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Original Research

An open-label study to determine the maximum tolerated dose of oral ESK-440 administered as a single agent in patients with advanced or metastatic solid tumors

Russell J. Schilder [a], Drew Rasco [b], Manish R. Sharma [c,d,*]

[a] Gynecologic Medical Oncology, Early Drug Development Unit, Sidney Kimmel Cancer Center, Thomas Jefferson University, 233 S 10th St, Philadelphia, PA, USA
[b] START Center for Cancer Research, 4383 Medical Dr # 3046, San Antonio, TX, USA
[c] Affiliation at time of study: University of Chicago, Chicago, IL, USA
[d] START Center for Cancer Research - Midwest (START Midwest), 5800 Foremost Dr SE Suite 100, Grand Rapids, MI, USA

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ABSTRACT

Purpose: Anaplastic lymphoma kinase (ALK) dysregulation is implicated in numerous cancers. Tyrosine kinase inhibitors (TKIs) targeting ALK have improved disease outcomes, but resistance mechanisms are common. This first-in-human trial evaluates ESK-440, a dual inhibitor of ALK and focal adhesion kinase, as a novel strategy for cancers with resistance to ALK-targeting TKIs.

Methods: This phase 1, open-label, dose-finding study evaluated the maximum tolerated dose (MTD), safety, efficacy, and pharmacokinetics of ESK-440 in participants with advanced or metastatic solid tumors (ClinicalTrials.gov: NCT01922752). A 3 + 3 dose-escalation design, with daily doses ranging from 25 to 700 mg/day of ESK-440 for each 28-day treatment cycle (6 to 8 cycles) was utilized to identify the MTD. A phase 1b was planned to further evaluate ESK-440 safety and antitumor activity at the MTD but was not performed due to sponsor decision.

Results: 32 participants were enrolled and 24 (75 %) completed cycle 1 of treatment. Three dose-limiting toxicities, all grade 3 nausea, were reported ($n = 1$, 500 mg; $n = 2$, 700 mg). The MTD was determined to be 500 mg daily. The most frequent adverse events (AEs) were fatigue and nausea (53 % each) and vomiting (38 %). Seven participants (22 %) withdrew from treatment due to AEs and 4 deaths occurred, none related to ESK-440. No participant had a complete or partial response; the best overall response was stable disease in 7 participants.

Conclusions: **ESK-440 was safe and tolerable with a maximum tolerated dose of 500 mg daily**; however, the study was terminated early based on sponsor decision.

Introduction

Anaplastic lymphoma kinase (ALK) is a highly conserved receptor tyrosine kinase that has been implicated in several human cancers [1]. ALK can undergo oncogenic translocation, fuse with different protein partners, and become constitutively active driving various malignancies [2]. When fused with echinoderm microtubule-associated protein-like 4 (EML4-ALK), the fusion gene is responsible for about 5 % of non–small cell lung cancer (NSCLC) [3]. Additionally, mutations and rearrangements of ALK are implicated in anaplastic large cell lymphomas (ALCLs) and neuroblastomas [1].

Current treatments for ALK-driven cancers involve the use of tyrosine kinase inhibitors (TKIs) to target ALK, which have improved overall survival rates for patients with ALK-driven cancers [4,5]. However, resistance to these therapies develop in most patients, limiting the clinical benefit of current generation TKIs to combat these diseases [4, 6–8]. Tumor resistance is developed through multiple mechanisms, including drug-induced activating mutations, gene amplification,

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; $AUC_{0\text{-}24}$, area under the plasma curve from time zero to the 24-h time point; $AUC_{0\text{-}t}$, area under the plasma curve from time zero to the time of the last measurable concentration; $AUC_{0\text{-}\infty}$, area under the plasma curve from time zero to infinity; C_{max}, the maximum plasma concentration; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FAK, focal adhesion kinase; MTD, maximum tolerated dose; PK, pharmacokinetics; SAE, serious adverse event; $t_{1/2}$, the terminal elimination half-life; TKI, tyrosine kinase inhibitor; T_{max}, the time to achieve C_{max}.

* Corresponding author at: Co-Director of Clinical Research, START Midwest, 5800 Foremost Drive SE, Suite 100, Grand Rapids, MI 49546, USA.
E-mail addresses: russell.schilder@jefferson.edu (R.J. Schilder), drew.rasco@startresearch.com (D. Rasco), manish.sharma@startresearch.com (M.R. Sharma).

