The difficult targets - PIK3CA

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Potential conflicts of interest

Employment and Leadership
- Universität Duisburg-Essen, Universitätsklinikum Essen, Ruhrlandklinik

Scientific Advice
- AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Lilly, Novartis

Stock Ownership
- none

Honoraries for Educational Lectures
- Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Novartis

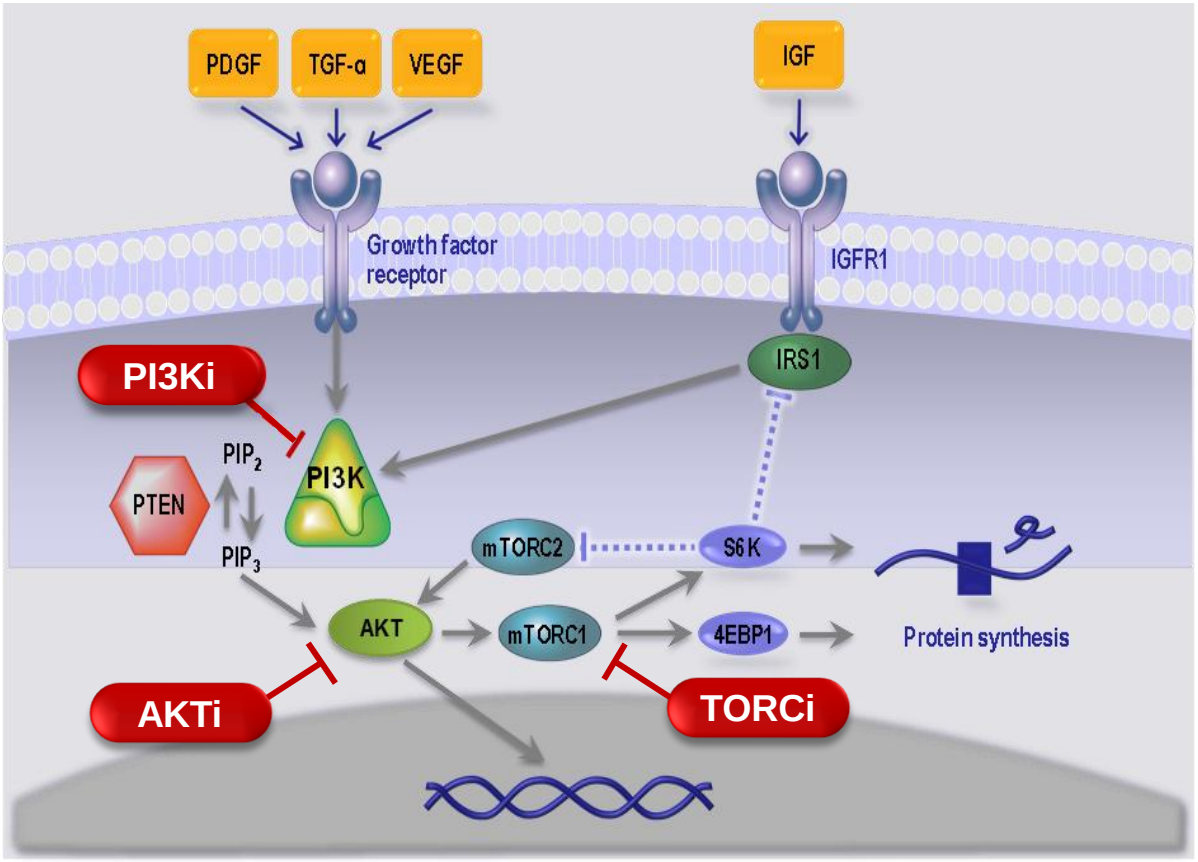
Research Grants to Institution
- Boehringer Ingelheim, Bristol-Myers Squibb, Novartis

Expert Testimony
- Medical Boards, Courts, Public Funding Agencies, Universities

Others
- Universität Duisburg-Essen (Patents)

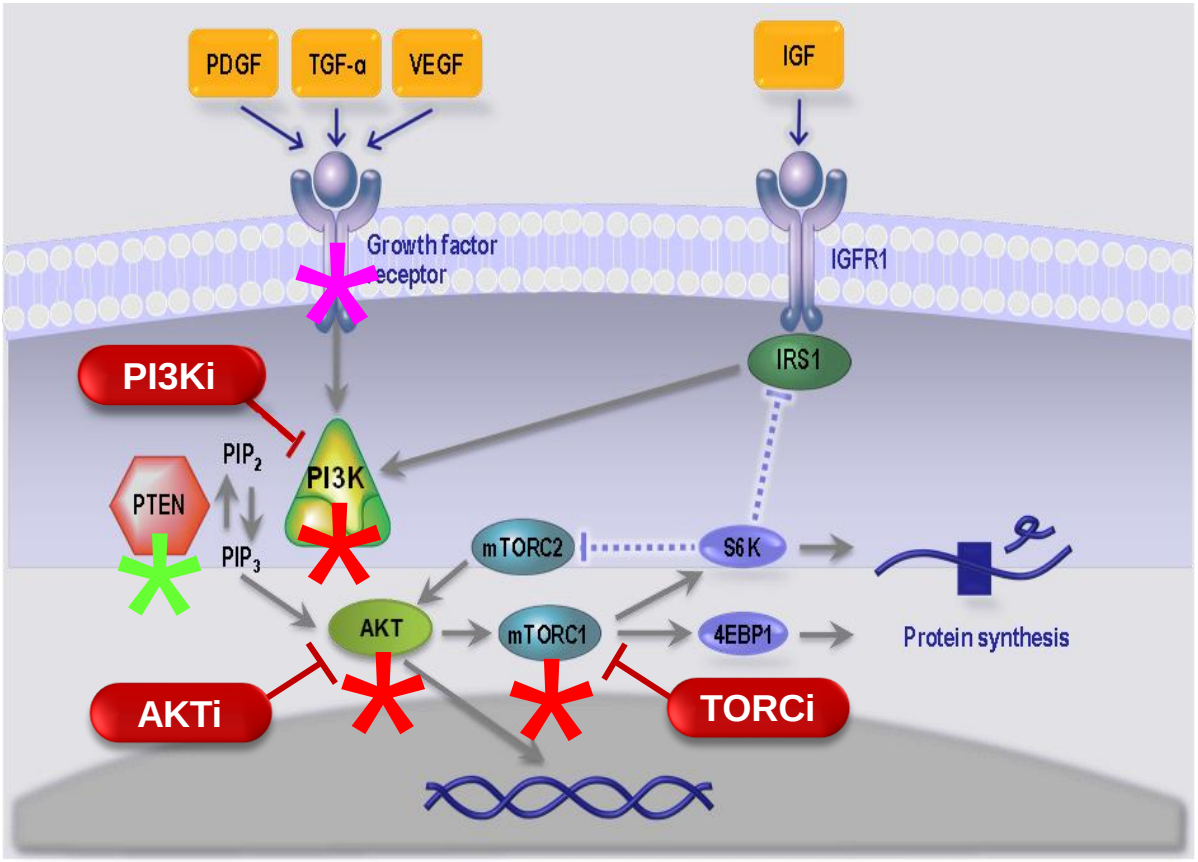
Phosphoinositide-3-kinase signaling pathway

