Selection and Sequencing of Therapy for Patients with ER-Positive Metastatic Breast Cancer

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Results for Pivotal CDK 4/6 Inhibitor Trials

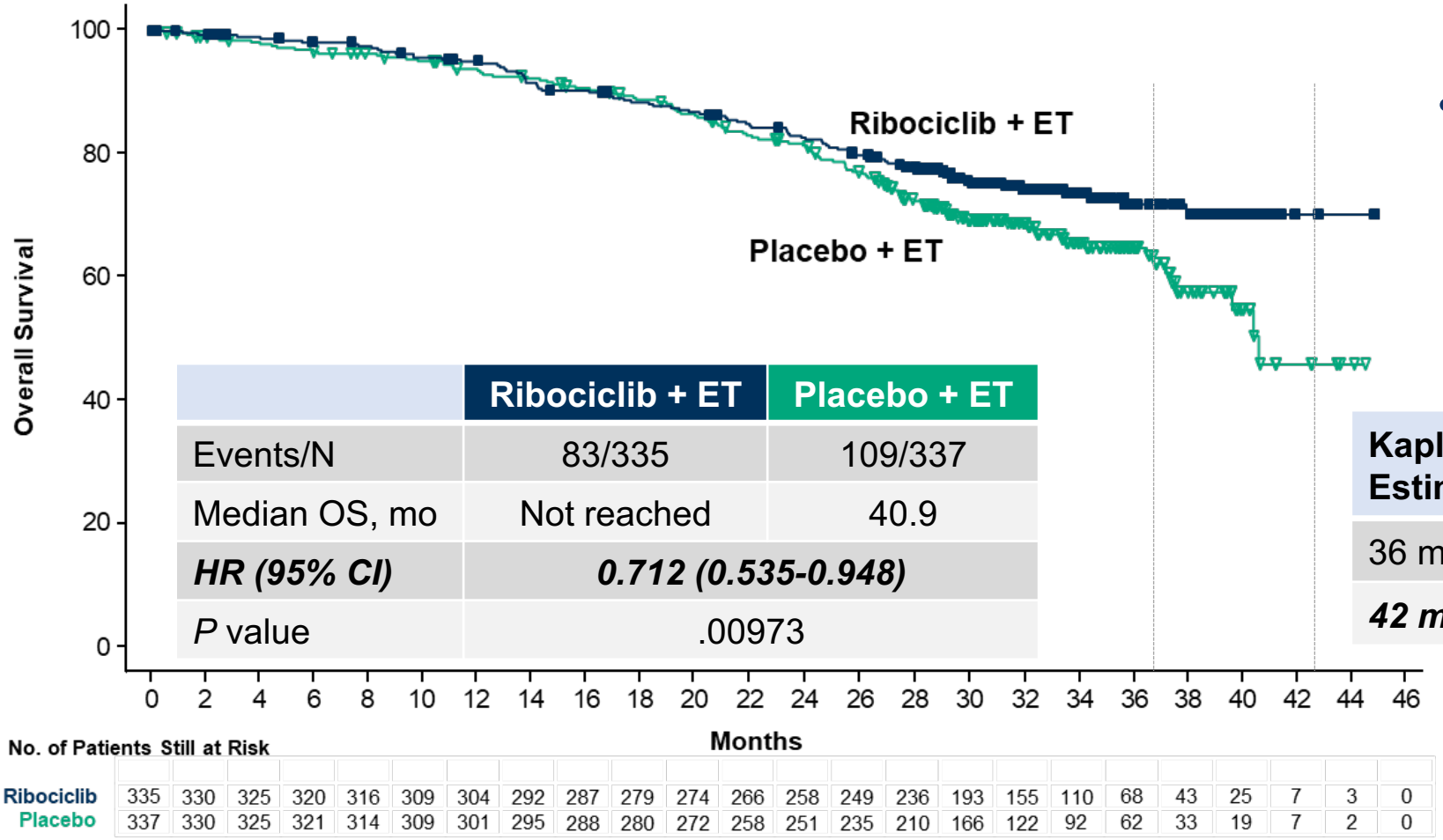
Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

a. Missing survival data (ie, pts who withdrew consent or were lost to follow-up) and were censored (assumed to be alive) at time of analysis: 13% in palbo+AI arm vs 21% in control arm.
b. 27% of patients in control arm went on to receive a CDK4/6i (24% received palbociclib).
c. PFS/OS data reported for approved AI subset.

AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5*. Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

MONALEESA-7: Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

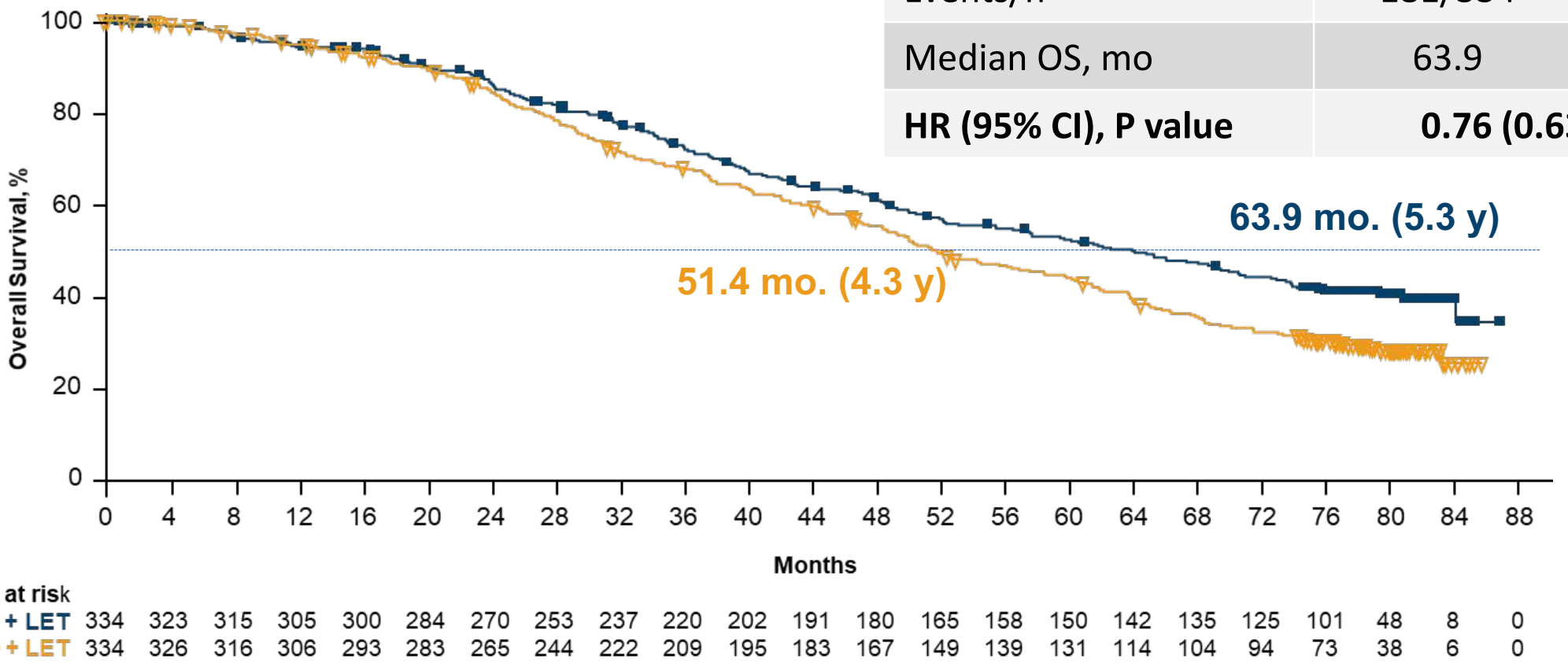
Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 mo	71.9%	64.9%
42 mo	***70.2%***	***46.0%***