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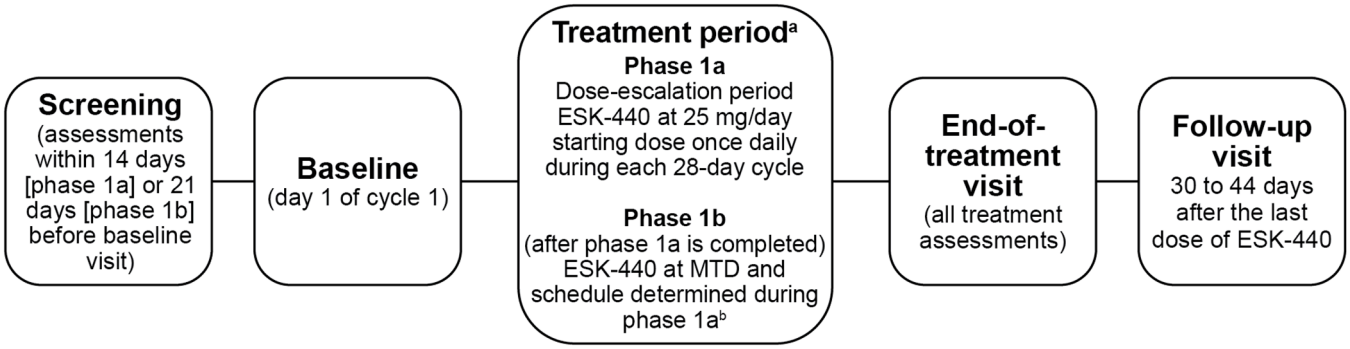

Fig. 1. Study Design.
MTD, maximum tolerated dose.
[a]Patients were treated in 28-day treatment cycles for 6 to 8 cycles.
[b]Phase 1b was not conducted.

and/or induced resistance or alternate signaling pathways [7–9]. Therefore, new strategies are needed to improve treatment outcomes in patients with ALK-driven malignancy, including methods to overcome drug resistance or therapies targeting additional pathways involved in tumor development and growth.

Focal adhesion kinase (FAK) is a signaling molecule that helps regulate cell adhesion, migration, and survival [10]. Focal adhesion kinase is activated or expressed in a variety of solid tumors, including breast, ovarian, NSCLC, prostate, and head and neck squamous cancer, and is often observed in metastatic tumors [9]. Focal adhesion kinase activation facilitates cell survival, migration, invasion, and angiogenesis, all critical steps in metastatic progression [9,11].

ESK-440 (previously CEP-37440) is a novel, selective, and potent dual inhibitor of ALK and FAK. In preclinical studies, ESK-440 showed low nanomolar potencies for both kinases, dose-dependent antitumor efficacy in multiple ALK- and FAK-driven xenograft models, and activity against clinically relevant resistance mutations [9,10]. Additionally, ESK-440 displayed favorable *in vivo* pharmacokinetics and acceptable oral bioavailability in all tested species, prompting further study in human clinical trials [9]. This phase 1 study is a first-in-human dose escalation trial to assess the safety, efficacy, and pharmacokinetics (PK) of ESK-440.

Materials and methods

Study design

This was an open-label, first-in-human, dose-finding study of daily oral ESK-440 in participants with advanced or metastatic solid tumors (Fig. 1). In phase 1a, a 3 + 3 dose-escalation design was utilized to determine the maximum tolerated dose (MTD) of ESK-440 and to evaluate safety and tolerability, PK, and preliminary efficacy. Phase 1b was planned to further assess the safety and antitumor activity of ESK-440 in an expanded population at the MTD determined in phase 1a. Although there were no safety concerns during phase 1a, phase 1b was not conducted based on sponsor decision. This manuscript will present the results of phase 1a.

The study was approved by the ethics committee at every participating institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

Study population

Key inclusion criteria for participation in the study included adults with recurrent, locally advanced, or metastatic disease with histologic or cytologic evidence of a solid neoplasm for which no standard therapy is available, or has progressed despite standard therapy, or was intolerant to standard therapy. Study participants were also required to have an (Eastern Cooperative Oncology Group) ECOG performance score ≤2. Participants with ALK-positive NSCLC were required to have had prior crizotinib in order to be eligible for the study. Key exclusion criteria for the study included an active infection requiring antibiotics; uncontrolled hypertension or diabetes; an active second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers for which a participant was treated with curative intent; primary brain tumor; or prior ALK-inhibitor–related toxicity. The full inclusion/exclusion criteria can be found in the supplemental materials (**Item S1**).

