

**A phase 1 dose-escalation study of the
safety, pharmacokinetics and
pharmacodynamics of XL765, a
PI3K/TORC1/TORC2 inhibitor
administered orally to patients with
advanced solid tumors**

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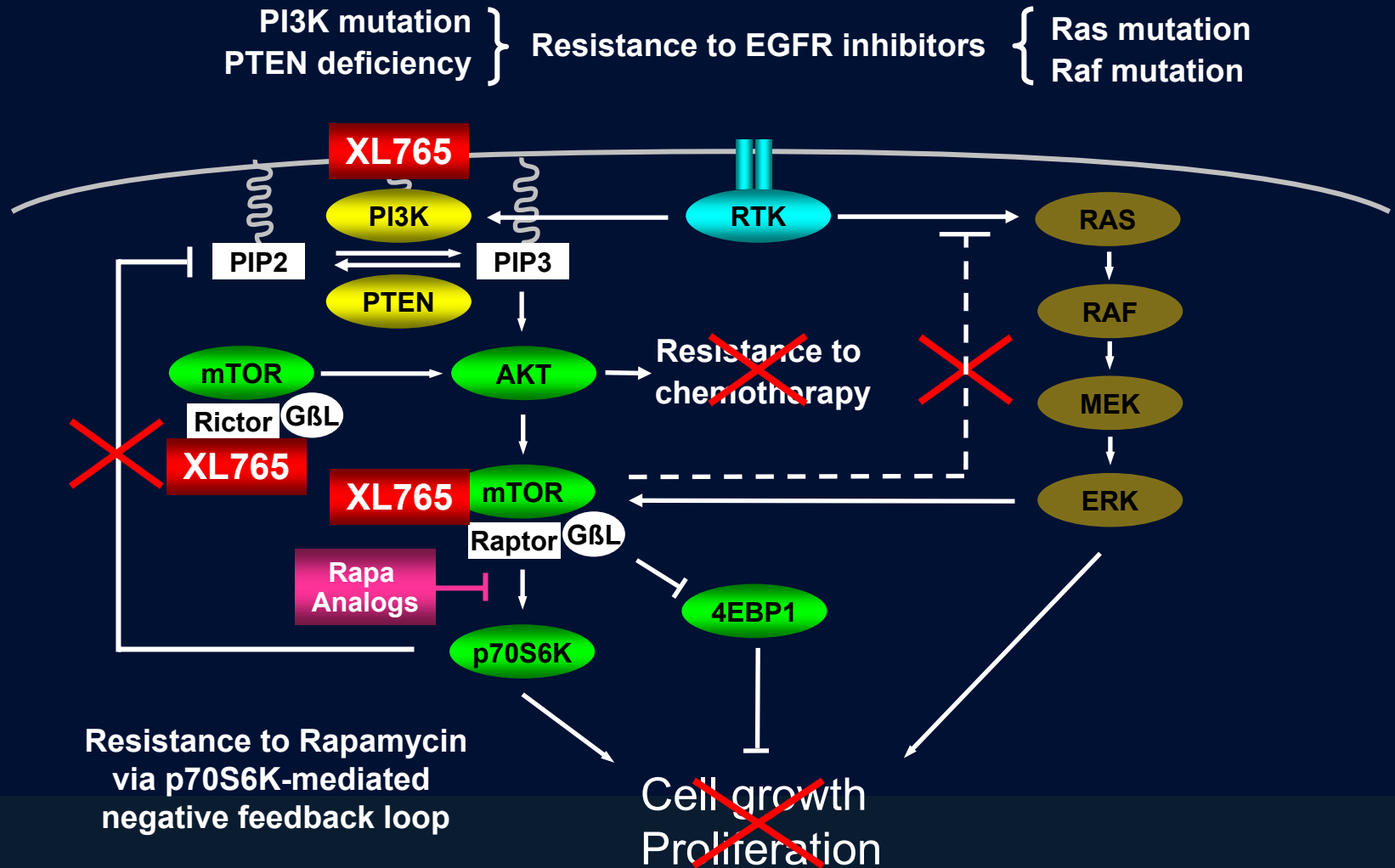
Disclosures

- P. LoRusso: Study Investigator
- B. Markman: Study Investigator
- J. Taberner: Study Investigator
- E. Heath: Study Investigator
- A. Patnaik: Study Investigator
- K. Papadopoulos: Study Investigator

