Inhibiting CDK4/6, PIK3CA, and PARP in mBC

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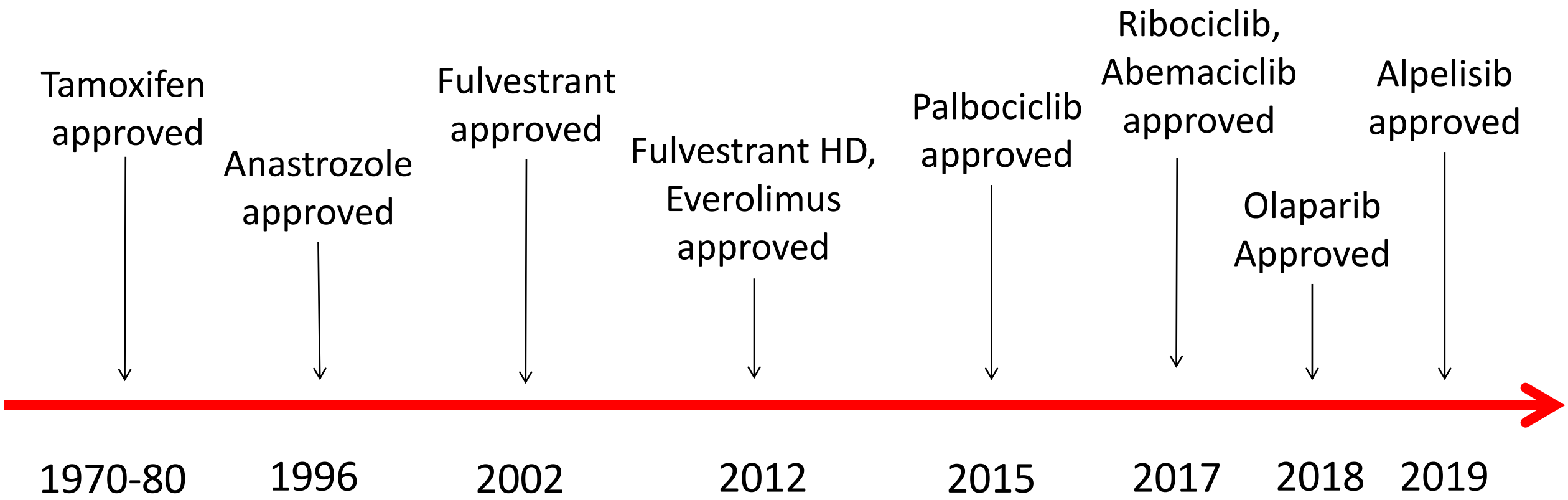
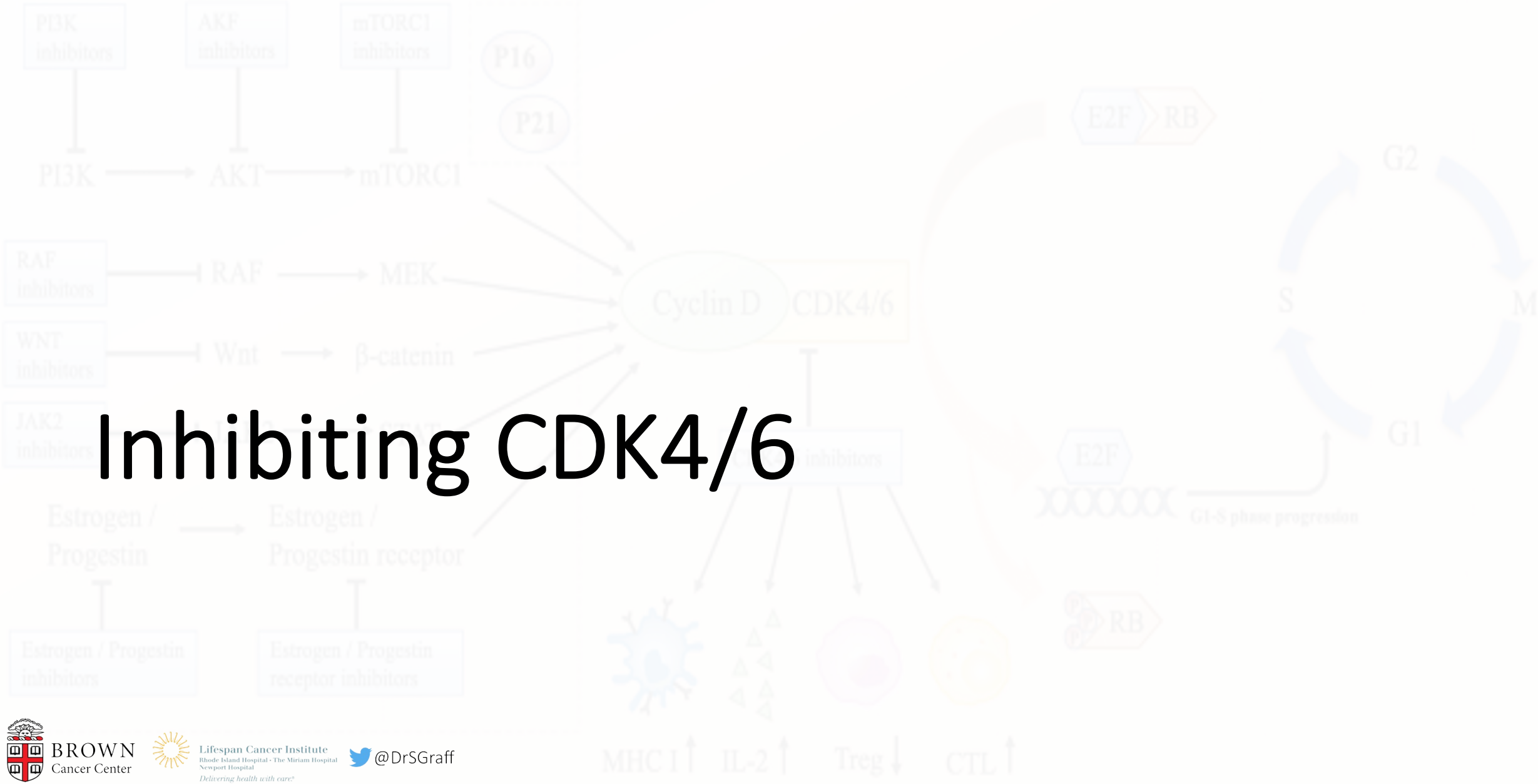
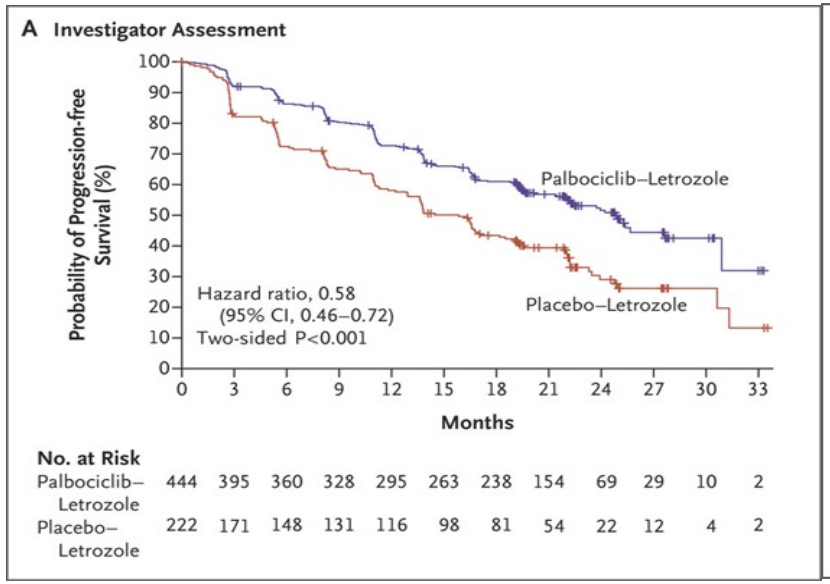
Changing Landscape of ER-positive Metastatic Breast Cancer

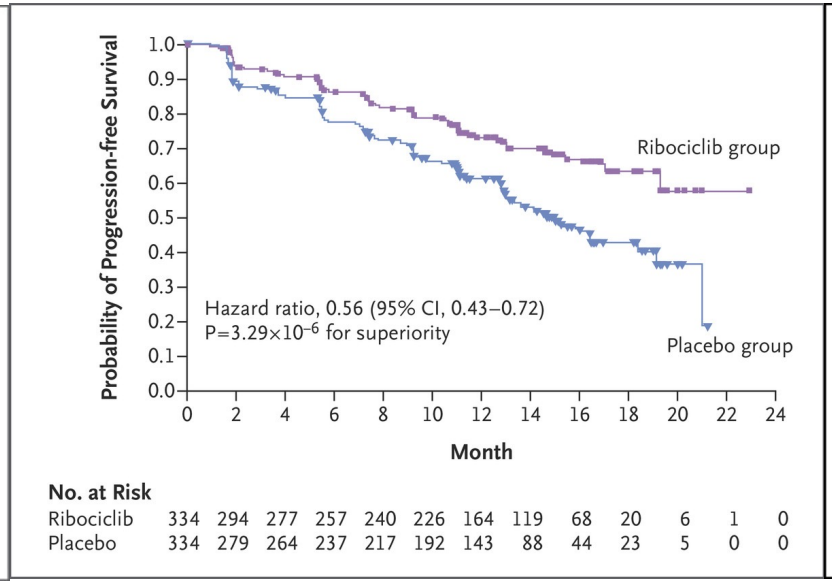


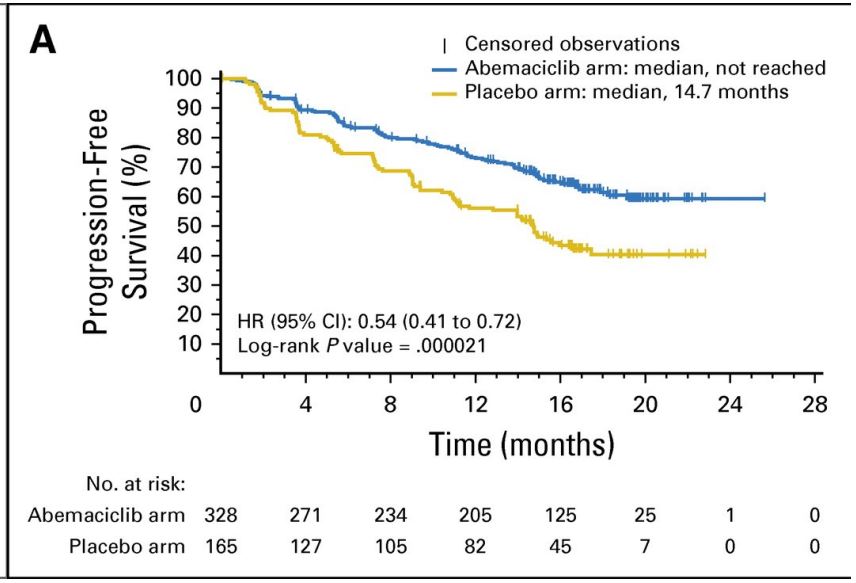
Inhibiting CDK4/6



CDK4/6 Inhibitors: Front Line







PALOMA-2
ORR: 55.3%, HR: 0.58

MONALEESA-2
ORR: 52.7%, HR: 0.56

MONARCH-3
ORR: 59.2%, HR: 0.54

Finn RS, NEJM 2016; Hortobagyi, Annals Onc 2018; Goetz MP AACR 2018;

