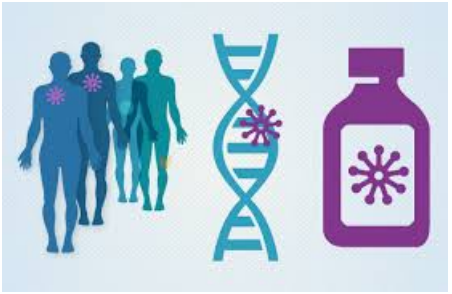

Targeted Therapy for Metastatic HR+/HER2- Breast Cancer: CDK4/6 and PI3K Inhibitors

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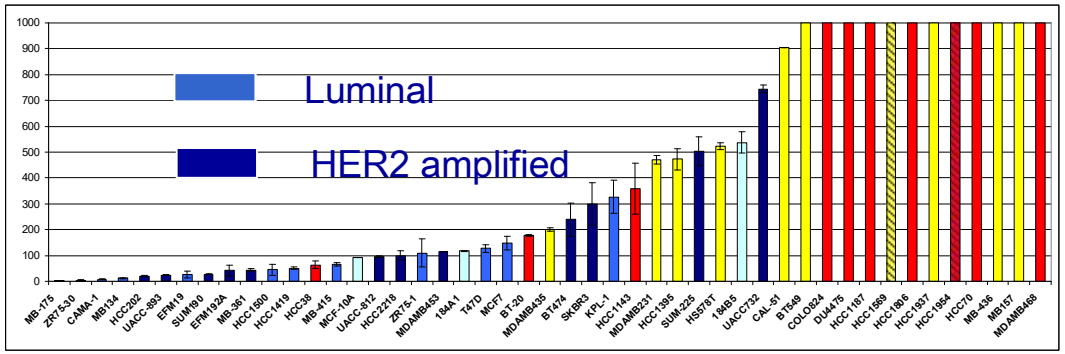
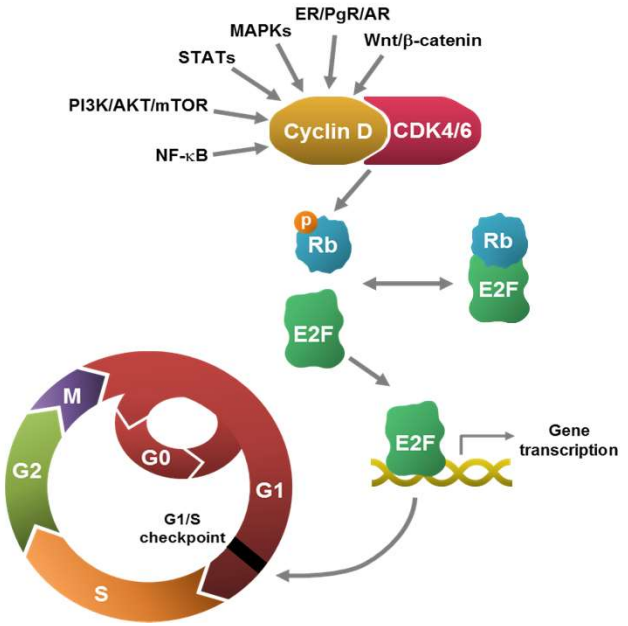
Cyclin-Dependent Kinase 4/6 Inhibitors[1,2]

- Growth of HR+ BC is dependent on cyclin D1, a transcriptional target of ER[1]
- Cyclin D1 activates CDK4/6 causing G1-S phase transition and cell cycle entry[1]
- Endocrine-resistant cell lines are dependent on cyclin D1 and CDK4/6[1]
- CDK4/6i prevent CDK4/6-mediated phosphorylation of Rb[1]





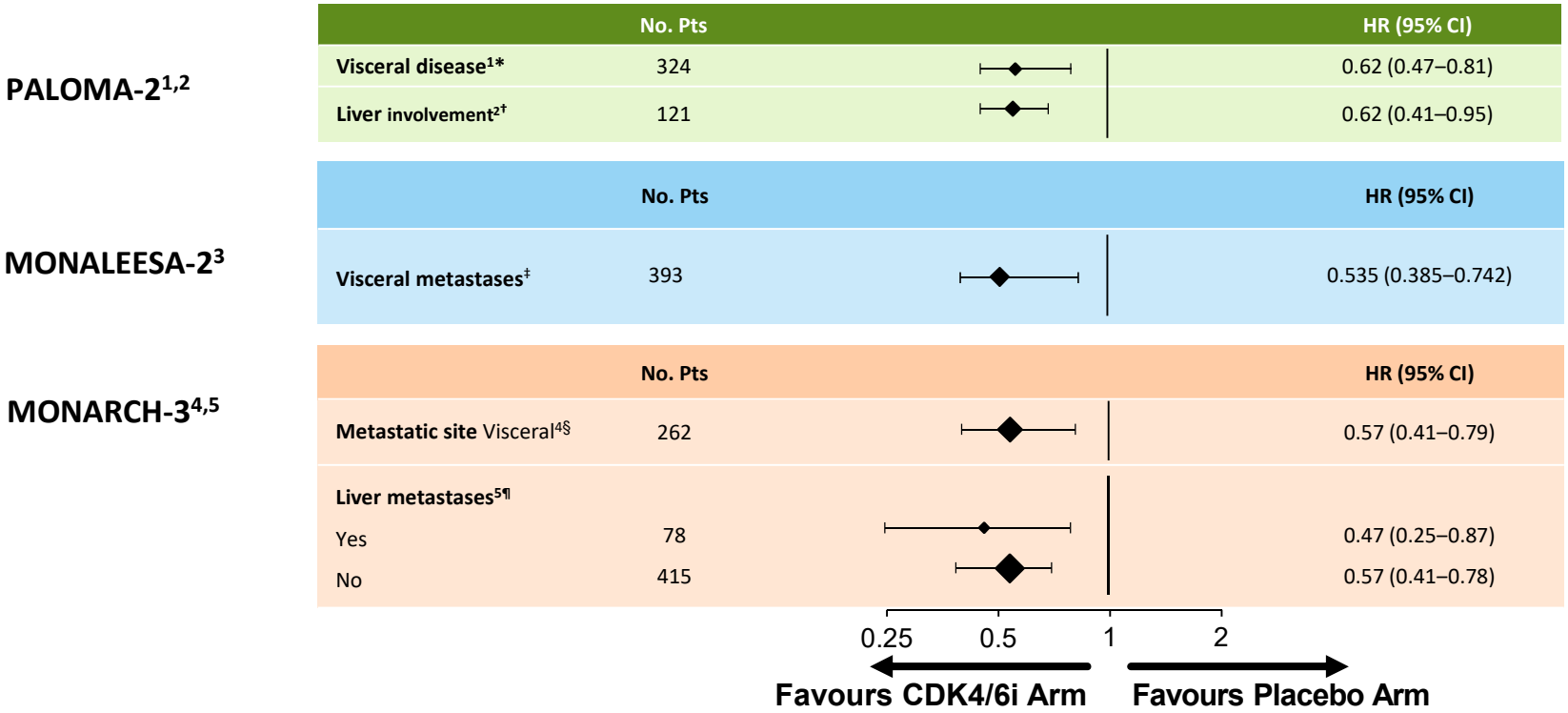
Inhibiting cyclin D–CDK4/6 may prevent cell cycle progression

BC=breast cancer; CDK4/6=cyclin-dependent kinase 4 and 6; CDK4/6i=cyclin-dependent kinase 4 and 6 inhibitors; ER=endoplasmic reticulum; HER2=human epidermal growth factor receptor 2; HR+=hormone receptor-positive; Rb=retinoblastoma. **1.** Created from Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov* 2015;14(2):130–146; **2.** Extracted from Finn RS, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11(5):R77.

CDK4/6i: Phase III First-Line Studies in HR+ MBC

	Paloma-2 Finn et al, NEJM 2016; Rugo et al BCRT 2019	**Monaleesa-2** Hortobagyi et al, NEJM 2016; Ann Oncol 2018; Slamon JCO 2018	**Monarch-3** Goetz et al,JCO 2017; Johnston et al, NPJ Breast 2019	**Monaleesa-7** Tripathy et al Lancet Oncol 2018; Im et al, NEJM 2019
Study design	**Letrozole/Pla vs Let/Palbociclib (1:2)**	**Letrozole/Pla vs Let/Ribociclib (1:1)**	**Letrozole/Pla vs Let/Abemaciclib (1:2)**	**AI or TAM/Pla vs AI or Tam+OS/Ribociclib (1:1)**
Eligibility	**Postmenopausal** **First line**	**Postmenopausal** **First line**	**Postmenopausal** **First line**	**Pre/perimenopausal** **One prior chemo allowed (14%)**
No. of pts	666 *No progression on AIs*	668 *No progression on AIs*	493 *No progression on AIs*	672 DFI≤12 mo: 30% 60% no prior E rx
PFS	**14.5 vs 27.6 mo** HR 0.56 (0.46-0.69) p<0.000001	**16.0 vs 25.3 mo** HR 0.556 (0.43-0.72); p=0.00000329 (HR 0.577 with fulvestrant in ML-3)	**14.8 vs 28.2 mo** HR 0.54 (0.418-0.698) P=0.00002	**13.0 vs 23.8 mo.** HR 0.55 (0.44-0.69) P<0.0001 PFS2 sign longer
OS	Not enough events at median FU of **38 months** No pre-planned interim OS analysis	Not enough events in ML2 ML3 reported	Not enough events	Yes Median FU **34.6 mo** Pre-planned interim analysis

