Which of the following (in addition to bone-targeted treatment) would you recommend for treatment of metastatic ER-negative, HER2-positive breast cancer (in lung and bone) in a patient who received 1 year of adjuvant trastuzumab combined with chemotherapy with disease recurrence 18 months later?

1. **Trastuzumab + single agent chemotherapy**
2. **Trastuzumab + pertuzumab + taxane**
3. **Lapatinib + single agent chemotherapy**
4. **Trastuzumab emtansine (TDM-1)**
5. **TDM-1 + pertuzumab**
6. **TDM-1 + pertuzumab + taxane**

Which of the following (in addition to bone-targeted treatment) would you recommend for treatment of metastatic ER-negative, HER2-positive breast cancer (in lung and bone) in a patient who received 1 year of adjuvant trastuzumab combined with chemotherapy with disease recurrence 18 months later?

1. Trastuzumab + single agent chemotherapy
   
   9.4%
2. Trastuzumab + pertuzumab + taxane
   
   50%
3. Lapatinib + single agent chemotherapy
   
   4.7%
4. Trastuzumab emtansine (TDM-1)
   
   18.8%
5. TDM-1 + pertuzumab
   
   8.6%
6. TDM-1 + pertuzumab + taxane
   
   8.6%

Clinical Opinion Poll Question #5: Optimal Anti-HER2 Approach in Metastatic HER2+ Breast Cancer

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

Recommendations HER2-targeted therapy is recommended for patients with HER2-positive advanced breast cancer, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis. Trastuzumab, pertuzumab, and taxane for first-line treatment and T-DM1 for second-line treatment are recommended. In the third-line setting, clinicians should offer other HER2-targeted therapy combinations or T-DM1 (if not previously administered) and may offer pertuzumab, if the patient has not previously received it. Optimal duration of chemotherapy is at least 4 to 6 months or until maximum response, depending on toxicity and in the absence of progression. HER2-targeted therapy can continue until time of progression or unacceptable toxicities. For patients with HER2-positive and estrogen receptor–positive/progesterone receptor–positive breast cancer, clinicians may recommend either standard first-line therapy or, for selected patients, endocrine therapy plus HER2-targeted therapy or endocrine therapy alone.

Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099.

First-Line HER2+ Metastatic Breast Cancer (MBC): CLEOPATRA

- Double-blind, placebo-controlled phase III trial
  - Docetaxel 75 mg/m^2 escalated to 100 as tolerated, about 6 cycles
  - Trastuzumab and pertuzumab (PER) / placebo q3w
- Primary endpoint
  - Independently assessed PFS
- 808 patients centrally confirmed HER2+ MBC
  - Adjuvant therapy
    - 53% no prior chemo
    - 10% prior trastuzumab
    - 49% ER+, 24% received endocrine therapy

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529. Swain SM, et al. *Lancet Oncol.* 2013;14(6):461-471.

CLEOPATRA: Results and Perspective

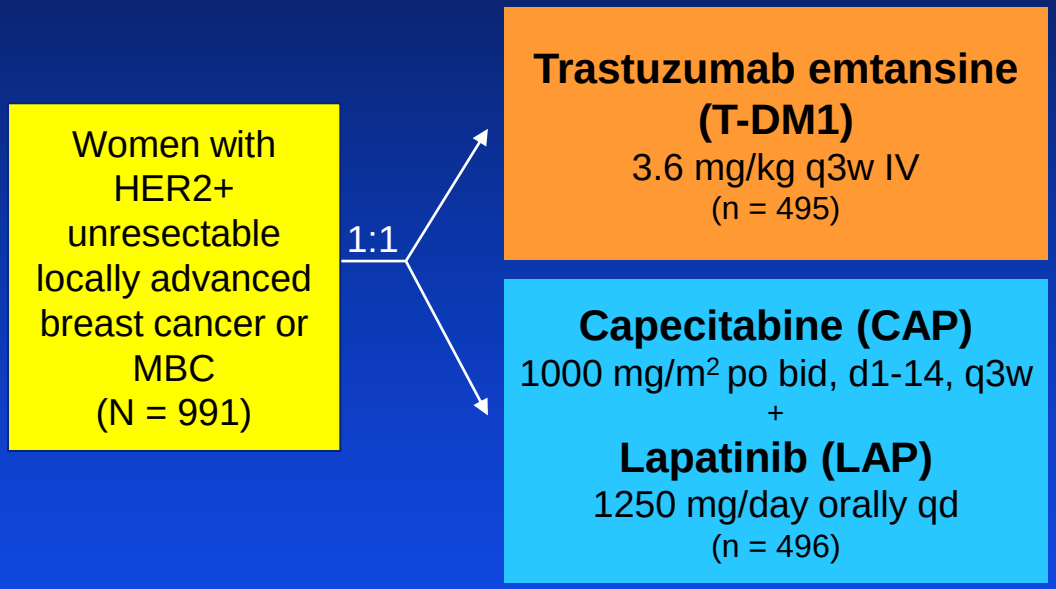
- PFS benefit seen in essentially all predefined subsets
- Complete response rare at 4%-5.5% (Partial response 65%-75%)
- Survival impact is practice changing

