ESMO DEEP DIVE:
BREAST CANCER

ER+ METASTATIC BREAST CANCER: REFINING PRACTICE AND STEERING RESEARCH

Peter Schimd, *Chair*

Barts Cancer Institute
London

ESMO WEBINAR SERIES

ESMO

PROGRAMME AND SPEAKERS

3 July 2024

5 min	**Welcome and introduction** Peter Schmid
25 min	**How to tackle endocrine resistance? Current concepts and ongoing research** Stephen Johnston
25 min	**Breakthrough research on the Role of liquid biopsy and molecular analysis** Francois-Clement Bidard
25 min	**What to do with endocrine refractory patients? Current concepts and ongoing research** Alessandra Gennari
15 min	**LIVE Discussion and Q&A** All

Peter Schmid
Chair
Barts Cancer Institute
London

Stephen Johnston
Speaker
Royal Marsden NHS Foundation Trust & Institute of Cancer Research

François-Clément Bidard
Speaker
Institut Curie & UVSQ/Université Paris-Saclay

Alessandra Gennari
Speaker
University of Piemonte Orientale; Maggiore della Carità Hospital

LEARNING OBJECTIVES

- To acquire a deeper understanding of the clinical course of breast cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for breast cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO DEEP DIVE: BREAST CANCER

THANK YOU FOR YOUR ATTENTION

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO WEBINAR SERIES

ESMO DEEP DIVE: BREAST CANCER

ER+ METASTATIC BREAST CANCER: REFINING PRACTICE AND STEERING RESEARCH

How to tackle endocrine resistance? Current concepts and ongoing research

Stephen R D Johnston

Professor of Breast Cancer Medicine

Royal Marsden Hospital & The Institute of Cancer Research, London, UK

ESMO WEBINAR SERIES

DECLARATION OF INTERESTS

Stephen Johnston

Consulting or Advisory Role:
Eli Lilly, Puma Biotechnology, Pfizer, Novartis, Sanofi Genzyme

Speaker Honoraria:
Pfizer, Novartis, Eisai, Eli Lilly, AstraZeneca, Roche/Genentech, Sanofi Genzyme

Research Funding:
Laboratory Studies: Pfizer, Puma Biotechnology
Clinical Trials: Eli Lilly, Pfizer, AstraZeneca, Novartis, Roche/Genentech

TACKLING ENDOCRINE RESISTANCE IN METASTATIC BREAST CANCER (MBC)

Current Questions in Clinical Practice

1. **What is Endocrine Resistance ?**
   - ESMO definitions
   - What are the Key Mechanisms for Endocrine Resistance ?

2. **How to select Endocrine Treatment (ET) options for Endocrine Resistance in ER+ MBC ?**
   - How to overcome Primary (De-Novo) Endocrine Resistance in 1st-line setting ?
   - Mutation testing in 2nd line setting – when and how to test ?

3. **Current Research: Testing Emerging Treatments for Endocrine Resistance in Breast Cancer ?**
   - Lessons from Pre-surgical Clinical Models to identify Biomarkers of Endocrine Resistance

Definitions of Endocrine Resistance in ER+ MBC

PRIMARY ENDOCRINE RESISTANCE

Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE

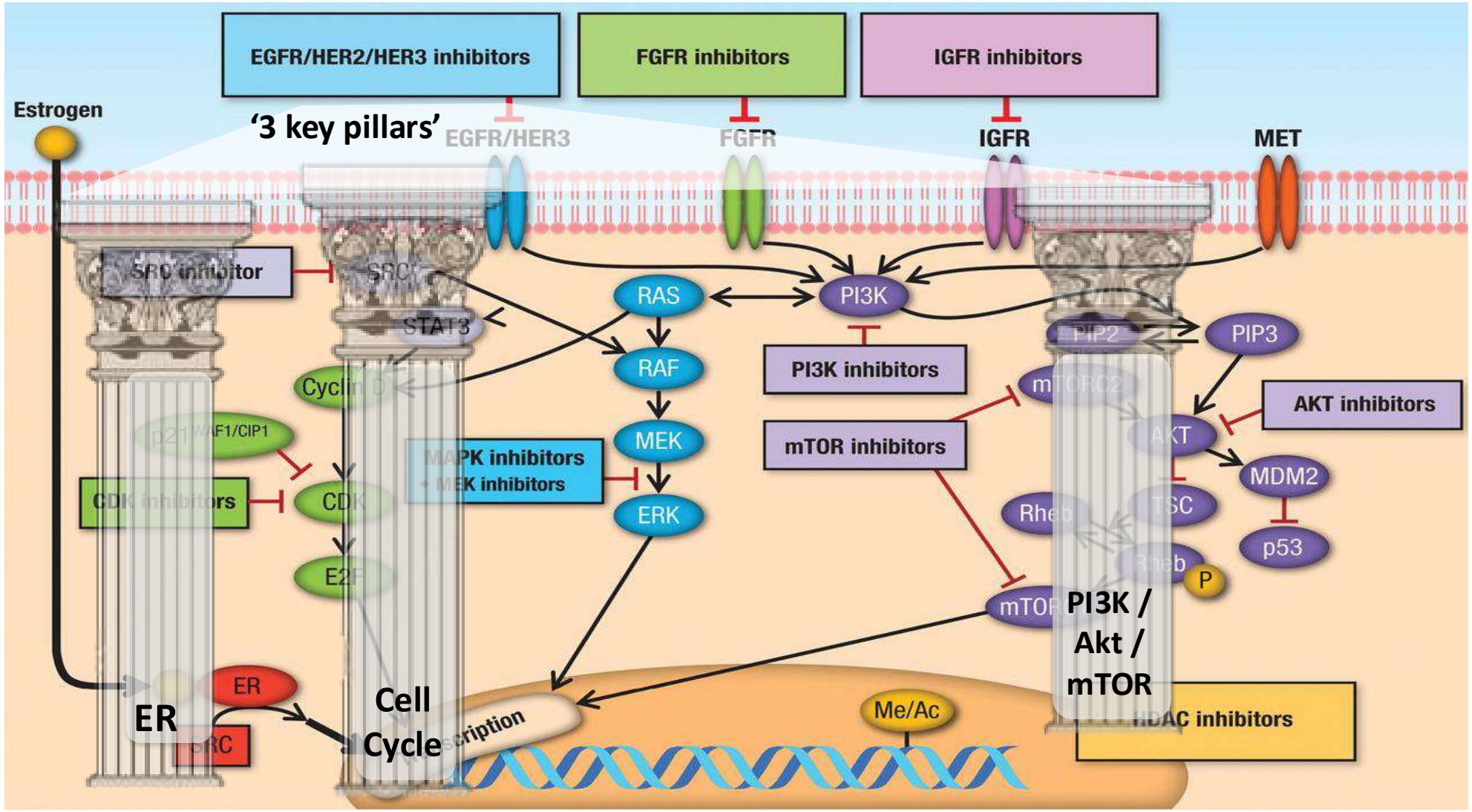
Relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for MBC, while on ET

European School of Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

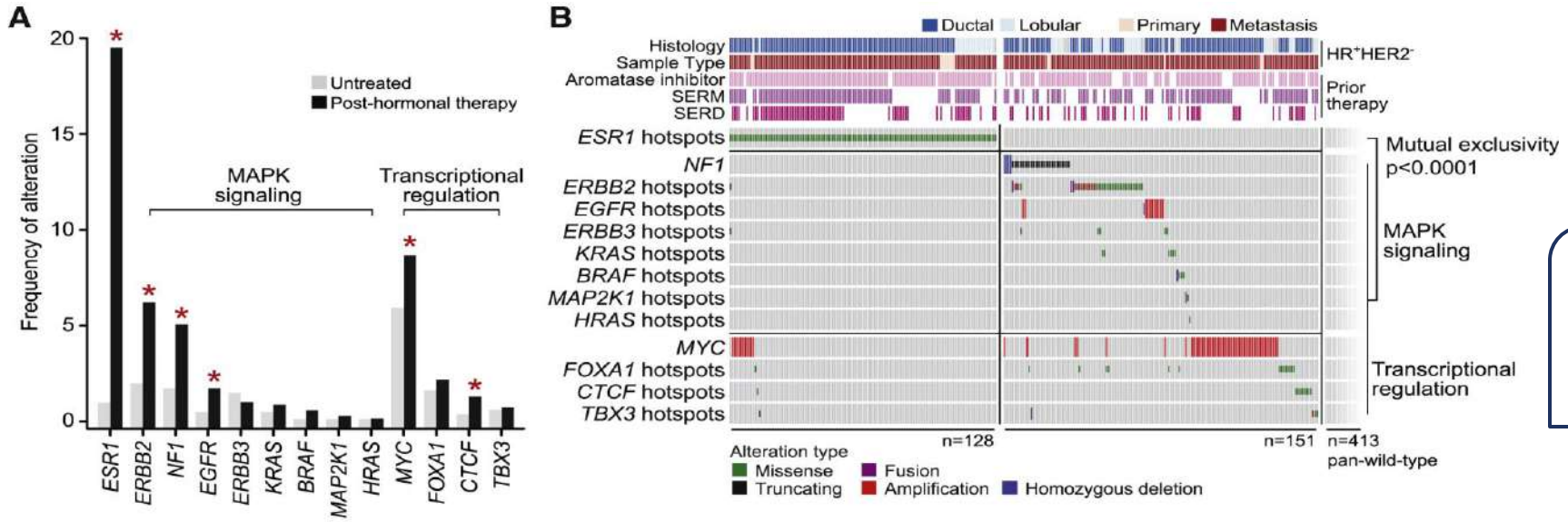
Network of intra-cellular signaling pathways involved in Endocrine Resistance in HR+ BC

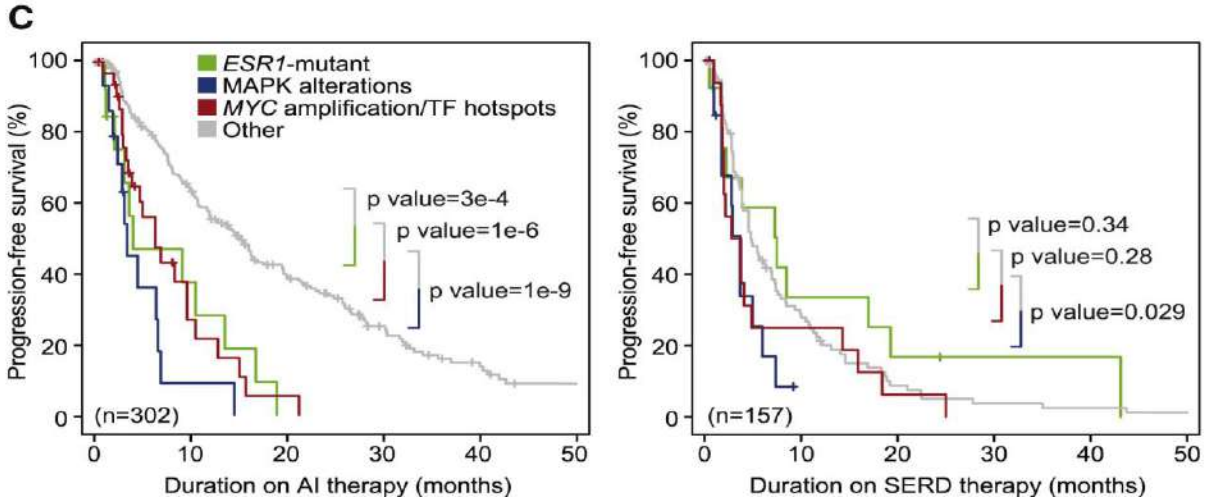


JNCI

Johnston S. J Natl Cancer Inst. 2015;107(10)

Genetic landscape of "endocrine-resistant" advanced breast cancer





N = 1,501 HR+ HER2- tumours

n = 809 Rx naïve tumours
n = 692 post-endocrine Rx

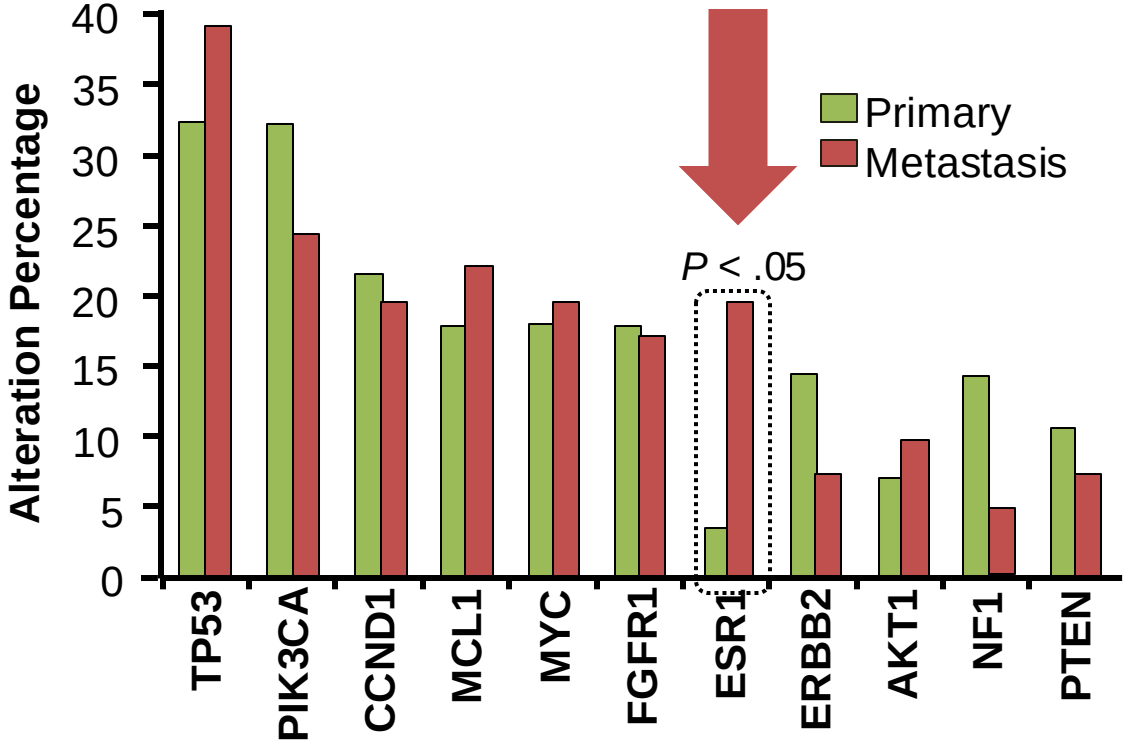
Key Findings in ER+ Endocrine Resistant MBC:

1. Mutations in ESR1 and MAPK Signalling most common, but mutually exclusive
2. Functional Role: Mutations are biological determinants of response to subsequent next line of Rx (AI vs SERDs)

Razavi P et al. Cancer Cell. 2018:34:427-38.

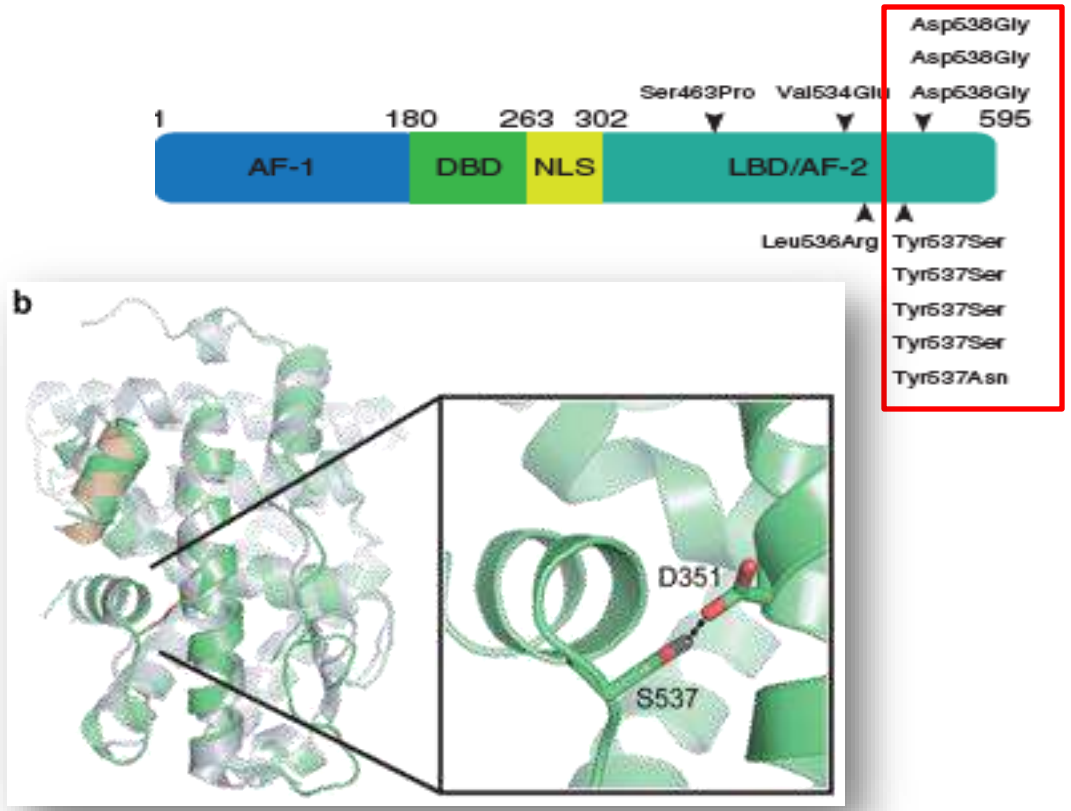
Genomic mutations in ER+ advanced breast cancer

Genomic alterations in ER+ tumors



***ESR1* mutations occur in ~20% of endocrine resistant ER positive breast cancer**

Cluster of mutations in amino acids 537-538 in ligand-binding domain reported in AI pretreated pts, conferring constitutive activation



Zhang Q.X et al. Cancer Res 1997 Li S et al. Cell Reports 2013 Toy W et al. Nat Gen 2013
Robinson DR et al. Nat Gen 2013 Merenbakh-Lamin K et al. Cancer Res 2013 Jeselsohn R et al. Clin Cancer Res 2014

ESR1 mutations in SoFEA trial

HR+ve Metastatic Breast Cancer
with prior sensitivity to NSAI (n = 723)

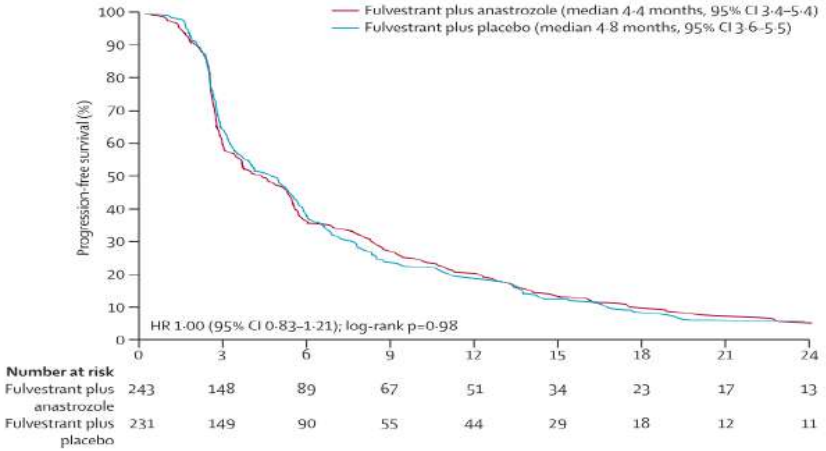
N=161 blood samples available for testing

Fulvestrant arms merged for analysis

Fulvestrant 250mg + Placebo

Fulvestrant 250mg + Anastrozole

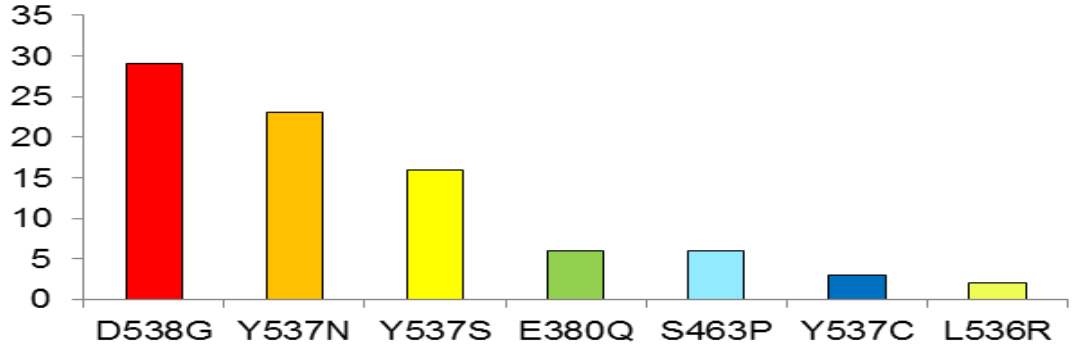
Exemestane



Johnston SR, et al. Lancet Oncol. 2013;14(10):989-98

39.1% patients (63/161) had *ESR1* mutations detected in baseline plasma

ESR1 mutations polyclonal in 49.1%



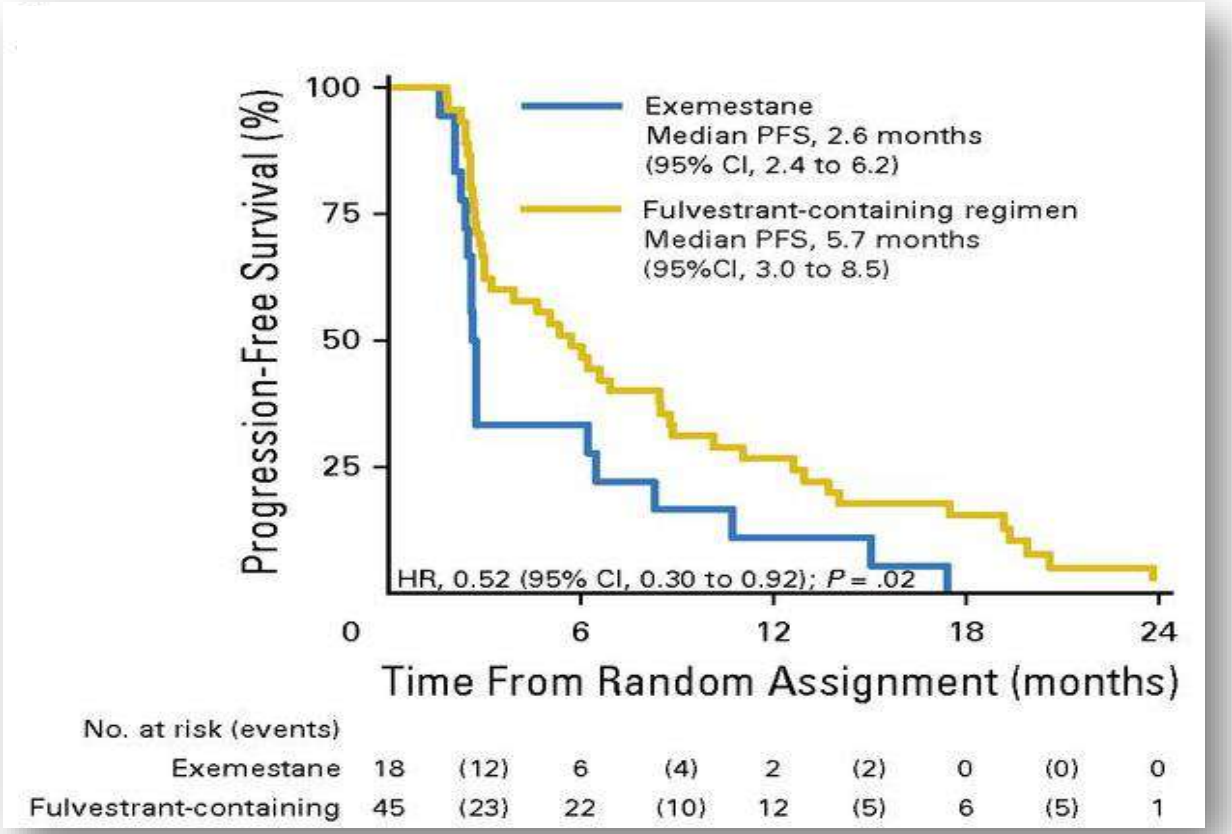
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Plasma *ESR1* Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer

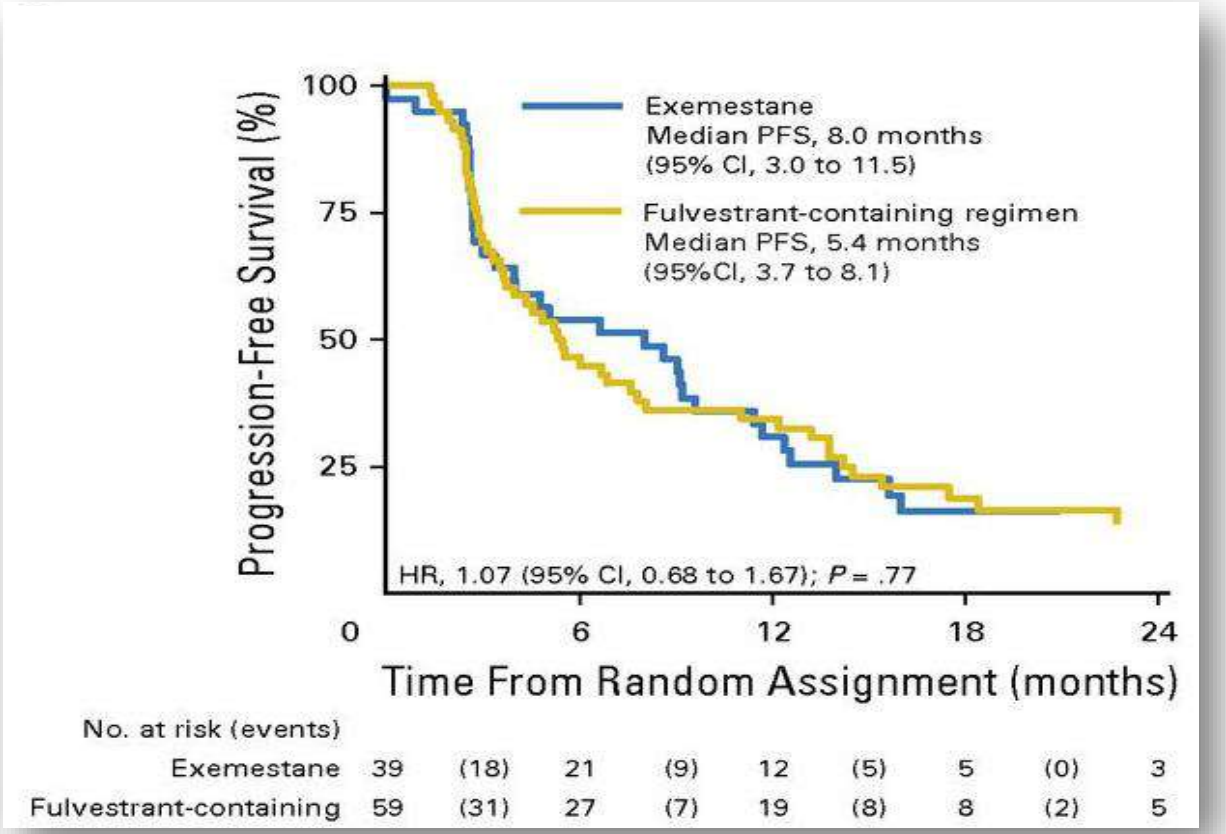
Charlotte Fribbens, Ben O'Leary, Sarah Hrebien, Isaac Garcia-Murillas, Matthew Beaney, Mitch Dowsett, and Nicholas C. Turner, Institute of Cancer Research; Charlotte Fribbens, Ben O'Leary, Stephen R.D. Johnston, and Nicholas C. Turner,

Charlotte Fribbens, Ben O'Leary, Lucy Kilburn, Sarah Hrebien, Isaac Garcia-Murillas, Matthew Beaney, Massimo Cristofanilli, Fabrice Andre, Sherene Loi, Sibylle Loibl, John Jiang, Cynthia Huang Bartlett, Maria Koehler, Mitch Dowsett, Judith M. Bliss, Stephen R.D. Johnston, and Nicholas C. Turner

***ESR1* mutated**



***ESR1* wild type**



Fribbens C, et al. J Clin Onc. 2016;34(25):2961-8

RESEARCH ARTICLE | OCTOBER 27 2023

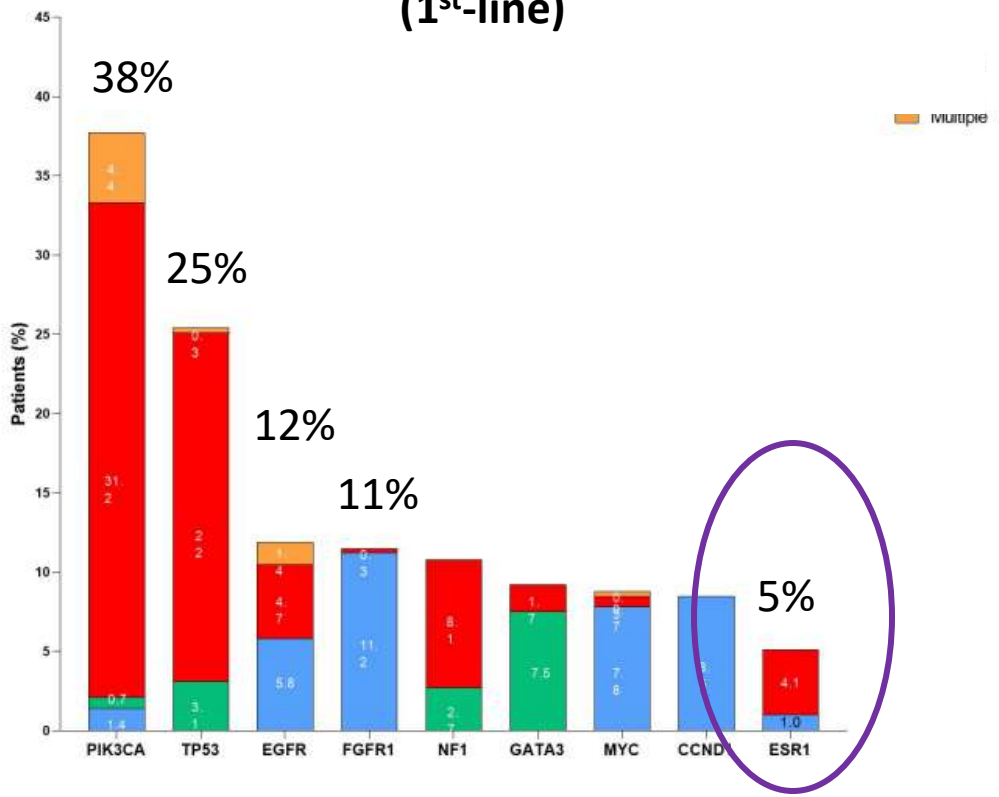
Landscape of baseline and acquired genomic alterations in circulating tumor DNA with abemaciclib alone or with endocrine therapy in advanced breast cancer

Matthew P. Goetz ; Erika P. Hamilton ; Mario Campone ; Sara A. Hurvitz ; Javier Cortes ; Stephen Johnston ; Antonio Llombart-Cussac ; Peter A. Kaufman ; Masakazu Toi ; Guy Jerusalem ; Hillary Graham ; Hong Wang ; Valerie M. Jansen ; Lacey M. Litchfield ; Miguel Martin

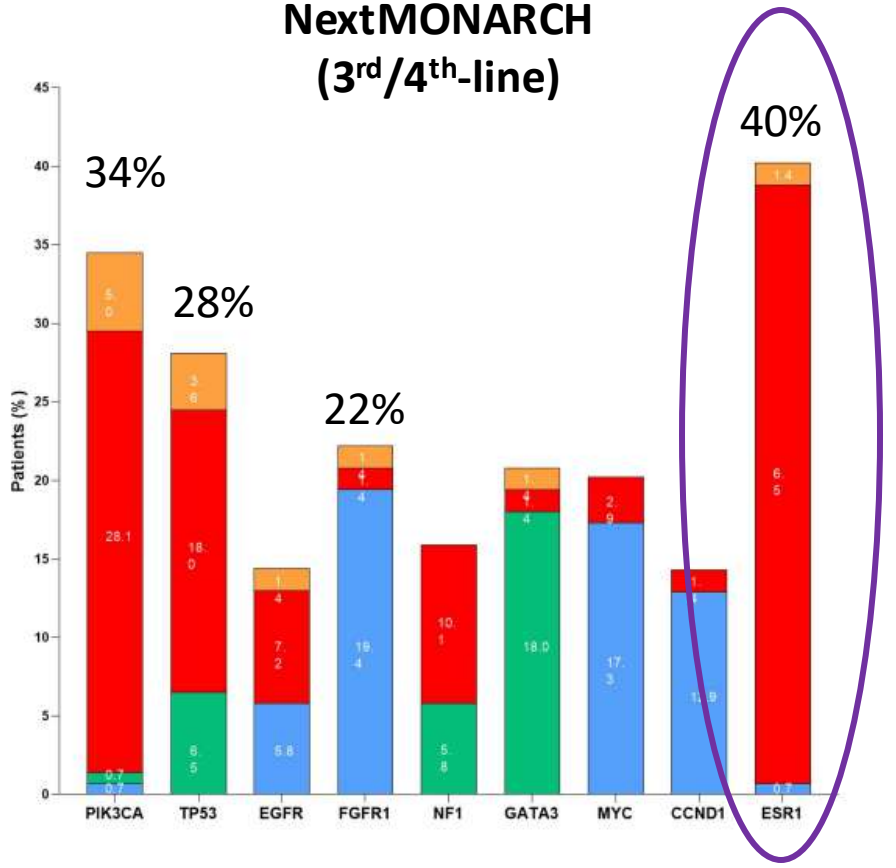
81% M-3 and 90% NM patients had at least one genomic alteration detected in ctDNA at baseline:

- amplifications (copy number alterations)
- point mutations (single nucleotide variants)
- insertions / deletions
- multiple

MONARCH-3 (1st-line)

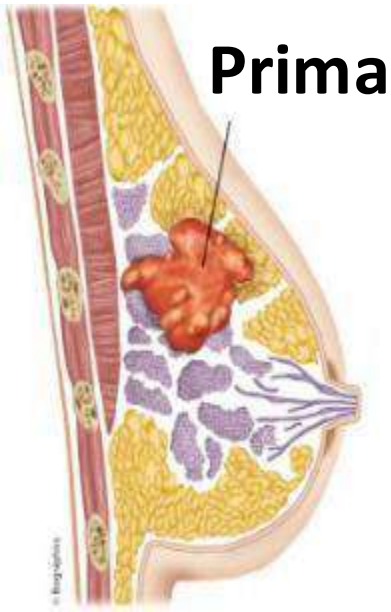


NextMONARCH (3rd/4th-line)



Goetz MP et al. Clin Cancer Res. 2023 Oct 27. doi: 10.1158/1078-0432.CCR-22-3573.

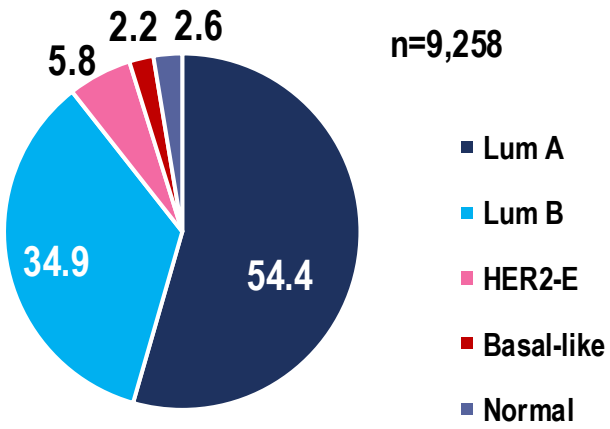
Subtype in HR+/HER2-negative metastatic breast cancer



Primary Tumor

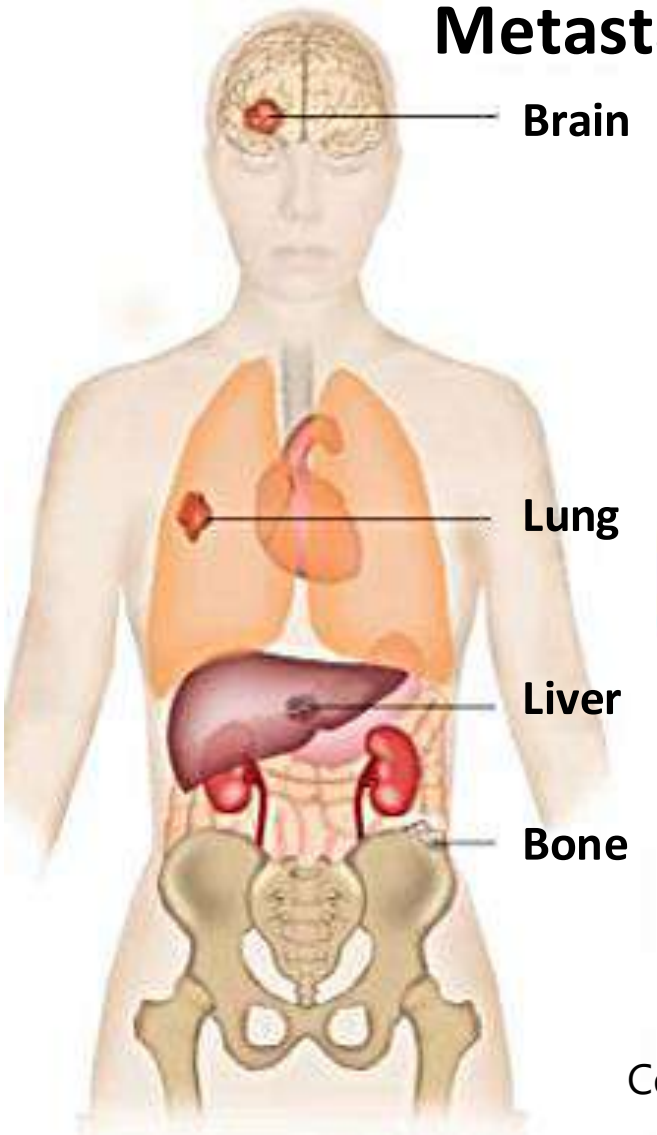
Treatment

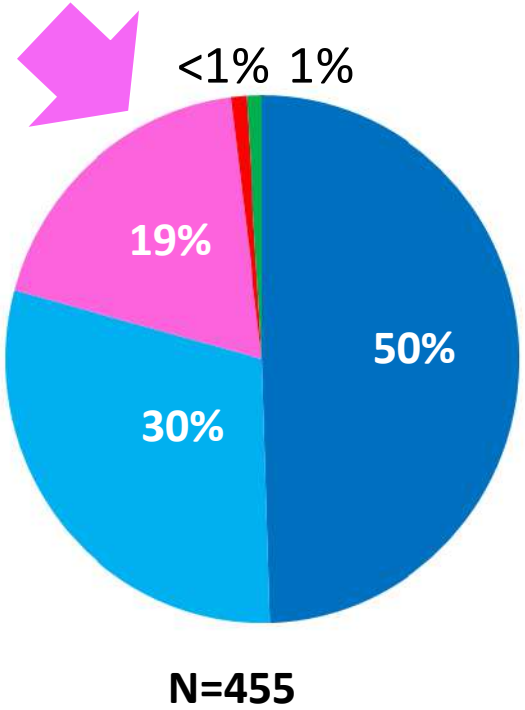
Tumor Evolution



Cejalvo et al. *Cancer Treatment Rev*. 2018.