Targeted agents in clinical development



Phosphoinositide-3-kinase signaling pathway

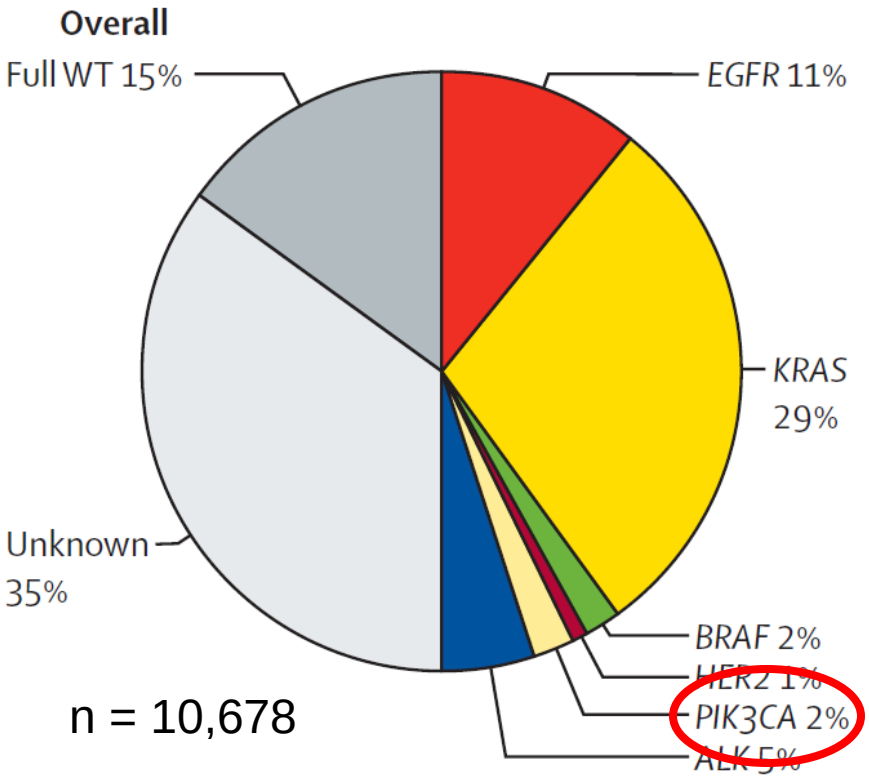
Recurring genomic aberrations in lung cancer



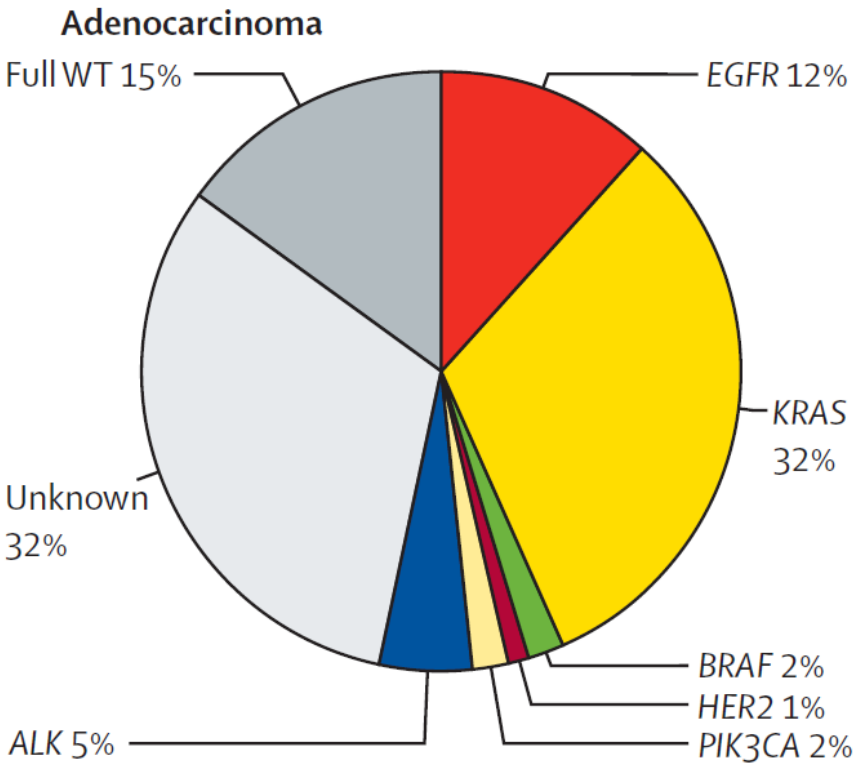
www.cancer.sanger.ac.uk/cosmic

Prospective screening for PI3K pathway aberrations

French Cooperative Thoracic Intergroup (IFCT)



