

A Phase I Dose-Escalation and Pharmacokinetic (PK) Study of XL647, a Novel Spectrum Selective Kinase Inhibitor, Administered Orally Daily to Patients With Advanced Solid Malignancies (ASM)

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INTRODUCTION

- EGFR (epidermal growth factor receptor), HER2 (human epidermal growth factor receptor 2), and VEGFR2/KDR (vascular endothelial growth factor receptor 2/kinase insert domain-containing receptor) are involved in the growth and metastasis of tumors.
- There is increasing evidence of a close relationship between the EGFR- and VEGFR2-mediated signaling pathways.¹ Simultaneous inhibition of these pathways may provide improved efficacy and help delay the emergence of resistance.
- XL647 is a new chemical entity that inhibits multiple receptor tyrosine kinases including EGFR, VEGFR2, and HER2 in preclinical studies (Figure 1).
- XL647 has preclinical activity against the T790M mutant form of EGFR,² which is resistant to erlotinib.³
- In vitro defined lapatinib resistance mutations in HER2 are sensitive to XL647 (data not shown).⁴

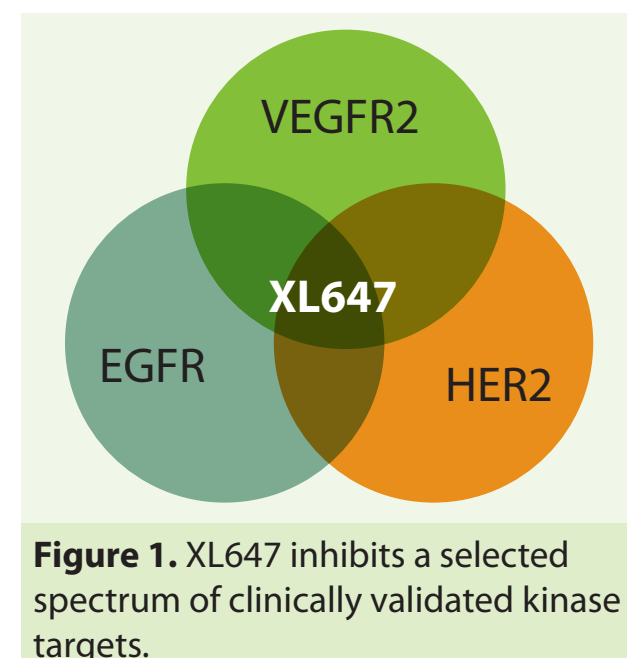


Figure 1. XL647 inhibits a selected spectrum of clinically validated kinase targets.

OBJECTIVES

- The primary objective of this study is to determine the maximum tolerated dose (MTD) and to evaluate the safety of daily oral administration of XL647.
- The secondary objective is to evaluate the plasma PK of daily oral administration of XL647.
- The exploratory objectives are to:
 - Assess the pharmacodynamic effects of XL647.
 - Evaluate effects of XL647 on vascular permeability of tumors using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

METHODS

Study Design

- This is a Phase I, nonrandomized, open-label, dose-escalation study conducted at 2 sites in the USA.

Key Inclusion Criteria

- Adult patients (age ≥ 18 years) with histologically confirmed metastatic or unresectable solid tumors for which known effective measures do not exist or are no longer effective
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; life expectancy > 3 months, and adequate hematologic, renal, and hepatic function

Key Exclusion Criteria

- Chemotherapy or radiotherapy within 30 days (nitrosoureas or mitomycin C within 6 weeks) prior to entering the study
- Known brain metastases
- QTc of > 0.45 seconds

Study Treatments

- XL647 is administered orally once daily. Cycles are repeated every 28 days.
- Cohorts of 3 to 6 patients were enrolled to receive escalating doses levels of XL647 with a starting dose level of 75 mg.
 - The maximum dose escalation was 100% as long as no Grade 2 or higher XL647-related adverse events (AEs) were observed in the previous cohort during the first 28 days of dosing.
 - The maximum dose escalation was 50% in the event of Grade 2 or higher XL647-related AEs in the previous cohort during the first 28 days of dosing.
- Following determination of the MTD, an expanded cohort (to receive 300 mg XL647 daily) is currently being enrolled.
 - Up to 15 new patients will be enrolled into this cohort.
 - At least 6 of these patients will undergo pre- and post-treatment DCE-MRI evaluation of the effects of XL647 on the vascular permeability of tumors.
- In the absence of progressive disease or unacceptable XL647-related toxicity, patients may continue to receive XL647 treatment on the same dosing schedule for up to 1 year.