CDK4/6 Inhibitors: Second Line

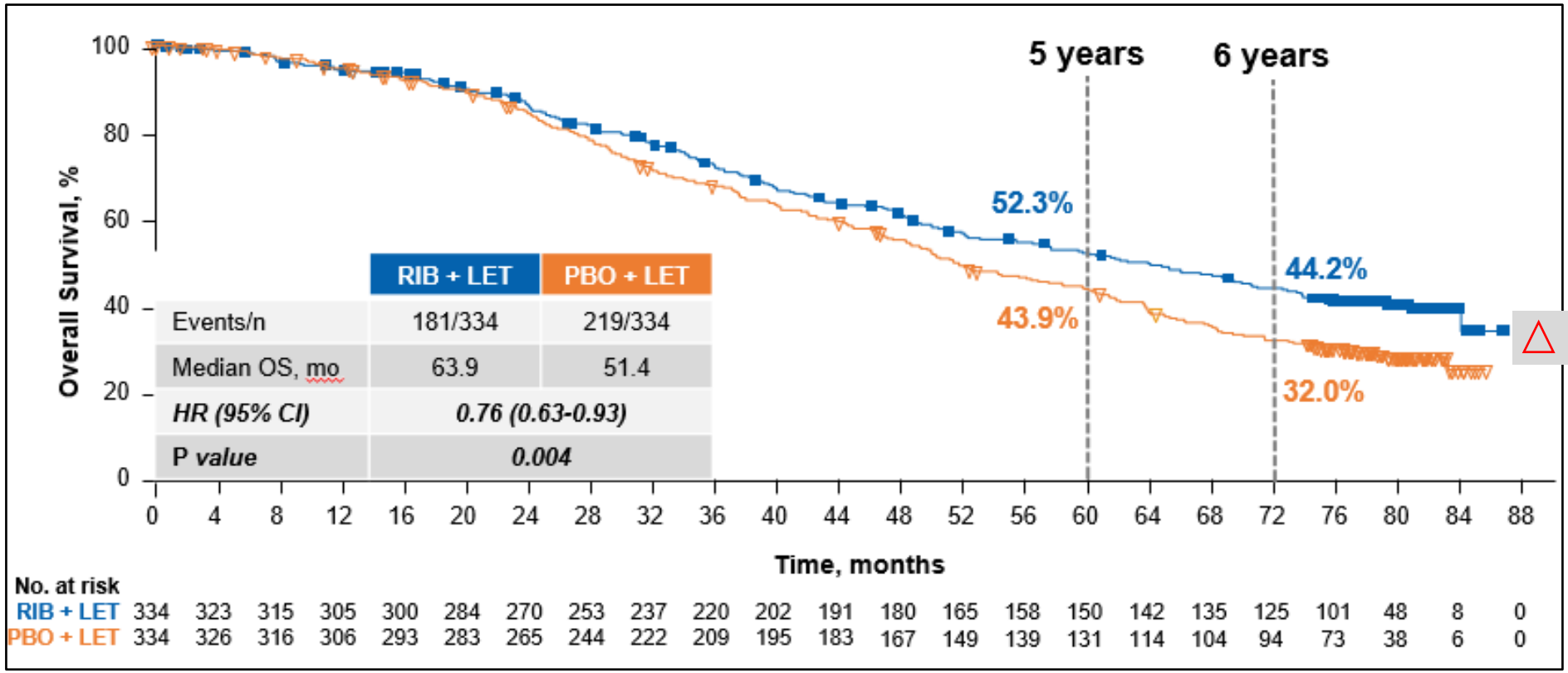
- PALOMA-3 (Turner NC, NEJM 2015): Fulvestrant +/- palbociclib:
  - HR 0.50 with 11.2 month PFS
- MONARCH-2 (Sledge G, JCO 2017): Fulvestrant +/- abemaciclib:
  - HR 0.55 with 16.4 month PFS
- MONALEESA-3 (Slamon DJ, ASCO 2018): Fulvestrant =/- ribociclib:
  - HR 0.57 with 14.6 month PFS

CDK4/6 Inhibitors: Toxicity Profiles

	Palbociclib	Ribociclib	Abemaciclib
Neutropenia	+++	+++	++
Anemia	++	++	++
Thrombocytopenia	+		
Fatigue	+	+	+
Diarrhea	+	+	++
Nausea			+
QTc Prolongation		+	

MONALEESA-2: Letrozole +/- Ribociclib in 1L HR+/HER2- MBC

Overall Survival after median follow up of 80 months



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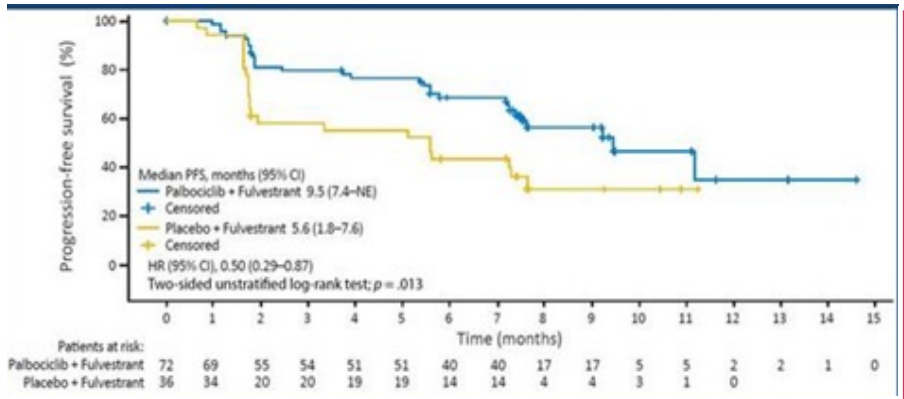
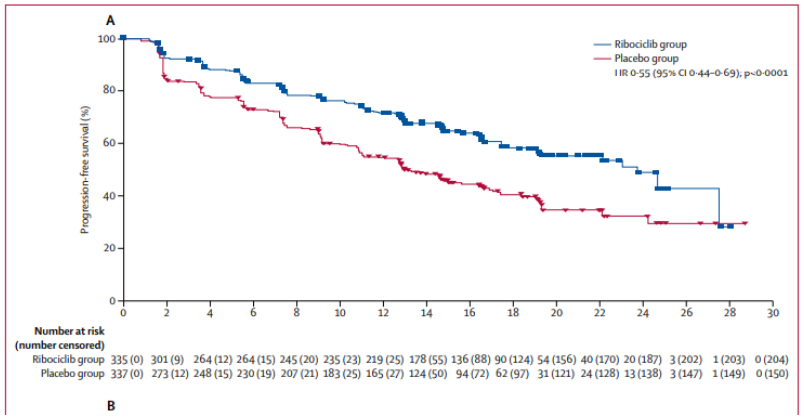
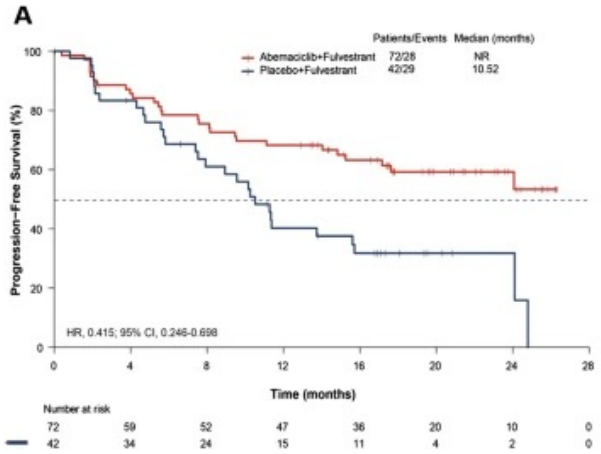
Is There *Anybody* Who Doesn't Benefit from CDK4/6 Inhibitors?

CDK 4/6 Inhibitors: Premenopausal Women







PALOMA-3
Fulvestrant + goserelin
+/- palbociclib
HR 0.50 (n=106)

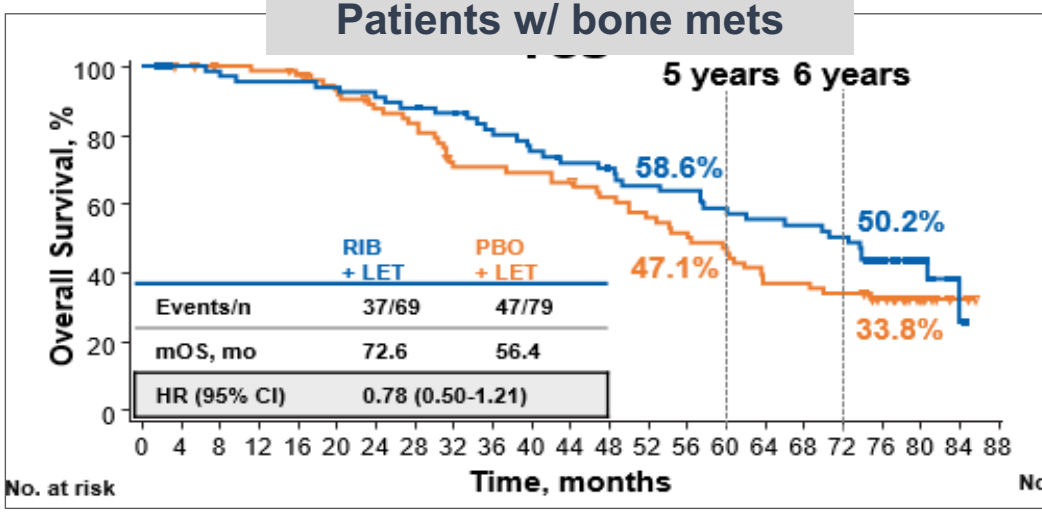
MONALEESA-7
(Tam or NSAI) + goserelin
+/- ribociclib
HR 0.55 (n=335)

MONARCH-2
Fulvestrant + goserelin
+/- abemaciclib
HR 0.45 (n=114)

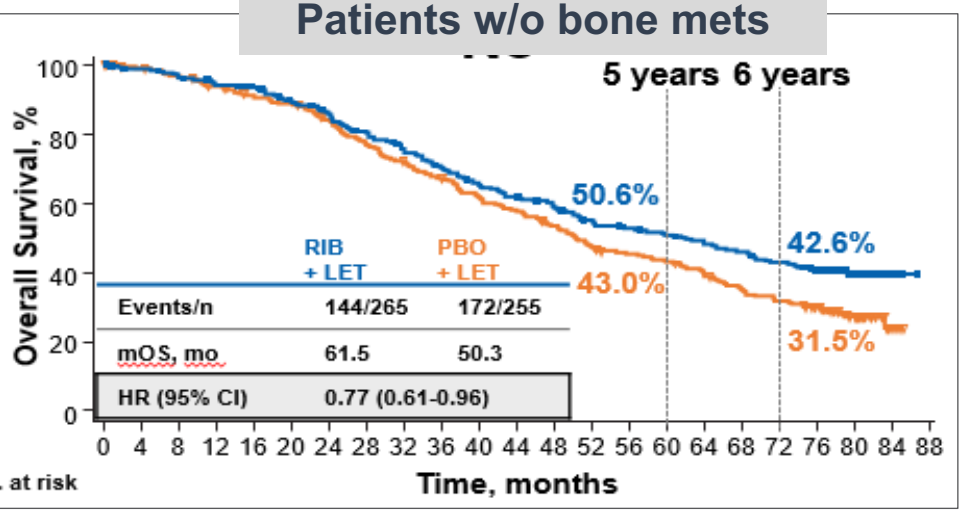
Loibl, Oncologist 2017; Tripathy D, SABCS 2017; Neven, ASCO 2018.

