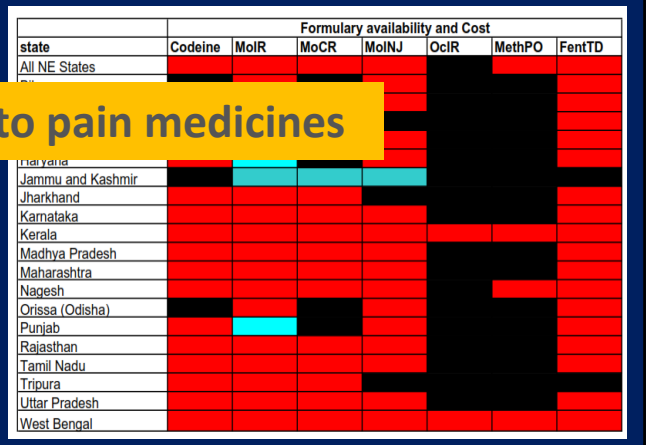
Latin A+ Caribbean



Africa



Indian States



- Phased implementation TARGET: prioritise access to pain medicines

Many governments are failing patients with cancer in the delivery of adequate pain relief !

Cherny et al, Ann Oncol 2013; 24 (Supplement 11): xi7–xi13.

The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.
(LoE/GoR: Expert opinion/A) (100%)

■ **PI TARGET: multidisciplinarity**

All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy to understand information about their disease and its management.
Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable,
(LoE/GoR: 1/A) (97%)

■ **PI TARGET: patient information**

From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care.
The approach must be personalized to meet the needs of the individual patient.
(LoE: Expert opinion/A) (100%)

■ **PI TARGET: psychosocial/supportive**

The medical community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients' well being, length of life and preferences should always guide decisions.
(LoE/GoR: Expert opinion/A) (100%)

- **PI TARGET: resource-appropriate, value-based decisions**

We strongly recommend the use of objective scales, such as the ESMO Magnitude of Clinical Benefit Scale or the ASCO Value Framework, to evaluate the real magnitude of benefit provided by a new treatment and help prioritize funding, particularly in countries with limited resources.
(LoE/GoR: Expert opinion/A) (88%)

- **PI TARGET: value frameworks**

The ABC community strongly supports the use of biosimilars both for treatment of breast cancer (i.e. trastuzumab) and for supportive care (i.e. growth factors).
To be used, the biosimilar must be approved after passing the stringent development and validation processes required by EMA or FDA or other similarly strict authority.
(LoE/GoR: I/A) (90%)

- **PI TARGET: biosimilars**

Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone.
(LoE/GoR: II/A) (67%)

- **PI TARGET: scale-up resource-appropriate radiology /lab availability (LABC vs M1?)**

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.
(LoE/GoR: I/A) (93%)

- **PI TARGET: scale-up availability endocrine treatments**

Many trials in ER+ ABC have not included pre-menopausal women.
Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.
(LoE/GoR: Expert Opinion/A) (95%)

- **PI TARGET: focus on endocrine treatment for PREMENOPAUSAL**

PALLIATIVE / SUPPORTIVE CARE

Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.
(LoE/GoR: I/A) (100%)

<u>Early</u> introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.
(LoE/GoR: I/A) (100%)

Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.
(LoE/GoR: I/A) (100%)

- **PI TARGET: ensure palliation and pain control, access to morphine, focus on QOL**

Alternative therapies (i.e. therapies used instead of scientifically based medicines) are <u>not recommended</u> in any phase or stage of cancer treatment.
(LoE/GoR: NA/E)

- **PI TARGET: educate on lack of efficacy of alternative treat.**

Implementation does not equal copying

- Many patients are treated as we speak with very limited resources
- In the process of PI (A-->B) situation analysis is key (=A)
- Stake holders involvement
- Setting the goals (=B)
- Numerous target/goals for phased implementation
- Lots of work to do in the afternoon panel!