Tumor Assessments

- Tumor measurements are performed at baseline and then approximately every 8 weeks thereafter. Responses are determined using RECIST and are to be confirmed with a follow-up tumor assessment at ≥ 30 days.

Pharmacokinetic/Pharmacodynamic Assessments

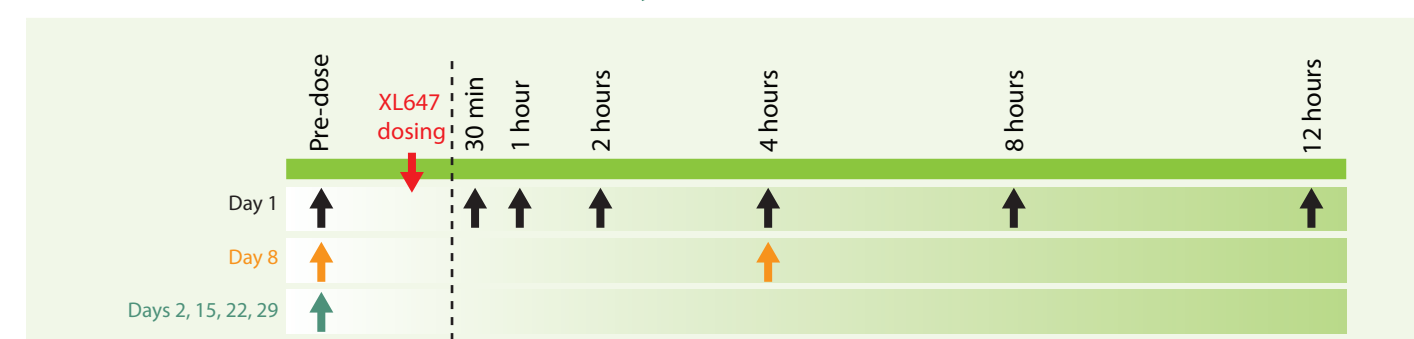


Figure 2. Phase I study design: timepoints of pharmacokinetic sample collections in the dose escalation cohorts.

- Dose escalation cohorts:** Patient blood samples were collected for PK analysis at the timepoints indicated in Figure 2. Baseline pharmacodynamic samples were collected (pre-dose on Day 1) and at various times during the study (including on Days 2, 8, 15, 22, and 29).
- Expanded MTD cohort:** Extensive post-dose sampling on Day 22 was added to the existing sampling scheme (data not shown).
- PK plasma samples were analyzed for XL647 concentration using a validated LC/MS/MS method. Exposure was determined using noncompartmental methods.
- Estimated AUC at steady state was calculated as the Day 1 AUC times the accumulation ratio, where the accumulation ratio was calculated as the mean trough concentration on Days 15, 22, and 29 divided by the trough concentration on Day 2.
- Dose proportionality was assessed using a power model.
- Receptor pathway effects were assessed by measurement of phosphorylated ERK1/2 and AKT in patient scalp or eyebrow hair follicles obtained pre- and post-dose.

RESULTS

- This is an interim analysis of an ongoing study; data presented have not been audited.
- The study has enrolled 26 patients as of September 27, 2007. Baseline characteristics and treatment status are shown in Tables 1 and 2. Safety data are available for 24 patients and response data are available for 21 evaluable patients.

