

**A phase 1 study of XL228, a potent
IGF1R / AURORA / SRC inhibitor,
in patients with solid tumors or
hematologic malignancies**

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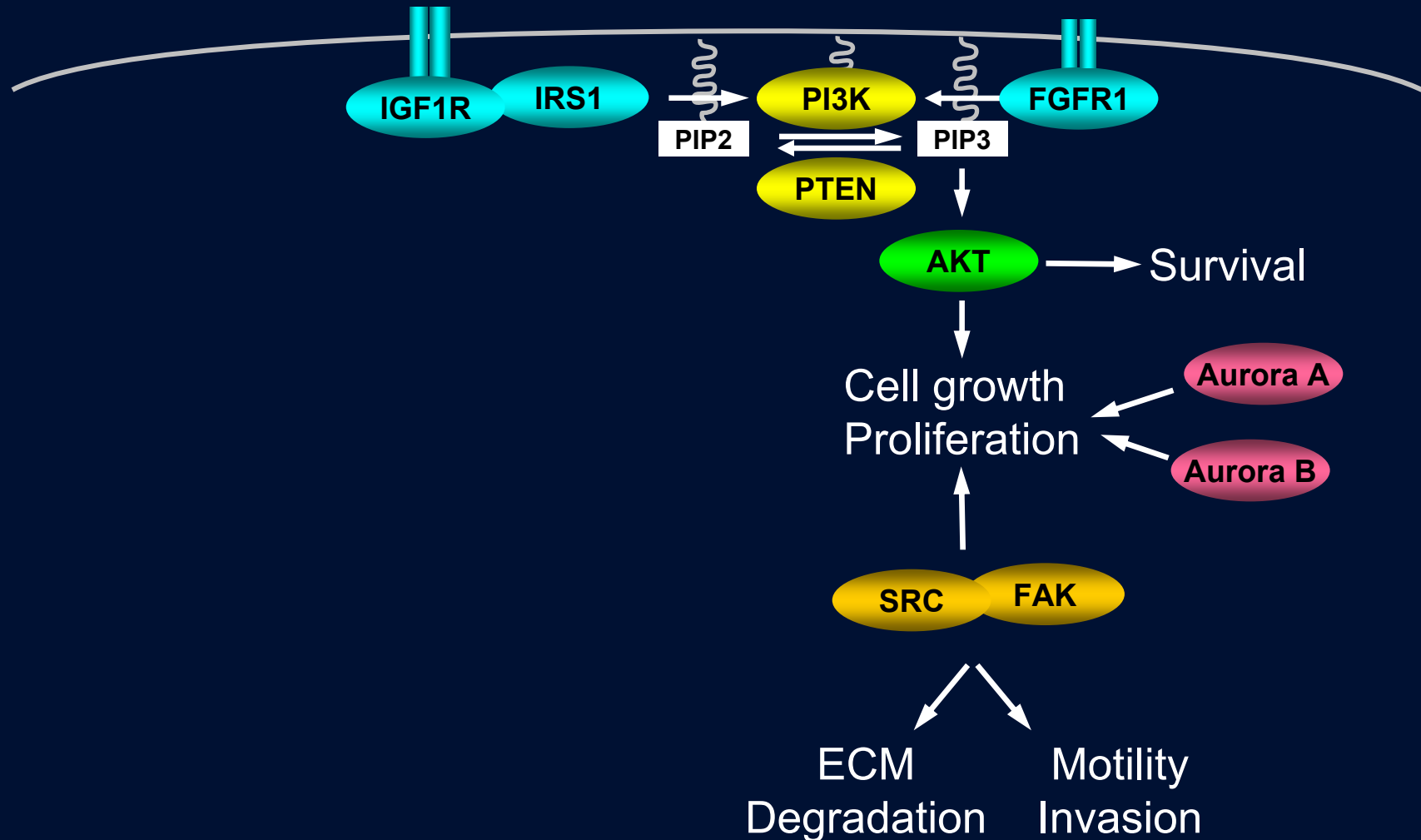
Disclosures

- D. Smith: Study Investigator
- C. Britten: Study Investigator
- H. Hurwitz: Study Investigator