Efficacy in Patients with Visceral Metastases: 1L RCTs



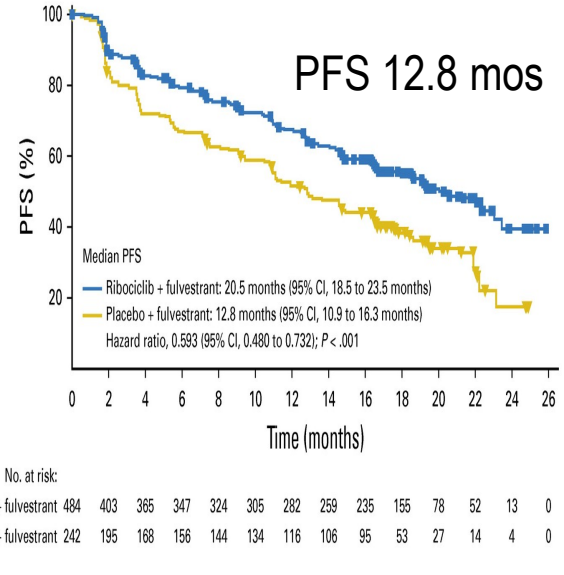
Cross-trial comparisons need to be taken with caution. *Median ITT population follow-up: 37.6 months; †Median ITT population follow-up: 23.0 months; ‡Median ITT population follow-up: 26.4 months; § Median ITT population follow-up: 26.7 months (final analysis); ¶Median follow-up was 17.8 months. ITT=intent to treat; Pts=patients; RCT=randomised controlled trial; 1L=first-line. **1.** Rugo HS, et al. Breast Cancer Res Treat. 2019;174:719–729; **2.** Turner NC, et al. Ann Oncol. 2018;29:669–680; **3.** Hortobagyi G, et al. Breast Cancer Research 2018;20:123; **4.** Johnston S, et al. NPJ Breast Cancer. 2019 Jan 17;5:5; **5.** Goetz MP, et al. J Clin Oncol 2017;35:3638–3646.

CDK 4/6i: Comparison of Trials in Patients with Progression on Prior NSAI. Prior Therapy Matters!

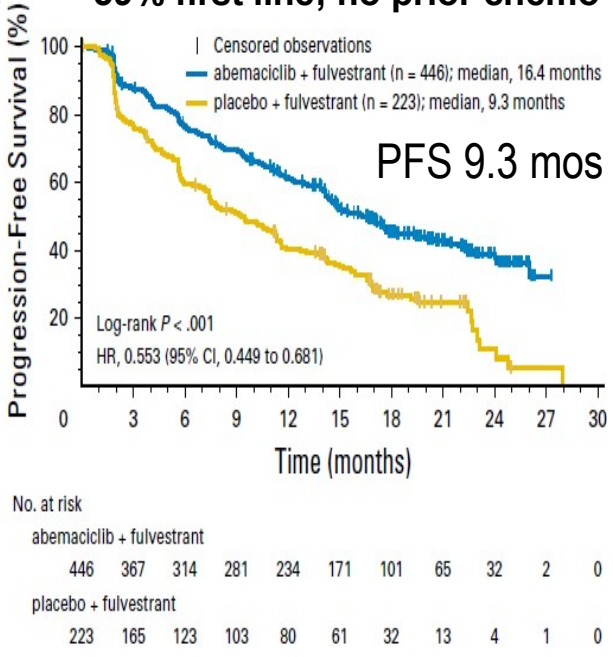
	PALOMA 3 Turner et al, NEJM 2015, NEJM 2018	MONARCH 2 Sledge et al, JCO 2017 JAMA Oncol, 2019	MONALEESA 3 Slamon et al, JCO 2018 NEJM 2020
Study design	**Fulv/pla vs fulv/ palbociclib**	**Fulv/pla vs fulv/ abemaciclib**	**Fulv/pla vs fulv/ ribociclib**
Patient #	**521**	**699**	**726; 345 (2nd line)**
PFS (mo) p value (HR)	**4.6 vs 11.2 P<.000001 (HR 0.497)**	**9.3 vs 16.9 P<.0001 (HR 0.536)**	**2nd line: 9.1 vs 14.6 (HR 0.571) 1st line: 19.6 vs 33.6 (HR 0.55)**
Time from randomization to chemotherapy	**8.8 vs 17.6 mo (HR 0.583)**	**22.1 vs 50.2 mo (HR 0.625)**	**29.5 vs NR mo (HR 0.696) PFS 2: 29.4 vs 39.8 mo (HR 0.670)**
Prior chemotherapy for metastatic disease	**31-36%**	**None**	**None**
Prior endocrine Rx	**Any number of lines**	**1**	**0 or 1**
OS	**28 vs 34.9 mo HR 0.791 (0.626-0.999) P=0.0246 (NS)**	**37.3 vs 46.7 mo HR 0.757 (0.606-0.945) P=0.0137**	**ITT: HR 0.72 (0.57–0.92), p=0.00455 2nd line 32.5 vs 40.2 mo, HR 0.73 (0.53-1.00)**

PFS Data of Fulvestrant + CDK 4/6 inhibitor Phase III Trials

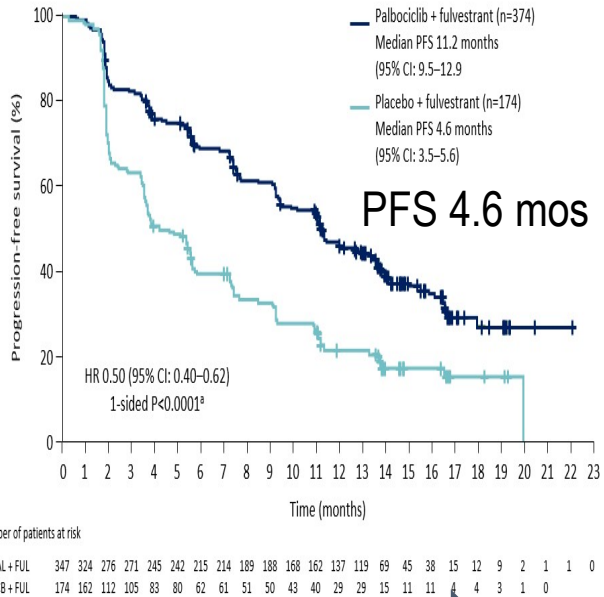
MONALEESA-3[1]
59% first line; no prior chemo



MONARCH-2[2]
59% first line; no prior chemo



PALOMA-3[3]
22% first line; 34% prior chemo



As level of pretreatment increases, PFS as well as time to chemo in control arm decreases

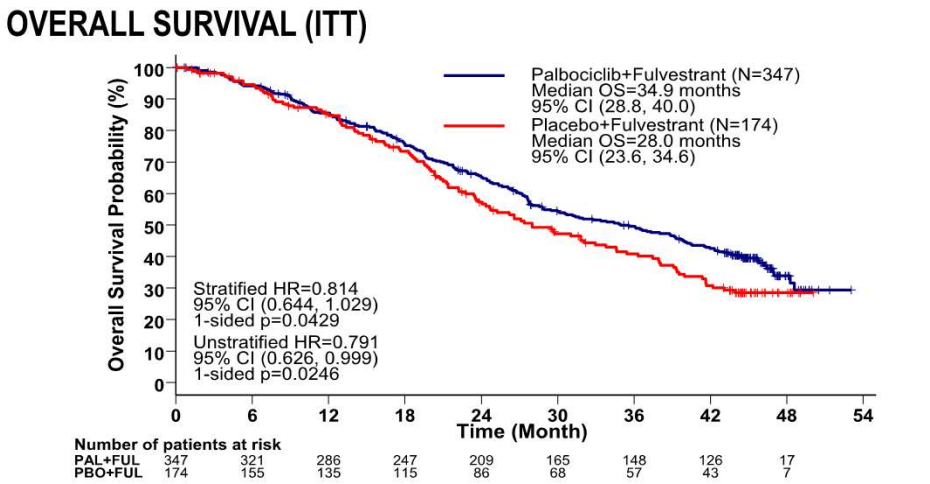
Courtesy/adapted from Loible, ESMO 2019

1. Slamon D et al *JCO* 2018;36:2465-72; 2. Sledge GW et al *JCO* 2017;35:2875-84; 3. Turner N et al. NEJM 2016

OS Benefit from CDK4/6i with Fulvestrant: Decreasing Benefit with Increasing Line of Therapy