Table 1. Baseline Characteristics

Characteristic	No. of patients (N = 26)
Median age (range), years	62 (41-79)
Sex (M/F)	18/8
Race	
Asian	6
White	20
Tumor type	
Non-small cell lung cancer	7
Colon carcinoma	3
Esophageal carcinoma	3
Adenoid cystic carcinoma	2
Multiple tumor types ^a	11
ECOG status	
0	11
1	14
2	1
Did not receive prior radiation	15
Received prior radiation	11
Did not receive prior chemotherapy	2
Received prior chemotherapy	24
Median number of regimens (range)	3 (1-7)

ECOG: Eastern Cooperative Oncology Group
^aOne case each of angiosarcoma, appendiceal adenocarcinoma, bladder cancer, fibrosarcoma, desmoplastic squamous cell carcinoma, duodenal adenocarcinoma, gastrointestinal stromal tumor, liposarcoma, ovarian carcinoma, sarcoma, and thymoma.

Table 2. Summary of Study Status

Status	No. of patients (N = 26)
On treatment	6
Off treatment	20
Reason for discontinuation	
Progressive disease	16
Adverse event*	2
Withdrew consent	2

*Grade 3 pneumonitis; Grade 3/4 drug-induced transaminitis.

Safety

- The MTD is 300 mg.
- Three dose-limiting toxicities (DLTs) occurred:
 - One event of Grade 3 study drug-induced pneumonitis occurred in 1 of 3 patients enrolled at 300 mg.
 - The cohort was expanded, and no further DLTs were observed.
 - Two events of clinically asymptomatic Grade 3 QTc prolongation occurred in 2 of 4 patients enrolled at 350 mg based on machine-read ECG.
 - These events were downgraded to Grade 2 following subsequent manual re-reads.
 - Central ECG laboratory re-analysis for all ECGs is in progress.
- The most common treatment-related AEs were Grade 1 and 2 diarrhea, dysgeusia, fatigue, rash, and clinically asymptomatic QTc prolongation (Table 3).
- A total of 10 serious AEs were reported in 6 patients; of these events 2 were considered possibly or probably related to XL647. These 2 drug-related events of Grade 3 study drug-induced pneumonitis and grade 4 myocardial infarction occurred in the same patient.

Table 3. Summary of Related Adverse Events (Reported by $> 10\%$ of Patients; n = 24)

Adverse events (AEs)*	No. patients (%) with Grade 1	No. patients (%) with Grade 2	No. patients (%) with Grade ≥ 3	Total no. patients (%) with related AEs
Diarrhea	13 (54)	5 (21)	1 (4)	19 (79)
Rash ^b	9 (38)	10 (42)	0	19 (79)
Fatigue	7 (29)	1 (4)	2 (8)	10 (42)
Dry skin	6 (25)	5 (21)	0	11 (46)
Dysgeusia	6 (25)	1 (4)	0	7 (29)
Nausea	7 (29)	0	0	7 (29)
Hypophosphataemia	2 (8)	3 (13)	0	5 (21)
QTc interval prolonged	2 (8)	2 (8)	1 (4)	5 (21)
Dry mouth	3 (13)	1 (4)	0	4 (17)
Abdominal pain	3 (13)	0	0	3 (13)
Alanine aminotransferase increase	2 (8)	0	1 (4)	3 (13)
Alopecia	3 (13)	0	0	3 (13)
Aspartate aminotransferase increase	2 (8)	0	1 (4)	3 (13)
Gamma-glutamyltransferase increase	1 (4)	2 (8)	0	3 (13)

*Adverse events graded using the Common Terminology for Adverse Events Version 3.0. Terms are the Preferred Term/MedDRA 10.0.

^bRash includes acne, dermatitis acneiform, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular.

Expanded MTD cohort

- Enrollment is ongoing; DCE-MRI evaluation of the effects of XL647 on tumor vascular permeability will be performed in a subset of patients in this cohort.

Tumor Response

- As of 15 October 2007, 11 of 21* evaluable patients achieved prolonged stable disease (> 3 months), 4 of whom are currently on study and 7 of whom developed progressive disease (Table 4).

