NEW HORIZONS IN HER2 NEGATIVE BREAST CANCER

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COI

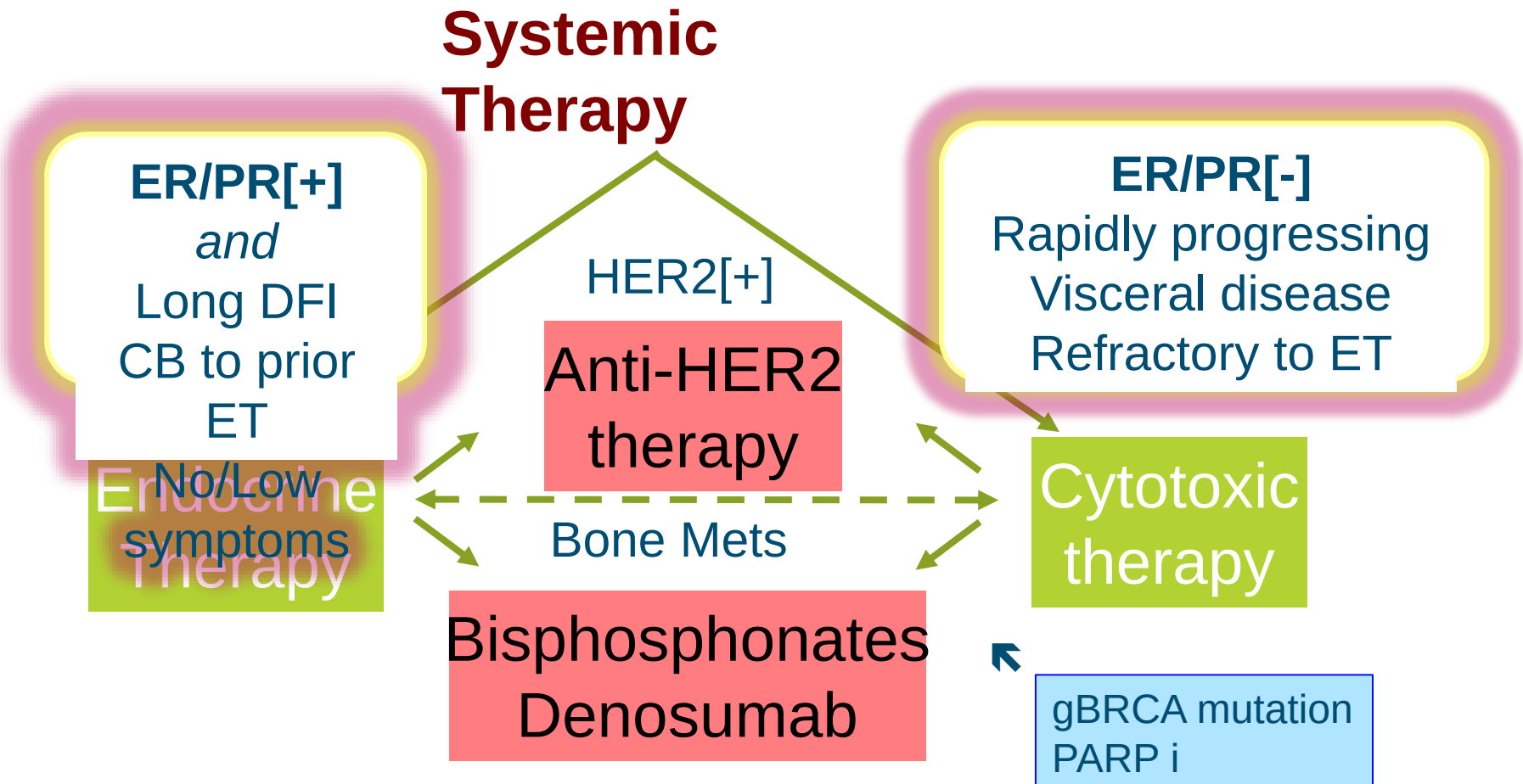
- Boards
  - Susan G Komen Scientific Advisory Board
  - Breast International Group Executive Board
- Pharmaceutical Company Associations
  - Advisory Boards – AstraZeneca, Roche, Novartis, Pfizer, Oncotheryon, Nanostring, Merck
  - Research Funding – Pfizer, AstraZeneca, Novartis, BMS

Goals in the Treatment of ABC

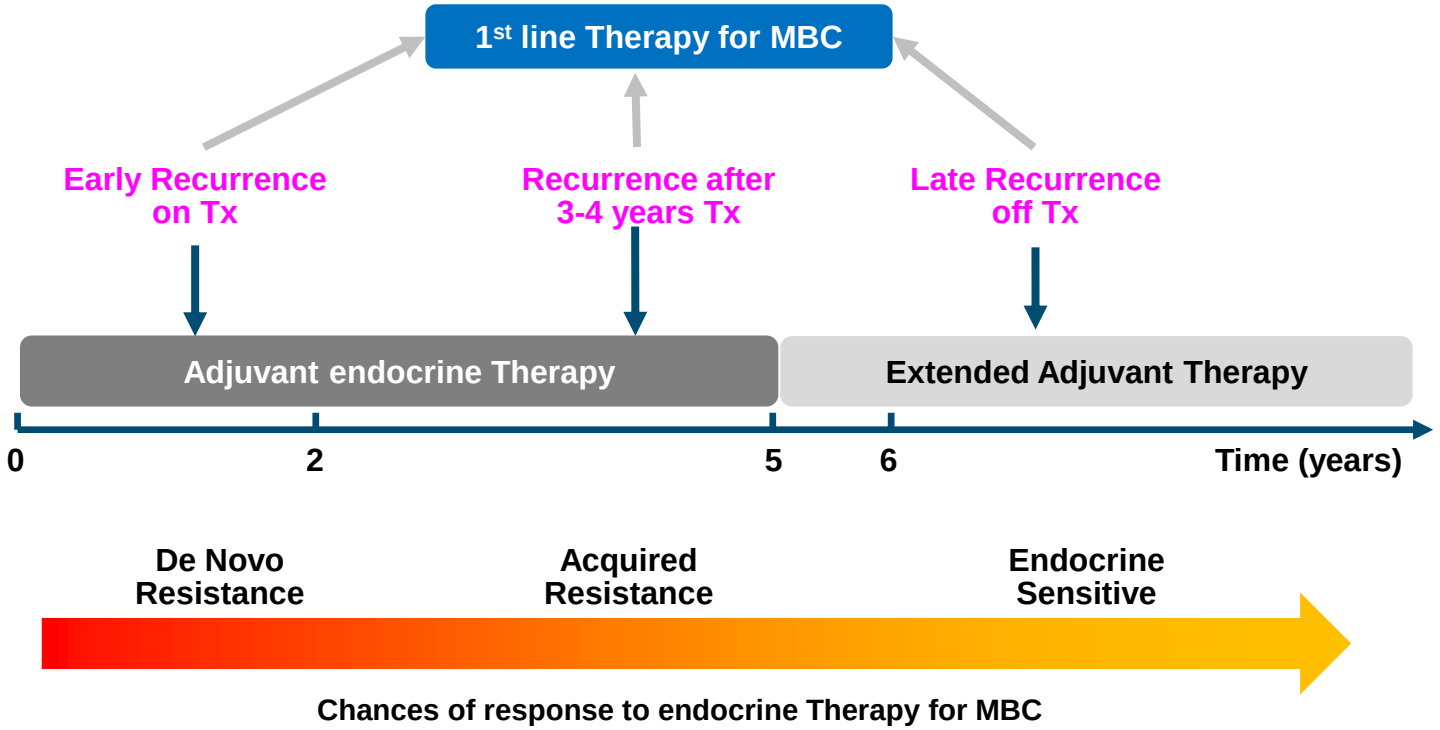
- Metastatic/advanced breast cancer (ABC) is incurable yet treatable with a median survival of only 24 months
  - Treatment aims:
    - Maintain or improve quality of life
    - Increase disease free progression
    - Prolongation of survival
  - A large number of active agents and combinations are available
  - Standard management is still debatable

ESMO/NCCN Guidelines

Treatment Algorithms for Advanced Breast Cancer



Defining Endocrine Sensitivity/Resistance with adjuvant Therapy



Primary and Secondary ET Resistance (per ESMO guidelines)

- Primary ET Resistance: progression
  - while on the first 2 years of adjuvant ET
  - while on the first 6 months of 1st line ET for MBC

- Secondary ET Resistance: progression
  - after 2 years while on adjuvant ET
  - within 12 months of completing adjuvant ET
  - after 6 months while on ET for MBC

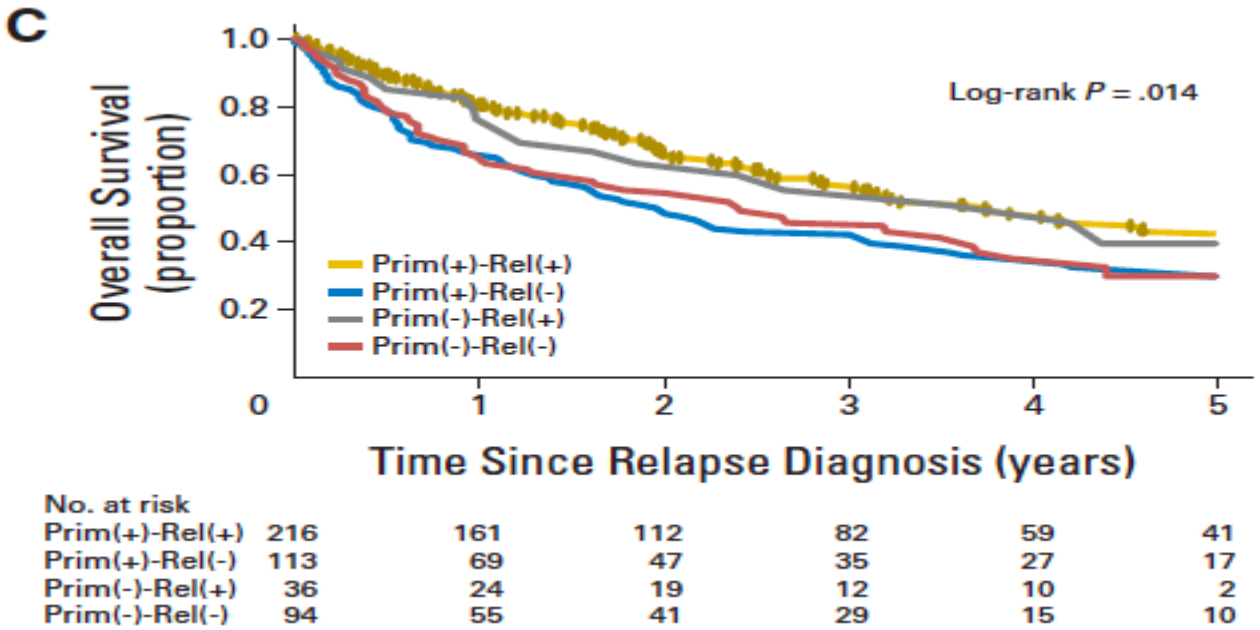
Cardoso F et al. *The Breast* 6:489-502, 2014; 5. Cardoso F et al. *Ann Oncol* 25:1871-88, 2014.

Visceral Crisis

- Defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease
  - Potential for an imminent catastrophic problem leading to a clinical indication for a more rapidly efficacious therapy
  - Examples: significant liver metastases causing significant dysfunction, lymphatic/lung metastases with severe symptoms, bone marrow replacement causing significant cytopenias
- Chemotherapy is a key option based on the severity and immediacy of the disease
- Visceral disease without visceral crisis can be treated with ET which may provide the most durable response

Cardoso F, et al. Ann Oncol. 2014;1-18

Importance of biopsy …Clonal alterations of ER may occur Primary cancer vs. biopsy of relapse



The blue depicts patients with ER+ primary tumours while the biopsy from the relapse was ER-

Lindström/Karlsson, JCO 2012

First-Line Endocrine Therapy in Advanced Breast Cancer: Choice of ET ± CDK 4/6 Inhibitor

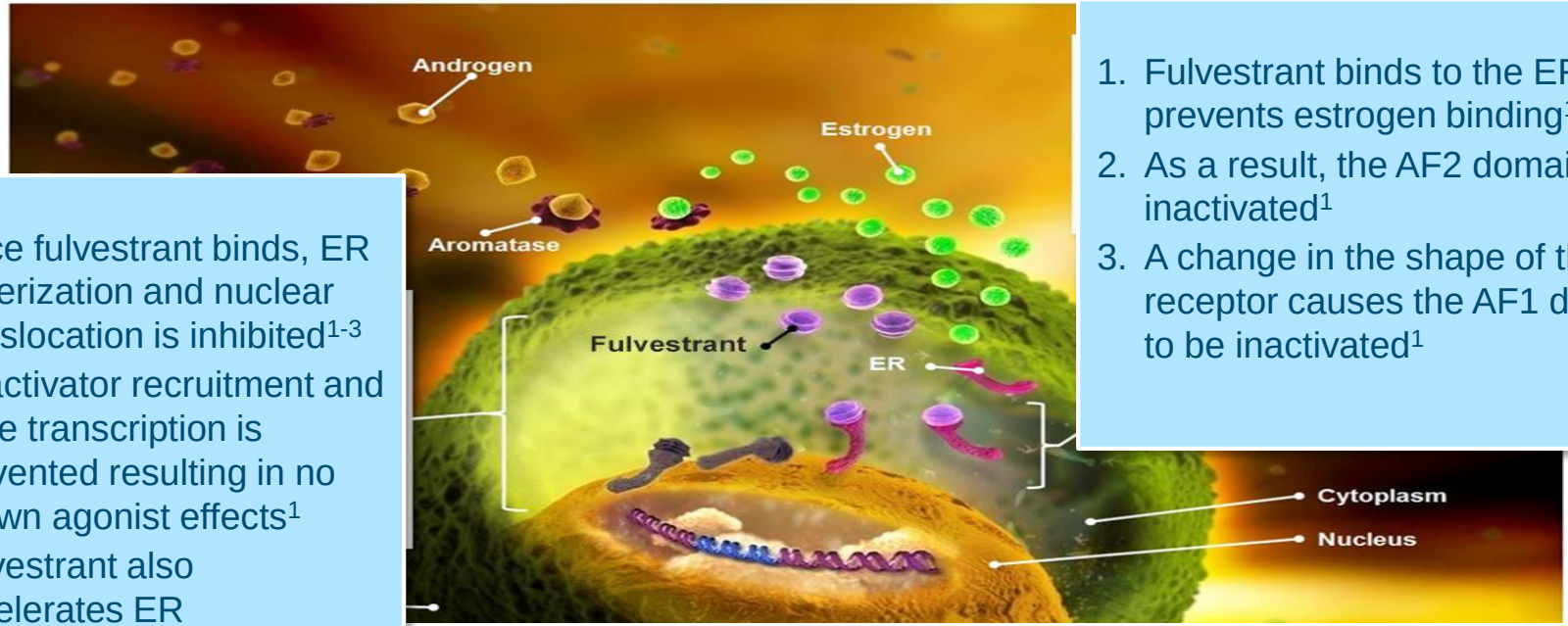
Monotherapy (Fulvestrant)

