Current and Future Role of CDKi

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NH Hotel Vienna Airport

Dislosures

- Research funding: Celgene, Lilly, Novartis, Pfizer, Samsung
- Advisory role: Amgen, AstraZeneca, Lilly, MSD, Novartis, Pierre Fabre,Pfizer, Roche, Samsung
- Speakers buearau: Amgen, AstraZeneca, Celgene, Lilly, Novartis, Pierre Fabre, Pfizer, Roche

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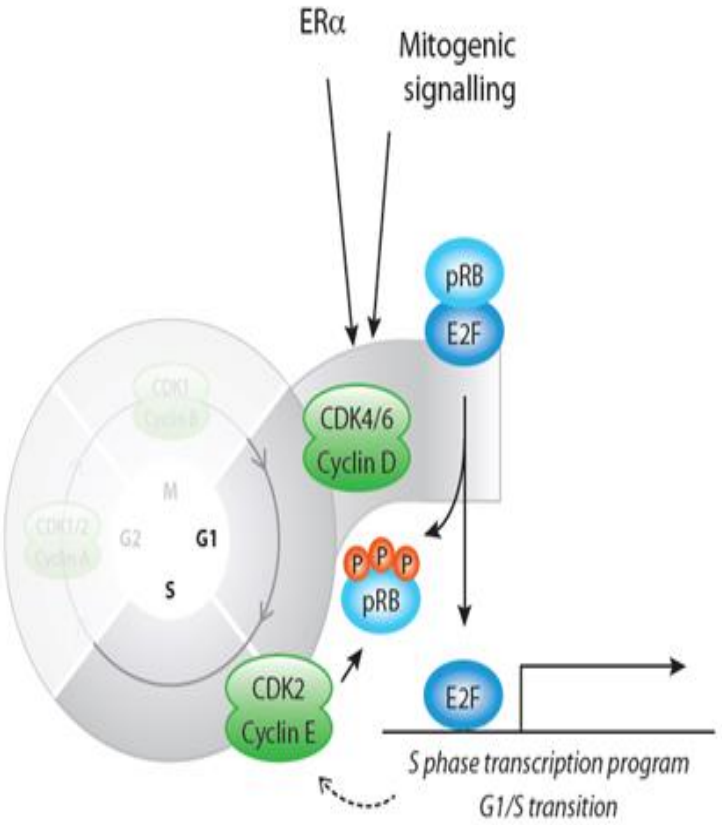
CDK 4/6 inhibitors in breast cancer

- 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]



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.

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

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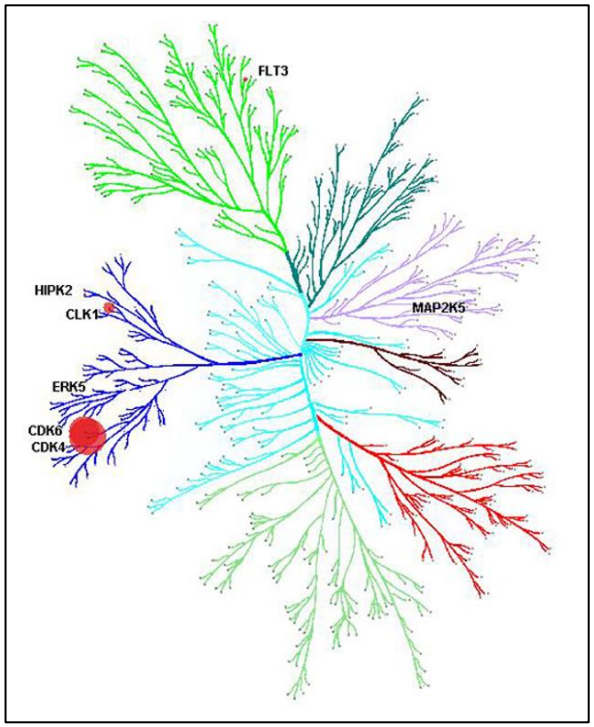
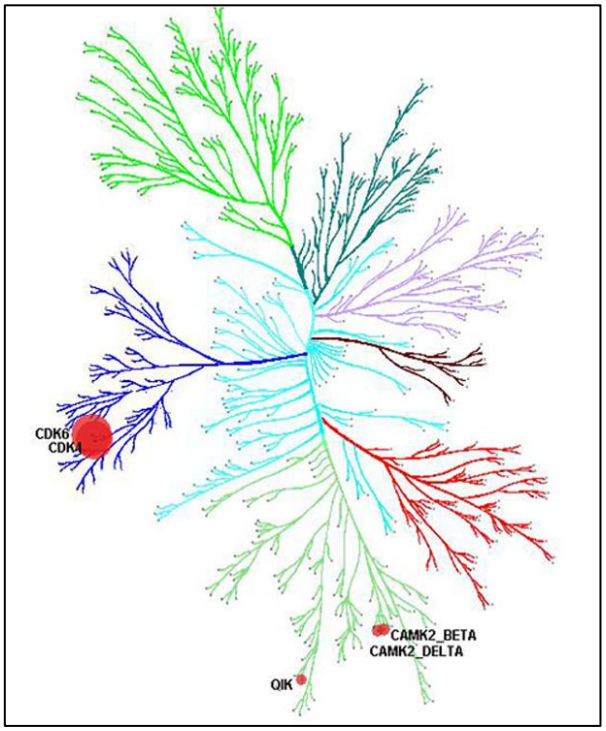
Target Profiles of CDK4/6 Inhibitors in Tumor Cell Assays

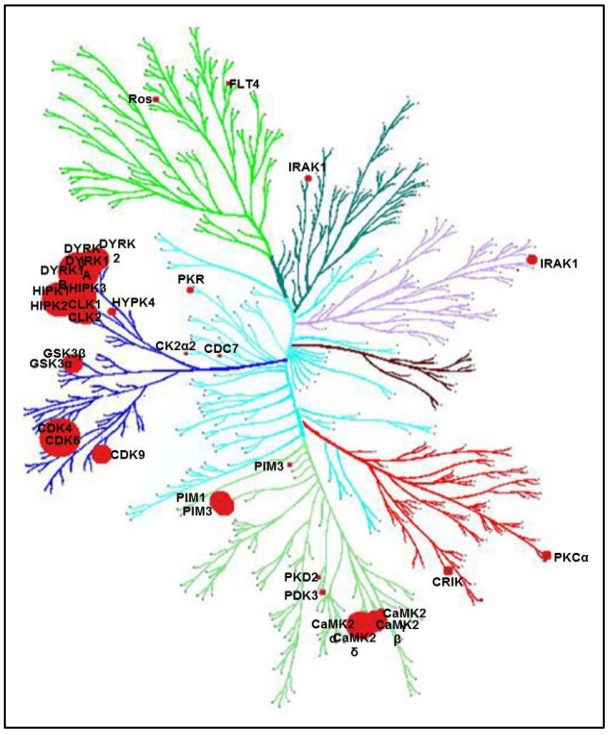
Palbociclib



Ribociclib



Abemaciclib



Selectivity

- 1x
- 10x
- 100x

NSAF, normalized spectral abundance factor.

Chen P, et al. *Molec Cancer Ther*. 2016.

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Table 1: Clinical trial data for CDK4/6 inhibitors for HR+/HER2-negative advanced breast cancer

	Study	Phase	Arms	Description	Median PFS Hazard Ratio (95% CI)	ORR	Median OS Hazard Ratio (95% CI)
1st line	PALOMA-1 / TRIO-18	II	2	Palbociclib/letrozole vs. letrozole	20.2 vs. 10.2 mo 0.488 (0.319-0.748)	55.0% vs. 39.0%	37.5 vs. 34.5 mo 0.897 (0.623 – 1.294)
1st line	PALOMA-2	III	2	Palbociclib/letrozole vs. placebo/letrozole	24.8 vs. 14.5 mo 0.58 (0.46-0.72)	55.3% vs. 44.4%	Pending
1st line	MONALEESA-2	III	2	Ribociclib/letrozole vs. placebo/letrozole	25.3 vs. 16.0 mo 0.568 (0.457-0.704)	52.7% vs. 37.1%	Pending
1st line	MONALEESA-7	III	2	Ribociclib/OFS/AI or tamoxifen vs. placebo/ OFS/AI or tamoxifen	23.8 vs. 13.0 0.553 (0.441-0.694)	51.0% vs. 36.0%	Pending
1st line	MONARCH-3	III	2	Abemaciclib/AI vs. placebo/AI	NR vs. 14.7 mo 0.543 (0.409-0.723)	59.0% vs. 44.0%	Pending
1st and 2nd line	MONALEESA-3	III	2	Ribociclib/Fulvestrant vs.. placebo/Fulvestrant	20.5 vs.. 12.8 mo 0.593 (0.480 to 0.732)	40.9% vs.. 28.7%	Pending
2nd line	PALOMA-3	III	2	Palbociclib/fulvestrant vs. placebo/fulvestrant	9.5 vs. 4.6 mo 0.46 (0.36-0.59)	24.6% vs. 15.0%	34.9 vs.. 28.0 mo 0.81 (0.64-1.03)
2nd line	MONARCH-2	III	2	Abemaciclib/fulvestrant vs. placebo/fulvestrant	16.4 vs. 9.3 mo 0.553 (0.449-0.681)	48.1% vs. 21.3%	Pending
Later line	MONARCH-1	II	1	Abemaciclib	6.0 mo	19.7%	17.7 mo