Table 4. Response to Treatment

Dose (mg)	Primary diagnosis	Best response ^a	Time on study (days)
75	Desmoplastic squamous cell	SD	198
75	Colon adenocarcinoma	SD	126
150	Synovial cell sarcoma	SD	197
150	Adenoid cystic carcinoma	SD	125
150	Thymoma	SD	122
200	Squamous cell carcinoma of the esophagus	SD	137
300	Ovarian carcinoma	SD	287 ^b
300	Liposarcoma	SD	280 ^b
300	Angio-sarcoma	SD	245 ^b
300	GIST	SD	92 ^b
200/300 ^c	Adenocystic carcinoma	SD	306

^aPatients had to display stable disease (SD) for > 3 months; ^bCurrently on study; ^cPatient started at 200 mg/day and was escalated to 300 mg/day when MTD was reached. *5 patients did not have assessments: 2 are too early; 1 withdrew consent after receiving 5 days of study drug; 2 were withdrawn due to adverse events

Pharmacokinetics

- A high interpatient variability in exposure was observed.
- Exposure (AUC) increased approximately in proportion to the dose.
- Based on the median value for all patients, XL647 accumulated approximately 3.8-fold in plasma with repeated daily dosing.
- Apparent steady-state plasma concentrations were reached by approximately Day 15 for most cohorts.
- Average exposure was calculated at the MTD in two Phase I studies examining different dosing schedules: once-daily, repeated every 28-days (300 mg/day) and the Intermittent 5 days on followed by 9 days off (Intermittent 5 & 9), repeated every 14 days (approximately 350 mg/day). At the MTD, the estimated average concentration (Cavg) over 28 days for once-daily dosing was 399 ng/mL (the estimated mean AUC at steady state [hr·ng/mL] divided by 24 [hr]). This value was approximately 2-fold higher than the 28-day average concentration determined for the Intermittent 5 & 9 regimen (199 ng/mL, which was calculated as the Day 1 AUC₀₋₂₄ [hr·ng/mL] $\times 10 / (28 \times 24)$ [hr]).

