Thank you for joining us.
The program will commence momentarily.

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Monday, August 17, 2020

5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

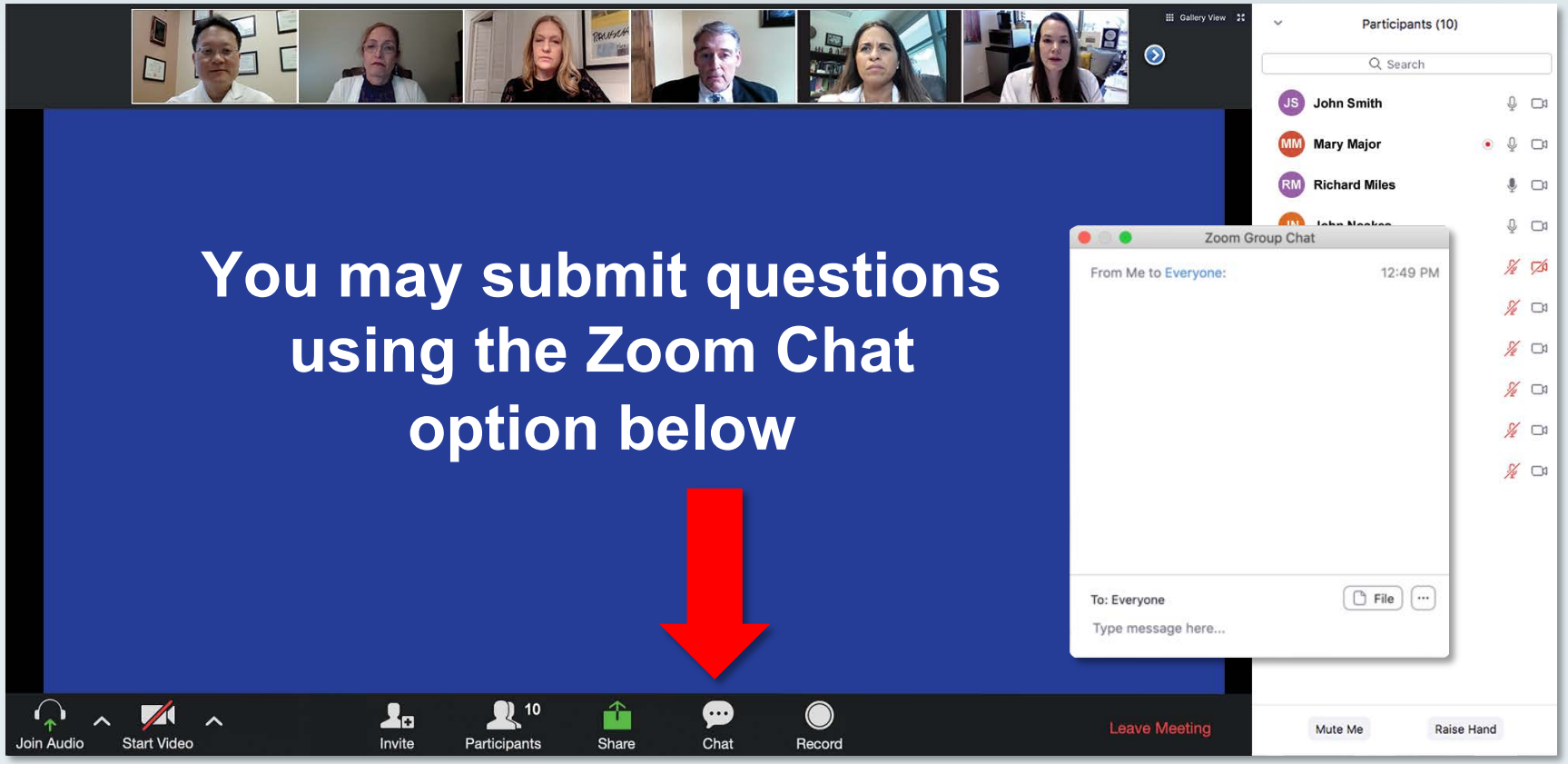
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

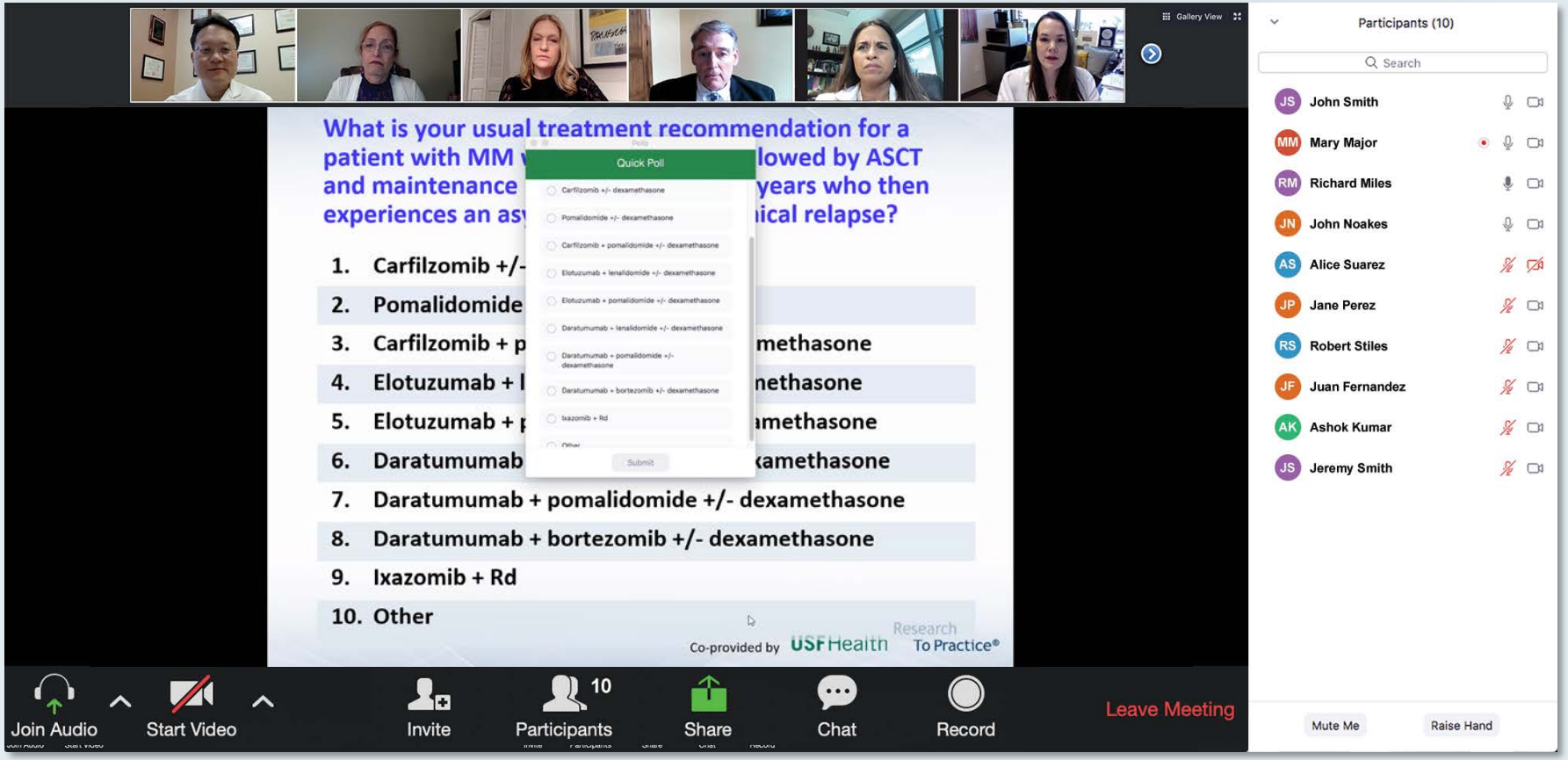
RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



Feel free to submit questions **now before** the program commences and **throughout the program.**

Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

Commercial Support

This activity is supported by educational grants from AbbVie Inc, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Merck, Puma Biotechnology Inc and Seattle Genetics.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seattle Genetics, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc, Tolero Pharmaceuticals and Verastem Inc.

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Dr Kaklamani — Disclosures

Consulting Agreements	Amgen Inc, AstraZeneca Pharmaceuticals LP, Athenex, Celldex Therapeutics, Eisai Inc, Immunomedics Inc, Puma Biotechnology Inc
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Bristol-Myers Squibb Company
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Genomic Health Inc, Novartis, Pfizer Inc, Puma Biotechnology Inc

Dr Tolaney — Disclosures

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Upcoming Live Webinars

Tuesday, August 18, 2020
5:00 PM – 6:00 PM ET

Current Questions and Controversies in the Management of Lung Cancer

Faculty
Leora Horn, MD, MSc

Moderator
Neil Love, MD

Wednesday, August 19, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Noopur Raje, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Thursday, August 20, 2020
5:00 PM – 6:00 PM ET

Clinical Investigator Perspectives on the Current and Future Role of PARP Inhibition in the Management of Ovarian Cancer

Faculty
Don S Dizon, MD

Moderator
Neil Love, MD

Friday, August 21, 2020
12:00 PM – 1:00 PM ET

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

Faculty
Brad S Kahl, MD

Moderator
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RTP RESEARCH TO PRACTICE

Faculty

Virginia Kaklamani, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in
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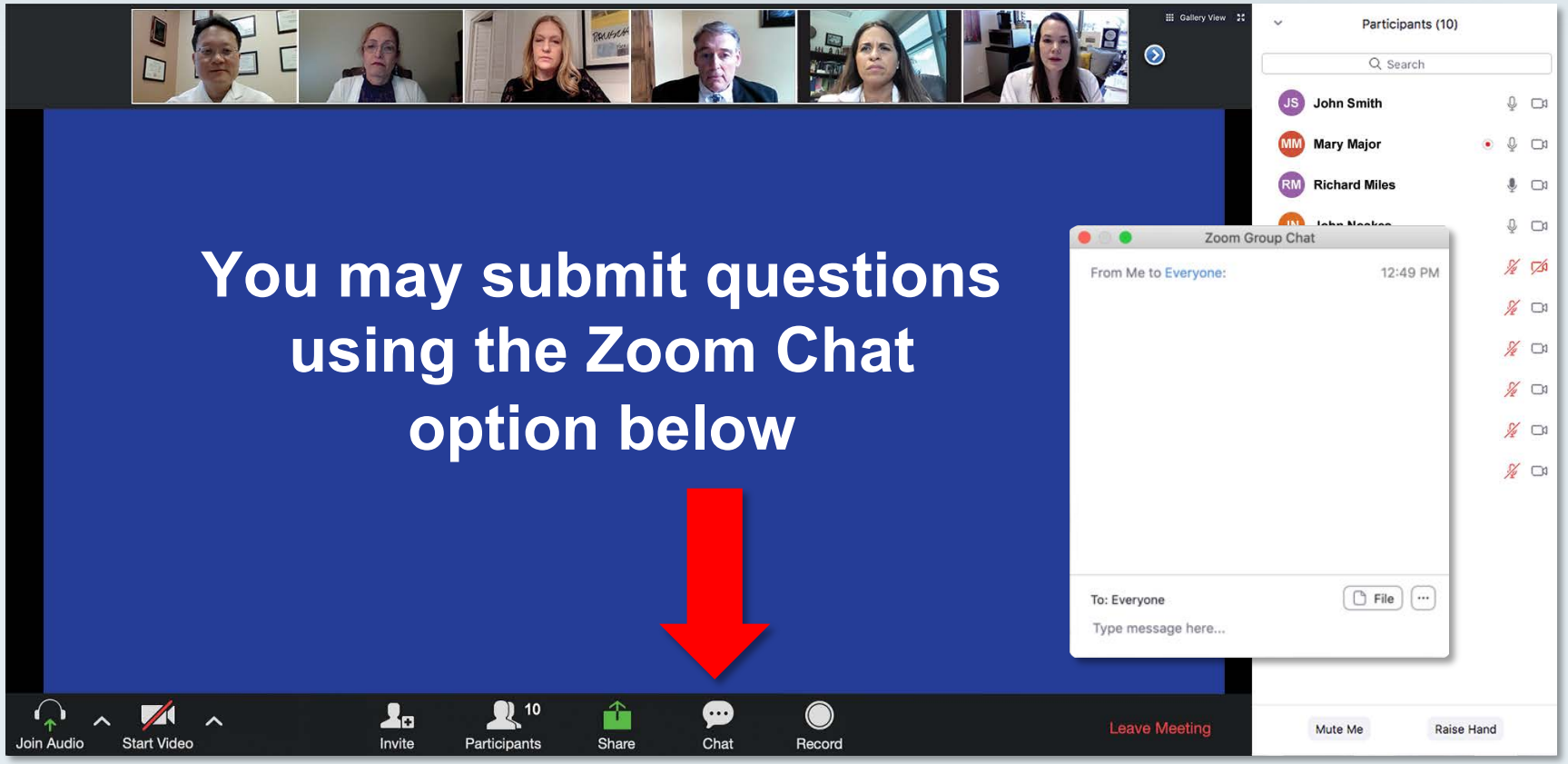
Dr Love and Faculty Encourage You to Ask Questions



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ONCOLOGY TODAY

WITH DR NEIL LOVE

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Exploring the Role of Immune Checkpoint Inhibitor Therapy and Other Novel Strategies in Gynecologic Cancers

A Virtual Meet The Professor Series

Starting August 2020

Participating Faculty

Michael J Birrer, MD, PhD
Robert L Coleman, MD
David M O'Malley, MD
Richard T Penson, MD, MRCP
Matthew A Powell, MD
Brian M Slomovitz, MD
Krishnansu S Tewari, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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Download the RTP Live app on your smartphone or tablet to access program information, including slides being presented during the program:

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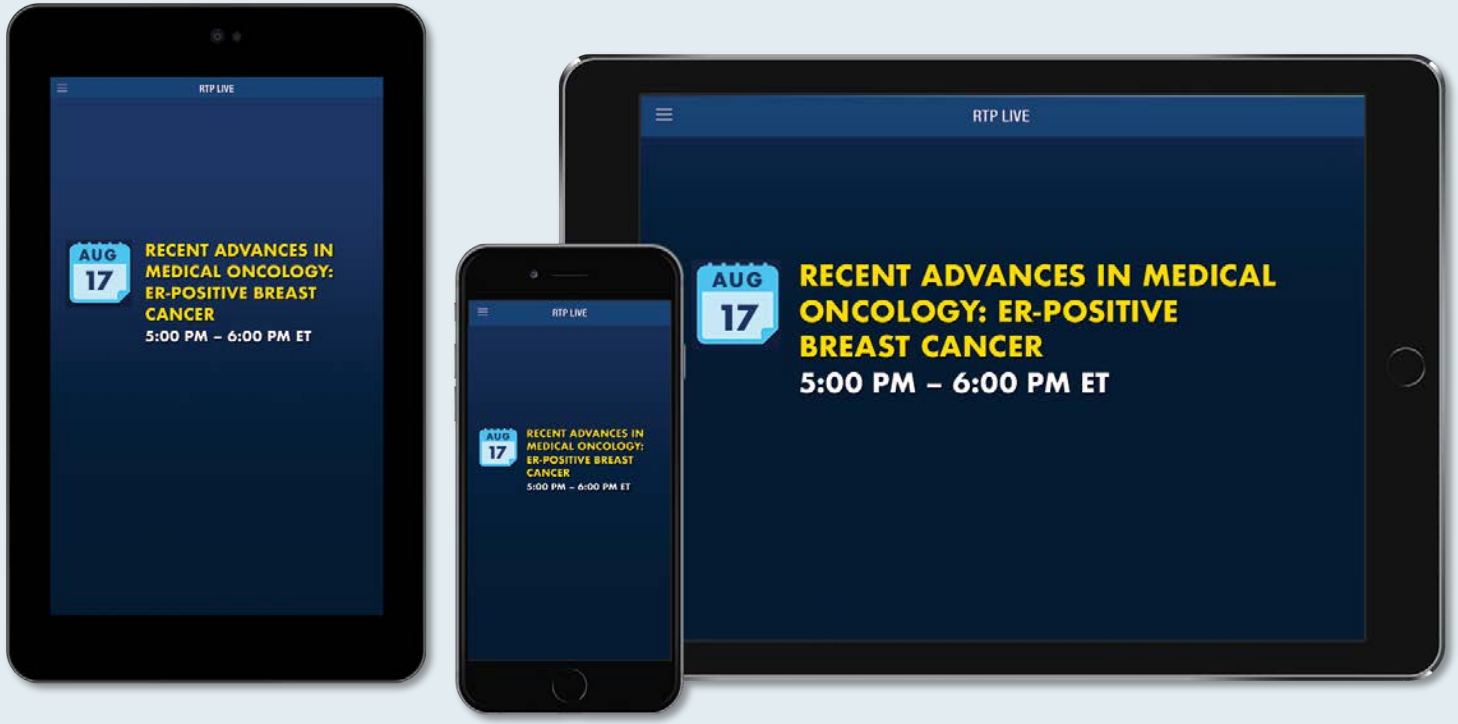

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

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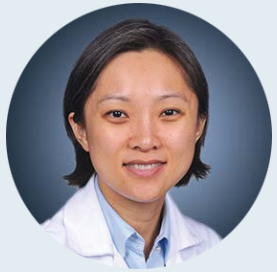
Community Oncologists

Patricia A DeFusco, MD
Hartford HealthCare Cancer Institute
Hartford Hospital
Hartford, Connecticut

Nick C Leasure, MD
Tower Health Medical Group
Reading, Pennsylvania

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina



Yanjun Ma, MD, PhD
Tennessee Oncology, a Partner of OneOncology
Murfreesboro, Tennessee

Maen Hussein, MD
Florida Cancer Specialists and Research Institute
The Villages, Florida

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Module 1: Localized Disease — Dr Kaklamani

- Faculty Cases
  - A 48-year-old woman with ER-positive bilateral breast cancer
  - A 55-year-old woman with ER-positive breast cancer
- Cases/Questions from General Medical Oncologists
  - A premenopausal woman with 2 ER-positive primary breast cancers
  - A 70-year-old woman with Stage I ER-positive breast cancer

Module 2: Metastatic Disease — Dr Tolaney

- Faculty Cases
  - A 56-year-old woman with ER-positive metastatic breast cancer (mBC)
  - A 60-year-old woman with ER-positive mBC
- Cases/Questions from General Medical Oncologists
  - An elderly woman with ER-positive mBC
  - A 54-year-old woman with ER-positive mBC
  - A 60-year-old woman with ER-positive mBC
  - A woman with ER-positive mBC who experiences disease progression on a CDK4/6 inhibitor
  - A woman with ER-positive mBC who develops diabetes on a PI3K inhibitor

Case Presentation (Dr Kaklamani): A 48-year-old woman with ER-positive breast cancer

1. 48 yo woman with bilateral breast cancer.
   - R breast cancer: 1.6cm Grade 3 ER+ PR+ HER2- LN-
   - L Breast Cancer: 1.3 cm grade 2 ER+ PR+ HER2-

2. Ordered Onco*type* DX on both tumors
   - R tumor: Onco*type* Recurrence score 25
   - L tumor: Onco*type* Recurrence score 16

3. What adjuvant treatment should we recommend?

Case Presentation (Dr Kaklamani): A 55-year-old woman with ER-positive breast cancer

1. 55 yo woman undergoes breast conserving surgery and is found to have L breast cancer 3.2cm with 4/15+ LN. Her tumor is ER+ PR- HER2-.
2. Adjuvant therapy recommendations:
   - Should we give chemotherapy and what regimen?
   - Should we offer CDK4/6 inhibitor with endocrine therapy?

A premenopausal woman presents with 2 Grade 2, ER/PR-positive, HER2-negative primary tumors measuring 1.5 and 0.5 cm and is found at surgery to have 1 positive node. Would you order a genomic assay for this patient?

a. No
b. Yes, the 21-gene assay
c. Yes, the 70-gene signature
d. Yes, Prosigna® PAM50
e. Yes, Breast Cancer Index
f. Yes, other

A premenopausal woman presents with 2 Grade 2, ER/PR-positive, HER2-negative primary tumors (1.5 and 0.5 cm) and 1 positive node. A 70-gene signature is ordered and indicates a low risk of recurrence. Would you recommend adjuvant chemotherapy?

a. No
b. Yes, dose-dense AC → q2wk paclitaxel
c. Yes, dose-dense AC → weekly paclitaxel
d. Yes, TC
e. Yes, other chemotherapy

Dr Ma: A premenopausal woman with 2 ER-positive, HER2-negative primary breast cancers

YanJun Ma, MD

- Two primaries – 1.5 and 0.5 cm, both Grade 2, highly ER/PR-positive, HER2-negative, Ki67: 15%
- At surgery, 2-cm nodal metastasis
- MammaPrint®: Ultra-low risk

Question

- What adjuvant treatment would you recommend – chemotherapy, endocrine therapy, both?

Would you recommend adjuvant chemotherapy for a 70-year-old woman with an ER-positive, HER2-negative, T1cN0M0 IDC with focal perineural invasion and a 21-gene Recurrence Score® of 25 who has a history of atrial fibrillation and Type II diabetes?

a. Yes
b. No
c. I would discuss it as an option and say there may or may not be benefit

Dr Favaro: A 70-year-old woman with Stage I ER-positive, HER2-negative breast cancer

Justin Peter Favaro, MD, PhD

- PMH: Atrial fibrillation, diabetes but fit enough for chemotherapy
- Stage I (T1CN0) right-sided, ER-positive, PR-negative, HER2-negative breast cancer; Focal perineural invasion
- Oncotype DX® RS: 25

Question

- Could there be some benefit for adjuvant chemotherapy at the upper limit of lower-risk Oncotype DX Recurrence Scores®?

A 60-year-old woman presents with a 3.5-cm ER/PR-positive, HER2-negative IDC and wishes to undergo breast-conserving surgery but needs tumor shrinkage in order to achieve a good cosmetic result. How would you generally approach neoadjuvant therapy?

A 21-gene assay is ordered and this patient receives a Recurrence Score® (RS) of 10 (low). How would you generally approach neoadjuvant therapy?

	Approach to neoadj Tx	Approach to neoadj Tx if RS = 10
 LISA A CAREY, MD	Administer neoadjuvant ET	Administer ET
 VIRGINIA KAKLAMANI, MD, DSC	Order the 21-gene assay	Administer ET
 IAN E KROP, MD, PHD	Order the 21-gene assay	Administer ET
 JOYCE O'SHAUGHNESSY, MD	Depends on grade and Ki-67	Administer ET
 HOPE S RUGO, MD	Order 70-gene signature (through I-SPY 2)	Administer ET
 SARA M TOLANEY, MD, MPH	Order the 21-gene assay	Administer ET

ET = endocrine therapy

A 57-year-old postmenopausal woman is diagnosed with a 1.3-cm ER/PR-positive, HER2-negative IDC. She has 1 positive sentinel lymph node. Would you order a genomic assay for this patient?

 LISA A CAREY, MD	Yes, PAM50 assay
 VIRGINIA KAKLAMANI, MD, DSC	Yes, the 21-gene assay
 IAN E KROP, MD, PHD	Yes, the 21-gene assay
 JOYCE O'SHAUGHNESSY, MD	Yes, the 70-gene signature
 HOPE S RUGO, MD	Yes, the 21-gene assay
 SARA M TOLANEY, MD, MPH	Yes, the 21-gene assay

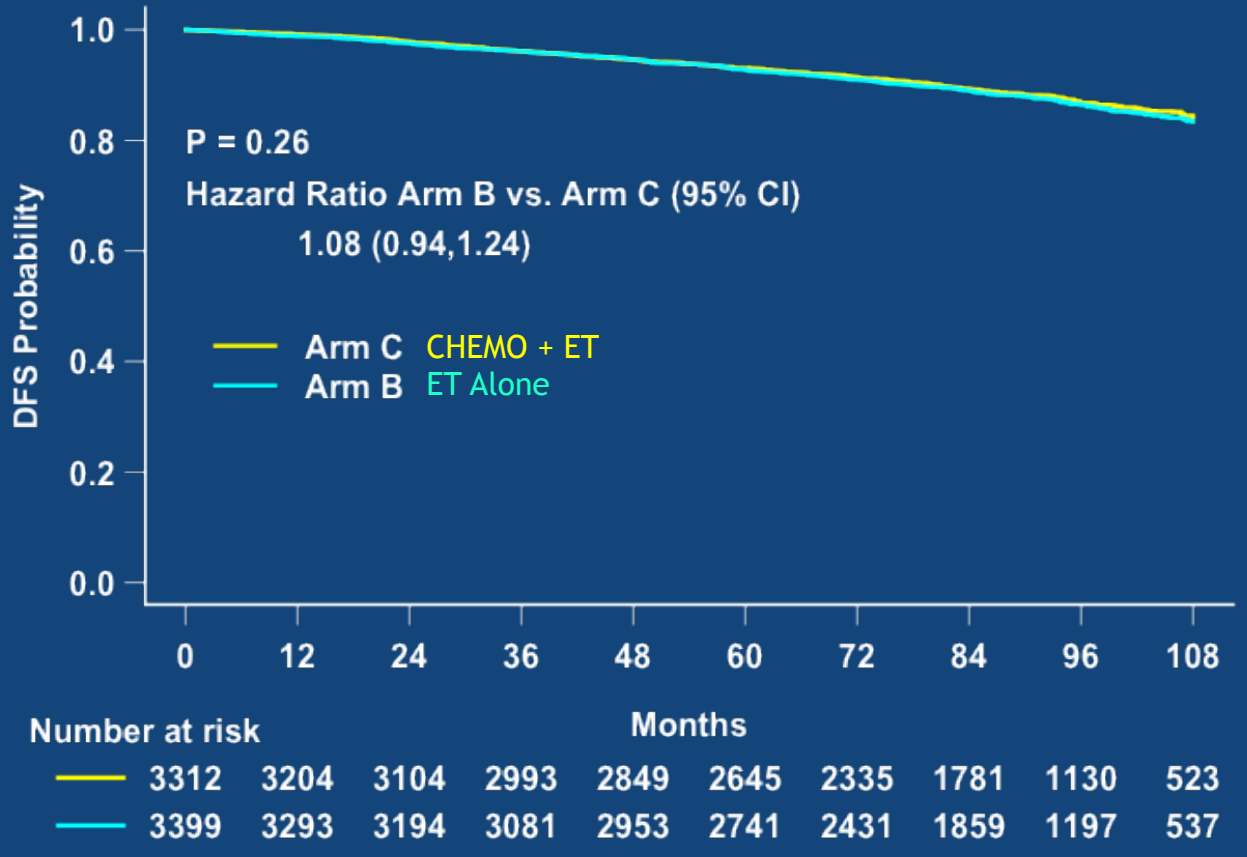
Have you administered or would you administer a CDK4/6 inhibitor to a patient with ER-positive breast cancer in the neoadjuvant or adjuvant setting off protocol?