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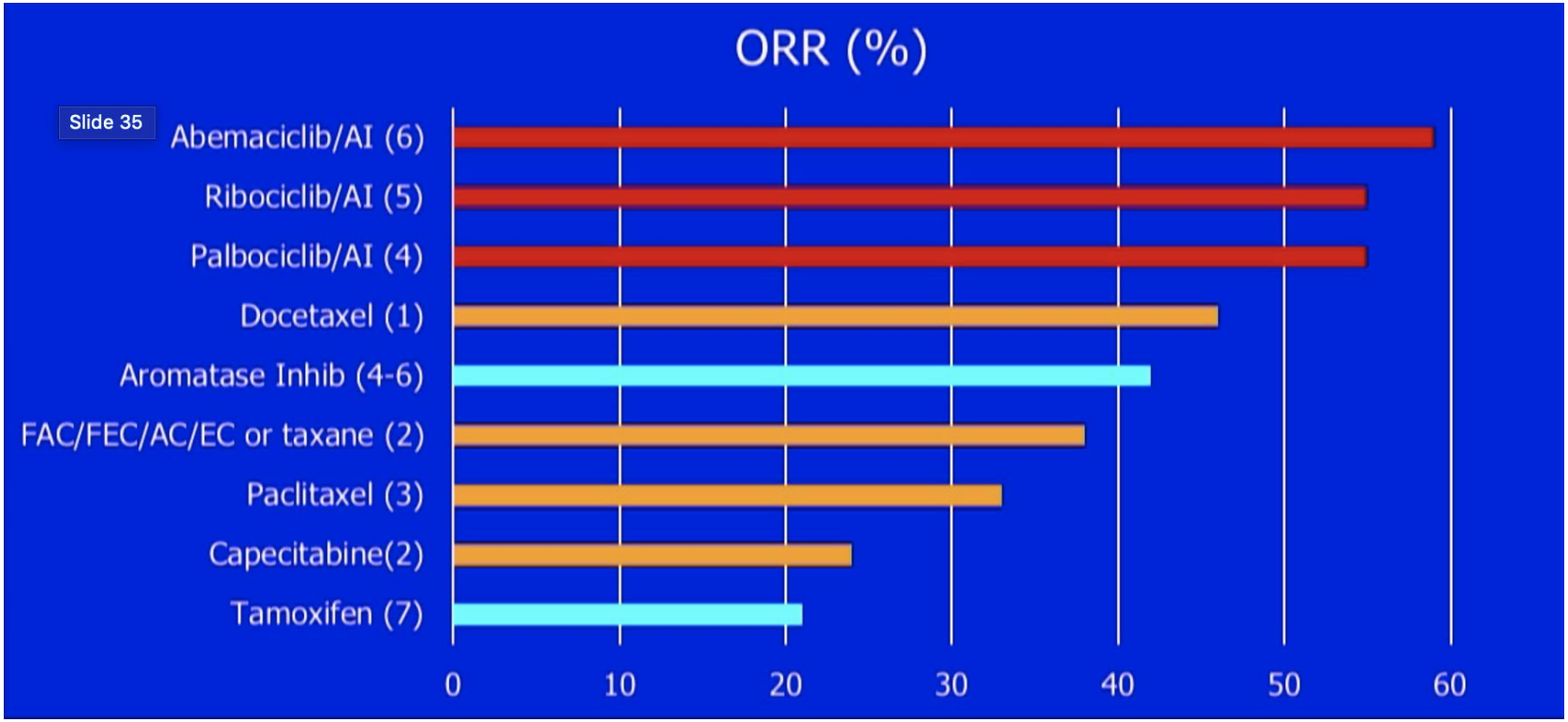
CDK 4/6 inhibitors and ORR



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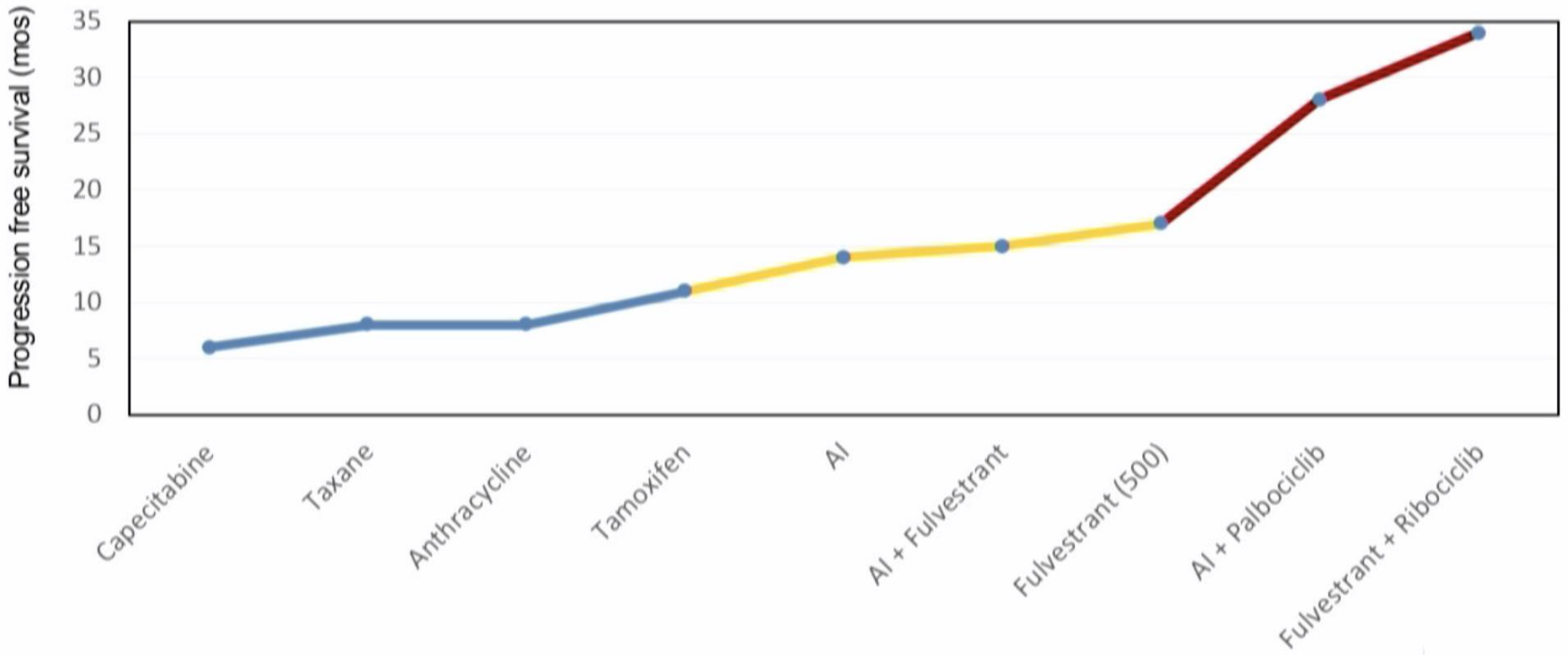
CDK 4/6 inhibitors and PFS



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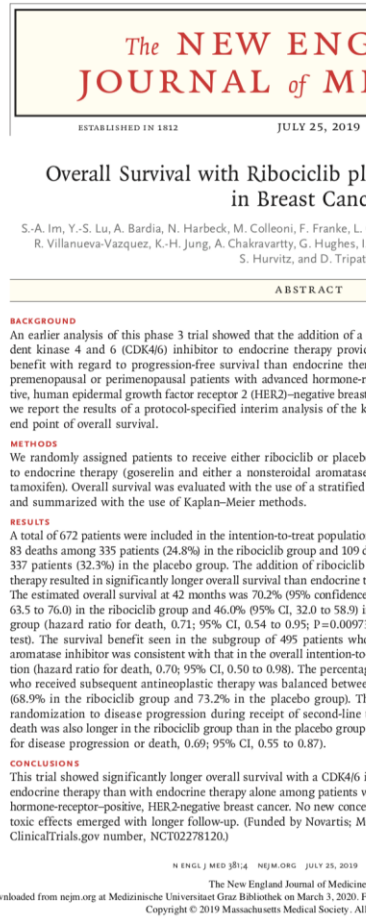
CDK 4/6 inhibitors and OS



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Overall Survival with Ribociclib pl
in Breast Canc

S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L.
R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I
S. Hurvitz, and D. Tripat

ABSTRACT

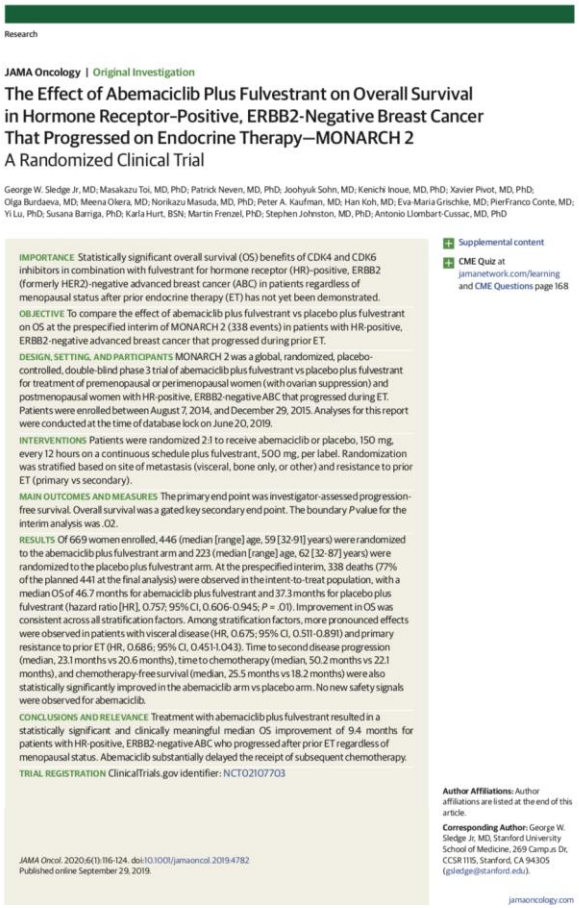
BACKGROUND
An earlier analysis of this phase 3 trial showed that the addition of a
dent kinase 4 and 6 (CDK4/6) inhibitor to endocrine therapy provi
benefit with regard to progression-free survival than endocrine the
premenopausal or perimenopausal patients with advanced hormone-r
tive, human epidermal growth factor receptor 2 (HER2)–negative breast
we report the results of a protocol-specified interim analysis of the k
end point of overall survival.

METHODS
We randomly assigned patients to receive either ribociclib or placeb
to endocrine therapy (goserelin and either a nonsteroidal aromatase
tamoxifen). Overall survival was evaluated with the use of a stratified
and summarized with the use of Kaplan–Meier methods.

RESULTS
A total of 672 patients were included in the intention-to-treat populatio
83 deaths among 335 patients (24.8%) in the ribociclib group and 109 d
337 patients (32.3%) in the placebo group. The addition of ribociclib
therapy resulted in significantly longer overall survival than endocrine t
The estimated overall survival at 42 months was 70.2% (95% confidence
63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) i
group (hazard ratio for death, 0.71; 95% CI, 0.54 to 0.95; P=0.0097
test). The survival benefit seen in the subgroup of 495 patients wh
aromatase inhibitor was consistent with that in the overall intention-to
tion (hazard ratio for death, 0.70; 95% CI, 0.50 to 0.98). The percentag
who received subsequent antineoplastic therapy was balanced betwee
(68.9% in the ribociclib group and 73.2% in the placebo group). Th
randomization to disease progression during receipt of second-line
death was also longer in the ribociclib group than in the placebo group
for disease progression or death, 0.69; 95% CI, 0.55 to 0.87).

CONCLUSIONS
This trial showed significantly longer overall survival with a CDK4/6 i
endocrine therapy than with endocrine therapy alone among patients v
hormone-receptor–positive, HER2-negative breast cancer. No new conce
toxic effects emerged with longer follow-up. (Funded by Novartis; M
ClinicalTrials.gov number, NCT02278120.)

