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Clinical Trial Results

Phase I Dose-Escalation Study of Pilaralisib (SAR245408, XL147), a Pan-Class I PI3K Inhibitor, in Combination With Erlotinib in Patients With Solid Tumors

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Author Summary

Abstract

Background. This phase I study evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics of pilaralisib (SAR245408), an oral pan-class I phosphoinositide 3-kinase (PI3K) inhibitor, in combination with erlotinib, an epidermal growth factor receptor (EGFR) inhibitor.

Methods. In a 3 + 3 dose-escalation study, patients with advanced solid tumors received pilaralisib capsules once daily (21 days per 28-day cycle; 50–600 mg) plus erlotinib tablets once daily (28 days per 28-day cycle; 100 or 150 mg). An MTD expansion cohort of patients with non-small cell lung cancer who had previously received treatment with an EGFR inhibitor was included.

Results. Thirty-five patients were enrolled. Only one patient had an *EGFR* activating mutation. One dose-limiting toxicity was reported (grade 4 drug reaction or rash with eosinophilia and systemic symptoms). MTD was pilaralisib 400 mg plus erlotinib 150 mg. The most commonly reported treatment-related adverse events were rash (62.9%), diarrhea (42.9%), and fatigue (40.0%). Pilaralisib PK findings were consistent with previous studies, suggesting erlotinib had no effect on pilaralisib pharmacokinetics. Pharmacodynamic analyses indicated moderate inhibition of PI3K, mitogen-activated protein kinase, and EGFR pathways. Of 27 evaluable patients, one had a partial response (3.7%) and 14 (51.9%) had stable disease. There was no association between molecular alterations of PI3K pathway components and clinical activity.

Conclusion. Pilaralisib plus erlotinib had limited antitumor activity. Safety findings were similar to recent studies of single-agent pilaralisib or other PI3K inhibitors. ***The Oncologist*** 2015; 20:245–246

Discussion

In non-small cell lung cancer (NSCLC), resistance to EGFR inhibitors occurs through several mechanisms, including activation of parallel or downstream pathways, such as the PI3K and mammalian target of rapamycin (mTOR) pathway [1, 2]. In vitro studies suggest that PI3K pathway inhibition can overcome resistance to EGFR inhibition [3, 4]; therefore, combining PI3K and EGFR inhibitors is a rational therapeutic strategy.

Pilaralisib is a highly selective, reversible, pan-class I PI3K inhibitor. In a phase I dose-escalation study in patients with solid tumors, pilaralisib showed clinical activity, and the MTD was established as 600 mg once daily [5].

The current phase I dose-escalation study (ClinicalTrials.gov identifier NCT00692640) evaluated MTD, safety, PK, pharmacodynamics, and efficacy of pilaralisib in combination with the EGFR inhibitor erlotinib in patients with advanced solid tumors, including patients with NSCLC who had previously received an EGFR inhibitor.

Thirty-five patients were enrolled; 57% had NSCLC. There was one dose-limiting toxicity: grade 4 DRESS syndrome (drug reaction or rash with eosinophilia and systemic symptoms)

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Table 1. Treatment-related AEs occurring in ≥20% of patients and all treatment-related grade 3/4 AEs in patients treated with pilaralisib and erlotinib once daily

	Pilaralisib dose + erlotinib dose, *n* (%)								
AE	**50 mg + 100 mg, *n* = 3**	**50 mg + 150 mg, *n* = 3**	**75 mg + 150 mg, *n* = 3**	**100 mg + 150 mg, *n* = 3**	**200 mg + 150 mg, *n* = 3**	**NSCLC: 400 mg + 150 mg, *n* = 10**	**Non-NSCLC: 400 mg + 150 mg, *n* = 7**	**600 mg + 150 mg, *n* = 3**	**Total, *N* = 35**
Any grade	3 (100)	3 (100)	2 (66.7)	3 (100)	3 (100)	10 (100)	6 (85.7)	3 (100)	33 (94.3)
Rash	2 (66.7)	2 (66.7)	1 (33.3)	3 (100)	3 (100)	3 (30.0)	5 (71.4)	3 (100)	22 (62.9)
Diarrhea	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	4 (40.0)	3 (42.9)	2 (66.7)	15 (42.9)
Fatigue	2 (66.7)	2 (66.7)	0	1 (33.3)	1 (33.3)	5 (50.0)	2 (28.6)	1 (33.3)	14 (40.0)
Nausea	0	2 (66.7)	2 (66.7)	3 (100)	1 (33.3)	2 (20.0)	2 (28.6)	0	12 (34.3)
Vomiting	1 (33.3)	0	1 (33.3)	2 (66.7)	1 (33.3)	4 (40.0)	2 (28.6)	1 (33.3)	12 (34.3)
Decreased appetite	1 (33.3)	0	2 (66.7)	0	0	5 (50.0)	1 (14.3)	0	9 (25.7)
Asthenia	0	0	0	1 (33.3)	0	4 (40.0)	2 (28.6)	1 (33.3)	8 (22.9)
Folliculitis	0	0	0	0	0	5 (50.0)	2 (28.6)	0	7 (20.0)
Grade 3/4	0	0	0	0	1 (33.3)	0	2 (28.6)	1 (33.3)	4 (11.4)
Diarrhea	0	0	0	0	1 (33.3)	0	0	0	1 (2.9)
Blood amylase increased	0	0	0	0	0	0	1 (14.3)	0	1 (2.9)
DRESS syndrome	0	0	0	0	0	0	0	1 (33.3)	1 (2.9)
Intracardiac thrombus	0	0	0	0	0	0	1 (14.3)	0	1 (2.9)

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.
Abbreviations: AE, adverse event; DRESS syndrome, drug reaction or rash with eosinophilia and systemic symptoms.

(Table 1). The MTD was determined to be pilaralisib 400 mg in combination with erlotinib 150 mg. Safety findings were similar to recent studies of single-agent pilaralisib or other PI3K inhibitors [5–9].

Day 21 PK parameters were consistent with previous findings for pilaralisib monotherapy at steady state [5] (Table 2), suggesting that erlotinib does not interact with pilaralisib pharmacokinetically. Exposure on day 21 increased in a less than dose-proportional manner; geometric mean maximum concentration and area under the concentration-time curve increased over the 12-fold dose range of pilaralisib (50–600 mg) by 6.91- and 7.91-fold, respectively.

Pharmacodynamic analyses in tumor and skin samples indicated moderate inhibition (61%–67% and 31%–66%, respectively) of PI3K, mitogen-activated protein kinase, and EGFR pathways. *PIK3CA* amplification or mutation was detected in three patients, phosphatase and tensin homolog protein deficiency was detected in three patients, and an *EGFR* activating mutation was detected in one patient.

In 27 evaluable patients, the best response was a partial response in one patient (3.7%) and stable disease in 14 patients (51.9%). Thirteen patients had progression-free survival for ≥90 days. The limited efficacy was consistent with the modest pharmacodynamic activity observed and with recent studies combining PI3K/mTOR pathway inhibitors and EGFR inhibitors [9, 10]. The combination of pilaralisib and erlotinib is no longer being investigated in solid tumors.

Author disclosures and references available online.