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A Phase 1 Safety and Pharmacokinetic (PK) Study of the PI3K Inhibitor XL147 (SAR245408) in Combination with Paclitaxel (P) and Carboplatin (C) in Patients with Advanced Solid Tumors

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INTRODUCTION

- 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 cytotoxic agents, including paclitaxel and carboplatin (Figure 1).
- XL147 is a potent, orally bioavailable inhibitor of the Class I PI3K family of lipid kinases, with IC_{50} values in the nanomolar range in biochemical assays.
- XL147 inhibits phosphorylation of downstream effectors of PI3K in preclinical models and in surrogate tissues and tumors in an ongoing single-agent Phase 1 study (Shapiro et al. 2009).
- In preclinical xenograft models, XL147 potentiates the antitumor efficacy of paclitaxel and carboplatin without exacerbating toxicity.
- Based on these preclinical and clinical data, a study combining XL147 with paclitaxel and carboplatin was initiated in patients with advanced solid tumors.

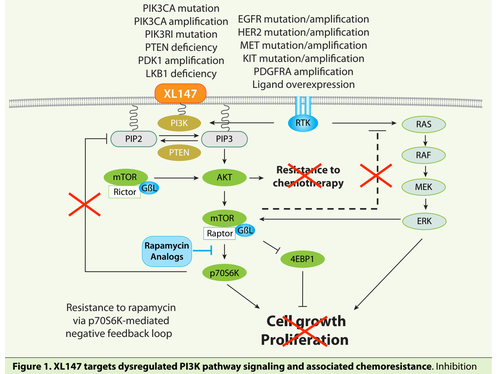

Figure 1. XL147 targets dysregulated PI3K pathway signaling and associated chemoresistance. Inhibition of PI3K precludes pAKT and pERK induction associated with specific mTOR/Raptor (TORC1) inhibition (Shapiro et al. 2009).

OBJECTIVES

Primary

- Evaluation of safety and maximum tolerated dose (MTD) of XL147 administered in combination with paclitaxel and carboplatin in patients with advanced solid tumors
  - Part A: Standard "3+3" escalation design in various solid tumors: Paclitaxel will be dose-escalated up to 175 mg·m^{-2} and carboplatin up to AUC 6. MTD-A expansion in six patients with endometrial and six patients with ovarian cancer (Figure 2).
  - Part B: Standard "3+3" escalation design in non-small cell lung cancer (NSCLC): XL147 starting dose will be 75% of the XL147 MTD-A dose. Paclitaxel will be dose-escalated up to 225 mg·m^{-2} and carboplatin remains at AUC 6. MTD-B expansion in six patients with NSCLC (Figure 2).

Secondary

- Investigation of the relationship between selected biomarkers and efficacy and safety outcomes
- Assessment of plasma pharmacokinetics (PK) of XL147, paclitaxel, and carboplatin when given in combination
- Evaluation of the preliminary antitumor activity of XL147 in combination with carboplatin and paclitaxel

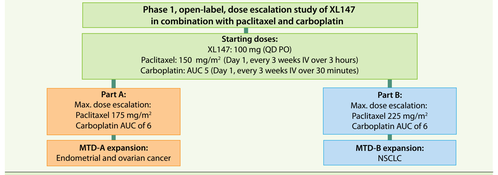

Figure 2. Study design and treatment schedule.

METHODS

Key Eligibility Criteria

- Patients (≥ 18 years old) with histologically confirmed metastatic or unresectable solid tumor for which known effective measures do not exist or are no longer effective
- ECOG performance status ≤ 1
- Fasting plasma glucose < 120 mg/dL
- No prior treatment with a PI3K inhibitor
- No cytotoxic chemotherapy or biological agents within 4 weeks (nitrosoureas or mitomycin C within 6 weeks)
- No small-molecule kinase inhibitors within 14 days (or 5 half-lives of the drug or active metabolites, whichever is longer)

Assessments

- Tumor assessments at baseline and every 6 weeks thereafter
- PK sampling: Full profile in Cycle 1 and on Cycle 2 Day 1; limited sampling in Cycle 3+
- Pharmacodynamic assessments
  - Plasma
  - Optional tumor, hair, buccal mucosa, and skin
  - Mandatory tumor biopsies for Expanded MTD Cohorts

RESULTS

- This is an analysis of preliminary data from an ongoing study.
- Sixteen patients have been enrolled as of 22 Oct 2009.
- Baseline characteristics and treatment status are shown in Tables 1 and 2.
- Safety and response data are available for 15 patients and are shown in Tables 3 and 4.

Table 1. Baseline Characteristics

Characteristic	Patients (n = 16)
Median age (range), years	51 (25–81)
Sex (male/female)	4/12
Race	
Black	1
Asian	3
White	12
Tumor type	
Breast cancer	5
Cervical cancer	2
Other tumor types[a]	9
ECOG status	
0	4
1	12
Received prior radiation	11
Received prior taxane/prior platinum therapy	10/12
Median number of prior chemotherapy regimens (range)	4 (1-10)

ECOG, Eastern Cooperative Oncology Group.
[a]One case each of vulvar, tonsillar (squamous cell carcinoma [SCC]), parotid, primary peritoneal, colorectal, esophageal (adenocarcinoma), melanoma (clear cell carcinoma), endometrial and tongue (SCC) cancer.