- Exelixis is the sponsor of this study

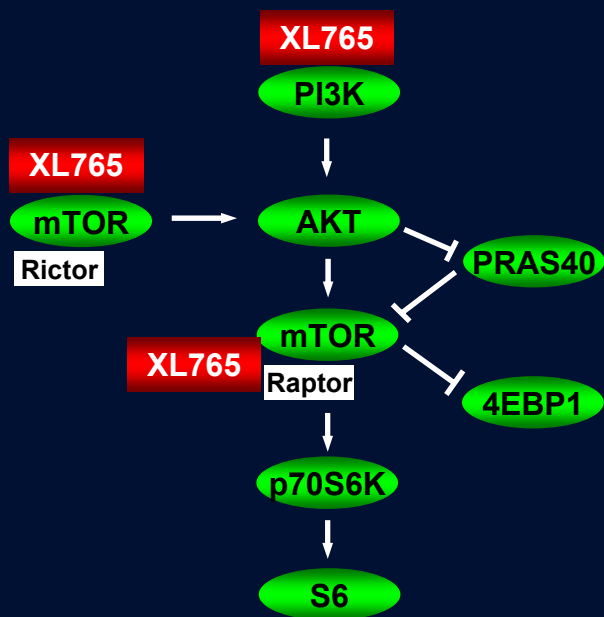
- R. Shazer and L. Nguyen are employed at Exelixis and are stockholders of Exelixis

XL765 Inhibits PI3K Signaling Pathway



XL765: A Potent PI3K/TORC1/TORC2 Inhibitor

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



Family	Kinase	IC ₅₀ (nM)	
PI3K	Class IA	PI3K α	39
		PI3K β	113
		PI3K δ	43
	Class IB	PI3K γ	9
Class III	VPS34	9060	
PIKK (PI3K-related)	DNA-PK	150	
	mTOR/Raptor (TORC1)	190	
	mTOR/Rictor (TORC2)*	908	
ERK pathway	BRAF/CRAF	>10000	
	MEK	>10000	

Highly selective in panel of > 120 kinases

* Immunoprecipitated from cells

XL765 Phase 1: Study Objectives

- Primary
 - Safety and tolerability of escalating doses of XL765
 - MTD administered orally, once and twice daily for 28 days
- Secondary
 - Pharmacokinetics
 - PK profile on Day 1 and Day 28
 - Pharmacodynamics
 - PBMCs and plasma
 - Optional sampling of hair, skin, tumor
 - Mandatory tumor biopsy, FDG-PET for expanded MTD cohort
- Exploratory
 - Anti-tumor activity
 - Long-term safety and tolerability

XL765 Phase 1: Study Design

- 3 + 3 ascending dose design, XL765 given orally
 - Continuous daily dosing schedule, BID and QD
- Standard Phase 1 eligibility and DLT criteria
- MTD expansions to assess preliminary anti-tumor activity
- Exploratory cohorts with tumor genetic alterations affecting PI3K pathway

XL765 Phase 1: Patient Demographics

Age, median yrs (range, n = 50)	61 (23-81)
Male / Female, n	24 / 26
ECOG, 0 / 1 / 2	17 / 31 / 2
Prior radiotherapy, n (%)	26 (52)
Prior chemotherapy, n (%)	48 (96)
Tumor (n = 48)	
Colon/Rectum	12 / 2
Breast	9
Lung	5
Prostate	2
Endometrium	2
Kidney	2
Sarcoma	2
Others	12