Protocol-specified key secondary end point.
Im S-A, et al. *New Engl J Med*. 2019;381:307-316.

MONALEESA-2: Letrozole ± Ribociclib – Overall Survival

Final Analysis at 400 death events: Improvement in median OS of 12.5 mo

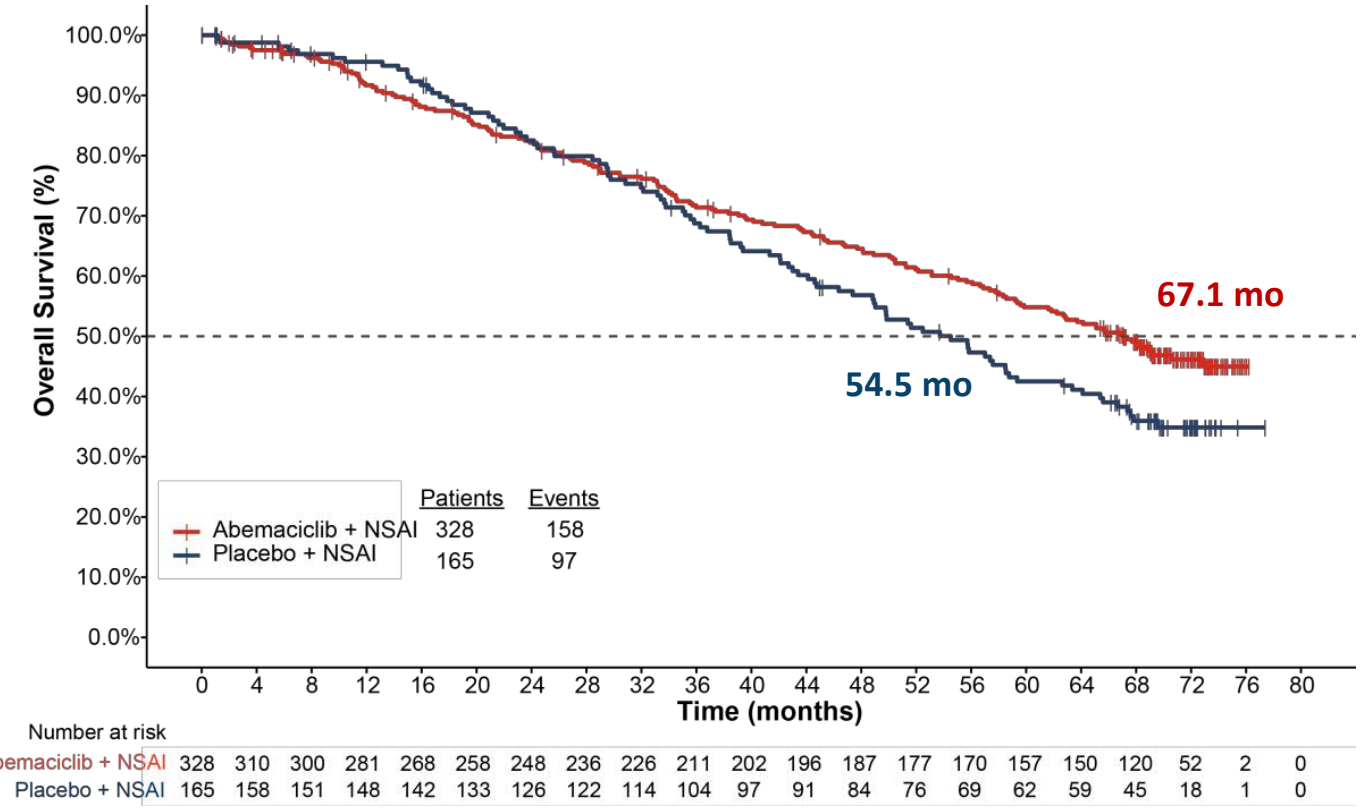
	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI), P value	**0.76 (0.63-0.93), .004**	



Key secondary end point.

Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR.

MONARCH-3: NSAI ± Abemaciclib – Overall Survival



	abemaciclib + NSAI	placebo + NSAI
Median OS, (months)	67.1	54.5
HR (95% CI; *P* value)	0.754 (0.584-0.974) p-value 0.0301*	
Pre-planned OS IA2 Analysis Data cut: 02 Jul 2021		

*p-value did not reach threshold for statistical significance at this interim

31.5% of patients in the control arm and 10.1% in the abemaciclib arm received a subsequent CDK4 & 6 inhibitor

At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months.

