

Cyclin inhibitors
Where are we now and
where are they headed in
the future

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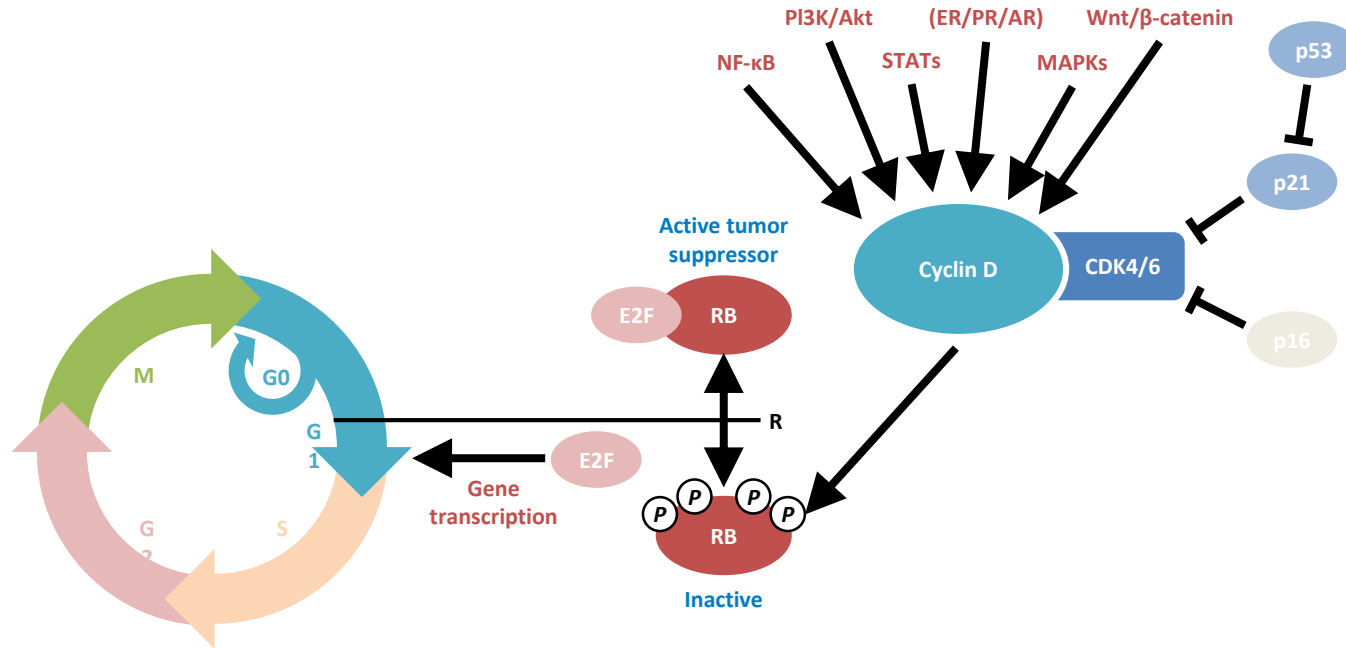
HM CIOCC, Madrid

SOLTI Group

Cyclin inhibitors

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Regulation of the G1/S Checkpoint

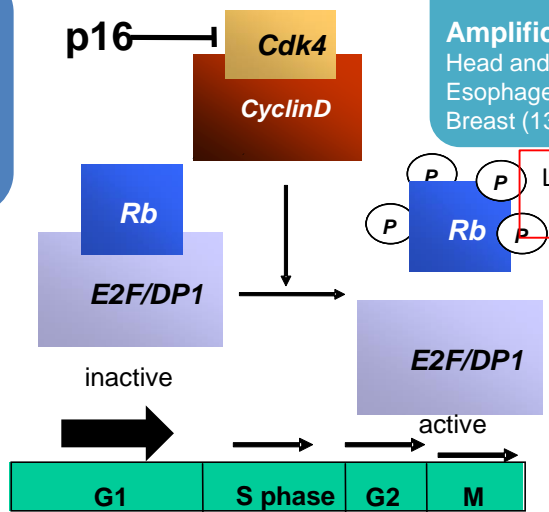


AR, androgen receptor; ER, estrogen receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; PI3K, phosphoinositide-3 kinase; PR, progesterone receptor; R, restriction point; RB, retinoblastoma; STAT, signal transducer and activator of transcription

The Rb/Cdk4-6/Cyclin D Pathway is Dysregulated in Many Human Cancers

Cdk4
Amplification/Mutation:
 Amplified: Gliomas (50%)
 Mutated: Melanoma (R24C)

Rb Inactivation (deletion):
 Retinoblastoma (100%)
 SCLC (90%)
 NSCLC (30%)
 Gliomas (14%)



2º más frecuentemente amplificado en cáncer

Cyclin D1-11q13
Amplification: Head and Neck (43%)
 Esophageal (34%)
 Breast (13%)
Expression: t(11;14) translocations
 MC Lymphoma (most)
 Myeloma (34%)

Locus más frecuentemente deleccionado en cáncer

P16, p15, p18, p19 (INK4A / CDKN2A)
Deletion/Mutation/Methylation
 Glioblastoma (70%)
 Mesothelioma (55%)

CIP/KIP: p21, p27, p57
 Protein degradation

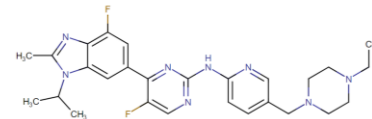
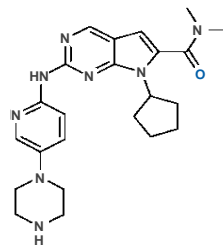
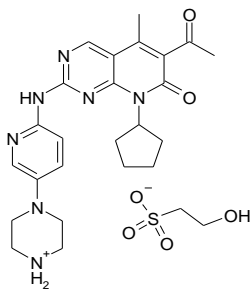
- E2F control genes essential for cell cycle progression
- Retinoblastoma (Rb) susceptibility protein prevents progression from the G1 phase to S phase through its interaction with E2F transcription family members

Cyclin D, CDK 4 and 6 required for tumor initiation and tumor maintenance

Approximately, 80% of human neoplasms maintain functional Rb and ^{3,4}

- Translocation and amplification of D-cyclins⁵
- Amplification of CDK4/6⁵
- Inactivation of p16

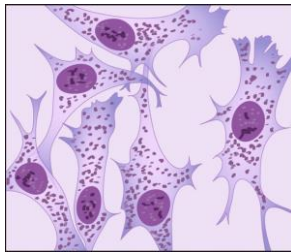
CDK4/6 inhibitors



Target	Palbociclib IC50 (μM)	Ribociclib IC50 (μM)	Abemaciclib IC50 (μM)
CDK4/Ciclin D1	0.011	0,010	0.002
CDK6/Ciclin D2 D3	0.009 – 0.015	0.039	0.010
CDK1/Ciclin B	> 10	113	1,627
CDK2/Ciclin A	> 10	76	0.5

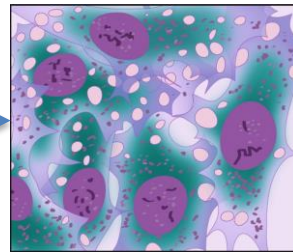
CDK4/6 inhibitors

Palbociclib PD0332991 Pfizer	CDK4(9-11nM) and CDK6 (15nM)	G1 arrest	Phase III: breast, lung Phase II: breast, lung, HN, MM, AML, ALL, gastrointest, hepatocell, ovarian, prostate, melanoma, liposarc, urothelial, endometrial, astrocytoma, oligodendrog.
Ribociclib LEE011 Novartis	CDK4(10nM) and CDK6(39nM)	G1 arrest	Phase III: breast Phase II: breast, melanoma, liposarc, prostate, lung, uterine, GI, ovarian, glioma, hepatocel, teratoma, pancreatic, colorectal
Abemaciclib LY835219 Eli Lilly	CDK4(2nM), CDK6(10nM), HIPK2(31nM), PIM1(50nM), CDK9(57nM), DYRK2(61nM), CK2(117nM), GSK3B(192nM)	G1 arrest	Phase III: breast, lung Phase II: breast, lung, melanoma, mantle cell lymphoma

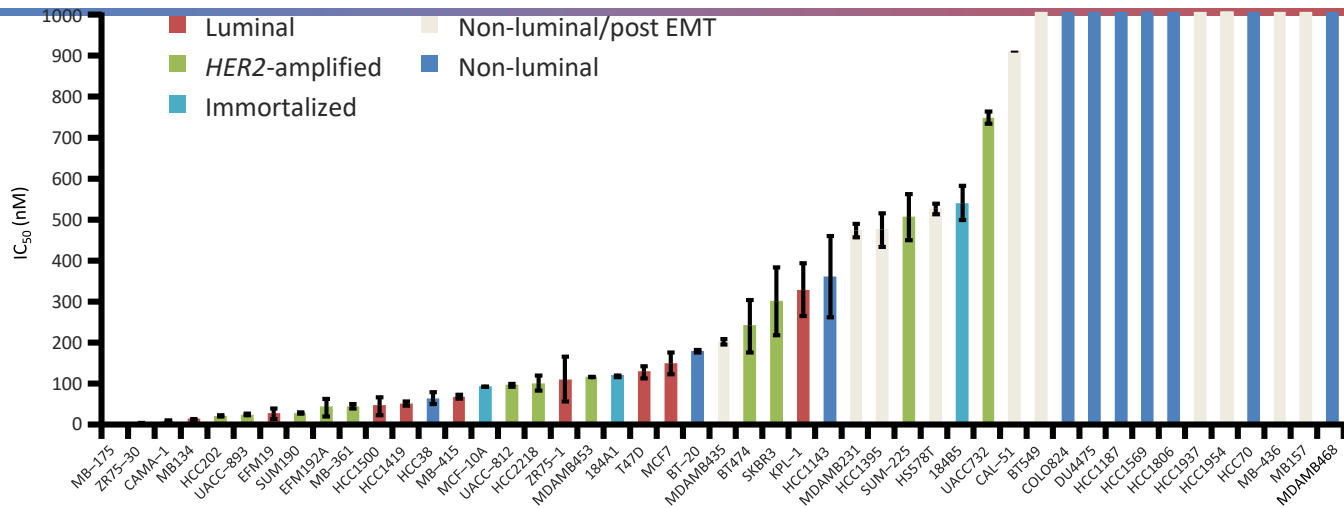


CDK 4/6 inhibition

Senescent state



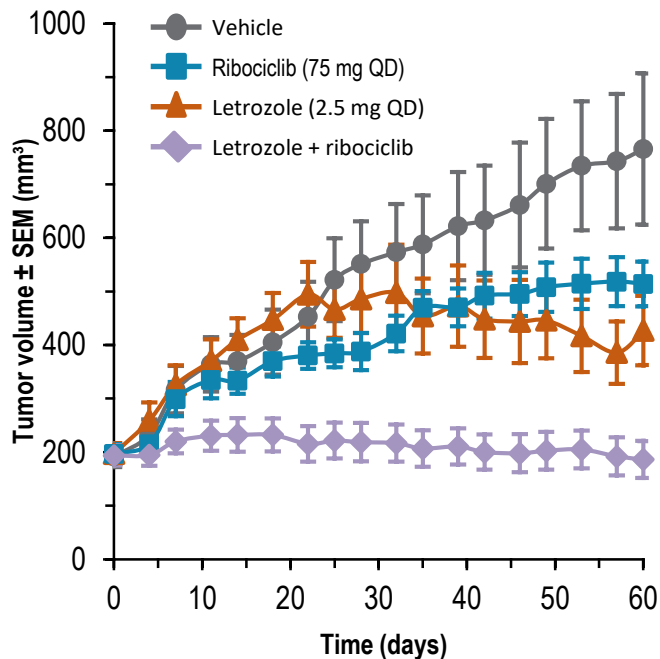
Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines In Vitro



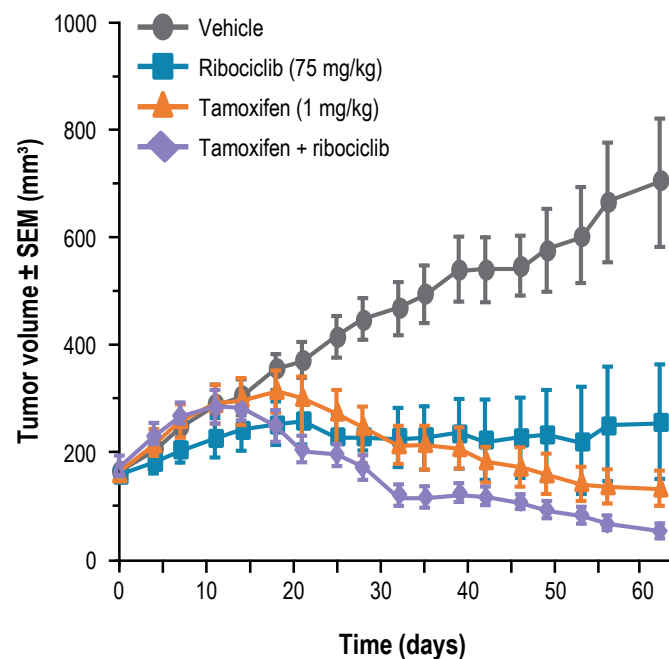
Luminal ER+ and *HER2*-amplified breast cancer cell lines are most sensitive to CDK4/6 inhibition of proliferation

Preclinical activity of ribociclib-based combinations*

Ribociclib + letrozole¹



Ribociclib + tamoxifen²



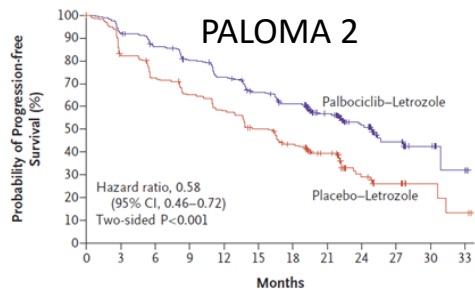
QD, once daily; SEM, standard error of the mean.