N ENGL J MED 381;4 NEJM.ORG JULY 25, 2019



Research

JAMA Oncology | Original Investigation

The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2
A Randomized Clinical Trial

George W. Sledge Jr, MD; Masakazu Toi, MD, PhD; Patrick Neven, MD, PhD; Joohyuk Sohn, MD; Kenichi Inoue, MD, PhD; Xavier Pivot, MD, PhD; Olga Burdaeva, MD; Meena Okera, MD; Norikazu Masuda, MD, PhD; Peter A. Kaufman, MD; Han Koh, MD; Eva-Maria Grischke, MD; PierFranco Conte, MD; Yi Lu, PhD; Susana Barriga, PhD; Karla Hurt, BSN; Martin Frenzel, PhD; Stephen Johnston, MD, PhD; Antonio Llombart-Cussac, MD, PhD

IMPORTANCE Statistically significant overall survival (OS) benefits of CDK4 and CDK6 inhibitors in combination with fulvestrant for hormone receptor (HR)–positive, ERBB2 (formerly HER2)-negative advanced breast cancer (ABC) in patients regardless of menopausal status after prior endocrine therapy (ET) has not yet been demonstrated.

OBJECTIVE To compare the effect of abemaciclib plus fulvestrant vs placebo plus fulvestrant on OS at the prespecified interim of MONARCH 2 (338 events) in patients with HR-positive, ERBB2-negative advanced breast cancer that progressed during prior ET.

DESIGN, SETTING, AND PARTICIPANTS MONARCH 2 was a global, randomized, placebo-controlled, double-blind phase 3 trial of abemaciclib plus fulvestrant vs placebo plus fulvestrant for treatment of premenopausal or perimenopausal women (with ovarian suppression) and postmenopausal women with HR-positive, ERBB2-negative ABC that progressed during ET. Patients were enrolled between August 7, 2014, and December 29, 2015. Analyses for this report were conducted at the time of database lock on June 20, 2019.

INTERVENTIONS Patients were randomized 2:1 to receive abemaciclib or placebo, 150 mg, every 12 hours on a continuous schedule plus fulvestrant, 500 mg, per label. Randomization was stratified based on site of metastasis (visceral, bone only, or other) and resistance to prior ET (primary vs secondary).

MAIN OUTCOMES AND MEASURES The primary end point was investigator-assessed progression-free survival. Overall survival was a gated key secondary end point. The boundary *P* value for the interim analysis was .02.

RESULTS Of 669 women enrolled, 446 (median [range] age, 59 [32-91] years) were randomized to the abemaciclib plus fulvestrant arm and 223 (median [range] age, 62 [32-87] years) were randomized to the placebo plus fulvestrant arm. At the prespecified interim, 338 deaths (77% of the planned 441 at the final analysis) were observed in the intent-to-treat population, with a median OS of 46.7 months for abemaciclib plus fulvestrant and 37.3 months for placebo plus fulvestrant (hazard ratio [HR], 0.757; 95% CI, 0.606-0.945; *P* = .01). Improvement in OS was consistent across all stratification factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR, 0.675; 95% CI, 0.511-0.891) and primary resistance to prior ET (HR, 0.686; 95% CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months), time to chemotherapy (median, 50.2 months vs 22.1 months), and chemotherapy-free survival (median, 25.5 months vs 18.2 months) were also statistically significantly improved in the abemaciclib arm vs placebo arm. No new safety signals were observed for abemaciclib.

CONCLUSIONS AND RELEVANCE Treatment with abemaciclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement of 9.4 months for patients with HR-positive, ERBB2-negative ABC who progressed after prior ET regardless of menopausal status. Abemaciclib substantially delayed the receipt of subsequent chemotherapy.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02107703

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 168

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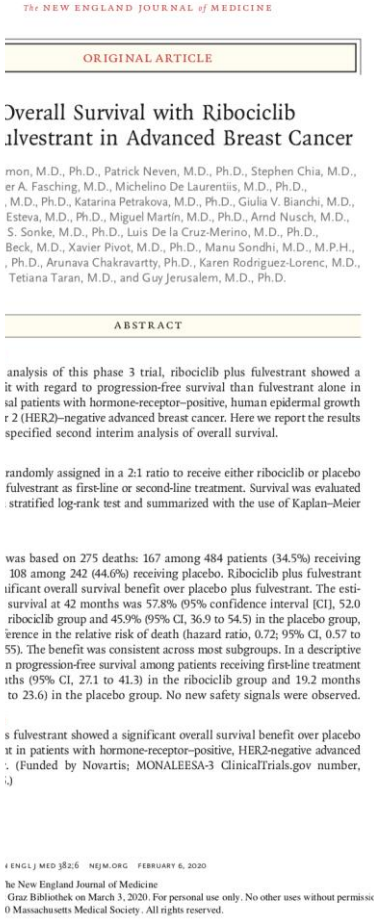

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Ribociclib
ılvestrant in Advanced Breast Cancer

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Tetiana Taran, M.D., and Guy Jerusalem, M.D., Ph.D.

ABSTRACT

analysis of this phase 3 trial, ribociclib plus fulvestrant showed a
it with regard to progression-free survival than fulvestrant alone in
sal patients with hormone-receptor–positive, human epidermal growth
r 2 (HER2)–negative advanced breast cancer. Here we report the results
specified second interim analysis of overall survival.

randomly assigned in a 2:1 ratio to receive either ribociclib or placebo
fulvestrant as first-line or second-line treatment. Survival was evaluated
stratified log-rank test and summarized with the use of Kaplan–Meier

was based on 275 deaths: 167 among 484 patients (34.5%) receiving
108 among 242 (44.6%) receiving placebo. Ribociclib plus fulvestrant
ificant overall survival benefit over placebo plus fulvestrant. The esti-
survival at 42 months was 57.8% (95% confidence interval [CI], 52.0
ribociclib group and 45.9% (95% CI, 36.9 to 54.5) in the placebo group,
erence in the relative risk of death (hazard ratio, 0.72; 95% CI, 0.57 to
55). The benefit was consistent across most subgroups. In a descriptive
n progression-free survival among patients receiving first-line treatment
nths (95% CI, 27.1 to 41.3) in the ribociclib group and 19.2 months
to 23.6) in the placebo group. No new safety signals were observed.

s fulvestrant showed a significant overall survival benefit over placebo
nt in patients with hormone-receptor–positive, HER2-negative advanced
. (Funded by Novartis; MONALEESA-3 ClinicalTrials.gov number,
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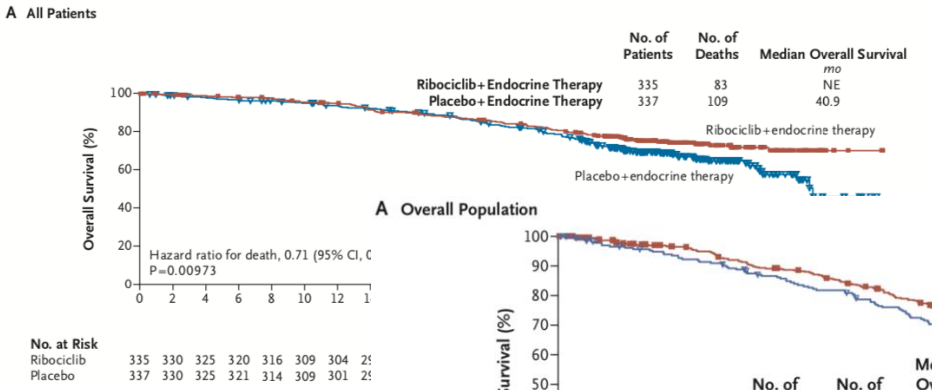
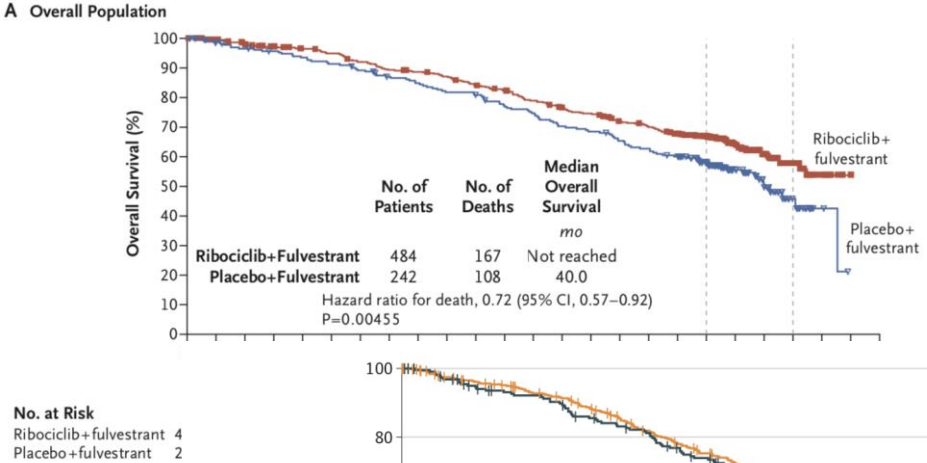
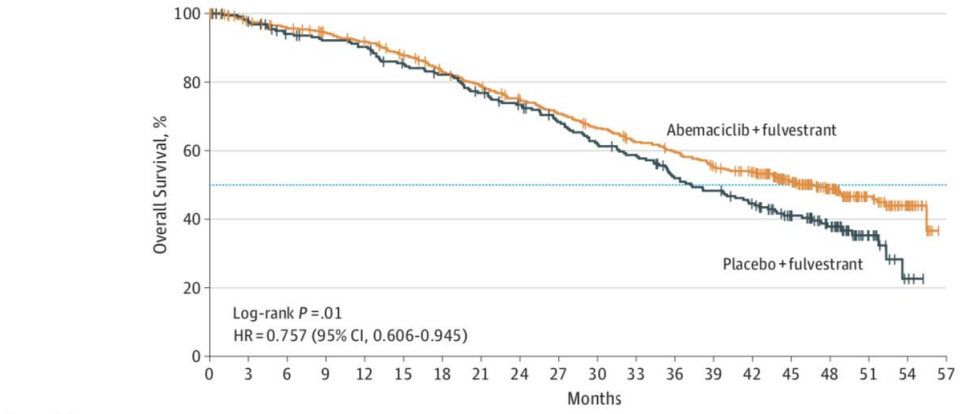
OS benefit