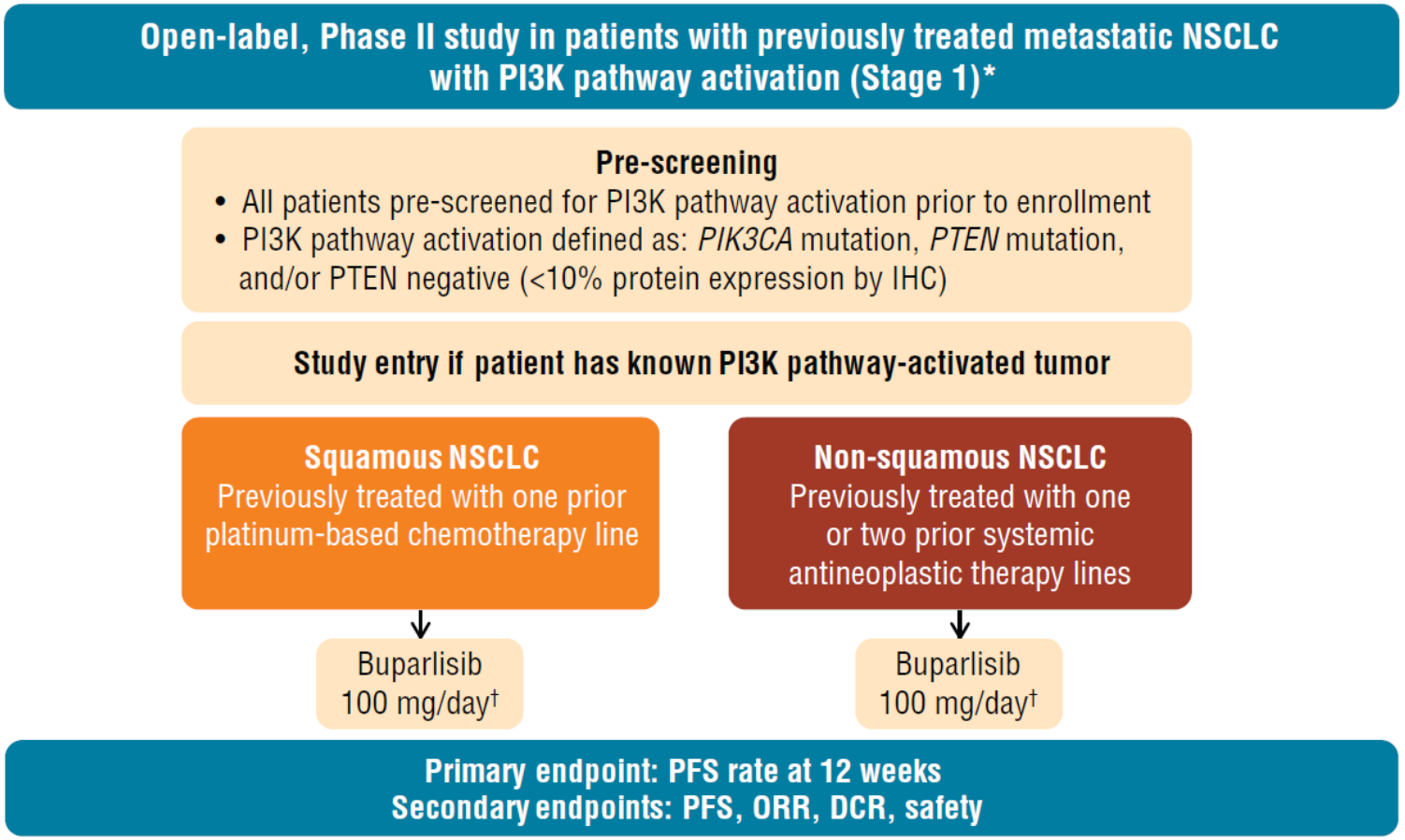
n = 10,678



Lancet 2016 [Epub ahead of print]

Class I PI3K inhibition in PI3K-activated lung cancer

Two-stage phase II study of buparlisib (BASALT-1)



J Thorac Oncol. 10:1319 (2015)

Class I PI3K inhibition in PI3K-activated lung cancer

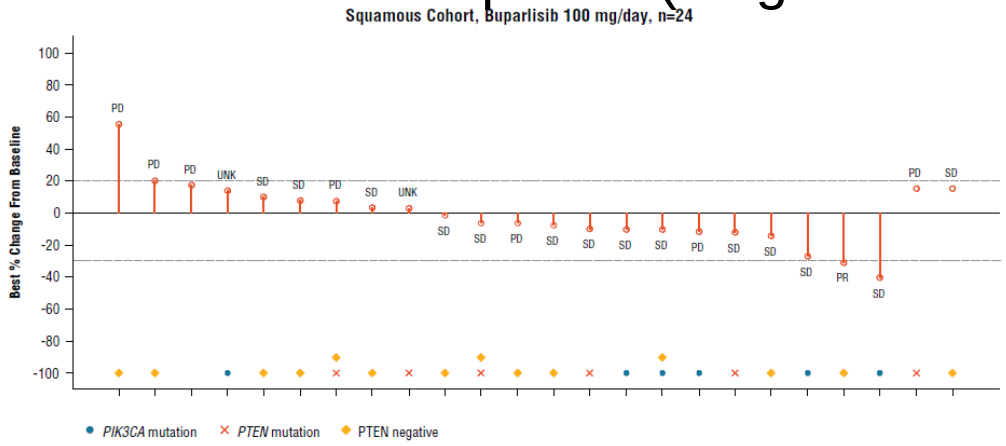
Biomarker prescreening results from BASALT-1

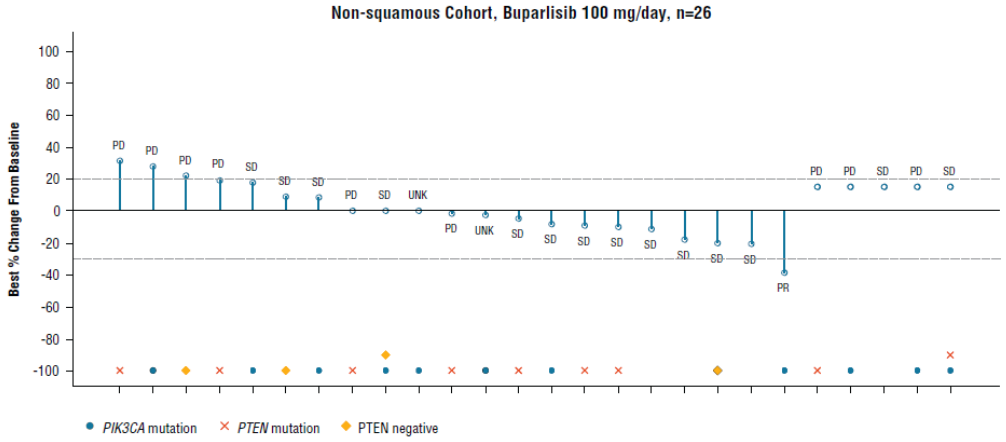
PI3K pathway status	Squamous (N=668) n (%)	Non-squamous (N=574) n (%)	Total (N=1242)* n (%)
PI3K pathway activation†	103 (15.4)	65 (11.3)	168 (13.5)
PIK3CA mutation	n‡=388 (58.1)	n‡=349 (60.8)	n‡=737 (59.3)
Yes	26 (6.7)	22 (6.3)	48 (6.5)
No	362 (93.3)	327 (93.7)	689 (93.5)
Unknown	69	95	164
Missing	211	130	341
PIK3CA mutation only	21 (5.4)	15 (4.3)	36 (4.9)
PTEN Mutation	n‡=394	n‡=342	n‡=736
Yes	25 (6.3)	36 (10.5)	61 (8.3)
No	369 (93.6)	306 (89.5)	675 (91.7)
Unknown	61	90	151
Missing	213	142	355
PTEN mutation only	18 (4.6)	29 (8.5)	47 (6.4)
PTEN Negative	n‡=444	n‡=358	n‡=802
Yes	64 (14.4)	16 (4.5)	80 (10)
No	380 (85.6)	342 (95.5)	722 (90.0)
Unknown	17	32	49
Missing	207	184	395
PTEN negative only	53 (11.9)	12 (3.4)	65 (8.1)