XL765 Phase 1: Study Status

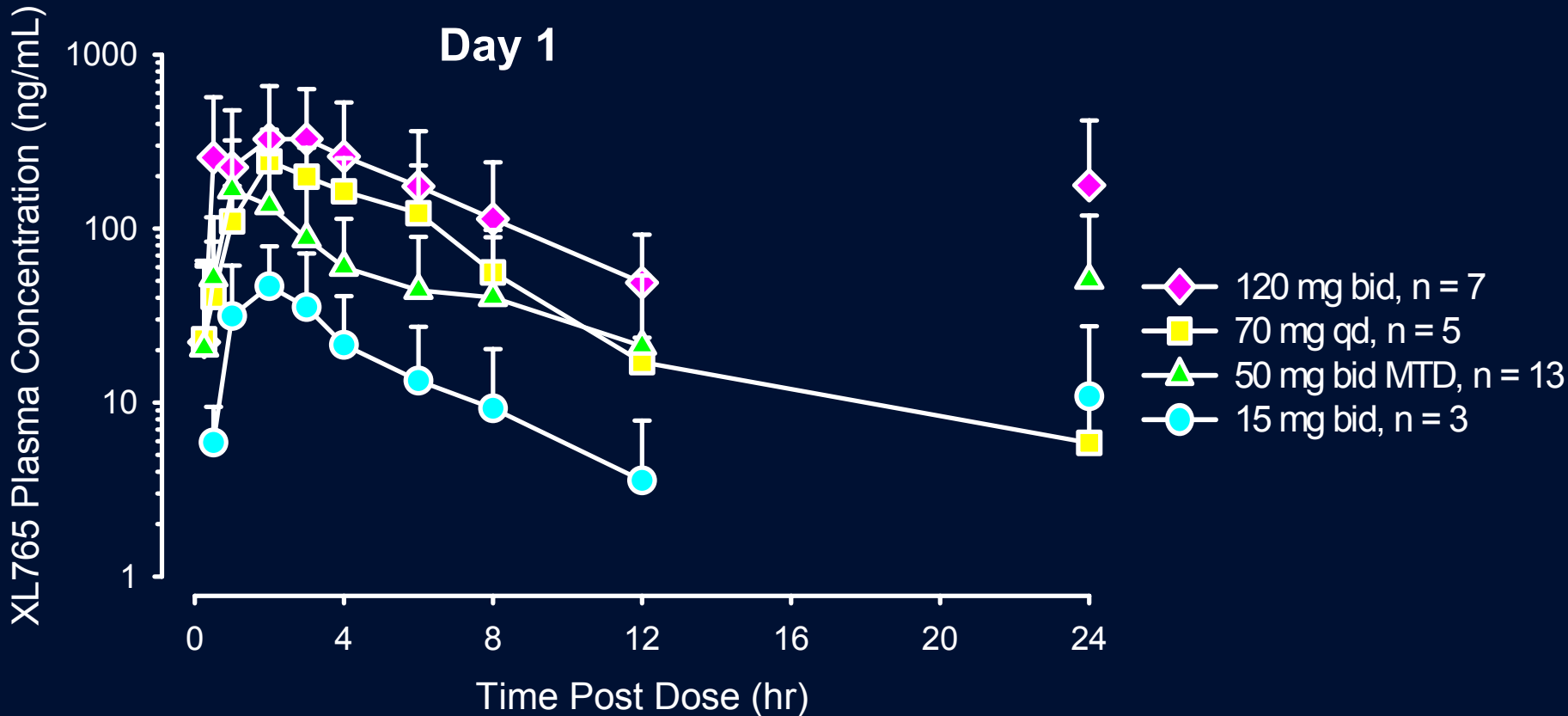
Unit Dose (mg)	# Subjects	Toxicity
BID Schedule		
15	3	None
30	7	None
50 MTD	11	None
60	10	Gr 1 LFT elevation in 2/10 subjects; Gr 3 nausea and Gr 2 vomiting; Gr 2 pruritic rash
120 MAD	7	Gr 1-4 LFT elevation in 5/7 subjects; Gr 3 hypophosphatemia and anorexia
QD Schedule		
70	5	None
90	1	Enrolling
100 MAD	7	Gr 2 dyskinesia; Gr 3 rash, fatigue