	Slamon, et al N = 469*		Marty, et al N = 186		CLEOPATRA N = 808		AVEREL N = 424	
	-TRAS	+TRAS	-TRAS	+TRAS	-PER	+PER	-BEV	+BEV
PFS/TTP, months	4.6	7.3	6.1	11.7	12.4	18.5	13.7	16.5
OS, months	20	26	23	31	**37.6**	**42.6+**	38.3	38.5

BEV, bevacizumab

Slamon D, et al. *N Engl J Med*. 2001;344(11):783-792. Mass RD, et al. *Clin Breast Cancer*. 2005;6(3):240-246. Marty M, et al. *J Clin Oncol*. 2005;23(19):4265-4274. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. Swain SM, et al. *Lancet Oncol*. 2013;14(6):461-471. Gianni L, et al. *J Clin Oncol*. 2013;31(14):1719-1725.

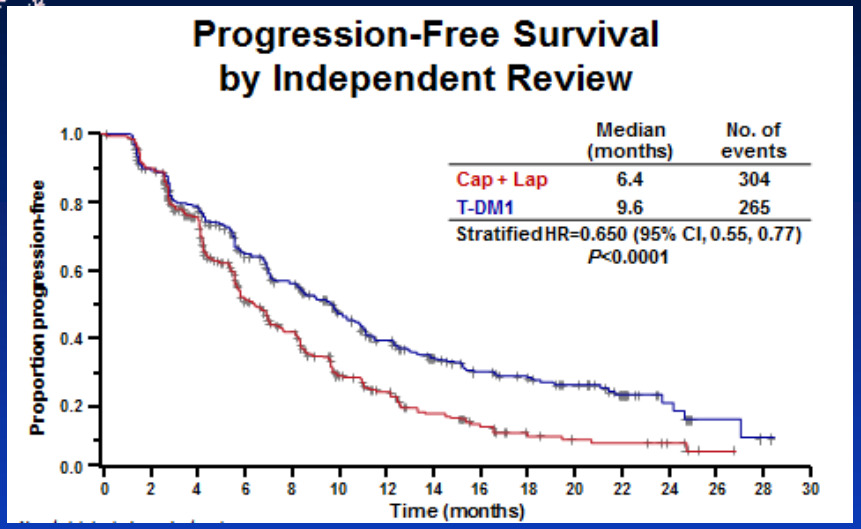
Refractory HER2+ MBC: EMILIA

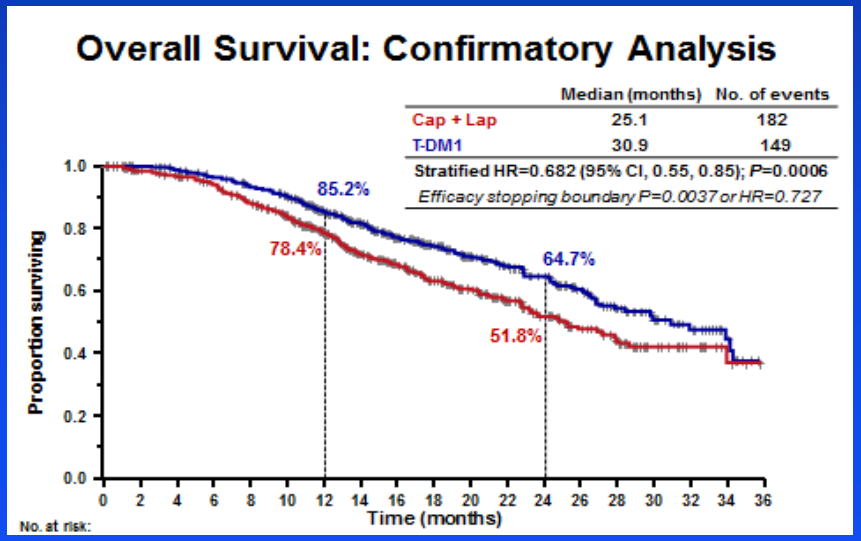


- **Primary endpoints**