Metastases





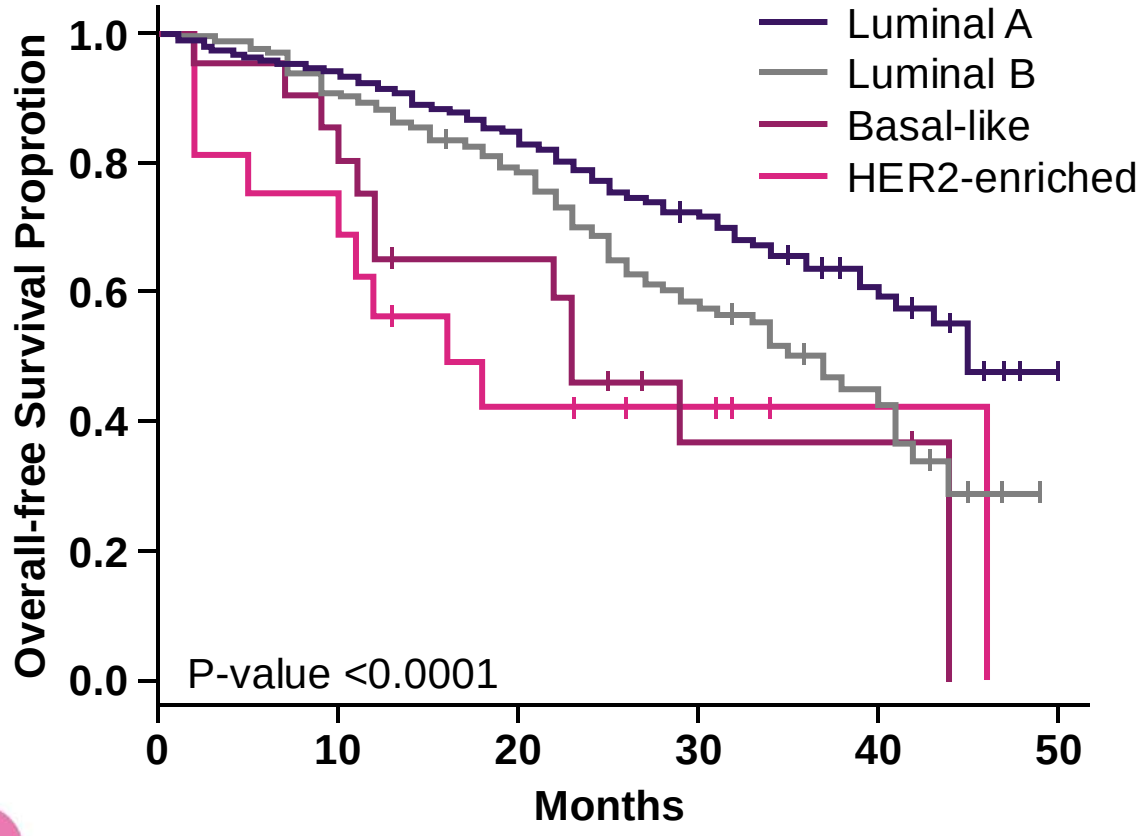
N=455

Cejalvo et al. *Cancer Res*. 2017
Finn R et al. SABCS 2017

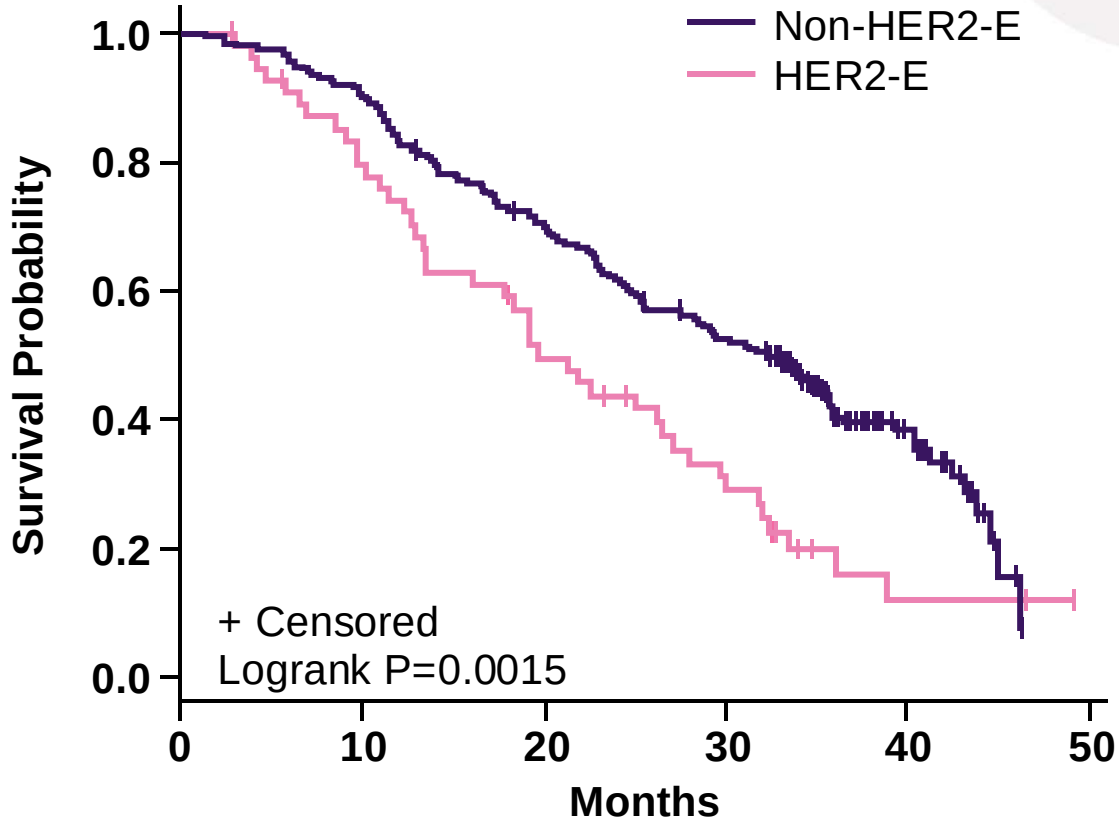
HER2-enriched Subtype and Overall Survival in HR+/HER2-neg Metastatic Breast Cancer (N=905)

~80% of the samples were from the primary tumour

EGF30008 clinical trial (N=644)[1]

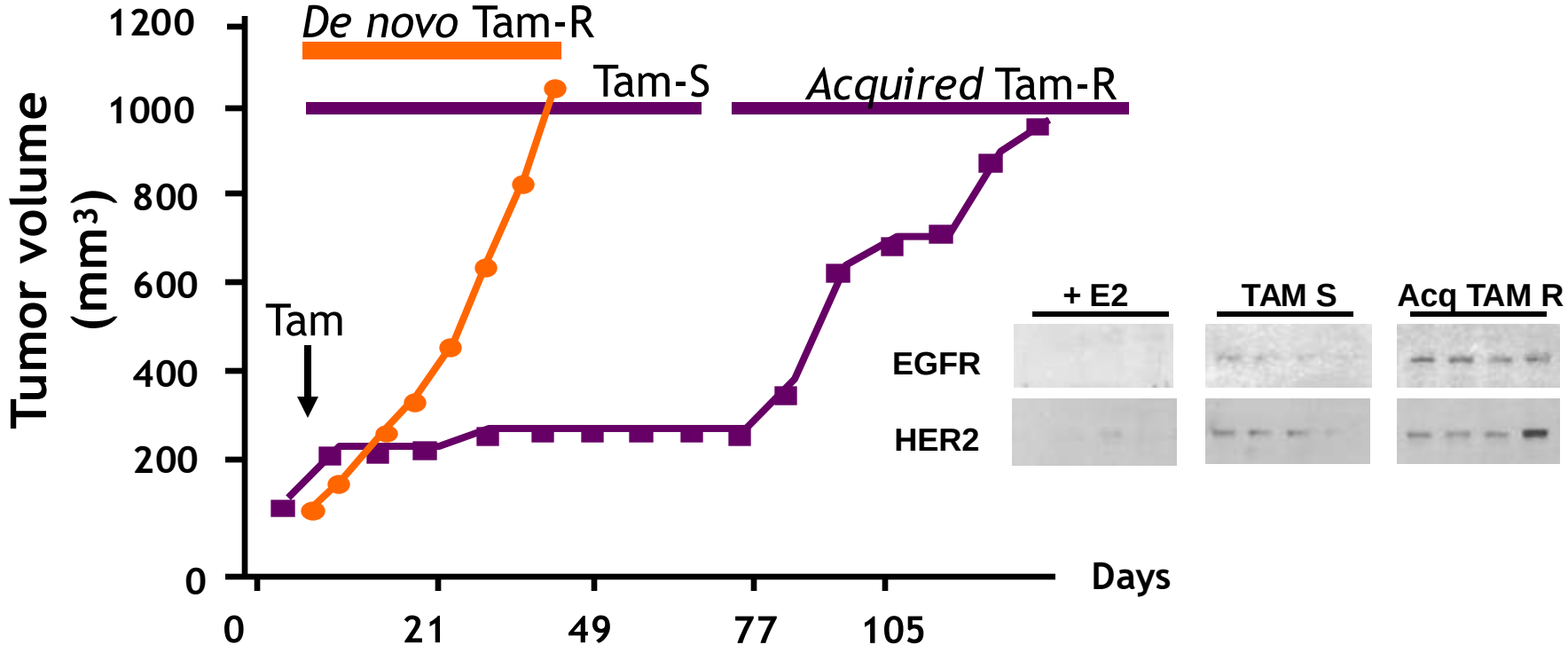


BOLERO-2 clinical trial (N=261)[2]



1. Prat A et al. JAMA Oncology. 2016;2(10):1287-1294;
2. 2. Prat A et al. Oncologist. 2019;24(7):893-900.

Can targeting growth factor receptors in ER+ HER2- MBC delay PFS when added to endocrine therapy?



Osborne et al, JNCI 1994

1st-line clinical trials in ER+ HER2- MBC:

- In 2 small phase II studies, gefitinib + tamoxifen/anastrozole improved PFS in subset endocrine naïve patients (median PFS 14.6 vs 8.2 months)[1, 2]

1. *Osborne et al. Clin Can Res. 2011;17:1147-59*
2. *Cristofanilli et al. Clin Can Res. 2010;16:1904-14*

Can targeting growth factor receptors in ER+ HER2- MBC delay PFS when added to endocrine therapy?

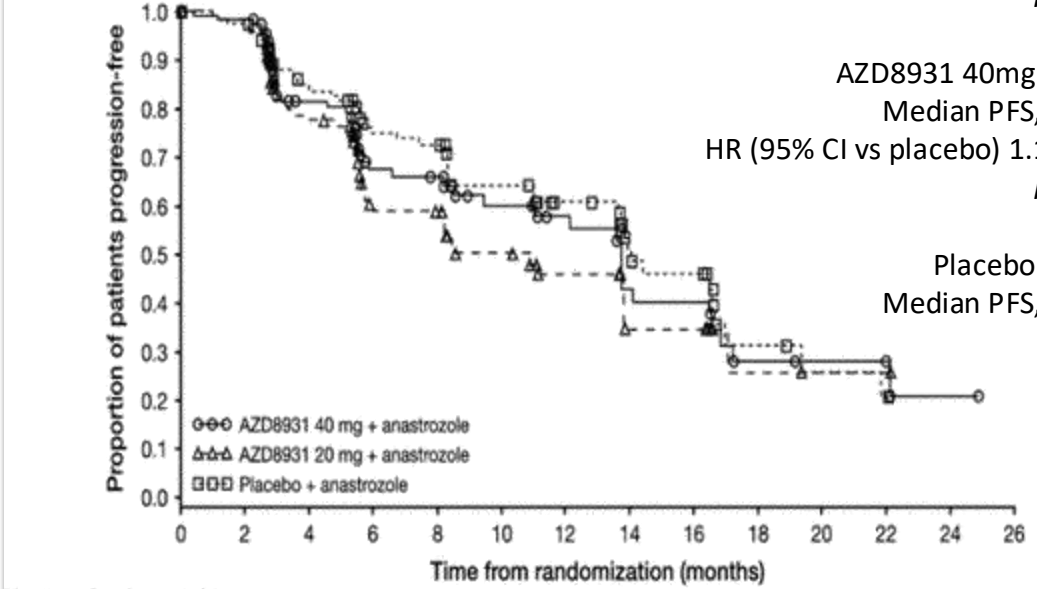
MINT: PFS

Endocrine-therapy naïve

AZD8931 20mg + anastrozole
Median PFS, **10.9 months**
HR (95% CI vs placebo) 1.37 (0.91-2.06)
P value: 0.135

AZD8931 40mg + anastrozole
Median PFS, **13.8 months**
HR (95% CI vs placebo) 1.16 (0.77-1.75)
P value: 0.485

Placebo + anastrozole
Median PFS, **14.0 months**



Number of patients at risk:

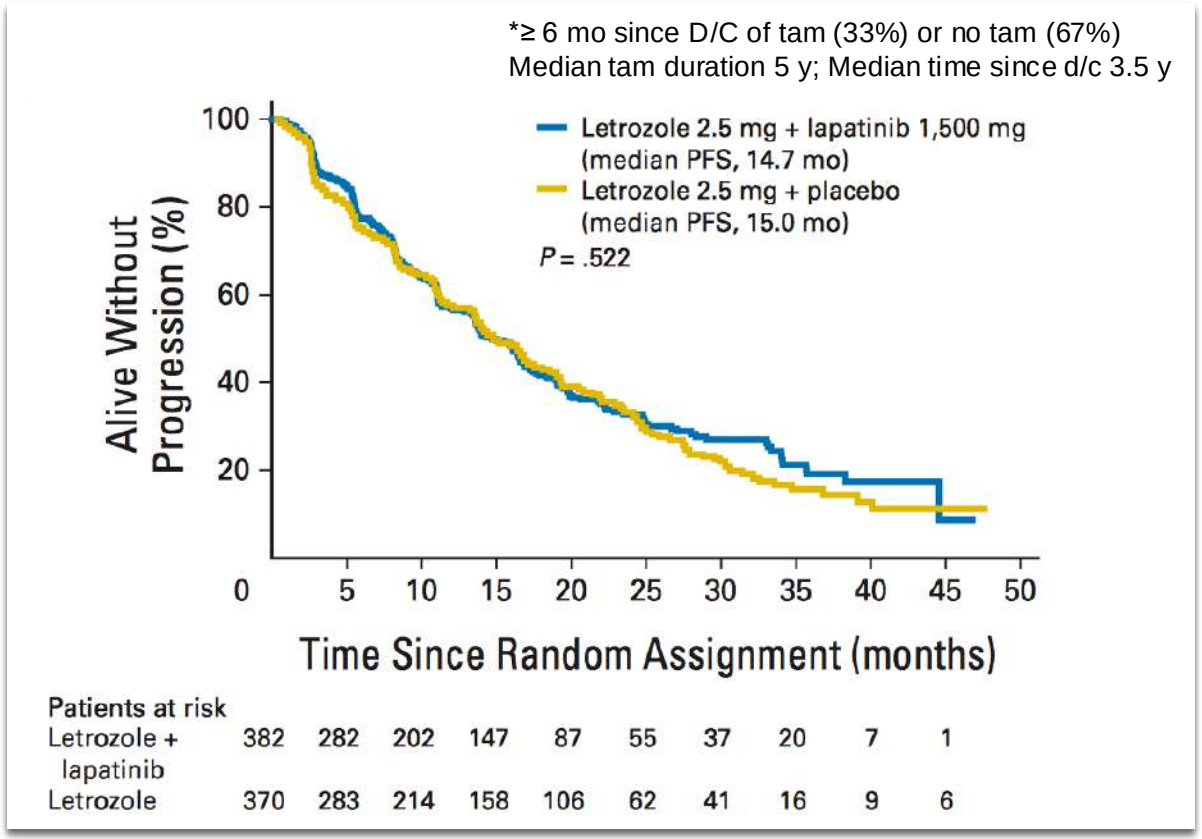
AZD8931 40 mg	120	113	72	42	40	28	24	17	16	7	5	4	2	0
AZD8931 20 mg	118	110	69	39	37	26	19	10	10	3	1	1	0	0
Placebo	121	114	76	53	51	37	29	20	17	7	5	4	0	0

Johnston S et al. Br Ca Res Treat. 2016;160:91-9

EGF30008: PFS

Endocrine sensitive*

*≥ 6 mo since D/C of tam (33%) or no tam (67%)
Median tam duration 5 y; Median time since d/c 3.5 y



Patients at risk

Letrozole + lapatinib	382	282	202	147	87	55	37	20	7	1
Letrozole	370	283	214	158	106	62	41	16	9	6

Johnston S et al. J Clin Oncol. 2009;27:5538-46

Cyclin Dependent Kinase (CDK) 4/6 in ER+ Breast Cancer

- The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER
- Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle[1]
- Resistance to endocrine therapy is associated with continued dependence on Cyclin D1 & CDK 4/6

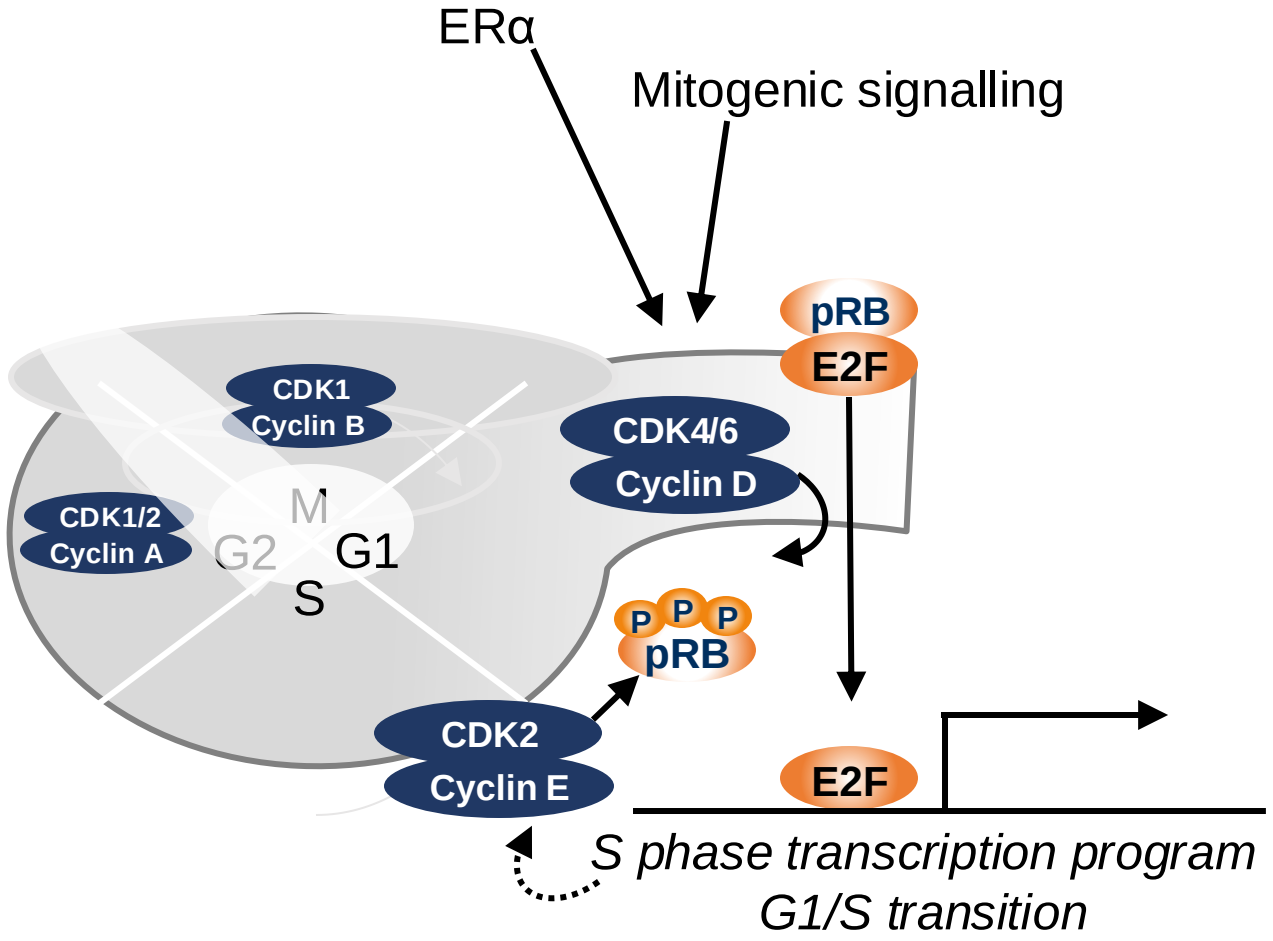
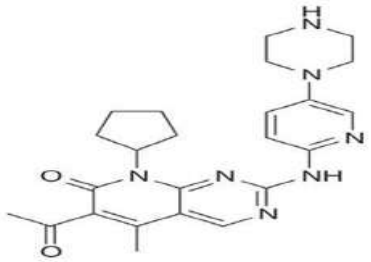
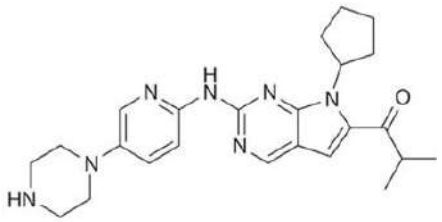


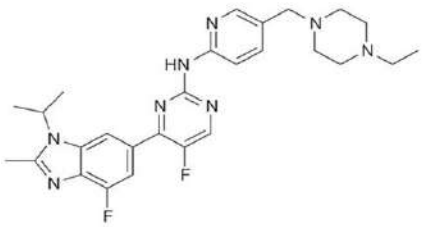
Figure adapted from Asghar, et al. Nat Rev Drug Dis. 2015;14:130-146

Selective CDK 4/6 inhibitors

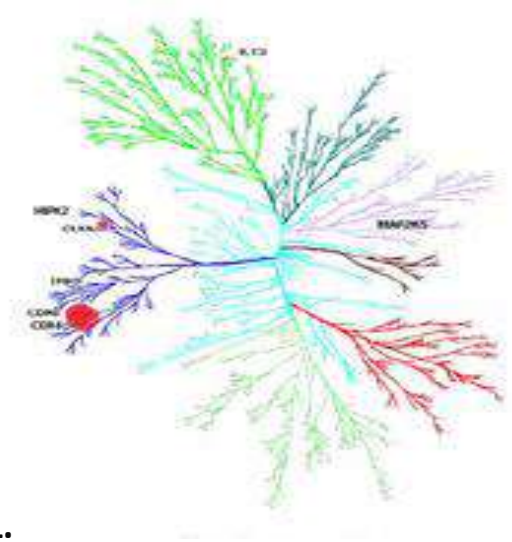
IC_{50}	Palbociclib	Ribociclib	Abemaciclib
CDK4	9–11 nM	10 nM	2 nM
CDK6	15 nM	39 nM	5 nM
CDK2	>10 µM	>50 µM	>500 nM
CDK9	ND	ND	57 nM

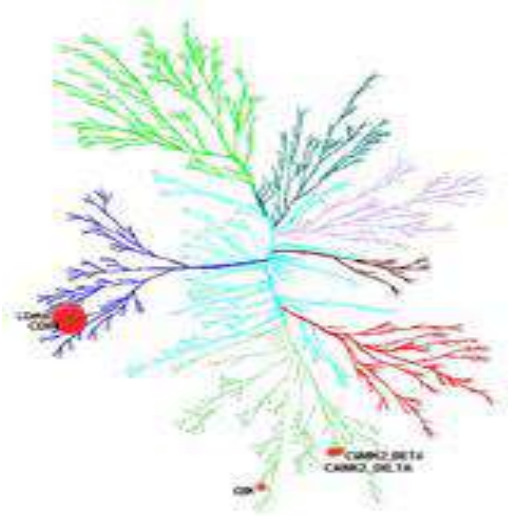






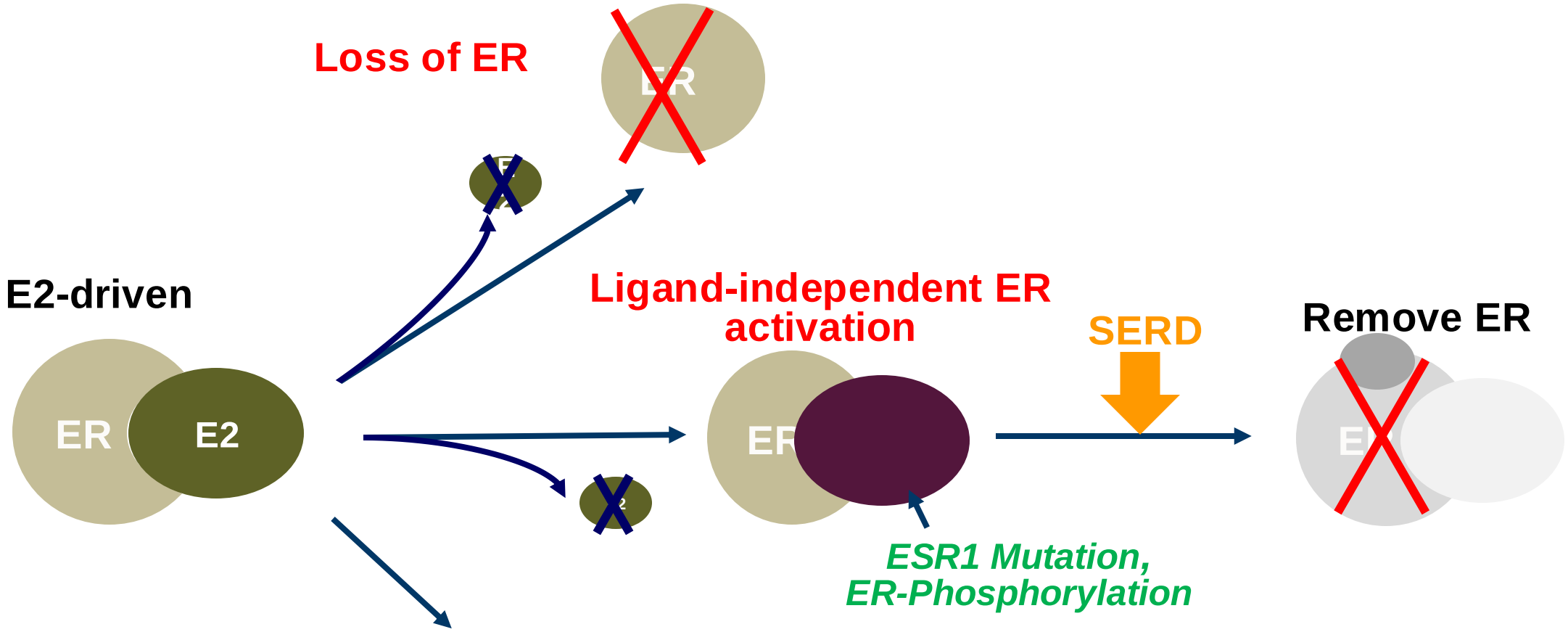
Kinase selectivity tree: Bigger circles = more inhibition





Chen P, et al. *Mol Cancer Ther* 2016;15:2273–81.
Asghar U, et al. *Nat Rev Drug Discov* 2015;14:130–46;

Mechanisms of Endocrine Resistance & Therapeutic Strategies



Slide adapted courtesy Peter Schmid

TACKLING ENDOCRINE RESISTANCE IN METASTATIC BREAST CANCER (MBC)

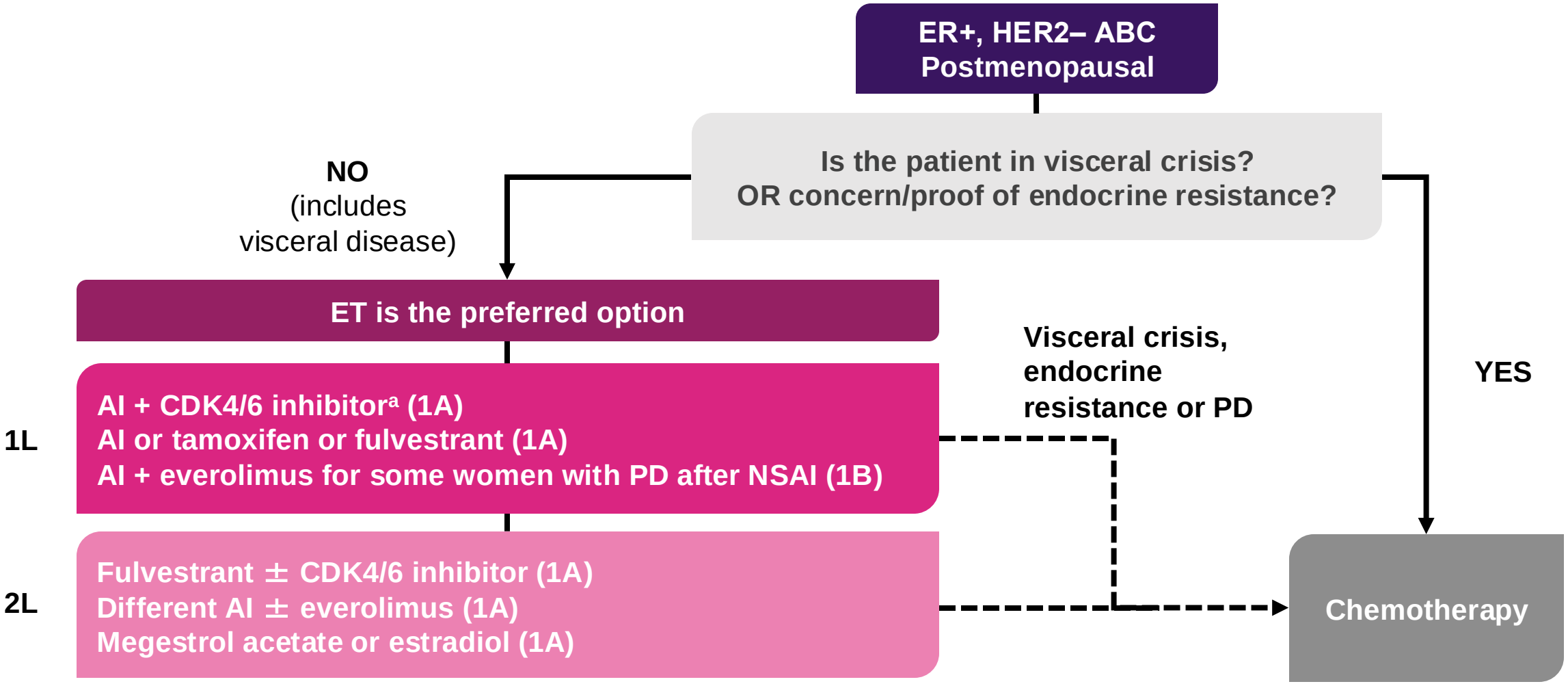
Current Questions in Clinical Practice

1. **What is Endocrine Resistance ?**
   - ESMO definitions
   - What are the Key Mechanisms for Endocrine Resistance ?

2. **How to select Endocrine Treatment (ET) options for Endocrine Resistance in ER+ MBC ?**
   - How to overcome Primary (De-Novo) Endocrine Resistance in 1st-line setting ?
   - Mutation testing in 2nd line setting – when and how to test ?

3. **Current Research: Testing Emerging Treatments for Endocrine Resistance in Breast Cancer ?**
   - Lessons from Pre-surgical Clinical Models to identify Biomarkers of Endocrine Resistance

ESMO ABC4 guidelines: Postmenopausal patients with ER+, HER2– ABC



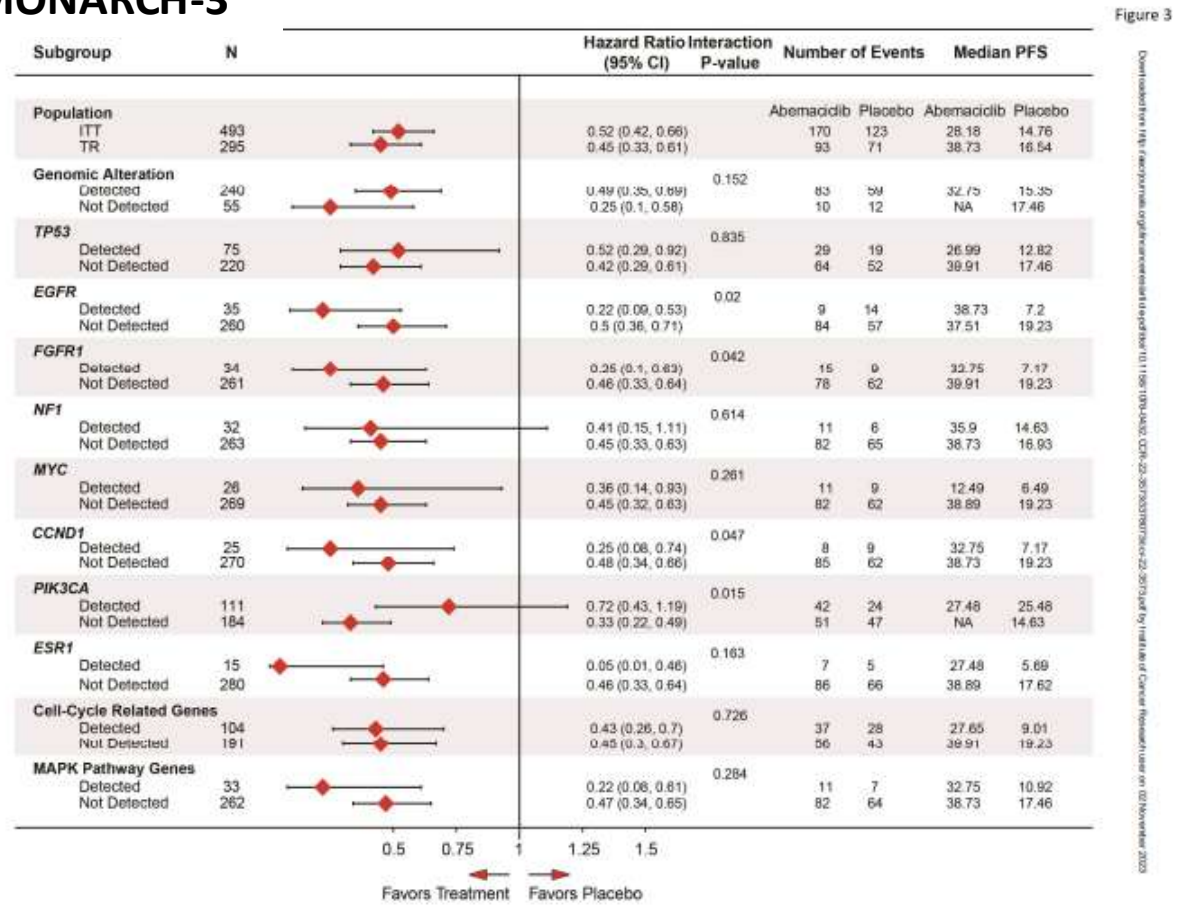
[a] Except for relapse <12 months from finishing adjuvant AI.

Adapted from Cardoso F et al. Ann Oncol 2018;29:1634–57.

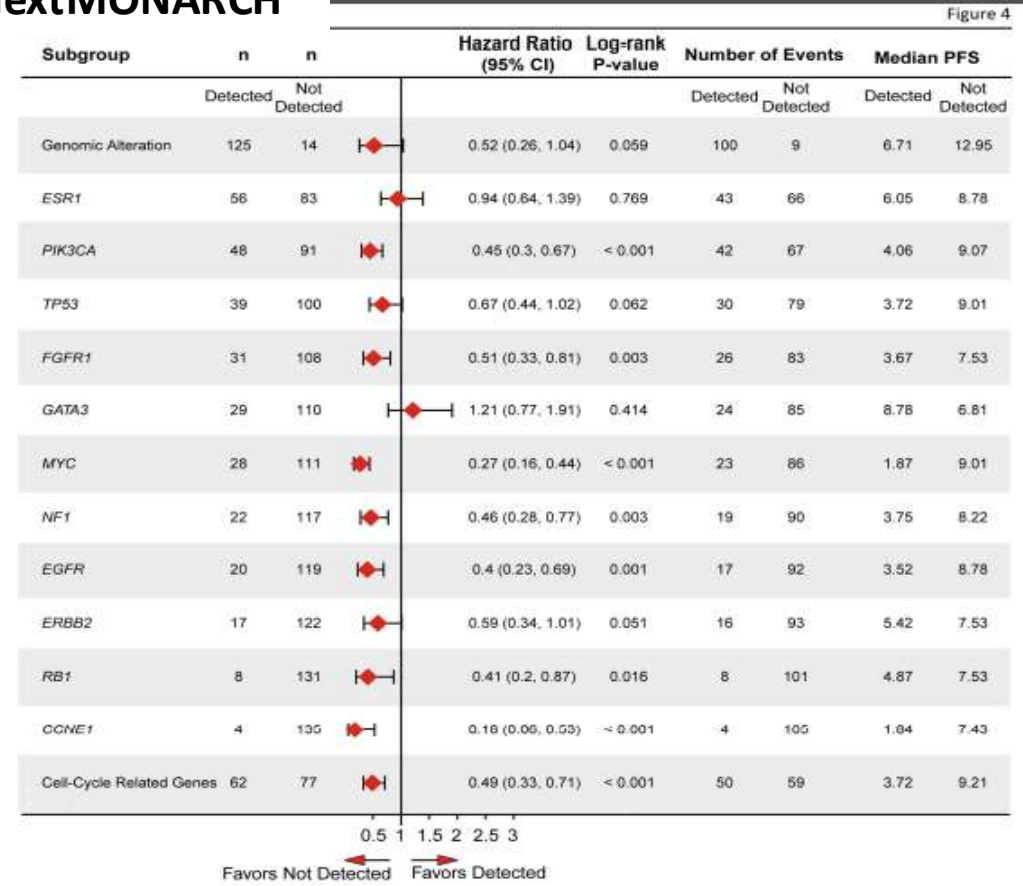
PARIS 2022 ESMO congress

Baseline Mutations – Prognosis and CDK 4/6i Predictive Outcome

MONARCH-3



NextMONARCH



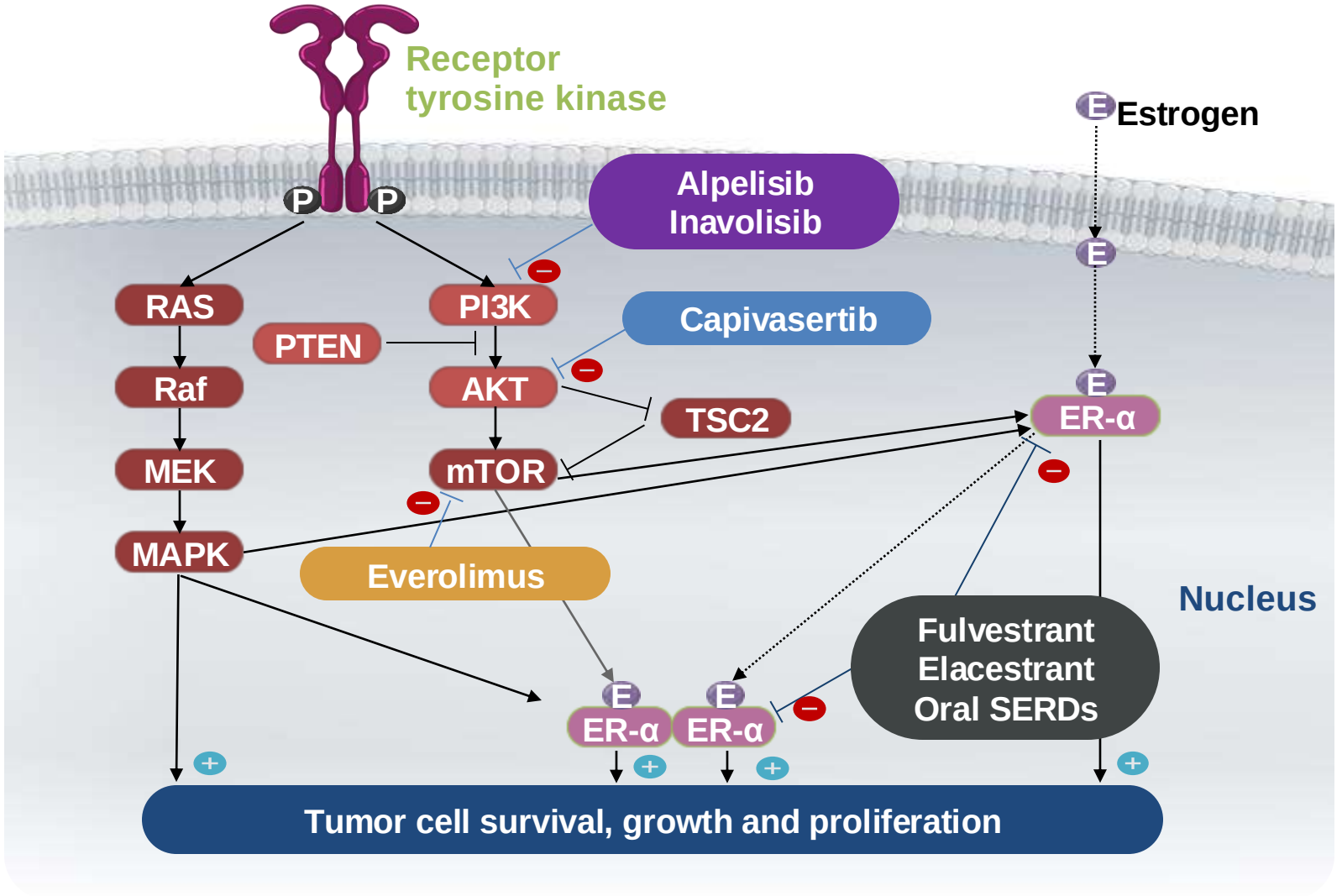
Abemaciclib Benefit seen regardless of Mutations

Prognosis poorer if Mutations present

Goetz MP et al. Clin Cancer Res. 2023 Oct 27. doi: 10.1158/1078-0432.CCR-22-3573.

Targeting the Endocrine Resistance Signaling Pathway beyond CDK 4/6 inhibitors in ER+ Breast Cancer

- **Endocrine Resistance** is associated with either *ESR1* mutations, and/or activation of cross-talk signaling pathways
- **PI3K** activating mutations are the most common (30-40%) finding in endocrine resistant breast cancer
- **AKT** activation can be caused AKT mutations, PTEN loss or upstream PI3K oncogenic mutations



ASCO Guidelines for HR+ HER2- Metastatic Breast Cancer

Journal of Clinical Oncology®

ASCO special articles

Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update

Harold J. Burstein, MD, PhD[1]; Mark R. Somerfield, PhD[2]; Debra L. Barton, PhD, RN[3]; Ali Dorris, MBA, MFA[4]; Lesley J. Fallowfield, DPhil[5]; Dharamvir Jain, MD[6]; Stephen R. D. Johnston, MD, PhD[7]; Larissa A. Korde, MD[8]; Jennifer K. Litton, MD[9]; Erin R. Macrae, MD[10]; Lindsay L. Peterson, MD, MSCR[11]; Praveen Vikas, MBBS[12]; Rachel L. Yung, MD[13]; and Hope S. Rugo, MD[14]

abstract

PURPOSE To update recommendations of the ASCO systemic therapy for hormone receptor (HR)-positive metastatic breast cancer (MBC) guideline.

METHODS An Expert Panel conducted a systematic review to identify new, potentially practice-changing data.