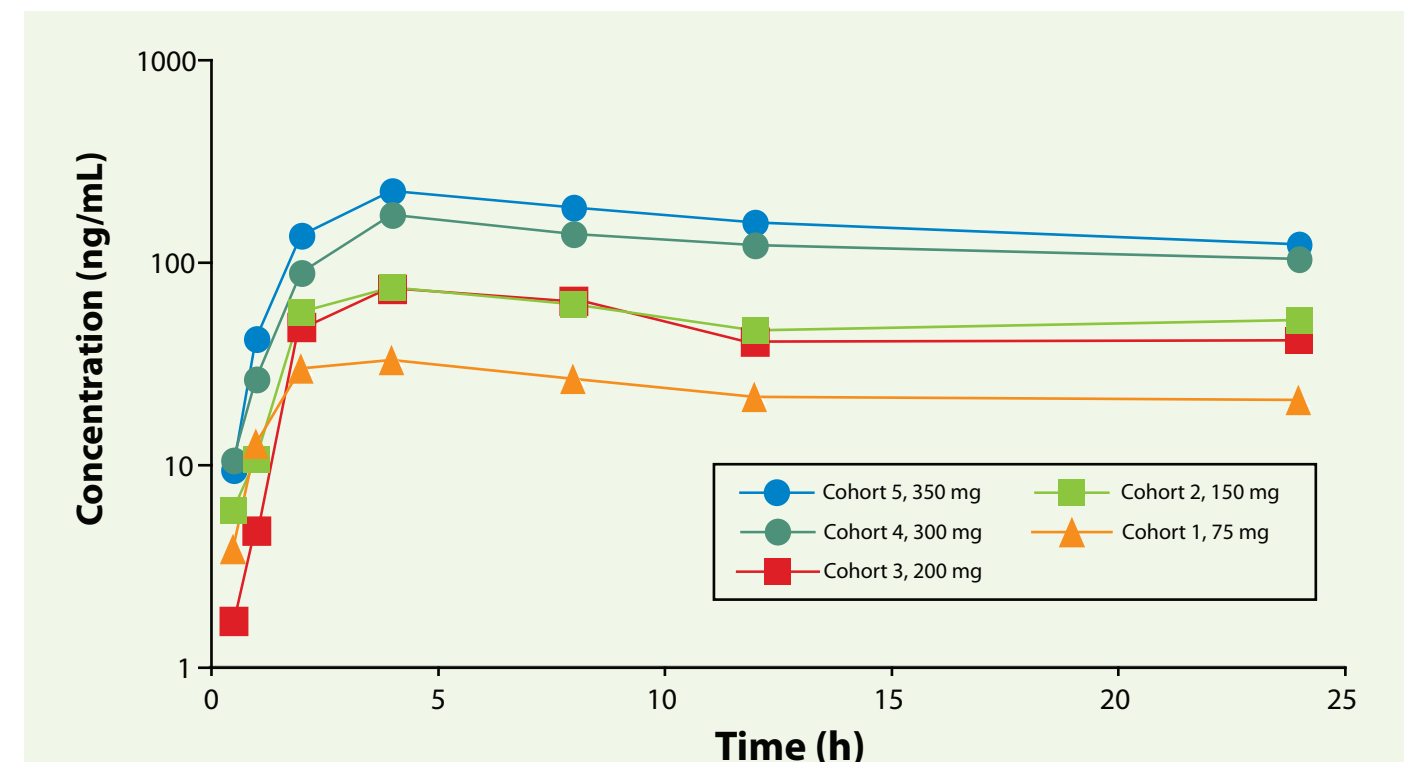


Figure 3. Cohort mean pre-dose plasma concentrations of XL647 on Day 1.