Monaleesa 7



Monaleesa 3



Monarch 2

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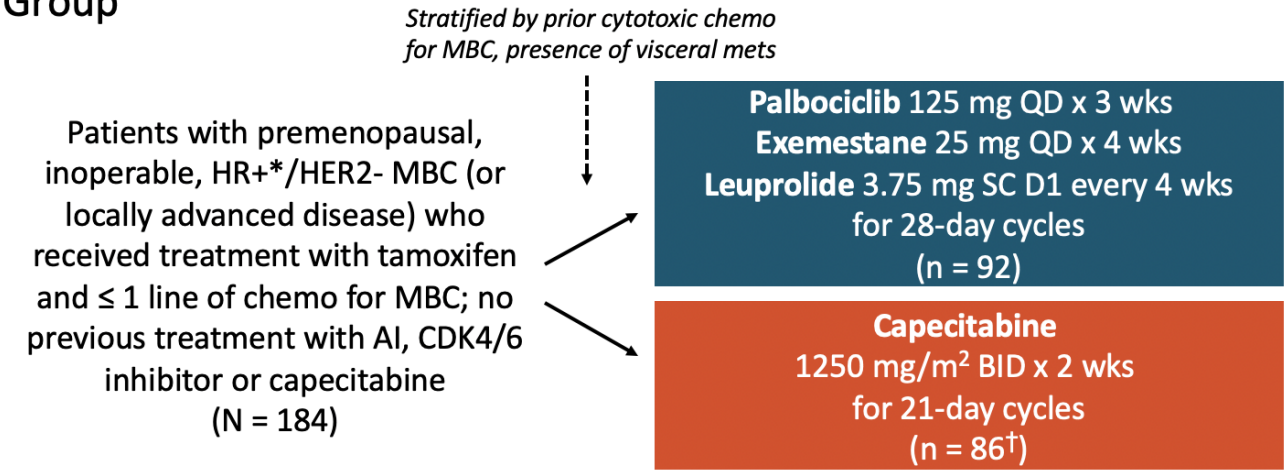
Young- PEARL study design

- Prospective, multicenter, open-label phase II study by the Korean Cancer Study Group



- Primary endpoint: PFS (investigator assessed)
- Secondary endpoint: DCR, OS, safety, QoL, biomarkers

*ER and/or PgR positive. †92 patients randomized, but 6 withdrew before receiving first dose of treatment

Park. ASCO 2019. Abstr 1007.

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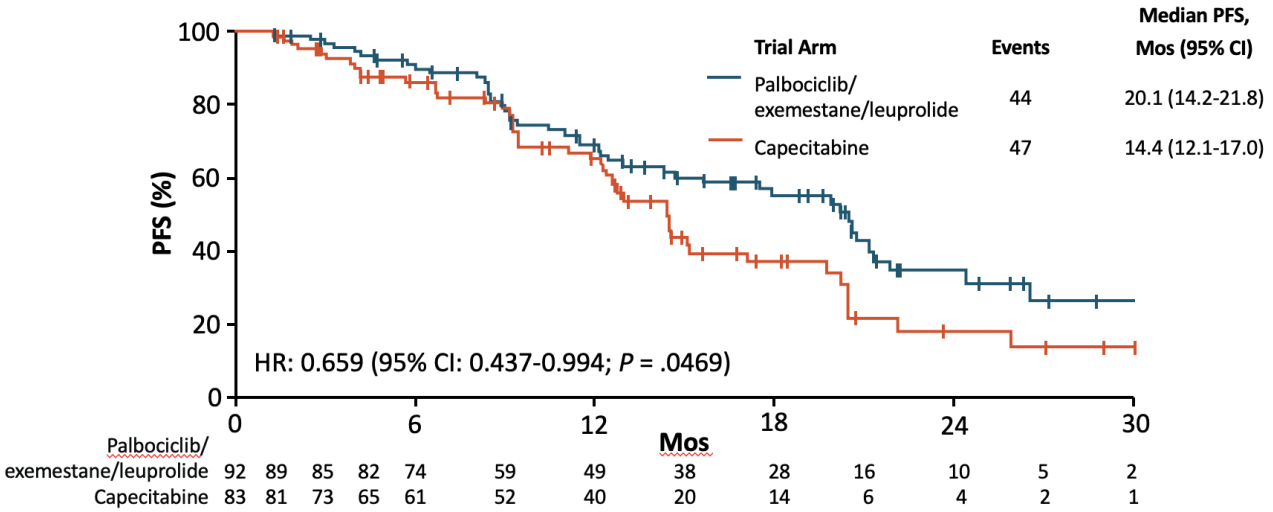

Investigator Assessed PFS

Response, n (%)	Palbociclib/Exemestane/ Leuprolide (n = 92)	Capecitabine (n = 86)	*P* Value
ORR (n = 178)	37 (37.0)	29 (34.9)	.781
▪ Measurable (n = 119)	31 (50.8)	26 (44.8)	.387
DCR (n = 178)	89 (96.7)	78 (94.0)	.480
▪ Measurable (n = 119)	58 (95.1)	51 (87.9)	.262
CBR* (n = 178)	74 (80.4)	58 (69.9)	.105
▪ Measurable (n = 119)	48 (78.7)	38 (65.5)	.134

*CR + PR + SD ≥ 24 wks.

Response Rates

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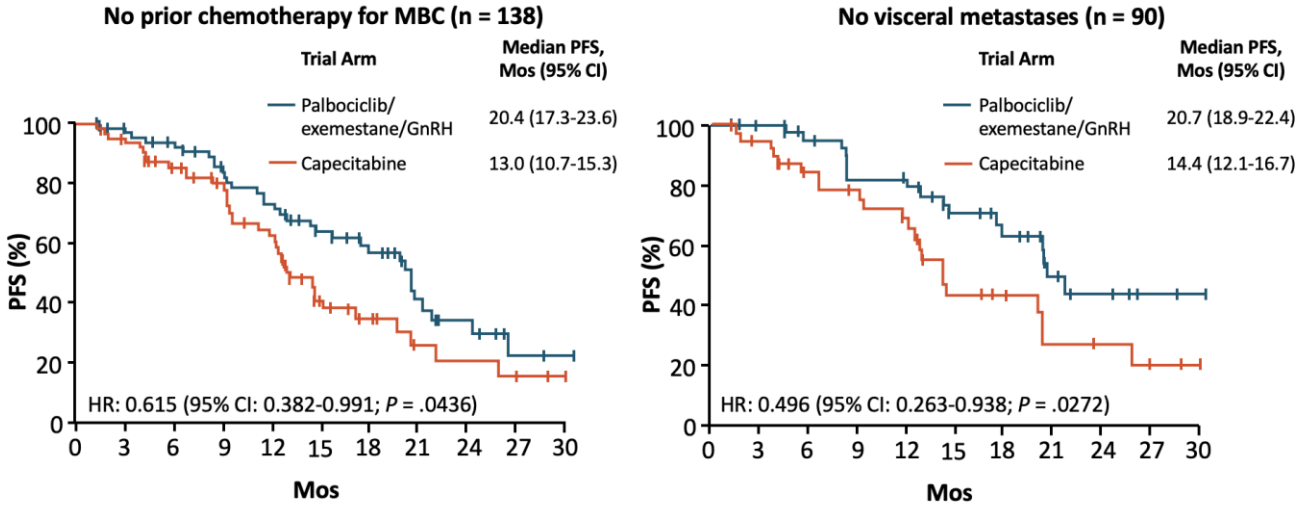
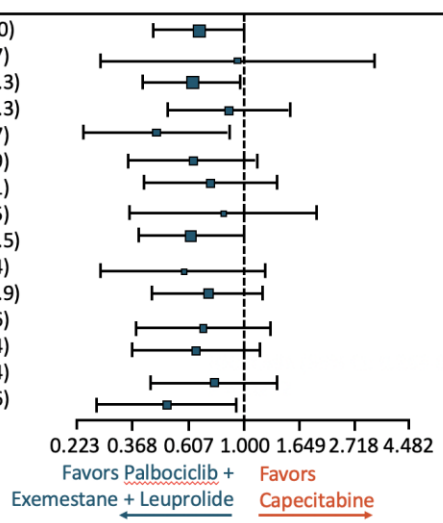


Subgroup		n (%)	*P* Value	HR (95% CI)
All patients		178 (100)	.0469	0.659 (0.436-0.998)
Age (yrs)	≤ 35	19 (10.7)	.9242	0.941 (0.272-3.263)
	> 35	159 (89.3)	.0367	0.629 (0.405-0.977)
ECOG PS	0	102 (57.3)	.6016	0.864 (0.499-1.497)
	1-2	76 (42.7)	.0134	0.449 (0.233-0.866)
Prior lines of treatment for MBC	0	87 (48.9)	.1118	0.626 (0.350-1.121)
	≥ 1	91 (51.1)	.2992	0.731 (0.402-1.328)
Previous chemotherapy for MBC	Yes	40 (22.5)	.6500	0.824 (0.355-1.915)
	No	138 (77.5)	.0436	0.615 (0.382-0.991)
Objective response	Yes	63 (35.4)	.1378	0.573 (0.272-1.209)
	No	112 (62.9)	.1894	0.717 (0.434-1.182)
No. of metastatic site	1	99 (55.6)	.2149	0.686 (0.376-1.252)
	≥ 2	79 (44.4)	.1308	0.643 (0.361-1.146)
Visceral metastases	Yes	88 (49.4)	.3434	0.762 (0.433-1.341)
	No	90 (50.6)	.0272	0.496 (0.263-0.938)



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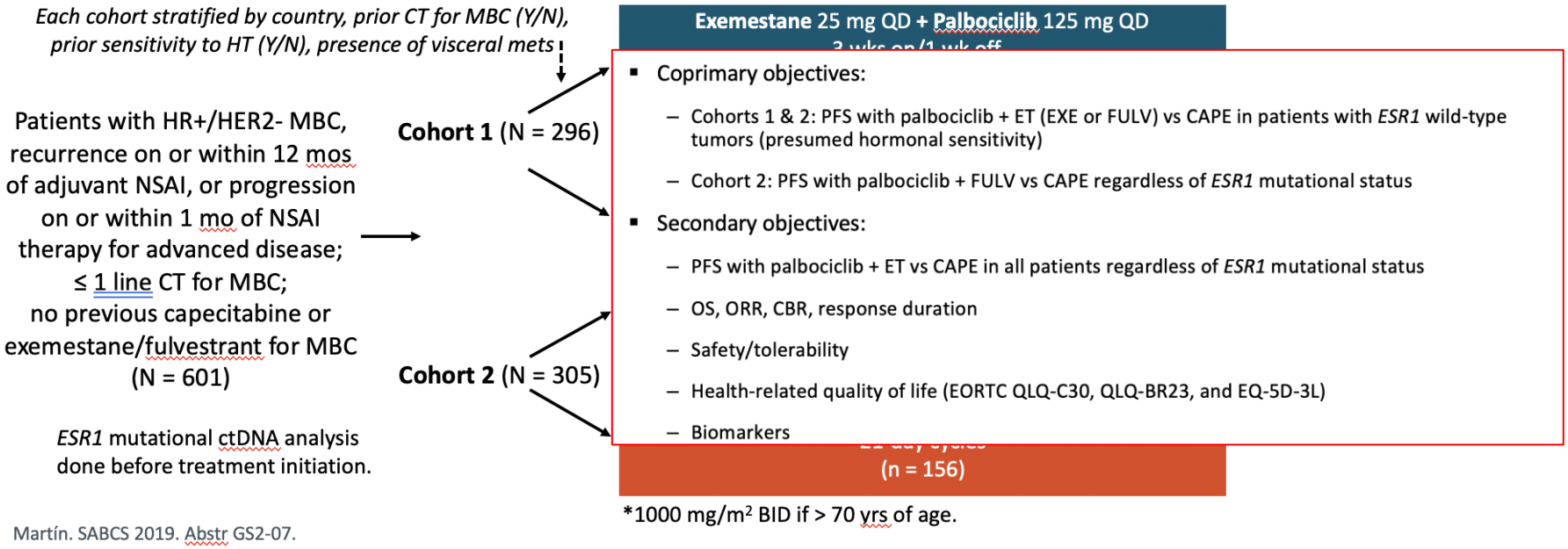
PEARL Study Design

- Phase III, international, randomized study with 2 cohorts; 4 countries, 37 sites (GEICAM, CECOG)
  - Cohort 1 recruited March 2014 to September 2016; Cohort 2 recruited May 2016 to July 2018



*1000 mg/m^2 BID if > 70 yrs of age.