MONALEESA-2

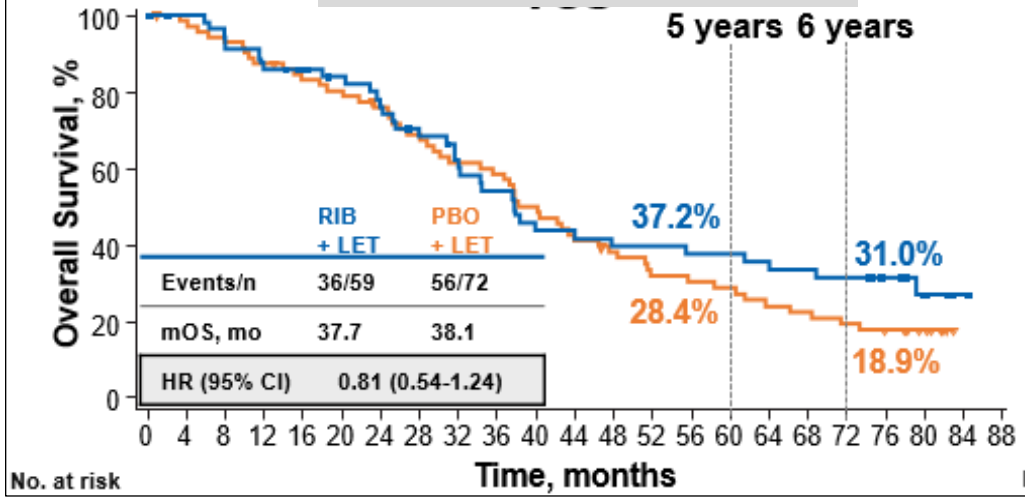
Patients w/ bone mets



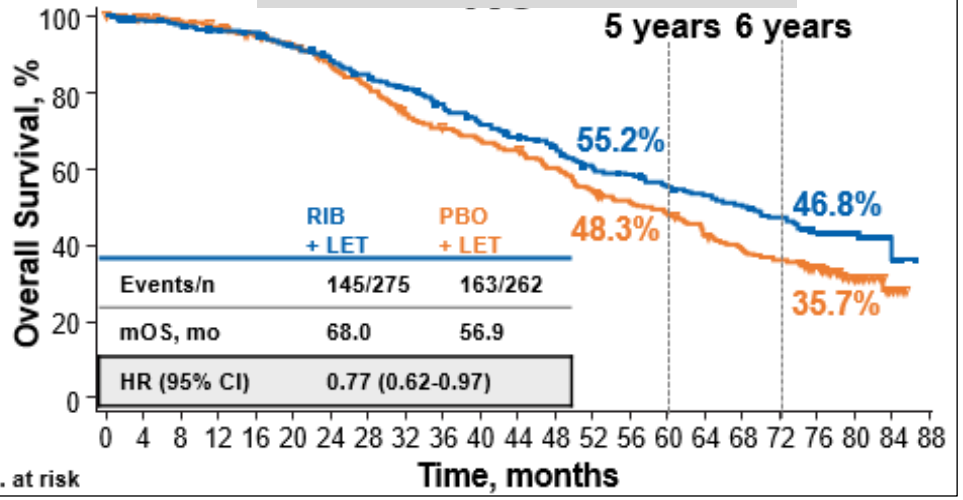
Patients w/o bone mets



Patients w/ liver mets

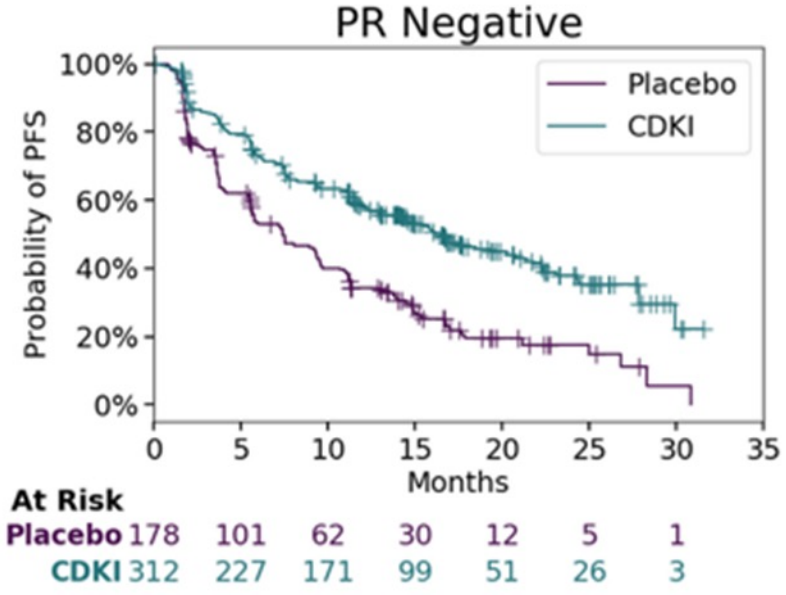


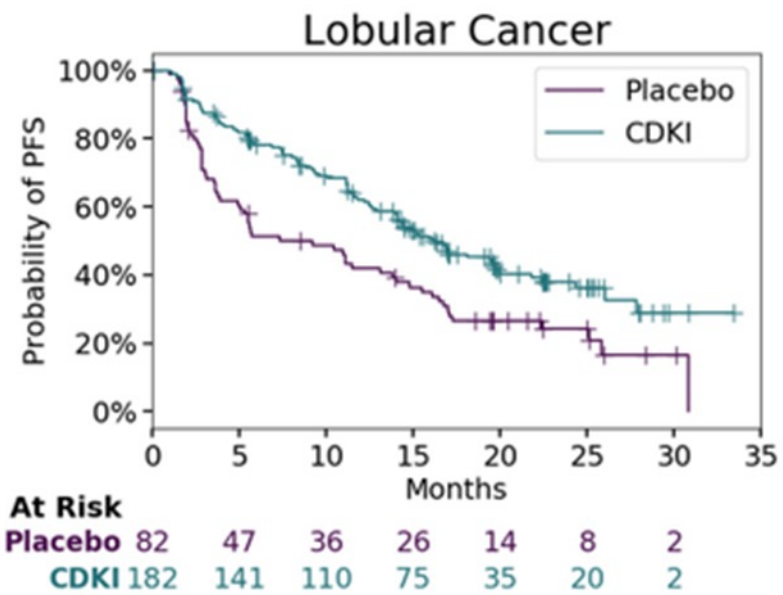
Patients w/o liver mets

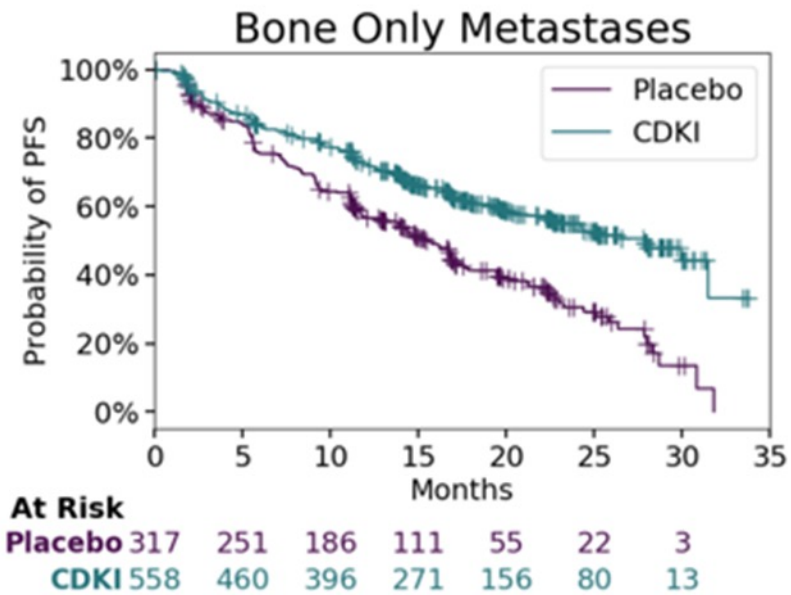


O'Shaughnessy J et al GS2-01, SABCS 2021

FDA Pooled Analysis, Gao *et al* ASCO18





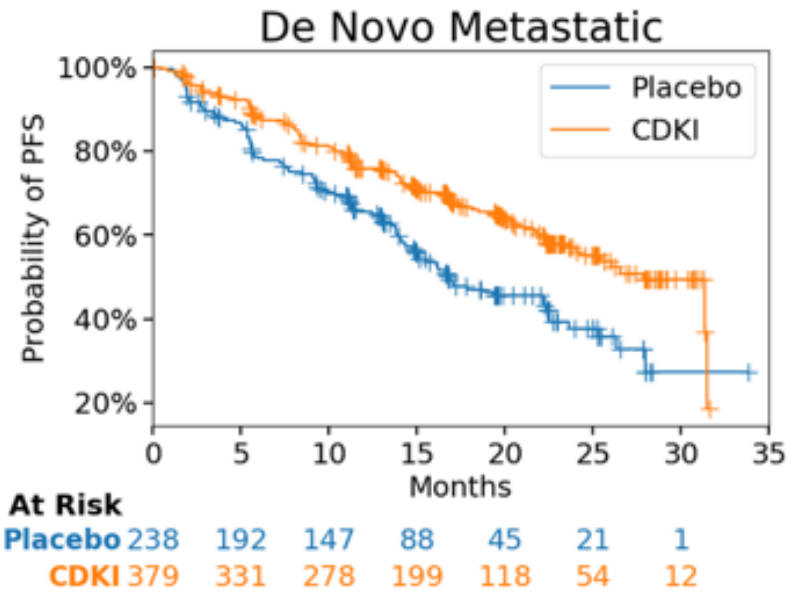


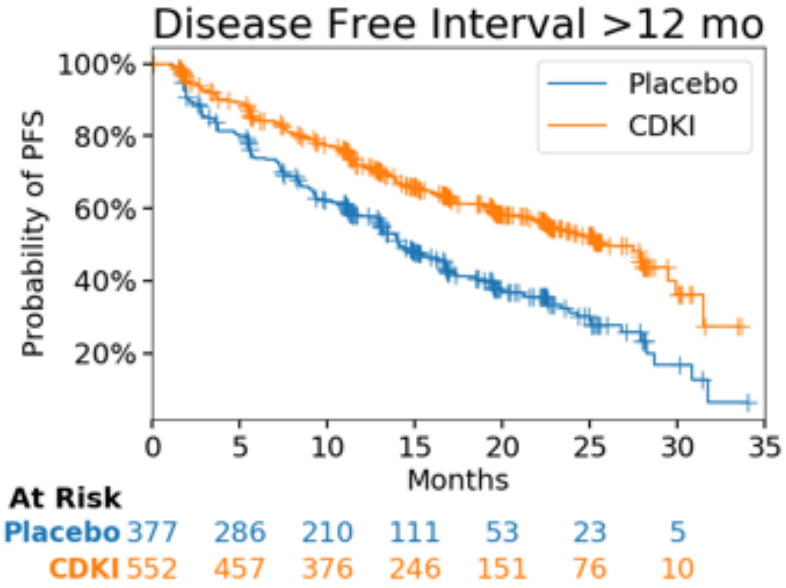
PR negative (N=490):
- PFS: 16.5 vs. 7.4 mo
- Δ 9.1 months
- HR 0.50 (0.40-0.64)

Lobular cancer (N=264):
- PFS 16.1 vs. 9.2 mo
- Δ 6.9 months
- HR 0.58 (0.42-0.80)

Bone only mets (N=875):
- PFS 27.9 vs. 15.5 mo
- Δ 12.4 months
- HR 0.55 (0.45-0.67)

FDA Pooled Analysis, Gao et al ASCO 18





De novo metastatic (N=617):

- PFS 27.8 vs. 16.8 mo
- Δ 11.0 months
- HR 0.59 (0.46-0.76)

Disease free interval >12mo (N=929)

- PFS 25.7 vs. 14.2 mo
- Δ 11.5 months
- HR 0.55 (0.46-0.67)

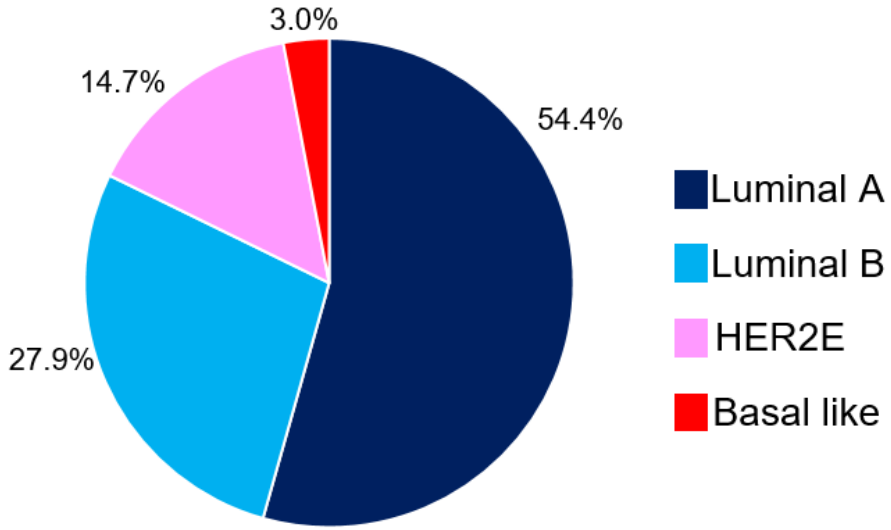
Pooled analysis from MONALEESA-2, -3, -7 trials

✓ Ribociclib + ET demonstrated statistically **significant PFS and OS benefit** in three phase 3 clinical trials (MONALEESA-2, -3, -7) in patients with HR+/HER− MBC

1. This retrospective exploratory analysis evaluated the **association of intrinsic subtype with OS** in pts from these 3 trials

2. Primary and metastatic tumor samples underwent gene expression profiling using a customized NanoString nCounter GX 800-gene panel including 36/50 PAM50 genes

Subtype distribution in the pooled MONALEESA dataset

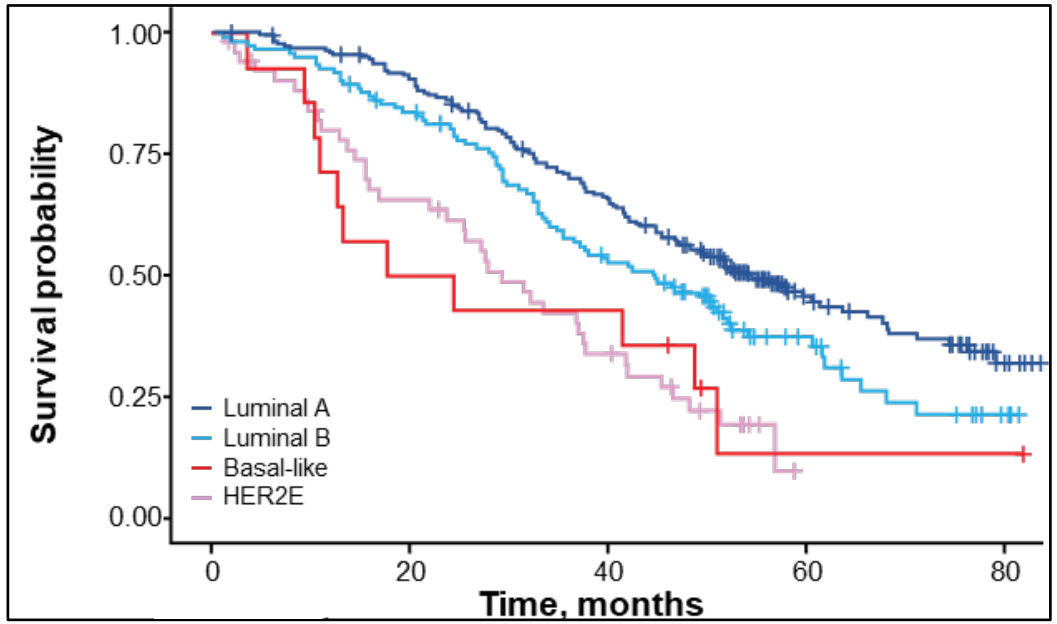


Carey LA et al SABCS 2021

Intrinsic subtype was prognostic for OS

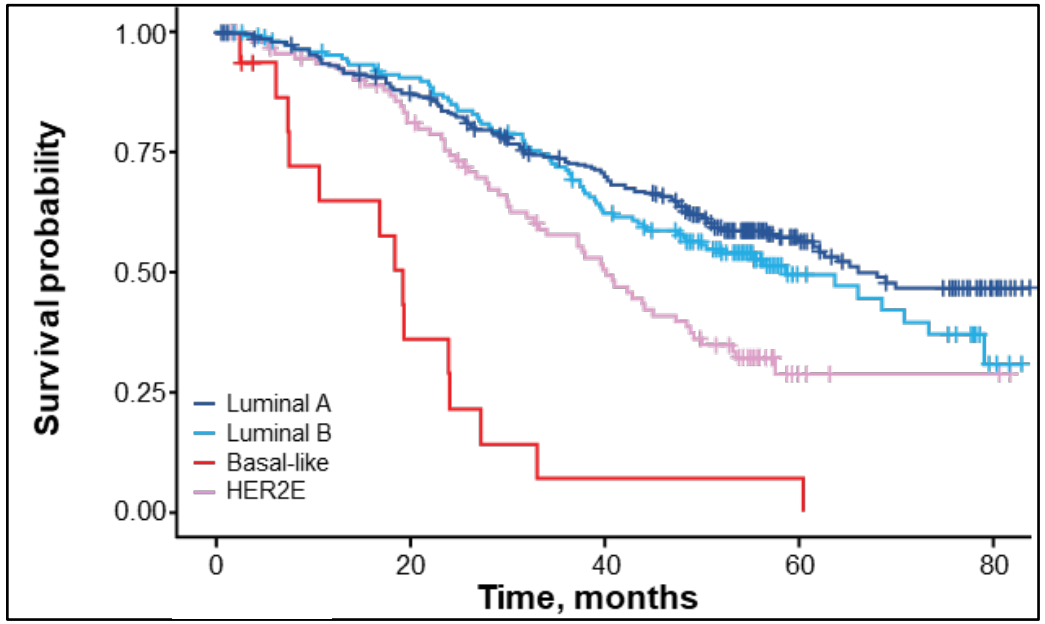
Placebo + ET

	n (%)	Median OS, mo
Luminal A	222 (54)	54.6
Luminal B	124 (30)	44.9
HER2E	52 (13)	29.4
Basal-like	14 (3)	21.2