  - **OS**
  - **PFS by independent review**
  - **Safety**

Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

EMILIA: Results

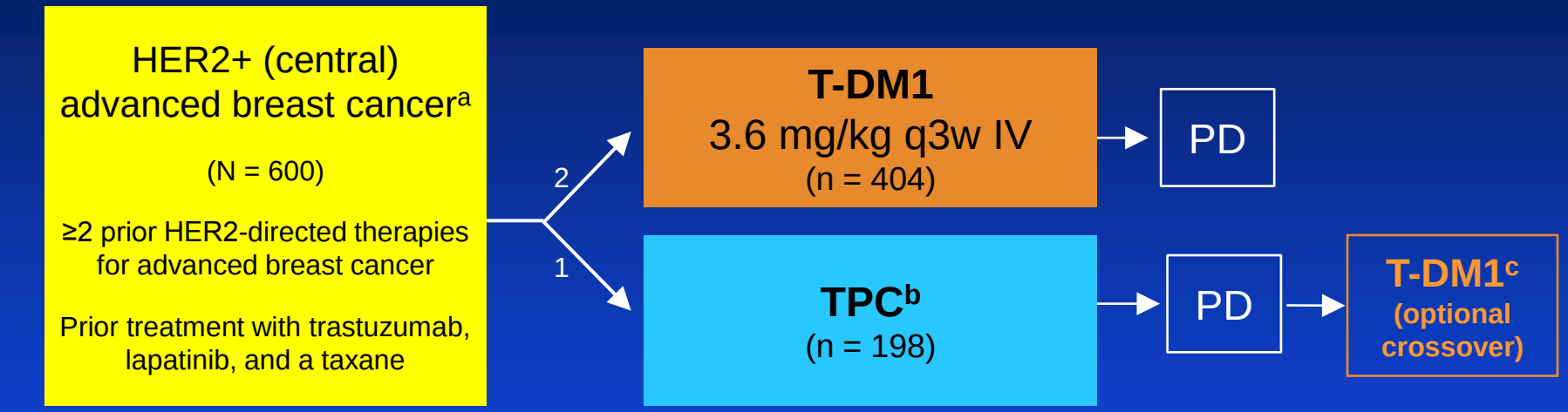




- Cardiac dysfunction rare
  - All grades: 3.1% vs 1.8%
  - Grade 3: 0.4% vs 0.2%
- Common toxicities
  - Low grade fatigue, nausea, diarrhea
- Unique toxicities
  - Thrombocytopenia
    - 13% grade 3
  - Modest increase in AST and ALT
- PFS in patients with CNS mets at baseline (n = 95)
  - 12.9 months LAP + CAP vs 26.8 months T-DM1
- New standard following progression on trastuzumab based therapy

Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

TH3RESA: Phase III Trial of T-DM1 vs Treatment of Physician's Choice (TPC)