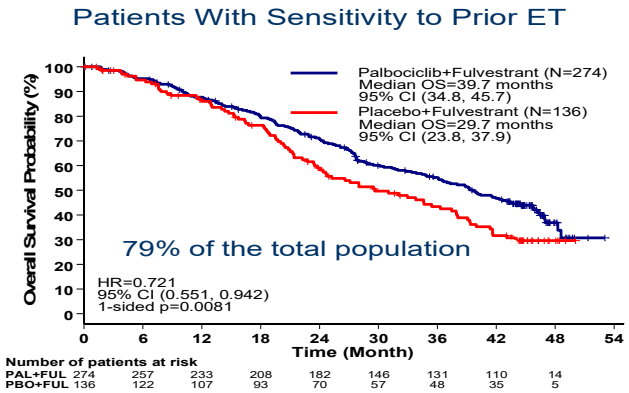
	N	Prior chemotherapy	Lines of endocrine therapy	OS (placebo vs CDK4/6i)
Paloma 3	521	Yes (~33%)	Any number	28 vs 34.2 mo HR 0.791
Endocrine sensitive (79%)	410			29.7 vs 39.7 mo HR 0.721
Monaleesa 3 (2nd line/early relapse)	346	No	1	32.5 vs 40.2 mo HR 0.73
Monarch 2	669	No	1	37.3 vs 46.7 mo HR 0.757

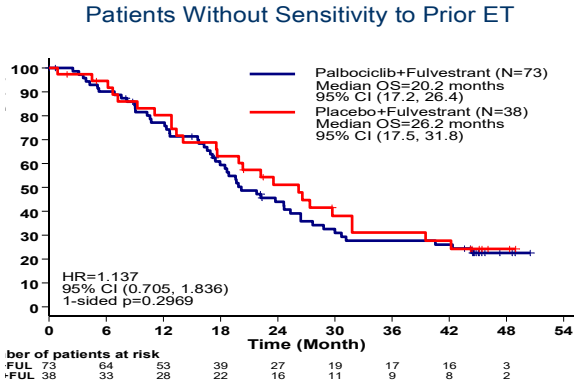
Overall Survival PALOMA-3



- **Absolute improvement in median OS in the palbociclib arm vs the placebo arm was 6.9 months.**

The prespecified significance threshold was 1-sided 0.0235 which was adjusted for two interim OS analyses

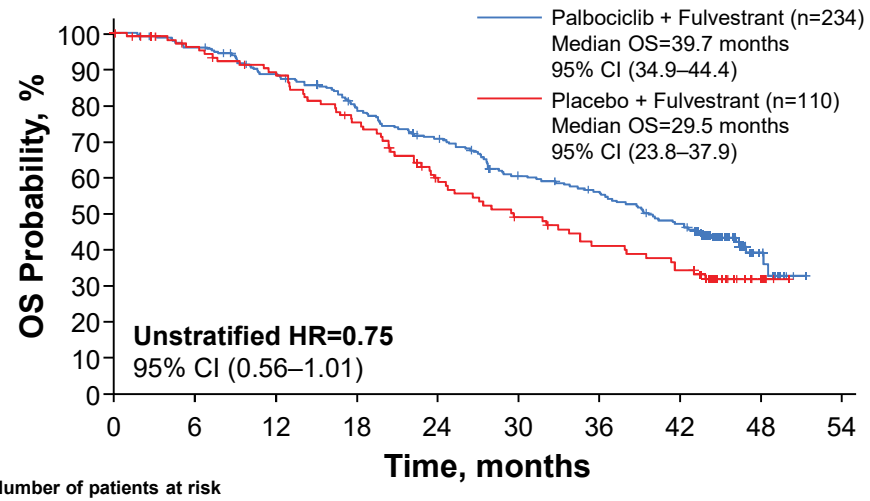




Turner NC, et al. *N Engl J Med*. 2018;379(20):1926-1936.

OS in Patients Without and With Prior CT in ABC (Overall Population)

Without Prior CT in ABC (66% of ITT)

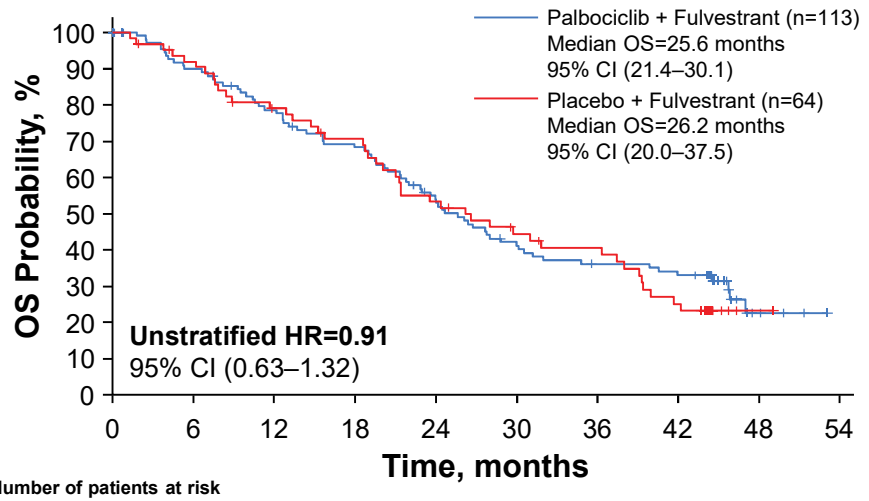


Number of patients at risk

PAL+FUL	234	223	202	175	154	124	113	94	13
PBO+FUL	110	98	88	74	55	44	36	30	6

Absolute difference in median OS with palbociclib: +10.2 months

With Prior CT in ABC (34% of ITT)



Number of patients at risk

PAL+FUL	113	98	84	72	55	41	35	32	4
PBO+FUL	64	57	47	41	31	24	21	13	1

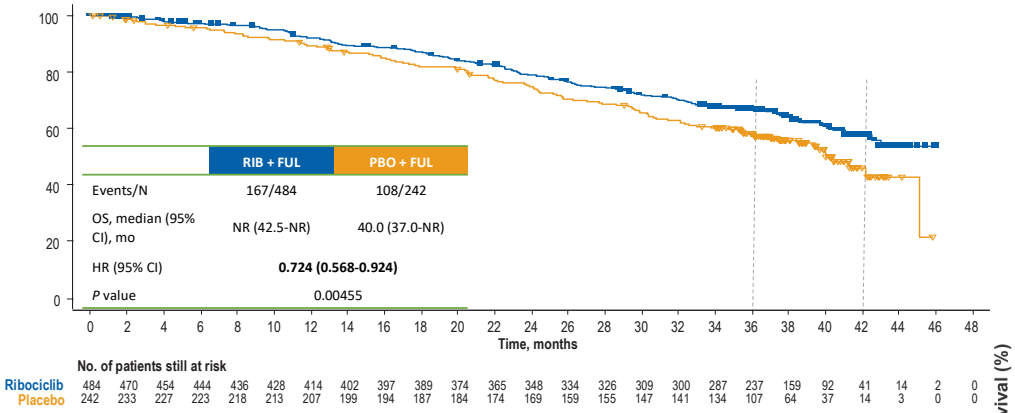
Absolute difference in median OS with palbociclib: -0.6 months

ABC=advanced breast cancer; CI=confidence interval; CT=chemotherapy; FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PAL=palbociclib; PBO=placebo.

Rugo et al, EBCC 2020

Overall Survival MONALEESA-3: Combined 1st and 2nd line

The relative reduction in risk of death with RIB was 28%



- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* < 0.01129)

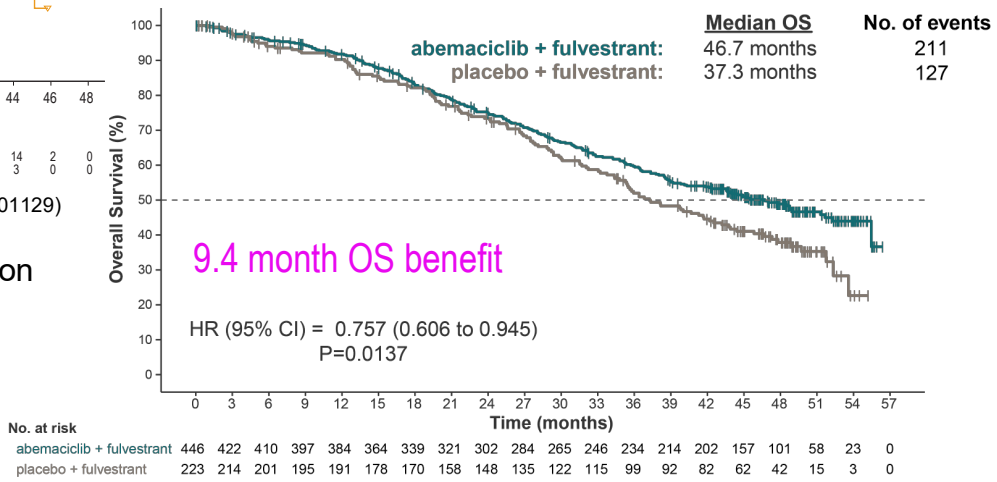
OS by line of therapy was consistent with overall population