Ribociclib + ET

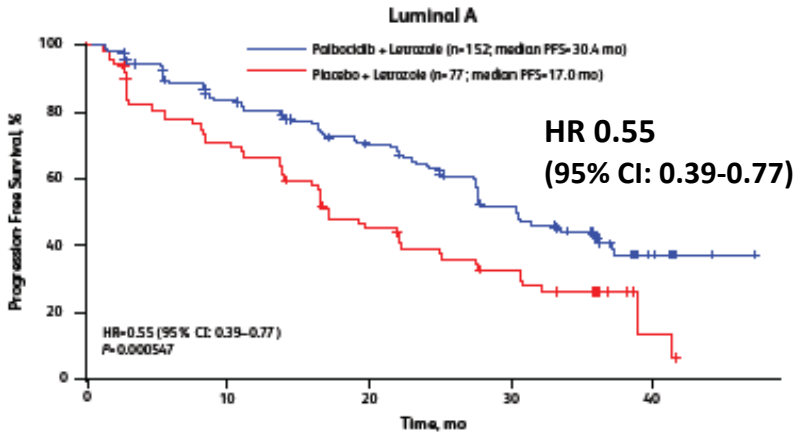
	n (%)	Median OS, mo
Luminal A	320 (55)	68.0
Luminal B	154 (26)	58.8
HER2E	95 (16)	40.3
Basal-like	16 (3)	19.4



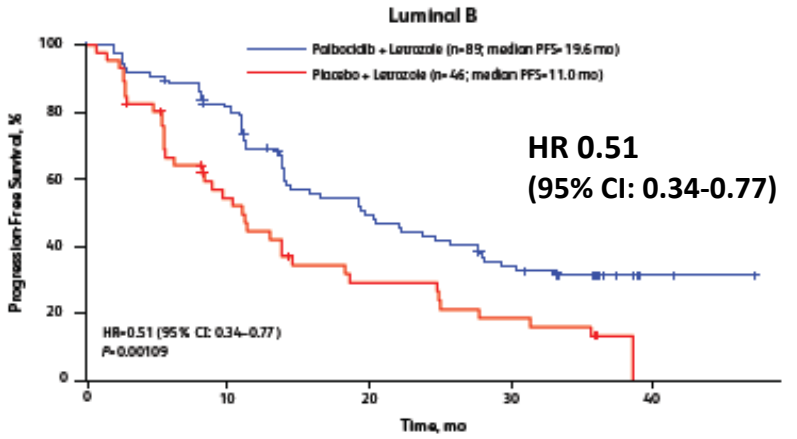
Carey LA et al SABCS 2021

Molecular Subtype, Finn *et al* ASCO18

PALOMA-2
(N=364)

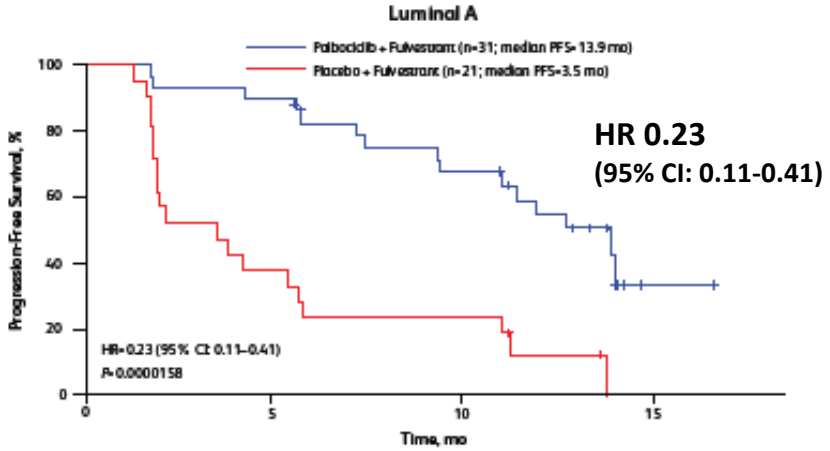


HR 0.55
(95% CI: 0.39-0.77)

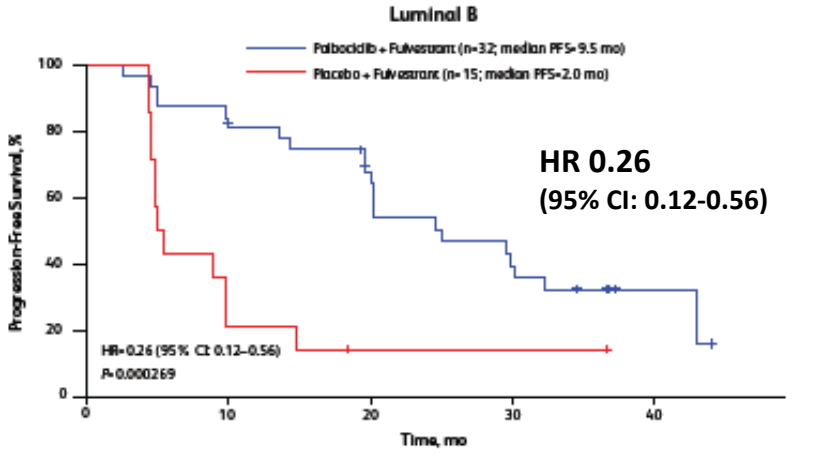


HR 0.51
(95% CI: 0.34-0.77)

PALOMA-3
(N=142)



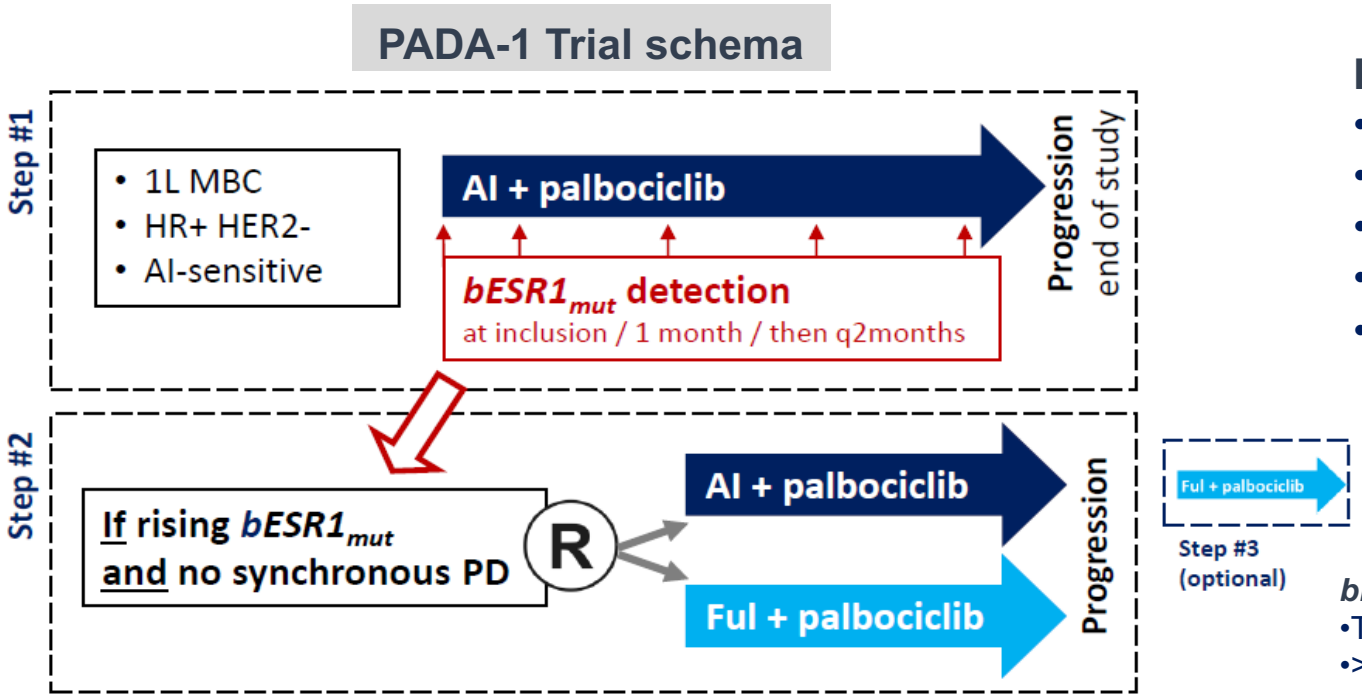
HR 0.23
(95% CI: 0.11-0.41)



HR 0.26
(95% CI: 0.12-0.56)

PADA-1: ctDNA ESR1 monitoring to inform therapy

- ESR1 mutations are rare at diagnosis of MBC; however, frequency is ~ 30-40% following tx 1L AI
- Can we prevent/delay tumor progression in pts receiving 1L AI + palbociclib by targeting ESR1 mutations with a switch to fulvestrant (continuing palbociclib) as soon as ESR1mut are detectable in ctDNA?



Key eligibility:
- HR+ (>10%) HER2-mBC
- No relapse on/<12m from adjuvant AI
- No prior systemic therapy for mBC
- Absence of visceral crisis
- Measurable or evaluable disease

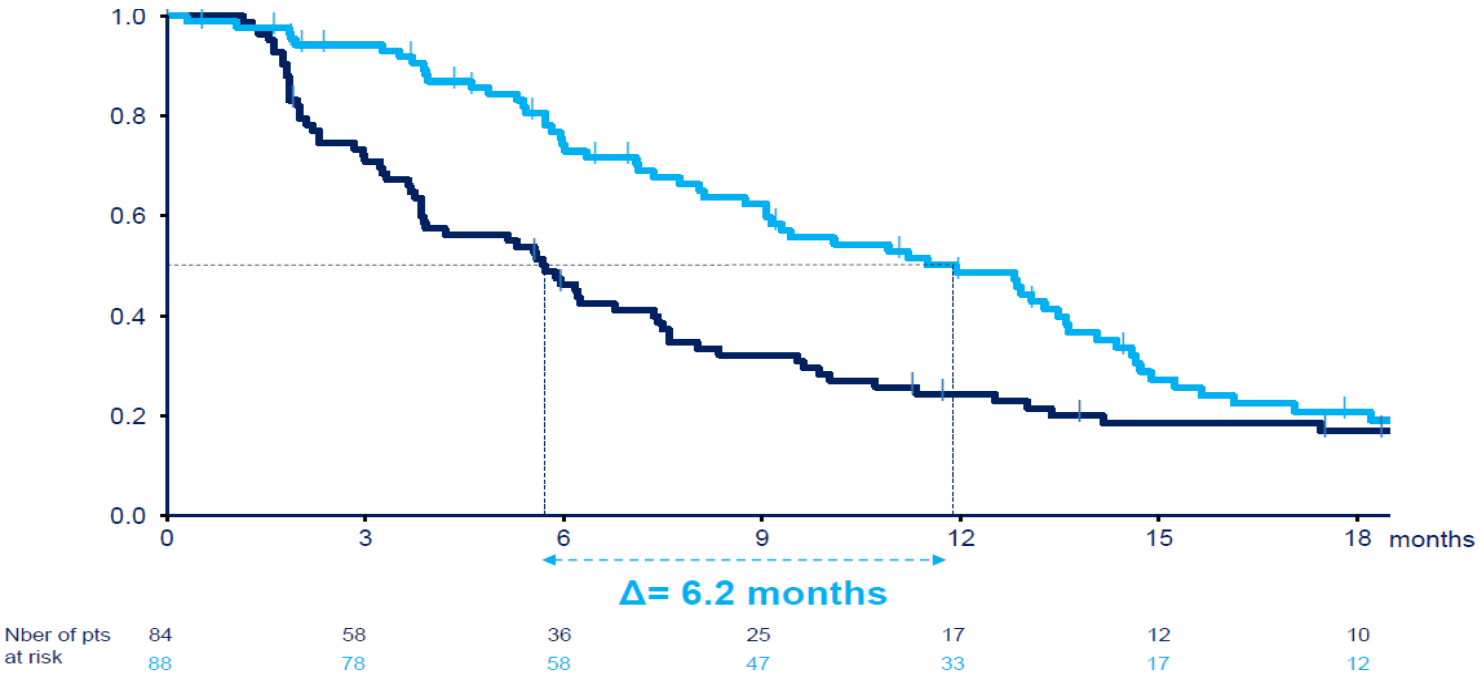
***bESR1mut*monitoring with ddPCR:**
- Targets E380, P535, L536, Y537, D538 mutations [1]
- >12,000 samples analyzed in real time