RESULTS Fifty-one articles met eligibility criteria and form the evidentiary basis for the recommendations.

RECOMMENDATIONS Alpelisib in combination with endocrine therapy (ET) should be offered to postmenopausal patients, and to male patients, with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA*-mutated, ABC, or MBC following prior endocrine therapy with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor. Clinicians should use next-generation sequencing in tumor tissue or cell-free DNA in plasma to detect *PIK3CA* mutations. If no mutation is found in cell-free DNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations. There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for HR-positive, HER2-negative MBC. For *BRCA1* or *BRCA2* mutation carriers with metastatic HER2-negative breast cancer, olaparib or talazoparib should be offered in the 1st-line through 3rd-line setting. A nonsteroidal aromatase inhibitor (AI) and a CDK4/6 inhibitor should be offered to postmenopausal women with treatment-naïve HR-positive MBC. Fulvestrant and a CDK4/6 inhibitor should be offered to patients with progressive disease during treatment with AIs (or who develop a recurrence within 1 year of adjuvant AI therapy) with or without one line of prior chemotherapy for metastatic disease, or as first-line therapy. Treatment should be limited to those without prior exposure to CDK4/6 inhibitors in the metastatic setting.

Additional information can be found at www.asco.org/breast-cancer-guidelines.

Insufficient data for routine ESR1 mutation testing?

Burstein HJ et al, J. Clin. Oncol. 2021;39(35):3959-3977.

Capivasertib in Advanced ER+ Breast Cancer: FAKTION Trial

- >50% of ER+ MBC tumours have activated PI3K/AKT/PTEN pathway
- Capivasertib is a potent and selective inhibitor of all 3 isoforms of AKT
- In Phase II FAKTION trail, addition of capivasertib to fulvestrant doubled median PFS (10.3 vs 4.8 mo, HR 0.58)

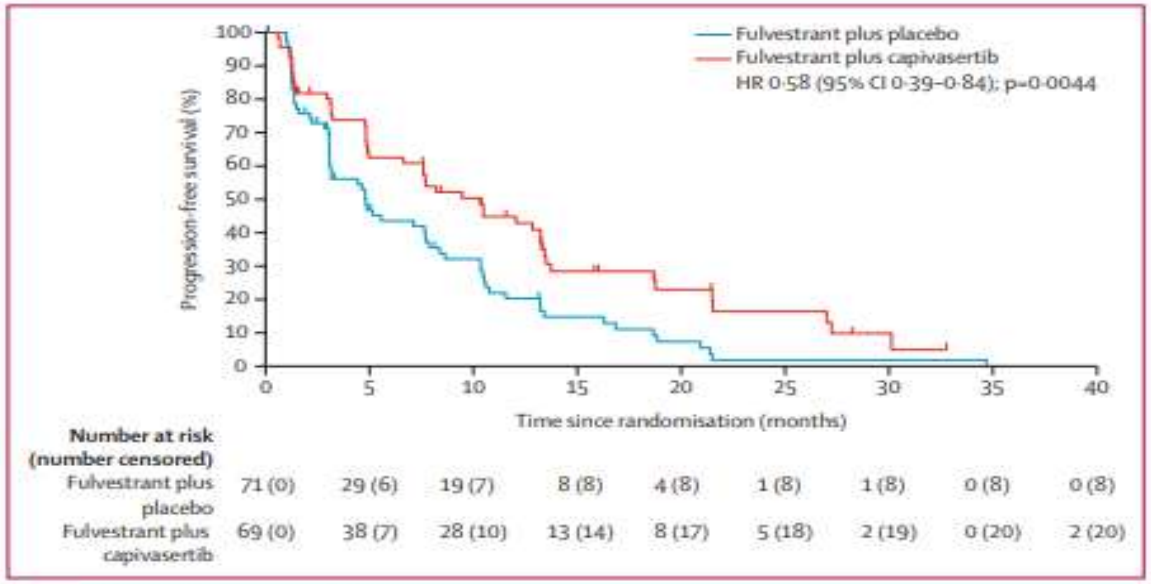
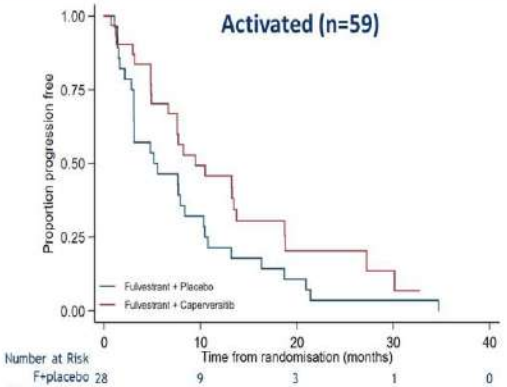
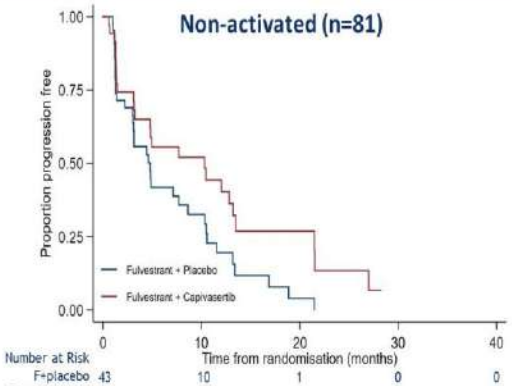


Figure 2: **Progression-free survival**
HR=hazard ratio.

Progression Free Survival by PI3K/AKT/PTEN pathway activation status



	Fulvestrant + Placebo (n=28)	Fulvestrant + Capivasertib (n=31)
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	



	Fulvestrant + Placebo (n=43)	Fulvestrant + Capivasertib (n=38)
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	

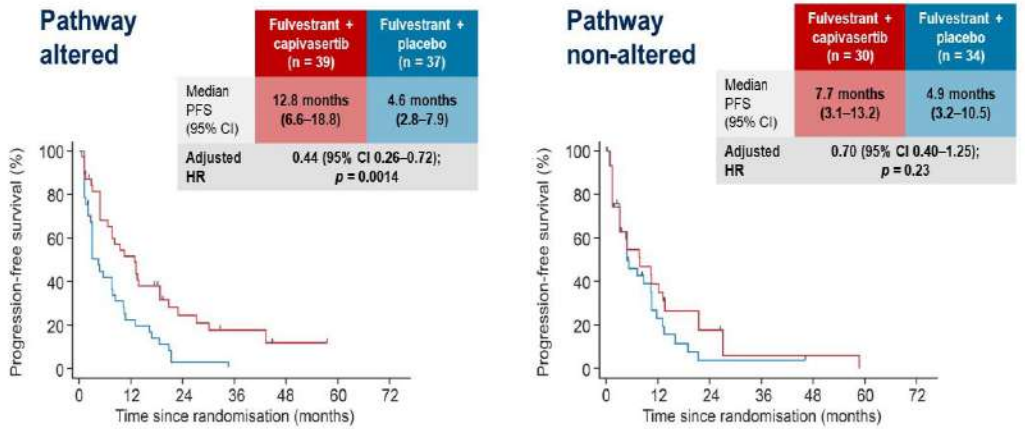
- Benefit appeared independent of activated pathway, albeit only tested for limited *PIK3CA* mutations by ddPCR and PTEN protein loss by IHC
- *AKT1* not examined

Jones RL et al, Lancet Oncol 2020;21:345-57.

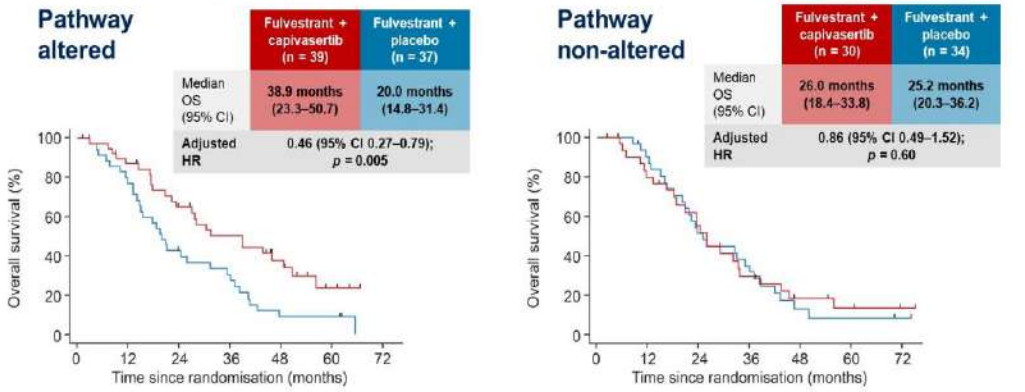
Capivasertib in Advanced ER+ Breast Cancer: FAKTION Trial

- Updated efficacy data after median 60 months follow-up
- Expanded NGS testing used to identify *AKT1* E17K mutation, additional activating *PIK3CA* mutations, and *PTEN* alterations predicted to result in loss of function
- PI3K/AKT/PTEN alterations found in 54% of participants in ITT population (vs 42% using original ddPCR / IHC methods)
- PFS and OS data indicated that capivasertib mainly benefited the pathway alerted subgroup
  - median PFS 12.8 mo vs 4.6 mo (HR 0.44; p = 0.0014)
  - median OS 39.8 mo vs 20.0 mo (HR 0.46; p = 0.005)
- Results of Phase III CAPitello-291 trial (NCT04305496) awaited

FAKTION: PFS in the expanded pathway altered and pathway non-altered subgroups



FAKTION: OS in the expanded pathway altered and pathway non-altered subgroups



PARIS 2022 ESMO congress

Stephen R D Johnston

Howell S et al, Lancet Oncol 2022; online June 4th.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

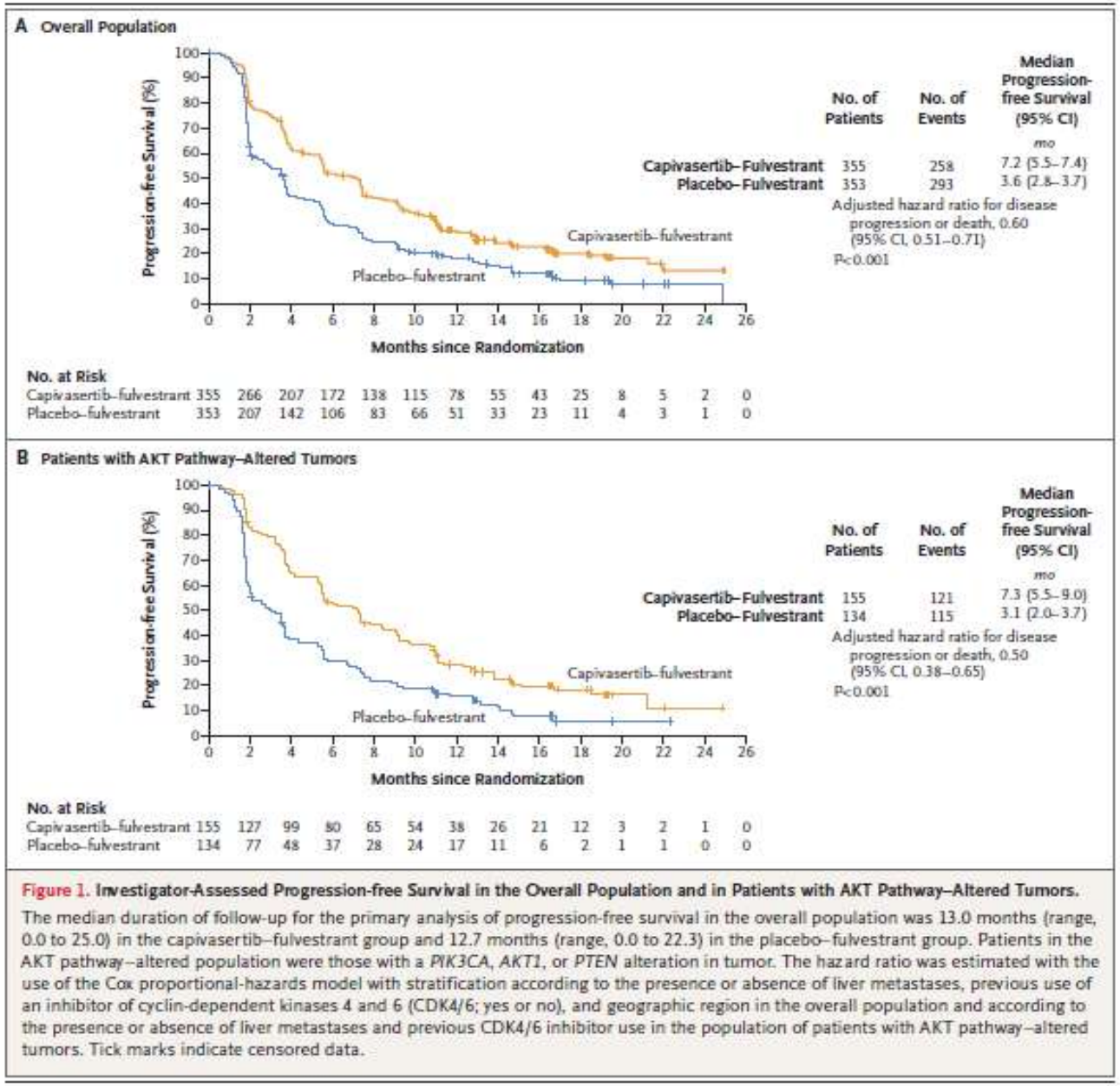


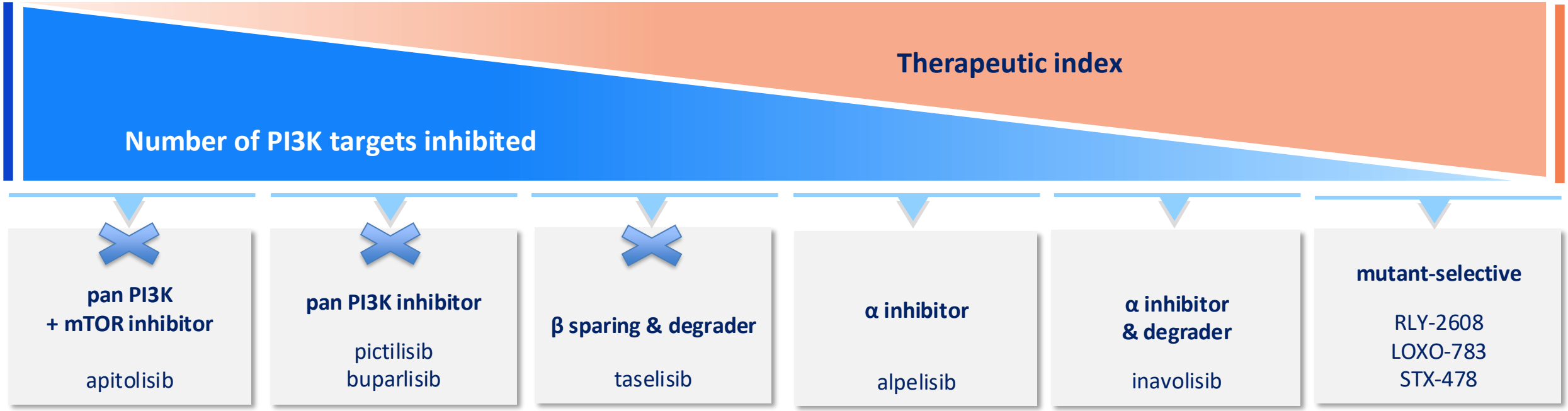
Figure 1. Investigator-Assessed Progression-free Survival in the Overall Population and in Patients with AKT Pathway–Altered Tumors.

The median duration of follow-up for the primary analysis of progression-free survival in the overall population was 13.0 months (range, 0.0 to 25.0) in the capivasertib–fulvestrant group and 12.7 months (range, 0.0 to 22.3) in the placebo–fulvestrant group. Patients in the AKT pathway–altered population were those with a *PIK3CA*, *AKT1*, or *PTEN* alteration in tumor. The hazard ratio was estimated with the use of the Cox proportional-hazards model with stratification according to the presence or absence of liver metastases, previous use of an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6; yes or no), and geographic region in the overall population and according to the presence or absence of liver metastases and previous CDK4/6 inhibitor use in the population of patients with AKT pathway–altered tumors. Tick marks indicate censored data.

Turner N et al, NEJM 2023

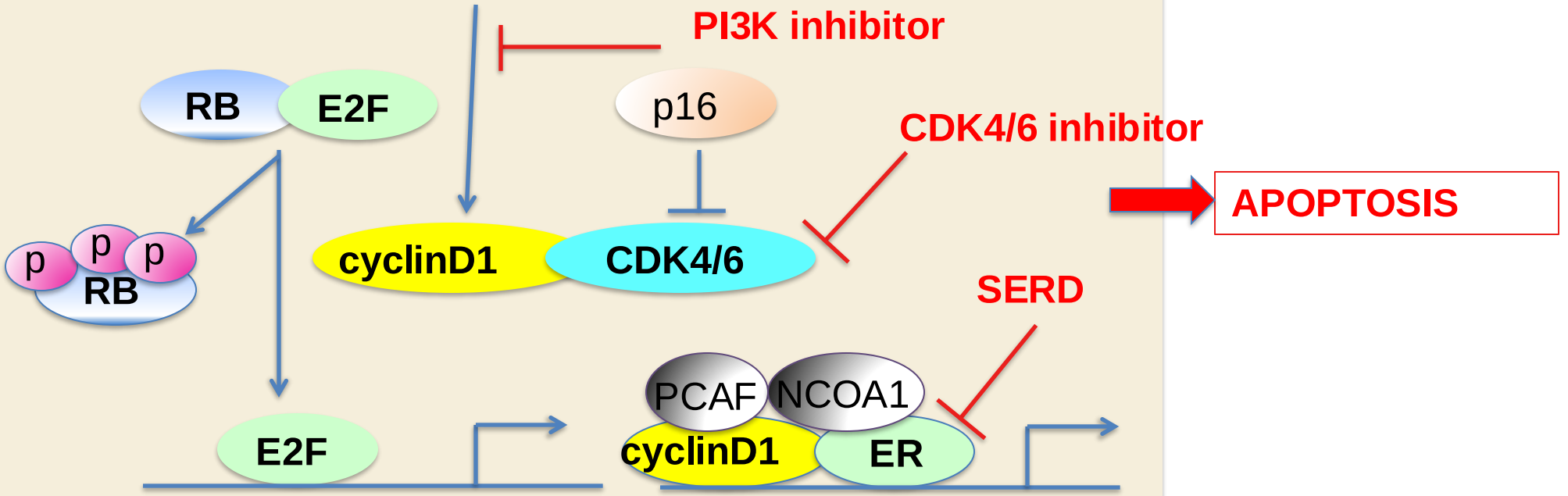
Progress in Inhibiting PI3K!

- **PI3Kα** is the most important isoform as an oncogenic targetv
- **Therapeutic index** needs to be improved for better safety, combinability, and efficacy



Can we improve therapeutic targeting by triplet therapy?

Ligand-independent ER & PI3K pathway activation activate a unique ER/E2F/CDK4 dependent program

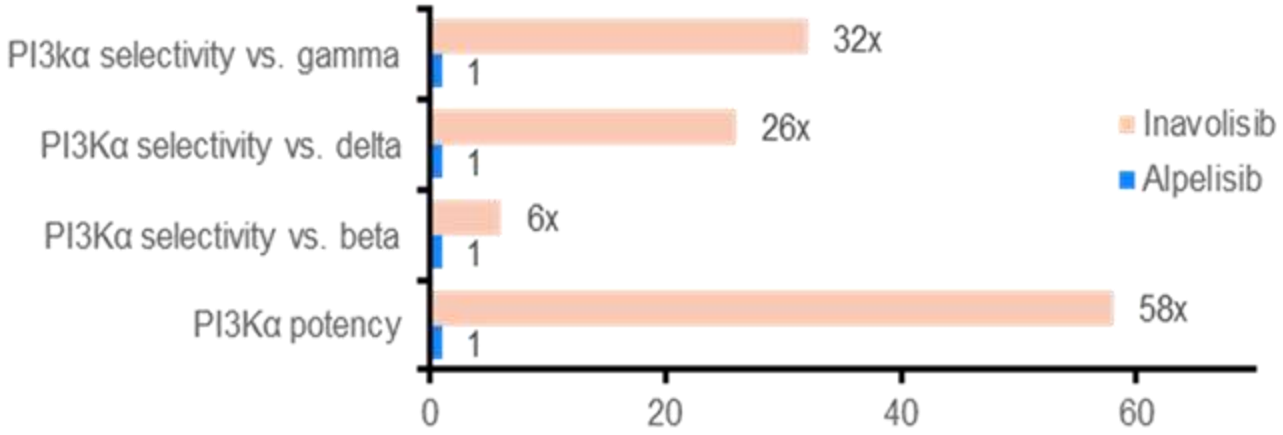


Miller TW et al. Cancer Discov 2011; 1(4): 338-351;
Vora SR et al. Cancer Cell 2014; 26(1): 136-149.

Inavolisib: Highly Potent & Selective PI3Kα Inhibitor that Facilitates Specific Degradation of Mutated PI3Kα

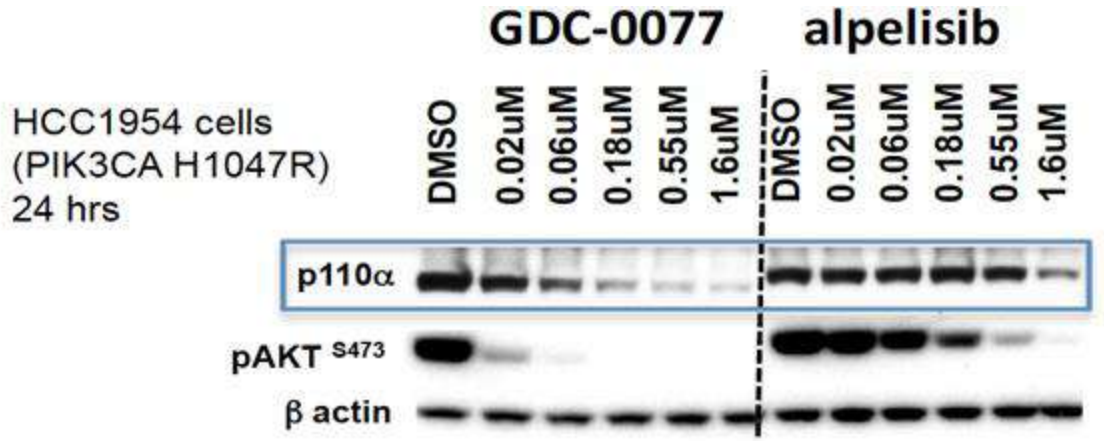
High potency and specificity for PI3Kα

Inavolisib has higher potency and selectivity for PI3Kα inhibition compared to alpelisib*



Mutant-specific degradation of PI3Kα

Inavolisib facilitates mutant PI3Kα degradation that leads to sustained pathway inhibition



Inavolisib potently inhibits mutant PI3K pathway signaling and cell viability through unique HER2-dependent mutant p110a degradation resulting in prolonged pathway suppression.

* Adapted from Song et al, Cancer Discovery 2022; Edgar et al, AACR 2017

Slide Courtesy of Hope Rugo

ASCO rapid recommendations

Testing for *ESR1* Mutations to Guide Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update

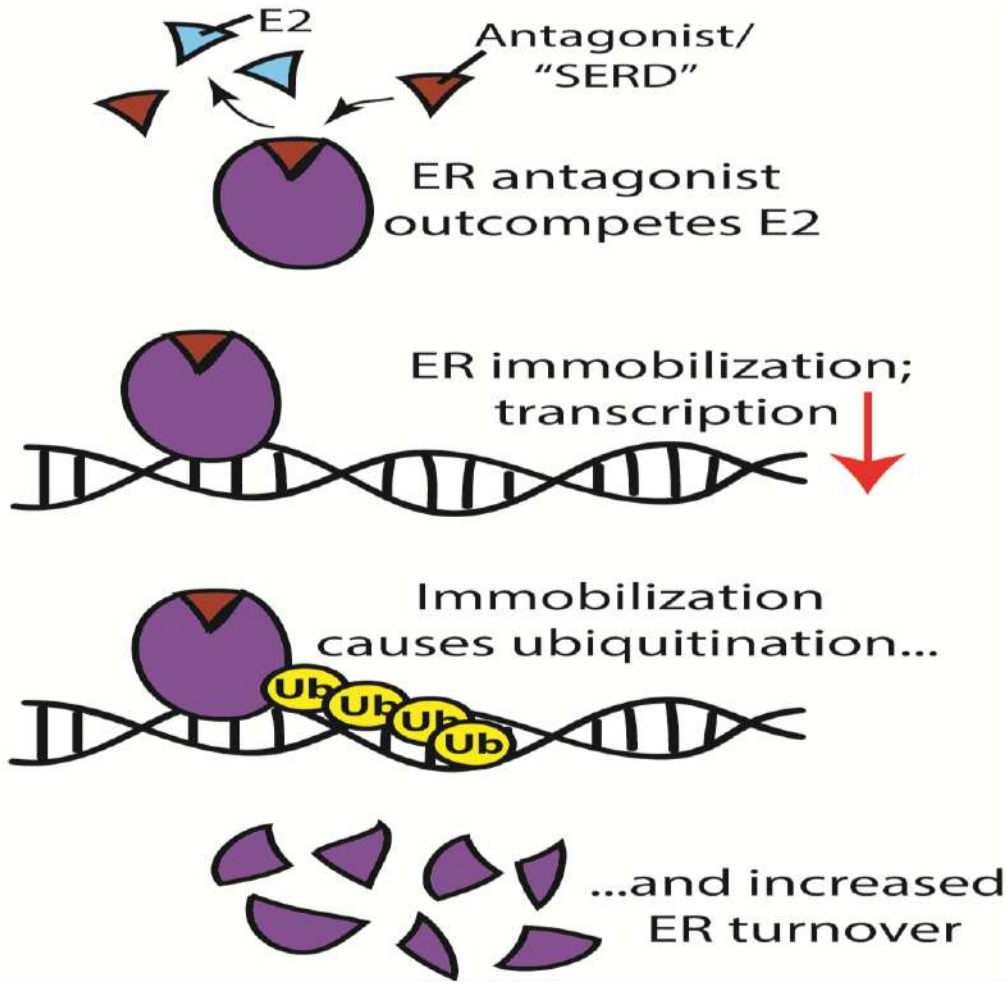
Harold J. Burstein, MD, PhD[1]; Angela DeMichele, MD[2]; Mark R. Somerfield, PhD[3]; and N. Lynn Henry, MD, PhD[4]; for the Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options. See the Appendix for disclaimers and other important information (Appendix 1 and Appendix 2, online only).

Burstein HJ et al, J. Clin. Oncol. 2023.

Selective Estrogen Receptor Downregulators / Degraders (SERDs): ER destabilization follows ER inhibition

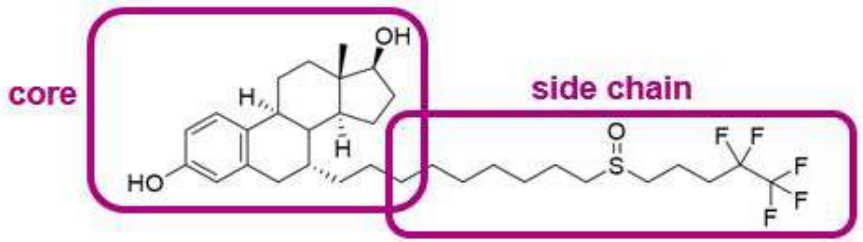
Mechanism of Action



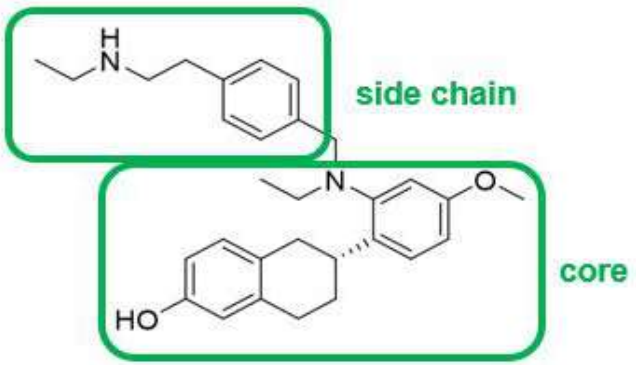
Adapted from Ciara Metcalfe SABCS 2018

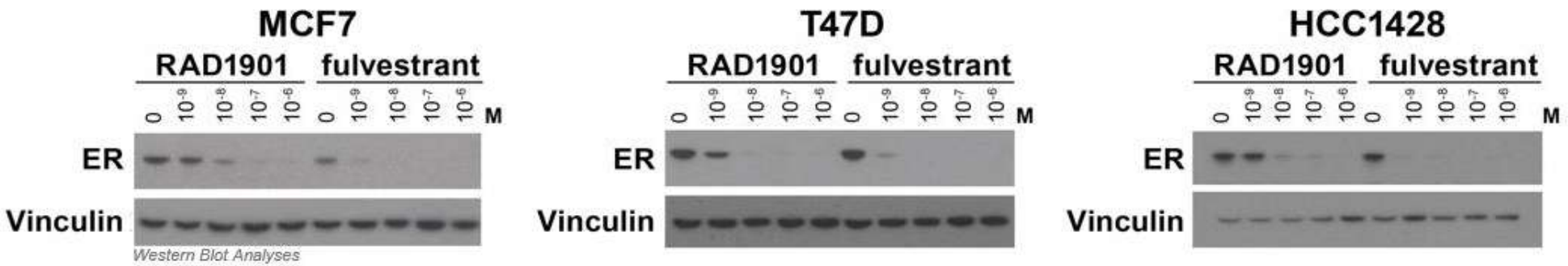
Elacestrant (RAD1901) is an oral SERD with a distinct chemical structure

Fulvestrant (Faslodex, AstraZeneca)
Approved, Marketed



Elacestrant (RAD1901)



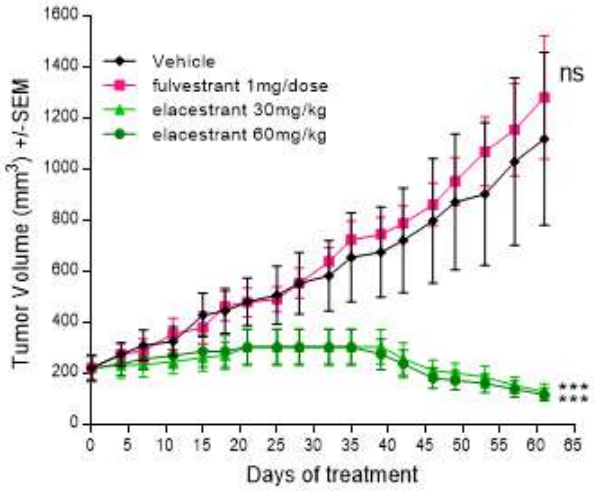


Bihani et al. Clin Cancer Res 2017

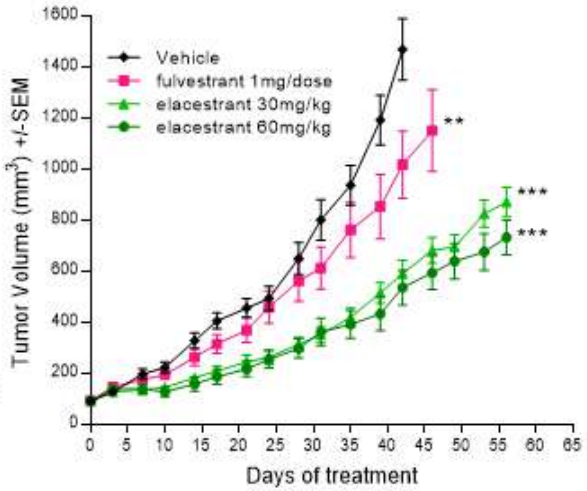
Elacestrant demonstrated greater anti-tumor activity than fulvestrant in PDX models regardless of ESR1 mutational status

ESR1^{wt}

PDX Model: ST986
Patient treatment history: naïve



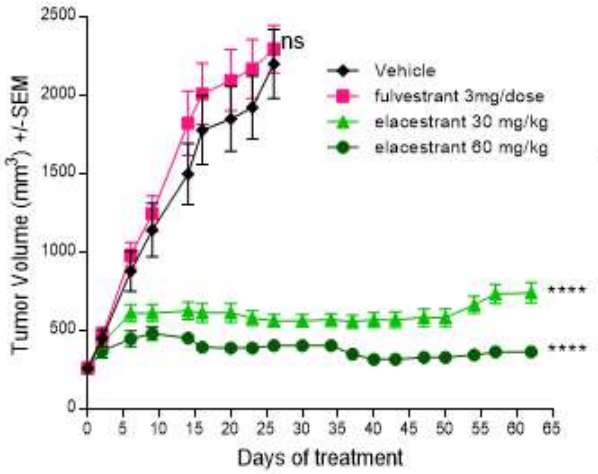
PDX Model: HBCx-3
Patient treatment history: naïve



ESR1^{mut}

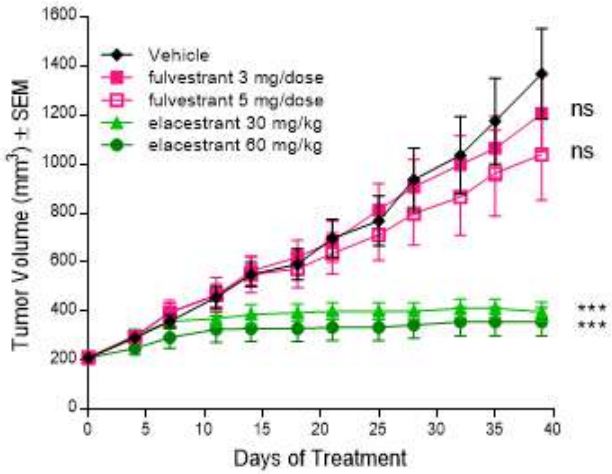
PDX Model: ST941-HI
Patient treatment history: AI

ESR1:Y537S



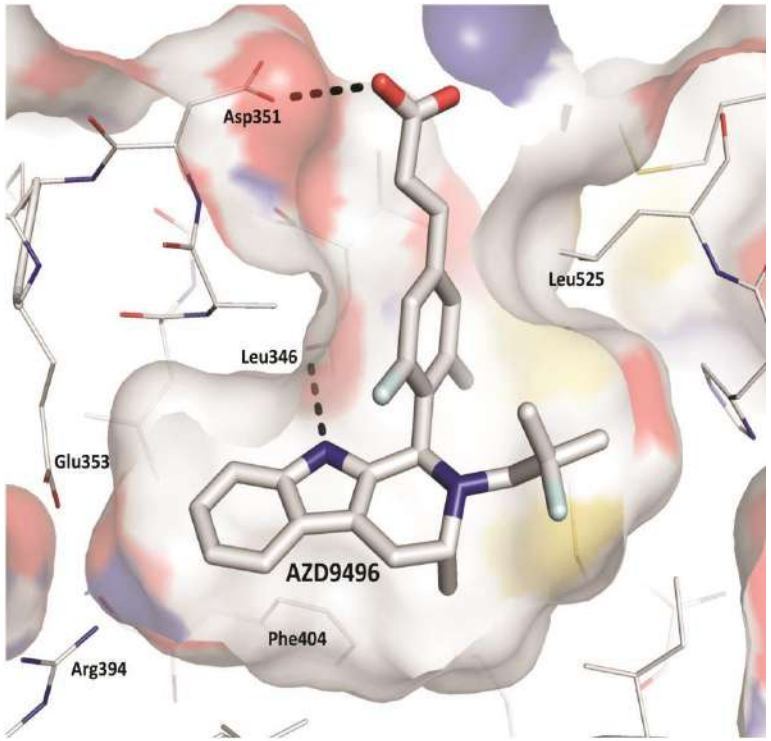
PDX Model: ST2535-HI
Patient treatment history: tam, AI, fulv

ESR1:D538G



Patel et al. SABCS 2018

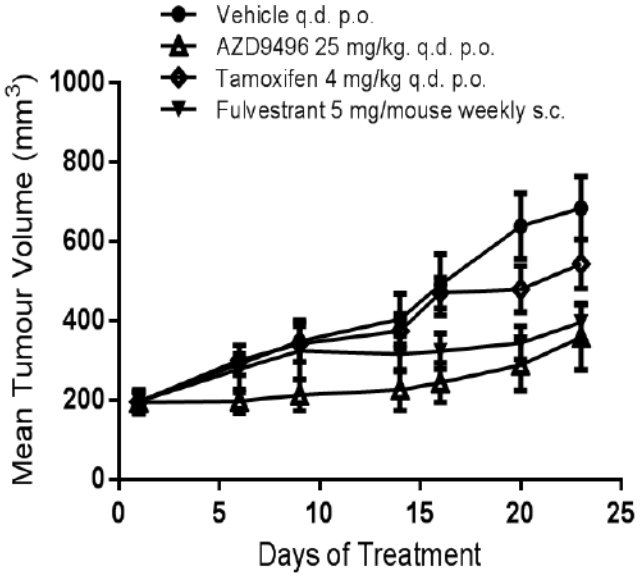
AZD9496: An oral estrogen receptor inhibitor that blocks growth of ER+ and *ESR1* mutant breast tumors in pre-clinical models

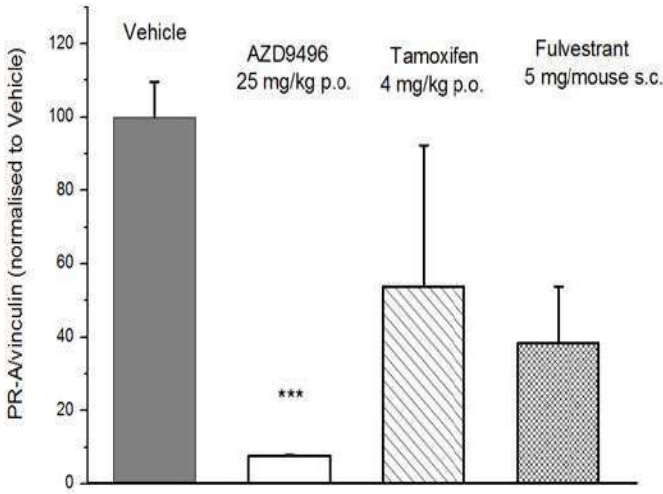


In-vitro binding to ERα mutant LBDs

	ERα LBD binding IC50 nM	
	AZD9496 nM	Fulvestrant nM
wt	0.2	1.6
D538G	0.5	3.3
Y537S	0.6	3.8