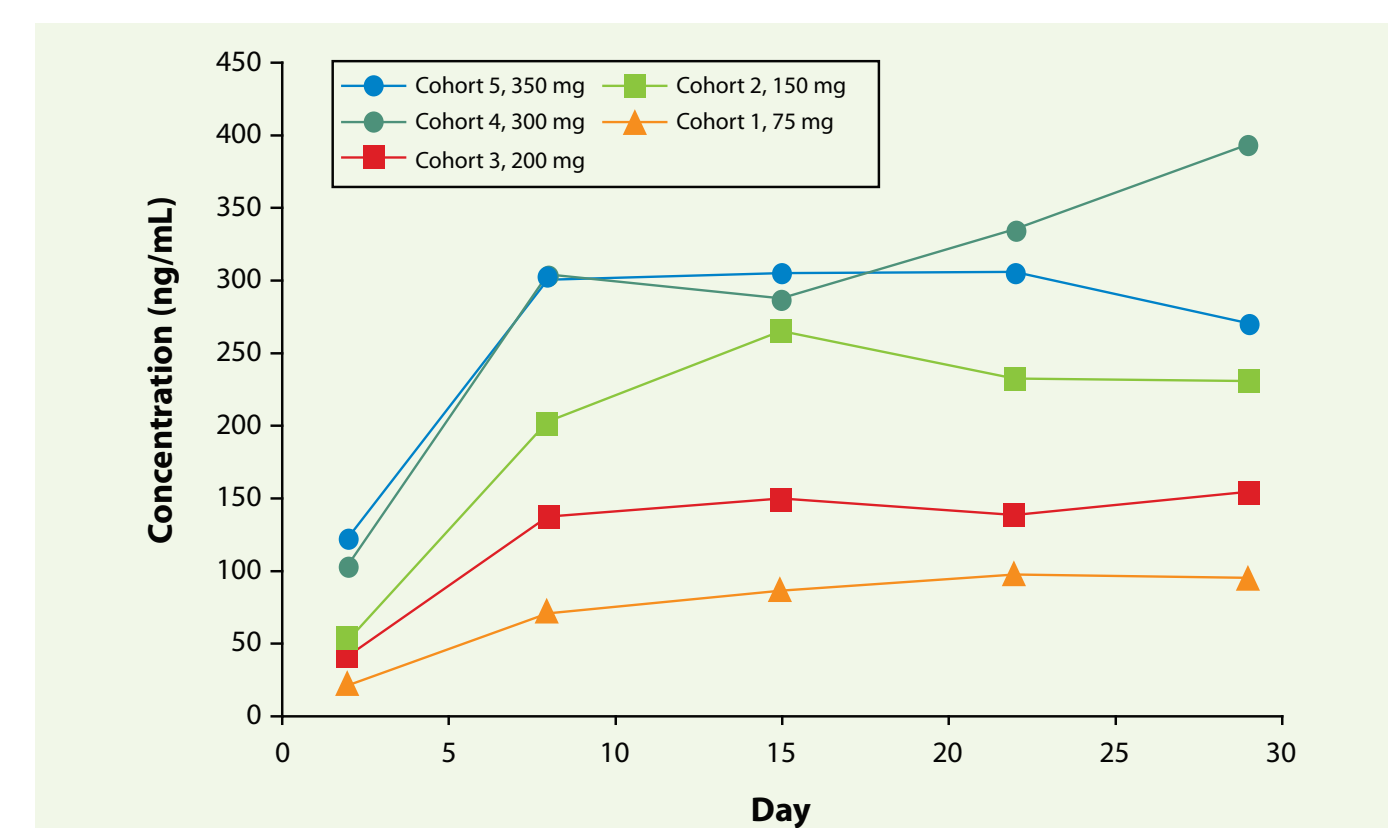


Figure 4. Cohort mean pre-dose (trough) plasma concentrations of XL647 over Cycle 1.