- Most efficacious ET single agent
- Proven PFS and OS benefit in first- and second-line ET
- Well-tolerated
- Increased cost compared with AI -- proportionate with previous improved ETs
- Patient selection
  - Comorbidities
  - Prior treatment/tolerance
  - Disease characteristics/site of disease
- Biological – Percent ER, Ki67, *ESR* status

ET + CDK 4/6 Inhibitor

- Improved PFS over ET alone
- No proven OS benefit yet
- Increased toxicity compared with ET alone
- Availability
- Affordability
- Patient selection
  - “Only ER”

Fulvestrant: Mechanism of Action



1. Fulvestrant binds to the ER and prevents estrogen binding[1,2]
2. As a result, the AF2 domain is inactivated[1]
3. A change in the shape of the receptor causes the AF1 domain to be inactivated[1]

4. Once fulvestrant binds, ER dimerization and nuclear translocation is inhibited[1-3]
5. Coactivator recruitment and gene transcription is prevented resulting in no known agonist effects[1]
6. Fulvestrant also accelerates ER degradation[2]

n function 2; ER = estrogen receptor

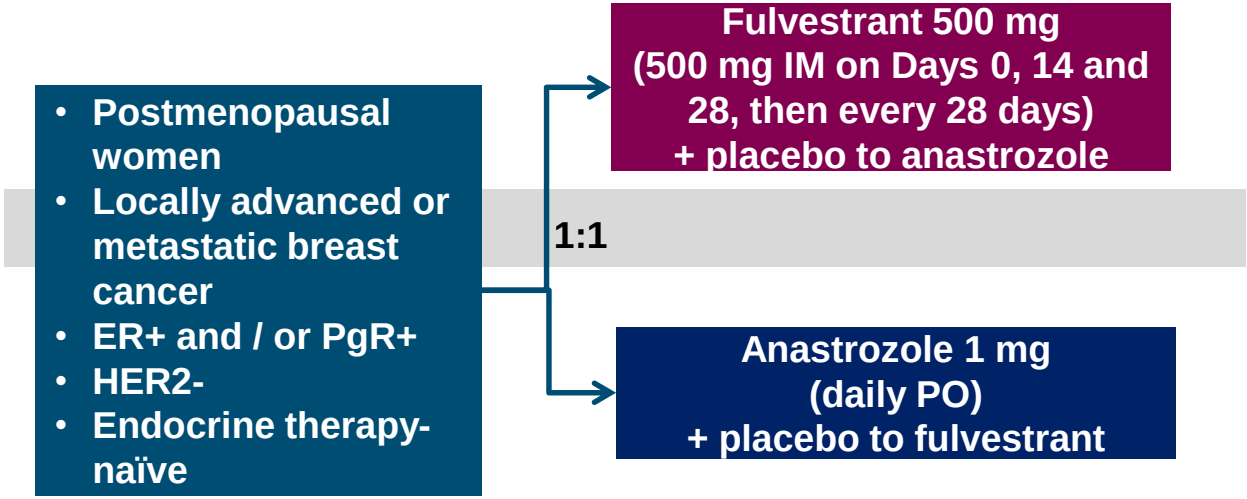
1. Howell A. *Int J Gynecol Cancer.* 2006;16(suppl 2):521-523. **2.** Carlson RW. *Clin Breast Cancer.* 2005;6(suppl 1):S5-S8. **3.** Wakeling AE. *Endocr Relat Cancer.* 2000;7:17-28.

Comparison of Recent First Line Studies For ER-Positive ABC using Fulvestrant

Trial, Author	Treatment/Setting	No. Patients	TTP/PFS, mos	ORR, %	CBR, %
Mehta et al[a]	Anastrozole vs anastrozole + fulvestrant (250 mg)	345 349	13.5 15.0	NR NR	70 73
Bergh et al[b]	Anastrozole vs anastrozole + fulvestrant (250 mg)	256 258	10.2 10.8	33.6 31.8	55.1 *55.0*
FIRST[c]	Anastrozole vs fulvestrant 500 mg	103 102	OS = 48.4 months 54.1 months		
FALCON[d]	Anastrozole vs fulvestrant 500 mg	230 232	16.6 13.8	46 45	78 74

a. Mehta RS, et al. N Engl J Med. 2012;367:435-444 b. Bergh J, et al. J Clin Oncol. 2012;30:1919-1925. c. Ellis MJ, et al. J Clin Oncol. 2015;33:3781-3787. d. Robertson J, et al. Lancet. 2016.

FALCON: PHASE III STUDY DESIGN



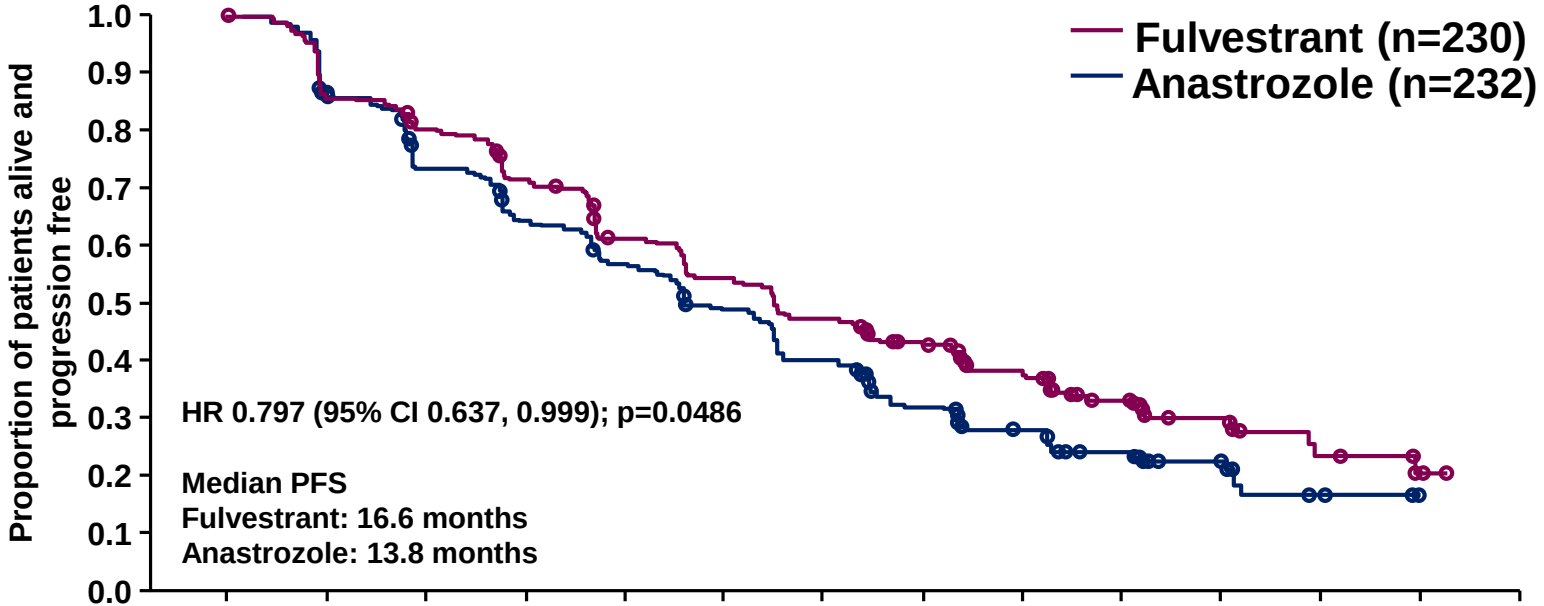
Primary endpoint: PFS[a]

Secondary endpoints

- OS[b]
- ORR
- CBR
- DoR, EDoR
- DoCB,
- EDoCB
- HRQoL (FACT-B total and TOI)
- Safety

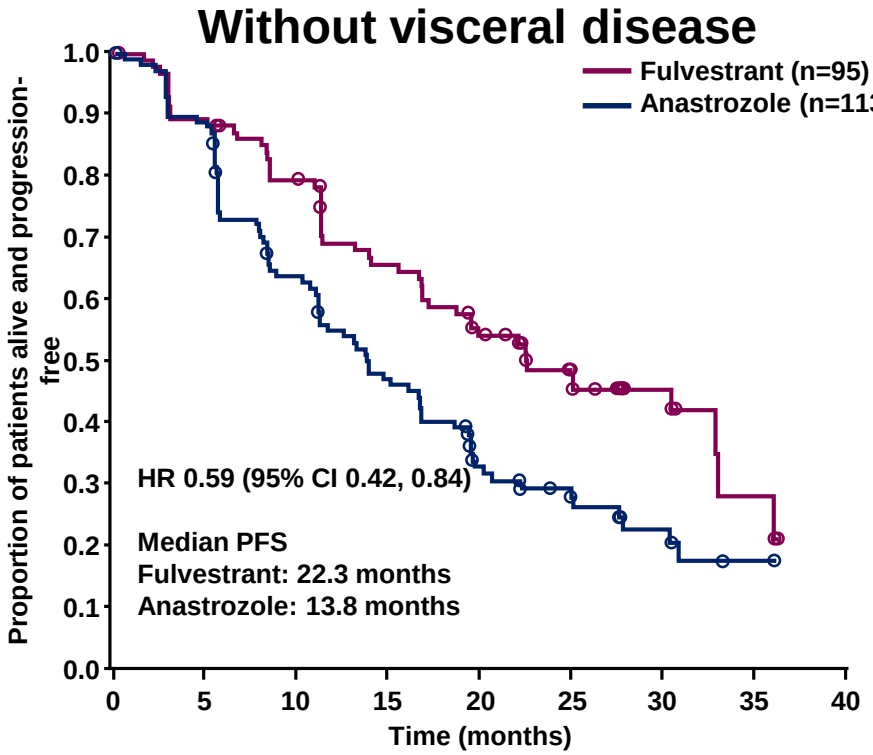
- Randomised, double-blind, parallel-group, international, multicentre study
- Follow-up for disease progression and survival
- Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test)
- Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease
- Subgroup analysis of PFS for pre-defined baseline covariates

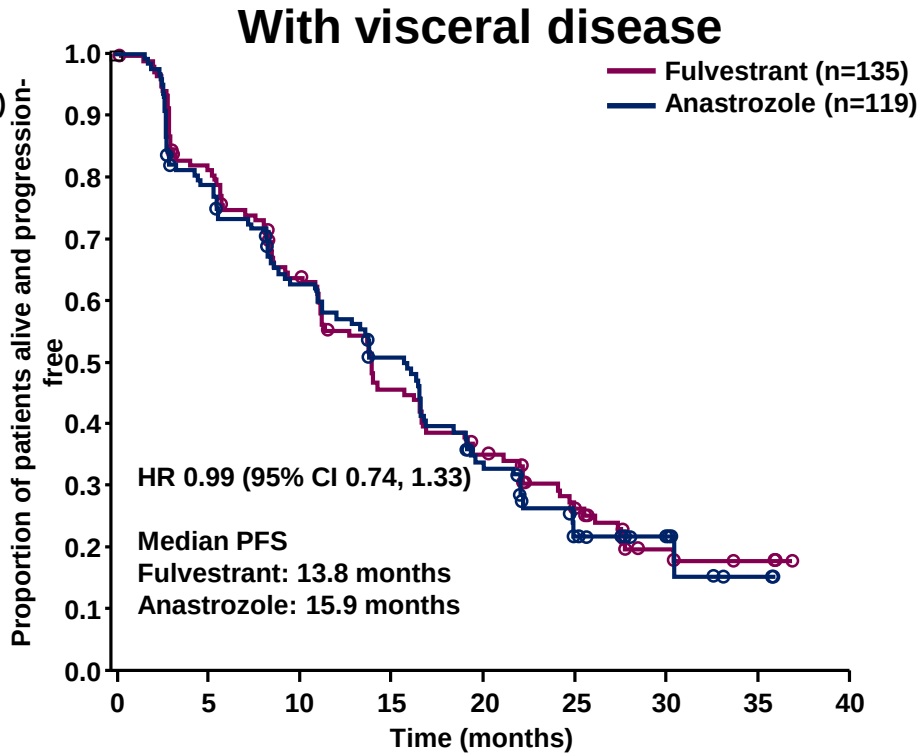
FALCON: PRIMARY ENDPOINT, PFS



A circle represents a censored observation

FALCON: PFS IN PATIENTS WITH OR WITHOUT VISCERAL DISEASE

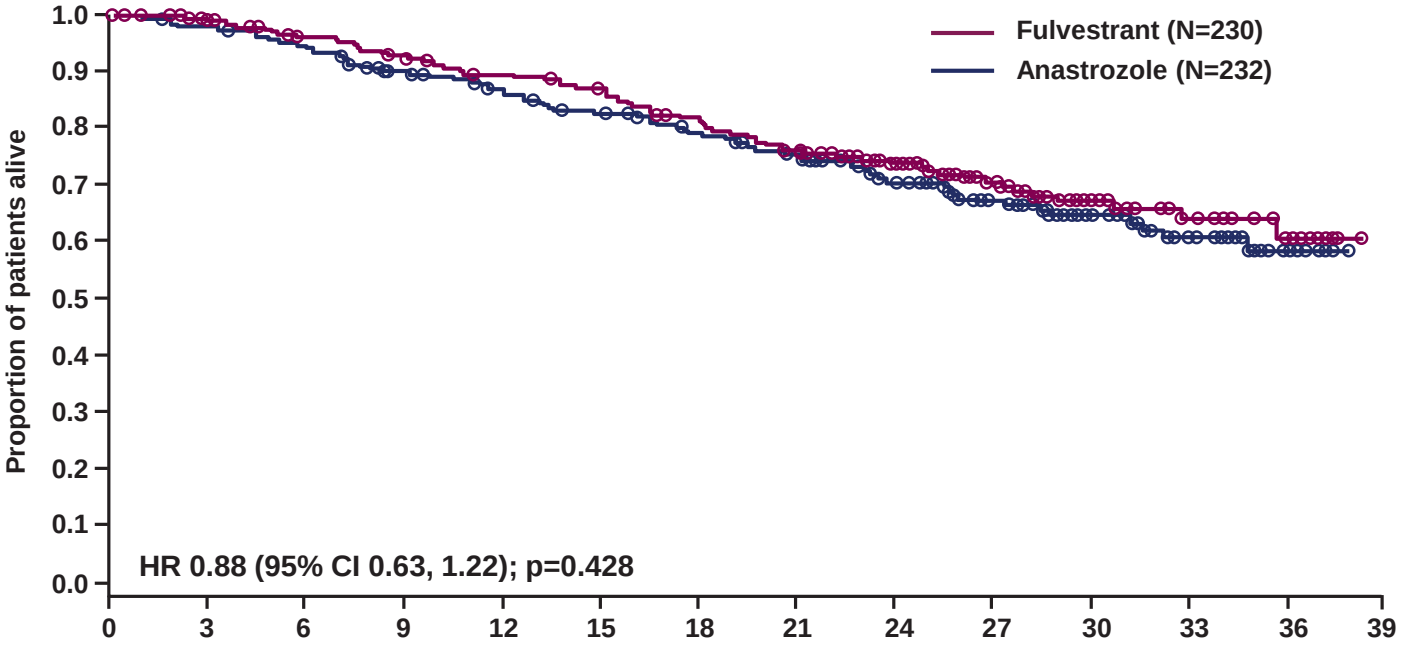




Post hoc interaction test $p<0.01$

A circle represents a censored observation

FALCON: OS (31% MATURITY)



