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A Phase 1 Safety and Pharmacokinetic (PK) Study of PI3K/TORC1/TORC2 Inhibitor, XL765 (SAR245409), in Combination with Erlotinib in Patients (pts) with Advanced Solid Tumors

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INTRODUCTION

- Erlotinib is an EGFR inhibitor and is approved in the United States for recurrent locally advanced or metastatic non-small cell lung carcinoma (NSCLC) and in combination with gemcitabine for patients with locally advanced, unresectable or metastatic pancreatic cancer.
- Activation of the phosphatidylinositol-3 kinase (PI3K) pathway is a common occurrence in many human tumors. In particular, amplification of or activating mutations in the PIK3CA gene (which encodes the p110α catalytic subunit of PI3K), or loss of function/deletion mutations in the gene encoding its antagonist PTEN have been found with high frequency in a wide range of tumor types.
- PI3K pathway signaling has been implicated as a mediator of resistance to EGFR inhibitors.
- XL765 is an oral, selective inhibitor of Class I PI3Ks, as well as TORC1 (mTOR/Raptor complex) and TORC2 (mTOR/Rictor complex).
- In preclinical studies, XL765 has demonstrated dose-dependent target modulation and efficacy in tumor xenograft models.
- In an ongoing Phase 1 single-agent clinical study, XL765 has exhibited robust pharmacodynamic activity in diverse solid tumors (Lo Russo et al, 2009).
- Based on these preclinical and clinical data, a study combining XL765 with erlotinib was initiated in patients with advanced solid tumors.

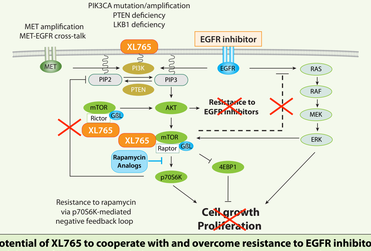

Figure 1. Potential of XL765 to cooperate with and overcome resistance to EGFR inhibitors. Combined inhibition of PI3K/mTOR precludes pAKT and pERK induction associated with specific mTOR/Raptor (TORC1) inhibition (LoRusso et al. 2009).

OBJECTIVES

Primary

- Evaluation of the safety and tolerability of XL765 administered in combination with erlotinib in patients with solid tumors refractory to standard treatments
- Determination of the maximum tolerated dose (MTD) of XL765 administered in combination with erlotinib in patients with refractory solid tumors

Secondary

- Evaluation of pharmacokinetics (PK) of XL765 and erlotinib when given in combination
- Evaluation of preliminary efficacy

Exploratory

- Evaluation of pharmacodynamic effects, identification of surrogate and predictive biomarkers

METHODS

Study Design

- Phase 1, non-randomized, open-label, safety, and PK dose escalation study
- A 2 week run-in of single agent erlotinib during the dose escalation part of the study

Expanded MTD Cohort

- Once the preliminary MTD has been established, 9–12 additional patients with non-small cell lung cancer (NSCLC) will be enrolled.

Key Eligibility Criteria

- Dose Escalation: Patients with solid tumors, prior treatment with standard therapies
- Cohort Expansion: Patients with advanced or metastatic NSCLC, prior treatment with erlotinib or gefitinib
- Archival or fresh tumor tissue identified and designated for central lab analysis
- Fasting plasma glucose ≤ 160 mg/dL
- No prior treatment with a PI3K inhibitor
- No small-molecule kinase inhibitor (excluding erlotinib) or hormonal agents within 14 days (or 5 times the half-life of the drug or active metabolites, whichever is longer)
- Subjects enrolling into the MTD cohort with accessible tumor for biopsies must provide pre-treatment and on-treatment tumor biopsies

Study Treatment

- XL765 is administered orally daily on two schedules (28-day cycles)
  - Once-daily (qd) dosing
  - Twice-daily (bid) dosing
- Erlotinib is administered once daily
  - Starting dose 100 mg qd; maximum dose 150 mg qd

Assessments

- Tumor assessments at baseline and every 8 weeks thereafter while on treatment
- Full PK profile for run-in and Cycle 1; limited sampling in Cycle 2+
- Pharmacodynamics assessments:
  - Plasma
  - Optional tumor, hair, buccal mucosa, and skin
  - Mandatory tumor biopsies for expanded MTD cohort
  - Optional FDG-PET imaging

RESULTS

- This is an analysis of preliminary data from an ongoing study.