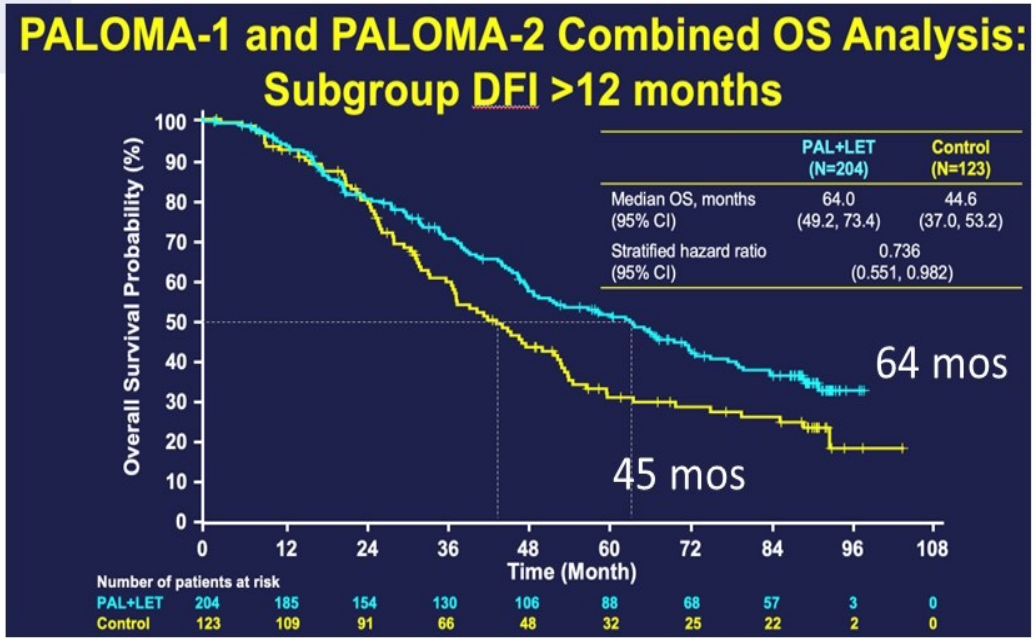
Key secondary end point.
Goetz M. et al. ESMO 2022. Abstract LBA15

Why are there OS differences between the studies?

Randomized P3 Trials	PALOMA-2 * Palbociclib	MONALEESA-2 Ribociclib	MONALEESA-7 Ribociclib	MONALEESA-3 Ribociclib 1L Cohort
De novo mBC	38%	34%	41%	20%
Disease-free interval				
DFI ≤ 12 mos	22%	1%	7%	0%
DFI > 12 mos	40%	NR	53%	80%
DFI > 24 mos	NR	60%	NR	NR

- DFI ≤ 12 mos in Paloma 1 ~ 35%
- Combined OS analysis with PALOMA-1 planned
- Analysis by DFI subgroup unplanned

No substantial differences in prior therapy, visceral disease, use of subsequent CDK46i in placebo arm, other variables



Limitations:
- Post hoc analyses
- Definition of "missing survival data"

- Paloma-2: Missing survival data and were censored at time of analysis: 13% in palbo+AI arm vs 21% in control arm. 27% of pts in control arm went on to receive a CDK4/6i (24% received palbo).

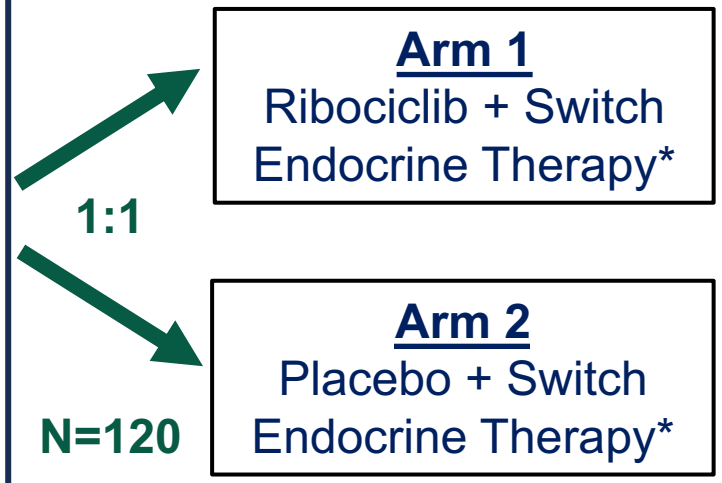
Finn et al NEJM 2016; Hortobagyi et al. NEJM 2016; Tripathy et al Lancet Oncol 2018; Slamon et al. NEJM 2020

Adopted from Claudine Isaacs

Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed



Primary Endpoint

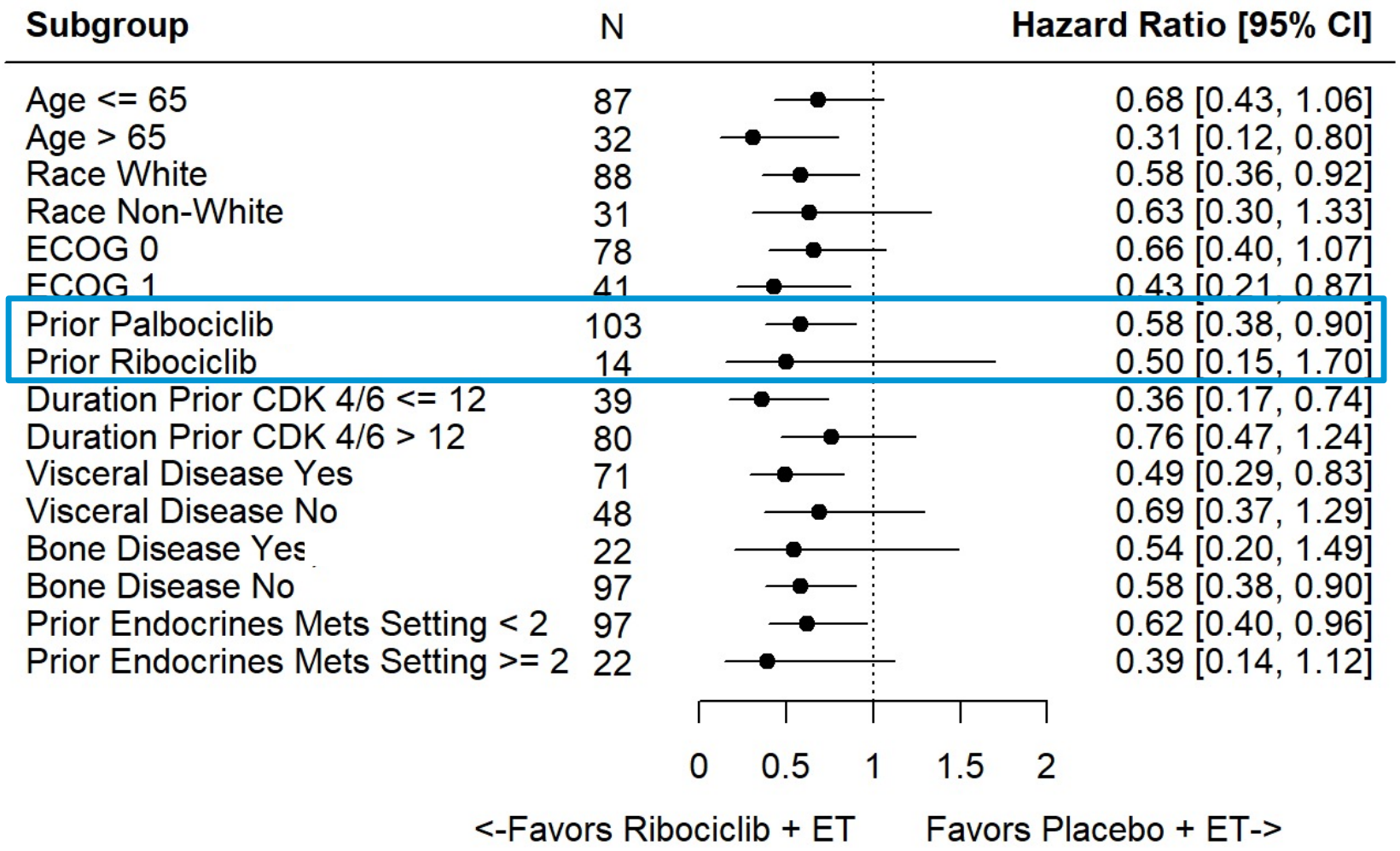
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

