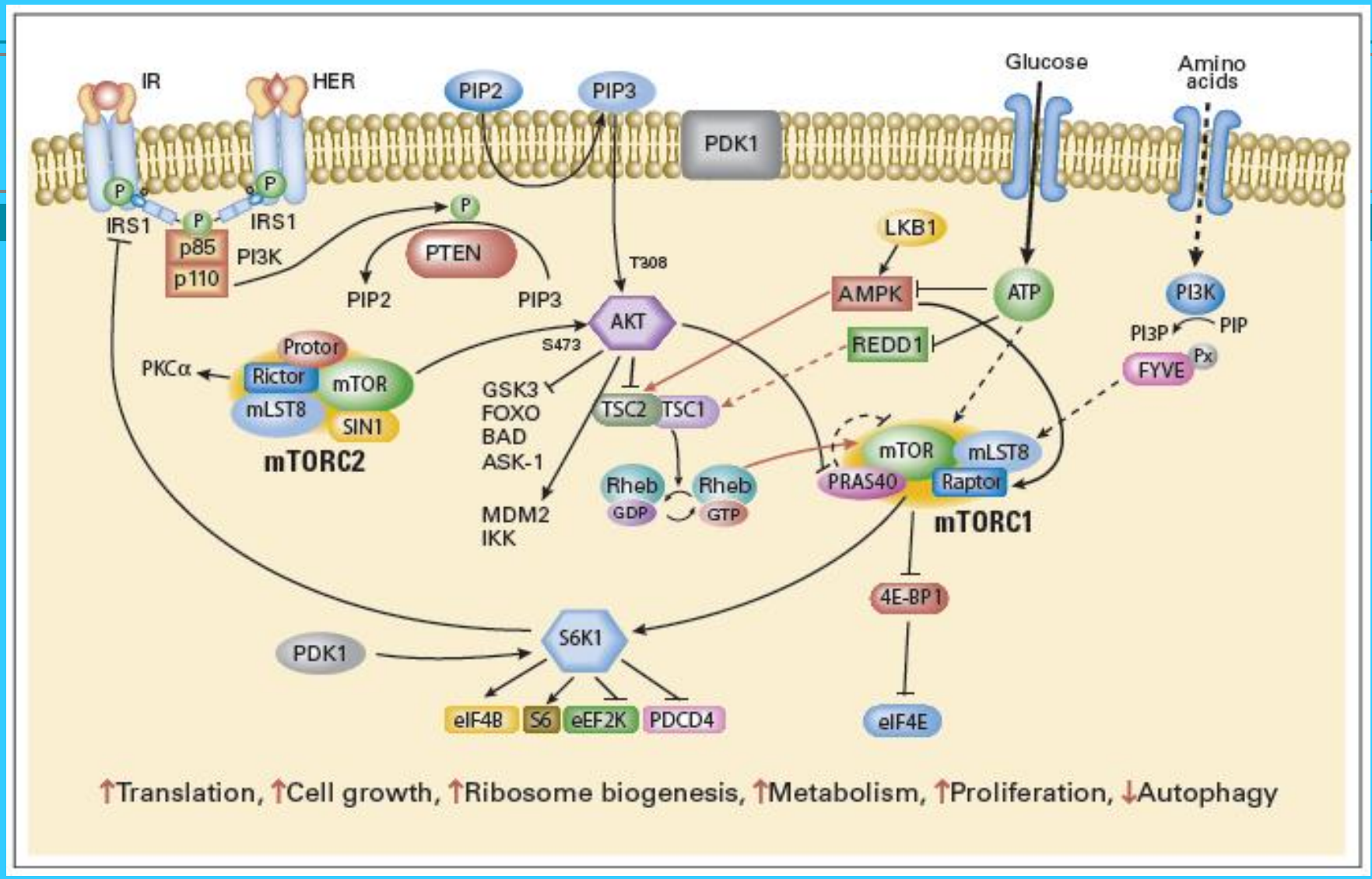
Agents Targeting the PI3K pathway

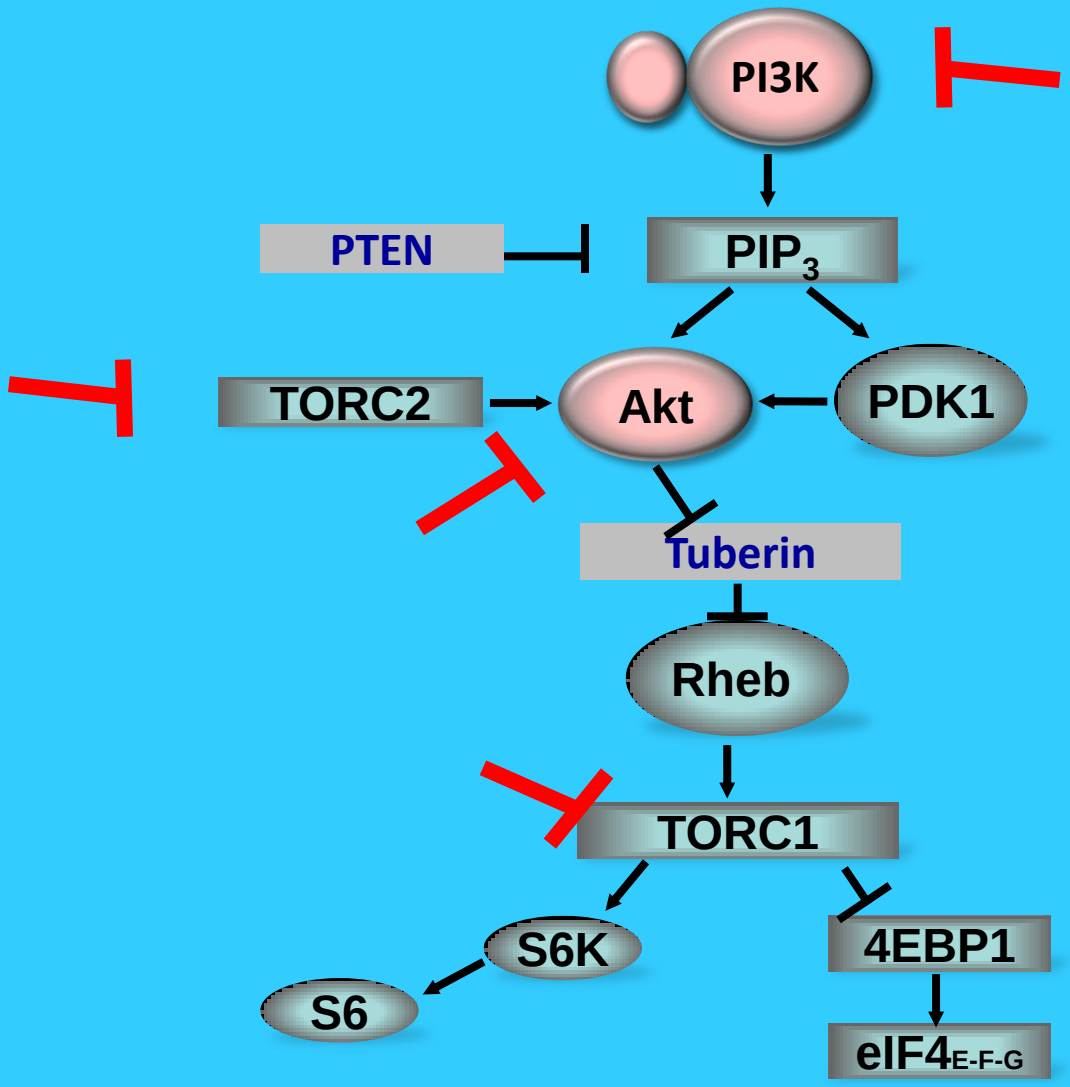
Patricia Mucci LoRusso, D.O.
Director – Experimental Medicine
Karmanos Cancer Institute
Detroit, MI

PI3K Pathway



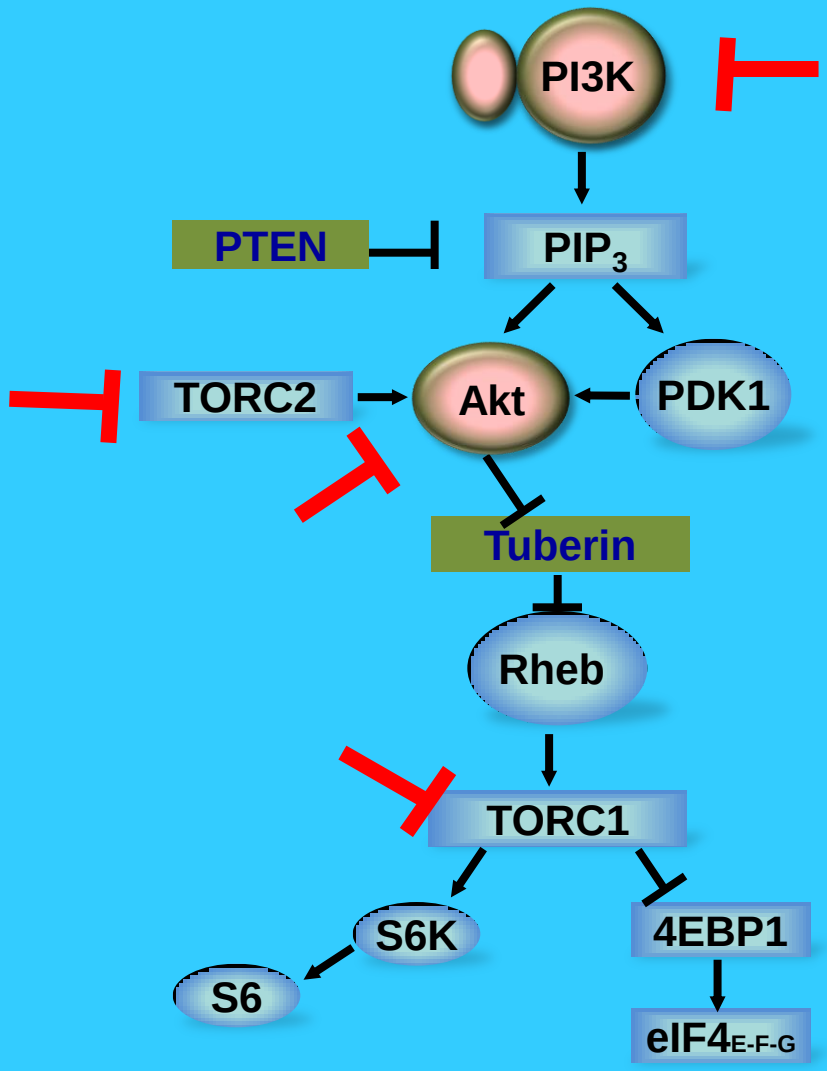
Meric-Bernstam and Gonzalez-Angulo, J Clin Oncol 2009

Strategies to Target the PI3K Pathway



PI3K Pathway Inhibitors

Agent	Company	Molecular targets
BYL719	Novartis	PI3Kα
GDC-0032	Genentech	PI3Kα
INK-1117	Intellikine	PI3Kα
XL-147	Exelixis/Sanofi	Pan-PI3K
NVP-BKM120	Novartis	Pan-PI3K
GDC-0941	Genentech	Pan-PI3K
PKI-587	Pfizer	Pan-PI3K
XL-765	Exelixis/Sanofi	PI3K / mTOR
NVP-BEZ-235	Novartis	PI3K / mTOR
NVP-BGT-226	Novartis	PI3K / mTOR
PF-4691502	Pfizer	PI3K/mTOR
AZD8055	Astrazeneca	mTOR (catalytic)
INK 128	Intellikine	mTOR (catalytic)
MK-2206	Merck	AKT1,2,3
GDC-0068	Genentech	AKT



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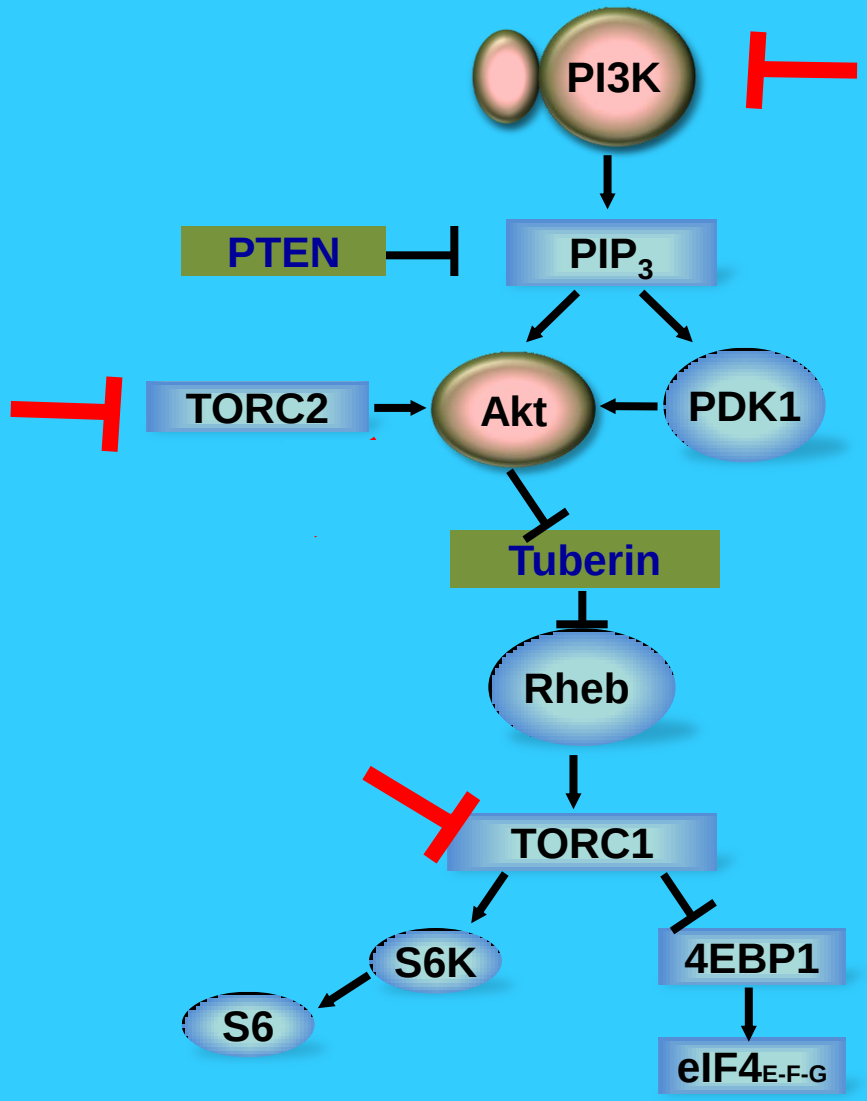
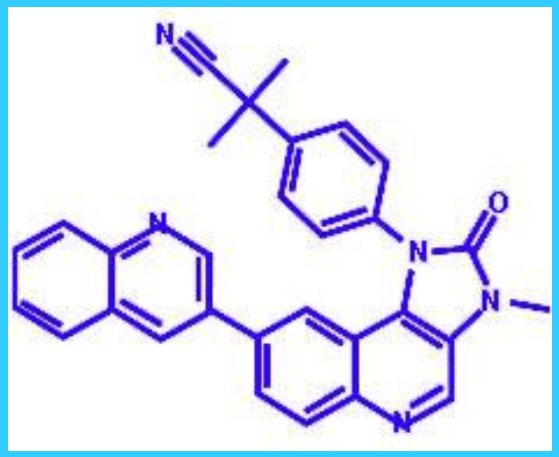


BEZ235

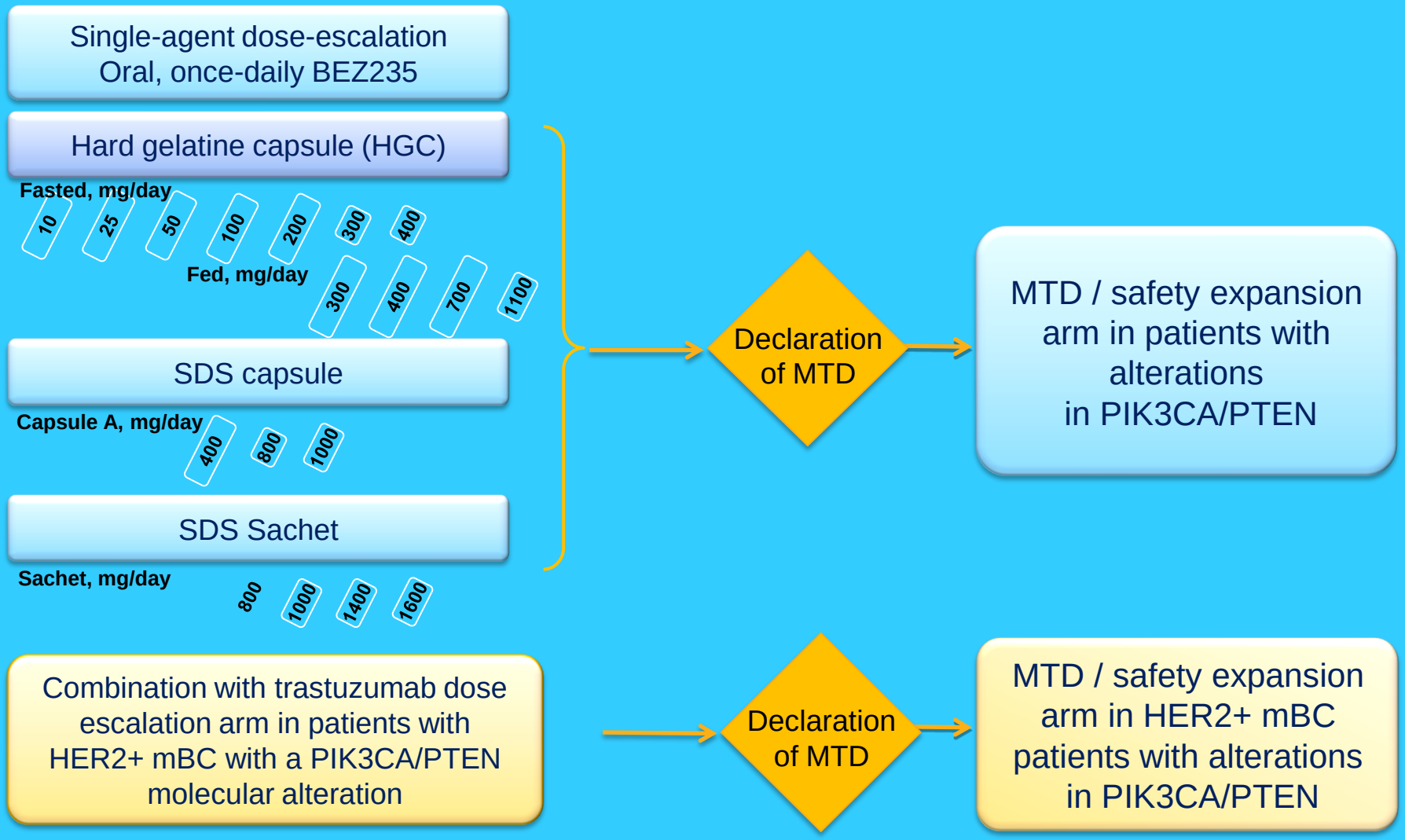


	Enzyme	IC_{50} nM/L
Class I PI3K	p110α	4.0 ± 2
	P110α-H1047R	4.6 ± 0.8
	P110α-E545K	5.7 ± 1.0
	p110β	75 ± 45
	p110 δ	7 ± 6
	p110 γ	5 ± 4
	mTOR	20.7
Panel of 18 other protein kinases		>10,000

- Potent, specific, oral PI3K and mTORC1/2 inhibitor
- Broad antiproliferative effect across different tumor types
- Pro-apoptotic effect in PI3K-pathway activated tumor models
- Antiangiogenic

Maira *et al*. *Mol Cancer Ther* 2008;7:1851–63
Serra *et al*. *Cancer Res* 2008;68:8022–30

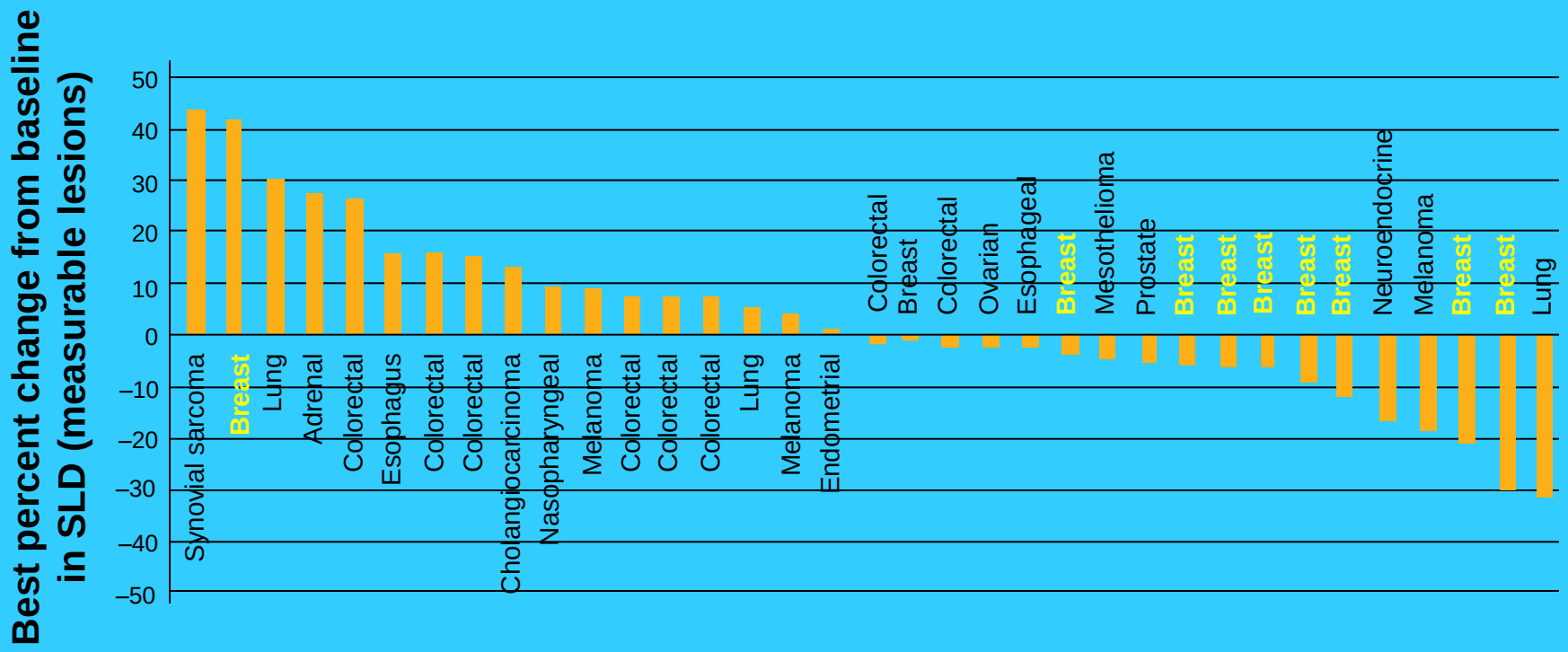
BEZ235 Phase I Study: Study Design



BEZ235 Phase I Study: Preliminary Clinical Activity

- Single-agent activity
  - 2 radiologic responses with HGC
    - ER+ mBC: (1100 mg/day, response duration 9+ months)
    - Lung cancer (Cowden syndrome: 700 mg/day, response duration 8 months on BEZ235, 10+ months off BEZ235)
  - 1PR with SDS capsule
    - **ER+ mBC**
- 1 PR in combination with trastuzumab (HER2+ mBC)
- Disease stabilization
  - 14 patients with SD ≥ 4 months w/ HGC
  - Several SD > 3 months w/ SDS
  - 2 patients on study > 22 months (ER+ mBC, HRPC)

BEZ235 Phase I:
Reduction in Tumor Burden as per CT



- **18 out of 35 evaluable patients had tumor shrinkage as per central review**

NOVARTIS

Burris et al ASCO 2010 Abstract #3005 Clinical Science Symposium

BEZ235 Phase I:
Retrospective Analysis of Tumor Mutation Status

N=59	n
Tumor samples[a]	51 (86%)
Evaluable for *PIK3CA* Status[b]	48
Wild-type	43 (90%)
Mutation	5 (10%)
Evaluable for PTEN Status[c]	51
Wild-type	39 (76%)
Mutated	7 (14%)
Protein level low (H-score < 40)	10 (20%)
Protein level medium (H-score 40-90)	12 (24%)
Protein level high (H-score >90)	26 (51%)
Tumors with PI3K pathway activation (any PIK3CA/PTEN alterations)	19 (37%)