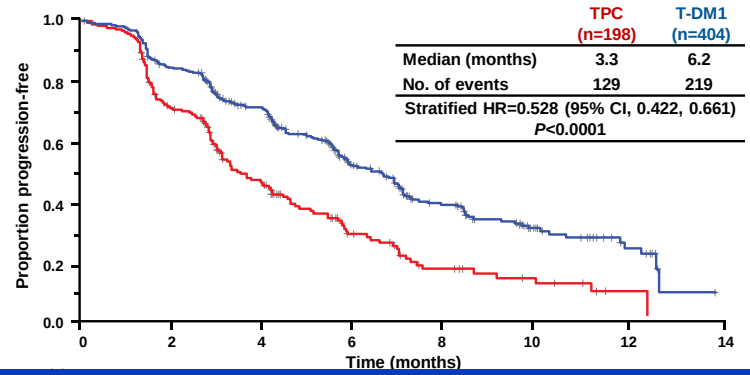


- Stratification factors
  - World region
  - No. of prior regimens for advanced breast cancet
  - Presence of visceral disease
- Primary endpoints
  - PFS by investigator
  - OS
- Secondary endpoints
  - ORR by investigator
  - Safety

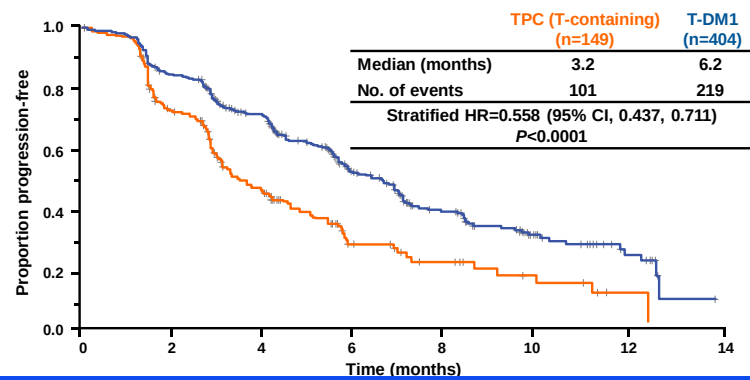
Wildiers H, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract LBA15. Krop IE, et al. *Lancet Oncol.* 2014;15(7):689-699.

TH3RESA: PFS and Comparison With Trastuzumab Regimen Beyond Progression

PFS by Investigator Assessment



PFS for Patients Treated With Trastuzumab-Containing Regimens



- PFS: 3 months benefit
- OS: Analysis still early
  - 44 events vs 61 events
  - HR 0.552
  - *P* = .0034 (14.9 vs NE)
- Less toxic than "standard" options

Wildiers H, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract LBA15. Krop IE, et al. *Lancet Oncol.* 2014;15(7):689-699.

Selected Ongoing First-Line MBC Trials

- VELVET (n = 210)
  - Trastuzumab/pertuzumab/vinorelbine
- MARIANNE (n = 1092)
  - Comparing 3 options
    - (Trastuzumab + taxane) vs (T-DM1 + pertuzumab) vs (T-DM1 + placebo)
- PERTAIN (n = 250)
  - Comparing an aromatase inhibitor vs chemo up front +/- pertuzumab

Summary of Considerations for Clinical Practice (1)