*Patient-derived ER+ breast cancer xenograft model (HBX34) used for both analyses.

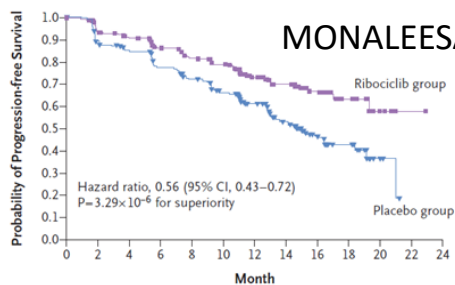
1. O'Brien NA, et al. *Cancer Res* 2014;74(suppl 19):abst 4756;

2. Caponigro G, et al. *Keystone Symposia – Kinases: Next-Generation Insights and Approaches* 2017:oral.

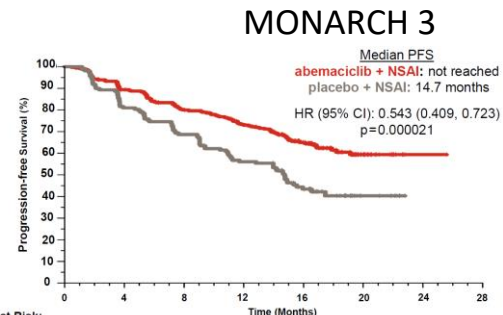
CDK4/6 inhibitors as first line in MBC in combination with AI



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33
Palbociclib-Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo-Letrozole	222	171	148	131	116	98	81	54	22	12	4	2



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0



Patients at Risk:	0	4	8	12	16	20	24	28
abemaciclib arm	328	271	234	205	125	25	1	0
placebo arm	165	127	105	82	45	7	0	0

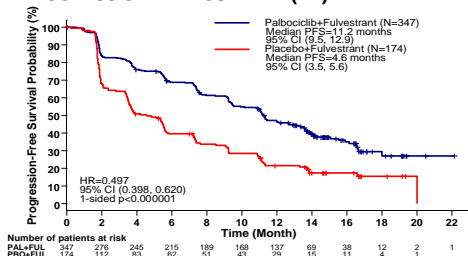
PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p=.000102

Agent	Line	PFS HR	p	CBR (%)	ORR (%)
Palbociclib	1st (P2)	0,58	<,0001	85%	55% (Δ 10%)
Ribociclib	1st (ML2)	0,56	<,0001	80%	53% (Δ 15%)
	1st (ML7)	0,55	<,0001	79%	41% (Δ 11%)
Abemaciclib	1st (MN3)	0,54	<,0001	78%	59% (Δ 15%)

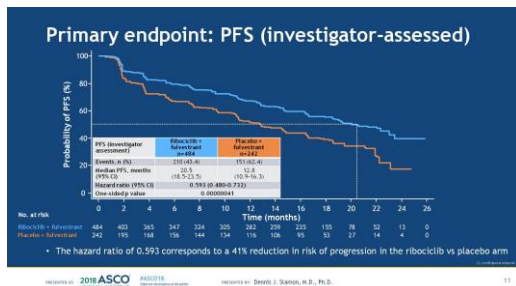
CDK4/6 inhibitors as second line in MBC in combination with fulvestrant

PALOMA 3

FINAL PROGRESSION-FREE SURVIVAL (ITT)¹



MONALEESA. 3

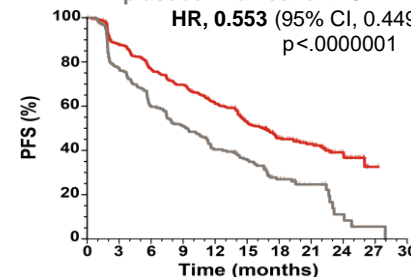


MONARCH 2 Median PFS¹

abemaciclib + fulvestrant: 16.44 months (N=446)

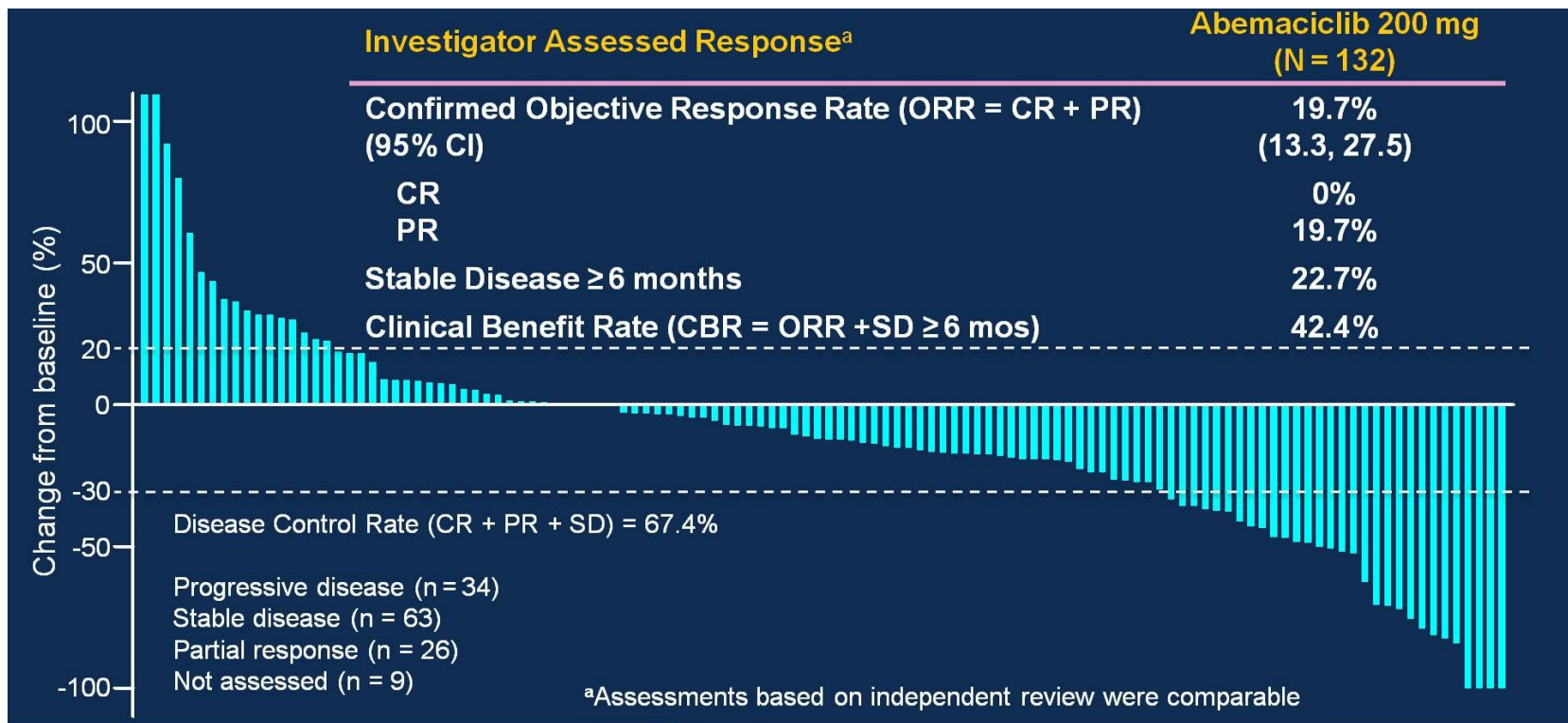
placebo + fulvestrant: 9.27 months (N=223)

HR, 0.553 (95% CI, 0.449 to 0.681)
p<.0000001



Agent	Line	PFS HR	p	CBR (%)	ORR (%) [eval.]
Palbociclib	2 nd	0,46	< ,0001	67%	25% (Δ 14%)
Ribociclib	1 st - 2 nd	0,59	< ,0001	70%	41% (Δ 12%)
Abemaciclib	2 nd	0,55	< ,0001	NK	48% (Δ 27%)

CDK4/6 inhibitors as monotherapy in pretreated MBC



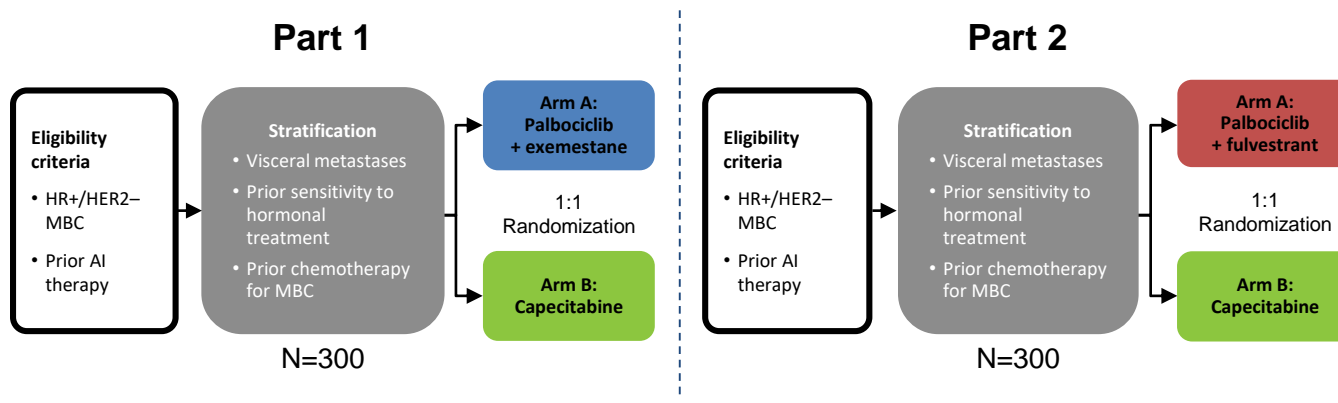
CDK4/6 inhibitors in pretreated MBC vs chemo

Agent	Trial	N	Prior CT lines mBC	Overall RR	Median PFS (mo)	Median OS (mo)
CDK 4/6 inh	PALOMA3	521	0-1	19 vs 9%	11,2 vs 4,6 (HR 0,49)	34,9 vs 28 (HR 0,81) P3
	MONALEESA 3	726	0	32,4 vs 21,5%	14,6 vs 9,1 (HR 0,56)	
	MONARCH 2	669	0	35,2 vs 16,1%	16,4 vs 9,2 (HR 0,55)	
	MONARCH 1	132	3-4	19,7%	5,9	
Capecitabine	Phase III	546	0 – 2	19,9	4,2 mo	14,5
Eribulin	Phase III	544	0 - 2	16,1	4,1 mo	15,9

PEARL

Phase III study of Palbociclib in combination with endocrine therapy (Exemestane or Fulvestrant) versus chemotherapy (Capecitabine) in HR+/HER2- MBC patients with resistance to NSAI

[NCT02028507](#)



Primary endpoint: PFS

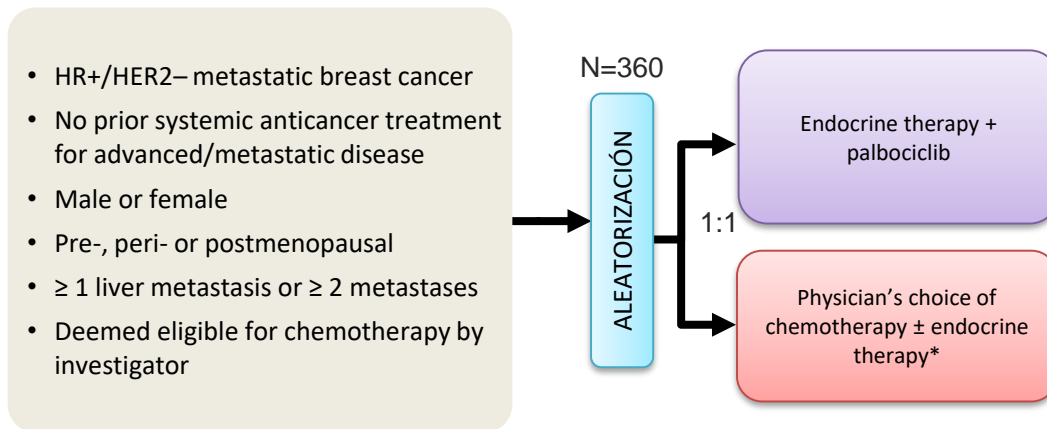
- In all Part 2 patients regardless of *ESR1* mutational status
- In all patients with WT *ESR1* at study entry