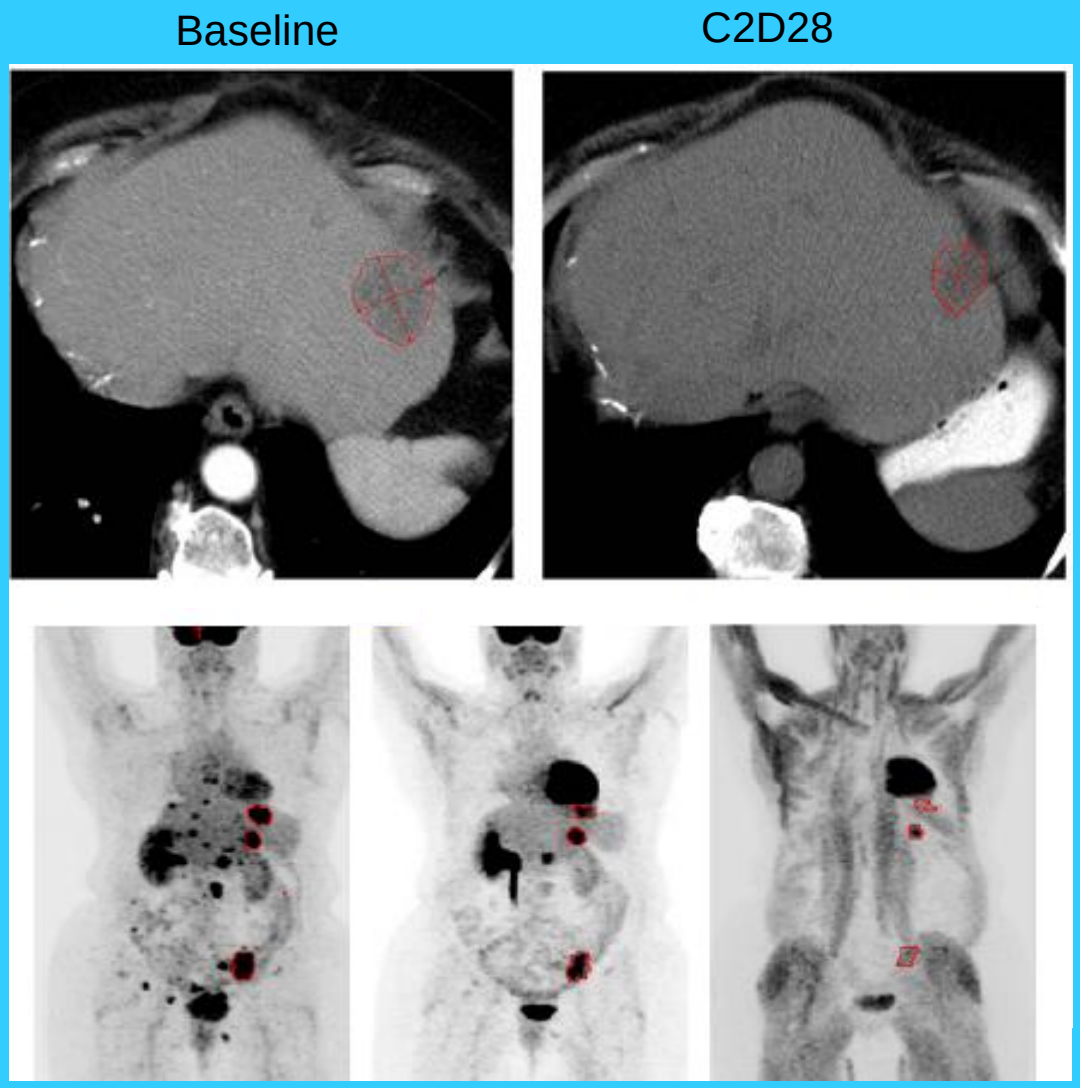
[a] Population enrichment was not employed. Samples available for 51/ 59 patients, some analyses incomplete due to sample quantity or quality

[b] SNaPshot genotyping, exons 9 and 20

[c] Genomic DNA sequencing of *PTEN* exons 1-9, Semiquantitative IHC

Burris et al ASCO 2010 Abstract #3005
Clinical Science Symposium

BEZ235 Clinical Activity in Breast Cancer

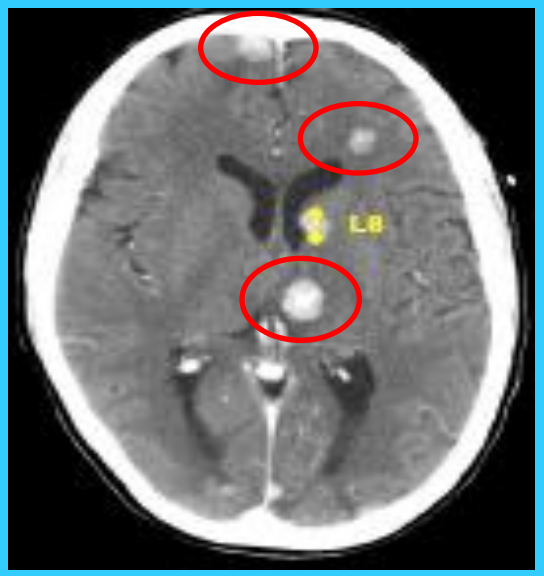


BEZ235 @1100 mg/day:

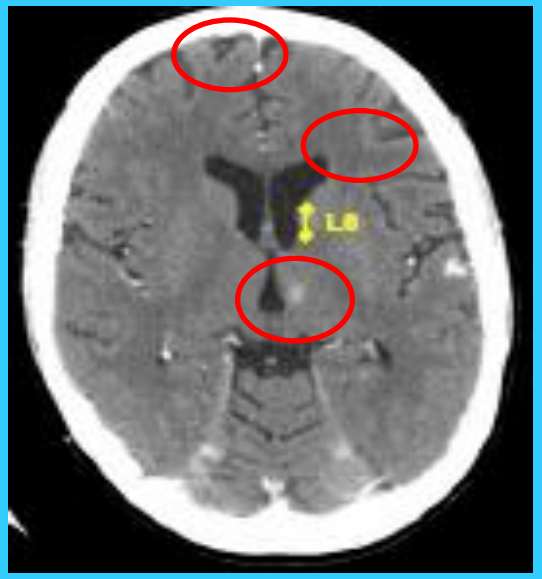
- ER+ breast cancer
- PI3K status unknown

BEZ235 - Responses in combination with trastuzumab (HER2+ Breast cancer)

Baseline:



Cycle 2:



BEZ235 (400 mg+trastuzumab)

HER2+ Breast Ca. Trastuzumab pre-treated, PI3K mutation

PI3K Pathway Inhibitors

Agent	Company	Molecular targets
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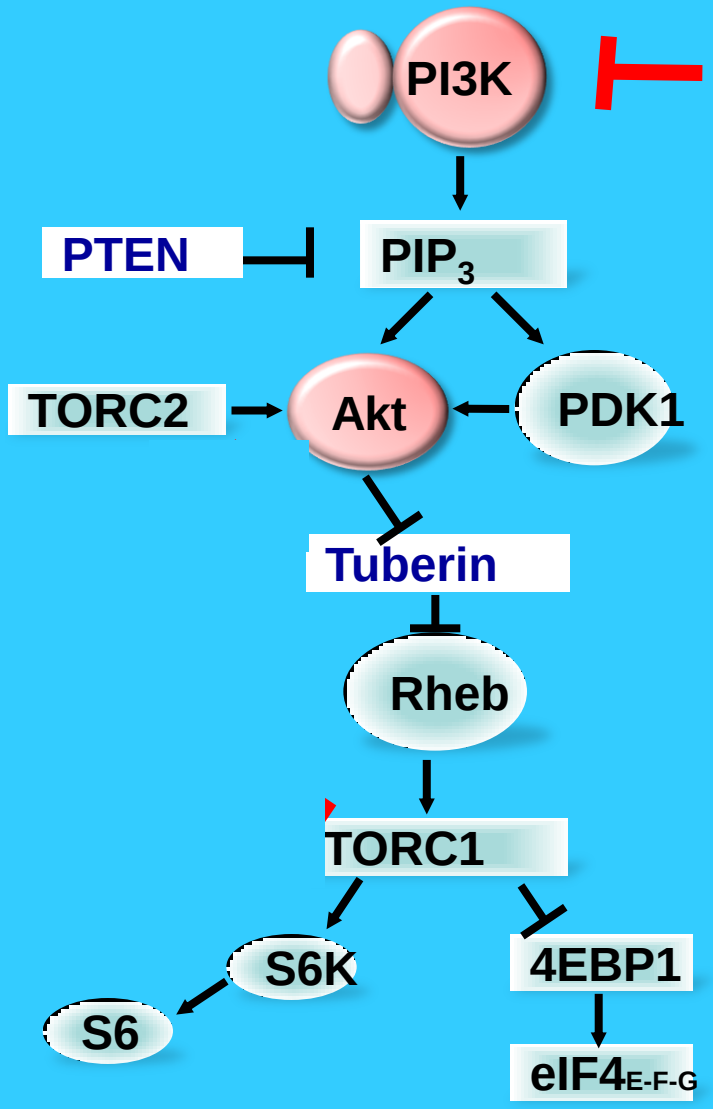
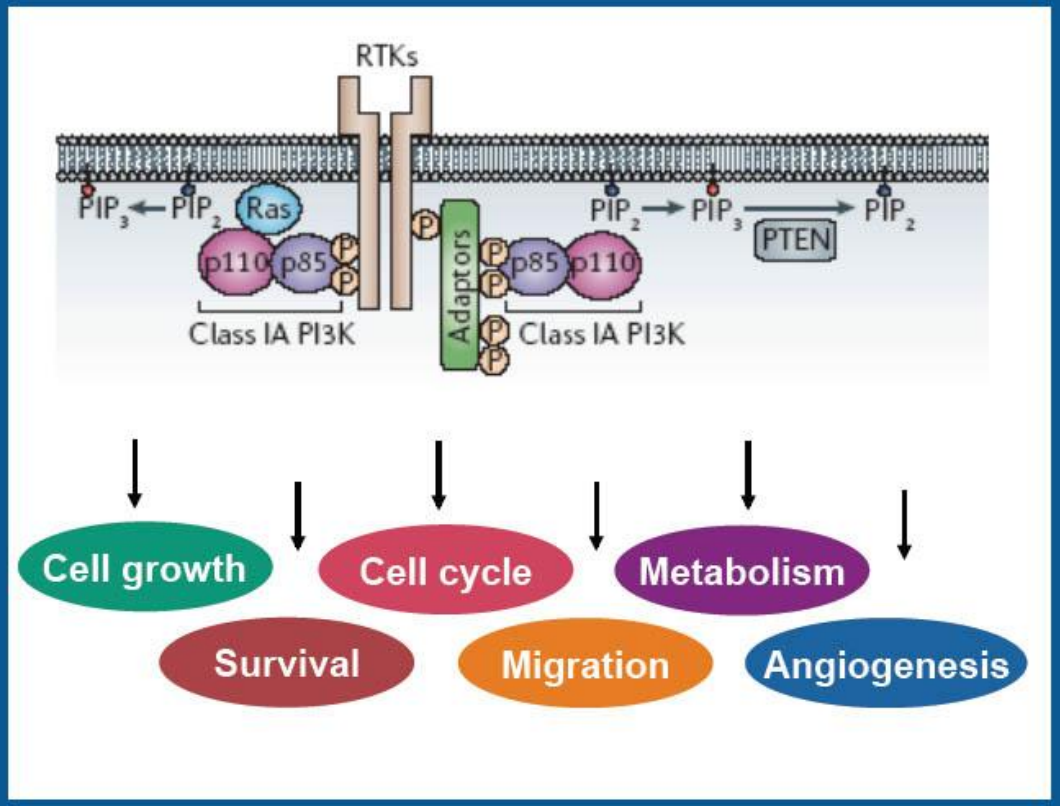
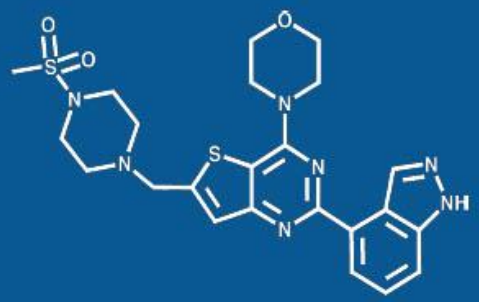


Novartis

GDC-0941 – Inhibitor of Class I PI3K

- The PI3K-PTEN-AKT signaling pathway is dysregulated in a wide variety of cancers.
- GDC-0941 is a pan-inhibitor of Class I PI3K demonstrating activity in xenograft models of breast, ovarian, lung, and prostate cancers.





Biochemical potency
(IC50)

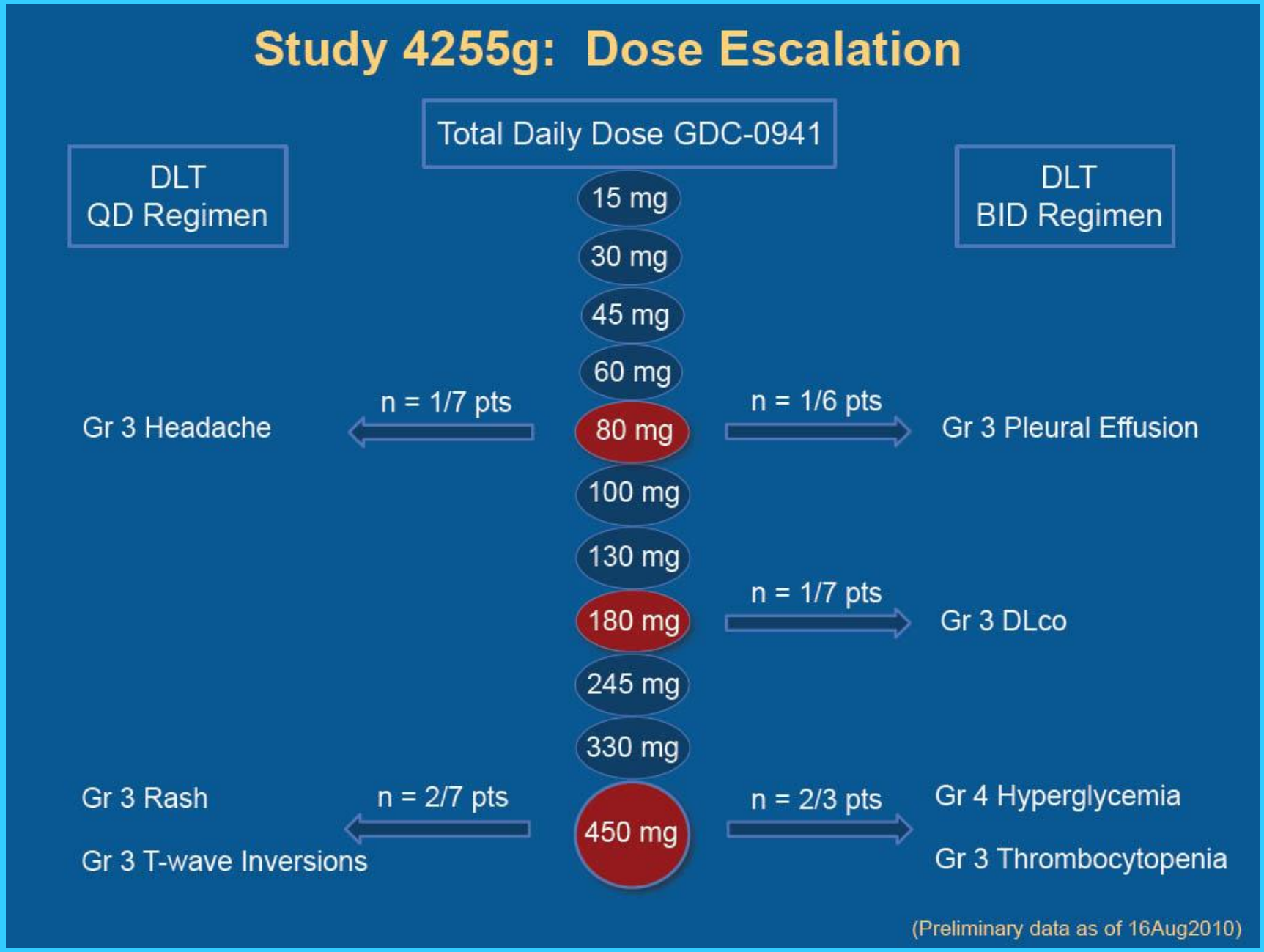
- p110α: 0.003 μM
- p110β: 0.033 μM
- p110γ: 0.075 μM
- p110δ: 0.003 μM

- mTOR: 0.58 μM*

* K_{iapp} value

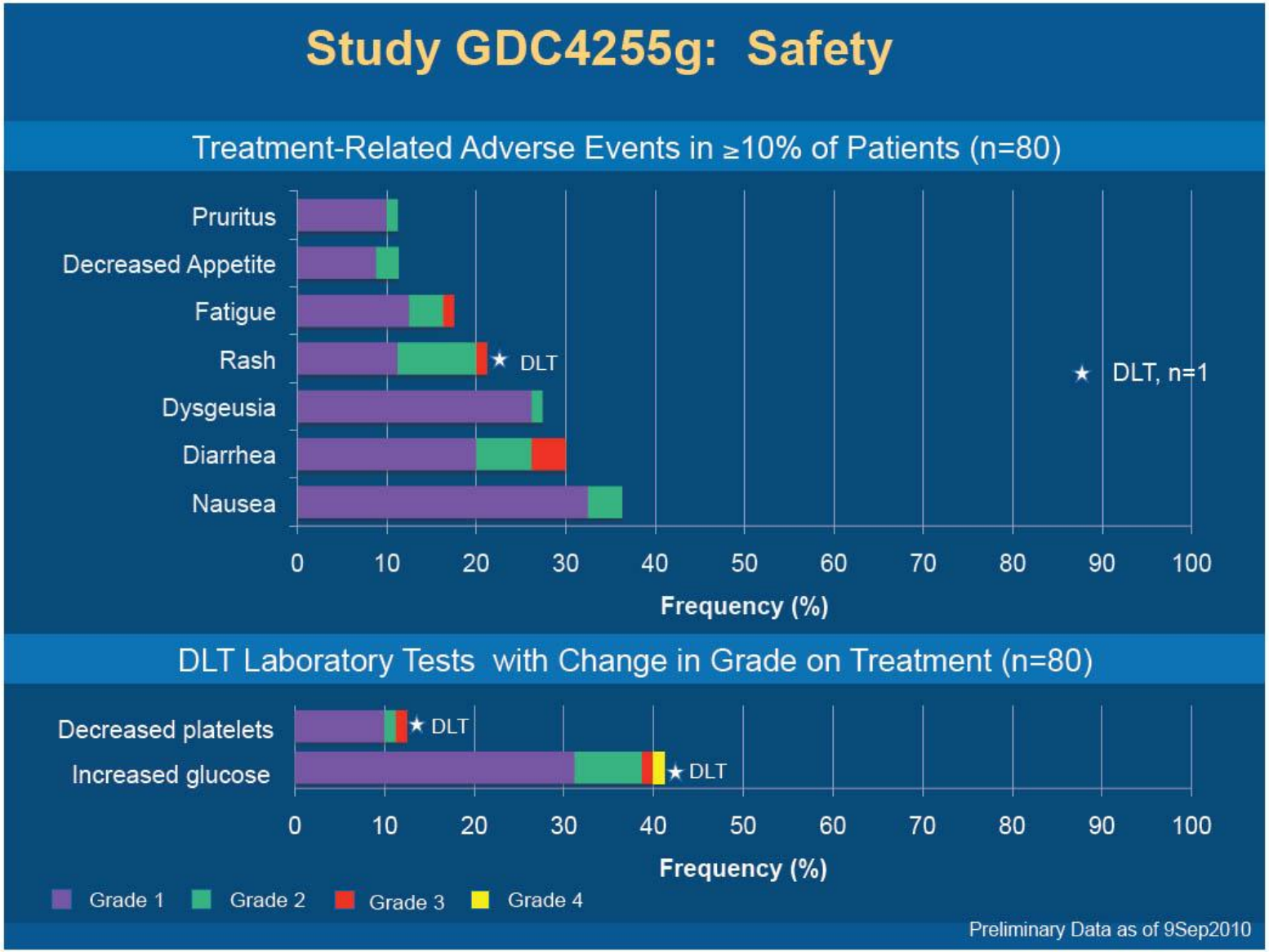
Wagner, et al. 2010 ESMO

Study 4255g: Dose Escalation



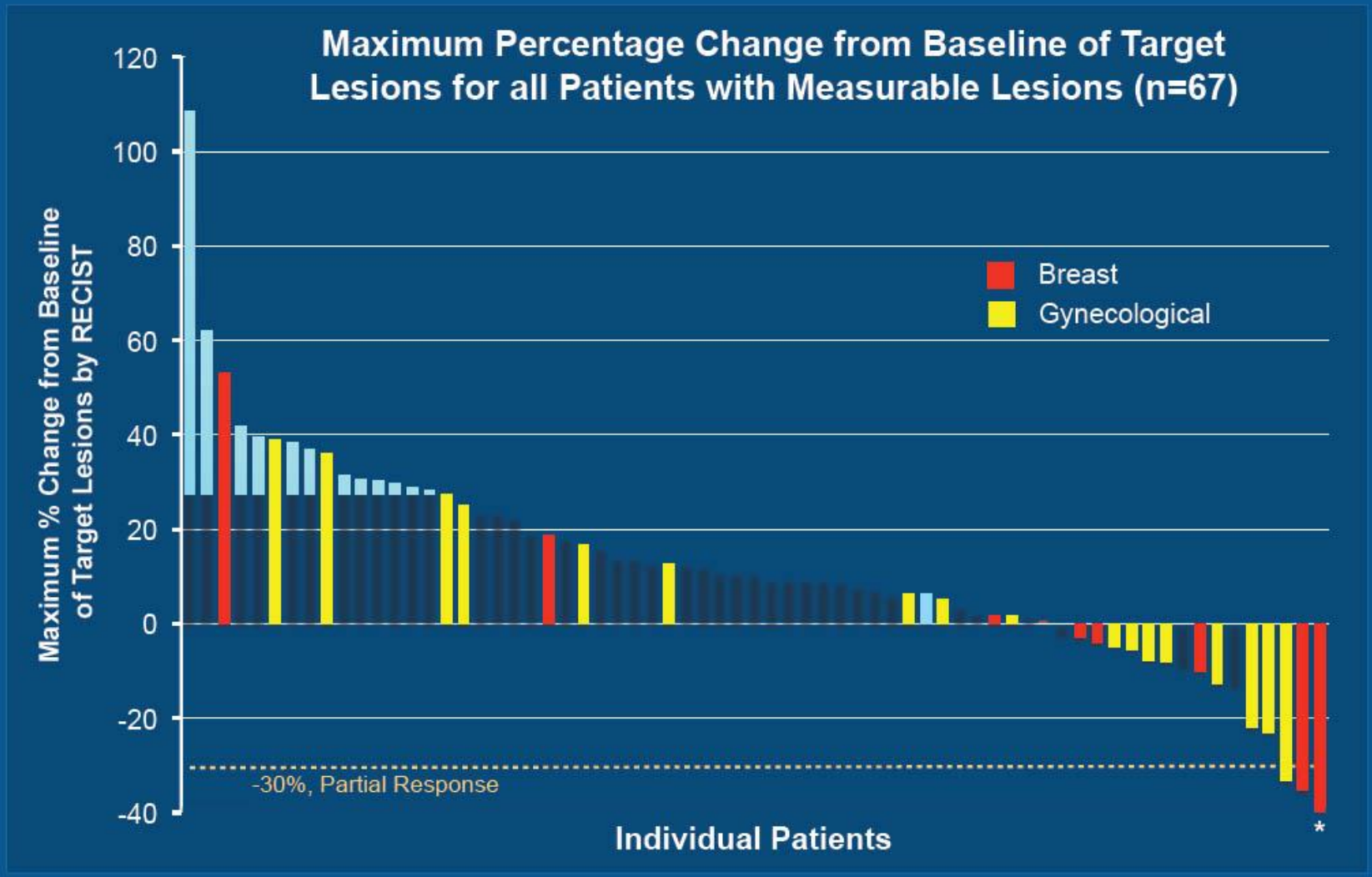
Wagner, et al. 2010 ESMO

Study GDC4255g: Safety



Wagner, et al. 2010 ESMO

Study GDC4255g: Patient Target Lesion Data



* Disease progression due to worsening of multiple non-target lesions

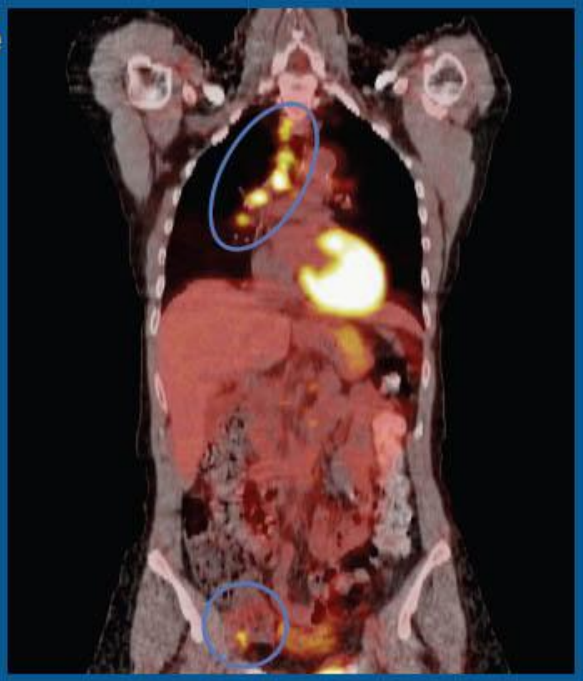
Preliminary Data as of 01Sep 2010

Wagner, et al. 2010 ESMO

Study GDC4255g: Clinical Activity #2

- 48 y/o woman with endocervical adenocarinoma
  - Dx 2003; lymph node mets; prior XRT and 5 systemic treatment regimens
    - 330 mg TDD (165/165 mg) GDC-0941 with AUC ~22.4 μM•hr
  - archival tumor tissue: PIK3CA mutation at E545K, normal PTEN expression
  - RECIST response: 33% decrease (uPR) in target lesions by end C4; still on study
    - ^{18}FDG-PET: 80% decrease in mean SUVmax of 6 measured regions of interest (ROI) with 3 regions disappearing by end C2