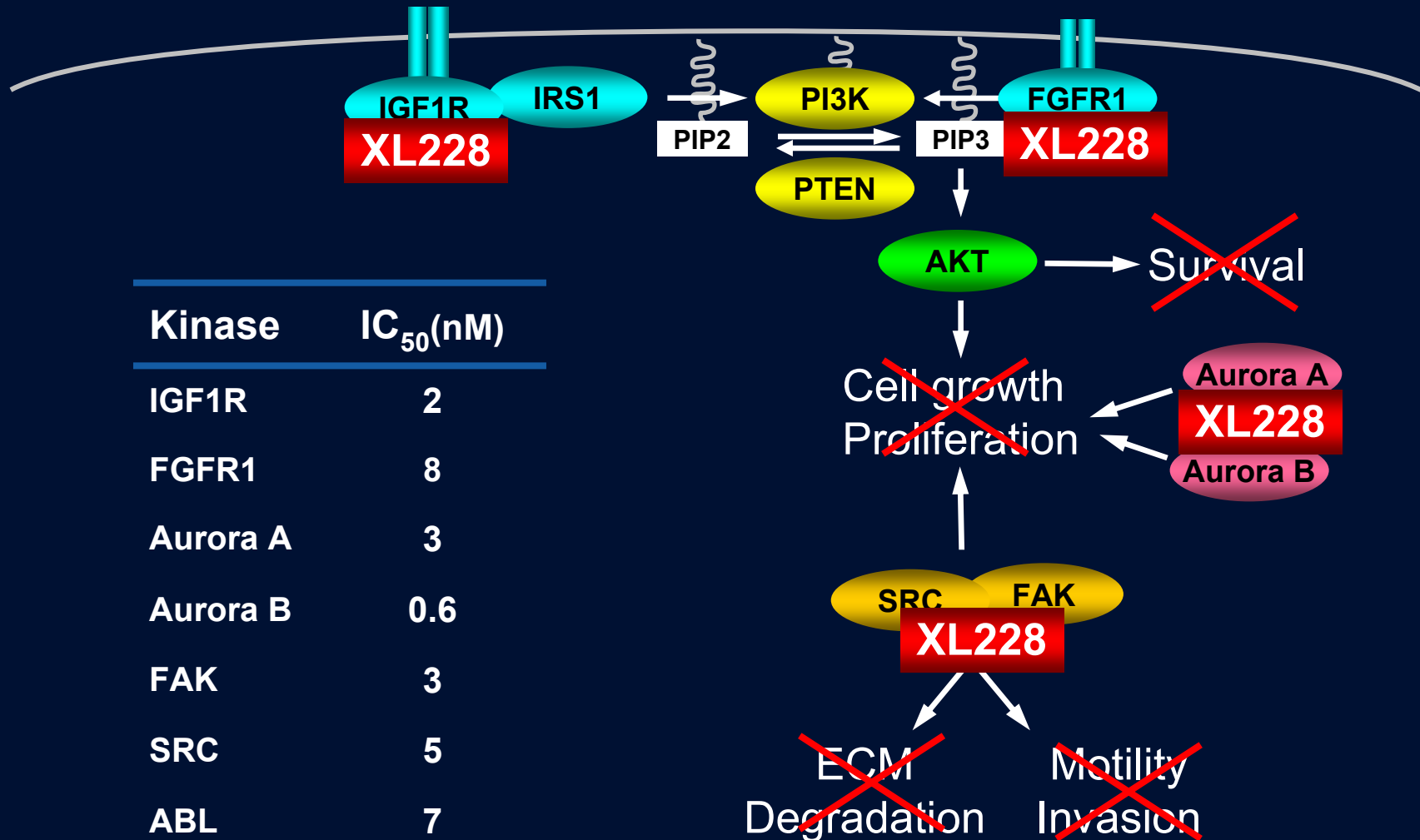
- Exelixis is the sponsor of this study

- D. Clary, L. Nguyen, and P. Woodard are employed at Exelixis, Inc. and are stockholders of Exelixis.