Tumor Regressions in *ESR1* Mutant MCF-7 Xenograft Models

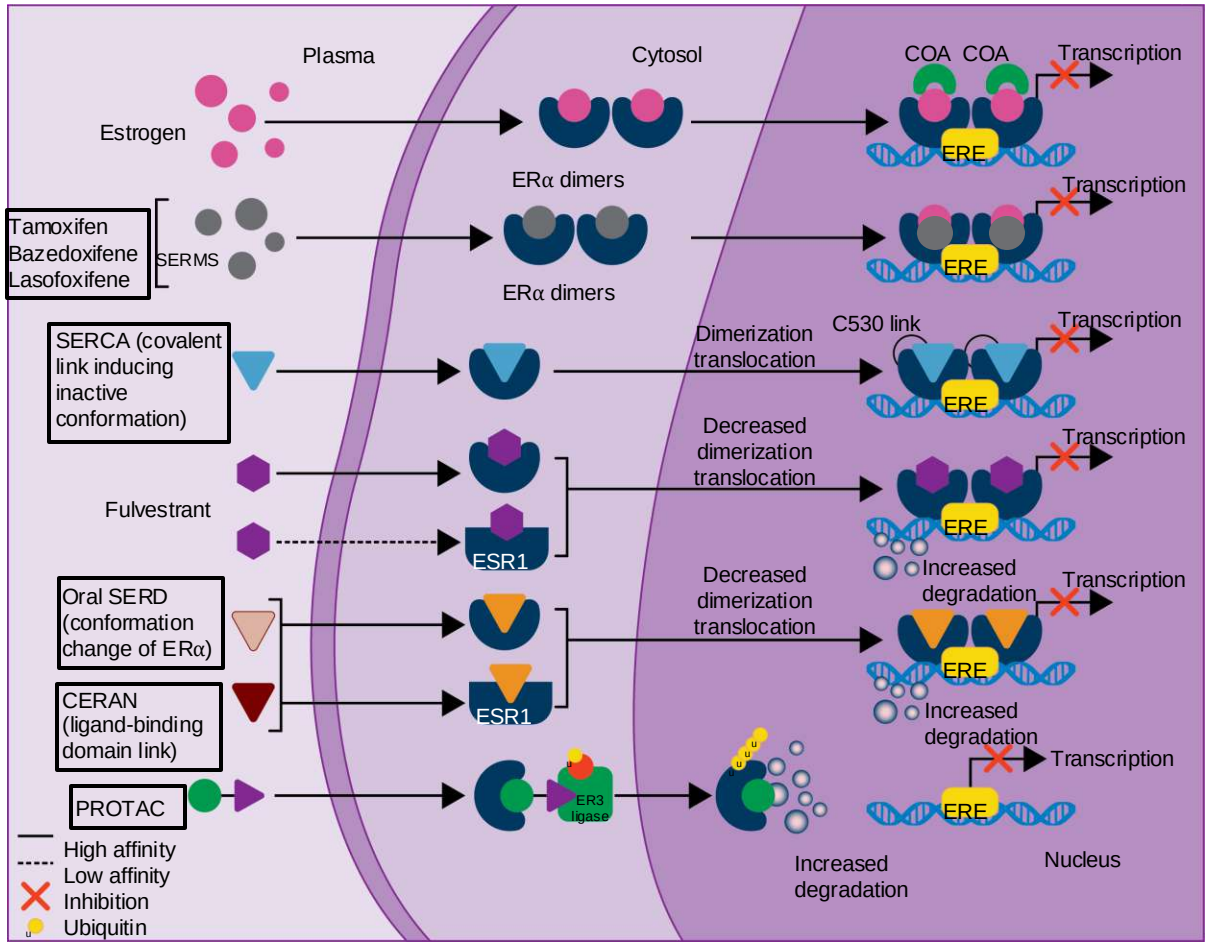


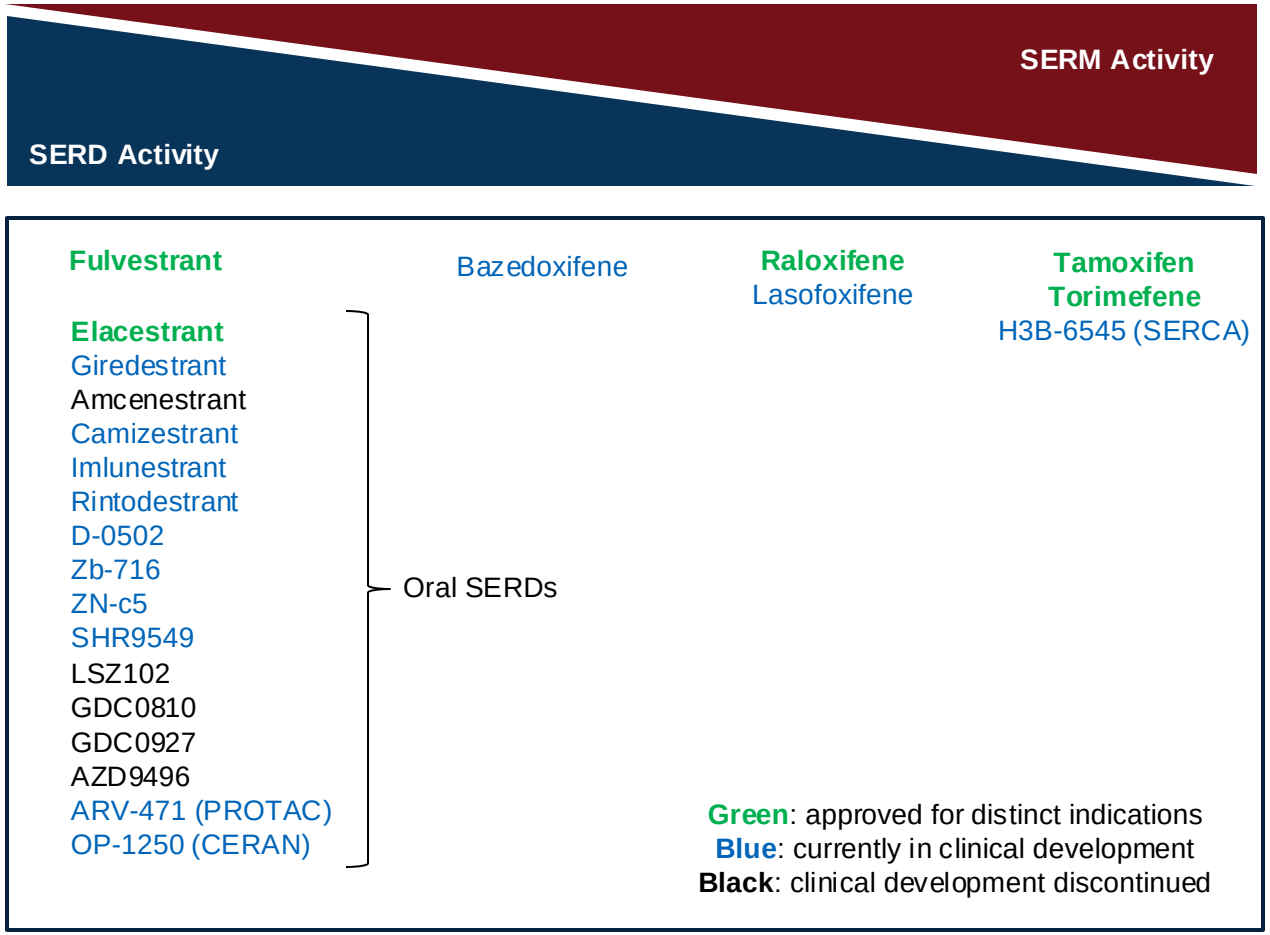


Weir HM et al. Cancer Res 2016 76; 3307-18

Several Novel Endocrine Agents in Development [1,2]

Ultimate goal: downregulate ERα with an agent that has an optimal therapeutic index and improved efficacy

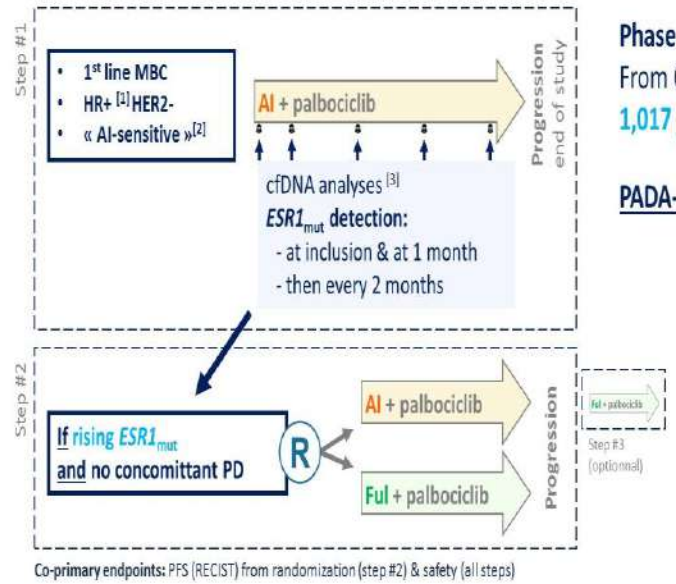




1. McDonnell DP et al. J Clin Oncol. 2021;39:1383-1388
2. Ferraro E et al. Cancer Treat Rev. 2022;109:102432.

Biomarker driven selection of ET backbone in 1L ET + CDK4/6i therapy for HR+ MBC: PADA-1

Study design: PAlbociclib & ctDNA for *ESR1*$_{mut}$ detection (PADA-1)



Co-primary endpoints: PFS (RECIST) from randomization (step #2) & safety (all steps)

[1] ER and/or PR ≥ 10%
[2] "AI-sensitive": no prior AI or DFI>12 months from adjuvant AI completion
[3] centralized ddPCR assay cfcDNA from 4 mL of plasma (Jeannot, Oncogene 2020)

Phase 3
From 04.2017 to 01.2019
1,017 patients included in step #1

PADA-1 is still ongoing
As of April 1st, 2020
Median FU = 21.2 months (0-34.5)

N= 452 pts still in step #1

N= 565 pts went out of step #1

N= 135 randomizations (24%) in step #2
Rising *ESR1mut* detected before progression; Target N=200

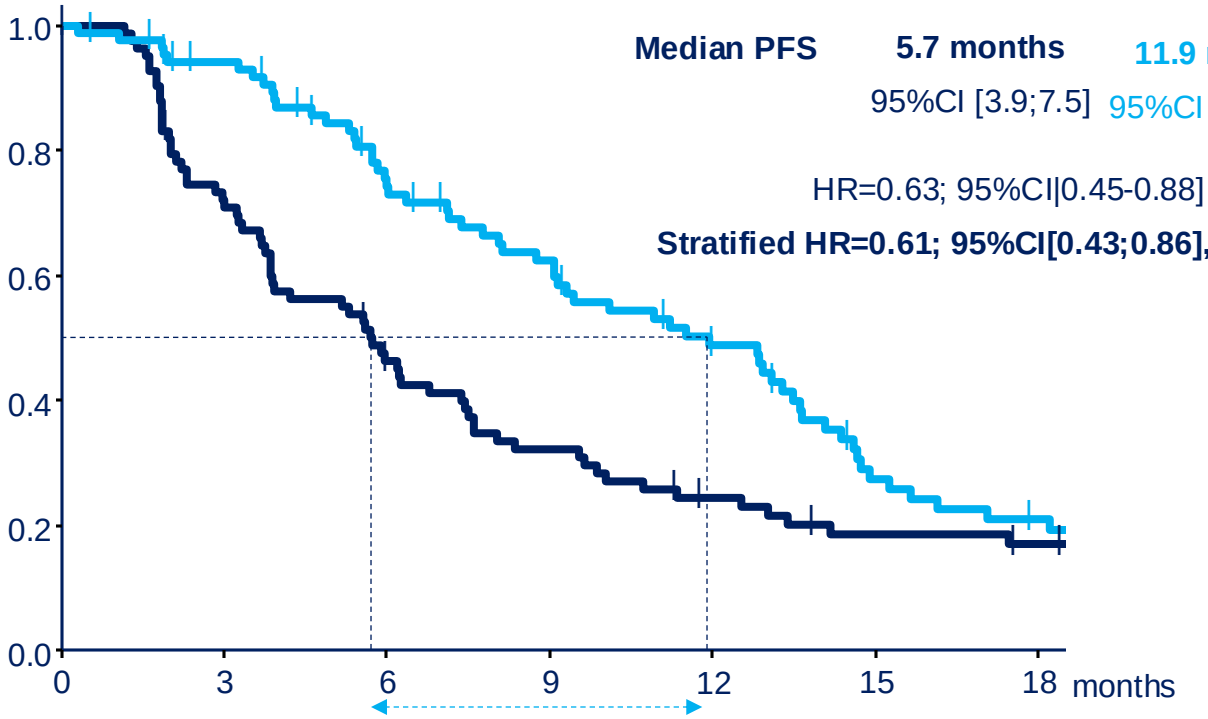
N= 354 progressions
Both ESR1wild-type & ESR1mut concomitant to RECIST progression

N= 76 pts out of study
Patient/investigator decision

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Francois-Clement BIDARD, MD PhD; fcbidard@curie.fr

Median FU in step #2: 26 months (range: 0-36m); N=136 PFS events



Bidard FC et al, J Clin Oncol 2022

TACKLING ENDOCRINE RESISTANCE IN METASTATIC BREAST CANCER (MBC)

Current Questions in Clinical Practice

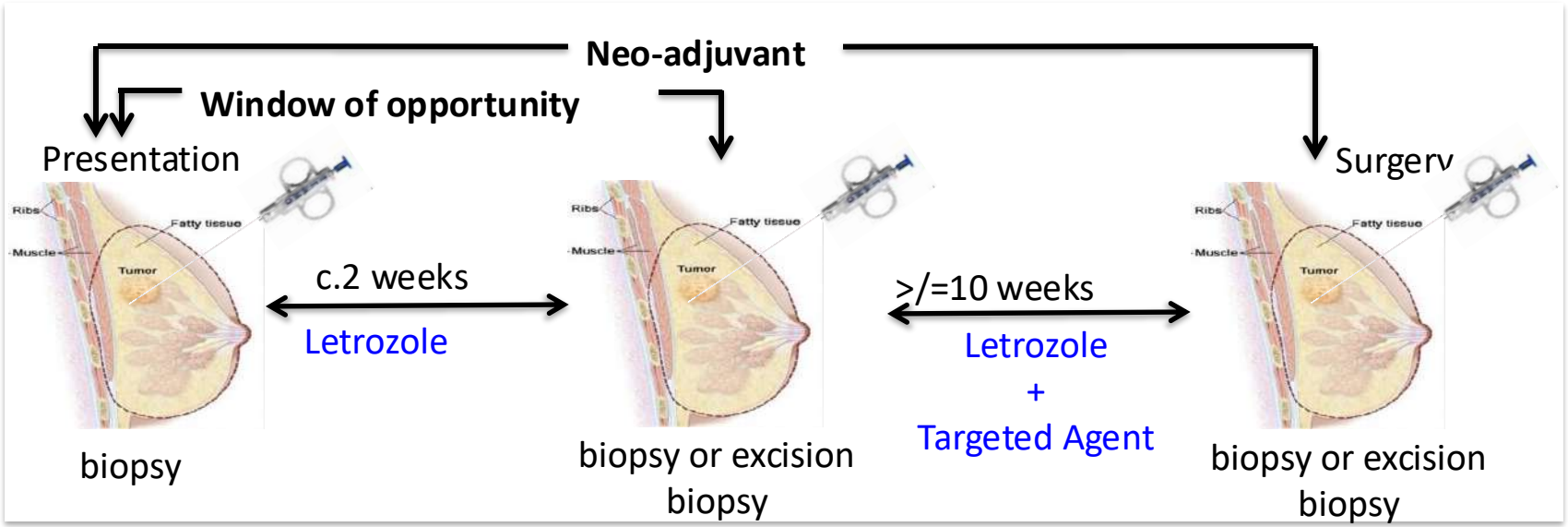
1. **What is Endocrine Resistance ?**
   - ESMO definitions
   - What are the Key Mechanisms for Endocrine Resistance ?

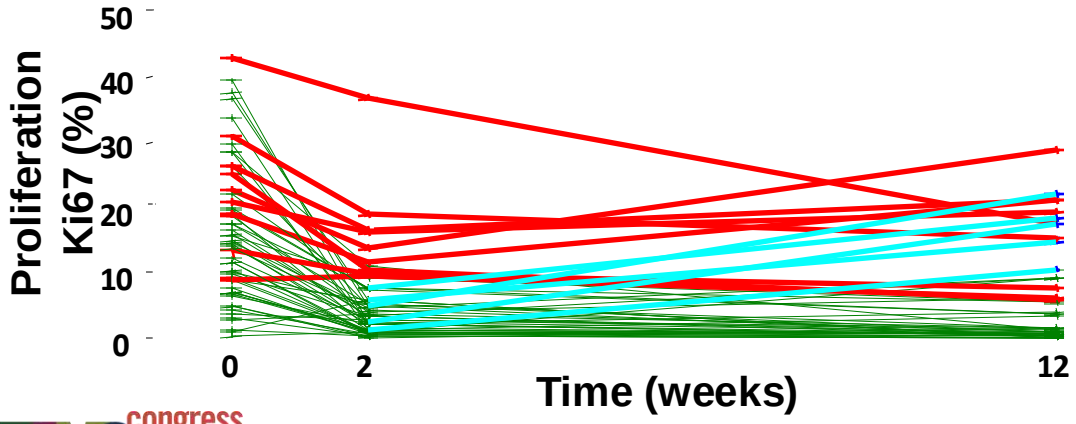
2. **How to select Endocrine Treatment (ET) options for Endocrine Resistance in ER+ MBC ?**
   - How to overcome Primary (De-Novo) Endocrine Resistance in 1st-line setting ?
   - Mutation testing in 2nd line setting – when and how to test ?

3. **Current Research: Testing Emerging Treatments for Endocrine Resistance in Breast Cancer ?**
   - Lessons from Pre-surgical Clinical Models to identify Biomarkers of Endocrine Resistance

Improving Endocrine Responsiveness in ER+ Early Breast Cancer

Role of Dynamic Ki-67 as Biomarker of Endocrine Response

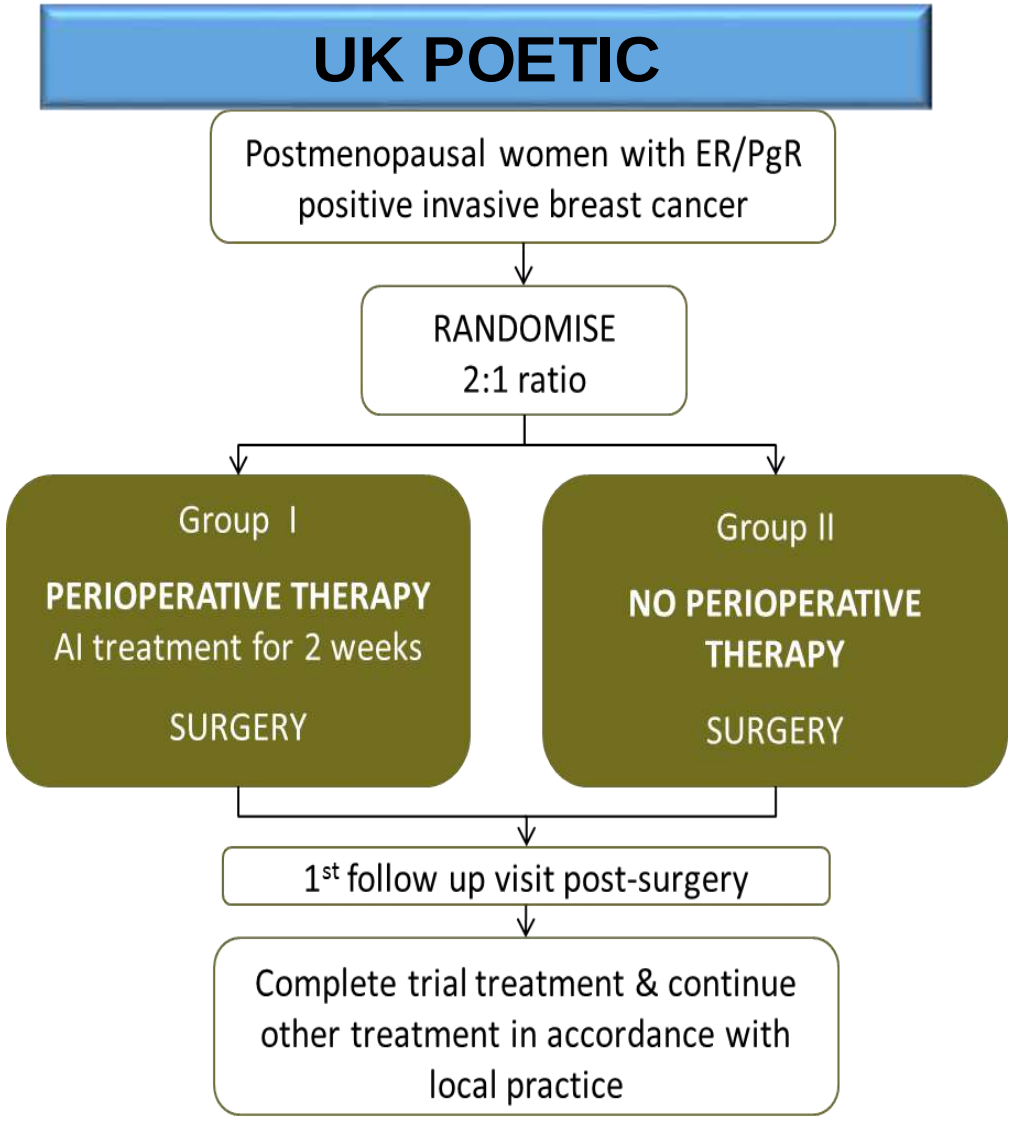




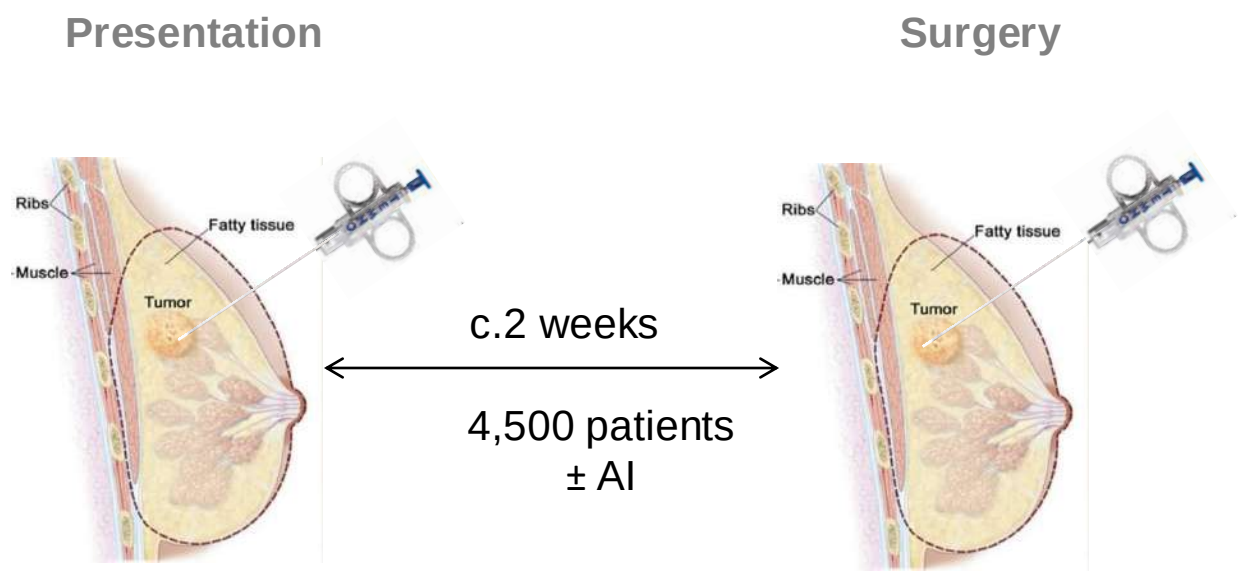
- **Measure impact of adding Targeted Agent on E-independent Ki67 (ie. de-novo or acquired endocrine resistance)**
- **Detect biomarkers for resistance / response**

Dowsett et al JNCI 2007 99; 167

Predicting endocrine resistance in ER+ primary breast cancer

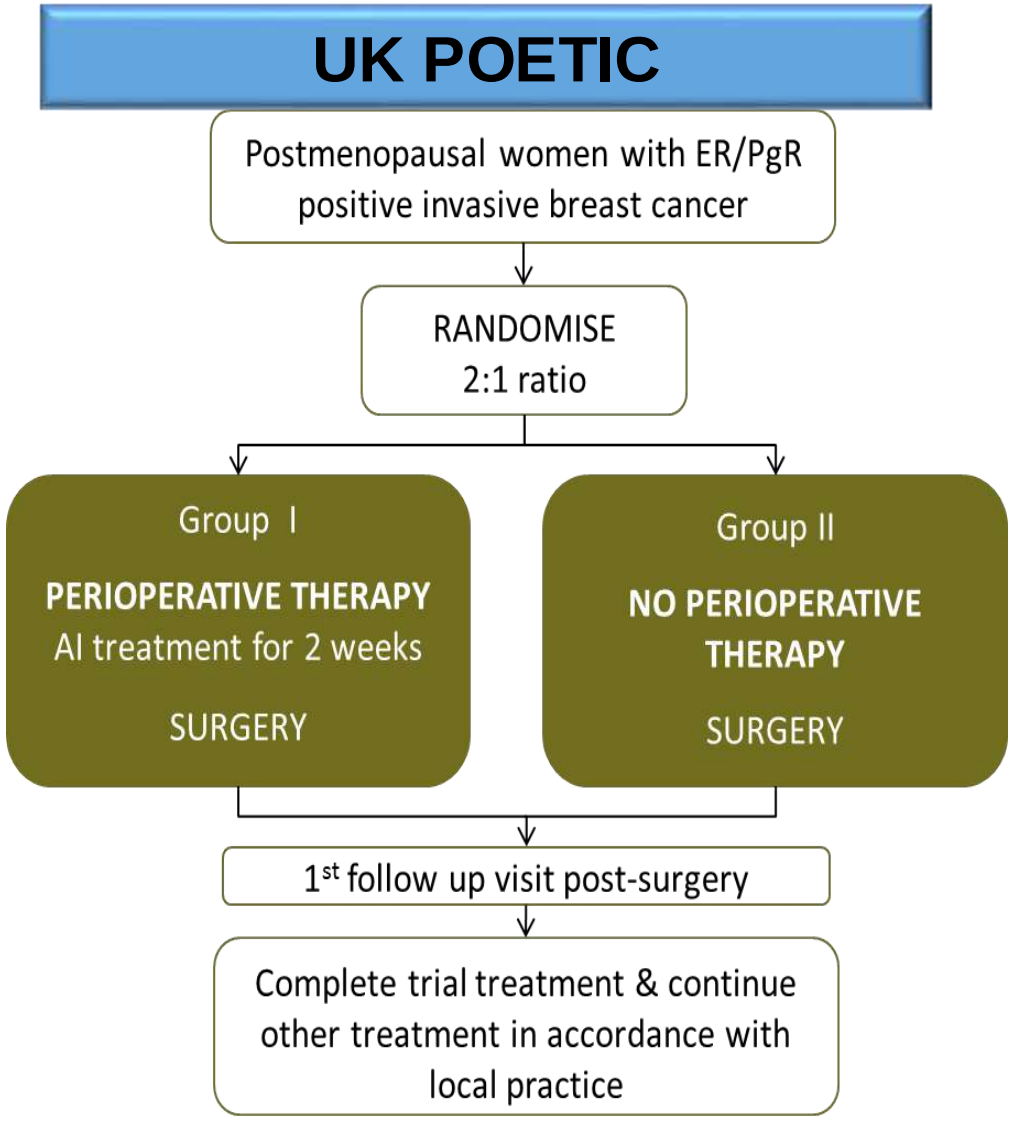


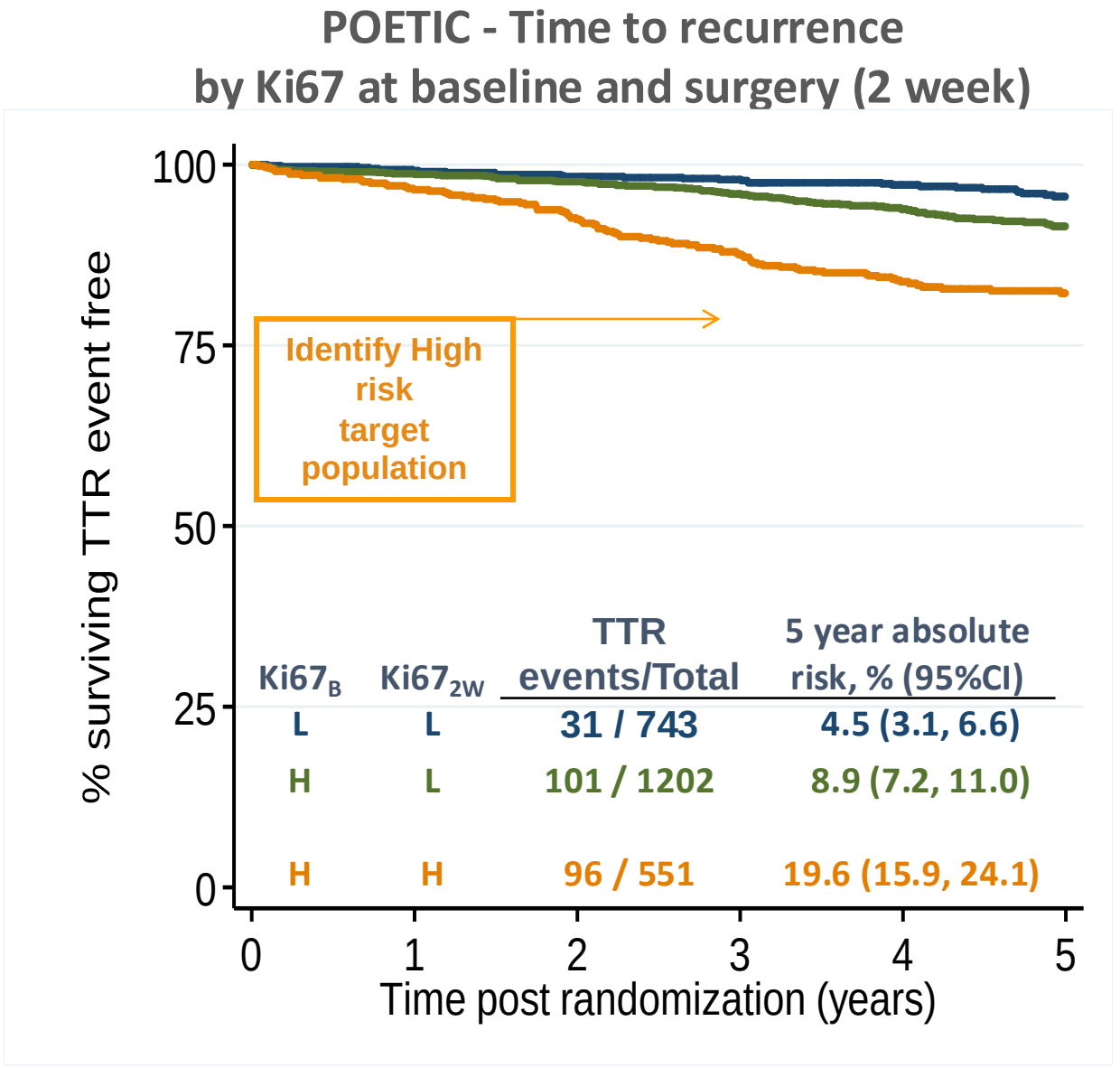
POETIC TRIAL
Peri-Operative Endocrine Therapy for Individualised Care
In ER+ primary breast cancer



Robertson et al., SABCS 2017 & Smith et al., Lancet Oncol. Nov 2020

Predicting endocrine resistance in ER+ primary breast cancer





Robertson et al., SABCS 2017 & Smith et al., Lancet Oncol. Nov 2020

nature communications

Article

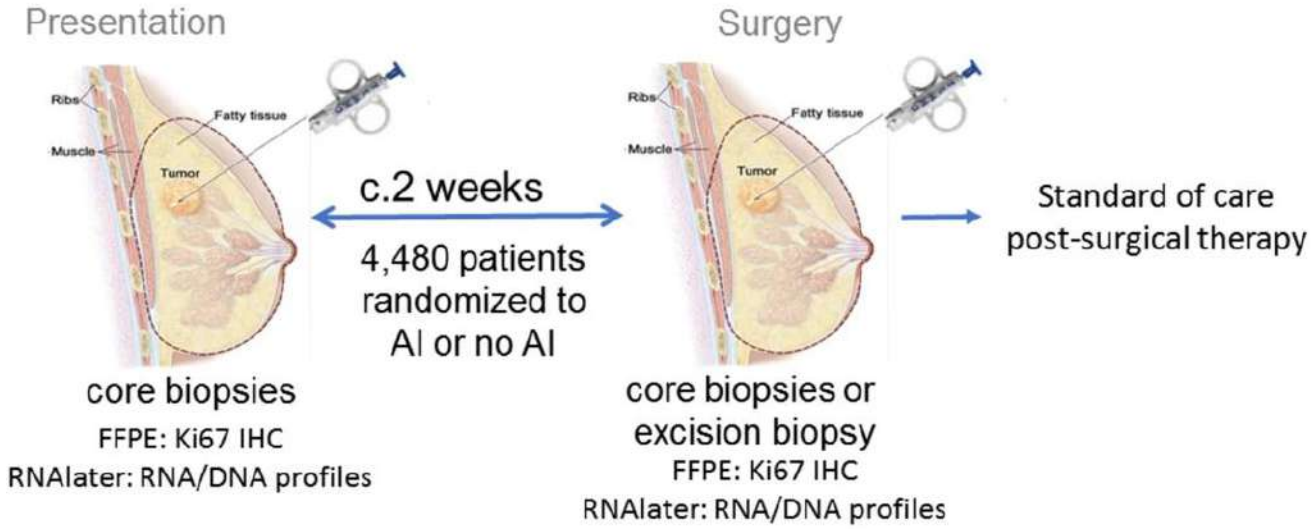
https://doi.org/10.1038/s41467-023-39613-z

Molecular profiling of aromatase inhibitor sensitive and resistant ER+HER2- postmenopausal breast cancers

POETIC TRIAL

PeriOperative Endocrine Therapy for Individualised Care

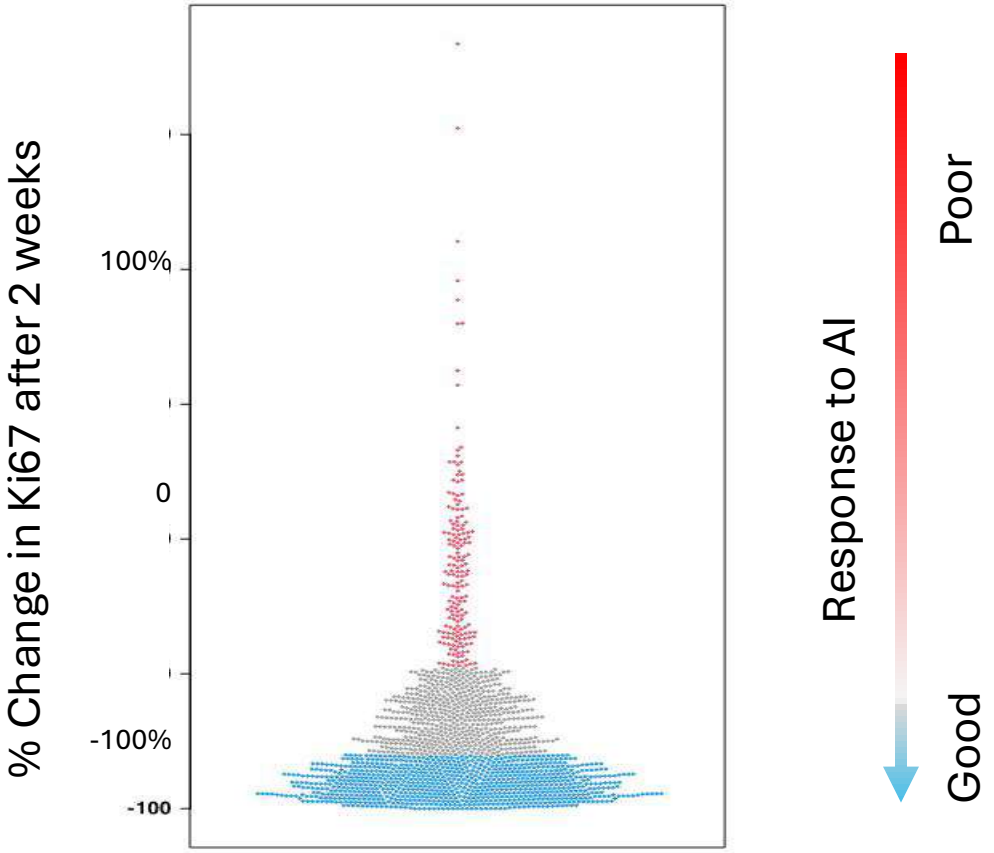
ER+ primary breast cancer



Co-primary analyses: (i) comparison of recurrence-free survival between randomized groups
(ii) comparison of prognostic importance of Ki67 at baseline and 2 weeks in AI-treated group

POETIC Bookend Study

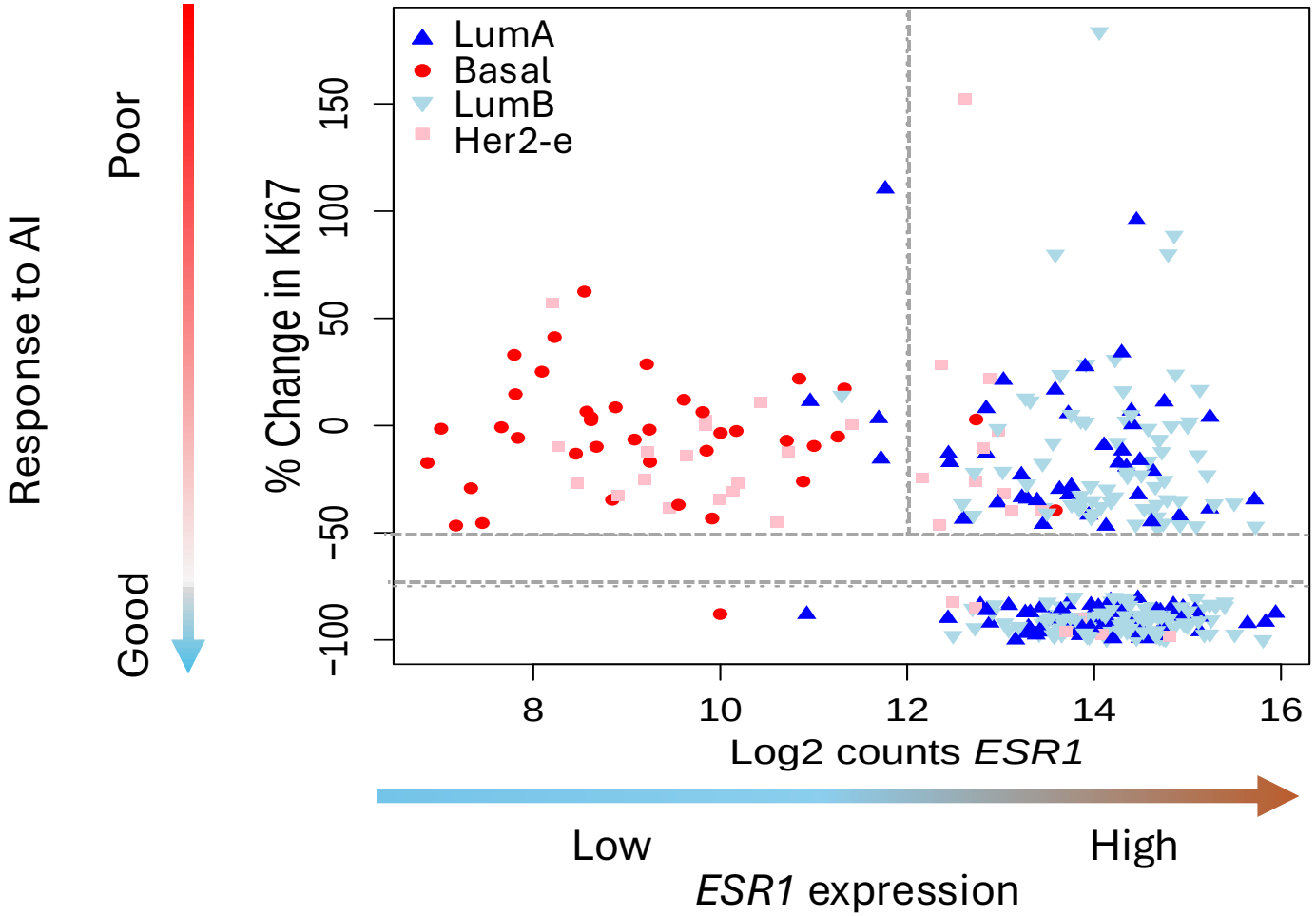
Top15% of Poor Responders
vs Good Responders

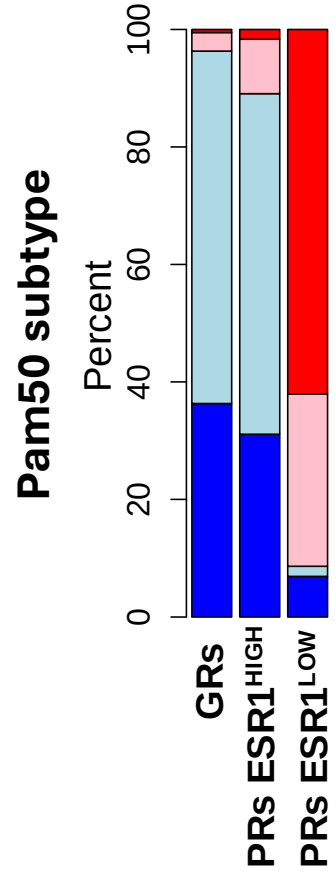


Schuster, E.F. et al. Nat Comm 14, 4017 (2023)

Poor Responders (PRs) to AI have low *ESR1* expression & non-Luminal Subtype

Good Responders (GRs) and PRs with high *ESR1* expression have similar percentage of LumA/B subtypes, suggesting poorer prognosis of LumB subtypes might not be related to response to AI