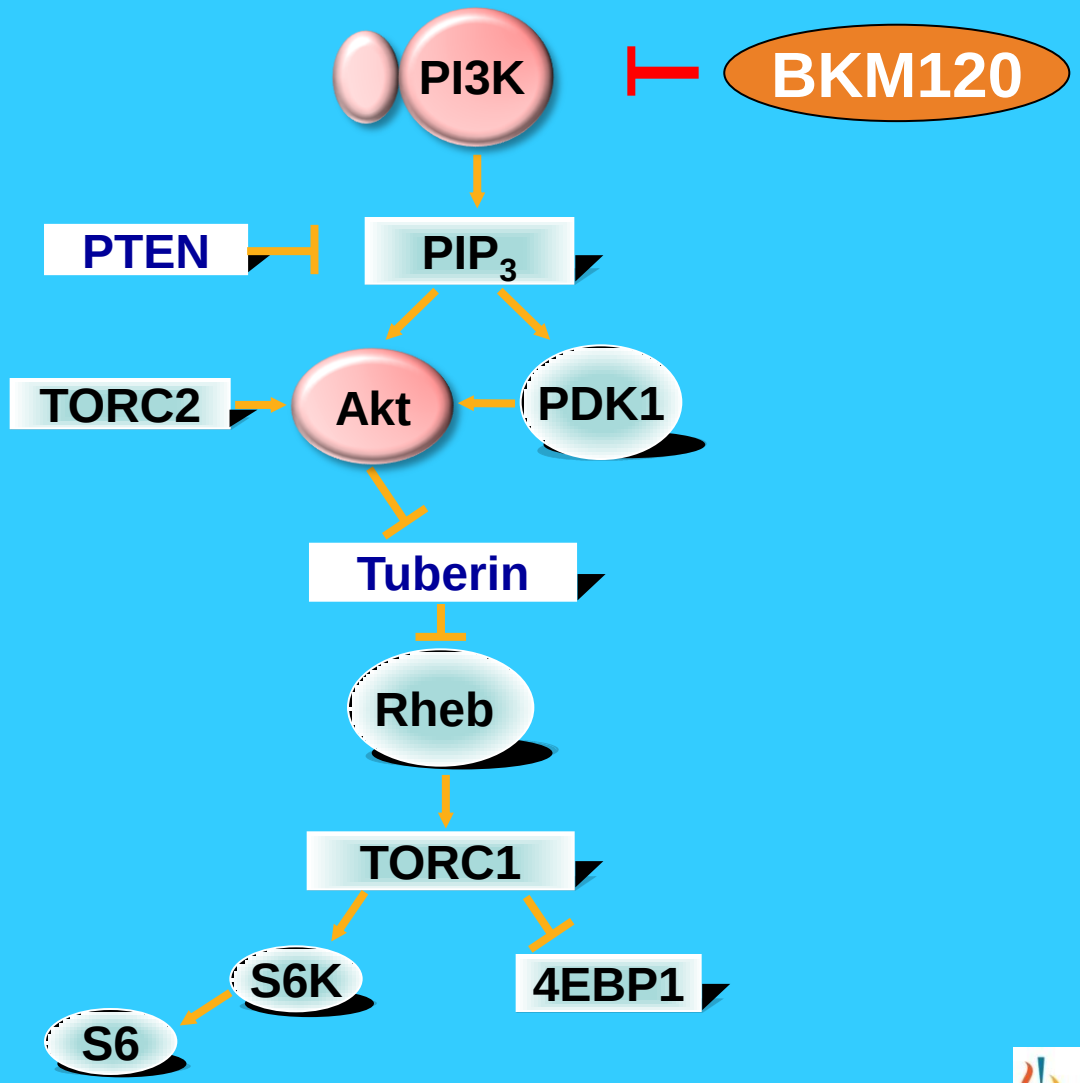
Baseline



End of Cycle 2

Wagner, et al. 2010 ESMO

Novartis PI3K Pathway Inhibitors: BKM120

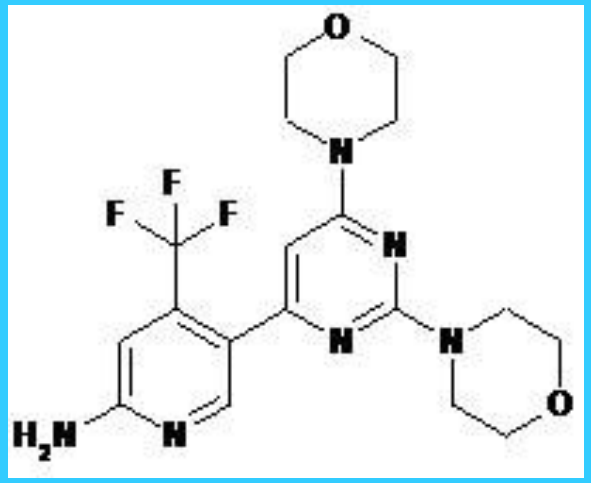


Baselga et al ASCO 2010 Abstract #3003 Clinical Science Symposium

NOVARTIS

BKM120

	Enzyme	IC_{50} (nM)
Class I PI3Ks	**p110α**	**52 ± 37**
	p110α–H1047R	**58 ± 2**
	p110α–E545K	**99 ± 6**
	p110β	**166 ± 29**
	p110δ	**116**
	p110γ	**262 ± 94**
Class III PI3Ks	mTOR	4610 ± 1860
	DNAPK	>5000
Panel of >18 protein kinases		>10000

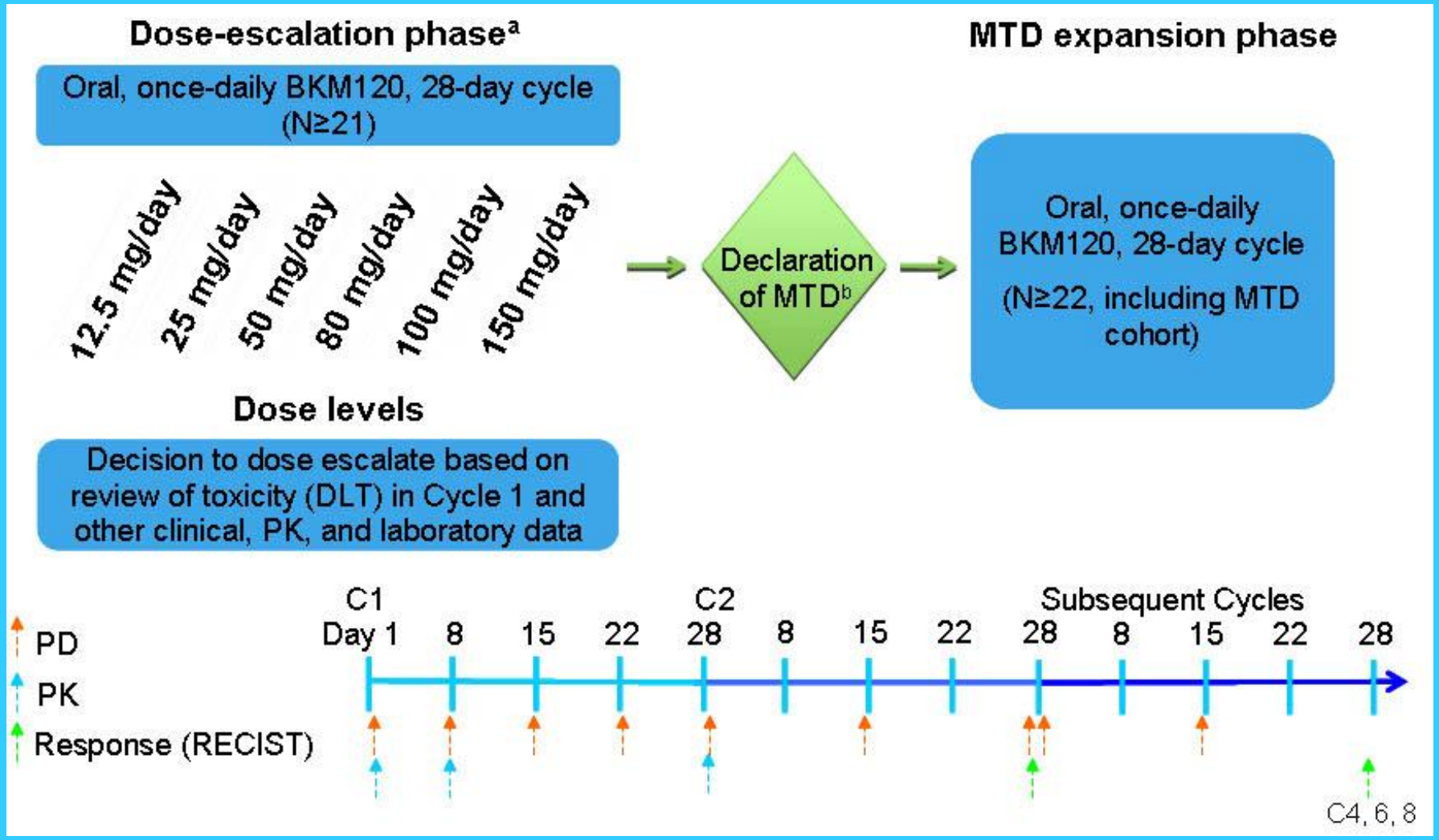


- ATP competitive, highly specific inhibition of class I PI3K
- Antiproliferative activity in tumor cell lines (GI_{50} 158–1010 nM)
- Pro-apoptotic activity in PIK3CA-mutated breast cancer cell lines
- Potent anti-tumor activity in tumor xenograft models with or without PI3K/PTEN mutations

Voliva *et al.* Poster Presn. AACR 2010. Abstr 4098
Maira *et al.* Poster Presn. AACR 2010. Abstr 4097

BKM120 Phase I: Study Design

Phase IA, Multicenter, Open-label, Single-agent, Dose-escalation Study in Patients with Advanced Solid Tumors



[a] Bayesian logistic regression model using overdose control; [b] Defined as the highest drug dosage not causing DLT in >33% of patients during the first treatment cycle

Baselga et al ASCO 2010

BKM120 Phase I: Tumor Mutation status

Tumor samples[a]	n (%)
Evaluable for *PIK3CA* status[b]	30 (86)
Wild-type	29 (83)
Mutation	1 (3)
Evaluable for *PTEN* status[c]	26 (74)
Wild-type	23 (66)
Mutated	3 (9)
Evaluable for PTEN expression[d]	29 (83)
Protein level low or null	12 (34)
Protein level not low	17 (49)
Tumors with PI3K pathway activation (any PIK3CA/PTEN alterations)	15 (43)
Evaluable for *KRAS* status[e]	28 (80)
Wild-type	18 (51)
Mutation	10 (29)

[a] Samples available for 30/35 patients, some analyses incomplete due to sample quantity or quality
[b] SNaPshot genotyping assay of exons 9 and 20
[c] Genomic DNA sequencing *PTEN* exons 1–9
[d] Semiquantitative IHC Dako M3627 antibody
[e] Genomic DNA sequencing

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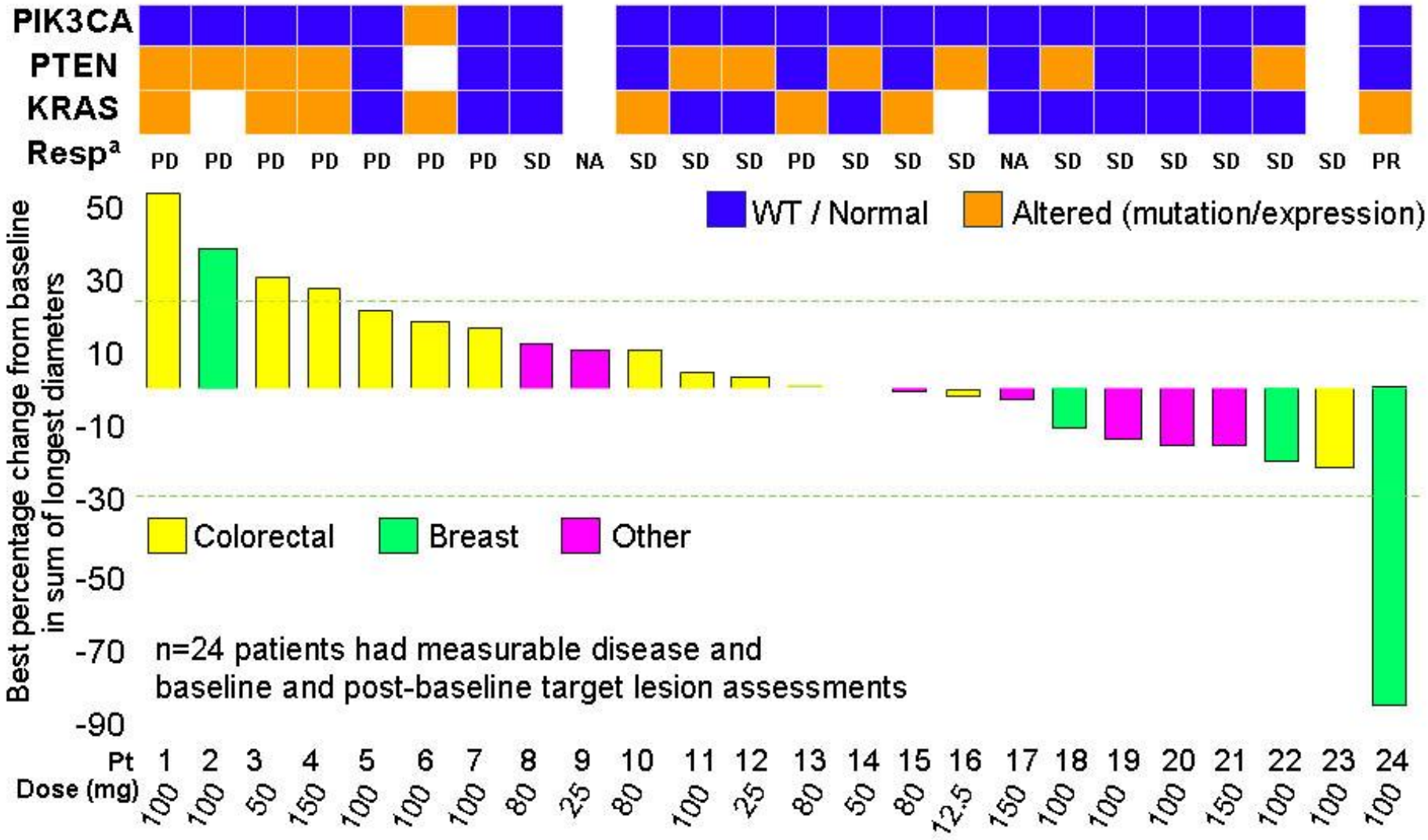
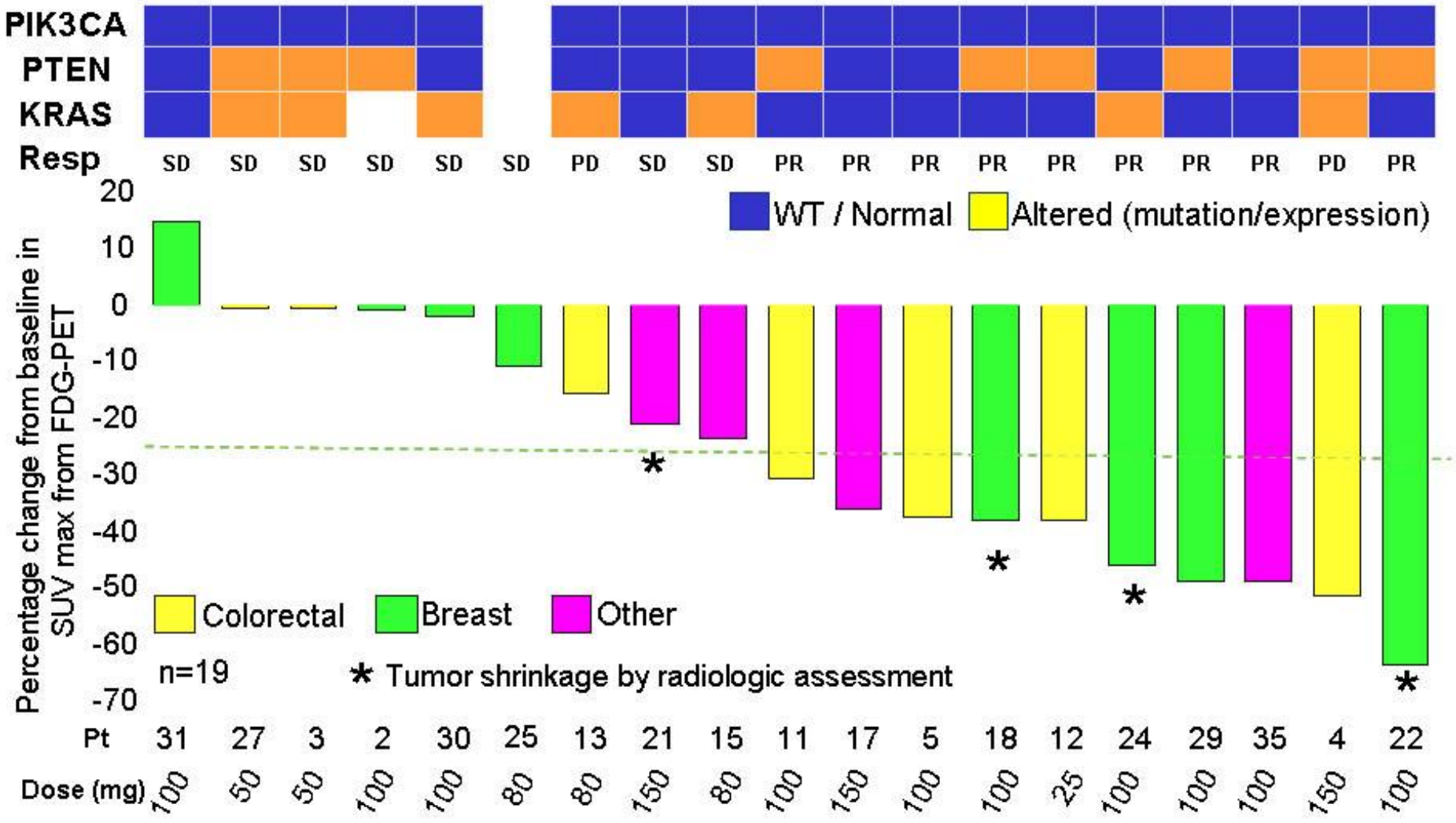
BKM120 Phase I: Clinical Efficacy By Radiologic Assessment And Overall Response



[a]Response as per investigator; NA, not available

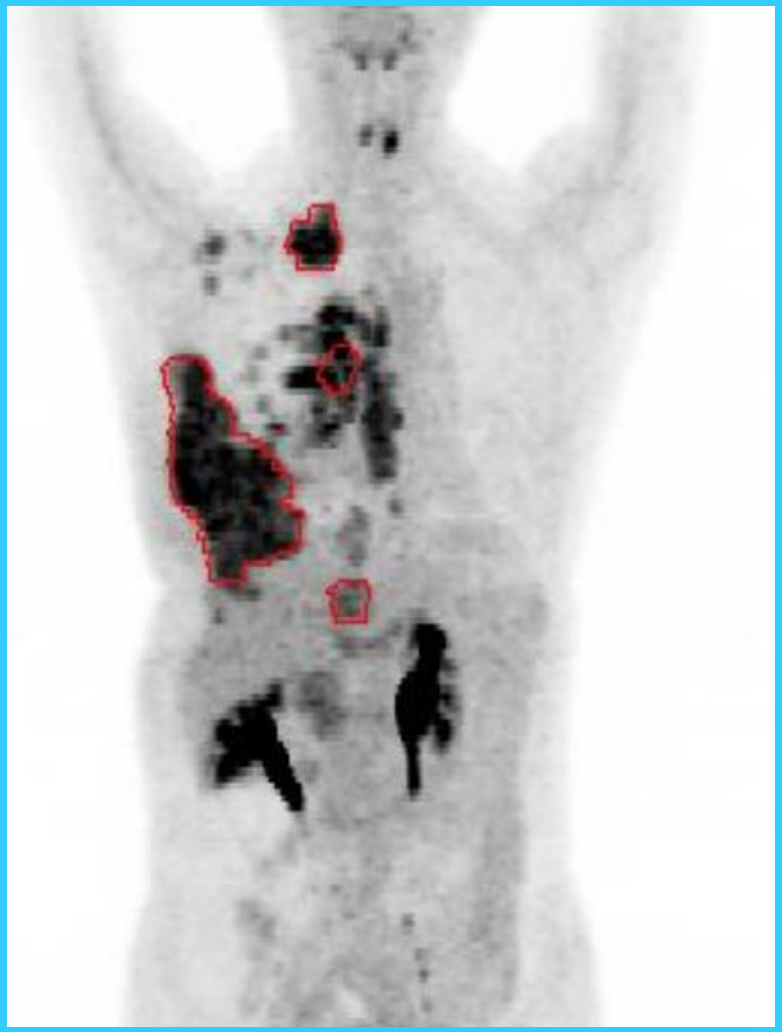
BKM120 Phase I: Tumor Metabolic Response As Per ^{18}FDG-PET[a]