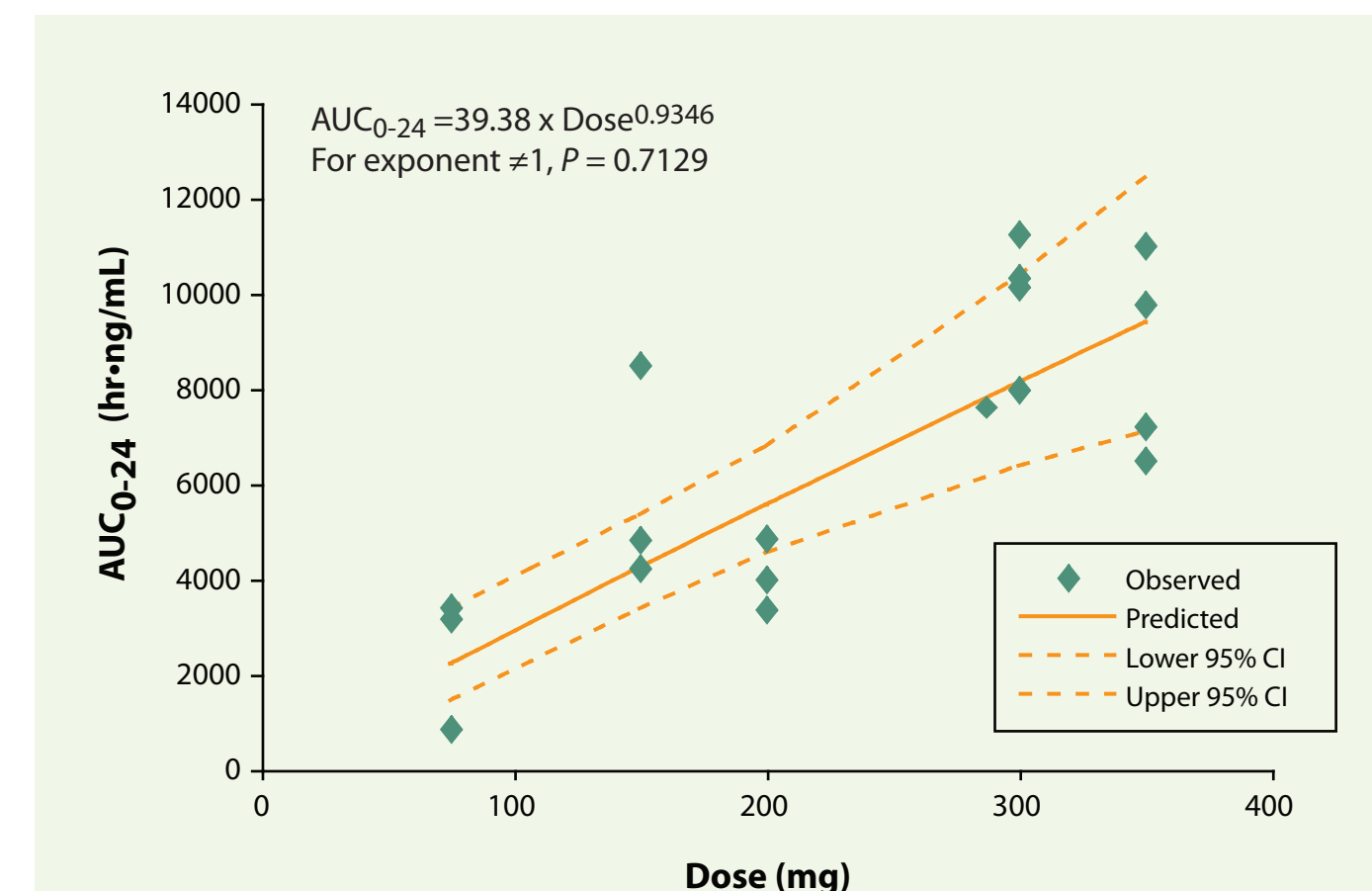


Figure 5. Estimated plasma XL647 AUC at steady state versus administered daily dose.

Pharmacodynamic Analyses

Drug-Induced Pharmacodynamic Changes in the EGFR Signal Pathway in a Surrogate Tissue (Eyebrow Follicles)

- Phosphorylated ERK and AKT were examined in eyebrow follicles by immunofluorescence (3 patients in cohort 2, 2 patients in cohort 3).
- In cohort 2 a pharmacodynamic response was detected over the course of the treatment with XL647:
 - Levels of phospho-ERK were decreased (up to 77%) in all 3 patient eyebrow samples.
 - Levels of phospho-AKT were decreased (up to 71%) in 2 of 3 patient eyebrow samples.
- In cohort 3, inhibition of phospho-AKT and phospho-EGFR were detected in 1 of 2 patients at 4 hours post-dose.