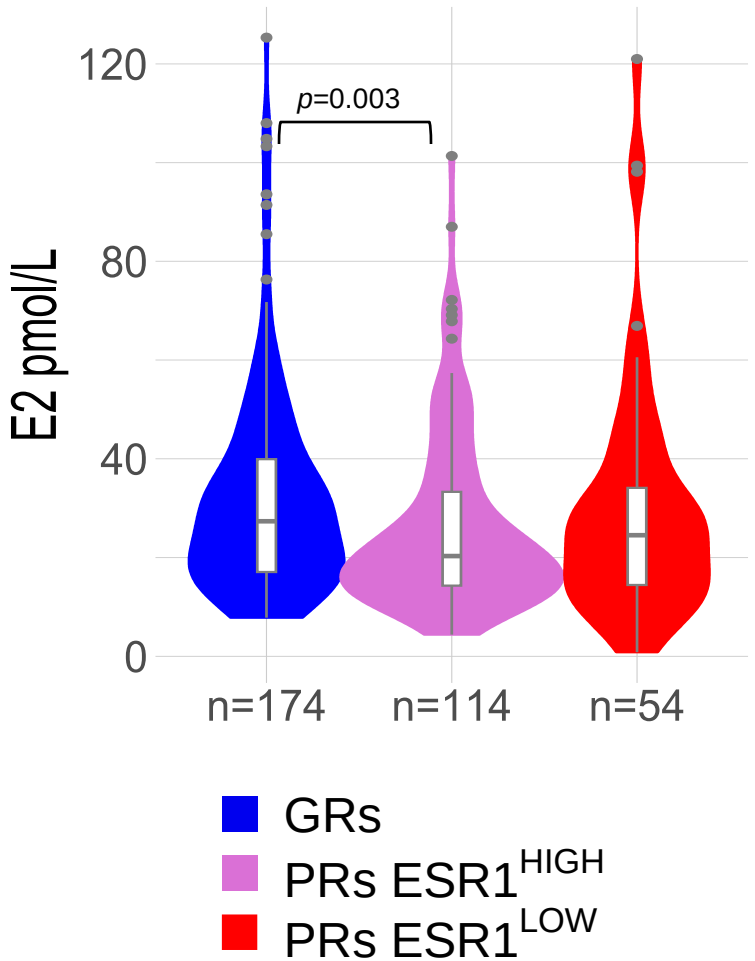


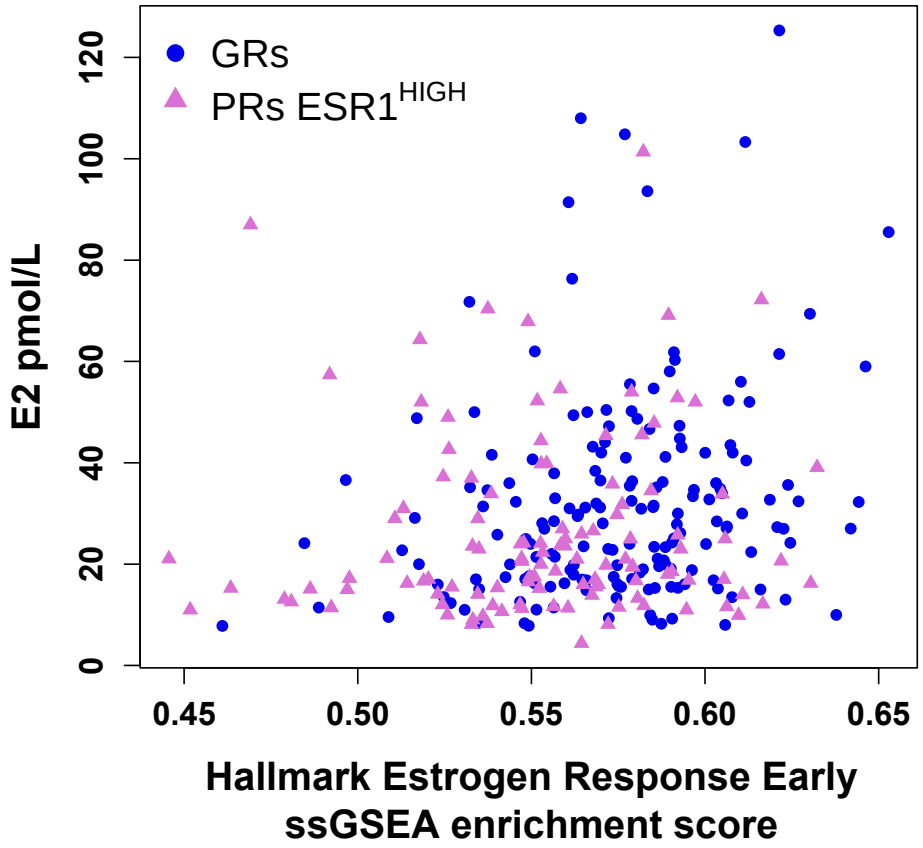


Schuster, E.F. et al. Nat Comm 14, 4017 (2023)

Estradiol (E2) levels are lower in Poor Responders with ESR1^{HIGH}

E2 levels correlate with expression of estrogen regulated genes

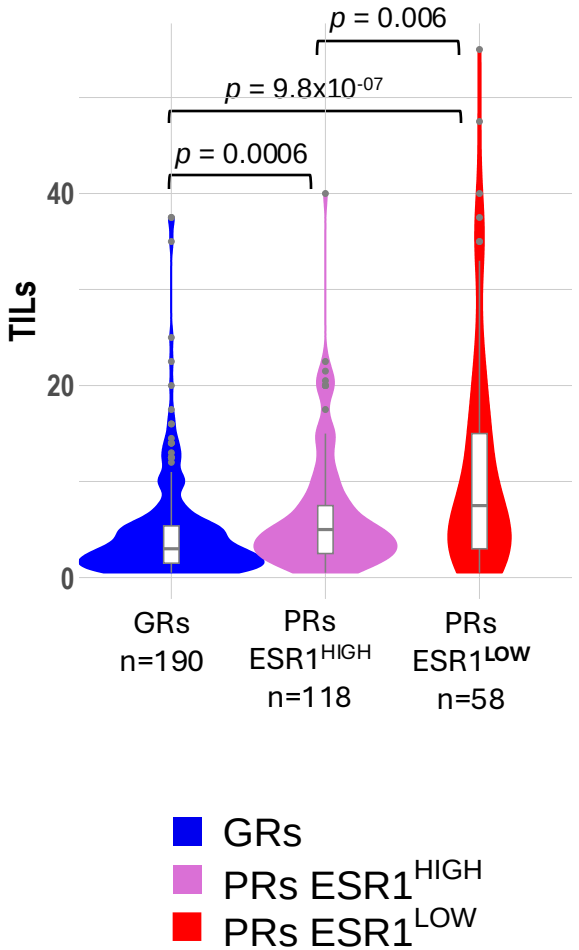


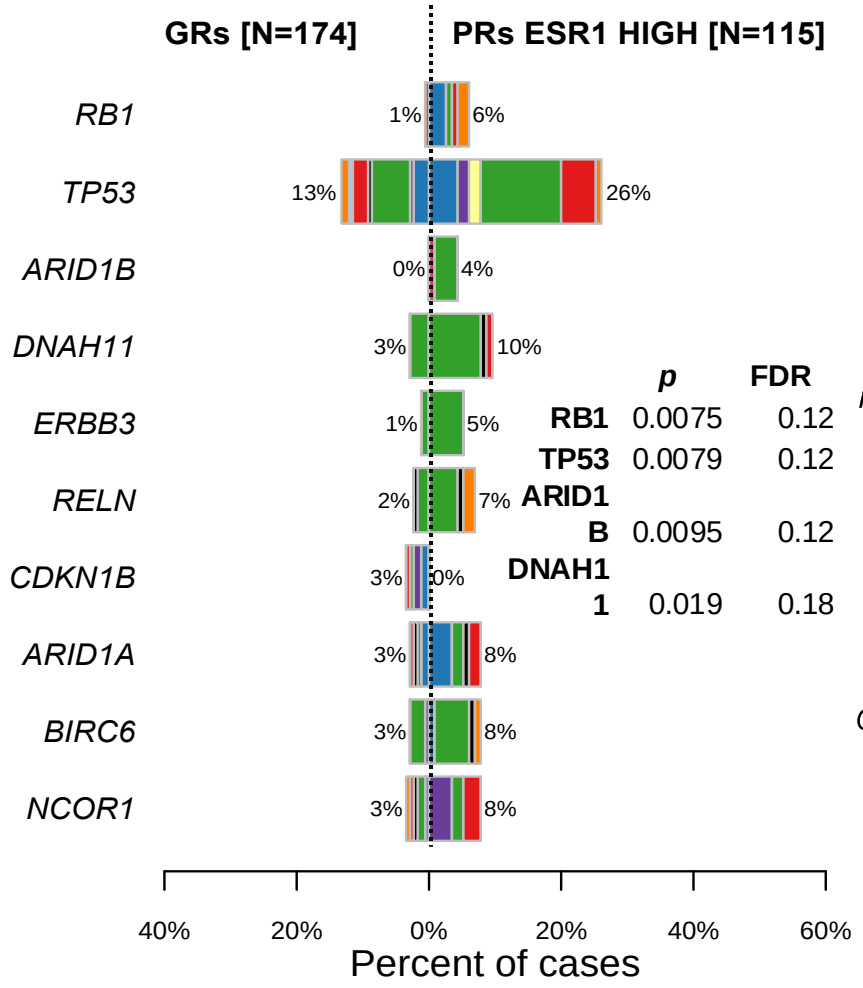


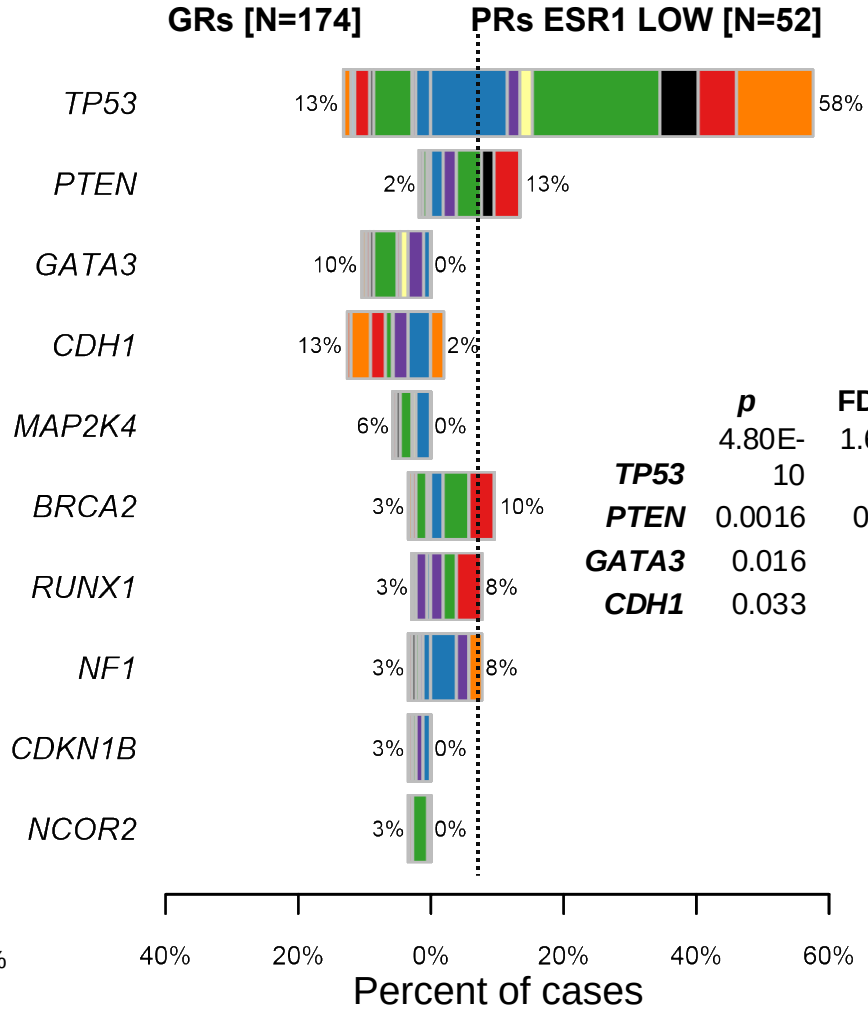
FDR = 0.01, Spearman correlation

Schuster, E.F. et al. Nat Comm 14, 4017 (2023)

Tumor infiltrating lymphocytes (TILs) & TP53 mutations higher in Poor Responders to AIs







Frame_Shift_Del
Multi_Hit
Splice_Site
Frame_Shift_Ins
Nonsense_Mutation
In_Frame_Del
Missense_Mutation
Nonstop_Mutation
In_Frame_Ins

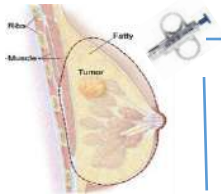
Schuster, E.F. et al. Nat Comm 14, 4017 (2023)

POETIC-A: Pre-Operative Endocrine Therapy for Individualised Care - Adjuvant

Trial Design [1]

Postmenopausal
ER+ Early Breast Cancer
≥1.5 cm IDC / ILC
Gr 2/3

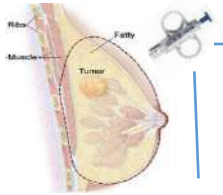
Diagnostic biopsy



ER- or HER2+ → **ineligible**

ER+ and HER2-

2 weeks to 6 months pre-op Aromatase Inhibitor



Core-cut/excision at surgery

Ki67 < 8% → **ineligible**

Ki67 ≥ 8%

Complete standard of care treatment, (ie loco-regional Radiotherapy and Adjuvant Chemotherapy if indicated)

ClinTrials.gov. NCT04584853

Prospectively Stratified as either **AIR-CIS** Biomarker assay Sensitive or Resistant/Unknown **(Aromatase Inhibitor Resistant, CDK4/6 Inhibitor Sensitive)**

RANDOMISE

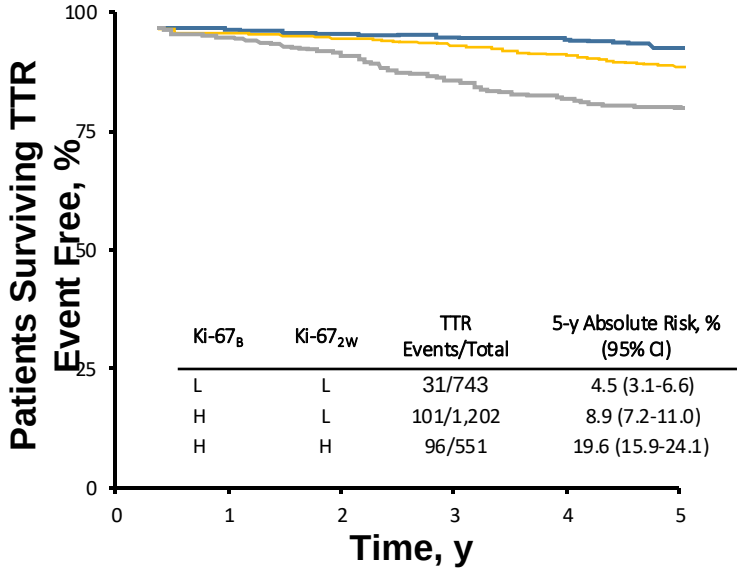
ET only

ET + abemaciclib

Clinical end-point: Time to Recurrence

Original POETIC Trial [2]

Poor Ki-67 response to 2 wk AI associated with 20% 5-y risk of relapse in ER+ EBC
(Smith I et al. *Lancet Oncol.* 2020)

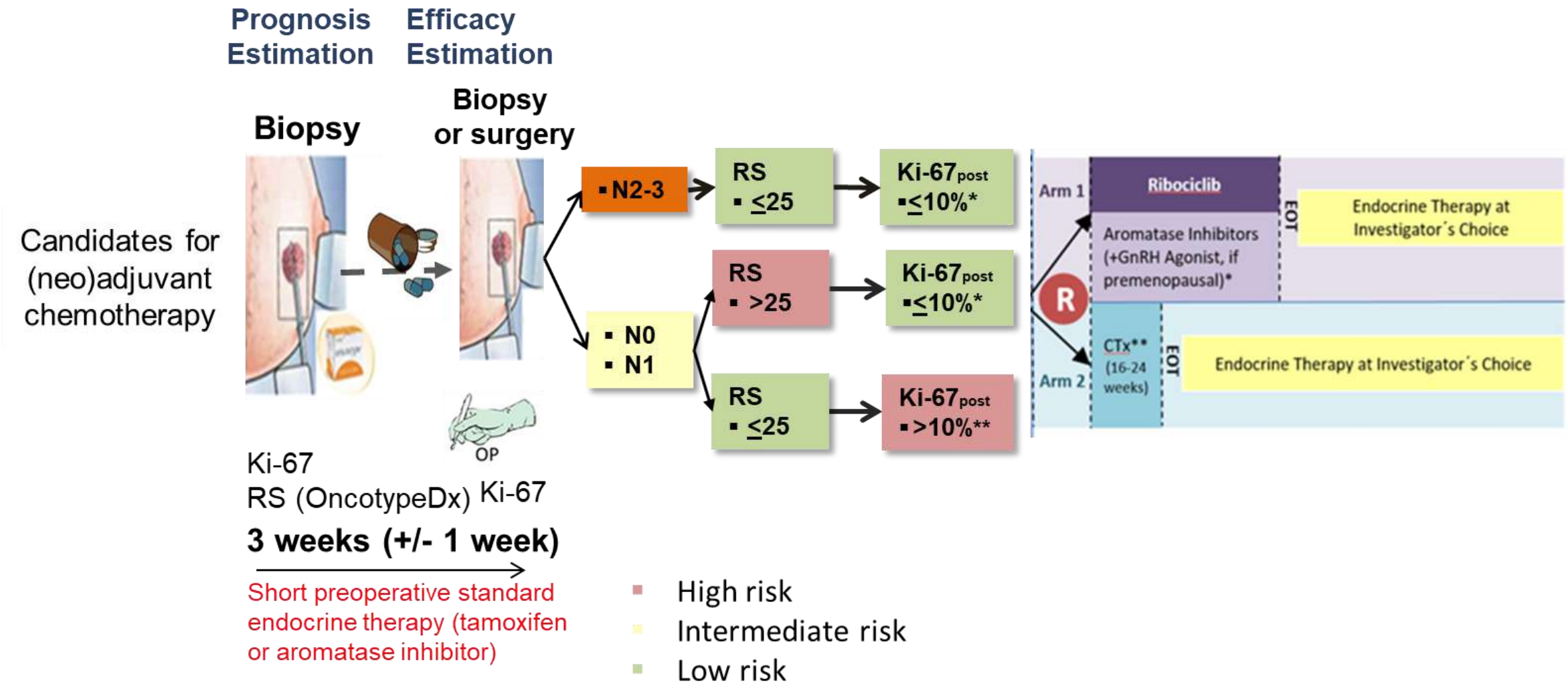


$Ki\text{-}67_B$	$Ki\text{-}67_{2W}$	TTR Events/Total	5-y Absolute Risk, % (95% CI)
L	L	31/743	4.5 (3.1-6.6)
H	L	101/1,202	8.9 (7.2-11.0)
H	H	96/551	19.6 (15.9-24.1)

1. https://clinicaltrials.gov/ct2/show/study/NCT04584853.
2. Smith I et al. *Lancet Oncol.* 2020;21:1443-1454.

POETIC-A

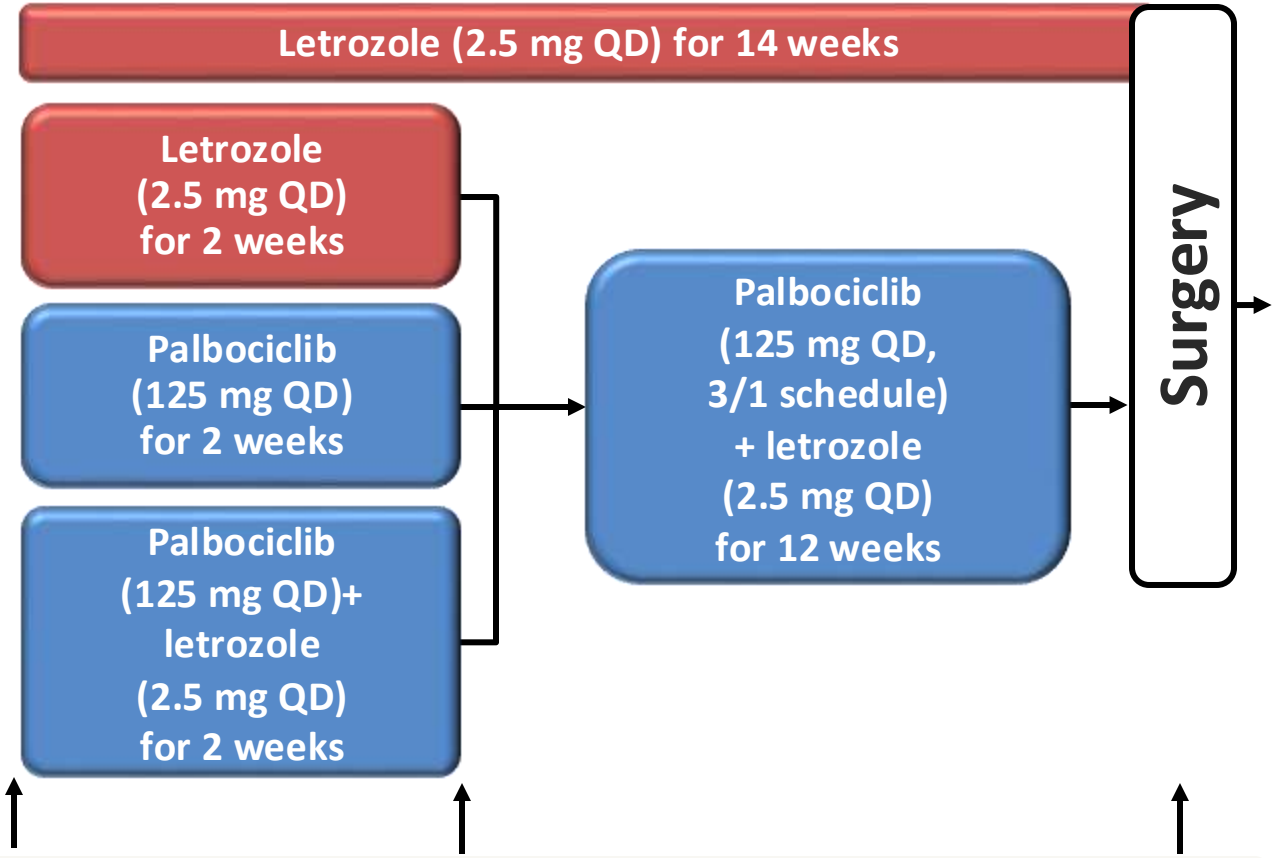
ADAPT^{cycle} - study design



Harbeck N, et al. J Clin Oncol 2020 38, no. 15_suppl. # TPS601

Randomised Phase II Neo-adjuvant Study (PALLET) (RMH/ICR-CTSU and NSABP)

- Localized ER+ HER– invasive early BC (≥2 cm)
- Suitable for neoadjuvant therapy with letrozole
- Post-menopausal
- N=301



Tumor samples: biopsies taken before treatment, and at 2 and 14 weeks

Primary Endpoints:
- Change in the proliferation marker Ki67 at week 14
- Clinical response at week 14

Secondary Endpoints:
- Ki67 at 2 weeks
- ypCR after 14 weeks
- Complete Cell Cycle Arrest (CCCA)
- PEPI score at 14 wk
- Safety & tolerability

Exploratory Endpoints:
- Biomarkers that predict benefit
- Molecular effects of therapy

Stratification:
- Country

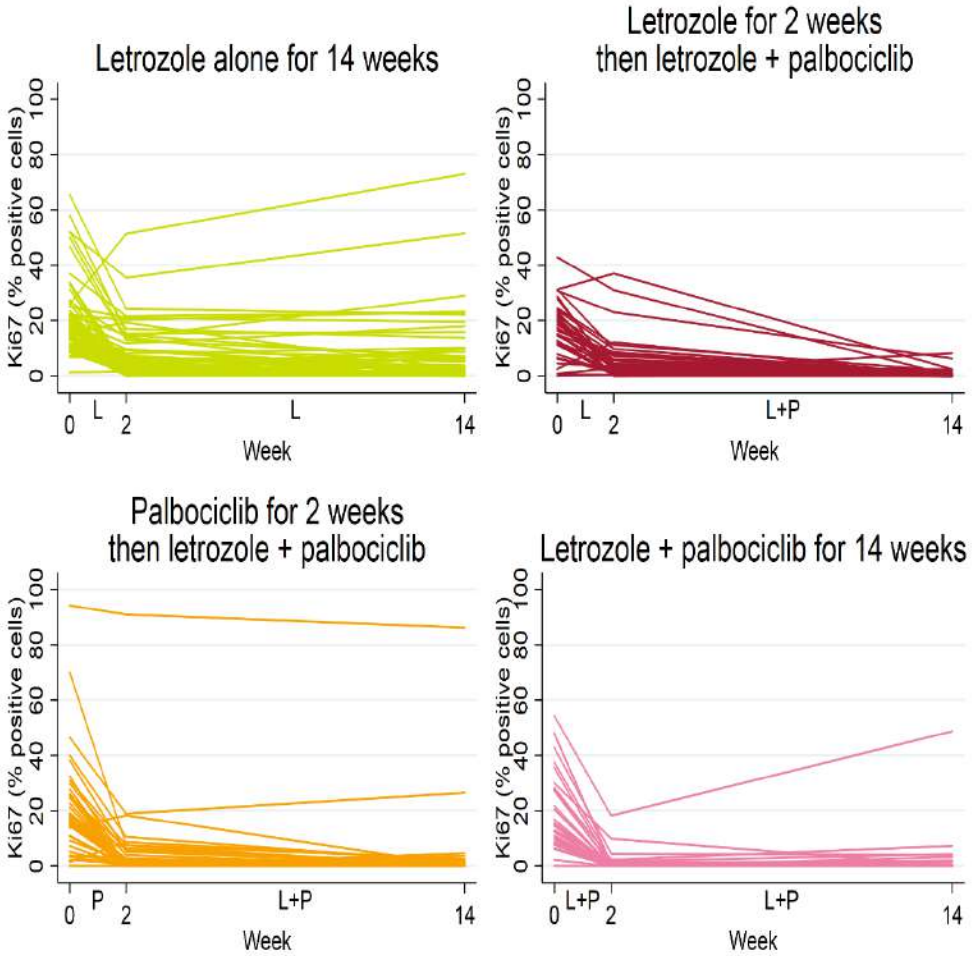
ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

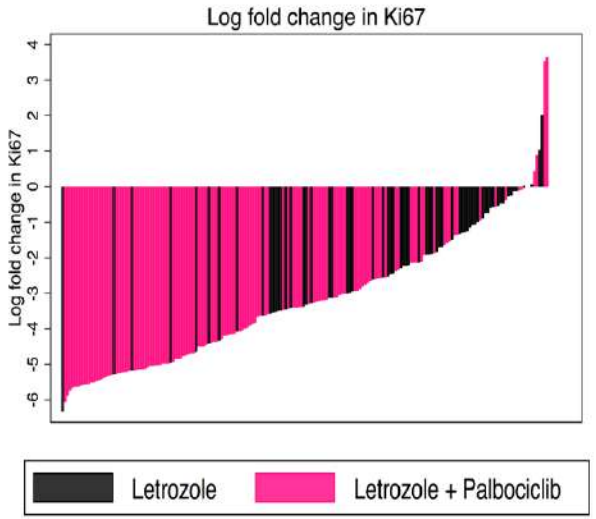
NSABP National Surgical Adjuvant Breast and Bowel Project

CANCER RESEARCH UK

Neo-adjuvant CDK 4/6 Inhibitor Therapy (PALLET Trial): Co-primary Endpoints: Anti-Proliferative (Ki-67) & Clinical Response



Ki67 at week 14



Complete Cell Cycle Arrest (CCCA) at 14 week:

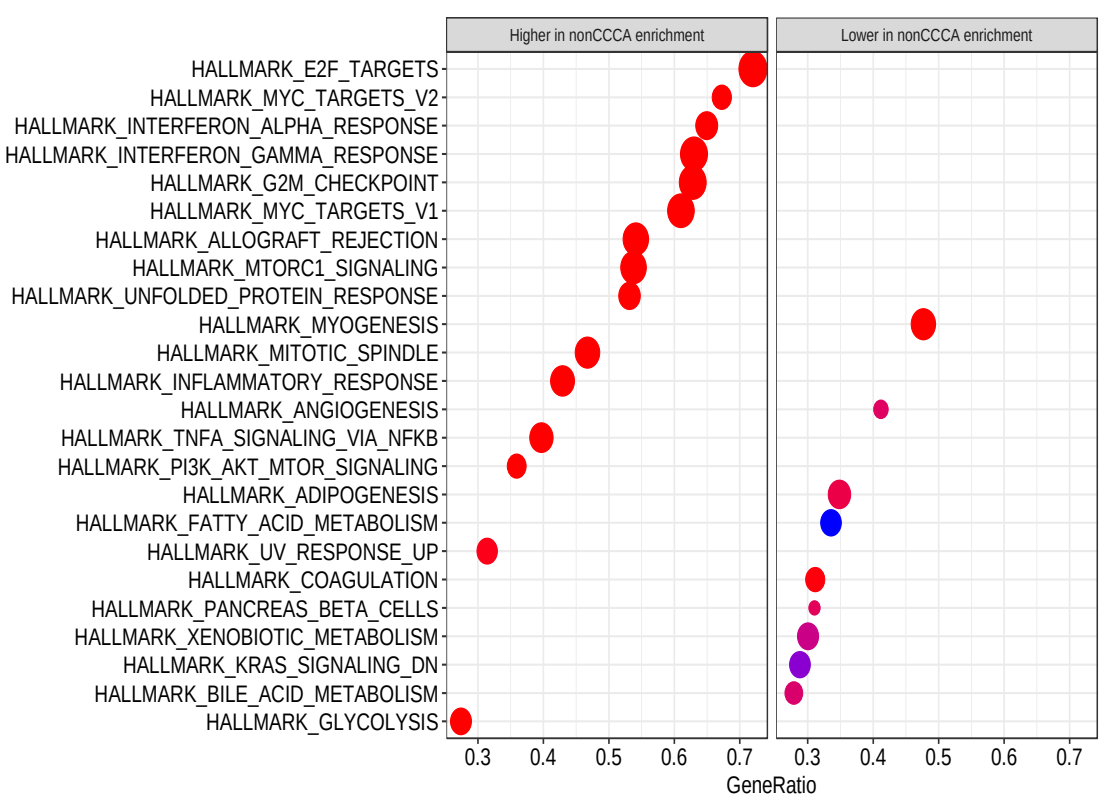
Palbo + Let 90%
Let alone 59% (p<0.001)

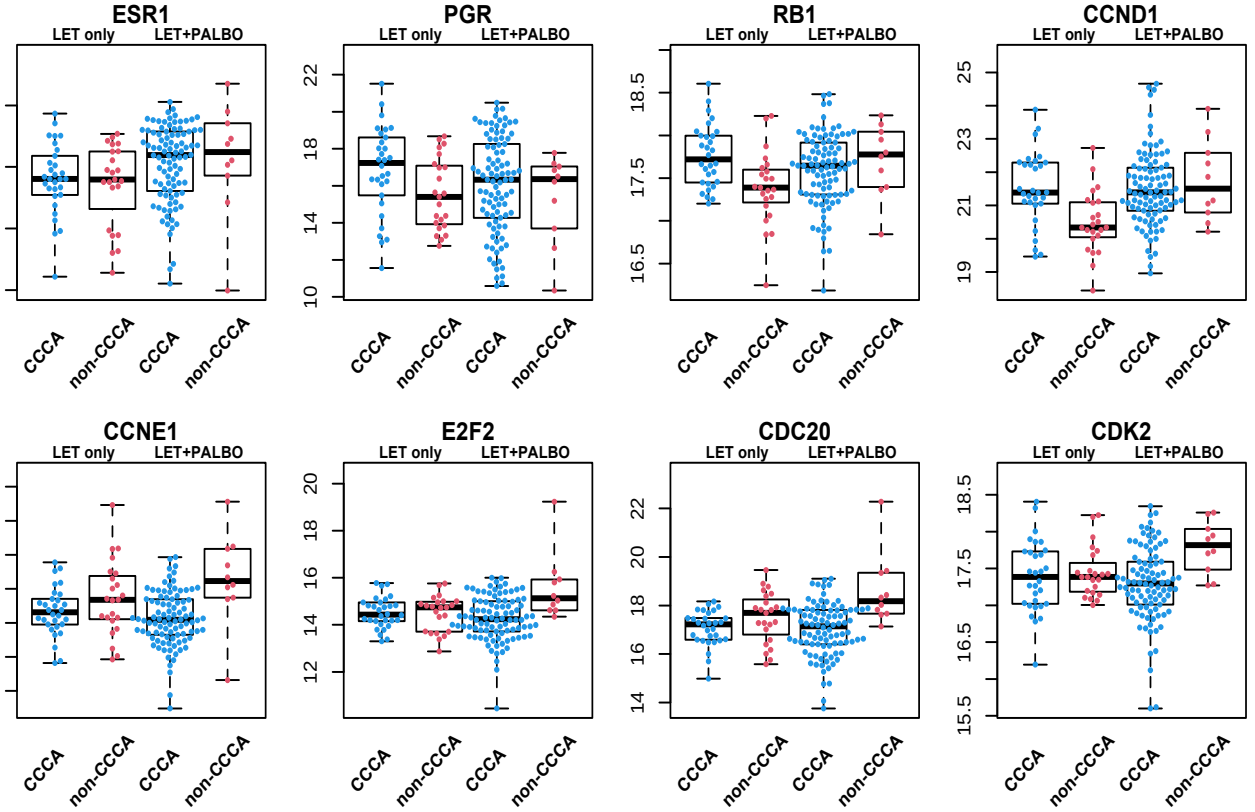
No significant difference in objective radiological response
Letrozole alone = 49.5%
Letrozole + Palbo = 54.4%

pCR Rate
Letrozole alone = 3%
Letrozole + Palbo = 3%

Johnston S et al. J Clin Oncol. 2019 Jan 20;37(3):178-189.

Biomarkers of resistance to Palbociclib in ER+ primary breast cancer in the PALLET trial





PALBOCICLIB resistance was associated with:

CCCA = complete cell cycle arrest
non-CCCA = non complete cell cycle arrest

- higher baseline Ki67 and proliferation gene expression
- higher expression of cyclin-E1, CDK2 and genes related with E2F transcription/ regulation, MYC signaling, interferon response and mTOR signaling

Schuster EF et al. SABCS 2020 PS5-01

CDK4/6 Resistance: Re-wiring of cell signalling pathways

Adaptive network changes make it difficult to identify dominant drivers

Strategies against CDK4/6 resistance

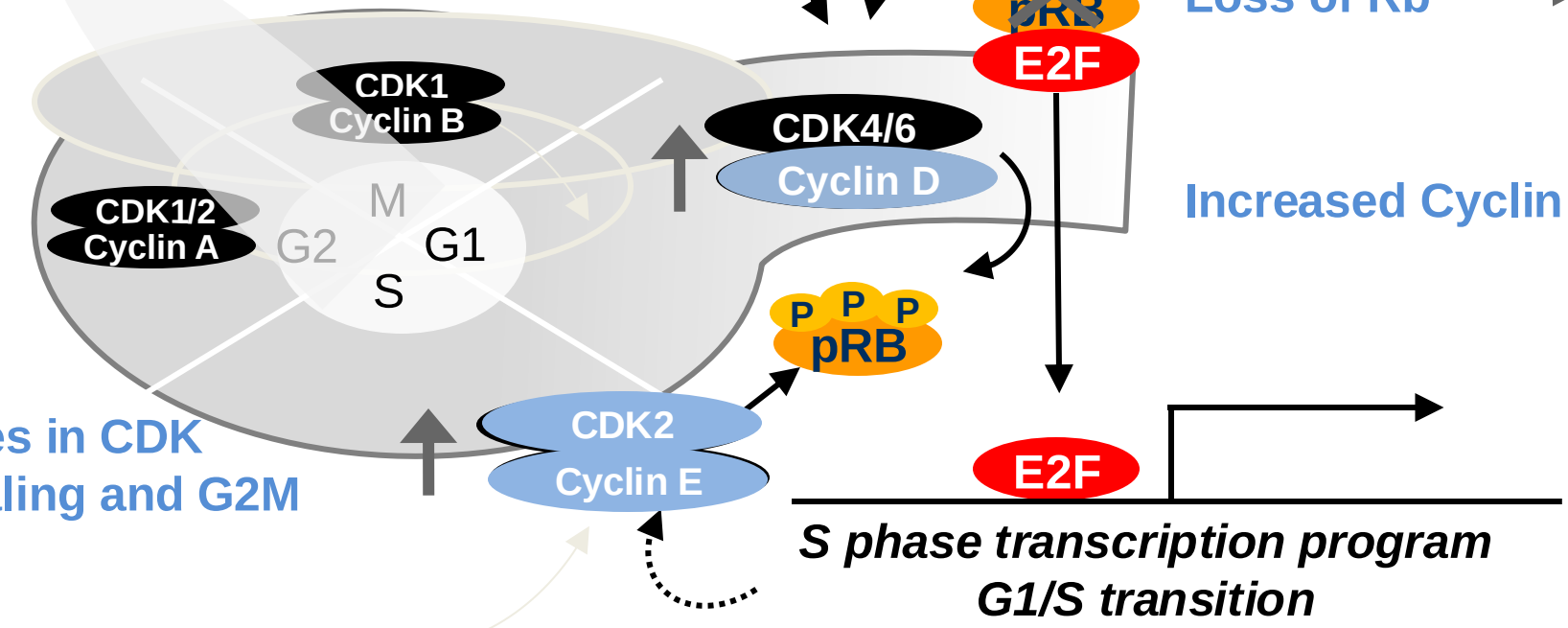
1. Switch to other CDK4/6i + endocrine therapy
2. Target other cell cycle regulators (CDK1/2, CDK7, Wee-1)
3. Co-targeting other cell signalling pathways (mTOR, PI3-K)

ER transcriptional activity

ERα

Mitogenic signalling

Up-regulation of PI3K/AKT/mTOR pathway



Adaptive changes in CDK and Cyclin signaling and G2M checkpoints

Slide adapted courtesy Peter Schmid

Lenihan SABCS 2016; Martin et al, SABCS 2016

TACKLING ENDOCRINE RESISTANCE IN METASTATIC BREAST CANCER (MBC)

Take Home Messages

1. **Endocrine Resistance**

   - De-Novo in 10-15% 1st-line Endocrine Naïve MBC – more likely Basal / HER2-E subtypes
   - Somatic Mutations vary in frequency, & not predictive (except *PIK3CA*) of resistance to CDK 4/6 inhibitors

2. **Acquired Endocrine Resistance occurs eventually in almost all ER+ MBC**

   - *ESR1* mutations most common, often mutually exclusive to *Akt/PIK3CA* pathway alterations
   - Biomarker testing in tumour / plasma now recommended in 2nd-line to select therapies
   - Acquired HER2-low a very common finding – therapies cannot prevent it, but ADCs may target it (new paradigm)

3. **Pre-op Therapy model can find new Biomarkers of Endocrine Resistance in Breast Cancer**

   - Dynamic Ki-67 as predictor of endocrine resistance, allowing potentially better selection of therapies
   - Deep-dive genomic & transcriptomic analyses showing immune signatures as possible endocrine resistance signal

ESMO DEEP DIVE: BREAST CANCER

Acknowledgements for Slides

Gene Schuster, Aleix Prat, Nick Turner, Peter Schmid, Nadia Harbeck

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

ER+ METASTATIC BREAST CANCER

BREAKTHROUGH RESEARCH ON THE ROLE OF LIQUID BIOPSY AND MOLECULAR ANALYSIS

Francois-Clement Bidard

Institut Curie, FR

ESMO WEBINAR SERIES

DISCLOSURES

Research fundings

GE Healthcare, Pfizer, Prolynx, Menarini Silicon Biosystems, Merck KGaA, MSD, Novartis, Personalis, Pfizer, Roche, SAGA Diagnostics, Tempus

Advisory boards

AstraZeneca, Daiichi-Sankyo, Exact Sciences, GE Healthcare, Gilead, Inatherys, Lilly, Menarini/Stemline, Novartis, Pfizer, Roche, SAGA Diagnostics

Speaker

AstraZeneca, Daiichi-Sankyo, Lilly, Menarini/Stemline, Pfizer

Travel support

AstraZeneca, Daiichi-Sankyo, Pfizer, Novartis

HR+ mBC: MAJOR CHANGES AHEAD !

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Median PFS: 24 mo. // Overall survival gain → PD

Current 2nd line options

- PD — Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- PD — Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → PD — Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- PD — Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → PD — PARPi (mPFS 6-7 mo, no OS gain)
- PD — 1st line chemo (mPFS 8-9 mo, no OS data)

N=2 radiologically significant tumor growths +/- appearance of new metastatic sites

No clinical utility data available for RECIST-based management

HR+ mBC: MAJOR CHANGES AHEAD !

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Median PFS: 24 mo. // Overall survival gain → PD

Current 2nd line options

- PD → Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- PD → Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → PD → Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- PD → Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → PD → PARPi (mPFS 6-7 mo, no OS gain)
- PD → 1st line chemo (mPFS 7-9 mo, no OS data)

2024

- post-MONARCH: Fulvestrant + abemaciclib (mPFS 6 mo)
- DB-06: T-DXd (mPFS 13.2 mo)
- EMBER-3: Imlunestrant + abemaciclib

HR+ mBC: MAJOR CHANGES AHEAD !

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Median PFS: 24 mo. // Overall survival gain → **PD**

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

- Pragmatic tools that detect ET failure
- **Building new treatment strategies**

- post-MONARCH: Fulvestrant + abemaciclib (mPFS 6 mo)
- DB-06: T-DXd (mPFS 13.2 mo)
- EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

PD

Get out !

Detecting & acting on *de novo* resistance

SAFIR-03

Chemo / ADC / targ. ther.

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

- post-MONARCH: Fulvestrant + abemaciclib
- DB-06: T-DXd
- EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Maximizing ET exposure / avoiding 1 PD event

Stay in !