Dy *et al*., WCLC (2013)

Class I PI3K inhibition in PI3K-activated lung cancer

Best treatment response (stage I of BASALT-1)

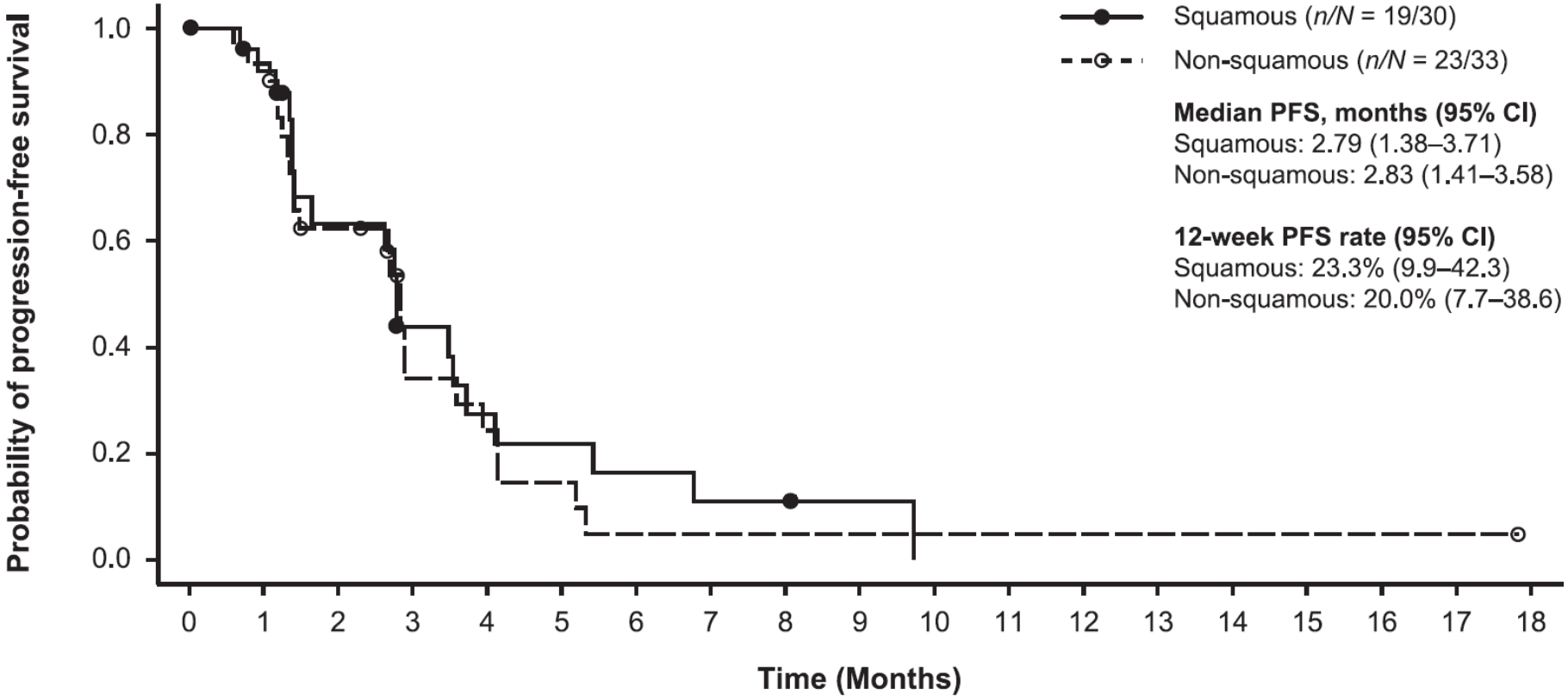




Soria *et al.*, ESMO (2014)

Class I PI3K inhibition in PI3K-activated lung cancer

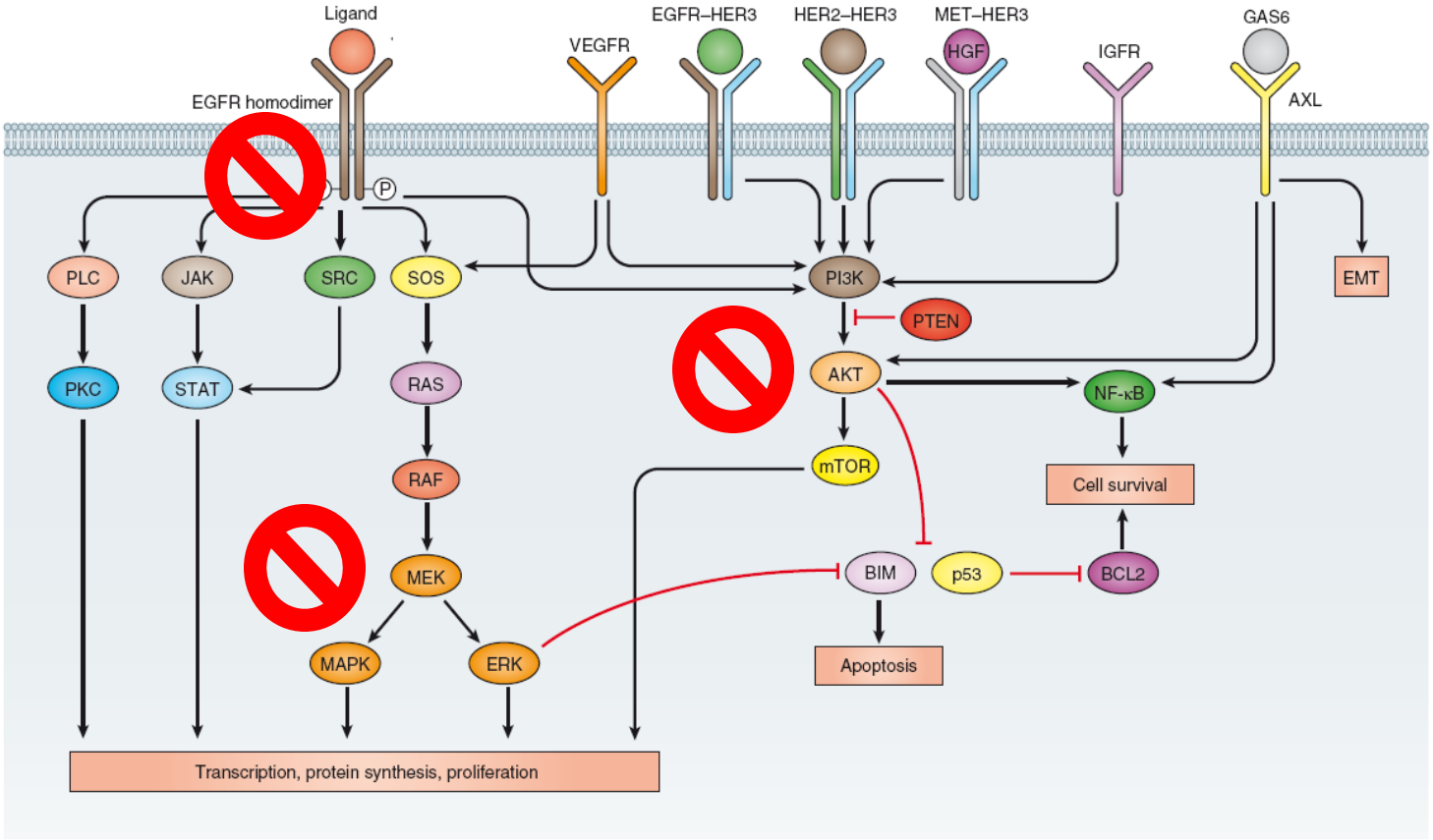
Progression-free survival (stage I of BASALT-1)