Table 2. Summary of Study Status

Status	Patients (n = 16)
On treatment	4
Off treatment	12
Reason for discontinuation	
Progressive disease	11
Patient request	1

Cohort (No. of Patients)	XL147/C/P (mg/AUC/mg·m^{-2})	Time on Study (Weeks)	Active Patients, n
1 (n = 3)	100/5/150	5–20	0
2 (n = 3)	150/5/150	6–40	0
3 (n = 3)	200/5/150	7–24	0
4 (n = 3)	200/6/175	15–33+	1
5 (n = 3)	400/6/175	11–24+	2
6 (n = 1)	600/6/175	3+	1

Safety

- The MTD has not been established.
- There have been no dose-limiting toxicities (DLTs).
- The most common treatment-related hematologic adverse events (AEs) were neutropenia, anemia, and thrombocytopenia.
- The most common treatment-related non-hematologic AEs were fatigue and nausea.
- One patient experienced a serious AE that was considered related to study treatment: Grade 4 thrombocytopenia that occurred approximately 3 months after starting study treatment. The event resolved; study treatment was re-introduced without recurrence.
- Five patients had a dose reduction of carboplatin and/or paclitaxel; no dose reductions of XL147 were reported.

Table 3. Summary of Treatment Related Adverse Events for ≥ 20% of Patients [number of patients (%), n= 15]

Adverse Events[a]	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Hematologic					
Neutropenia	—	1 (7)	3 (20)	4 (27)	8 (53)
Anemia	2 (13)	3 (20)	2 (13)	—	7 (47)
Thrombocytopenia	—	3 (20)	2 (13)	2 (13)	7 (47)
Non-Hematologic					
Fatigue	4 (27)	4 (27)	—	—	8 (53)
Nausea	5 (33)	—	—	—	5 (33)
Diarrhea	4 (27)	—	—	—	4 (27)
Neuropathy Peripheral	3 (20)	1 (7)	—	—	4 (27)
Rash	—	4 (27)	—	—	4 (27)
Alopecia	3 (20)	—	—	—	3 (20)
Anorexia	2 (13)	1 (7)	—	—	3 (20)
Vomiting	2 (13)	—	—	1 (7)	3 (20)

[a]Adverse events graded using the Common Terminology for Adverse Events Version 3.0; terms are the Preferred Term/MedDRA 10.0.
[b]One additional Grade 3 and two additional Grade 4 adverse events termed "neutrophil count decreased" were reported.

Antitumor Activity

- As of 22 Oct 2009, 15 patients were evaluable for tumor response assessment.
- Four patients had a confirmed partial response:
  - One patient with tonsillar cancer (SCC) achieved a 63% decrease of target lesions after Cycle 6.
  - One patient with cervical cancer (adenocarcinoma) achieved a 42% decrease of target lesions after Cycle 4.
  - One patient with esophageal cancer (SCC) achieved a 45% decrease of target lesions after Cycle 2.
  - One patient with tongue cancer (SCC) achieved a 72% decrease of target lesions after Cycle 3 (Figure 4).
- One patient with triple-negative, inflammatory breast cancer (mutant p53 and LKB-1) experienced regression of cutaneous lesions after Cycle 2.
- Twelve of the 15 evaluable patients continued on study ≥12 weeks, with four patients remaining on study ≥ 24 weeks.

Table 4. Antitumor Activity

Tumor Type	Best Response[a]	XL147/C/P (mg/AUC/mg·m^{-2})	Time on Study (Weeks)	Most Recent Therapy (Weeks on Prior Therapy)	Prior Taxane or Platinum Therapy	Molecular Alteration Status[b]
Breast cancer	SD	100/5/150	20	Dasatinib/ Gemcitabine (8)	Yes/No	NA
Breast cancer	SD[c]	100/5/150	21	Paclitaxel (24)	Yes/Yes	LKB1 mut, TP53 mut
Tonsillar	cPR (63% ↓)	150/5/150	40[d]	Bevacizumab/ Cetuximab (11)	No/Yes	NA
Parotid	SD	200/5/150	24[e]	Docetaxel (15)	Yes/Yes	NA
Peritoneal	SD	200/5/150	20	Bevacizumab/ Temsirolimus (22)	Yes/Yes	NA
Cervical	cPR (42% ↓)	200/6/175	33+	Cisplatin (4)	No/Yes	PIK3CA polymorph
Esophageal	cPR (45% ↓)	200/6/175	20	Bevacizumab (3)	Yes/Yes	PIK3CA mut
Melanoma	SD	400/6/175	24+	Interleukin-2 (4)	No/No	EGFR amp; TP53 polymorph
Tongue	cPR (72% ↓)	400/6/175	15+	Investigational (8)	No/Yes	NA

cPR, confirmed partial response; SD, stable disease; mut, mutation; polymorph, polymorphism; amp, amplification by qPCR; NA, not available.
[a]Patients with SD for ≥ 16 weeks.
[b]Genes analyzed included PIK3CA, PTEN, KRAS, EGFR, TP53, except for cervical cancer patient
[c]Regression of cutaneous lesions observed after 2 cycles
[d]Carboplatin and paclitaxel discontinued as of CSD1.
[e]Carboplatin and paclitaxel discontinued as of CSD1.