Detecting & tackling secondary resistance

PADA-1 & SERENA-6

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

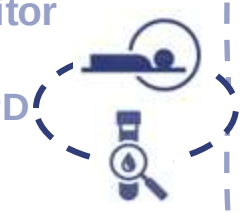
- post-MONARCH: Fulvestrant + abemaciclib
- DB-06: T-DXd
- EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

PD



Finding the best of the two worlds

Biomarker workup for CT vs ET treatment decision

Current 2nd line options

PD Fulvestrant single agent (mPFS ~2 mo, no OS gain)

PD Elacestrant single agent (mPFS ~4mo, no OS gain)

PIK3CA/AKTmut → PD Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)

PD Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)

gBRCAmut → PD PARPi (mPFS 6-7 mo, no OS gain)

PD 1st line chemo (mPFS 7-9 mo, no OS data)

post-MONARCH: Fulvestrant + abemaciclib

DB-06: T-DXd

EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

PD

Finding the best of the two worlds

Biomarker workup for CT vs ET treatment decision

Finding patients with long PFS on ET rechallenge

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

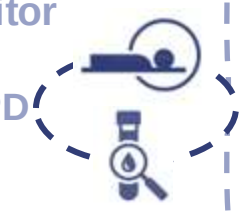
- post-MONARCH: Fulvestrant + abemaciclib
- DB-06: T-DXd
- EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

PD



Finding the best of the two worlds

Biomarker workup for CT vs ET treatment decision

Finding patients with long PFS on ET rechallenge

Avoiding detrimental ET in other patients

ECLECTIC

Current 2nd line options

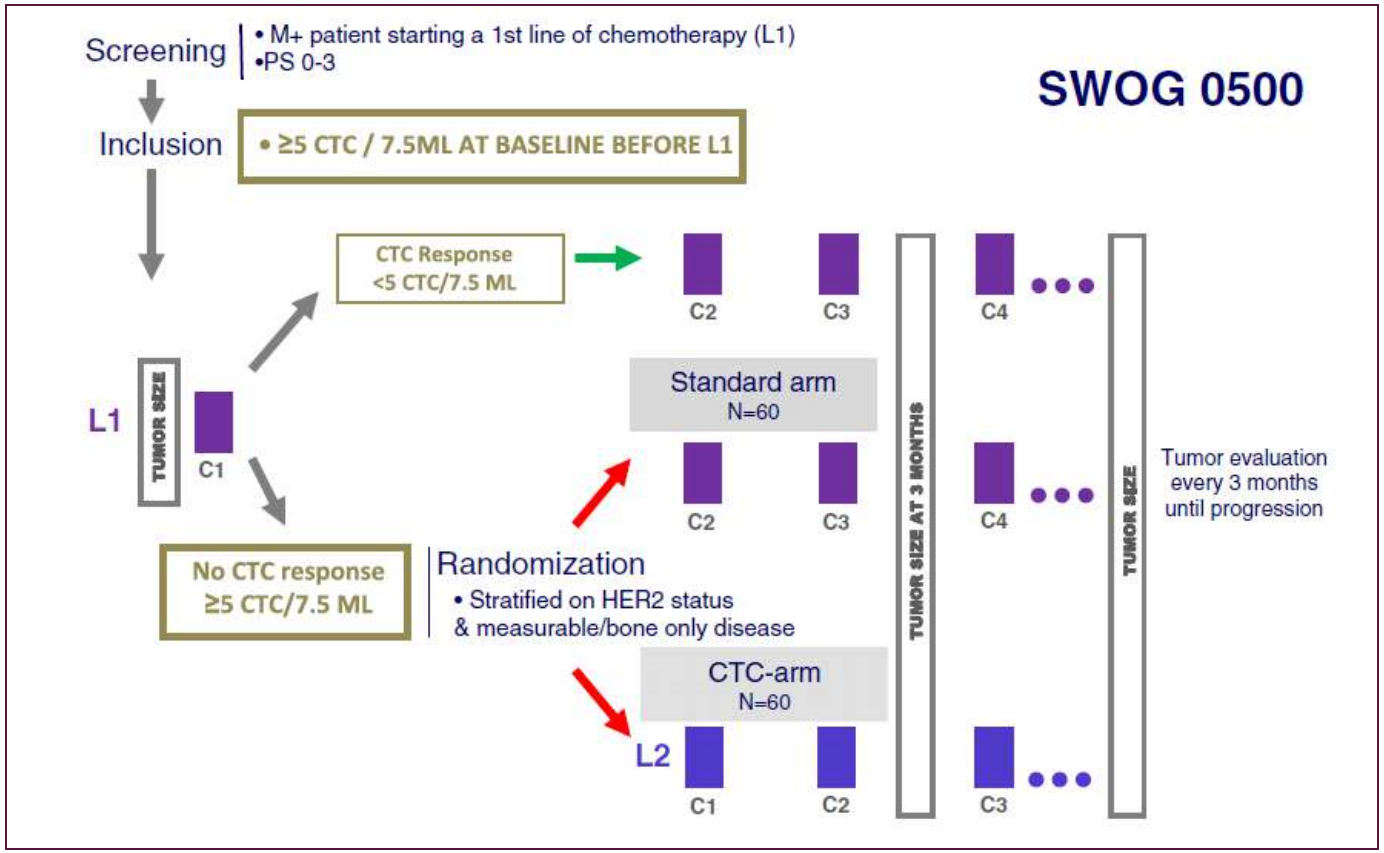
- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

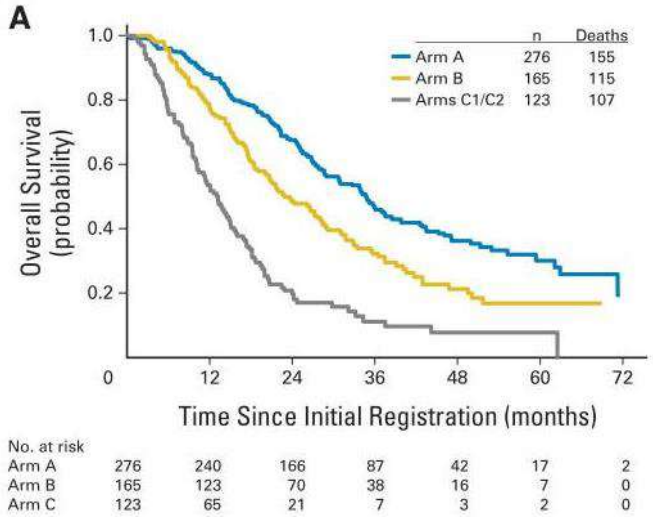
post-MONARCH: Fulvestrant + abemaciclib

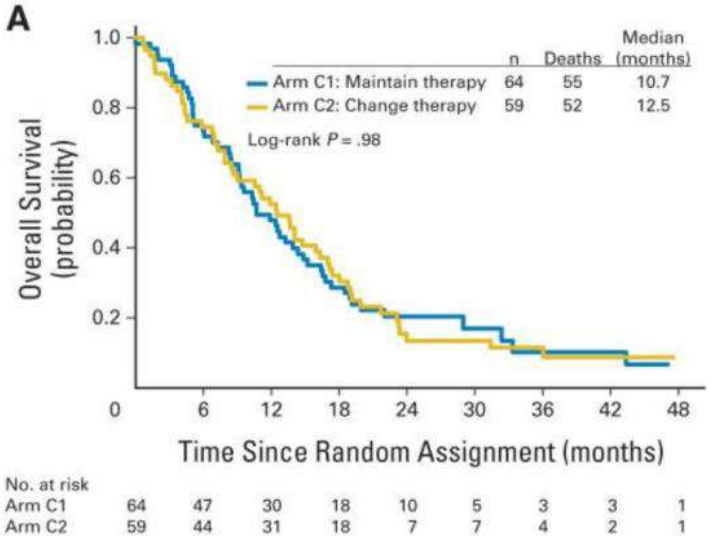
DB-06: T-DXd

EMBER-3: Imlunestrant (+ abemaciclib)

EARLY RESISTANCE DETECTION - HISTORY

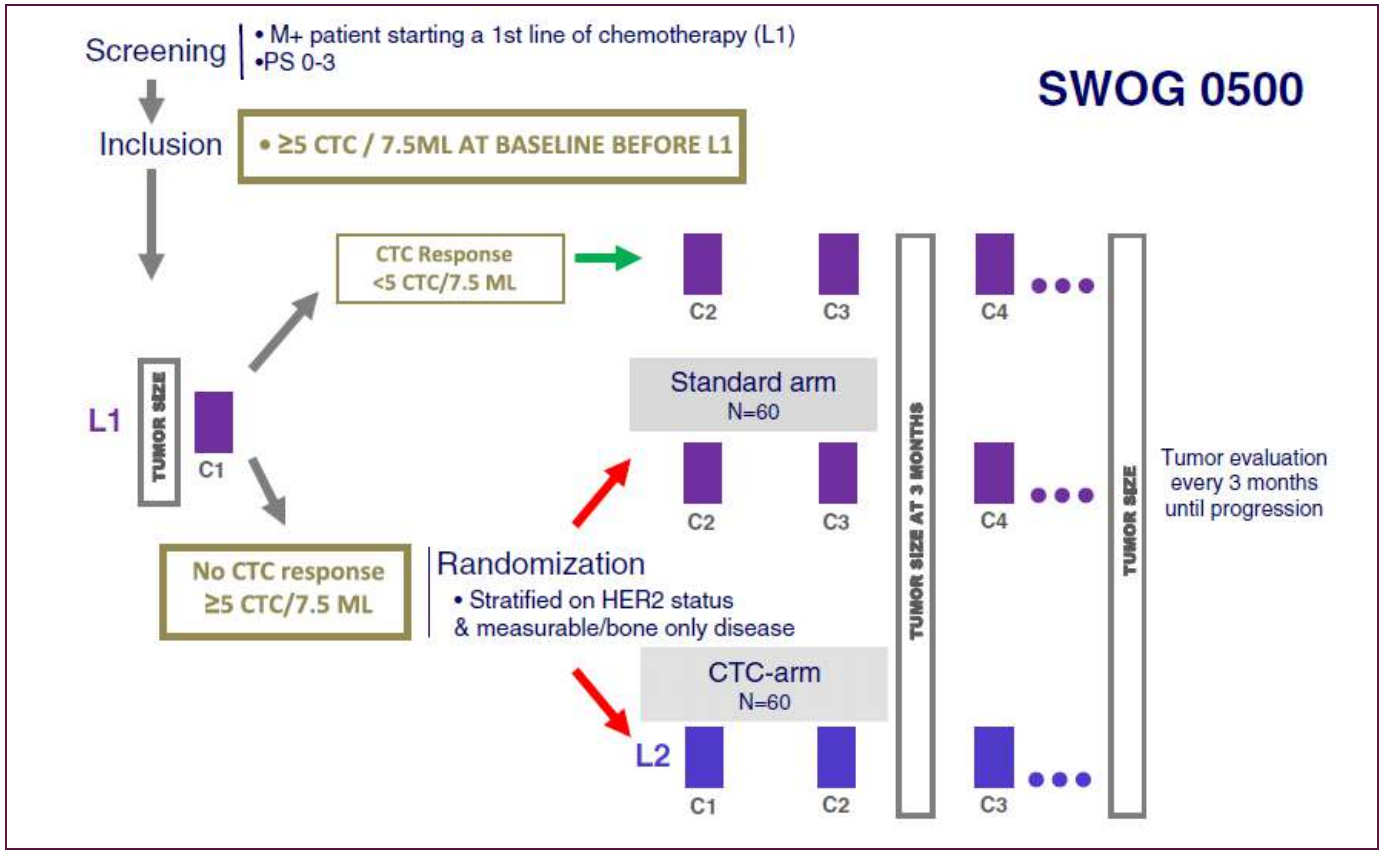


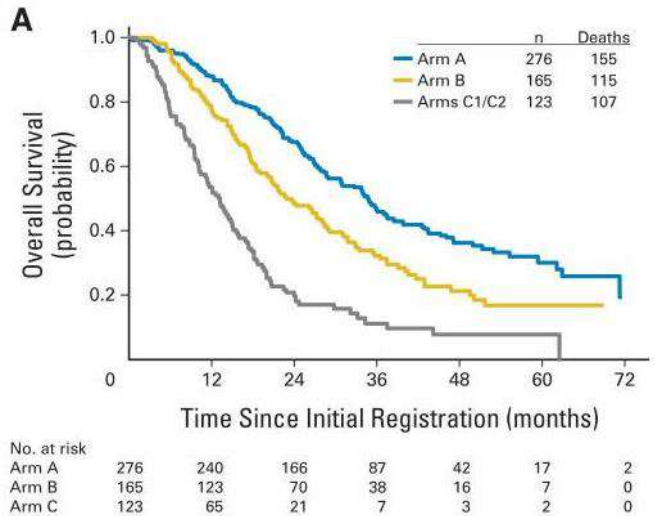


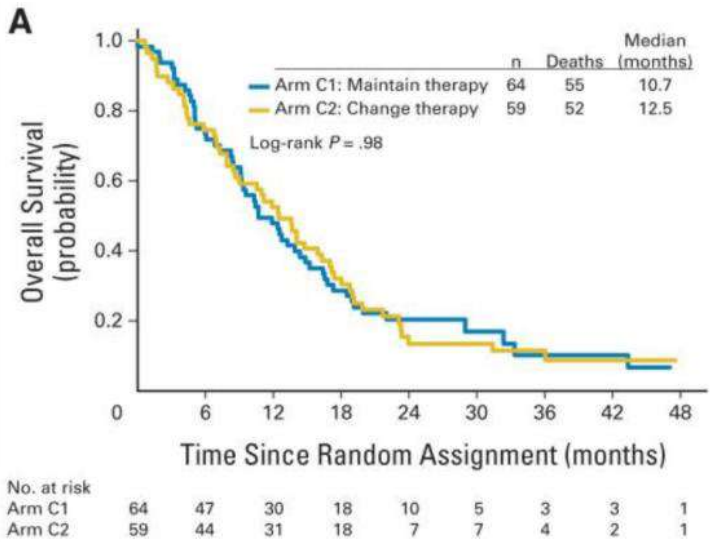


- Smerage JCO 2014

EARLY RESISTANCE DETECTION - HISTORY







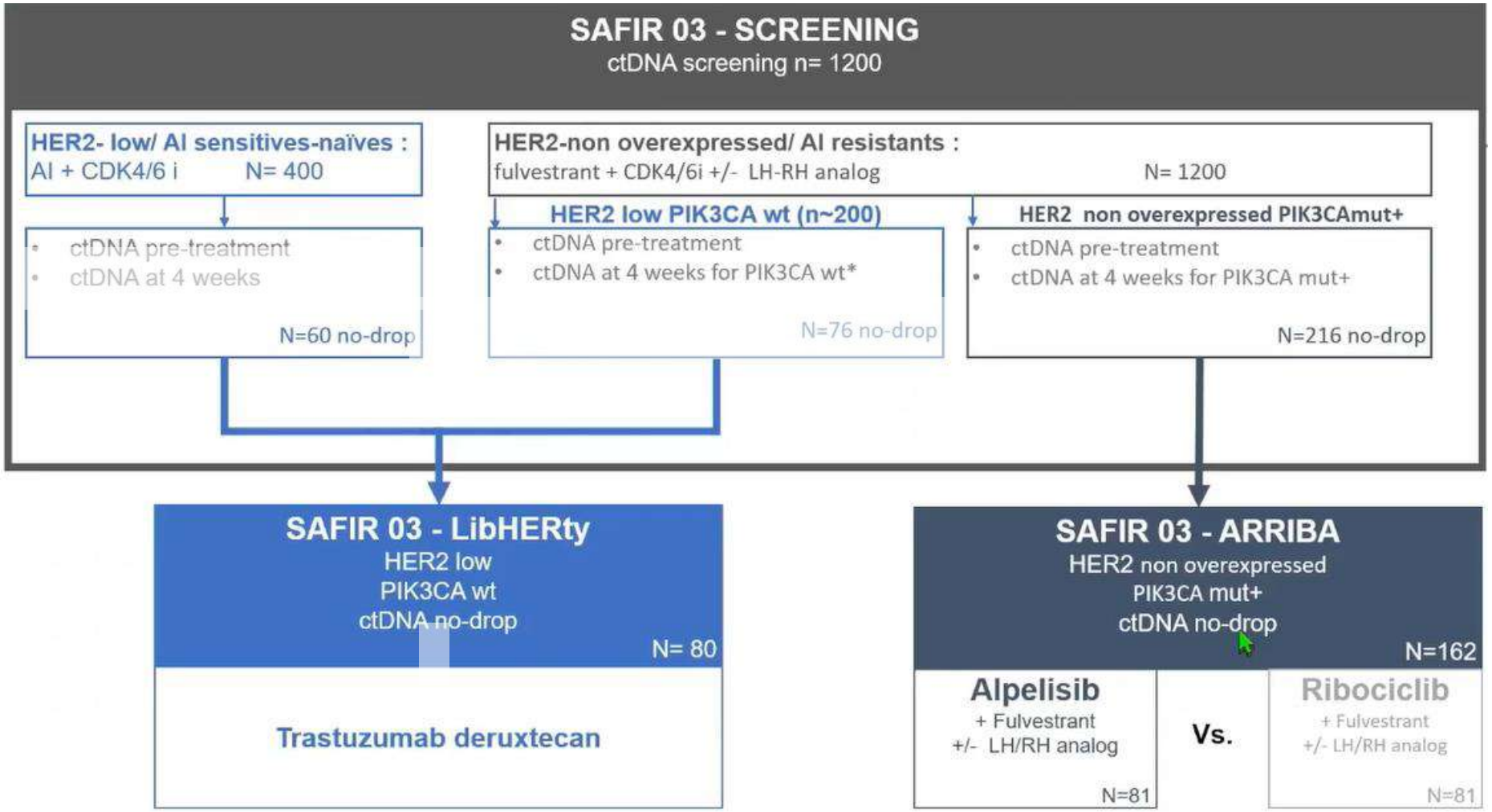
Failure to show clinical utility

- No change in mechanism of action (in a population selected to be chemoresistant)
- Short lead time between CTC assesment & standard CT

- Smerage JCO 2014

EARLY RESISTANCE DETECTION – SAFIR03

UCBG
unicancer
Personalized Medicine Group
unicancer

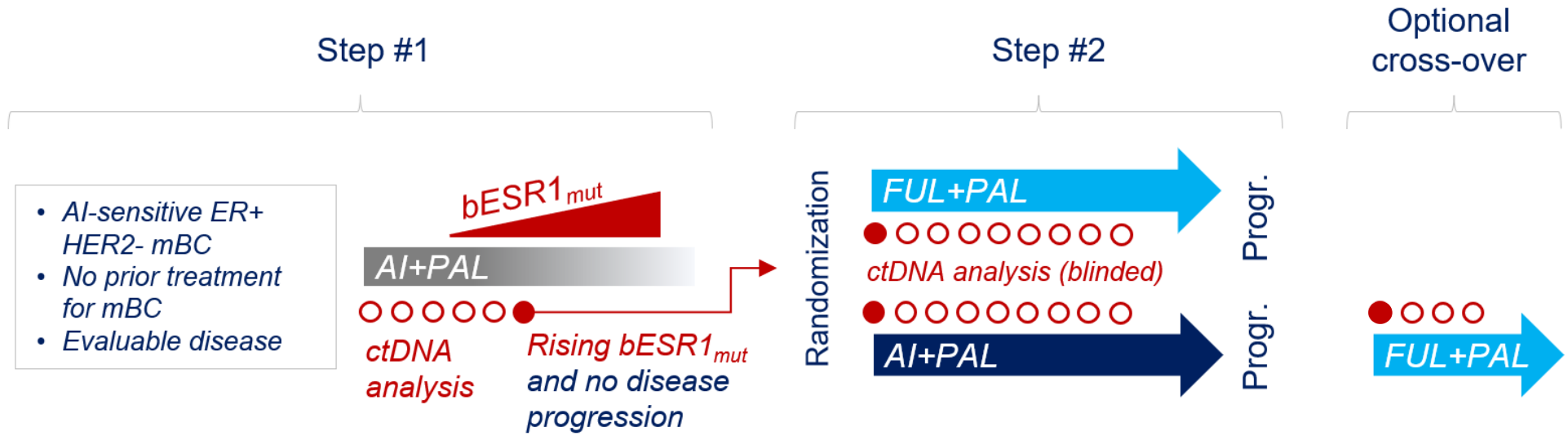


F André, ESMO breast 2024

LATE / ACQUIRED RESISTANCE – PADA-1

PADA-1

- Strategy: **to target rising *bESR1$_{mut}$* when they become detectable during 1L treatment with AI+Palbociclib (PAL)** [1]



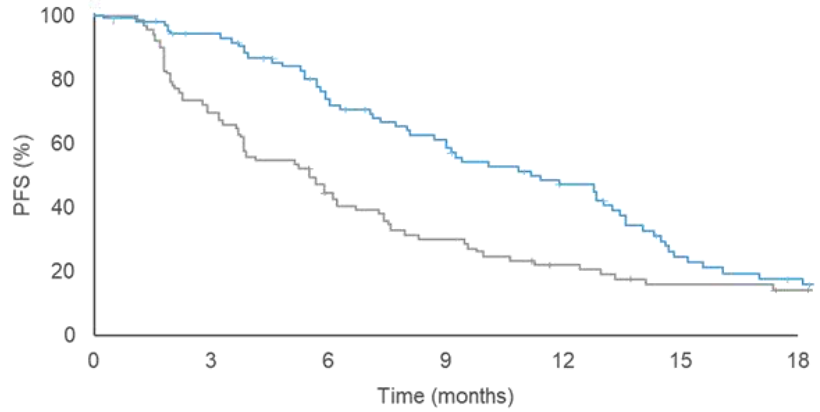
LATE / ACQUIRED RESISTANCE – PADA-1

Step 1
AI + palbociclib

Step 2
If *ESR1*m and no concomitant PD…

PFS1 From Randomization

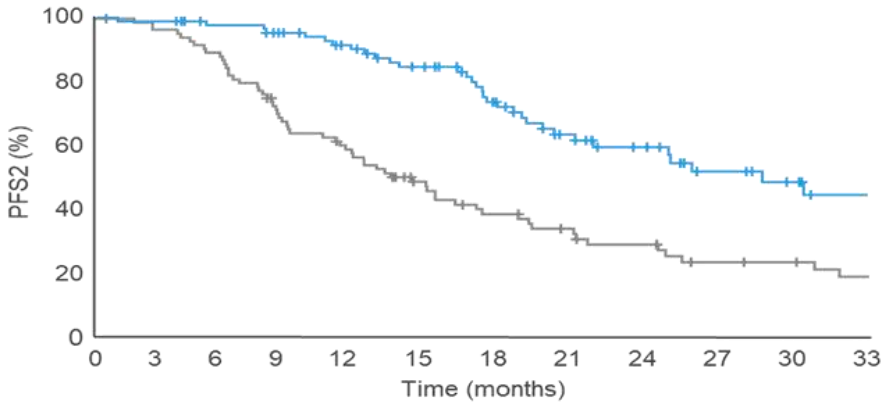
	FUL + PAL	AI + PAL
mPFS (95% CI), mo	12.8 (9.3, 14.7)	5.8 (3.9, 7.5)
Hazard ratio (95% CI)	**0.54** (0.38, 0.75)	



FC Bidard, Lancet Oncol 2022

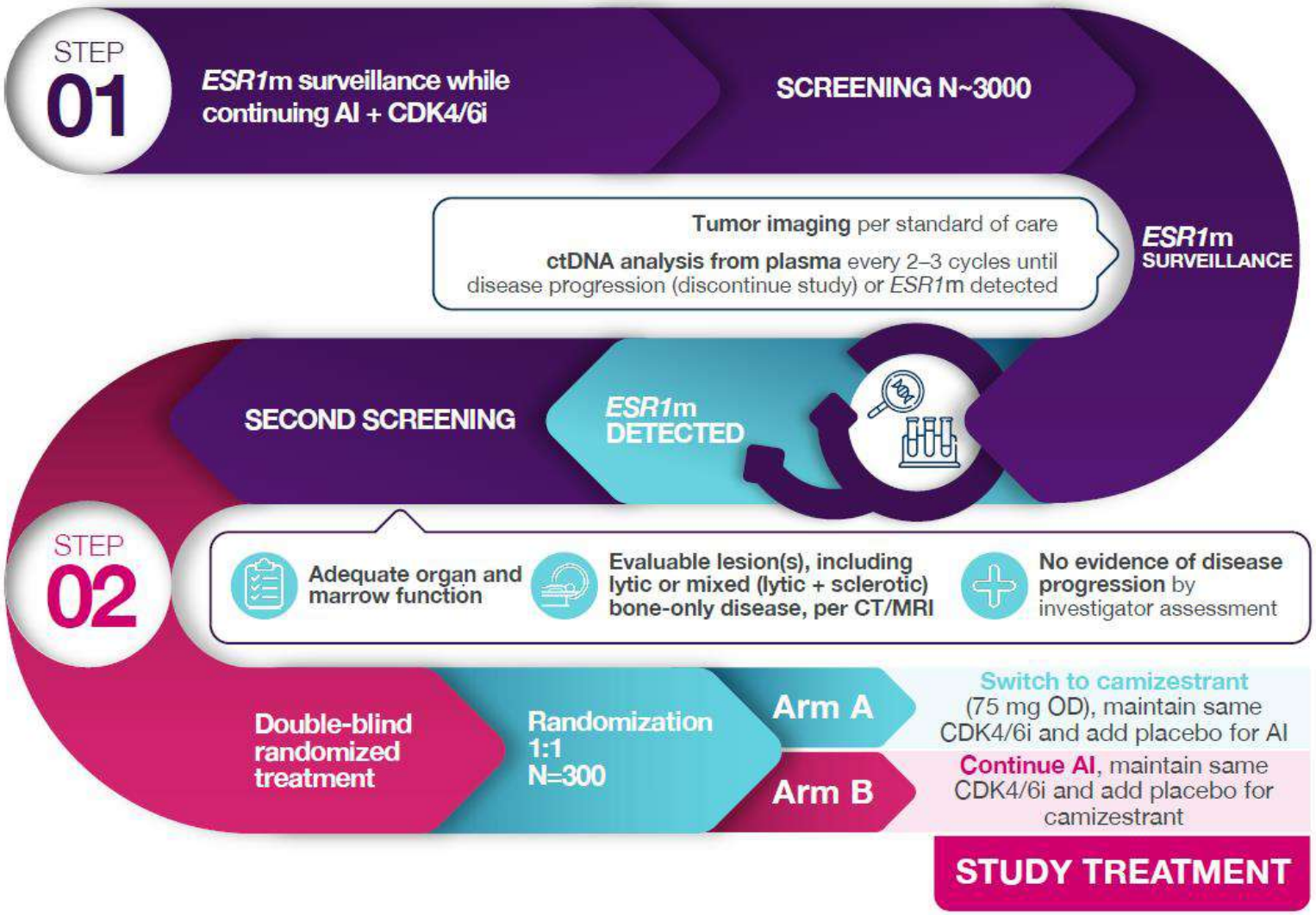
PFS2 From Randomization

	FUL + PAL	AI + PAL
mPFS2 (95% CI), mo	29.4 (21.9, NR)	14.0 (11.0, 18.6)
Hazard ratio (95% CI)	**0.37** (0.24, 0.56)	



FC Bidard, ASCO 2023

LATE / ACQUIRED RESISTANCE – SERENA-6



- Turner (…) Bidard, Future Oncol 2023

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Maximizing ET exposure / avoiding 1 PD event

Stay in !

Detecting & tackling secondary resistance

PADA-1 & SERENA-6

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

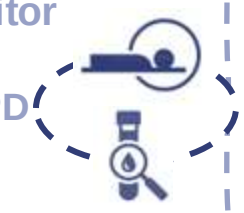
- post-MONARCH: Fulvestrant + abemaciclib
- DB-06: T-DXd
- EMBER-3: Imlunestrant + abemaciclib

TRIALS & CONCEPTS

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

PD



Finding the best of the two worlds

Biomarker workup for CT vs ET treatment decision

Current 2nd line options

- **PD** Fulvestrant single agent (mPFS ~2 mo, no OS gain)
- **PD** Elacestrant single agent (mPFS ~4mo, no OS gain)
- PIK3CA/AKTmut → **PD** Fulvestrant + PIK3CAi/AKTi (mPFS 6-7 mo, no OS gain)
- **PD** Fulvestrant/AI + mTORi (mPFS 6-7 mo, no OS gain)
- gBRCAmut → **PD** PARPi (mPFS 6-7 mo, no OS gain)
- **PD** 1st line chemo (mPFS 7-9 mo, no OS data)

- post-MONARCH: Fulvestrant + abemaciclib
- DB-06: T-DXd
- EMBER-3: Imlunestrant + abemaciclib

FLUORO-ESTRADIOL PET/CT

- FDA cleared for clinical use

"for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or mBC."

- EMA cleared / Approved for reimbursement in France

"in patients with initially ER+ mBC with early relapse after endocrine therapy, when biopsy is deemed impossible and hormone therapy is an option".

- Performances investigated since >15 years - now marketed by GE Healthcare

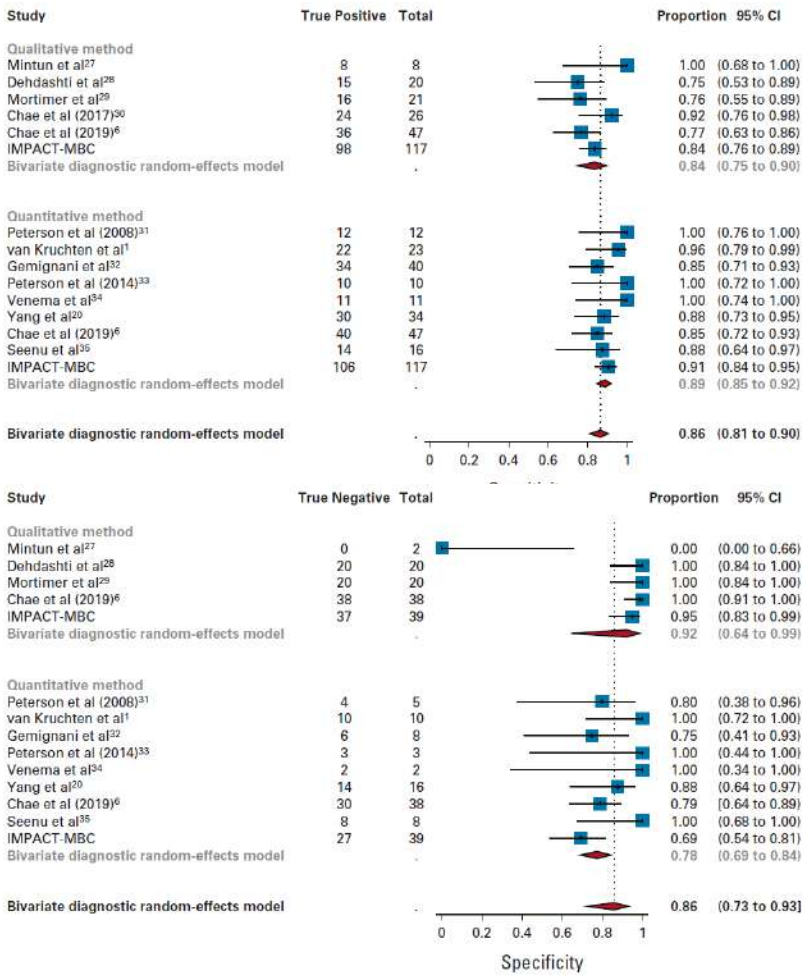
FLUORO-ESTRADIOL PET/CT

original reports

Clinical Validity of 16α-[18F] Fluoro-17β-Estradiol Positron Emission Tomography/Computed Tomography to Assess Estrogen Receptor Status in Newly Diagnosed Metastatic Breast Cancer

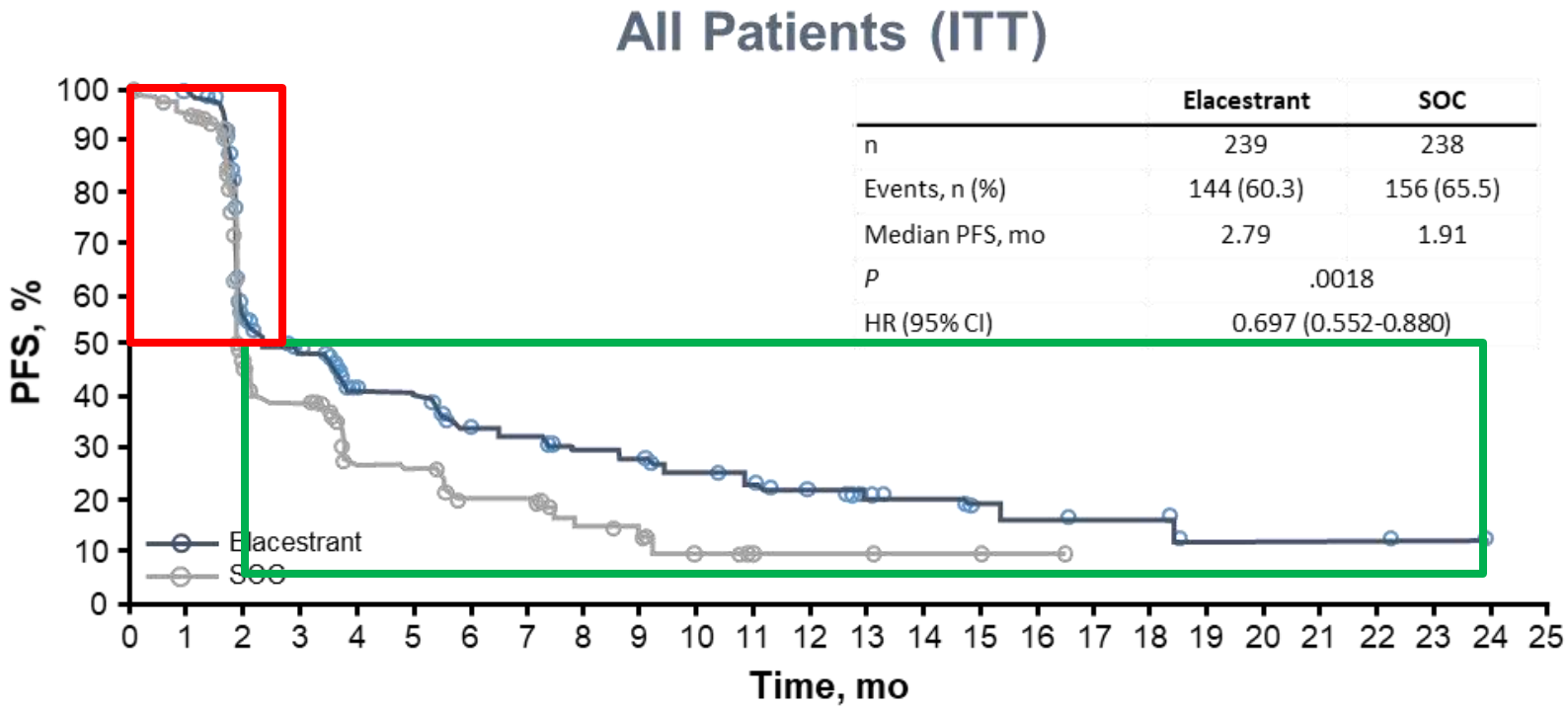
Jasper J.L. van Geel, MD[1]; Jorianne Boers, MD[1]; Sjoerd G. Elias, MD, PhD[2]; Andor W.J.M. Glaudemans, MD, PhD[3]; Erik F.J. de Vries, PhD[3]; Geke A.P. Hospers, MD, PhD[1]; Michel van Kruchten, MD, PhD[1]; Evelien J.M. Kuip, MD, PhD[4]; Agnes Jager, MD, PhD[5]; Willemien C. Menke-van der Houven van Oordt, MD, PhD[6]; Bert van der Vegt, MD, PhD[7]; Elisabeth G.E. de Vries, MD, PhD[1]; and Carolina P. Schröder, MD, PhD[6] on behalf of the IMPACT-Metastatic Breast Consortium

	Participants (n = 181)	
	ER IHC Status of the Biopsied Lesion	
Result	**Positive (n = 132)**	**Negative (n = 49)**
Whole-body [18F]FES-PET result		
Positive (n = 135)	125	10
Negative (n = 46)	7	39
Sensitivity	95 (89 to 97)	
Specificity	80 (66 to 89)	
PPV	93 (87 to 96)	
NPV	85 (72 to 92)	



➔ should detect accurately the ~**15-20%** of mBC pts with **ER loss** at time of progression

POST-CDK4/6I, SINGLE AGENT ENDOCRINE T.: EMERALD



	Elacestrant	SOC
n	239	238
Events, n (%)	144 (60.3)	156 (65.5)
Median PFS, mo	2.79	1.91
P	.0018	
HR (95% CI)	0.697 (0.552-0.880)	

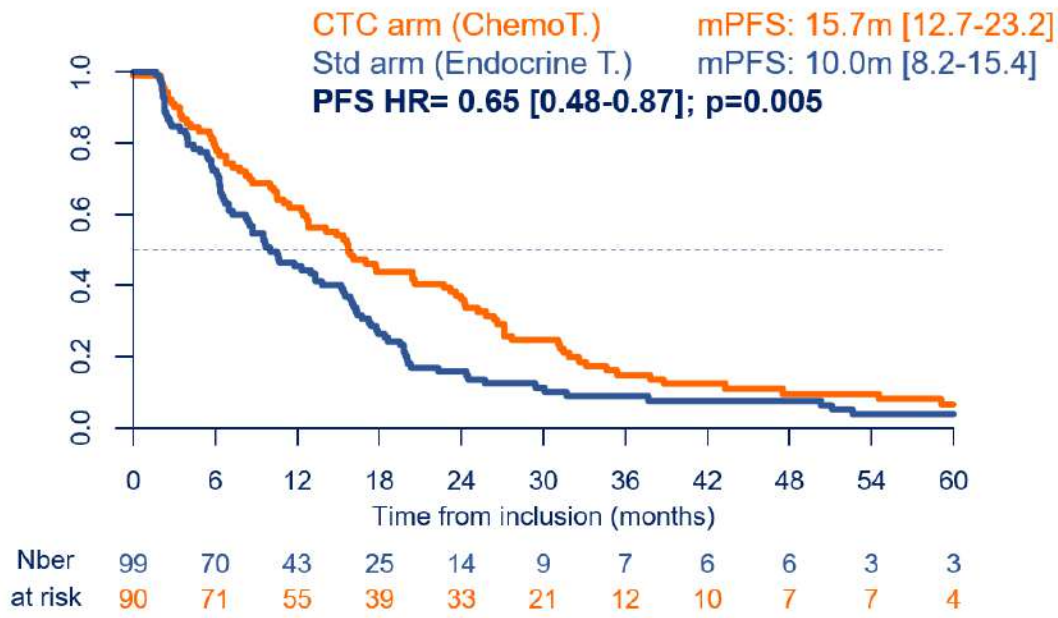
Bidard FC, *et al,* J Clin Oncol, 2022

CIRCULATING TUMOR CELLS – STIC TRIAL

In patients eligible to 1st line endocrine therapy (by investigator) AND a high CTC count

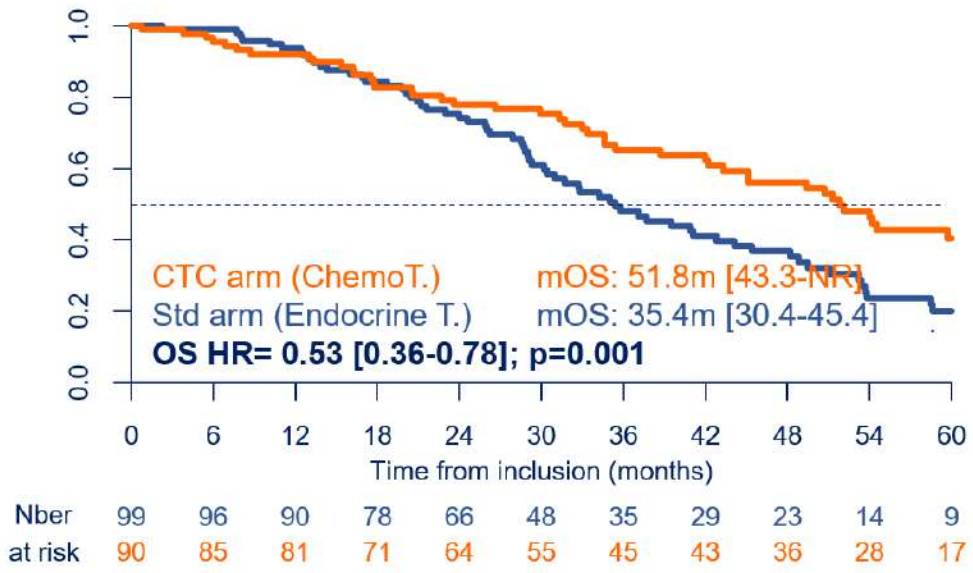
Both PFS and OS were very significantly improved when randomized to chemotherapy

Progression-Free Survival



Bidard FC, *et al,* JAMA Oncol, 2021

Overall Survival



Bidard FC, *et al,* J Clin Oncol, 2023

ECLECTIC

- **N=300** ER+ HER2- mBC pts
- Received AI+CDK4/6i for >6 months
- No prior chemotherapy for mBC
- No visceral crisis
- Eligible for 2nd line endocrine therapy

NCT06195709

Bidard FC *et al.*, TiP ASCO 2024

institut Curie

ECLECTIC

NCT06195709

Bidard FC *et al.*, TiP ASCO 2024

- **N=300** ER+ HER2- mBC pts
- Received AI+CDK4/6i for >6 months
- No prior chemotherapy for mBC
- No visceral crisis
- Eligible for 2nd line endocrine therapy

Biomarker workup

Predictive
^{18}F-FES PET/CT

High FES uptake
- in **all** tumor sites
- in **most** tumor sites & sites with low FES uptake amenable to local therapy

Low FES uptake
- in ≥3 tumor sites
- not amenable to local therapy

ECLECTIC

NCT06195709

Bidard FC *et al.*, TiP ASCO 2024

- **N=300** ER+ HER2- mBC pts
- Received AI+CDK4/6i for >6 months
- No prior chemotherapy for mBC
- No visceral crisis
- Eligible for 2nd line endocrine therapy

Biomarker workup

Predictive
^{18}F-FES PET/CT

Prognostic
CTC count
+ ctDNA banking

High FES uptake
- in **all** tumor sites
- in **most** tumor sites & sites with low FES uptake amenable to local therapy

AND

Low CTC count
<5 CTC/7.5mL

Low FES uptake
- in ≥3 tumor sites
- not amenable to local therapy

AND /OR

High CTC count
≥5 CTC/7.5mL

ECLECTIC

NCT06195709

Bidard FC *et al.*, TiP ASCO 2024

- **N=300** ER+ HER2- mBC pts
- Received AI+CDK4/6i for >6 months
- No prior chemotherapy for mBC
- No visceral crisis
- Eligible for 2nd line endocrine therapy

Biomarker workup

Predictive
^{18}F-FES PET/CT

Prognostic
CTC count *+ ctDNA banking*

High FES uptake
- in **all** tumor sites
- in **most** tumor sites & sites with low FES uptake amenable to local therapy

AND

Low CTC count
<5 CTC/7.5mL

Low FES uptake
- in ≥3 tumor sites
- not amenable to local therapy

AND /OR

High CTC count
≥5 CTC/7.5mL

Allocated type of therapy

Arm A (N=142)

2nd line **ET** (SoC, physician choice)

+/- local treatment of sites with low FES SUV

ECLECTIC

NCT06195709

Bidard FC *et al.*, TiP ASCO 2024

institut Curie

- **N=300** ER+ HER2- mBC pts
- Received AI+CDK4/6i for >6 months
- No prior chemotherapy for mBC
- No visceral crisis
- Eligible for 2nd line endocrine therapy

Biomarker workup

Predictive
^{18}F-FES PET/CT

Prognostic
CTC count
+ ctDNA banking

High FES uptake
- in **all** tumor sites
- in **most** tumor sites & sites with low FES uptake amenable to local therapy

AND

Low CTC count
<5 CTC/7.5mL

Low FES uptake
- in ≥3 tumor sites
- not amenable to local therapy

AND /OR

High CTC count
≥5 CTC/7.5mL

Allocated type of therapy

R

Arm A (N=142)
2nd line **ET** (SoC, physician choice)
+/- local treatment of sites with low FES SUV

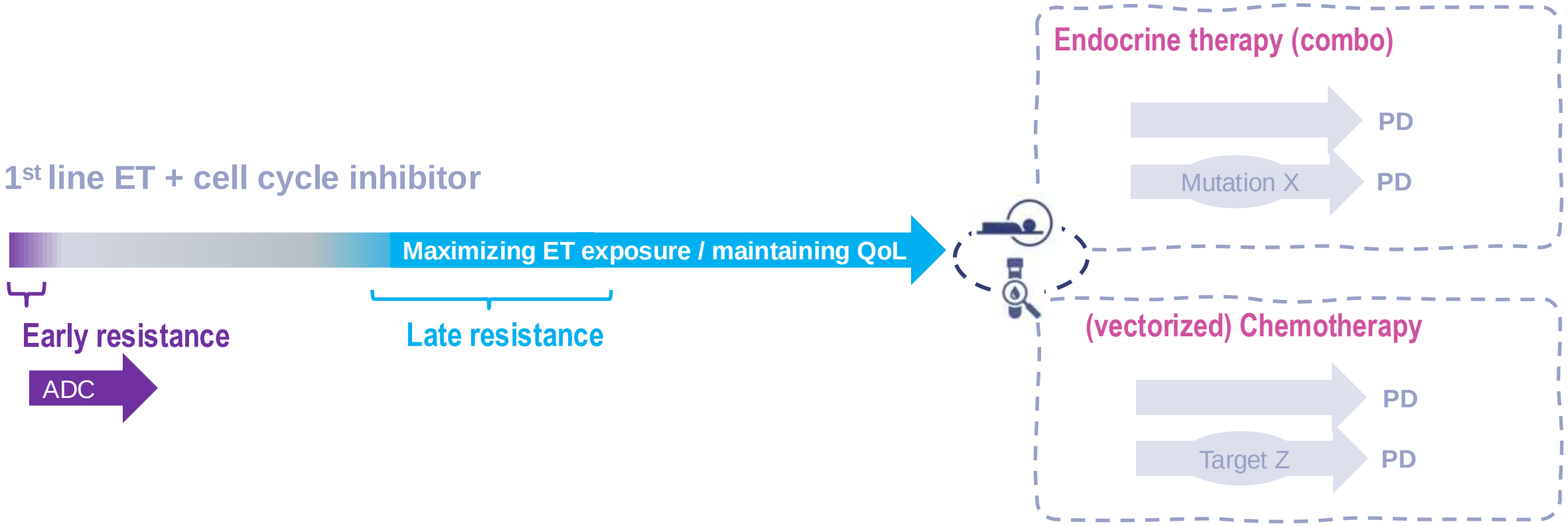
Arm B (N=79)
1st line **CT/ADC** (SoC, phys. choice)

Arm C (N=79)
2nd line **ET** (SoC, physician choice)

Iry endpoint:
- PFS (arm B vs C)

IIry endpoints:
- PFS (arm A)
- OS, ORR, DCR, CBR
- Toxicity
- QoL

WHAT (A CLOSE) FUTURE MIGHT LOOK LIKE ?