	Neoadjuvant	Adjuvant
 LISA A CAREY, MD	I have not but would for the right patient	I have not but would for the right patient
 VIRGINIA KAKLAMANI, MD, DSC	I have	I have not but would for the right patient
 IAN E KROP, MD, PHD	I have not but would for the right patient	I have not but would for the right patient
 JOYCE O'SHAUGHNESSY, MD	I have not and would not	I have not and would not
 HOPE S RUGO, MD	I have	I have
 SARA M TOLANEY, MD, MPH	I have	I have

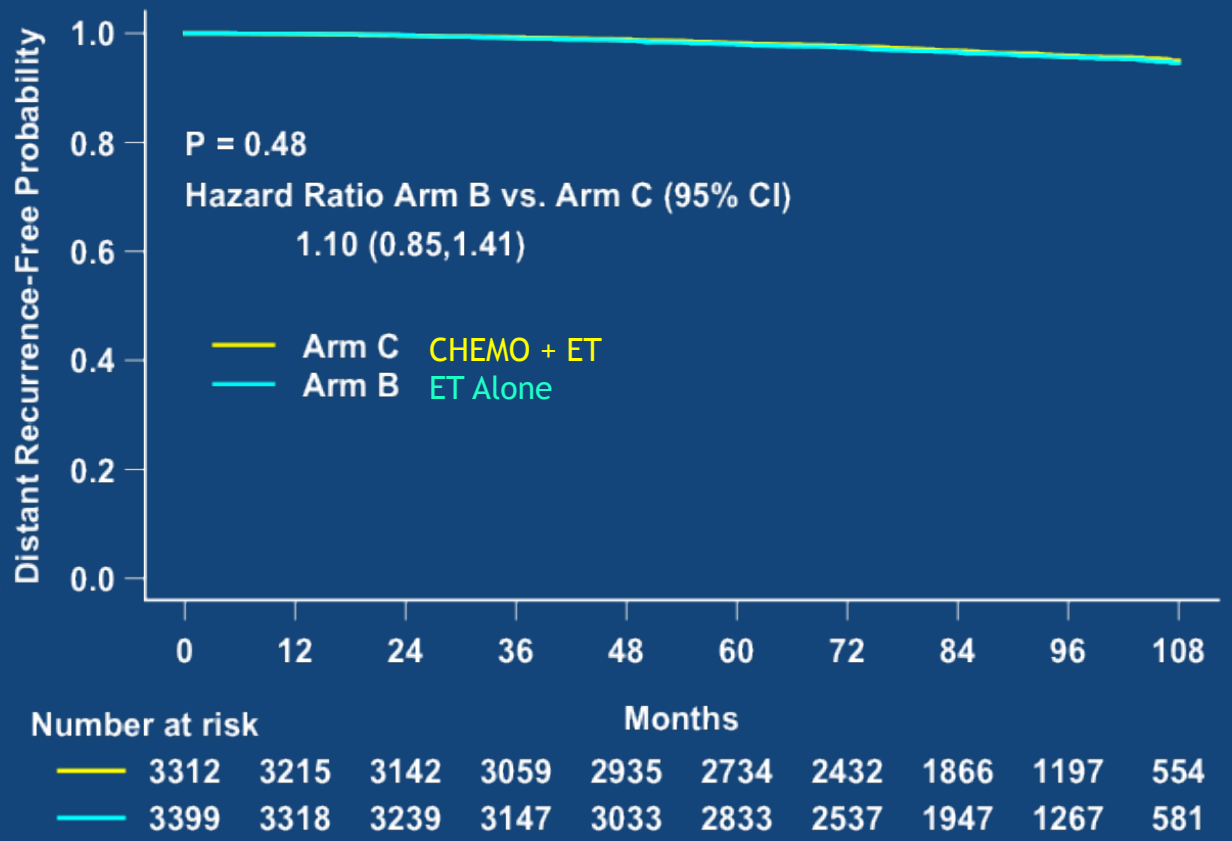
TAILORx Results — ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant

Primary Endpoint
Invasive Disease-Free Survival



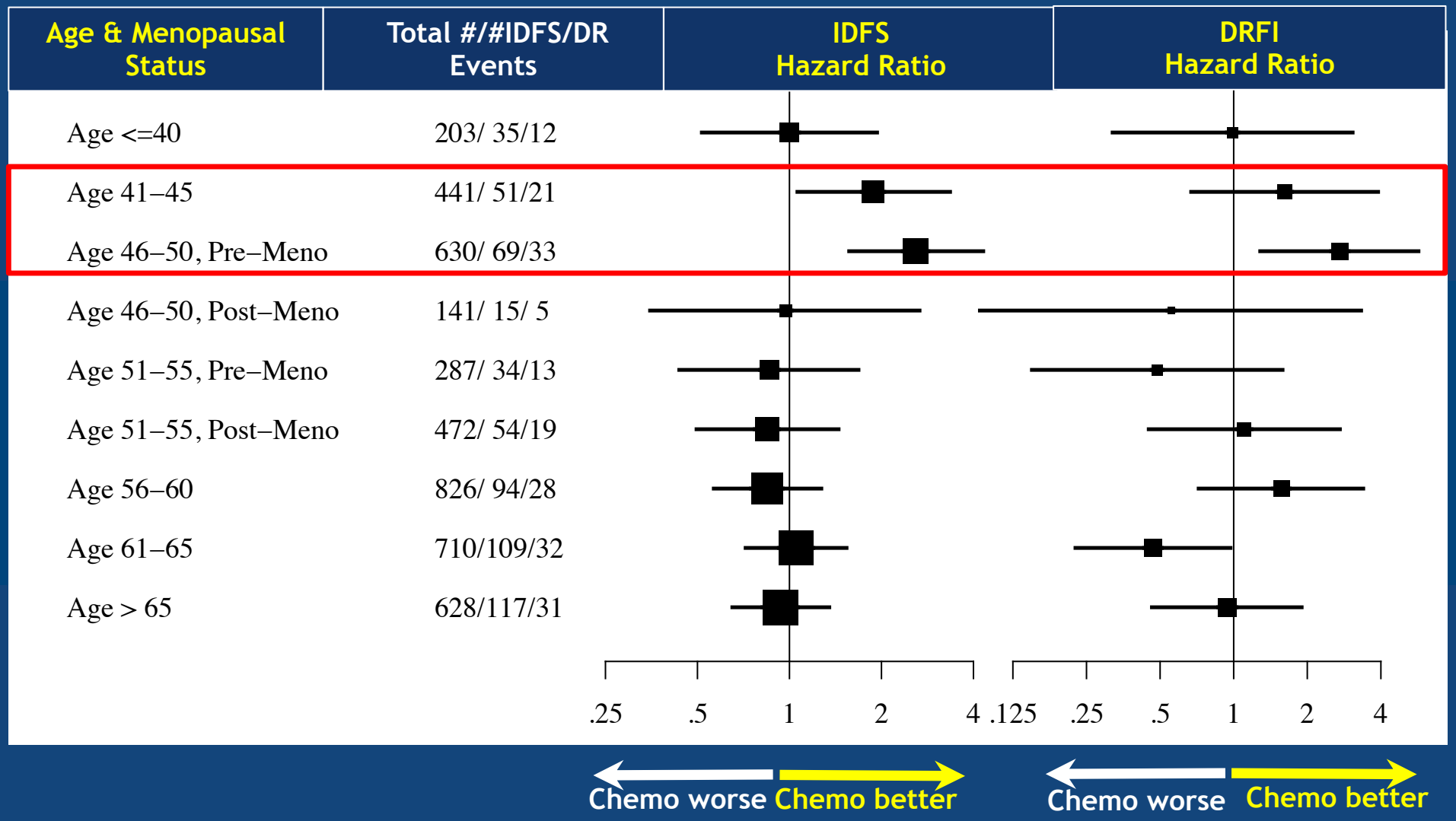
Secondary Endpoint
Distant Relapse-Free Interval



Sparano et al. *N Engl J Med* 2018; 379(2):111-21

Courtesy of Virginia Kaklamani, MD DSc

TAILORx: Exploratory Analysis - Impact of Age and Menopausal Status on Chemotherapy Benefit for RS 16-25



Sparano et al. *N Engl J Med* 2019; 26;381(13):1290-1

Courtesy of Virginia Kaklamani, MD DSc

Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding Treatment in Women ≤ 50 Years

- **Low risk:** T ≤ 1 cm & high grade, ≤ 2 cm & int. grade, ≤ 3 cm & low grade
- **High risk:** not meeting low risk criteria

Integrated RS and Clinical Risk (CR)

Low Integrated Risk (58%)
< 5% Distant Recurrence

- **RS 0-10 & Any CR** (1.8% ±0.9%*) with tam#
- **RS 11-20 & Low CR** (3.2% ±1.2%*) with tam#

Tamoxifen alone adequate
No Chemotherapy

High Integrated Risk (31%)
> 10% Distant Recurrence

- **RS 21-25** (13.1% ±2.9%*) with tam#
  RS 16-20 & High CR (11.9% ± 3.9%) with tam#

Consider chemotherapy or OFS + AI as an alternative to chemotherapy

- **RS 26-100 & High CR** (15.2% ±3.3%*) with tam# plus chemo

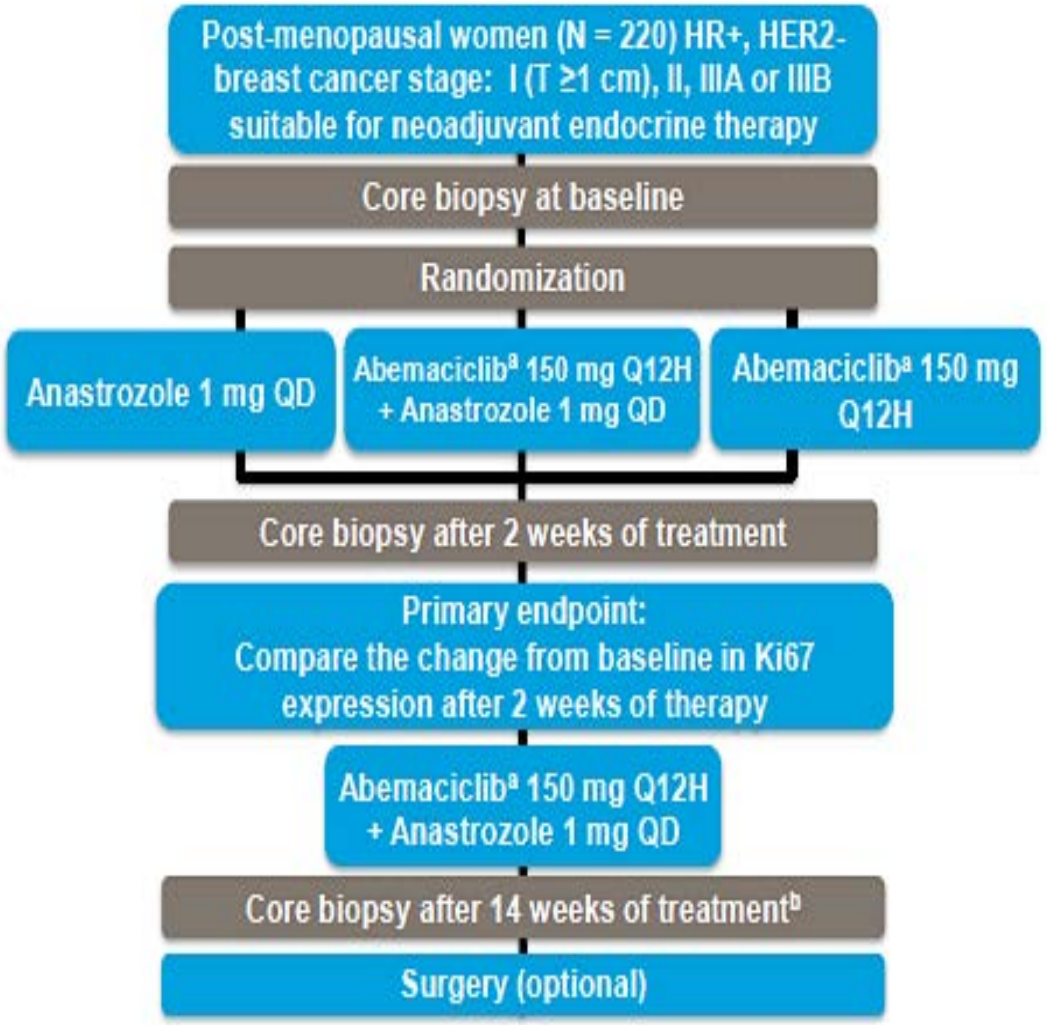
Chemotherapy and consider OFS + AI in addition to chemotherapy

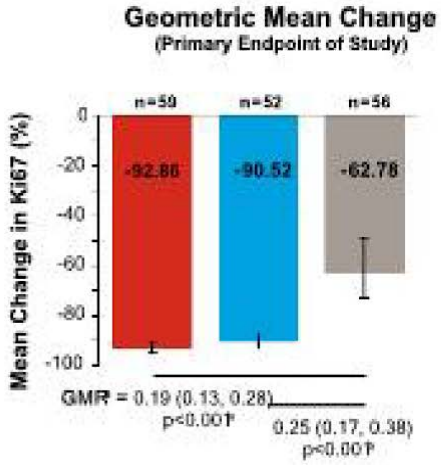
*Kaplan Meier estimates of 9-year distant recurrence rates
tamoxifen in 78% (including 35% who crossed over to an AI), or OFS ± AI in 13%; 9% AI other