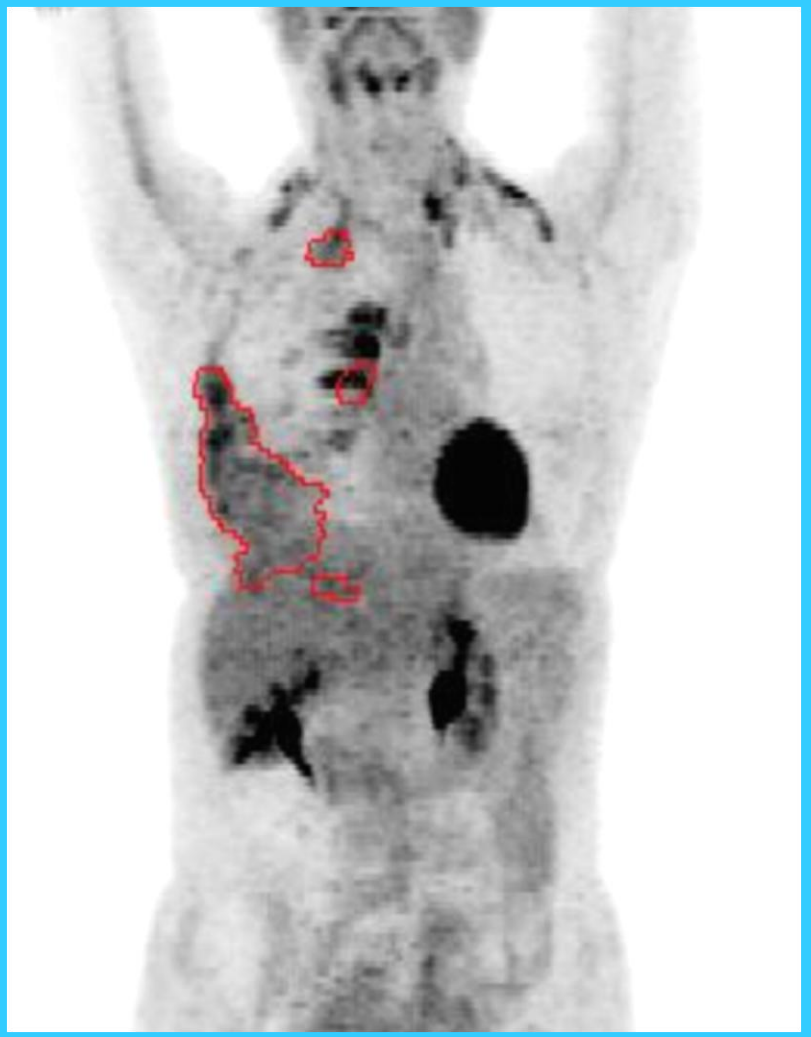
[a]Cycle 1, Day 28

BKM120 – Clinical Activity

Breast Cancer: her2+, PIK3CA WT



Baseline
Patient 500-108

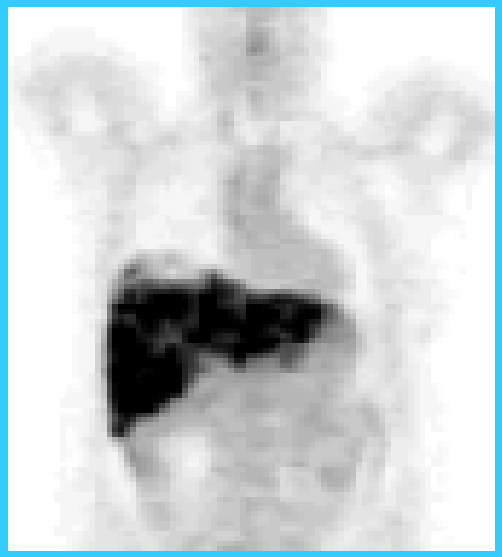


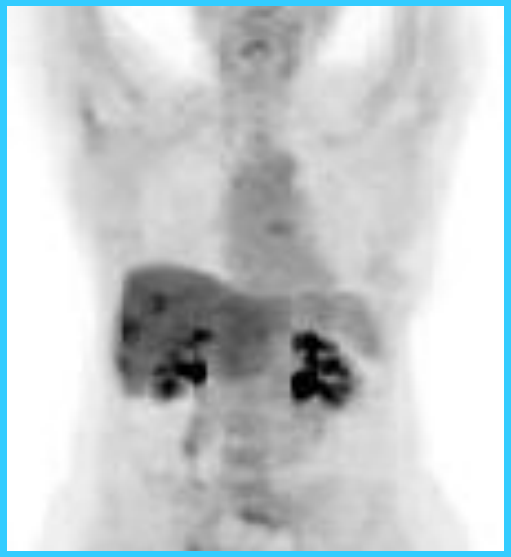
Cycle 1

BKM120 - Clinical Activity

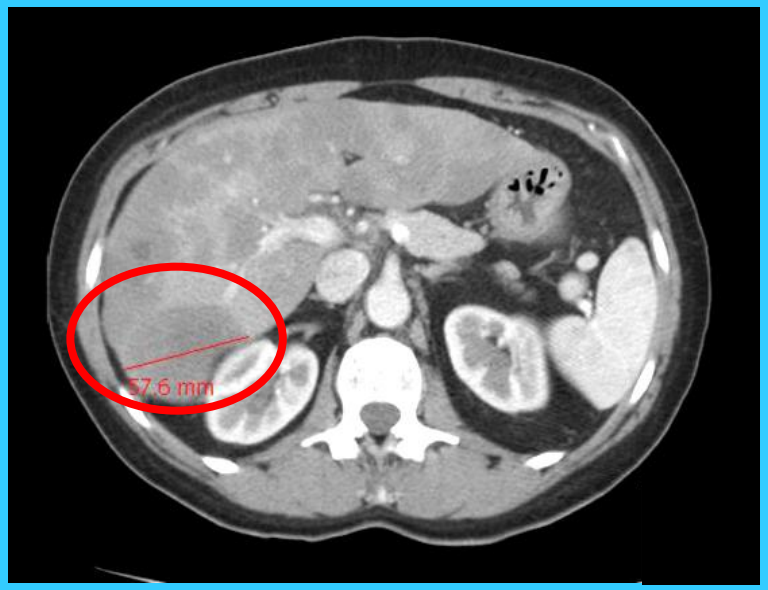
Breast Cancer: PIK3CA mutant

PET SCAN

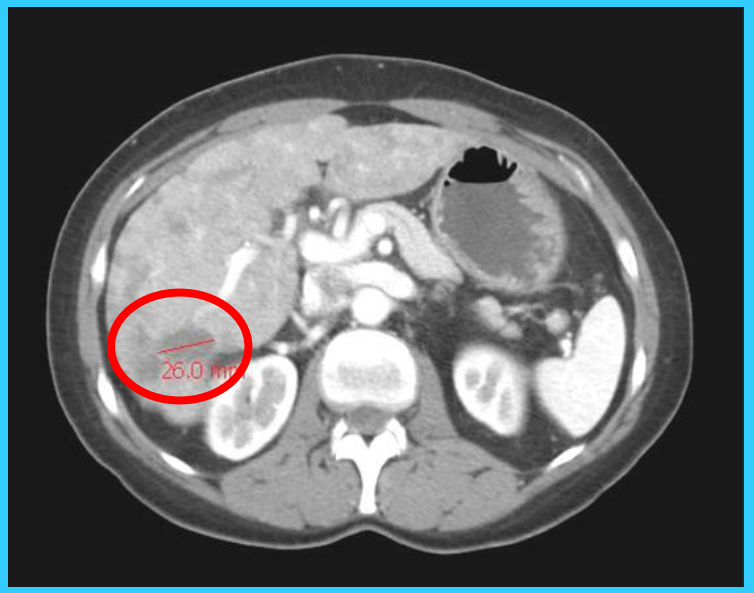




CT SCAN



Baseline

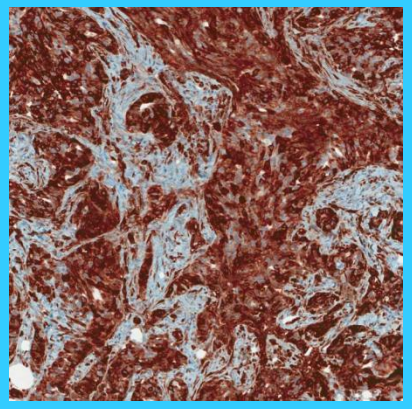


Cycle 4

BKM120 Shows PD Effect in Paired Tumor Biopsies from Patients Treated at 100mg

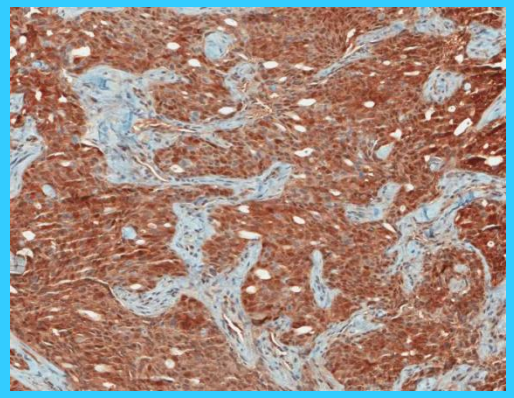
Biopsy	Diagnosis	PI3K MT	pTEN	Tumor content	pS6 (1+/2+/3+)	pAkt (1+/2+/3+)	p4EBP1 (1+/2+/3+)	Ki67%
Base line	**Salivary Gland**	**MT***	**Neg*/ WT**	80%	0-20-80	0-100-0	0-0-100	80
C2D1				70%	60-10-30 ↓	80-20-0 ↓	0-30-70	50 ↓

* Local assessment as PIK3ca mutation and PTEN expression



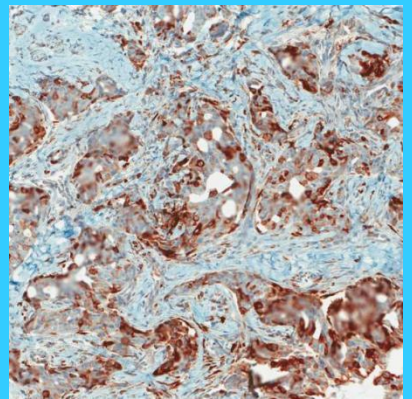
pS6

Base line

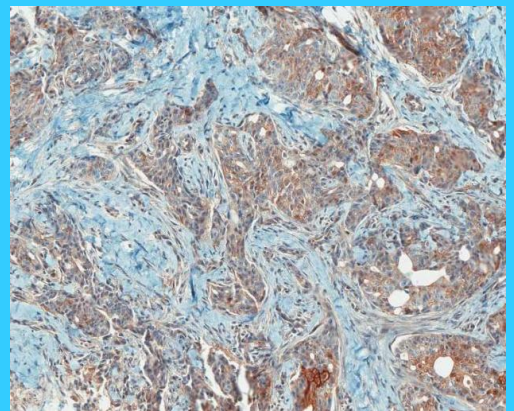


pAKT

Base line

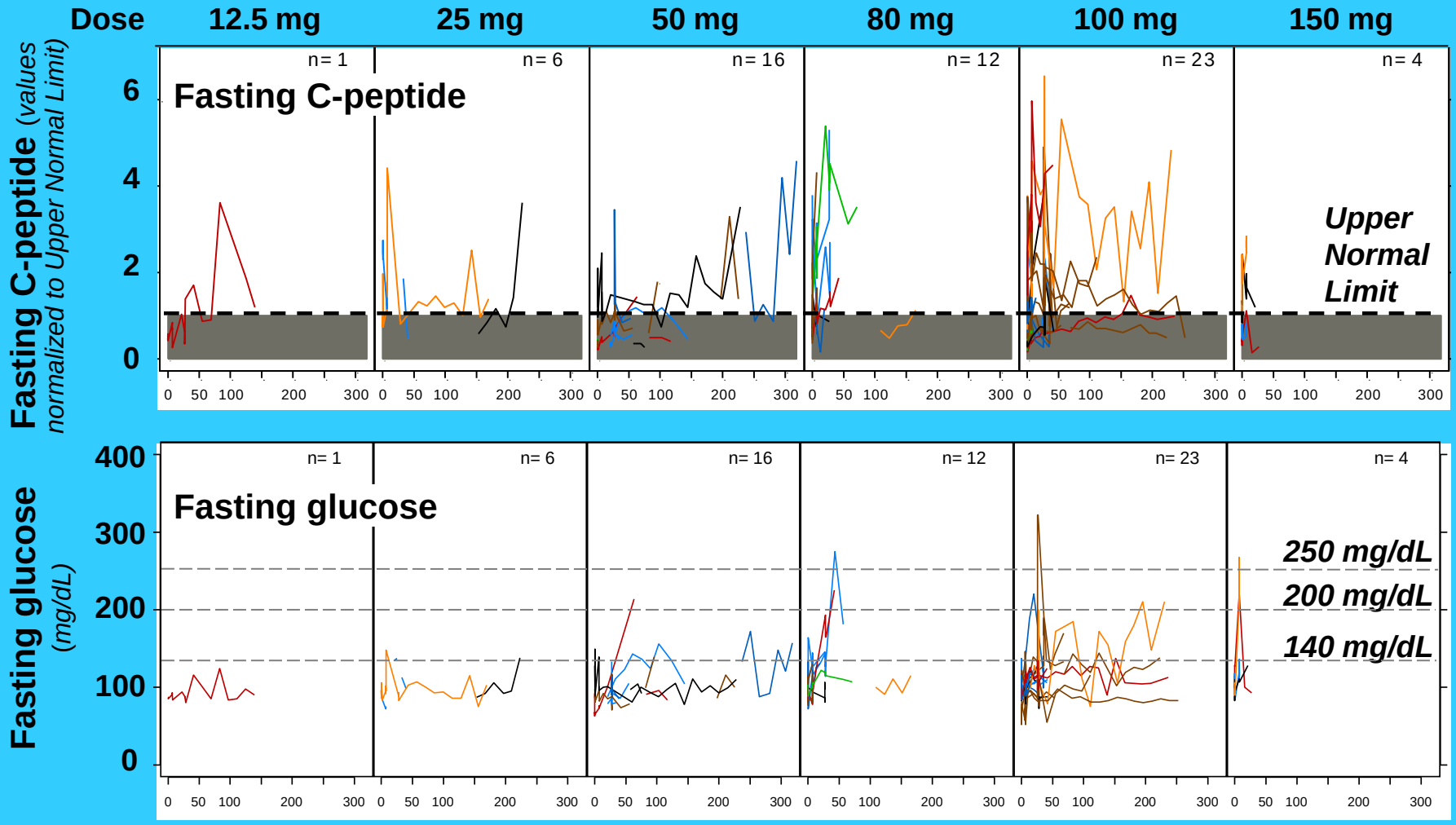


C2D1



C2D1

BKM120 Phase I: Endogenous C-peptide Increases Can Compensate for Bkm120-induced Hyperglycemia



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Most Frequent AEs - All Grades*

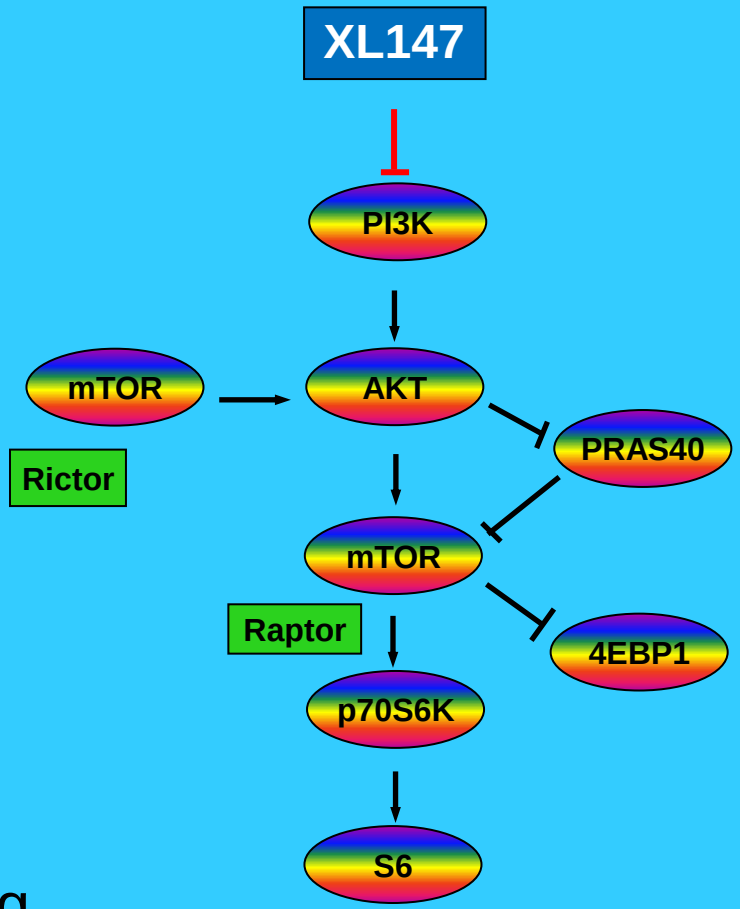
- Decreased appetite (33%)
- Rash (27%)
- Diarrhea (27%)
- Nausea (27%)
- Fatigue (24%)
- Hyperglycemia (24%)
- Anxiety (20%)
- Depression (18%)
- Mucositis (17%)

*First 66 pts included in analysis
Suspected drug related

XL147: a potent and selective PI3K inhibitor

Family		Kinase	IC_{50} (nM)
PI3K	Class IA	PI3Kα	39
		PI3Kβ	383
		PI3Kδ	36
	Class IB	PI3Kγ	23
	Class III	VPS34	6975
PIKK (PI3K-related)		DNA-PK	4750
		mTOR	>15000
ERK Pathway		BRAF/CRAF	>10000
		MEK	>10000

Highly selective in panel of > 120 kinases

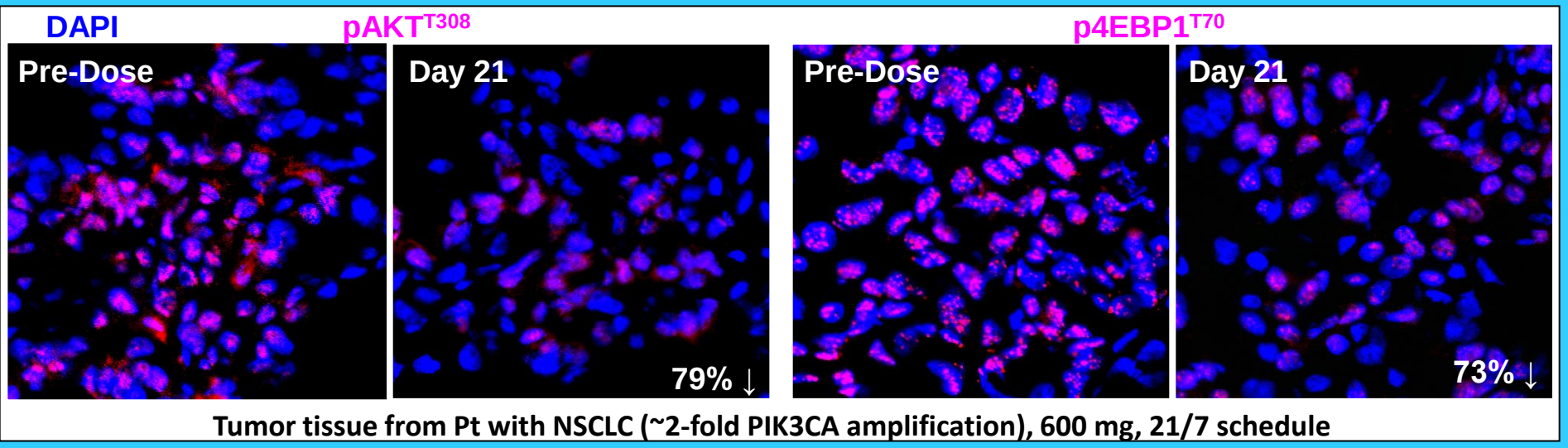


- ATP competitive and reversible binding
- Oral administration
- Preclinical efficacy in PI3K, PTEN, and KRAS mutant xenografts

Robust PI3K Pathway Inhibition in Diverse Tumors

Tumor	Dose (mg)	% Decrease			TUNEL (Fold-Increase)
		pAKT^{T308}	p4EBP1^{T70}	Ki67	
Leiomyosarcoma[1,2]	600	82	68	15	NC
Merkel Cell Carcinoma[1,2]	600	77	48	22	1.5
Hamartoma (Cowden)[3]	600	76	62	NC	NC
NSCLC[4]	600	79	73	29	1.6
NSCLC[5]	600	42	48	37	NC
Parotid Carcinoma[6,7]	900	44	39	NC	NC

[1] pAKT^{S473}, pPRAS40^{T246}, pS6$^{S240/S244}$ comparable reductions evident
[2] No mutations detected in PIK3CA, PTEN, KRAS
[3] Germline PTEN R233X mutation
[4] PIK3CA ~2-fold amplified
[5] Tumor mutational analysis in progress
[6] PTEN C250X mutation, HER2 amplified
[7] Initial dose halted and dose-reduced
NC, No change



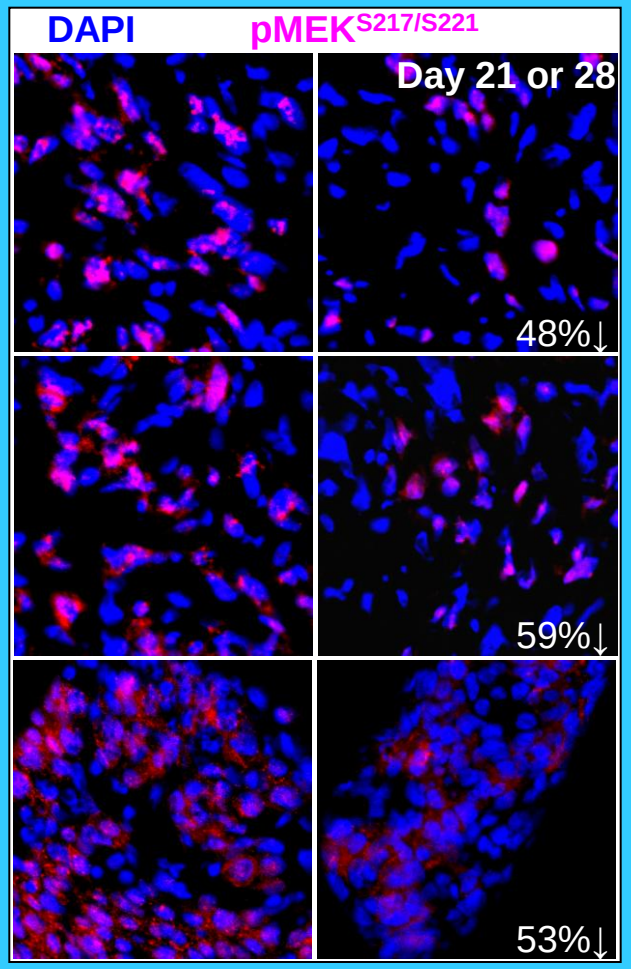
Tumor tissue from Pt with NSCLC (~2-fold PIK3CA amplification), 600 mg, 21/7 schedule

XL147 Inhibits ERK Pathway in Tumors: pMEK

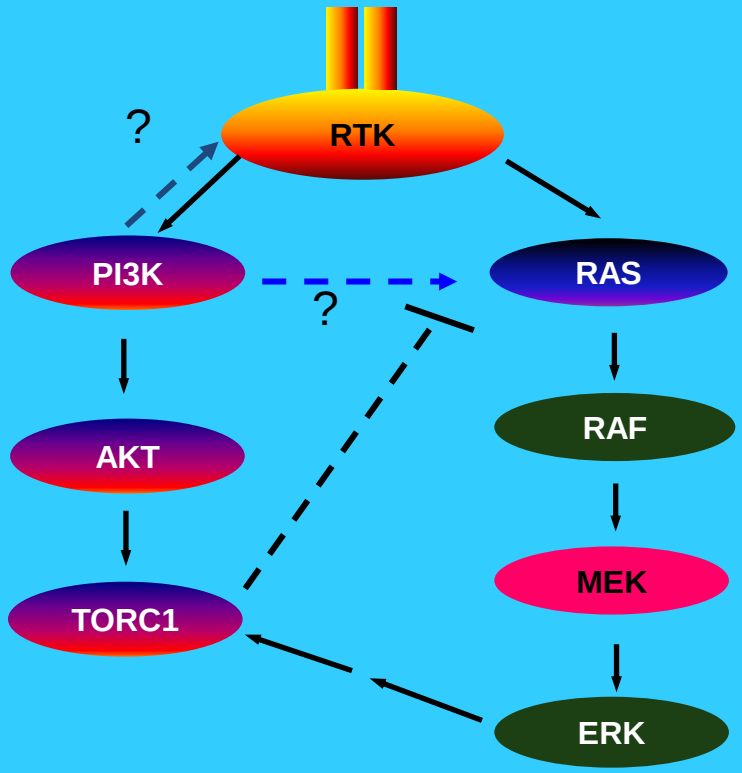
Merkel Cell Carcinoma[a] (600 mg)

Leiomyosarcoma[a] (600 mg)

Tongue SCC[b] (600 mg)



- Reduction in pMEK evident across diverse tumors
- Reduction in total MEK not evident