J Thorac Oncol. 10:1319 (2015)

Phosphoinositide-3-kinase signaling pathway

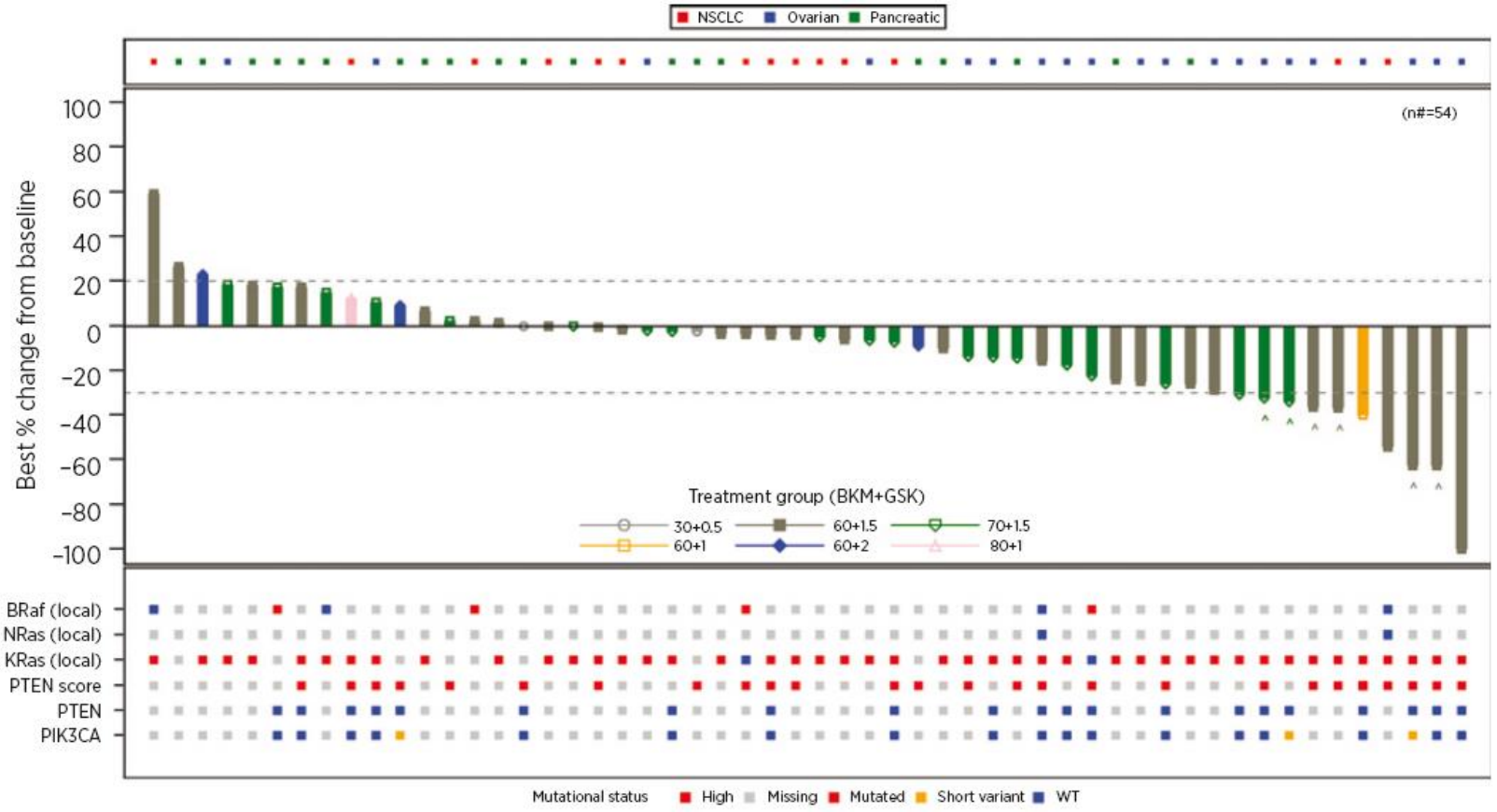
Horizontal pathway inhibition in lung cancer



Nat Med. 19:1389 (2013)