XL765 Phase 1: Adverse Events¹ for ≥10% Subjects on BID and QD Schedules

Number of subjects (%), n = 50

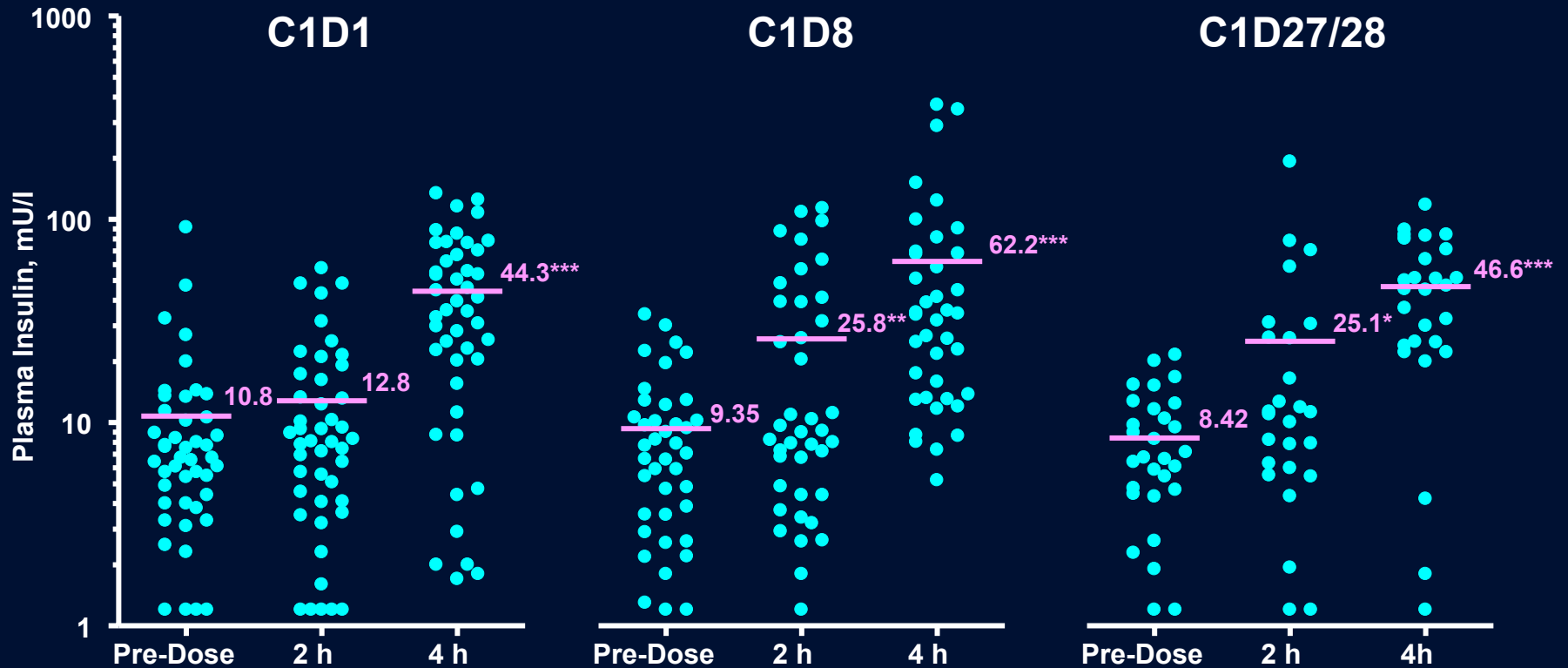
Adverse Event	Grade 1-2	Grade 3	Grade 4	All Grades
Nausea	16 (32)	2 (4)	-	18 (36)
Diarrhea	16 (32)	-	-	16 (32)
Fatigue	11 (22)	3 (6)	-	14 (28)
Anorexia	11 (22)	2 (4)	-	13 (26)
Vomiting	10 (20)	1 (2)	-	11 (22)
Transaminase increase ²	8 (16)	1 (2)	2 (4)	11 (22)
Cough	7 (14)	-	-	7 (14)
GGT increased	5 (10)	2 (4)	-	7 (14)
Asthenia	5 (10)	1 (2)	-	6 (12)
Alk Phos increased	6 (12)	-	-	6 (12)
Constipation	6 (12)	-	-	6 (12)
Abdominal pain	5 (10)	-	-	5 (10)
Hyperglycemia	5 (10)	-	-	5 (10)

XL765 Phase 1: Clinical Pharmacokinetics



- Median T_{max} = 2 hr (range: 0.3 - 6)
- $t_{1/2, ss}$ = 6.3 hr (range: 2 - 17)
- Low to moderate accumulation
- C_{max} increases with dose
- $AUC_{0-\tau}$ increases with dose
- Lower C_{min} (C_{24}) observed for qd