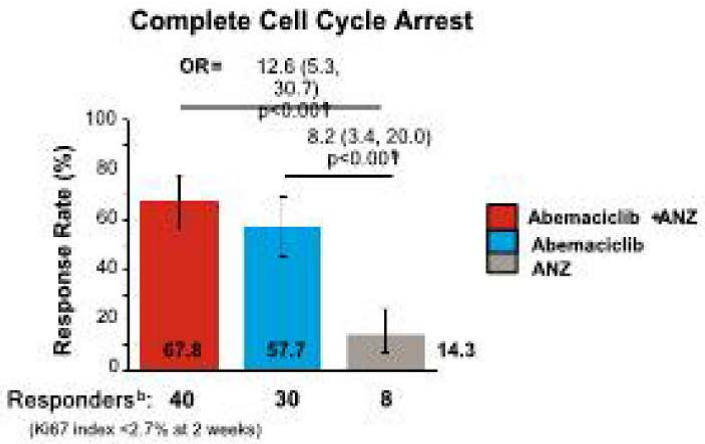
Courtesy of Virginia Kaklamani, MD DSc

neoMONARCH: HR positive

Neoadjuvant Anastrozole +/-Abemaciclib





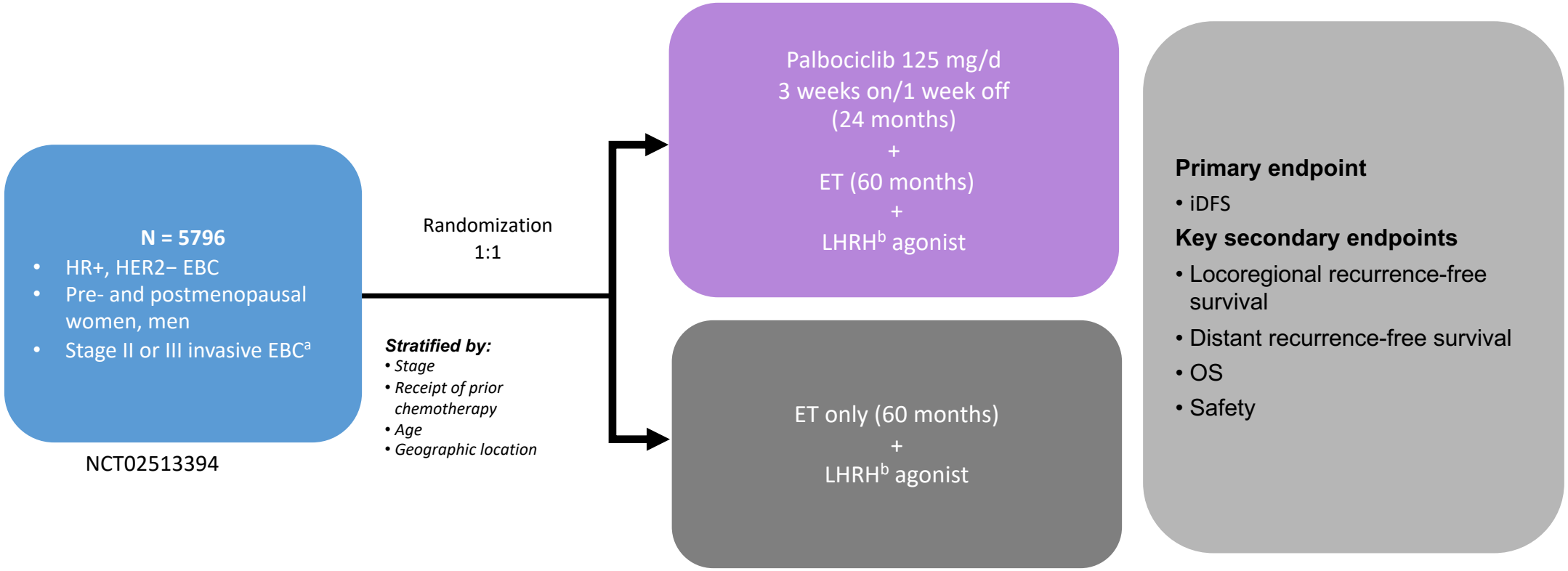


Key Findings

- The two Abemaciclib arms showed a greater drop in Ki67 from baseline to 2 weeks, with >90% of patients' tumors having a significant drop in Ki67 vs patients treated with anastrozole alone
- After 2 weeks, the combination induced a more potent cell-cycle arrest (defined as Ki67 <2.7%)

Courtesy of Virginia Kaklamani, MD DSc

PALLAS: Study design[1,2]



Patients will be treated with physician's choice of ET.

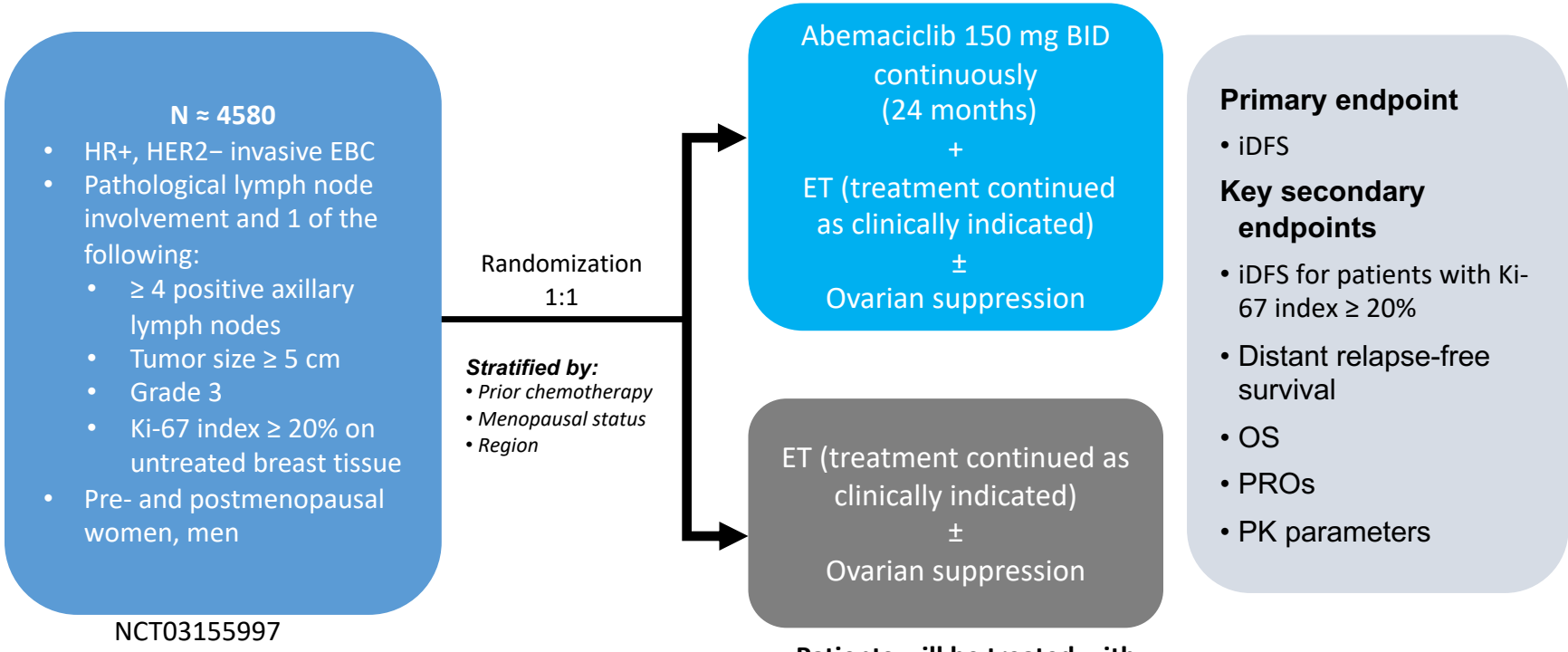
EBC, early breast cancer; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; iDFS, invasive disease-free interval; LHRH, luteinizing hormone–releasing hormone; OS, overall survival; PRO, patient-reported outcome.

[a] Stage IIA limited to maximum 1000 patients. [b] Premenopausal patients.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02513394. Accessed June 9, 2020.
2. Mayer E, et al. *Cancer Res*. 2016;76(4 suppl) [abstract OT1-03-21].

Courtesy of Virginia Kaklamani, MD DSc

MonarchE: Study design[1,2]



NCT03155997

Patients will be treated with physician's choice of ET.

2 high-risk cohorts will be randomized to each treatment:
1. ITT high risk, based on clinical pathological features
2. Ki-67 high risk, based on Ki-67 alone[3]

BID, twice daily; EBC, early breast cancer; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; iDFS, invasive disease-free survival; ITT, intent to treat; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03155997. Accessed June 9, 2020. 2. Rastogi P, et al. *Cancer Res*. 2018;78(4 suppl) [abstract OT3-05-05].
3. DKG. https://www.marienkrankenhaus.org/fileadmin/user_upload/Publikationen/Studien_des_Brustzentrums_2017-07-25.pdf. Accessed March 21, 2020.

Courtesy of Virginia Kaklamani, MD DSc

PALLAS update

- Press release on May 29, 2020, communicating that the trial is unlikely to show a statistically significant improvement in the primary endpoint of iDFS
- Alliance update May 2020
  - Palbociclib discontinuation rate of ≈ 36%
    - Early discontinuation within first 3 months: 9.5%
    - ≈ 65% due to toxicity (≈ 40% protocol-defined toxicity, ≈ 25% nonprotocol-defined toxicity)

MonarchE update

- Press release on June 16, 2020, communicating that abemaciclib in combination with standard adjuvant endocrine therapy (ET) has met the primary endpoint of invasive disease-free survival (IDFS), significantly decreasing the risk of breast cancer recurrence or death compared to standard adjuvant ET alone
- pre-planned interim analysis
- completion date, estimated for June 2027. At the time of the interim analysis, the IDFS results are considered definitive

CDK, cyclin-dependent kinase; ET, endocrine therapy; iDFS, invasive disease-free survival; NA, not available.

Courtesy of Virginia Kaklamani, MD DSc

Courtesy of Virginia Kaklamani, MD DSc

NATALEE: Study design[1,2]

N ≈ 4000
- HR+, HER2− EBC
- Pre- and postmenopausal women, men
- Anatomical stage II[a]
- Anatomical stage III

NCT03701334

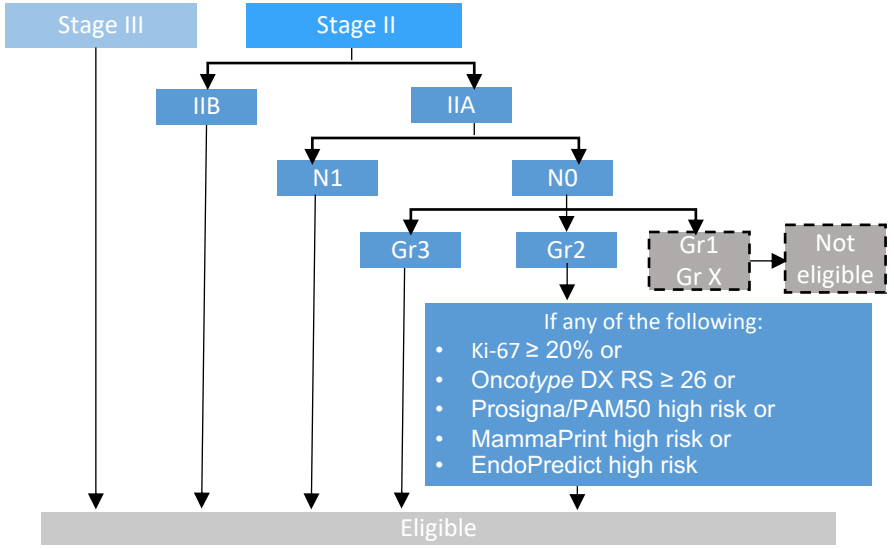
Randomization 1:1

Stratified by:
- *Anatomical stage*
- *Menopausal status*
- *Prior (neo)adjuvant chemotherapy*
- *Geographic region*

Ribociclib 400 mg/d
3 weeks on/1 week off
(36 months)
+
Letrozole 2.5 mg/d or anastrozole 1 mg/d[b]
(60 months)
+
LHRH[c] agonist
N ≈ 2000

Letrozole 2.5 mg/d or anastrozole 1 mg/d[b]
(60 months)
+
LHRH[c] agonist
N ≈ 2000

Eligibility by Anatomical Stage



Primary endpoint
- iDFS

Key secondary endpoints
- Recurrence-free survival
- Distant disease-free survival
- OS
- PROs
- PK parameters
- Safety and tolerability

EBC, early breast cancer; GR, grade; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; iDFS, invasive disease-free survival; LHRH, luteinizing hormone–releasing hormone; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome.

[a] Stage IIB or IIA N1. Stage IIA N0 included if grade 3 or if grade 2 and (Ki-67 ≥ 20% or Oncotype DX Breast Recurrence Score ≥ 26 or Prosigna/PAM50 categorized as high risk or MammaPrint categorized as high risk or EndoPredict EPclin Risk Score categorized as high risk).[3] [b] Treatment with NSAI may start up to 12 months before study treatment start date. [c] Goserelin in premenopausal women and men.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed June 9, 2020. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597]. 3. Data on file. Novartis Pharmaceuticals Corp; 2020.