Number of patients at risk														
Fulvestrant	230	221	208	200	188	180	168	153	129	92	57	31	17	0
Anastrozole	232	223	213	197	186	175	164	155	122	94	61	37	18	0

Median follow up 25.0 months
A circle represents a censored observation

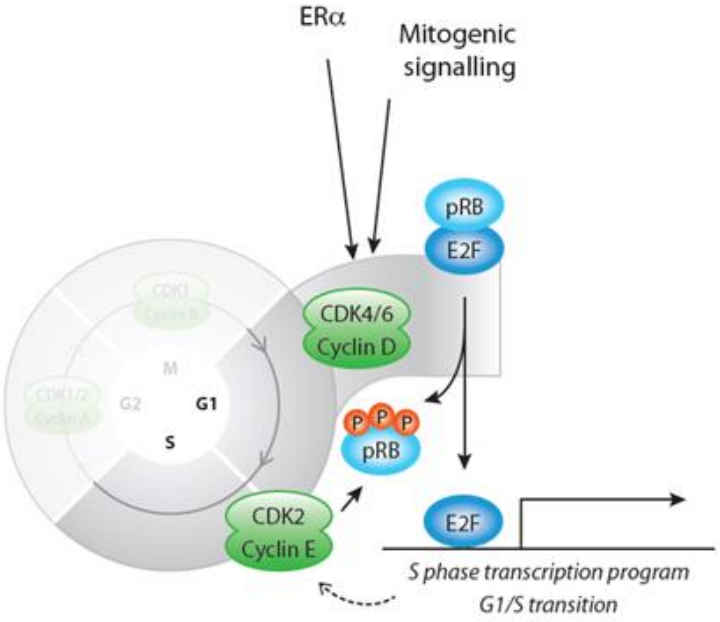
FALCON: SECONDARY ENDPOINTS

Endpoint	Fulvestrant (N=230)	Anastrozole (N=232)	
ORR[a]	46.1% (89 / 193)	44.9% (88 / 196)	Odds ratio (95% CI) 1.07 (0.72, 1.61); p=0.729
CBR	78.3% (180 / 230)	74.1% (172 / 232)	Odds ratio (95% CI) 1.25 (0.82, 1.93); p=0.305
Median DoR	20.0 months	13.2 months	-
Median DoCB	22.1 months	19.1 months	-
EDoR	11.4 months	7.5 months	Ratio (95% CI) 1.52 (1.23, 1.89); p<0.001
EDoCB	21.9 months	17.5 months	Ratio (95% CI) 1.26 (1.13, 1.39); p<0.001
Median time to deterioration in FACT-B total score	13.8 months	11.1 months	HR (95% CI) 0.84 (0.66, 1.07); p=0.159

[a] In patients with measurable disease at baseline

CDK4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge.
- 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]
- Cell line models of endocrine resistance remain dependent on Cyclin D1 and CDK4/6.[2,3]
- Suggestion that continuous dosing may be more effective



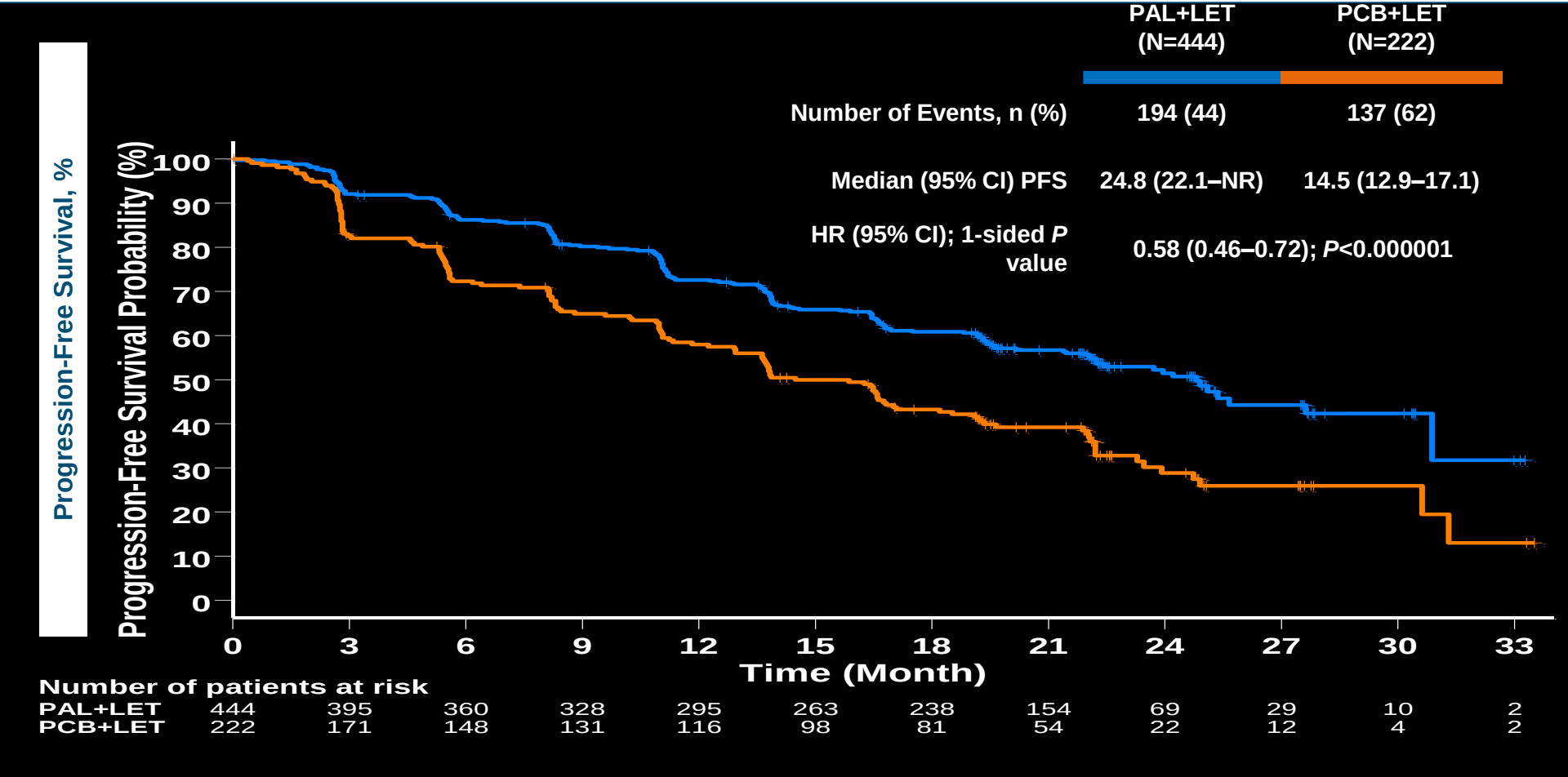
CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Miller T, et al. *Cancer Discov.* 2011; 1:338-51.
3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

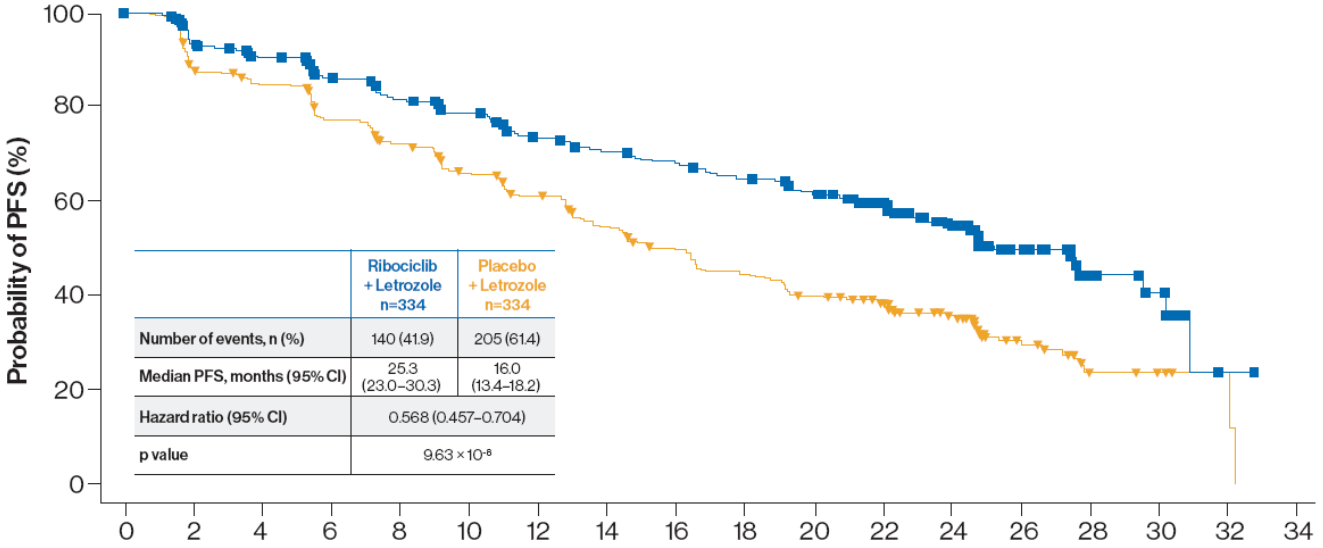
Palbociclib Phase III Advanced Breast Cancer

Study Name	Design	Setting	Intervention	Current Status
Paloma 1	Randomized Phase II	Advanced first line; ER+ HER2-	Letrozole +/- Palbociclib	HR: 0.488 p=0.0004; median PFS 20.2 vs 10.2 mo (IA) (Finn et al Lancet Oncol 2015)
Paloma 2	Randomized Phase III	Advanced first line; ER+ HER2-	Letrozole +/- Palbociclib	HR =0.58 Median PFS 24.8 vs 14.5 mo (p 0.000001) Finn, NEJM 2017
Paloma 3	Randomized Phase III	Advanced second line; ER+ HER2-	Fulvestrant +/- Palbociclib	HR 0.422 (P<0.000001), median PFS 9.2 vs 3.8 mo (IA) Turner NEJM 2015

PALOMA 2 PFS: Investigator-Assessed (ITT Population)



RIBOCICLIB: MONALESSA 2 Update



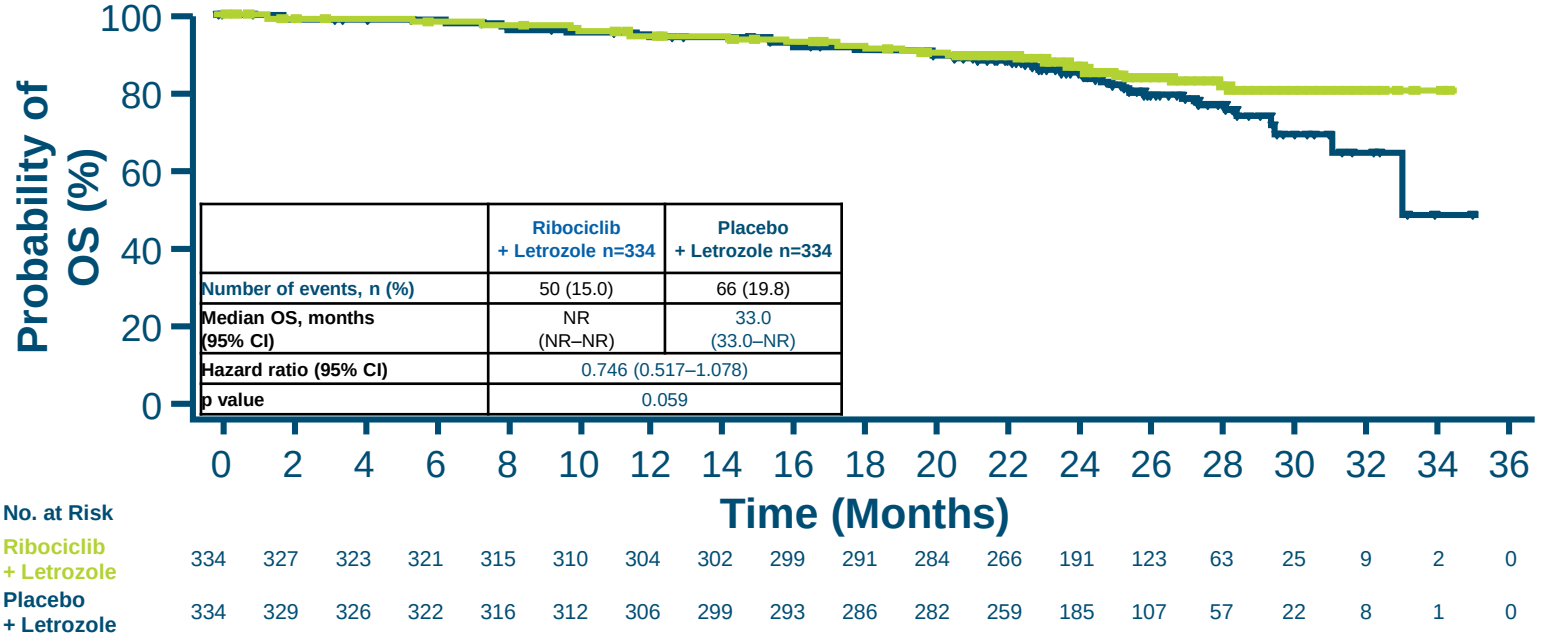
	Ribociclib + Letrozole n=334	Placebo + Letrozole n=334
Number of events, n (%)	140 (41.9)	205 (61.4)
Median PFS, months (95% CI)	25.3 (23.0–30.3)	16.0 (13.4–18.2)
Hazard ratio (95% CI)	0.568 (0.457–0.704)	
p value	9.63×10^{-8}	

No. at Risk																		
Ribociclib + Letrozole	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
Placebo + Letrozole	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

CI, confidence interval; PFS, progression-free survival.
Data cut-off: January 2, 2017.