Landmark Analysis

KM Estimate	RIB + FUL	PBO + FUL
36 months	67.0%	58.2%
42 months	57.8%	45.9%

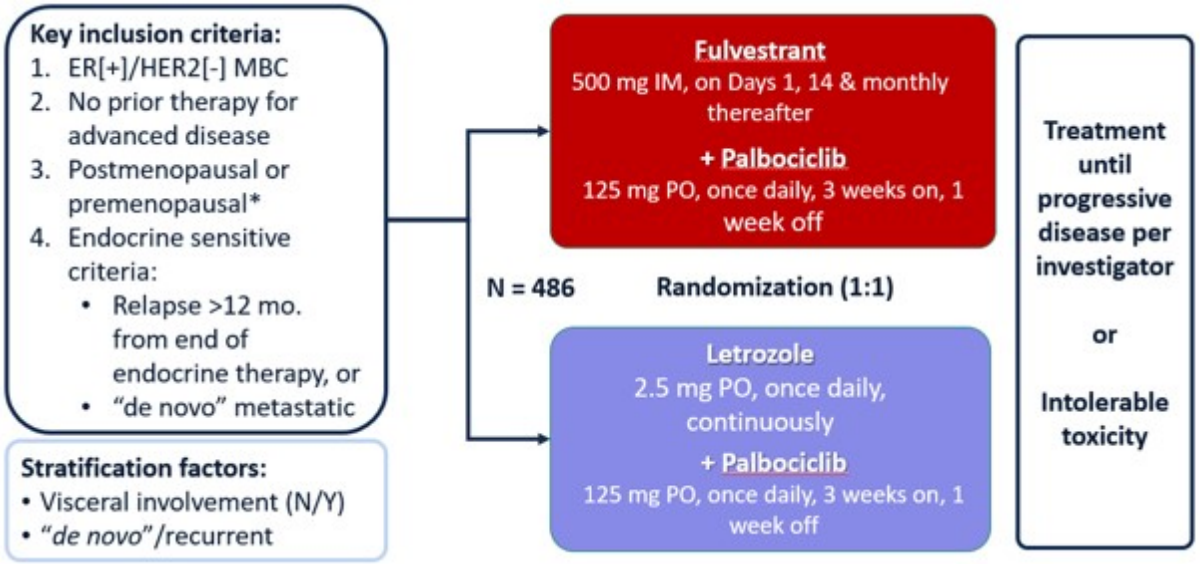
Slamon D et al. ESMO 2019; *N Engl J Med*. 2020;382(6):514-524

OVERALL SURVIVAL MONARCH-2



Sledge G et al. ESMO 2019; JAMA Oncology 2019 [Epub ahead of print]

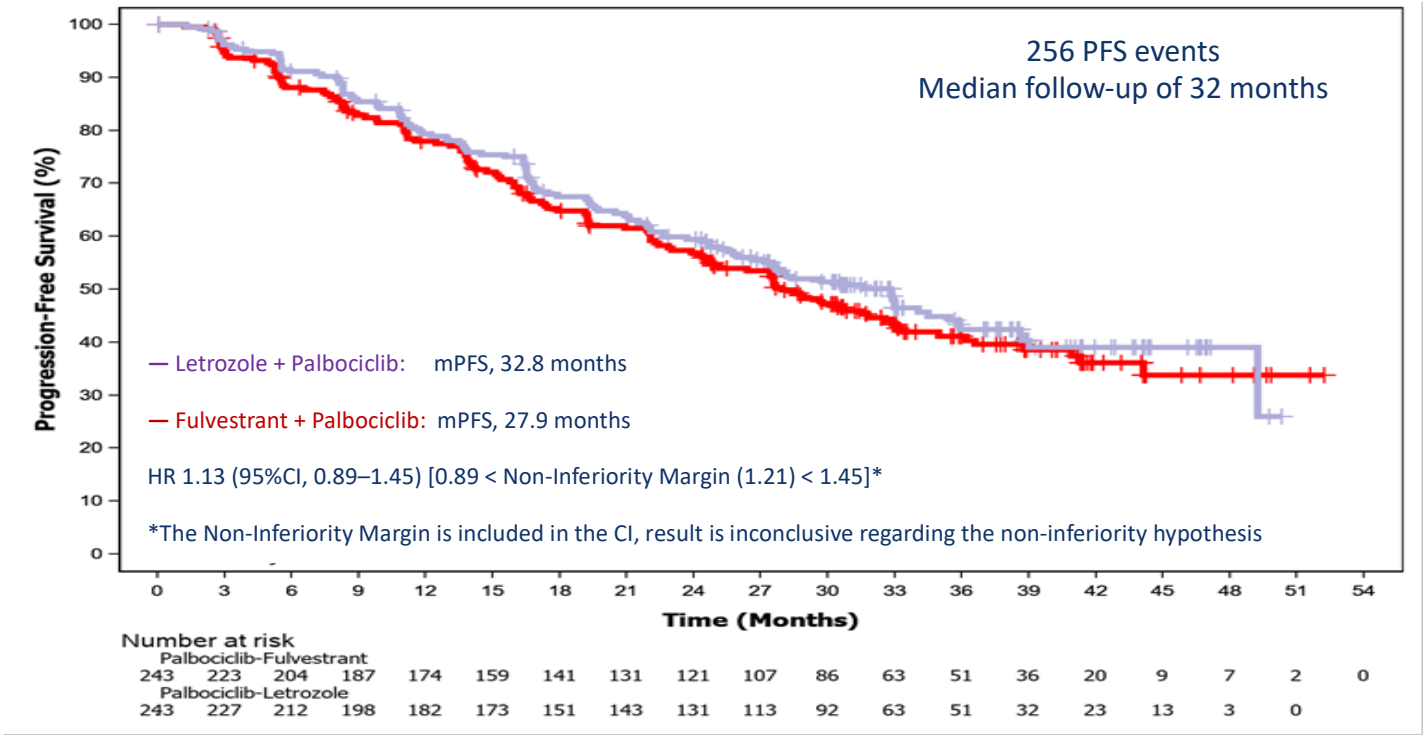
Is There an Optimal Endocrine Partner in Combination with CDK4/6i? The Parsifal Trial



Characteristics	Fulvestrant+ Palbociclib (N=243)	Letrozole+ Palbociclib (N=243)
Prior therapies in EBC, n (%)		
Chemotherapy		
Neoadjuvant	25 (10.3)	21 (8.6)
Adjuvant	73 (30)	71 (29.2)
Endocrine therapy		
Tamoxifen	87 (35.8)	90 (37.0)
Aromatase inhibitors	65 (26.7)	52 (21.4)
Both	39 (16.0)	31 (12.8)

Llombart-Cussac et al, ASCO 2020

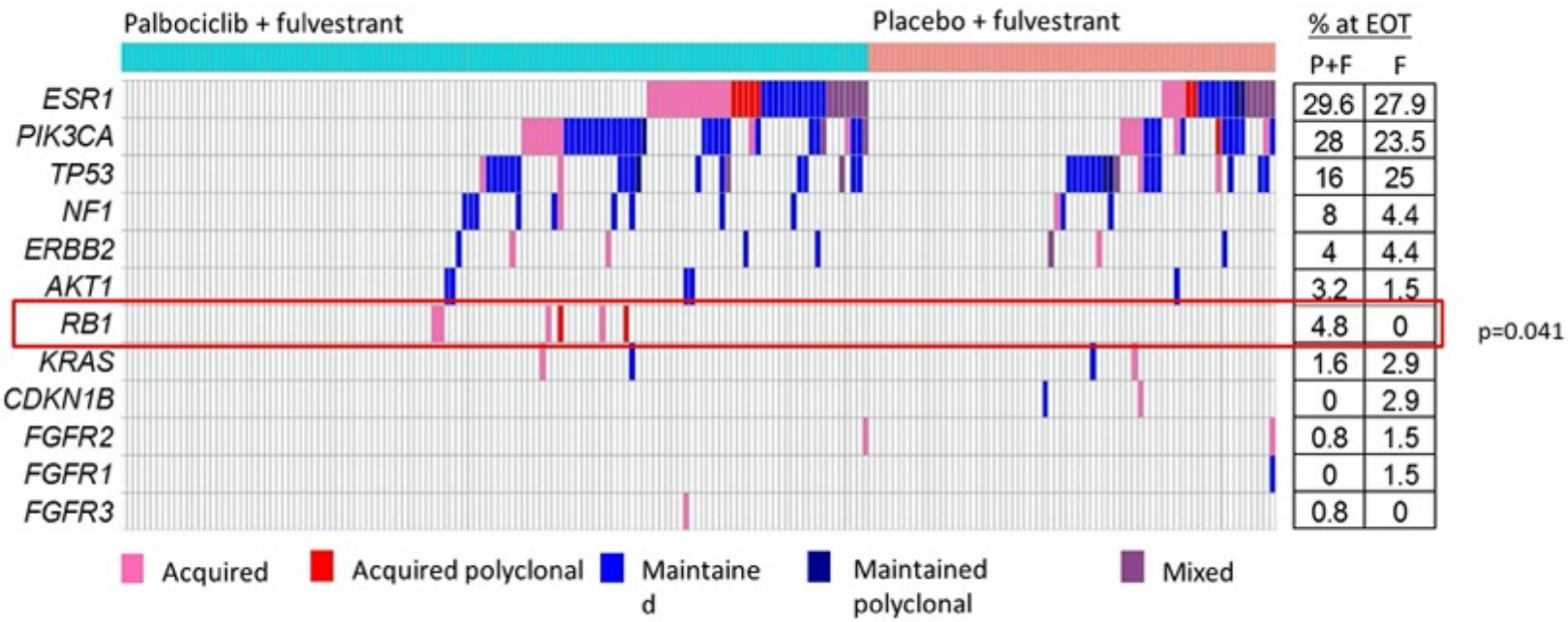
PARSIFAL: PFS ITT Analysis



- Trial initially designed with a superiority design (HR 0.70) with N=486
- If superiority was not achieved, design changed to a non-inferiority analysis with a non-inferiority margin of 1.21