CDK4/6 inhibitor adjuvant phase III trial designs

	NATALEE	PALLAS	MonarchE	PENELOPE-B
Study population	• High (stage III) and intermediate risks (stage IIB and IIA N1 or N0 G3 or N0G2 with Ki-67 ≥ 20% or high risk by: Onco*type* DX, MammaPrint, EndoPredict, or PAM50) • ≈4000 pts	• High (stage III) and intermediate risks (stage II) • 5796 pts (stage IIA limited to maximum of 1000 patients)	• High risk 2 cohorts - ITT (clinical pathological features) - Ki-67 • ≈ 4580 pts	• High risk (residual invasive disease after neoadjuvant therapy for ≥ 16 weeks [including 6 weeks of taxane] and CPS-EG ≥ 3 or score 2 if ypN+) • Pre- and postmenopausal women • Men excluded • 1250 pts
Node status	Node-positive/-negative	Node-positive/-negative	Node-positive only	Node-positive/-negative
Time from ET start	≤ 12 months	≤ 6 months	≤ 12 weeks	NS
Time from BC surgery	NS	NS	≤ 16 months	< 16 weeks
CDK4/6 trt duration	3 years	2 years	2 years	13 cycles (≈ 1 year)
ET partner	AI (± ovarian suppression)	Tamoxifen or AI (± ovarian suppression)	Tamoxifen or AI (± ovarian suppression)	Tamoxifen or AI (± ovarian suppression)
Primary endpoint	iDFS	iDFS	iDFS	iDFS
Timelines	• Start of study: December 7, 2018	• Start of study: August 2015 • May 2020 study stopped for futility	• Start of study: July 12, 2017	• Start of study: November 2013

AI, aromatase inhibitor; BC, breast cancer; CDK, cyclin-dependent kinase; CPS-EG, clinical-pathological stage-estrogen/grade; ET, endocrine therapy; iDFS, invasive disease-free survival; ITT, intent to treat; NS, not specified; ypN+, postneoadjuvant therapy pathological node positive.

Courtesy of Virginia Kaklamani, MD DSc

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Module 1: Localized Disease — Dr Kaklamani

- Faculty Cases
  - A 48-year-old woman with ER-positive bilateral breast cancer
  - A 55-year-old woman with ER-positive breast cancer
- Cases/Questions from General Medical Oncologists
  - A premenopausal woman with 2 ER-positive primary breast cancers
  - A 70-year-old woman with Stage I ER-positive breast cancer

Module 2: Metastatic Disease — Dr Tolaney

- Faculty Cases
  - A 56-year-old woman with ER-positive mBC
  - A 60-year-old woman with ER-positive mBC
- Cases/Questions from General Medical Oncologists
  - An elderly woman with ER-positive mBC
  - A 54-year-old woman with ER-positive mBC
  - A 60-year-old woman with ER-positive mBC
  - A woman with ER-positive mBC who experiences disease progression on a CDK4/6 inhibitor
  - A woman with ER-positive mBC who develops diabetes on a PI3K inhibitor

Case Presentation (Dr Tolaney): A 56-year-old woman with ER-positive mBC

- 56 yo woman who originally presented with a stage II ER+ HER2- breast cancer in 2003, and had received adjuvant ACx4, followed by 5 yrs of tamoxifen
- 2010: Presented with back pain, imaging demonstrated several lytic lesions in the spine, biopsy confirmed ER+ HER2- disease
- 2010-2015: Letrozole
- 2015-2016: Fulvestrant
- 2016-2018: capecitabine, progressed with new liver mets
- 2018-2020: Tamoxifen + abemaciclib

ctDNA analysis: PIK3CAm (no ESR1)

- 2020: Fulvestrant + alpelisib
  - Baseline HbA1c: 6.2
  - Day 7 fasting glucose 410
  - Alpelisib held, started metformin
  - Restarted alpelisib with dose reduction (Decreased from 300 mg to 250 mg)

Case Presentation (Dr Tolaney): A 60-year-old woman with ER-positive mBC

- 60 yo woman
  - 2000: bilateral mastectomies: multicentric grade 2 IDC, largest 1.2 cm, 0/3 LN ER+, PR+ HER2-
    - AC x4
    - Tamoxifen x5yrs
  - 2016: Presented with cough and back pain: CT revealed pulmonary nodules and spine MRI with likely mets
  - 2016: L4 biopsy: c/w original breast primary, ER+, PR+, HER2-
  - 2017: Letrozole/palbociclib, required dose reduction to 75 mg due to low ANC, and still required dose holds, so switched to abemaciclib
  - 2020: Progression with new liver lesion
  - ctDNA: ESR1, no PIK3CA
  - Enrolled on randomized trial of SERD vs endocrine choice
  - Received SERD, has been on for 4 months with continued reduction in nodes, and just progressed with increase in liver met
  - Getting liver biopsy

A 65-year-old woman presents with de novo ER-positive/HER2-negative mBC with asymptomatic liver and bone metastases. What would be your most likely approach?

a. Observe off treatment
b. Palbociclib + fulvestrant
c. Palbociclib + letrozole
d. Ribociclib + fulvestrant
e. Ribociclib + letrozole
f. Abemaciclib + fulvestrant
g. Abemaciclib + letrozole
h. Other

Challenging Questions and Cases

An elderly woman with ER-positive mBC

A 54-year-old woman with ER-positive mBC

A patient who presents with ER-positive, HER2-negative mBC with liver and bone metastases is stable on palbociclib/letrozole and is found on imaging to have asymptomatic disease progression. Genomic testing reveals a PIK3CA mutation. What would you recommend?

a. Continue palbociclib/letrozole
b. Continue palbociclib and switch endocrine therapy
c. Continue endocrine therapy and switch CDK4/6 inhibitor
d. Switch to alpelisib/fulvestrant
e. Other

A patient with ER-positive mBC experiences asymptomatic disease progression on palbociclib/letrozole. Genomic testing reveals a PIK3CA mutation. Her baseline fasting glucose is 130 mg/dL and hemoglobin A1c = 6.5%. Would you recommend alpelisib/fulvestrant for this patient?

a. No
b. Yes, with standard-dose alpelisib
c. Yes, with reduced-dose alpelisib

Challenging Questions and Cases

A 60-year-old woman with ER-positive mBC

A woman with ER-positive mBC who experiences disease progression on a CDK4/6 inhibitor

A woman with ER-positive mBC who develops diabetes on a PI3K inhibitor

A woman presents with de novo ER-positive, HER2-negative metastatic breast cancer with asymptomatic bone metastases. Which endocrine-based treatment would you most likely recommend?

	Age 65	Age 80
 LISA A CAREY, MD	Palbociclib + letrozole	Palbociclib + letrozole
 VIRGINIA KAKLAMANI, MD, DSC	Palbociclib + letrozole	Palbociclib + letrozole
 IAN E KROP, MD, PHD	Palbociclib + letrozole	Palbociclib + letrozole
 JOYCE O'SHAUGHNESSY, MD	Palbociclib + letrozole	Palbociclib + letrozole
 HOPE S RUGO, MD	Letrozole and then I rotate which CDK4/6 inhibitor	Palbociclib + letrozole
 SARA M TOLANEY, MD, MPH	Palbociclib + letrozole	Palbociclib + letrozole

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?

 LISA A CAREY, MD	Palbociclib + fulvestrant
 VIRGINIA KAKLAMANI, MD, DSC	Palbociclib + fulvestrant
 IAN E KROP, MD, PHD	Palbociclib + fulvestrant
 JOYCE O'SHAUGHNESSY, MD	Palbociclib + fulvestrant
 HOPE S RUGO, MD	CDK4/6 inhibitor + fulvestrant
 SARA M TOLANEY, MD, MPH	Palbociclib + fulvestrant

A 65-year-old woman has completed 5 years of adjuvant anastrozole for an ER-positive, HER2-negative IDC but has now developed minimally symptomatic bone metastases 2 years after completing adjuvant hormonal therapy. Which endocrine-based treatment would you most likely recommend?

 LISA A CAREY, MD	Palbociclib + letrozole
 VIRGINIA KAKLAMANI, MD, DSC	Palbociclib + fulvestrant
 IAN E KROP, MD, PHD	Palbociclib + fulvestrant
 JOYCE O'SHAUGHNESSY, MD	Palbociclib + fulvestrant
 HOPE S RUGO, MD	CDK4/6 inhibitor + letrozole
 SARA M TOLANEY, MD, MPH	Palbociclib + letrozole

A patient who developed metastatic disease after adjuvant anastrozole for ER-positive, HER2-negative breast cancer is receiving palbociclib/fulvestrant and experiences disease progression. Genomic testing is positive for a PIK3CA mutation. The patient has Type II diabetes requiring insulin. Which endocrine-based treatment would you most likely recommend next?

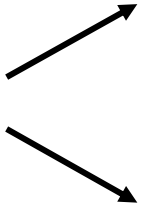
 LISA A CAREY, MD	Exemestane/everolimus
 VIRGINIA KAKLAMANI, MD, DSC	Alpelisib/other endocrine therapy
 IAN E KROP, MD, PHD	Alpelisib/fulvestrant
 JOYCE O'SHAUGHNESSY, MD	Exemestane/everolimus
 HOPE S RUGO, MD	Alpelisib/other endocrine therapy
 SARA M TOLANEY, MD, MPH	Fulvestrant/everolimus

PARSIFAL: Does choice of endocrine backbone matter?

International, open-label, randomized phase II trial

Stratified by visceral involvement, de novo vs recurrent disease

Women with histologically confirmed HR+/HER2- locally advanced/metastatic BC that is endocrine sensitive by ABC3 consensus; no previous systemic tx for metastatic disease; no DFI ≤ 12 mos with previous (neo)adjuvant endocrine tx; postmenopausal or premenopausal receiving ovarian suppression; ECOG PS 0-2
(N = 486)



Palbociclib 125 mg PO QD 3 wks on, 1 wk off +
Fulvestrant 500 mg IM on Days 1, 14, 29 then QM
(n = 243)

Palbociclib 125 mg PO QD 3 wks on, 1 wk off +
Letrozole 2.5 PO QD
(n = 243)

Until PD or intolerable toxicity

Primary endpoint: investigator-assessed PFS

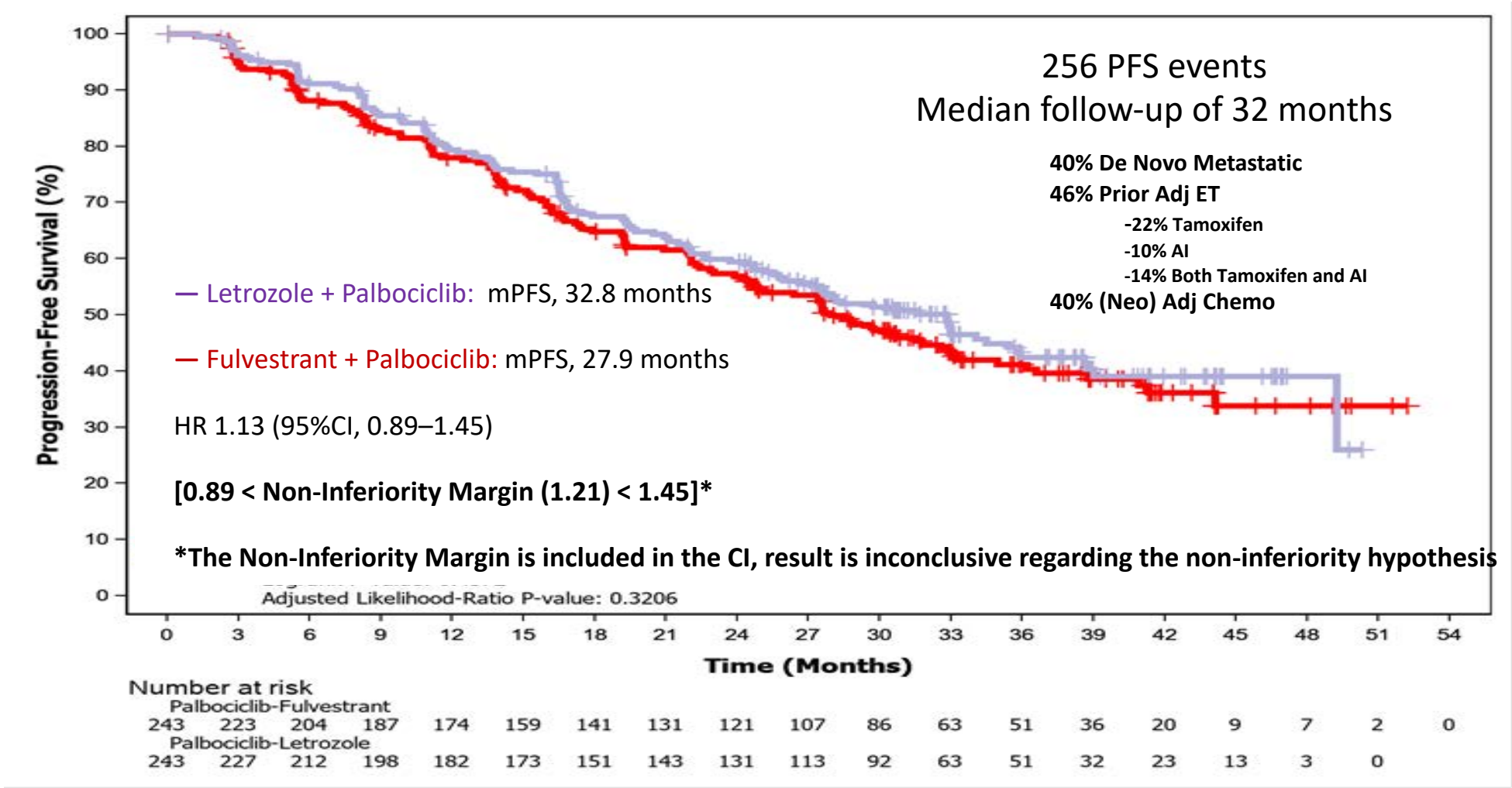
Assumed median PFS of 22 mos for palbociclib + letrozole; study had 80% to detect HR of 0.70 for fulvestrant + palbociclib (31.3 mos) with final analysis after 254 events in 486 patients

If superiority not demonstrated, performed noninferiority analysis (noninferiority margin: HR of 1.21)

