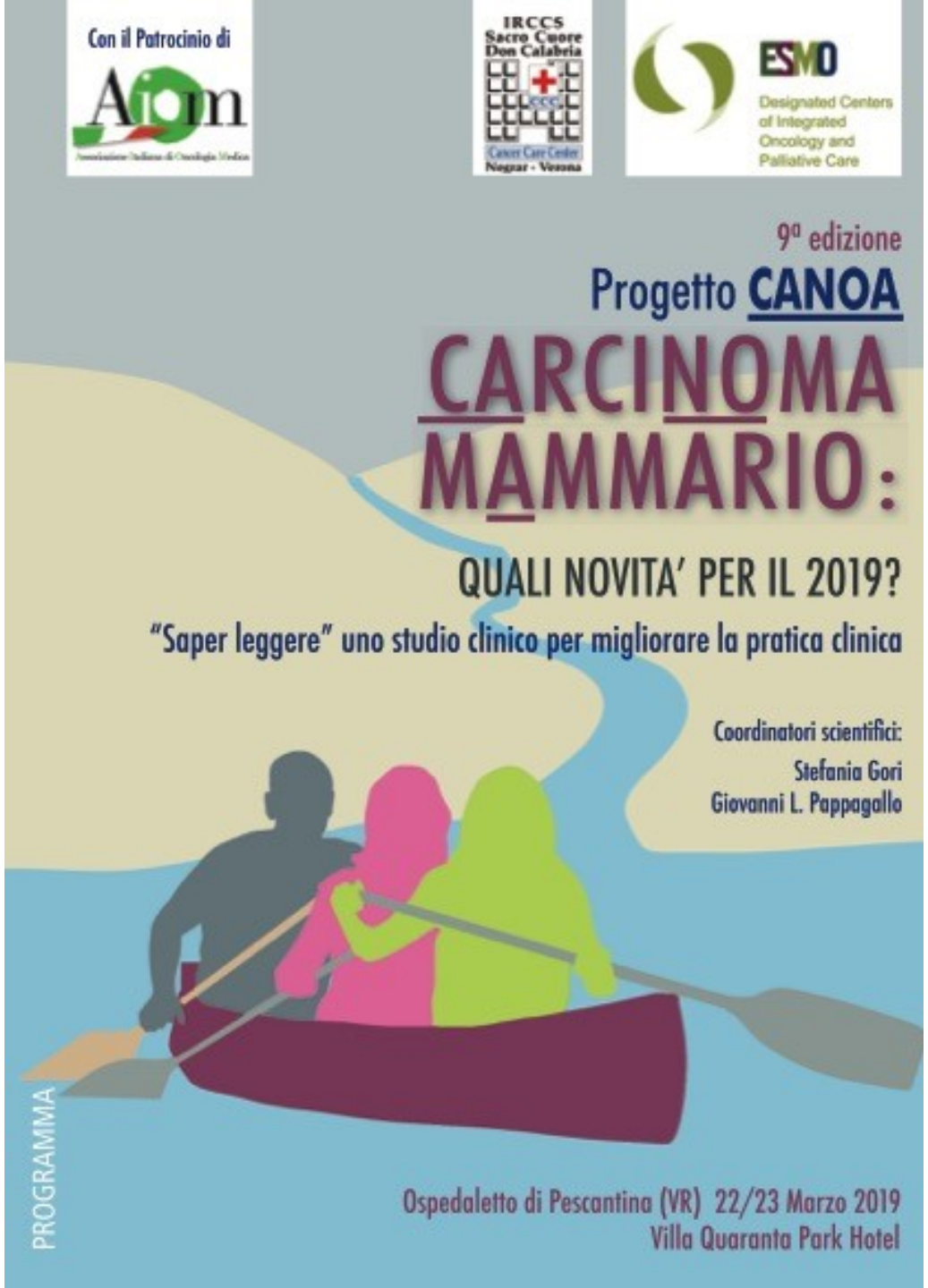


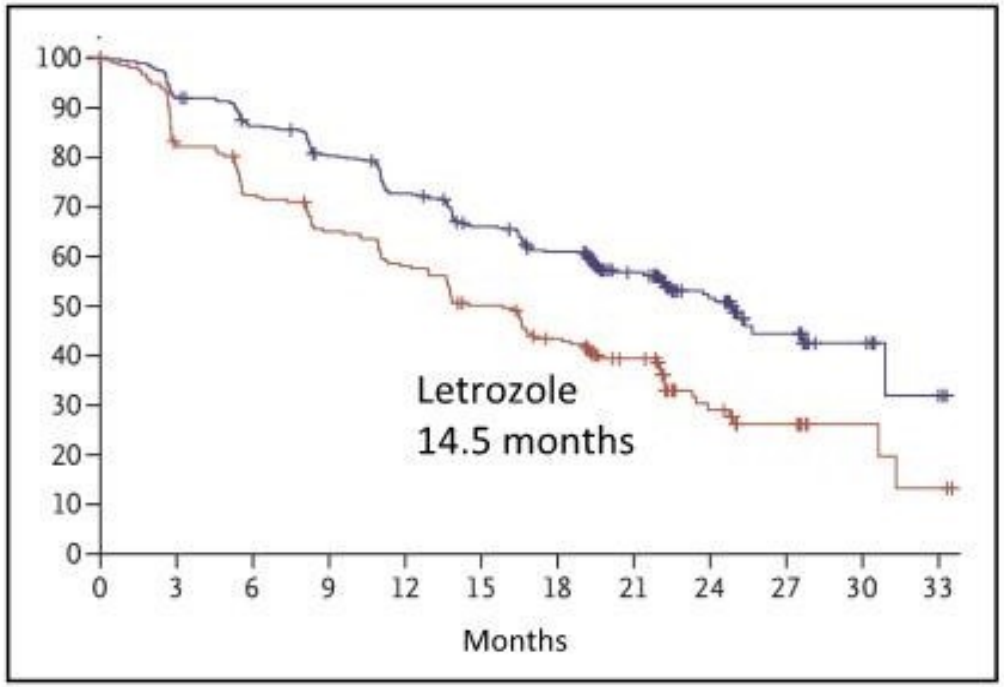
Quale impatto nella pratica clinica

Prof.ssa Grazia Arpino

Università di Napoli Federico II

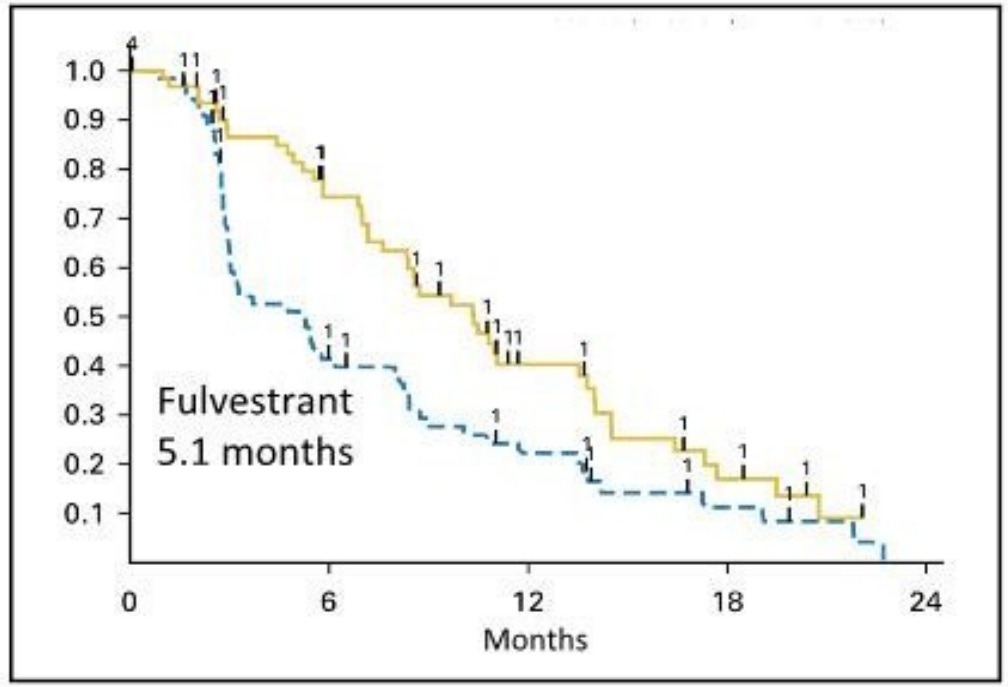
Endocrine therapy resistance is almost inevitable

First line: PALOMA-2



Finn *NEJM* 2016

Second line: PrE0102



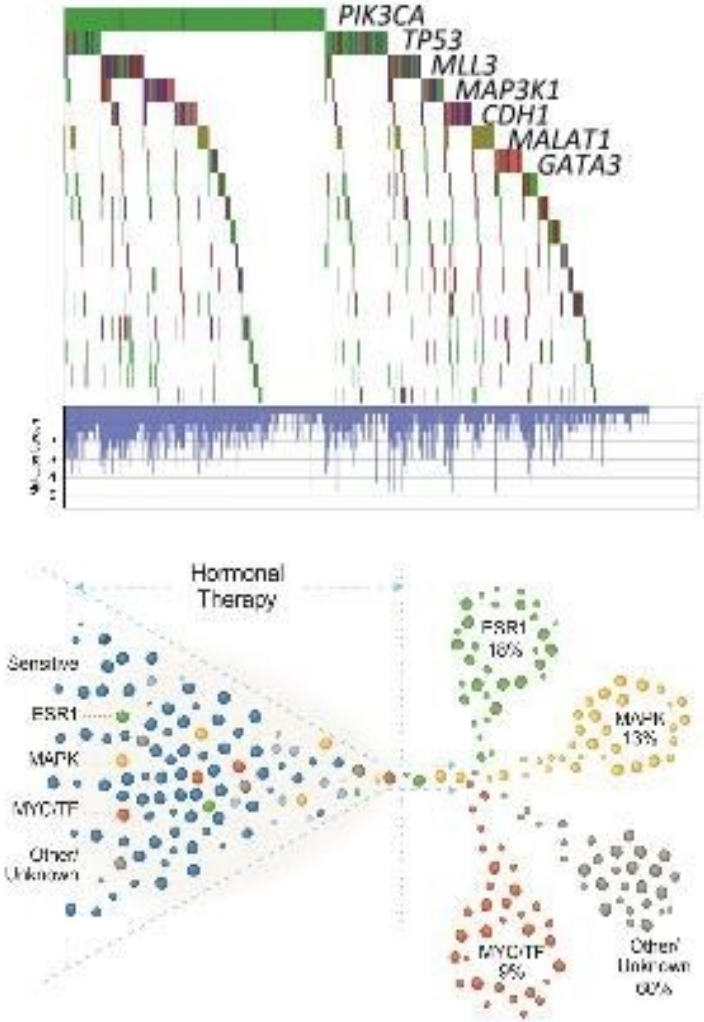
Kornblum *JCO* 2018

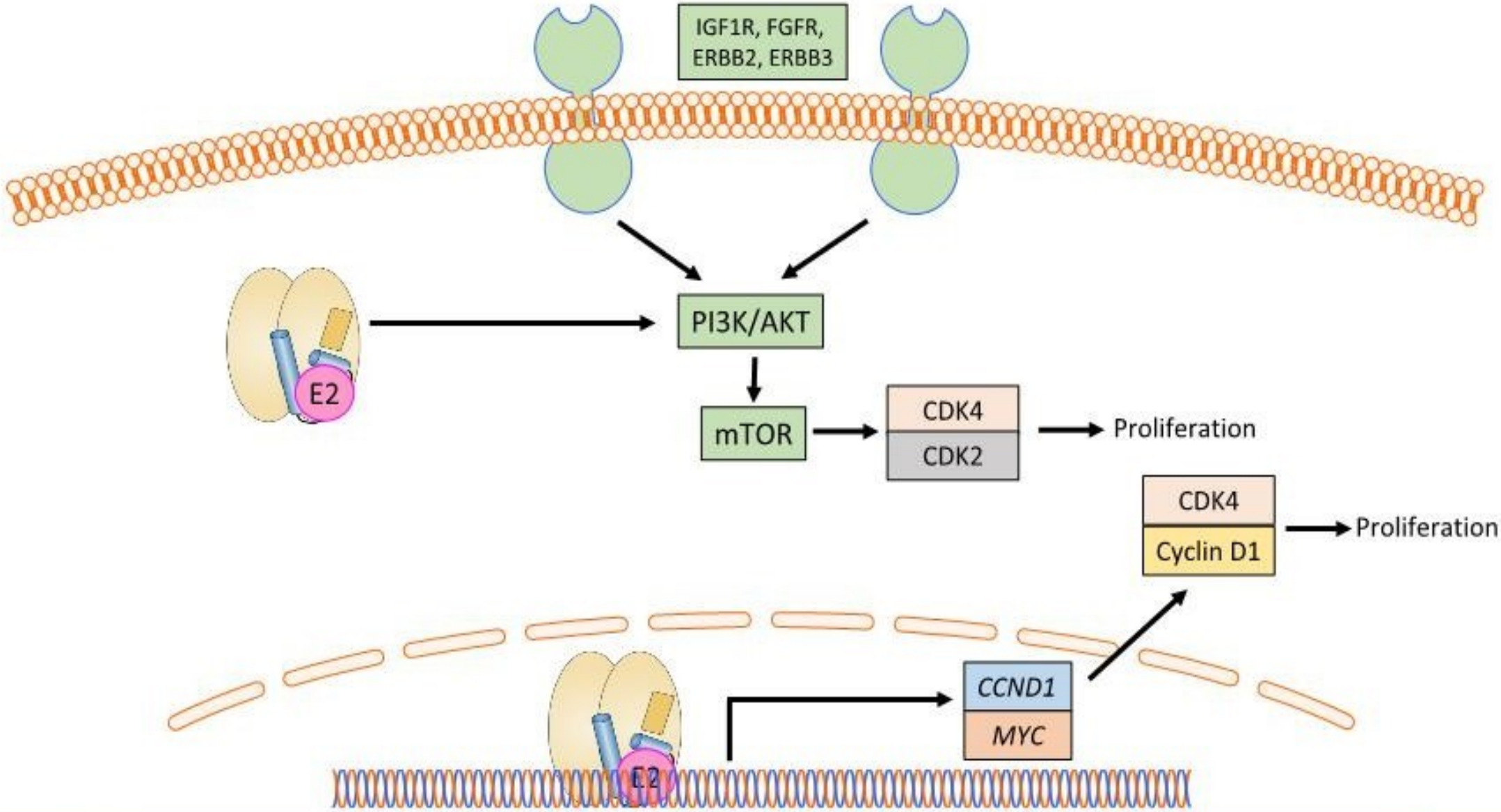
Hormone receptor positive breast cancer is a heterogeneous disease

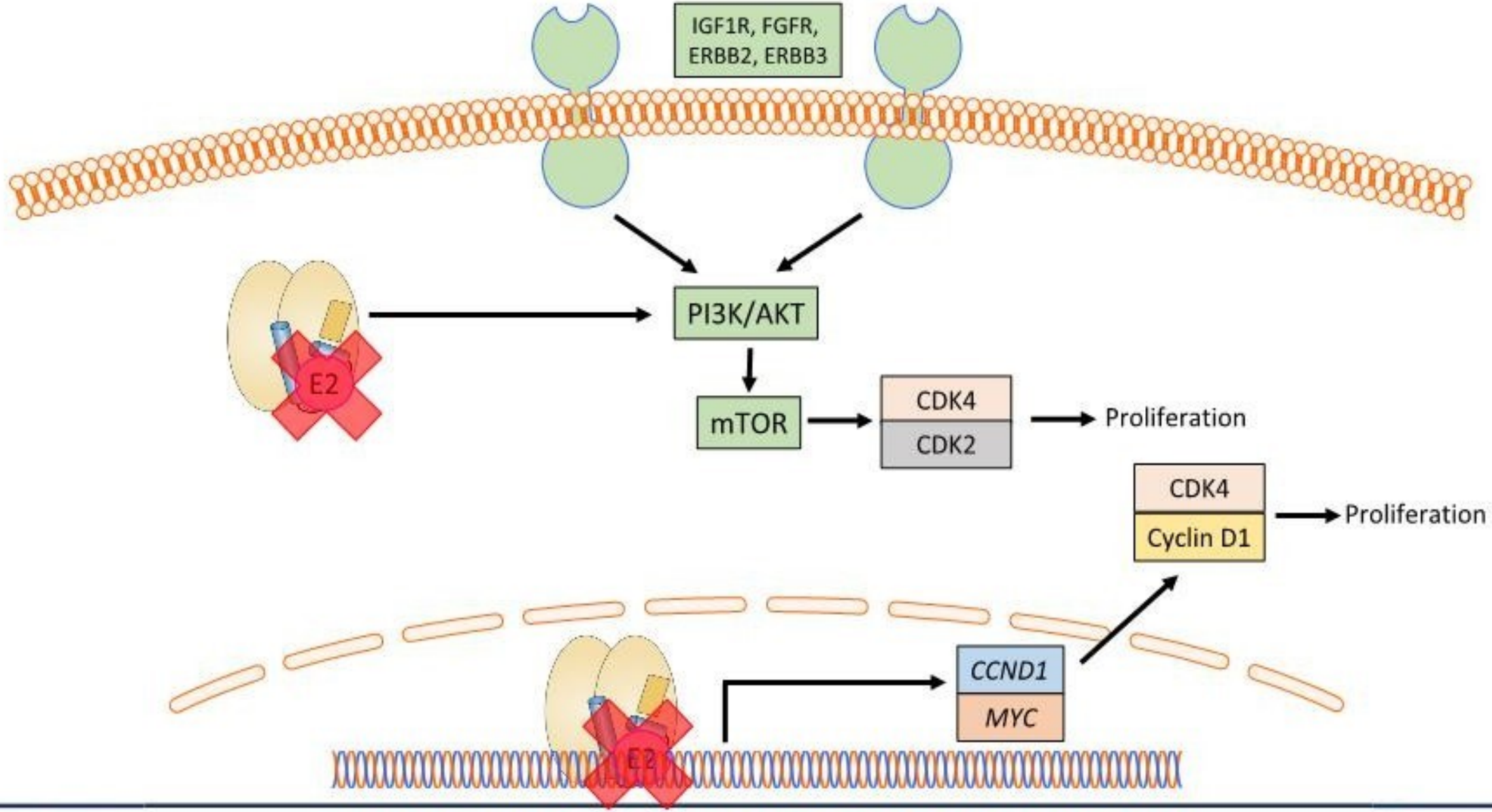
Primary and resistant/metastatic tumors are different entities

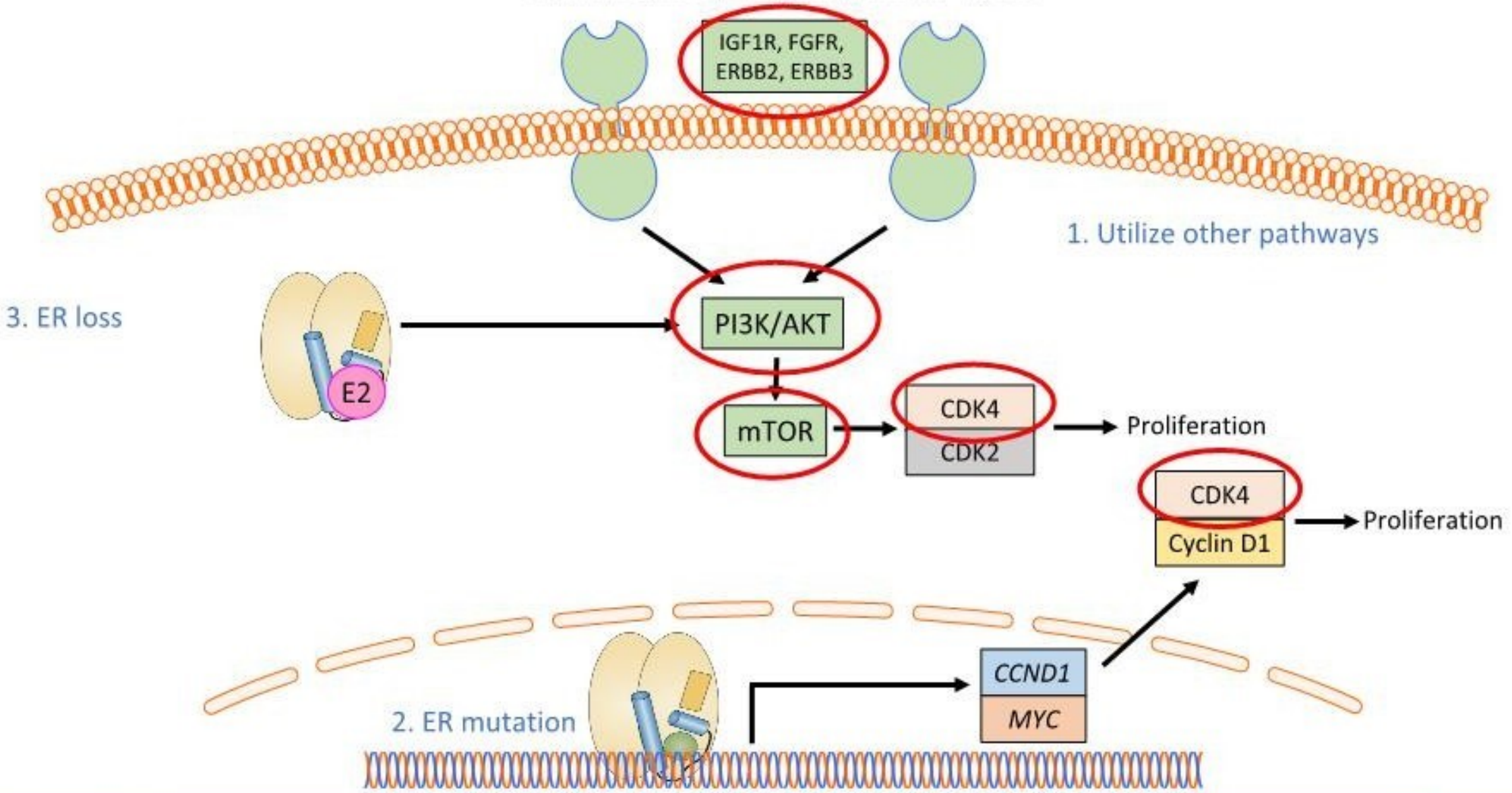
Gene expression

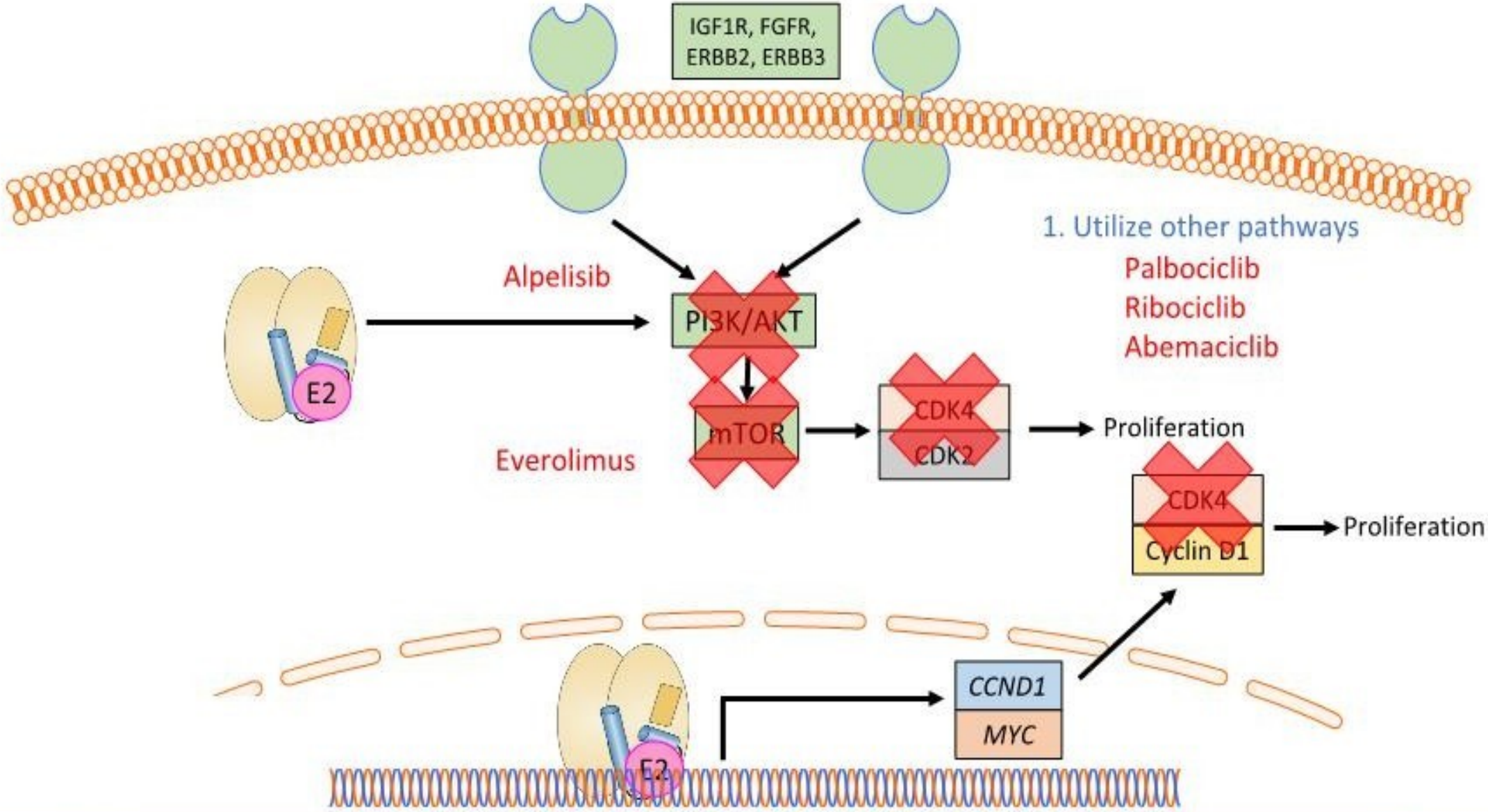
DNA mutations




IGF1R, FGFR,
ERBB2, ERBB3
E2
PI3K/AKT
mTOR
CDK4
CDK2
Proliferation
CDK4
Cyclin D1
Proliferation
CCND1
MYC
E2