Martín. SABCS 2019. Abstr GS2-07.

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Patients characteristics

Characteristic	Cohort 1		Cohort 2	
	EXE + PALBO (n = 153)	CAPE (n = 143)	FULV + PALBO (n = 149)	CAPE (n = 156)
Genomic subtype, n (%)	(n = 122)	(n = 112)	(n = 122)	(n = 126)
▪ Luminal A/Luminal B	61 (50.0)/49 (40.2)	61 (54.4)/42 (37.5)	58 (47.5)/43 (35.3)	52 (41.3)/58 (46.0)
▪ HER2-enriched	5 (4.1)	4 (3.6)	11 (9.0)	9 (7.1)
▪ Basal-like/normal-like	2 (1.6)/4 (3.3)	0/4 (3.6)	0/5 (4.1)	0/7 (5.8)
No. previous lines of HT for MBC, n (%)				
▪ 0	30 (19.6)	31 (21.7)	38 (25.5)	44 (28.2)
▪ 1	82 (53.6)	70 (49.0)	85 (57.0)	90 (57.7)
▪ 2	35 (22.9)	34 (23.8)	12 (8.1)	9 (5.8)
▪ 3/Maintenance after CT	3 (2.0)/3 (2.0)	4 (2.8)/4 (2.8)	1 (0.7)/12 (8.1)	1 (0.6)/12 (7.7)
Previous HR for MBC, n (%)				
▪ AI	106 (69.3)	105 (73.4)	111 (74.5)	109 (69.9)
▪ Fulvestrant	44 (28.8)	35 (24.5)	0	1 (0.6)
▪ Tamoxifen	16 (10.5)	17 (11.9)	12 (8.1)	16 (10.3)
Previous CT for MBC, n (%)	105 (68.6)	102 (71.3)	108 (72.5)	115 (73.7)
Line of therapy at study entry, %				
▪ 1st/2nd/≥ 3rd	17.6/41.2/41.2	21.7/35.0/43.3	25.5/51.0/23.5	27.6/50.6/21.8

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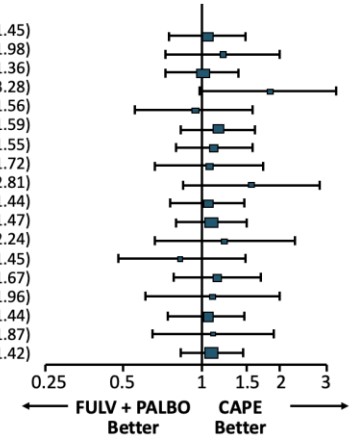
PEARL: PFS by Subgroup for Cohort 2 (n = 305)

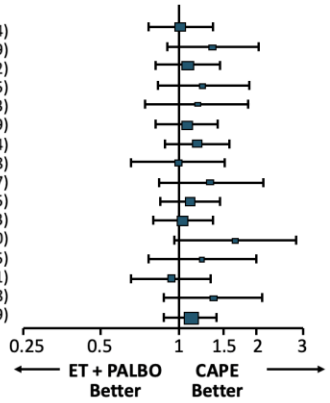
Subgroup	FULV + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
Visceral	72/97 (74.2)	68/102 (66.7)	1.04 (0.75-1.45)	0.811
Nonvisceral	36/52 (69.2)	26/54 (48.1)	1.19 (0.72-1.98)	0.497
Yes prior sensitivity to HT	84/119 (70.6)	72/122 (59.0)	0.99 (0.73-1.36)	0.974
No prior sensitivity to HT	24/30 (80.0)	22/34 (64.7)	1.79 (0.98-3.28)	0.057
Yes prior CT for MBC	31/41 (75.6)	28/41 (68.3)	0.93 (0.55-1.56)	0.784
No prior CT for MBC	77/108 (71.3)	66/115 (57.4)	1.15 (0.82-1.59)	0.419
Age < 65 yrs	73/93 (78.5)	63/103 (61.2)	1.10 (0.79-1.55)	0.566
Age ≥ 65 yrs	35/56 (62.5)	31/53 (58.5)	1.06 (0.65-1.72)	0.814
One site	38/56 (67.9)	15/35 (42.9)	1.54 (0.85-2.81)	0.155
Multiple sites	70/93 (75.3)	79/121 (65.3)	1.05 (0.76-1.44)	0.786
Measurable lesions	81/116 (69.8)	78/126 (61.9)	1.08 (0.79-1.47)	0.630
Nonmeasurable lesions	27/33 (81.8)	16/30 (53.3)	1.20 (0.65-2.24)	0.558
Treatment line: 1st	26/38 (68.4)	25/42 (59.5)	0.83 (0.47-1.45)	0.503
Treatment line: 2nd	54/76 (71.1)	50/78 (64.1)	1.14 (0.77-1.67)	0.515
Treatment line: ≥ 3rd	28/35 (80.0)	19/32 (59.4)	1.09 (0.60-1.96)	0.786
ESR1: WT	76/102 (74.5)	60/98 (61.2)	1.03 (0.73-1.44)	0.880
ESR1: Mutated	25/38 (65.8)	30/48 (62.5)	1.10 (0.64-1.87)	0.734
All	108/149 (72.5)	94/156 (60.3)	1.08 (0.82-1.42)	0.599



*Unadjusted Cox *P*-value comparing FULV + PALBO vs CAPE in each subgroup.

PEARL: PFS by Subgroup for *ESR1* WT (n = 393)

Subgroup	ET + PALBO Events/N (%)	CAPE Events/N (%)	HR (95% CI)	*P* Value*
Visceral	108/137 (78.8)	81/115 (70.4)	1.00 (0.75-1.34)	.996
Nonvisceral	53/69 (76.8)	45/71 (63.4)	1.33 (0.89-1.99)	.165
Yes prior sensitivity to HT	111/148 (75.0)	84/132 (63.6)	1.07 (0.81-1.42)	.634
No prior sensitivity to HT	50/58 (86.2)	42/55 (76.4)	1.22 (0.81-1.85)	.335
Yes prior CT for MBC	44/57 (77.2)	33/46 (71.7)	1.16 (0.74-1.83)	.516
No prior CT for MBC	117/149 (78.5)	93/141 (66.0)	1.06 (0.81-1.39)	.678
Age < 65 yrs	111/130 (85.4)	84/125 (67.2)	1.16 (0.87-1.54)	.302
Age ≥ 65 yrs	50/76 (65.8)	42/62 (67.7)	0.98 (0.65-1.48)	.927
One site	54/74 (73.0)	29/45 (64.4)	1.30 (0.82-2.07)	.260
Multiple sites	107/132 (81.1)	97/141 (68.8)	1.10 (0.83-1.45)	.514
Measurable lesions	128/169 (75.7)	102/149 (68.5)	1.02 (0.79-1.33)	.878
Nonmeasurable lesions	33/37 (89.2)	24/37 (64.9)	1.63 (0.95-2.80)	.078
Treatment line: 1st	37/49 (75.5)	36/57 (63.2)	1.21 (0.76-1.95)	.423
Treatment line: 2nd	77/96 (80.2)	55/74 (74.3)	0.92 (0.65-1.31)	.652
Treatment line: ≥ 3rd	47/60 (78.3)	35/54 (64.8)	1.34 (0.86-2.08)	.191
All	161/206 (78.2)	126/187 (67.4)	1.10 (0.87-1.39)	.425



*Unadjusted Cox *P*-value comparing ET + PALBO vs CAPE in each subgroup.

Martín. SABCS 2019. Abstr GS2-07. Reproduced with permission.

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Response rates

Response, %	Cohort 2			*ESR1* WT		
	FULV + PALBO (n = 149)	CAPE (n = 156)	Odds Ratio (95% CI)	ET + PALBO (n = 206)	CAPE (n = 187)	Odds Ratio (95% CI)
ORR (CR + PR)	27	33	0.73 (0.42-1.27)	28	37	0.67 (0.42-1.08)
CBR	49.0	48.1	1.06 (0.67-1.66)	50.5	50.3	1.03 (0.69-1.53)

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Conclusion 1

- CDK 4/6 inhibitors have significantly impacted current treatment of patients with hormon receptor positive metastatic/ advanced breast cancer

- Their use early on in the treatment course has been associated with PFS and OS benefit, and superior or comparable response rates

- It will be crucial to define patients who may not benefit from the treatment, so far the only grup may be patients without any endocrine response, hyothesis generating