Treatment benefit was consistent across pre-specified patient subgroups, including ECOG performance status, age, prior therapies, and *de novo* ABC

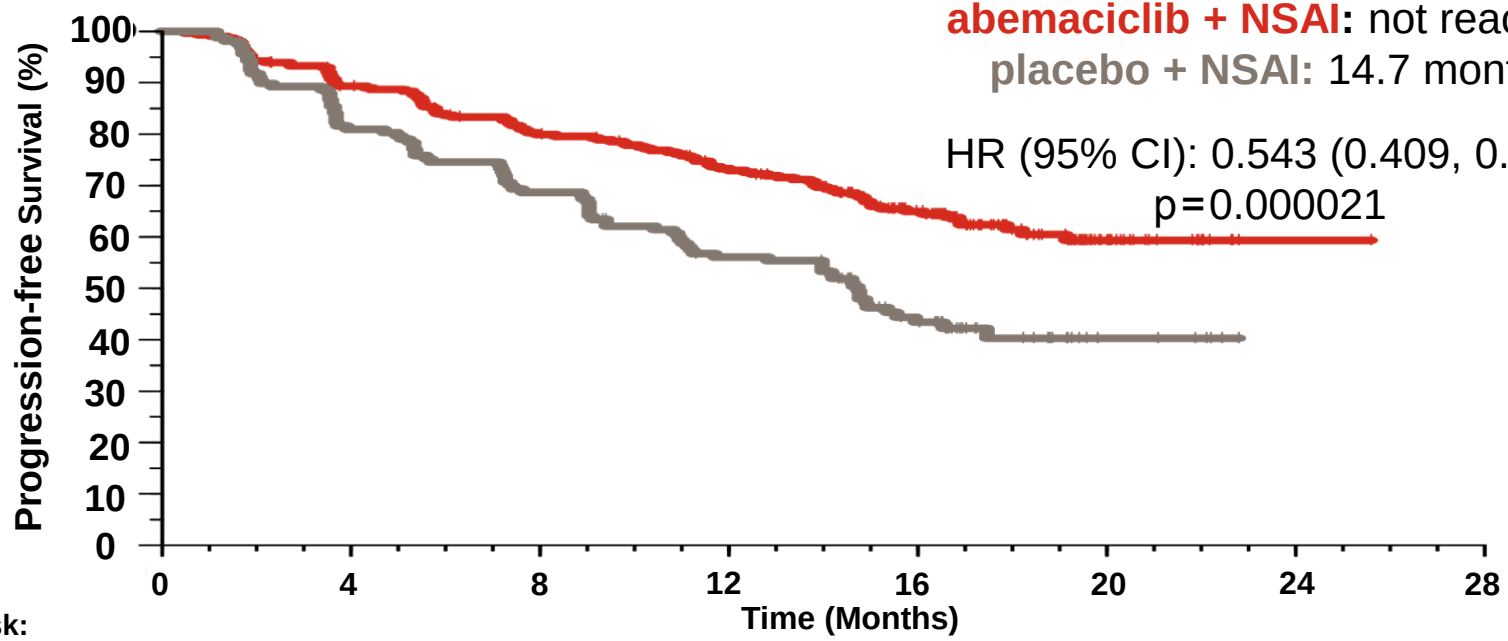
RIBOCICLIB: MONALEESA 2 locally assessed overall survival



Data cut-off: January 2, 2017.

Abbreviations: CI, confidence interval; NR, not reached; OS, overall survival.

ABEMACICLIB: MONARCH 3 : PFS



Patients at Risk:								
abemaciclib arm	328	271	234	205	125	25	1	0
placebo arm	165	127	105	82	45	7	0	0

PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p=.000102

Trend Trial

- TREnd trial: phase 2 trial (n=115) of pabloclib as single agent vs as combination with endocrine in pts who progressed on endocrine therapy

  - ORR: 11% with combination and 7% alone
  - PFS: 10.8 mo with combination and 6.5 mo alone

  - Should we start with monotherapy and add in? or start with combination?
    Development of resistance?

PALOMA 3 Study Design

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received goserelin.

2:1 Randomization

N=521

Stratification:

- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

n=347

Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)

n=174

Placebo (3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)

Primary Endpoint = PFS

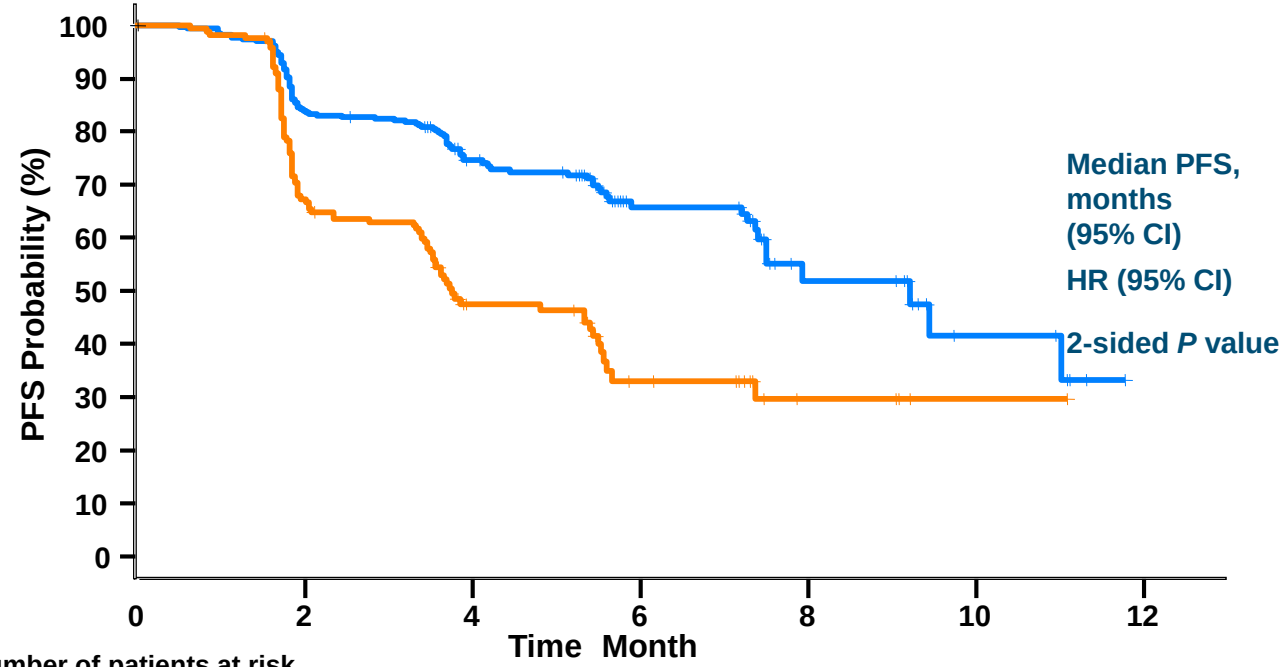
Secondary Endpoints = Response, CBR, OS, Safety, Biomarkers, Patient Related Outcomes

- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

†administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov NCT01942135

Primary Endpoint: PFS (ITT Population)



	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

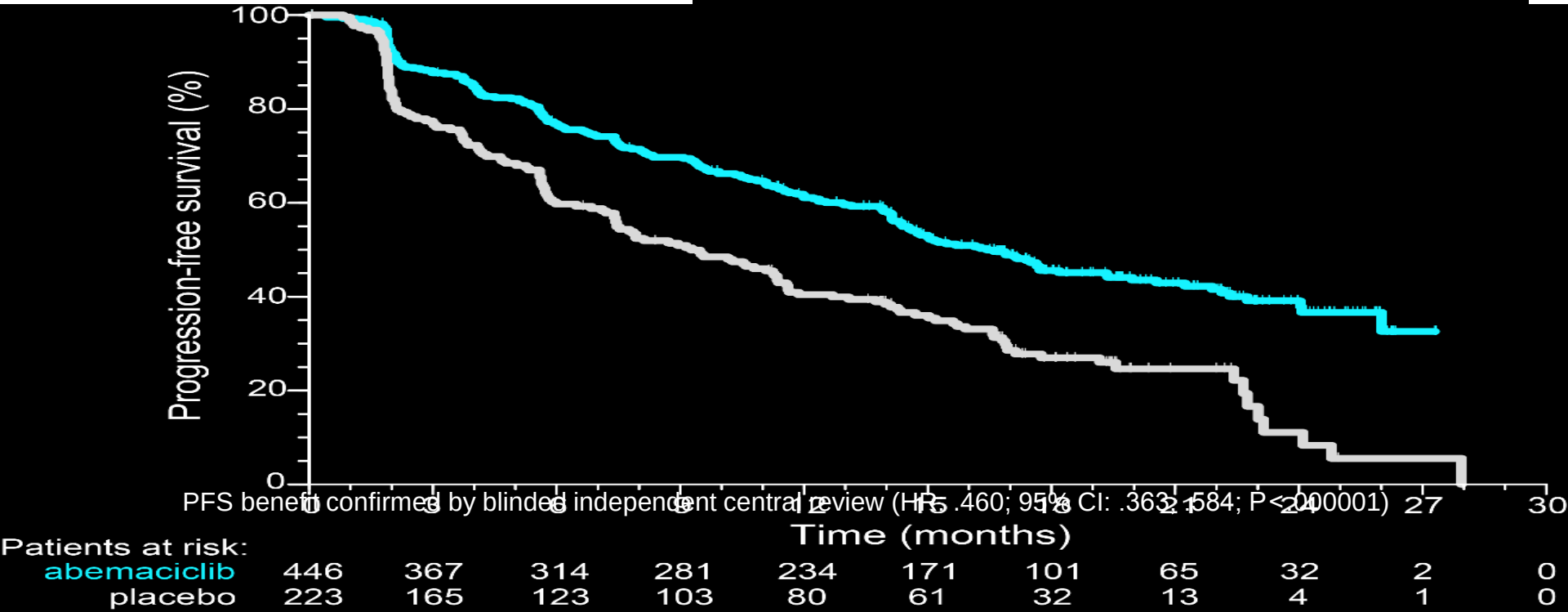
CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

MONARCH 2: Primary Endpoint: PFS (ITT)

Median PFS

abemaciclib + fulvestrant: 16.4 months

placebo + fulvestrant: 9.3 months



PFS benefit confirmed by blinded independent central review (HR .460; 95% CI: .363, .584; P <.000001)

Differences in PK, PD, dosing, and toxicity between the three CDKi

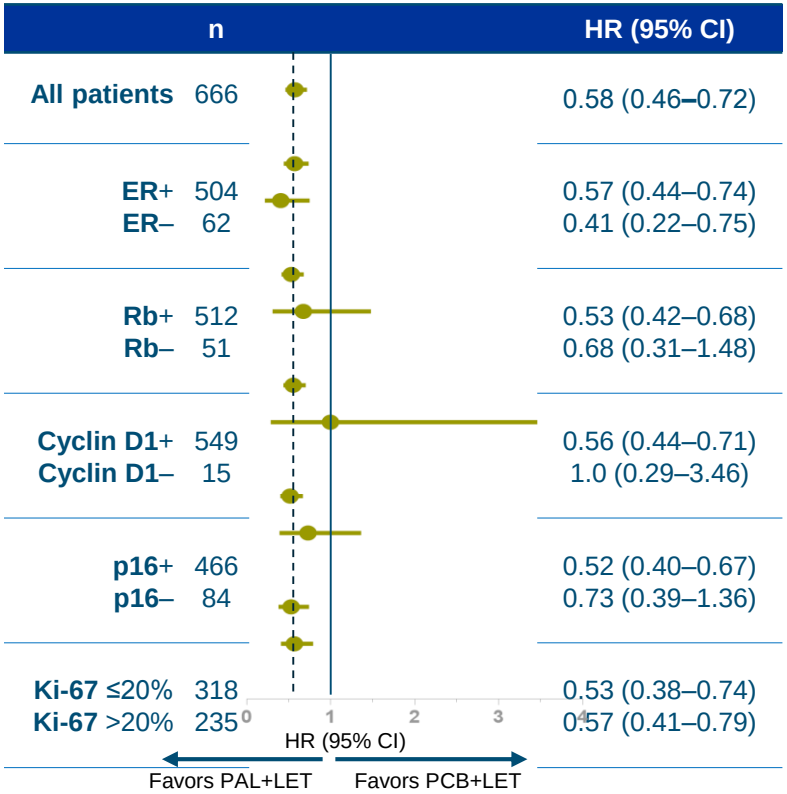
	Palbociclib	Ribociclib	Abemaciclib
PK	**T_{max} 4.2–5.5 hours $t_{1/2}$ 25.9–26.7 hours**	**T_{max} 4 hours $t_{1/2}$ 24–36 hours**	**T_{max} 4–6 hours $t_{1/2}$ 17–38 hours (Crosses blood:brain barrier)**
PD	**Reduced Rb phosphorylation in paired tumour biopsies, along with reduced fluorothymidine-PET uptake**	**Reduced Rb phosphorylation and Ki67 expression in paired tumour biopsies**	**Reduced Rb phosphorylation and TOPO IIα expression in paired tumour and skin biopsies**
Dosing	**125 mg daily (3 weeks, 1-week drug holiday) or 200 mg daily (2 weeks, 1-week drug holiday)**	**600 mg daily (3 weeks, 1-week drug holiday)**	**200 mg twice daily (continuous dosing)**
Major dose-limiting toxicities	**Neutropenia, thrombocytopenia**	**Neutropenia, thrombocytopenia**	**Fatigue**
Other reported adverse events	**Anaemia, nausea, anorexia, fatigue, diarrhoea**	**Mucositis Prolonged ECG QTc interval Elevated creatinine Nausea**	**Diarrhoea Neutropenia**