Status: Recruitment closed. Primary completion: Q3 2019

ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02028507>

PADMA

A Phase III/IIIb of Palbociclib + Endocrine Therapy Versus Physician's Choice of Chemotherapy, With or Without Endocrine Therapy, in the First Line Setting for HR+/HER2- Metastatic Breast Cancer



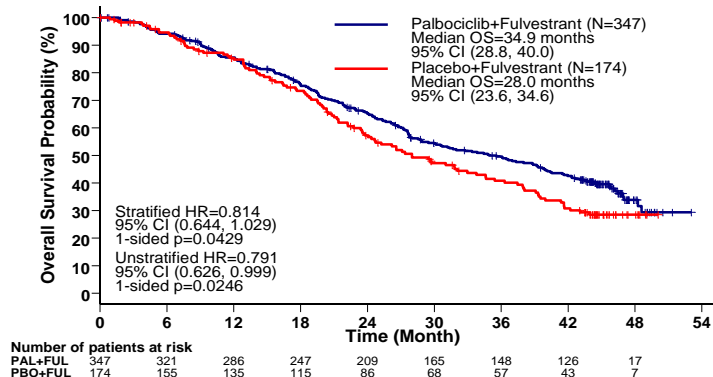
Primary endpoint: Time to treatment failure

Secondary endpoints: Time to first subsequent therapy. Time to second subsequent therapy. OS at 36 months. HRQOL (FACT-B). Daily monitoring treatment impact. Safety. Tolerability. Compliance

Status: Recruiting. Primary completion: Q2 2021

CDK4/6 inhibitors : OS

OVERALL SURVIVAL (ITT)

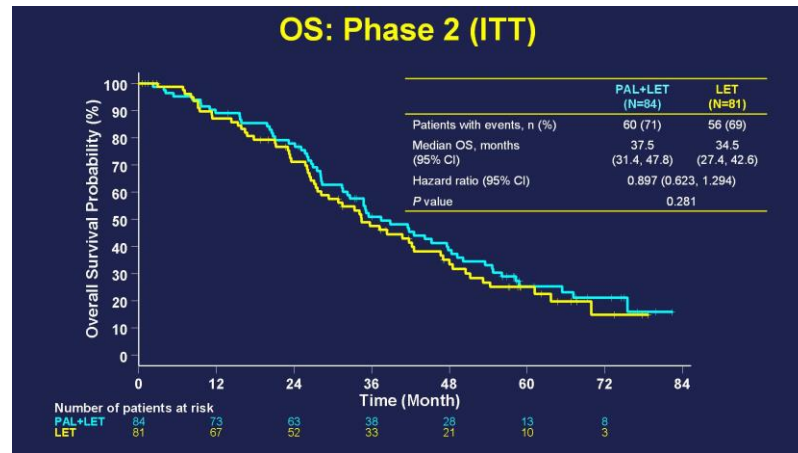


• Absolute improvement in median OS in the palbociclib arm vs the placebo arm was 6.9 months.

PALOMA 3

Cristofanilli M, NEJM 2018

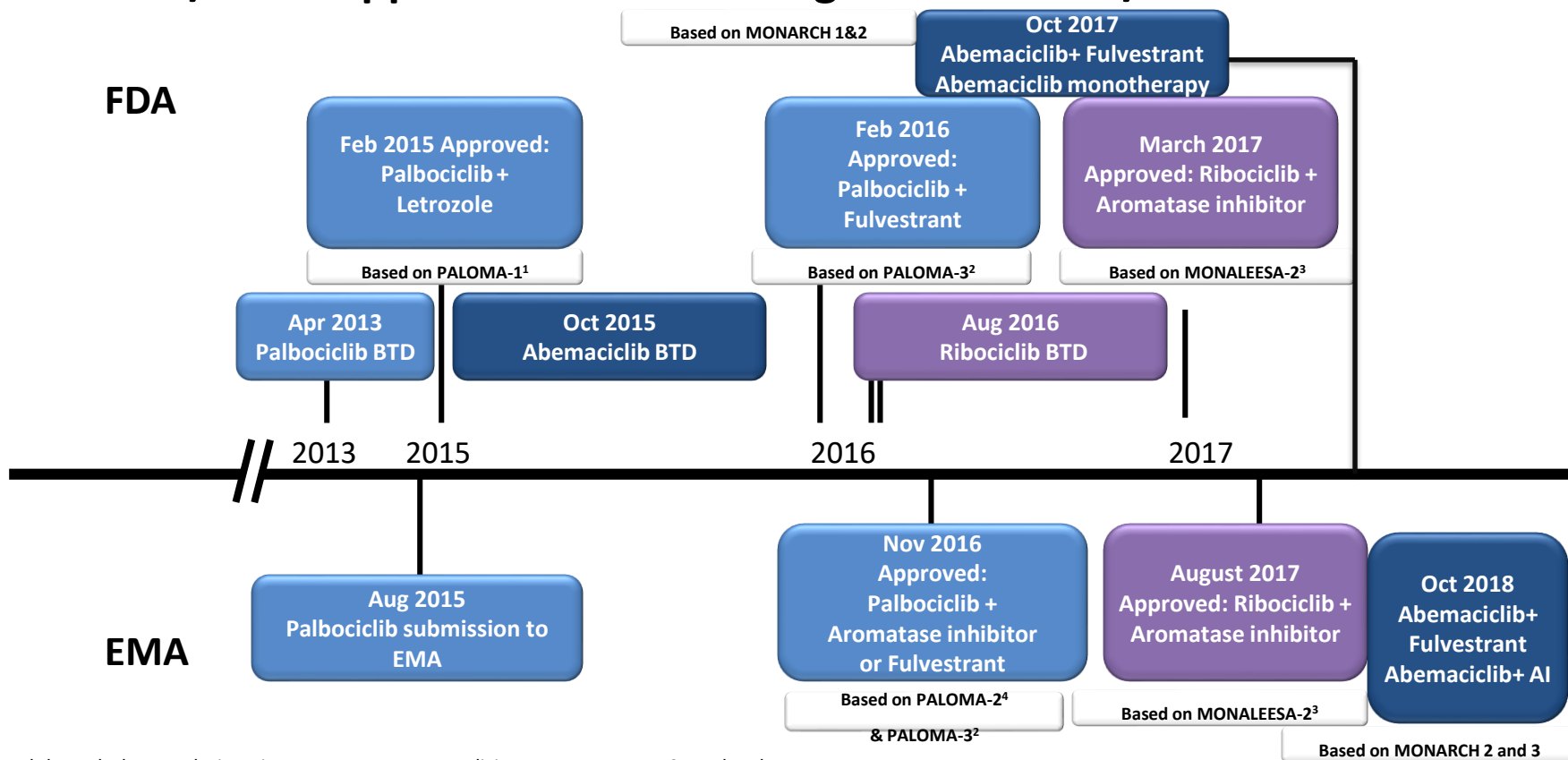
OS: Phase 2 (ITT)



PALOMA 1

Finn R, ASCO 2017

CDK4/6 inh approved for the management of HR+/HER2- mBC



BTD, breakthrough therapy designation; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; mBC, metastatic breast cancer

- Created from www.FDA.gov; www.ema.europa.eu/ema/;
- 1. Clinicaltrials.gov. 2017.NCT00721409;; 2. NCT01942135;
- 3. NCT01958021; 4. NCT01740427

Cyclin inhibitors

Where are we now and
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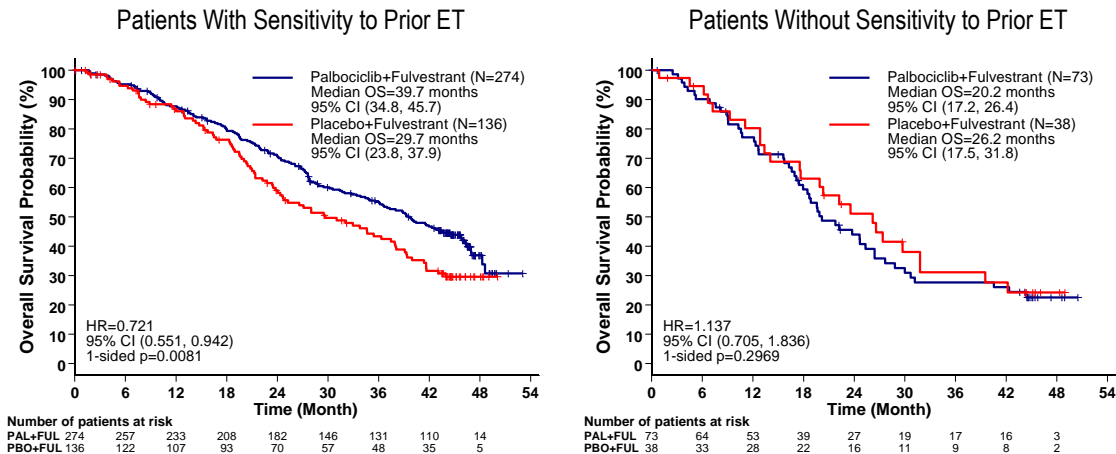
Cyclin inhibitors

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Biomarkers

Biomarkers: Sensitivity to prior endocrine treatment

OVERALL SURVIVAL BY SENSITIVITY TO PRIOR ET

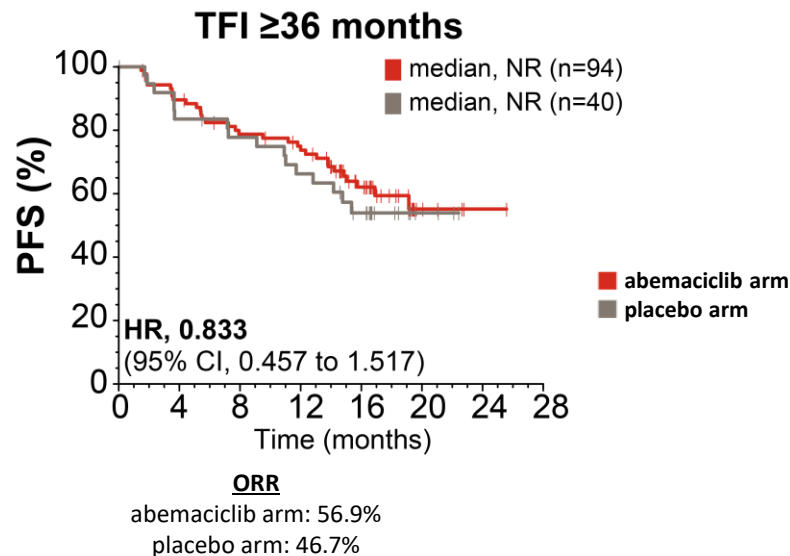
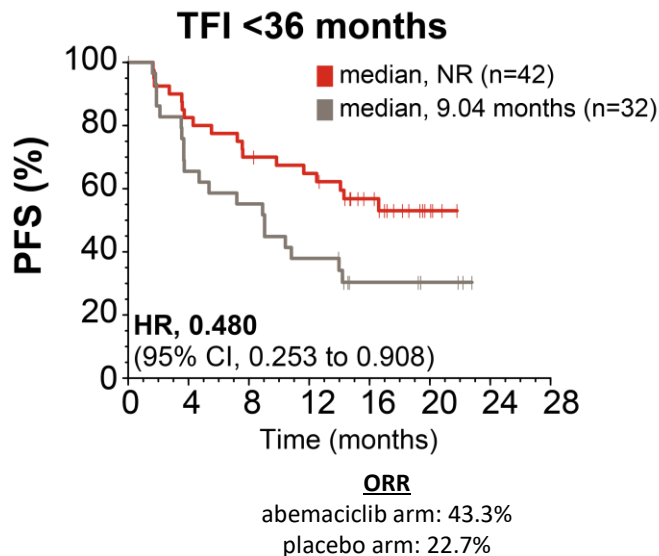


In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months.