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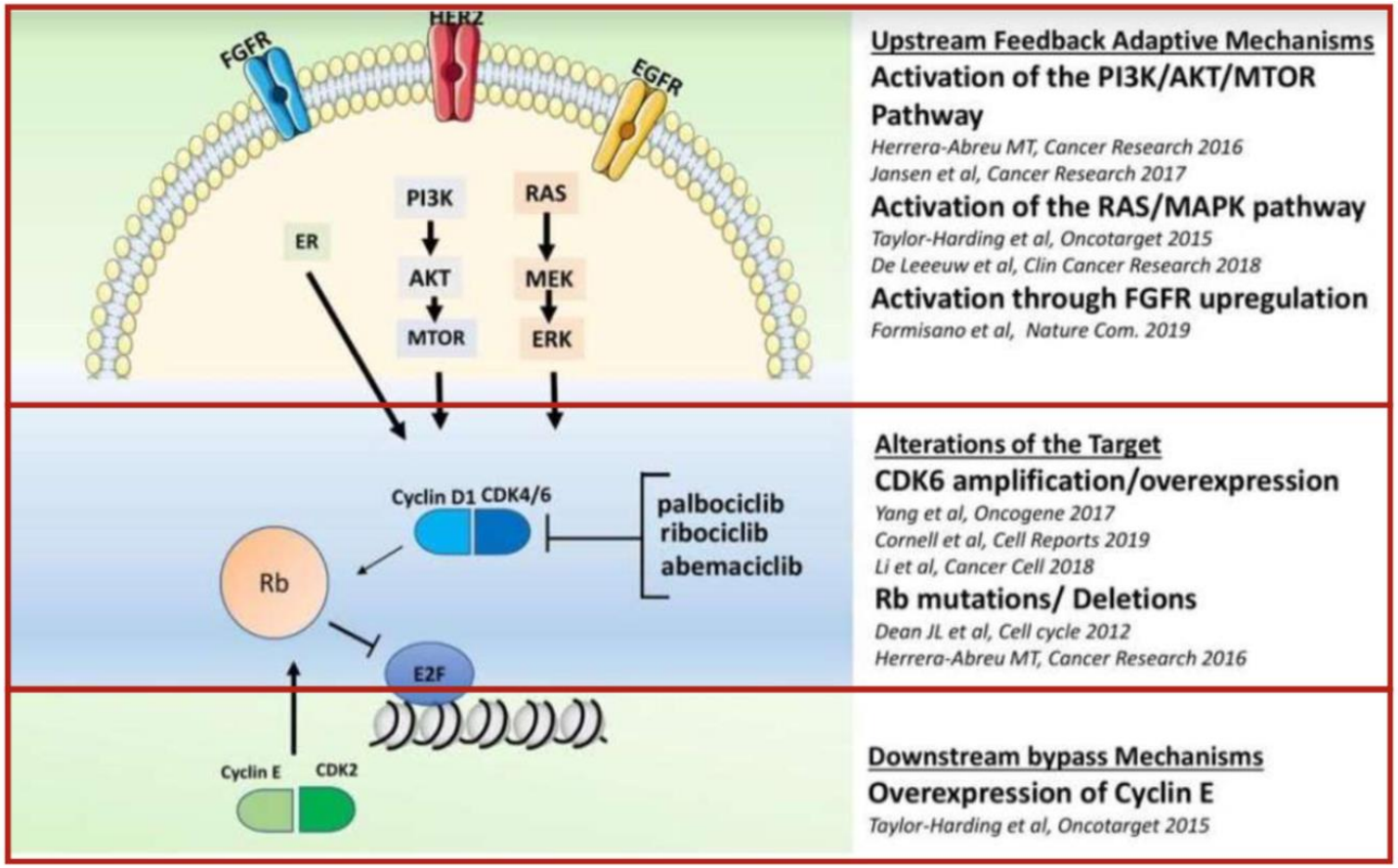
Resistance mechanisms



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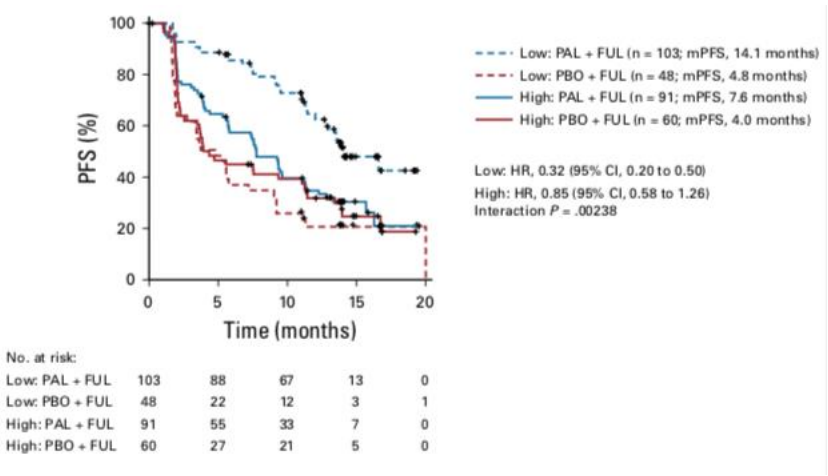
original report

Cyclin E1 Expression and Palbociclib Efficacy in Previously Treated Hormone Receptor–Positive Metastatic Breast Cancer

Nicholas C. Turner, MD, PhD[1]; Yuan Liu, PhD[2]; Zhou Zhu, PhD[2]; Sherene Loi, MD, PhD[3]; Marco Colleoni, MD[4]; Siby
Angela DeMichele, MD, MSCE[6]; Nadia Harbeck, MD, PhD[7]; Fabrice André, MD, PhD[8]; Mohamed Amine Bayar, M
Stefan Michiels, PhD[8]; Zhe Zhang, MS[2]; Carla Giorgetti, PhD[9]; Monica Arnedos, MD[8]; Cynthia Huang Bartlett, MI
Massimo Cristofanilli, MD[11]



Turner et al

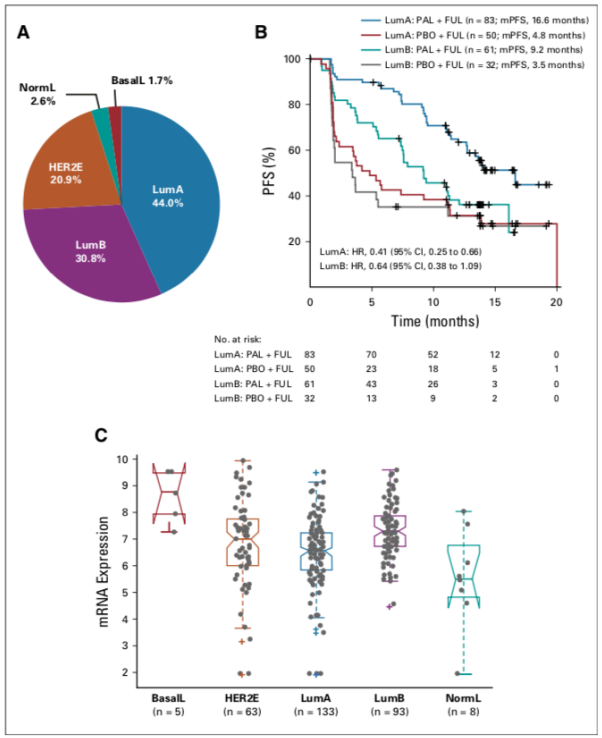


FIG 5. Intrinsic molecular subtype and efficacy of palbociclib (PAL). (A) Intrinsic subtype distribution of tumors in the PALOMA-3 trial. (B) Progression-free survival (PFS) in luminal A (LumA) and B (LumB) tumors. (C) Cyclin E1 (*CCNE1*) mRNA expression by intrinsic molecular subtype. BasalL, basal-like; FUL, fulvestrant; HER2E, human epidermal growth factor receptor 2–enriched; HR, hazard ratio; mPFS, median progression-free survival; NormL, normal-like; PBO, placebo.

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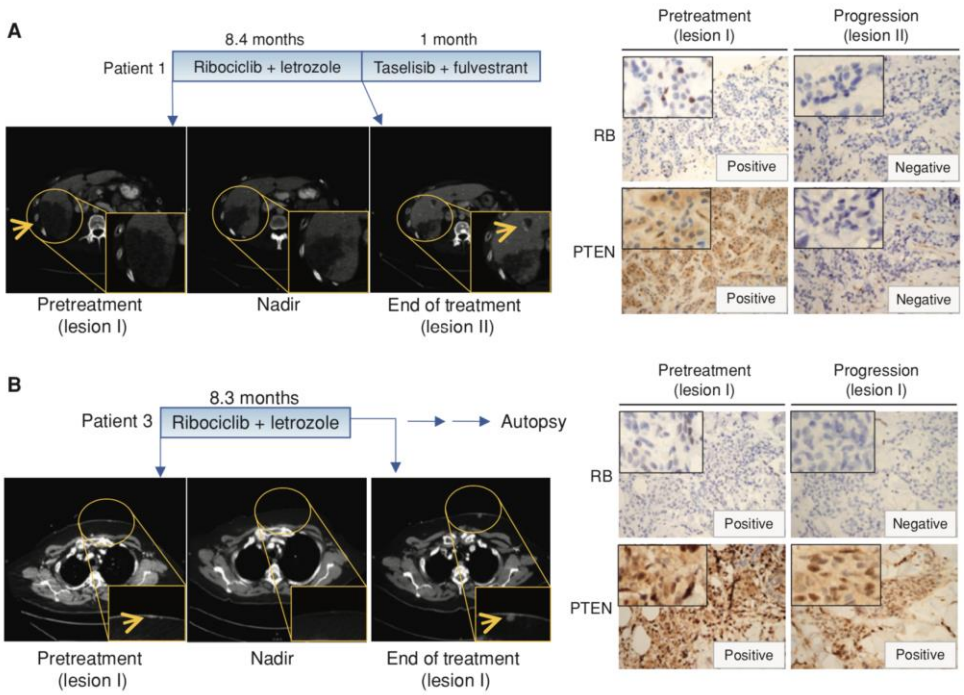
PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3Kα Inhibitors in Breast Cancer

Carlotta Costa[1], Ye Wang[1], Amy Ly[2], Yasuyuki Hosono[3], Ellen Murchie[1], Charlotte S. Walmsley[1], Tiffany Huynh[2], Christopher Healy[1], Rachel Peterson[1], Shogo Yanase[3], Charles T. Jakubik[1], Laura E. Henderson[1], Leah J. Damon[1], Daria Timonina[1], Ioannis Sanidas[1], Christopher J. Pinto[1], Mari Mino-Kenudson[2], James R. Stone[1], Nicholas J. Dyson[1], Leif W. Ellisen[1], Aditya Bardia[1], Hiromichi Ebi[3,4,5], Cyril H. Benes[1], Jeffrey A. Engelman[1], and Dejan Juric[1]

AKT activation is relevant
PTEN loss obsergved in progression biopsies
AKT activation → p27 phosphorylation →
stabilisation of CDK4/cyclinD1 →
CDK 4 and CDK2 activation
An AKT inhibitor can restore the sensitivity