Toxicity in 1st line	Palbociclib	Ribociclib	Abemaciclib
Dosing schedule	3 wks on, one wk off	3 wks on, one wk off	Continuous
≥Gr 3 neutropenia	66%	59.6%	21.1%
Febrile neutropenia	1.6%	1.5%	<1%
≥Gr 3 diarrhea (all grade)	1% (26%)	1.2% (35%)	9.5 (81%)
Gr2/3 QTc prolongation	-	3/0.3 (↑with TAM)	-
≥Gr 3 AST/ALT increase	-	5.7/9.3% All grade ML3 13.7%	3.8/7%
Dose reduction/discontin due to AEs	36% / 9.7%	51% / 7.4%	43.4% / 19.6%
Alopecia	33%	33%	27%
Increased creatinine	-	-	98% (nl fcn)
VTE/PE	0.9 vs 1.4%	NR	4.9 vs 0.6%

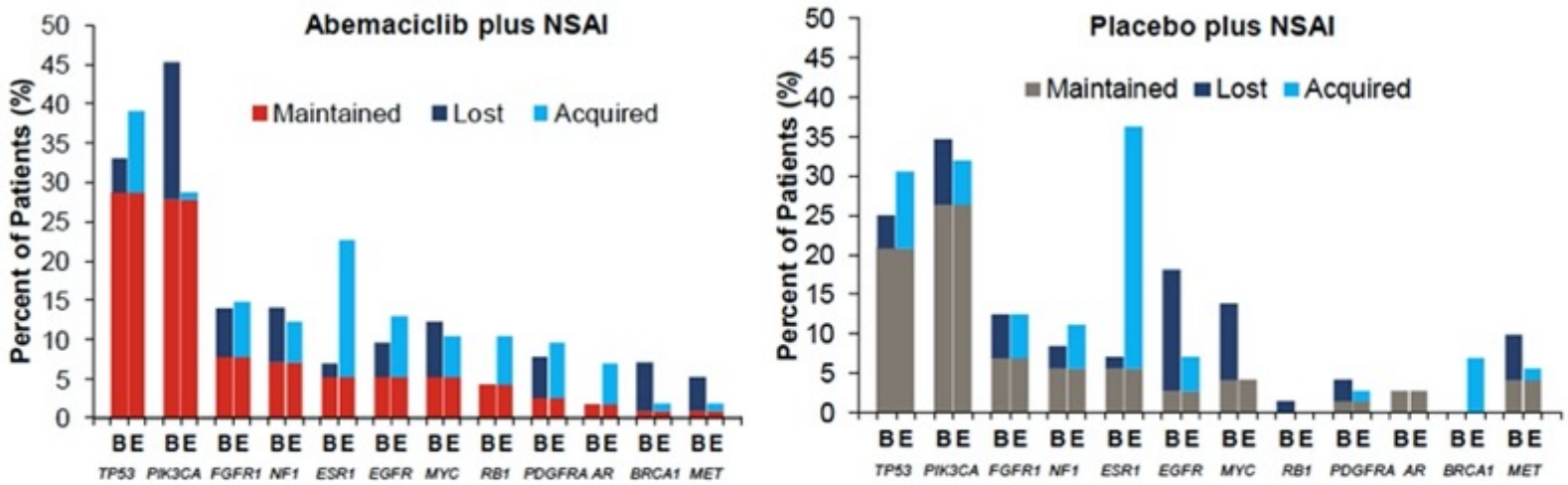
ctDNA mutation landscape at end of treatment in PALOMA3



RB1 mutations acquired in 4.8% (6/125) patients on palbociclib and fulvestrant

O'Leary *et al* Cancer Discov 2018

MONARCH3 paired ctDNA analysis

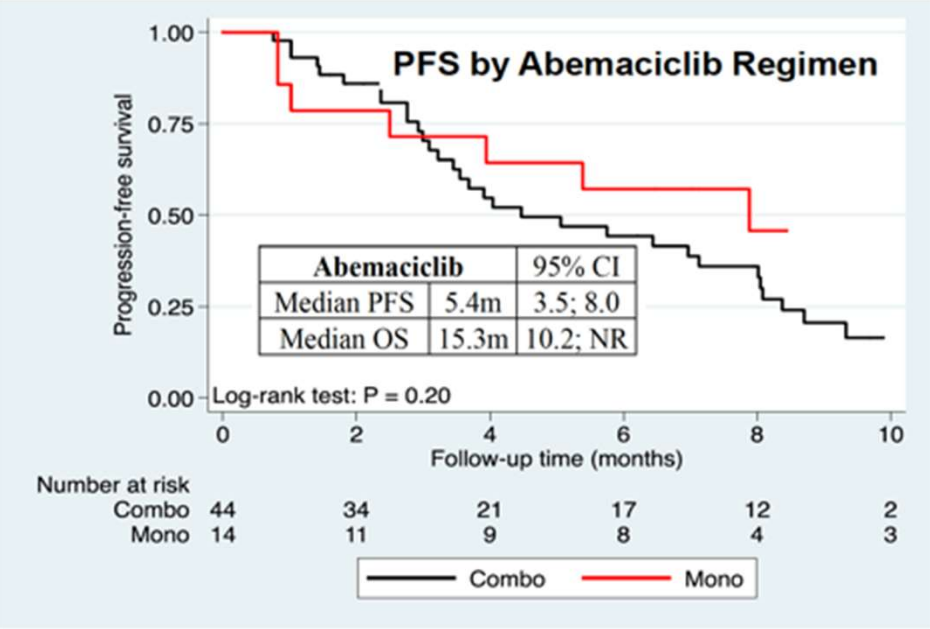


RB1 mutations selected in 6% of abemaciclb group, and 0% placebo p = 0.008

ESR1 alterations less frequently selected with abema vs placebo (17% vs 31%, p = 0.038)

CDK4/6i after CDK4/6i: Is There Efficacy?

- 4 institution collaboration
  - 58 patients treated with abema post ribo or palbo
    - 20 sequential CDK4/6i; 38 non-sequential CDK4/6i
    - 27 (46.6%) with clinical benefit



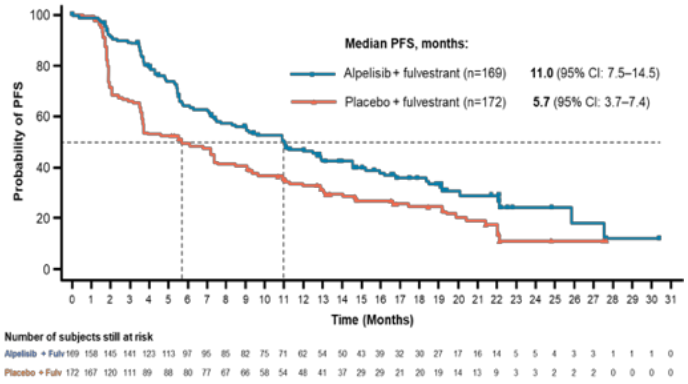
- Ongoing MAINTAIN trial[2]
  - HR+ mBC
  - Disease progression on an AI and CDK4/6i
- Ongoing PALMIRA trial[3]
  - HR+/HER2- ABC
  - Disease progression on LET/FUL and palbociclib after obtaining clinical benefit

1. Wander S, Spring L, Niemierko A, Kambadakone A, Kim LSL, Xi J, et al. A multi-center analysis of abemaciclib after progression on palbociclib in patients with hormone-receptor postive (HR+)/HER2- metastatic breast cancer. ASCO 2019. Abstract 1057; **2.** Clinicaltrials.gov. NCT02632045. https://clinicaltrials.gov/ct2/show/NCT02632045; 3. Clinicaltrials.gov. NCT03809988. https://clinicaltrials.gov/ct2/show/NCT03809988.

Gain-of-Function PI3K Mutations

- PI3K pathway hyperactivation due to *PIK3CA* mutations contributes to endocrine resistance
- *PIK3CA* is one of the most frequently mutated genes in BC, occurring in approximately 40% of HR+, HER2– ABCs
- The presence of a *PIK3CA* mutation is a negative prognostic factor in HR+, HER2– ABC

SOLAR-1: Primary Endpoint of Locally Assessed PFS in the *PIK3CA*-mutant Cohort with Alpelisib, an Alpha Specific PI3K Inhibitor



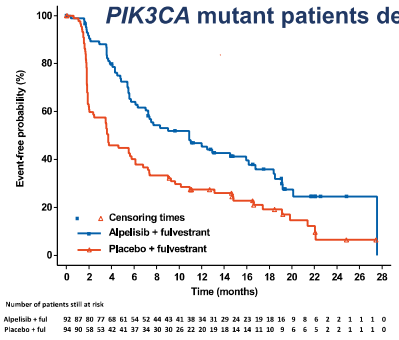
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.

Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
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)	
One-sided *P* value	0.00065	

Similar results when PI3K mutation determined in plasma using ctDNA

Only 6% had prior exposure to a CDK4/6i

Locally Assessed PFS by Tissue or Plasma ctDNA Mutation Status



	ALP + FUL		PBO + FUL		
	Event n/N (%)	Median PFS	Event n/N (%)	Median PFS	HR
Patients with *PIK3CA* mutation: tissue	103/169 (60.9)	11.0	129/172 (75.0)	5.7	0.65
Patients with *PIK3CA* mutation: plasma	57/92 (62,0)	10,9	75/94 (79,8)	3,7	0,55
Patients without *PIK3CA* mutation: tissue	49/115 (42.6)	7.4	57/116 (49.1)	5.6	0.85
Patients without *PIK3CA* mutation: plasma	92/181 (50.8)	8.8	103/182 (56.6)	7.3	0.80

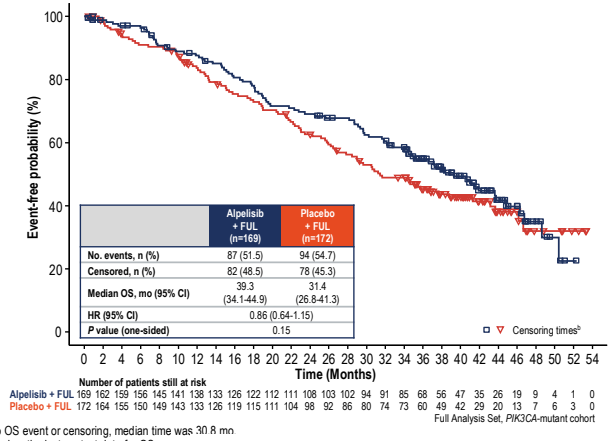
ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; QD, once daily.

Andre et al, NEJM 2019;
Juric et al, SABCS 2018

SOLAR-1: Overall Survival

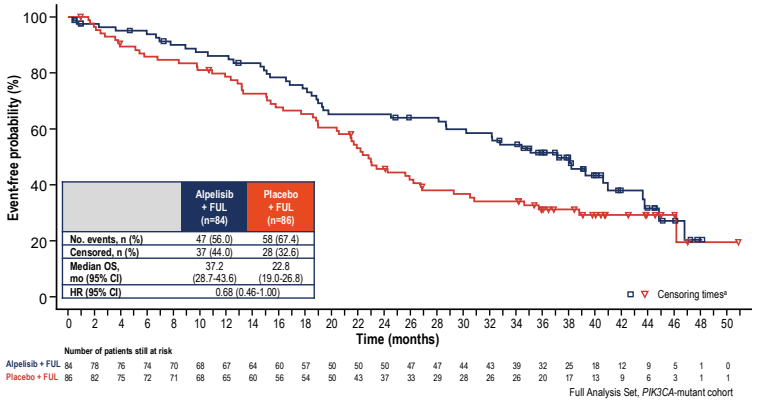
SOLAR-1: OS in Patients in *PIK3CA*-mutant Cohort[a]

- mOS was prolonged by 7.9 mo for patients in the alpelisib + fulvestrant arm
- Final OS analysis in the *PIK3CA*-mutant cohort did not cross the prespecified O'Brien-Fleming efficacy boundary (1-sided $P \leq 0.0161$)



[a]Between randomisation to OS event or censoring, median time was 30.8 mo.
[b]Date of censoring is defined as the last contact date for OS.

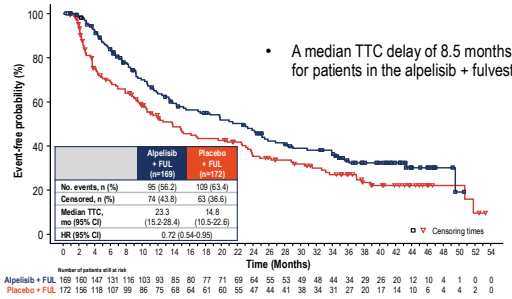
SOLAR-1: OS in Patients With Lung and/or Liver Metastases



[a]Date of censoring is defined as the last contact date for OS.

SOLAR-1: Time to First Chemotherapy[a]

- A median TTC delay of 8.5 months was observed for patients in the alpelisib + fulvestrant arm



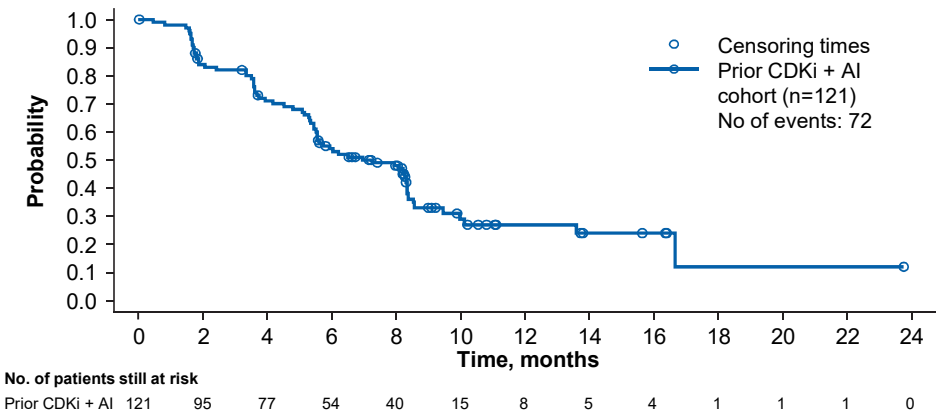
Post hoc exploratory analysis, *PIK3CA*-mutant cohort
TTC, time to chemotherapy.
[a]Time to chemotherapy is defined as time from randomisation for first chemotherapy, censored at last contact date or death.

Andre et al, ESMO 2020

BYLieve Cohort A: Primary Endpoint and PFS Results

(prior AI + CDK4/6i as last treatment)

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Rugo HS et al. ASCO 2020 Abstract 1006

PFS Effect of Alpelisib Over Standard Treatments in Real-World Setting[a]

Analysis Method (In Patients With *PIK3CA* Mutation)	**BYLieve Prior CDKi +AI (Cohort A) Alpelisib + Fulvestrant median-PFS (mo)** (95% CI), n	**Flatiron/FMI Standard Treatment median-rwPFS (mo)** (95% CI), n
Unadjusted results	**7.3** (5.6-8.3), n=120	**3.6** (3.1-6.1), n=95
Weighting by odds	**7.3** (5.6-8.3), n=120	**3.7** (3.1-6.1), n=116
Propensity score matching	**8.0** (5.6-8.6), n=76	**3.5** (3.0-5.4), n=76
Exact matching	**6.5** (5.3-8.3), n=61	**3.4** (2.9-3.9), n=61

Matched analysis comparing BYLieve with RWE standard treatment in post-CDK4/6i setting further supports use of alpelisib + fulvestrant

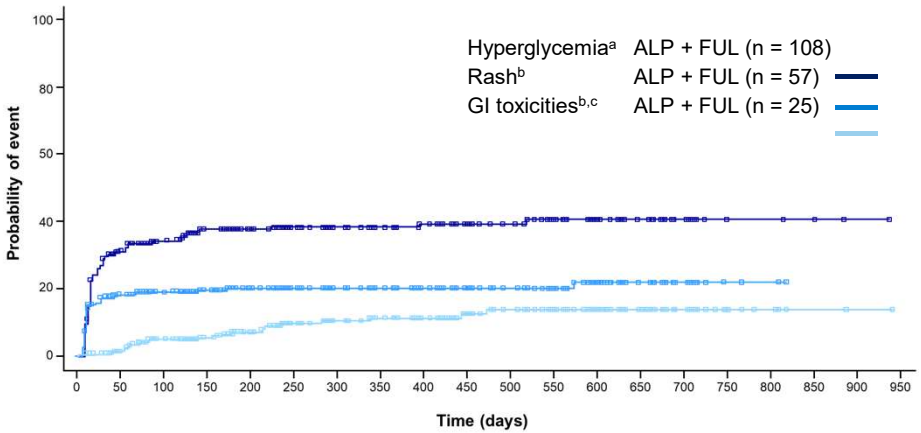
[a]PFS comparison is based on PFS per RECIST v1.1 in BYLieve and real-world PFS in Flatiron/FMI.