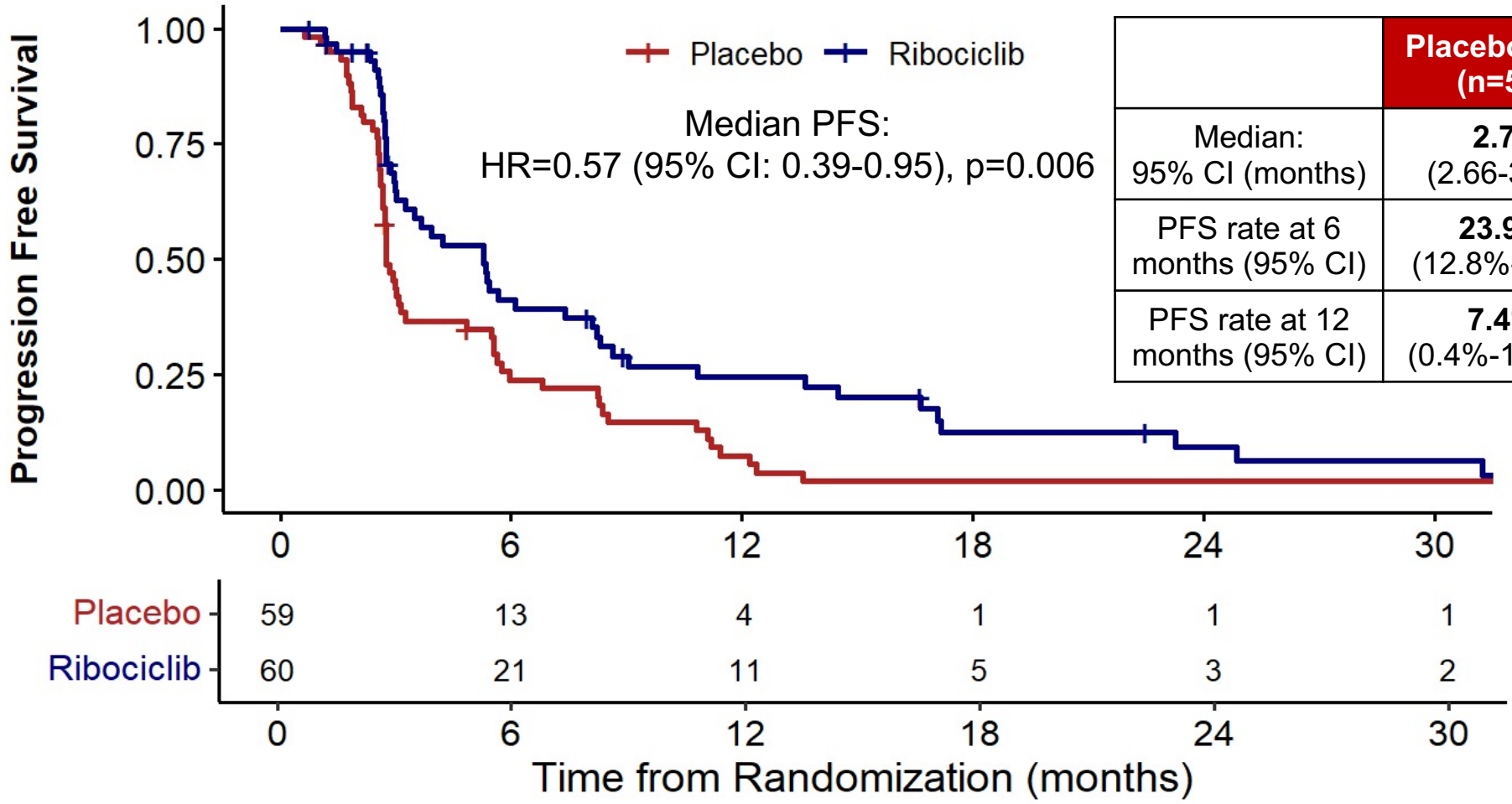
- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

Progression Free Survival by Subgroup



PRESENTED BY:
Kevin Kalinsky, MD, MS

Progression Free Survival



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

PACE Trial: Schema

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

1:2:1 randomization; stratified by exposure to chemo between CDK4/6i and entry onto trial

N=220

RANDOMIZE

Fulvestrant: 500 mg IM C1D1,15, then q28d

Fulvestrant: 500 mg IM C1D1,15, then q28d
Palbociclib: 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)

Fulvestrant: 500 mg IM C1D1,15, then q28d
Palbociclib: 125 mg PO qd 1-21d in a 28d cycle
Avelumab: 10 mg/kg IV q14d

Baseline archival tissue
Baseline ctDNA, CTC

ctDNA

ctDNA, CTC

ctDNA

ctDNA

Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

NOTE: Dr Kalinsky to submit PACE slides once presented at SABCS 2022, Thursday, Dec 8th, 9:45 am CT

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial

BYLieve
Alpelisib (BYL719) in patients with PIK3CA mutant, HR+, HER2- advanced breast cancer