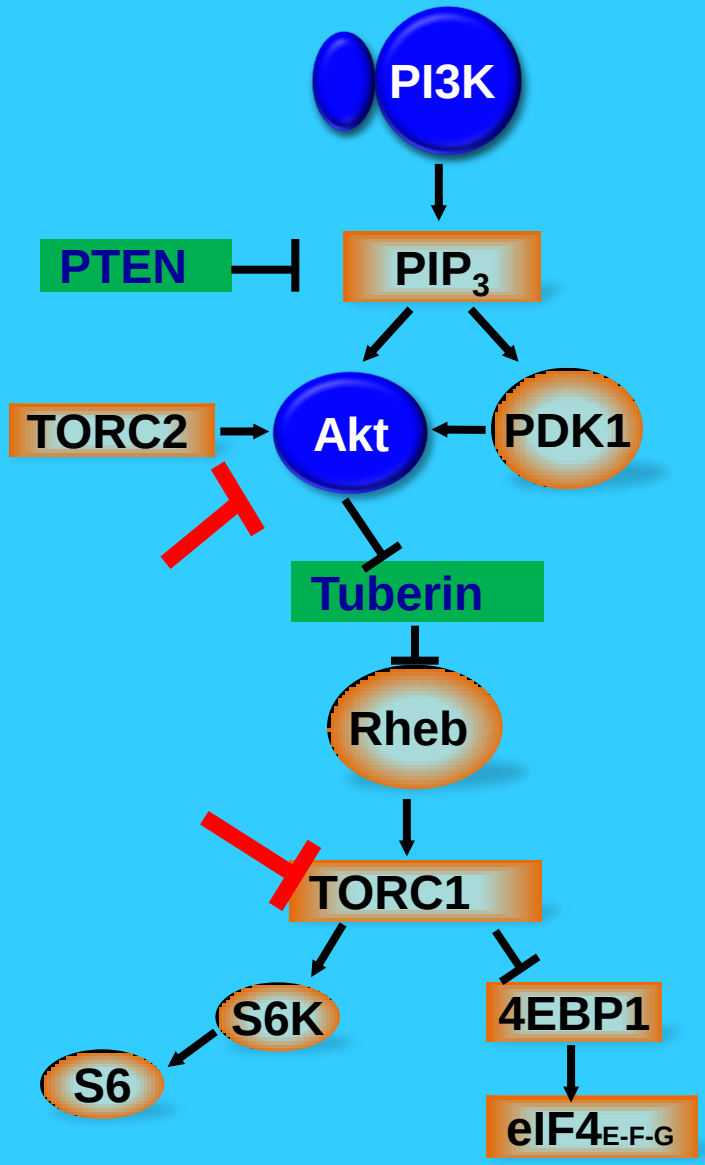


[a] No mutations detected in PIK3CA, PTEN, KRAS
[b] PIK3CA E545K mutation; no mutations detected in PTEN, KRAS

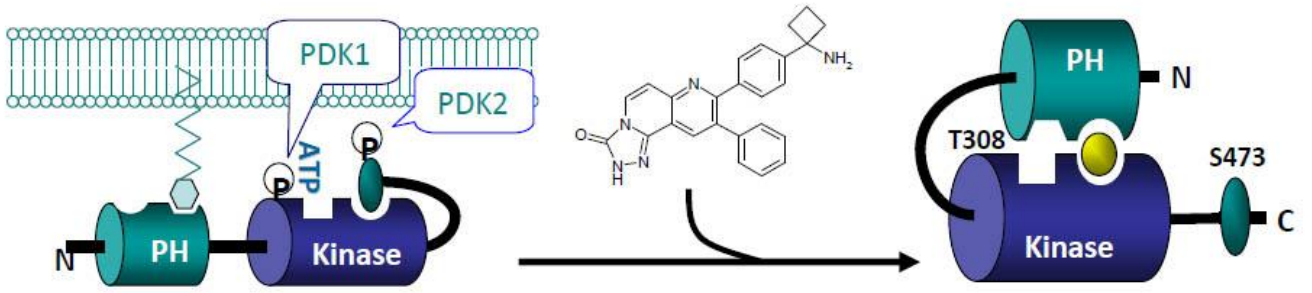
Edelman G, ASCO 2010:Abstr 3004

PI3K Pathway Inhibitors

Agent	Company	Molecular targets
BYL719	Novartis	PI3Kα
GDC-0032	Genentech	PI3Kα
INK-1117	Intellikine	PI3Kα
XL-147	Exelixis/Sanofi	Pan-PI3K
NVP-BKM120	Novartis	Pan-PI3K
GDC-0941	Genentech	Pan-PI3K
PKI-587	Pfizer	Pan-PI3K
XL-765	Exelixis/Sanofi	PI3K / mTOR
NVP-BEZ-235	Novartis	PI3K / mTOR
NVP-BGT-226	Novartis	PI3K / mTOR
PF-4691502	Pfizer	PI3K/mTOR
AZD8055	Astrazeneca	mTOR (catalytic)
INK 128	Intellikine	mTOR (catalytic)
MK-2206	Merck	AKT1,2,3
GDC-0068	Genentech	AKT



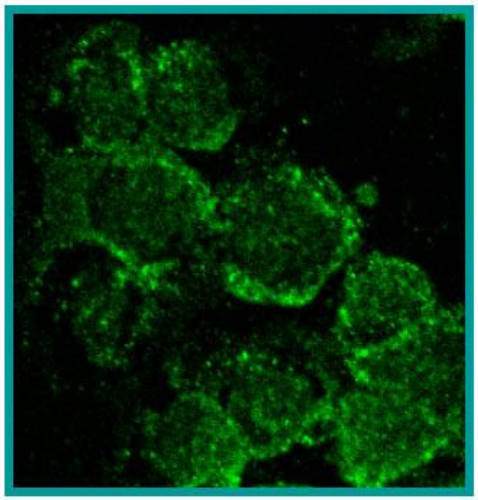
Proposed MoA of MK-2206, an Allosteric AKT inhibitor



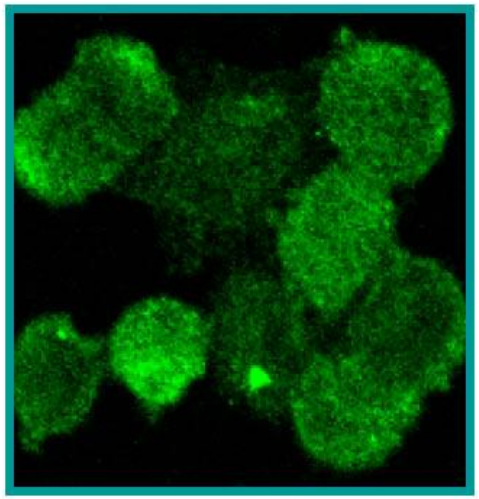
Active AKT

MK-2206

Inhibited AKT
(Incapable of membrane localization)



Vehicle



AKTi-1/2C
tool compound

Public disclosed

Dose escalation and expansion cohorts

	Dose	No. of patients		No. of cycles	No. of patients with DLTs	
		Enrolled	Dose reduced			
Every other day (QOD)	30 mg	3	-	10	-	
	60 mg	6	-	15	-	MTD
	90 mg	7	6	13	4	
	75 mg	3	3	13	3	
Weekly (QW)	90 mg	3	-	11	-	
	135 mg	4	-	7	-	
	200 mg	6	1	20	1	MTD*
	300 mg	3	2	9	3	
	250 mg	3	2	3	2	
	QOD cohort expansions†	45	2	94	6	

†Including mandatory biopsy cohort, ovarian and castration resistant prostate cancer cohorts, and DCE-MRI cohort

Public disclosed

Dose-limiting toxicities

Cycle 1 (all cycles)

DLT	60 mg QOD	75 mg QOD		90 mg QOD		200 mg QW	250 mg QW	300 mg QW
	Grade 3	Grade 2	Grade 3	Grade 3	Grade 4	Grade 3	Grade 3	Grade 3
Rash	6 (8)	-	2 (2)	3 (3)	1 (1)	1 (1)	2 (2)	3 (3)
Diarrhea	-	1*(1)	-	-	-	-	-	-
Hyperglycemia	1 (1)	-	0 (1)	-	-	-	-	-
Pruritus	-	-	0 (1)	1 (1)	-	-		-

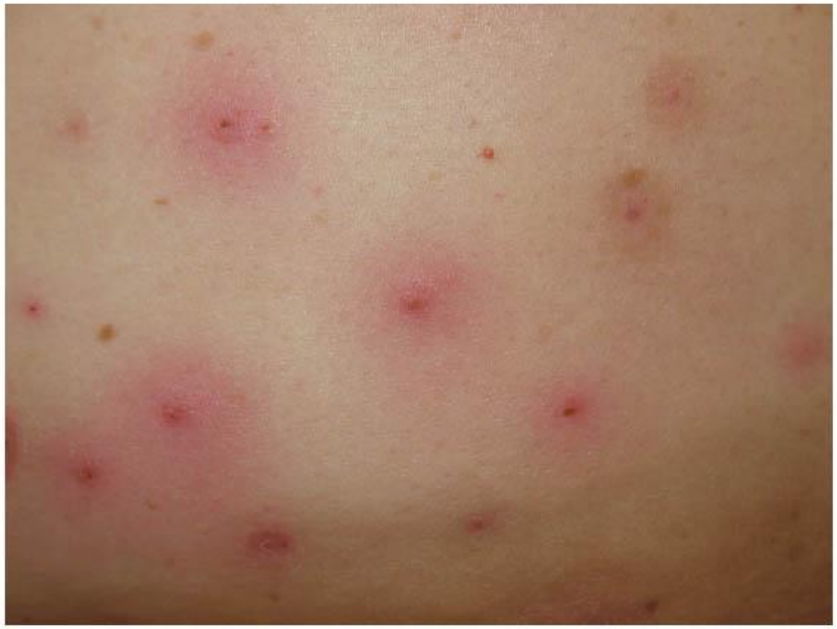
*Required dose reduction

The QOD and QW MTD was established at 60 mg and 200 mg†, respectively

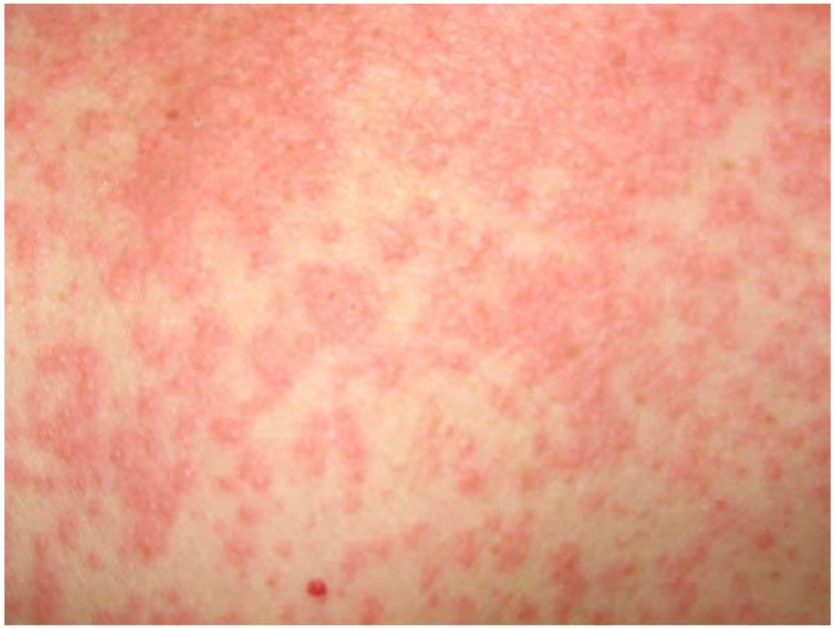
†Preliminary QW MTD

Public disclosed

Drug-related skin rash



Grade 1-2



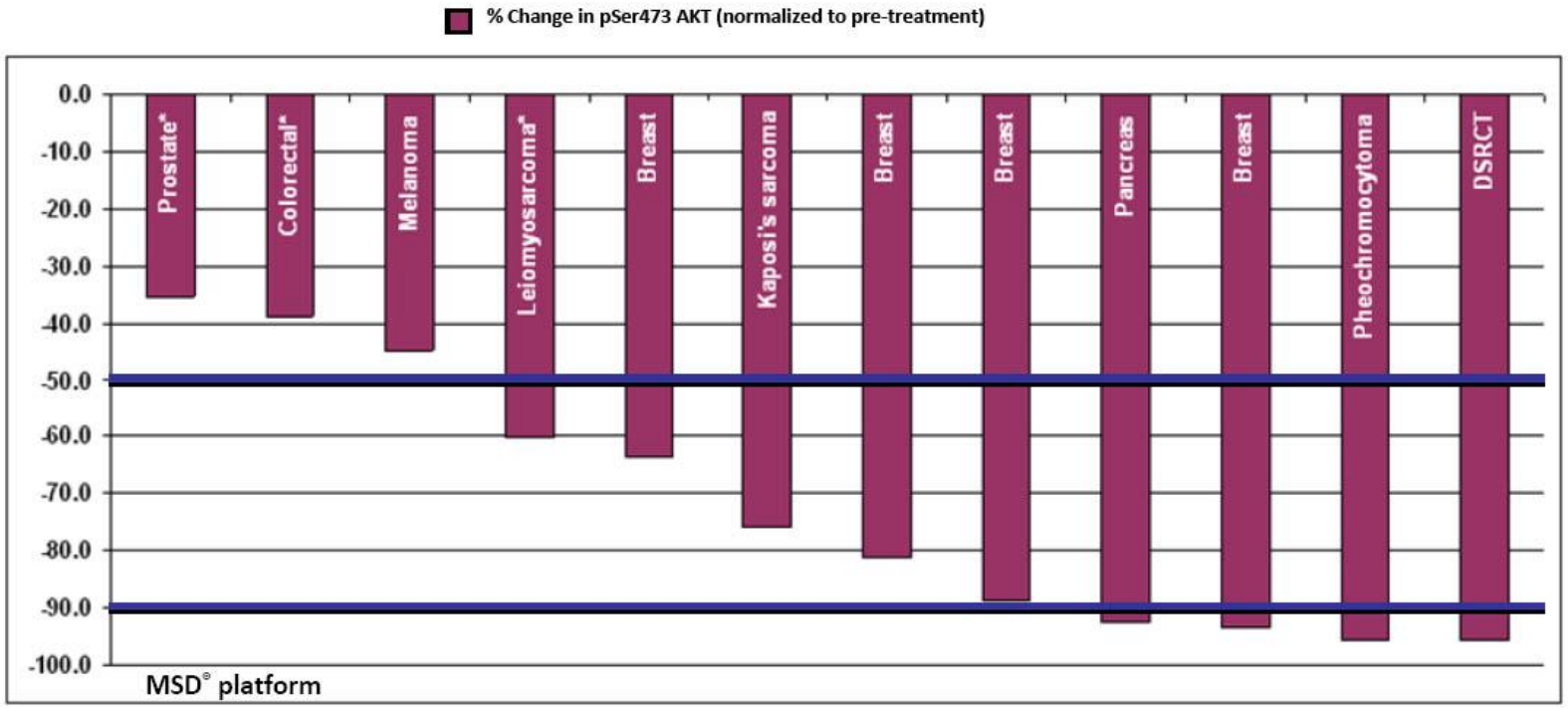
Grade 3-4

Fully reversible on drug discontinuation

Public disclosed

Tumor PD 60 mg QOD (MTD)

n = 12



- Tumor pSer473 AKT decreased post-MK-2206 in all 12 patients
- ≥ 50% decrease of pSer473 AKT in 9 of 12 patients

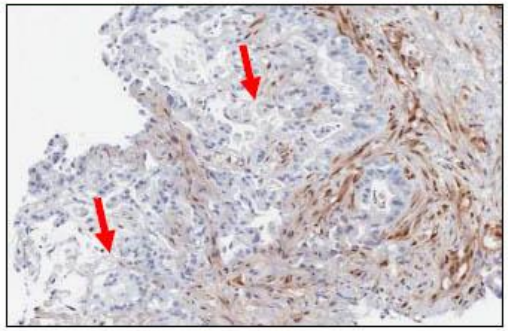
AKT TARGET MODULATED IN TUMOR

Clinical Development Lab, Merck and *Clinical PD Biomarker Group, The Institute of Cancer Research

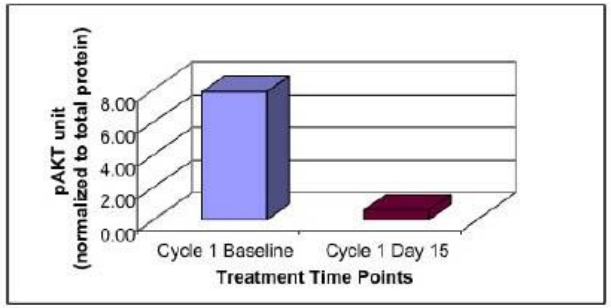
Public disclosed

Case study: Metastatic pancreatic cancer (MK-2206 60 mg QOD)

- 72 year-old male with metastatic pancreatic cancer
- Multiple prior therapies
- *Loss of PTEN expression (tumor)*
- *G12D KRAS mutation (tumor)*



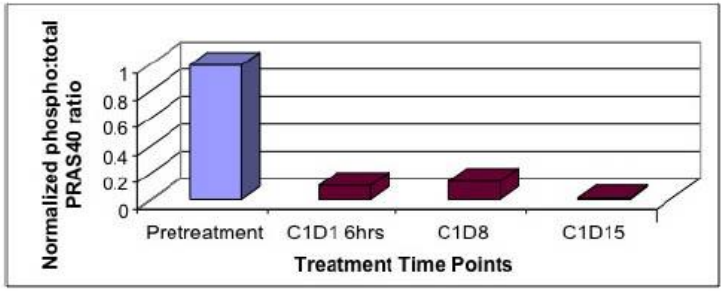
MSD® platform



Tumor PD

↓ pSer473 AKT

Immunofluorescence assay



Hair follicles

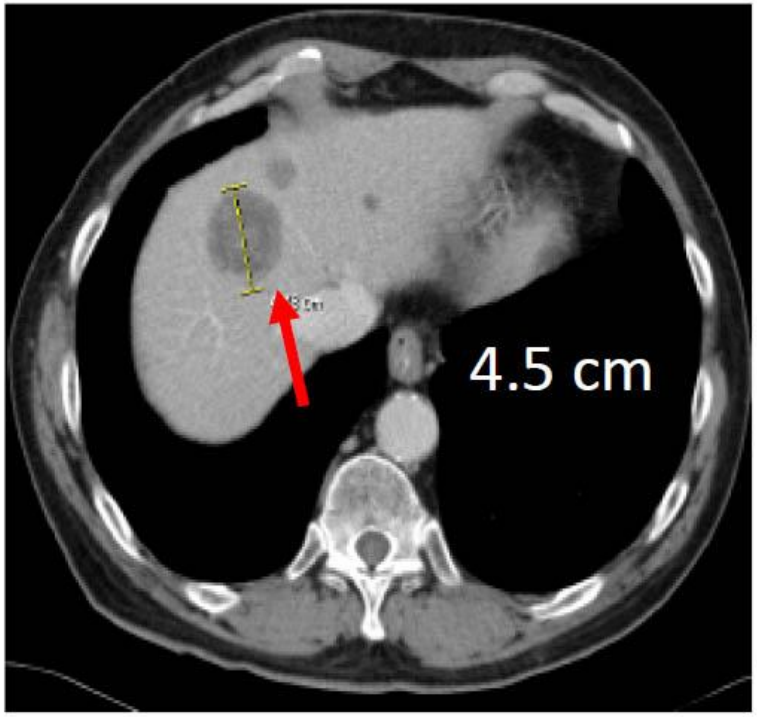
↓ pThr246 PRAS40

Clinical Development Lab, Merck and Clinical PD Biomarker Group, The Institute of Cancer Research

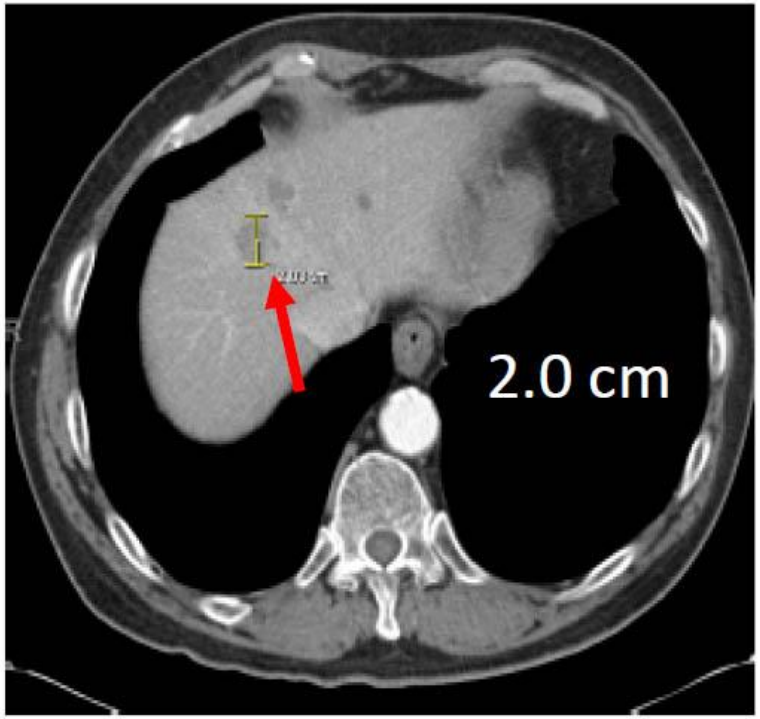
Public disclosed

Case study: Metastatic pancreatic cancer (MK-2206 60 mg QOD)

- 50% shrinkage of largest hepatic lesion after 4 months of MK2206
- RECIST response of 23%
- ~65% decrease in CA19-9 tumor marker



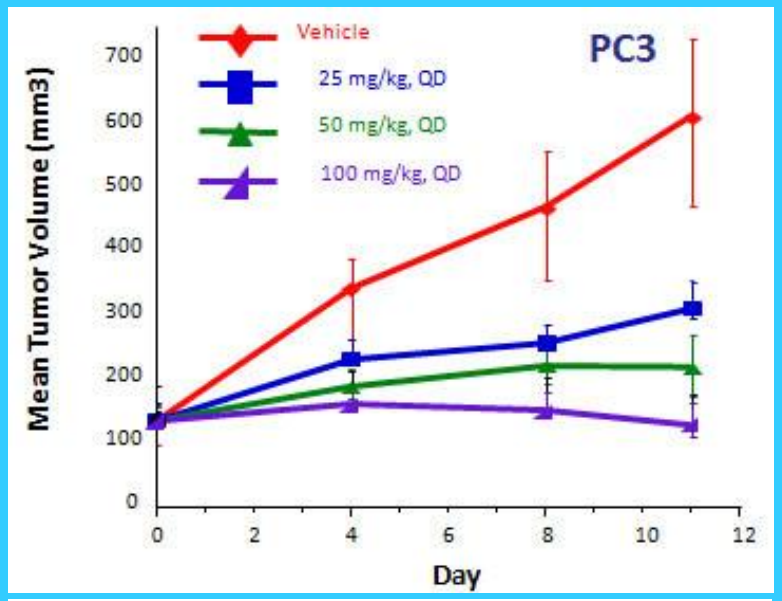
Baseline

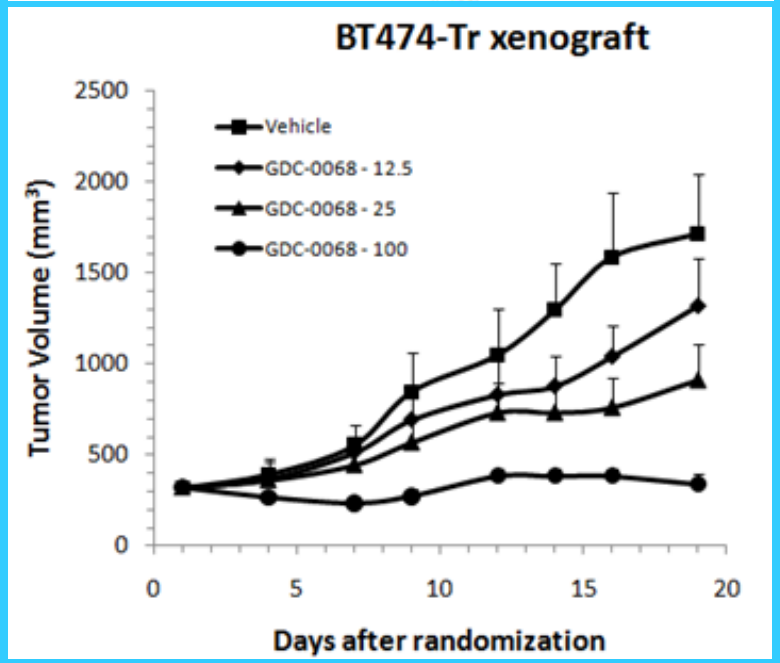


4 months on MK-2206

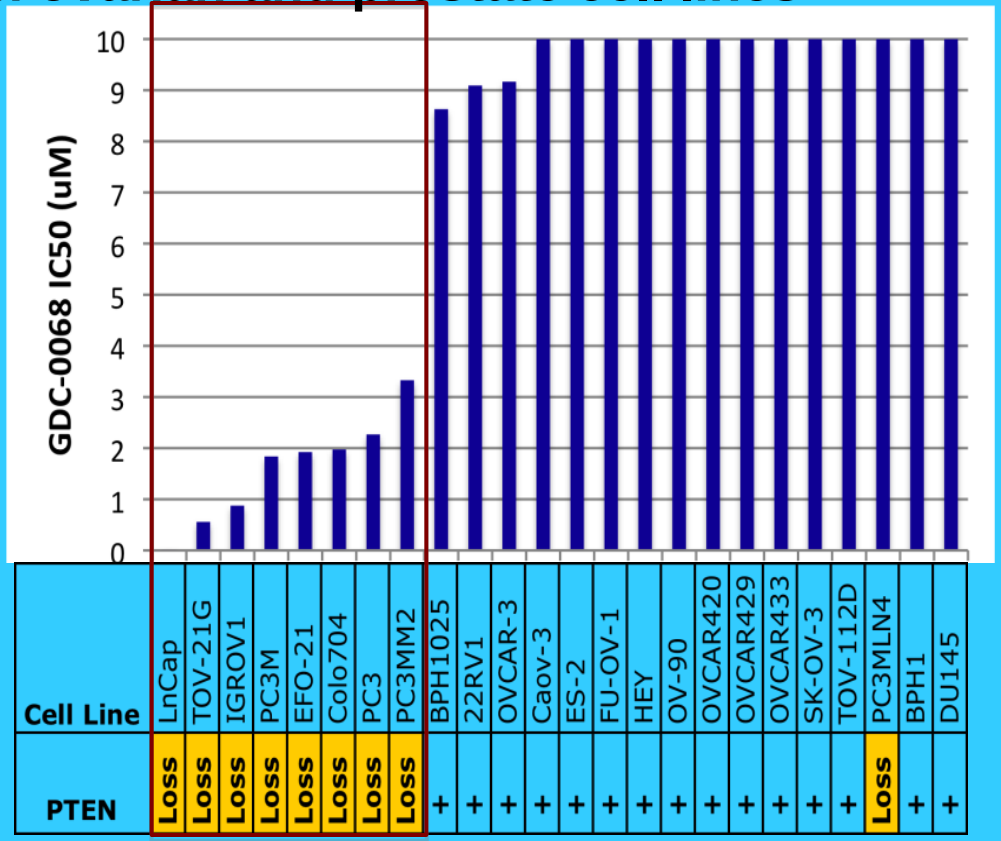
Public disclosed

GDC-0068, a Specific Akt Inhibitor





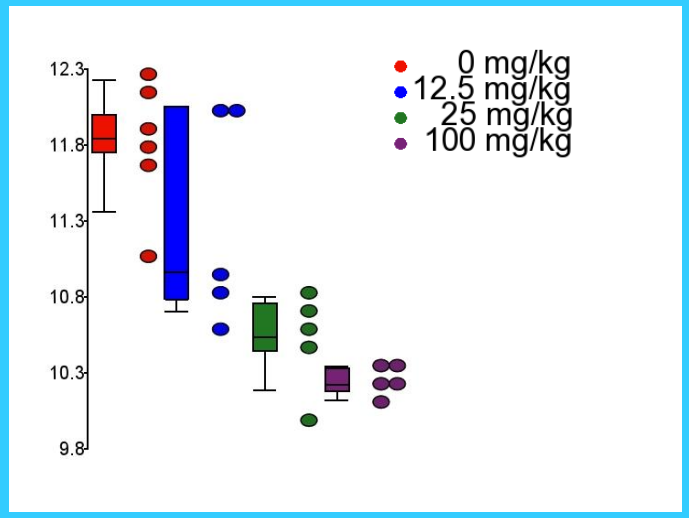
PTEN loss drives GDC-0068 sensitivity in ovarian and prostate cell lines