Study treatment and dose escalation

The starting dose for the study corresponds to approximately 1/10th of the highest non-severely toxic dose (HNSTD) in the most sensitive species tested. In rats, the highest dose of ESK-440 administered, 30 mg/kg, corresponded to the HNSTD. The starting dose in humans was determined to be 25 mg/day. Subsequent dose levels up to 700 mg/day were determined using a modified Fibonacci schema, depicted in **Table S1.**

Participants at each dose level were treated with oral ESK-440 daily for a 28-day period, which defines the does-limiting toxicity (DLT) window and is considered 1 cycle of therapy, for 6 to 8 cycles. Participants were not enrolled at a higher dose until the previous cohort was filled. A conventional 3 + 3 design was used when enrolling successive cohorts of 3 to 6 participants during dose escalation (**Table S2**). If a DLT was reported, an additional 2 or 3 participants were added to the cohort at that particular dose level, for a maximum of 6 participants per cohort. The MTD was based on DLT assessment during cycle 1 only and was defined as the highest dose at which fewer than one-third of the participants in a cohort experienced a DLT.

DLTs were defined as any adverse event considered by the investigator as related or potentially related to ESK440 as follows: grade 4 neutropenia lasting 7 days or more; grade 3 or grade 4 neutropenia with fever greater than 38.5°C; grade 3 thrombocytopenia lasting 7 days or more; grade 3 thrombocytopenia with bleeding requiring platelet transfusion; grade 4 thrombocytopenia ($\leq$25000/mm^3); grade 4 anemia; grade 3 transaminitis lasting 1 week or more or any grade 4 transaminitis; grade 4 vomiting or diarrhea; grade 3 nausea, vomiting, or diarrhea that persists for 48 h or more despite optimal medical intervention; QTcF greater than 500 msec; delay of treatment for >2 weeks for any cause; any other grade 3 or 4 nonhematologic adverse events.

The total sample size for the study was estimated to be approximately 30 individuals based on enrolling 3 to 6 participants per dose

Table 1
Disposition of participants.

	Number (%) of participants								
	25 mg/day (n = 3)	50 mg/day (n = 3)	100 mg/day (n = 4)	150 mg/day (n = 3)	250 mg/day (n = 4)	350 mg/day (n = 4)	500 mg/day (n = 6)	700 mg/day (n = 5)	Overall (N = 32)
Enrolled	3 (100)	3 (100)	4 (100)	3 (100)	4 (100)	4 (100)	6 (100)	5 (100)	32 (100)
PK population	3 (100)	3 (100)	3 (75)	3 (100)	4 (100)	4 (100)	5 (83)	5 (100)	30 (94)
Safety population	3 (100)	3 (100)	4 (100)	3 (100)	4 (100)	4 (100)	6 (100)	5 (100)	32 (100)
Completed cycle 1	3 (100)	3 (100)	3 (75)	3 (100)	3 (75)	3 (75)	5 (83)	1 (20)	24 (75)
Reasons for not completing cycle 1									
Death	0	0	1 (25)	0	0	0	0	0	1 (3)
Adverse event	0	0	0	0	0	0	1 (17)	2 (40)	3 (9)
Withdrawal by participant	0	0	0	0	0	0	0	1 (20)	1 (3)
Clinical progression	0	0	0	0	1 (25)	1 (25)	0	1 (20)	3 (9)
Completed study	0	1 (33)	1 (25)	1 (33)	2 (50)	1 (25)	2 (33)	0	8 (25)
Reasons for not completing study									
Death	1 (33)	0	1 (25)	0	1 (25)	0	0	0	3 (9)
Adverse event	0	0	0	0	0	1 (25)	1 (17)	2 (40)	4 (13)
Withdrawal by participant	1 (33)	0	1 (25)	0	1 (25)	0	3 (50)	2 (40)	8 (25)
Lost to follow-up	1 (33)	0	1 (25)	0	0	1 (25)	0	0	3 (9)
Other	0	2 (67)	0	2 (67)	0	1 (25)	0	1 (20)	6 (19)
Death <30 days after study	1 (33)	0	1 (25)	0	1 (25)	0	0	1 (20)	4 (13)

PK, pharmacokinetics.

level tested. There was no intrapatient dose escalation allowed in the study. Participants who discontinued therapy without completing a cycle for a reason other than a DLT were replaced. After cycle 1, the start of a new cycle could occur within a 3-day window or be continuous. After cycle 2, the start of cycle 3 could be delayed by 1 week if determined to be warranted clinically by the investigator.

Participants who, after cycle 1, experienced a DLT during any treatment cycle, were to have their dose reduced one level for the remainder of their participation in the study. Participants were allowed 2 dose reductions before removal from the study.

Study assessments and statistical analyses

The safety population included all participants who received 1 or more doses of ESK-440. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and their severity graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 criteria. Adverse effects (AEs), serious AEs (SAEs), and DLTs were summarized using descriptive statistics by system organ class and preferred term.