Thank you !

Questions/collaborations:
francois-clement.bidard@curie.fr

ESMO DEEP DIVE:
BREAST CANCER

WHAT TO DO WITH ENDOCRINE REFRACTORY PATIENTS? CURRENT CONCEPTS AND ONGOING RESEARCH

Alessandra Gennari, MD PhD

Dept of Traslational Medicine - University of Piemonte Orientale

Head, Division of Oncology - Maggiore University Hospital, Novara, Italy

ESMO WEBINAR SERIES

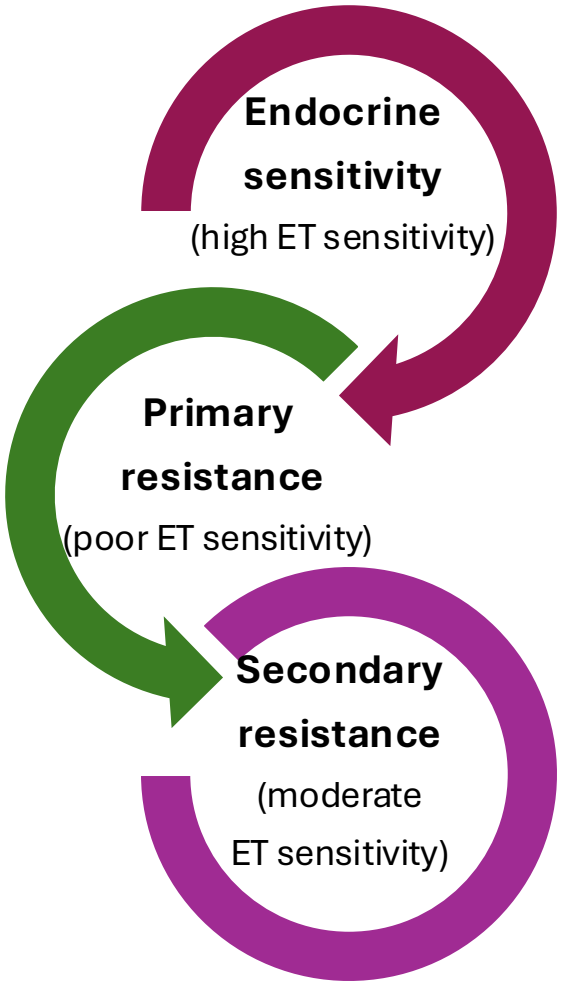
DECLARATION OF INTERESTS

- Consultancy/advisory role/speaker bureau: Astra Zeneca, Daichii-Sankyo, Eisai, Exact Sciences, Gentili, Gilead, MSD, Pfizer, Novartis, Organon, Seagen, Lilly, Roche

- Non profit research support: AIRC, Italian Association for Cancer Research, MIUR Dept of Excellence, LILT Novara, University of Piemonte Orientale, Italian Ministry of Health, EraNET Transcan

- Scientific Board in IBCSG; Membership/affiliation: LILT

DEFINITION OF ENDOCRINE SENSITIVITY/RESISTANCE



Relapse at least 12 months after the completion of adjuvant endocrine therapy or patients not treated for advanced disease

Relapse within 24 months while the patient was receiving adjuvant endocrine therapy or progression within 6 months while the patient was receiving endocrine therapy for advanced disease

Relapse after at least 24 months of adjuvant endocrine therapy and within 12 months after ending adjuvant endocrine therapy, or progression after at least 6 months of endocrine therapy for advanced disease

Cardoso F, et al. Ann Oncol 2018

6TH AND 7TH INTERNATIONAL CONSENSUS GUIDELINES FOR THE MANAGEMENT OF ADVANCED BREAST CANCER (ABC GUIDELINES 6 AND 7)

Endocrine sensitivity/resistance **ET NAÏVE**: unknown if there is sensitivity or resistance to endocrine therapy (ET) since has never received ET. **PRIMARY ENDOCRINE RESISTANCE** is defined as: Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET-based therapy for ABC (note: this definition is the same regardless of whether therapy included a CDK4/6i or not). **SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE** is defined as: All other clinical situations of endocrine-resistance. Examples include: 1) Relapse while receiving adjuvant ET but after at least 2 years; 2) PD after at least 6 months of 1st line ET-based therapy for ABC; 3) PD after any duration of 2nd+ line ET-based therapy for ABC; 4) Known *ESR1* mutation (note: definition unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs) **ENDOCRINE INSENSITIVITY** is defined as: PD within 2 months of later-line ET-based therapy for ABC and no additional ET-based approaches likely to result in clinically meaningful benefit.	Expert opinion/NA	95%

F Cardoso et al, The Breast 2024

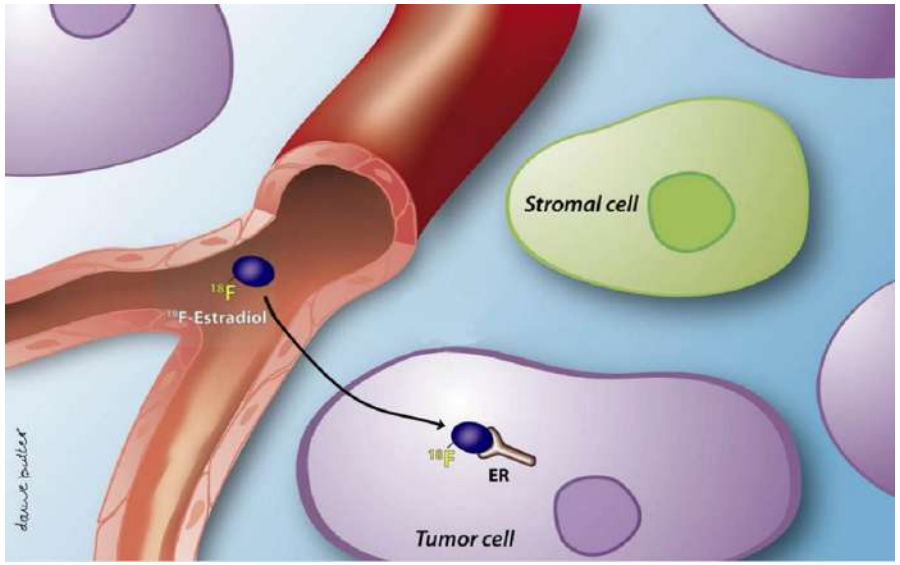
RESISTANCE TO ENDOCRINE THERAPY CAN BE CLASSIFIED BY CLINICAL AND MOLECULAR VARIABLES

Clinical	**Primary**[1–3] **Disease progression within the first 6 months of first-line ET** for aBC	**Secondary**[1–3] **Disease progression ≥6 months after initiating ET** for aBC
Molecular	***De novo***[4,5] Alterations of the **PI3K/AKT/mTOR, RAS-MAPK, FGFR1** pathways, or **RB1** loss, **TP53** activation, etc.	**Acquired**[5] Mechanisms of resistance **occurring after prior endocrine therapy in aBC**

1. Gennari A, et al. Ann Oncol. 2021;12:1475–1495; 2. Rasha F, et al. Mol Cell Endocrinol. 2021;532:111322; 3. Patel R, et al. NPJ Breast Cancer. 2023;9:20; 4. Rani A, et al. Front Endocrinol (Lausanne) 2019;10:245; 5. Xu P, et al. Acta Pharmacol Sin 2021;42:171–178; 6. Brett JO, Breast Cancer Res. 2021;23(1):85

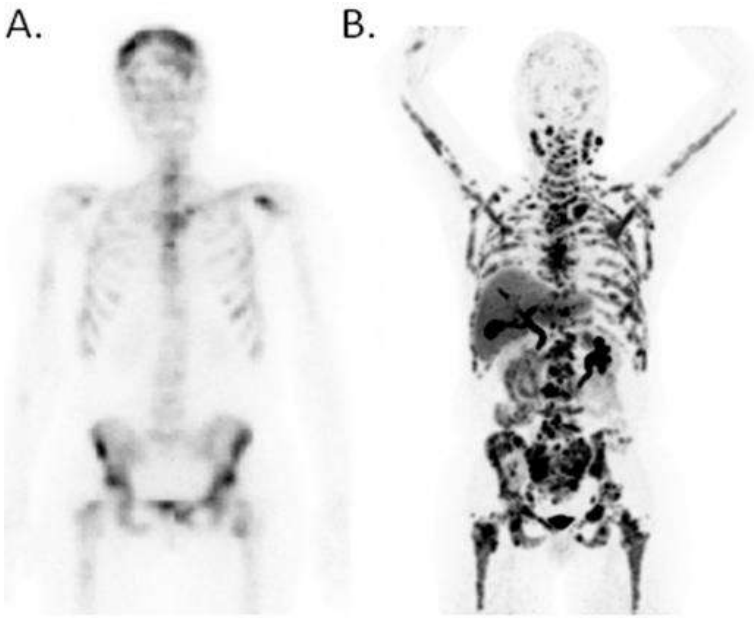
18F-FES PET/CT

- 18F-fluoroestradiol Positron Emission Tomography (18F-FES PET/CT), have been proposed as whole-body imaging to assess overall ER expression at different metastatic sites.
- PET technology combined with CT scans is a potent approach for determining the stage of breast cancer and its response to treatment.
- Retrospective evidence suggests a link between 18F-FES PET/CT uptake (SUV) and the presence and performance of ER in BC tissues.



- 18F-FES PET/CT has been recommended as a predictive diagnostic marker of endocrine sensitivity in patients treated with endocrine therapy.
- Approved by FDA in 2023

FES-PET IDENTIFIES ER+ LESIONS



Bonescan FES-PET

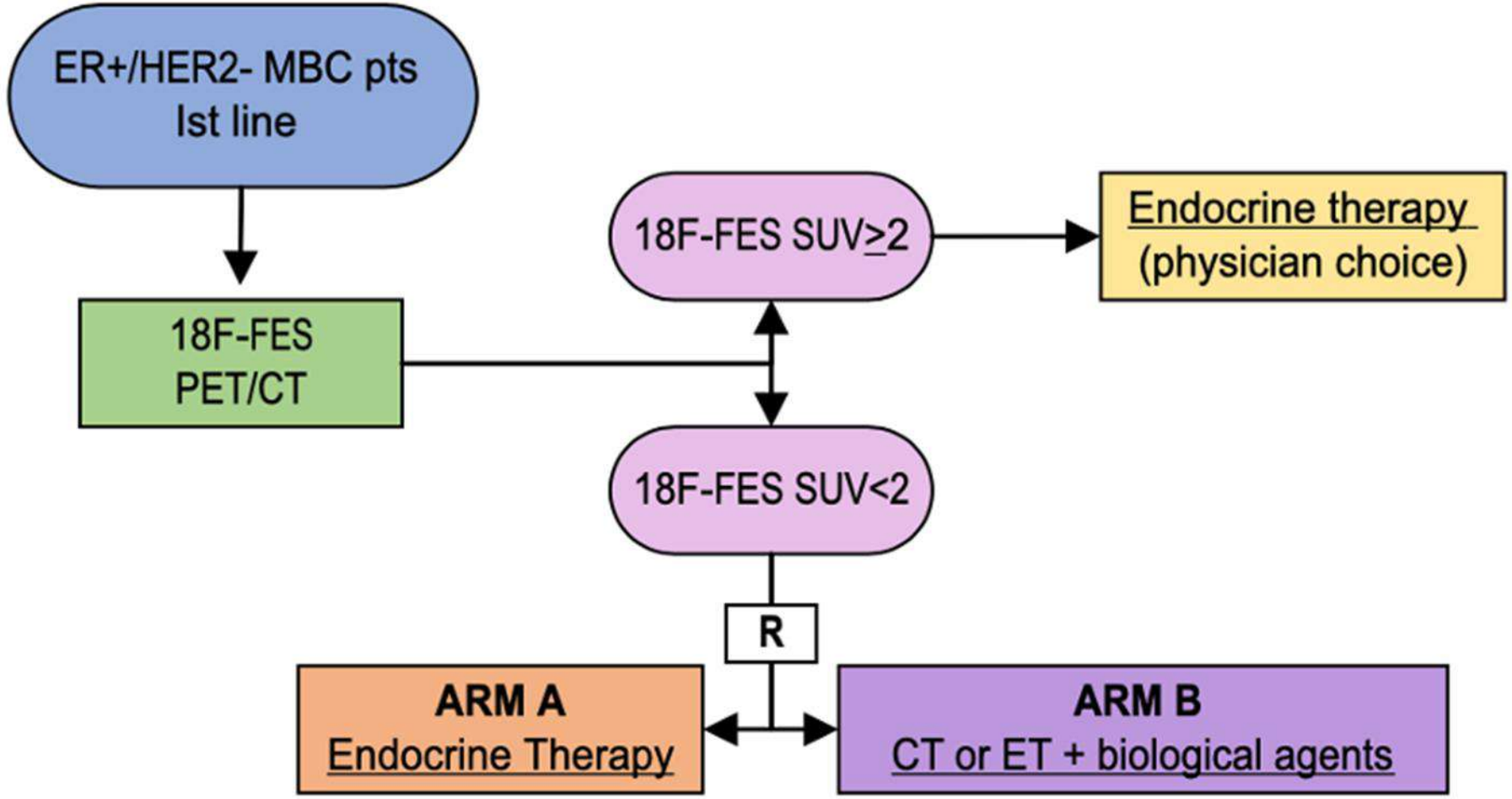
- FES uptake related to ER expression

  in MBC pts with ER+ primary (n=33):
  - more lesions (n=398) than on conventional imaging (n=319)
  - change in therapy (48%)

Van Kruchten et al, Lancet Oncol 2013

ET-FES TRIAL DESIGN

ERA-NET TRANSCAN JTC 2011



A Gennari et al, Ann Oncol 2024

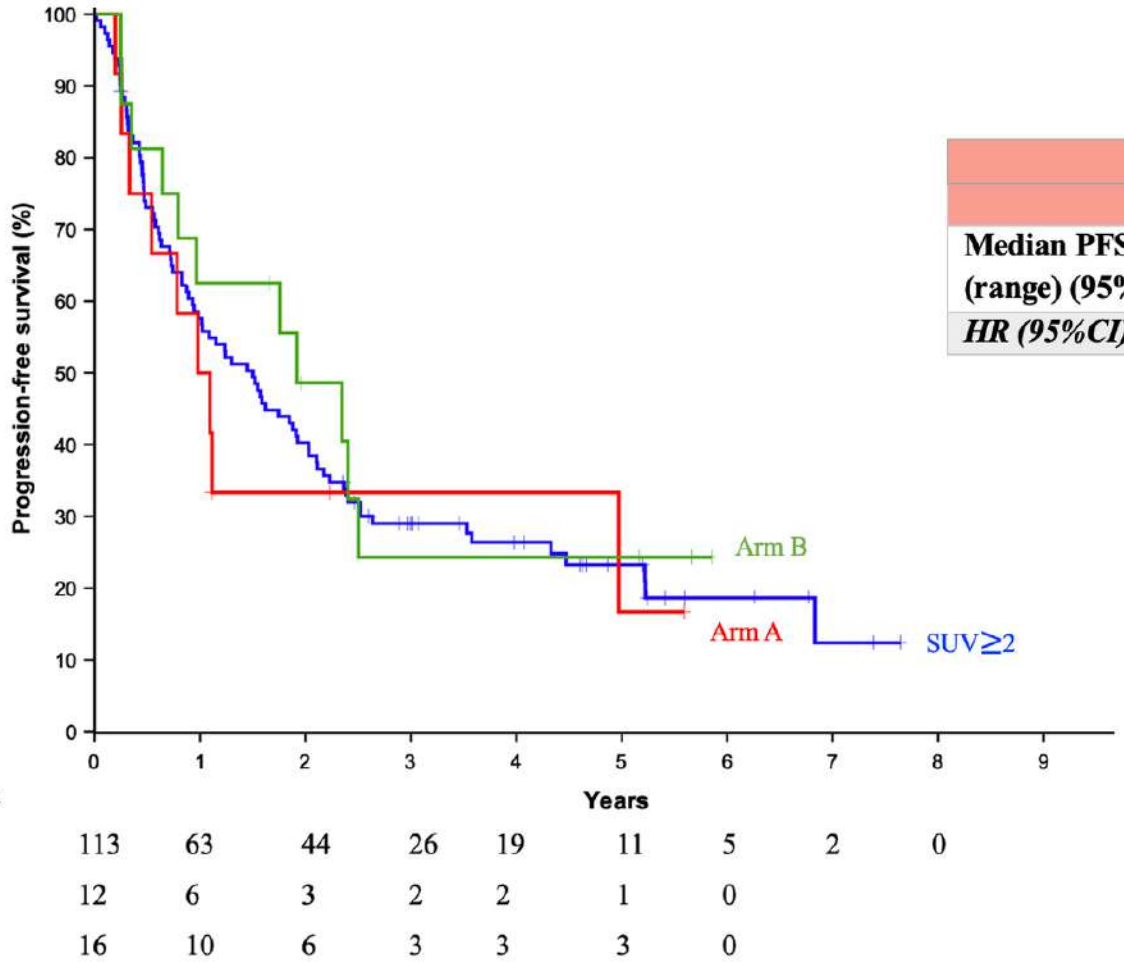
RESULTS

Table 3. Characteristics of the patients at baseline

Patients characteristics	Registered (n=113)	ARM A (n=13)	ARM B (n=16)	Total (n=142)
Median age (range) – yrs	66 (36-90)	60 (38-79)	62 (38-87)	65 (36-90)
Menopausal status – no. (%)				
Pre/peri-menopausal	14 (12.4)	2 (15.4)	5 (31.3)	21 (14.8)
Post-menopausal	98 (86.7)	11 (84.6)	11 (68.8)	120 (84.5)
ECOG Performance Status – no. (%)				
0	89 (78.8)	10 (76.9)	14 (87.5)	113 (79.6)
1	24 (21.2)	3 (23.1)	2 (12.5)	29 (20.4)
Hormone receptors status – no. (%)				
ER > 50%	100 (88.5)	13 (100.0)	15 (93.7)	128 (90.1)
Disease-free interval – no. (%)				
DFI ≤24 mos	11 (9.7)	1 (7.7)	1 (6.3)	13 (9.2)
DFI > 24 mos	75 (66.4)	9 (69.2)	14 (87.5)	98 (69.0)
Metastatic ab initio	27 (23.9)	3 (23.1)	1 (6.2)	31 (21.8)
Previous treatment – no. (%)				
Prior Neoadjuvant/Adiuvant CT	68 (60.2)	9 (69.2)	11 (68.8)	88 (62.0)
Prior adjuvant ET	78 (69.0)	8 (61.5)	13 (81.3)	99 (69.7)
Site of metastases – no. (%)				
Bone only	41 (36.3)	4 (30.8)	5 (31.3)	50 (35.2)
Bone + other	31 (27.4)	3 (23.1)	0 (0.0)	34 (23.9)
Visceral any	38 (33.6)	5 (38.5)	6 (37.5)	49 (34.5)
Soft tissue any	37 (32.7)	5 (38.5)	6 (37.5)	48 (33.8)
Other	8 (7.1)	1 (7.7)	1 (6.3)	10 (7.0)

A Gennari et al, Ann Oncol 2024

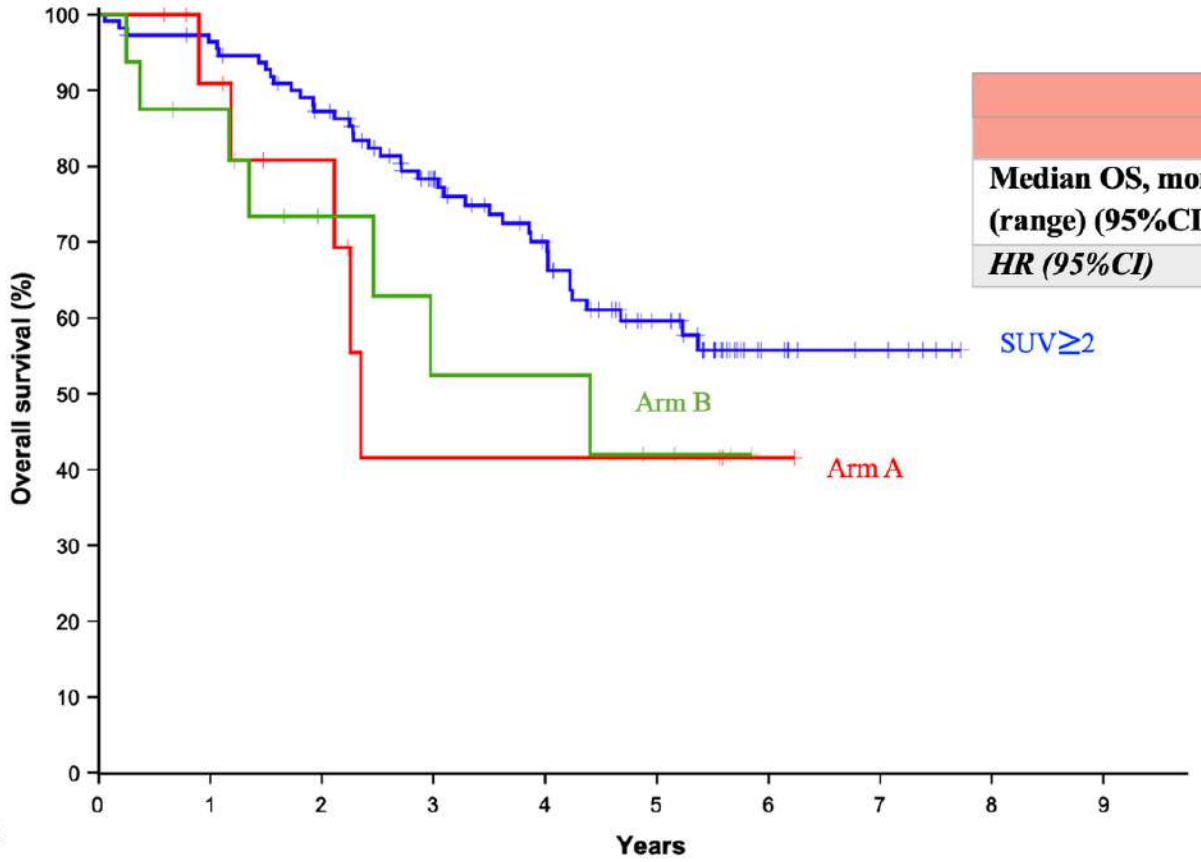
PROGRESSION FREE SURVIVAL



		18F-FES SUV<2	
	18F-FES SUV≥2	Arm A	Arm B
Median PFS, months (range) (95%CI)	18.0 (11.2-23.1)	12.4 (3.1-59.6)	23.0 (7.7-30.0)
HR (95%CI)		0.71 (0.29-1.72)	

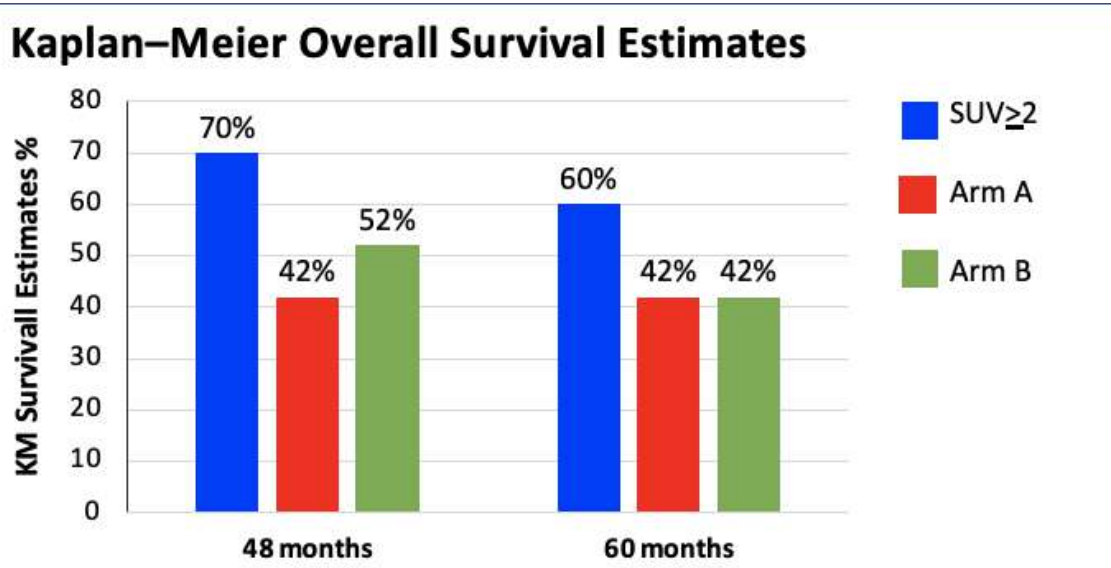
A Gennari et al, Ann Oncol 2024

OVERALL SURVIVAL



		18F-FES SUV<2	
	18F-FES SUV≥2	Arm A	Arm B
Median OS, months (range) (95%CI)	*Not reached*	*28.2 (14.2-NE)*	*52.8 (16.2-NE)*
HR (95%CI)		*0.97 (0.31-3.09)*	

No. at risk									
SUV≥2	113	106	93	71	56	37	11	6	0
Arm A	13	10	7	3	3	3	1	0	
Arm B	16	13	7	5	5	3	0		

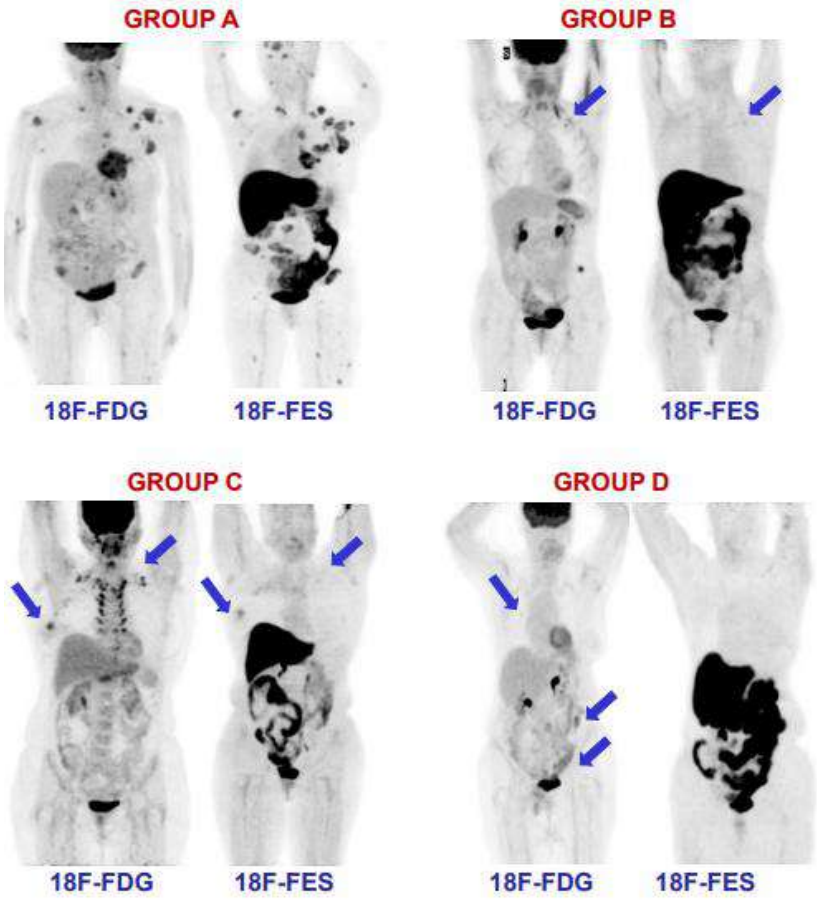


A Gennari et al, Ann Oncol 2024

HETEROGENEITY BETWEEN 18F-FES AND 18F-FDG IN ET-FES STUDY

PTS INCLUDED IN THE ANALYSIS	N° Pts	%
Group A 18F-FES & 18F-FDG ALL LESIONS 18F-FES POSITIVE	53/79	67.1%
Group B 18F-FES & 18F-FDG 50% OF LESIONS 18F-FES POSITIVE	11/79	13.9%
Group C 18F-FES & 18F-FDG 25% OF LESIONS 18F-FES POSITIVE	5/79	6.3%
Group D 18F-FES & 18F-FDG ALL LESIONS 18F-FES NEGATIVE	10/79	12.7%

Overall, 26/79 (33%) patients, with ER+ MBC had heterogeneous 18F-FES SUV uptake



The use of ET in discordant cases (B/C/D) was associated with a 79% increase in the risk of PD

A Gennari et al, presented at ESMO 2017

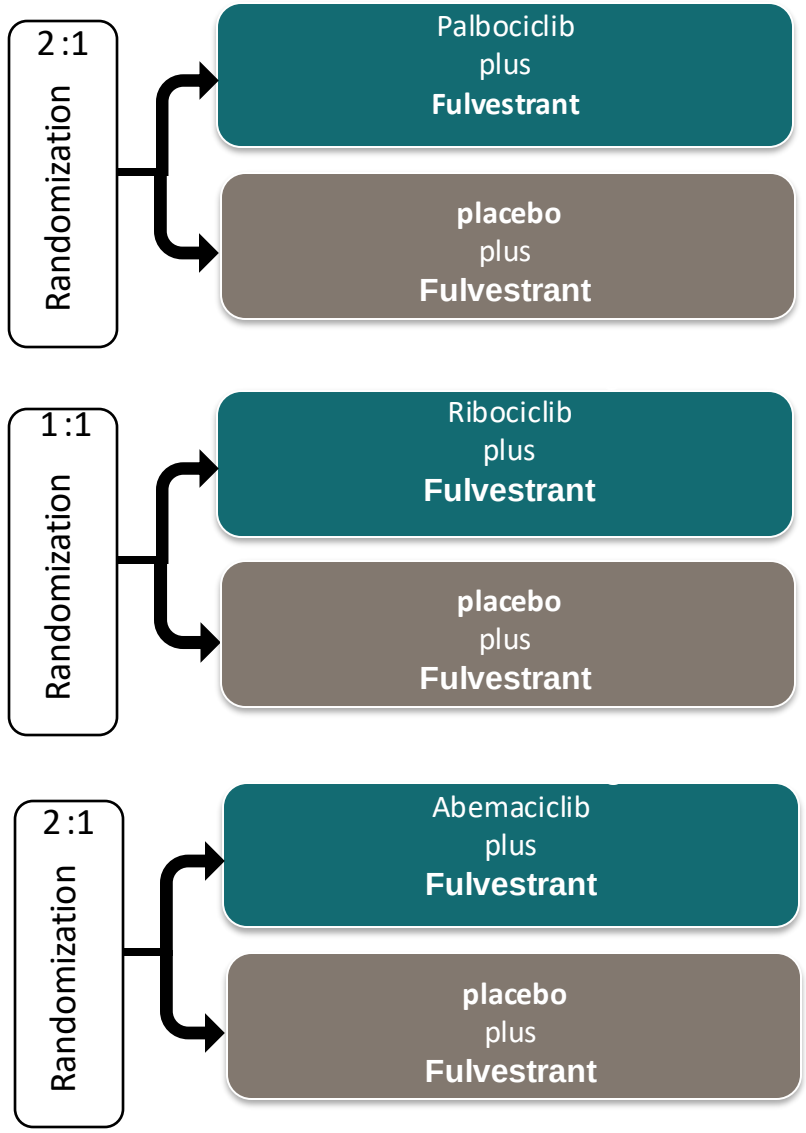
ESMO SCALE FOR ACTIONABILITY OF MOLECULAR TARGETS - ESCAT

Gene or protein	Alteration	Prevalence	ESCAT score
ER	**Protein expression ≥ 1% by IHC** **ESR1 mutation**	**75%** **40%**	**NA** **II-A**
ERBB2	Amplifications or 3+ (IHC) **HER2-low (IHC (1+, 2+ NA)**	15%-20% **40%-50%**	I-A **II-B. - IA/IIA**
	Hotspot mutations	4%	II-B
BRCA1/2	**Germline mutations**	**4%**	**I-A**
	Somatic mutations	3%	II-A
PALB2	Germline mutations	1%	II-A
PD-L1 (TNBC)	Expression by IHC on ICs and tumour cells (CPS)	40%	I-A
PIK3CA (ER+, HER2-)	**Hotspot mutations**	**30%-40%**	**I-A**
MSI	MSI-H	1%-2%	I-C
NTRK	Fusions	<0.1%	I-C
ESR1 (ER+, HER2-)	**Mutations (mechanism of resistance)**	**30%**	**II-A**
AR (TNBC)	AR expression (not validated)	?	II-B
AKT1^{E17K}	Mutations	5%	II-B

ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)

ENDOCRINE RESISTANT DISEASE: 1ST LINE

- **ER+, HER2- MBC**
- **Pre/peri & Postmenopausal**
- **Progressed on prior ET:**
  - **–On or within 12 mos adjuvant**
  - **–On therapy for MBC**



PALOMA-3[1]

MONALEESA-3[2]

MONARCH-2[3]

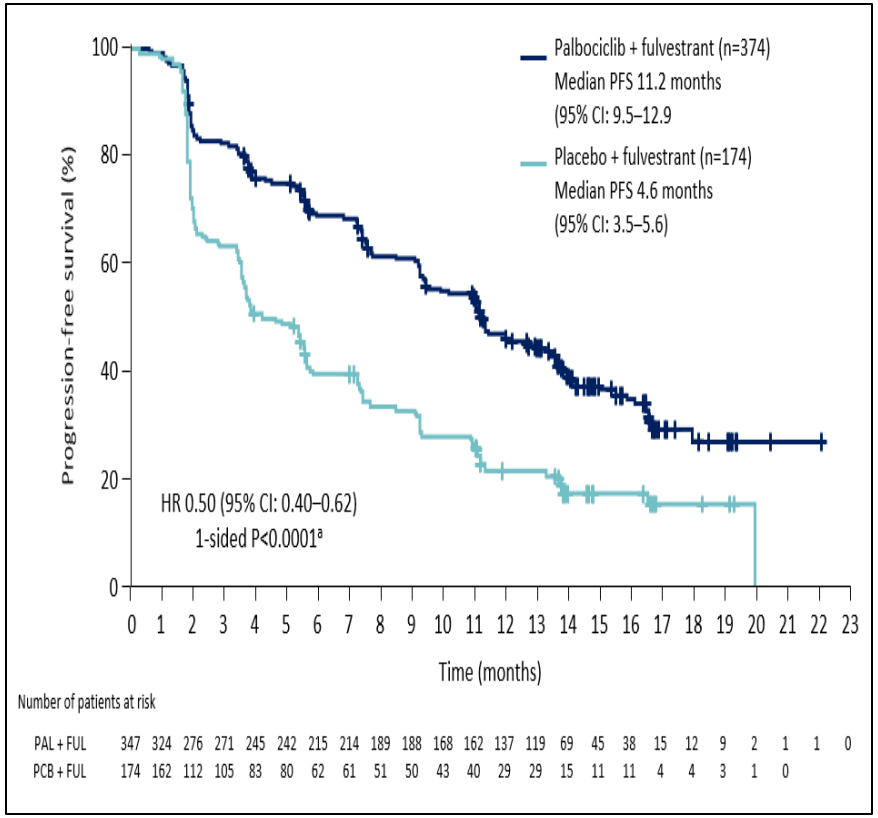
Primary endpoint:
Investigator-assessed PFS

[1]Turner NC, et al. N Engl J Med 2015; [2]Slamon D et al, J Clin Oncol 2018; [3]Sledge G, et al. J Clin Oncol 2017