Sensitivity to GDC-0068 driven by PI3K mutations and/or PTEN loss depending on tumor type

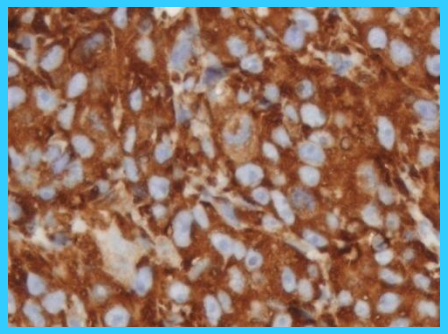
IHC/IF and RPPA: Complementary platforms to demonstrate PD changes

pS6 RPPA

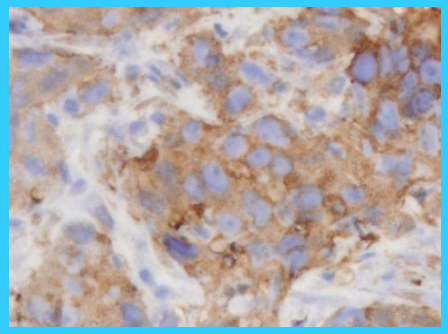


pS6 IHC

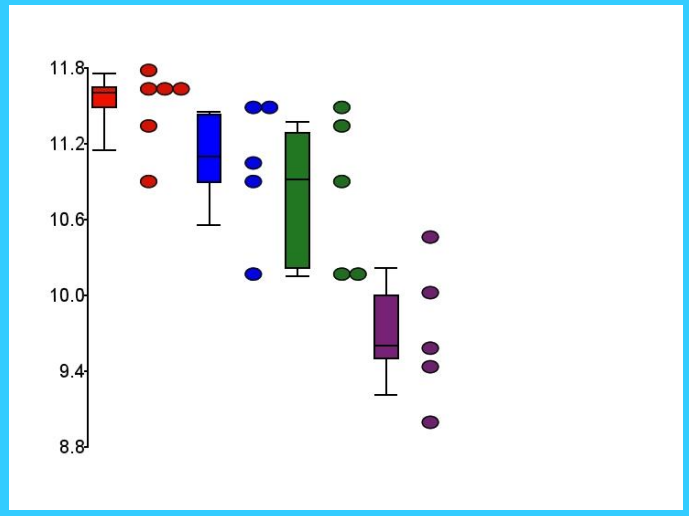
Vehicle



GDC-0068

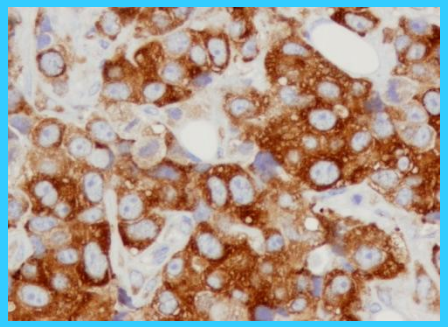


peIF4G RPPA

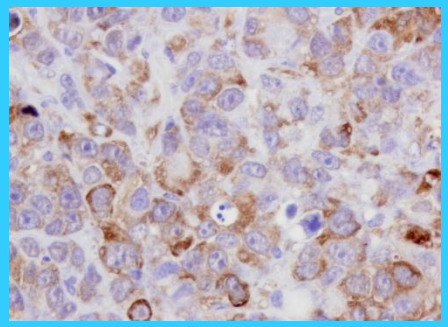


peIF4G IHC

Vehicle



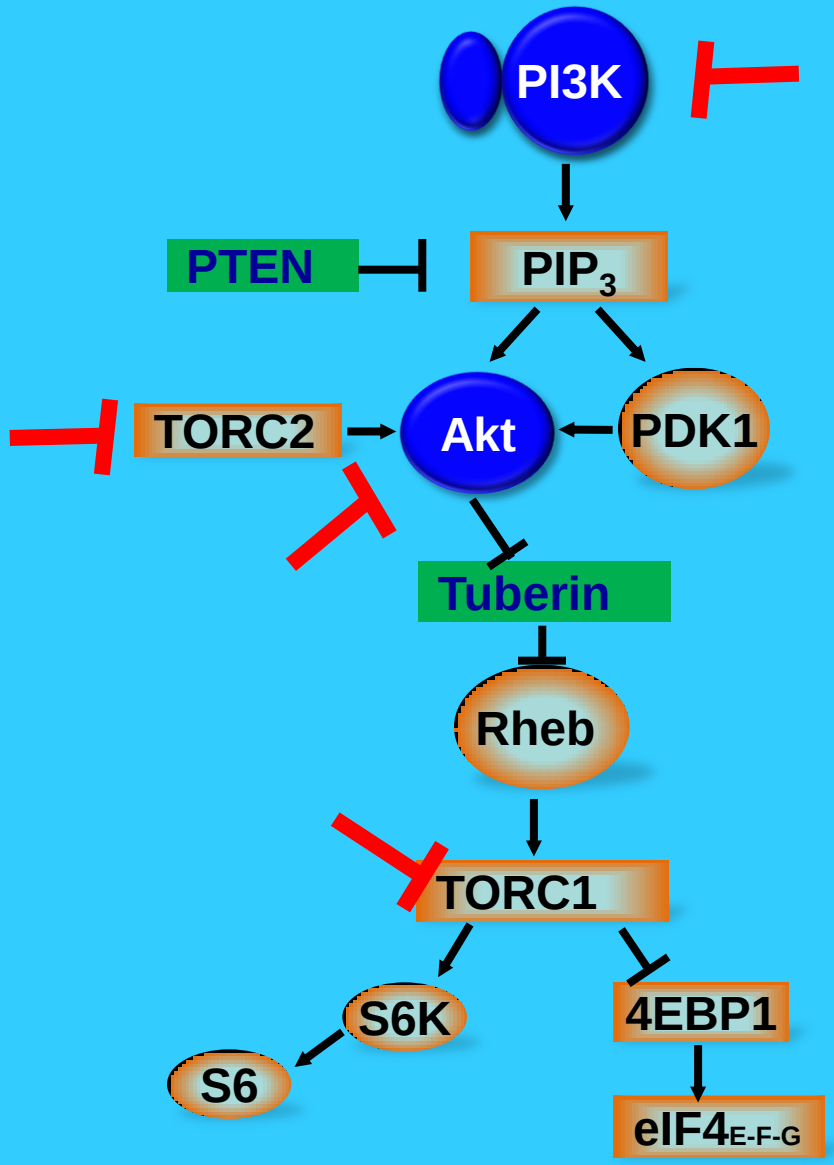
GDC-0068



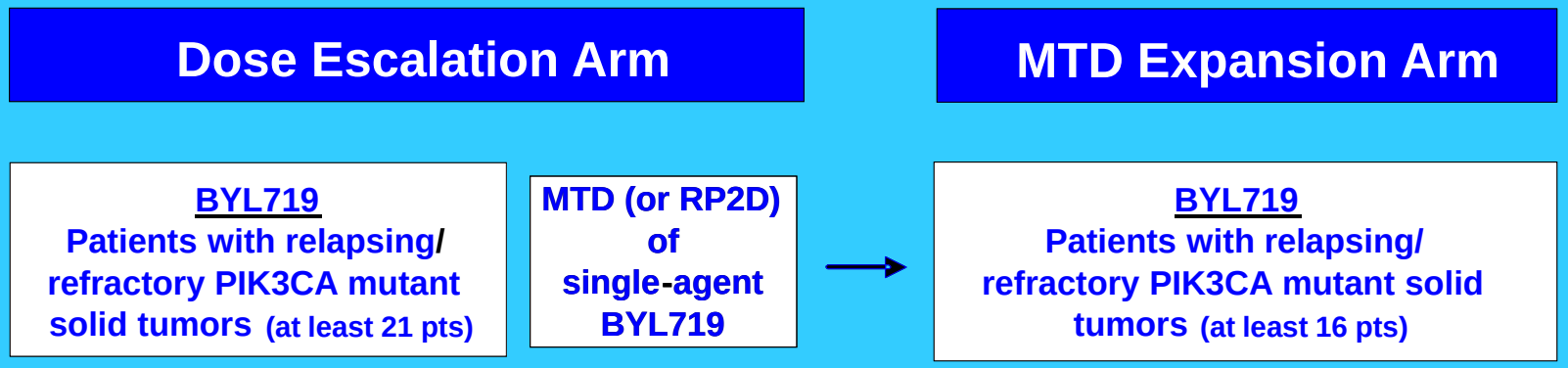
GDC-0068 reduces pS6 and peIF4G levels in BT474-Tr xenografts

PI3K Pathway Inhibitors

Agent	Company	Molecular targets
BYL719	Novartis	PI3Kα
GDC-0032	Genentech	PI3Kα
INK-1117	Intellikine	PI3Kα
XL-147	Exelixis/Sanofi	Pan-PI3K
NVP-BKM120	Novartis	Pan-PI3K
GDC-0941	Genentech	Pan-PI3K
PKI-587	Pfizer	Pan-PI3K
XL-765	Exelixis/Sanofi	PI3K / mTOR
NVP-BEZ-235	Novartis	PI3K / mTOR
NVP-BGT-226	Novartis	PI3K / mTOR
PF-4691502	Pfizer	PI3K/mTOR
AZD8055	Astrazeneca	mTOR (catalytic)
INK 128	Intellikine	mTOR (catalytic)
MK-2206	Merck	AKT1,2,3
GDC-0068	Genentech	AKT



BYL719 Phase I Study – Design Overview



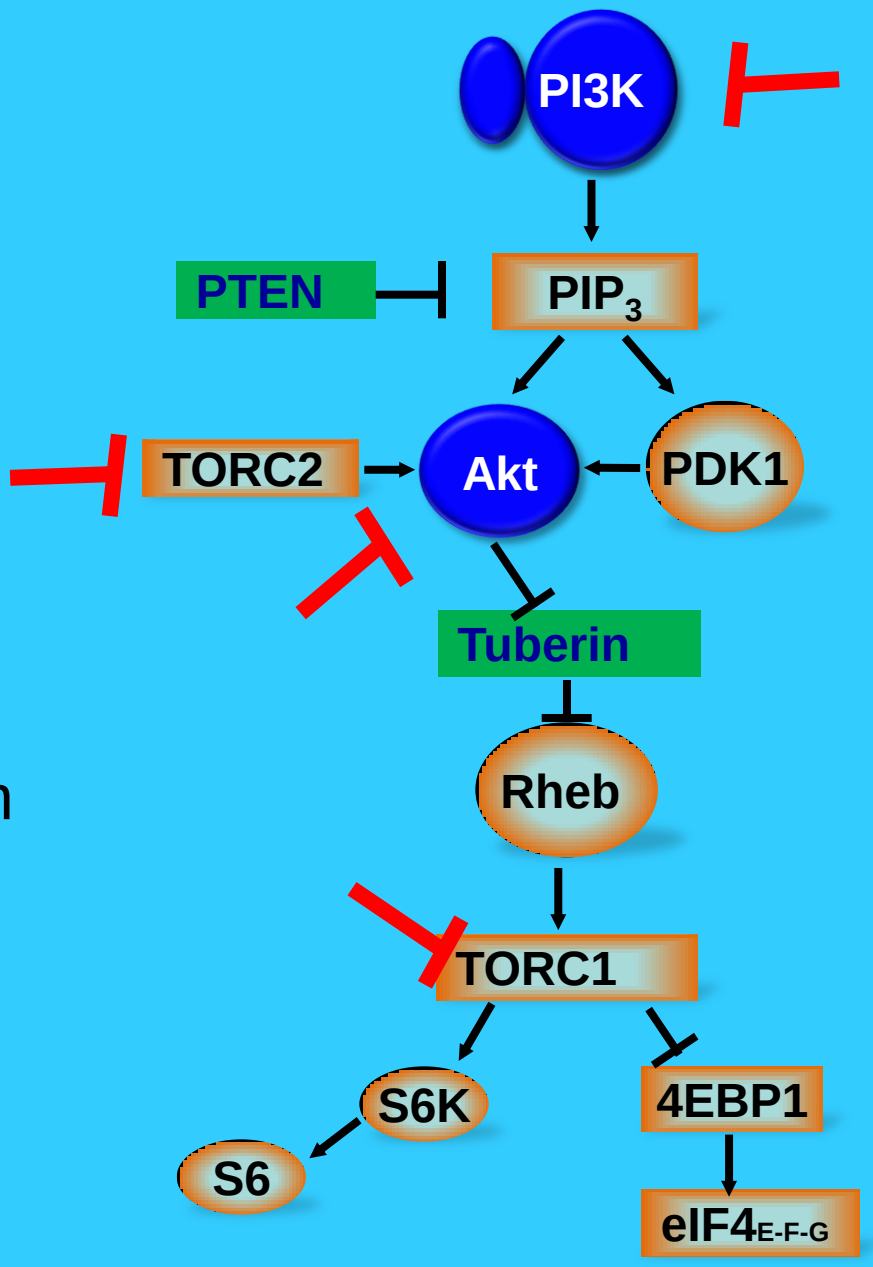
- Key objective to determine MTD (or RP2D) and to evaluate safety and tolerability.
- Main inclusion criteria:
  - -Patients with histologically confirmed, advanced unresectable solid tumors who have progressed within 3 months before screening/baseline visit on standard therapy .
    - **Only patients who have confirmed *PIK3CA* mutation will be allowed for screening.**
  - -Availability of a tumor tissue sample.
    - Archival tissue (or fresh tumor biopsy) and **locally documented *PIK3CA* mutation are mandatory** for study enrollment.
- Treatment: per os, once daily

What has Become of the “Wonder Target” of Cancer Drug Therapy????

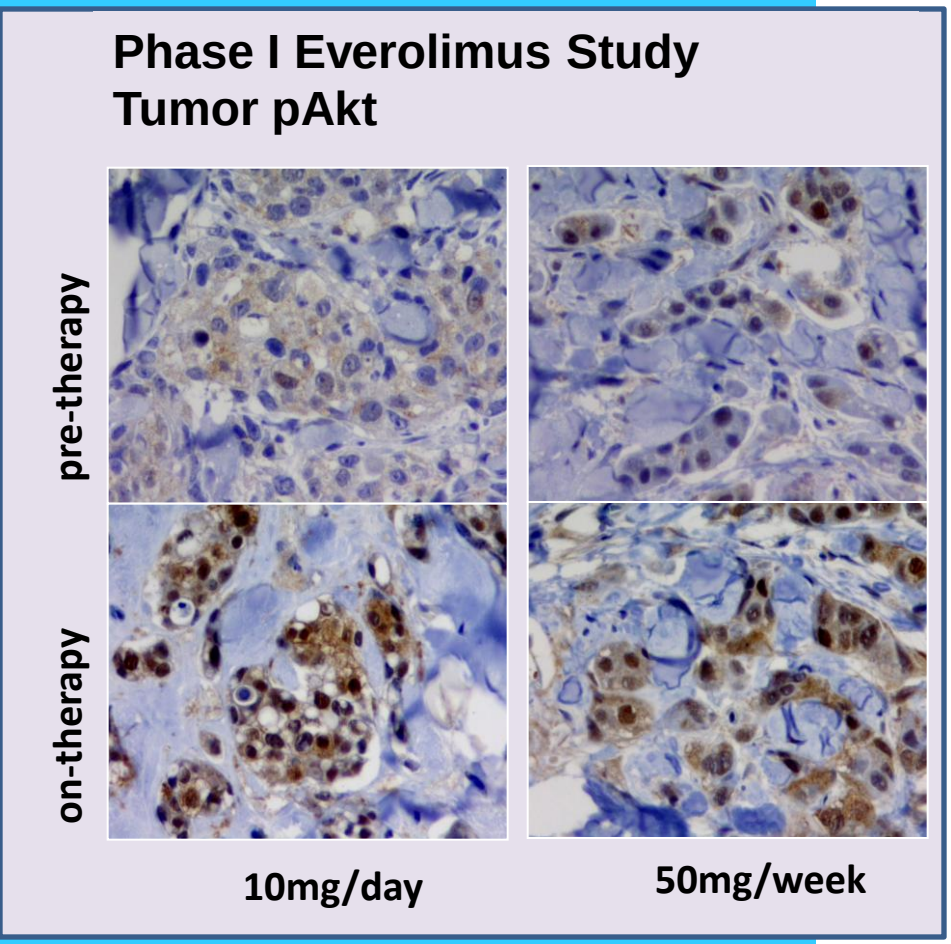
- It is clearly obvious that hitting PI3K alone, even in tumors that demonstrate mutational/deletion status, is insufficient to impact long term effects
- Combinations will be of utmost importance, but are limited by many challenges

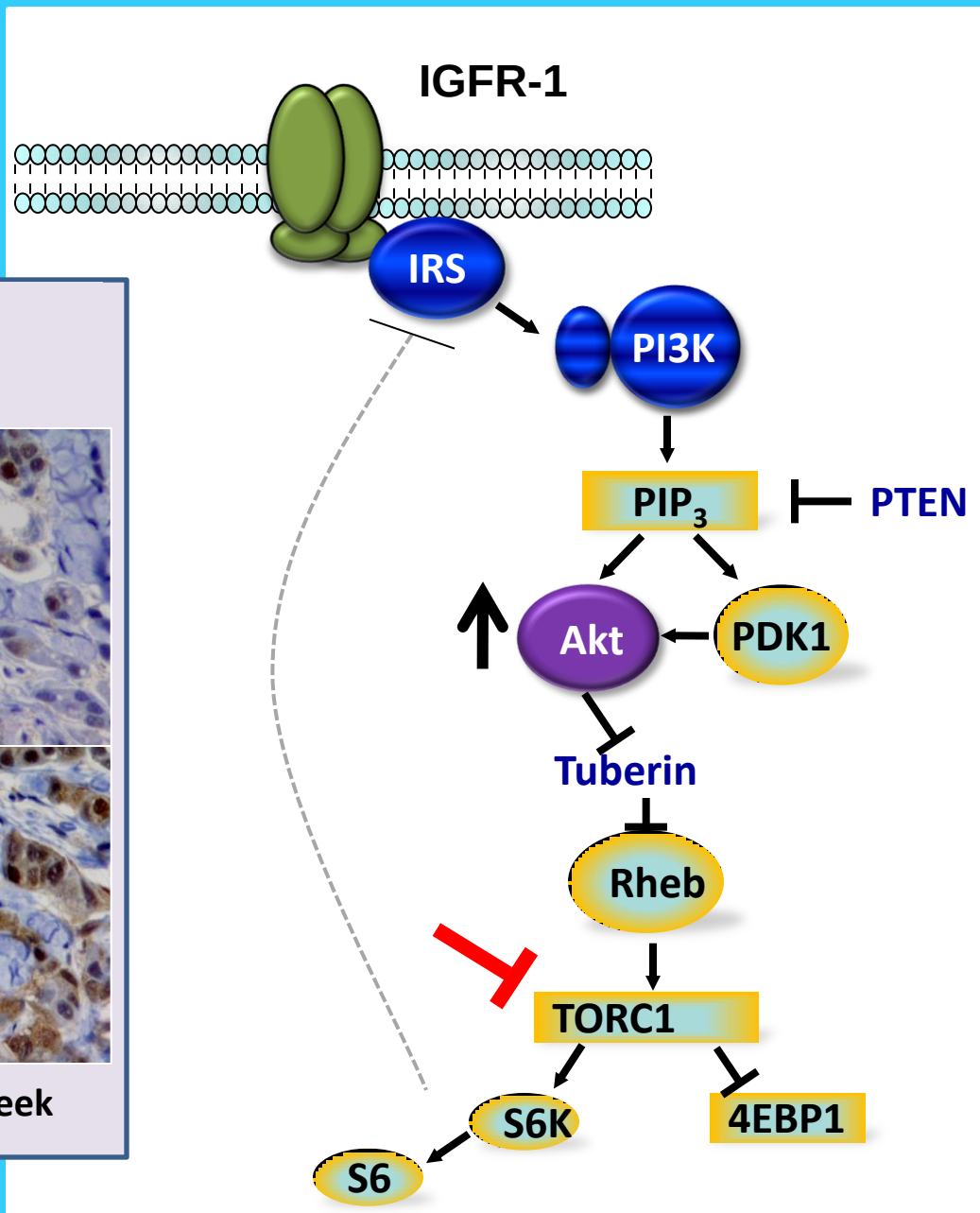
Strategies to target the PI3K pathway: Issues to address

- Best target on the pathway?
  - Will toxicities differ?
    - Probably yes
    - It may preclude combinatorial approaches
  - Diverse clinical activity profile?
  - Will activity be dependent on specific mutations?
  - Will specific inhibitors have an improved safety profile?
- Patient selection
  - Mutational status to be known upfront
- Compensatory pathway activation
  - Combinatorial approaches
  - Tumor specific
    - IGF1R in luminal B tumors
    - HER2 in HER2 overexpressing tumors
    - MEK in basal type