Combined PI3K and MEK inhibition in lung cancer

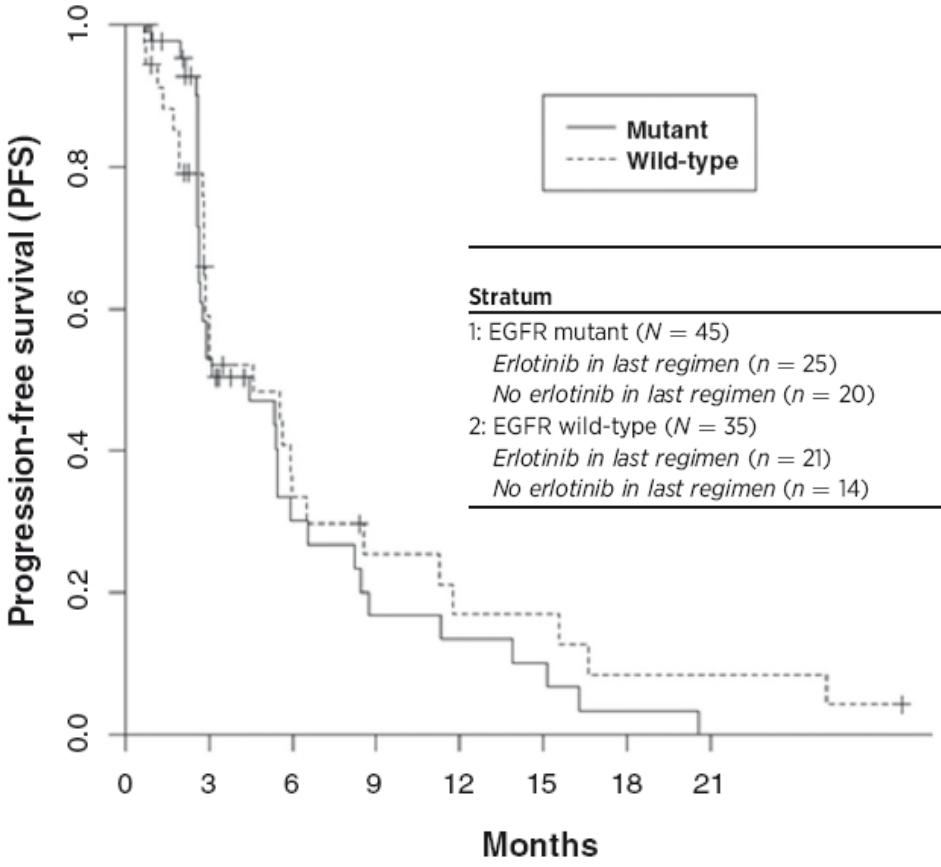
Phase Ib study of buparlisib plus trametinib



Clin Cancer Res. 21:730 (2015)

Combined PI3K and AKT inhibition in lung cancer

Phase II study of erlotinib plus MK-2206

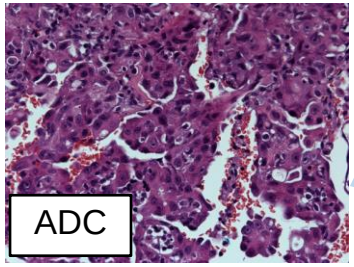


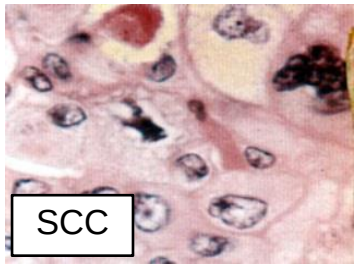
Stratum	Response rate, *n* (%)	DCR at 12 weeks, *n* (%)
1: EGFR mutant (*N* = 45)	4 (9%)	18 (40%)
Erlotinib in last regimen (*n* = 25)	2 (8%)	8 (32%)
No erlotinib in last regimen (*n* = 20)	2 (10%)	10 (50%)
2: EGFR wild-type (*N* = 35)	1 (3%)	15 (43%)
Erlotinib in last regimen (*n* = 21)	0 (0%)	10 (48%)
No erlotinib in last regimen (*n* = 14)	1 (7%)	5 (36%)

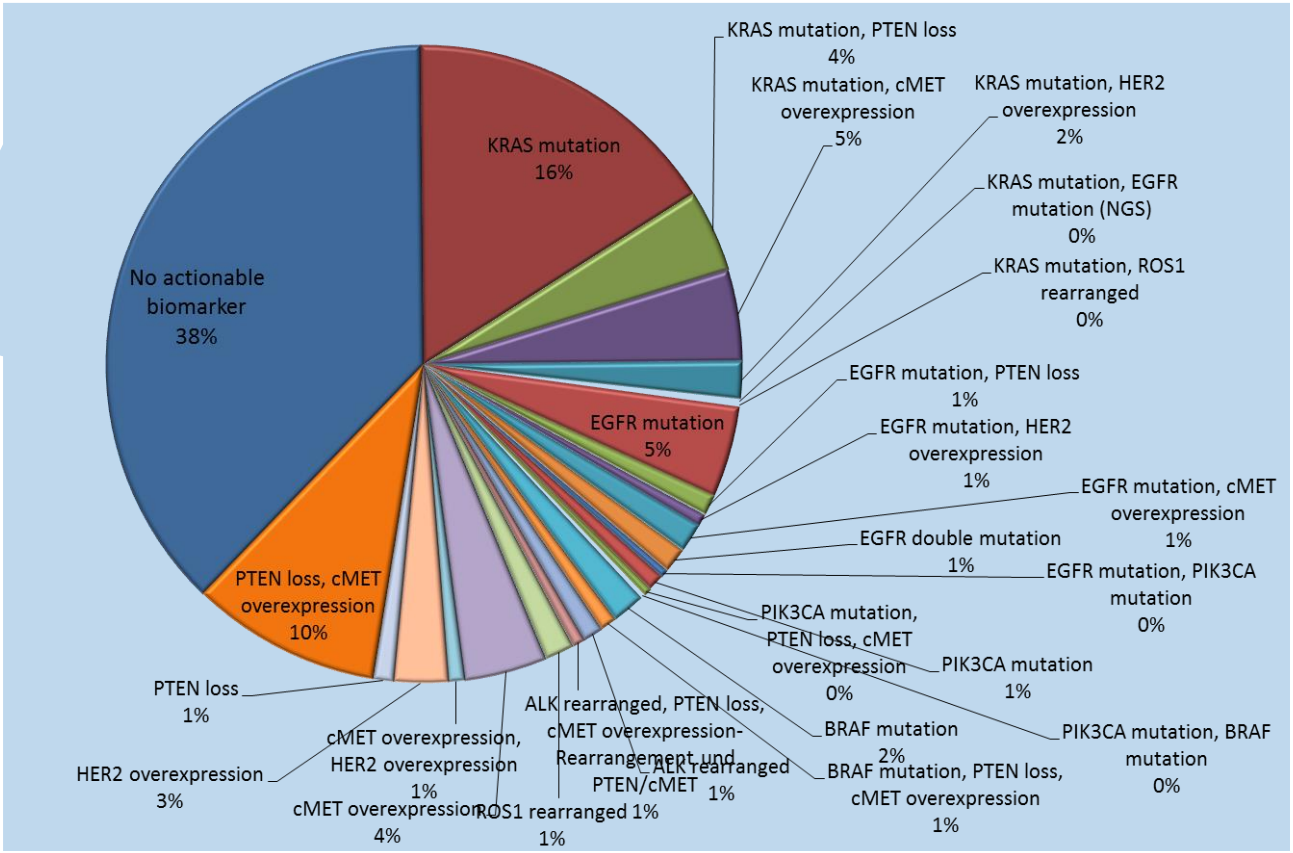
Clin Cancer Res. 21:4321 (2015)