Rugo HS et al. ASCO 2020 Abstract 1006

Time Course of Adverse Events in SOLAR-1

- The most common grade ≥3 AEs in the ALP arm were hyperglycemia, rash, and diarrhea
- In the ALP arm, hyperglycemia and/or rash were typically experienced in the first few weeks of treatment with ALP + FUL, whereas GI toxicities could occur at any time during study therapy
- Median time to onset and median time to improvement by ≥1 grade are shown in the table below

Probability of First Occurrence of Grade 3 AESI Events



Time to Onset and Time to Improvement of AESIs

	Median time to onset, days	Median time to improvement by ≥1 grade, days
Hyperglycemia	15	6
Rash	13	11
Diarrhea	139	18

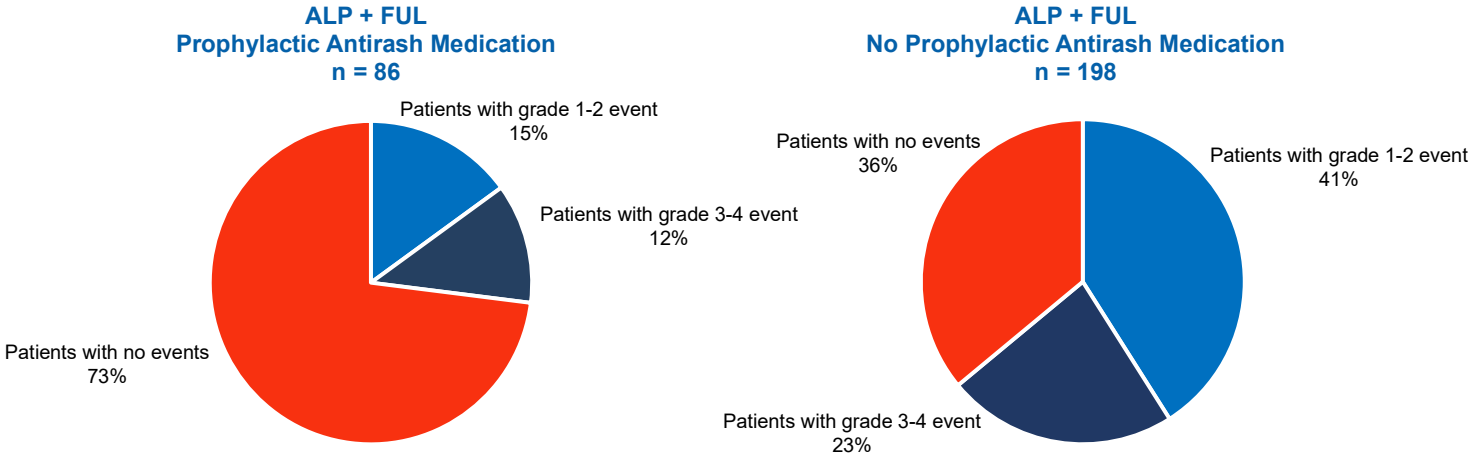
AE, adverse event; AESI, adverse event of special interest; ALP, alpelisib; FUL, fulvestrant; GI, gastrointestinal; PBO, placebo.

[a] Based on laboratory values rather than single preferred term.
[b] Based on grouped terms.
[c] Of the grade ≥ 3 gastrointestinal (GI) toxicities, 76% of them were grade ≥ 3 diarrhea.

Rugo HS et al, Annals Onc 2020

Understanding and Modifying Toxicity

- Understanding timelines and (to some degree) mechanism helps develop effective prophylactic and management strategies
  - EX: steroid mouthwash for everolimus stomatitis has essentially eliminated this toxicity
  - For alpelisib, antihistamine prophylaxis markedly reduces rash



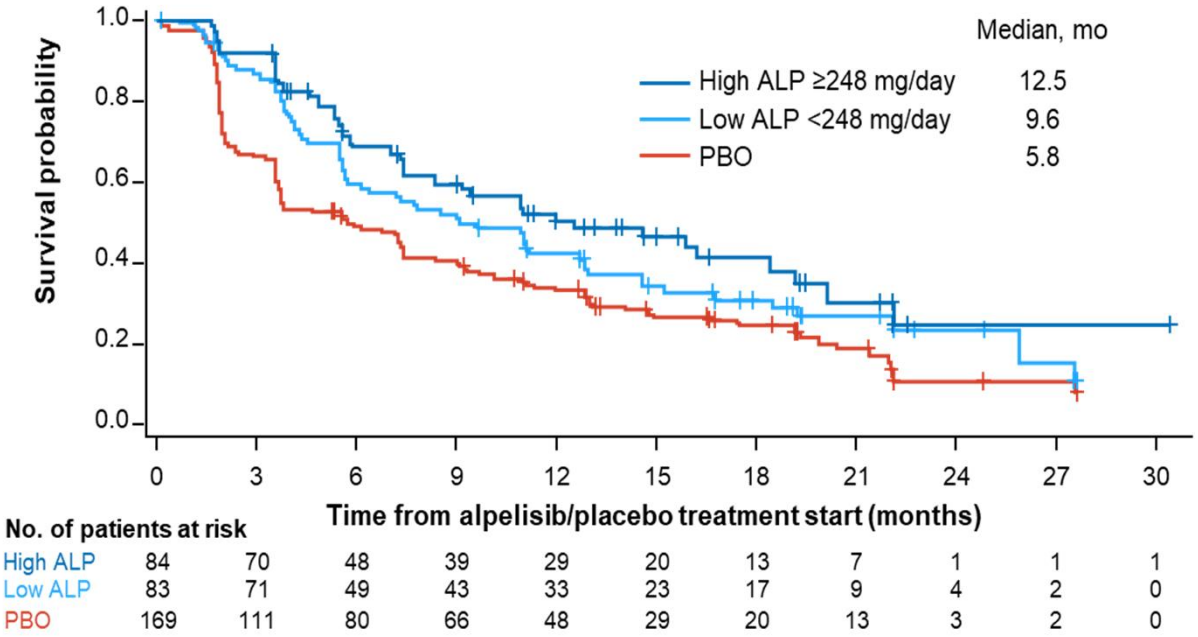
Rugo HS et al, Ann Oncol 2020

Results: Treatment Exposure

- For patients with *PIK3CA* mutations in the ALP arm, the median duration of exposure was 5.5 months for ALP and 8.2 months for FUL
  - Median dose intensity was 248 mg/day

- **PFS benefit with ALP versus PBO was maintained in patients requiring lower doses of ALP for AE management**

PFS by Median Dose Intensity in the *PIK3CA*-mutant Cohort



AE, adverse event; ALP, alpelisib; FUL, fulvestrant; PBO, placebo, *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival

Rugo et al, Ann Oncol 2020

Efficacy of Everolimus in AI-Pretreated HR-Positive Advanced BC

Study	Phase	N	Study Arms	Population	Median PFS, Mos	HR	*P* Value
PrE0102[1]	II	131	Everolimus + FULV vs placebo + FULV	Overall	10.3 vs 5.1	0.61	.02
TAMRAD[2]	II	111	Everolimus + TAM vs TAM	Overall	8.6 vs 4.5‡	0.54	.002
BOLERO-2[3-5]	III	724	Everolimus + EXE vs placebo + EXE	▪ Overall[3] ▪ *PIK3CA*mut tumor*[4] ▪ *PIK3CA*mut ctDNA†[5]	▪ 7.8 vs 3.2 ▪ 6.7 vs 2.8 ▪ 6.9 vs 2.7	▪ 0.45 ▪ 0.51 ▪ 0.37	▪ < .0001 ▪ Not reported ▪ Not reported

*n = 302. †n = 550. ‡TTP.

1. Kornblum. J Clin Oncol. 2018;36:1556. 2. Bachelot. J Clin Oncol. 2012;30:2718. 3. Yardley. Adv Ther. 2013;30:870. 4. Hortobagyi. J Clin Oncol. 2016;34:419. 5. Moynahan. Br J Cancer. 2017;116:726.

FAKTION: Capivasertib + Fulvestrant for AI-Resistant ER+/HER2- Metastatic Breast Cancer

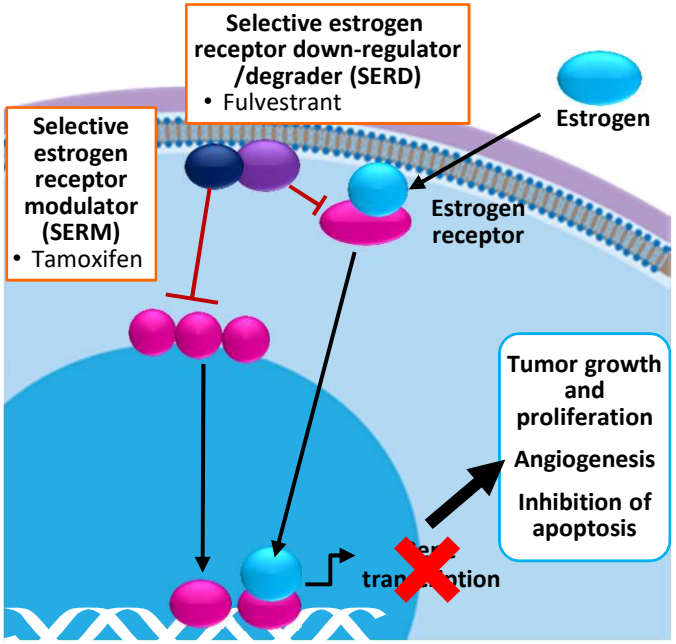
- Randomized phase II study of capivasertib + FULV vs placebo + FULV (N = 140)
  - Relapse or progression on an AI
  - Capivasertib (AZD5363): selective, oral AKT inhibitor
- Capivasertib + FULV improved PFS in endocrine-resistant MBC vs placebo + FULV, meeting the primary endpoint of PFS
  - Trend toward improvement in OS
- Ongoing Phase III CAPitello291 Trial
- IPATunit150: ipatasertib with palbociclib and fulvestrant

Outcome	CAP + FULV (n = 69)	PBO + FULV (n = 71)
Median PFS, mos	10.3	4.8
	HR: 0.57 (95% CI: 0.39-0.84) 2-sided *P* = .0035	
Median OS, mos	26.0	20.0
	HR: 0.59 (95% CI: 0.34-1.05) 2-sided *P* = .071	

- Similar benefit was observed in patients with PI3K/AKT/PTEN-activated and nonactivated tumors
- 39% of patients in the capivasertib + FULV arm required dose reductions, primarily due to diarrhea and rash, and 12% discontinued due to toxicity

Jones RH, et al. ASCO 2019. Abstract 1005.