Questions in Treatment of ER+ ABC

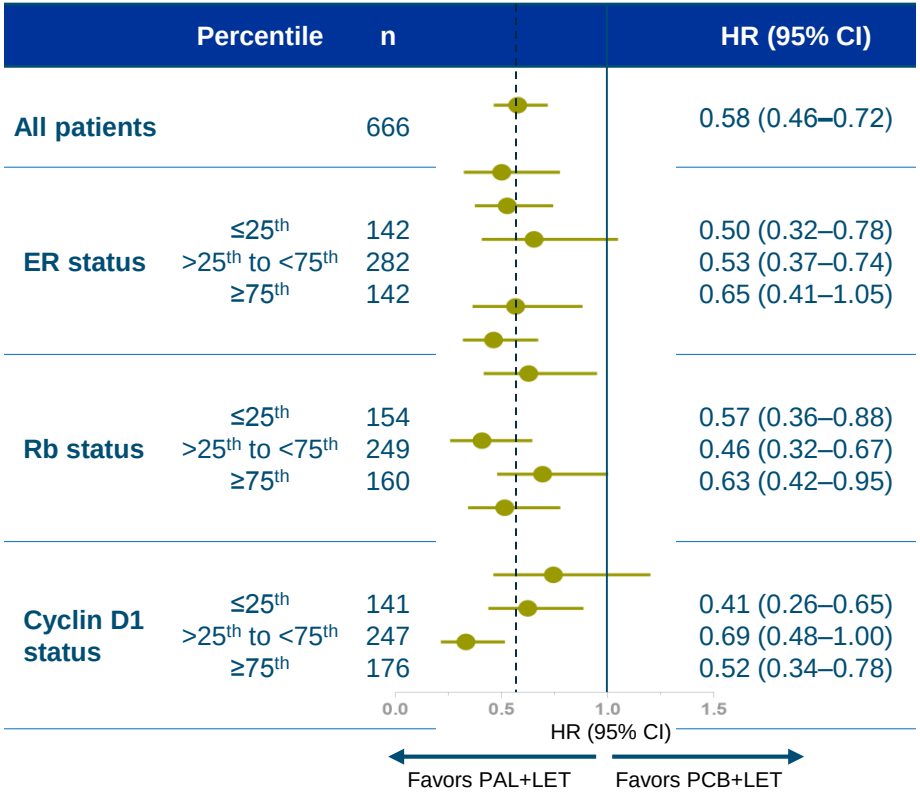
- First line
  - Visceral vs non visceral
  - Primary vs Secondary Resistance
  - Survival benefit ?
- Second line
  - Prior exposure and response
  - Visceral vs non visceral
- Beyond
  - Is there a role for rechallenge of a class with a different partner? Or a different agent? Or a combination of agents?
  - What about the role of ctDNA in the clinic
  - What about the role of ESR1 mutations

Subgroup Analysis of PFS by Biomarker for PALOMA2

Qualitative Analysis



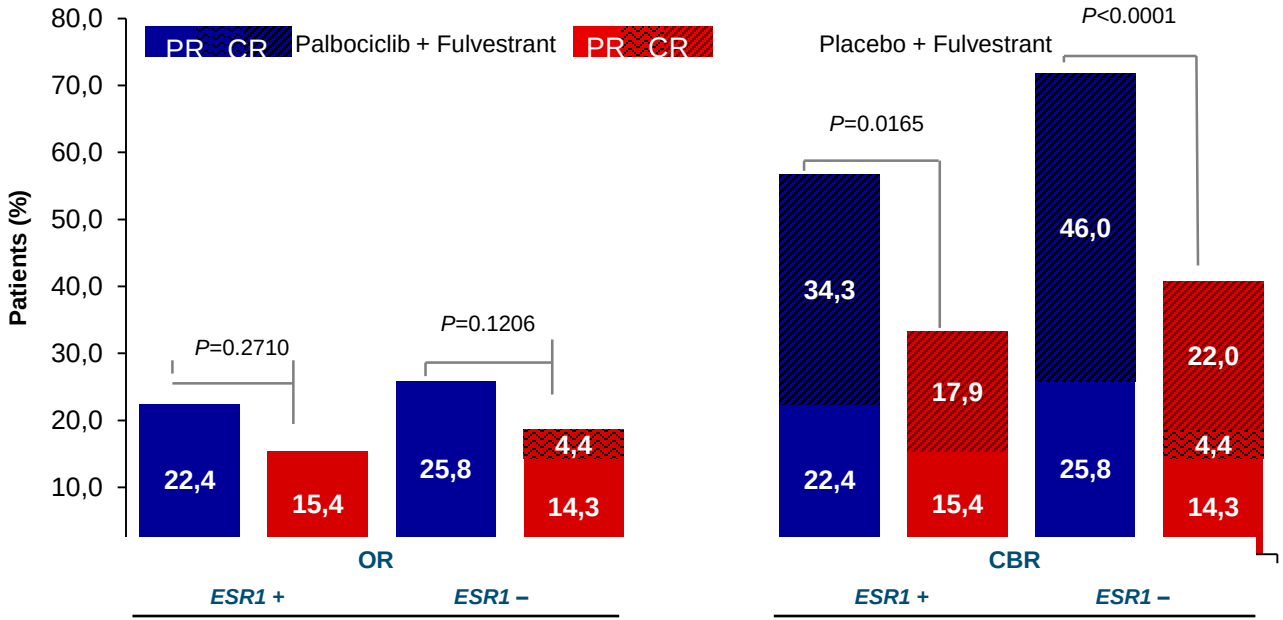
Quantitative Analysis



hazard ratio; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

PALOMA 3: Efficacy of Palbociclib Plus Fulvestrant in Patients With MBC and *ESR1* Mutations in Circulating Tumor DNA

Response by *ESR1* Mutation Status



Odds Ratio (95% CI)	1.59 (0.51–5.49)	1.51 (0.79–2.99)	2.62 (1.07–6.54)	3.70 (2.13–6.44)

CBR=clinical benefit response; CR=complete response; OR=objective response; PR=partial response; SD=stable disease ≥24 months.

N. Turner, ASCO 2016

EVEROLIMUS: Adverse Events

Most Common Adverse Events (AEs)

- **Fatigue**
- **Stomatitis**
- **Rash**
- **Anorexia**
- **Diarrhea**

Less frequent but clinically relevant:

- **Hyperglycemia**
- ***Pneumonitis: Rare but potentially fatal***

Significant % (about 20%) of EVE–treated patients required a dose reduction

Clinical Management Strategy

- **Focus on patient awareness and early intervention**
- **Importance of well defined management & dose reduction/delay or drug discontinuation guidelines**

(they exist for stomatitis, pneumonitis, hyperglycemia)

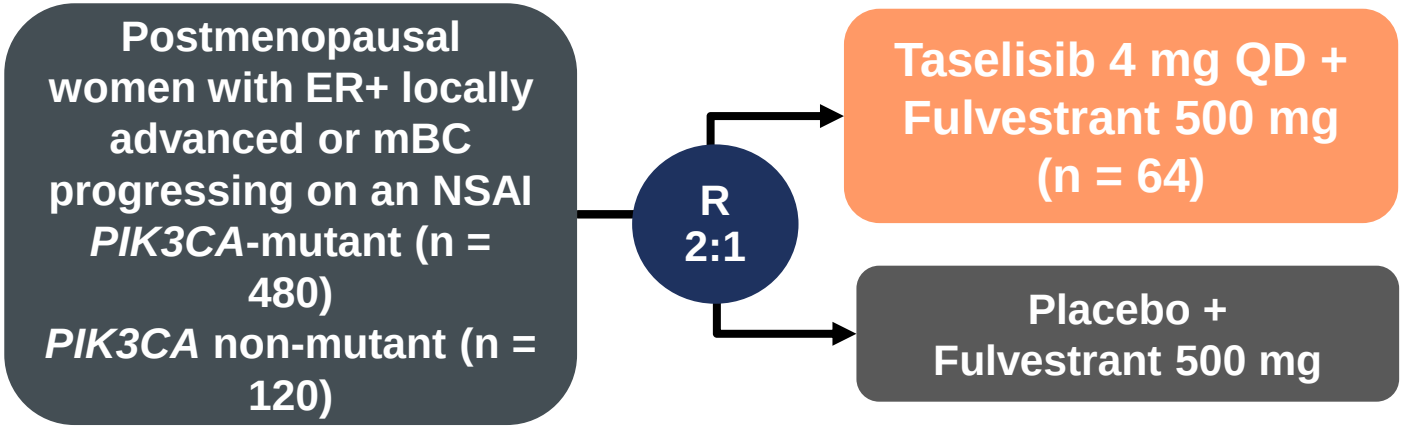
Are TORC kinase inhibitors better everolimus? - MANTA Trial

Investigator-initiated academic Trial (Sponsor: QMUL); funding received from AstraZeneca
Coordinating centre: CECM (within Barts Cancer Institute)

Trial open in 60 sites across the UK, Germany, Spain, and Portugal
Additional 30 sites to open in France, Hungary, Korea, Romania and Georgia in next 3 months

Queen Mary University of London · ECMC · NCRN · Barts Health NHS Trust

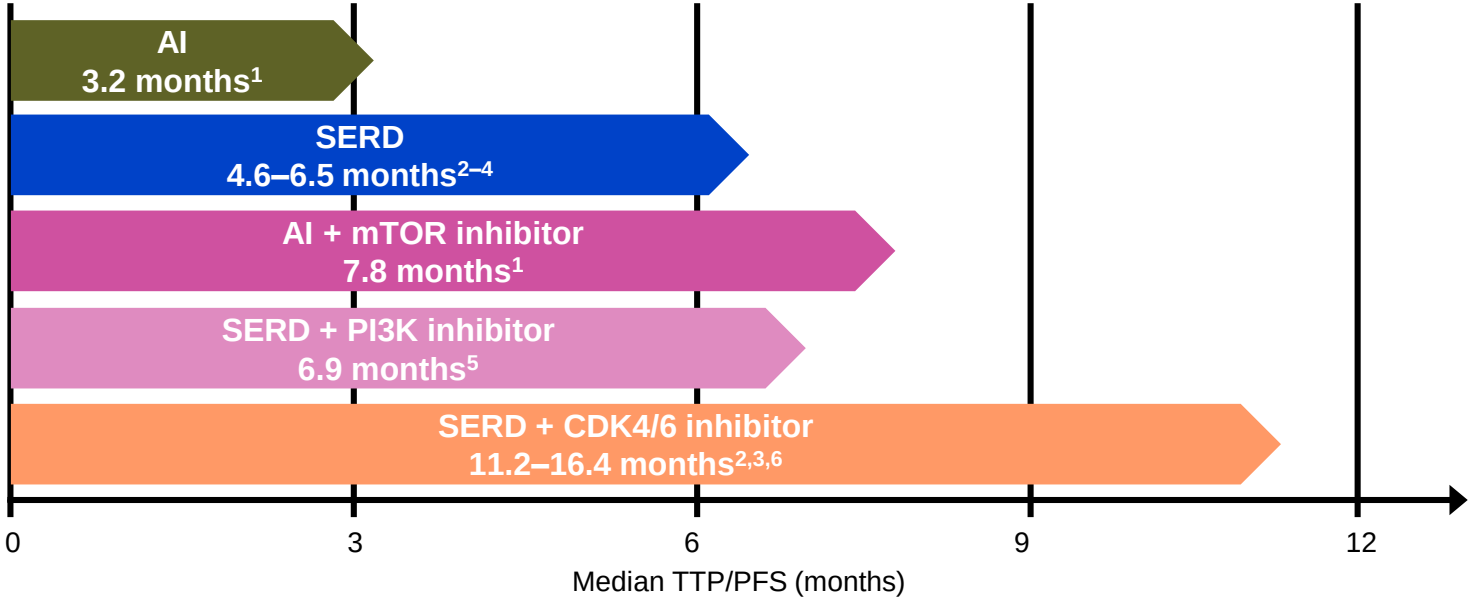
Taselisib + Fulvestrant in PIK3CA-Mutant mBC: SANDPIPER Trial



- Randomized, double-blind, placebo-controlled, phase 3 trial
- Randomization stratified by visceral disease, endocrine sensitivity, geographic region
- Primary endpoint: Investigator assessed PFS in pts with PIK3CA-mutant tumors
- Secondary endpoints: OS, ORR, CBR, DOR, safety, pharmacokinetics, patient-reported outcomes

Baselga J, et al. *J Clin Oncol.* 2015;33:Abstract TPS629.

Evolution of therapy for endocrine-resistant metastatic breast cancer



AI, aromatase inhibitor; CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; SERD, selective oestrogen receptor degrader; TTP, time-to-progression

1. Yardley DA, et al. *Adv Ther* 2013;30:870–84;
2. Palbociclib EU SmPC, May 2017;
3. Turner NC, et al. SABCS 2016 (Abstract P4-22-06);
4. Di Leo A, et al. *J Clin Oncol* 2010;28:4594–600;
5. Baselga J, et al. *Lancet Oncol* 2017;18:904–16;
6. Sledge GW, *et al. J Clin Oncol* 2017:35;25:2874–84.