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

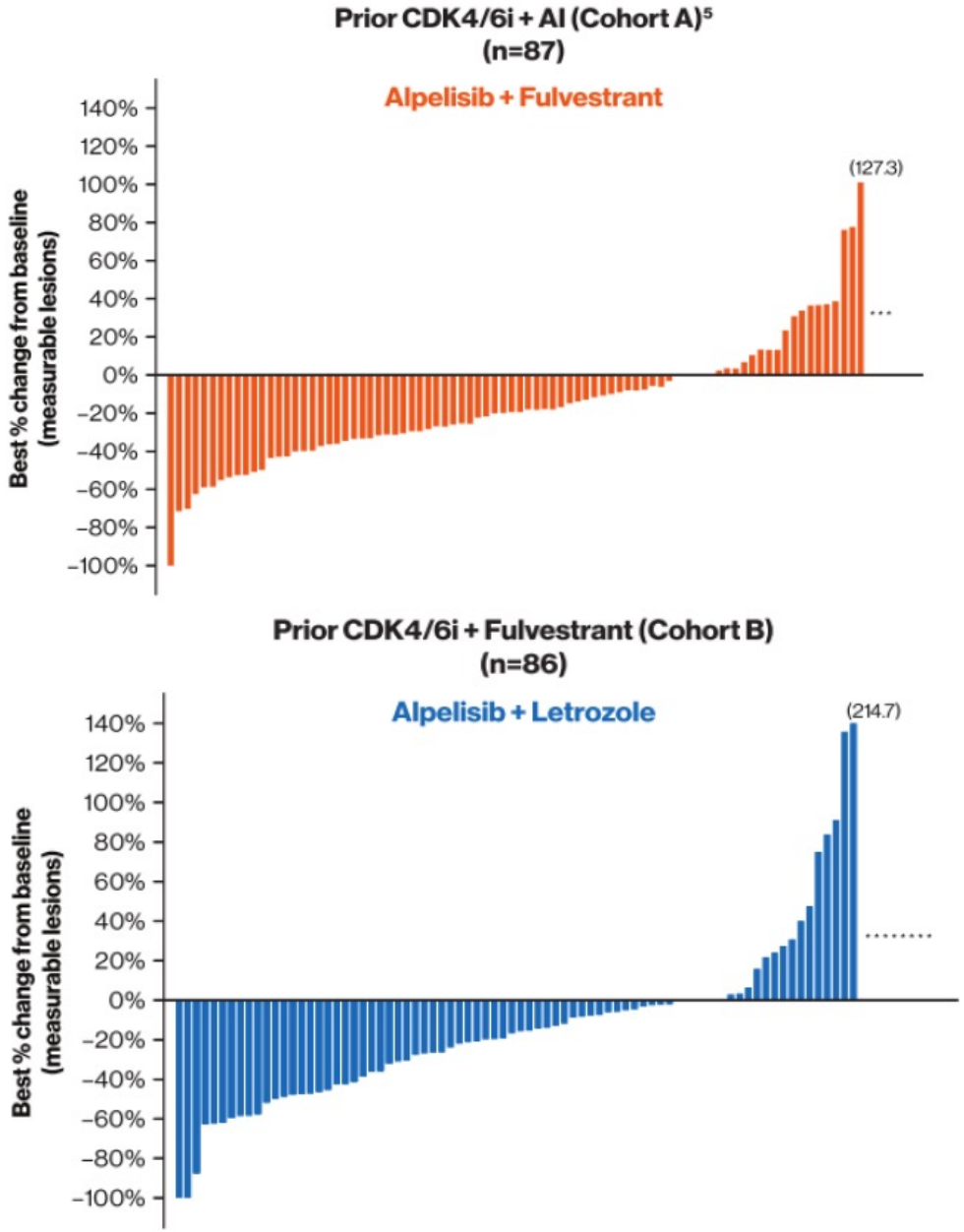
(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

- Rugo HS, et al. Lancet Oncol. 2021;22:489-498; Rugo HS, et al. ASCO 2020. Abstract 1006.

BYLieve Study of Alpelisib After CDK4/6i: Efficacy

Endpoint	BYLieve Trial[a,b]	
	Cohort A[a] Prior AI	Cohort B[b] Prior FULV
N	121	115
Alive, no PD @ 6 mo	50.4% met endpoint	46.1% met endpoint
Median PFS (mo)	7.3 mo	5.7 mo
ORR	21.0%	17.8%
CBR	42.0%	31.7%



a. Rugo HR, et al. ASCO 2020. Abstract 1040; b. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

Summary of Selected Outcomes: BYLieve And SOLAR-1

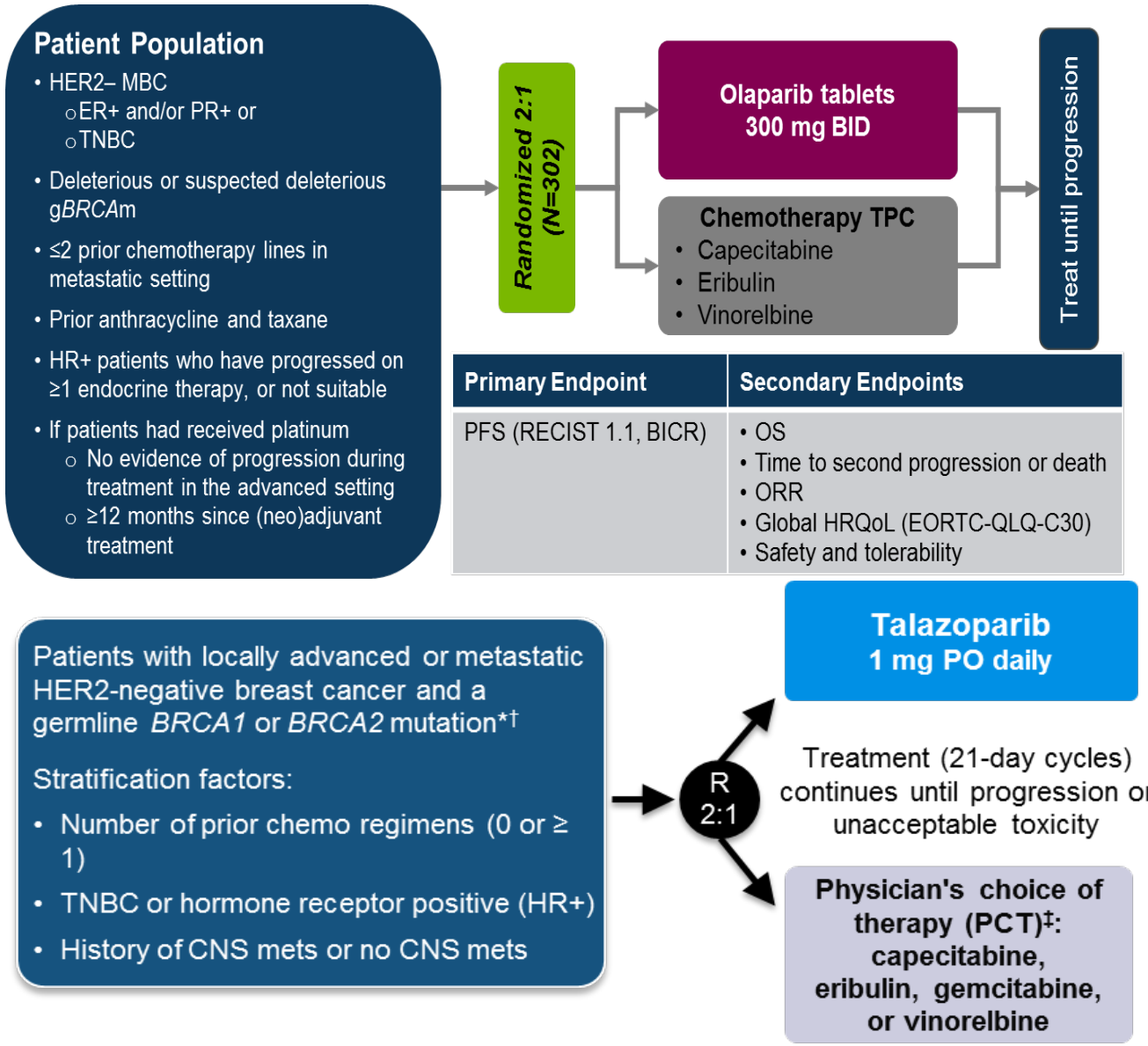
Endpoint	SOLAR-1 Trial Prior CDKi[a]		BYLieve Trial[b,c]	
	FULV + PBO	FULV + Alpelisib	Cohort A[b]	Cohort B[c]
N	11	9	121	115
Alive, no PD @ 6 mo	≈ 20%	44.4%	50.4%	46.1%
Median PFS (mo)	1.8 mo	5.5 mo	7.3 mo	5.7 mo
ORR	NR	NR	21.0%	17.8%
CBR	NR	NR	42.0%	31.7%

a. André F, et al. *N Engl J Med*. 2019;380:1929-1940; b. Rugo HR, et al. ASCO 2020. Abstract 1040; c. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

PARP Inhibitors

- **OlympiAD**

- **EMBRACA**

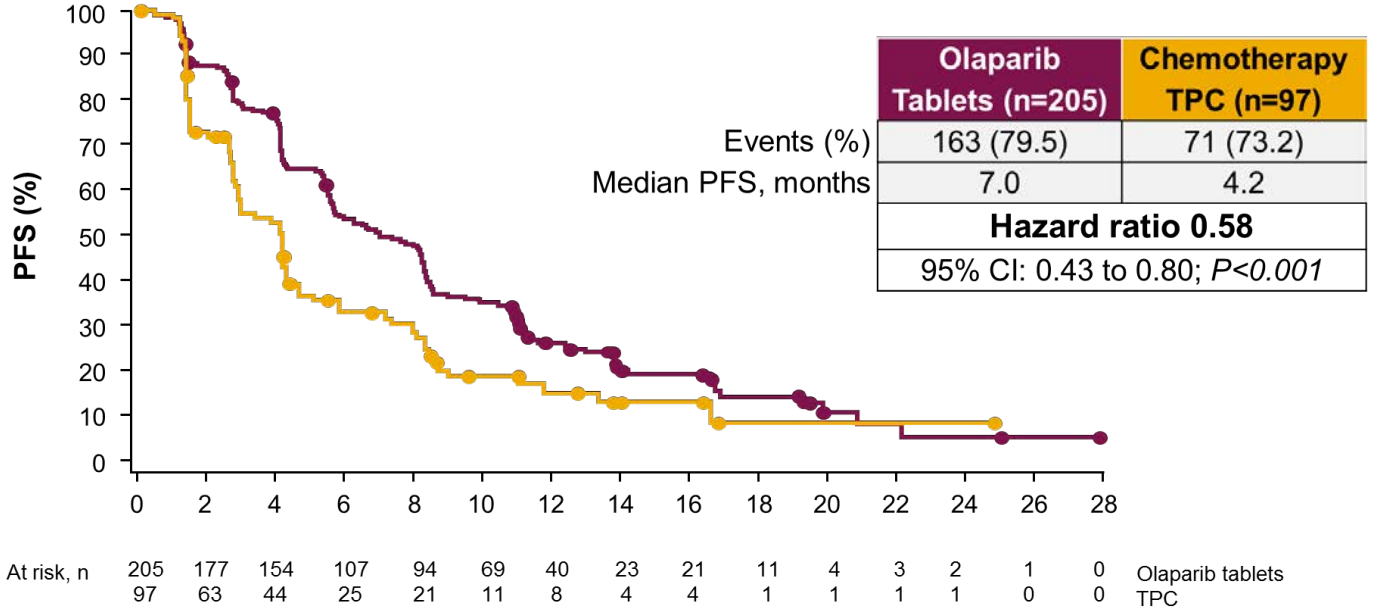


Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

Litton JK, et al. N Engl J Med 2018;379:753-763. Robson M, et al. N Engl J Med 2017;377:523-533.