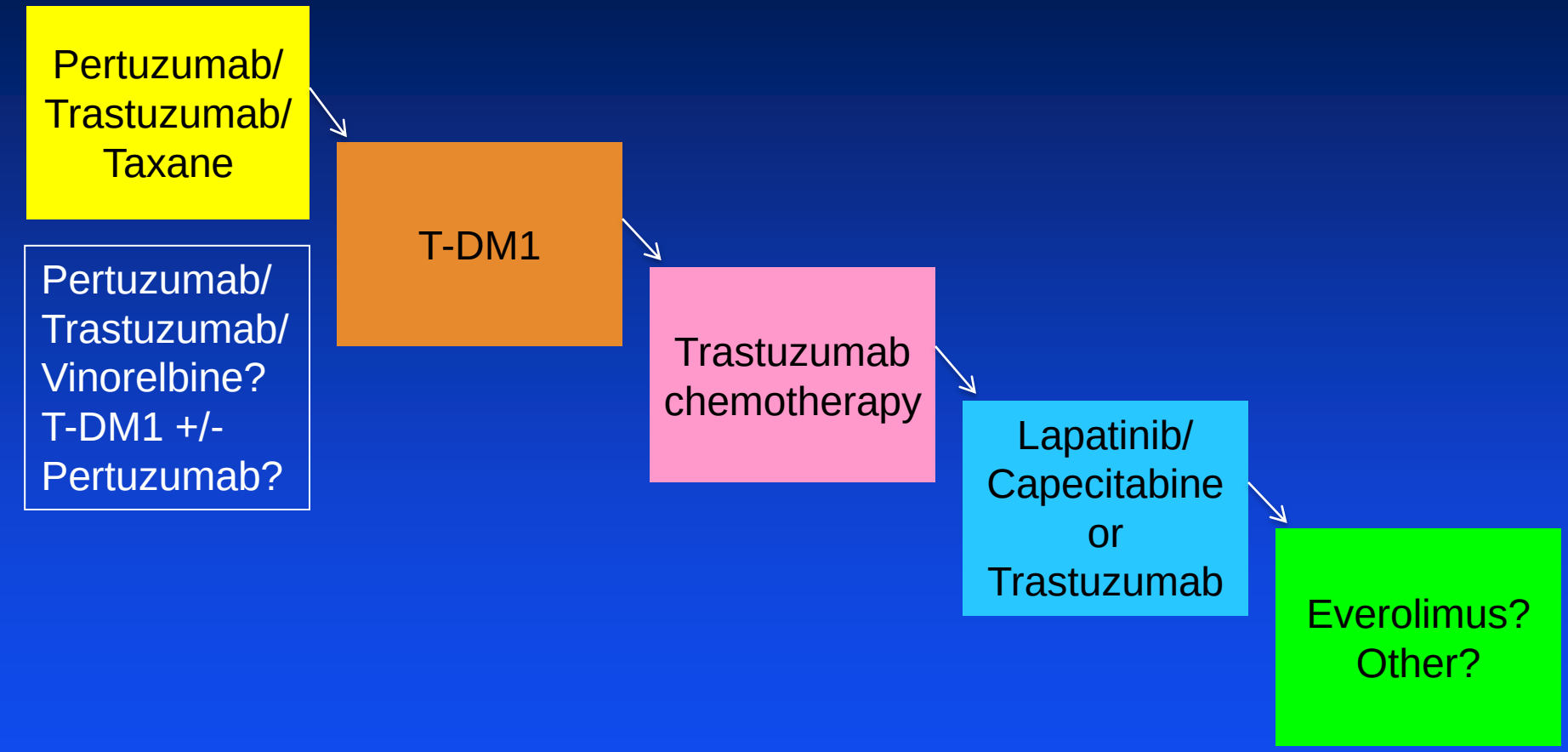
- Pertuzumab approved in first-line setting in combination with trastuzumab/docetaxel
- T-DM1 an effective treatment for HER2+ MBC progressing on trastuzumab
  - Toxicities are unique but generally well tolerated
- Lapatinib + chemotherapy associated with more toxicity, less efficacy than trastuzumab in first-line metastatic setting

Summary of Considerations for Clinical Practice (2)

- Lapatinib/trastuzumab or capecitabine still an option for later line therapy or in special settings (low EF, brain mets)
- No role for bevacizumab (for systemic disease)
- No clear role for everolimus
- More research needed related to brain mets
- Tumor biopsies, plasma DNA and molecular analysis of CTCs important for research

EF, ejection fraction; CTCs, circulating tumor cells

Considerations for Clinical Practice (3)



Multiple agents in clinical trials: inhibitors of mTOR, HSP90, TKs, vaccines, PD-1, PD-L1

Collaborators

NIH
NCI
BCRF
26.2 with Donna Foundation

Feb 13-15, 2015

5K, relay, half and full marathon
breastcancermarathon.com

Feb 13-14, 2015

CME Course: Advances in Systemic Therapies for Breast Cancer
Mayo Clinic Simulation Center, Jacksonville, FL

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions