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GRUPPI ONCOLOGICI MULTIDISCIPLINARI

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

Alterazioni del pathway PIK3CA/AKT/PTEN: significato biologico, incidenza e caratteristiche delle pazienti

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Declaration of interests

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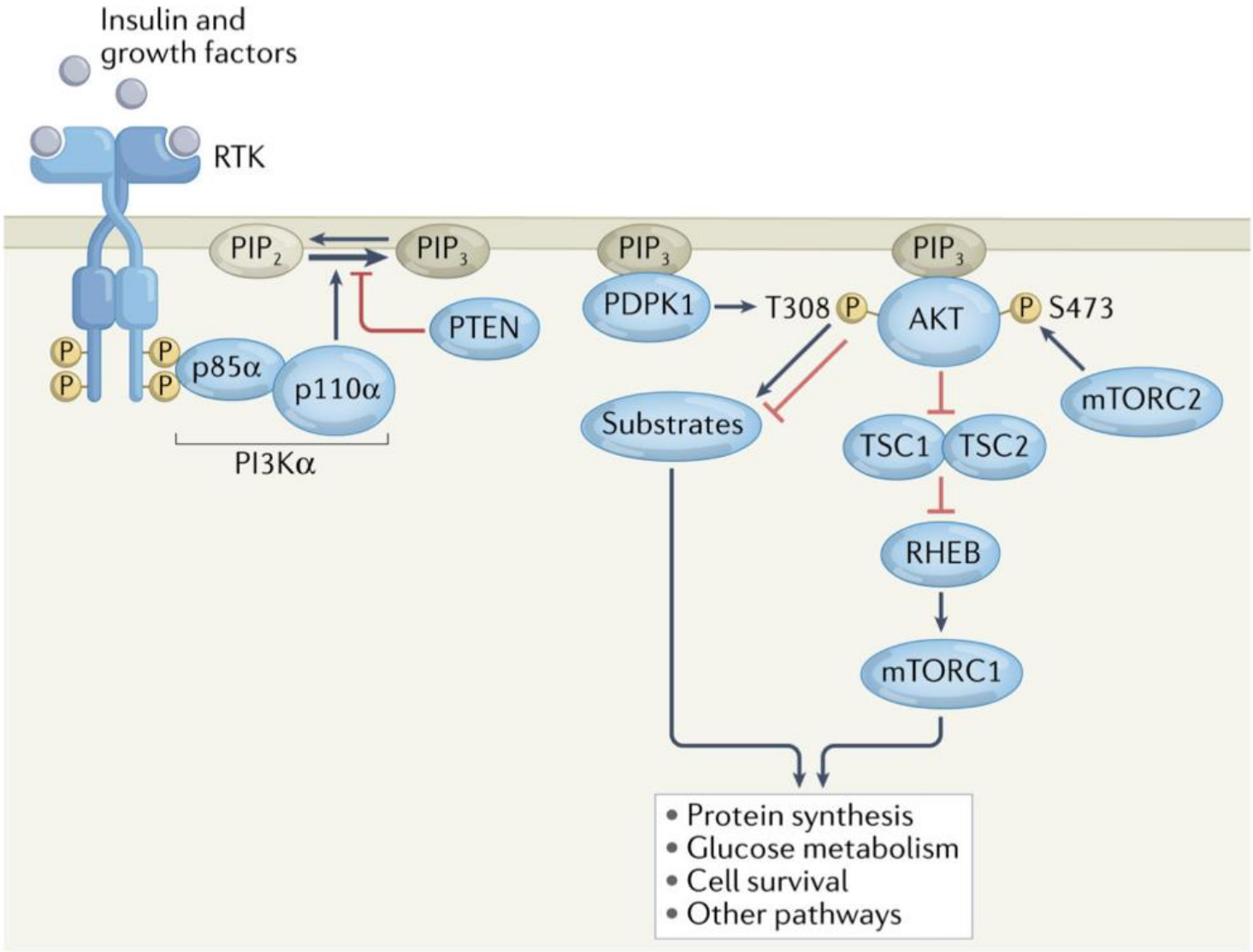
Non profit research support: GILEAD

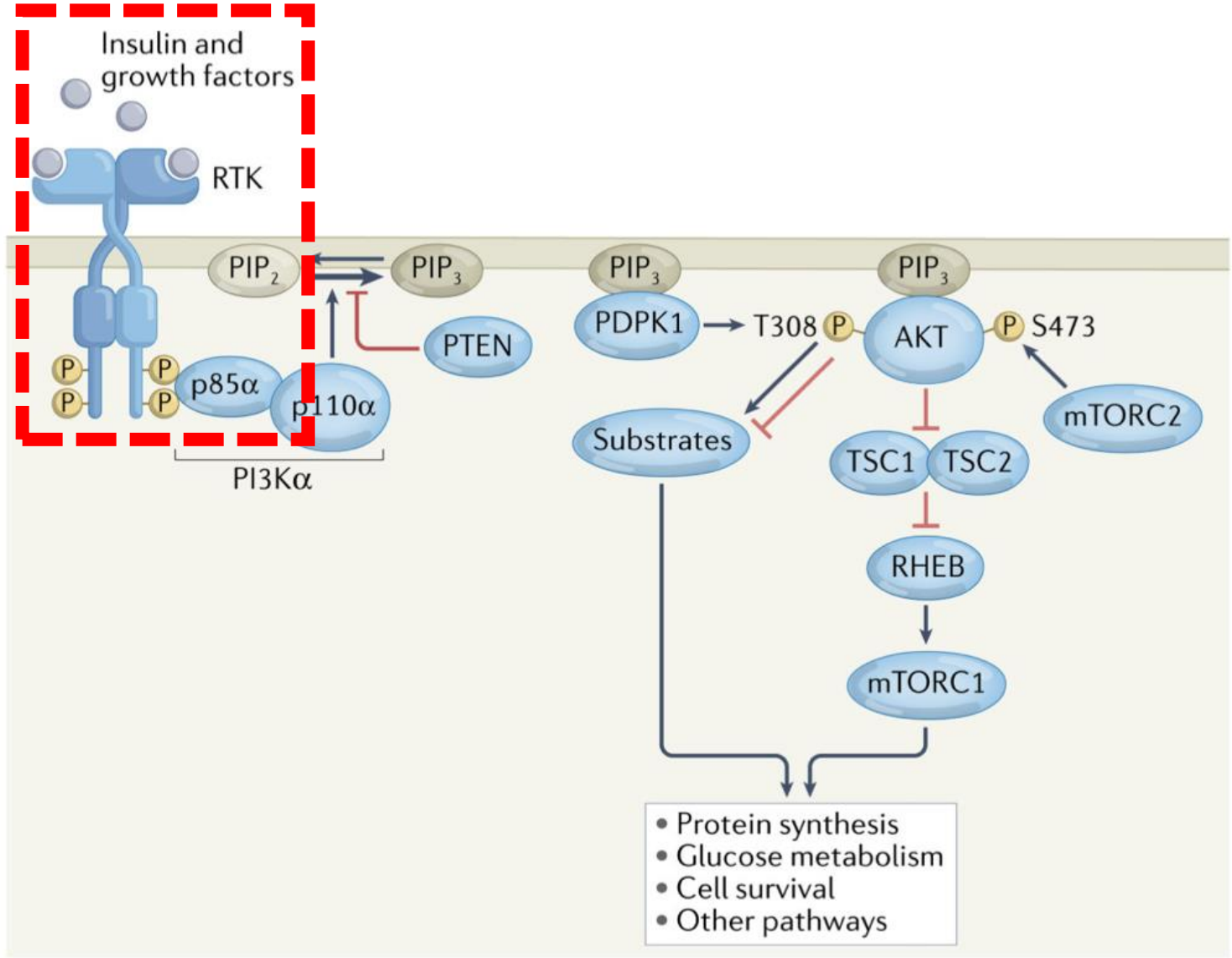
PI3K pathway in non-malignant cells



Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

PI3K pathway in non-malignant cells

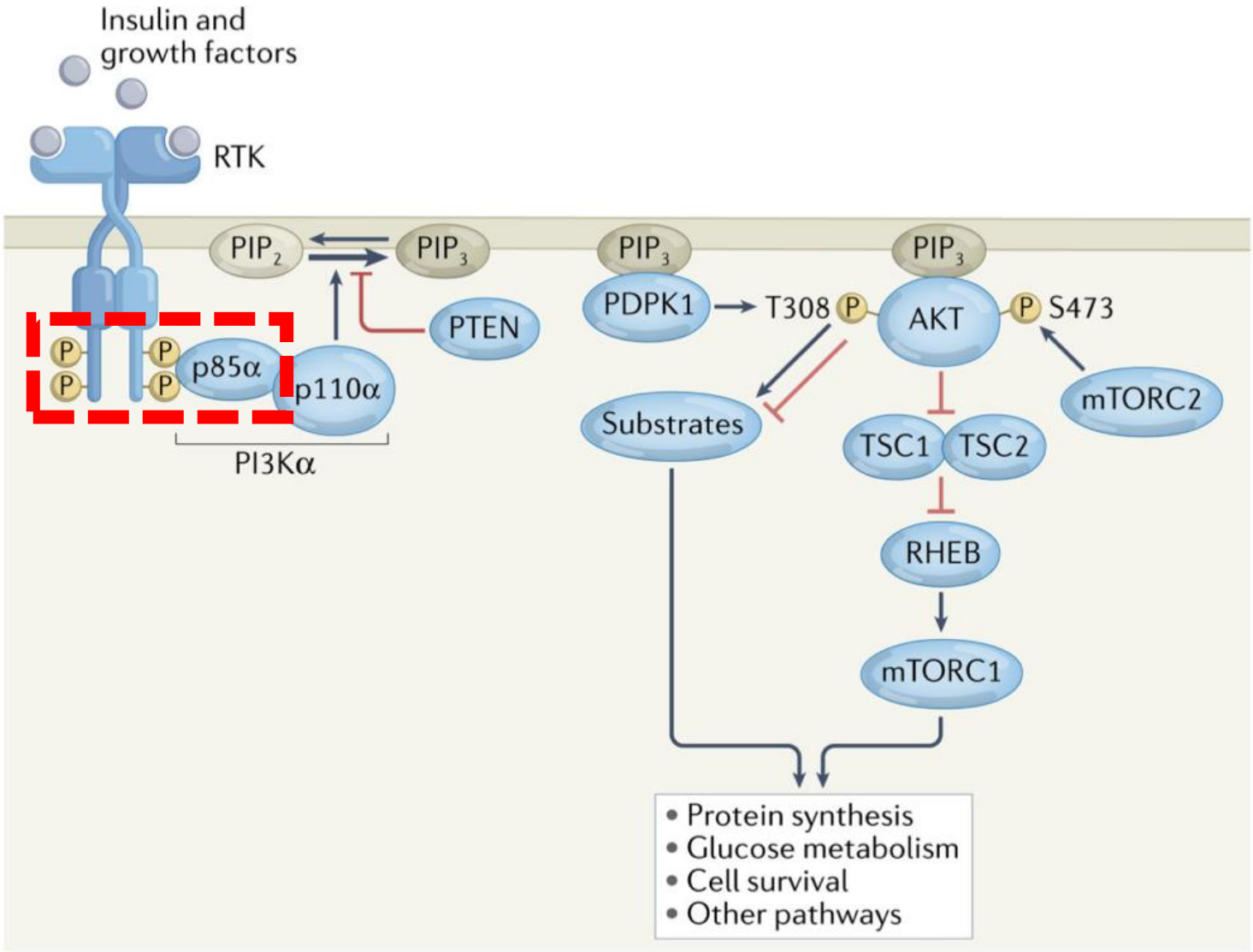
Insulin and other growth factors stimulate receptor tyrosine kinases (RTKs), leading to phosphorylation at C-terminal domain tyrosine residues.



Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

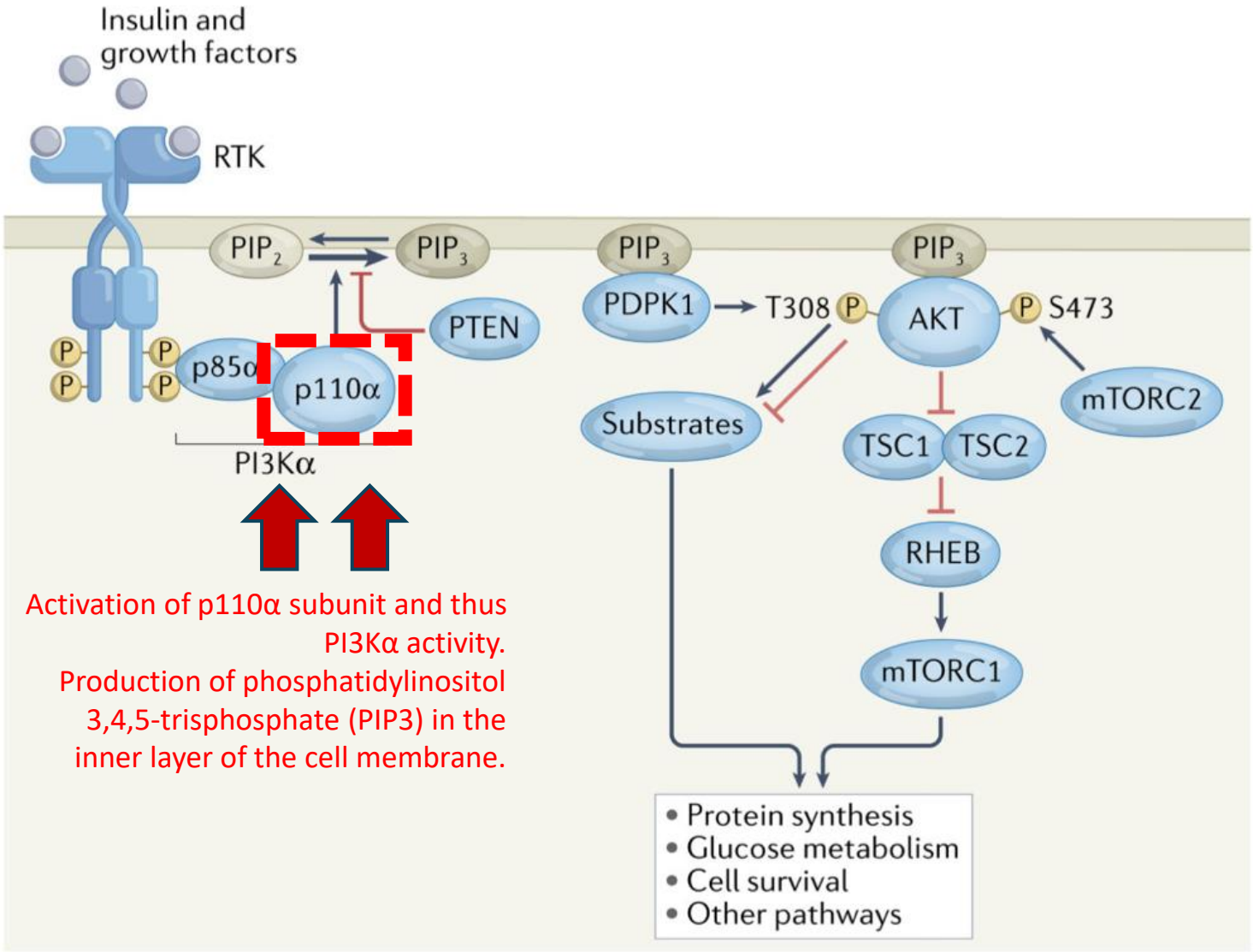
PI3K pathway in non-malignant cells

These phosphotyrosines bind to the regulatory p85α subunit of phosphatidylinositol 3-kinase-α (PI3Kα)



Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

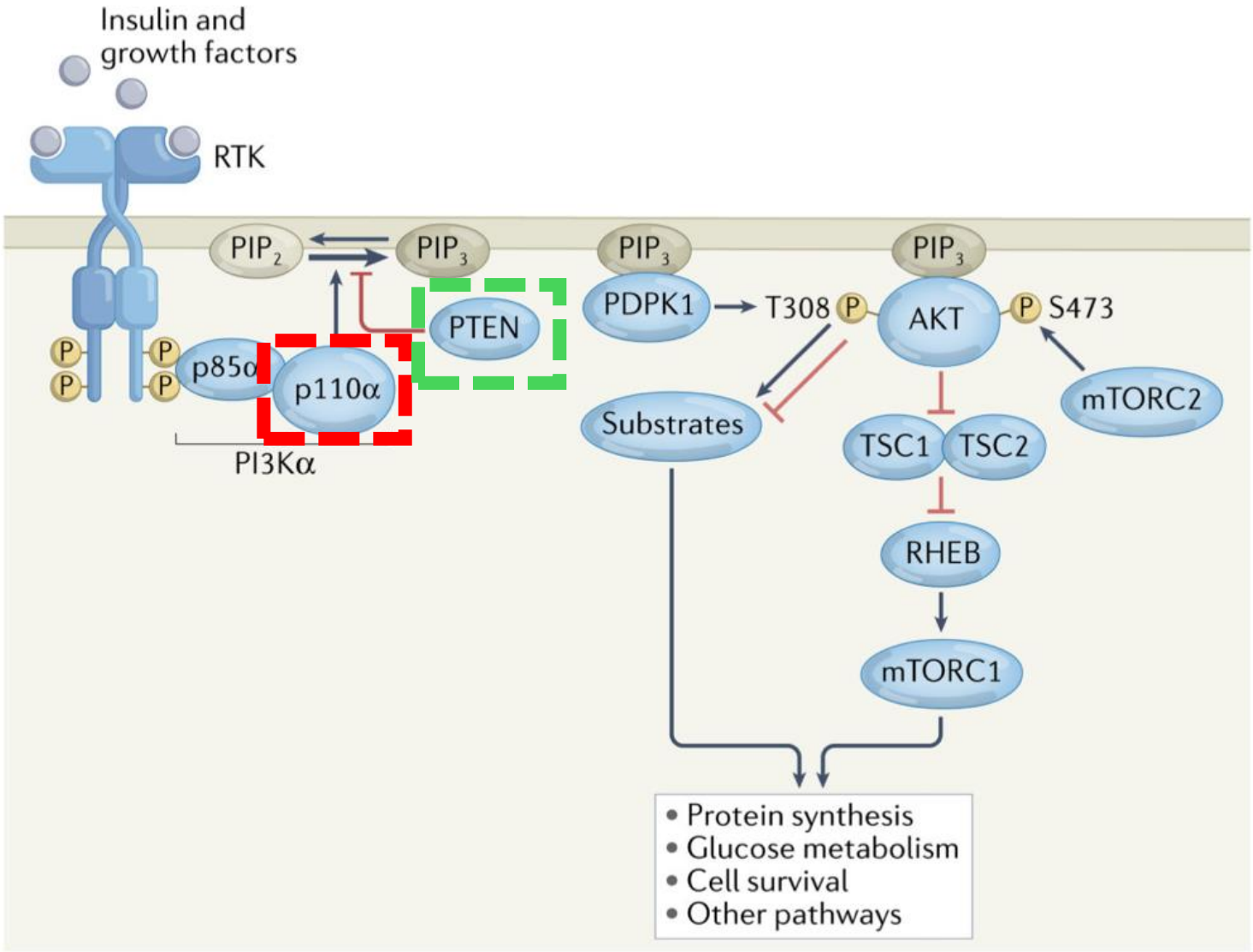
PI3K pathway in non-malignant cells



Activation of p110α subunit and thus PI3Kα activity.
Production of phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the inner layer of the cell membrane.

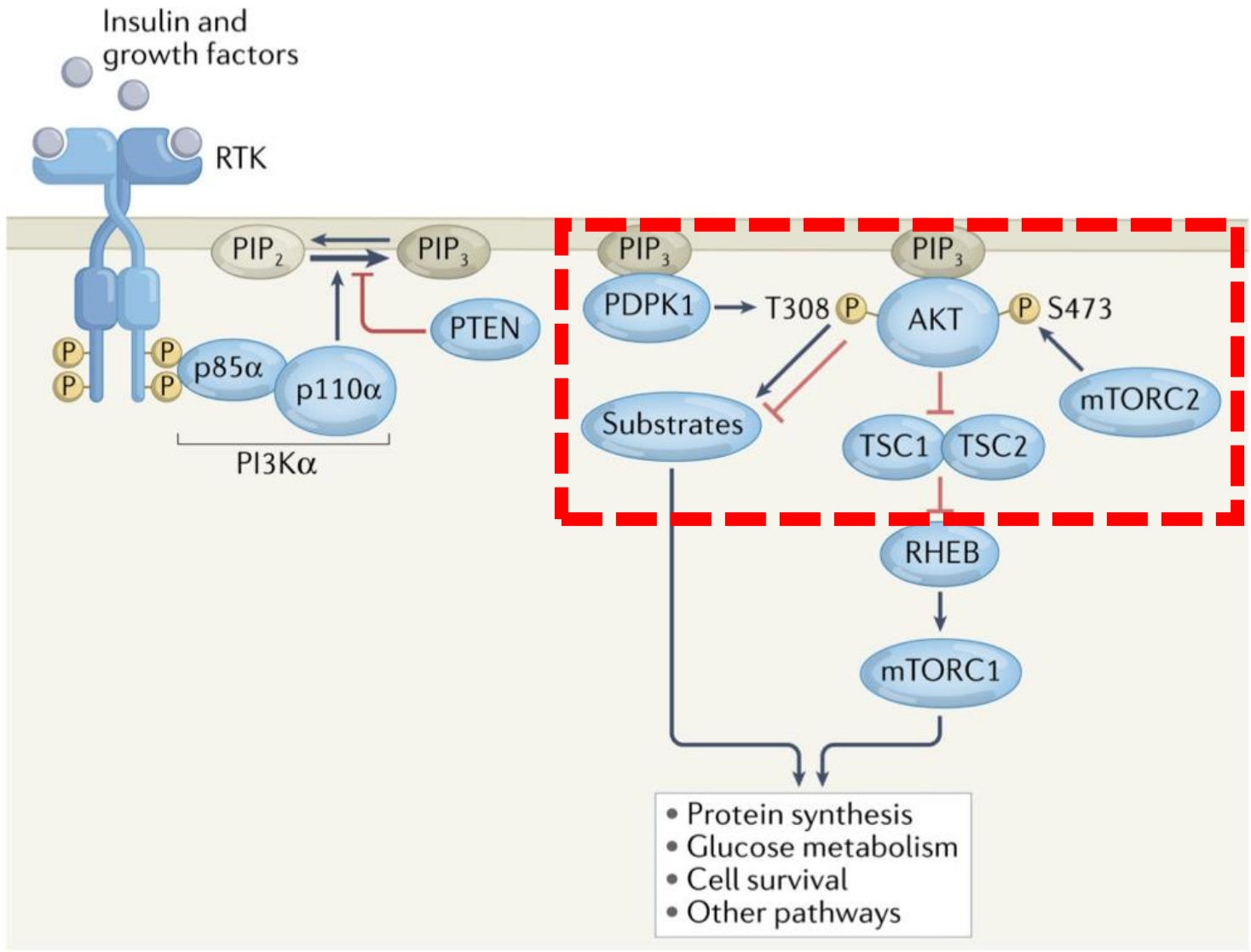
Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

PI3K pathway in non-malignant cells



Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

PI3K pathway in non-malignant cells



PIP3 recruits the serine/threonine kinases PDPK1 and AKT to the plasma membrane.

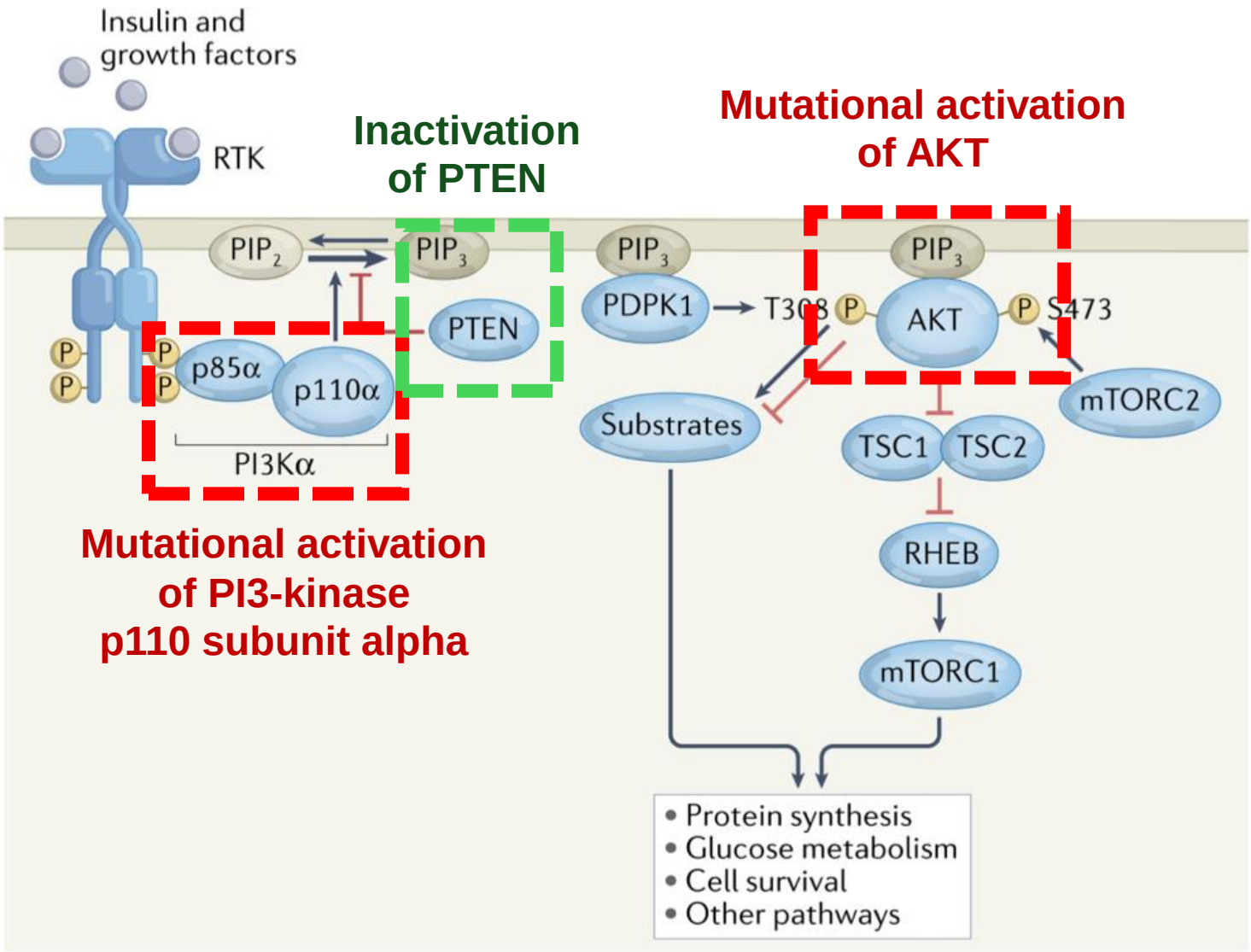
PDPK1 and the mTOR complex 2 (mTORC2) phosphorylate AKT

AKT phosphorylates multiple cellular substrates, including tuberin (TSC2)

Activation of mTOR complex 1 (mTORC1)

Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

Disruption of the PI3K pathway in cancer



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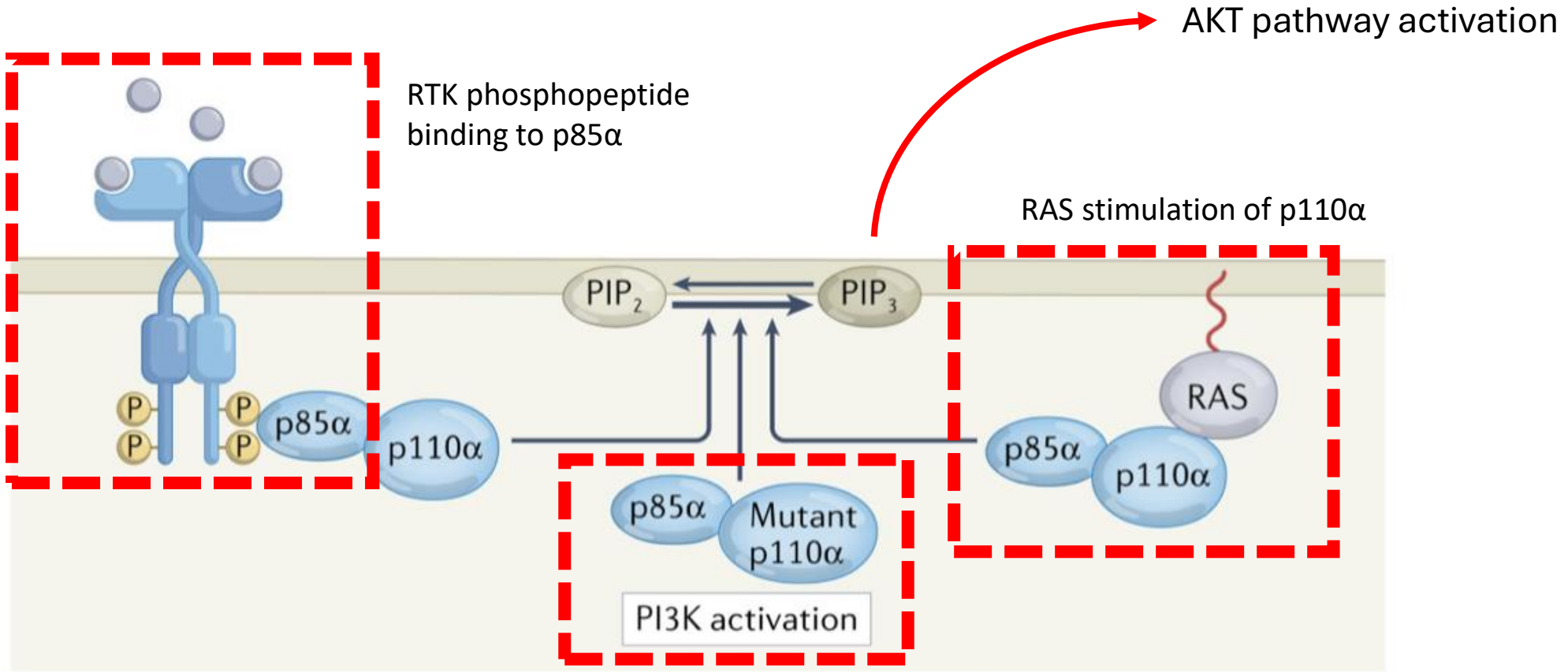
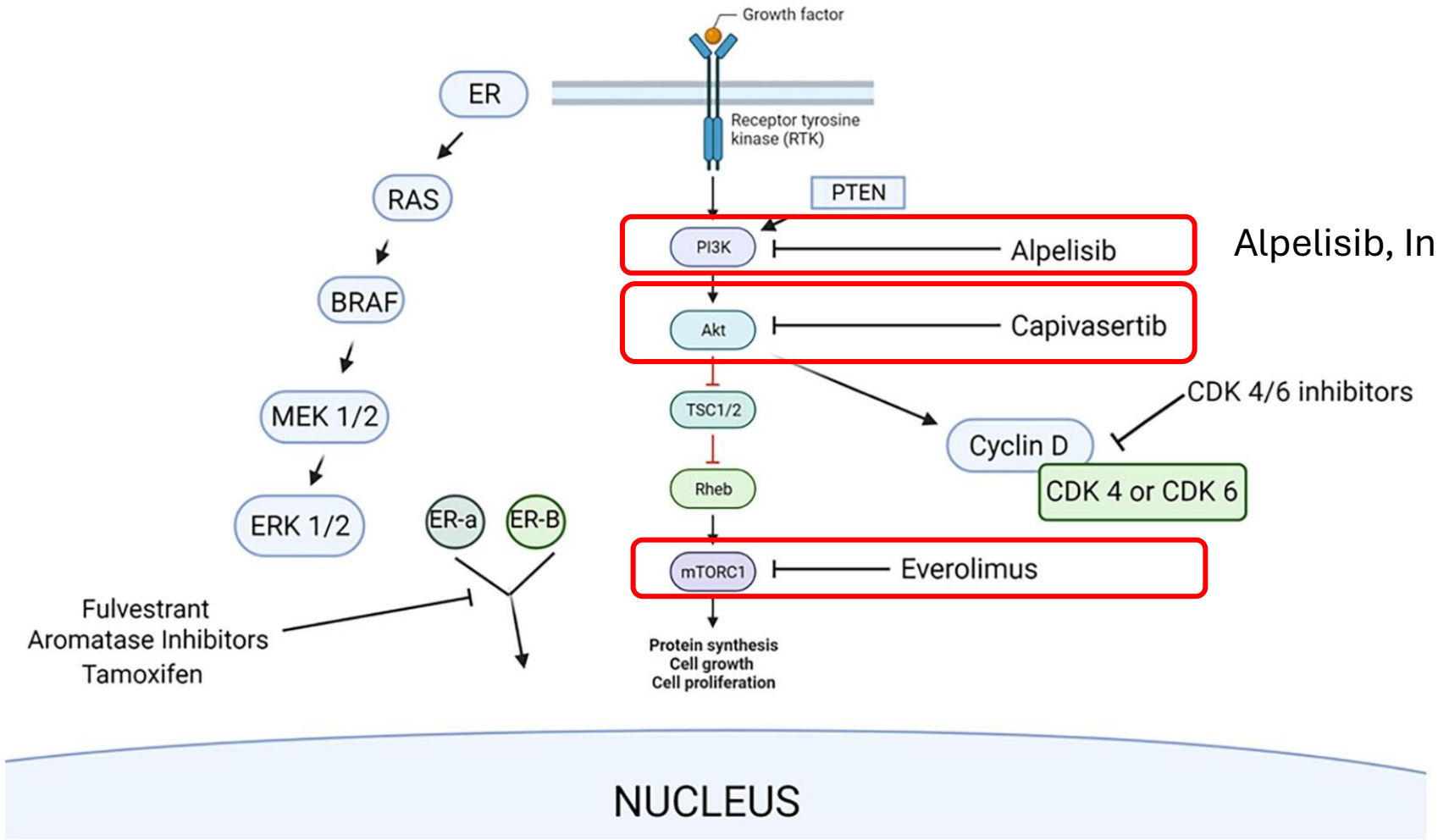


Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

Target agents in PI3K pathway



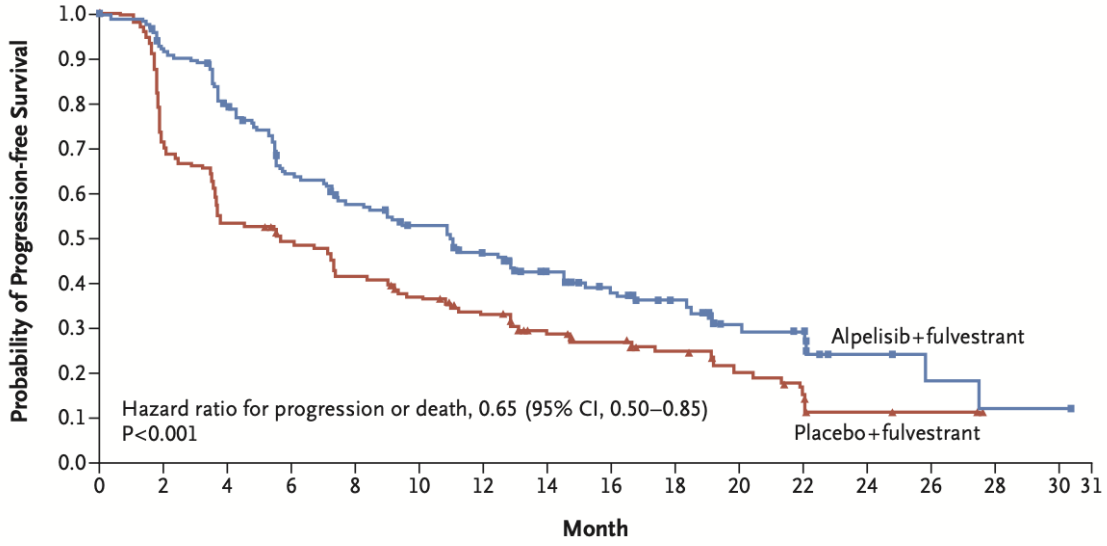
Alpelisib, Inavolisb, ect..

Luboff AJ et al. *Ann Pharmacother*. 2024;58(12):1229-1237

PFS with Fulvestrant + Alpelisib/placebo

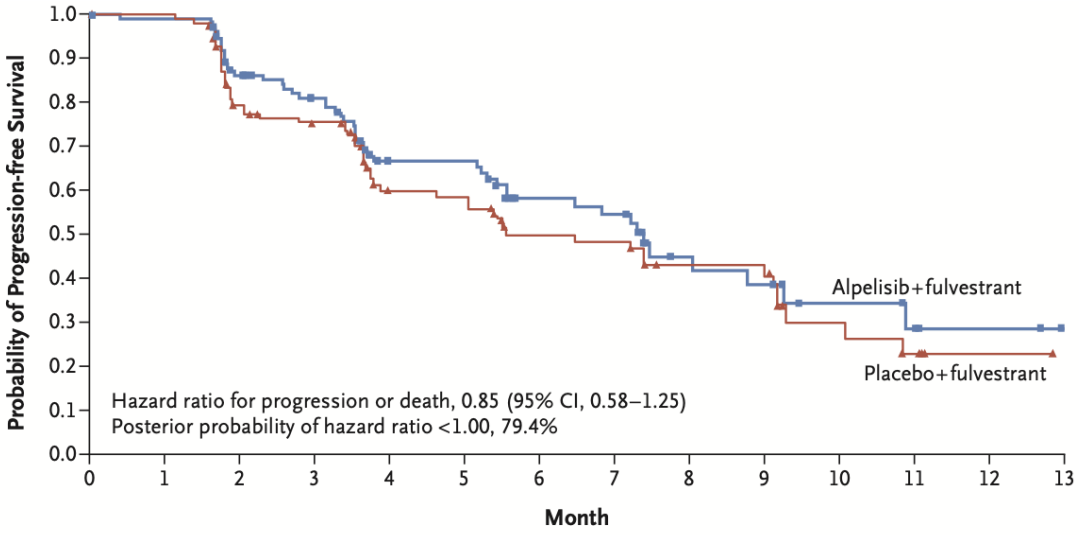
SOLAR-1 trial

Cohort with *PIK3CA-mutated* cancer



No. at Risk																	
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

Cohort without *PIK3CA-mutated* cancer



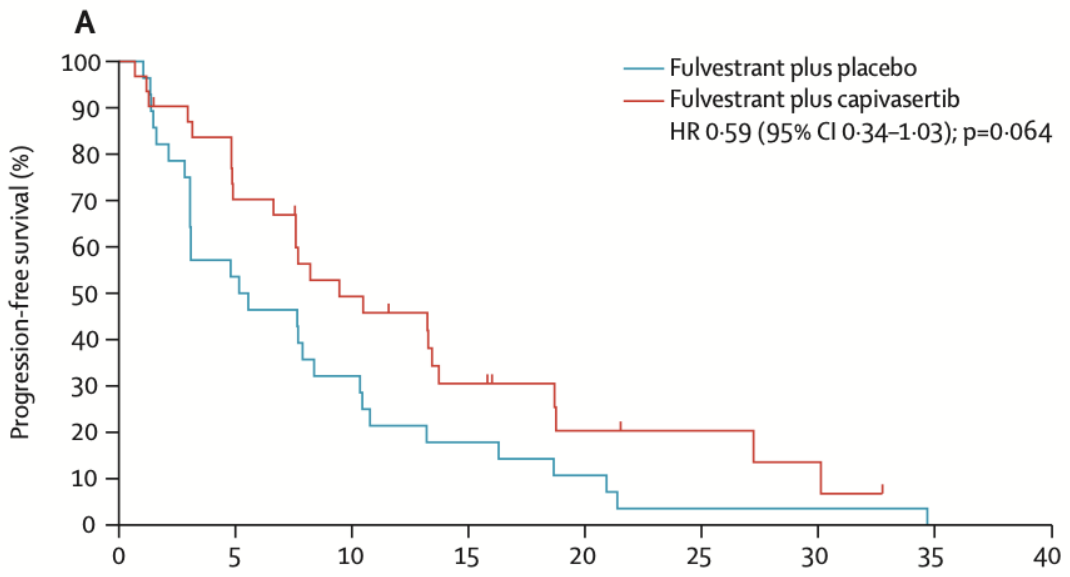
No. at Risk														
Alpelisib+fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo+fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0

André F et al. *N Engl J Med*. 2019;380(20):1929-1940

PFS with Fulvestrant + Capivasertib/placebo

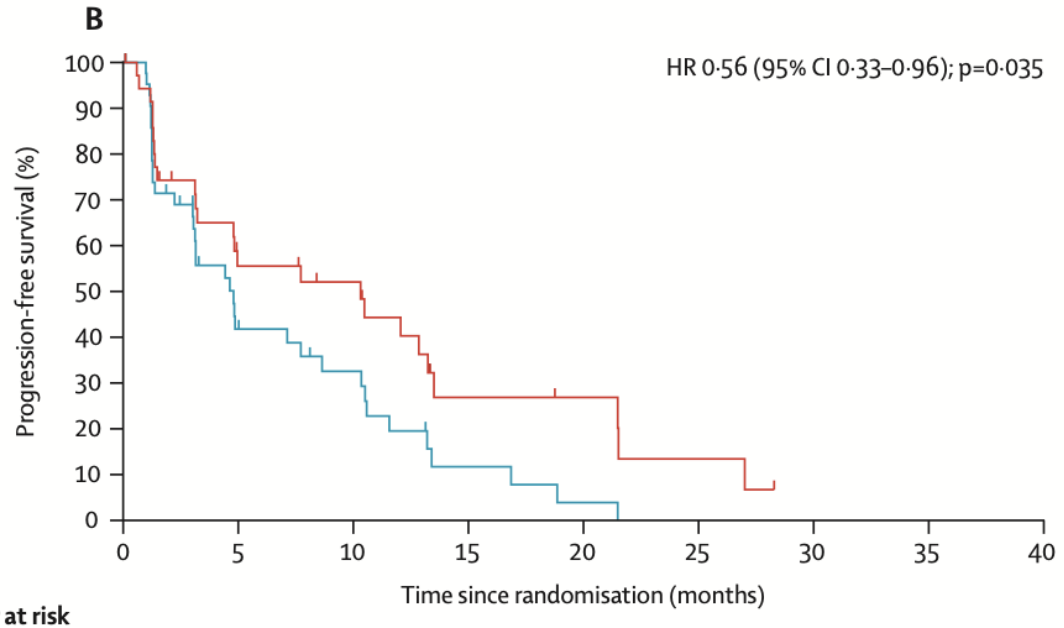
FAKTION trial

PI3K pathway altered subgroup



Number at risk (number censored)									
Fulvestrant plus placebo	28 (0)	15 (0)	9 (0)	5 (0)	3 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Fulvestrant plus capivasertib	31 (0)	21 (1)	14 (2)	8 (3)	4 (5)	3 (6)	2 (6)	0 (6)	0 (7)

PI3K pathway non-altered subgroup



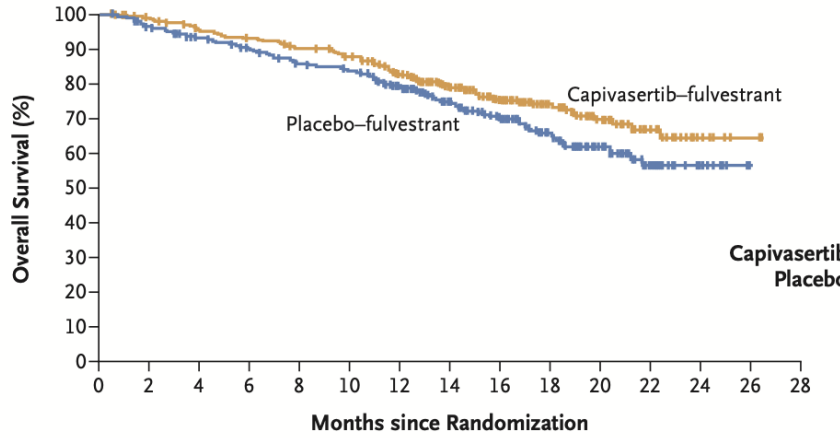
Number at risk (number censored)									
Fulvestrant plus placebo	43 (0)	14 (6)	10 (7)	3 (8)	1 (8)	0 (8)	0 (8)	0 (8)	0 (8)
Fulvestrant plus capivasertib	38 (0)	17 (6)	14 (8)	5 (11)	4 (12)	2 (12)	0 (13)	0 (13)	0 (13)

Jones RH et al. *Lancet Oncol*. 2020;21(3):345-357

PFS with Fulvestrant + Capivasertib/placebo

CAPitello-291 trial

A Overall Population

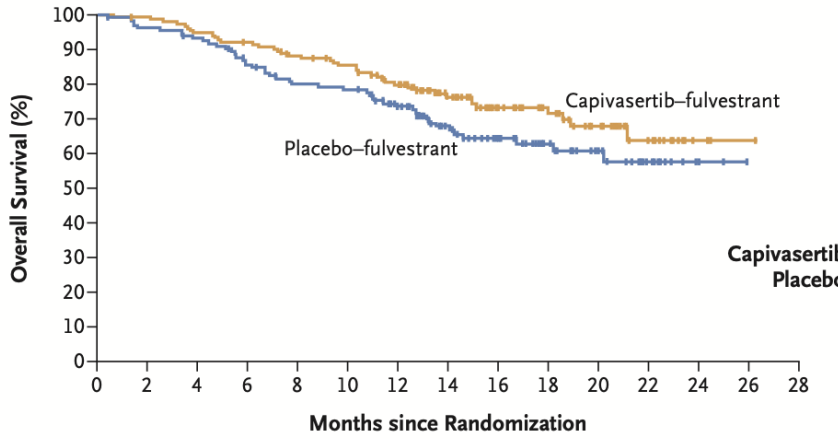


	No. of Patients	No. of Deaths
Capivasertib–Fulvestrant	355	87
Placebo–Fulvestrant	353	108

Adjusted hazard ratio for death, 0.74 (95% CI, 0.56–0.98)

No. at Risk															
Capivasertib–fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo–fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

B Patients with AKT Pathway–Altered Tumors



	No. of Patients	No. of Deaths
Capivasertib–Fulvestrant	155	41
Placebo–Fulvestrant	134	46

Adjusted hazard ratio for death, 0.69 (95% CI, 0.45–1.05)

No. at Risk															
Capivasertib–fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo–fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

Turner NC et al. *N Engl J Med*. 2023;388(22):2058-2070

PI3KCA mutation prevalence

Table 2 Description of Studies: Sample and Selected Demographics Relative to Clinical and Observational Studies of $HR^+/HER2^-$ mBC

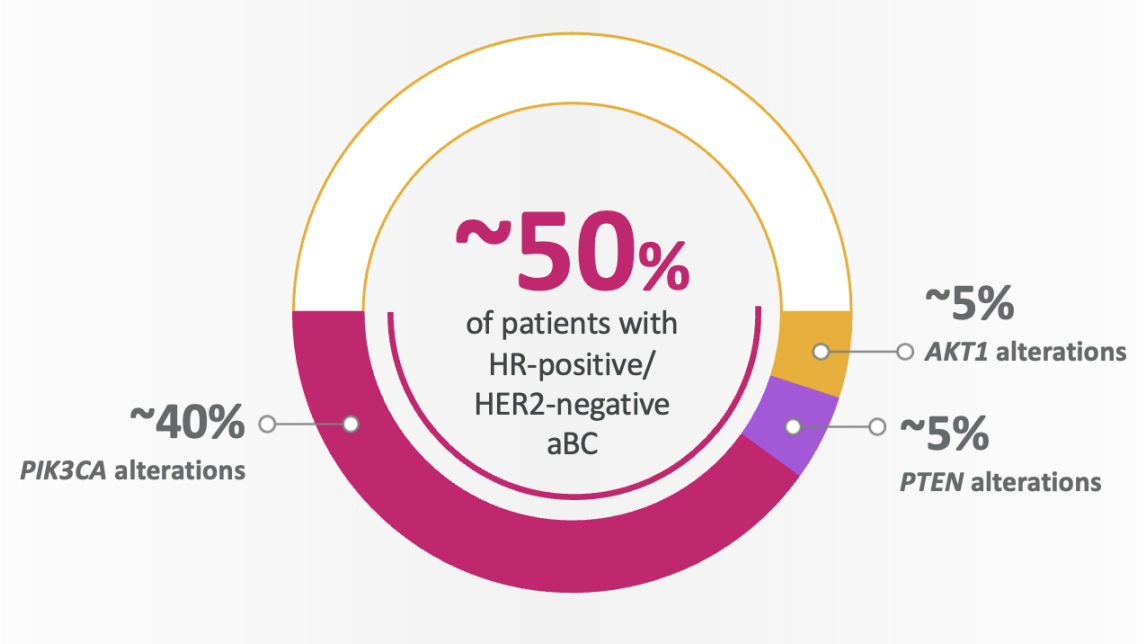
Study	Year	Study Phase	Type of Biopsy	Treatment Arms	$HR^+/HER2^-$ Sample Size Number	PIK3CA Mutant Number	PIK3CA Wild Type Number	PIK3CA Mutation Prevalence %	Median Age		ECOG PS, %				
									PIK3CA	Wild Type	0	1	2	3	Missing
Andre et al[18]	2018	III	Tissue	Placebo plus fulvestrant (SOLAR-1)	288	172	116	NA[a]	64	63	192	95	NR	NR	1
Juric et al[25]	2018	III	Liquid	Alpelisib plus fulvestrant	284	169	115	NA[a]	63	62	196	86	NR	NR	2
Baird et al[26]	2016	Ib	Liquid	Taselisib plus tamoxifen	30	4	26	13.3	53	37	63				
Baselga et al[27]	2018	III		Taselisib plus fulvestrant (SANDPIPER)	340	340	NR	NA[b]	NR	NR	NR	NR	NR		
	2018	III		Placebo plus fulvestrant	176	176	NR	NA[b]	NR	NR	NR	NR	NR		
Baselga et al[16]	2017	III	Tissue	Buparlisib plus fulvestrant (BELLE-2)	576	87[c]	199	30.4	62	58	40	2	<1		
Campone et al[28]	2017	III	Tissue	Placebo plus fulvestrant	571	113[c]	188	37.5	61	60	37	3	0		
Cristofanilli et al[29]	2016	III	Tissue	Palbociclib plus fulvestrant (PALOMA-3)	347	85[c]	180	32.1	58	57	57	43			
Turner et al[30]	2016	III	Tissue	Placebo plus fulvestrant	174	44[c]	86	33.8	56	55	63	35			
Di Leo et al[31]	2018	III	Tissue	Buparlisib plus fulvestrant (BELLE-3)	289	100[c]	132	43.1	60	60	39	1		1	
	2018	III	Tissue	Placebo plus fulvestrant	143	35[c]	81	30.2	62	64	34	1		2	
Dickler et al[32]	2016	II	Tissue	Taselisib plus fulvestrant	60	31	29	51.7	61	62	56.7	43.3			
Fleming et al[33]	2012	II	Tissue	Temsirolimus	21	5	16	23.8	NR	NR	48	52			
Hortobagyi et al[34]	2017	III	Tissue	Ribociclib plus letrozole	212	69	143	32.5	NR	NR	NR	NR	NR	NR	
	2017	III	Tissue	Placebo plus letrozole	215	55	142	25.6	NR	NR	NR	NR	NR	NR	
Juric et al[35]	2019	Ib	Tissue	Alpelisib plus fulvestrant	87	52	33	59.8	58	NR	NR	NR	NR		
Krop et al[36]	2016	II	Tissue	Pictilisib plus fulvestrant	89	38	45	42.7	60	68.5	31.5				
	2016	II	Tissue	Placebo plus fulvestrant	79	32	39	40.5	63	57	42				
Mayer et al[37]	2014	Ib	Tissue	Buparlisib plus letrozole (intermittent vs. continuous dosing)	51	16	35	31.4	55	NR	NR	NR	NR		
Mayer et al[38]	2016	Ib	Liquid	Alpelisib plus letrozole	26	16	10	61.5	53	NR	NR	NR	NR		
Moynahan et al[39]	2017	III	Liquid	Everolimus plus exemestane	357	169	188	47.3	NR	NR	NR	NR	NR	NR	
	2017	III	Liquid	Placebo plus exemestane	193	69	124	35.8	NR	NR	NR	NR	NR	NR	

Abbreviations: BELLE-2 = Buparlisib Breast Cancer Clinical Evaluation-2; BELLE-3 = Buparlisib Breast Cancer Clinical Evaluation-3; ECOG PS = Eastern Cooperative Oncology Group performance status; $HER2^-$ = human epidermal growth factor receptor 2-negative; HR^+ = hormone receptor-positive; mBC = metastatic breast cancer; NR = not reported; PALOMA-3 = Palbociclib: Ongoing Trials in the Management of Breast Cancer; *PIK3CA* = PIK3 p110α subunit, phosphatidylinositol-4,5- bisphosphate 3-kinase catalytic subunit alpha; SANDPIPER = A Study of Taselisib + Fulvestrant Versus Placebo + Fulvestrant in Participants With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy.

[a] *PIK3CA* mutation prevalence in SOLAR-1 is not reportable as such because patients were selected based on *PIK3CA* mutation status to enrich for tumors with a mutation.

[b] *PIK3CA* mutation prevalence in SANDPIPER is not reportable because only data on the *PIK3CA* population was reported at time of this publication.

[c] Only a subset of the total sample of $HR^+/HER2^-$ sample was tested for the *PIK3CA* mutation.



Courtesy of AstraZeneca Medical

Mollon LE et al. *Clin Breast Cancer*. 2020;20(3):e232-e243

Cancer Genome Atlas Network. *Nature*. 2012;490:61–70; Martorana F et al. *Front Pharmacol*. 2021;12:662232; Miricescu D et al. *Int J Mol Sci*. 2020;22(1):173; Smyth LM et al. *Cancer Discov.* 2020;10(4):526–535; Paplomata E, O'Regan R. *Ther Adv Med Oncol*. 2014;6(4):154–166.

New ET options for ET-resistant disease (biomarker selected)

	Primary	Secondary	Sensitive
eBC	Relapse on first 2 yrs of adj ET	Relapse <1y off adjuvant ET	Relapse > 1y off adj ET/ De novo mBC
mBC	PD ≤24 wks from start of ET for mBC	PD >24 wks from start of ET for mBC	PFS >12 mo with 1L ET+ CDK4/6is*

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Trial	Design	N.	Biomarker	Prior CDK %	Primary res %	<1y of adj ET	PFS mo.	HR
EMERALD[1]	SoC ET **Elacestrant**	**228**	**ESR1**	**100**	**~ 10** (ITT) **0** (ESR1mut)	**-**	1.9 **3.8**	0.55 (0.39-0.77)
EMBER-3[2]	SoC ET **Imlunestrant**	**661**	**ESR1**	**~ 60**	**~ 9** (ITT) **0** (ESR1mut)	**~ 30** (ITT) **20** (ESR1mut)	3.8 **5.5**	0.62 (0.46-0.82)
CAPItello-291[3]	Ful + Placebo **Ful+Capivasertib**	**289**	**AKT path**	**~ 70**	**~ 40**	**-**	3.1 **7.3**	0.50 (0.38-0.65)
INAVO-120[4]	SoC ET **Elacestrant**	**228**	**PIK3CA**	**1**	**34**	**66**	7.3 **15**	0.43 (0.32-0.59)
PALOMA-3[5] MONALEESA-3[6] MONARCH-2[7]	Fulv + Placebo **Ful+CDK4/6is**	-	-	**0**	- - **~ 25**	**~ 5** **~ 5** -	-	-

[1]Bidard FC K et al, JCO 2022; [2]Jhaveri KL et al, NEJM 2024; [3]Turner NC et al, NEJM 2023; [4]Turner NC et al, NEJM 2024 ; [5]Cristofanilli M et al, Lancet Oncol 2016; [6]Slamon DJ et al, JCO 2018; [5]Sledge GW et al, JCO 2017

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EMERALD[1]	SoC ET **Elacestrant**	**228**	**ESR1**	**100**	**~ 10** (ITT) **0** (ESR1mut)	-	1.9 **3.8**	0.55 (0.39-0.77)
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PALOMA-3[5] MONALEESA-3[6] MONARCH-2[7]	Fulv + Placebo **Ful+CDK4/6is**	-	-	**0**	- - **~ 25**	**~ 5** **~ 5** -	-	-

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Targeting AKT pathway in ET-resistant disease: CAPItello-291

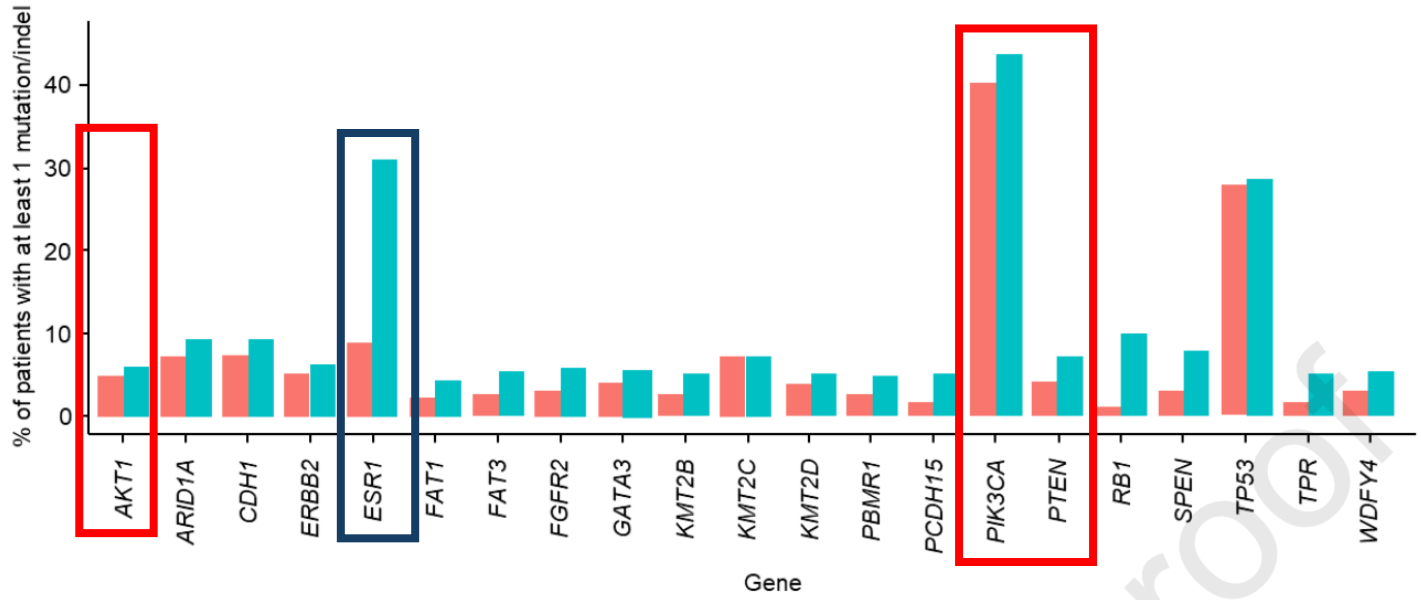
Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	**2 (0.6)**	**2 (0.6)**
	PIK3CA and *PTEN*	**4 (1.1)**	**9 (2.5)**
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing **in tumor tissue** with the **FoundationOne®CDx assay** (and Burning Rock assay in China)

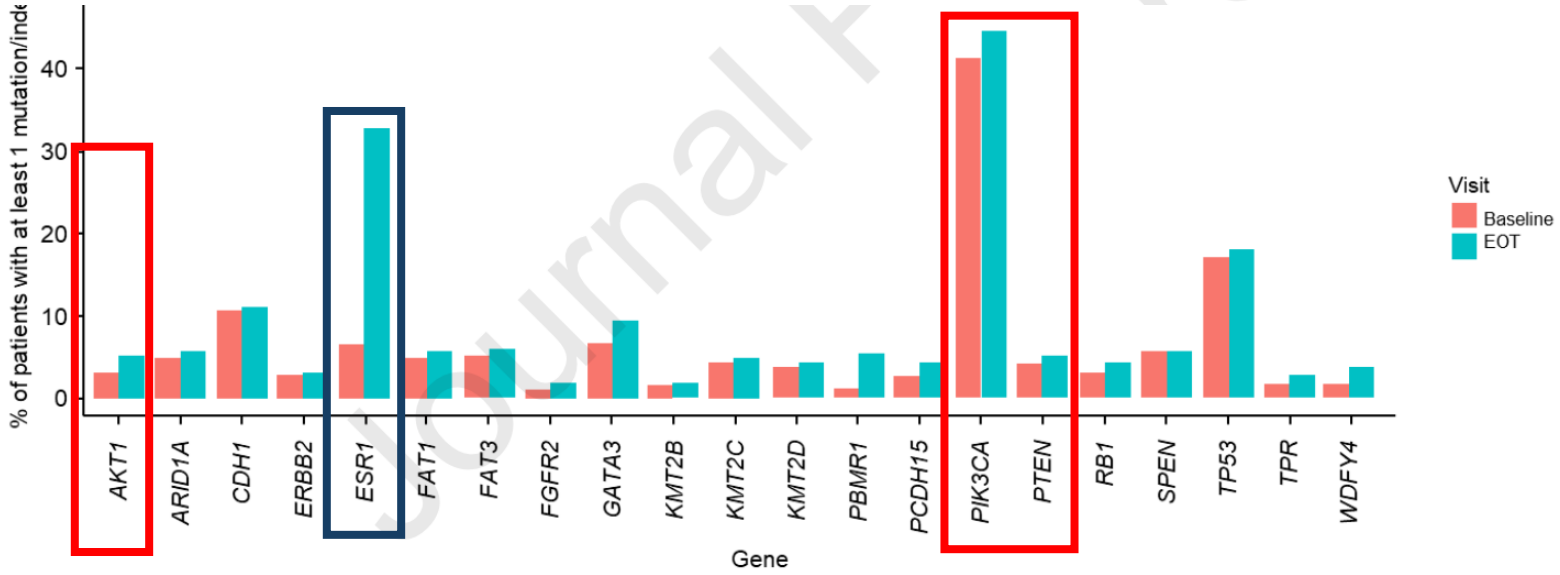
Turner NC et al, SABCS 2022 and NEJM 2023

Prevalence of gene alterations at baseline vs EOT with ribociclib plus ET vs placebo plus ET

Ribo + ET



ET + Placebo



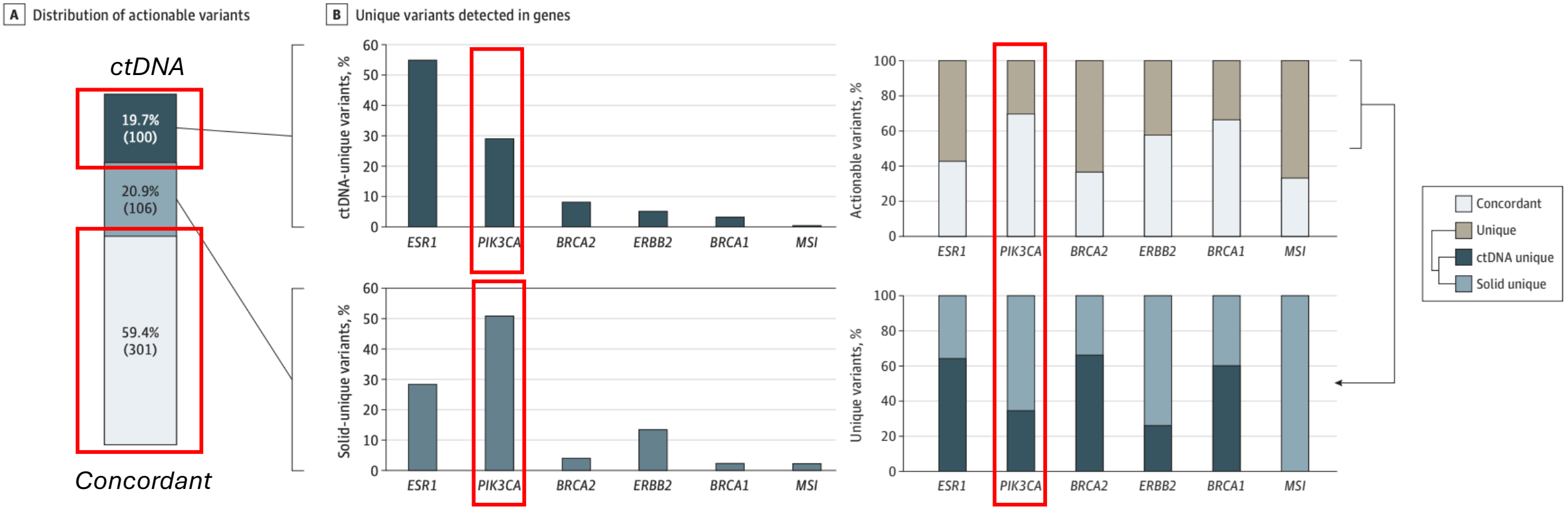
No difference in ESR1m with Ribo use

PI3KCA remains stable in time

Among Ribo users only **RB1 and SPEN** showed differences

André. F Annals of Oncol. 2024

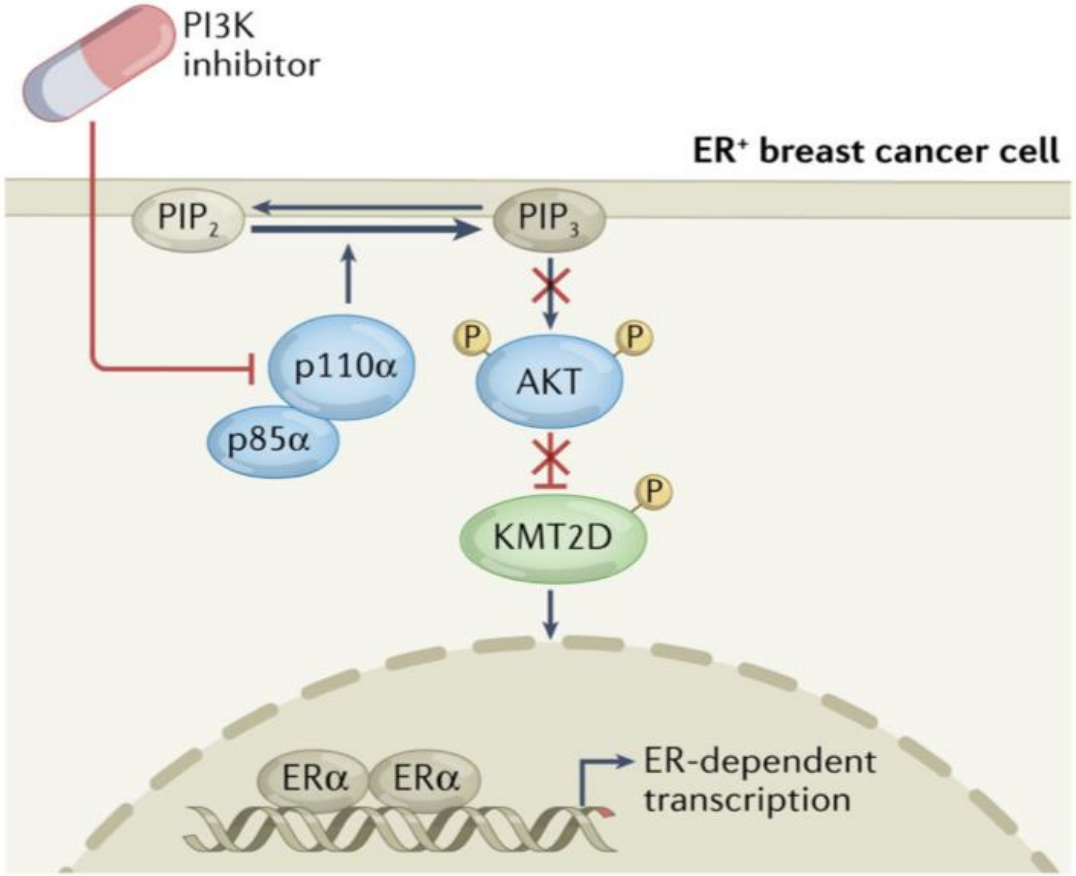
Liquid Biopsy or tissue Biopsy?

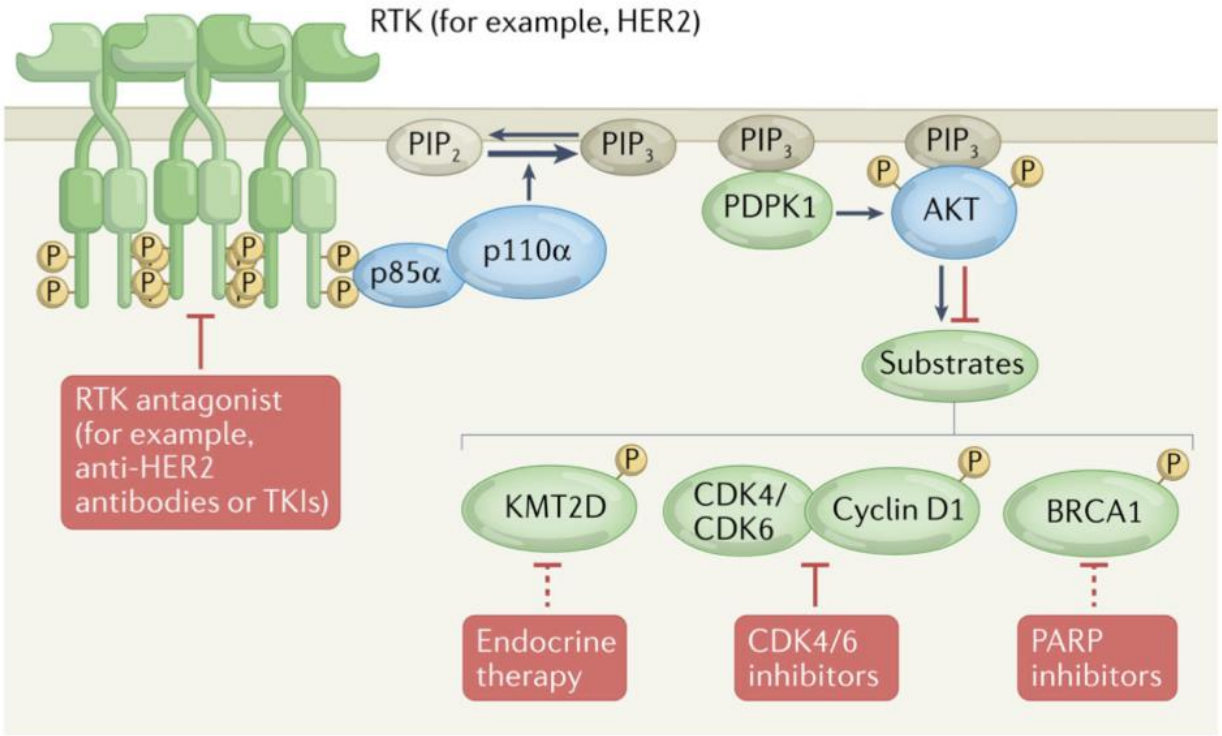


- **60 -80% concordance** between **tissue and ctDNA**
- **High ctDNA** identification of **actionable biomarkers**
- **19.7%** variants detected uniquely by **ctDNA → 55% ESR1**

Iams W JAMA Network 2024

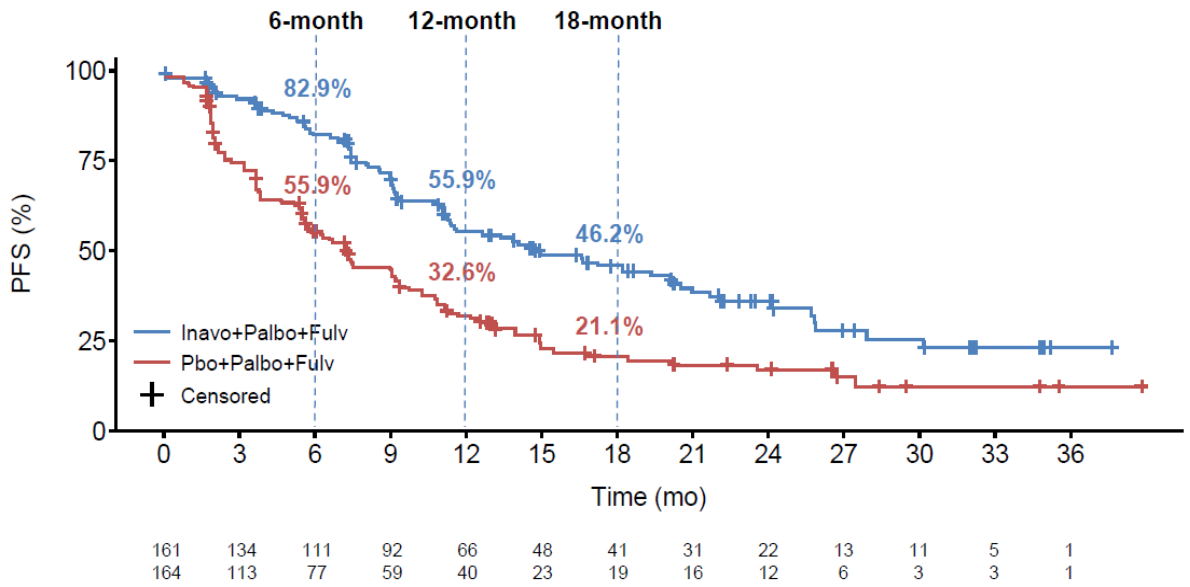
PI3K mechanism of resistance in breast cancer



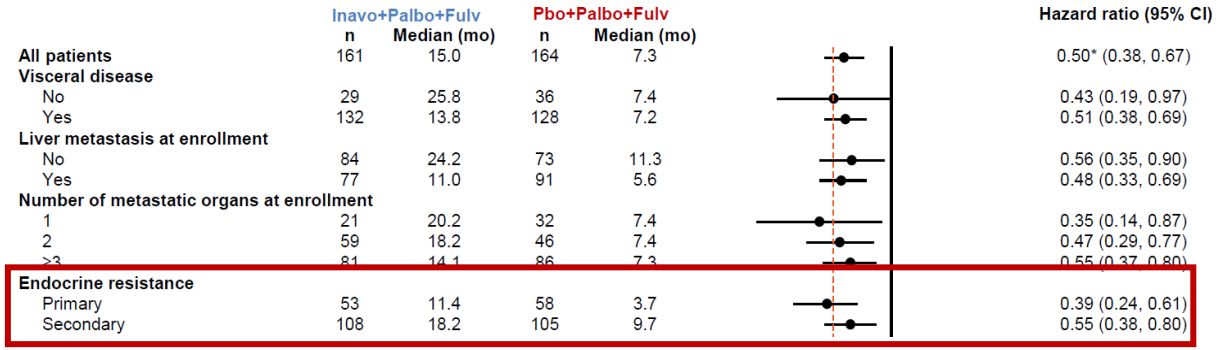


Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

Targeting PIK3CA + CDK4/6is in ET-resistant disease: INAVO-120

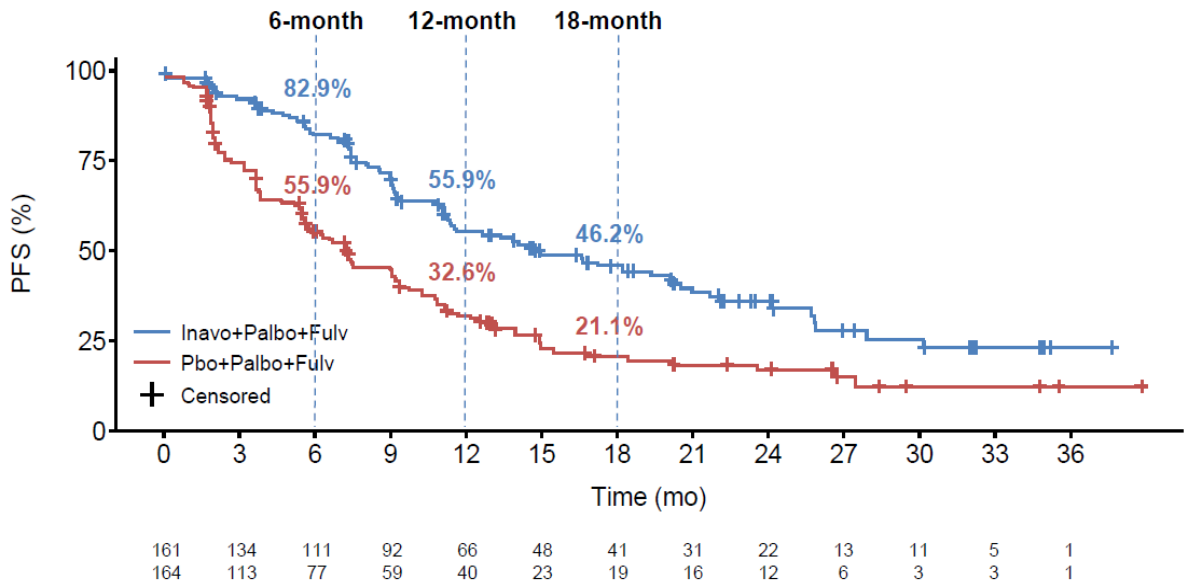


	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	



Jhaveri KL et al, SABCS 2023; Turner NC et al NEJM 2024

Targeting PIK3CA + CDK4/6is in ET-resistant disease: INAVO-120



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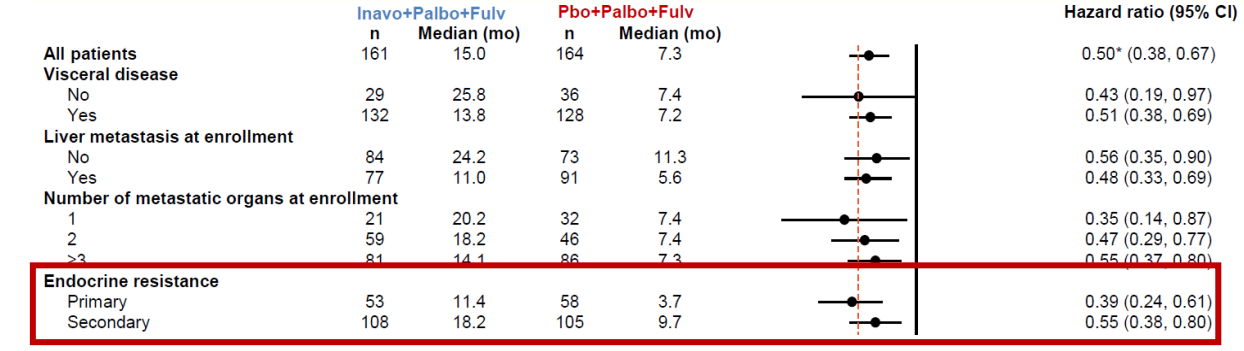
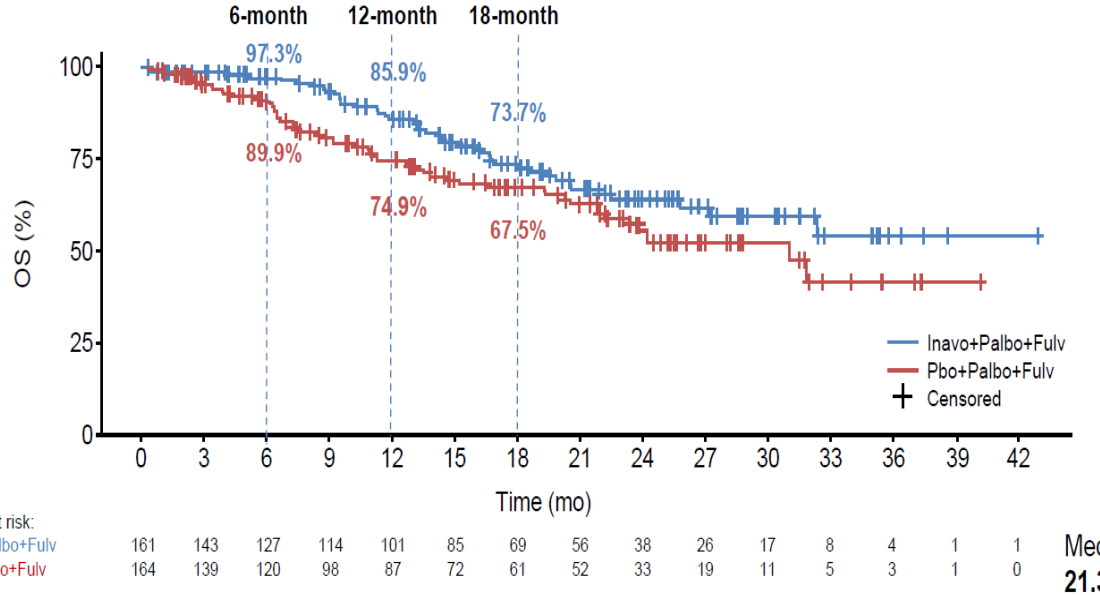




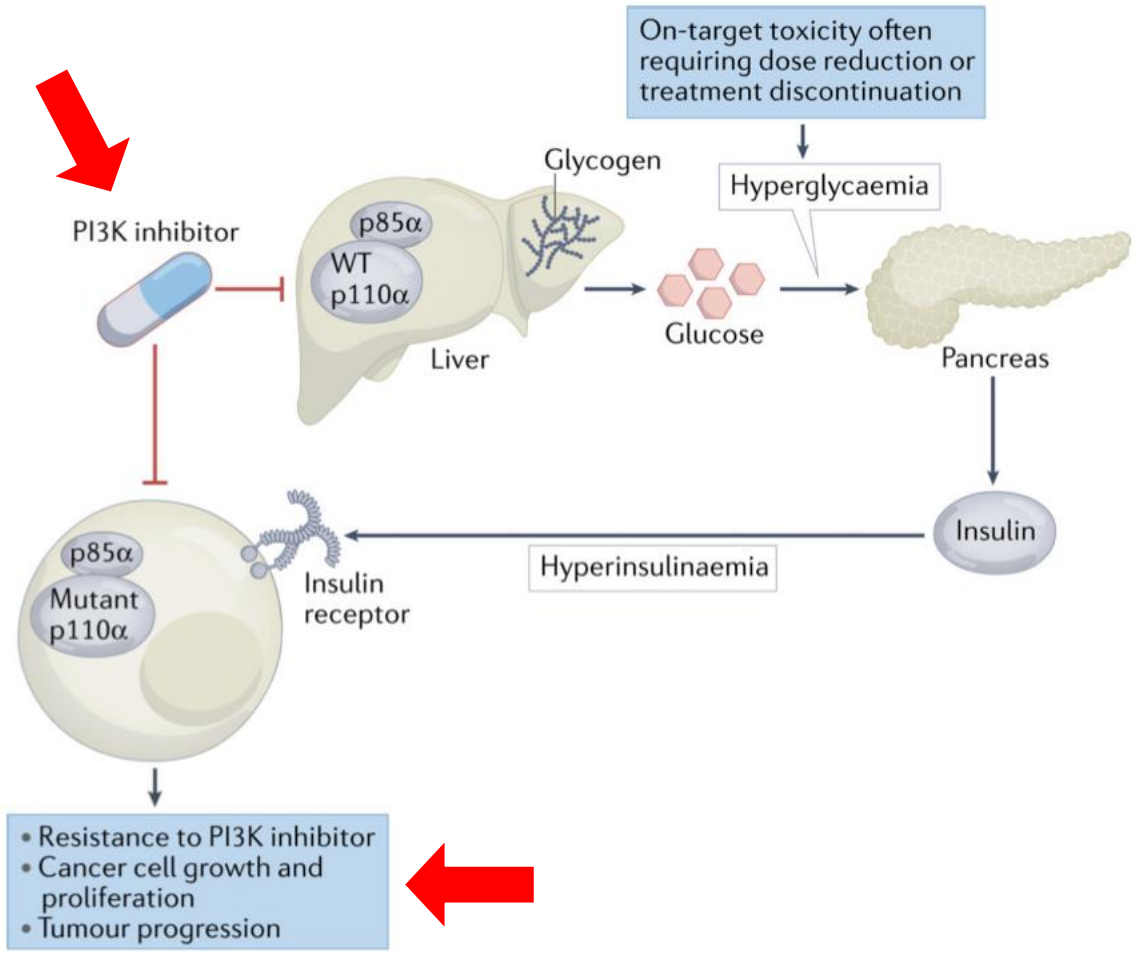
Median follow-up: **21.3 months**

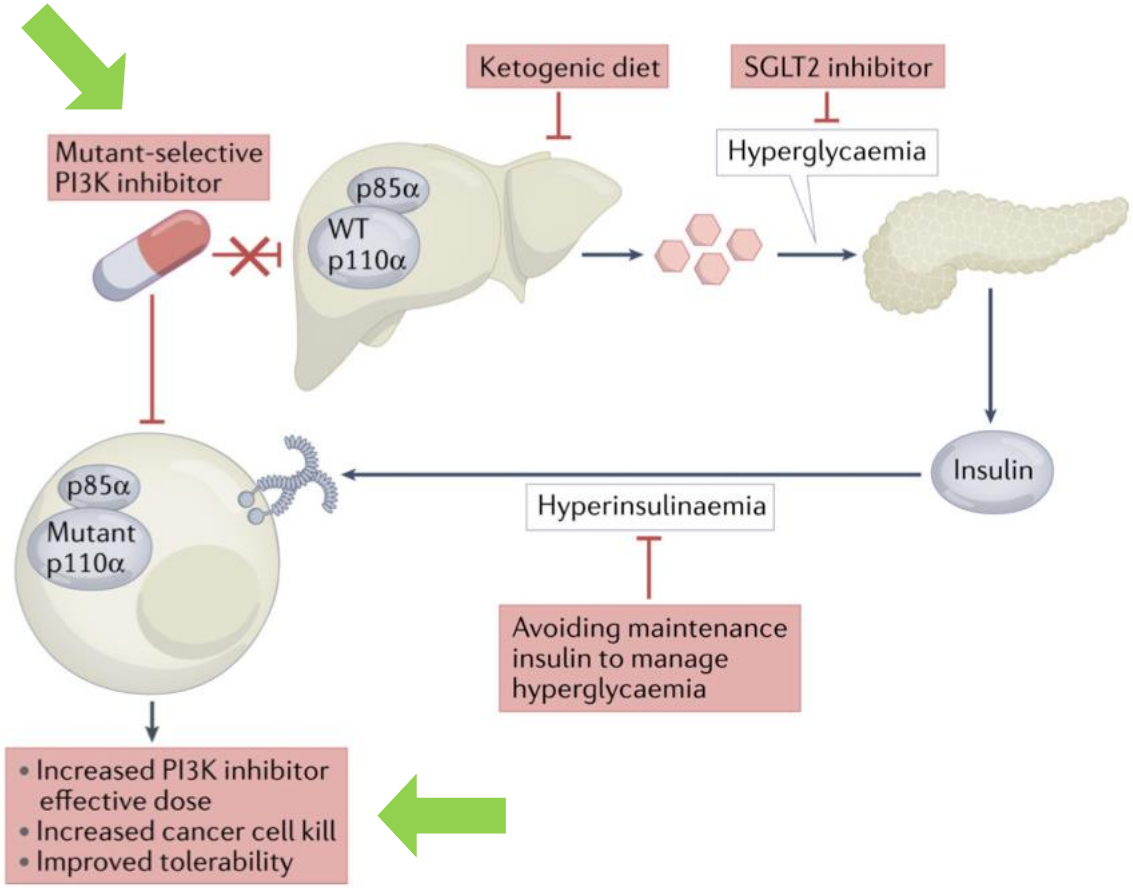
The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Jhaveri KL et al, SABCS 2023; Turner NC et al NEJM 2024

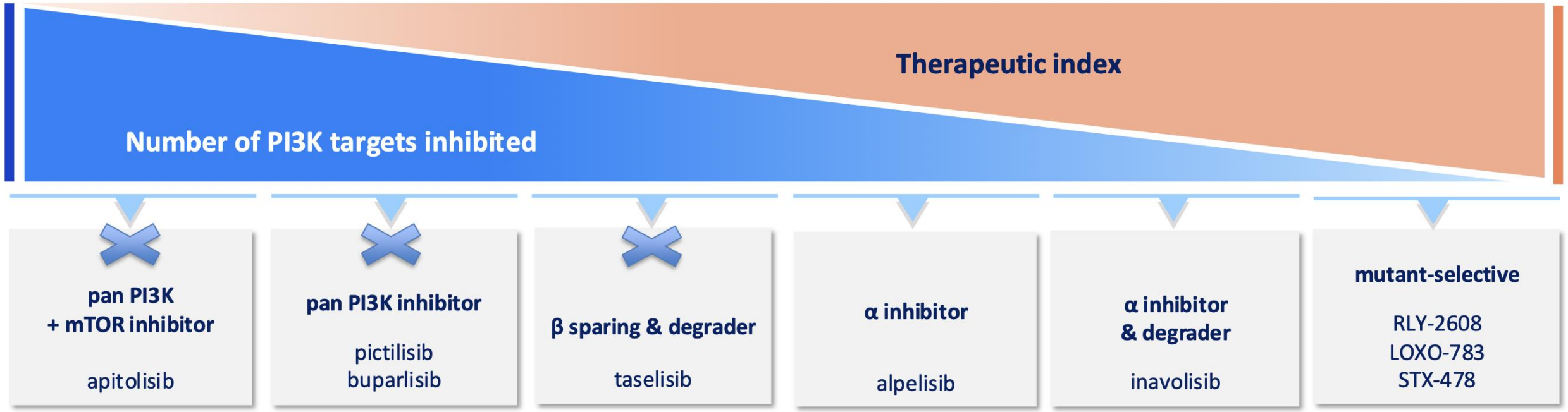
PI3K inhibitors effect on metabolism





Vasan N et al. *Nat Rev Clin Oncol*. 2022;19(7):471-485

PIK3 target inhibitors development



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Grazie per l'attenzione

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