PALOMA 3

Cristofanilli M, NEJM 2018

Biomarkers: Sensitivity to prior endocrine treatment



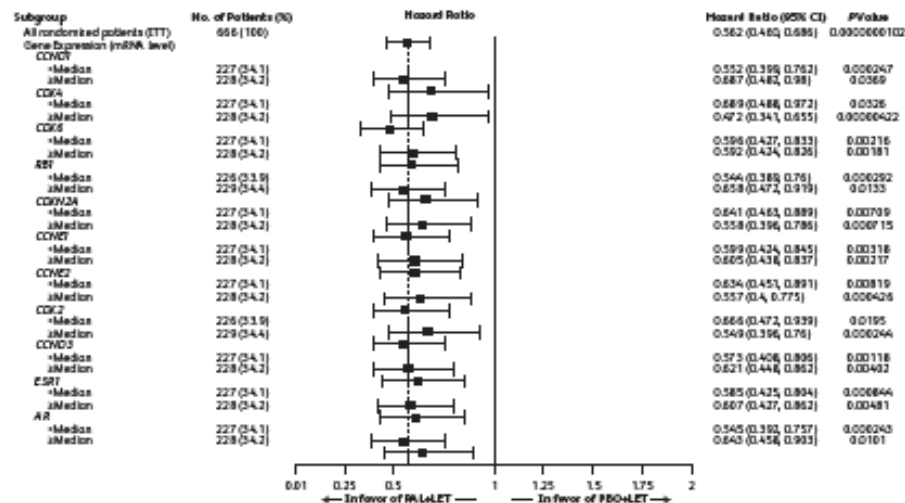
Note: Study protocol required an interval greater than 12 months from the end of adjuvant ET until relapse. The 36-month cutoff was arbitrarily selected to be as short as possible while providing an adequate sample size.

1. Goetz MP et al. *J Clin Oncol.* 2017;35(32):3638-46

2. Di Leo A et al. *Annals of Oncology.* 2017;28 (suppl_5): v605-v649

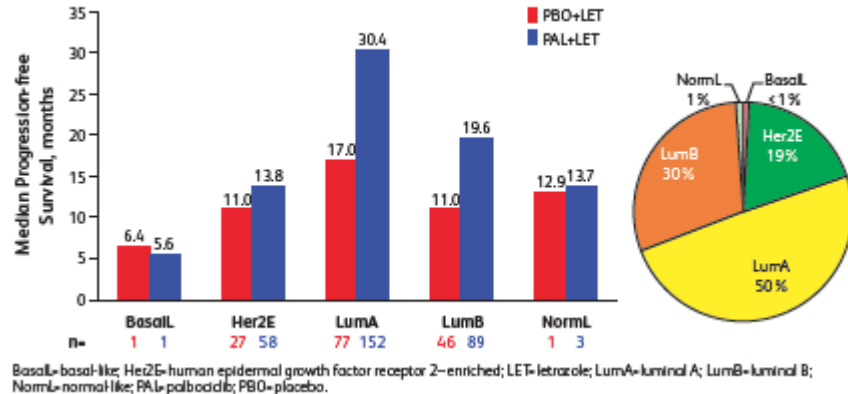
Biomarkers: Intrinsic subtypes

Figure 2. Subgroup Analysis Based on Target Gene Expression in the Cyclin D-CDK4/6-RB Pathway

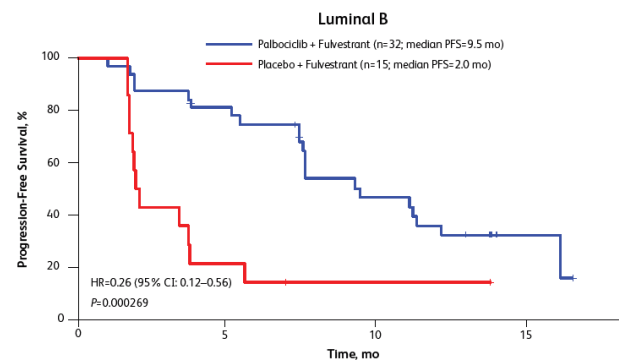
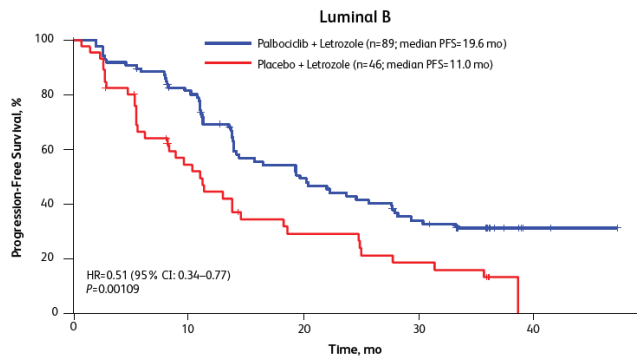
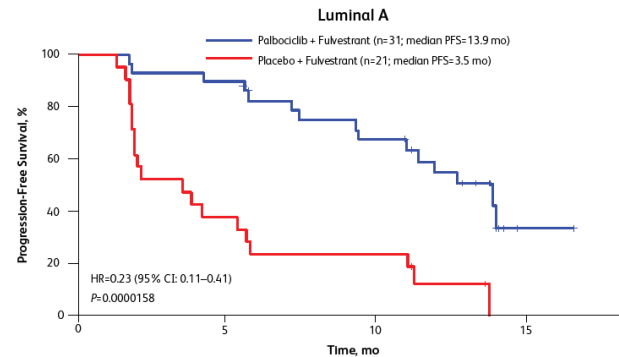
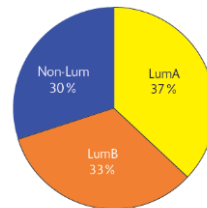
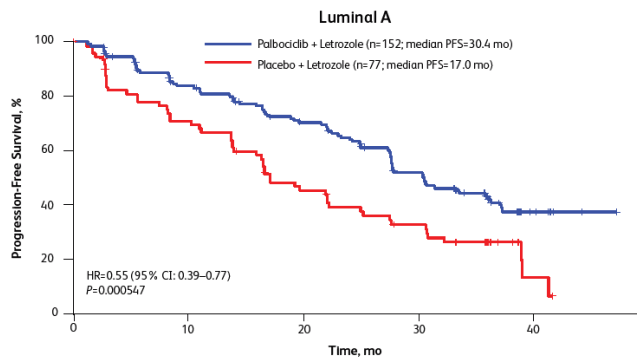
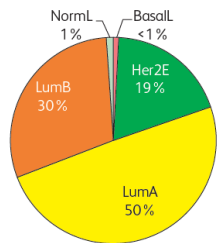


ITT=Intent-to-treat; LET=letrozole; PAL=palbociclib; PBO=placebo.

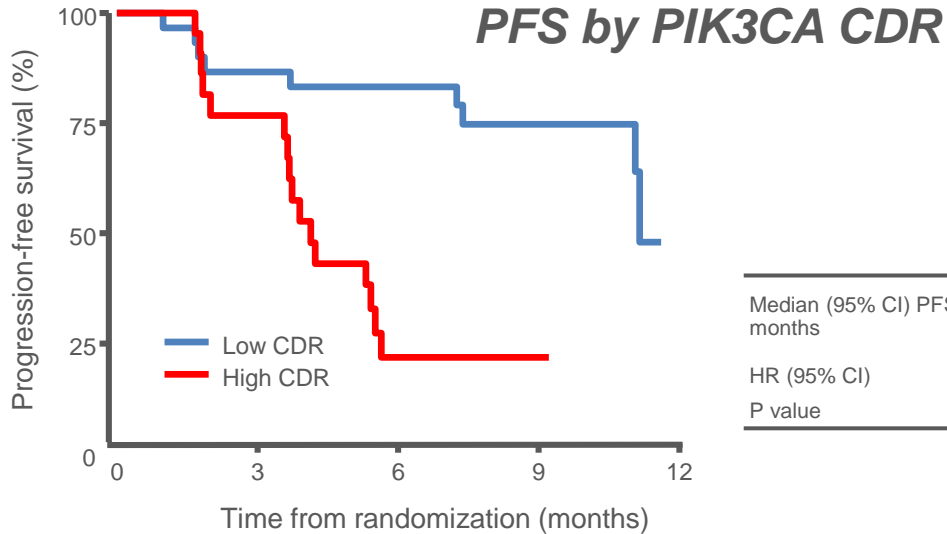
Figure 6. Median PFS in Patients With Various Intrinsic Molecular Subtypes



Biomarkers: Intrinsic subtypes



PIK3CA ctDNA Dynamics Predicted Palbociclib Outcome (PALOMA 3)



Number at risk (events)									
Low CDR:	30	(4)	26	(1)	20	(2)	13	(2)	1
High CDR:	22	(5)	16	(11)	4	(0)	1	(0)	0

	Low CDR (n=30)	High CDR (n=22)
Median (95% CI) PFS, months	11.2 (11.1–Undefined)	4.1 (3.6–5.5)
HR (95% CI)	4.92 (1.98–12.26)	
P value	0.0002	

CDR, circulating DNA ratio; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival. O'Leary B, *et al.* Nature Communications. 2018

La dinámica temprana de ctDNA de *PIK3CA* predice la supervivencia libre de progresión (SLP) en palbociclib + fulvestrant con mayor fuerza que la dinámica de *ESR1*. Gráfica de Kaplan-Meier para SLP de pacientes tratados con palbociclib + fulvestrant divididos en *PIK3CA* CDR₁₅ alta o baja usando un punto de corte optimizado calculado con el índice c de Harrell. Valor de q del test de log-rank corregido para descubrimientos falsos con Benjamini-Hochberg.

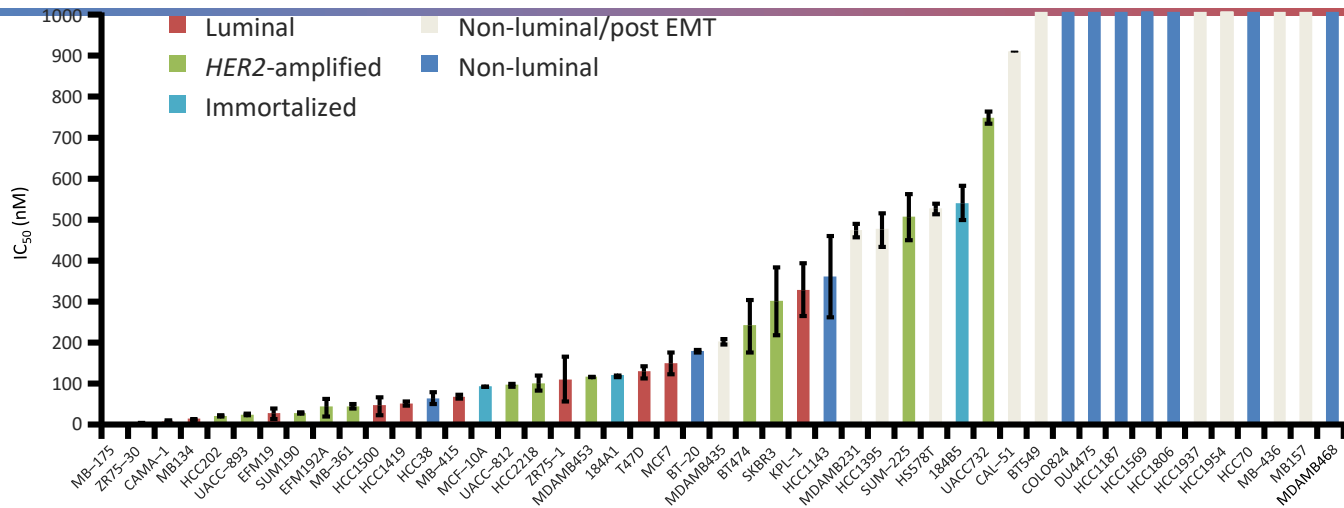
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Biomarkers