Table 1. Baseline Characteristics[a]

Characteristic	Once-Daily Dosing (n = 18)
Median age (range), years	60 (38-76)
Sex, M/F (n)	6/12
Race (n = 12)	
White	12
Black	0
Tumor type	
Non-small cell lung cancer	14
Other tumor types[b]	4
ECOG status (n = 12)	
0	5
1	7
Prior erlotinib/gefitinib treatment[c]	11
Prior radiation therapy (n = 12)	8
Medium number of regimens (range, n = 12)	4 (0-9)

ECOG, Eastern Cooperative Oncology Group.
[a] Eighteen patients enrolled and treated with erlotinib during the 14 day run-in period as of 03 Nov 2009; two patients discontinued before receiving XL765 + erlotinib. Based on monitored and unmonitored data.
[b] Liposarcoma, colon cancer, endometrial cancer, epidermoid carcinoma.
[c] One patient received gefitinib and erlotinib.

Table 2. Dose Escalation Summary[a]

Erlotinib administered at 100 mg qd on a 28 day cycle

Cohort	XL765 dose (mg)	Patients (n)	Dose-Limiting Toxicity
1	30 qd	5	—
2	50 qd	10	—
3	20 bid	1	—

[a] Includes patients that received at least one dose of XL765 as of 03 Nov 2009; based on monitored and unmonitored data of 16 patients enrolled as of 03 Nov 2009.

Table 3. Summary of Study Status

Status	Patients (n = 16)[a]
On treatment	6
Off treatment	10
Reason for discontinuation	
Progressive disease	8
Adverse event[b]	1
Withdrew consent	1

[a] Includes patients who received at least one dose of XL765 as of 03 Nov 2009; based on monitored and non-monitored data.
[b] Adverse events include: Grade 2 AST and ALT.

Safety

Table 4. Summary of Adverse Events Regardless of Causality (Reported in > 10% of Patients; n = 12)[a]

	Patients with			
Adverse Events (AEs)[b]	Grade 1 n (%)	Grade 2 n (%)	Grade 3[c] n (%)	Total n (%)
Diarrhea	5 (42)	1 (8)	—	6 (50)
Rash	5 (42)	1 (8)	—	6 (50)
Nausea	3 (25)	1 (8)	1 (8)	5 (42)
Fatigue	1 (8)	1 (8)	1 (8)	3 (25)
Vomiting	1 (8)	—	2 (17)	3 (25)
Anorexia	1 (8)	—	1 (8)	2 (17)
Asthenia	2 (17)	—	—	2 (17)
Blood cholesterol increase	1 (8)	1 (8)	—	2 (17)
Dehydration	—	1 (8)	1 (8)	2 (17)
Dizziness	2 (17)	—	—	2 (17)
Dry skin	2 (17)	—	—	2 (17)
Hypokalemia	1 (8)	—	1 (8)	2 (17)
Peripheral oedema	2 (17)	—	—	2 (17)

[a] Adverse events in database as of 07 Oct 2009 independent of attribution for patients that received at least one dose of XL765.
[b] Adverse events graded using the Common Terminology for Adverse Events Version 3.0; terms are the Preferred Term/MedDRA 10.0.
[c] No ≥ Grade 4 AEs were reported.

Serious adverse events have been reported in five patients

- None of these events were considered related to study treatment (XL765 + erlotinib).

Antitumor Activity

Table 5. Status of NSCLC Patients who Received Prior Erlotinib[a]

Histology	Weeks on prior erlotinib	Best response to prior erlotinib	Weeks from erlotinib failure to joining this study	XL765 dose (mg qd)[b]	Weeks on Study	Tumor Characteristics[c]
AD	50	SD	126	50	35 +	EGFR mut
SQ	4	SD	13	50	24	ND
AD	44	SD	NR[d]	30	16	NA
LC	12	SD	8	50	16 +	ND
AD	18	SD	89 (±2)	50	10	ND
AD	91	PR	10	50	8	NA
AD	22 (±4)[e]	SD[e]	235	50	8	EGFR mut PIK3CA amp
AD	37 (±4)	NR[f]	158	30	4	LKB1 mut p53 mut
AD	72	PR	4	50	1 +	NA
AD	24	SD	8	50	1 +	NA