Laboratory tests, vital signs, ECG data, ECOG performance status, and physical exams were collected or performed at screening and on days 1, 8, 15, and 22 of cycle 1; on days 1 and 15 of cycle 2; on day 1 of each subsequent cycle; at the end-of-treatment visit; and at the follow-up visit. Postbaseline QTcF measurements were classified according to the following categories: maximum absolute QTc interval prolongation, defined as ≤450, >450 to ≤480, >480 to ≤500, >500 msec, and maximum change from baseline in QTc interval, defined as ≤30, >30 to ≤60, >60 msec.

Efficacy was assessed by the proportion of participants who achieved a tumor response during the study, determined using RECIST v1.1 criteria. A responder was defined as a patient with a best response of complete response or partial response during study. Best observed response was listed, with no statistical analysis.

The PK population included all participants who had at least 1 PK measurement after receiving ESK-440. For PK evaluation, 3 mL blood samples were collected during cycle 1 on day 1 and day 15 at times: 0 (predose) and 0.5, 1, 2, 3, 4, 6, 8, and 24 h after ESK-440 administration. Concentrations of ESK-440 and its principal metabolite, CEP-38901, were determined by Covance using a validated high-performance liquid chromatography method with tandem mass spectrometric detection. The following PK parameters were determined: the maximum plasma concentration (C_{max}), the time to achieve C_{max} (t_{max}), the terminal elimination half-life ($t_{1/2}$), area under the plasma curve from time zero to the time of the last measurable concentration ($AUC_{0\text{-}t}$) or to the 24-h time point ($AUC_{0\text{-}24}$), and the area under the curve from time zero to infinity ($AUC_{0\text{-}\infty}$). Derived pharmacokinetic parameters for ESK-440 and its metabolite were summarized using descriptive statistics by dose group, including geometric mean, geometric CV%, arithmetic mean, CV%, and standard deviation of the arithmetic mean.

Results

Participant disposition

A total of 32 participants met the eligibility criteria and were enrolled in the study. These 32 participants were assigned to cohorts as follows: 3 participants in the 25 mg/day treatment group, 3 participants in the 50 mg/day treatment group, 4 participants in the 100 mg/day treatment group, 3 participants in the 150 mg/day treatment group, 4 participants in the 250 mg/day treatment group, 4 participants in the 350 mg/day treatment group, 6 participants in the 500 mg/day treatment group, and 5 participants in 700 mg/day treatment group. All 32 participants received at least 1 dose of ESK-440 and were evaluated for safety in the study.

Twenty-four (75 %) participants completed cycle 1 of treatment. Eight participants (25 %) completed the study, defined as completing 6 to 8 cycles of treatment and a follow-up visit. The most frequently reported reasons for withdrawal were withdrawal by participant (8 participants [25 %]), other (6 participants [19 %]), and adverse events (4 participants [13 %]). Four participants (13 %) died within 30 days of the last dose of ESK-440. Participant disposition is summarized in Table 1.

Demographics and other baseline characteristics

The treatment groups were well matched regarding age, race, weight, height, and other baseline characteristics as seen in Table 2. The most common tumor types among the study participants included the following: colorectal (6 participants, 19 %), breast (4 participants, 13 %), and lung, pancreas, and ovarian (2 participants each, 6 %). Twelve participants (38 %) had tumors classified as "other." In the phase 1a

Table 2
Baseline demographics and disease characteristics.