PI3K Compensatory Pathways: Rapalogs Activate Akt

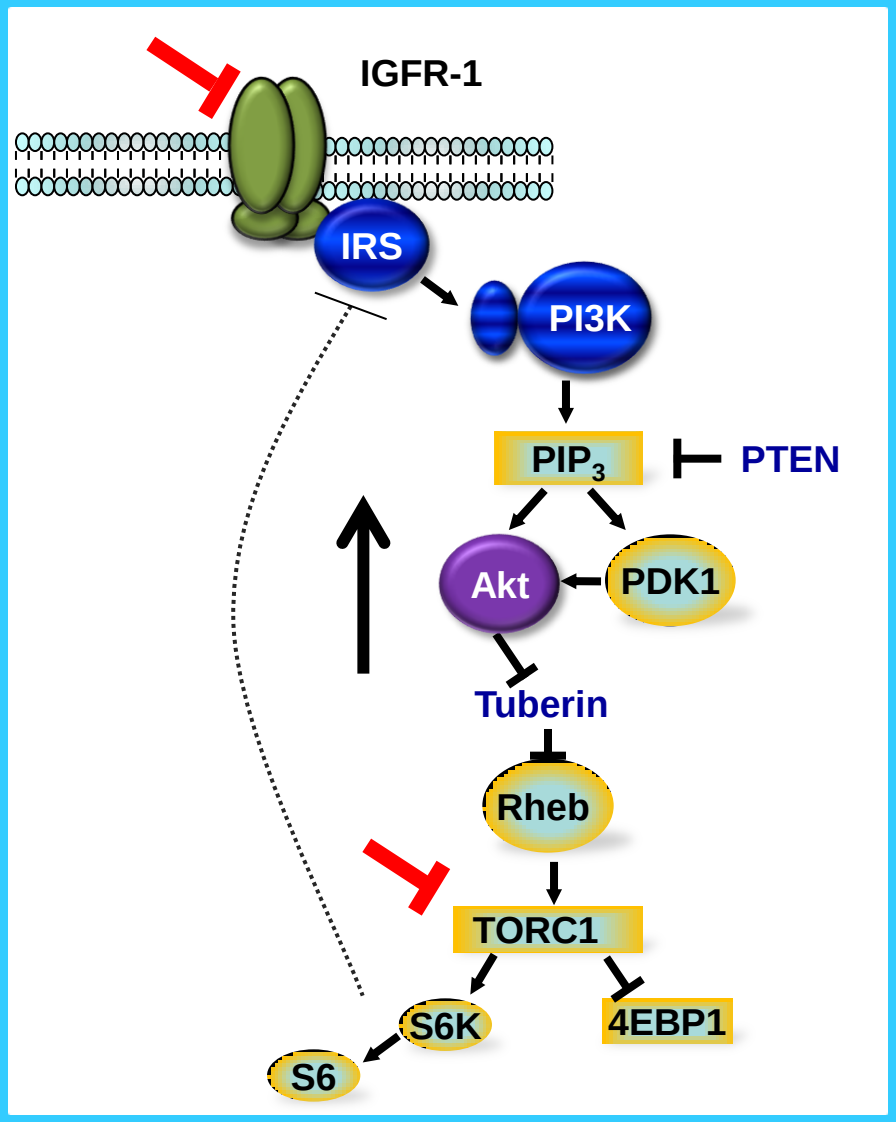




Tabernero *et al*. J. Clin Oncol. 2008

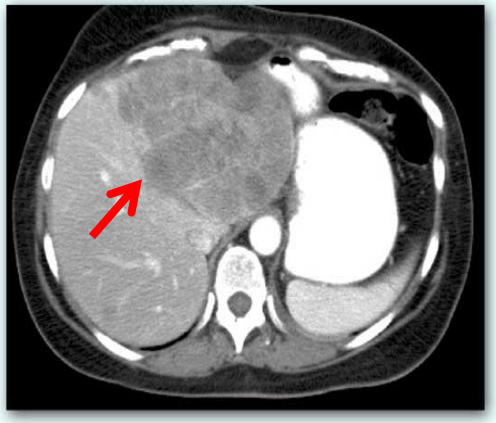
Targeting Compensatory Pathways

Suppress IGF-1R plus mTOR to prevent compensation by tumor cells

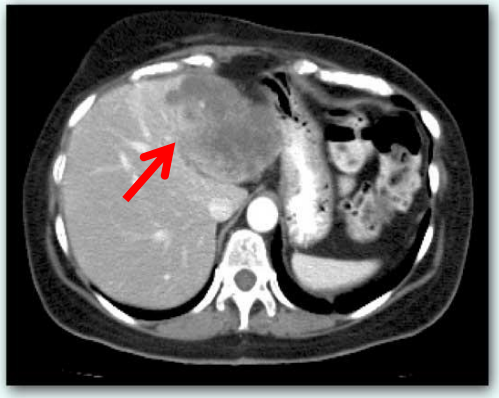


Patient had received 7 prior treatments

Before therapy

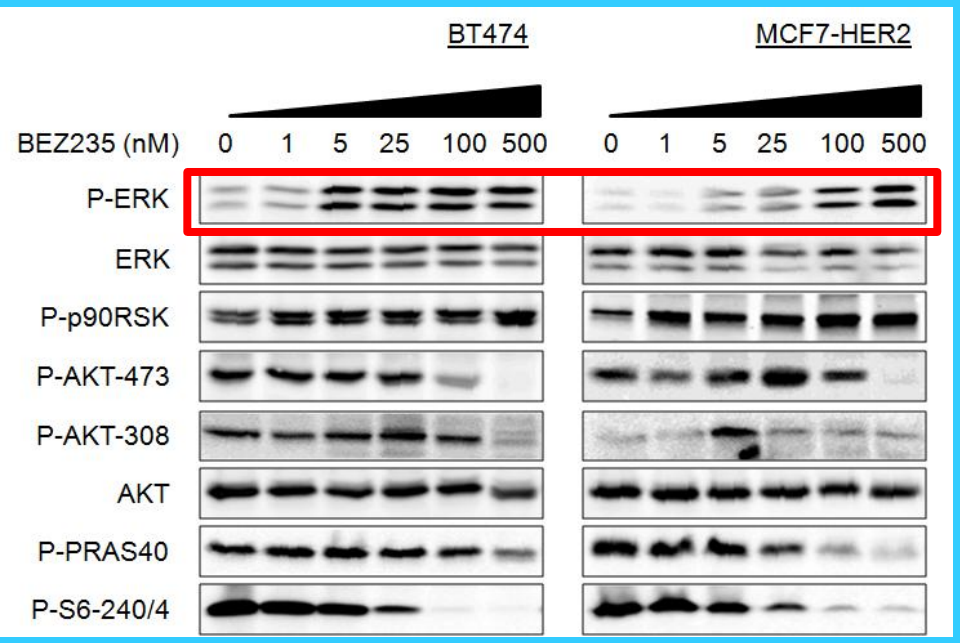


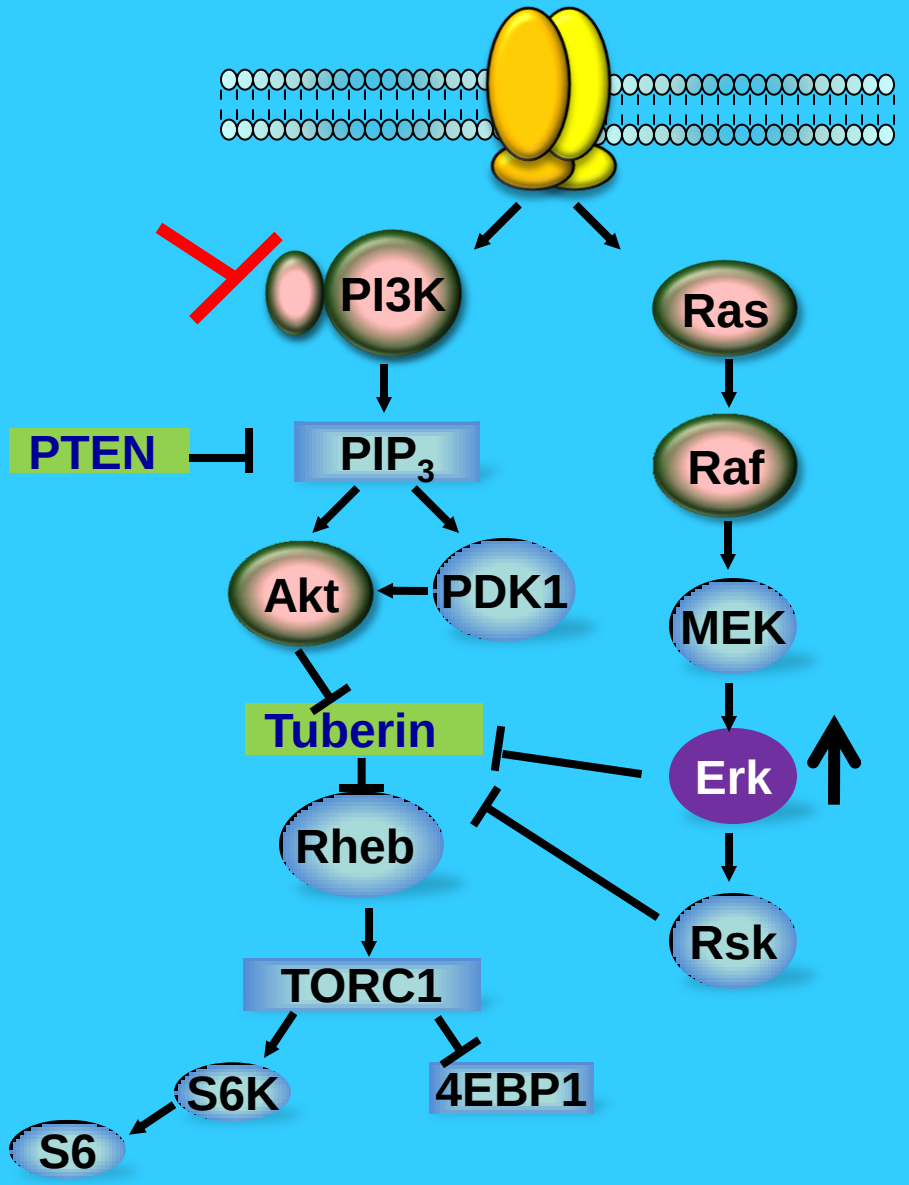
2 months later



Di Cosimo *et al*. ASCO 2010

PI3K Compensatory Pathways: PI3k inhibitors Activate ERK pathway

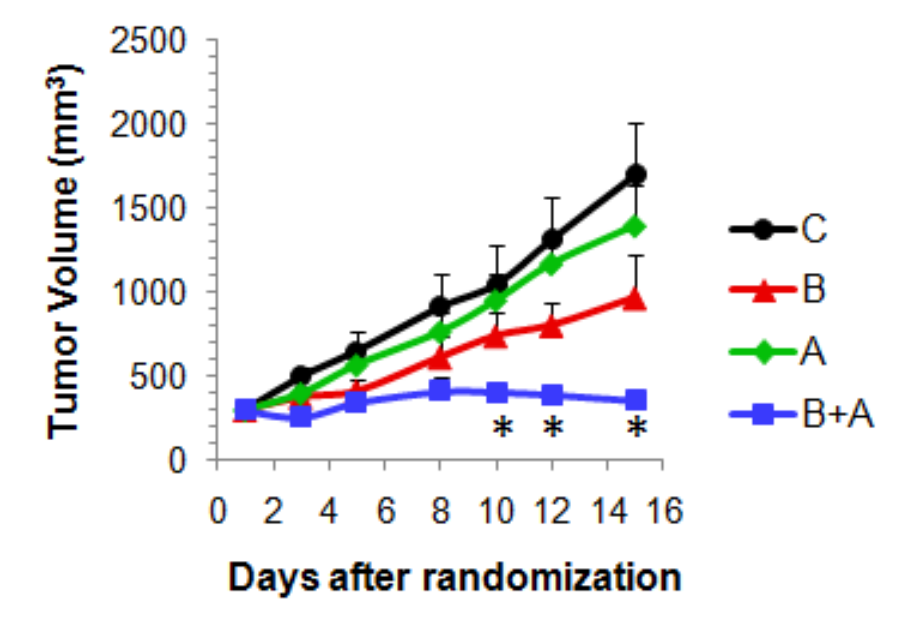




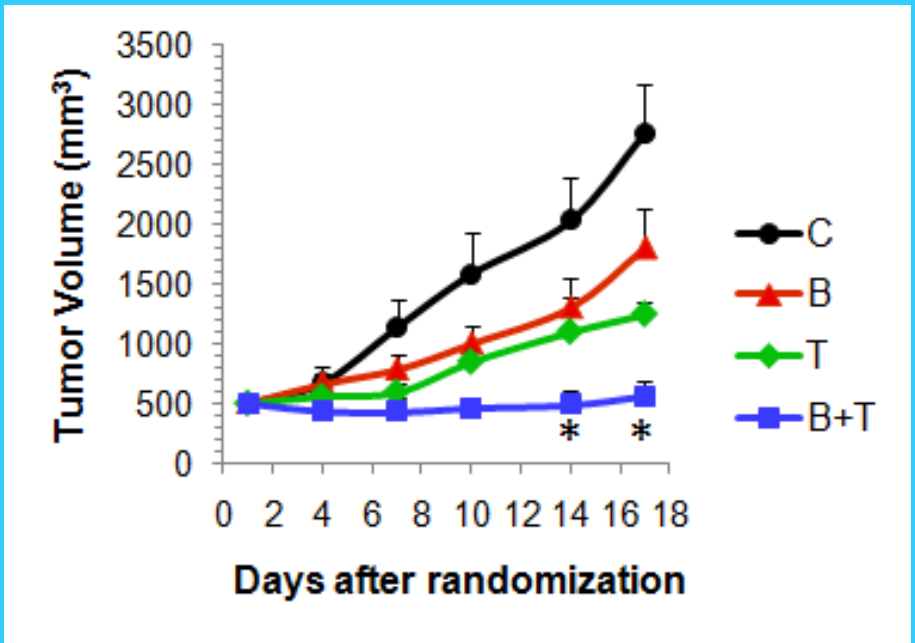
Serra *et al*. Oncogene. In Press

Combined Inhibition of PI3K/mTor and HER2 or PI3K/mTor and MEK Results in Tumor Growth Inhibition

BEZ235 + AZD6244



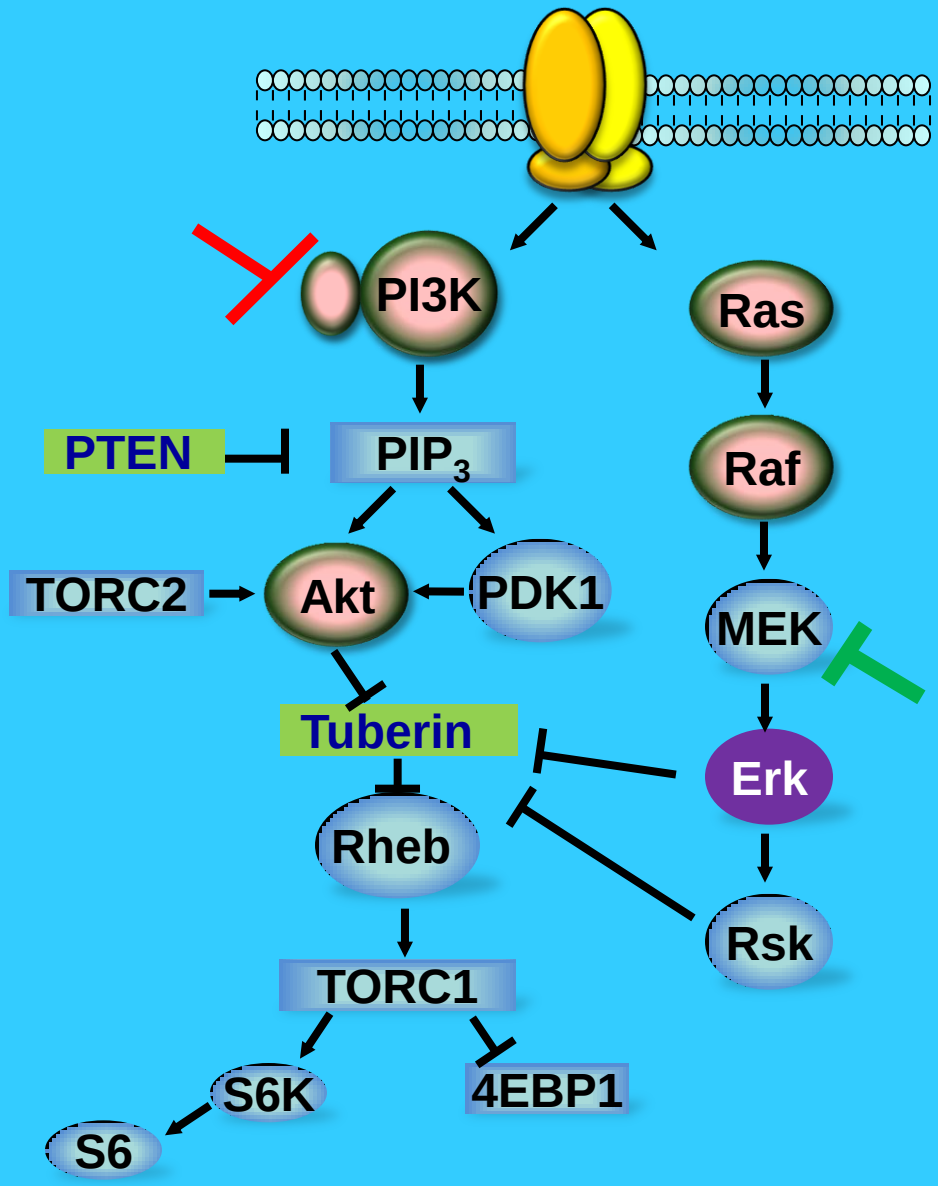
BEZ235 + trastuzumab



BT474-Tr xenografts

Combinatorial Studies: Issues to Consider

- Right patient population
- Feasibility
  - Toxicity
  - Dosing
  - Schedules
- Multiple-company studies



- The next generation of trials will need drug combinations with smarter trial designs and more select patient subsets to help answer key clinical questions related to this pathway

Thanks to All the Patients, their families, and the clinical teams that made execution and completion of these trials possible

Thank You!!!!

From Serendipity to Systematic Progress: Novel Clinical Trial Designs

1. Smaller, smarter clinical trials will provide answers

2. Combinatorial approaches to address compensatory pathways

3. Applying novel therapies earlier in the course of disease

4. Study of resistance will be key

PIK3CA Mutations in Patients with Advanced Cancers Treated in a Phase I Clinic

Janku F, Garrido-Laguna I, Hong DS, Tsimberidou AM, Naing A, Falchook GS, Wheler JJ, Moulder SL, Fu S, Piha-Paul SA, Kurzrock R

Investigational Cancer Therapeutics
(Phase I Clinical Trials Program)

The UT M. D. Anderson Cancer Center
1515 Holcombe Blvd.
FC8.2057, Box 0455
Houston, TX 77030

Methods

- *PIK3CA*mutation analysis was requested for patients referred for Phase I trials.
- Genomic DNA was isolated from archival tumors.
- PCR-based DNA sequencing of exon9 (helical domain) and exon20 (kinase domain) was performed.
- Patients with *PIK3CA*mutations were preferably treated, whenever possible, with regimens containing inhibitors of the PI3K/AKT/mTORsignaling pathway.

Results I

- *PIK3CA*mutation testing was requested for 146 samples from patients with various advanced tumors.
- Mutation analysis was available in 117 cases.

- *PIK3CA*mutations were detected in 14 (12%) of patients (Table 2).
- Exon9: 1 x c542; 1 x c545; 1 x c546.
- Exon20: 1 x c1043; 8 x c1047; 2 x c1049.

Table 1: Distribution of tumors

Tumor	Number	%
Ovarian cancer	23	20
Colorectal cancer	14	12
Cervical cancer	10	9
Breast cancer	11	9
Head & Neck cancer	10	9
Endometrial cancer	7	6
Melanoma	7	6
Soft tissue sarcoma	6	5
Renal cancer	4	3
Others	25	21

Tumor Type	Histology	*PIK3CA*	Other Mutations	% of Tested
Ovarian	Clear cell	C1047	*c600 BRAF*	
Ovarian	Endometrioid	C1047		
Ovarian	Clear cell	C1049		22
Ovarian	High grade	C542		
Ovarian	High grade	C546	*c61 KRAS*	
Endometrial	High grade	C1049		
Endometrial	Intermediate grade	C1047		43
Endometrial	Intermediate grade	C1049		
Breast	Invasive lobular ER+/PR+/HER2-	c1047		18
Breast	Invasive ductal ER+/PR-/HER2-	c1047		
Colon	Adenocarcinoma grade II	c1047	*c12 KRAS*	15
Colon	Adenocarcinoma grade II	C545	*c12 KRAS*	
Head & Neck	Poorly differentiated squamous	c1043		14
Small intestine	Adenocarcinoma grade II	c1047		100

Results II

- **Of the 14 patients with *PIK3CA*mutations, 10 were treated on a protocol that included a drug targeting the PI3K/AKT/mTORpathway**

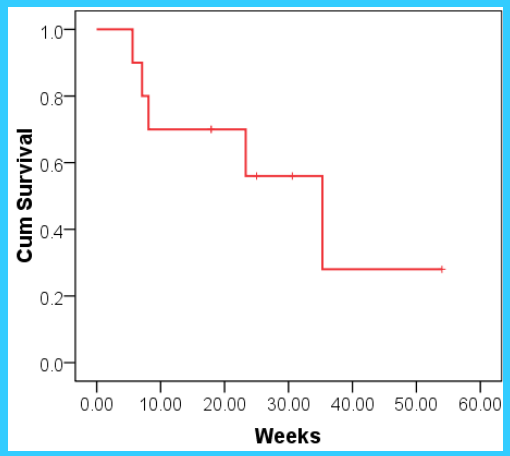
Table 3: Patients with *PIK3CA*mutations treated with combinations targeting the PI3K/AKT/mTORpathway.

Tumor	*PIK3CA*	Other Mutations	Treatment	RECIST %	TTP weeks
Ovarian	C1047	*BRAF*	mTOR based	-34	+17.9
Ovarian	C1049		mTOR based	-4	23.3
Ovarian	C542		mTOR based	-6	+17.9
Ovarian	C546	*KRAS*	mTOR based	-34	+30.6
Endometrial	C1049		mTOR based	-37	35.3
Endometrial	C1047		mTOR based	-60	+54
Endometrial	C1049		mTOR based	46	5.6
Breast	C1047		mTOR based	-37	+25
Colon	C1047	*KRAS*	PI3K based	87	7.1
Small intestine	C1047		mTOR based	20*	8.1

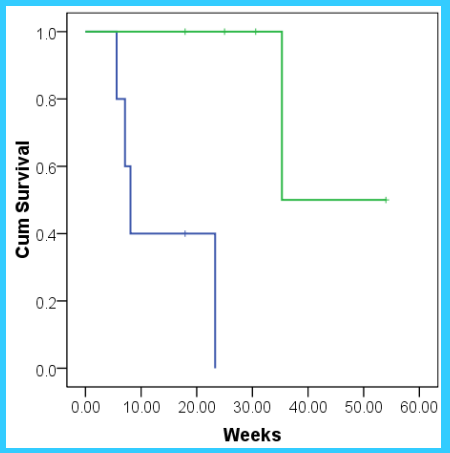
TTP, time to progression.
+ Patient continues on therapy without disease progression.
**Clinical progression.*

Figure 3: Kaplan-Meier PFS

A



B

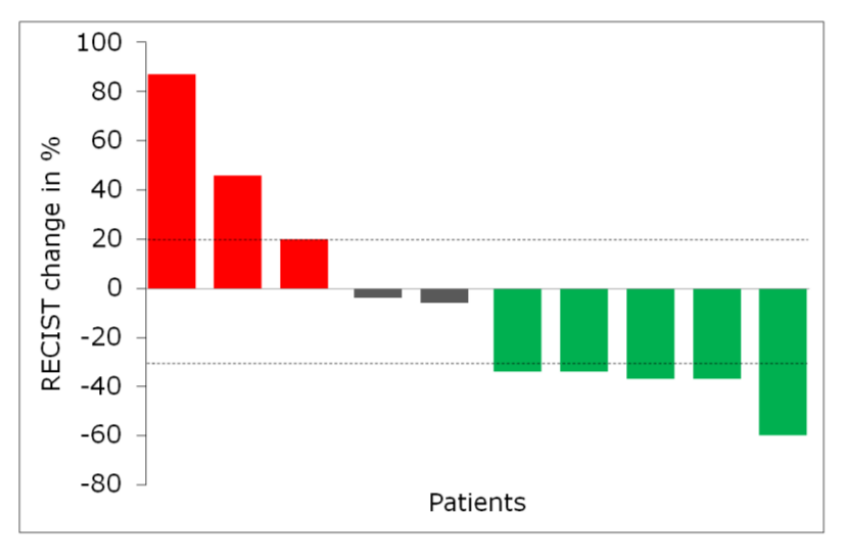


A. **PFS for all patients with *PIK3CA*mutations treated with combinations targeting the PI3K/AKT/mTORpathway. Median PFS estimate was 35.3 weeks (95% CI; 17.2,53.4).**

B. **PFS in responding patients (green) 35.3 weeks (95%CI;17.2,53.4) vs. combined stable disease and disease progression (blue) 8.1 weeks (95%CI;5.9-10.2); p=0.009, Log Rank.**

Results III

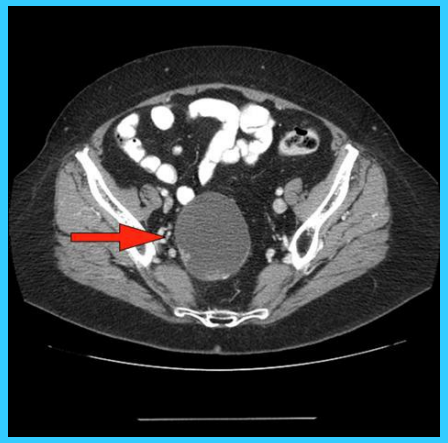
Figure 4: Waterfall plot of patients with *PIK3CA* mutations treated with a combination targeting the PI3K/AKT/mTORpathway. The response rate was 50%.**



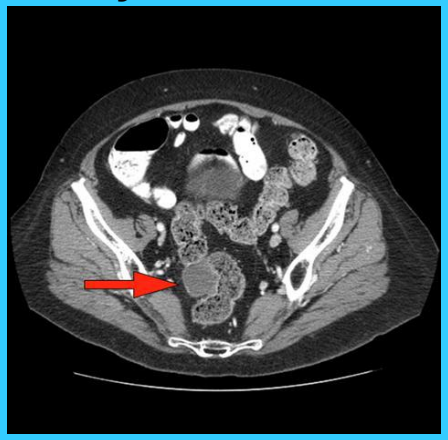
***Patients without PIK3CA mutation treated on same protocols demonstrated response rate 10% .*

Figure 5: Patient with endometrial cancer demonstrating partial response on anti-mTOR based therapy.

