Progression to CDK4/6 inhibitors: what next?

Antonio Frassoldati

Oncologia Clinica - Ferrara

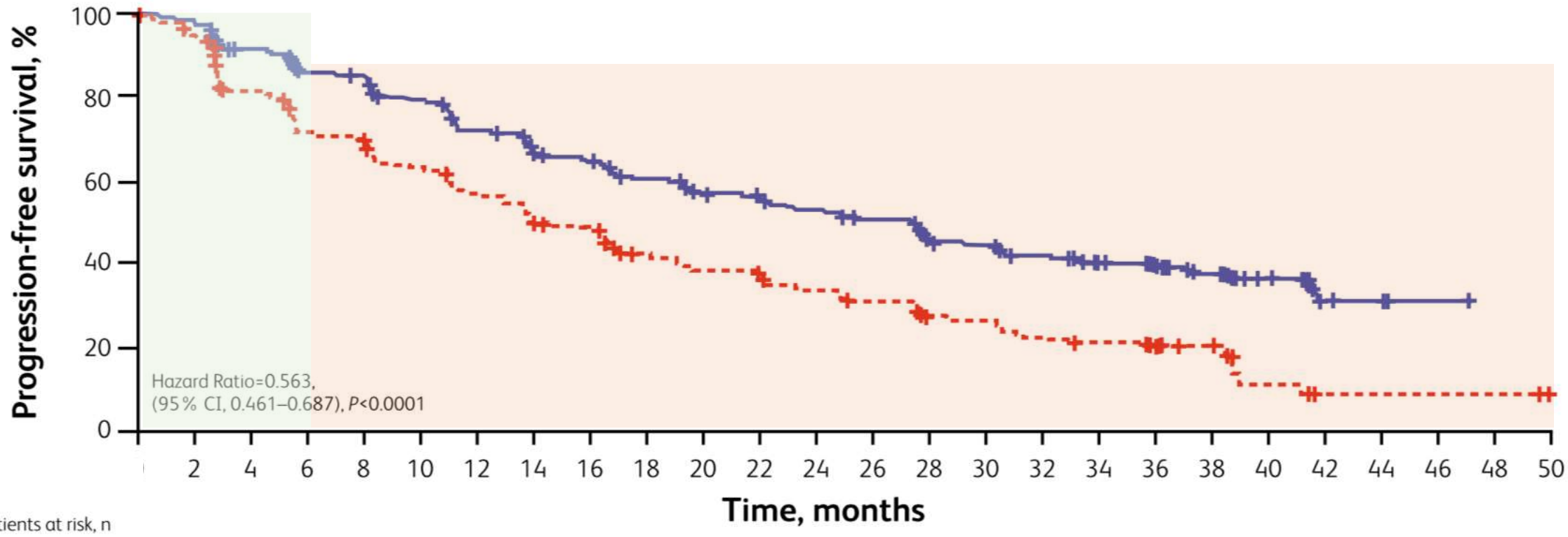
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Università degli Studi di Ferrara

Disclosure

- Grants for advisory board
  - Roche, Novartis, Pfizer
- Lectures
  - Novartis, Astrazeneca, Pfizer, Lilly
- Travel grants
  - Roche, Novartis, Astrazeneca, Lilly, Pfizer, Cellgene

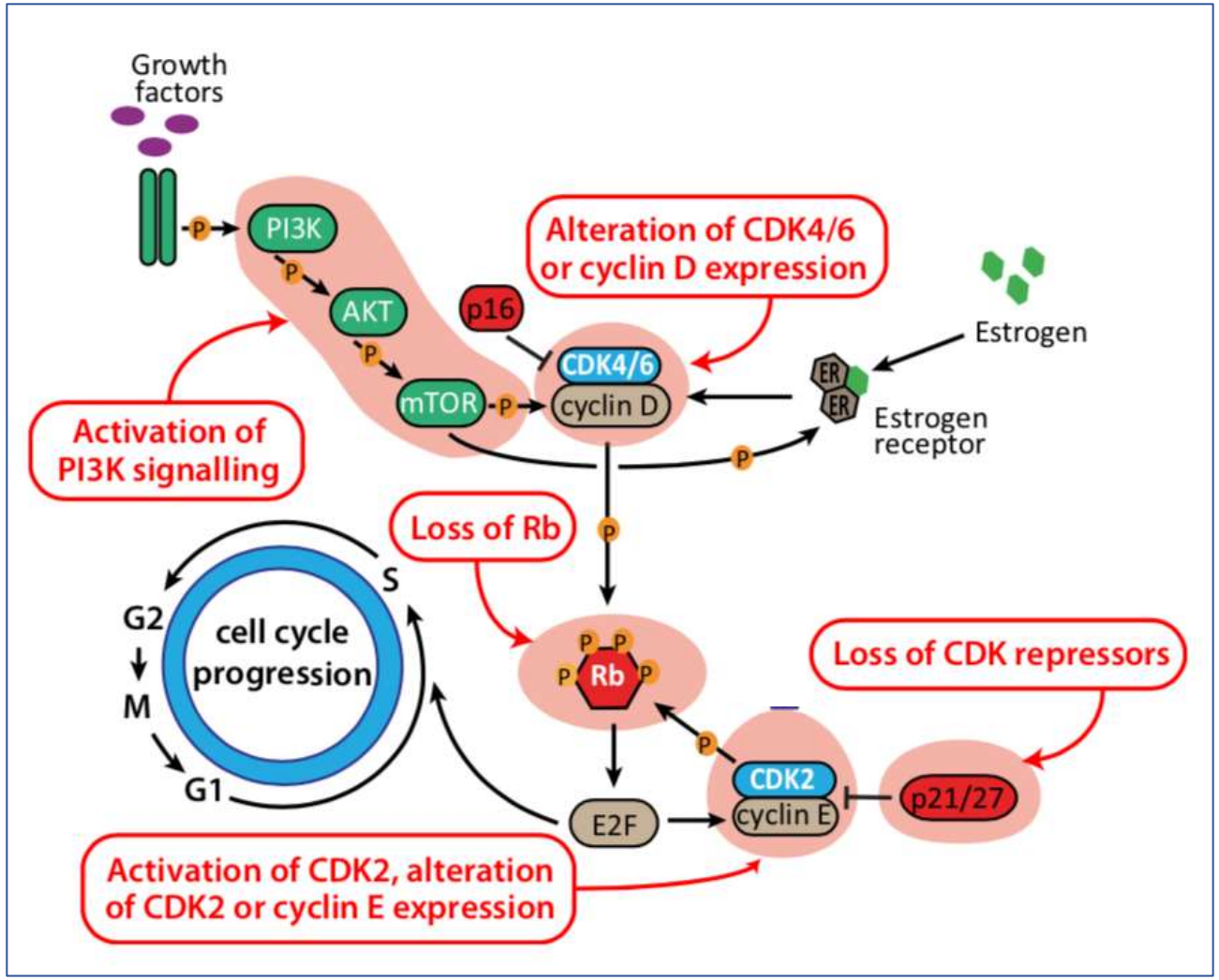
Disease progression occurs in the majority of patients treated with CDK4/6i + ET



Biological basis of progression

Early Progression

Mainly due to intrinsic characteristics or short-term adaptive pathways in BC cells



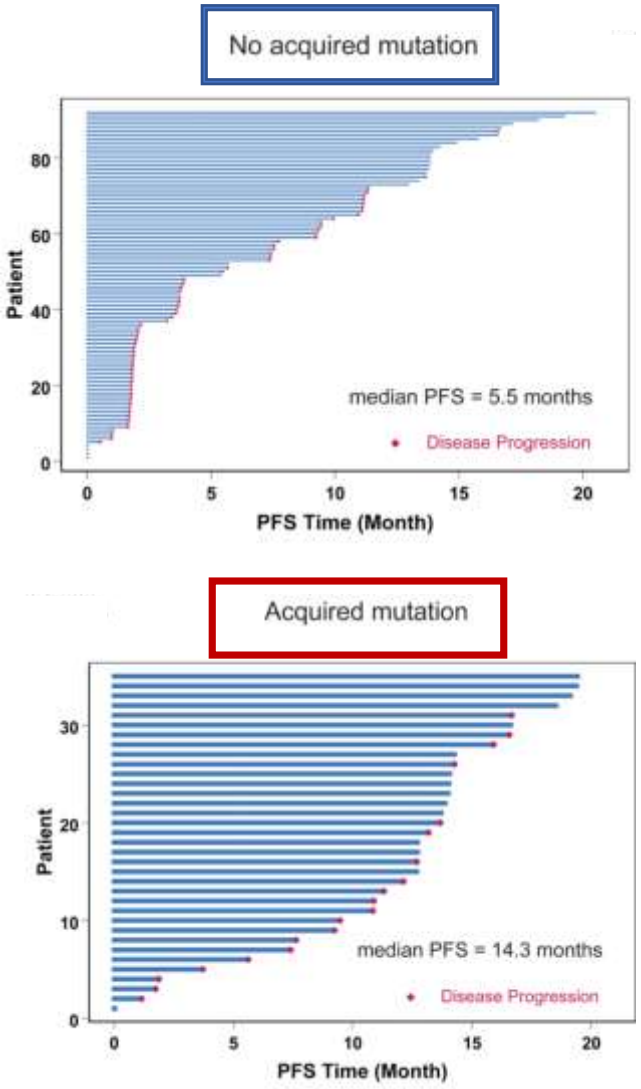
Late Progression

Mainly due to clonal and treatment-driven selections and long-term adaptive pathwys in BC cells

Portman, Endocrine-Related Canc 2019

Early and late progression have distinct mechanism of resistance

- **Short term adaptive changes**
  - Non-canonical complexes of cyclin D1 and CDK2 causes continued Rb phosphorylation.
  - Promotion of a proinflammatory, senescence-associated secretory phenotype (SASP) could augment insensitivity to CDK4/6 inhibitors

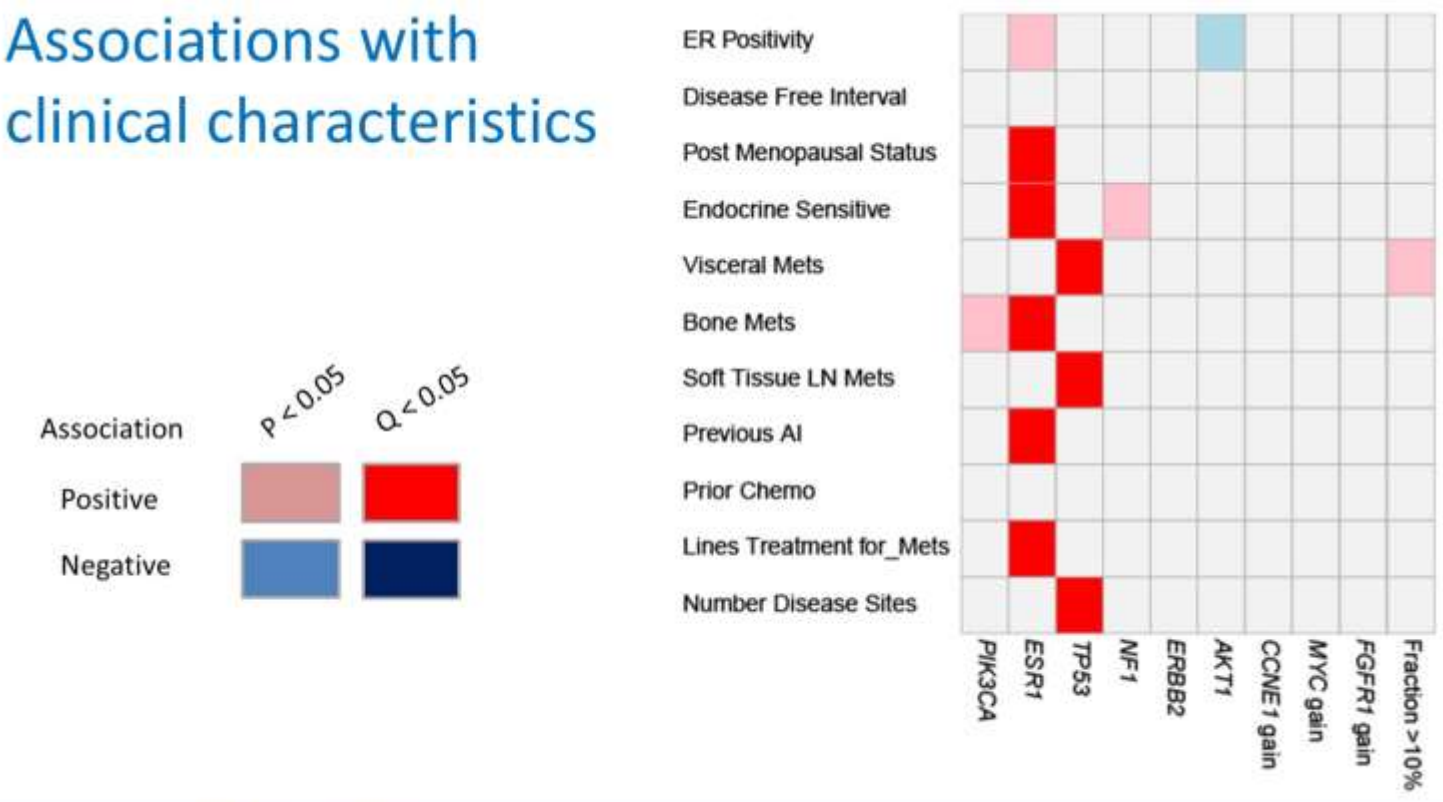


- **Long term adaptive changes**
  - Loss or mutation of Rb
  - Upregulation of CDK4 or CDK6 *(amplification or non-canonical activation)*
  - Cyclin E1, cyclin E2 and CDK2 upregulation
  - Deregulations or mutations in growth factor signalling pathways (PIK3, mTOR, NRAS, FGFR)

O'Leary, Canc Disc 2018

Clinical and biological point of interest

- Time to Progression
- Symptoms and PS
- Sites of disease progression
- Degree and function of involved organs
- Previous therapies

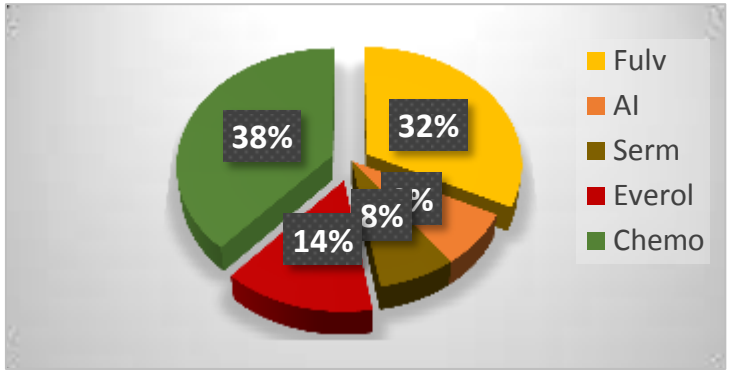


What next after CDK4/6i failure?

- **Stay on inhibition of signal transduction pathways**
  - Single:
    - Endocrine therapy alone
  - Double:
    - Exemestane plus everolimus
    - CDK4/6i beyond progression (same or different CDK4/6i & ET)
    - PIK3i plus ET (in unselected or selected population)
    - Growth factors inhibitors plus ET
  - Triple:
    - CDK4/6i plus ET plus other targeted agent
- **Change to chemotherapy**

Post-progression therapies in Randomized Clinical Trials

PL-2



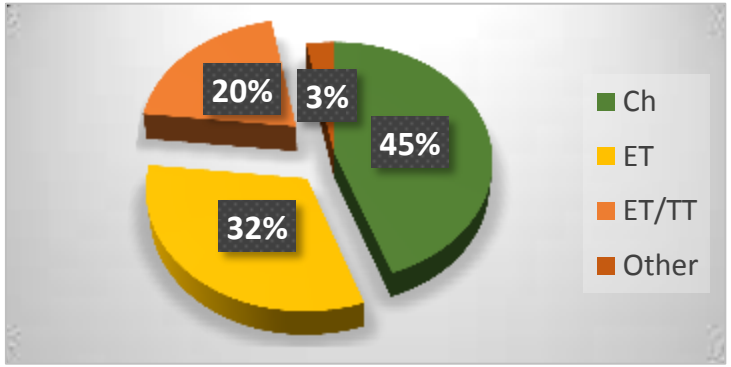
mPFS: 27.6 mos

mPFS2: 38.8 mos

mPFS2Ct: 40.4 mos

Rugo, BCRT 2019

ML-7



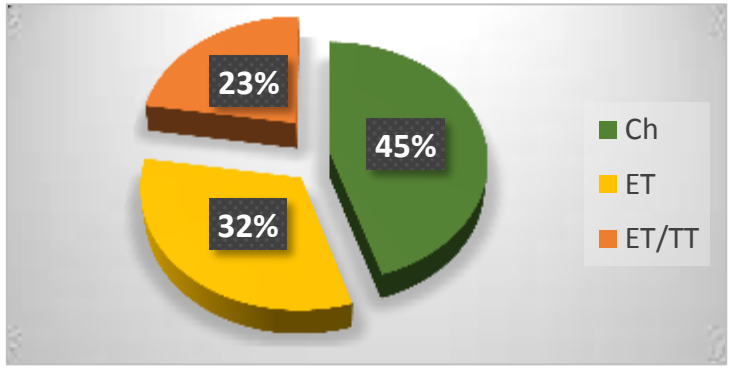
mPFS: 23.8 mos

mPFS2: Not reached*

* At 42 mos FU

Im, NEJM 2019

ML-3



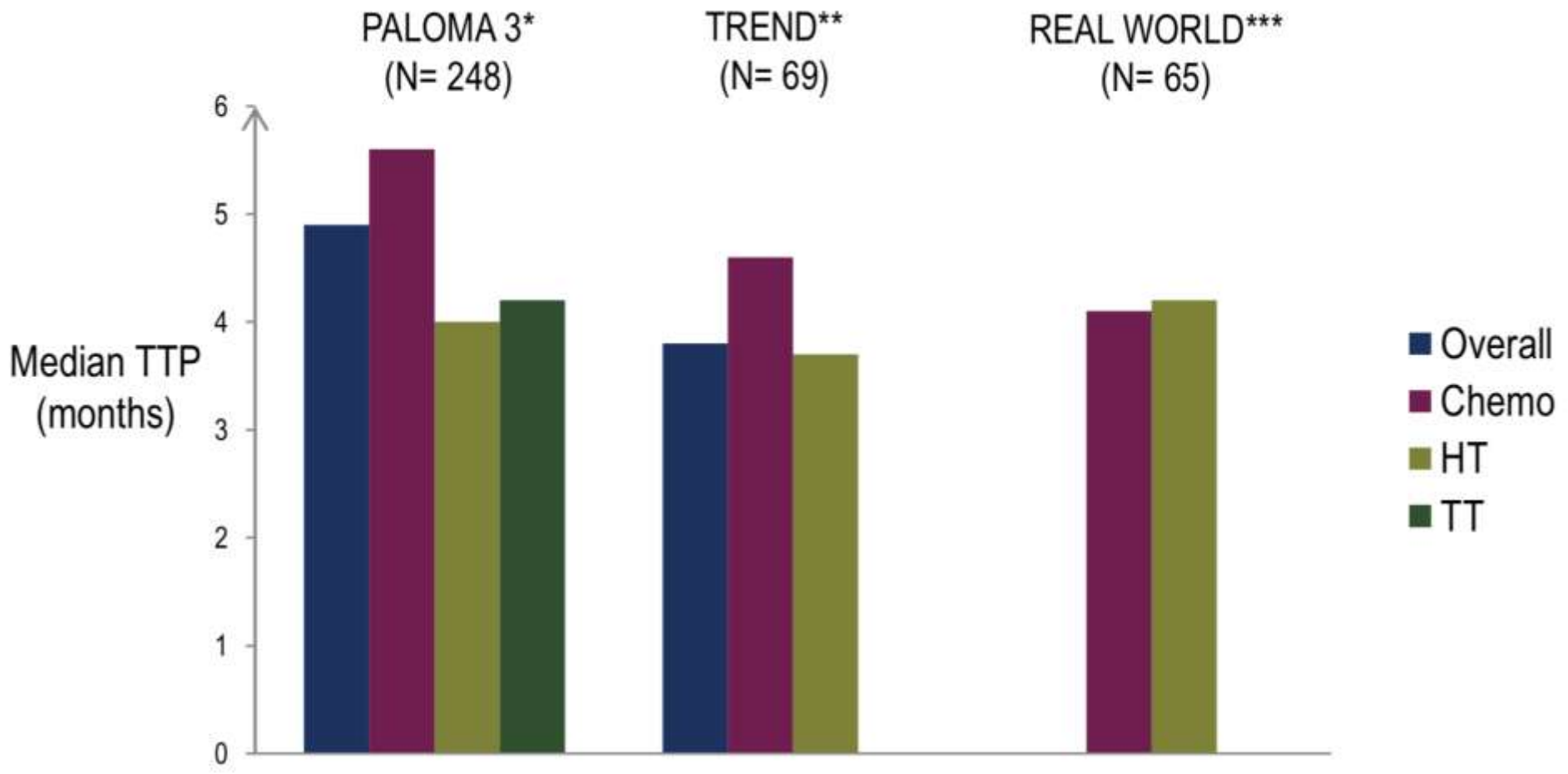
mPFS: 20.6 mos*

mPFS2: 39.8 mos

* R+F, 1° and 2° L

Slamon, ESMO 2019

Effect of subsequent treatment after CDK4/6i failure



No great differences in activity among different treatment options

Di Leo, ESMO 2019; Turner, NEJM 2018; Rossi BCRT 2019; Xi JNCCN 2019

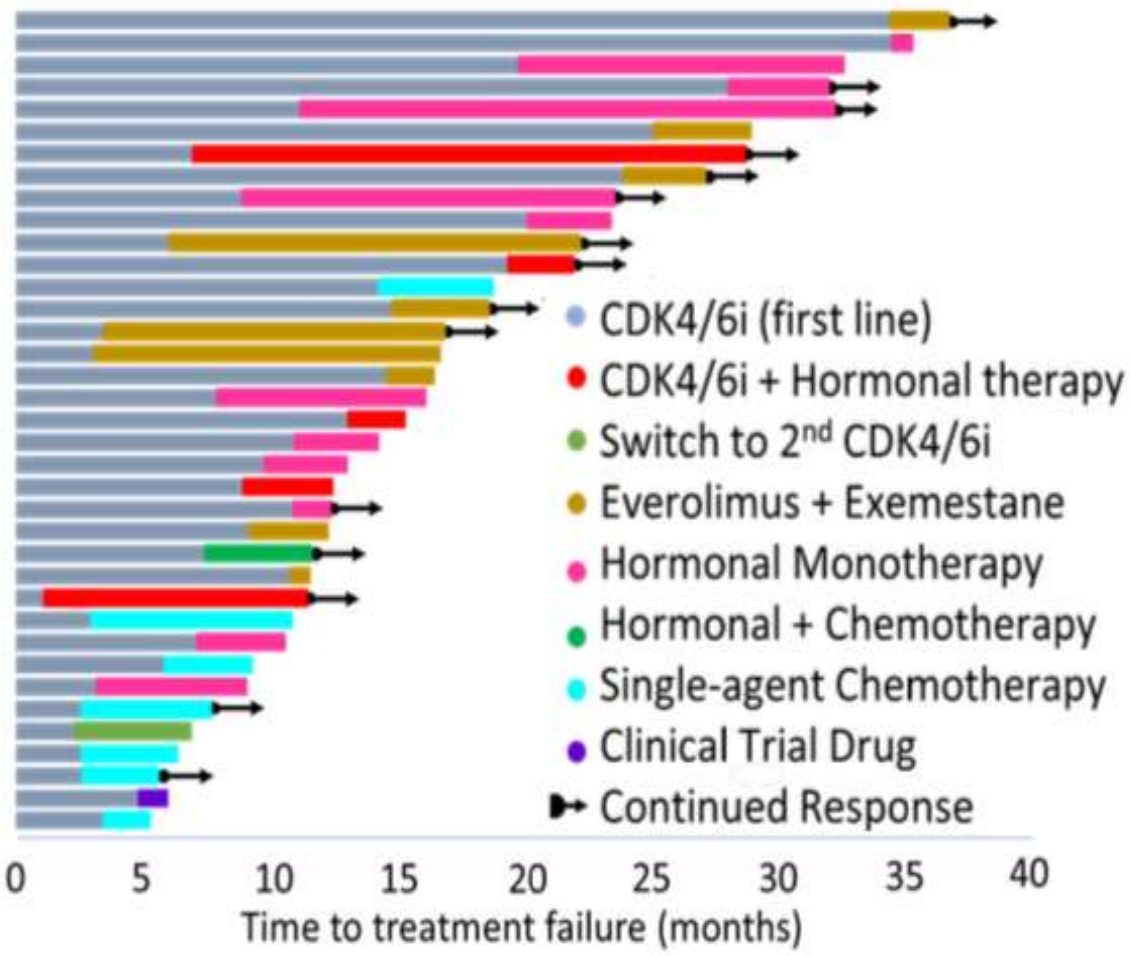
Treatment following progression on CDK4/6i
Real world data

Outcomes by treatment type:

Exemestane/everolimus:
N= 10
median TTF of 13.2 mo
95%CI 0.3 mo to NR

Single agent chemotherapy
N=8
median TTF of 4.1 mo
(95%CI 1.4-5.4mo)

Single agent hormonal treatment
N=11
median TTF of 3.1 mo
95%CI 1.4-5.4mo



Prolonged clinical responses lasting >12 months in patients receiving everolimus/ exemestane post-CDK4/6i

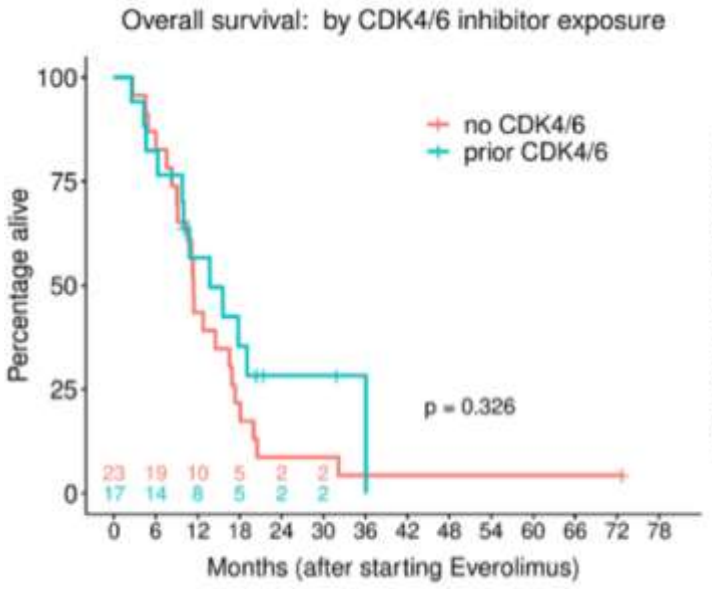
Giridhar, ASCO 2019

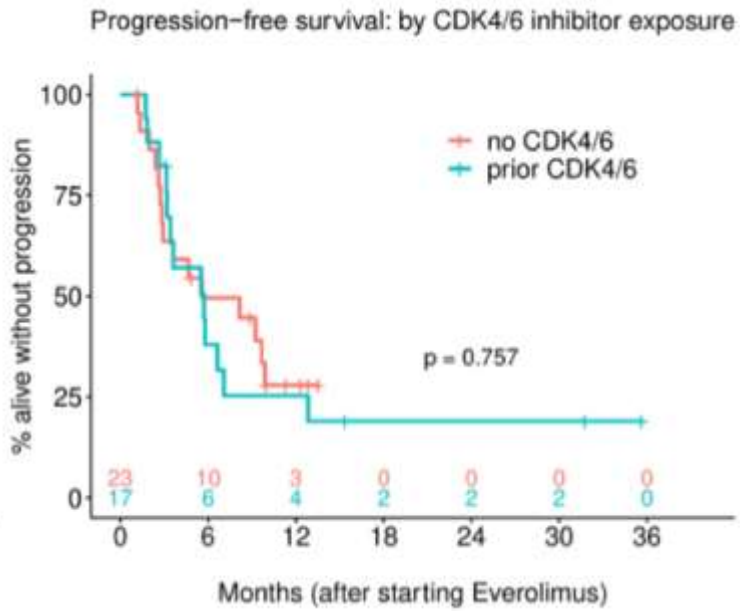
Everolimus + examestane in pts pretreated with CDK4/6i based Tx

Retrospective analysis

	Prior CDK4/6i n = 17	No prior CDK4/6i n = 23
Age at Diagnosis Median (Range)	55 years (31 – 78)	51 years (29 – 79)
Number Prior Systemic Therapies Median (Range)	1 (1 – 8)	2 (1 – 6)
Prior Systemic Therapies ≥1	8 (47%)	15 (65%)
CNS Metastases	1/17 (6%)	1/23 (4%)
Bone Metastases	14/17 (82%)	19/23 (83%)
Lung Metastases	9/17 (53%)	6/23 (26%)
Liver Metastases	5/17 (29%)	7/23 (30%)

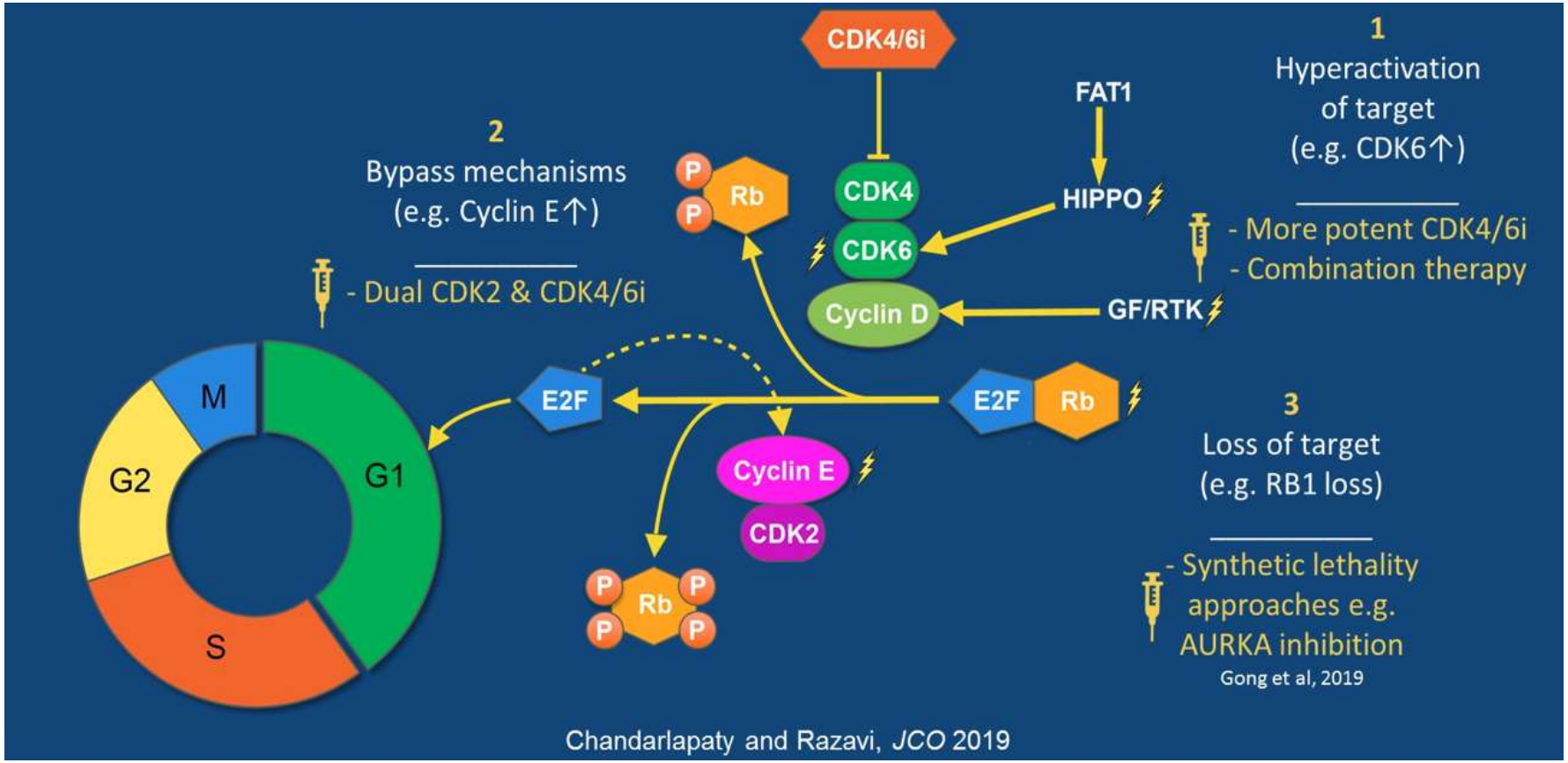
	Prior CDK4/6i n = 17	No prior CDK4/6i n = 23	P-value
Median Follow-Up	10.8 months	11.4 months	
PFS	5.7 months	5.6 months	0.757
PFS (1-year rate)	25.3%	27.9%	
OS	13.7 months	11.4 months	0.326
OS (1-year rate)	56.6%	43.5%	





Cook, ASCO 2019

CDK4/6i beyond progression?



Some observation in acquired resistance, like the *persistant downregulation of E2F related genes*, migth support the prosecution of CDK4/6 inhibition, others should suggest to stop them (like *Rb1 loss or high CCNE1/Rb1 ratio)*).

Treatments with CDK4/6i beyond progression
Retrospective analysis

- 135 pts patients treated with ≥ 2 lines of CDK4/6i
- Patients categorized based on reason for discontinuation of their first CDK4/6i:
  - cohort 1 – switch to alternate CDK4/6i due to toxicity;
  - **cohort 2** – retreatment with same CDK4/6i beyond progression with change of ET
  - **cohort 3**- switch to alternate CDK4/6i as monotherapy or with same or another ET.

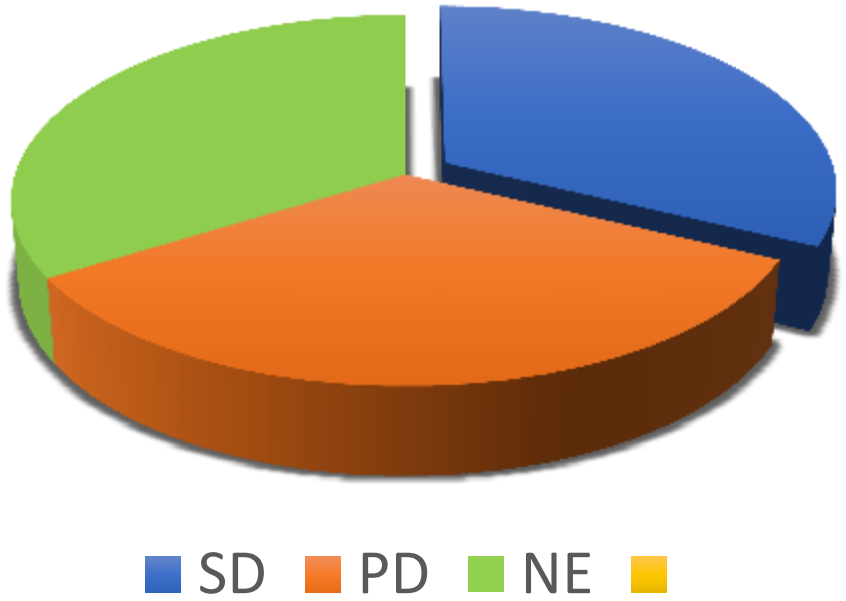
	Cohort 2	Cohort 3
	43 pts	84 pts
CDK4/6i+ET beyond PD	Same CDK4/6i	Different CDK4/6i
Tx line	Second	≥ Fifth
TTST2	**4.5 mos**	**4.4 mos**
TTST2 > 24 wks	35%	29%

dos Anjos, ASCO 2019

Treatments with CDK4/6i beyond progression
Real world data

- **58 pts** with HR+/HER2- MBC received **abemaciclib following PD on prior palbociclib.**
  - 20 pts (34%) received sequential courses of therapy, while 38 pts (66%) had at least one intervening non-CDK4/6i regimen.
- 44 pts (76%) received CDK4/6i in combination with ET (fulvestrant 52%; aromatase inhibitor 22%).
- 20 pts (34%) had early PD (< 90 days), while 21 pts (36%) had treatment duration > 6 months, including 10 who remain on treatment (range 181-413 days).

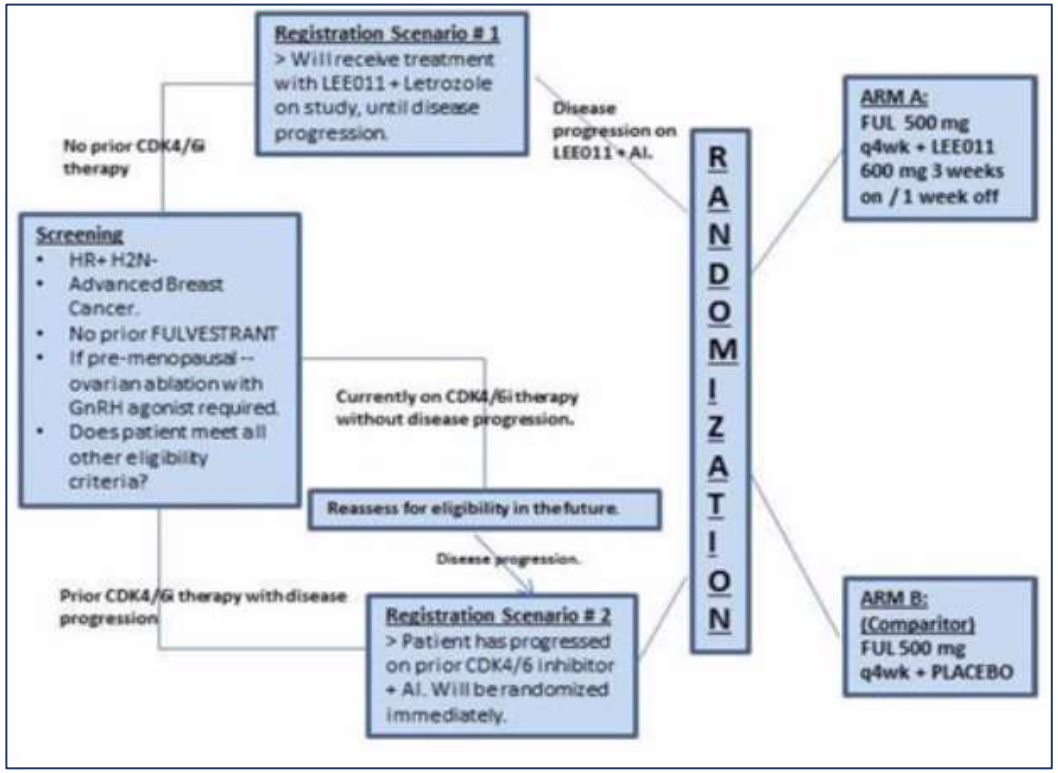
The median **PFS was 5.8 months** (95%CI 3.4 – 8.0).



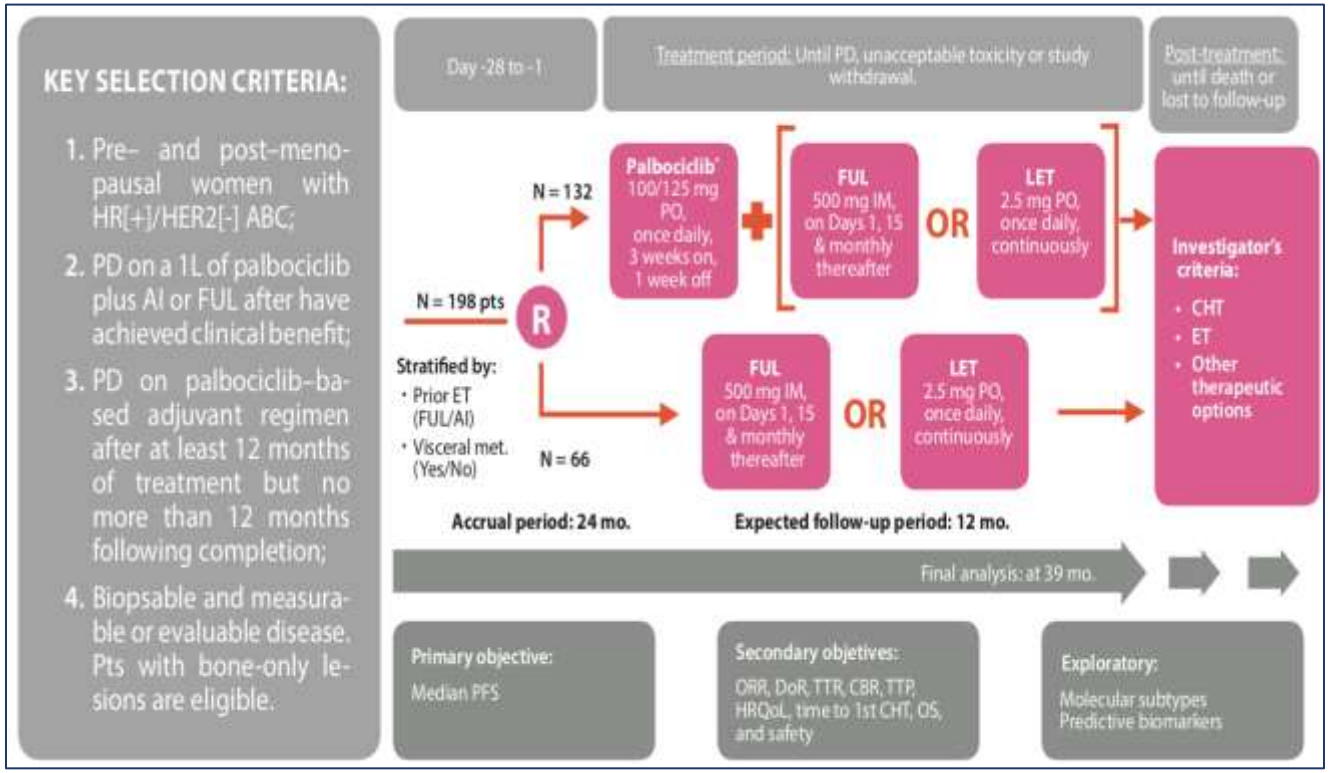
Wander, ASCO 2019

ET with or without CDK4/6i after Progression on ET Plus CDK 4/6i

MAINTAIN *Trial*



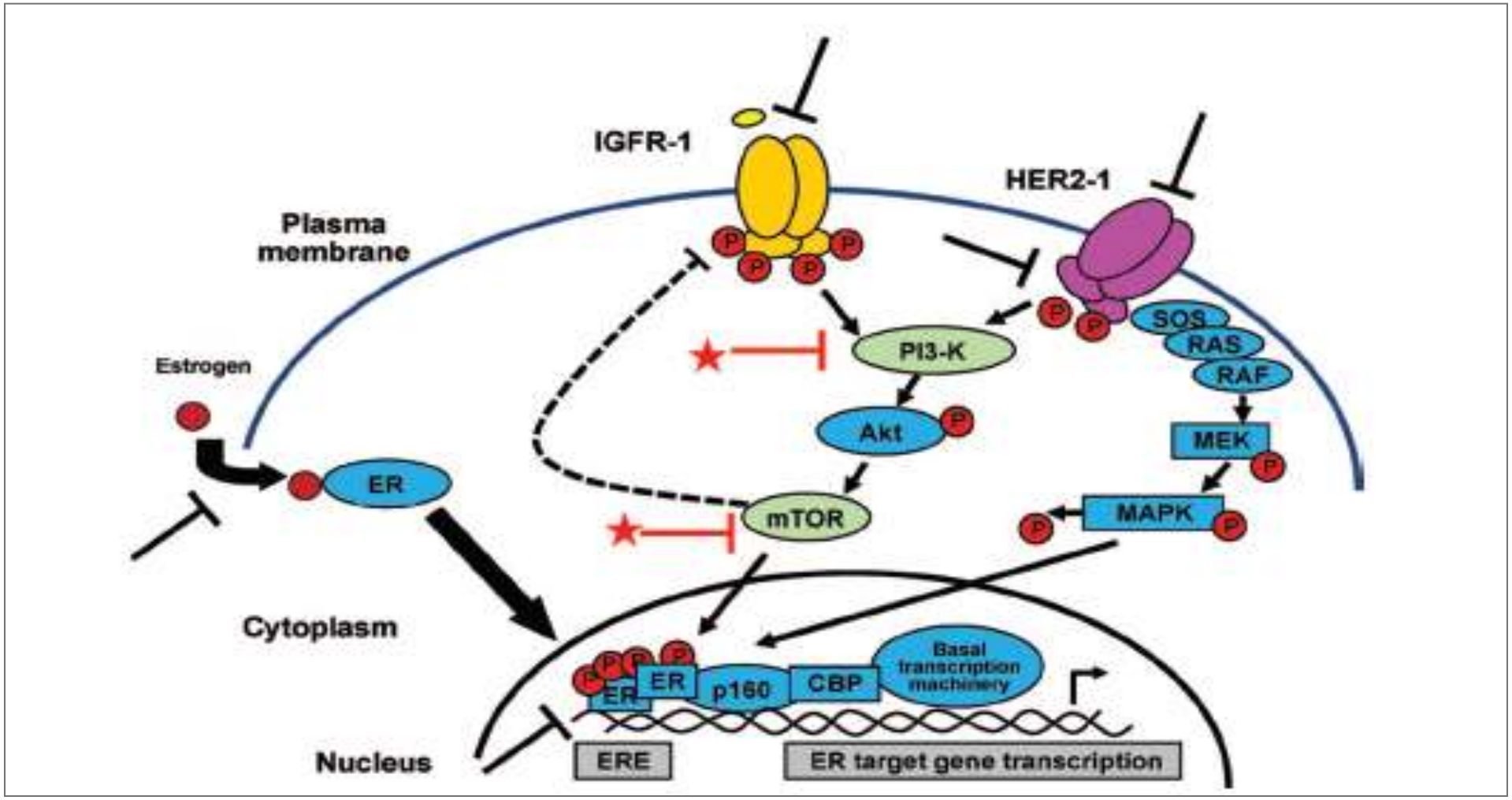
PALMIRA *Trial*



Kalinsky, SABCS 2017

Llombart Cussac , ESMO 2019

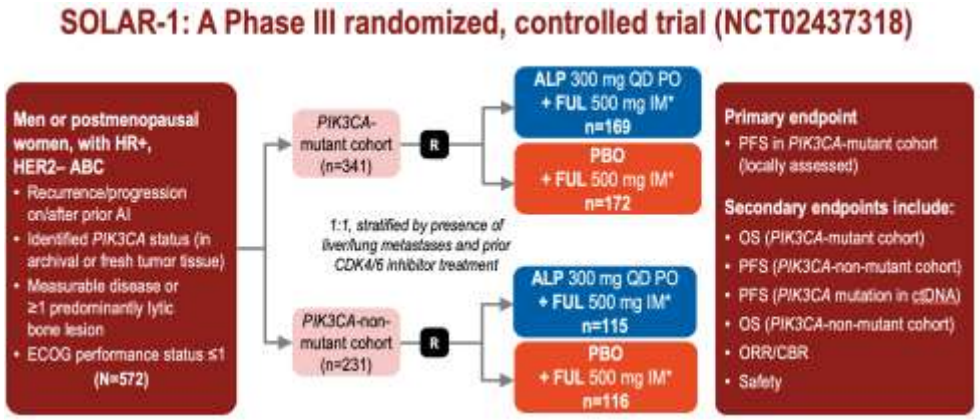
PI3K is an important intermediate of downstream pathways

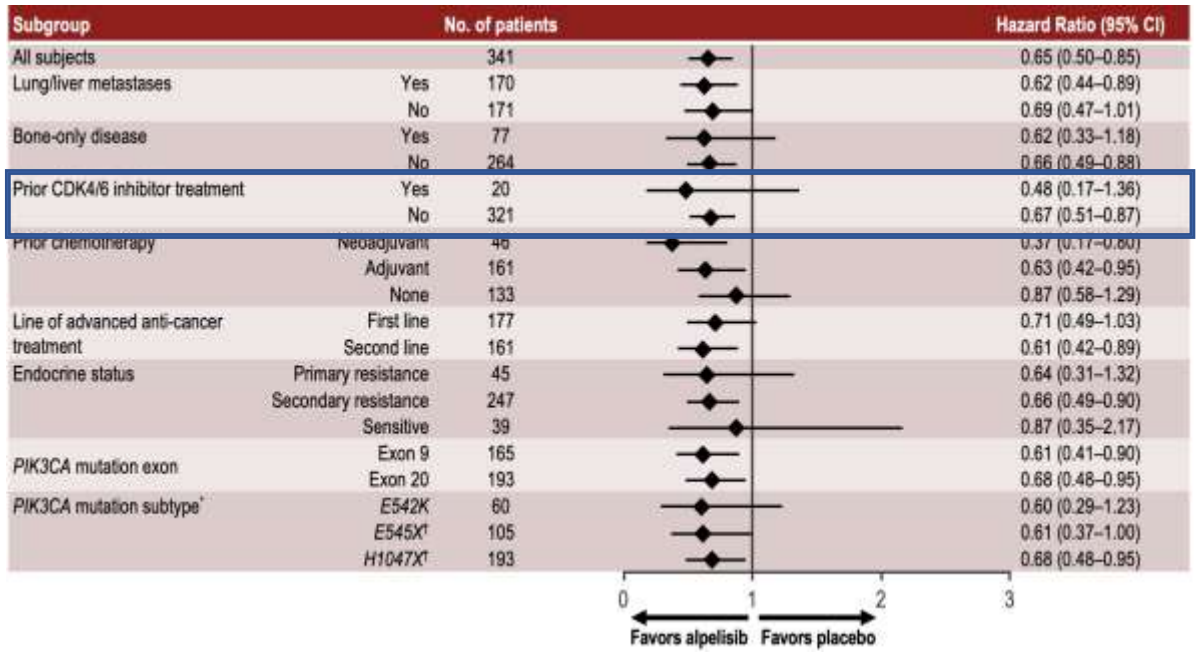


PI3K mutations, or activation by upstream GFr, can promote resistance to antiestrogen therapy, and can also mediate resistance to downstream mTOR inhibitors.

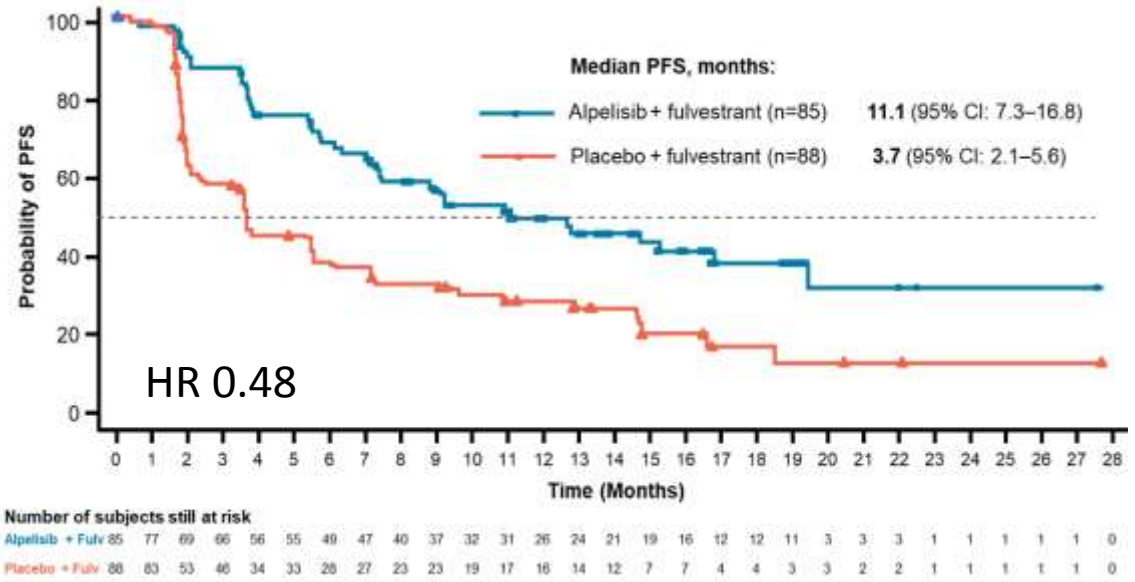
Baselga, The Oncologist 2011

PIK3CA Inhibitors in ER+/HER2- mBC resistant to AIs





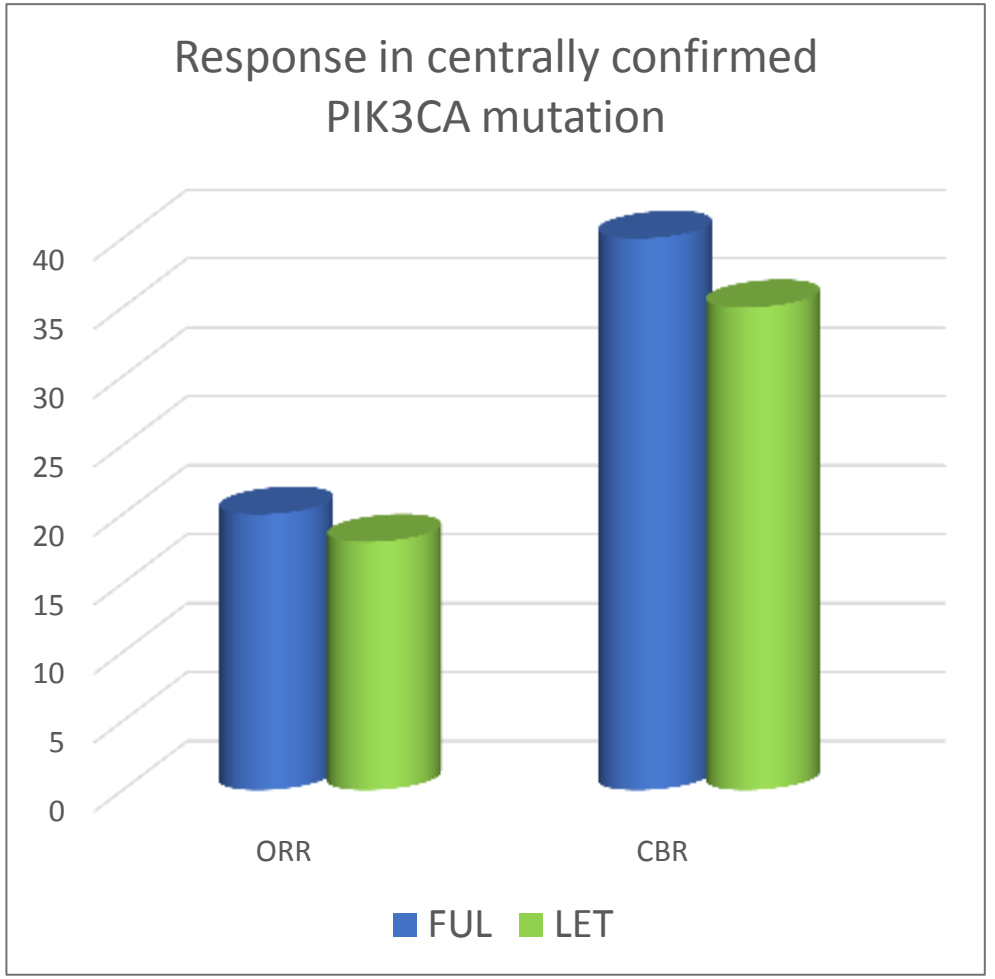
Efficacy in the PIK3CA mutant-cohort



Andrè, NEJM 2019

Alpelisib + ET **in pts with *PIK3CA*-mutated** mBC ***and*** **prior CDKi** - *BYLieve study*

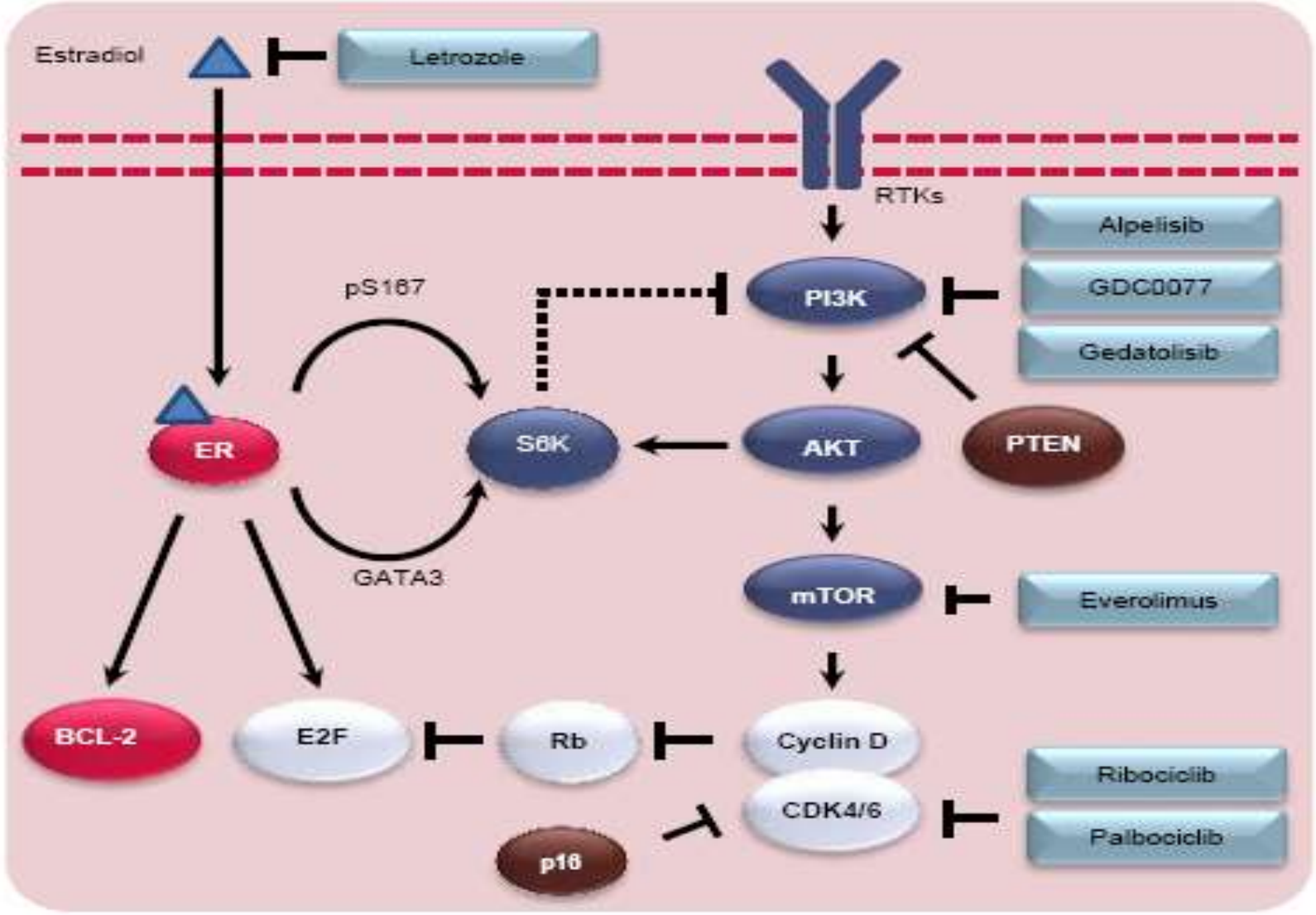
- First interim analysis
- 64 and 36 pts were enrolled in the *FUL* and *LET* cohorts; 39 pts (*FUL*, n=21; *LET*, n=18) evaluated until now
- Median relative ALP dose intensity was 93% (*FUL*) and 87% (*LET*).
- Most common grade ≥3 adverse events were hyperglycemia (38.1% (*FUL*) and 27.8% (*LET*)) and rash (4.8% (*FUL*) and 27.8% (*LET*)).



Rugo, ASCO 2019

PIK3/mTOR, Cyclin and ER pathways interactions

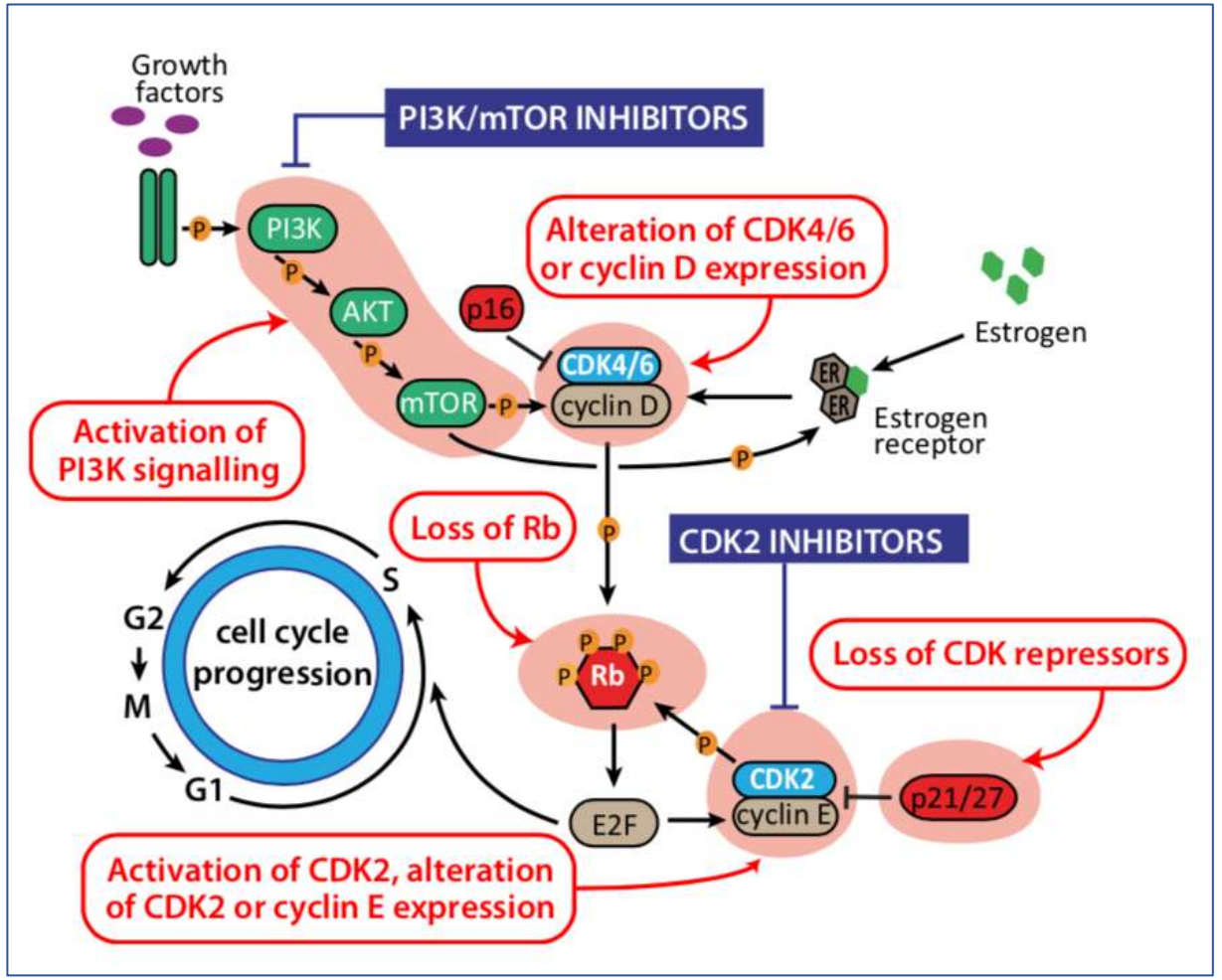
Vertical inhibition could be needed to overcome frequent genetic alteration and bypass pathways



Juric, ESMO 2017

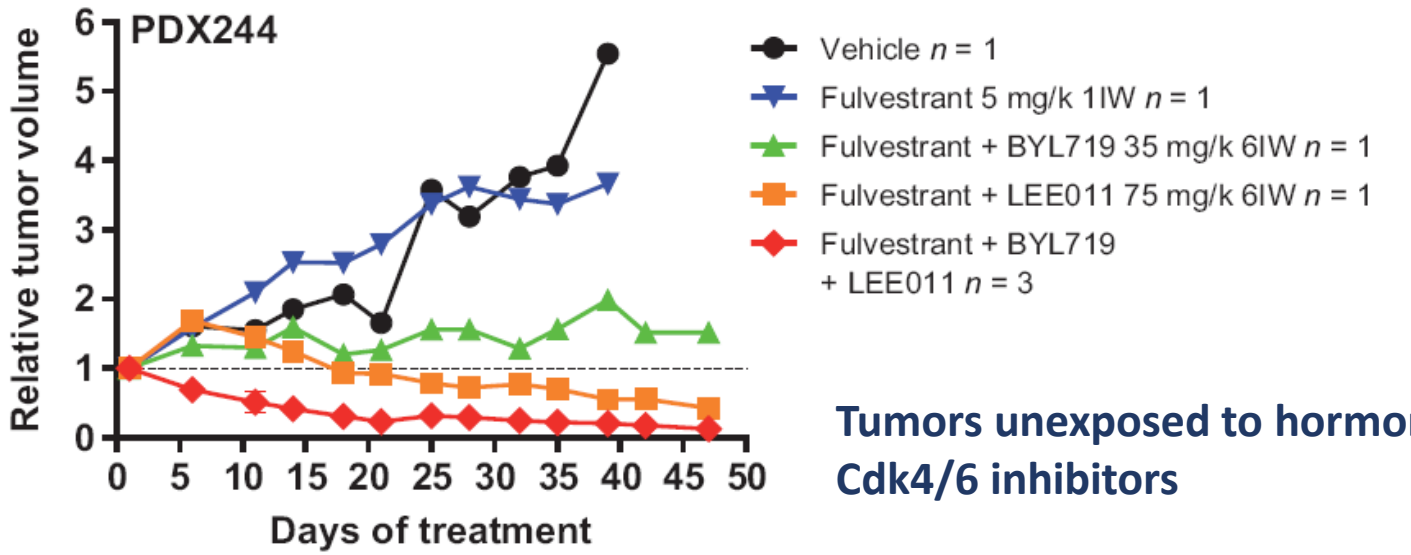
Rationale to combine CDK4/6i plus ET with PIK3i or mTORi

- Addition of a PI3K inhibitor to palbociclib delayed the resumption of S phase entry and abrogated the accumulation of cyclin D1 *(Herrera-Abreu et al. 2016).*
- mTOR pathway inhibition synergised with CDK4/6 inhibition to prevent resumption of proliferation of breast cancer cells, inducing a significant downregulation of E2F target genes *(Michaloglou et al. 2018).*
- Reduced mTOR signalling can augment senescence induced by CDK4/6 inhibition *(Yoshida et al. 2016)*



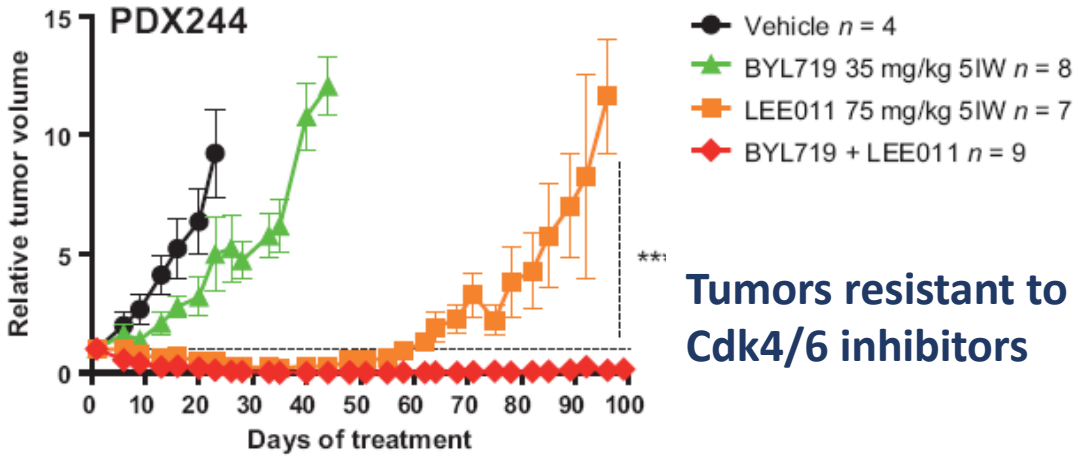
Portman, Endocrine-Related Canc 2019

Synergistic effect of CDK4/6 inhibitor and PIK3CA inhibitor in xenografts



Tumors unexposed to hormones and Cdk4/6 inhibitors

In palbociclib resistant tumor (due to Rb loss or mutation, or Cyclin E gain), **the combination seems not able to restore sensitivity to palbociclib, but early use of combination is able to prevent the onset of resistance**



Tumors resistant to Cdk4/6 inhibitors

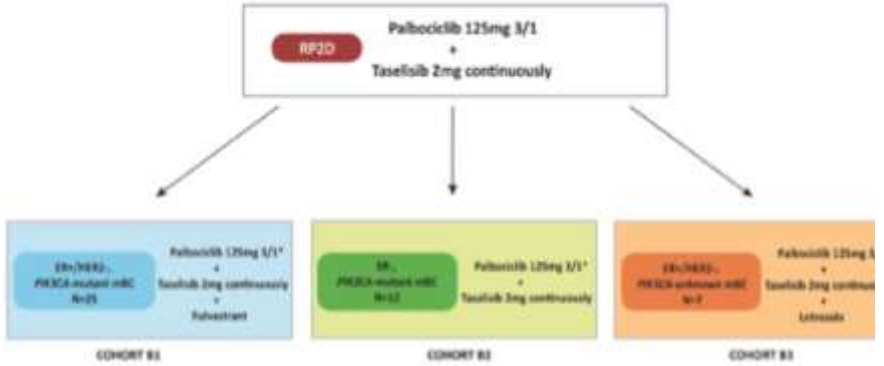
Herrera-Abreu, Canc Res 2016

Clinical trials with CDK4/6 inhibitors in combination with inhibitors of PI3k pathway and endocrine therapy

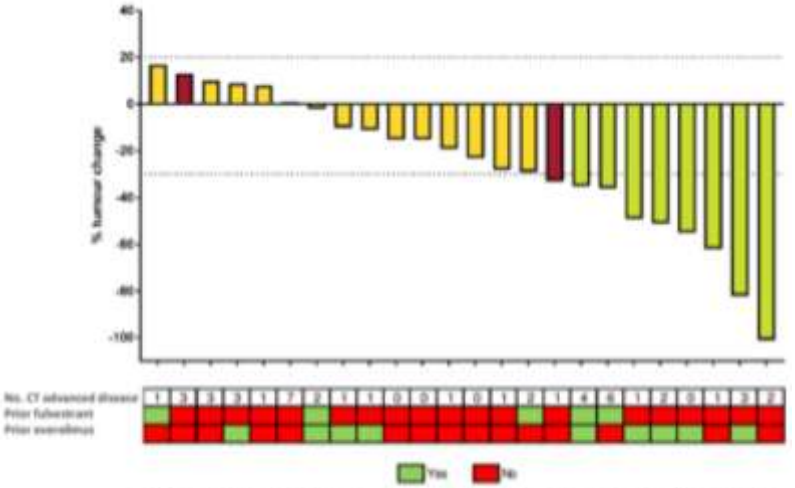
NCT number	Phase	Estimated/actual participants	PI3K pathway target	PI3K pathway inhibitor	Stage	Endocrine therapy/CDK4/6 inhibitor backbone
03006172	I	156	PI3 Kinase	GDC-0077	Advanced	AI, fulvestrant/palbociclib
02154776	I	13	PI3 Kinase	Buparlisib	Advanced	AI/ribociclib
01872260	Ib	253	PI3 Kinase	Alpelisib	Advanced	AI/ribociclib
02684032	I	120	PI3 Kinase/mTOR	Gedatolisib	Metastatic	AI, fulvestrant/palbociclib
01655225*	I	130	PI3 Kinase/mTOR/DNA-PK	LY3023414	Advanced	AI, fulvestrant/abemaciclib
02057133*	Ib	198	PI3 Kinase mTOR/DNA-PK	LY3023414 Everolimus	Metastatic	AI, fulvestrant/abemaciclib
01857193	Ib	132	mTOR	Everolimus	Advanced	AI/ribociclib
03128619	I, II	102	PI3 Kinase	Copanlisib	Stage I–IV	AI/palbociclib
02088684	Ib, II	70	PI3 Kinase	Alpelisib and buparlisib	Advanced	Fulvestrant/ribociclib
02732119	I, II	51	mTOR	Everolimus	Advanced	AI/ribociclib
02599714	I, II	54	mTORC1/2	Vistusertib	Metastatic	Fulvestrant/palbociclib
02871791	Ib, II	32	mTOR	Everolimus	Metastatic	AI/palbociclib

PIPA: taselisib (T) plus palbociclib (P) and fulvestrant (FUL) in *PIK3CA*-mutant (mt) ER-positive advanced breast cancer

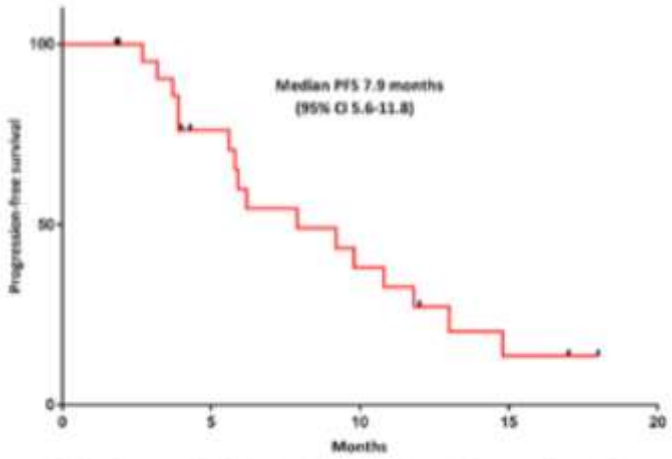
- 24 assessable patients
- Most common AEs were neutropenia (80%), fatigue (50%), mucositis (50%) and thrombocytopenia (30%).
- Most common grade 3/4 AEs were neutropenia (57%) and rash (11%).



Characteristic		B1 (n=25)
Median age, years	No. (range)	57 (42-74)
Median prior lines of therapy for advanced disease	No. (range)	3 (1-9)
Prior chemotherapy (CT) for advanced disease (%)	Yes	20 (80)
	No	5 (20)
Prior lines of CT for advanced disease	0	5
	1	9
	2	4
	>2	7
Prior ET for advanced diasease (%)	Yes	25 (100)
	No	0 (0)
Prior Tamoxifen for advanced disease (%)	Yes	4 (16)
	No	21 (84)
Prior AI for advanced disease (%)	Yes	23 (92)
	No	2 (8)
Prior everolimus (%)	Yes	10 (40)
	No	15 (60)
Prior fulvestrant (%)	Yes	6 (24)
	No	19 (76)

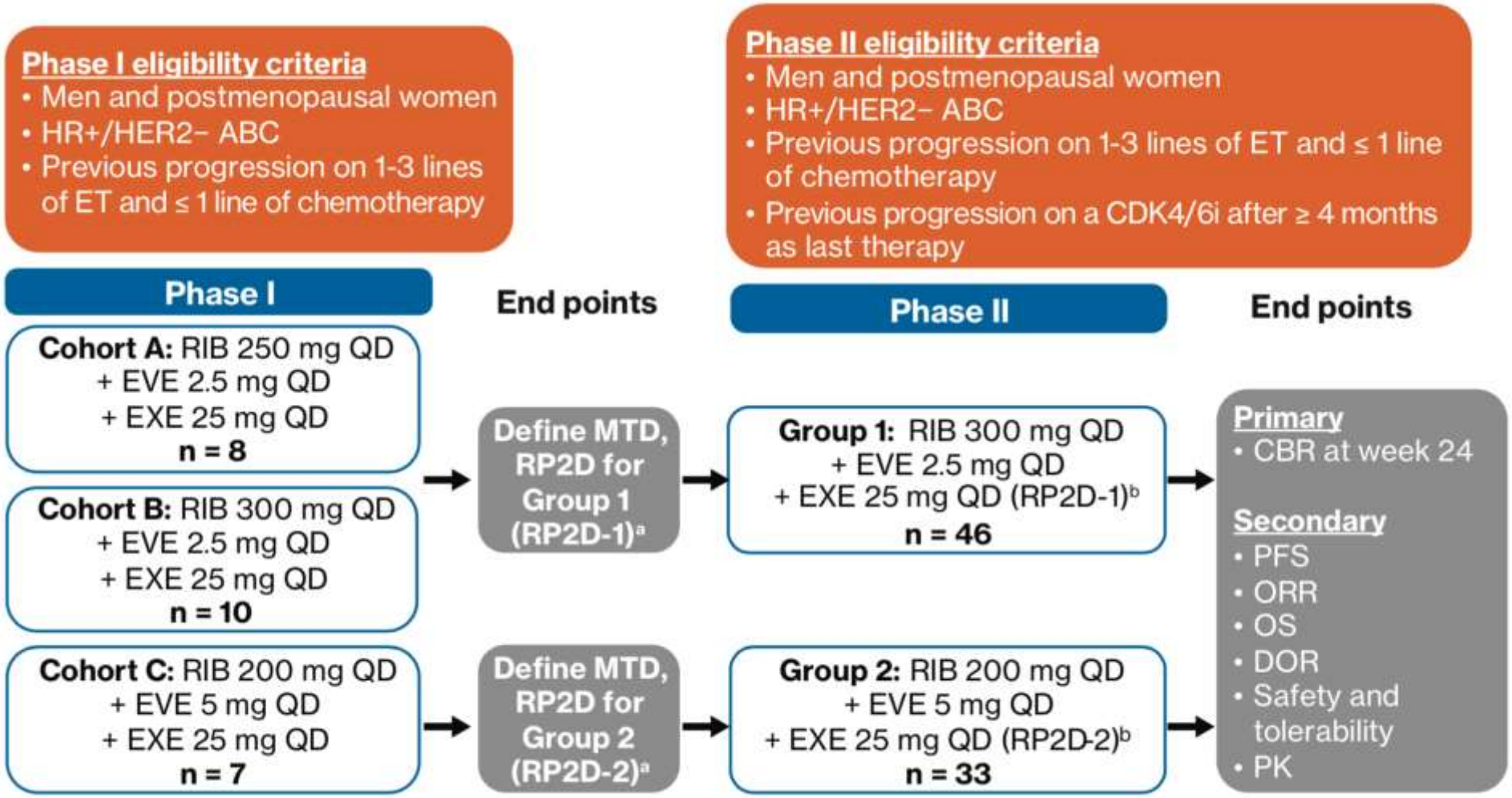


RECIST response as best tumour change and best overall response for 24 measurable *PIK3CA*-mutant ER+ve/HER2-ve breast cancer patients (cohort B1)



PFS for 24 assessable *PIK3CA*-mt ER+ve/HER2-ve mBC patients (cohort B1), all treated with palbociclib + taselisib + fulvestrant triplet

TRINITY-1 study design



A total of 95 ET-refractory and post-CDK4/6i evaluable for efficacy

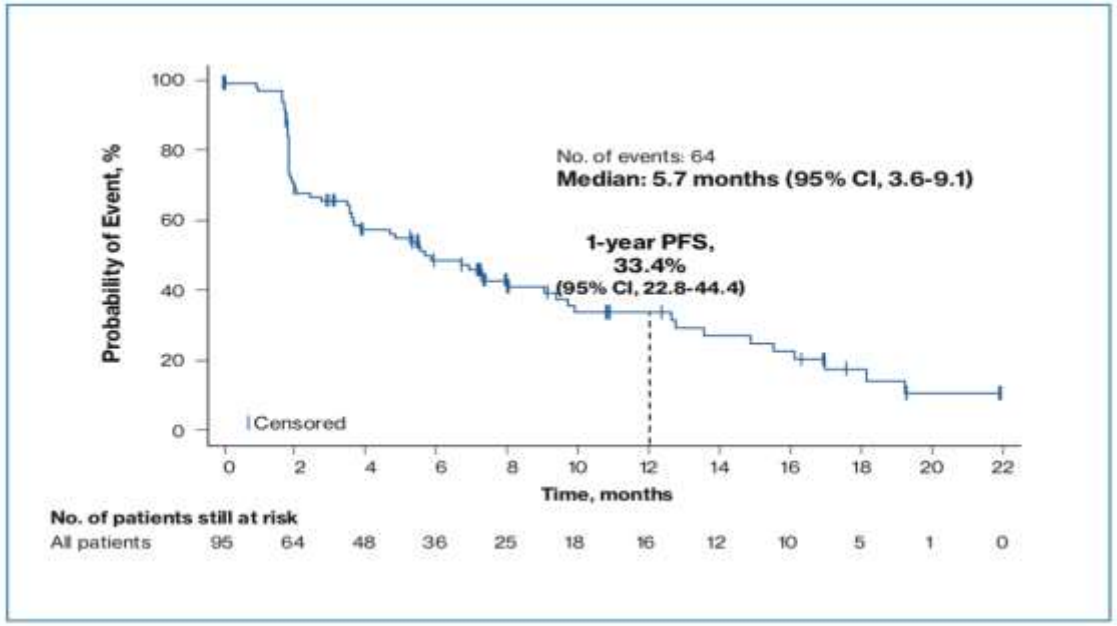
- Phase I: n = 17;
- Phase II: n = 78;

Baseline ctDNA *PIK3CA* and *ESR1* mutation analyses evaluated in 89 patients.

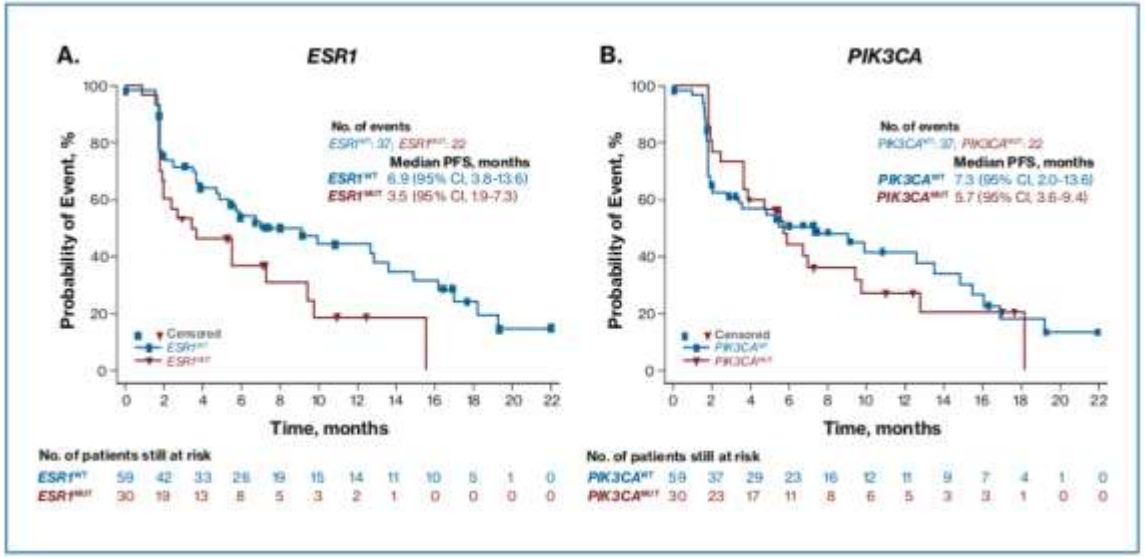
Bardia, ASCO 2019

Efficacy results of Everolimus+ Examestane+Ribociclib

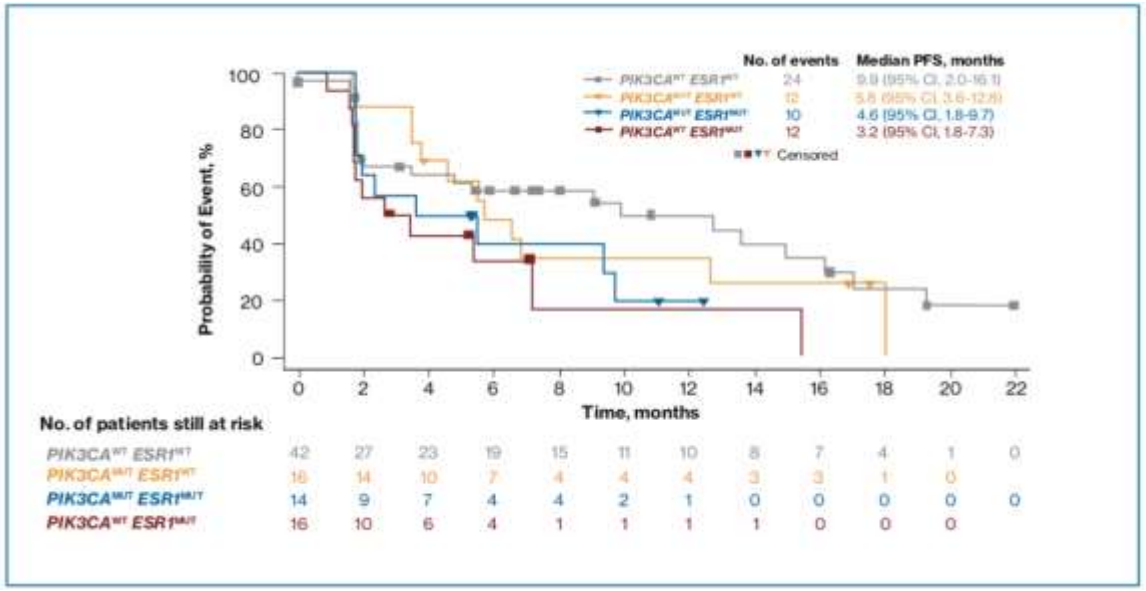
Best overall response	
ORR	8%
CBR 24w	39%
DCR	56%
DOR median	5.6 mos



Bardia, ASCO 2019

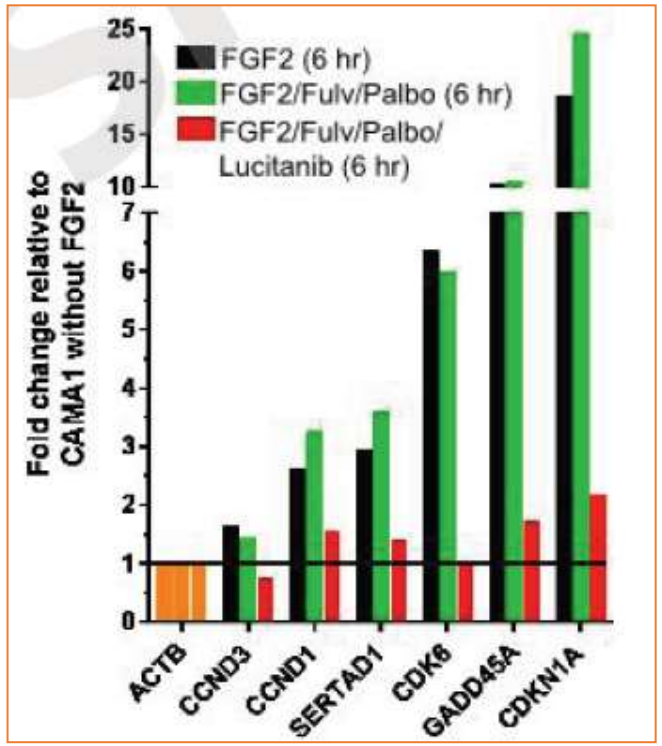


Progression-Free Survival per Baseline ctDNA Genotype: *ESR1* and *PIK3CA*



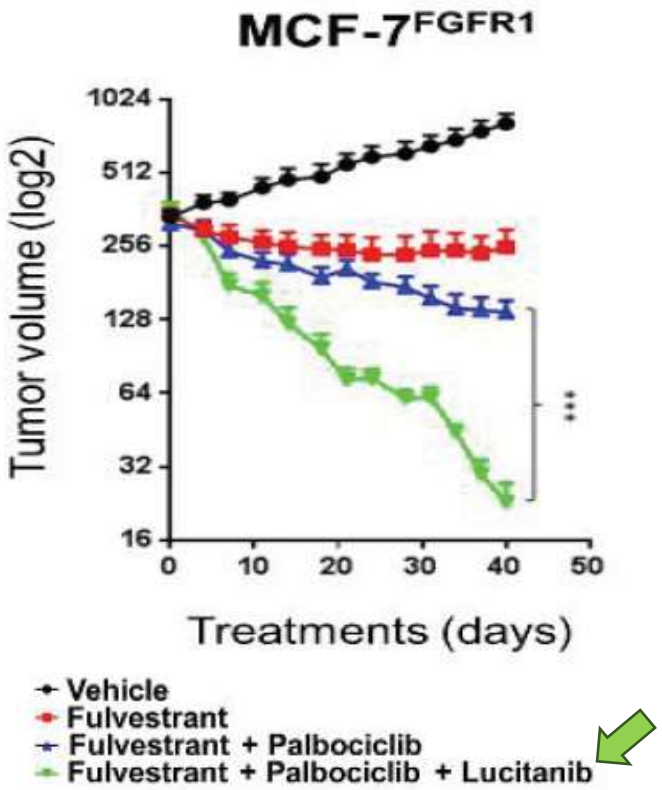
PFS per Baseline ctDNA Genotype: *PIK3CA* With or Without *ESR1*

FGFR1 amplification can induce resistance to CDK4/6 inhibitor



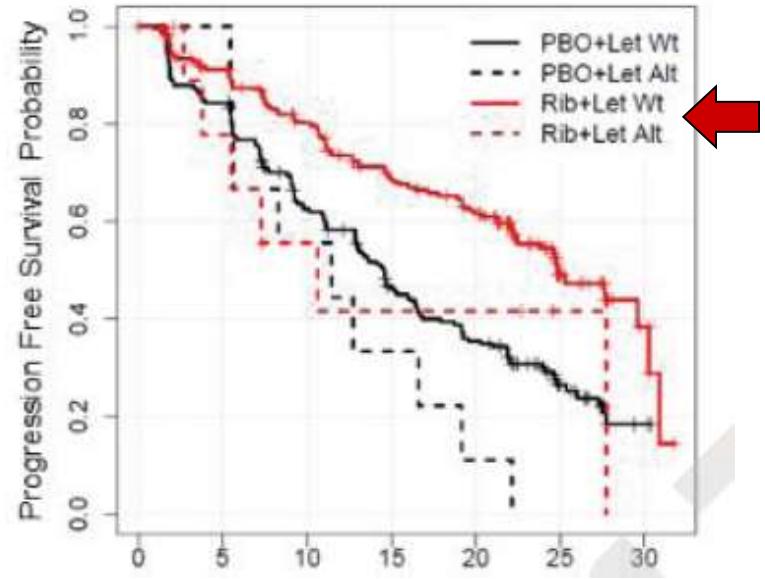
FGFR1 potently induces the expression of CCND1 and CDK6 mRNA

Formisano, SABCS 2017



CCND1 and ERK pathways are possible mechanisms of FGFR1-induced resistance

FGFR1 ampl in plasma tumor DNA correlates with resistance to ribociclib in Monaleesa2



Legend	Group	N	Median PFS	HR (95% CI)	p
	Rib + Let FGFR1/ZNF703 WT	202	24.84	2.14 (0.93 – 4.94)	$7.50e^{-02}$
	Rib + Let FGFR1/ZNF703 ALT	10	10.61		
	PBO + Let FGFR1/ZNF703 WT	205	14.59	1.61 (0.82 – 3.17)	$1.70e^{-01}$
	PBO + Let FGFR1/ZNF703 ALT	10	11.43		

Hortobagyi, SABCS 2017

Progression to CDK4/6i + ET - what next?

- Treatment after CDK4/6i plus ET failure is an unmet clinical need
- Several possible resistance mechanisms to be further studied for rational treatment strategy
- Available therapies (CTx, ET, TT) gain about 10 mos after first line CDKi, and about 4-6 months after second line
- No evidence of one option better than the others

  - ***CDK4/6 plus ET beyond progression*** supported by some preclinical evidences
  - ***mTOR-inhibitors plus ET*** possible usefull, but no data from prospective trials
  - ***PIK3-inhibitors plus ET*** effective in ER+/HER2- BC bearing PIK3 mutations, but very limited data after CDK4/6i failure
  - Combinations of ***PIK3i or mTORi plus CDK4/6i and ET*** have a strong rational, to be confirmed by ongoing trials