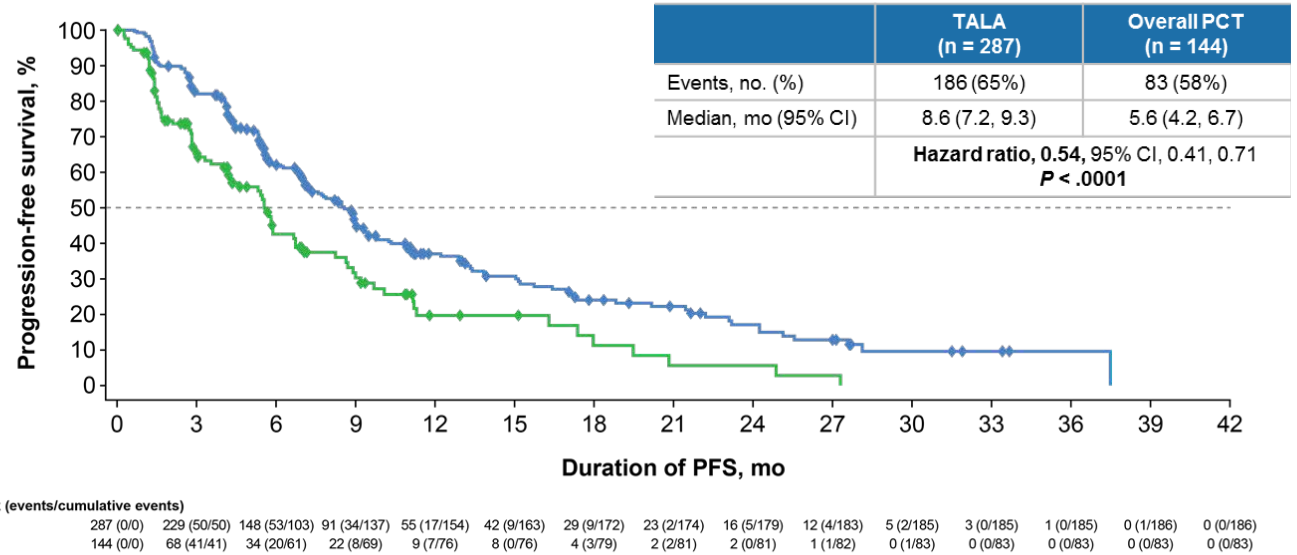
Progression-Free Survival

- **OlympiAD**



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

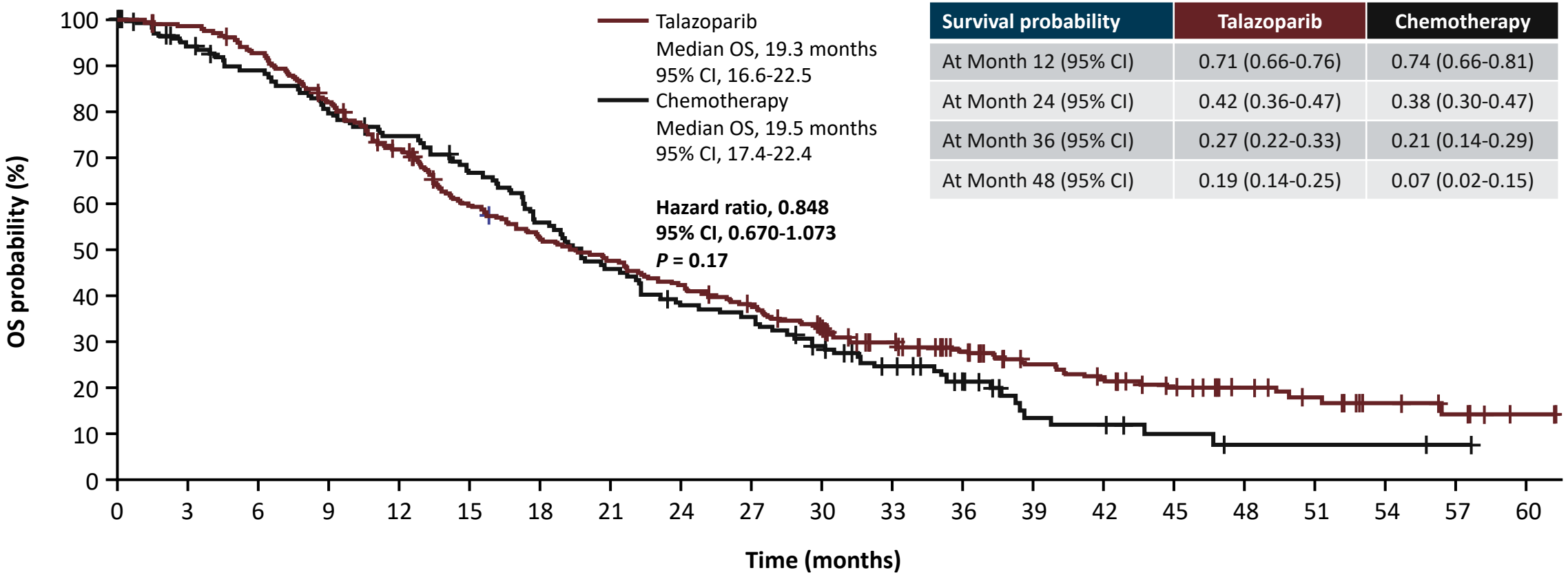
- **EMBRACA**



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

Litton JK, et al. N Engl J Med 2018;379:753-763. Robson M, et al. N Engl J Med 2017;377:523-533.

EMBRACA: Final OS



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
At Month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
At Month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
At Month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

Number of patients at risk

Talazoparib	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
Chemotherapy	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