IGF1R, FGFR,
ERBB2, ERBB3
PI3K/AKT
E2
mTOR
CDK4
CDK2
Proliferation
CDK4
Cyclin D1
Proliferation
CCND1
MYC
E2


IGF1R, FGFR,
ERBB2, ERBB3
1. Utilize other pathways
3. ER loss
E2
PI3K/AKT
mTOR
CDK4
CDK2
Proliferation
CDK4
Cyclin D1
Proliferation
2. ER mutation
CCND1
MYC


IGF1R, FGFR,
ERBB2, ERBB3
1. Utilize other pathways
Palbociclib
Ribociclib
Abemaciclib
Alpelisib
PI3K/AKT
E2
mTOR
Everolimus
CDK4
CDK2
Proliferation
CDK4
Cyclin D1
Proliferation
CCND1
MYC
E2

The Importance of the PI3K Pathway in HR+ Breast Cancer

- The PI3K pathway is frequently altered in HR+ breast cancer and has been implicated in resistance to endocrine therapies[1,2]
- Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signaling has been shown to promote estrogen-independent growth of ER+ breast cancer cells,[6,7] and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[8]

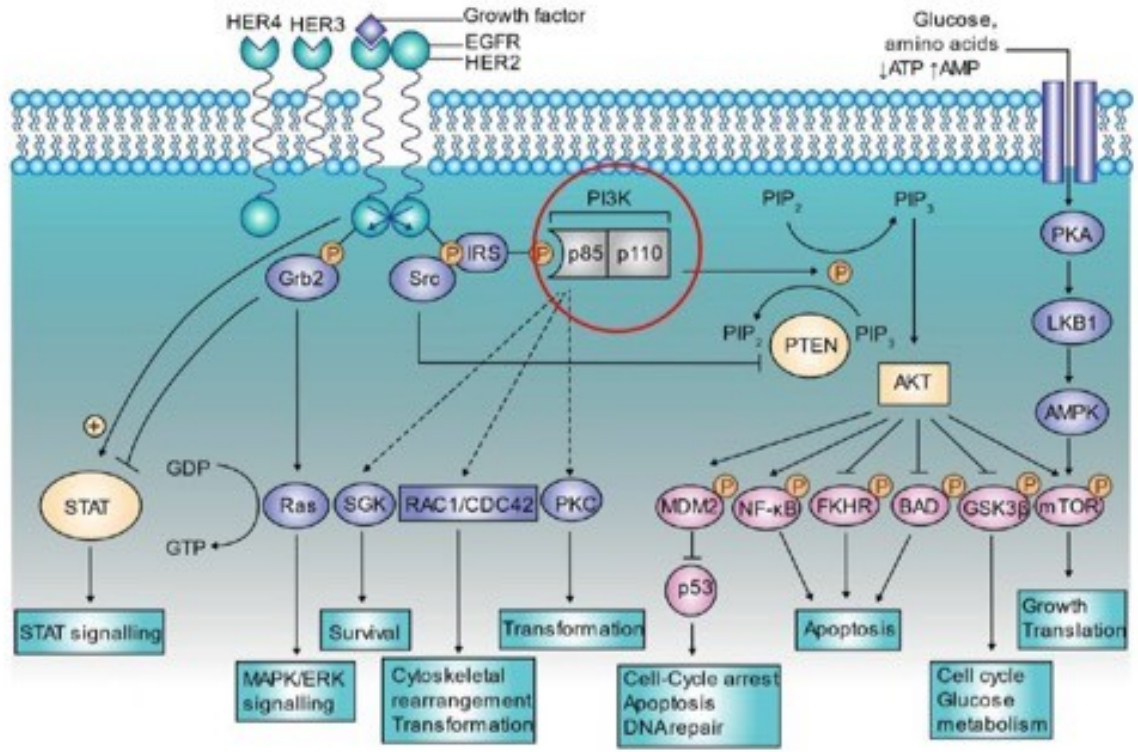
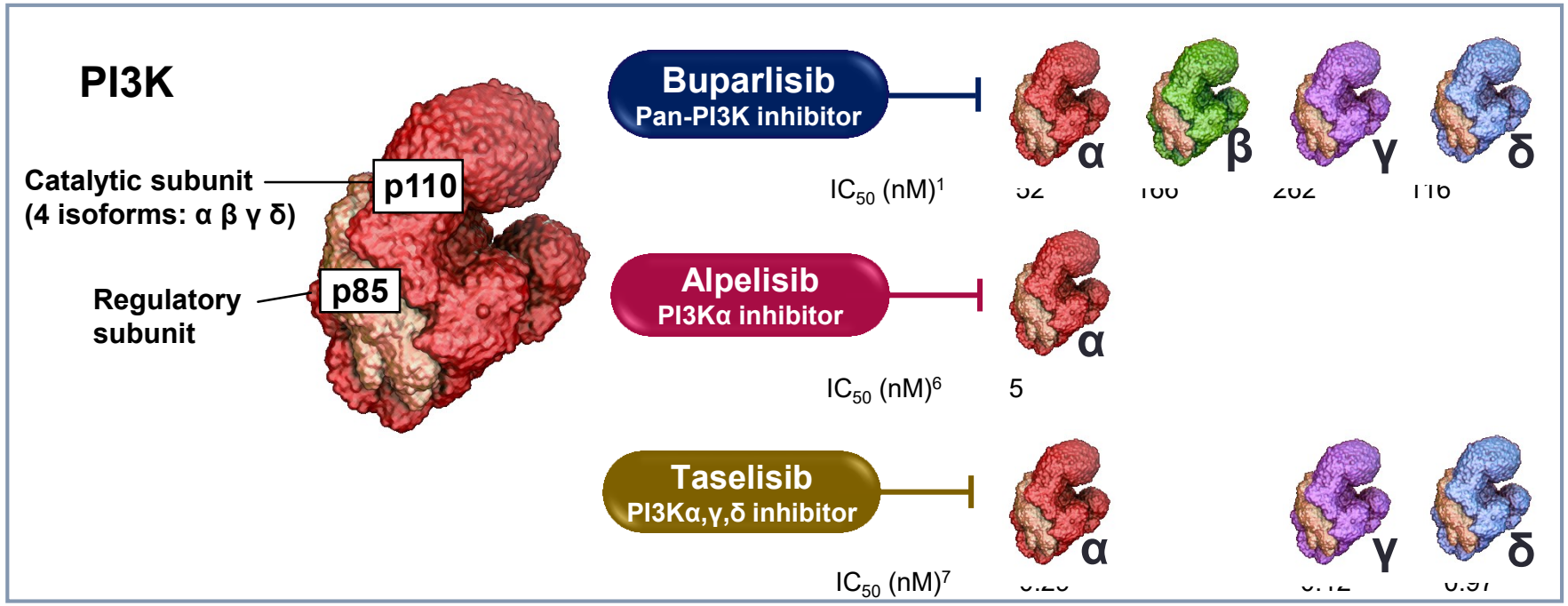


Figure reprinted by permission from Springer Nature: *Nature Reviews Drug Discovery*. Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery. Hennessy BT, et al. *Nat Rev Drug Discov*. 2005 Dec;4(12):988-1004. © 2005.

ER+, estrogen receptor-positive; HR+, hormone receptor-positive; P13K, phosphatidylinositol 3-kinase.

1. Miller TW, et al. *J Clin Oncol*. 2011;29(33):4452-4461. 2. Bosch A, et al. *Sci Transl Med*. 2015;7(283):283ra51. 3. Mayer IA, et al. *Clin Cancer Res*. 2017;23(1):26-34. 4. Loi S, et al. *Proc Natl Acad Sci U S A*. 2010;107(22):10208-10213. 5. Stemke-Hale K, et al. *Cancer Res*. 2008;68(15):6084-6091. 6. Miller TW, et al. *J Clin Invest*. 2010;120(7):2406-2413. 7. Crowder RJ, et al. *Cancer Res*. 2009;69(9):3955-3962. 8. Miller TW, et al. *Cancer Discovery*. 2011;1(4):338-351.

PI3K Inhibitors in Late Stage Clinical Development

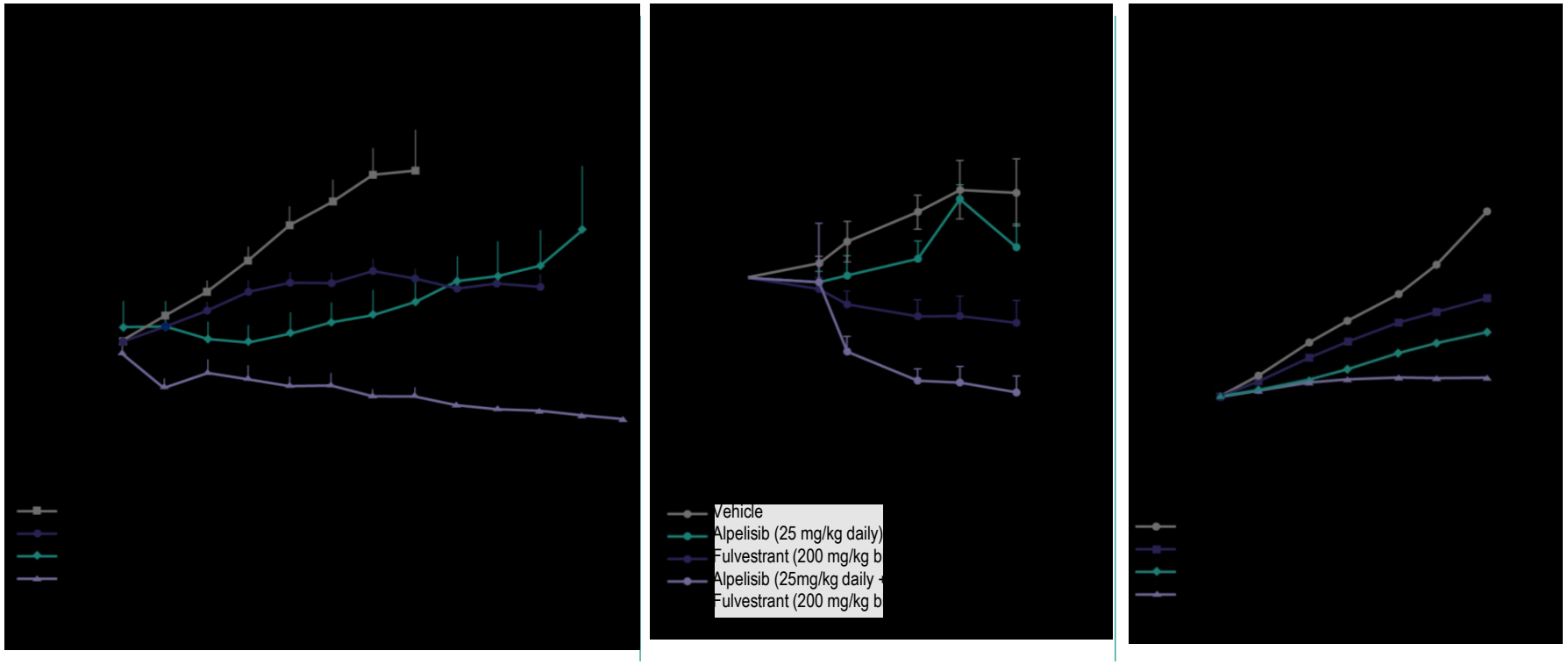


- Targeting all class I isoforms may ensure broad activity in tumors with a range of molecular drivers[2–5]
- Isoform-specific inhibitors may reduce off-target toxicity[5,6]

IC_{50}, half maximal inhibitory concentration

1. Maira SM *et al. Mol Cancer Ther* 2012;11:317–28; 2. Liu P *et al. Nat Rev Drug Discov* 2009;8:627–44; 3. Kang S *et al. Proc Natl Acad Sci U S A* 2006;103:1289–94; 4. Hernandez-Aya LF *et al. Oncologist* 2011;16:404–14; 5. Jia S *et al. Curr Opin Cell Biol* 2009;21:199–208; 6. Fritsch C *et al. Mol Cancer Ther 2014;13 1117-29*;
7. Ndubaku CO *et al. J Med Chem* 2013;56:4597–610

PI3K Inhibitors Demonstrate *in vivo* Anti-tumor Activity in Combination with Fulvestrant



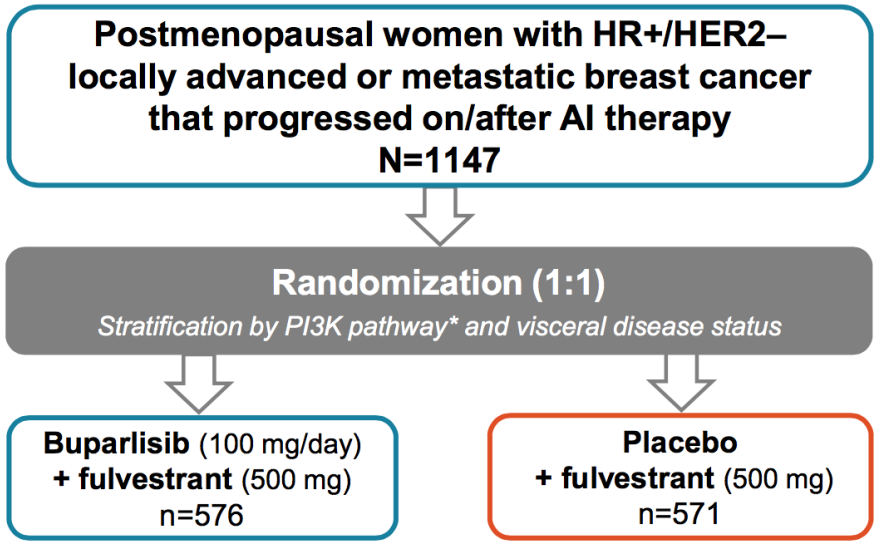
Combination with fulvestrant shows greater anti-tumor activity than either agent alone in MCF7 breast cancer xenograft models[1–3]

1. Miller TW *et al. Cancer Discov* 2011;1:338–351. 2. Bosch A *et al. Sci Transl Med* 2015;7:283ra51. 3. Taselisib, RO5537381 - F. Hoffmann-La Roche Ltd

Clinical development of Buparlisib

BELLE-2 Trial

BELLE-2 Study Design and Endpoints



Primary Endpoints

- **PFS** in the full population
- **PFS** in the main population (PI3K activated and non-activated, excluding status unknown*)
- **PFS** in the PI3K activated group* (*PIK3CA* mutation and/or PTEN loss)

Key Secondary Endpoint

- **Overall survival**

Other Secondary Endpoints

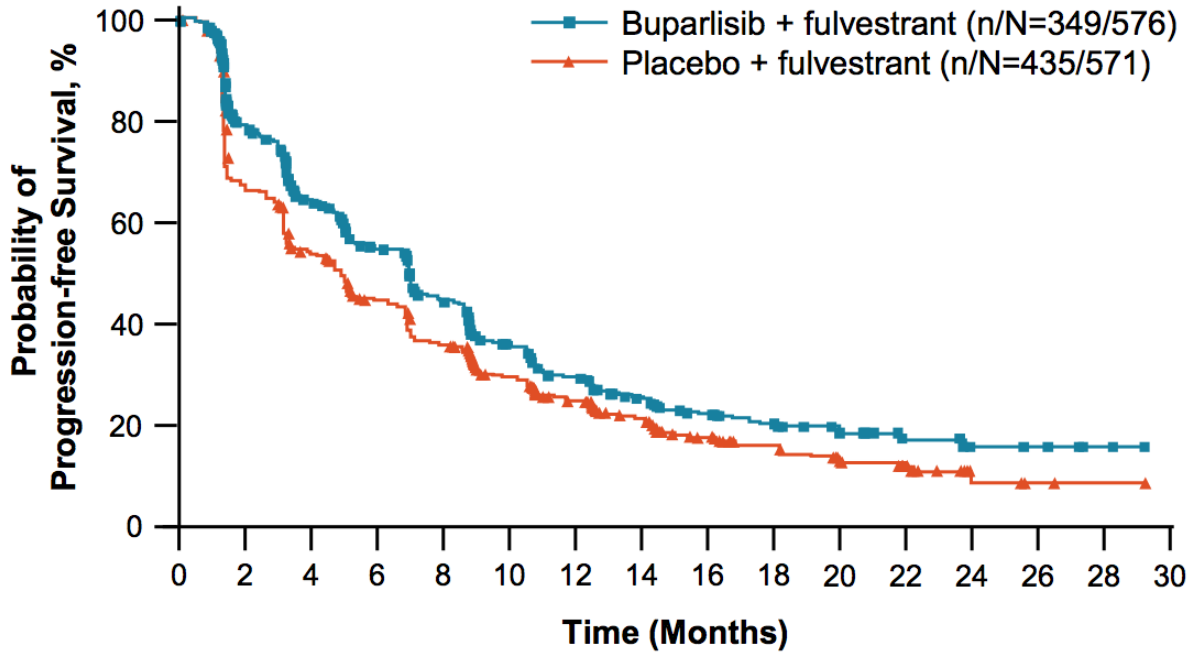
- **Overall response rate**
- **Clinical benefit rate**
- **Safety, pharmacokinetics, quality of life**

Exploratory Endpoint

- **PFS** by ctDNA *PIK3CA* mutation status†

Baselga et al. SABCS 2015

BELLE-2 Trial
Overall Results



Full Population (N=1147)	Buparlisib + Fulvestrant n=576	Placebo + Fulvestrant n=571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided *P* value	<0.001	

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided *P* value 0.003)
- Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

Baselga et al. SABCS 2015

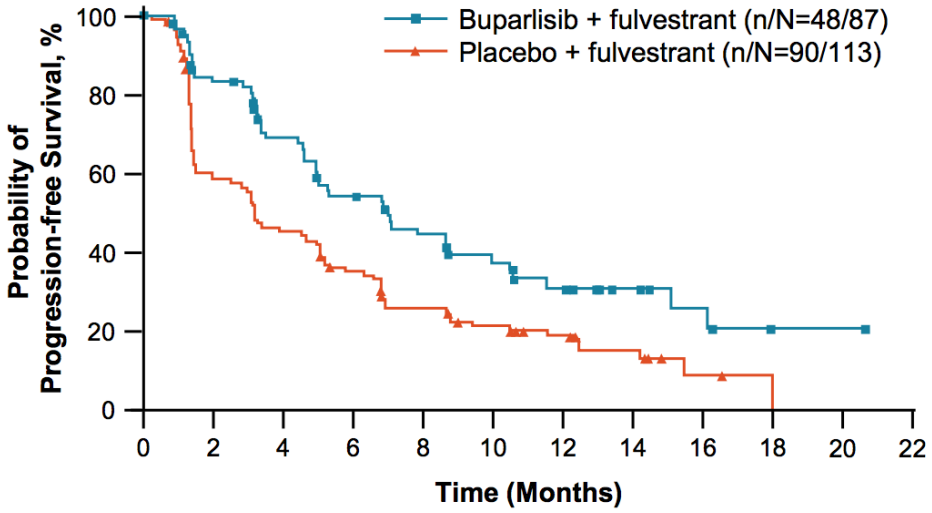
BELLE-2 Trial

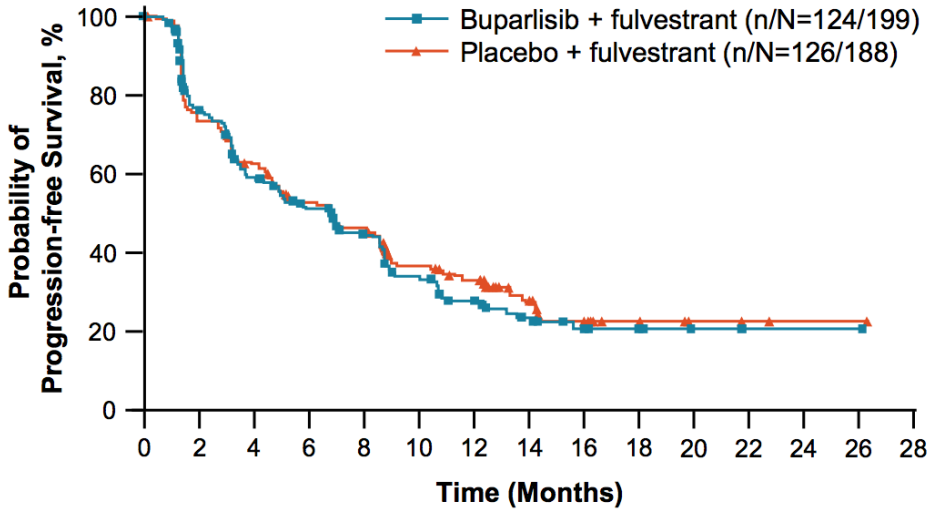
PFS according to PiK3CA status on ctDNA

ctDNA: circulating tumor DNA

ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	

ctDNA *PIK3CA* Non-mutant n=387	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	0.642	



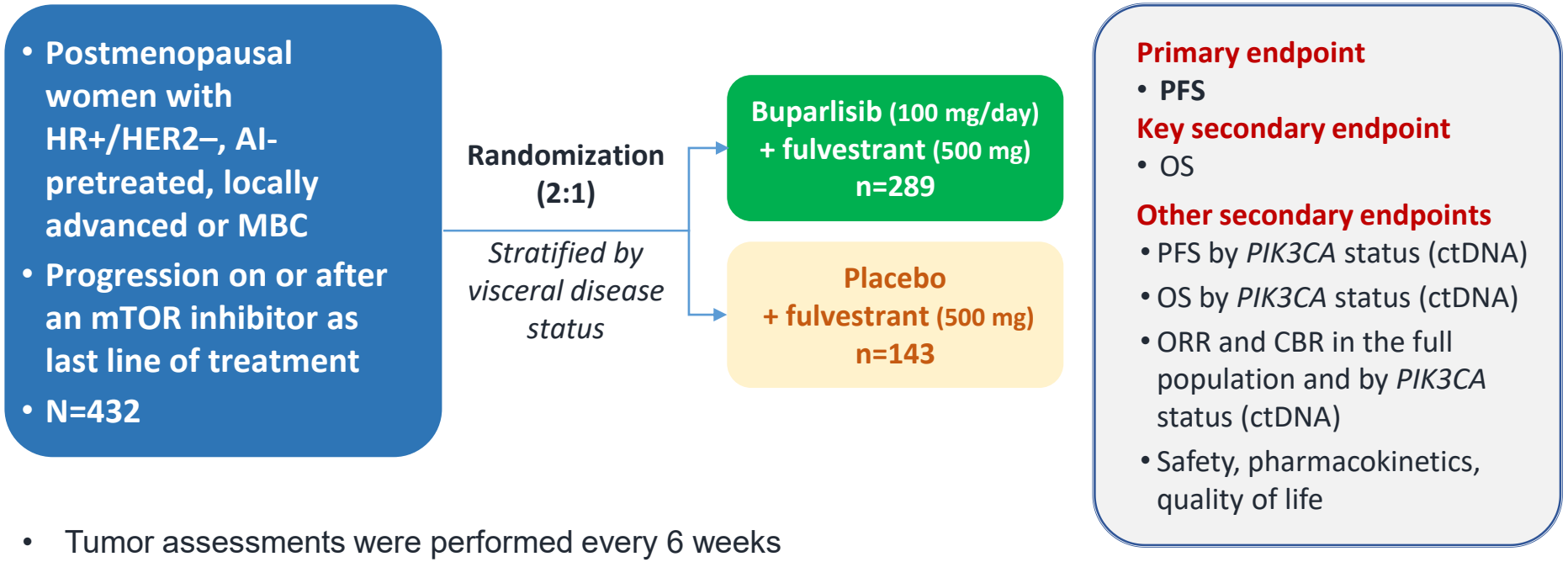


First evidence of potential utility for liquid biopsy in metastatic breast cancer!

Baselga et al. SABCS 2015

Clinical development of Buparlisib

BELLE-3 Trial

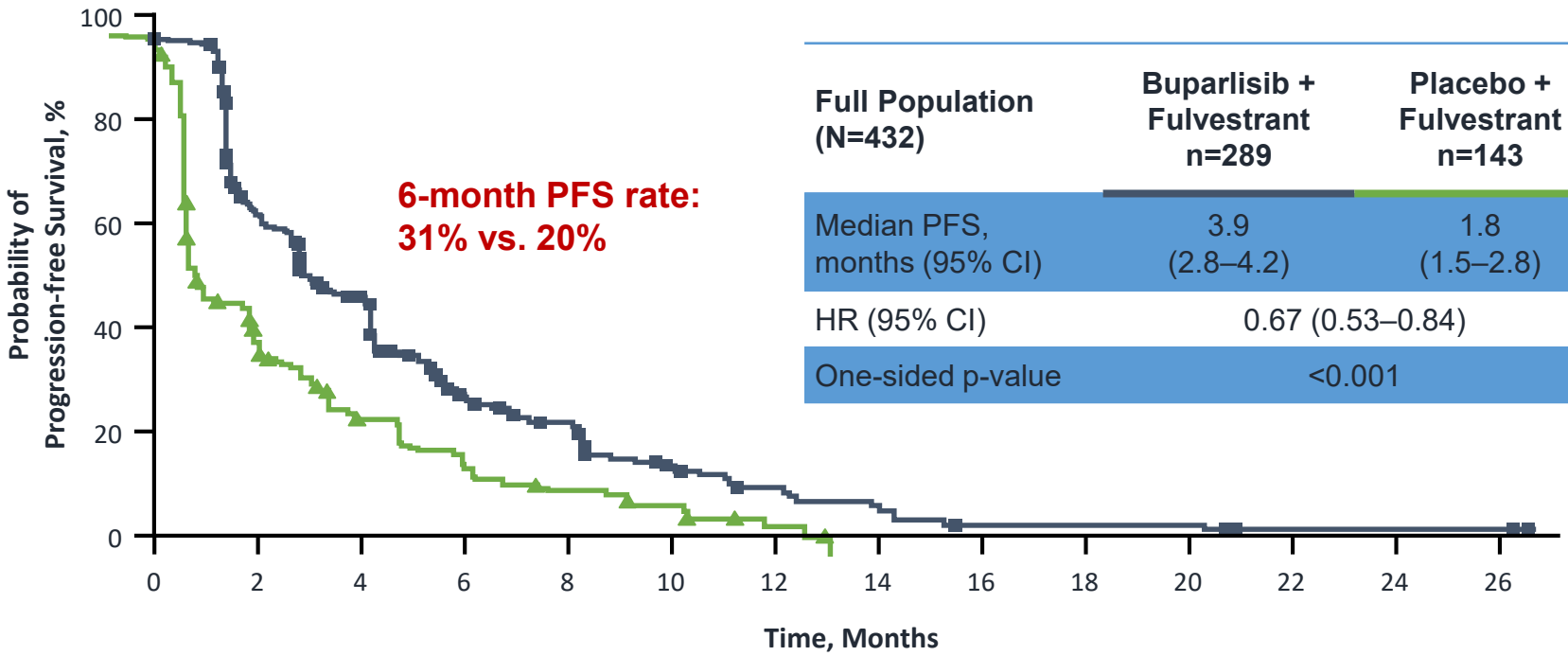


- Tumor assessments were performed every 6 weeks
- 90% power to detect a 33% risk reduction in PFS (disease progression or death) at one-sided α=0.025, based on the observation of 313 PFS events

AI, aromatase inhibitor; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors. BELLE-3: ClinicalTrials.gov NCT01633060.

Di Leo et al. SABCS 2016

BELLE-3 Trial
Overall Results



Full Population (N=432)	Buparlisib + Fulvestrant n=289	Placebo + Fulvestrant n=143
Median PFS, months (95% CI)	3.9 (2.8–4.2)	1.8 (1.5–2.8)
HR (95% CI)	0.67 (0.53–0.84)	
One-sided p-value	<0.001	

PFS results by independent central review were consistent with local assessment:

HR 0.57 (95% CI: 0.44–0.74; one-sided p<0.001)

Di Leo et al. SABCS 2016

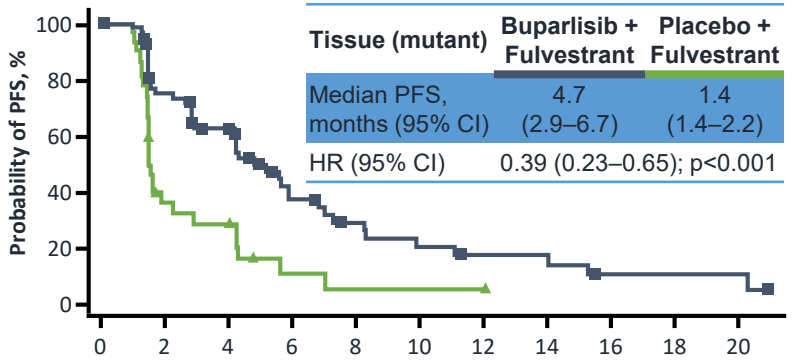
BELLE-3 Trial

PFS according to PIK3CA status

Primary tumor tissue (PCR) N=321

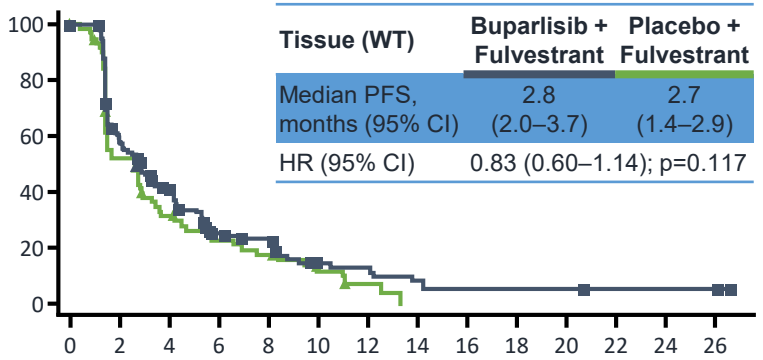
PIK3CA mutant: 34%

Mutant



Tissue (mutant)	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	4.7 (2.9–6.7)	1.4 (1.4–2.2)
HR (95% CI)	0.39 (0.23–0.65); p<0.001	

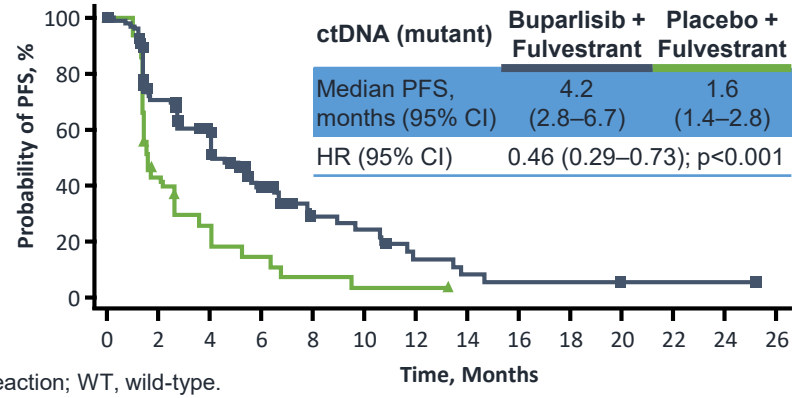
Wild-type



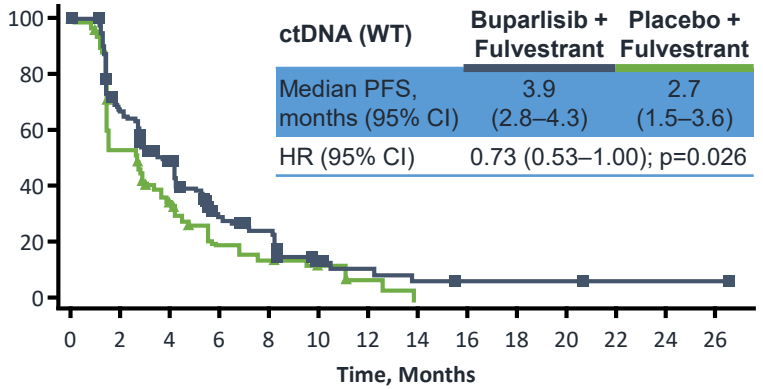
Tissue (WT)	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	2.8 (2.0–3.7)	2.7 (1.4–2.9)
HR (95% CI)	0.83 (0.60–1.14); p=0.117	

ctDNA samples at study entry (BEAMing) N=348

PIK3CA mutant: 39%



ctDNA (mutant)	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	4.2 (2.8–6.7)	1.6 (1.4–2.8)
HR (95% CI)	0.46 (0.29–0.73); p<0.001	

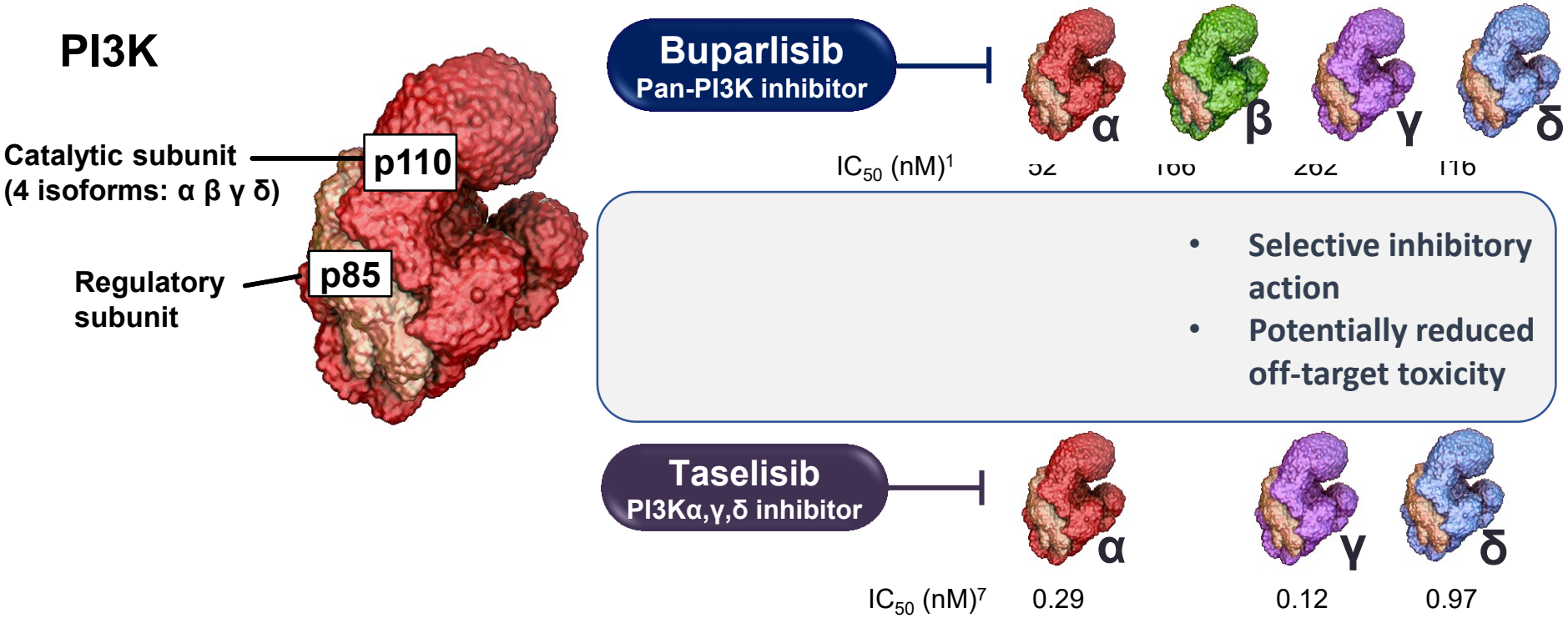


ctDNA (WT)	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	3.9 (2.8–4.3)	2.7 (1.5–3.6)
HR (95% CI)	0.73 (0.53–1.00); p=0.026	

PCR, polymerase chain reaction; WT, wild-type.
p-values are one-sided.

Di Leo et al. SABCS 2016

Pi3K inhibitors



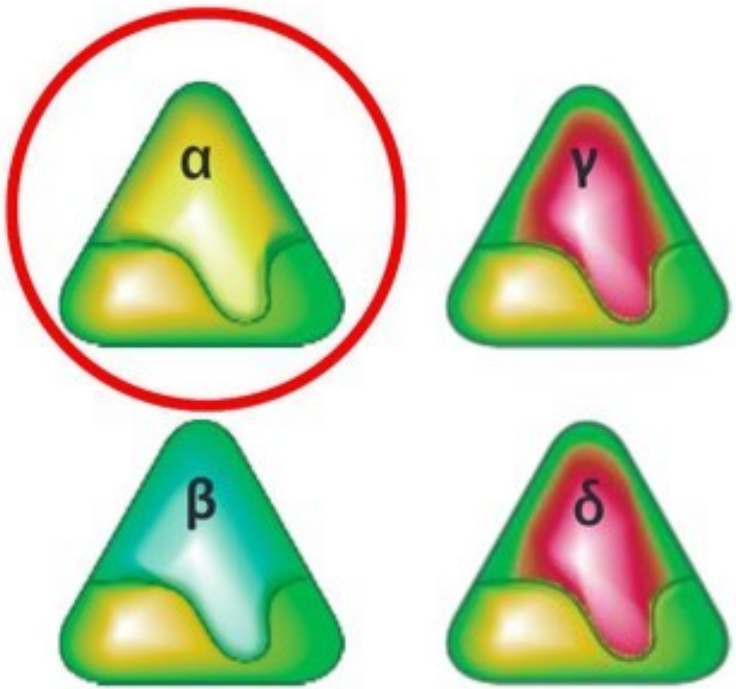
Targeting all class I isoforms may ensure broad activity in tumors with a range of molecular drivers[2–5]
Isoform-specific inhibitors may reduce off-target toxicity[5,6]

IC_{50}, half maximal inhibitory concentration

1. Maira SM *et al. Mol Cancer Ther* 2012;11:317–28; 2. Liu P *et al. Nat Rev Drug Discov* 2009;8:627–44; 3. Kang S *et al. Proc Natl Acad Sci U S A* 2006;103:1289–94;
4. Hernandez-Aya LF *et al. Oncologist* 2011;16:404–14; 5. Jia S *et al. Curr Opin Cell Biol* 2009;21:199–208; 6. Fritsch C *et al. Mol Cancer Ther 2014;13 1117-29*;
7. Ndubaku CO *et al. J Med Chem* 2013;56:4597–610

Selective Inhibition of PI3K-alpha Is a Promising Strategy in *PIK3CA*-Mutated Cancers

PI3K isoforms[1]

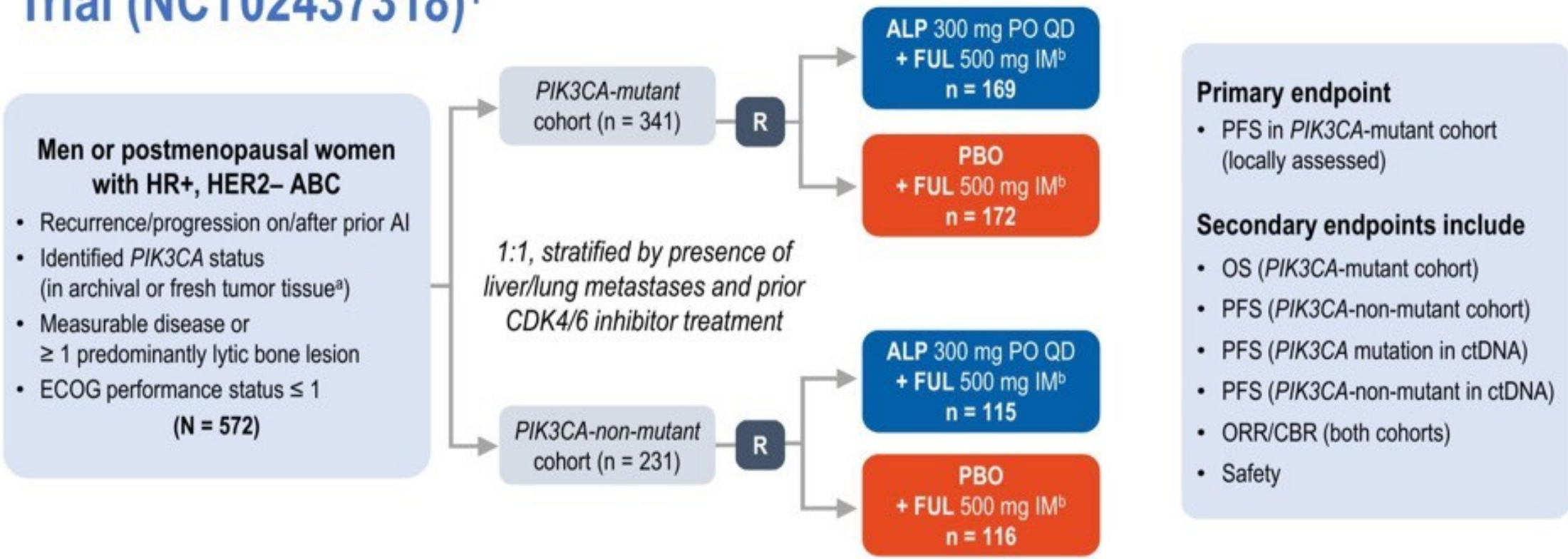


- While pan-PI3K and β-sparing inhibitors target multiple isoforms, alpelisib (BYL719) specifically targets the α-isoform[2]
- Alpelisib has demonstrated antitumor activity in preclinical models harboring *PIK3CA* alterations[2]
- In a phase 1b trial, alpelisib + fulvestrant provided a 9.1-mo median PFS in heavily pretreated patients with ER+ ABC and positive *PIK3CA* mutation status[3]

ABC, advanced breast cancer; ER+, estrogen receptor-positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral]. 2. Fritsch C, et al. *Mol Cancer Ther*. 2014;13(5):1117-1129. 3. Juric D, et al. *JAMA Oncol*. 2018;In press.

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)[1]



Primary endpoint

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

Secondary endpoints include

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

- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

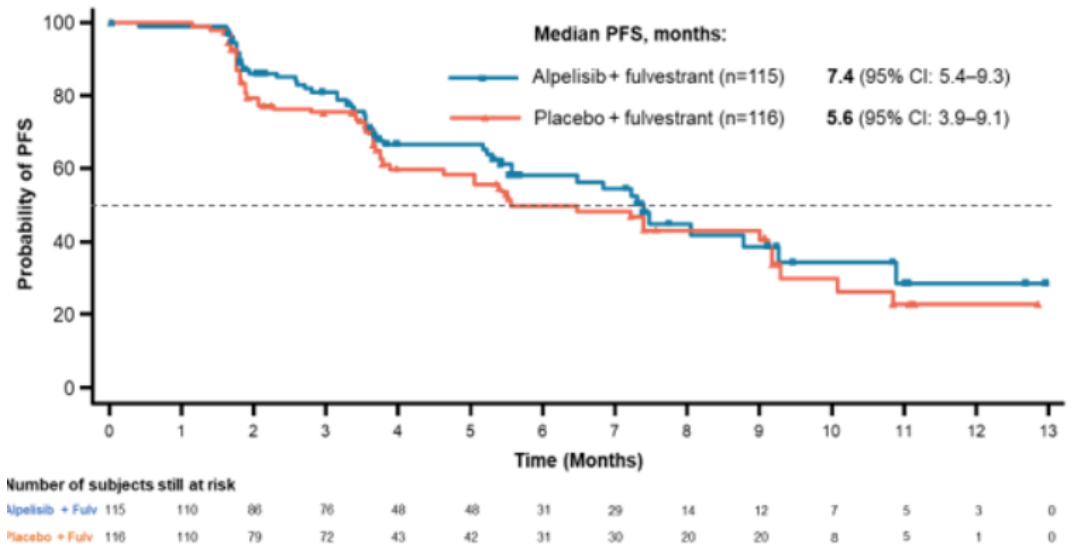
[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Proof of Concept: PFS in the *PIK3CA*-non-mutant cohort

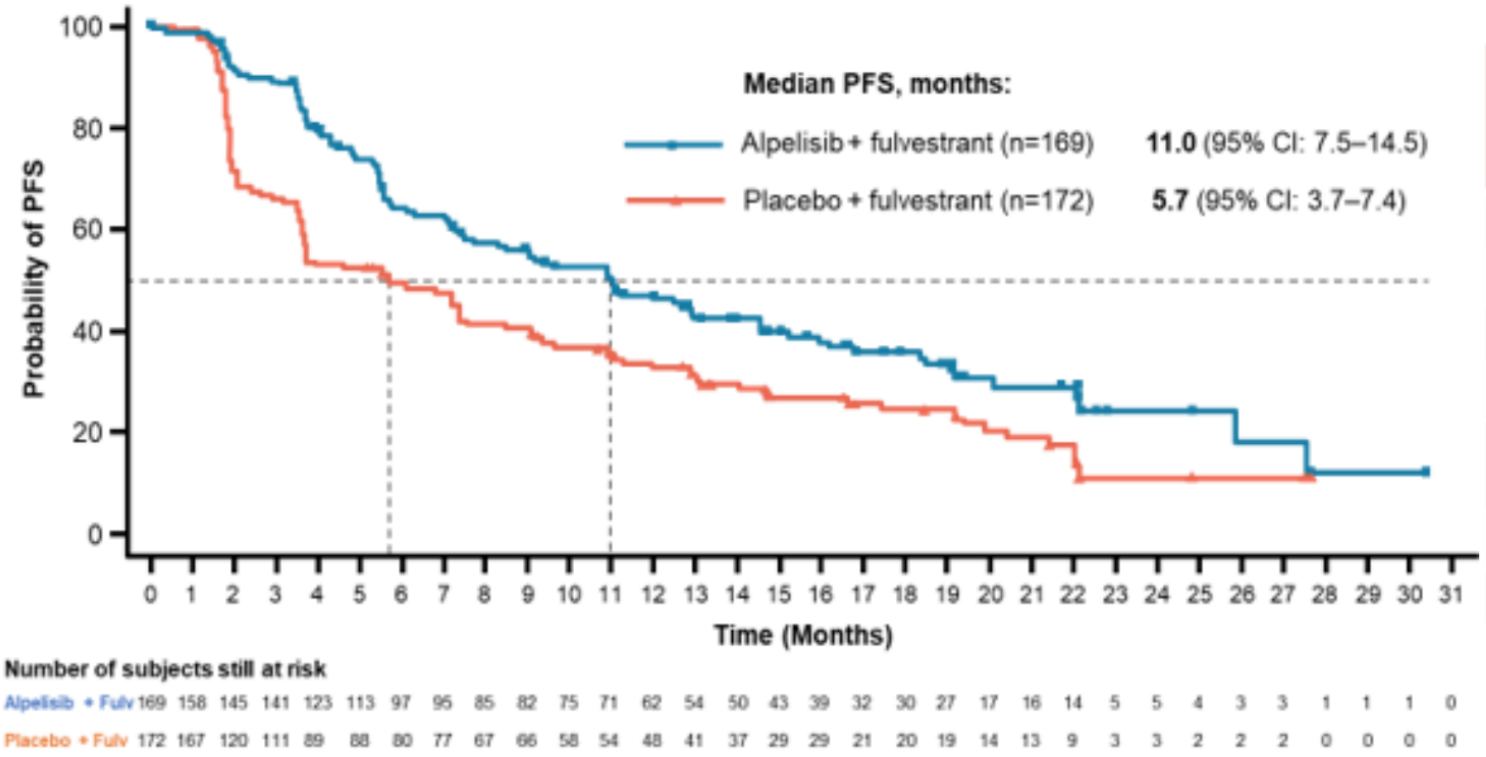
Proof of concept criteria were not met in the PIK3CA-non-mutant cohort



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Progression	47 (40.9)	57 (49.1)
Death	2 (1.7)	0
Censored	66 (57.4)	59 (50.9)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	
Posterior probability HR<1, %	79.4	

- Proof of concept criteria: estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1
- Patients with *PIK3CA*-non-mutant disease were followed up for safety alongside the *PIK3CA*-mutant cohort

Primary endpoint:
Locally assessed PFS in the *PIK3CA*-mutant cohort



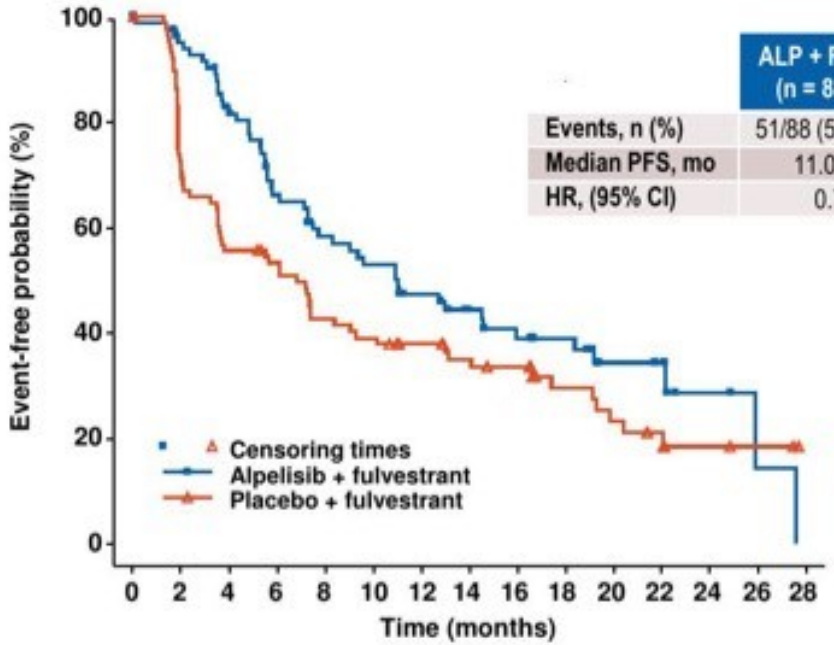
Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

- The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

PFS by Line of Therapy in the *PIK3CA*-mutant Cohort[a]

First-line (n = 177)

Defined as patients whose disease progressed ≤ 1 year after (neo)adjuvant ET (endocrine resistant) **or** whose disease progressed > 1 year after (neo)adjuvant ET (endocrine sensitive) (later excluded after protocol amendment)

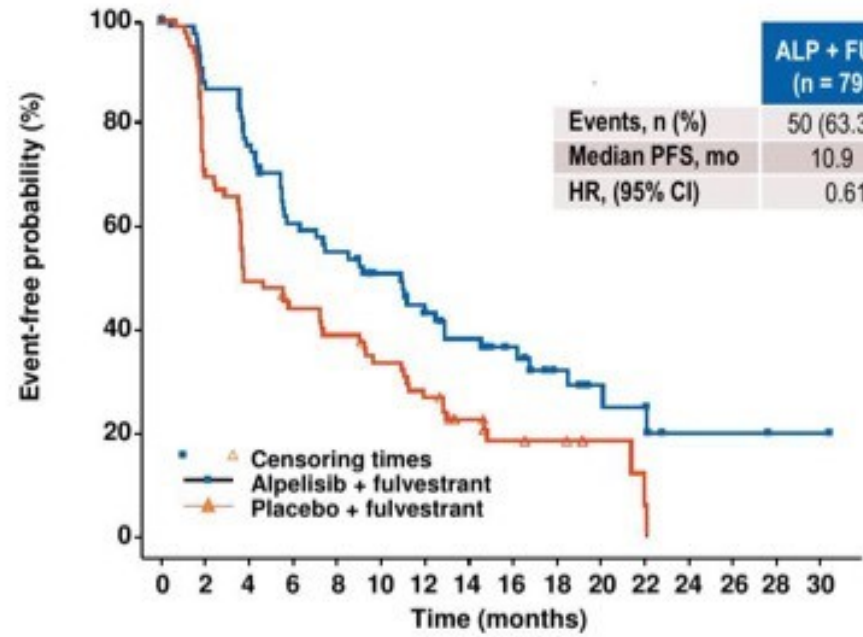


	ALP + FUL (n = 88)	PBO + FUL (n = 89)
Events, n (%)	51/88 (58.0)	64/89 (71.9)
Median PFS, mo	11.0	6.8
HR, (95% CI)	0.71 (0.49-1.03)	