XL765 Phase 1: Plasma Insulin

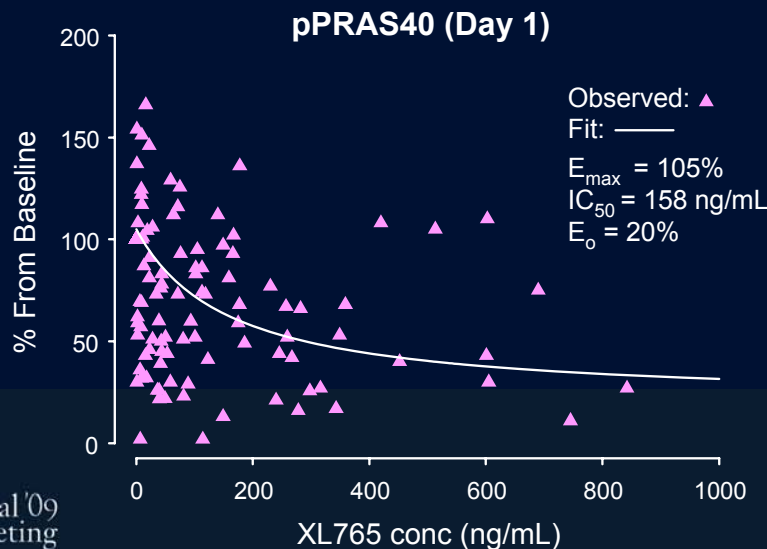
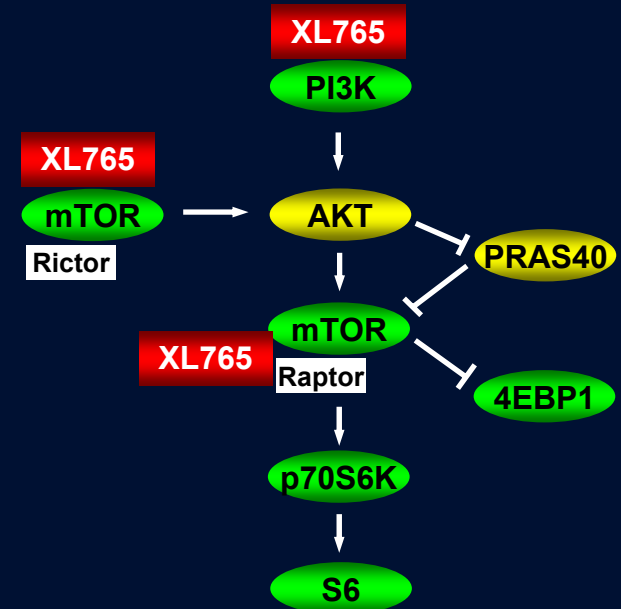
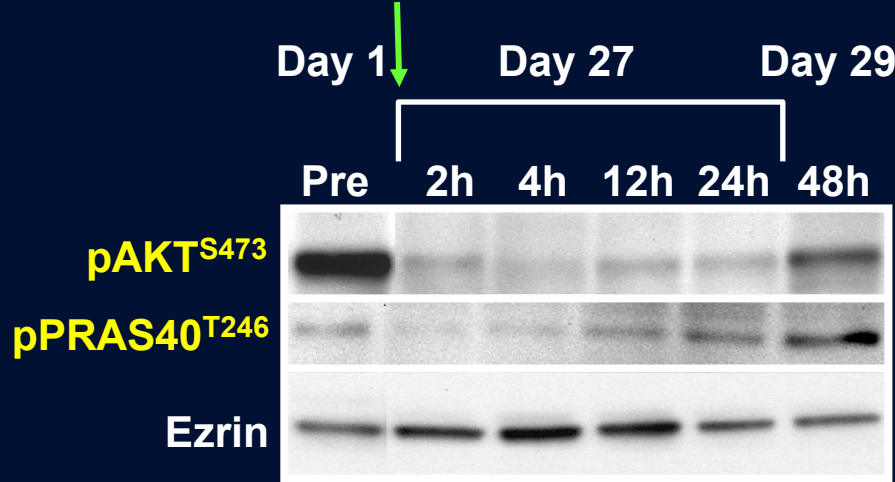


* $p < 0.05$; ** $p < 0.01$; *** $P < 0.0001$ vs. Pre-Dose

- Modest effect on fasting plasma insulin (2 h) after multiple doses of XL765
- No to minimal effect on plasma glucose