Patient DS

- 55 year old woman who presents with a T2N1 tumour, ER+, PR+ HER2 negative
- Well except for long standing back pain
- Partial mastectomy done showing a 3.5 cm, Grade II, ER 8/8, PR 6/8 HER2 negative, 1/ 6 nodes involved with a 1.5 cm mass, no extranodal disease

- Comes to medical oncologist without staging
- Staging finds multiple bone metastases, normal liver, possible increased hilar lymph nodes,
- Blood work normal except for elevation of CA15-3

Patient DS– de novo ABC

- She is put on zolendronic acid and
- Should she get

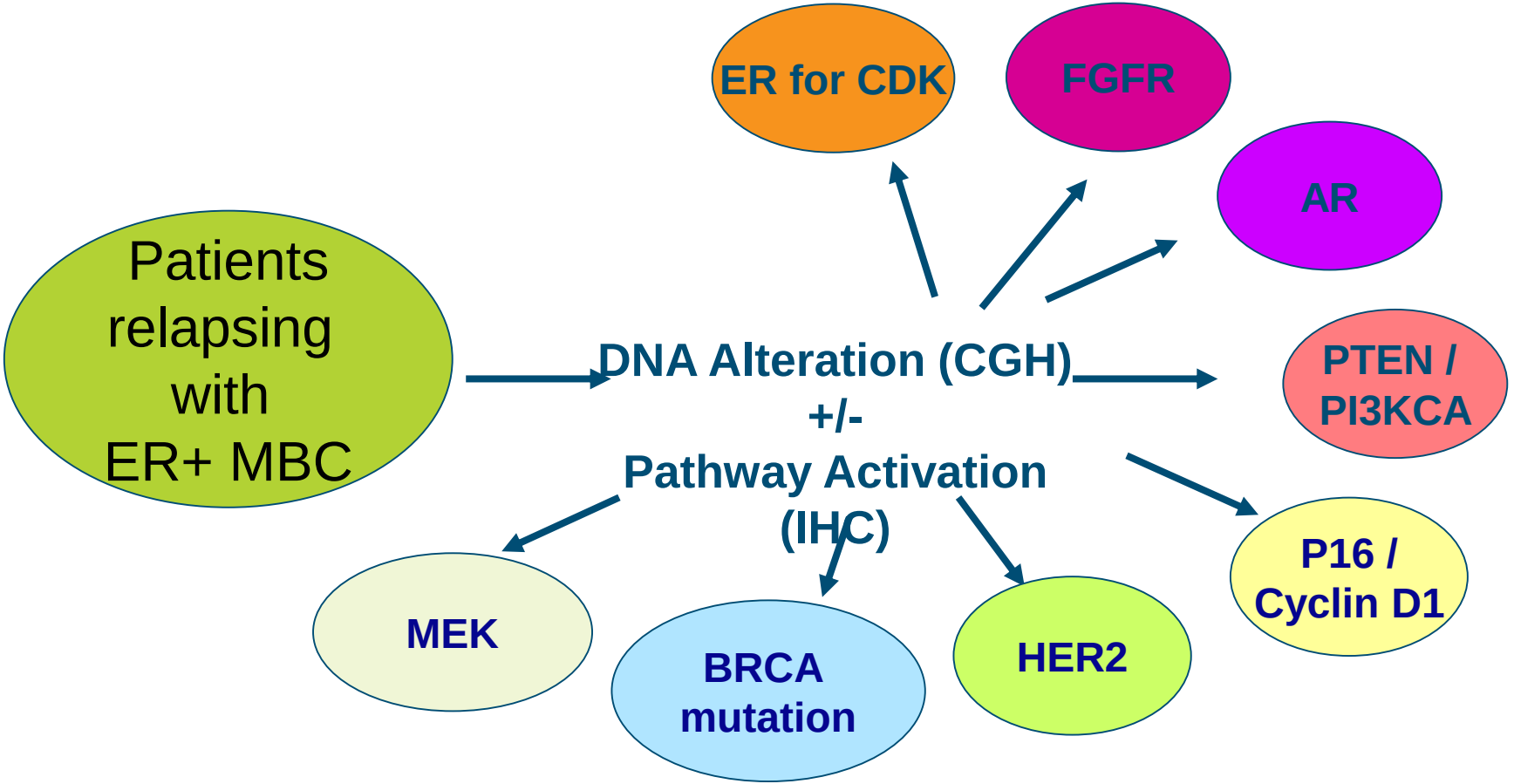
- AI alone and if no response add in CDK4/6?
- AI plus CDK4/6?
- Fulvestrant alone?

- Is there a correct answer?

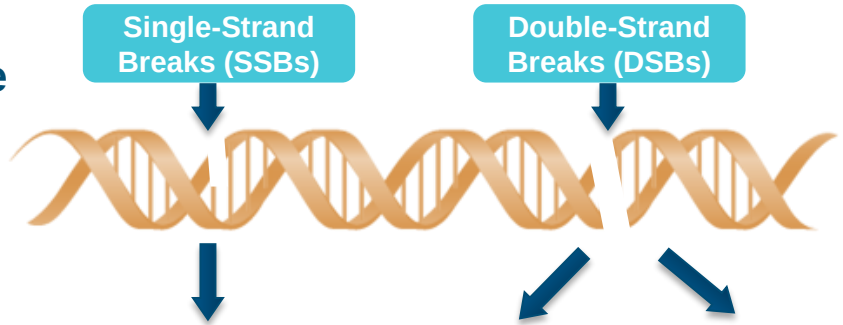
Ms DS

- She gets fulvestrant and has a 22 month of stable diseaase
- At the time of progression increased bone pain, increased bone mets with new lesions, and also growing supraclavicular and hilar nodes
- What is your second line therapy
- ? Letrozole and CDK4/6
- ?Fulvestrant and CDK4/6
- ?AI alone
- ?Exemestane and everolimus?

Biology-driven Treatment Options for ER+ MBC



DNA REPAIR IS MORE ERROR-PRONE WHEN BRCA1 OR BRCA2 PROTEINS ARE DEFICIENT



Two Major Mechanisms for the Repair of DNA Double-Stranded Breaks

1. **Homologous Recombination Repair (HRR)**
   - Non-functioning HRR may be due to BRCA 1 or BRCA 2 deficiency

2. **Non-Homologous End-Joining (NHEJ)**
   - Less precise, more error-prone

Non-functioning HRR results in:
- Accumulation of additional mutations
- Chromosomal instability
- Increased risk for malignant transformation

BER = base excision repair; HRR = homologous recombination repair; NHEJ = non-homologous end-joining.

1. Lord CJ, Ashworth A. *Nature.* 2012;481:287-94.
2. Marquard AM, et al. *Biomarker Res.* 2015;3:9
3. Curtin N. *Nat Rev Cancer.* 2012;12:801-17.
4. Frey MK, Pothuri B. *Gynecol Oncol Res Pract.* 2017;4:4.

PATIENTS WITH BRCA-MUTATED BREAST CANCER ARE YOUNGER WITH MORE AGGRESSIVE DISEASE

Comparison of clinicopathological characteristics of *BRCA* carriers and non-carriers at Oslo University Hospital (N = 440)

Characteristics of *BRCA* mutation-positive vs mutation-negative patients	
• Younger, mean 42 vs 58 yrs	P < 0.001
• Tumours of higher grade	P = 0.001
• ER negative	P < 0.001
• Triple-negative breast cancer	P < 0.001
• Tumours with higher Ki67 – Comparing mean – Comparing number with <30% activity	 P < 0.001 P = 0.004
• Family histories of breast and/or ovarian cancer	P = 0.035

Grindedal EM, et al. *BMC Cancer.* 2017;17:438

BRCA GERMLINE MUTATIONS ARE ASSOCIATED WITH POORER SURVIVAL OUTCOMES

Systematic Review and Meta-analysis:

- 60 studies met inclusion criteria (1996-2015)
- N = 105,220 breast cancer patients; n = 3588 *BRCA* mutation carriers (3.4%)

BRCA*-positive vs *BRCA*-negative Cases	**Overall Survival HR (95%CI)**	**Breast-Cancer Specific Survival HR (95%CI)**
BRCA1 - 17 OS studies - 14 BCSS studies	1.46 (1.12–1.91) P = 0.006 **46% increased risk of dying**	1.22 (0.91–1.63) P = 0.17
BRCA2 - 6 OS studies - 8 BCSS studies	1.10 (0.82–1.47) P = 0.54	1.34 (1.04–1.73) P = 0.02 **34% increased risk of dying from breast cancer**

*BRCA mutation tested negative patients represented the reference group; HR > 1 indicated a poorer outcome for the experimental group
BC = breast cancer; BCSS = breast cancer-specific survival; OS = overall survival; TNBC = triple-negative breast cancer.

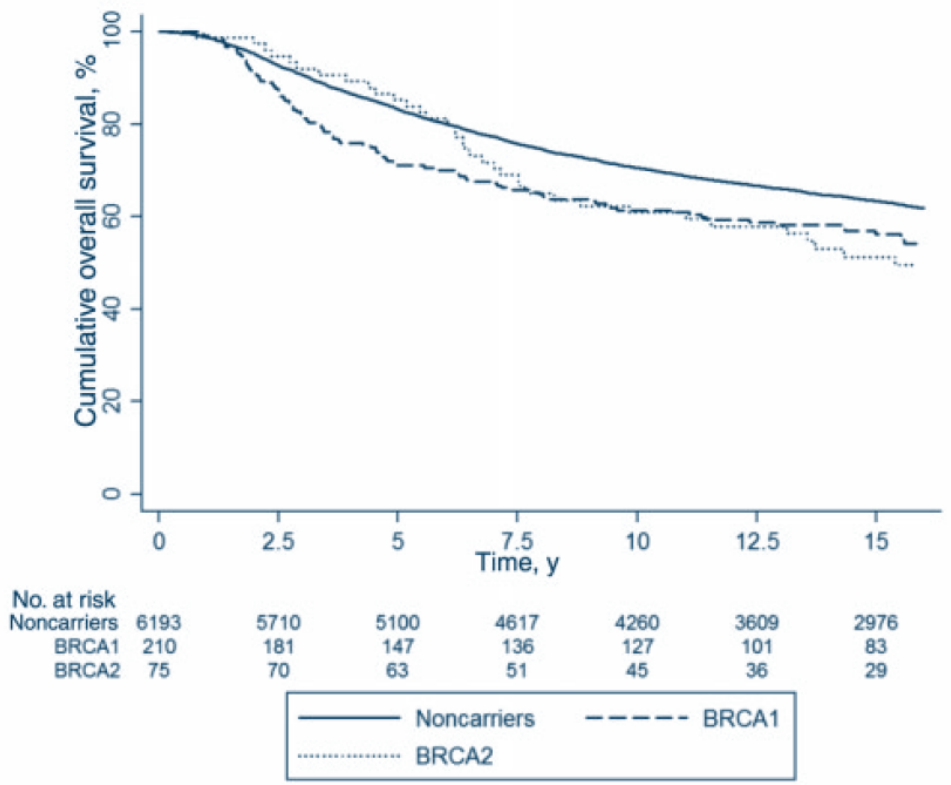
Baretta Z, et al. *Medicine*. 2016;95(40):e4975.

POORER SURVIVAL IN BRCA1/2 CARRIERS DIAGNOSED WITH BREAST CANCER BEFORE AGE 50

Cohort of Young, Invasive BC Patients (10 Dutch Hospitals)

- N = 6478
- Invasive BC diagnosis before age 50 years
- *BRCA1m,* 3.2%
- *BRCA2m,* 1.2%

10-year OS	
BRCA1m carriers	61.4%
BRCA2m carriers	60.9%
Non-carriers	70.4%



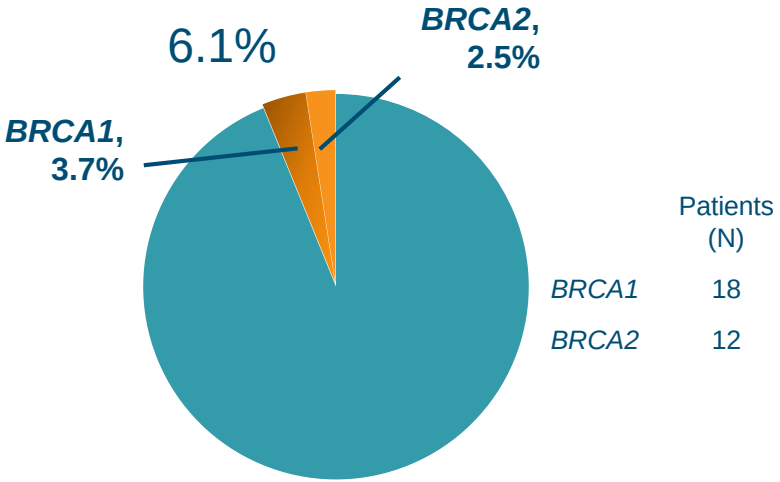
BC = breast cancer; OS = overall survival.

Schmidt MK, et al. *J Natl Cancer Inst.* 2017;109(8).

WHAT IS OUR UNDERSTANDING *BRCA* MUTATIONS PREVALENCE IN BREAST CANCER?

Germline BRCA Mutations

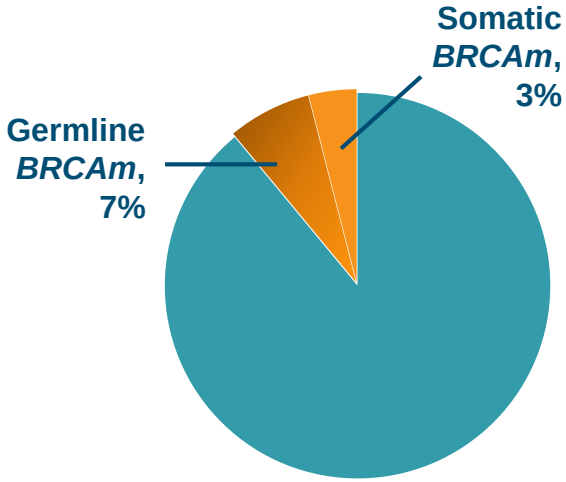
Dana Farber, Breast Cancer Patients (Stage I-III) Consenting to DNA Banking (N = 488), 2010-2012[1]



	Patients (N)
BRCA1	18
BRCA2	12

Germline vs Somatic Mutations

Sweden, Unselected Cohort of Breast Cancer Patients (N = 273), 2007-2009[2]



	Patients (N)
Germline *BRCA1*	10
Germline *BRCA2*	10
Somatic *BRCA1*	4
Somatic *BRCA2*	5

1. Tung N, et al. J Clin Oncol. 2016;34(13):1460-1468
2. Winter C, et al. Ann Oncol. 2016;27(8):1532-1538.

BRCA MUTATION PREVALENCE IN BREAST CANCER SUBTYPES: LIMITED DATA

Dana Farber Cohort (N=488), 2010-2012

	TNBC (n=87)	ER-Positive, HER2-Negative (n=301)	ER-Negative, HER2-Positive (n=37)	ER-Positive, HER2-Positive (n=63)
BRCA1	12.6%	1.7%	5.4%	0%
BRCA2	1.1%	3.3%	0.0%	1.6%

N = 499 Dana Farber stage I-III breast cancer patients consenting to DNA banking, 2010-2012

ER = estrogen receptor; TNBC = triple-negative breast cancer.

1. Tung N, et al. J Clin Oncol. 2016;34(13):1460-1468.

LIMITED FAMILY STRUCTURE CAN AFFECT IDENTIFICATION OF PATIENTS FOR *BRCA* TESTING

N = 1543
Women seen at US high-risk clinics for genetic cancer risk assessment (1997 – 2007)

N = 306
- Breast cancer before age 50
- No family history of breast or ovarian cancers in first- or second-degree relatives

	BRCA Mutation Carriers (%)		
	Limited Family Structure	Adequate Family Structure	P-value
N =306	13.7%	5.2%	0.02*
Aged < 40 y (n = 185)	15.4%	6.4%	0.08*
Aged ≥ 40 y (n = 121)	11.3%	3.4%	0.16†

*Using ^{2} test with continuity correction.
†Using 2-sided Fisher exact test.