***bESR1mut*:** ESR1 mutations detected in ctDNA from blood samples

Bidard F-C et al GS3-05, SABCS 2021

PADA-1: PFS after randomization to palbociclib + fulvestrant/AI

Median FU in step #2: 26 months (range: 0-36m)



	palbociclib + AI	palbociclib + FUL
Median PFS	5.7 months	11.9 months
	95%CI [3.9;7.5]	95%CI [9.1;13.6]

HR=0.63; 95%CI[0.45-0.88], p=0.007

Stratified HR=0.61; 95%CI[0.43;0.86], p=0.005

✓ with *bESR1mut* detection, mPFS doubled by switching from AI-palbo to FUL-palbo

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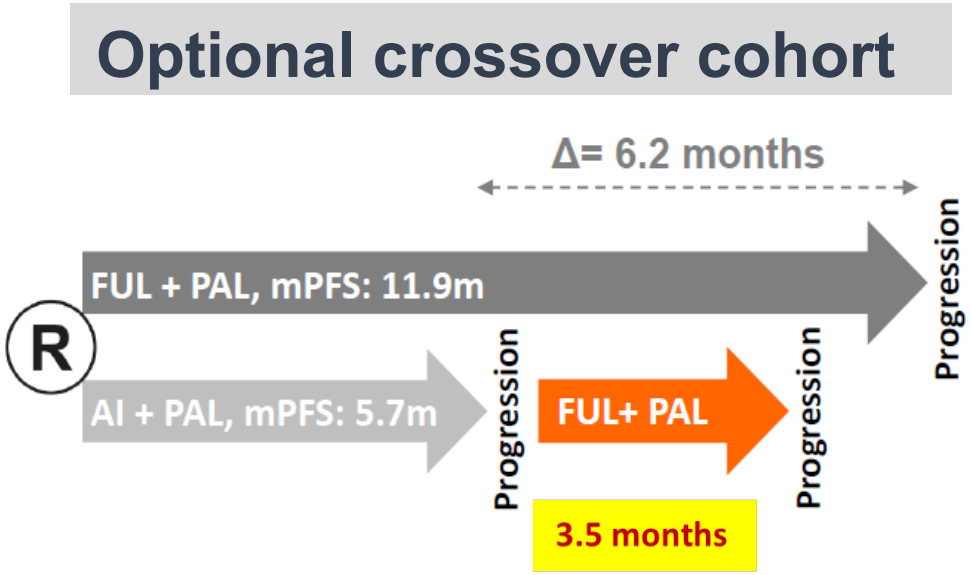
PADA-1: PFS in optional crossover cohort



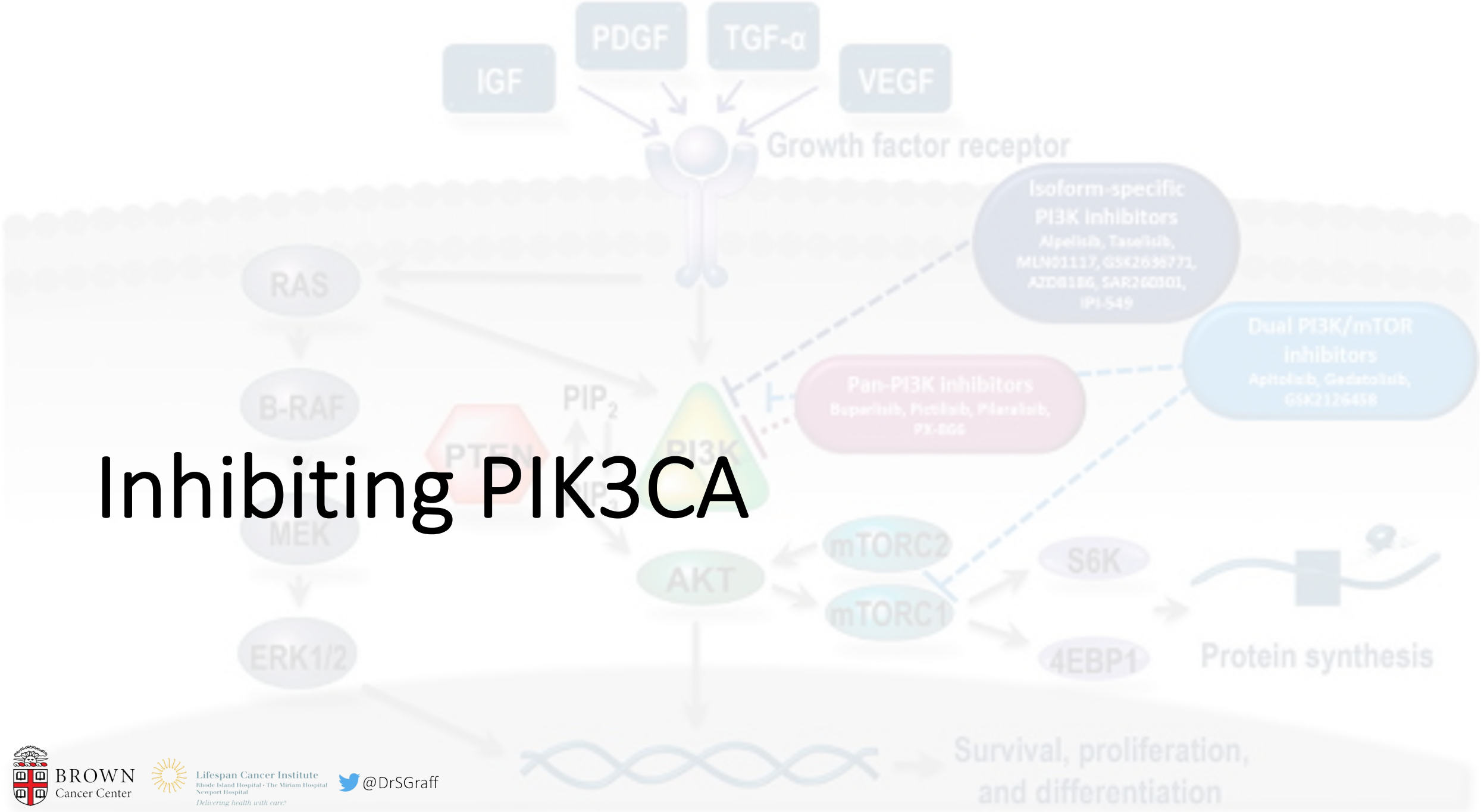
As of July 31st, 2021:

- N= 69 pts had a PD in the AI+PAL arm
- **N= 47 pts participated in the optional 2nd line cross-over cohort**
- Median FU in step #3: 14.7 months (range 0-17.3)

Median 2nd line PFS with FUL+PAL
3.5 months 95%CI=[2.7;5.1]

- ✓ Novel study demonstrating clinical utility of ***bESR1$_{mut}$*** monitoring and ability to optimize treatment
- ✓ The mPFS was doubled by the switch from AI-palbo to FUL-palbo
  - ✓ Crossover cohort = mPFS 9.2 months vs 11.9 months in switch cohort
- ✓ Phase 3 studies with similar study design using novel SERDs are being planned

Bidard F-C et al GS3-05, SABCS 2021



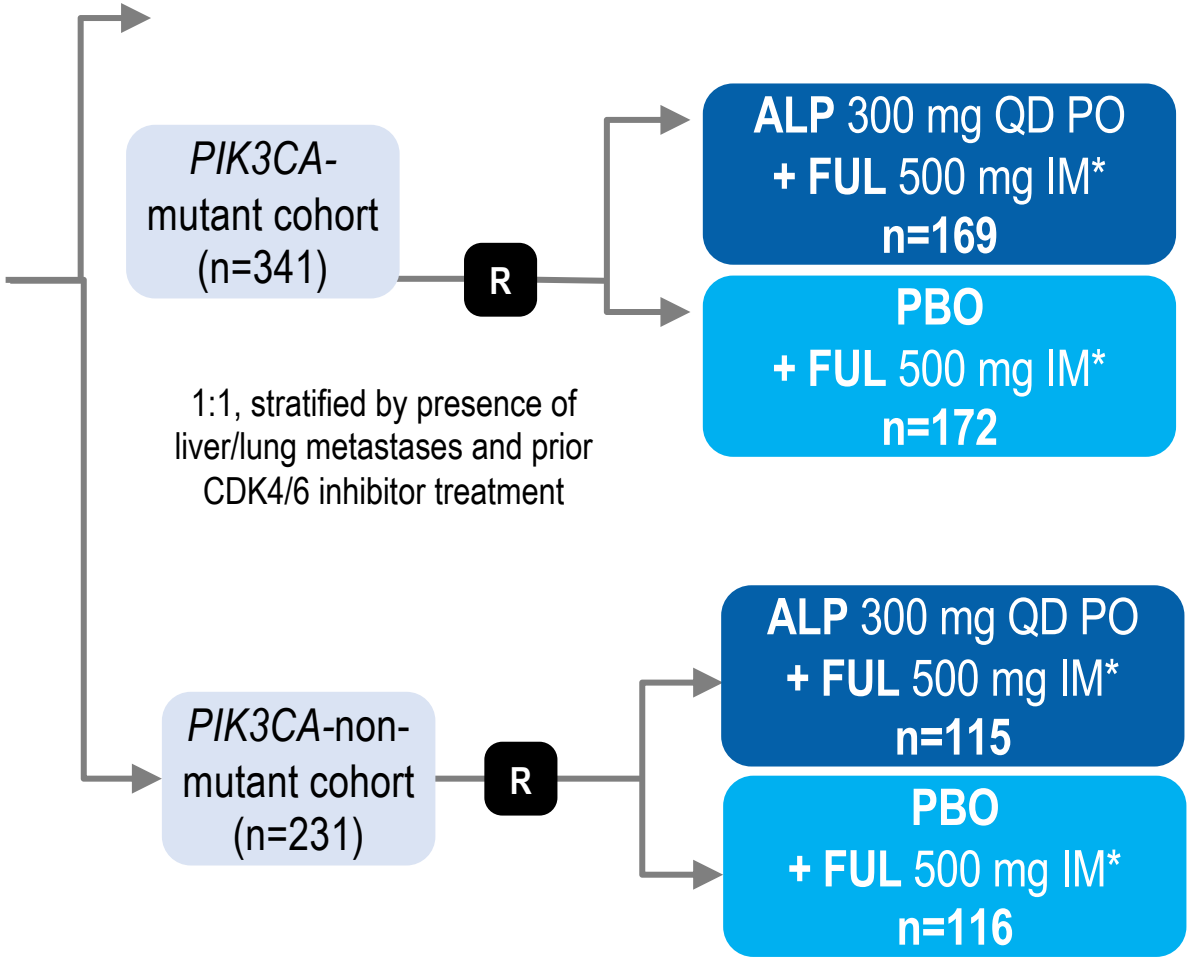
Inhibiting PIK3CA

SOLAR-1

Men or postmenopausal women, with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

(N=572)



Primary endpoint

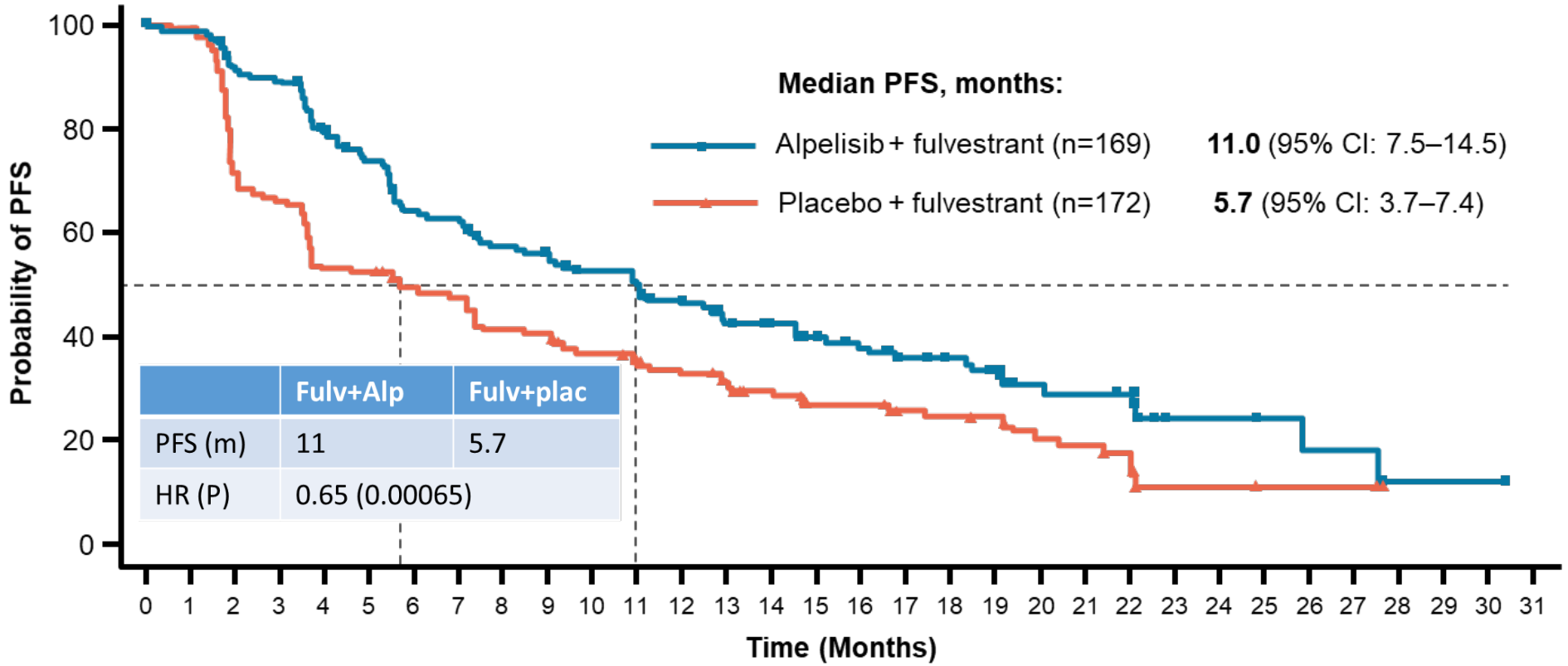
- PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include:

- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- OS (*PIK3CA*-non-mutant cohort)
- ORR/CBR
- Safety

F Andre et al. ESMO 2018

Locally Assessed PFS mPIK3CA cohort



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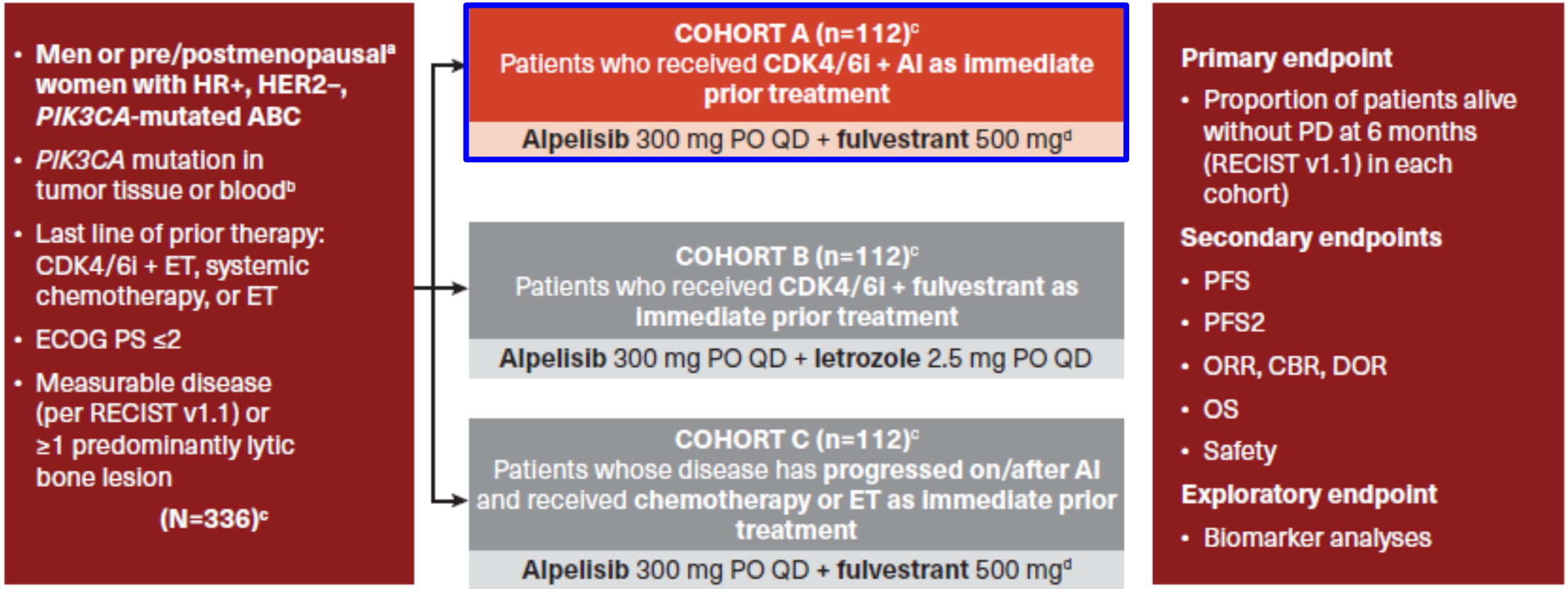
F Andre et al. ESMO 2018

SOLAR-1 Toxicity

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

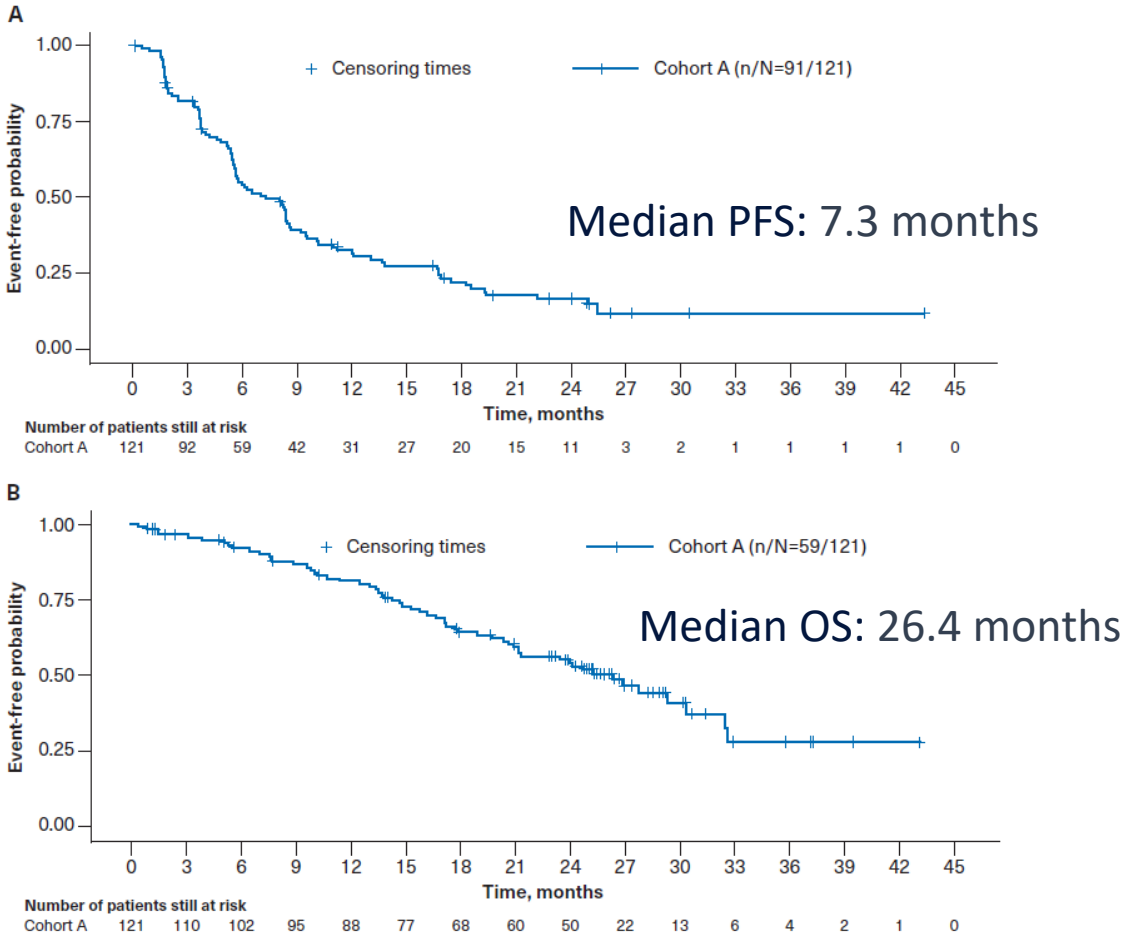
BYlieve: Alpelisib+ET in mPIK3CA HR+ MBC post CDK 4/6i

Question: But what about using PIK3CA inhibitors in a postCDK4/6 inhibitor world?



Ciruelos EM et al. SABCS 2021

BYlieve: Efficacy & safety after 18m f/u (Cohort A)



