A 55-year-old patient with T2N2M0 right breast cancer was treated with adjuvant chemotherapy with AC x 4 followed by weekly paclitaxel x 12. Her tumor was high grade, ER-25%, PR-5%, HER2 "1+" by IHC, Ki67- 25%. She develops metastatic disease with multiple liver metastases just 8 months after beginning anastrozole. Her ECOG performance status is 1 and liver function tests are normal. What would you recommend at this time?

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1. Exemestane + mTOR inhibitor (everolimus)

32.8%
2. Single agent chemotherapy

10.2%
3. Combination chemotherapy

19.5%
4. Chemotherapy + bevacizumab

22.7%
5. Chemotherapy + other targeted agent in a clinical trial

14.8%

Clinical Opinion Poll Question #3: Advanced High-Grade ER-Positive Breast Cancer: A Wolf in Sheep's Clothing?

Edith A. Perez, MD

Deputy Director at Large, Mayo Clinic Cancer Center

Serene M. and Frances C. Durling Professor of Medicine and Cancer Biology

Group Vice Chair, Alliance for Clinical Trials in Oncology

Director, Mayo Clinic Breast Cancer Translational Genomics Program

Mayo Clinic

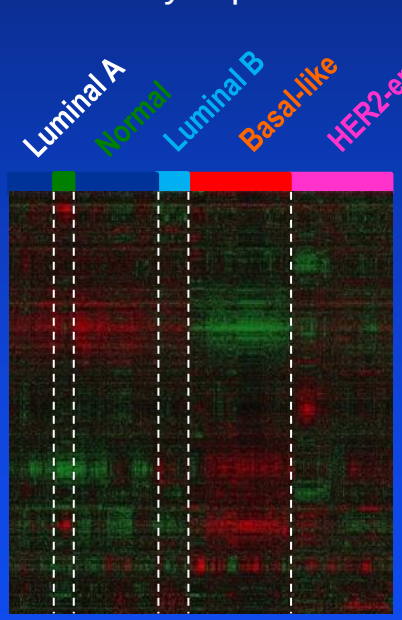
MAYO CLINIC

Considerations

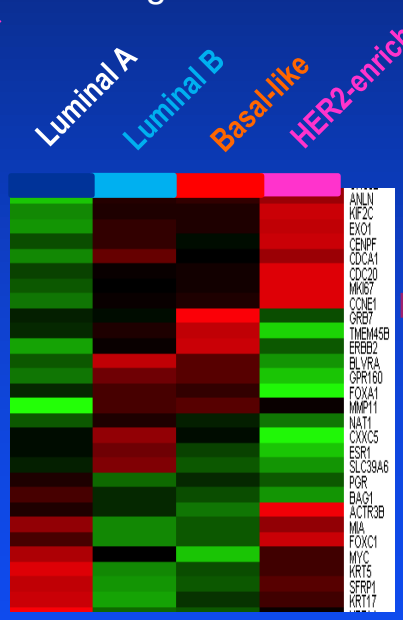
- HR vs concept of “luminal”
- Concept of primary vs secondary endocrine resistance
- Estrogen receptor
  - Is the target present?
  - Is the target mutated?
- Which hormonal therapy is best following tumor progression to a nonsteroidal aromatase inhibitor (AI)?
- What are some major mechanisms of resistance that can be targeted?
  - PI3K/AKT/mTOR?, FGF?, HDAC, CDK 4/6?

NanoString Technology, Prosigna Based on PAM50 Gene Signature

2000
Researchers first describe breast cancer intrinsic subtypes based on microarray experiments



2009
Researchers first describe PAM50 gene expression signature



2010
NanoString exclusively licenses PAM50 gene expression signature

2013
NanoString began marketing Prosigna in Europe, Israel and US after receipt of CE Mark and 510(k) clearance

prosigna™
Breast cancer
prognostic gene signature assay

Luminal definitions are based on gene profiling, not IHC

Definition of Clinical Endocrine Resistance (1)

- **Primary endocrine resistance**
  - **Recurrence within the first 2 years of adjuvant endocrine therapy while on endocrine therapy**
  - **Progression within first 6 months of initiating first-line endocrine therapy for the treatment of metastatic breast cancer (while on endocrine therapy)**

Definition of Clinical Endocrine Resistance (2)

- **Secondary clinical resistance**
  - **Recurrence during years 2-5 of adjuvant endocrine therapy (or within 12 months of completing adjuvant endocrine therapy)**
  - **Progression occurring 6 or more months after initiating endocrine therapy for metastatic disease while on endocrine therapy**

Endocrine Therapy After Nonsteroidal AI? Is There an Optimal Regimen?

- Exemestane (EXE)
- Exemestane + everolimus (EVE)
- Fulvestrant
- Tamoxifen
- Others?
- Or move to chemotherapy?