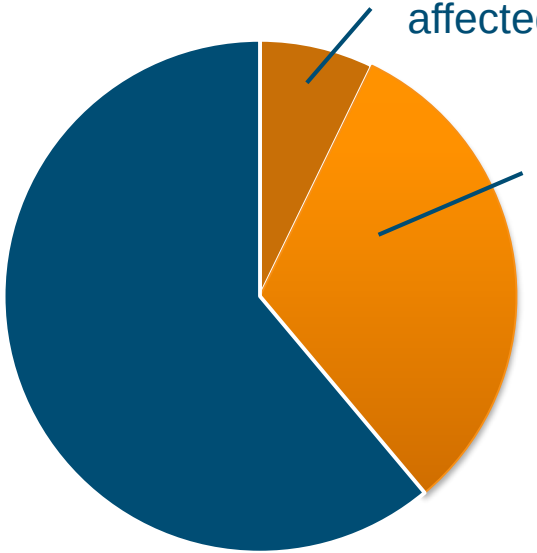
Limited family structure = fewer than 2 female relatives surviving beyond age 45 years in either parental lineage

Weitzel JN, et al. *JAMA.* 2007;297(33):2587-95.

IDENTIFICATION OF BRCA MUTATIONS LEADS TO MORE OPPORTUNITIES TO IDENTIFY UNAFFECTED CARRIERS

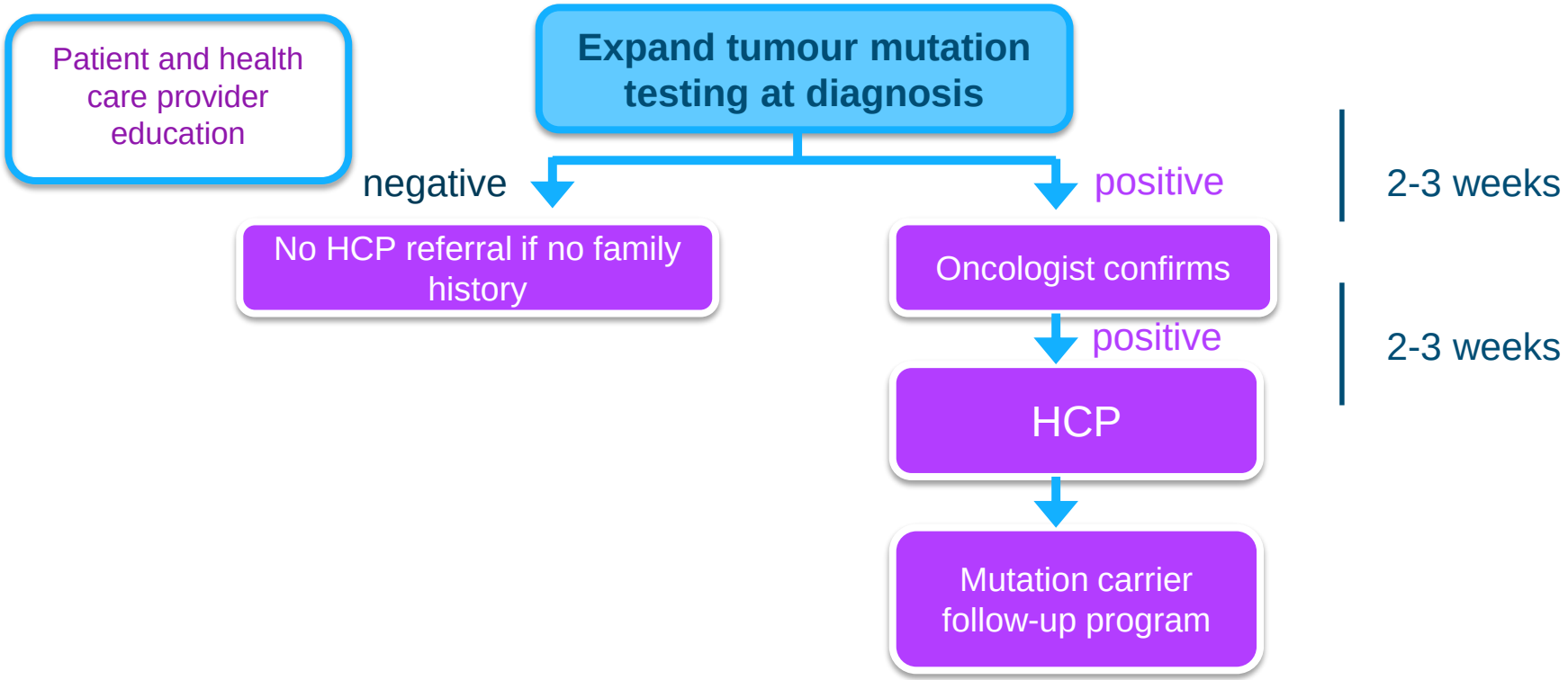
BRCA1 and *BRCA2* Testing in Ontario According to Established Criteria: Results from Mt. Sinai Hospital (2007-2014)

N = 763 women tested for a known family mutation

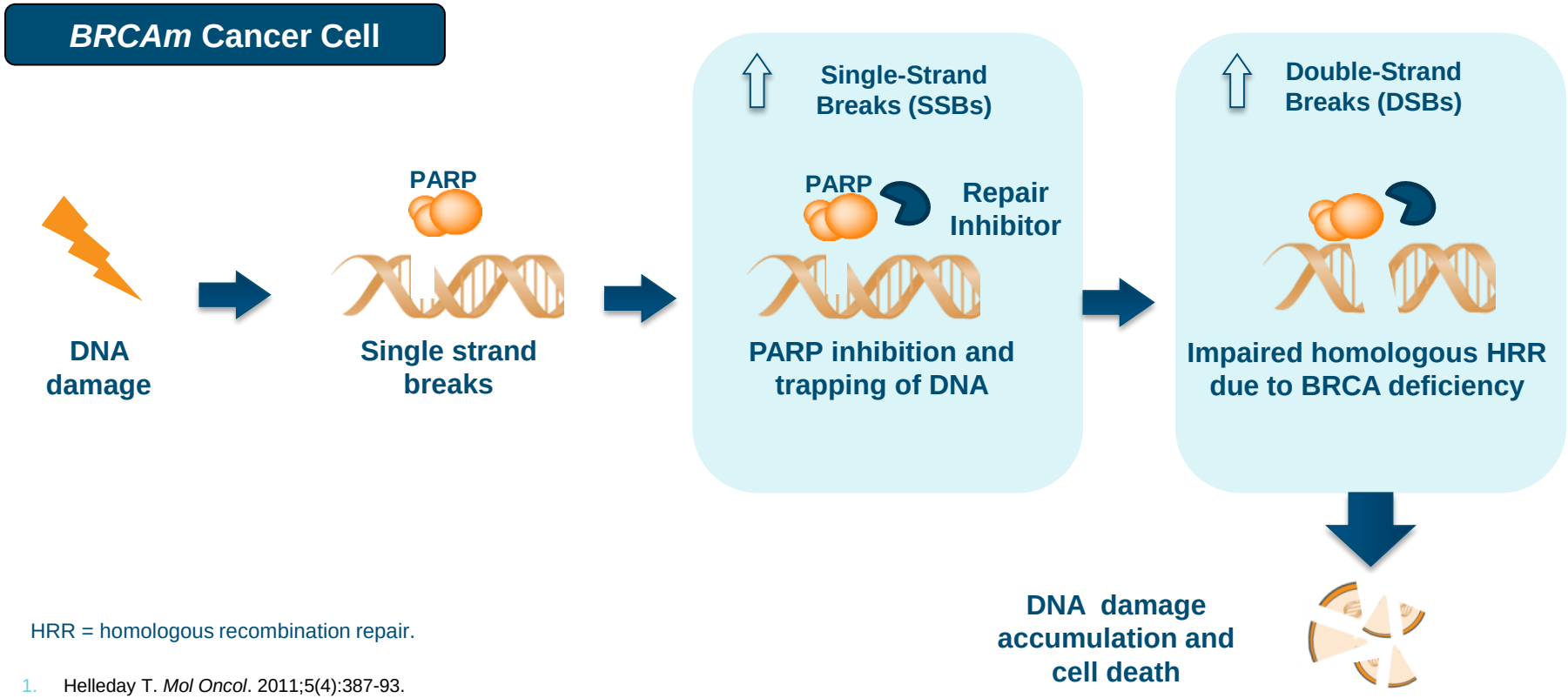


Finch A, et al. *Clin Genet,* 89: 304–11.

Changing Paradigms – is this the future?



RATIONALE FOR PARP INHIBITOR THERAPY IN BRCA-MUTATED TUMOURS



HRR = homologous recombination repair.

1. Helleday T. *Mol Oncol*. 2011;5(4):387-93.
2. Dziadkowiec K, et a. *Menopause Rev*. 2016;15(4):215-9.
3. Livraghi L, Garber JE. *BMC Med*. 2015 Aug 13;13:188.

PHASE 2 TRIAL OF OLAPARIB IN BRCA-DEFICIENT ADVANCED BREAST CANCER: PROOF OF CONCEPT

NCT00494234

- Recurrent, locally advanced or metastatic breast cancer
- *gBRCA1m* or *gBRCA2m*
- ≥ 1 chemotherapy regimen
- If HR+, ≥ 1 hormonal therapy

N=54

COHORT 1 (N=27)
Olaparib
400mg PO bid

COHORT 2 (N=27)
Olaparib
100mg PO bid

	COHORT 1 Olaparib 400 mg BID (N=27)	COHORT 2 Olaparib 100 mg BID (N=27)
Primary endpoint: ORR, n (%)	**11 (41%)** 95%CI(25-59)	**6 (22%)** 95%CI (11-41)
Complete response	1 (4%)	0
Partial response	10 (37%)	6 (22%)
Stable disease	12 (44%)	12 (44%)
Most Frequent Grade 3-4 AEs: n (%)		
Fatigue	4 (15%)	1 (4%)
Nausea	4 (15%)	0
Vomiting	3 (11%)	0
Anemia	3 (11%)	2 (7%)

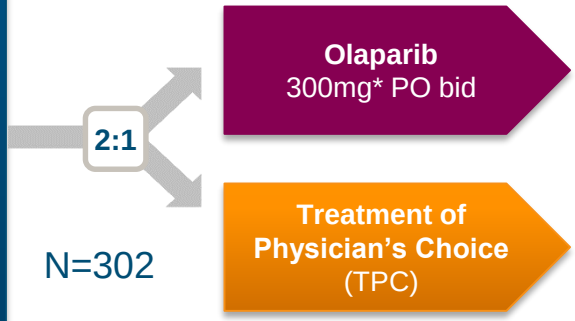
g*BRCA*m=germline BRCA mutation; HR+ = hormone receptor positive; ORR=objective response rate

Tutt A, et al. *Lancet.* 2010;376:235-44.

OLYMPIAD: STUDY DESIGN

NCT02000622

- g*BRCA*m MBC
- TNBC or HER2-negative, ER/PR positive
- ≤ 2 prior chemotherapy lines for MBC
- Previous treatment must include anthracycline and taxane
- HR+ disease progressed on ≥ 1 endocrine therapy, or not suitable
- If patients have received platinum therapy there should be:
  - No evidence of progression during treatment in the advanced setting
  - > 12 mo since (neo)adjuvant treatment and randomization



Primary endpoint
- PFS (RECIST 1.1, Independent Review)

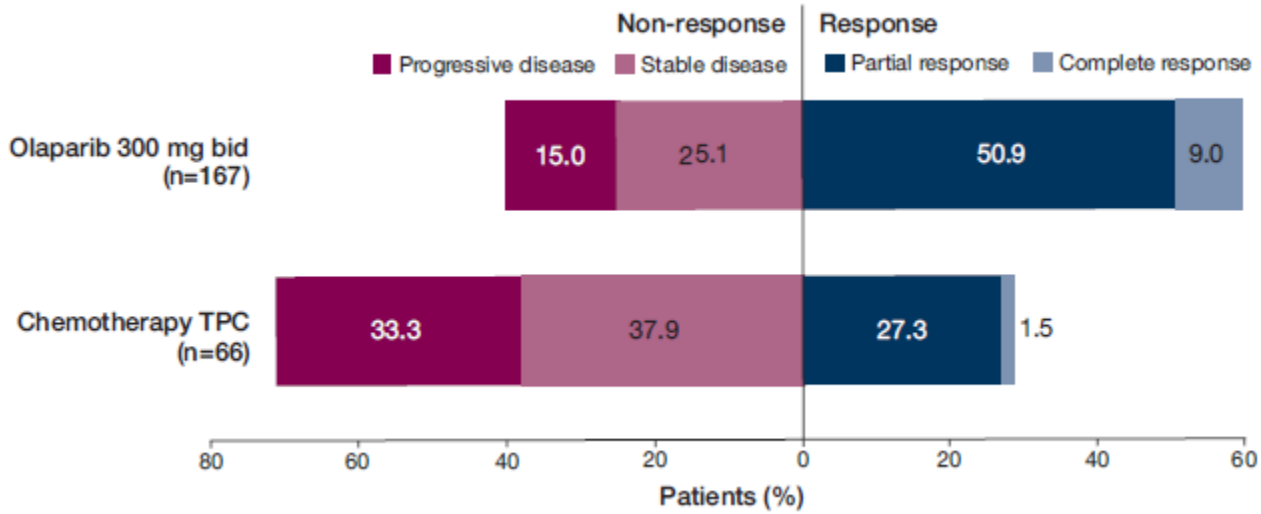
Secondary endpoints
- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad g*BRCA*m status
- HRQoL
- Safety and tolerability

* Tablet formulation (2 tablets twice daily)
g*BRCA*m=germline BRCA mutation; HER2=human epidermal growth factor 2; HR+ = hormone receptor positive; HRQoL=health-related quality of life; MBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; PO=oral; PR=progresterone receptor; TNBC=triple negative breast cancer; TPC=treatment of physician's choice; RECiST=_Response Evaluation Criteria in Solid Tumors.

Robson M, et al. *N Engl J Med*. 2017;377(6):523–33.