Secondary endpoints: PFS subgroup analyses, OS, response (RECIST v1.1), safety

Courtesy of Sara M Tolaney MD, MPH

PARSIFAL: No difference in PFS

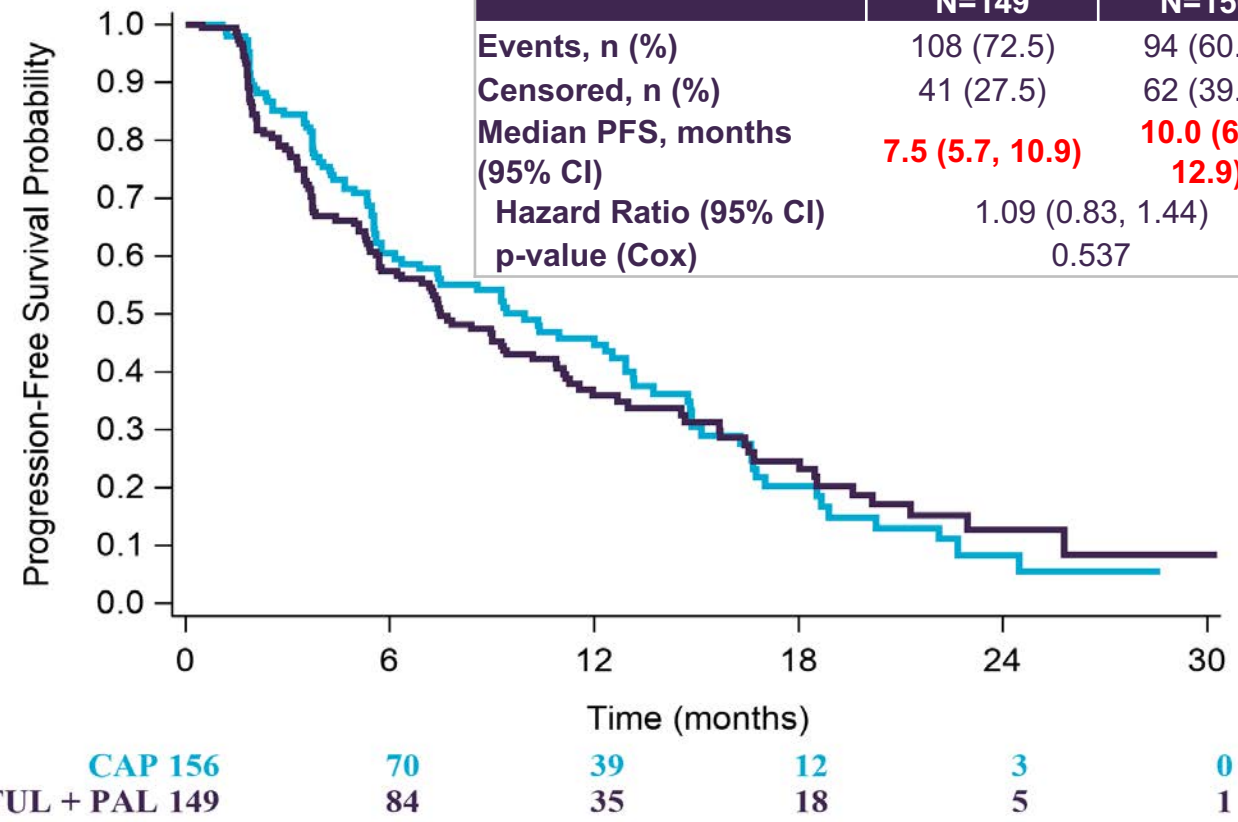


Courtesy of Sara M Tolaney MD, MPH

Is endocrine therapy + CDK4/6i as good as chemotherapy?

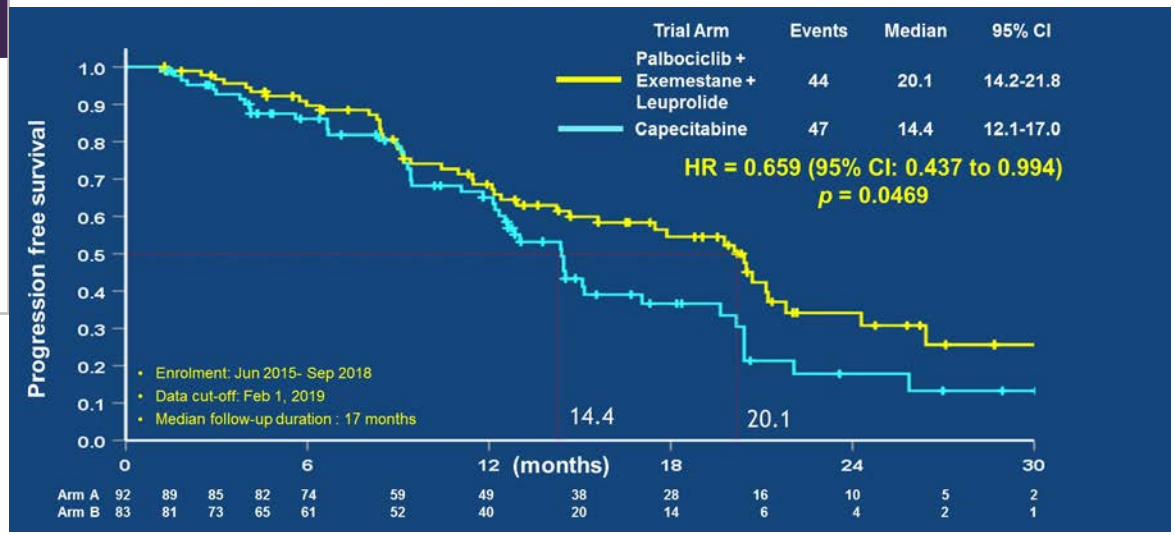
PEARL
Capecitabine vs Fulvestrant + palbociclib

	FUL + PAL N=149	CAP N=156
Events, n (%)	108 (72.5)	94 (60.3)
Censored, n (%)	41 (27.5)	62 (39.7)
Median PFS, months (95% CI)	7.5 (5.7, 10.9)	10.0 (6.3, 12.9)
Hazard Ratio (95% CI)	1.09 (0.83, 1.44)	
p-value (Cox)	0.537	



Martin M, et al. SABCS 2019

Young-PEARL
Capecitabine vs OS+ exemestane + palbociclib



Park YH et al, ASCO 2019

Courtesy of Sara M Tolaney MD, MPH

Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	QT Prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib (more) Palbociclib Ribociclib	Abemaciclib Ribociclib	Ribociclib	Abemaciclib (less) Palbociclib Ribociclib	Abemaciclib	Abemaciclib Palbociclib Ribociclib
Antidiarrheal therapy Increase oral hydration Notify HCP	LFTs before starting tx, Q2W x 2 mos, then: ▪ *abemaciclib,* as indicated ▪ *ribociclib,* at start of cycle x 4 cycles	EKG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of cycle x 6 cycles, then as indicated	CBC before starting tx, then: ▪ *abemaciclib,* Q2W x 2 mos, QM x 2 mos, then as indicated ▪ *palbociclib,* Days 1 and 15 of cycles 1-2, then as indicated ▪ *ribociclib,* Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Courtesy of Sara M Tolaney MD, MPH

Use of CDK4/6 inhibitors for metastatic HR+ breast cancer

- Combining CDK 4/6 inhibition with hormonal therapy is standard of care for first or second line metastatic therapy given significant increase in PFS and OS
  - Choice of endocrine backbone doesn’t seem to impact benefit
- No clear biomarker predictor for benefit outside of ER
- Similar outcomes for endocrine therapy + CDK4/6i when compared to chemotherapy even in patients with prior endocrine therapy for metastatic breast cancer and even among patients with luminal B tumors

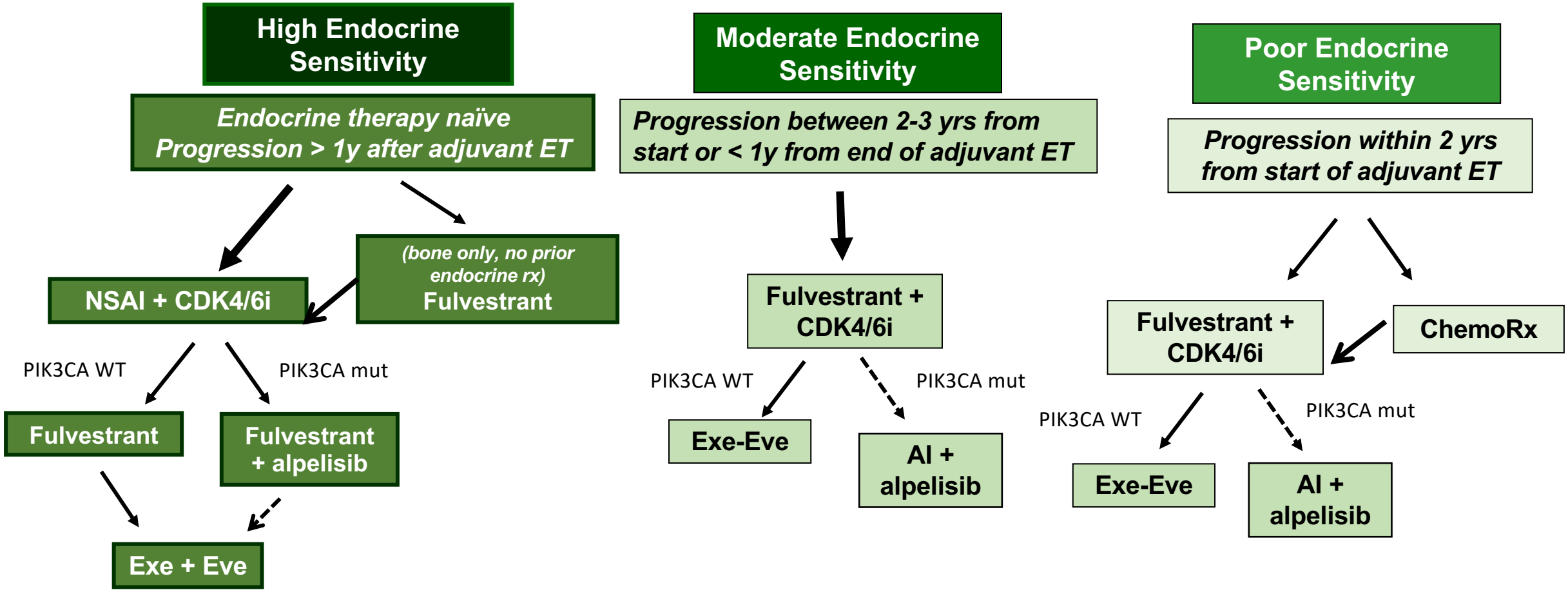
Courtesy of Sara M Tolaney MD, MPH

The Challenge Post-CDK4/6 Inhibition

- What are mechanisms of resistance to CDK4/6 inhibitor therapy?
- Is there a role to continue CDK4/6 inhibitors with subsequent lines of therapy?
- Are there biologically rational combinations to restore sensitivity to CDK4/6 inhibitors?

Courtesy of Sara M Tolaney MD, MPH

APPROACH TO THERAPY FOR METASTATIC HR+ BREAST CANCER



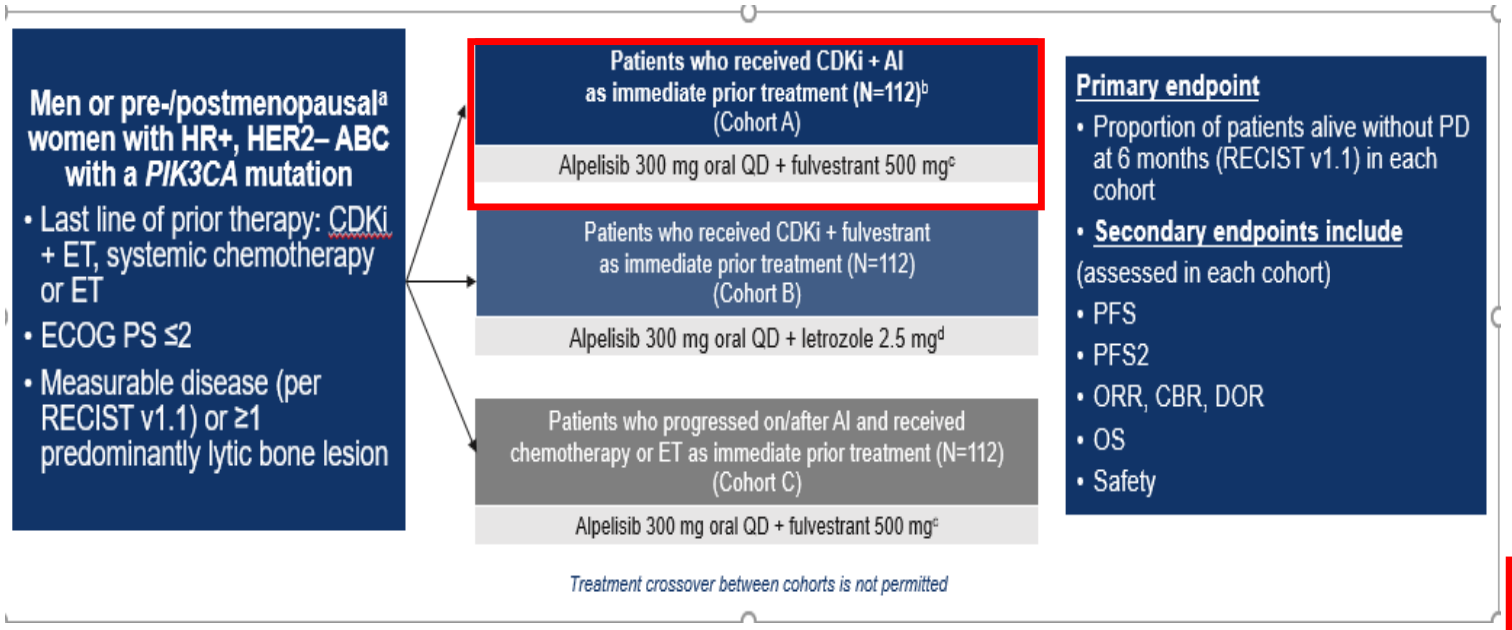
Courtesy of Sara M Tolaney MD, MPH

Summary

- CDK4/6 inhibitors have dramatically changed outcomes for patients with metastatic HR+ breast cancer
  - Double PFS, increase ORR, and improve OS
  - Similar outcomes when compared to chemotherapy, with less toxicity
  - Should be standard of care for all patients in the 1L setting
- Testing patients for PI3K mutations is important
  - Adding alpelisib to fulvestrant improves ORR and PFS for patients with PIK3CA mutations
- Oral SERDs are in development and may represent a novel strategy to better inhibit ER
- Many questions remain on how to best sequence therapy beyond CDK4/6 inhibition