Endocrine Therapy for Metastatic Breast Cancer

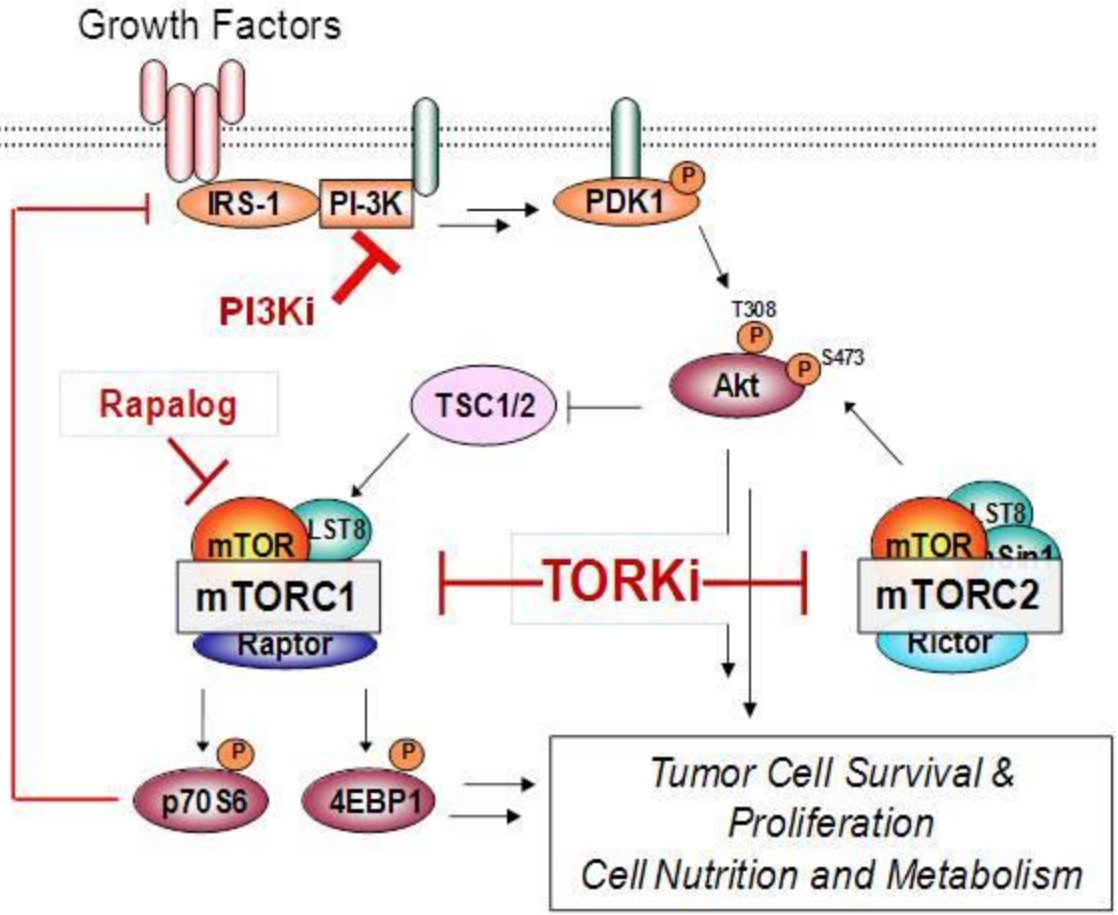
- EFECT trial
  - Response rate to second-line exemestane or fulvestrant 7%
    - Time to progression 3.7 months

Chia S, et al. *J Clin Oncol*. 2008;26(10):1664-1670.

New Targets for Metastatic ER+ Breast Cancer

- PI3K/mTOR
  - Major mechanism of tumor escape in the setting of long-term estrogen deprivation
  - PIK3CA mutations (oncogenic) are associated with better prognosis in early stage breast cancer
  - Are mutations in PI3K/PTEN/AKT predictive of benefit to drugs that target these pathways?
- FGF
- HDAC
- CDKs

Rationale for targeting TOR kinase



- PI3K/mTOR pathway dysregulated at high frequency in multiple tumors
- Inhibition of both TORC1 and TORC2 prevents feedback pathway upregulation
- differentiates this class of inhibitors from Rapalogs (predominantly TORC1 inhibitors)

Phase III BOLERO-2 Trial

	EVE + EXE n = 485	PBO + EXE n = 239	*P*	HR
PFS (months)				
Interim (7.6 month median follow-up)[1]	6.9	2.8	<0.001	0.43
Final (18 month median follow-up)[2]	7.8	3.2	<0.0001	0.45
OS (months)[3]	30.98	26.55	0.14	0.89

1. Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529. 2. Yardley DA, et al. *Adv Ther*. 2013;30(10):870-884. 3. Piccart M, et al. Presented at: European Breast Cancer Conference (EBCC-9), 2014, Glasgow, Scotland. EBCC 2014. Abstract #LBA1.