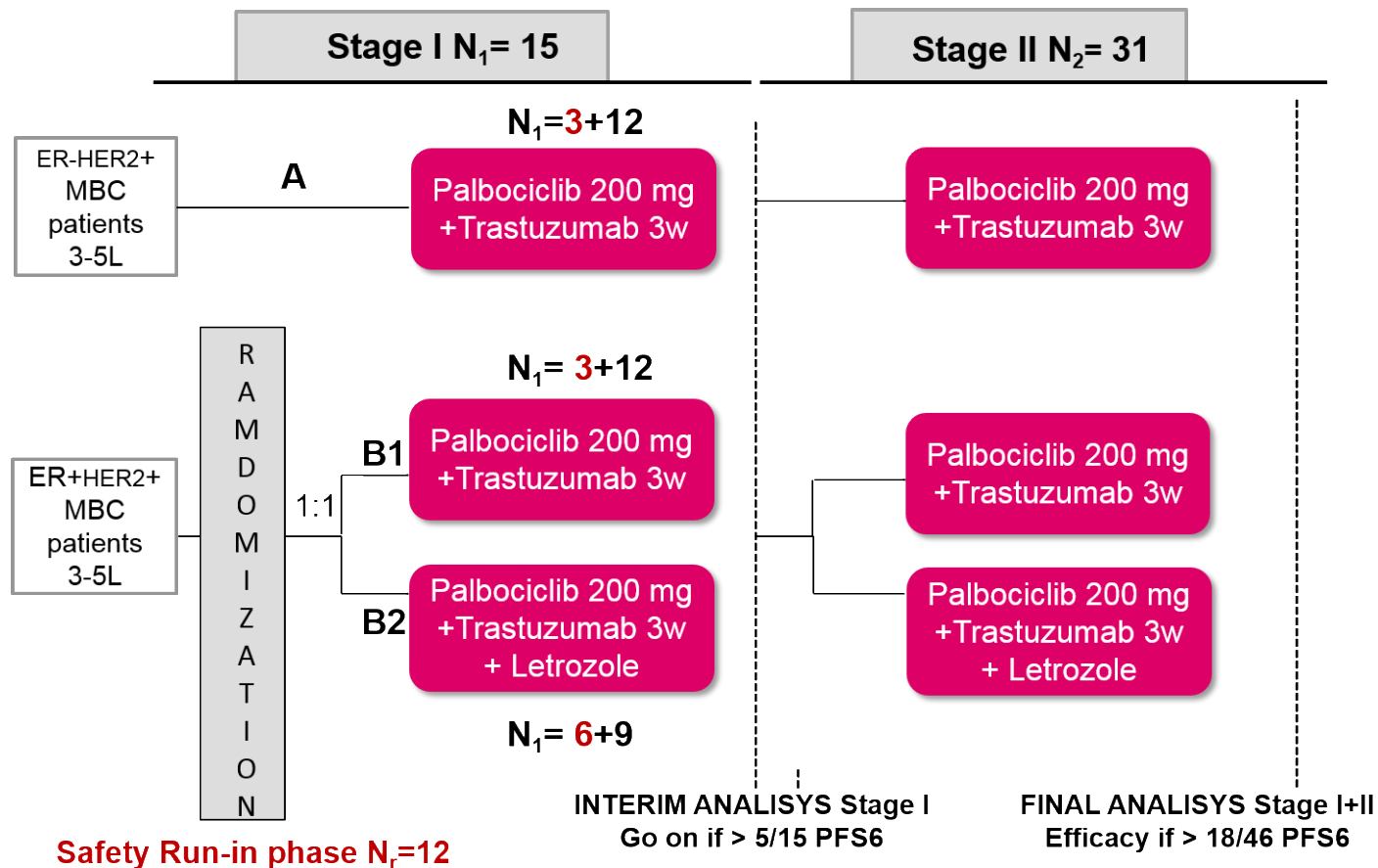
Breast cancer: HER2+

Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines In Vitro



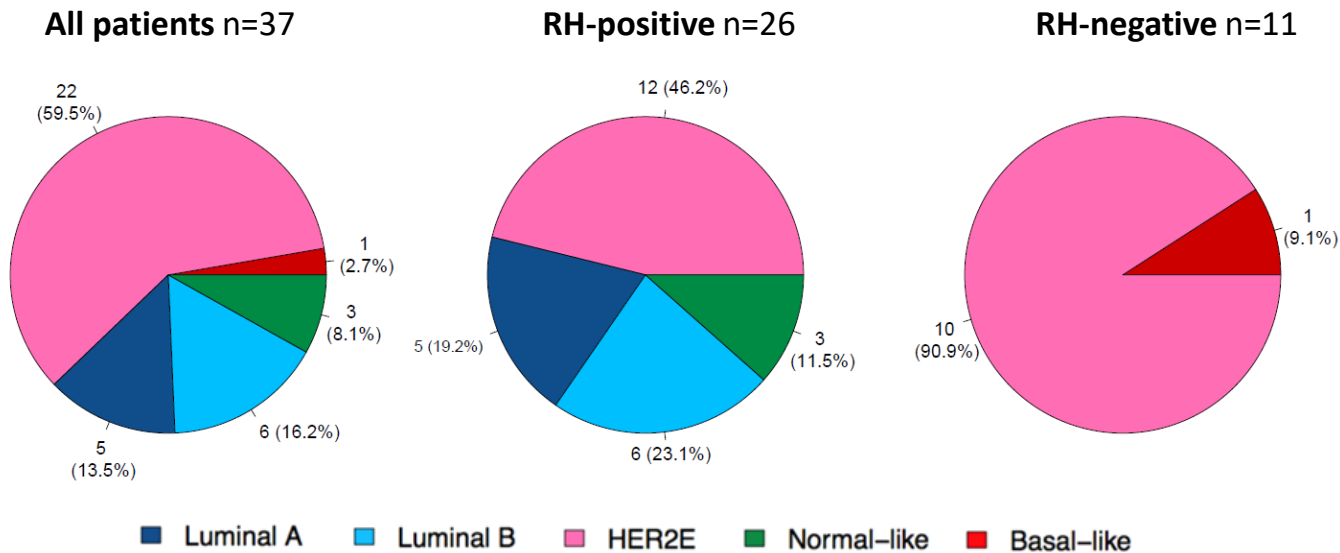
Luminal ER+ and HER2-amplified breast cancer cell lines are most sensitive to CDK4/6 inhibition of proliferation

PATRICIA 1 Design

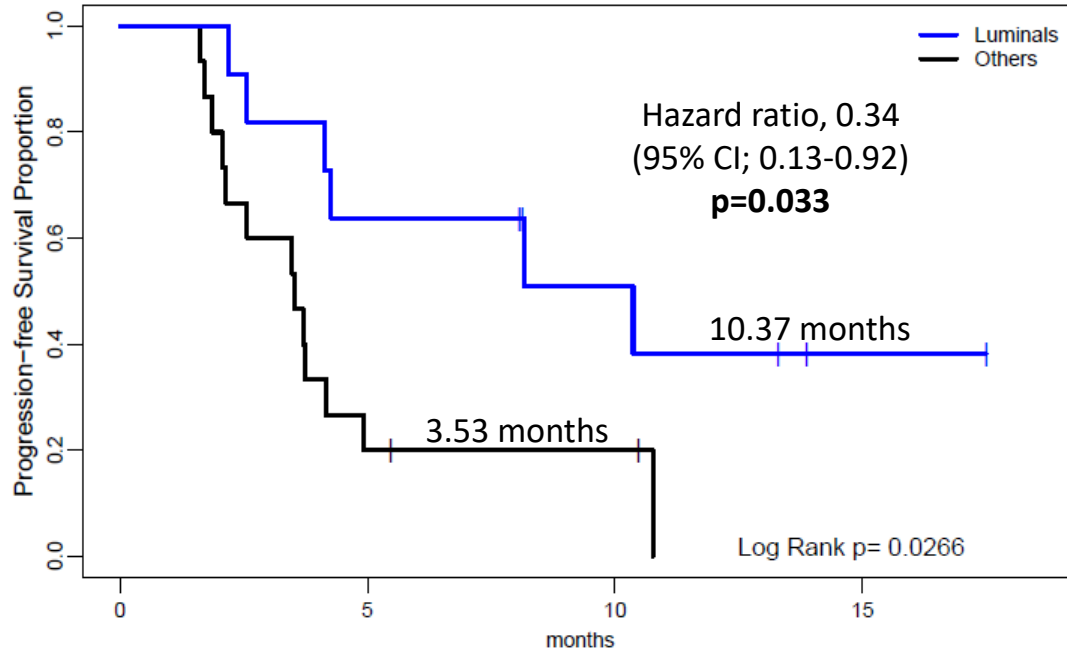


PATRICIA Trial

Distribution of the intrinsic subtypes



Progression-free survival (PFS) in Luminal versus others Cohort B



Luminals
Others

11
15

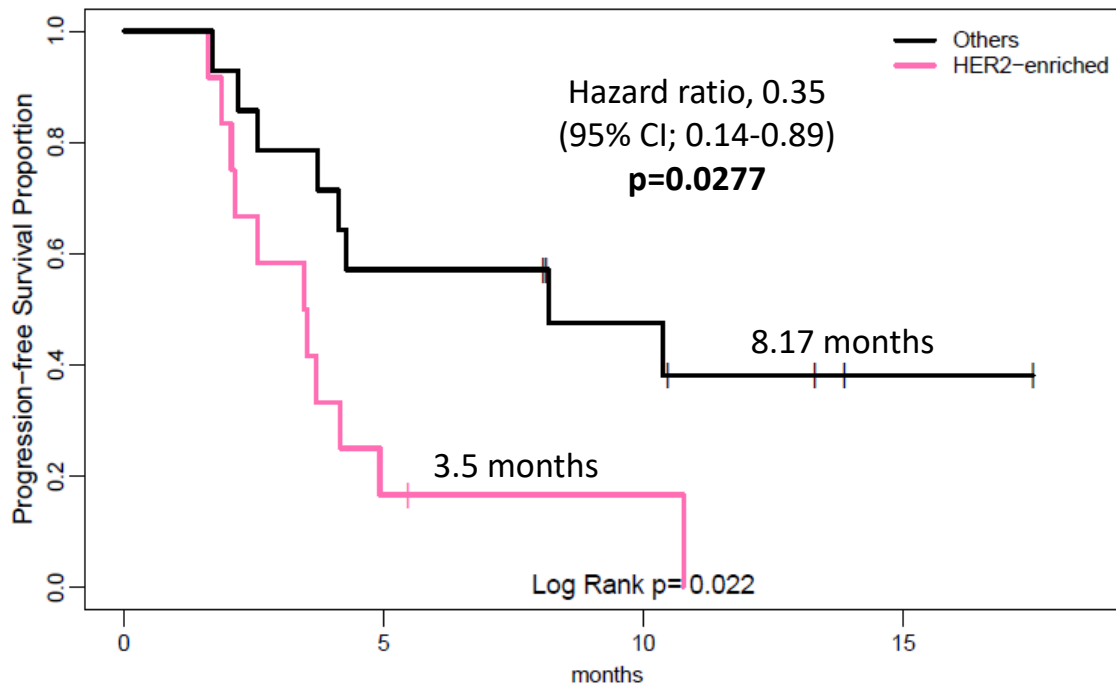
7
3

4
2

1

Ciruelos E, SABCS 2017

Progression-free survival (PFS) in HER2E versus others Cohort B



Others
HER2-enriched

14
12

8
2

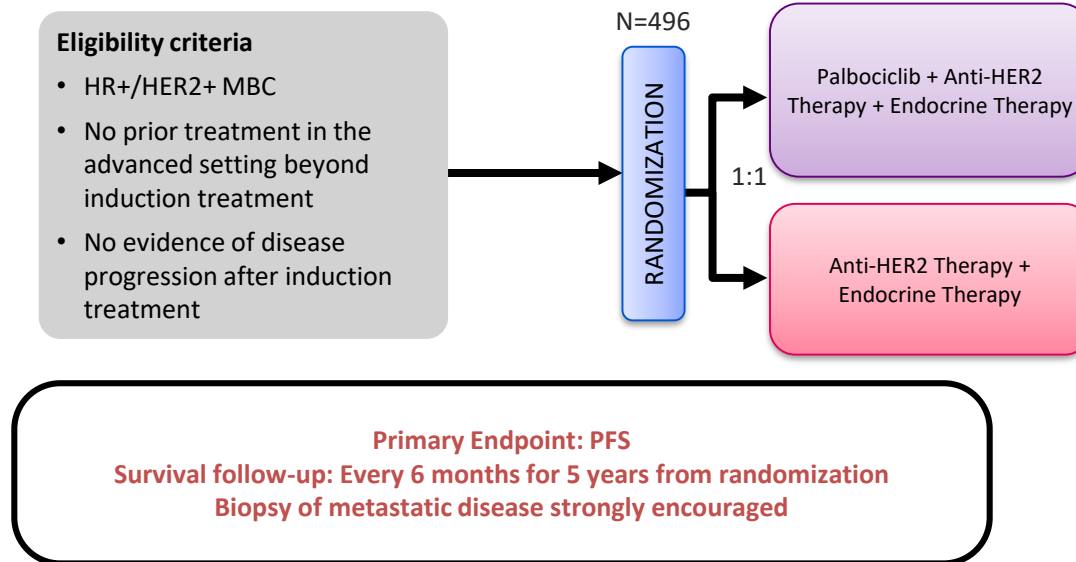
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1