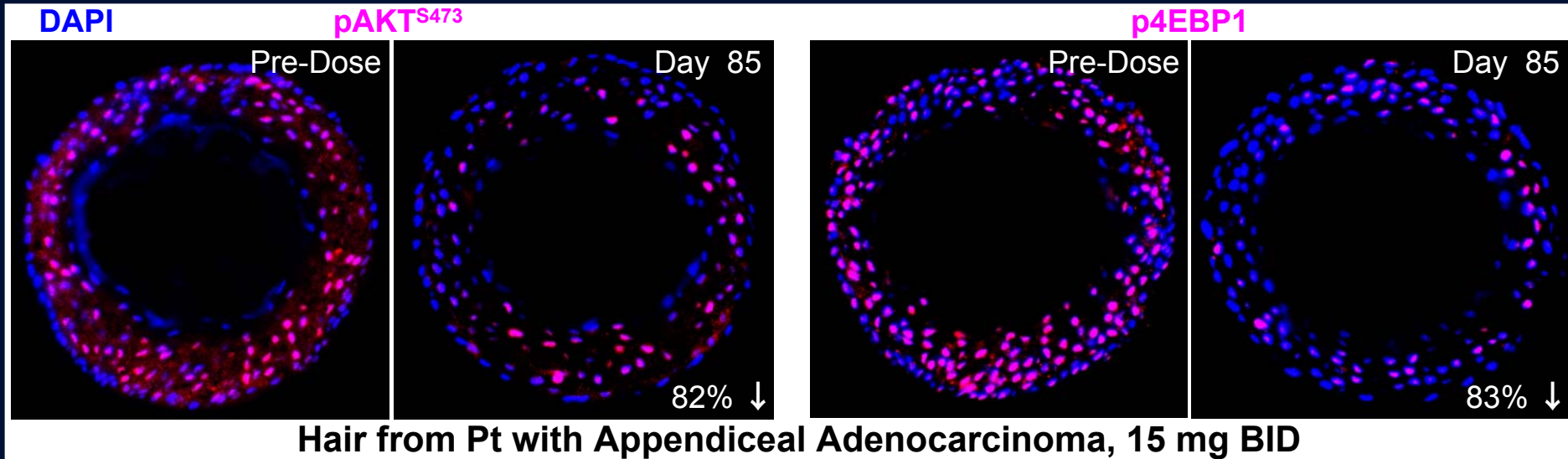
XL765 Phase 1: Pharmacodynamics in PBMCs

Last dose of Cycle 1 (70 mg QD)



- Trend suggests PD is exposure-dependent
- Reduction in multiple PI3K pathway readouts evident across doses
- QD comparable to BID

XL765 Phase 1: Pharmacodynamics in Hair

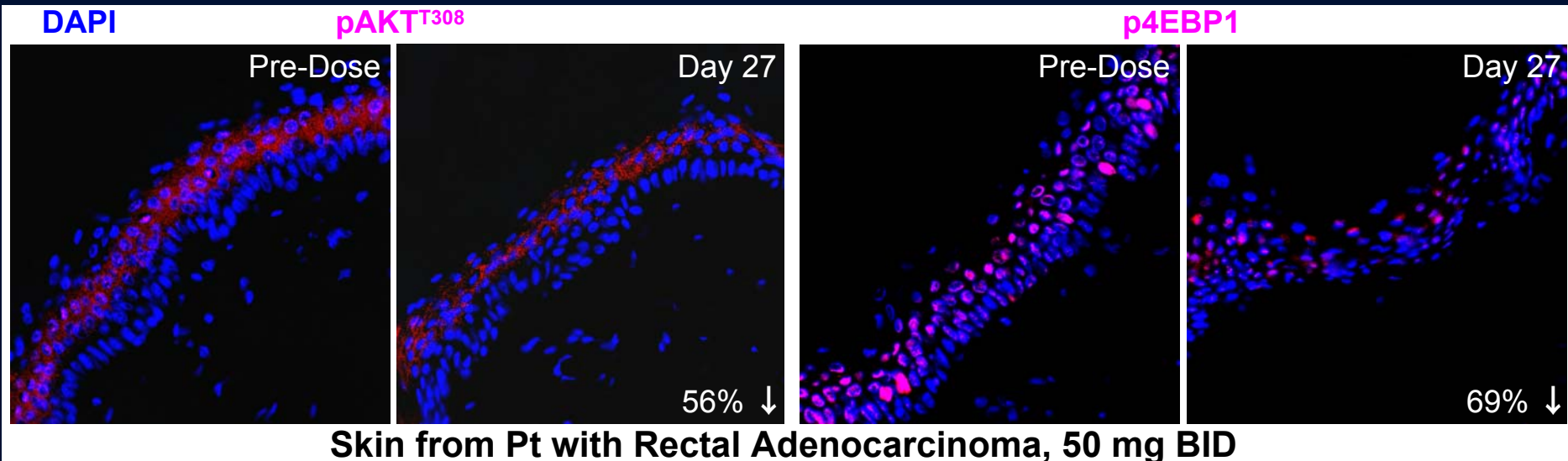


Patients (n)	% Decrease				
	pAKT ^{T308}	pAKT ^{S473}	pPRAS40 ^{T246}	p4EBP1 ^{T70}	pS6 ^{S240/S244}
4	70*	53-84	55-85	65-90	59-78

* n = 1 subject

- Inhibition of PI3K pathway at doses \geq 15 mg BID
- Progressive time-dependent inhibition in cases with serial post-dose samples