Endocrine Therapy for Metastatic Breast Cancer

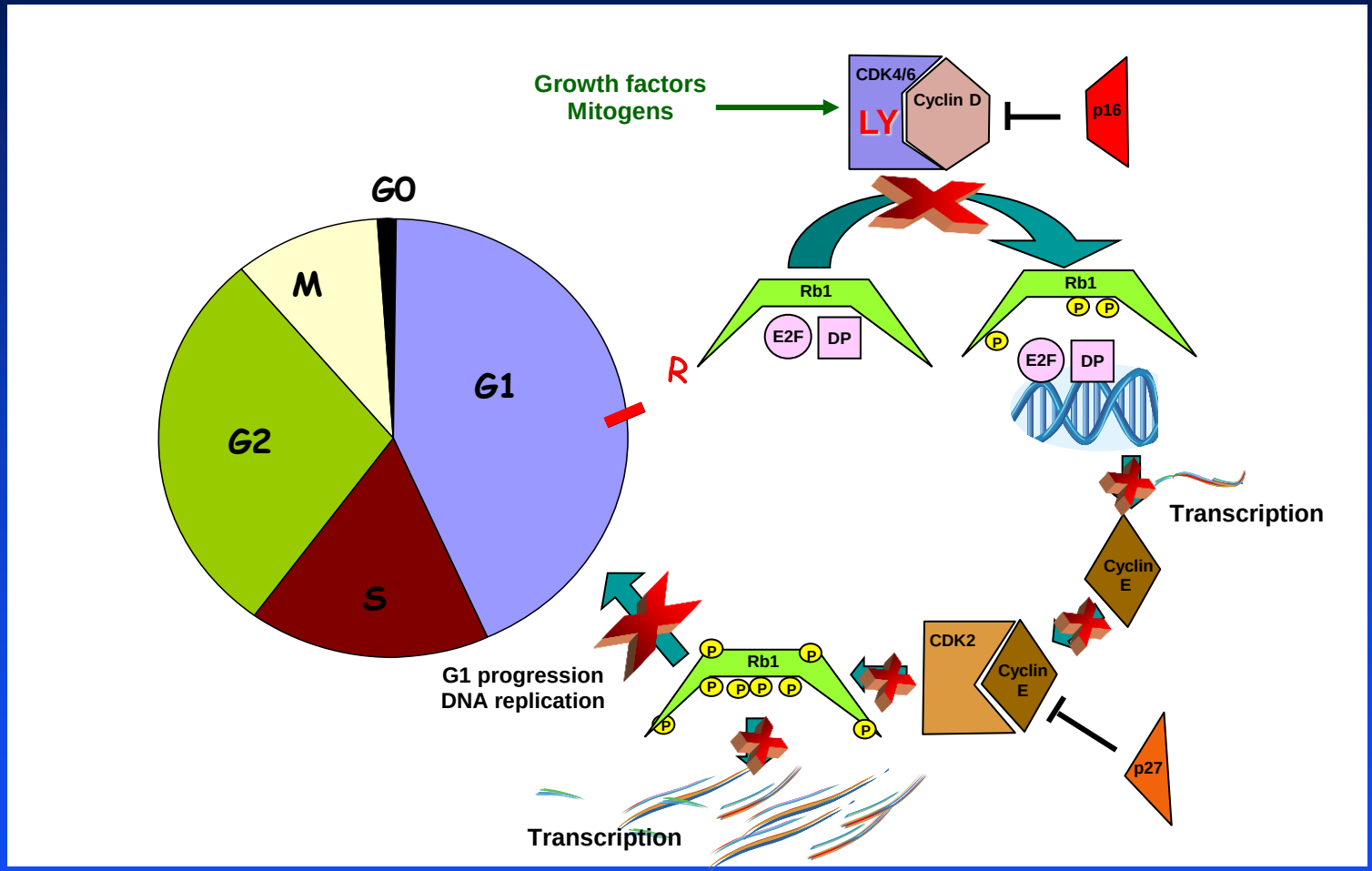
- BOLERO-2 study
  - Improved PFS with addition everolimus to exemestane, but additional toxicity
  - No improvement in median OS
- Novel approaches to improve the efficacy of endocrine therapy, while minimizing toxicity, are urgently required

Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529. Piccart M, et al. Presented at: ECCO 2014 .

Other Targets: CDK 4/6

Pfizer: Palbociclib
Lilly: Abemaciclib
Novartis: LEE011

CDK4/6 Regulates Grade 1→S Cell Cycle Progression



First-line Bevacizumab + Chemotherapy: Pooled Analysis

	BEV arm n=1439	non-BEV arm n = 1008	*P*	HR
Median PFS, months	9.2	6.7		0.64
ORR (in pts with measureable disease, n=1893), %	49%	32%	<0.0001	
Median OS, months	26.7	26.4		0.98

Miles DW, et al. *Ann Oncol.* 2013;24(11):2773-2780.

Question #3: My Opinion

A 55-year-old patient with T2N2M0 right breast cancer was treated with adjuvant chemotherapy with AC x 4 followed by weekly paclitaxel x 12. Her tumor was high grade, ER-25%, PR-5%, HER2"1+" by IHC, Ki67-25%. She develops metastatic disease with multiple liver metastases just 8 months after beginning anastrozole. Her ECOG performance status is 1 and liver function tests are normal. What would you recommend at this time?

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All of these are good options for management of this patient. None definitely proven to be better than the others in terms of OS…

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