	Endocrine sensitive patients		Endocrine resistant patients	
	ALP + FUL (n = 20)	PBO + FUL (n = 19)	ALP + FUL (n = 68)	PBO + FUL (n = 70)
Events, n (%)	11 (55.0)	9 (47.4)	40 (58.8)	55 (78.6)
Median PFS, mo	22.1	19.1	9.0	4.7
HR, (95% CI)	0.87 (0.35-2.17)		0.69 (0.46-1.05)	

Second-line (n = 161)

Defined as patients whose disease progressed > 1 year after (neo)adjuvant ET and while on or after 1 line of ET for ABC **or** patients with newly diagnosed ABC whose disease progressed while on or after 1 line of ET



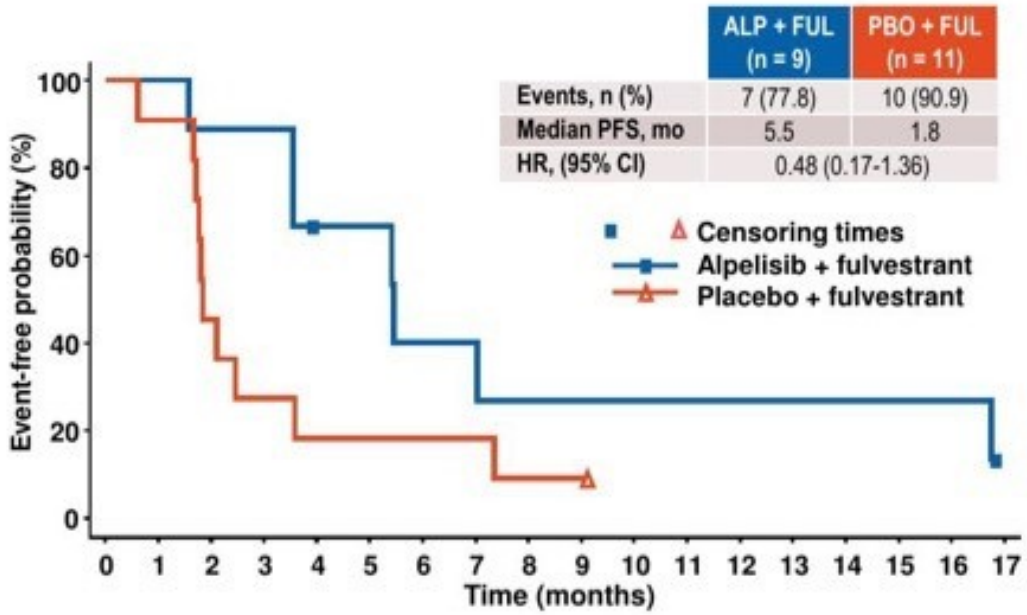
	ALP + FUL (n = 79)	PBO + FUL (n = 82)
Events, n (%)	50 (63.3)	65 (79.3)
Median PFS, mo	10.9	3.7
HR, (95% CI)	0.61 (0.42-0.89)	

ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.

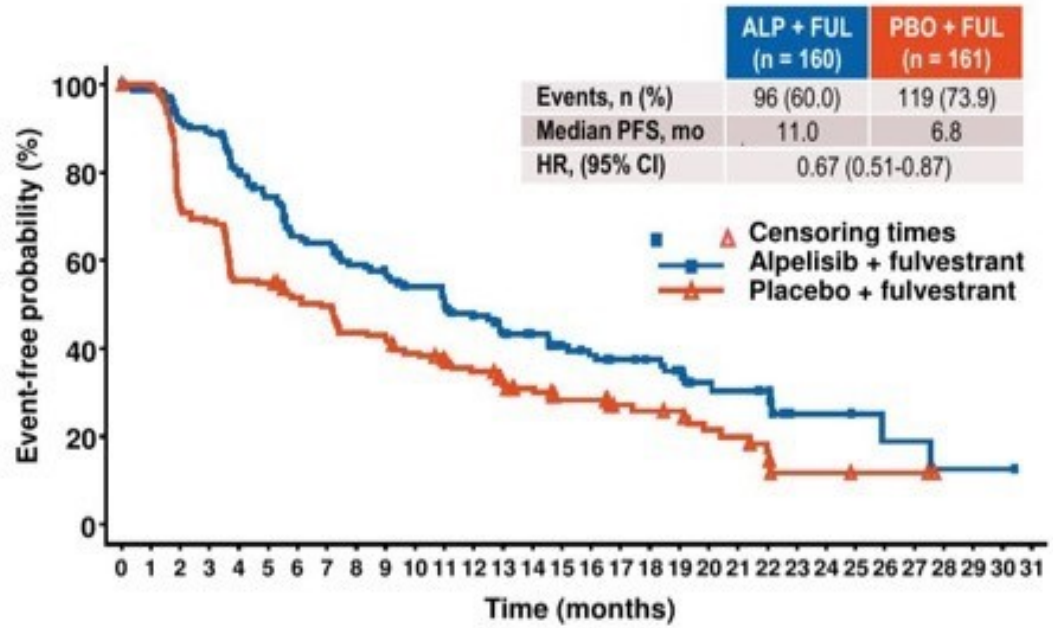
[a] Mutation status determined from tissue biopsy.

PFS by Prior CDK4/6 Inhibitor Treatment in the *PIK3CA*-mutant Cohort[a]

With Prior CDK4/6 inhibitor therapy



Without Prior CDK4/6 inhibitor therapy

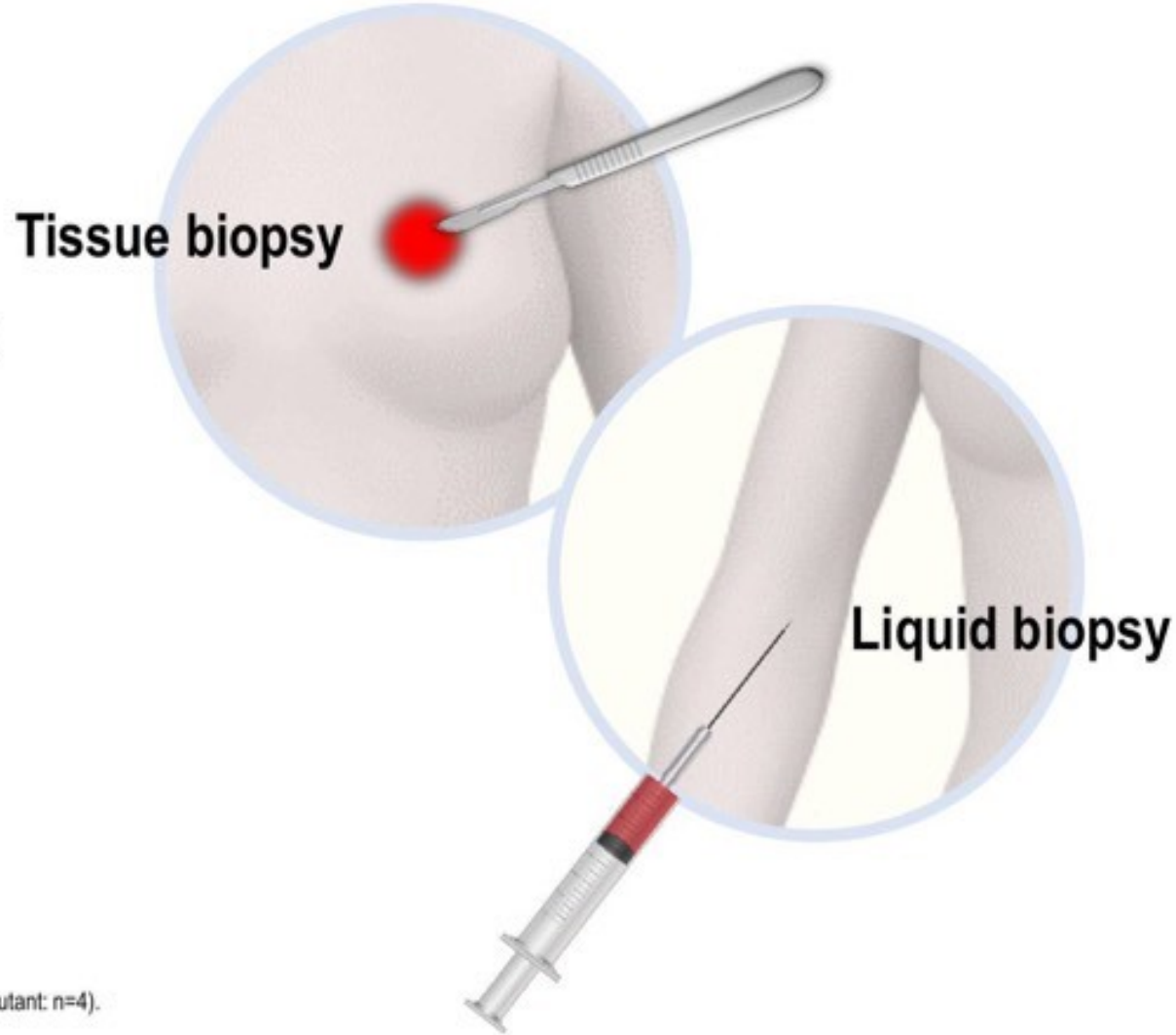


- Previous treatment with any CDK4/6 inhibitor was a stratification factor, however the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.
[a] Mutation status determined from tissue biopsy.

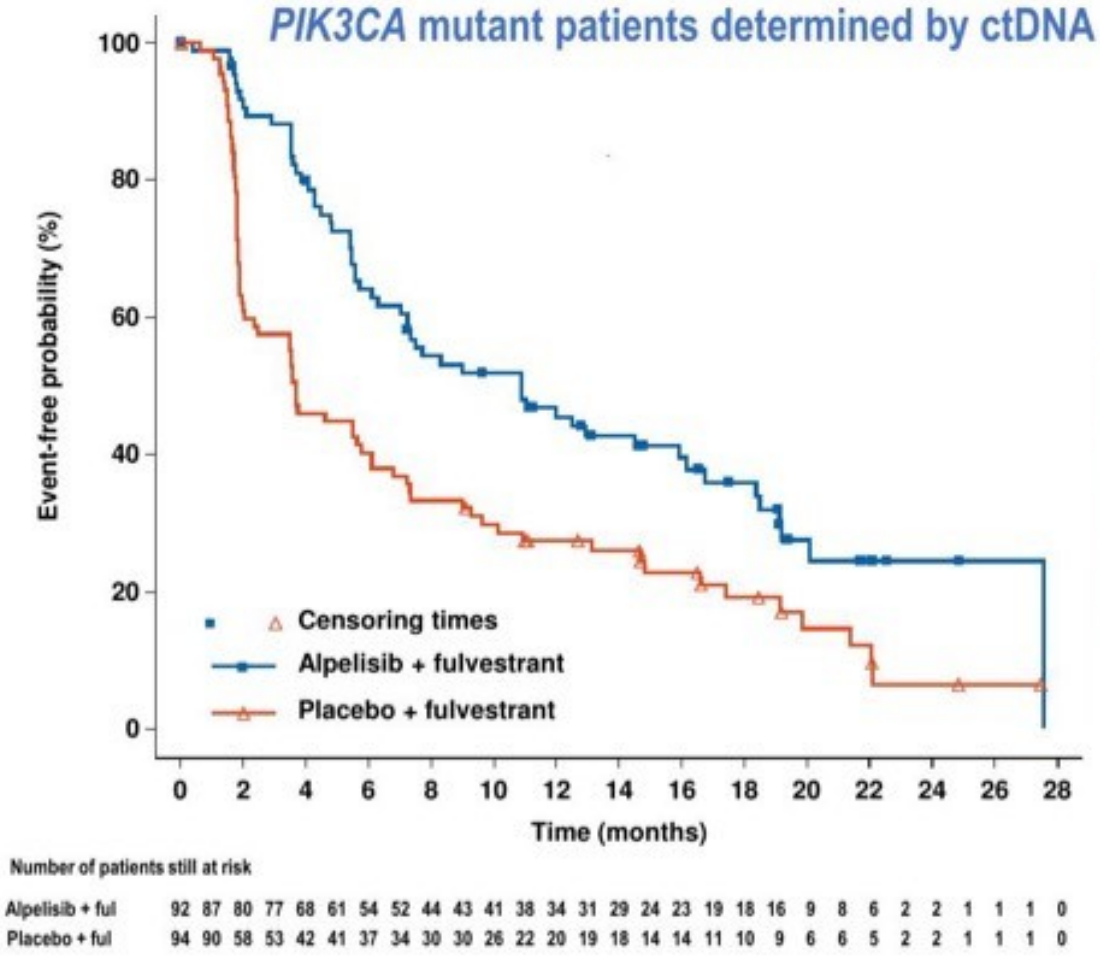
PIK3CA-mutational Analysis in SOLAR-1

- For the primary analysis of SOLAR-1, mutation status was determined from a tumor tissue sample
- Plasma ctDNA samples were also collected at baseline and analyzed by PCR to retrospectively assess PFS by *PIK3CA* mutation status as a secondary endpoint[a]
  - Mutation status defined by ctDNA was also used to assess PFS in the population (positive vs negative)



[a] Not all patients had mutation status determined from blood samples (missing patients – mutant: n=19, non-mutant: n=4).
ctDNA, circulating tumor DNA; PFS, progression-free survival.