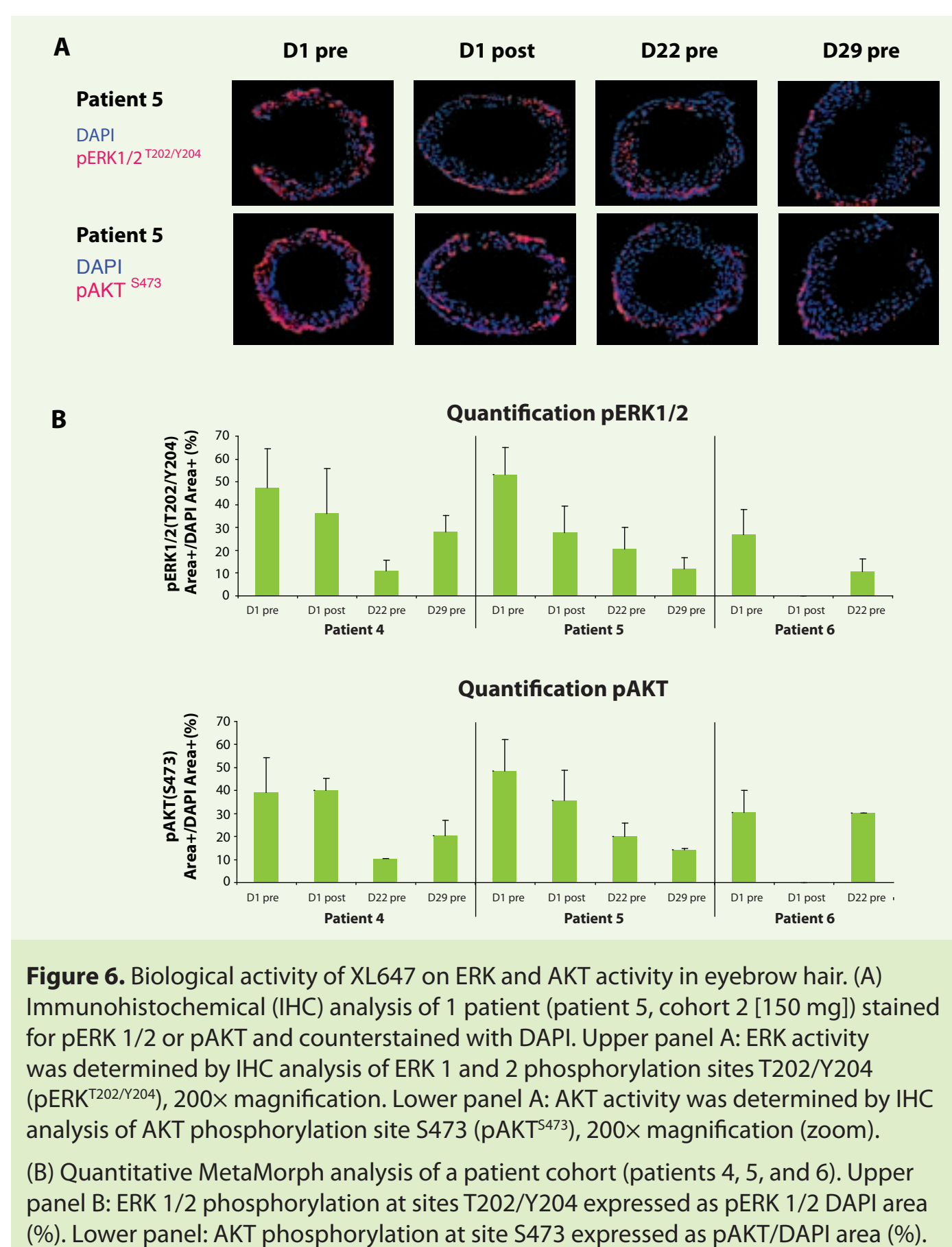


Figure 6. Biological activity of XL647 on ERK and AKT activity in eyebrow hair. (A) Immunohistochemical (IHC) analysis of 1 patient (patient 5, cohort 2 [150 mg]) stained for pERK 1/2 or pAKT and counterstained with DAPI. Upper panel A: ERK activity determined by IHC analysis of ERK 1 and 2 phosphorylation sites T202/Y204 (pERK^{T202/Y204}), 200x magnification. Lower panel A: AKT activity was determined by IHC analysis of AKT phosphorylation site S473 (pAKT^{S473}), 200x magnification (zoom). (B) Quantitative MetaMorph analysis of a patient cohort (patients 4, 5, and 6). Upper panel B: ERK 1/2 phosphorylation at sites T202/Y204 expressed as pERK 1/2 DAPI area (%). Lower panel B: AKT phosphorylation at site S473 expressed as pAKT/DAPI area (%).

CONCLUSIONS

- XL647 was generally well tolerated at doses up to 300 mg when administered orally daily over a 28-day cycle.
- The MTD has been determined to be 300 mg administered once daily.
- Exposure to XL647 increased approximately in proportion to dose.
- XL647 accumulated in plasma with repeated daily dosing, with steady state reached by approximately Day 15 for most cohorts.
- Once-daily administration of 300 mg XL647 is predicted to yield an approximately 2-fold increase in average exposure over a 28-day cycle versus intermittent 5 & 9 dosing with 350 mg and both regimens are generally well tolerated.
- Modulation of the phosphorylation levels of EGFR signaling intermediates was observed in eyebrow hair follicles upon XL647 treatment.

FUTURE STUDIES

Phase II studies are ongoing in non-small cell lung cancer and additional tumor types.

References

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