OLYMPIAD: OBJECTIVE RESPONSE IN EVALUABLE PATIENTS

- ORR was 59.9% in olaparib group vs 28.8% in TPC group

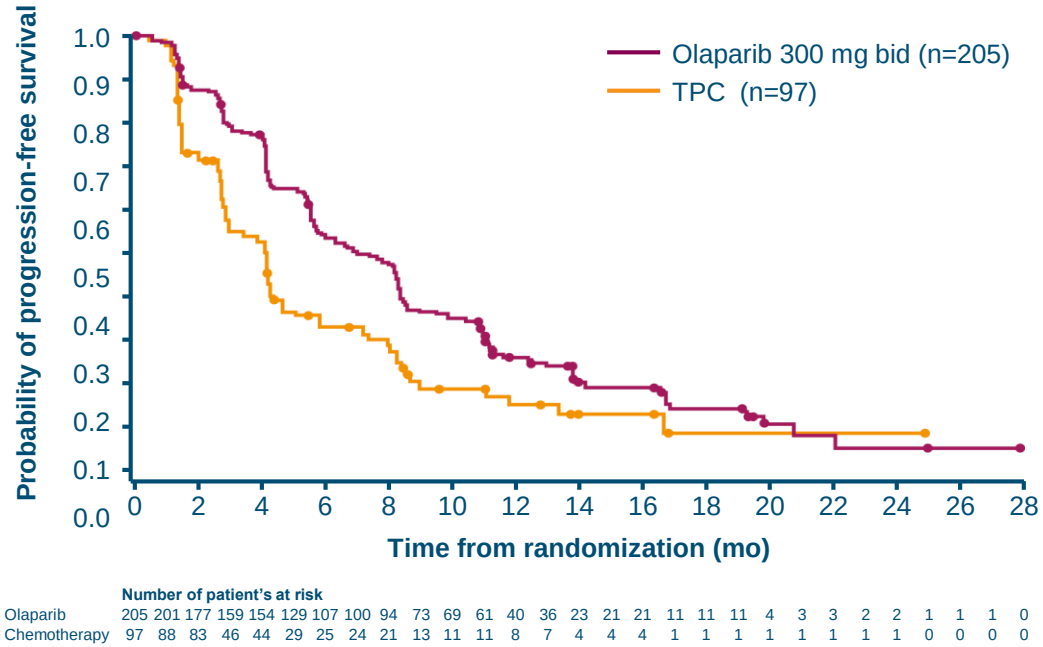


Stable disease was for ≥5 weeks, recorded ≥6 weeks after randomisation.
ORR = objective response rate; TPC = treatment of physician's choice.

Delaloge S, et al. ESMO 2017*;* abst. 2434 (poster 243PD).

OLYMPIAD: PROGRESSION-FREE SURVIVAL

- Risk of progression or death reduced by >40%



	Olaparib n=205	TPC n=97
Events (%)	163 (79.5%)	71 (73.2%)
Median (mo)	7.0	4.2
	HR = 0.58 95% CI (0.43, 0.80) P<0.001	
PFS free at 12m (%)	25.9	15.0

PFS = progression-free survival; TPC = treatment of physician's choice.

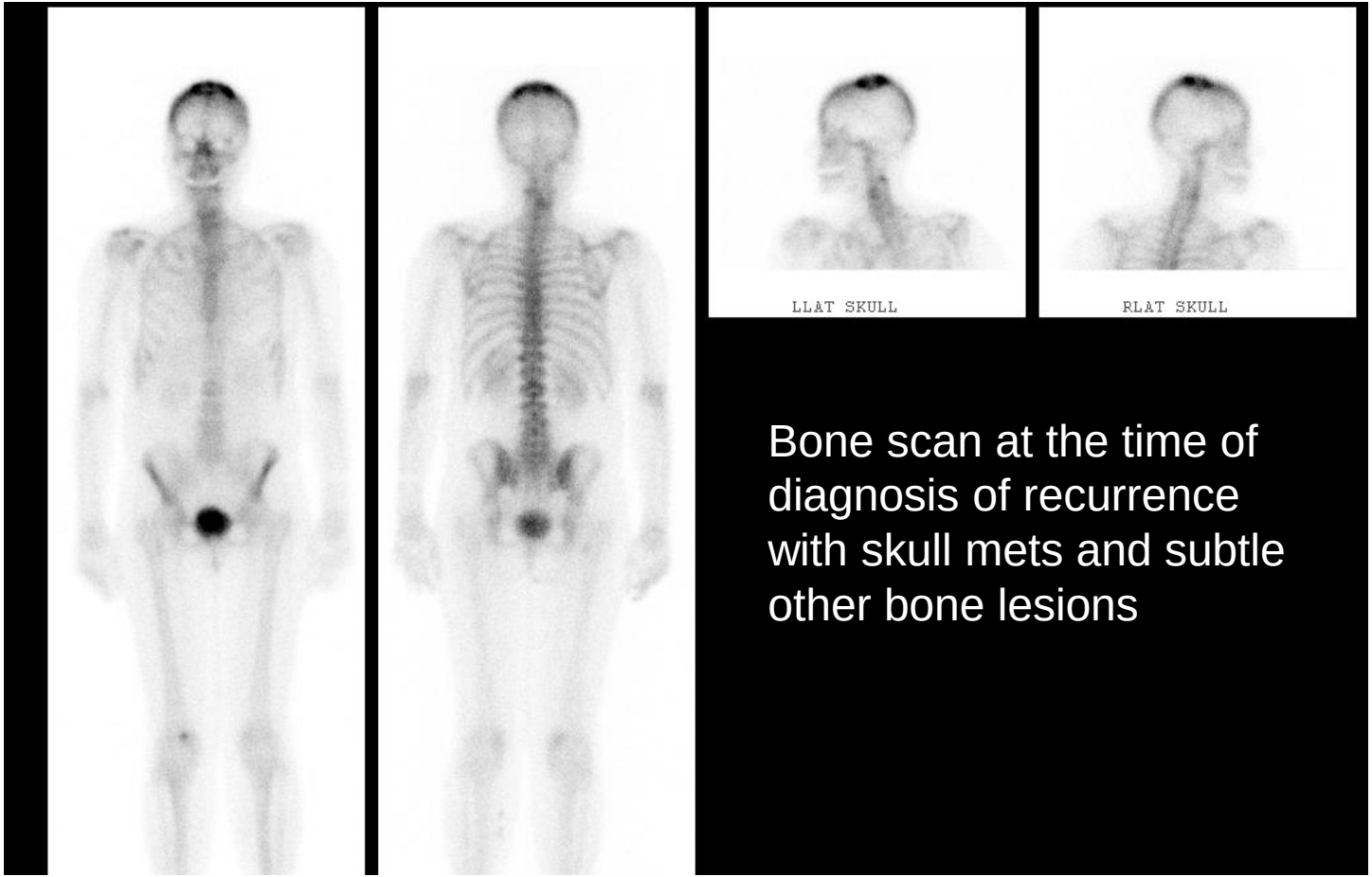
Robson M, et al. *N Engl J Med*. 2017;377(6):523–33.

62 YEAR OLD WITH BRCA 2+ ABC

- 1991 age 36 presented with DCIS treated with right partial mastectomy and RT
- 1996 presented with Stage IIIB ER+ HER2 neg left breast cancer, partial mastectomy
- Treated with CMF, RT and tamoxifen
- gBRCA 2 diagnosed in 2011, BSO 2011
- 2012 presented with bone mets bx proven ER+, PR+, HER2 neg
- Letrozole x18 months, faslodex x6 mo, exemestane and everolimus x 5 mo stopped with toxicity, tamoxifen x 2 months
- Late 2015 progressive bone mets and liver mets –

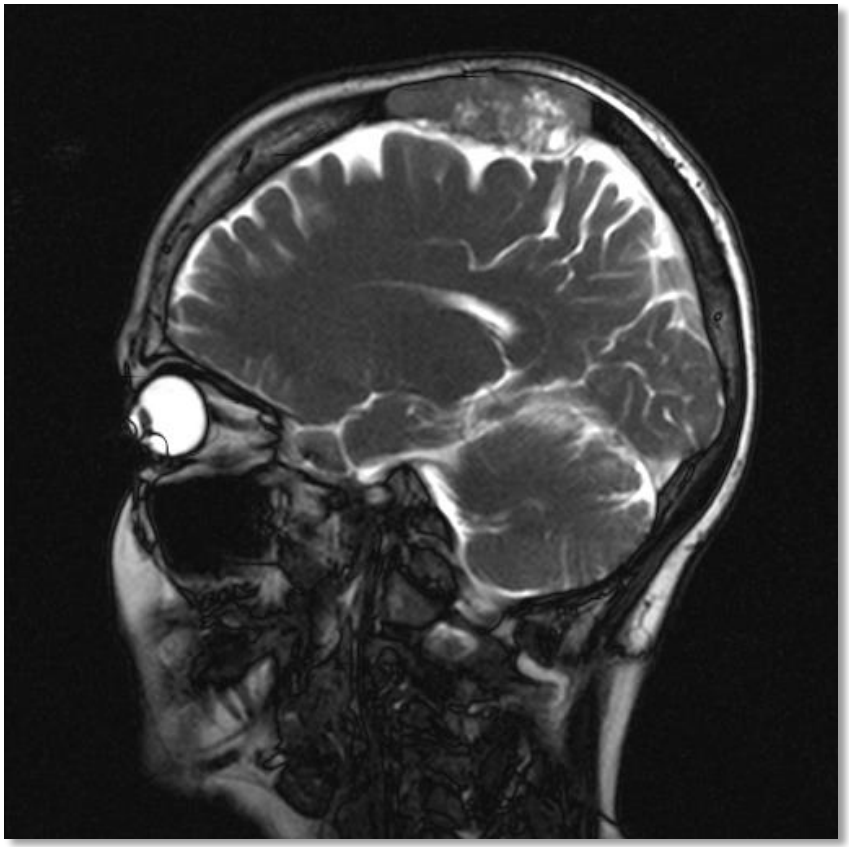
62 YEAR OLD WITH BRCA 2+ ABC

- Capecitabine with good response for 15 months before bone progression
- Cementoplasty
- Started on gemcitabine/cisplatin with good response but ototoxicity after 3 doses and she stopped with bad tinnitus
- July 2017 started on olaparib
- Severe nausea, dose decreased to half and then increased
- Continues with good partial response in bone and liver
- Tired but otherwise asymptomatic

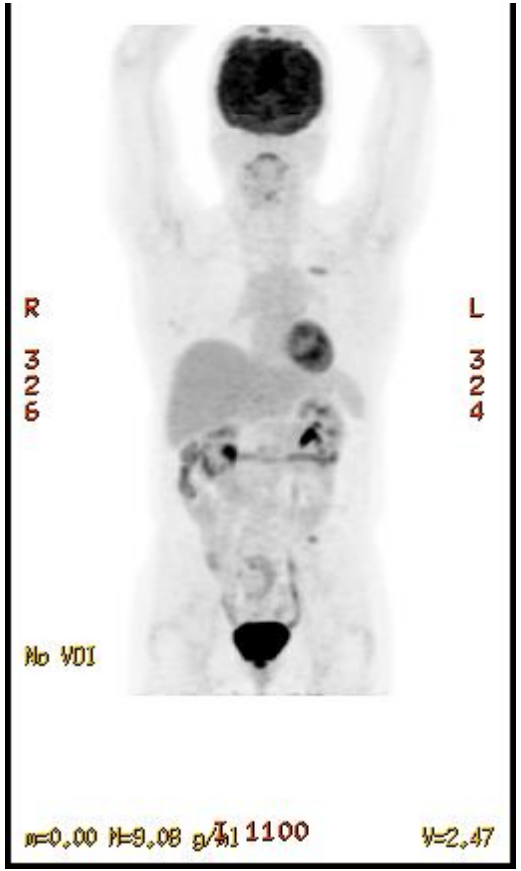


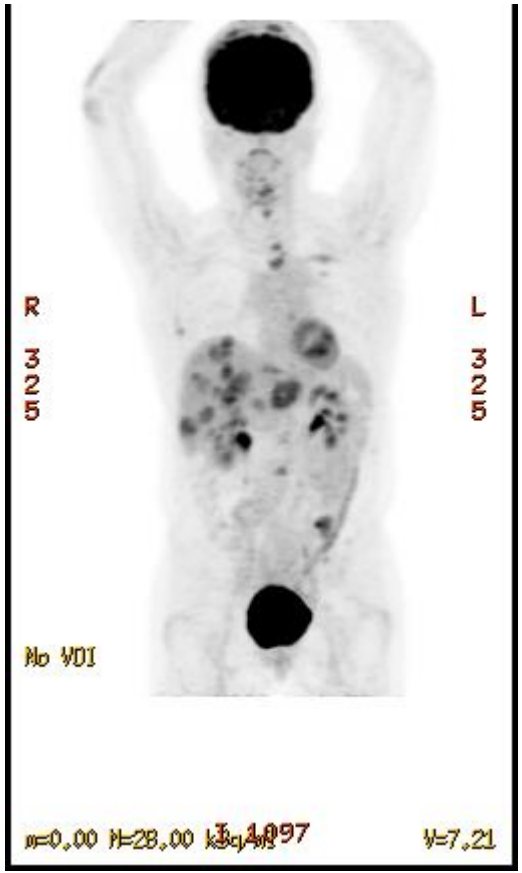
Bone scan at the time of diagnosis of recurrence with skull mets and subtle other bone lesions

MRI 2012: Skull Bone Metastases



PET scans in March 2017 after response to cisplatin/gemcitabine and in summer of 2017 with progression pre-olaparib





MS YC

- At 28 presented with a Grade 3, 4.5 cm, ER+, PR+, HER2 negative tumour with 2 nodes involved.
- Presented to med onc after surgery and treated with ddACT and RT to regional area
- Found to have BRCA2 mutation – no family history
- Treated with bilateral mastectomies with immediate recon
- Treated with tamoxifen by her med onc
- 2 years later interested in POSITIVE trial for pregnancy
- Prior to enrollment presented to ER with severe back pain
- Scans showed extensive bone and liver mets

MS YC

- Started on gemcitabine/carboplatin with excellent response
- Bone mets decreased, liver lesions disappeared on PET/CT
- After 6 cycles decision of further therapy
  - ? Zoladex/letrozole and CDK4/6
  - ? Olaparib
    ? Other

  - Also she is questioning her opportunity for a pregnancy

SUMMARY

- We have increasing options for treatment of HER2 negative tumours but we have a long way to go to understand predictive markers and BEST treatments
- For gBRCA – ER+ and ER- may have different selection of when to use PARPi
- For endocrine positive tumours the sequencing of the treatments is not clear
- Molecular markers may provide clues in the future with additional laboratory tools

Missing Data : Can We Predict Who Will Benefit and Who will not?