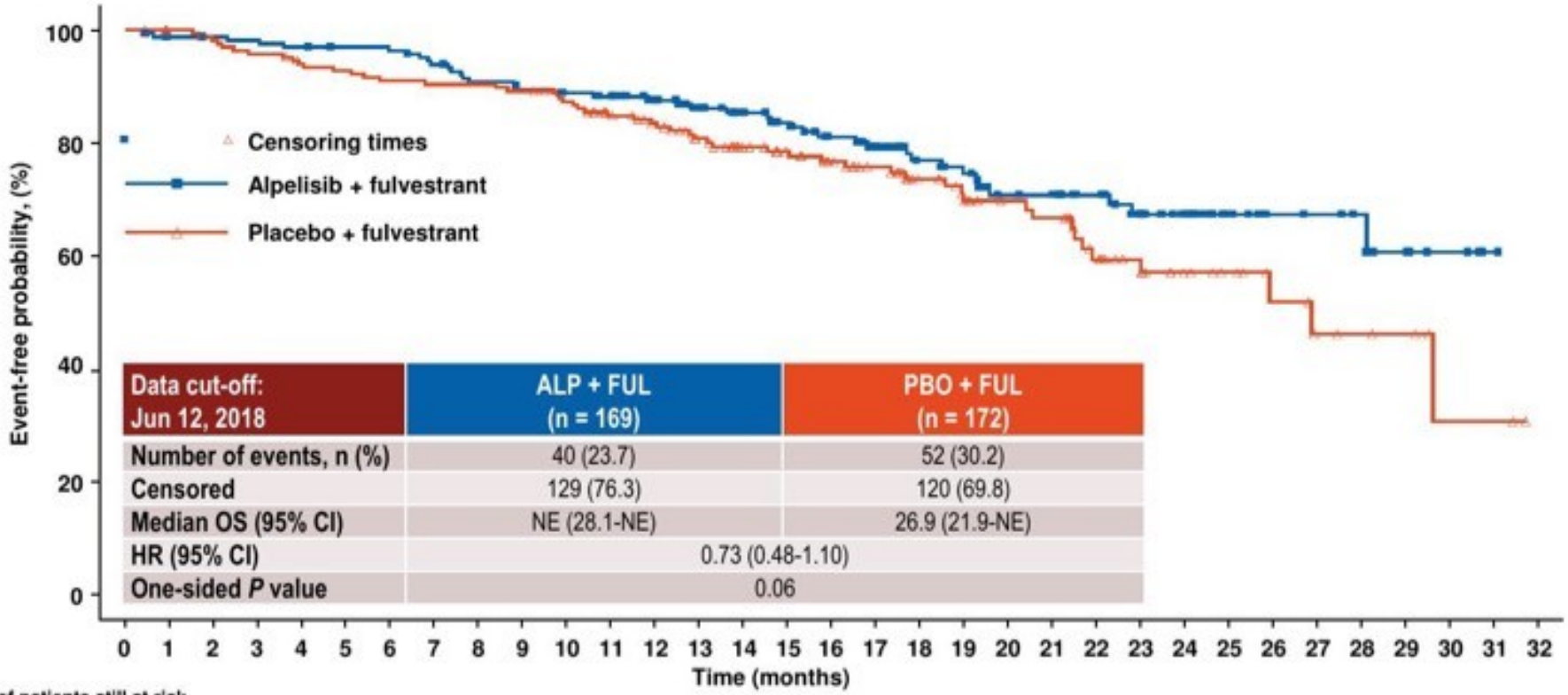
Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status



	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.

Key Secondary Endpoint: Overall Survival in the *PIK3CA*-mutant Cohort[a]



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of events, n (%)	40 (23.7)	52 (30.2)
Censored	129 (76.3)	120 (69.8)
Median OS (95% CI)	NE (28.1-NE)	26.9 (21.9-NE)
HR (95% CI)	0.73 (0.48-1.10)	
One-sided *P* value	0.06	

Number of patients still at risk

Alpelisib + fulv	169	163	162	161	159	157	156	151	145	142	139	137	129	117	107	97	88	79	67	63	53	52	44	35	28	17	13	12	10	7	4	1	0
Placebo + fulv	172	168	164	160	155	153	150	149	149	147	142	132	125	112	99	91	81	74	60	53	45	43	32	24	17	14	10	7	6	5	2	2	0

OS data at this first interim analysis were immature; as of the cut-off date, 52% of the planned number of events for the final OS analysis were included

Median OS follow-up time from randomization date to event/censoring date was 15.9 months (range 0.4-31.7 months).

[a] Mutation status determined from tissue biopsy.

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; QD: daily

Adverse events in the total population

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

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

Adverse Events by *PIK3CA* Mutational Status[a]

	PIK3CA-mutant cohort						*PIK3CA*-non-mutant cohort					
	ALP + FUL (n = 169)			PBO + FUL (n = 171)			ALP + FUL (n = 115)			PBO + FUL (n = 116)		
AEs ≥ 20% in either arm, %	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any AE	168 (99.4)	116 (68.6)	20 (11.8)	152 (88.9)	46 (26.9)	11 (6.4)	114 (99.1)	67 (58.3)	13 (11.3)	112 (96.6)	41 (35.3)	4 (3.4)
Hyperglycemia	110 (65.1)	54 (32.0)	8 (4.7)	15 (8.8)	0	1 (0.6)	71 (61.7)	39 (33.9)	3 (2.6)	13 (11.2)	1 (0.9)	0
Diarrhea	92 (54.4)	13 (7.7)	0	19 (11.1)	1 (0.6)	0	72 (62.6)	6 (5.2)	0	26 (22.4)	0	0
Nausea	77 (45.6)	4 (2.4)	0	34 (19.9)	0	0	50 (43.5)	3 (2.6)	0	30 (25.9)	1 (0.9)	0
Rash	67 (39.6)	22 (13.0)	0	11 (6.4)	1 (0.6)	0	34 (29.6)	6 (5.2)	0	6 (5.2)	0	0
Decreased appetite	57 (33.7)	1 (0.6)	0	13 (7.6)	0	0	44 (38.3)	1 (0.9)	0	17 (14.7)	1 (0.9)	0
Stomatitis	45 (26.6)	5 (3.0)	0	11 (6.4)	0	0	25 (21.7)	2 (1.7)	0	7 (6.0)	0	0
Weight decreased	45 (26.6)	6 (3.6)	0	1 (0.6)	0	0	31 (27.0)	5 (4.3)	0	5 (4.3)	0	0
Vomiting	43 (25.4)	0	0	16 (9.4)	0	0	34 (29.6)	2 (1.7)	0	12 (10.3)	1 (0.9)	0
Fatigue	40 (23.7)	5 (3.0)	0	26 (15.2)	0	0	29 (25.2)	5 (4.3)	0	23 (19.8)	3 (2.6)	0
Alopecia	36 (21.3)	0	0	5 (2.9)	0	0	20 (17.4)	0	0	2 (1.7)	0	0

[a] Mutation status determined from tissue biopsy.

PI3K Pathway Inhibitors in Clinical Development

Rapalogs
Everolimus Temsirolimus Deforolimus
mTOR kinase inhibitors
MLN0128 AZD2014 OSI-027 CC-223

Dual PI3K/mTOR inhibitors
BGT226 XL765 GDC-0980
AKT inhibitors
Perifosine MK2206 XL418 GDC-0068 (ipatasertib) GSK2141795 GSK2110183 AZD5363

Pan-PI3K inhibitors
Pictilisib (GDC-0941) Buparlisib (BKM120) XL147 PX-866 BAY 80-6946 CH5132799
P110α-specific PI3K inhibitors
Alpelisib (BYL719) MLN1117 Taselisib (GDC-0032, p110β sparing, also targets p110γ and δ)
P110β-specific PI3K inhibitors
AZD8186 SAR260301 GSK2636771

Adapted from Ma CX, *American Journal of Hematology/Oncology*. 2015;11:23-29

Recommendations from the ESO-ESMO ABC-2 Panel

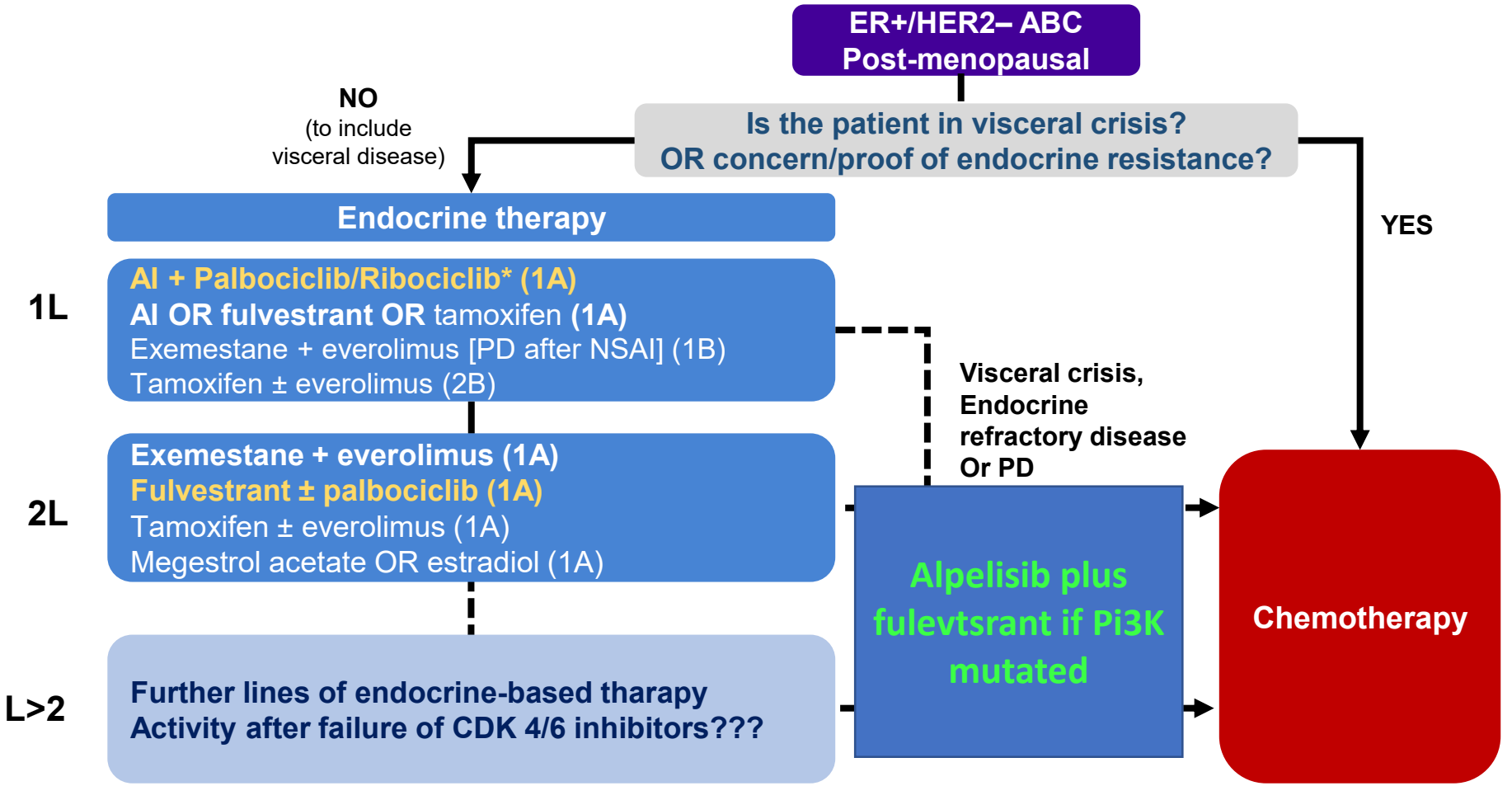
The main goal of treatment in metastatic breast cancer is to prevent disease progression while maintaining physical efficiency and quality of life during the course of the chronic disease.

- **"Endocrine therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response"**

- **Level of evidence IA**

- **Votes: 100% yes, 29 voters (of 43 members)**

ESO-ESMO ABC3 international consensus guidelines



*Except for relapse <12 mths from finishing adjuvant AI
AI, aromatase inhibitor; NSAI, non-steroidal AI; PD, progressive disease

Adapted from Cardoso F, *et al. Ann Oncol.* 2016 [Epub 5 December].