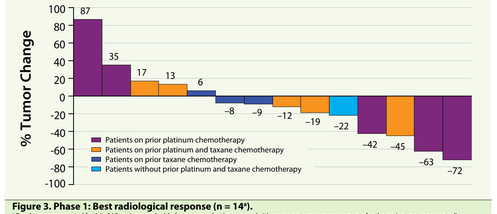

Figure 3. Phase 1: Best radiological response (n = 14[a]).
[a] Results are represented for 14 of 15 patients evaluable for response by time on study (there are no tumor measurements for the patient not represented).

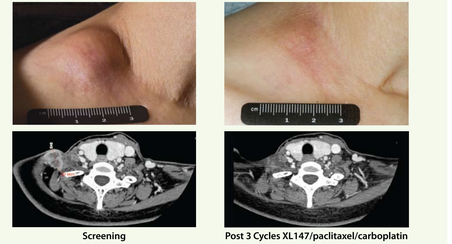

Figure 4. Right neck lymph node metastasis of a 44-year-old female with SCC of the tongue (PTEN deficiency by immunohistochemistry). Patient had previously been treated with chemoradiation (XRT, 5-FU, cetuximab, cisplatin) and an investigational mTOR inhibitor. (A) A decrease in size was evident after three cycles of once-daily dosing with 400 mg XL147 in combination with paclitaxel 175 mg/m^2 and carboplatin AUC 6 (I.V. Day 1 of each cycle). (B) Sequential CT scans showing subdermal granulation tissue or scarring tissue in the right supraclavicular fossa but no compelling evidence for tumor post-XL147/paclitaxel/carboplatin treatment.

Pharmacokinetics

- XL147 apparent clearance (CL/F) values when given in combination with paclitaxel and carboplatin are consistent with values from a single agent study (30-400 mg dose).
  - Paclitaxel or carboplatin does not have a major impact on XL147 PK.

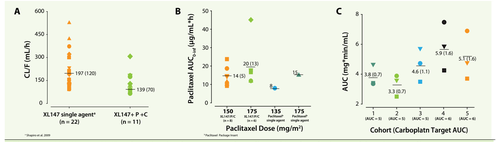

Figure 5. (A) XL147 CL/F values in single agent and paclitaxel/carboplatin combination studies. (B) Paclitaxel AUC in XL147/P/C combination versus published data for paclitaxel alone. (C) Observed free carboplatin AUC versus target AUC in XL147/P/C combination study.

- Paclitaxel AUC when given in combination with XL147 and carboplatin is consistent with published single-agent paclitaxel AUC values.
  - XL147 does not have a major impact on paclitaxel PK.
- Observed free carboplatin AUC values are in the range of target AUC values.
  - No major impact of XL147 or paclitaxel on carboplatin PK.

Pharmacodynamics

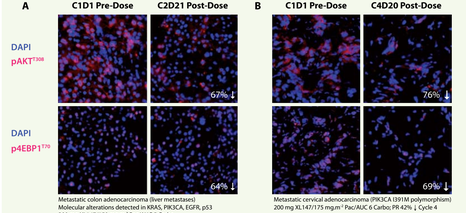

Figure 6. Administration of the combination of XL147 with paclitaxel and carboplatin inhibits PI3K and ERK/MAPK pathway signaling in paired tumor biopsies from patients with colon adenocarcinoma (A) and cervical adenocarcinoma (B). Cryopreserved tumor biopsy samples were serially sectioned at 10 microns. Twenty serial sections were obtained from each sample. Following immunostaining, up to 12 non-overlapping representative fields were captured at 400× magnification and quantified. (A) Post-dose changes also evident in pERK (73% ↓), Ki67 (32% ↓), and TUNEL (2.4-fold ↑). (B) Post-dose changes also evident in pERK (70% ↓), Ki67 (33% ↓), and TUNEL (2.3-fold↑). Decrease in pERK consistent with XL147 single agent study (Shapiro et al. 2009).

CONCLUSIONS

- XL147 at doses up to 400 mg in combination with paclitaxel/carboplatin is generally well tolerated.
- The MTD has not yet been established.
- No major PK interaction
- Inhibition of PI3K pathway signaling was evident in matched tumor biopsies, consistent with that observed in diverse tumors in an ongoing single-agent Phase 1 trial of XL147 (Shapiro et al. 2009).
- Four patients have experienced a confirmed PR.
  - All PRs occurred in patients who had been previously treated with a platinum-containing regimen.
- Twelve patients continued on study ≥12 weeks, with four patients remaining on study ≥ 24 weeks.

Reference
Shapiro et al. ASCO Annual Meeting 2009
http://www.exelixis.com/downloads/XL147-001_ASCO-2009.pdf

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics: Discovery, Biology, and Clinical Applications, November 15-19, 2009, Boston, MA

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