Prospective screening for PI3K pathway aberrations

Advanced or metastatic pulmonary adenocarcinomas (WTZ-POP)







Schuler, Schmid *et al*., West German Cancer Center (2015)

Prospective screening for PI3K pathway aberrations

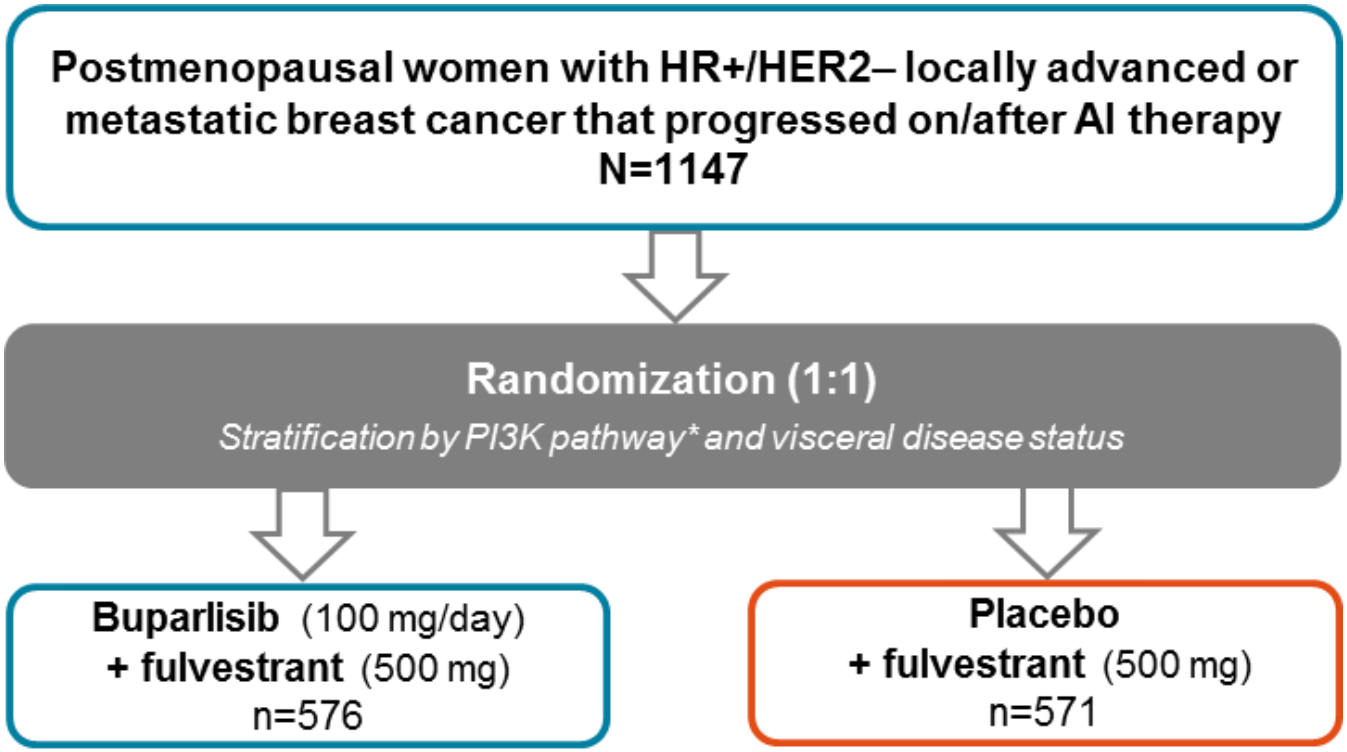
„Oncogenic driver“ or disease modifier in lung cancer?

PIK3CA mutation	Additional oncogenic „driver“
61%	none
23%	*EGFR* mutation
8%	*BRAF* mutation
8%	*CMET* amplification

Schuler, Schmid *et al*., West German Cancer Center (2015)

Class I PI3K inhibition in luminal breast cancer

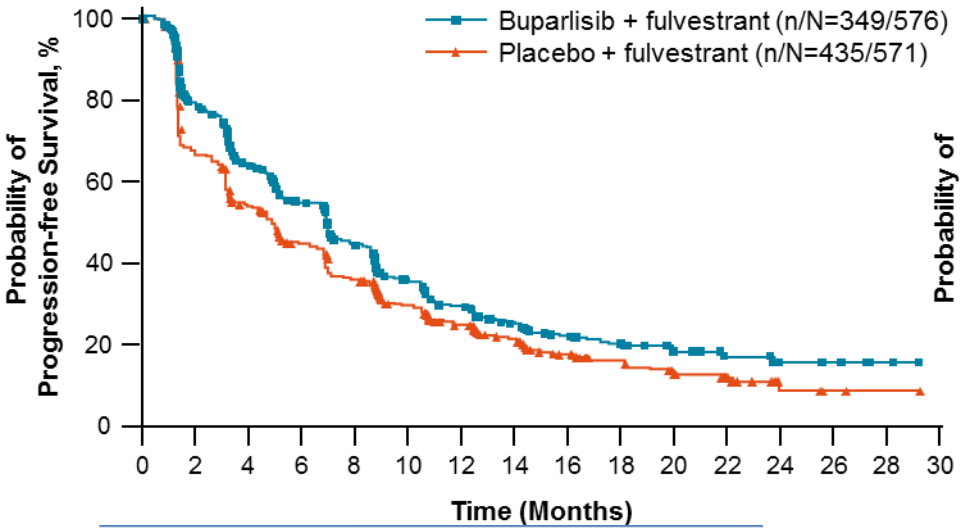
Phase III study of fulvestrant ± buparlisib (BELLE-2)