XL228 Targets in Cancer



XL228 Targets in Cancer



Kinase	IC ₅₀ (nM)
IGF1R	2
FGFR1	8
Aurora A	3
Aurora B	0.6
FAK	3
SRC	5
ABL	7

Study Objectives

- Primary
 - Safety, tolerability, MTD of XL228 administered weekly as 1 hour infusions
- Secondary
 - Pharmacokinetics (PK), renal elimination
 - Preliminary safety and anti-tumor activity in MTD expansion cohorts (CRC, lung, and multiple myeloma)
- Exploratory
 - Pharmacodynamics
 - Evidence of anti-tumor activity
 - Safety of extended dosing

Study Design

- 3 + 3 ascending dose design, weekly infusions
 - Twice-weekly schedule also to be evaluated
- Drug-related DLTs assessed during first 28-d cycle
 - Gr3 and Gr4 non-hematological toxicities despite optimal prophylaxis or treatment
 - Gr4 neutropenia ≥ 4 days or with documented fever or infection
 - Any other Gr4 hematological toxicity
 - Treatment-emergent AEs requiring dose reduction
 - Inability to receive $\geq 75\%$ of doses due to toxicity
- MTD is defined as highest dose level with $< 33\%$ of subjects experiencing a DLT during first cycle

Key Eligibility Criteria

■ Inclusion

- Refractory solid tumor, lymphoma, or multiple myeloma

■ Exclusion

- Previous treatment with IGF1R inhibitor
- Treatment with potent CYP3A4 inhibitor or inducer
- Inability to measure QT interval or risk of QT prolongation
- Bradycardia, arrhythmia, or history of significant heart disease within past 6 months

Study Status

- 42 subjects enrolled as of 18May2009
 - Demographic and safety data available for 33 subjects
 - 40 evaluable for clinical activity
- Weekly schedule
 - Seven dose levels evaluated (0.45 – 8.0mg/kg)
 - MAD is 8.0mg/kg
 - 2 of 5 subjects with DLTs (Gr3, Gr4 neutropenia)
 - MTD is 6.5mg/kg
 - 1 of 6 subjects with DLT (Gr3 hyperglycemia with dose reduction)

Patient Demographics (N=33)

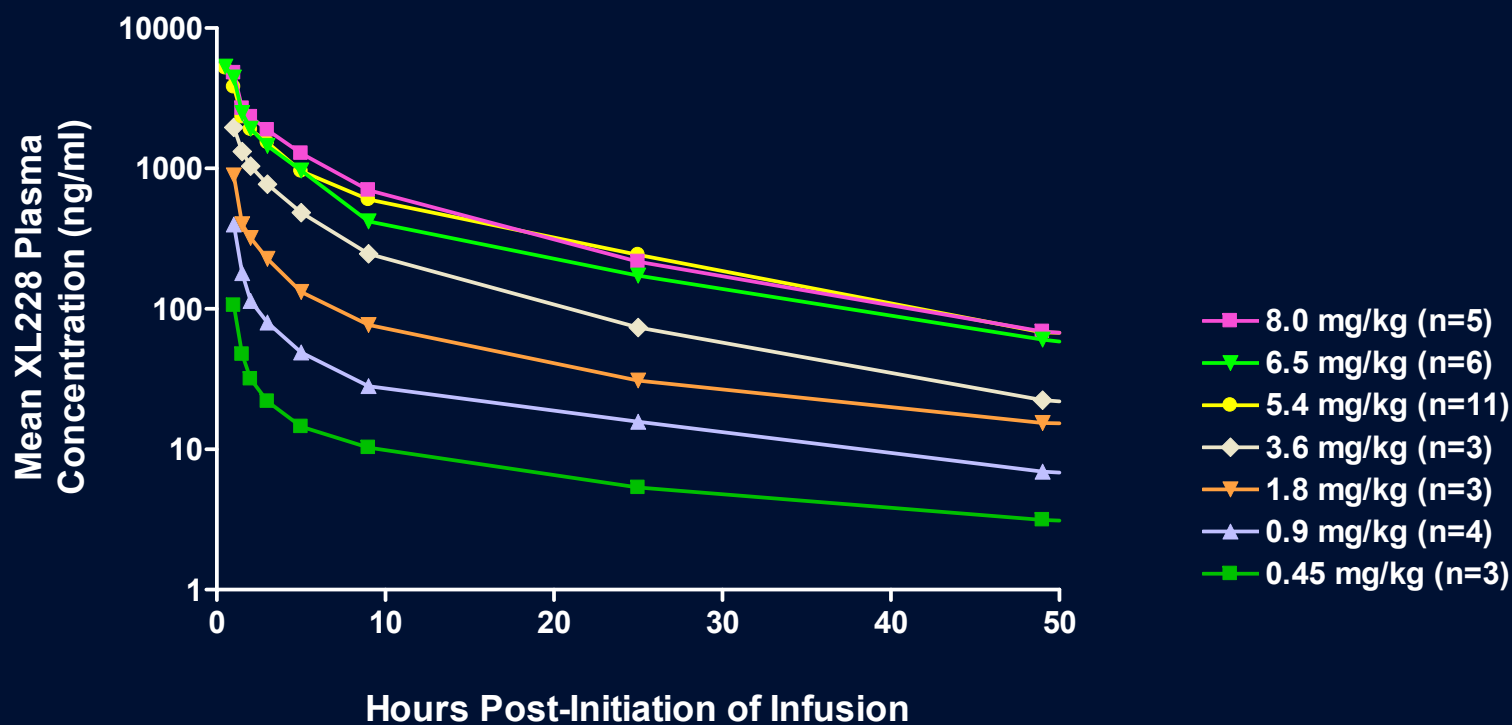
Age, median yrs (range)	63 (23-87)
Male / Female	23 / 10
ECOG 0 / 1 / 2	14 / 15 / 4
Prior radiotherapy	13 (39%)
Median prior anti-cancer regimens (range)	4 (0-8)
Diagnosis	
Colon	5
Sarcoma	5
NSCLC	3
Head and neck	3
SCLC	2
Pancreas	2
Prostate	2
Renal	2
Others	9