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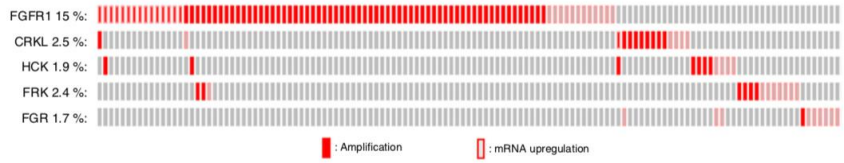
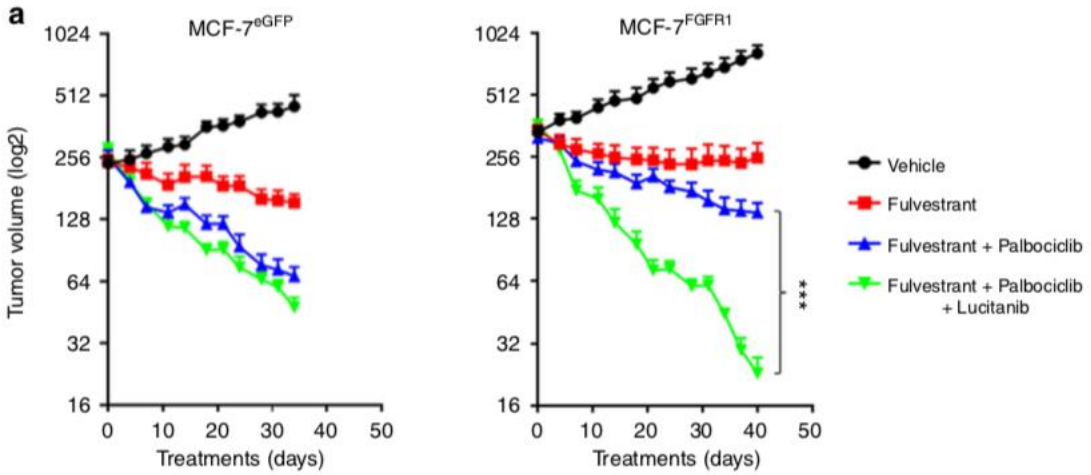
ARTICLE

https://doi.org/10.1038/s41467-019-09068-2 OPEN

Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer

Luigi Formisano[1], Yao Lu[1], Alberto Servetto[2], Ariella B. Hanker[1,2,3], Valerie M. Jansen[1], Joshua A. Bauer[4], Dhivya R. Sudhan[1,2], Angel L. Guerrero-Zotano[1], Sarah Croessmann[1], Yan Guo[5], Paula Gonzalez Ericsson[3], Kyung-min Lee[1], Mellissa J. Nixon[1], Luis J. Schwarz[1], Melinda E. Sanders[3,6], Teresa C. Dugger[1], Marcelo Rocha Cruz[7], Amir Behdad[7], Massimo Cristofanilli[7], Aditya Bardia[8], Joyce O'Shaughnessy[9], Rebecca J. Nagy[10], Richard B. Lanman[10], Nadia Solovieff[11], Wei He[11], Michelle Miller[12], Fei Su[12], Yu Shyr[5], Ingrid A. Mayer[1,3], Justin M. Balko[1] & Carlos L. Arteaga[1,2,3]





FGFR amplifications and mutations are more common on progression

FGFR inhibitors are a testable Therapeutic strategy (lucatinib, Erdafitinib)

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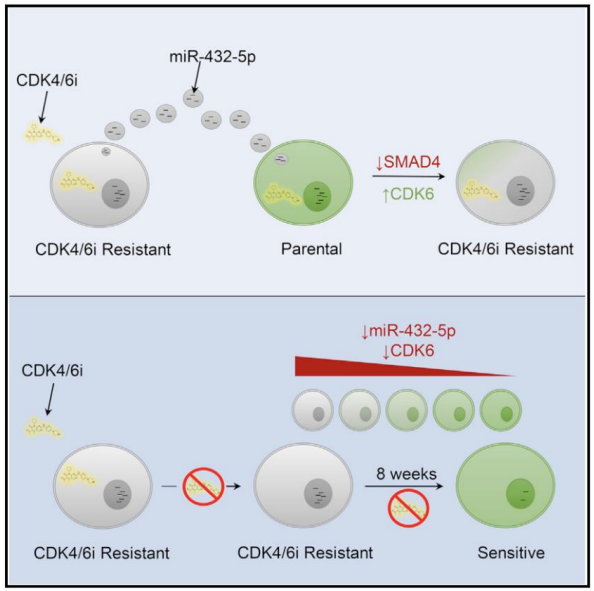
Article

Cell Reports

MicroRNA-Mediated Suppression of the TGF-β Pathway Confers Transmissible and Reversible CDK4/6 Inhibitor Resistance

Graphical Abstract



Authors

Liam Cornell, Seth A. Wander, Tanvi Visal, Nikhil Wagle, Geoffrey I. Shapiro

Correspondence

geoffrey_shapiro@dfci.harvard.edu

In Brief

Cornell et al. demonstrate a mechanism of acquired CDK4/6 inhibitor resistance that is independent of inherent genetic mutations, is conferred through extracellular signaling, and is reversible *in vitro* and *in vivo*. Resistance was mediated by exosomal miRNA, causing increased expression of CDK6 to overcome G1 arrest and promote cell survival.

Acquired resistance can be driven by microRNA

And

Potentially reversible through a drug holiday

Role for RECHALLENGE?

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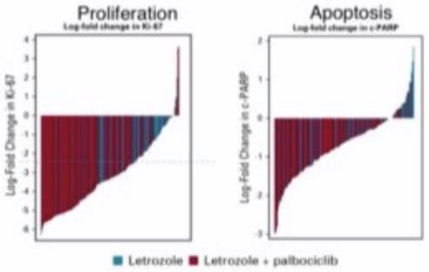
rapid communication

Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial

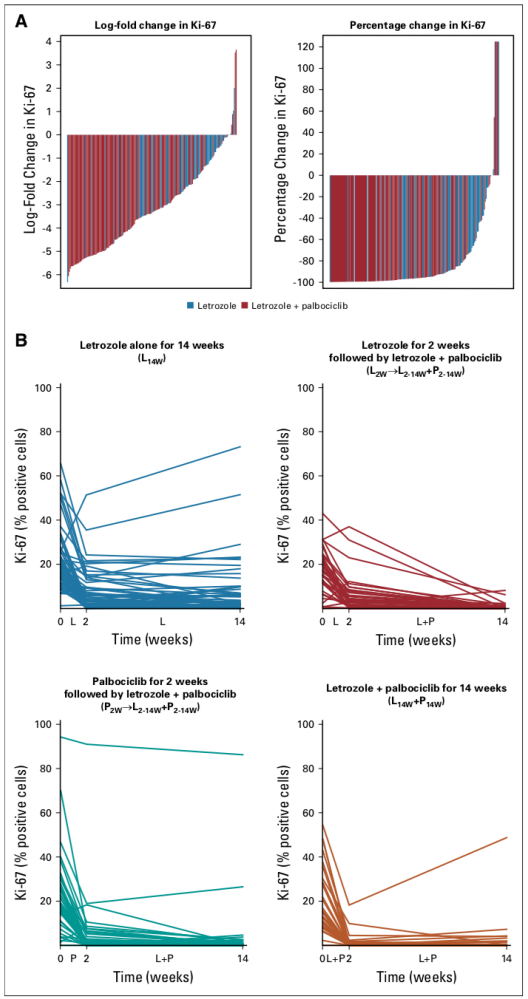
Stephen Johnston, MD, PhD[1]; Shannon Puhalla, MD[2]; Duncan Wheatley, MBBS[3]; Alistair Ring, MD[1]; Peter Barry, MBBS[1]; Chris Holcombe, MD[4]; Jean Francois Boileau, MD[5]; Louise Provencher, MD[6]; André Robidoux, MD[7]; Mothaffar Rimawi, MD[8]; Stuart A. McIntosh, PhD[9]; Ibrahim Shalaby, MD[10]; Robert C. Stein, MD, PhD[11,12]; Michael Thirlwell, MD[13]; David Dolling, PhD[14]; James Morden, MSc[14]; Claire Snowdon, MSc[14]; Sophie Perry, BSc[14]; Chester Cornman, MPH[15]; Leona M. Batten, BSc[14]; Lisa K. Jeffs, BA[14]; Andrew Dodson, MPhil[1,14]; Vera Martins, PhD[1]; Arjun Modi, MSc[1]; C. Kent Osborne, MD[8]; Katherine L. Pogue-Geile, PhD[15]; Maggie Chon U Cheang, PhD[14]; Norman Wolmark, MD[15]; Thomas B. Julian, MD[16]; Kate Fisher, MA[17]; Mairead MacKenzie[18]; Maggie Wilcox[18]; Cynthia Huang Bartlett, MD[19]; Maria Koehler, MD, PhD[20]; Mitch Dowsett, PhD[1,14]; Judith M. Bliss, MSc[14]; and Samuel A. Jacobs, MD[15]



CRR: 49.5 v 54.3% (p=0.2)
Mean log-fold change in Ki-67 favored combo
Mean log-fold change in apoptosis favored letrozole

CDK4/6i are cytostatic

Therapy is accompanied by less apoptosis



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Conclusion 2

- Increasing knowledge on resistance mechanisms
- Small puzzle peaces, combinatory strategies will be evaluated
- For now this data has no clinical impact, but it may soon change
- Lower proliferation does not reflect in increased apoptis- implications for early stage studies

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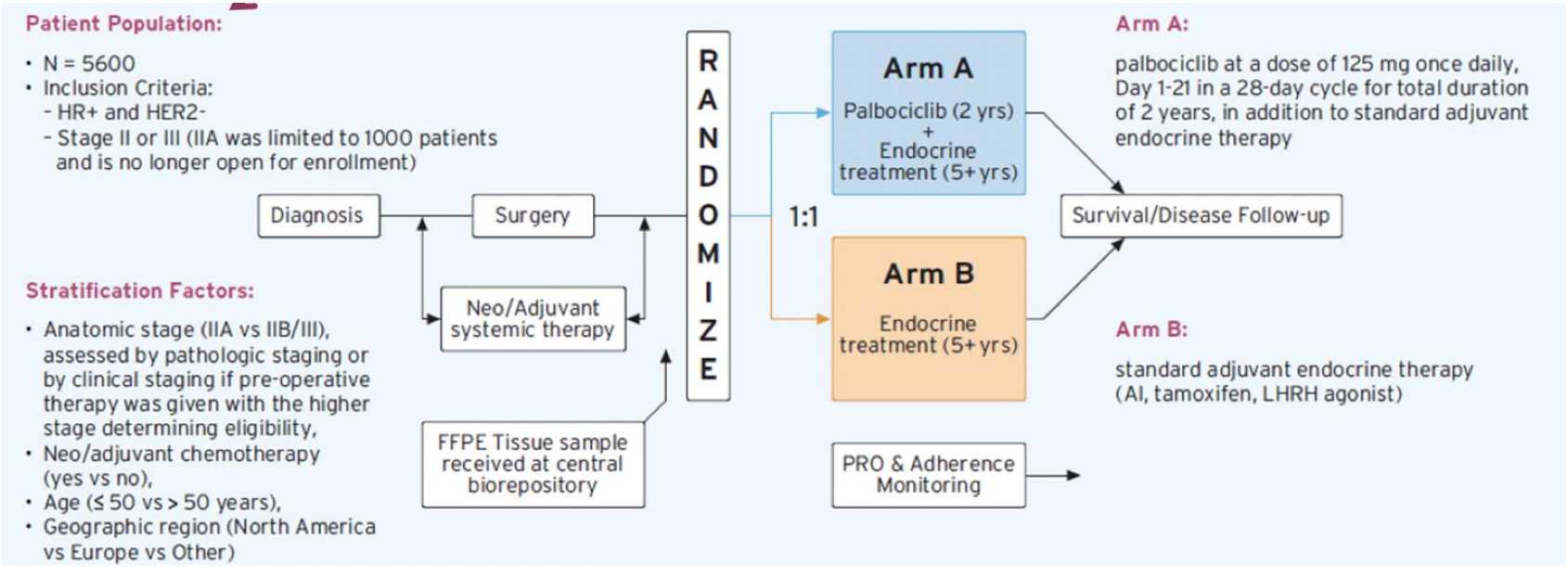
Adjuvant clinical trials with CDK 4/6 inhibitors