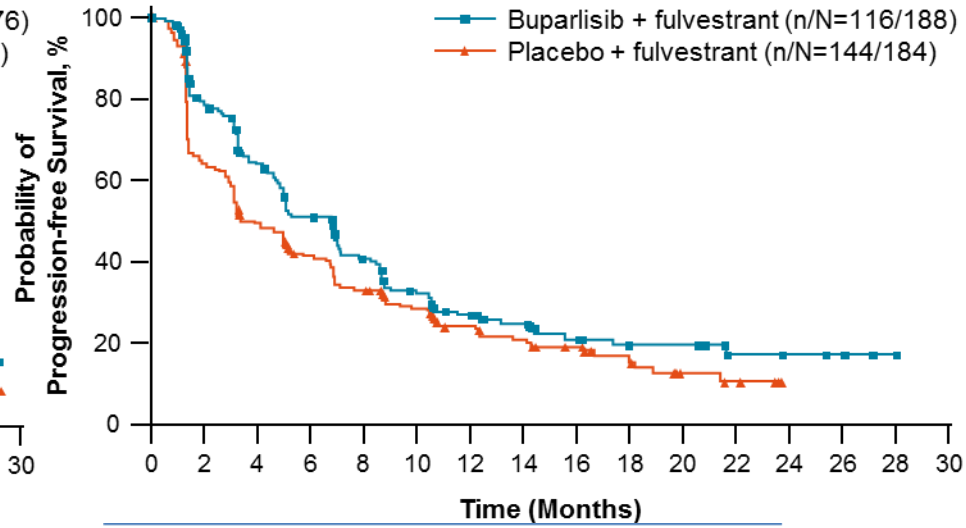
Baselga *et al*., SABCS S6-01 (2015)

Class I PI3K inhibition in luminal breast cancer

PFS in full and in PI3K-activated populations (archival biopsy)



Full Population (N=1047)	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	

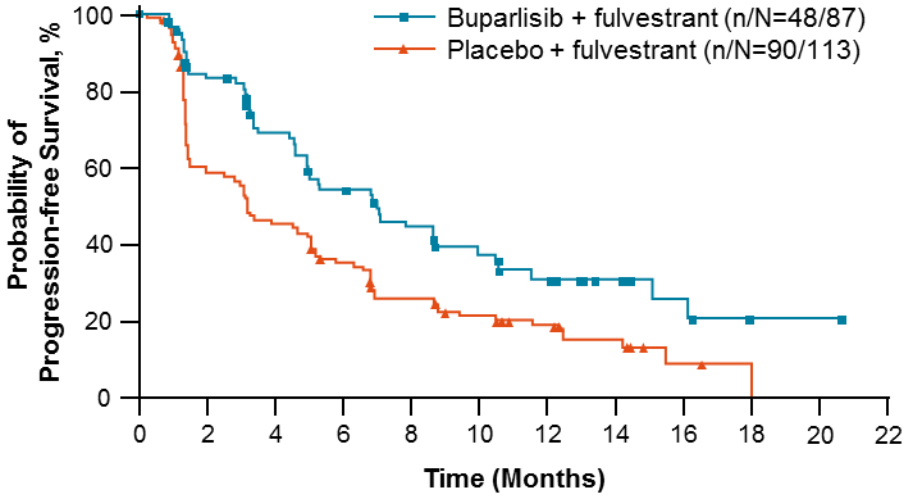


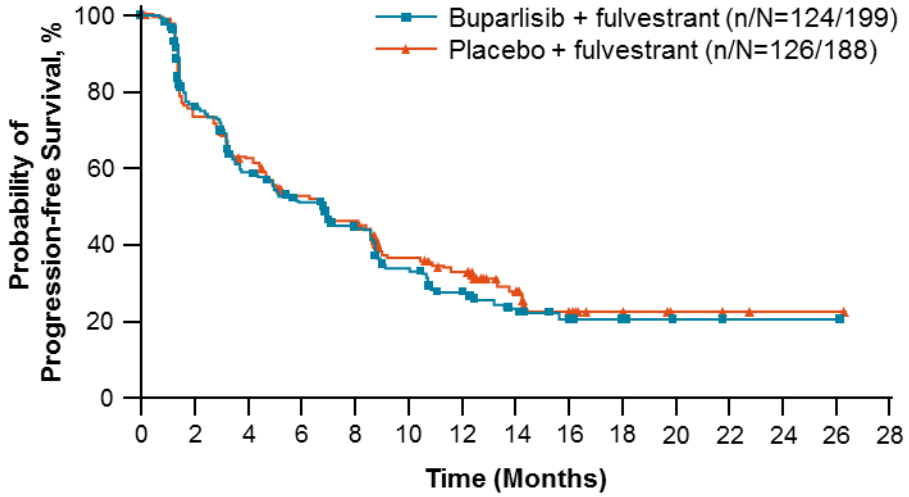
PI3K Activated Group (N=372)	Buparlisib + Fulvestrant n=188	Placebo + Fulvestrant n=184
Median PFS, months (95% CI)	6.8 (4.9–7.1)	4.0 (3.1–5.2)
HR (95% CI)	0.76 (0.60–0.97)	
One-sided *P* value*	0.014	

Baselga *et al*., SABCS S6-01 (2015)

Class I PI3K inhibition in luminal breast cancer

PFS in relation to *PIK3CA* mutation detected in ctDNA





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	

Baselga *et al*., SABCS S6-01 (2015)

Prospective screening for PI3K pathway aberrations

Discordant *PIK3CA* mutation prevalence in breast cancer

	Primary tumor		Metastasis		p (χ-square)
	N	% positive	*N*	% positive	
All	52		70		
PR	30	57.7	35	50.0	0.320
ER	34	65.4	49	70.0	0.509
HR	37	71.2	52	74.3	0.700
Her2/neu+	13	25.0	15	21.4	0.629
Her2/neu−/HR+	28	53.8	45	64.3	0.308
Her2/neu+/HR+	9	17.3	6	8.6	0.249
Her2/neu+/HR−	4	7.7	9	12.9	0.441
Triple negative	11	21.2	9	12.9	0.221
FGFR1 amplified	6	11.5	3	4.3	0.246
PI3KCA mutant	7	13.5	21	30	0.034*
PI3KCA amplified	1	1.9	2	2.9	0.471
PTEN loss	7	13.5	9	12.9	0.138

* Denotes statistically significant

Breast Cancer Res Treat. 142:81 (2013)

Targeting PIK3CA in lung cancer
Summary

- Clinical validation of *PIK3CA* mutations as biomarker for tractable dominant oncogenic dependency in stage IV lung cancer has failed
- Concomitant mutations of additional „oncogenic drivers“ frequently observed
- Questionable predictive value of *PIK3CA* mutation detection in archival tumor biopsy (breast cancer)
- Combination therapies involving PI3K pathway-targeting agents limited by clinical toxicities

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