Adverse Events (N=33)

AE Term	n (%) *			
	Grade 1-2	Grade 3	Grade 4	All Grades
Abdominal pain	7 (21)	2 (6)	-	9 (27)
Fatigue	5 (15)	2 (6)	-	7 (21)
Constipation	6 (18)	-	-	6 (18)
Dry Mouth	6 (18)	-	-	6 (18)
Nausea	6 (18)	-	-	6 (18)
Vomiting	6 (18)	-	-	6 (18)
Hypotension	5 (15)	-	-	5 (15)
Cough	3 (9)	1 (3)	-	4 (12)
Decreased Appetite	4 (12)	-	-	4 (12)
Dysgeusia	4 (12)	-	-	4 (12)
Hyperglycemia	3 (9)	1 (3)	-	4 (12)
Neutropenia	-	2 (6)	2 (6)	4 (12)

- Three subjects not included above have experienced drug-related SAEs: Gr3 vomiting (1 subject), medically significant Gr2 hypotension and bradycardia (1 subject), and Gr3 diarrhea (1 subject)

Pharmacokinetics

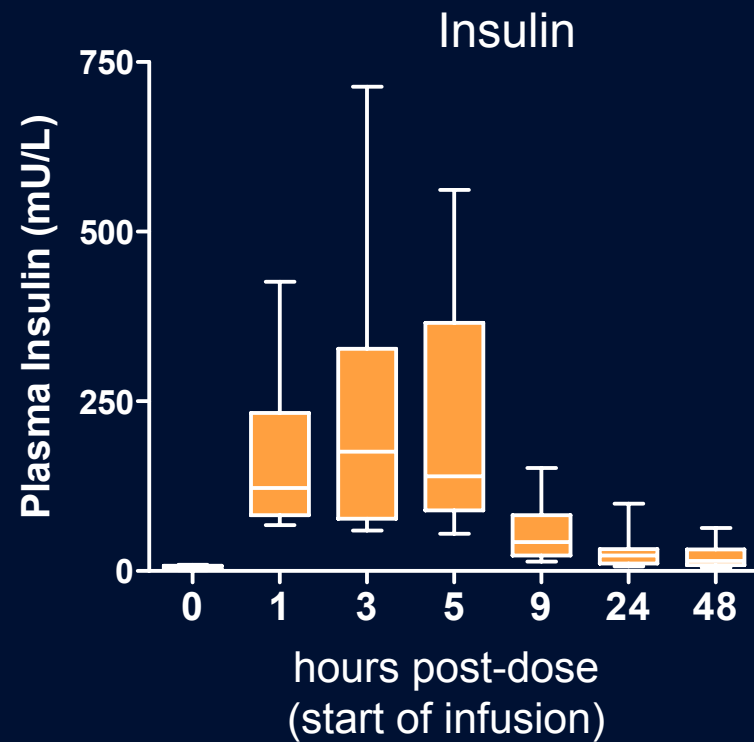
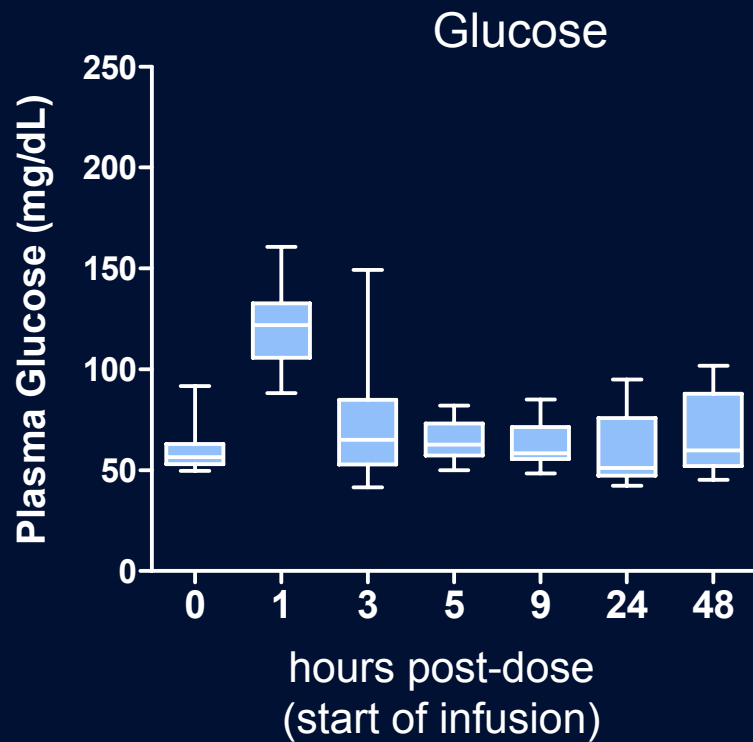