Courtesy of Sara M Tolaney MD, MPH

BYLieve: COHORT A: Alpelisib + Fulvestrant post AI + CDK4/6i



Endpoint	Prior CDKi + AI Cohort (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** (n=72; 95% CI, 5.6-8.3)

N=121 PIK3CA mutated tumors

Median F/U: 11.7 months
12%: CDK4/6i in adj setting
70%: 1 line (majority had ET)
6%: Chemo in 1st line
Primary Endo Resistance: 21%
Secondary Endo Resistance: 60%

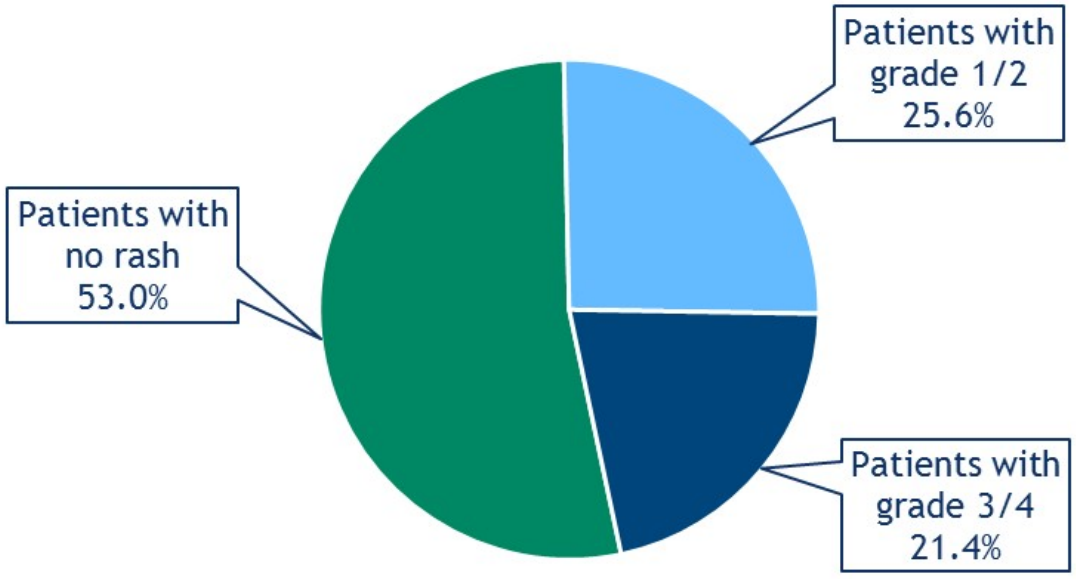
	BYLieve Cohort A	SOLAR-1
ORR	17.4% (21/121)	26.6% (45/169)
CBR*	45.5% (55/121)	62% (104/169)
ORR (measurable disease)	21% (21/100)	35.6% 45/126)
CBR* (Measurable disease)	42% (42/100)	57% (72/126)
Decrease in best % change from baseline	70.1% (n=87)	75.6% (n=116)
Median Relative Dose Intensity	89.9%	82.7%
AEs leading to discontinuation (≥ 1.5%)	20.5% (26/127)	25% (71/284)
Hyperglycemia	1.6% (2/127)	6.3% (18/284)
Rash	3.9% (5/127)	3.2% (9/284)

Rugo H et al, ASCO 2020

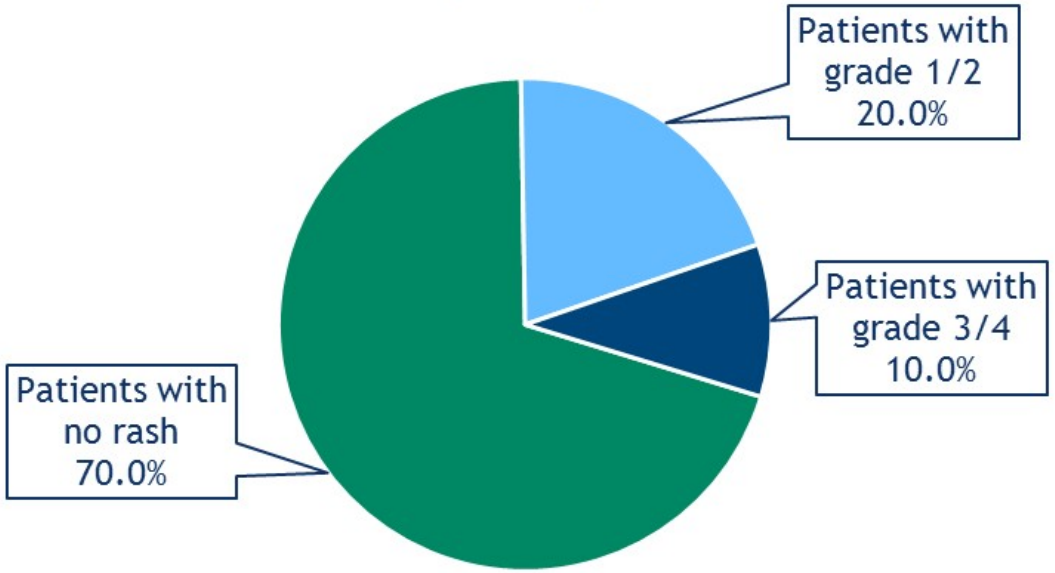
Courtesy of Sara M Tolaney MD, MPH

BYLieve: Incidence of rash with and without prophylactic antihistamines

Patients who did not receive antihistamines or received antihistamines after rash (n=117)



Patients who received antihistamines before rash or had no event (n=10)



Rugo H et al, ASCO 2020

Courtesy of Sara M Tolaney MD, MPH

How and when to utilize alpelisib?

- Adding alpelisib to fulvestrant resulted in a significant improvement in PFS and ORR in patients with PIK3CA mutations (~40% of HR+ breast cancer patients)
  - Testing all patients with metastatic HR+ breast cancer for PIK3CAm is recommended
  - Careful monitoring for hyperglycemia is important, with early initiation of metformin
  - Use of prophylactic antihistamines is recommended
- Questions remain:
  - Would there be benefit in patients who have received prior everolimus, and is there benefit for everolimus after alpelisib?
  - What is the optimal endocrine backbone in a patient with prior fulvestrant?

Courtesy of Sara M Tolaney MD, MPH

AKT Inhibition: FAKTION Ph I/II
Capivasertib (AZD5363) plus fulvestrant vs placebo plus fulvestrant in ER+ MBC

Phase 1b

3+3 design N=9 participants - Capivasertib Starting dose with fulvestrant 500mg: 400mg bd 4 days on / 3 days off

No DLT but 2 withdrawals in 9 participants - Dose not increased to the established single agent dose 480mg bd 4/7

Eligibility

- Post-menopausal women
- ER+/ HER2- Metastatic or unresectable LABC
- Prior AI therapy for MBC/LABC with PD **or** relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed

N = 140

R

1:1

Fulvestrant 500mg q4weeks + loading dose
Placebo bd 4 days on/3 off from C1D15 N=69

Fulvestrant 500mg q4weeks + loading dose
Capivasertib bd 4 days on/3 off from C1D15 N=71

Primary endpoint:

PFS in overall population

Secondary endpoints:

Safety and toxicity

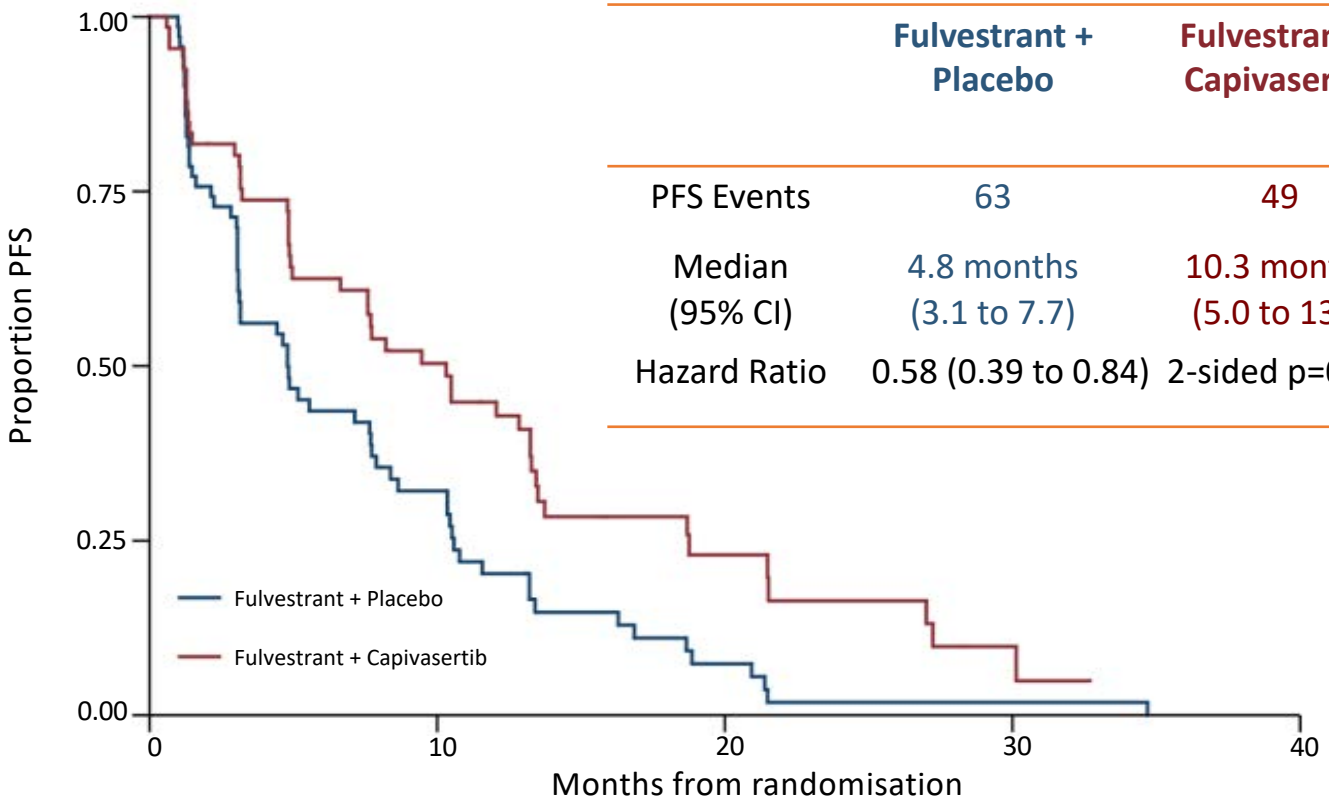
Objective Response rates, CBR and OS: in overall population and pathway activated