Ciruelos E, SABCS 2017

PATINA

Palbociclib in HR+/HER2+ 1st Line Maintenance MBC



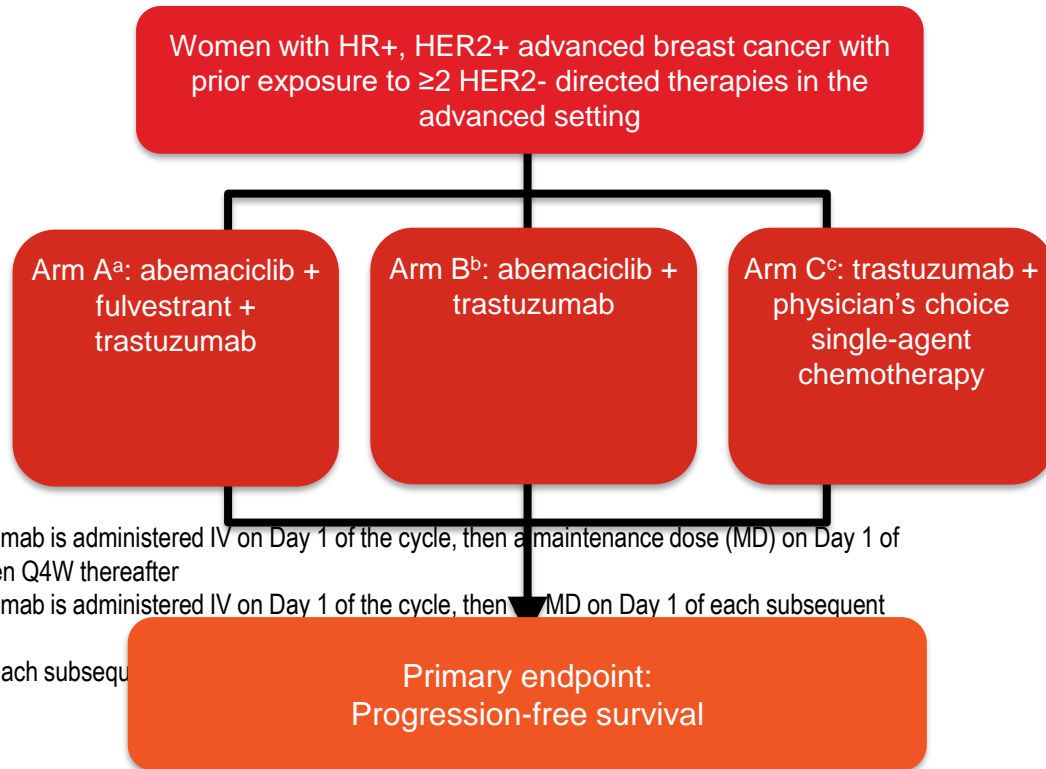
Status: Recruiting. Primary completion: Q2 2021

Abemaciclib: monarchHER I3Y-MC-JPBZ: Study Design

monarchHER: A Study Evaluating Abemaciclib Plus Trastuzumab With or Without Fulvestrant or Chemotherapy in Women With HR+, HER2+ Locally Advanced or Metastatic Breast Cancer After Prior Exposure to ≥ 2 HER2-directed Therapies for Advanced Disease

Phase 2

Recr. Closed Feb 2018



Participants continue study treatment until discontinuation criteria are met

^aAbemaciclib is administered PO Q12H on Days 1-21 of a 21-day cycle. Trastuzumab is administered IV on Day 1 of the cycle, then a maintenance dose (MD) on Day 1 of each subsequent cycle. Fulvestrant is administered IM on Days 1, 15, 29, and then Q4W thereafter

^bAbemaciclib is administered PO Q12H on Days 1-21 of a 21-day cycle. Trastuzumab is administered IV on Day 1 of the cycle, then a MD on Day 1 of each subsequent cycle

^cTrastuzumab is administered IV on Day 1 of the cycle, then an MD on Day 1 of each subsequent cycle. Chemotherapy is administered according to the product label

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Biomarkers

Breast cancer: HER2+

Toxicity profile

Toxicity profile

Grade 3 – 4 toxicities	Neutropenia	Febril Neutropenia	Anemia	Transaminitis	QTc(f)	Asthenia	DVT - PTE	Diarrea
Palbociclib	+++	+/-	+	+	-	+	-	-
Ribociclib	+++	+/-	+	++	++	+	-	-
Abemaciclib	++	+/-	++	+	-	++	++	+++

VTE known effect of abemaciclib + ET

	MONARCH 2		MONARCH 3		nextMONARCH1		
	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Abemaciclib + NSAID	Placebo + NSAID	Abemaciclib (150mg) + TAM	Abemaciclib (150mg)	Abemaciclib (200mg)
	(N=441)	(N=223)	(N=327)	(N=161)	(N=78)	(N=79)	(N=77)
VTE (all grade)^a	21 (4.8%)	2 (0.9%)	20 (6.1%)	1 (0.6%)	7 (9.0%)	4 (5.1%)	3 (3.9%) ^e
PE	11 (2.5%)	0	11 (3.4%) ^b	1 (0.6%)	4 (5.1%)	2 (2.5%)	2 (2.6%) ^f
DVT	10 (2.3%)	2 (0.9%)	9 (2.8%)	0	3 (3.8%)	2 (2.5%)	0
Grade ≥3	9 (2.0%)	1 (0.4%)	10 (3.1%)	1 (0.6%)	2 (2.6%)	3 (3.8%)	1 (1.3%)
Death	0	0	3 (0.9%) ^c	0	0	0	0
SAE	8 (1.8%) ^a	1 (0.4%)	9 (2.8%)	1 (0.6%)	3 (3.8%)	2 (2.5%)	1 (1.3%)
Discontinuations	2 (0.5%)	0	4 (1.2%) ^d	0	0	0	0
Dose reduction	2 (0.5%)	0	0	1 (0.6%)	0	0	0

^aAll VTEs classified as PE or DVT.

^b3 patients experienced both PE and DVT

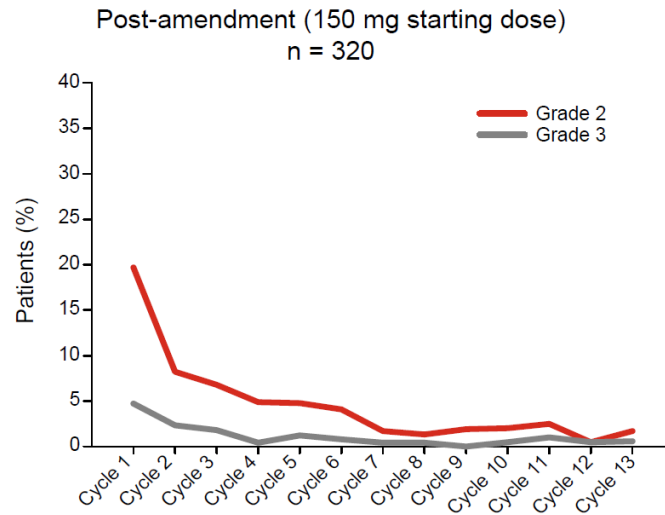
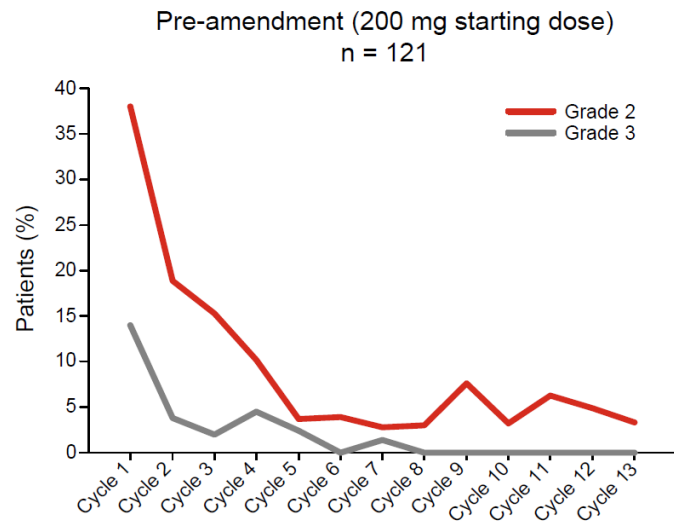
^cPE and DVT; Thromboembolism NFI (PE); Respiratory failure (possible PE) One fatal thromboembolism “no further information” classified as PE

^dincludes 3 patients who died

^eOne patient had preferred term “embolism” (vessel type unconfirmed)

^fOne DVT and 1 PE occurred in the same patient on the same day, reported here as PE

Diarrhea: known effect of abemaciclib



Events due to diarrhea	Pre- / post-amendment
Discontinuation	6.6% / 1.6%
Grade 2	43.8% / 27.2%
Grade 3	19.0% / 11.3%

Cyclin inhibitors

Where are we now and
**where are they headed in
the future**

Biomarkers

Breast cancer: HER2+

Toxicity profile

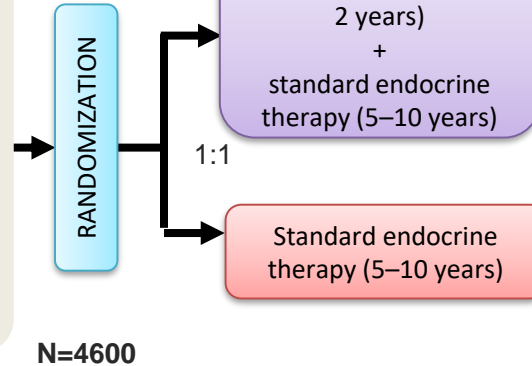
Early disease

PALLAS

PALbociclib CoLLaborative Adjuvant Study: A Randomized Phase III Trial of Palbociclib With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone for Hormone Receptor Positive (HR+) / Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Early Breast Cancer (PALLAS)

[NCT02513394](https://clinicaltrials.gov/ct2/show/study/NCT02513394)

- Pre- and postmenopausal women or men
- Stage IIA (limited to 1000 patients) or stage IIB/III early invasive breast cancer
- Histologically confirmed ER+ (and/or PR+), HER2–
- No more than 12 months since initial pathologic diagnosis
- No more than 6 months of adjuvant endocrine therapy
- Breast surgery for the current malignancy
- ECOG PS 0–1



Primary endpoint: Invasive disease-free survival

Secondary endpoints:

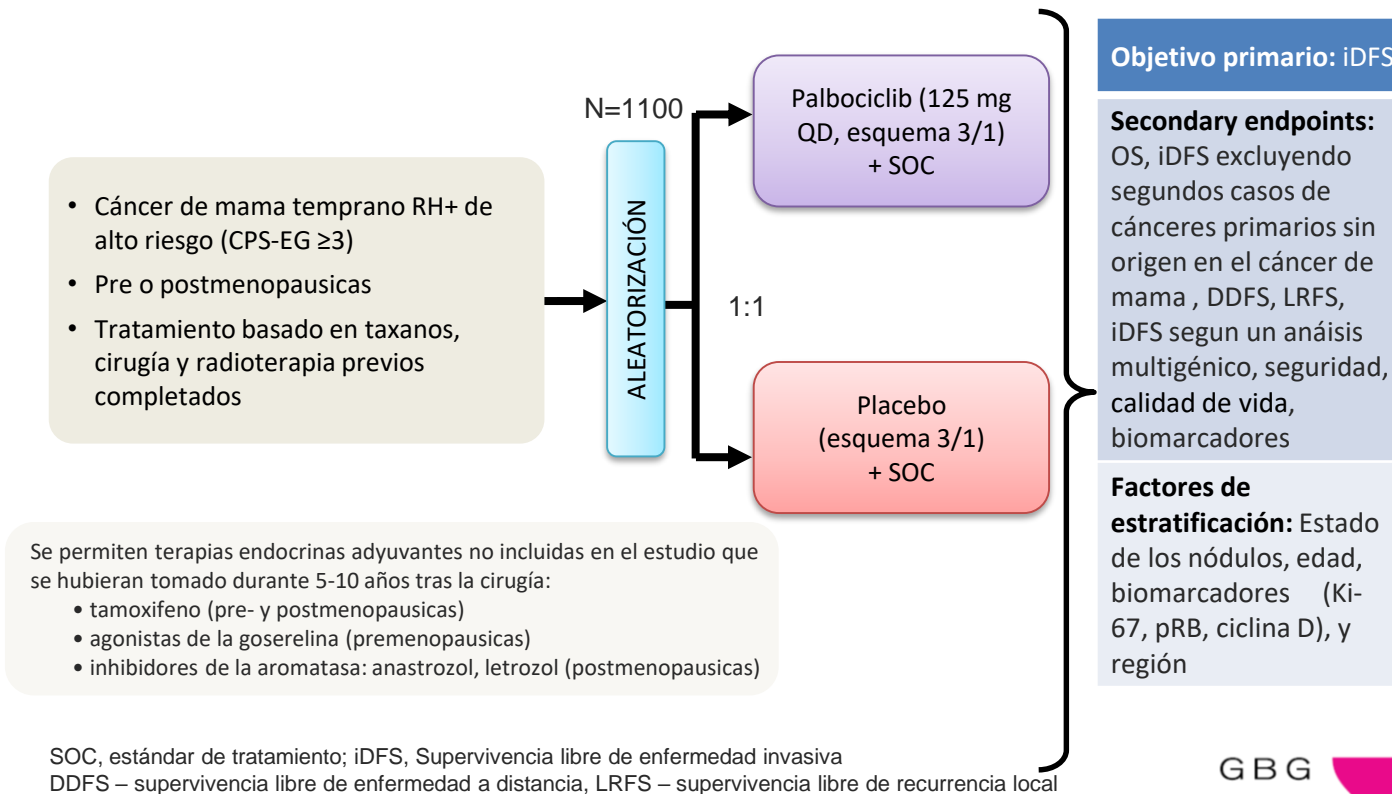
Invasive disease-free survival excluding secondary primary non-breast cancer.
Locoregional recurrences-free survival. Distant recurrence-free survival. Overall survival.
Safety