- C_{\max} and AUC_{0-t} increase with dose
- $T_{1/2}$ of 28h for 6.5mg/kg; minimal accumulation
- Large volume of distribution (V_{ss} 5 - 34 L/kg)

Pharmacodynamics

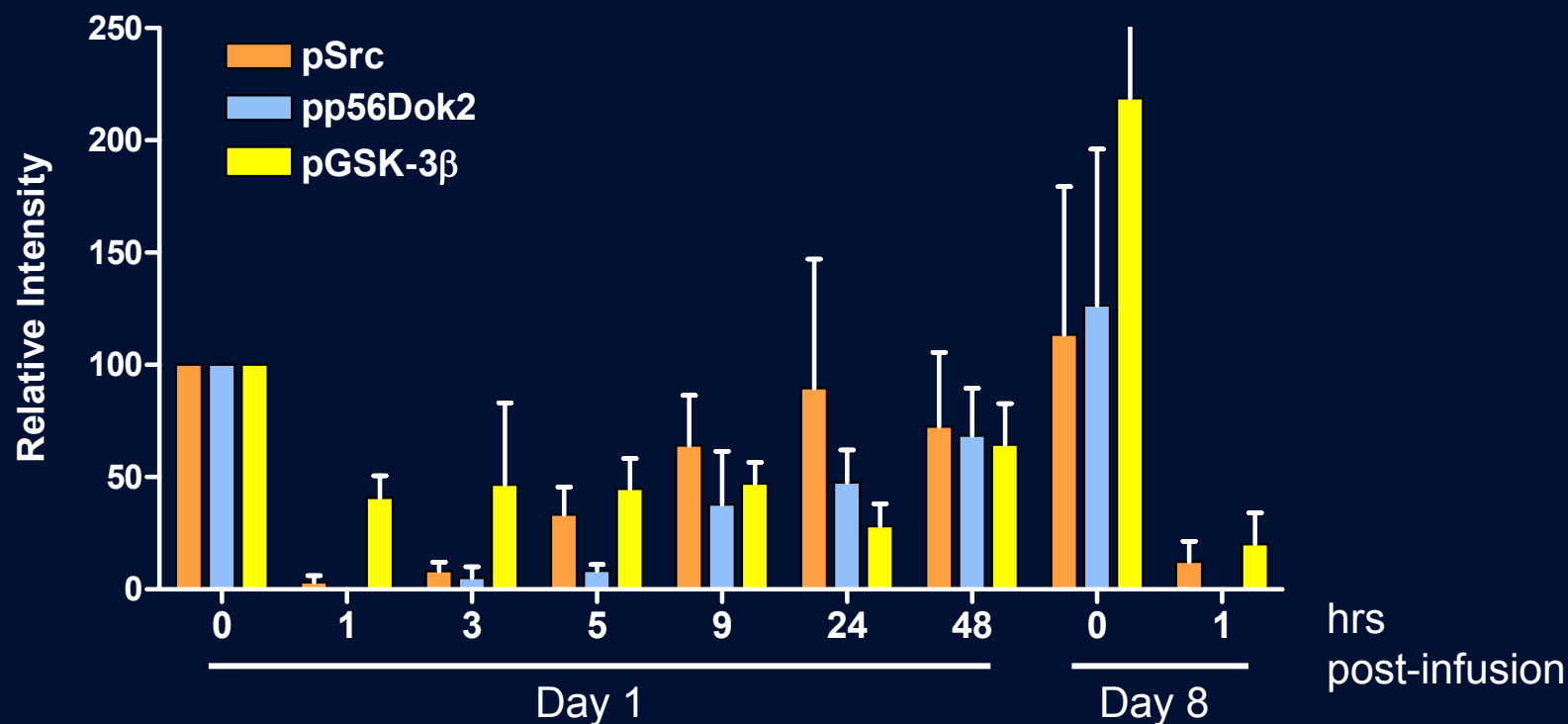
- Plasma
 - Upregulation of plasma glucose and insulin
- Peripheral blood mononuclear cells
 - IGF1R and SRC pathway phosphorylation monitored by immunoblot
- Normal and tumor tissues
 - Immunofluorescent analysis of IGF1R, SRC, FGFR, and Aurora pathway phosphoproteins.