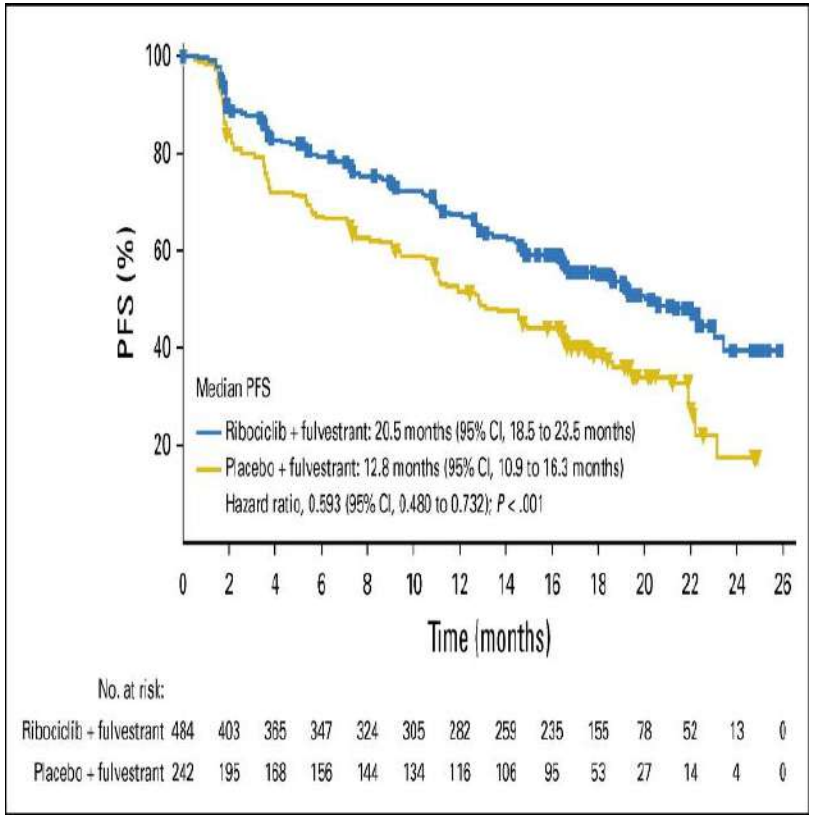
HR+ HER2- METASTATIC BREAST CANCER

Consistent PFS benefit in 2nd line for CDK 4/6i + fulvestrant

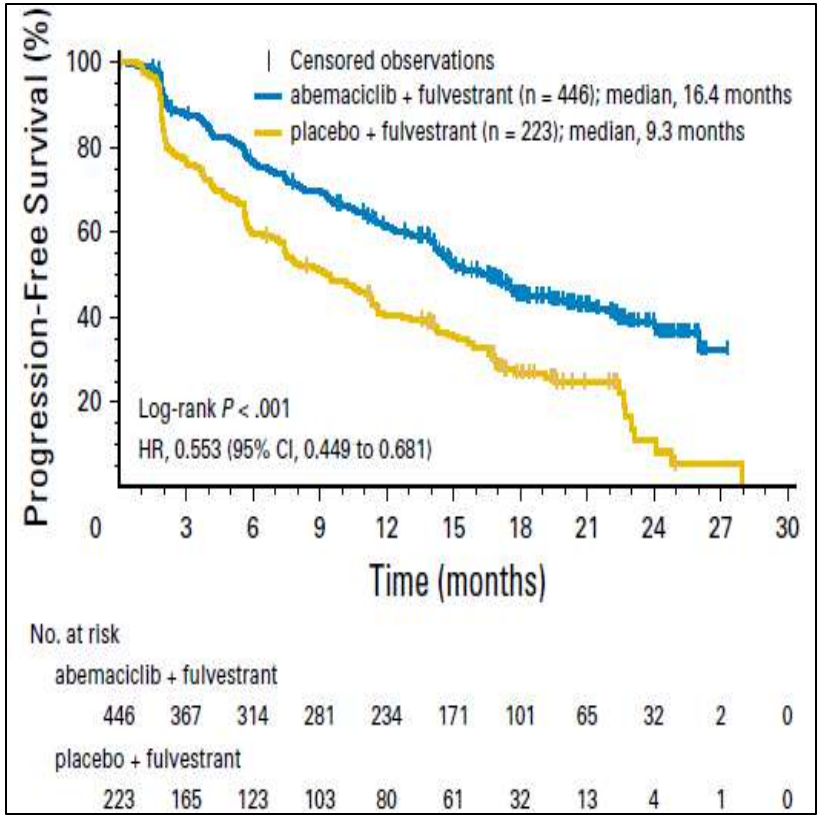
PALOMA-3



MONALEESA-3



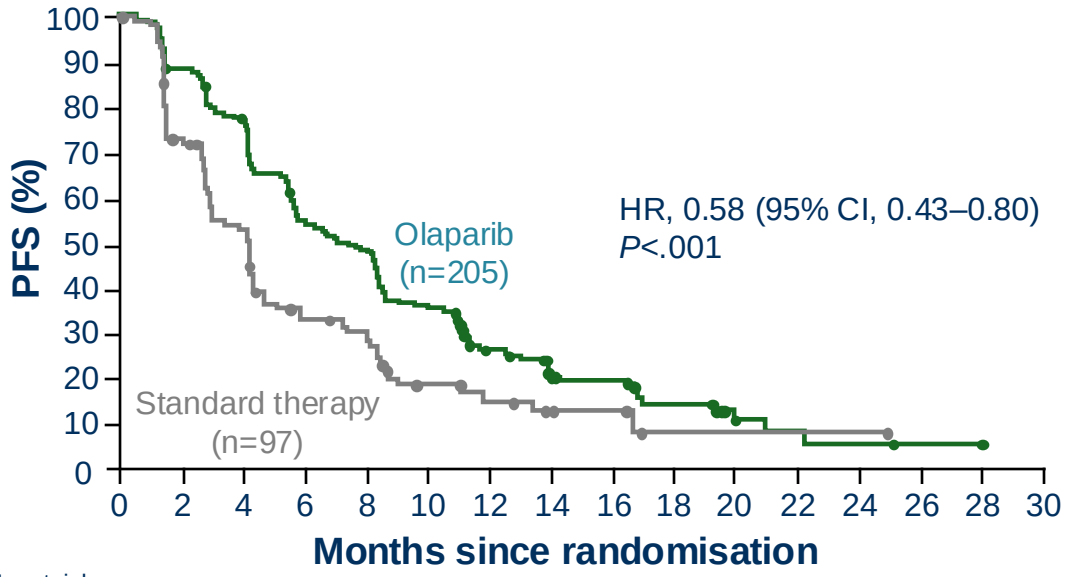
MONARCH-2



Turner N, et al. NEJM 2018; Slamon D, et al JCO 2018; Sledge GW, et al JCO 2017

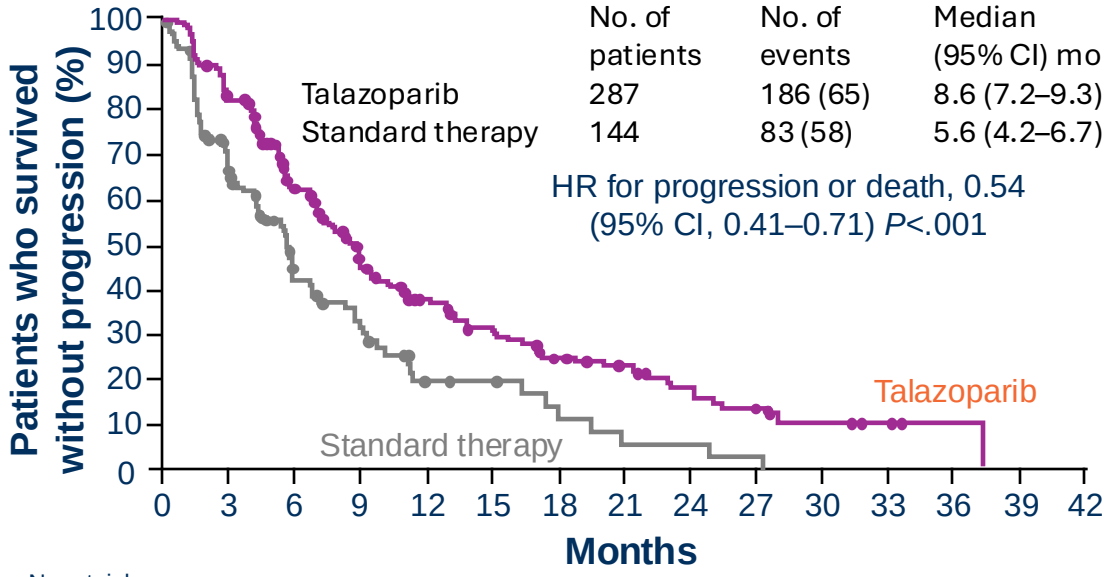
OLYMPIAD AND EMBRACA: PARP VS CT IN MBC

OlympiAD (olaparib) PFS



No. at risk

Olaparib	205	201	177	159	155	41	29	10	7	10	0	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	1	0	0	0	0		



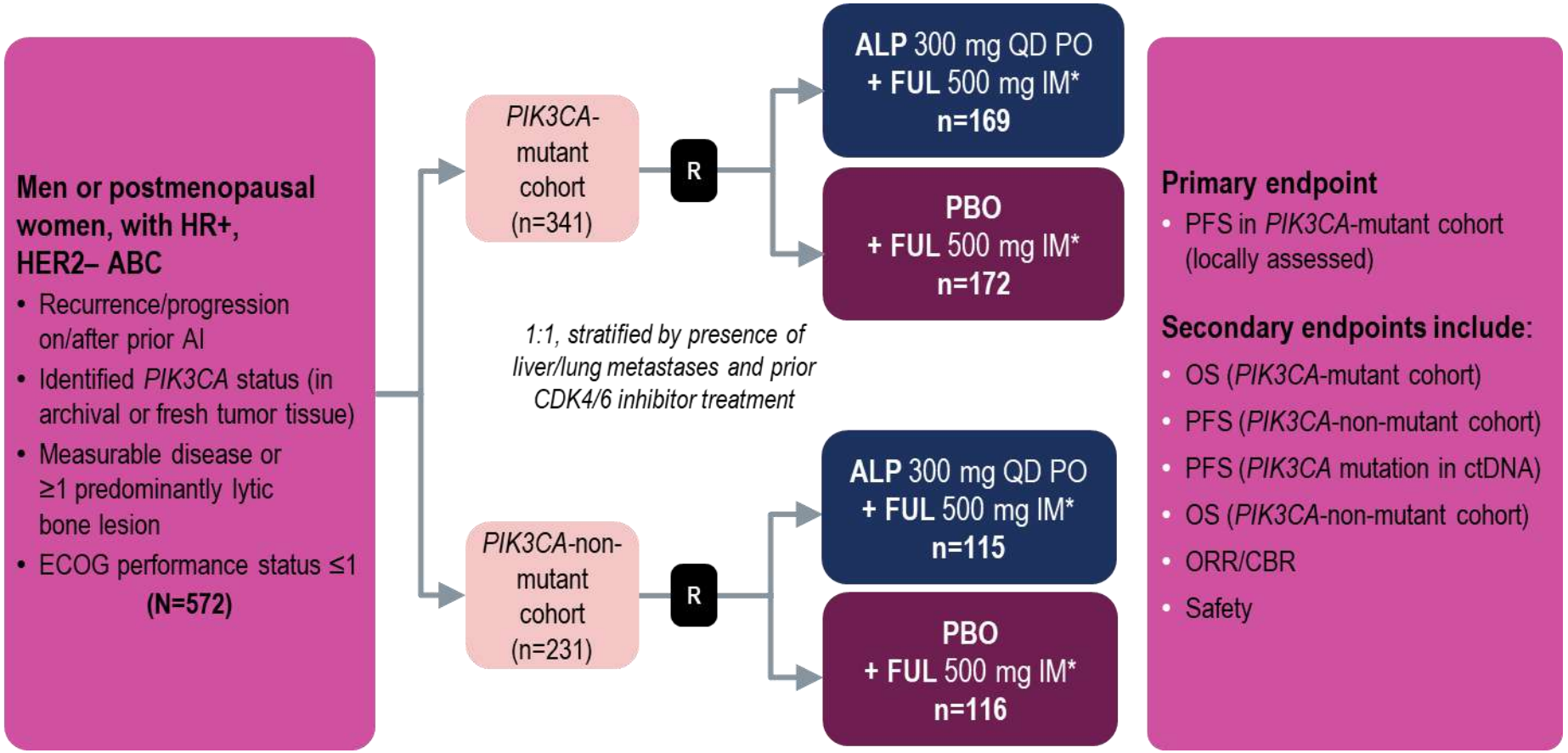
	No. of patients	No. of events	Median (95% CI) mo
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard therapy	144	83 (58)	5.6 (4.2–6.7)

No. at risk

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)												
Standard therapy	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)												

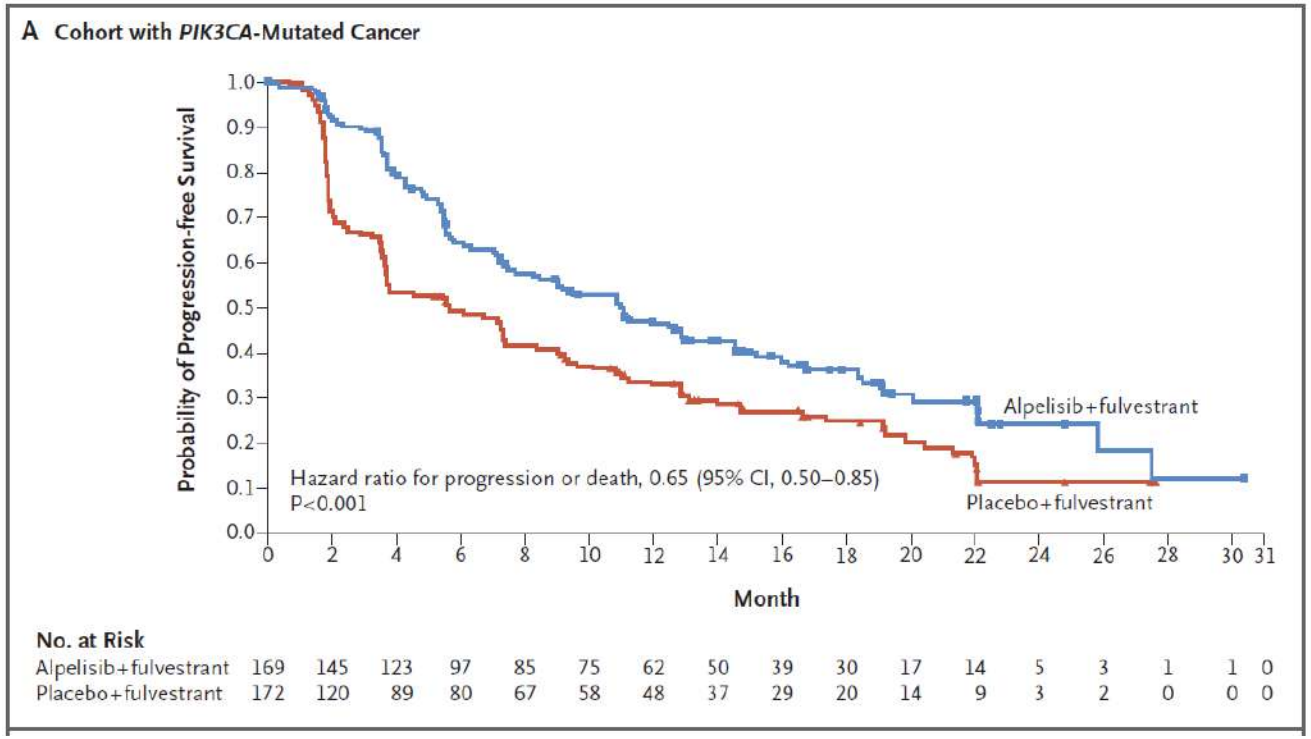
Robson M, et al. N Engl J Med. 2017; Litton J, et al. N Engl J Med. 2018

SOLAR-1: A PHASE III RANDOMIZED TRIAL OF ALPELISIB + FULVESTRANT IN PATIENTS WITH HR+/HER2- MBC PRETREATED WITH ET



André et al, NEJM 2019

SOLAR-1: Results – ESCAT IA

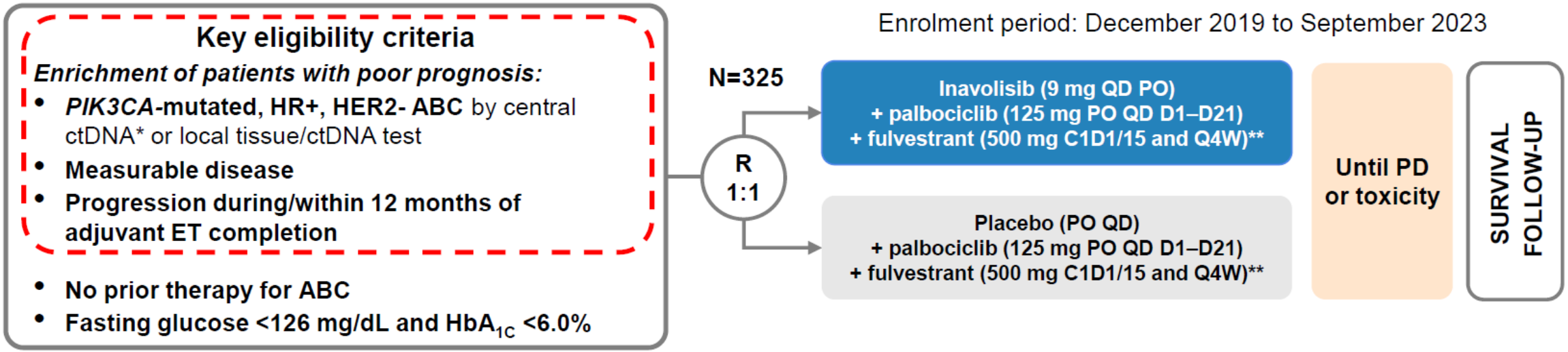


Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

Treatment with alpelisib–fulvestrant prolonged progression-free survival among patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously

Andrè et al, NEJM 2019

INAVO120: 1L inavolisib + palbociclib + fulvestrant in patients with PIK3CAm, HR+/HER2- mBC



Stratification factors:

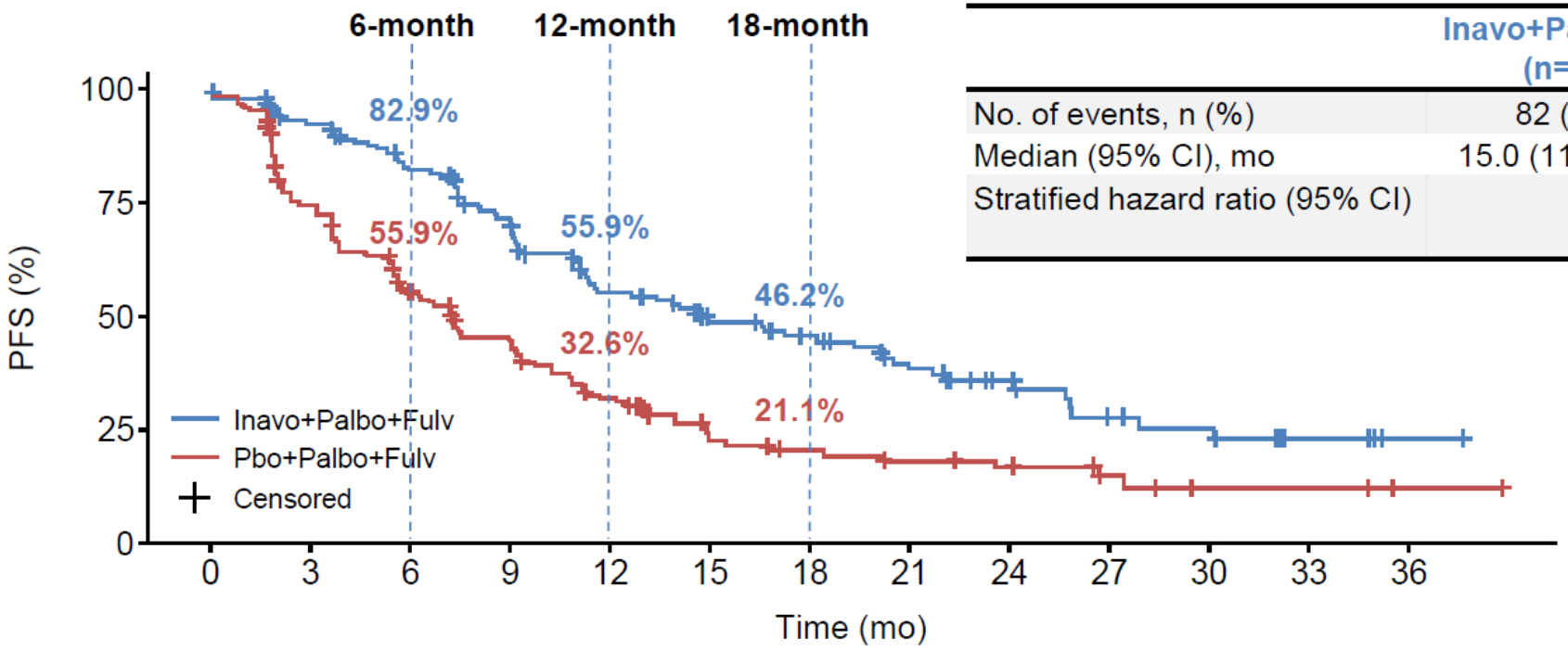
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

https://clinicaltrials.gov/ct2/show/NCT04191499

INAVO120: Primary endpoint PFS (investigator assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Jhaveri KL et al., SABCS 2023

INAVO120: Adverse events (any grade AEs ≥ 20 % incidence in either group)

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Jhaveri KL et al., SABCS 2023

CAPItello-291: capivasertib + fulvestrant in patients with HR+, HER2- aBC whose disease had progressed during or after AI therapy

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

https://classic.clinicaltrials.gov/ct2/show/NCT04305496

CAPITELLO-291: BASELINE AND TUMOR CHARACTERISTICS

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Median age; years (range)		59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female; n (%)		352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Post menopausal; n (%)		287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
Race; n (%)	White Asian Black or African American Other	201 (56.6) 95 (26.8) 4 (1.1) 55 (15.5)	206 (58.4) 94 (26.6) 4 (1.1) 49 (13.9)	75 (48.4) 48 (31.0) 2 (1.3) 30 (19.4)	76 (56.7) 35 (26.1) 1 (0.7) 22 (16.4)
Region*; n (%)	1 2 3	197 (55.5) 68 (19.2) 90 (25.4)	198 (56.1) 68 (19.3) 87 (24.6)	80 (51.6) 29 (18.7) 46 (29.7)	76 (56.7) 24 (17.9) 34 (25.4)
Metastatic sites; n (%)	Bone only Liver* Visceral	51 (14.4) 156 (43.9) 237 (66.8)	52 (14.7) 150 (42.5) 241 (68.3)	25 (16.1) 70 (45.2) 103 (66.5)	16 (11.9) 53 (39.6) 98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+ ER+/PR- ER+/PR unknown	255 (71.8) 94 (26.5) 5 (1.4)	246 (69.7) 103 (29.2) 4 (1.1)	116 (74.8) 35 (22.6) 4 (2.6)	101 (75.4) 31 (23.1) 2 (1.5)
Endocrine resistance; n (%)	Primary Secondary	127 (35.8) 228 (64.2)	135 (38.2) 218 (61.8)	60 (38.7) 95 (61.3)	55 (41.0) 79 (59.0)

*Baseline stratification factors. †One patient in the capivasertib + fulvestrant group was ER negative. Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia. Primary and secondary resistance were defined using the 4th ESO-ESMO International Consensus Guidelines for ABC.

Tuner et al., NEJM 2023

CAPITELLO-291: AKT PATHWAY ALTERATIONS

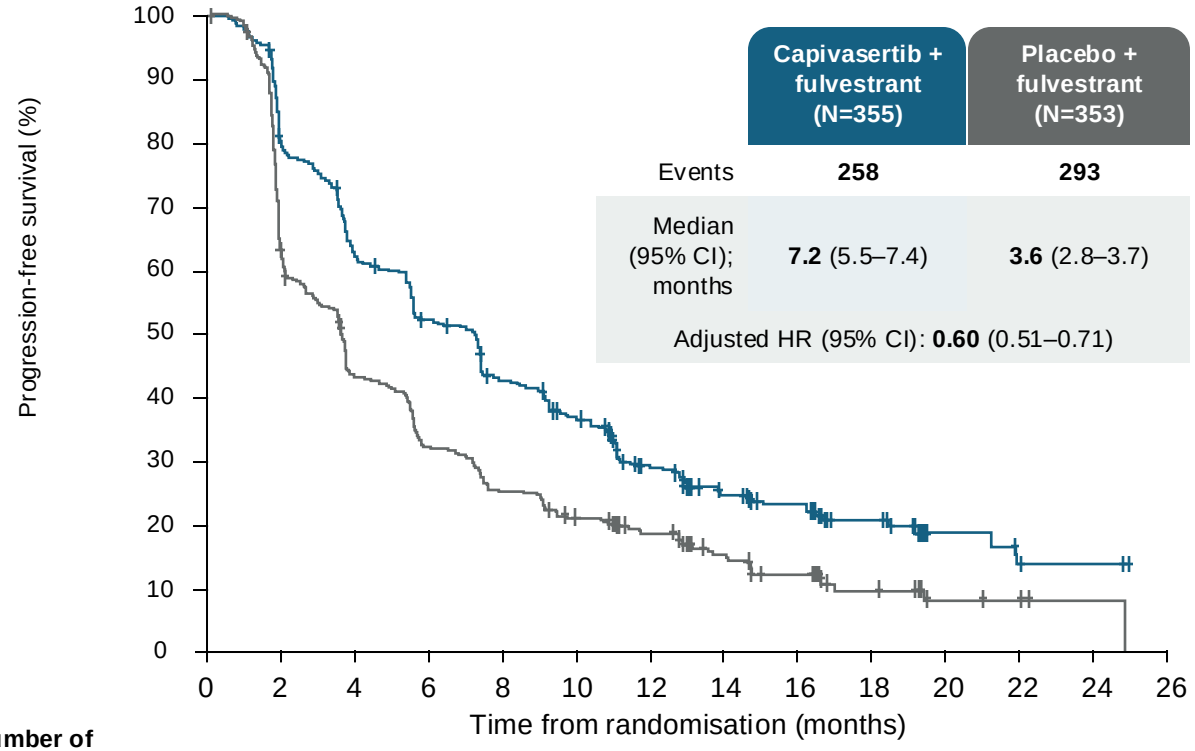
Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
	No sample available	10 (2.8)	4 (1.1)
	Preanalytical failure	39 (11.0)	34 (9.6)
	Post analytical failure	9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Tuner et al., NEJM 2023

CAPItello-291: PFS in overall and AKT pathway-altered populations

Overall population



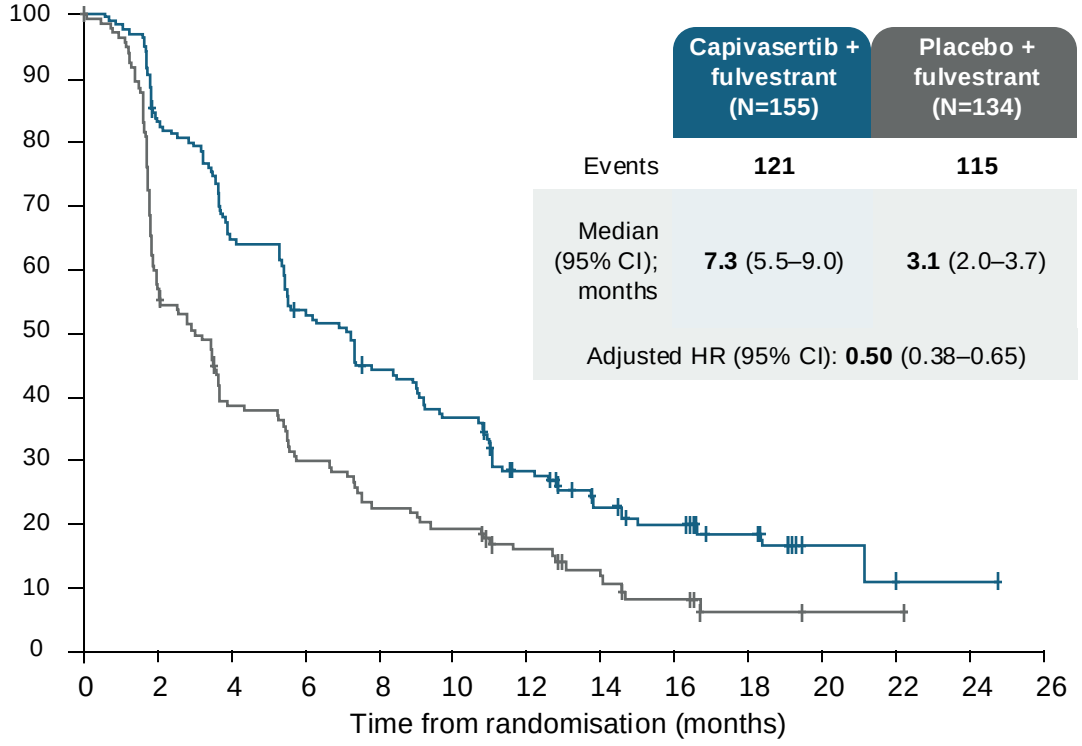
	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Events	**258**	**293**
Median (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)

Adjusted HR (95% CI): **0.60** (0.51–0.71)

Number of patients at risk

Capivasertib + fulvestrant	355	226	207	172	138	115	78	55	43	25	8	5	2	0
Placebo + fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Events	**121**	**115**
Median (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)

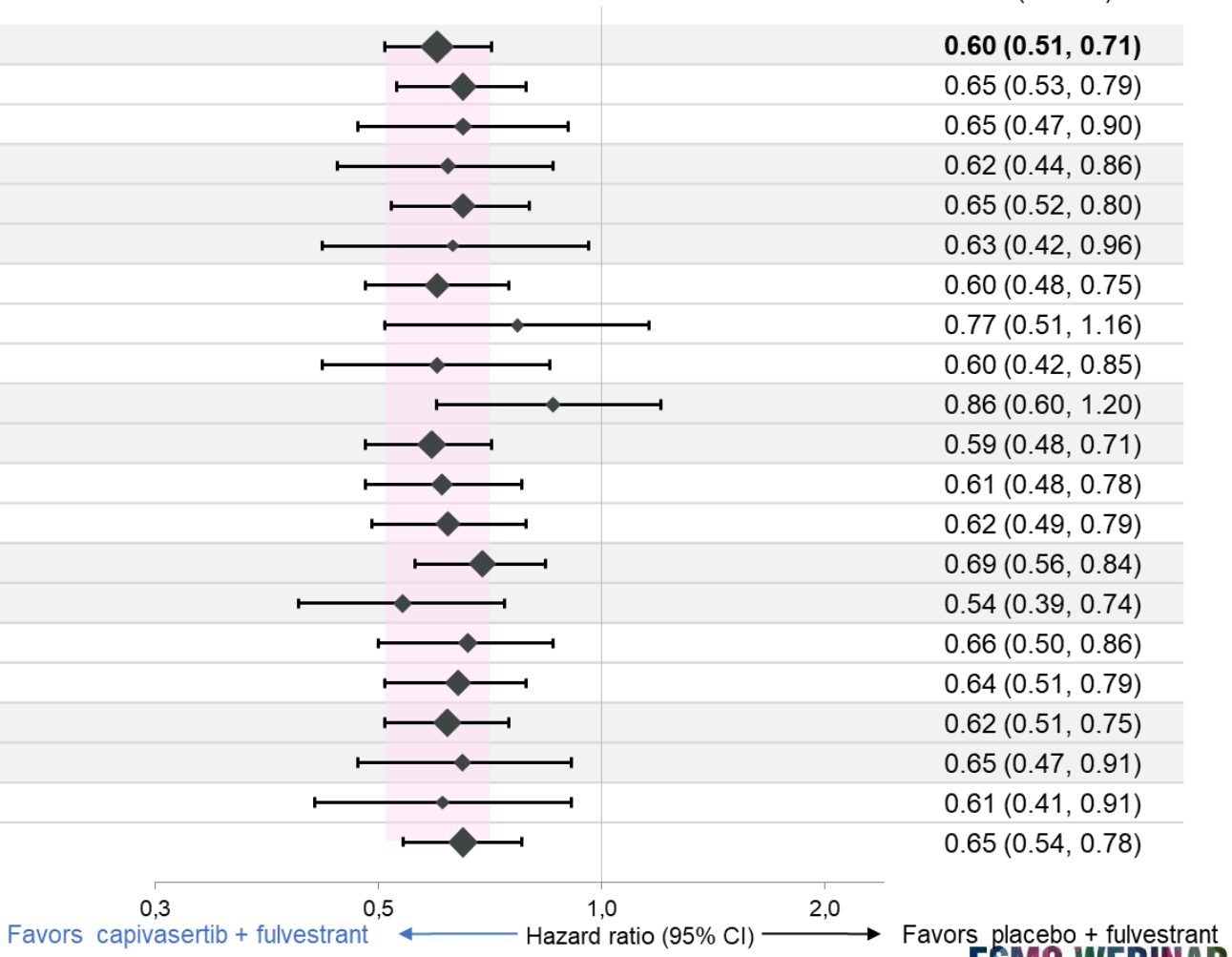
Adjusted HR (95% CI): **0.50** (0.38–0.65)

Capivasertib + fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

Tuner et al., NEJM 2023

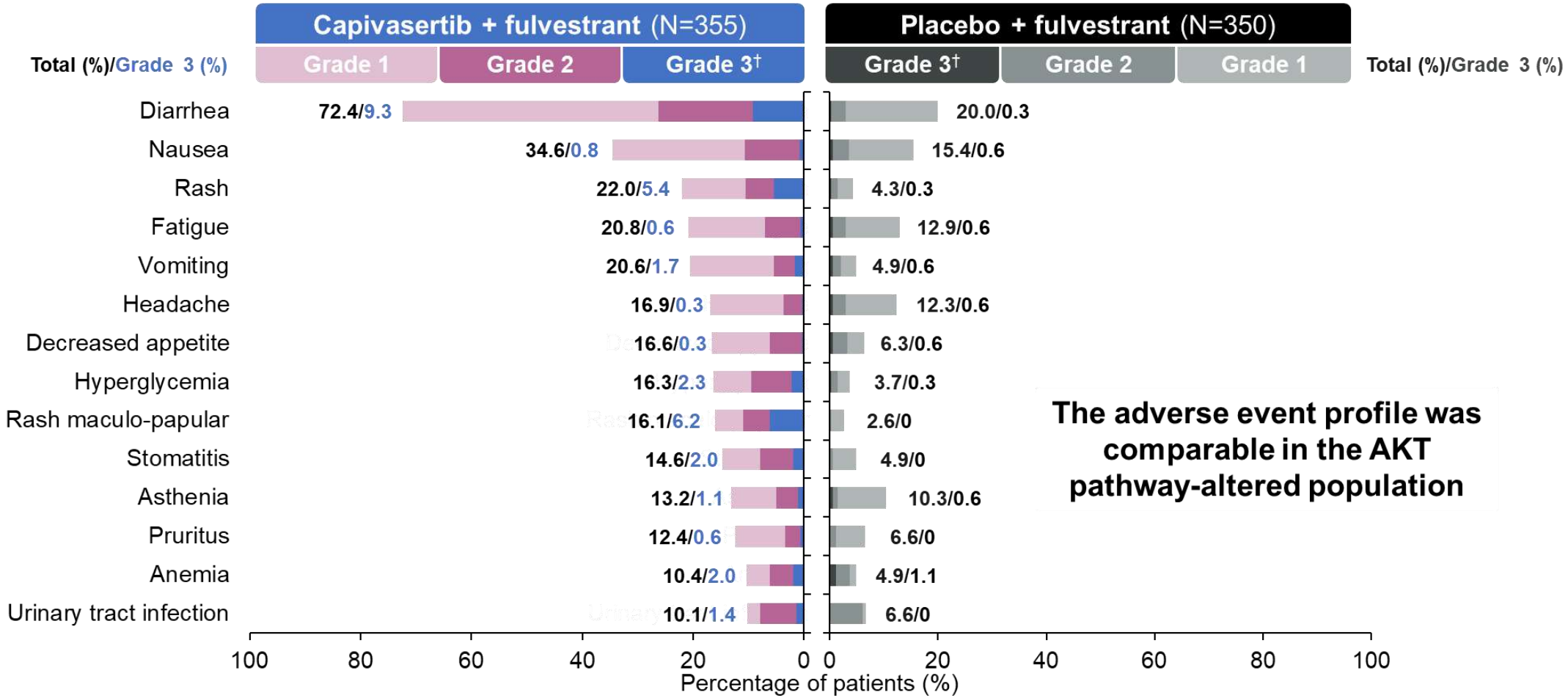
CAPITELLO-291: INVESTIGATOR-ASSESSED PFS BY SUBGROUP (OVERALL POPULATION)

		Number of patients	HR (95%CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



Tuner et al., NEJM 2023

CAPITELLO-291: ADVERSE EVENTS (>10% OF PATIENTS) – OVERALL POPULATION



The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

Tuner et al., NEJM 2023

Adverse Events from Phase III Trials: Inavolisib, Alpelisib, Capivasertib

Patients with key AEs,† %	INAVO120[1] Inavo + Palbociclib+ Fulvestrant (N=162)		INAVO120[1] Palbocilib + fulvestrant Control arm (n = 162)		SOLAR-1[2] Alpelisib + fulvestrant (n = 284)		CAPitello-291[3] Capivasertib + fulvestrant (n = 355)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperglycemia#	59	6	9	0	64	33	16	2
Diarrhea	48	4	16	0	58	7	72	9
Rash	25	0	17	0	54	20	38	12
Stomatitis*	51	6	27	0	25	3	15	2
Nausea	28	1	17	0	45	3	35	1
AEs leading to study treatment discontinuation	7	N/A	1	N/A	25	N/A	13	N/A

Cross-trial comparisons should be interpreted with caution due to differences in patient populations and AE reporting.

Notes:

†For INAVO120, the key AEs were assessed as a medical concept (grouped terms),

#Eligibility varied widely between trials. For INAVO120, FBG <126 and HGBA1c <6%; For SOLAR-1, HGBA1c < 6.5%; For Capitello-291, HGBA1c <8%

***For INAVO120, stomatitis grouped term includes mucosal inflammation.**

***For SOLAR-1 and CAPitello-291, stomatitis was reported as a single term; for Solar 1 mucosal inflammation was 18% for any Grade and 2% for Grade ≥3**

1. Jhaveri K, et al. SABCS 2023; 2. André F, *et al. N Engl J Med* 2019 3. Turner NC, et al. *N Engl J Med*. 2023

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
ERBB2	Amplifications	15%-20%	IA	Anti-HER2 monoclonal antibodies HER2 TKIs Anti-HER2 ADCs	Baselga et al., *N Engl J Med* 2012[55] Krop et al., *Lancet Oncol* 2014[56] Lin et al., *J Clin Oncol* 2020[57] Saura et al., *J Clin Oncol* 2020[58] Rugo et al., *JAMA Oncol* 2021[59]
	Hotspot mutations	4%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., *Nature* 2018[51] Smyth et al., *Cancer Discov* 2020[60] Li et al., *Ann Oncol* 2023[61]
PIK3CA	Hotspot mutations	30%-40%	IA (ER-positive HER2-negative ABC)	α-specific PI3K inhibitors*	André et al., *N Engl J Med* 2019[62] Rugo et al., *Lancet Oncol* 2021[63] Turner et al, *N Engl J Med* 2023[70]
ESR1	Mutations	30%-40%	IA (ER-positive HER2-negative ABC resistant to AI)	SERDs	Bidard et al., *J Clin Oncol* 2022[64] Bardia et al., *Cancer Res* 2023[65]
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%	IA	PARP inhibitors	Litton et al., *N Engl J Med* 2018[66] Robson et al., *Eur J Cancer* 2023[67]
	Somatic mutations	3%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68]
PTEN	Mutations/deletions	7%	I/II	AKT inhibitors	Schmid et al., *J Clin Oncol* 2020[69] Turner et al., *N Engl J Med* 2023[70]
AKT1	Mutations (p. E17K)	5%	I/II	AKT inhibitors	Kalinsky et al., *JAMA Oncol* 2021[71] Turner et al., *N Engl J Med* 2023[70]
PALB2	Germline pathogenic/likely pathogenic variants	1%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68] Gruber et al., *Nat Cancer* 2022[72]

ABC, advanced breast cancer; ADCs, antibody—drug conjugates; AI, aromatase inhibitors; ER, oestrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; HER, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; SERDs, selective oestrogen receptor degrader; TKIs, tyrosine kinase inhibitors.
*AKT inhibitors have shown efficacy in patients with PIK3CA mutated ER-positive HER2-negative ABC

RECOMMENDATIONS FOR THE USE OF NGS FOR PATIENTS WITH ADVANCED BREAST CANCER IN 2024

PI3K/AKT

- Capivasertib plus fulvestrant approved by FDA based on PFS (HR 0.60; P < 0.001), with a slightly greater benefit in AKT-pathway alterations (HR 0.50; P < 0.001) in a randomised phase III study.
- Based on these data, the FDA approved this combination for pretreated patients with ER+/HER2- ABC with PIK3CA/AKT1/PTEN alterations.
- There is no consensus among experts regarding whether AKT1/PTEN mutations should be classified as level I or II in this patient population, given the low prevalence, and the observed benefit may predominantly arise from PIK3CA mutations.
- Nevertheless, as the determination of AKT1/PTEN alterations can provide drug access to these patients, the group recommends carrying out tumour NGS.

Mosele MF et al., SABCS 2022

RECOMMENDATIONS FOR THE USE OF NGS FOR PATIENTS WITH ADVANCED BREAST CANCER IN 2024

- Tumour NGS can substitute germline BRCA1/2 testing in most of the patients
- Reclassification of ESR1 mutations to level IA,

- The NGS testing should be done after resistance to endocrine therapy to optimise the likelihood of detecting ESR1 mutations.
  - It is recommended to carry out tumour NGS of a tumour (or plasma) sample from a patient with ER+/HER2 - ABC as standard of care.
- Patients with high likelihood of harbouring germline BRCA1/2 mutations should undergo clinical genetic testing even if these alterations were not detected by tumour NGS.

It is recommended to carry out tumour NGS of a tumour (or plasma) sample from a patient with ER+/HER2 - ABC as standard of care

Mosele MF et al., SABCS 2022

ESMO DEEP DIVE: BREAST CANCER

Thank you!

Alessandra Gennari

alessandra.gennari@uniupo.it

@aledignus12

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org