XL765 Phase 1: Pharmacodynamics in Skin

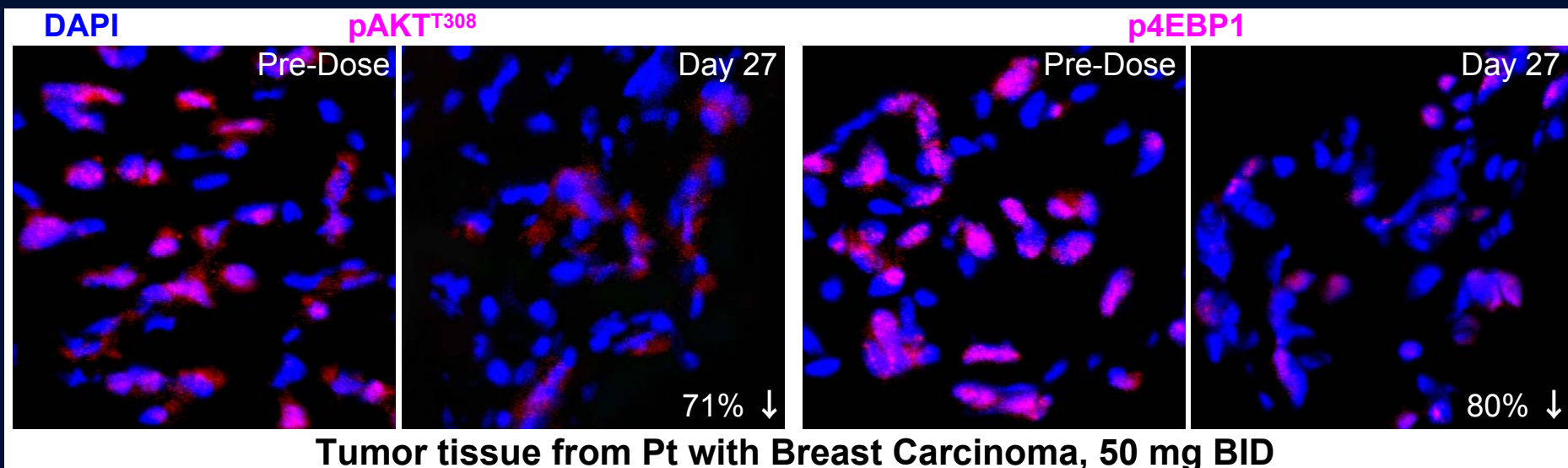


Patients (n)	% Decrease				
	pAKT ^{T308}	pAKT ^{S473}	pPRAS40 ^{T246}	p4EBP1 ^{T70}	pS6 ^{S240/S244}
12	46-92	42-81	66-82*	50-78	52-72*