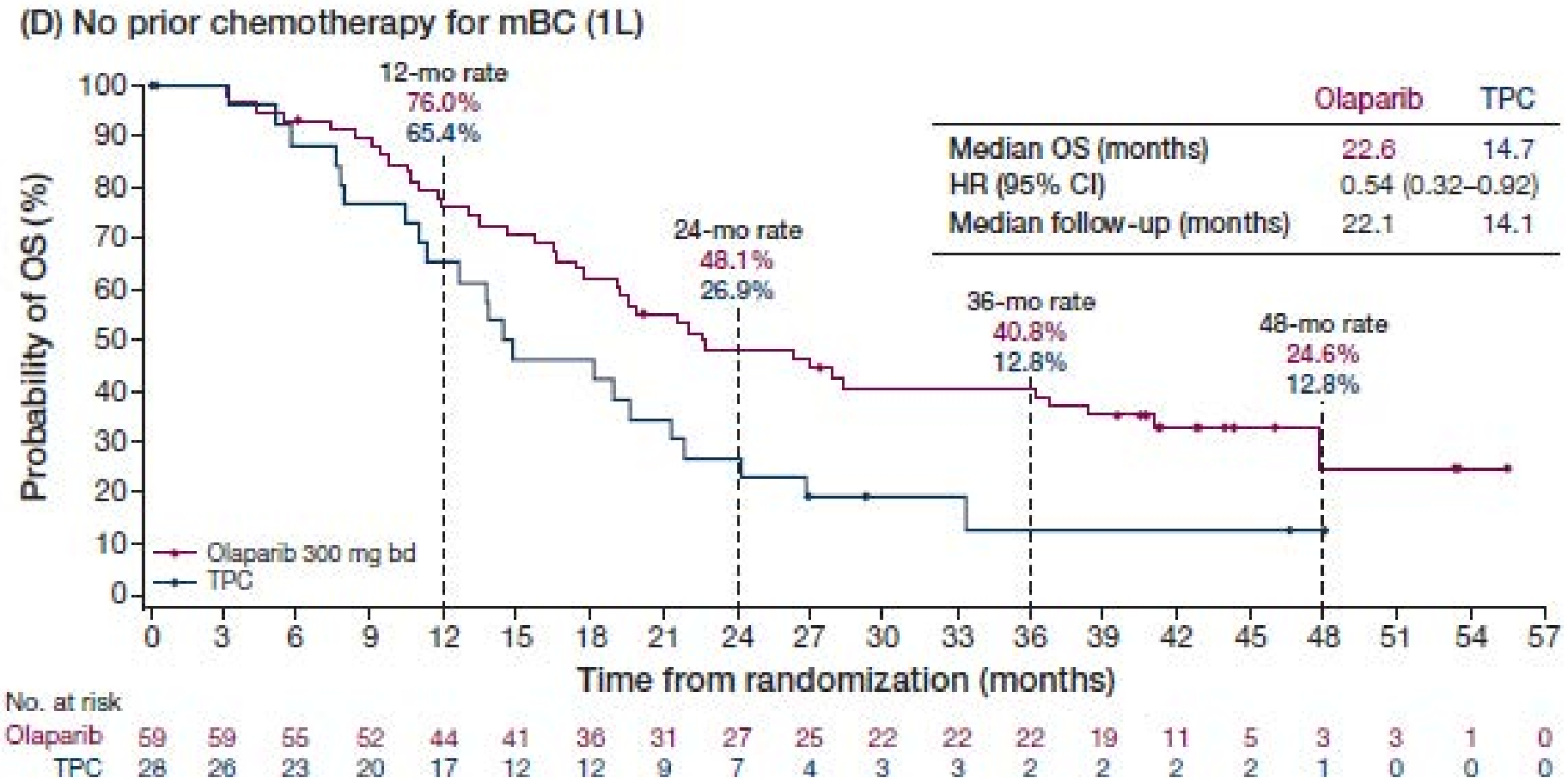
*ITT population

Litton JK, et al. AACR 2020. Abstract CT017.

OlympiAD: Extended OS Follow-Up

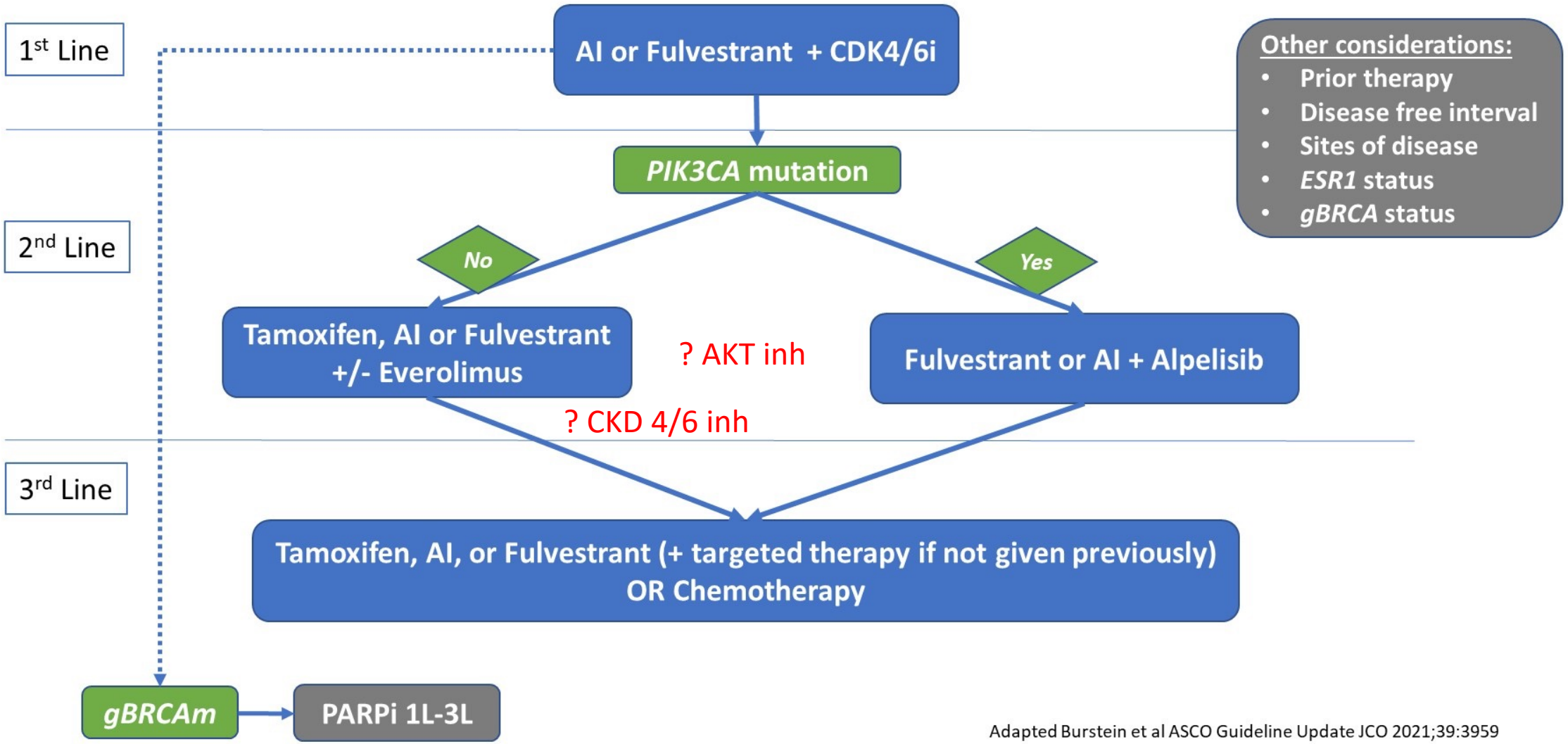
No statistically significant differences in survival curves in tissue receptor subtype

No new safety signal –No AML/MDS



Robson M, et al. SABCS 2019. PD4-03.

Current Approach: Treatment of HR+/HER2- mBC



Adapted Burstein et al ASCO Guideline Update JCO 2021;39:3959

Adopted from Claudine Isaacs