A. Pretreatment



B. 6 cycles.

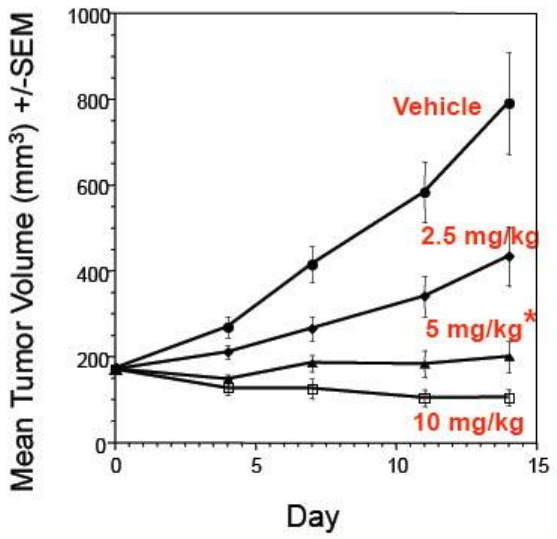


Conclusion

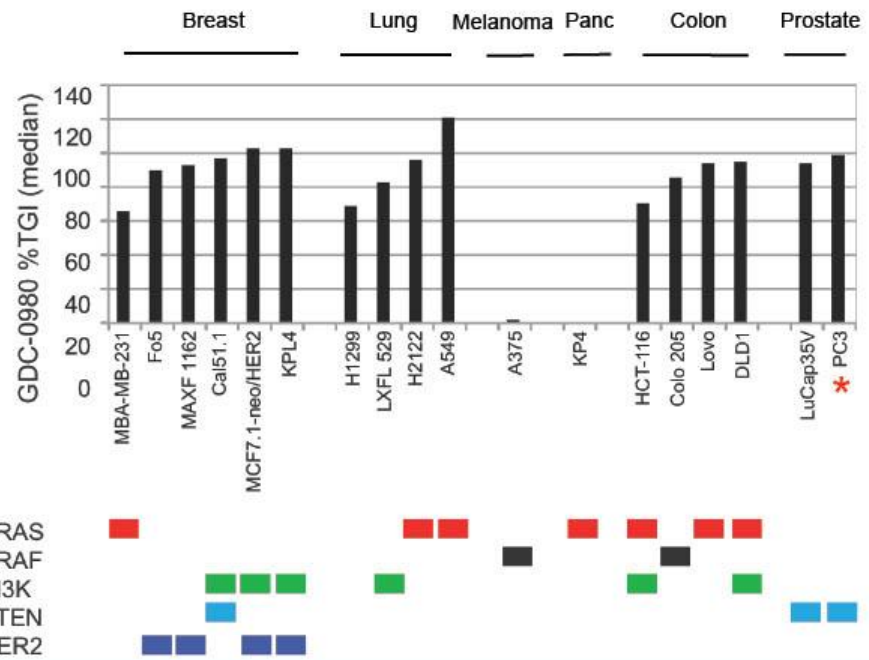
- *PIK3CA* mutations were detected in 12% of patients with various solid tumors.
- Mutations were detected most frequently in c1047 (kinasedomain) of *PIK3CA*.
- Patients with *PIK3CA* mutations had a 50% response rate when treated with a therapy containin PI3K/AKT/mTORinhibitors.

GDC-0980 Demonstrates Broad in vivo Efficacy

PC3 Prostate Cancer *
PTEN null
Treated with GDC-0980 QD



In vivo Efficacy of GDC-0980 by Tumor and Genotype



- GDC-0980 administered at 5 mg/kg QD
- 100% tumor growth inhibition (TGI) = stasis

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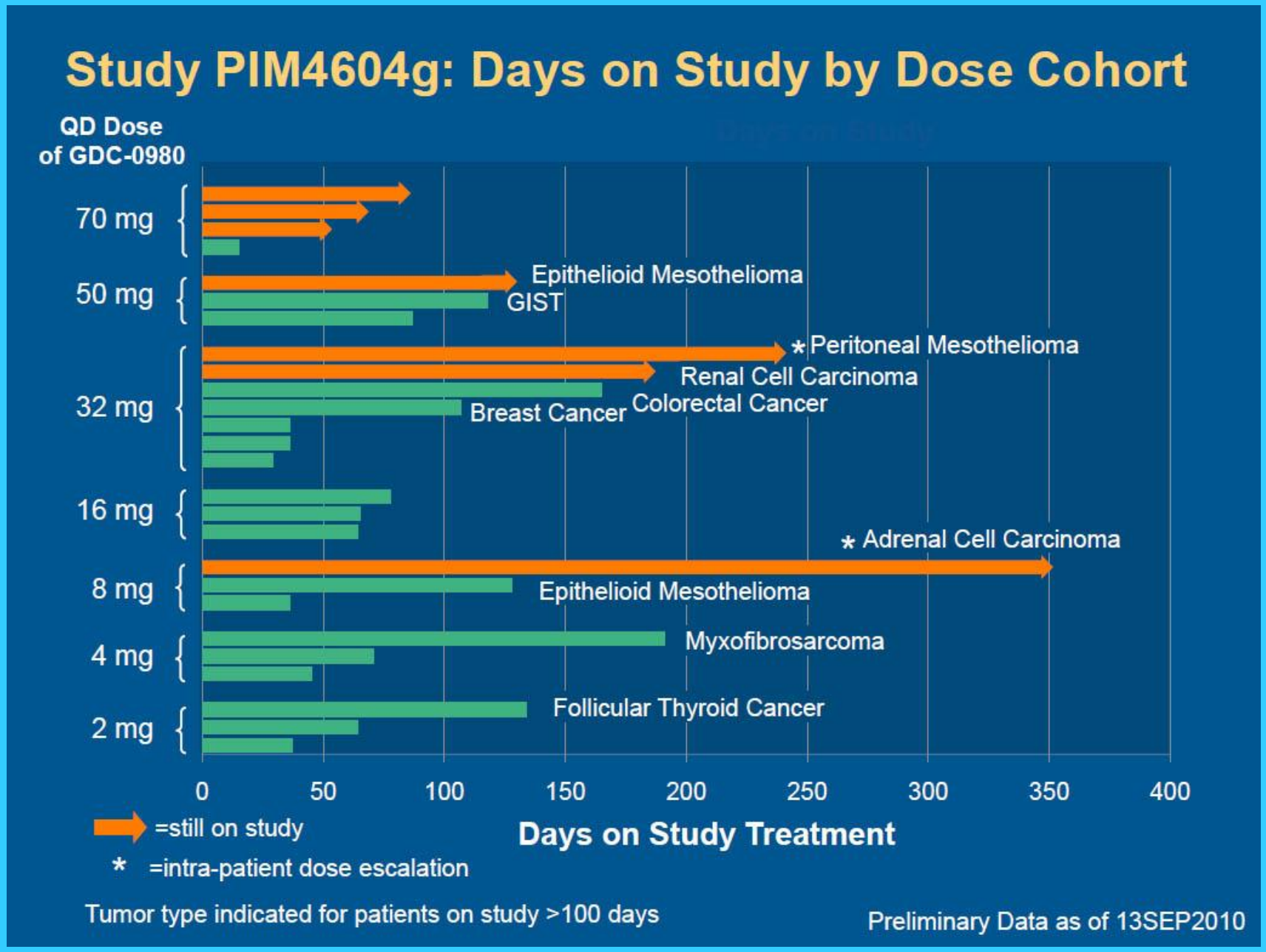

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Study PIM4604g: Safety Data Through 50 mg Dose

Treatment-related Adverse Events in ≥10% of Patients
AEs Grade ≤2 with exception of * a Grade 3 event

Adverse Event	2 mg (n=3)	4 mg (n=3)	8 mg (n=3)	16 mg (n=3)	32 mg (n=7)	50 mg (n=3)	All (n=22)
Diarrhea	2	1	1	1	3	2	10 (45.5%)
Fatigue	2		2	1	2*	2	9 (40.9%)
Rash					4	2	6 (27.3%)
Decreased appetite	1	2			2	1	6 (27.3%)
Abdominal pain				1	2		3 (13.6%)
Constipation	1	1			1		3 (13.6%)
Mucositis/oral pain		1		1		1	3 (13.6%)
Vomiting		1			2		3 (13.6%)

Grade 3 events reported: Grade 3 Fatigue (1 patient at 32mg)
Grade 3 Hyperglycemia (1 patient at 32mg)

Select Grade ≥ 3 Laboratory Values

↑ Glucose					1-G3		1 (4.5%)
↓ Lymphocytes		1-G3		1-G4		1-G3	3 (13.6%)

Data cutoff: 18AUG10

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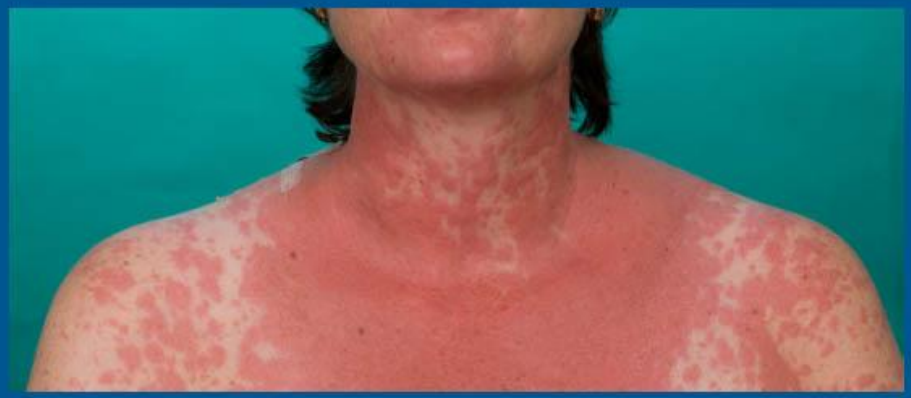
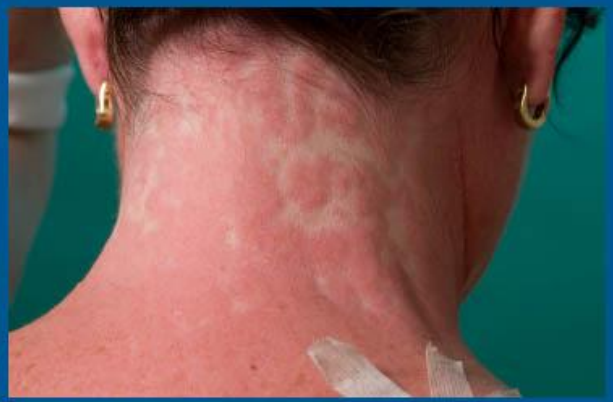
Study PIM4604g: Dose Limiting Toxicity

- Dose Limiting Toxicity of Grade 3 rash at 70 mg GDC-0980 (n=1/3 patients).
- Patient with triple negative breast cancer experienced G1 maculopapular pruritic rash after ~2 weeks of 70 mg QD and was treated with chlorpheniramine.
- The rash worsened to G3 1 week later. GDC-0980 was discontinued.
- Concurrent AEs: G2 fatigue, G2 conjunctivitis, G1 peripheral oedema, G1 mucositis, G1 thrombocytopenia
- Rash resolved to G1 after ~1 week after GDC-0980 discontinuation.





Preliminary Data as of 17 August 2010

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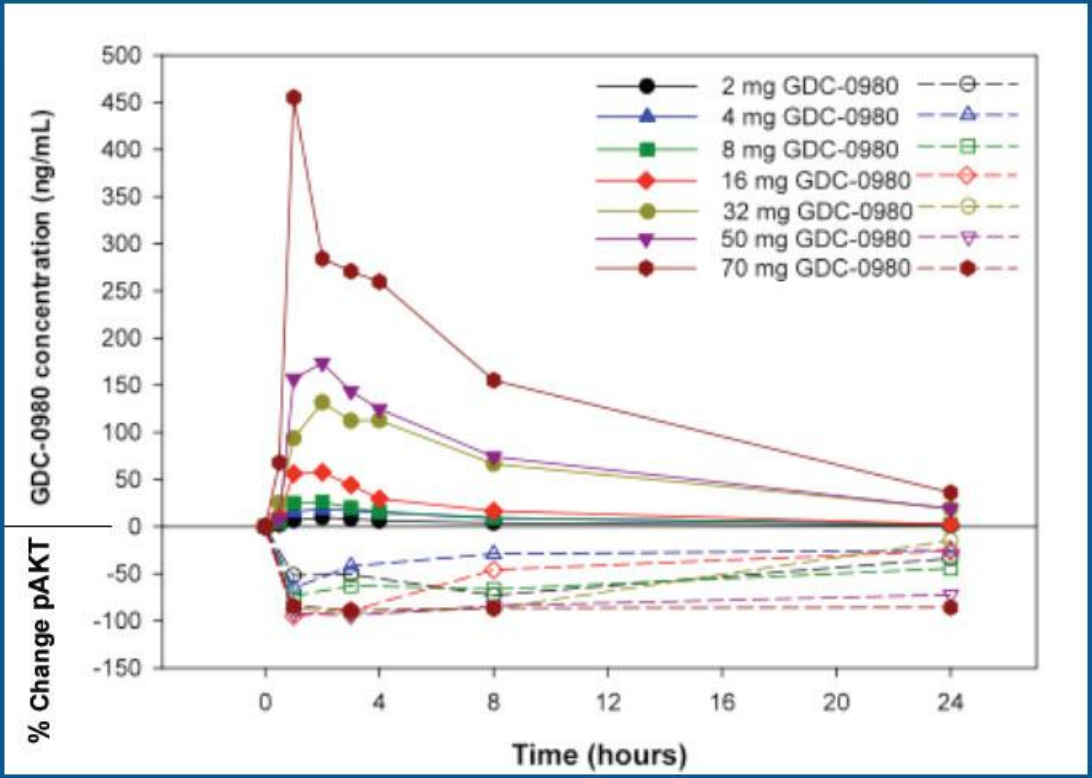
Study PIM4604g: Platelet Rich Plasma (PRP) pAKT Levels and GDC-0980 Concentration



- Significant decrease in pAkt is associated with GDC-0980 exposure
- pAKT demonstrates ≥90% decrease at GDC-0980 doses ≥ 16 mg
- pAKT decreases maintained at 24 hours at doses above 50 mg

*PRP collected simultaneously with most PK draws.

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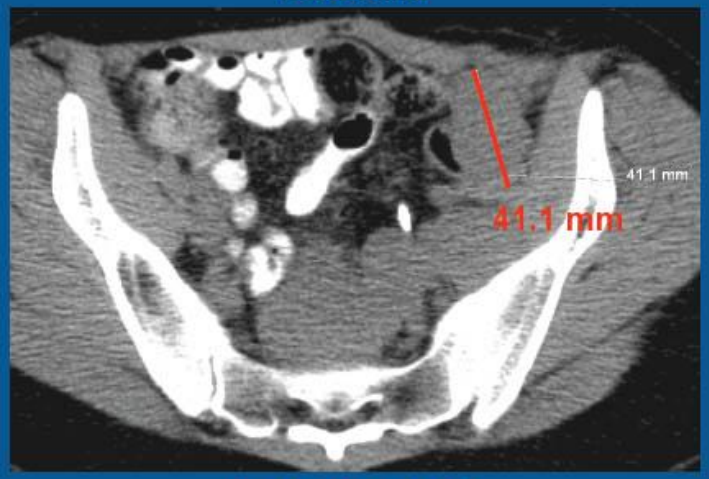
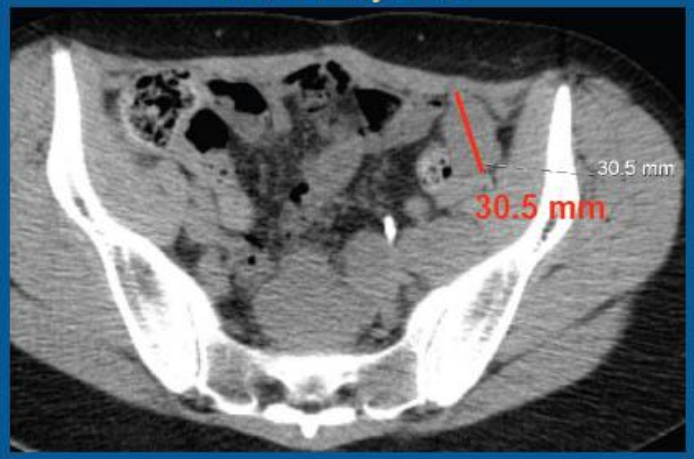
Study PIM4604g: Clinical Activity

- 35 y/o female with peritoneal mesothelioma cancer

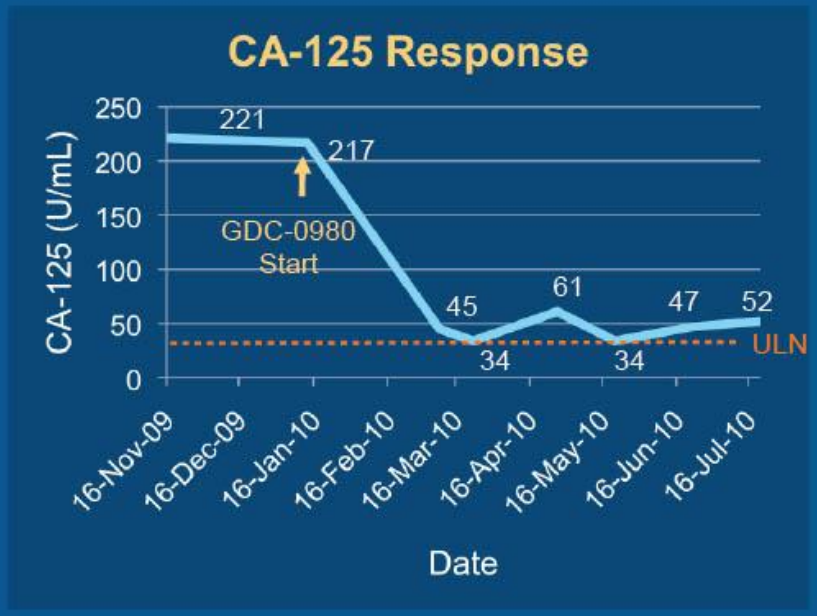
Baseline



End of Cycle 6



- Dx in 2003; prior thx with XRT and chemo
- 32 mg QD GDC-0980 with AUC ~4.4 µM•hr
- 94% decrease in pAKT in surrogate tissue
- RECIST Change: 29.6% decrease by end of C6
- CA-125 Response: normalized by end of C2



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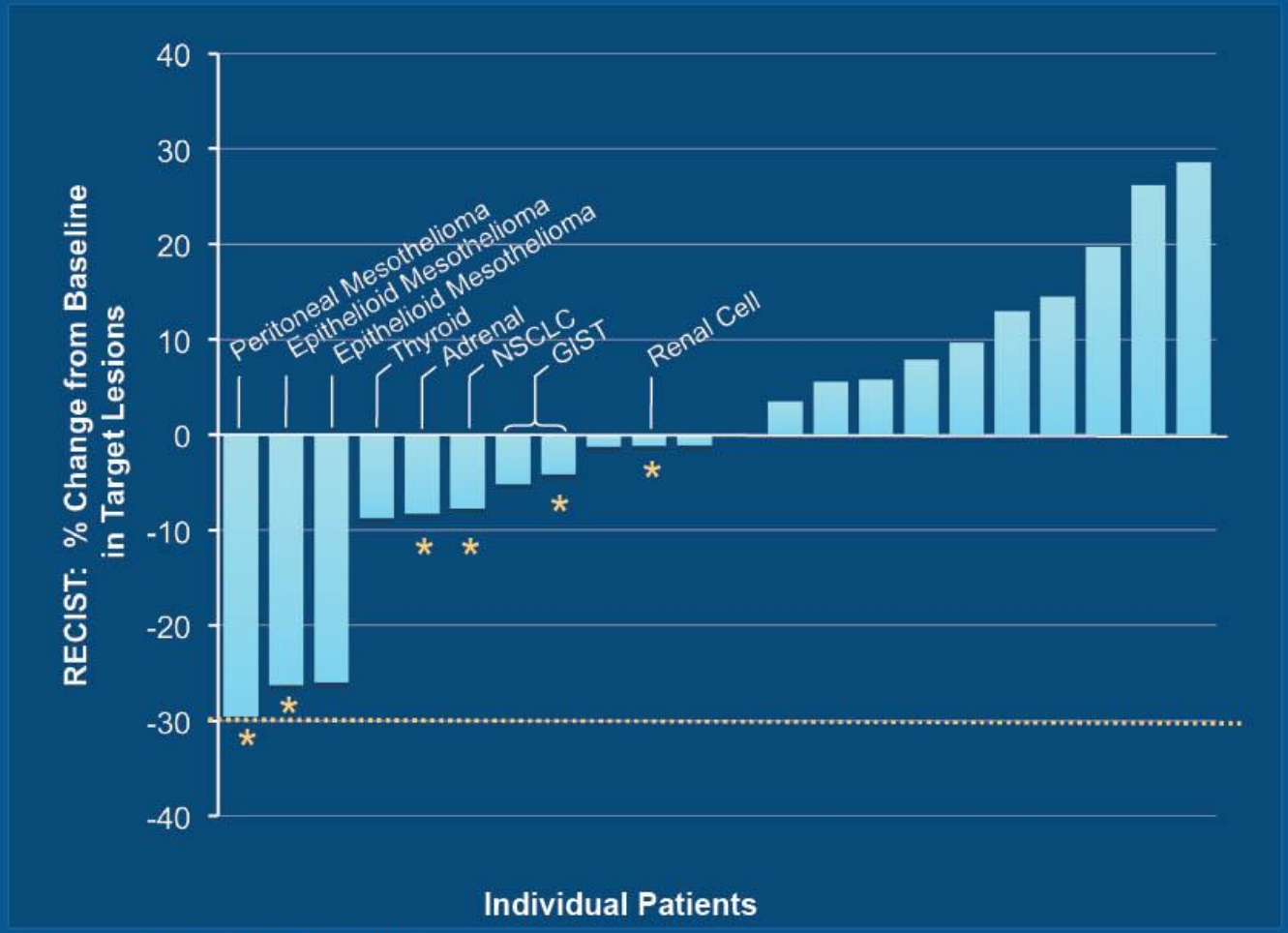
Study PIM4604g: Activity by RECIST



* Patient on study as of 10Sep2010

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- The Genentech PI3K inhibitors