Effects of Capivasertib on the PK of fulvestrant

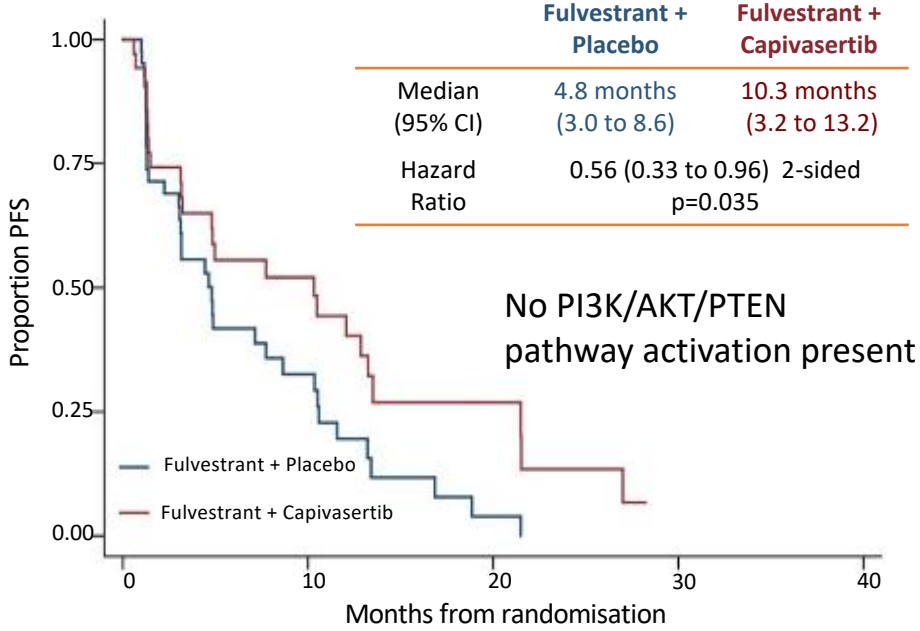
Jones et al, ASCO 2019

Courtesy of Sara M Tolaney MD, MPH

FAKTION: PFS ITT and by PI3K/AKT/mTOR pathway activation status

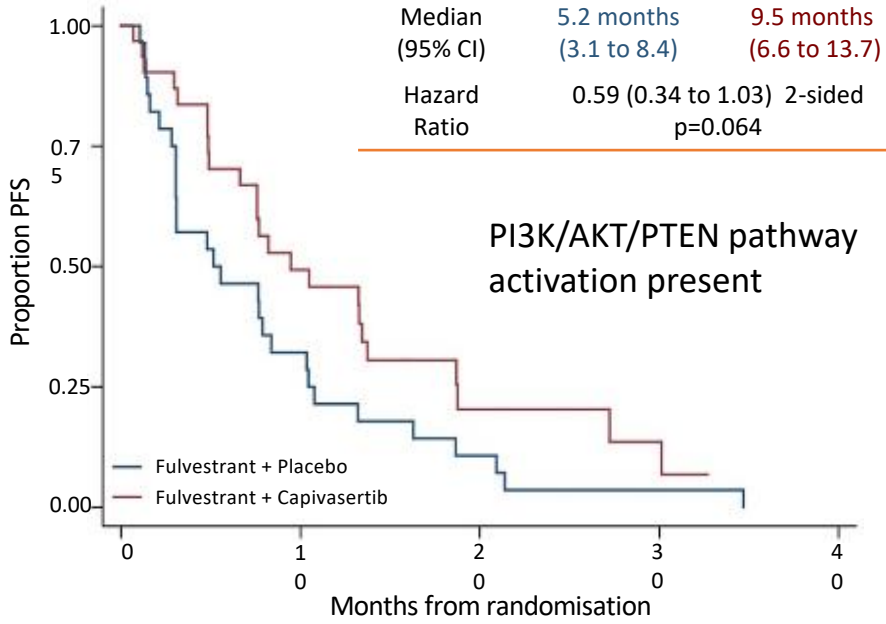


	Fulvestrant + Placebo	Fulvestrant + Capivasertib
PFS Events	63	49
Median (95% CI)	4.8 months (3.1 to 7.7)	10.3 months (5.0 to 13.2)
Hazard Ratio	0.58 (0.39 to 0.84) 2-sided p=0.004	



	Fulvestrant + Placebo	Fulvestrant + Capivasertib
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96) 2-sided p=0.035	

No PI3K/AKT/PTEN pathway activation present



	Fulvestrant + Placebo	Fulvestrant + Capivasertib
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03) 2-sided p=0.064	

PI3K/AKT/PTEN pathway activation present

Ongoing Phase III CAPItello-291 Trial

Jones et al, ASCO 2019

Courtesy of Sara M Tolaney MD, MPH

FAKTION: Notable toxicities

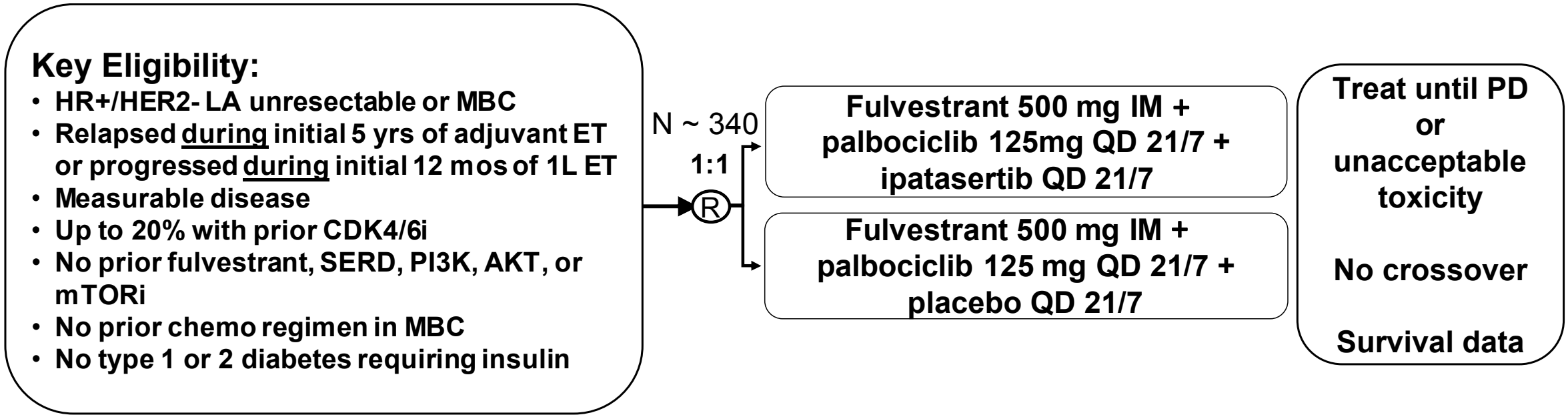
	Fulvestrant + Placebo (n=71)		Fulvestrant + Capivasertib (n=69)	
	All grades	CTCAE G3/4	All grades	CTCAE G3/4
Diarrhoea	25 (35%)	3 (4%)	56 (81%)	10 (14%)
Rash	13 (18%)	0	35 (51%)	14 (20%)
Hyperglycaemia	11 (16%)	0	29 (42%)	3 (4%)
Vomiting	15 (21%)	0	27 (39%)	2 (3%)
Infections	13 (18%)	1 (1%)	26 (38%)	2 (3%)
Oral mucositis	5 (7%)	0	10 (14%)	0
Nausea	36 (51%)	0	38 (55%)	0
Fatigue	41 (58%)	3 (4%)	40 (58%)	1 (1%)
Dizziness	1 (1%)	0	7 (10%)	0
Back pain	11 (16%)	0	17 (25%)	0

Other toxicities affecting >10%, but with similar distributions in each arm (or worse in placebo): abdominal pain; anorexia; arthralgia; non-cardiac chest pain; constipation; cough; dry mouth; dyspnea; extremity pain; flu symptoms; headache; injection site reactions; pain; pruritus; hot flashes.

Jones et al, ASCO 2019

Courtesy of Sara M Tolaney MD, MPH

A PHASE IB/III STUDY OF IPATASERTIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN HORMONE RECEPTOR POSITIVE AND HER2 NEGATIVE METASTATIC BREAST CANCER

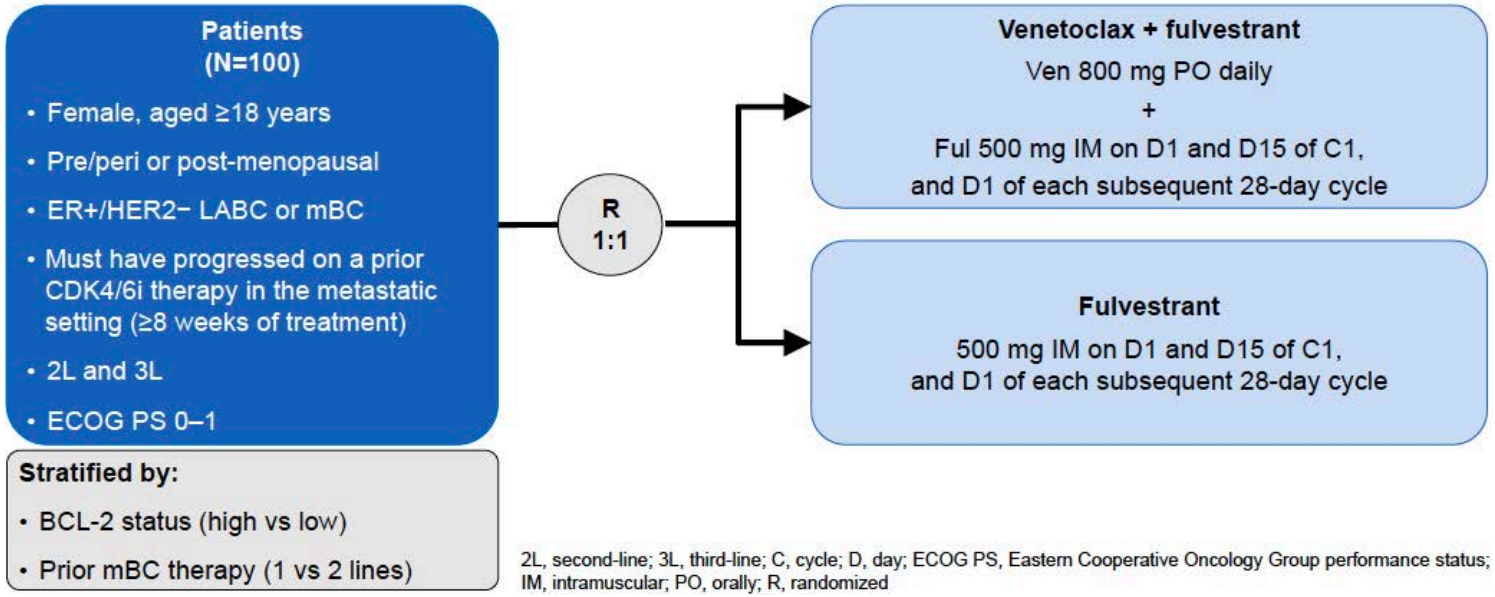


Courtesy of Sara M Tolaney MD, MPH

Other Targets: BCL-2 Inhibition (Venetoclax)

- BCL-2: anti-apoptotic molecule overexpressed in ~75% ER+ BC
- Encouraging activity seen with tamoxifen + venetoclax
  - ORR 54%, CBR 75%

VERONICA: Randomized phase 2



2L, second-line; 3L, third-line; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IM, intramuscular; PO, orally; R, randomized

Lindemann G et al, ASCO 2019

Courtesy of Sara M Tolaney MD, MPH

ESR1 mutations in Breast cancer

Trial	Study treatment	Patient population	Patients (n substudy/ total N on trial)	ESR1 mutation frequency
MONALEESA-2[2]	Letrozole +/- Ribociclib	1st line ER+ MBC	494/668	4.0%
BOLERO-2[3]	Exemestane +/- Everolimus	ER+ MBC after PD on ET	541/724	28.8%
FERGI[4]	Fulvestrant +/- Pictilisib	ER+ MBC after PD on ET	153/168	40.0%
PALOMA-3[5]	Fulvestrant +/- Palbociclib	ER+ MBC after PD on ET	195/521	25.3%
MONARCH 2[6]	Fulvestrant +/- abemaciclib	ER+ MBC after PD on ET	190/295	64.4%

1. C. Fribbens et al 2016; 2. G.N. Hortobagyi et al 2018; 3. S. Chandralapaty et al 2016; 4. J.M. Spoerkle et al 2016; 5. C. Fribbens et al 2016; 6. Tolaney S et al 2019

Slide adapted from Erika Hamilton

Courtesy of Sara M Tolaney MD, MPH

Several Oral SERDs in Various Phases of Development

Fulvestrant: only FDA approved SERD; efficacy may be limited by poor bioavailability

Oral SERDs may achieve higher exposures and have better activity

SERD	N	Prior treatments (%)	ESR1m	Preliminary efficacy	AEs (≥ 10%)
LSZ-102 Jhaveri K et al, SABCS 2018	74	Median ET: 3 (0-7) Ful: 58.9% CDKi: 57.5%	21% (?)	• ORR: 1.4% • DCR: 37,5%	Nausea 60%, Diarrhea 53%, Vomiting 26%
G1T48 Dees EC et al. ESMO 2019	26	Median ET: 3 (1-4) Ful: 84.6% CDKi: 76 %	50%	• ORR: 5.3% • CBR: 15.8%	Fatigue 31%, Diarrhea 27%, Hot Flush 27%, Nausea 15%
SAR439859 Campone M et al, SABCS 2019	16	Median ET: 2 (1-8) Ful: 56% CDKi: 75 %	68.8%	• ORR: 6.3% • CBR: 50%	Hot Flushes 31%, Diarrhea 25%%, Nausea 25%
RAD1901 Kaklamani K et al SABCS 2019	57	Median ET: 3 (1-7) Ful: 38% (?) CDKi: 52 %	50%	• ORR: 19.4% • CBR: 42.6	Nausea 50%, Vomiting 22%, LFT 15%
GDC-9545 Jhaveri et al, SABCS 2019	29	Median ET: 1 (1-2) Ful: 38% CDKi: 59%	52%	• ORR: 10% • CBR: 41%	Nausea 21%, Arthralgia 21%, Fatigue 21%, Diarrhea 17%
AZD9833 Hamilton EP et al, ASCO 2020	60	Median Prior Tx: 5 (1-9) Ful: 82% CDKi: 68%	45%	• ORR: 16.3% • CBR: 42%	Visual disturbance 53%, Bradycardia 45%, Nausea 18%
LSZ-102 + Ribociclib Jhaveri et al; ESMO Breast 2020	76	Median Prior Tx: 4 (0- 10) Ful: 61% CDKi: 41%	38%	• ORR: 16% • CBR: 36%	Nausea 51%, diarrhea 33%, Fatigue 29%, Neutropenia 28%
GDC-9545 (100mg) + Palbo Lim E et al, ASCO 2020	48	Median Prior Tx: 1 (0-2) Ful: 3 (7%) CDKi: 0	29%	• ORR: 33% • CBR: 81%	Neutropenia 77%, Fatigue 29%, Diarrhea 33%, Bradycardia 31%, Constipation 21%, Dizziness 19%, Nausea 21%, Anemia 17%, Thrombocytopenia 17%

Slide courtesy of Komal Jhaveri

Courtesy of Sara M Tolaney MD, MPH

Management of Breast Cancer in the Era of COVID-19

Challenging Questions and Cases

Current Questions and Controversies in the Management of Lung Cancer

A Meet The Professor Series

Tuesday, August 18, 2020

5:00 PM – 6:00 PM ET

Faculty

Leora Horn, MD, MSc

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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