* n = 6 subjects

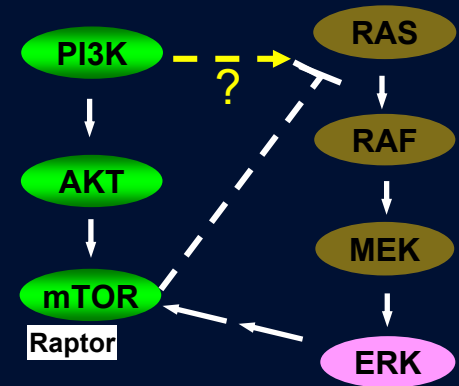
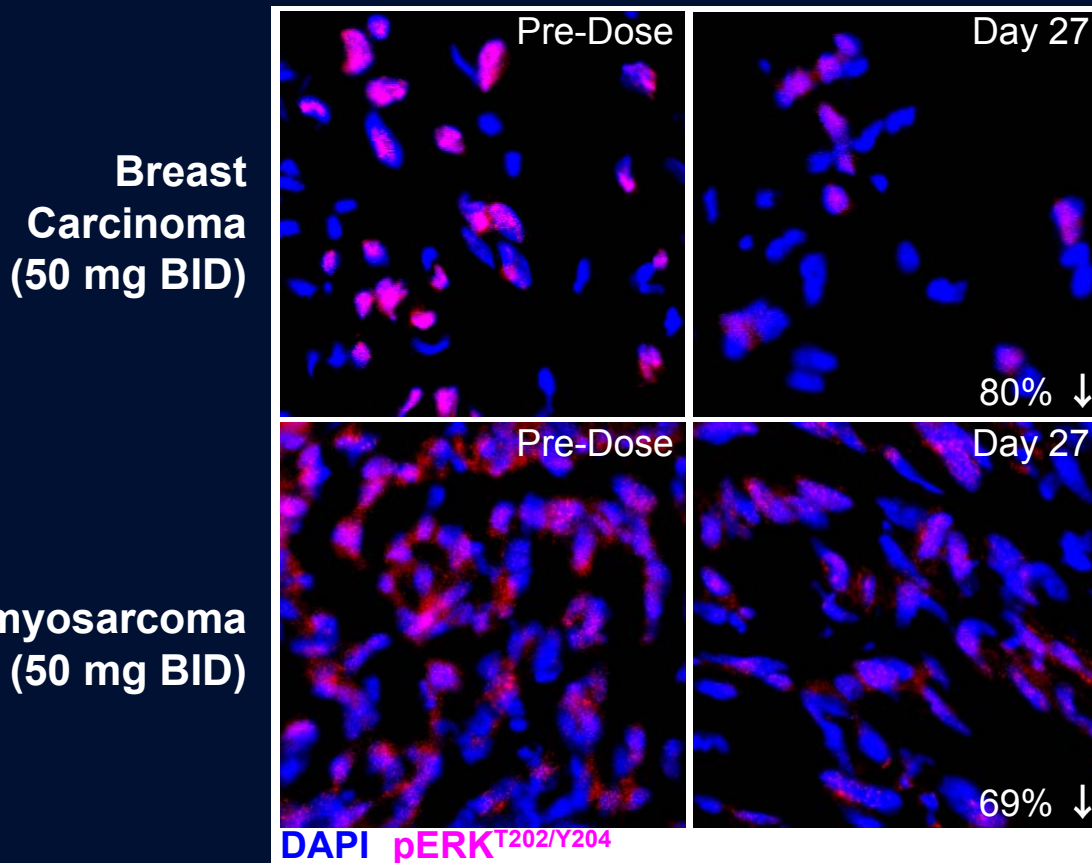
- Inhibition of PI3K pathway signaling across doses including 50 mg BID, 70 mg QD
- QD comparable to BID

Robust PI3K Pathway Inhibition in Diverse Tumors



Tumor	Dose (mg BID)	% Decrease				TUNEL (fold increase)
		pAKT ^{T308}	pAKT ^{S473}	p4EBP1 ^{T70}	Ki67	
Breast Carcinoma ^{1,2}	50	71	67	80	32	1.9
Mucinous Breast Ca ¹	50	76	76	70	44	1.8
Leiomyosarcoma ¹	50	74	70	66	26	2.1
Rectal Adenocarc ¹	50	61	68	65	43	1.3
Chondrosarcoma ³	60	83	94	89	53	1.4

XL765 inhibits ERK Pathway in Tumors



- Comparable pERK reduction in mucinous breast carcinoma (74% ↓) and rectal adenocarcinoma (62% ↓) - both also 50 mg BID
- pERK reduction contrasts with induction in clinic by TORC1 inhibitors
- Mechanistic basis for this reduction in pERK being explored
- Suggests interference with positive pathway cross-talk above TORC1

XL765 Phase 1: Anti-tumor Activity

Tumor Type	Dose	Best Response	Time on Study (Wks)	Most Recent Treatment	
				Agent	Wks
Mesothelioma ^a	60 BID	SD	41	Invest.	17
Appendiceal ^b Adeno	15 BID	SD	33	CPT-11/5-FU/ Leucovorin	14
Rectal Adeno ^b	50 BID	SD	24	NA	NA
Colon Adeno ^{b,c}	100 QD	SD	24	Panitumumab Irinotecan	8
NSCLC ^d	30 BID	SD	16	Docetaxel Cisplatin	6
Renal ^e	15 BID	SD	16	Sorafenib	182

^aTumor mutational analysis pending; ^bKRAS mutation; ^cEGFR amplified

^dMutations affecting PI3K pathway not detected; ^ePotential PIK3CA allelic loss; NA, not available

XL765 Phase 1: Summary

- Potent, selective inhibitor of PI3K/TORC1/TORC2
- Well tolerated at doses below MAD
- BID schedule: preliminary MTD 50 mg BID
- QD schedule: currently exploring 90 mg
- Robust pathway inhibition at well tolerated doses
 - QD comparable to BID
- 6 patients on study for 16 or more weeks
- 2 ongoing combination studies
 - Temozolomide; Erlotinib

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START

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