Median PFS: 7.3 months

Median OS: 26.4 months

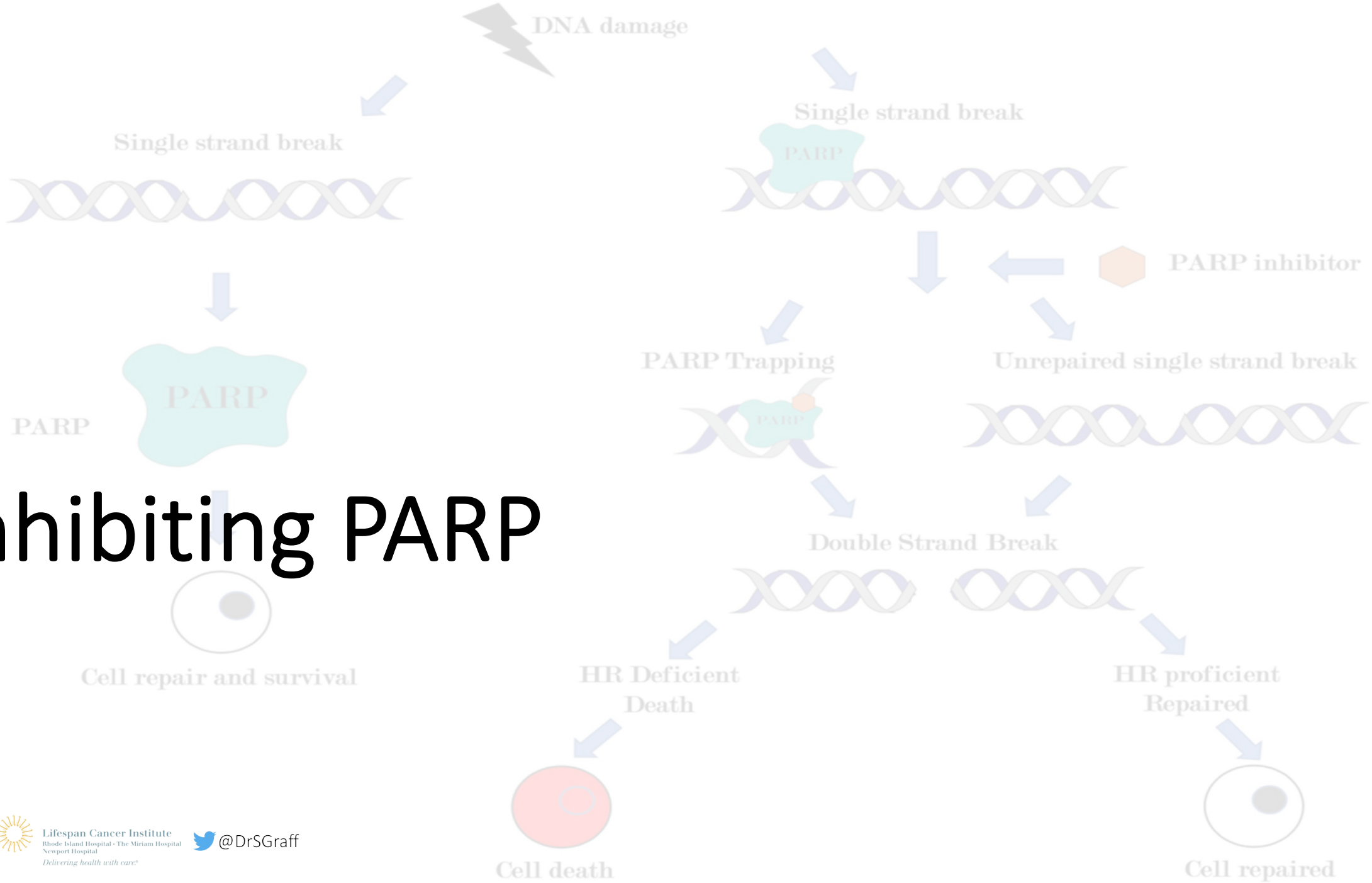
Adverse events

- Hyperglycemia ≥G3 in 29% of pts
- Rash ≥G3 in 10% of pts

✓ Longer exposure to alpelisib does not lead to cumulative toxicities

✓ Prophylactic use of antihistamines mitigated the incidence of rash

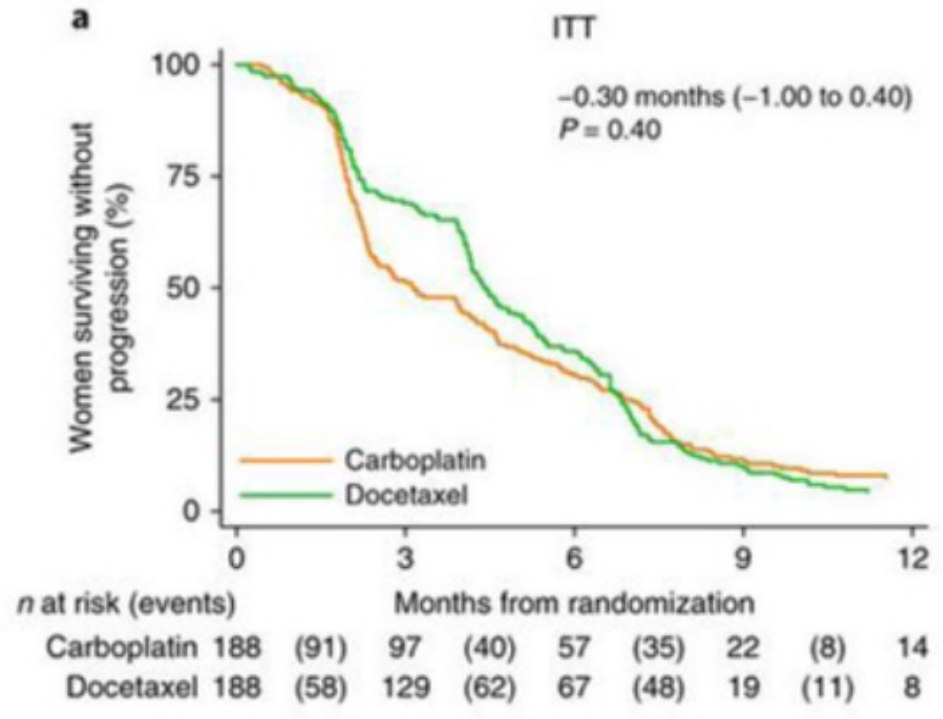
Ciruelos EM et al. SABCS 2021



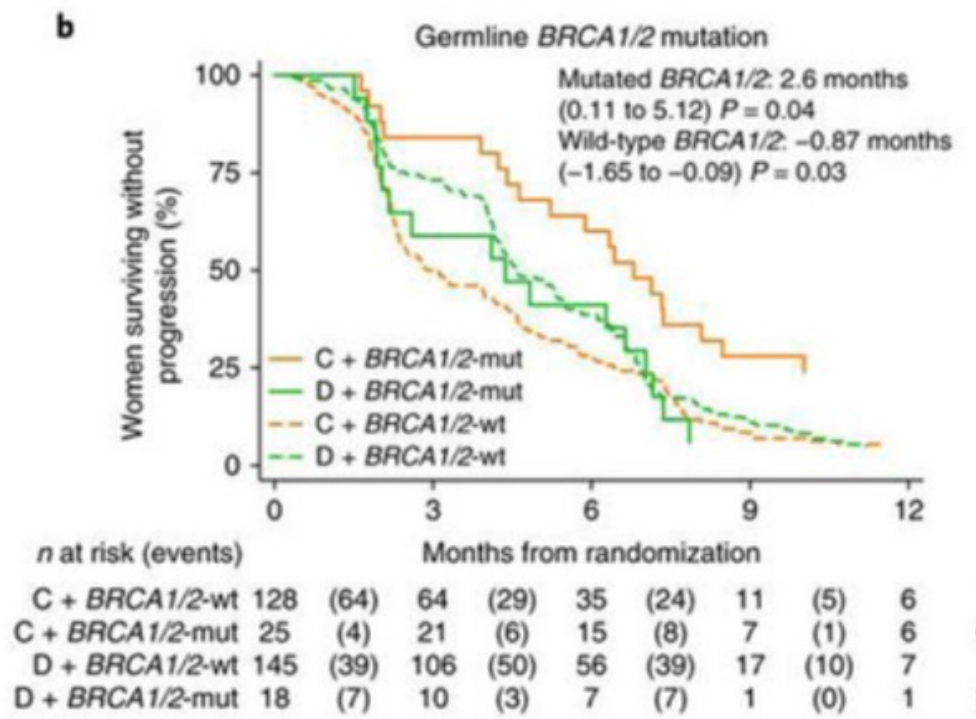
Inhibiting PARP

gBRCA status matters in TNBC

ITT Population: No difference



gBRCAm: Favors Platinum



Tutt Nat Med 2018 May;24(5):628-637

OlympiAD

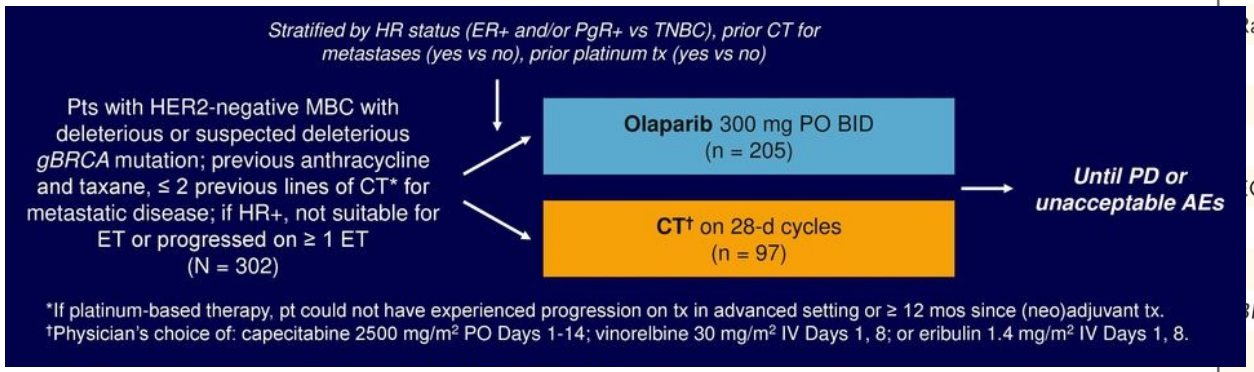
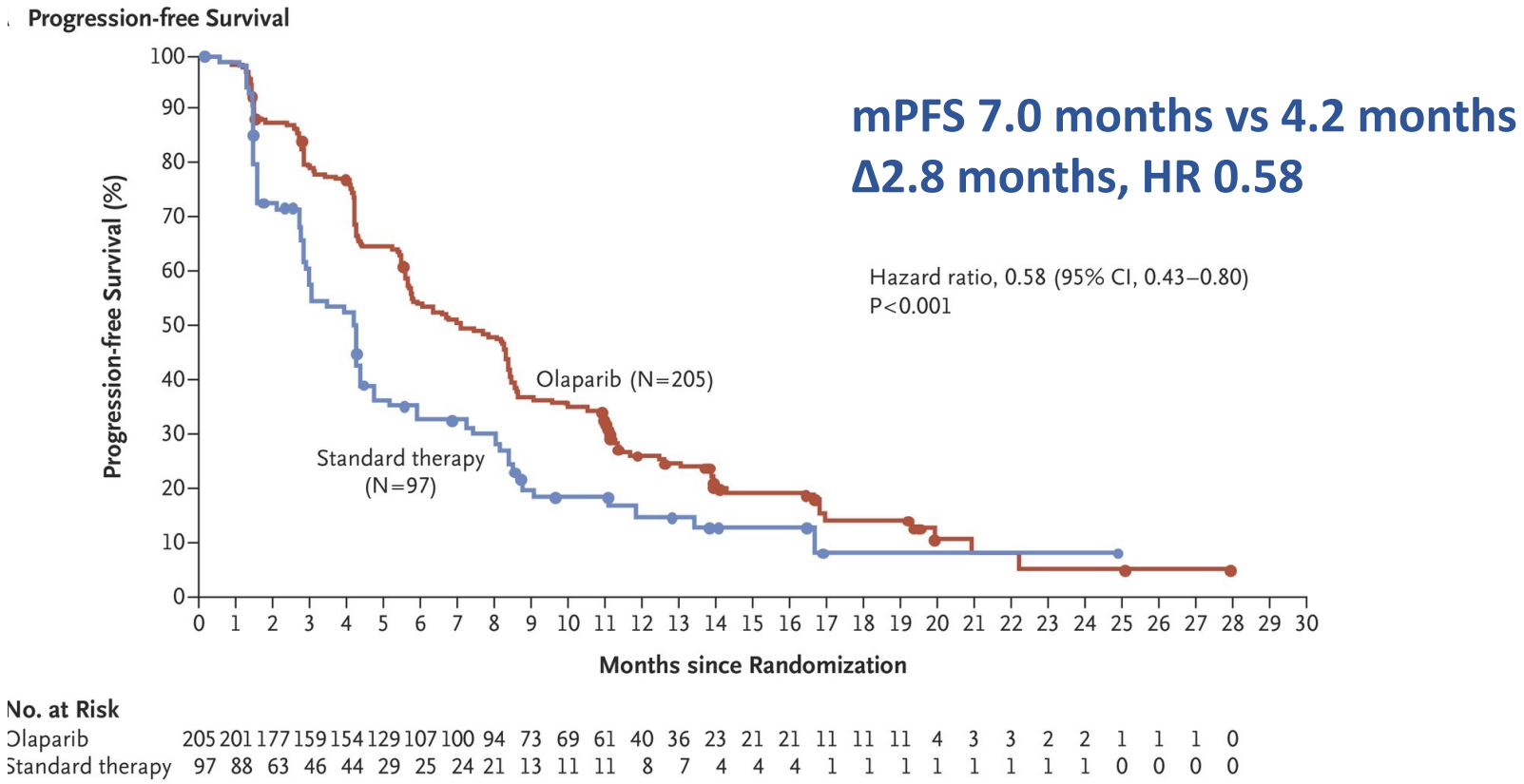


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

Robson M, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Aug 10;377(6):523-533.

OlympiAD

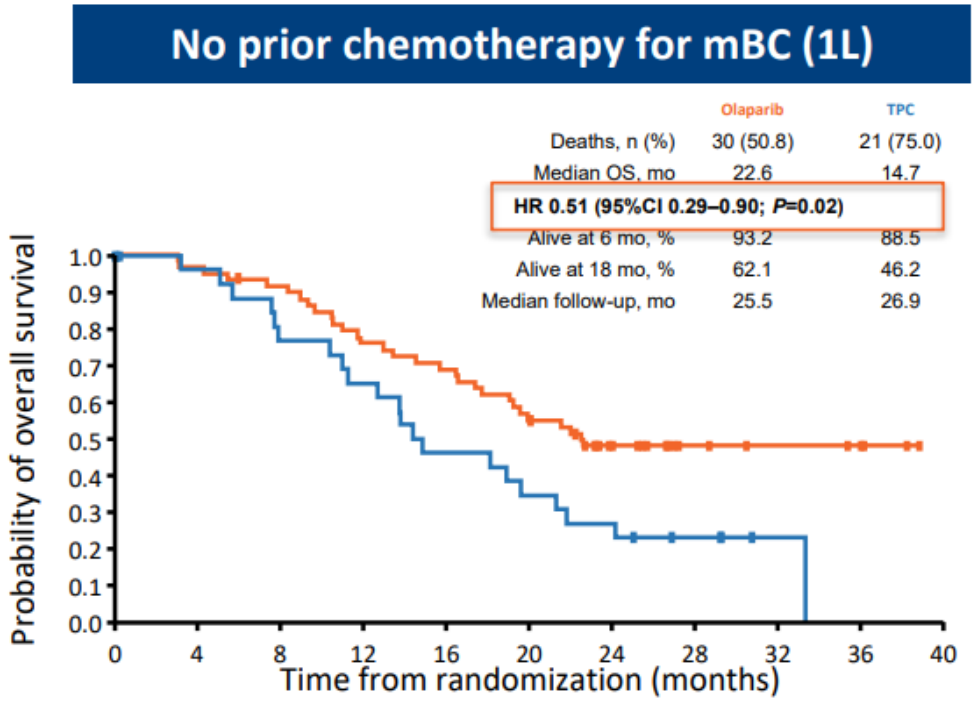


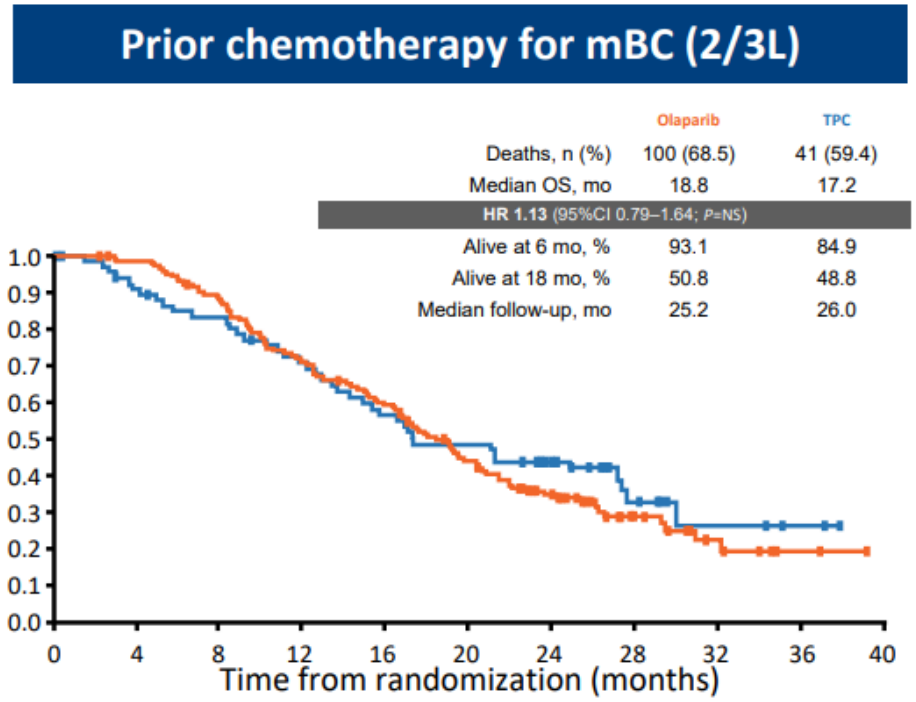
mPFS 7.0 months vs 4.2 months
Δ2.8 months, HR 0.58