PALLAS

PALbociclib CoLlaborative Adjuvant Study:
A randomized, phase 3 trial of Palbociclib with adjuvant endocrine therapy vs endocrine therapy alone for hormone receptor positive/HER2-negative breast cancer

PALLAS Study design



PALLAS
ABCSG 42 / AFT-05 / BIG 14-03

Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

ABCSG ALLIANCE FOUNDATION TRIALS, LLC BIG Pfizer Oncology

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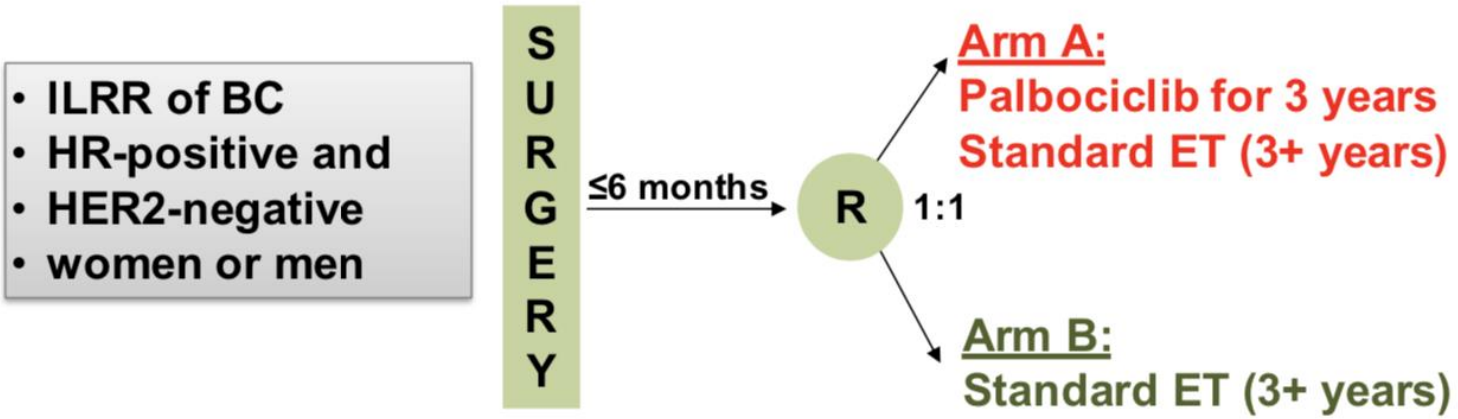
Adjuvant trial for local relapse

POLAR Trial Schema



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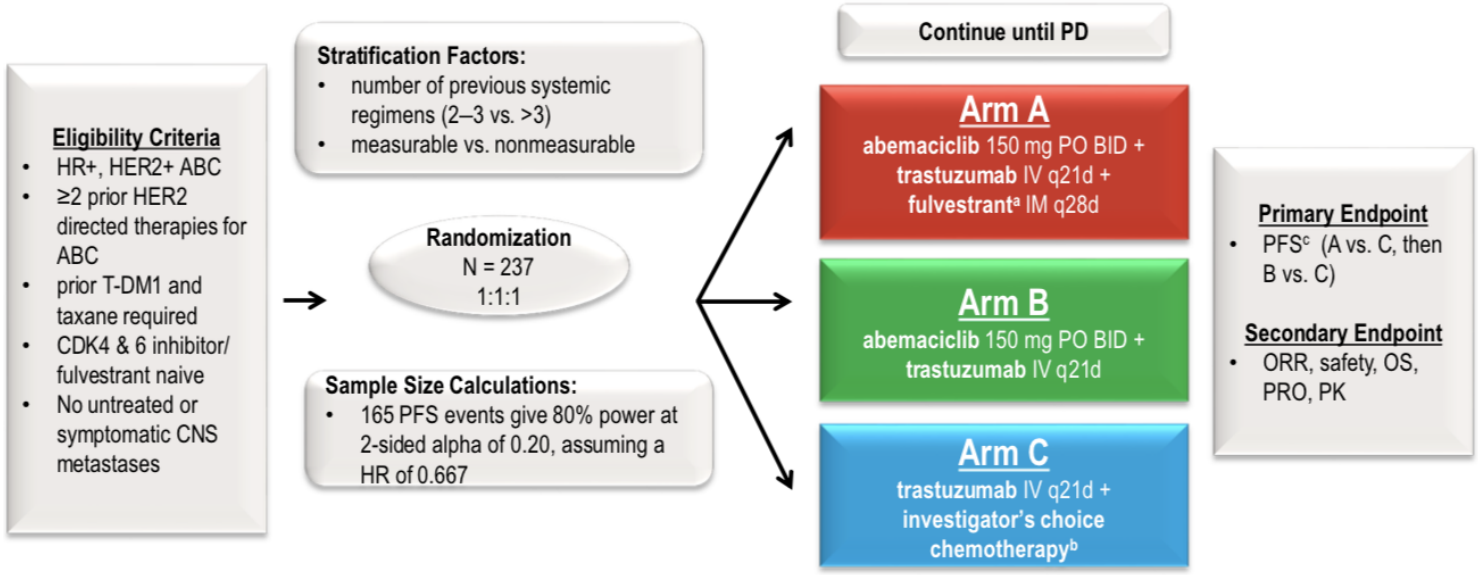
Triple positive breast cancer

monarcHER STUDY DESIGN



BARCELONA 2019 ESMO congress

Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

[a]Dosing per fulvestrant label

[b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

[c]investigator assessed

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MonarcHER

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

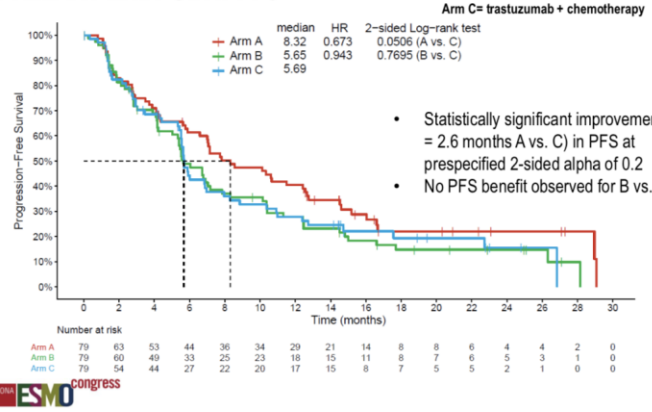
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

	Arm A N=79	Arm B N=79	Arm C [b] N=79
Median age, years (range)	55 (31-78)	54 (28-83)	57 (29-82)
Geographic distribution, n (%)			
Asia / Pacific	13 (16.5)	13 (16.5)	12 (15.2)
Europe	30 (38.0)	45 (57.0)	36 (45.6)
N. America	24 (30.4)	13 (16.5)	24 (30.4)
S. America	12 (15.2)	8 (10.1)	7 (8.9)
Metastatic Site, n (%)			
Visceral	58 (73.4)	56 (70.9)	48 (60.8)
Bone-only	7 (8.9)	3 (3.8)	7 (8.9)
Measurable disease, n (%)	70 (88.6)	68 (86.1)	69 (87.3)
Prior systemic therapies for ABC, n (%)			
2 to 3	35 (44.3)	44 (55.7)	40 (50.6)
More than 3	44 (55.7)	35 (44.3)	39 (49.4)
Prior endocrine therapy overall[a], n (%)	63 (79.7)	60 (75.9)	60 (75.9)
Tamoxifen in any setting	35 (44.3)	45 (57.0)	37 (46.8)
AI in any setting	46 (58.2)	42 (53.2)	42 (53.2)
Prior HER2 therapies for ABC, n (%)			
trastuzumab	77 (97.5)	76 (96.2)	79 (100.0)
trastuzumab emtansine	77 (97.5)	78 (98.7)	77 (97.5)
pertuzumab	43 (54.4)	37 (46.8)	39 (49.4)
lapatinib	35 (44.3)	37 (46.8)	31 (39.2)

[a]any of the following: letrozole, anastrozole, exemestane, tamoxifen
[b]most common chemotherapy: Vinorelbine (37.5%) , Capecitabine (26.4%) , Eribulin (16.7%), Gemcitabine (11.1%)

PRIMARY ENDPOINT: PFS

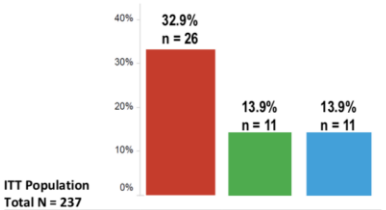
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

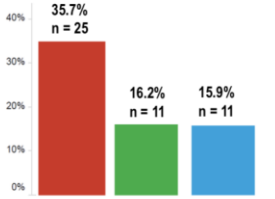
CONFIRMED BEST OVERALL RESPONSE RATE

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached



Measurable Disease
Total N = 207

	Arm A N=70	Arm B N=68	Arm C N=69
95% CI (%)	(24.5-46.9)	(7.4-24.9)	(7.3-24.6)
Stratified 2-sided p-value (vs Arm C)	0.0111	1.0000	-
Duration of Response, months	10.4	9.5	not reached

Toalaney et al, ESMO 2019

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CCR FOCUS

Cell Death and Cancer Therapy: Don't Forget to Kill the Cancer Cell!

Anthony Letai

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THANK YOU

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