Recr. Closed Nov 2018

Status: Recruiting. *End of recruitment:* Q4 2018 *Primary completion:* Q3 2020

ClinicalTrials.gov.
<https://clinicaltrials.gov/ct2/show/NCT02513394>

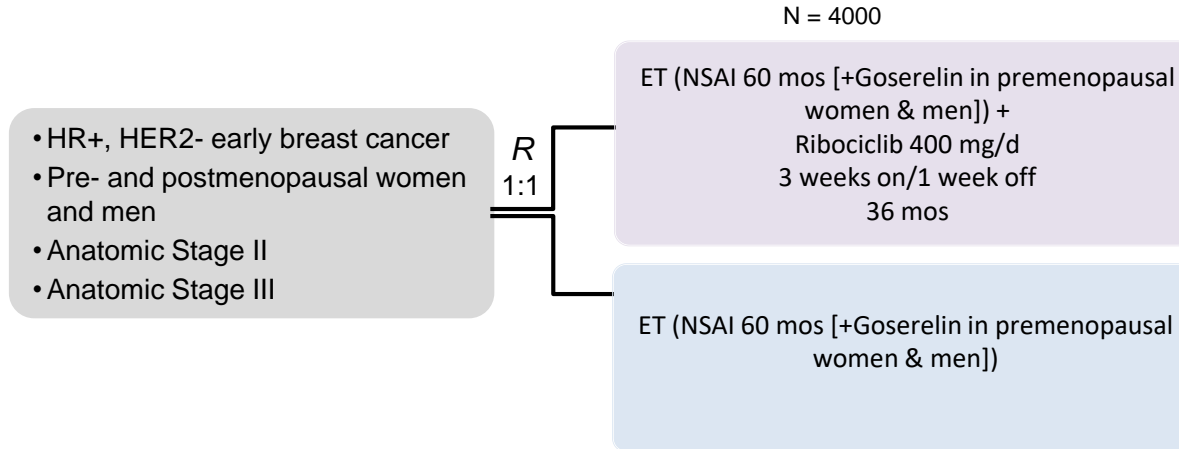
PENELOPE



Status: Recruitment closed. Primary completion: Q4 2020

NATALEE – Study Design

A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer.



End Points

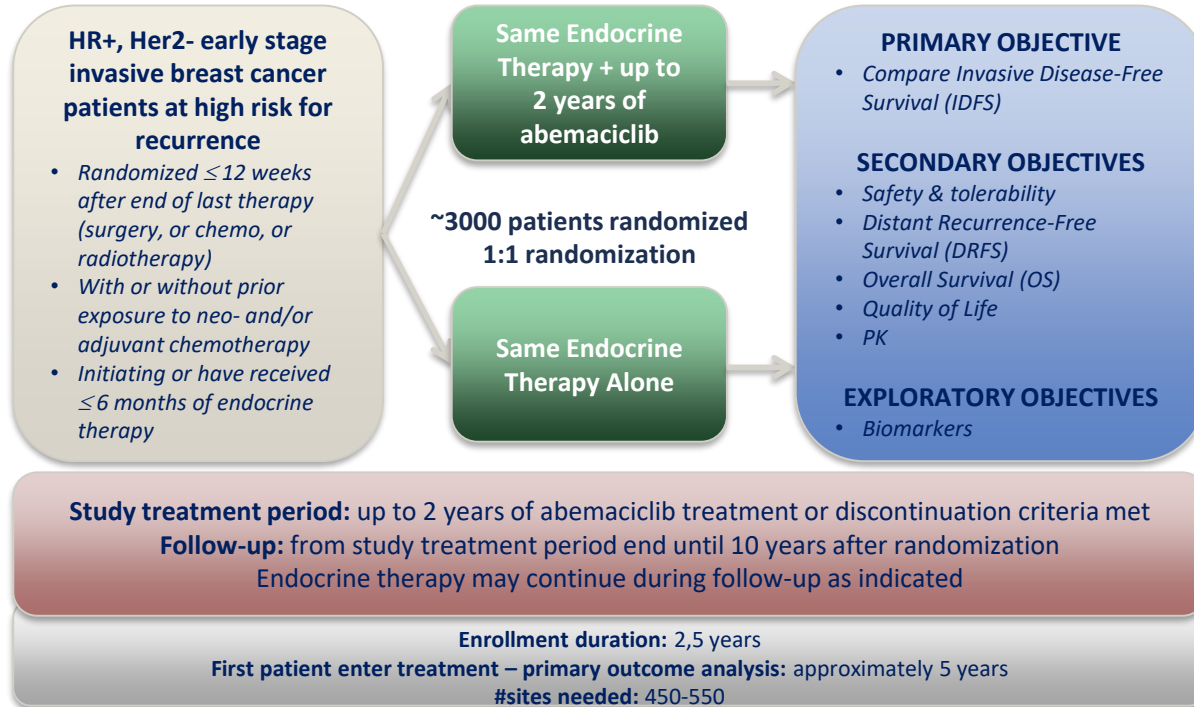
Primary: iDFS

Secondary: RFS, DDFS, OS, QoL, Safety

DDFS, distant disease-free survival; HER2-, human epidermal growth factor receptor-2-negative; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; QoL, quality of life; RFS, recurrence-free survival.

www.clinicaltrials.gov. "Natalee". <https://clinicaltrials.gov/ct2/show/record/NCT03701334> (accessed Nov, 5th, 2018)

MONARCH E: study design



Cyclin inhibitors

Where are we now and
**where are they headed in
the future**

Biomarkers

Breast cancer: HER2+

Toxicity profile

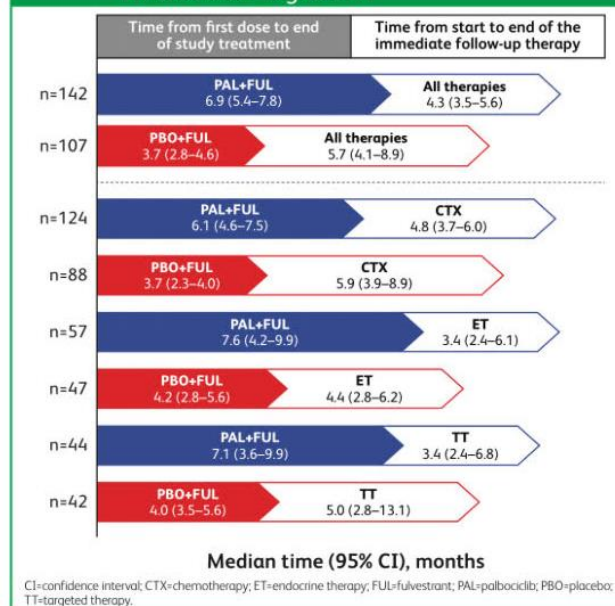
Early disease

After PD/ Resistance

After progression to CDK 4/6 inh: PALOMA3

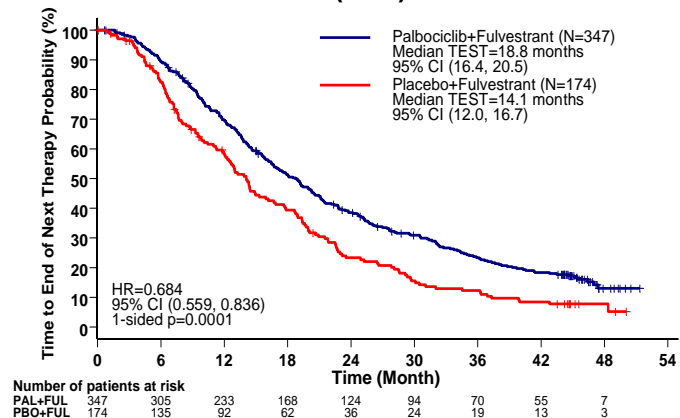
Patients who received ET, CT, or other therapy ANY TIME after progression on study treatment*, n	PAL+LET N=33	LET N=53
Patients who received ET, CT, or other therapy as the first subsequent treatment after progression on study treatment*, n (%)	33 (100.0)	53 (100.0)
Patients who received subsequent ET ANY TIME after progression on study treatment, n (%)	20 (60.6)	38 (71.7)
Time from randomization to first subsequent ET (days, median (range)) [†]	465.5 (239–1100)	368.5 (65–1102)
Duration of first subsequent ET (days, median (range)) [†]	153 (24–592)	151 (16–1135)
Patients who received ET as the first subsequent treatment after progression on study treatment, n (%)	15 (45.5)	32 (60.4)
Time from randomization to first subsequent ET (days) for patients who received ET as the first subsequent treatment, median (range) [§]	428.0 (239–825)	368.5 (65–1102)
Duration of first subsequent ET (days) for patients who received ET as the first subsequent treatment, median (range) [†]	149 (27–478)	151 (16–1135)

Figure 5. Kaplan-Meier Estimates of Treatment Durations For Patients on Poststudy Therapy for Disease Progression

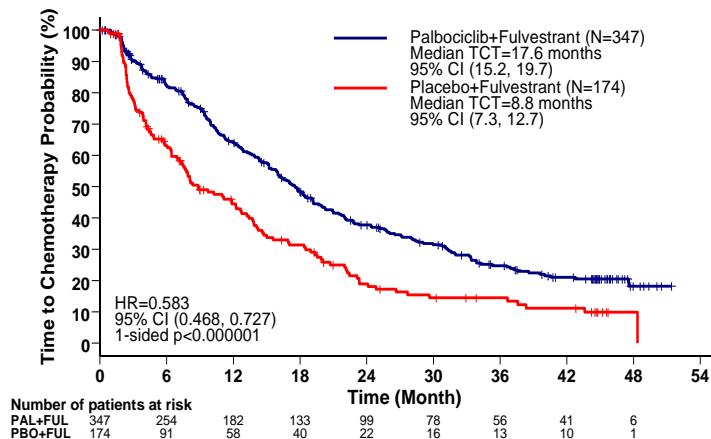


After progression to CDK 4/6 inh: PALOMA3

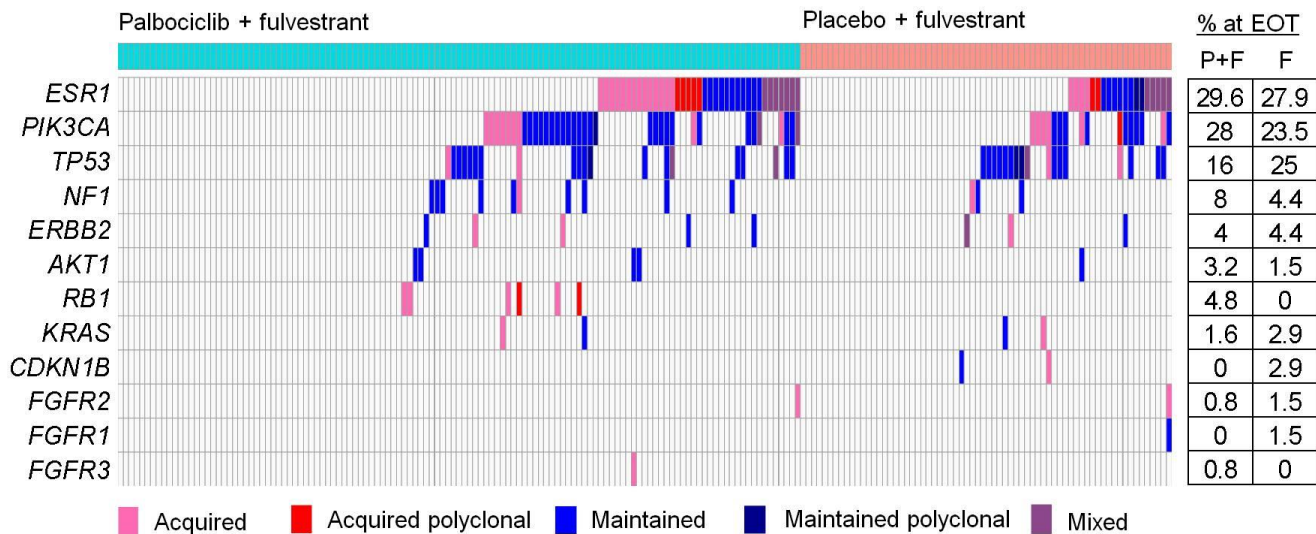
TIME FROM RANDOMIZATION TO END OF IMMEDIATE SUBSEQUENT LINE OF THERAPY POSTPROGRESSION (TEST)