Transient Modulation of Glucose and Insulin



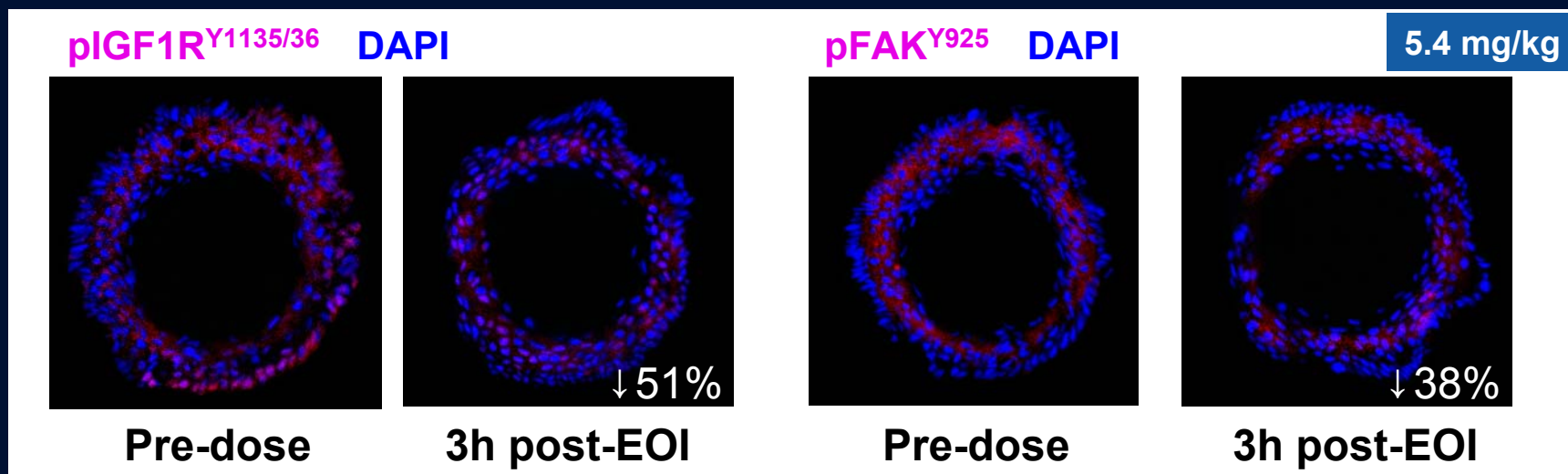
- Hyperglycemia is generally mild (Gr1 to Gr2), asymptomatic, and resolves within 2 hours

Pathway Phosphorylation in PBMC



- Transient inhibition of SRC and IGF1R/AKT pathway phosphorylation in peripheral blood mononuclear cells