AD, adenocarcinoma; amp, amplification by qPCR; LC, large cell carcinoma; mut, mutation; NA, not available; ND, no alteration detected; NR, not relevant PR, partial response; SD, stable disease; SQ, squamous carcinoma
[a] Includes patients who received at least one dose of XL765 as of 02 November 2009; Based on monitored and non-monitored data.
[b] Erlotinib administered at 100 mg qd on a 28 day cycle
[c] Minimum genomic analysis included PIK3CA and EGFR genes.
[d] Patient entered the study prior to erlotinib progression.
[e] Patient received gefitinib June 2004 – Aug 2006; response to gefitinib and erlotinib unavailable (minimum response of SD likely).
[f] Patient received erlotinib in maintenance setting after completion of chemoradiation treatment.

Pharmacokinetics

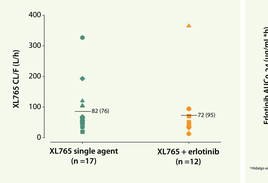

Figure 2. XL765 apparent clearance (CL/F) values when given in combination with erlotinib are consistent with values observed in XL765 single agent study (LoRusso et al. 2009).

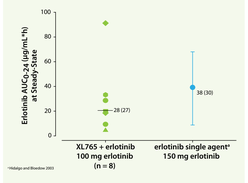

Figure 3. Erlotinib AUC_{SS} values when given in combination with XL765 are in the range of published erlotinib single agent values.

- Erlotinib does not have major impact on XL765 PK.
- XL765 does not have a major impact on erlotinib PK.

Pharmacodynamics

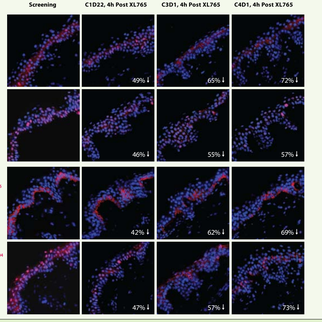

Figure 4. Reduction in PI3K and ERK/MAPK pathway signaling in serial skin biopsies from a patient with NSCLC Adenocarcinoma [prior Erlotinib, prolonged SD, EGFR (deletion (E746_A750))] administered 50 mg qd XL765 / 100 mg Erlotinib. (A) Progressive post-dose decreases in PI3K pathway readouts; (B) Progressive post-dose decreases in EGFR/MAPK pathway readouts.

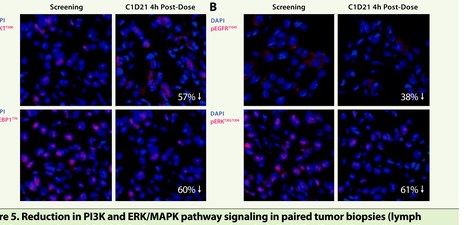

Figure 5. Reduction in PI3K and ERK/MAPK pathway signaling in paired tumor biopsies (lymph node) from a patient with NSCLC adenocarcinoma [prior erlotinib, LKB1 (D194N), p53 (M237I)] administered 30 mg qd XL765 / 100 mg Erlotinib. Cryopreserved tumor biopsy samples were serially sectioned at 10 microns. Twenty serial sections were obtained from each sample. Following immunostaining, up to 16 non-overlapping representative fields were captured at 400x magnification and quantified. (A) Post-dose decreases in PI3K pathway readouts; (B) Post-dose decreases in EGFR/MAPK pathway readouts. Also evident, post-dose decrease in Ki67 (36% ↓) and increase in TUNEL (1.6-fold ↑).

CONCLUSIONS

- XL765 in combination with erlotinib is generally well tolerated.
- MAD and MTD have not been established.
- Currently enrolling in qd and bid schedules.
- No major PK interaction between XL765 and erlotinib has been observed.
- Inhibition of PI3K and EGFR/MAPK signaling observed in skin and tumor tissues.
- Four of 10 NSCLC patients who had received prior erlotinib have been on study for 16 to 35+ weeks.

References.
Hidalgo and Bloedow. Semin Oncol. 2003;30(3 Suppl 7):25-33.
LoRusso et al. ASCO Annual Meeting 2009
http://www.exelixis.com/downloads/XL765-001_ASCO-2009.pdf

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