New Generation SERDS



SERDs inhibit the dimerization of ER[1]

Antagonism of ER activity by competitive binding, resulting in ER down-regulation[2]

FUL is approved for use in patients with progression on prior antiestrogen therapy[2]

- In the phase 3 FALCON study, benefit with first-line FUL vs AI in ET-naive patients was limited to patients without visceral disease[3]
- FUL is limited by method of administration (intramuscular injection)[4]

Novel oral SERDs are currently being investigated for postmenopausal women with HR+ ABC[4,5]

SERDs may have a role in treating tumors with *ESR1* mutations

ABC, advanced breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; FUL, fulvestrant; HR+, hormone receptor-positive; PMW, postmenopausal women; SERD, selective estrogen receptor down-regulator/degrader; SERM, Selective estrogen receptor modulators.

1. Fox EM, et al. *Front Oncol*. 2012;2:145; 2. Faslodex [package insert]. Wilmington, DE: AstraZeneca; 2010; 3. Robertson JFR, et al. *Lancet*. 2016 Nov 28 [Epub ahead of print]. 4. Garner F, et al. *Anticancer Drugs*. 2015;26(9):948-956; 5. Hamilton, E, et al. SABCS 2016. Abstract P6-12-03 [poster].

Oral SERD in ER+ MBC: Current Development Status

Company	Drug name	Current Development Status
Genentech	GDC-0810 GDC-927	Development Discontinued
Novartis	LSZ102	Development Discontinued
Radius Health	Elacestrant (RAD-1901)	Phase 3
Genentech	GDC-9545	Phase 2/3
Sanofi	SAR439859	Phase 2/3
G1 Therapeutics	G1T48	Phase 1 completed
Astra Zeneca	AZD9833	Phase 1/2

Need to be careful with cross-study comparisons –
Differences in prior lines of Rx, endocrine sensitivity, tumor biology

Slide credit: Aditya Bardia

Expanding New Directions

- Immunotherapy combinations
  - Beware enhanced toxicity (JPCE with; Rugo et al, AACR (abema/pembro/AI) and ASCO 2020 (abema/pembro)
- Triplet therapy to prevent/delay resistance
  - Toxicity has limited combinations with CDK4/6 and PIK3CA inhibitors
  - Suggestion of benefit in TRINITI trial with low dose everolimus
  - Future potential with AKTi in combination

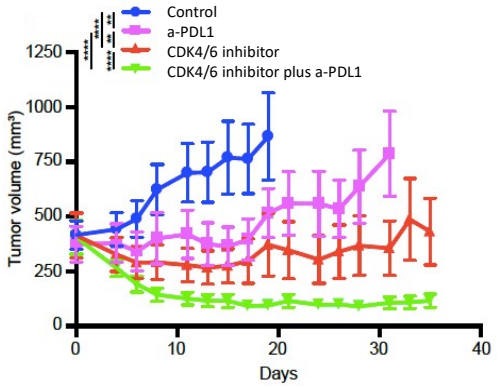
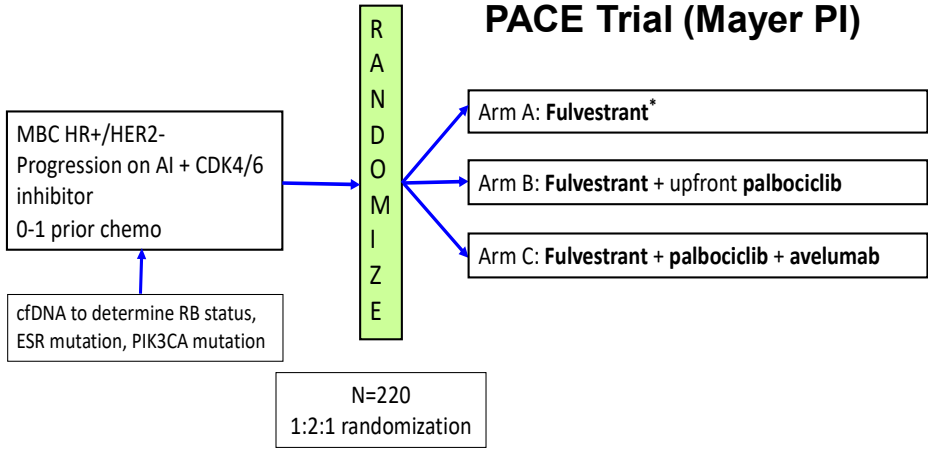
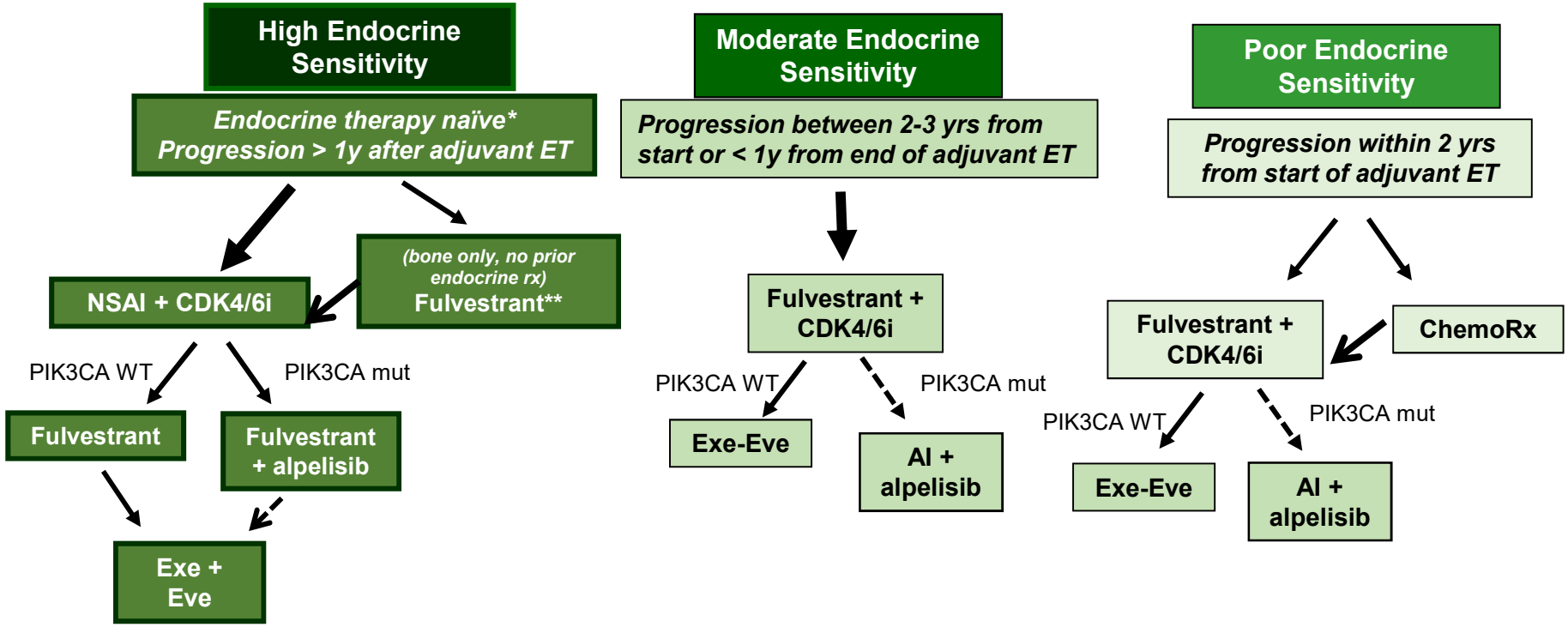


Figure 1: Preclinical experience combining CDK4/6 inhibitors and immunotherapy



Goel et al, Nature 2017

HR+HER2- ABC: Remarkable Progress Leads to Changing Paradigms



*De novo stage IV disease appears to be enriched in relative endocrine resistant disease
**No data comparing CDK4/6i combined with AI vs fulvestrant in the first line setting


Thank you!
UCSF Helen Diller Family
Comprehensive
Cancer Center