Skin and Hair Pharmacodynamics

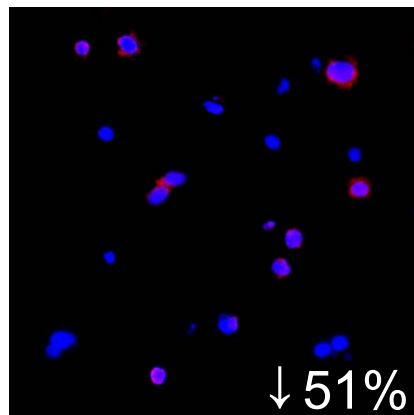
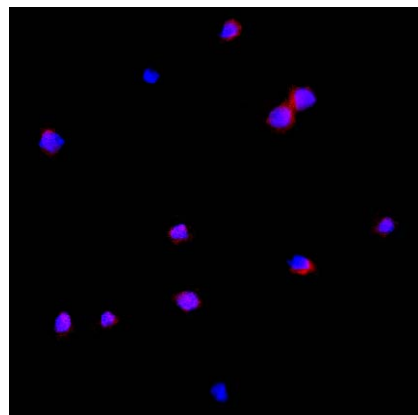


Tissue	Timepoint*	Dose (mg/kg)	↓pIGF1R	↓pIRS1	↓pAKT	↓pFAK	↓pFGFR1
Scalp Hair	D22 3 hrs post	5.4	39%	ND	41%	42%	39%
Eyebrow	D22 3 hrs post	5.4	51%	ND	45%	38%	43%
Eyebrow	D23 24 hrs post	5.4	29%	38%	ND	28%	30%
Skin	D21 3 hrs post	3.6	45%	36%	26%	28%	28%

- Pharmacodynamic effects at lower doses were less consistent

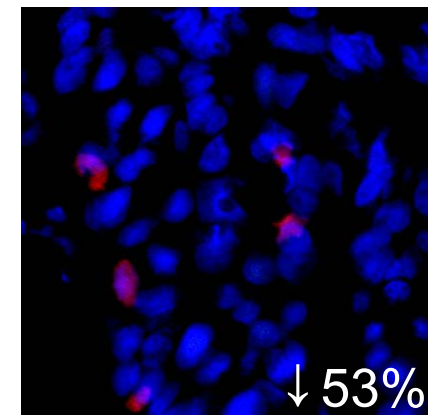
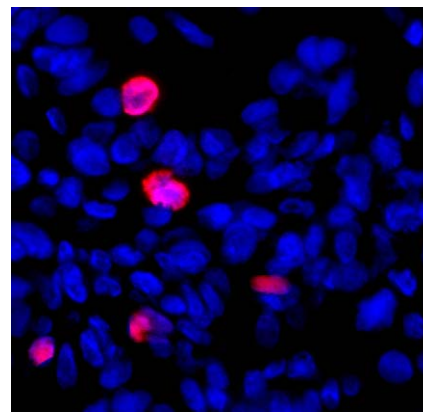
Tumor Pharmacodynamics

pIGF1R^{Y1135/36} DAPI



Inguinal node aspirate, SCLC

pHistone H3^{T3} DAPI



Liver metastasis, NSCLC

	Dose (mg/kg)	Timepoint*	↓pFAK	↓pIGF1R	↓pIRS1	↓pFGFR1	↓pHH3 (T3)	↓pHH3 (S10)
SCLC	5.4	D23 24 hrs	49%	51%	56%	ND	ND	ND
Eye brow	5.4	D23 24 hrs	28%	29%	38%	30%	ND	ND
NSCLC	3.6	D8 5 hrs	28%	n.s.	29%	30%	53%	39%

Pharmacodynamics Summary

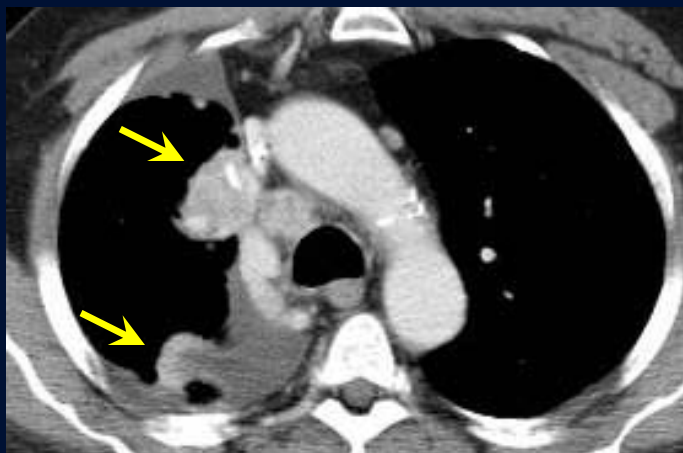
- IGF1R / Insulin receptor
 - Modulation of plasma glucose and insulin
 - Inhibition of IGF1R signaling in PBMC, normal tissue, and tumor samples
- SRC family kinases
 - Decreases in SRC substrate phosphorylation in PBMC, normal tissue, and tumor samples
- FGFR1
 - Inhibition of pFGFR1 in hair, skin, and tumor samples
- Aurora B
 - Inhibition of pHistone H3 in tumor tissue