TIME FROM RANDOMIZATION TO POST-PROGRESSION CHEMOTHERAPY (TCT)

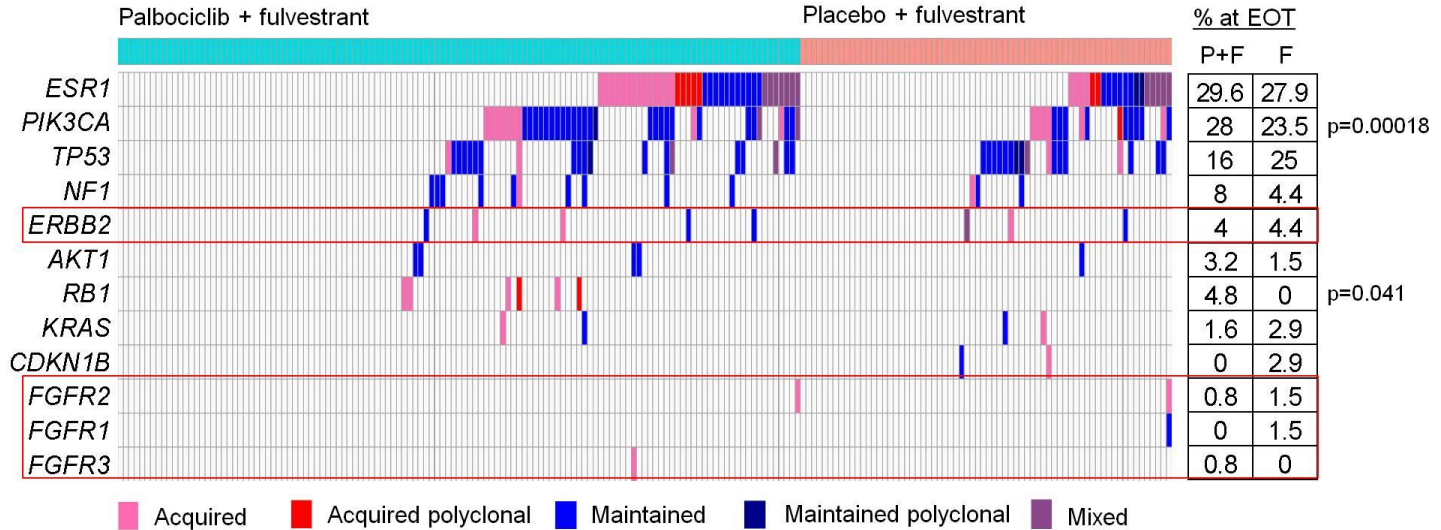


PALOMA3 end of treatment mutation landscape



- Patients with at least 1 acquired mutation(s): - 28.0% (35/125) palbociclib plus fulvestrant
 - 22.1% (15/68) fulvestrant alone

End of treatment growth factor receptor mutations



- Acquired mutations in *ERBB2* 2.1% (4/193) and *FGFR2/3* 1.6% (3/193)

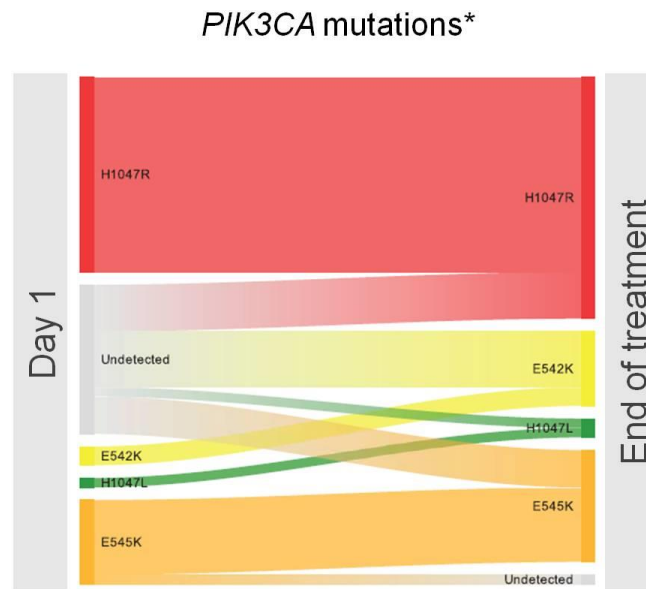
PIK3CA mutations are acquired in both treatment arms

	EOT		
	+	-	
Day 1	+	18.1% (35)	0% (0)
	-	8.3% (16)	73.6% (142)

p = 0.00018

PIK3CA mutations acquired in:

- 7.2% (9/125) patients on palbociclib plus fulvestrant and
- 10.3% (7/68) on fulvestrant alone



PRESENTED AT: **2018 ASCO**
ANNUAL MEETING

#ASCO18
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PRESENTED BY: Nicholas Turner

* both treatment groups combined
p values from McNemar's test

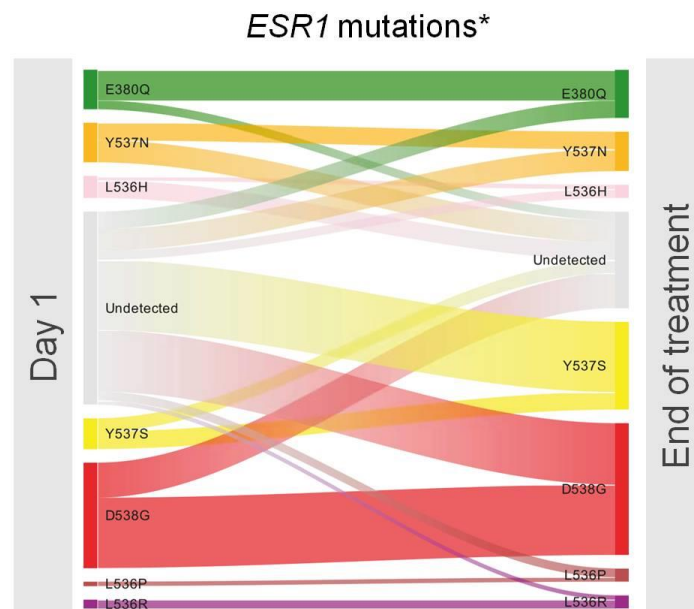
ESR1 mutations are both lost and acquired during treatment

		EOT	
		+	-
Day 1	+	16.1% (31)	6.7% (13)
	-	13.0% (25)	64.2% (124)

p = 0.07

ESR1 mutations acquired in:

- 15.2% (19/125) patients on palbociclib and fulvestrant
- 8.8% (6/68) on fulvestrant alone



PRESENTED AT: **2018 ASCO**
ANNUAL MEETING

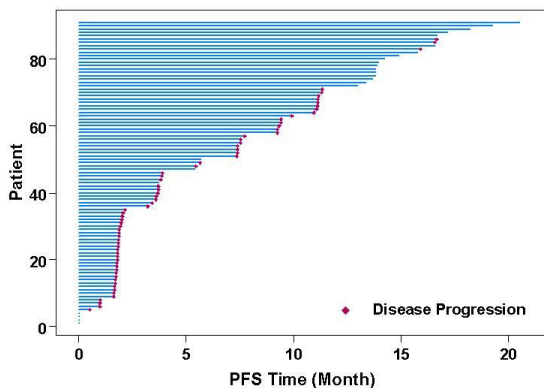
#ASCO18
Slides are the property of the author,
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PRESENTED BY: Nicholas Turner

* both treatment groups combined
p values from McNemar's test

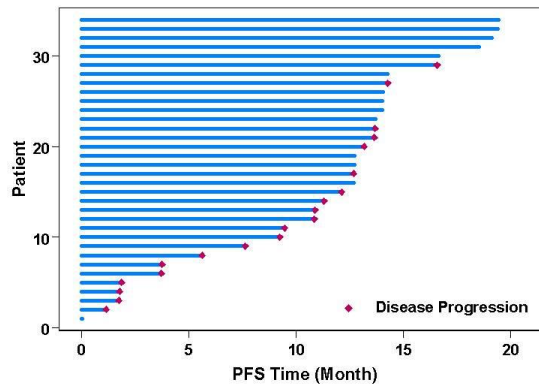
Time on palbociclib plus fulvestrant associates with acquisition of mutations

Patients without acquired mutation at EOT



Median 7.4 months

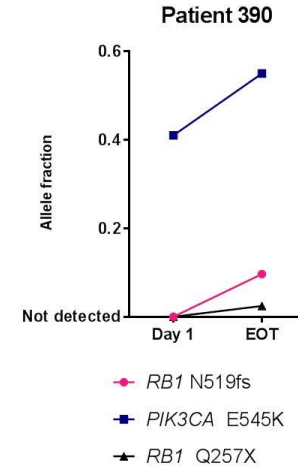
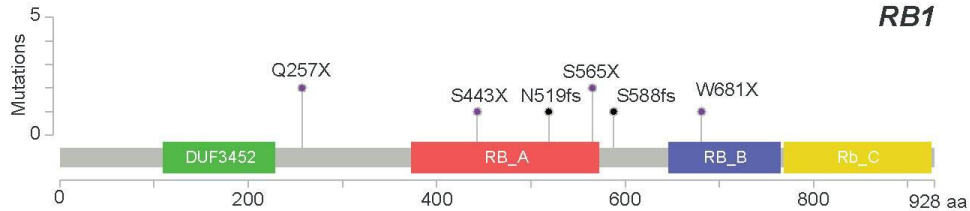
Patients with acquired mutation at EOT



Median 13.6 months

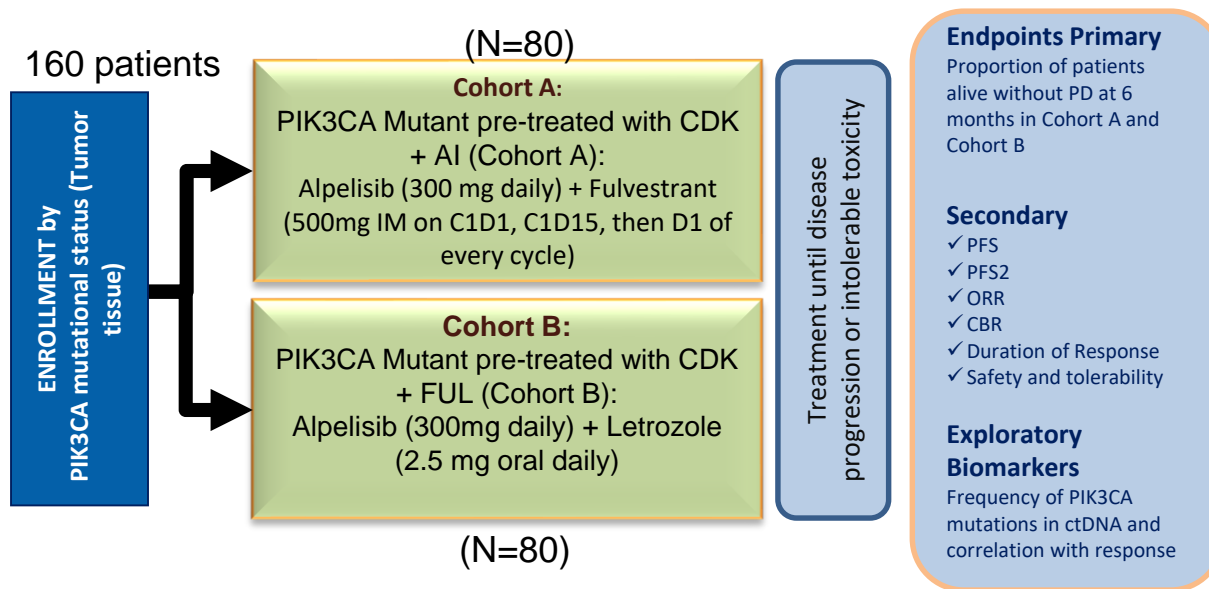
$p = 0.0066$

RB1 mutations are acquired on palbociclib



- No *RB1* mutations were detected at baseline 0% (0/193)
- *RB1* mutations were acquired in 4.8% (6/125) patients on palbociclib and fulvestrant 0% (0/68) on fulvestrant alone
- All *RB1* mutations were detected were truncating

CBYL719X2402 study: Post CDK Sequencing Study Design



Eligible patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after CDK 4/6 inhibitor combination with an AI or fulvestrant.

Cyclin inhibitors: Where are we now and where are they headed in the future

- Significant improvement in PFS, ORR, CBR, (OS non significant) and QL in 1st and 2nd line: New standard
- **Biomarkers:**
 - ER
 - intrinsic subtype
 - ctDNA dynamics
 - sensitivity to prior HT
- **Toxicities:**
 - help to decide based on patient`s characteristics
- **Early disease:**
 - need to wait
 - balance risks / benefit
- **Adquired resistance:**
 - somatic mutations / other
 - role of PIK3CA inhibitors