Hazard ratio, 0.58 (95% CI, 0.43–0.80)
P<0.001

Robson N Engl J Med 2017; 377:523-533 2017

OS: Prespecified Subgroups





Robson AACR 2018

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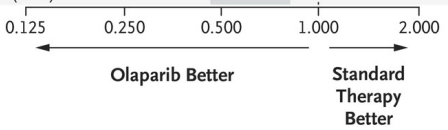
Subgroup Analysis

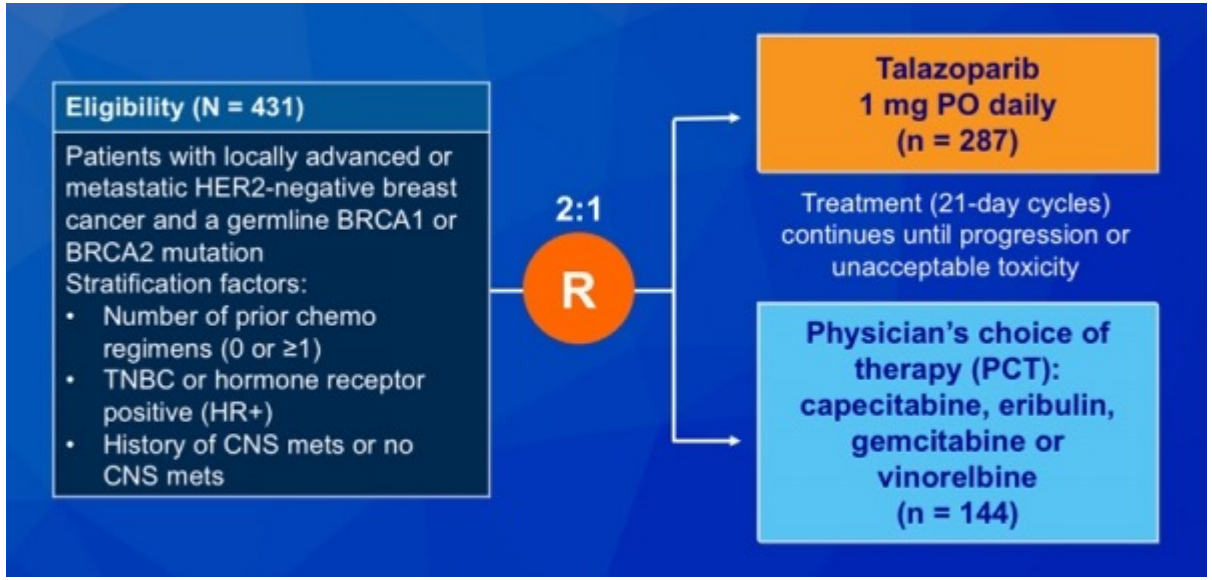
Subgroup	Olaparib	Standard Therapy	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	163/205 (79.5)	71/97 (73.2)	0.58 (0.43–0.80)
Previous chemotherapy for metastatic breast cancer			
Yes	119/146 (81.5)	51/69 (73.9)	0.65 (0.47–0.91)
No	44/59 (74.6)	20/28 (71.4)	0.56 (0.34–0.98)
Hormone-receptor status			
Hormone-receptor positive	82/103 (79.6)	31/49 (63.3)	0.82 (0.55–1.26)
Triple negative	81/102 (79.4)	40/48 (83.3)	0.43 (0.29–0.63)
Previous platinum-based therapy for breast cancer			
Yes	50/60 (83.3)	21/26 (80.8)	0.67 (0.41–1.14)
No	113/145 (77.9)	50/71 (70.4)	0.60 (0.43–0.84)
Measurable disease			
Yes	139/165 (84.2)	56/72 (77.8)	0.58 (0.43–0.80)
No	24/40 (60.0)	15/25 (60.0)	0.57 (0.30–1.12)
Progressive disease at the time of randomization			
Yes	127/159 (79.9)	53/73 (72.6)	0.60 (0.43–0.83)
No	36/46 (78.3)	18/24 (75.0)	0.72 (0.41–1.30)
BRCA mutation type			
BRCA1	94/114 (82.5)	41/50 (82.0)	0.54 (0.37–0.79)
BRCA2	64/84 (76.2)	30/45 (66.7)	0.68 (0.45–1.07)
Age			
<65 yr	154/194 (79.4)	67/93 (72.0)	0.66 (0.49–0.88)
≥65 yr	9/11 (81.8)	4/4 (100.0)	Not calculated
Region			
Asia	46/59 (78.0)	21/28 (75.0)	0.57 (0.34–0.97)
Europe	77/97 (79.4)	34/35 (75.6)	0.71 (0.48–1.08)
North America and South America	40/49 (81.6)	16/24 (66.7)	0.39 (0.22–0.73)
Race			
White	109/134 (81.3)	47/63 (74.6)	0.67 (0.48–0.95)
Other	54/71 (76.1)	24/34 (70.6)	0.51 (0.32–0.85)



PARPi Toxicity

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

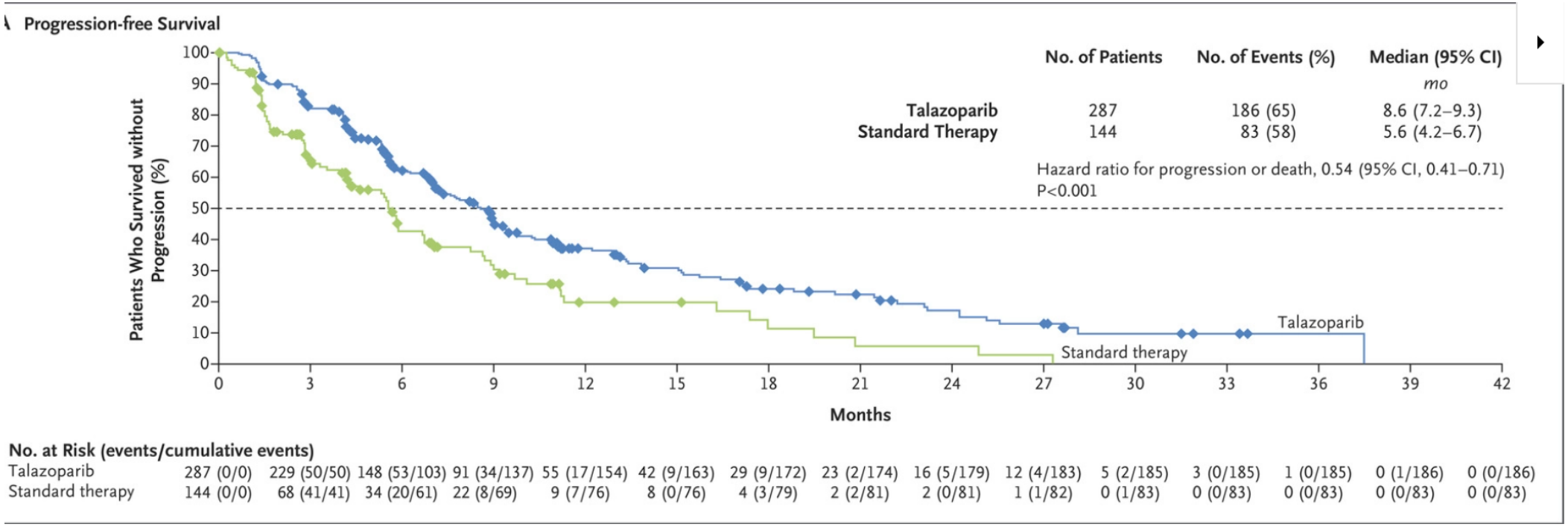
EMBRACA



Litton JK, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535.

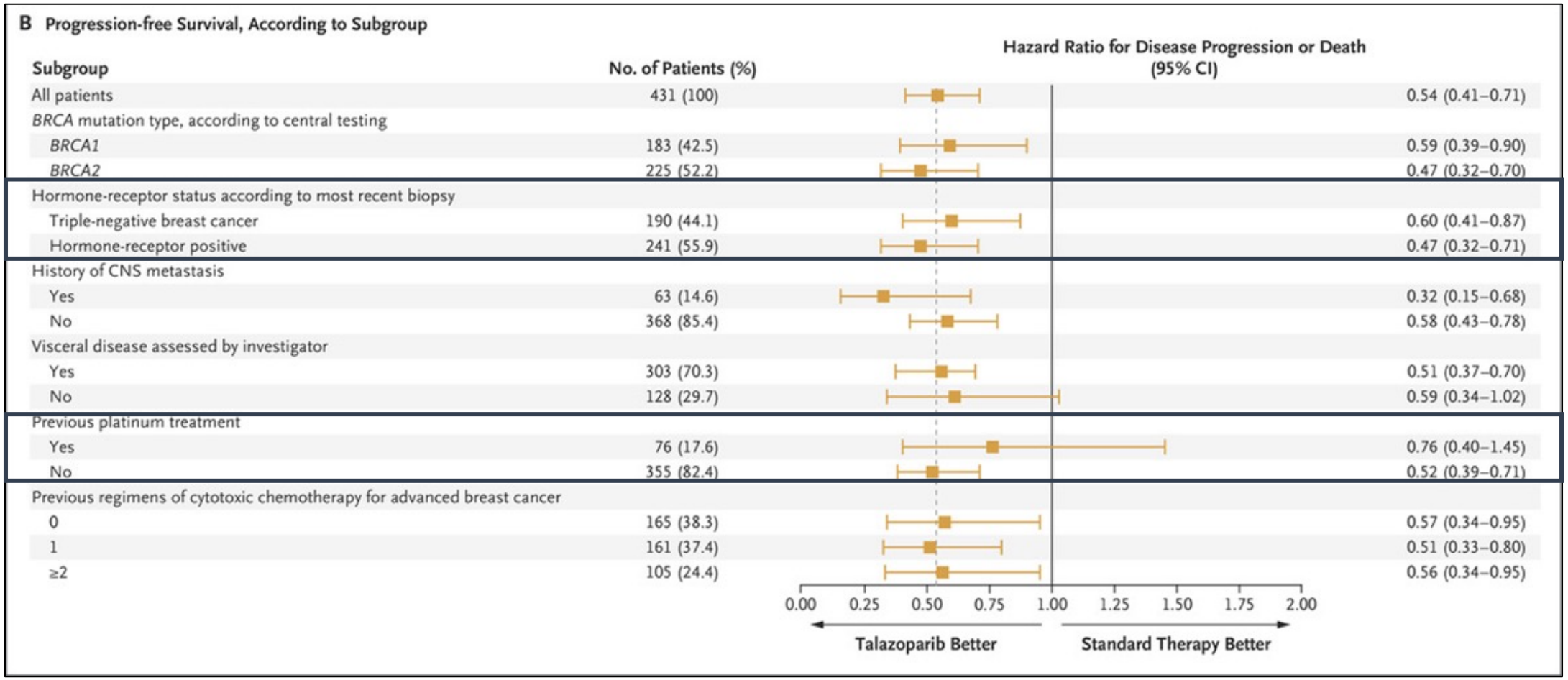
Characteristic	Talazoparib Group (N=287)	Standard-Therapy Group (N=144)
Age — yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age <50 yr — no. (%)	182 (63.4)	67 (46.5)
Female sex — %	98.6	97.9
ECOG performance status score — %†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breast cancer stage — no. (%)‡		
Locally advanced	15 (5.2)	9 (6.2)
Metastatic	271 (94.4)	135 (93.8)
Measurable disease assessed by investigator — no. (%)	219 (76.3)	114 (79.2)
History of CNS metastases — no. (%)	43 (15.0)	20 (13.9)
Visceral disease — no. (%)	200 (69.7)	103 (71.5)
Hormone-receptor status — no. (%)		
Triple-negative	130 (45.3)	60 (41.7)
Hormone-receptor–positive	157 (54.7)	84 (58.3)
BRCA status — no. (%)§		
BRCA1-positive	133 (46.3)	63 (43.8)
BRCA2-positive	154 (53.7)	81 (56.2)
<12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)	108 (37.6)	42 (29.2)
Previous adjuvant or neoadjuvant therapy — no. (%)	238 (82.9)	121 (84.0)
No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previous platinum therapy — no. (%)	46 (16.0)	30 (20.8)
Previous cytotoxic regimens for advanced breast cancer — no. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
3	12 (4.2)	8 (5.6)

EMBRACA



Litton N Engl J Med 2018; 379:753-763

Subgroup Analysis



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Conclusions

- Targeted inhibition of key pathways—CDK4/6, PIK3CA, and PARP—has been a successful strategy in the management of HR+ mBC and TNBC
- Targeted therapy may be most effective as an earlier line of therapy, as such…
- Testing for mPIK3CA and gBRCA status should be done early
- Monitoring for mESR1 may be a valuable strategy to extend the benefit of CDK4/6 inhibitors