Anti-Tumor Activity

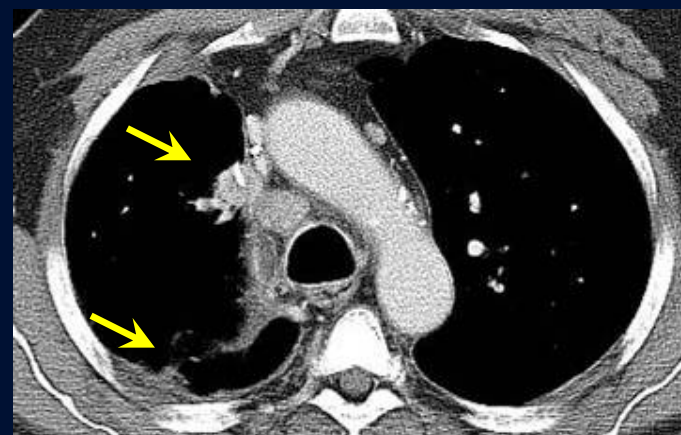
Tumor Type	Weeks on Study	Best Response	Dose Level (mg/kg)	# of Prior Regimens	Weeks on Most Recent Regimen
SCLC	58*	SD	0.45	1	carboplatin etoposide 21
CRC	56	SD	1.8	5	capecitabine oxaliplatin 44
NSCLC	48	cPR	5.4	5	pemetrexed 16
Pancreatic	35	SD	4.0	2	dasatinib gemcitabine 8
CRC	32 [†]	SD	1.8	3	panitumumab irinotecan 39
Leiomyosarcoma	32	SD	0.9	1	dasatinib 16
Liposarcoma	23	SD	4.0	4	temozolomide 24
Small Lymphocytic Lymphoma	22	SD	1.8	3	rituximab ifosfamide carboplatin etoposide 13

13 of 40 evaluable subjects (33%) have remained on treatment for \geq 12 weeks

Confirmed Partial Response: NSCLC



Baseline



Month 4

- Male, 63, African-American, ex-smoker (22 y); adenocarcinoma
- Sum of target lesions decreased **35%**; on study for 48 weeks

Prior Regimens	Duration	Outcome
1) surgery with adjuvant cisplatin / vinorelbine	1 cycle	Recurrence at 63 wks
2) carboplatin / gemcitabine	3 cycles	Progression at 9 wks
3) docetaxel	6 cycles	Response; progression at 50 wks
4) erlotinib	14 wks	Progression at 14 wks
5) pemetrexed	6 cycles	Progression at 20 wks

Summary

- Multi-targeted inhibitor of IGF1R, Aurora, FGFR, and SRC family kinases
- Generally well tolerated at the MTD of 6.5mg/kg
 - Drug-related SAEs of vomiting, hypotension, bradycardia, and diarrhea
- IGF1R, FGFR, Aurora and SRC pathway modulation
 - Tumor, skin, hair, plasma, and PBMC
- Evidence of single agent anti-tumor activity
 - Prolonged stable disease, including 6 patients on study for >26 weeks
 - Confirmed partial response in NSCLC patient
- Study expansion with cohorts of CRC, multiple myeloma, and lung cancer subjects

Acknowledgements

- XL228-002 patients and their families
- XL228-002 clinical site staff
 - Duke University
 - Dr. K Bullock, Dr. G Vlahovic, R Truax, S Savage, P Mitchell, K Coleman, S Norman
 - UCLA
 - Dr. E Garon, L Yonemoto, A Mayers
 - University of Michigan
 - Dr. R Chugh, S Robben, N Iqbal, M Schmidt
- Sponsor: Exelixis