	Number of participants								
	25 mg/day ($n = 3$)	50 mg/day ($n = 3$)	100 mg/day ($n = 4$)	150 mg/day ($n = 3$)	250 mg/day ($n = 4$)	350 mg/day ($n = 4$)	500 mg/day ($n = 6$)	700 mg/day ($n = 5$)	Overall (N = 32)
Age (y)									
Mean (SD)	62.0 (9.64)	56.3 (23.86)	63.8 (4.65)	63.7 (1.15)	62.5 (11.62)	67.0 (4.97)	62.8 (5.00)	67.4 (8.88)	63.5 (9.17)
Min, max	51, 69	29, 73	59, 90	63, 65	47, 74	60, 71	56, 97	58, 78	29, 78
Sex, n (%)									
Male	3 (100)	0	0	1 (33)	0	4 (100)	3 (50)	2 (40)	13 (41)
Female	0	3 (100)	4 (100)	2 (67)	4 (100)	0	3 (50)	3 (60)	19 (59)
Race, n (%)									
White	3 (100)	3 (100)	4 (100)	3 (100)	3 (75)	4 (100)	6 (100)	2 (40)	28 (88)
Black	0	0	0	0	1 (25)	0	0	0	1 (3)
Other/Pacific Islander	0	0	0	0	0	0	0	3 (60)	3 (9)
Ethnicity, n (%)									
Hispanic or Latino	1 (33)	1 (33)	0	0	1 (25)	1 (25)	0	3 (60)	7 (22)
Not Hispanic or Latino	2 (67)	2 (67)	4 (100)	3 (100)	3 (75)	3 (75)	6 (100)	2 (40)	25 (78)
Primary diagnosis, n (%)									
Head and neck	0	0	0	0	0	0	0	1 (20)	1 (3)
Lung	0	0	0	0	0	1 (25)	1 (17)	0	2 (6)
Breast	0	1 (33)	0	0	2 (50)	0	1 (17)	0	4 (13)
Colorectal	1 (33)	1 (33)	0	0	2 (50)	1 (25)	0	1 (20)	6 (19)
Pancreas	0	1 (33)	1 (25)	0	0	0	0	0	2 (6)
Renal	0	0	0	0	0	1 (25)	0	0	1 (3)
Ovarian	0	0	0	1 (33)	0	0	0	1 (20)	2 (6)
Melanoma	0	0	0	0	0	0	0	1 (20)	1 (3)
Prostate	0	0	0	0	0	0	1 (17)	0	1 (3)
Other*	2 (67)	0	3 (75)	2 (67)	0	1 (25)	3 (50)	1 (20)	12 (38)
ALK status, n (%)									
Positive	0	1 (33)	0	0	0	0	1 (17)	0	2 (6)
Negative	1 (33)	1 (33)	0	0	1 (25)	0	2 (33)	1 (20)	6 (19)
Missing	2 (67)	1 (33)	4 (100)	3 (100)	3 (75)	4 (100)	3 (50)	4 (80)	24 (75)
FAK status, n (%)									
Positive	0	0	0	0	0	0	1 (17)	0	1 (3)
Negative	1 (33)	2 (67)	0	0	1 (25)	0	0	1 (20)	5 (16)
Missing	2 (67)	1 (33)	4 (100)	3 (100)	3 (75)	4 (100)	5 (83)	4 (80)	26 (81)
ECOG performance status, n (%)									
0	0	3 (100)	0	1 (33)	2 (50)	1 (25)	0	0	7 (22)
1	3 (100)	0	4 (100)	2 (67)	2 (50)	3 (75)	6 (100)	5 (100)	25 (78)

* The category "Other" included thymic carcinoma and soft tissue sarcoma of the left shoulder in the 25 mg/day group; endometrial carcinoma, malignant myxoid solitary fibrous tumor, and cervical adenocarcinoma in the 100 mg/day group; squamous cell carcinoma (unknown primary) and endometrial serous carcinoma in the 150 mg/day group; myofibroblastic sarcoma of the right thigh in the 350 mg/day group; pleural mesothelioma, malignant mesothelioma, and adenoid cystic carcinoma breast cancer in the 500 mg/day group; and malignant mesothelioma in the 700 mg/day group.

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; FAK, focal adhesion kinase; SD, standard deviation.

Table 3
Adverse events.

	Number (%) of participants								
	25 mg/day ($n = 3$)	50 mg/day ($n = 3$)	100 mg/day ($n = 4$)	150 mg/day ($n = 3$)	250 mg/day ($n = 4$)	350 mg/day ($n = 4$)	500 mg/day ($n = 6$)	700 mg/day ($n = 5$)	Overall (N = 32)
Any AE	3 (100)	2 (67)	4 (100)	3 (100)	4 (100)	4 (100)	6 (100)	5 (100)	31 (97)
Grade 3-5 AE	3 (100)	1 (33)	2 (50)	1 (33)	1 (25)	2 (50)	1 (17)	4 (80)	15 (47)
Treatment-related AE	1 (33)	1 (33)	2 (50)	3 (100)	4 (100)	3 (75)	5 (83)	5 (100)	2 (75)
Deaths	1 (33)	0	1 (25)	0	1 (25)	0	0	1 (20)	4 (13)
Other serious AEs	2 (67)	1 (33)	2 (50)	1 (33)	1 (25)	1 (25)	1 (17)	0	9 (28)
Withdrawn from treatment due to AE	1 (33)	0	1 (25)	0	0	1 (25)	2 (33)	2 (40)	7 (22)
AEs occurring in >15 % of participants overall									
Fatigue	0	1 (33)	3 (75)	2 (67)	3 (75)	2 (50)	2 (33)	4 (80)	17 (53)
Nausea	1 (33)	1 (33)	0	0	3 (75)	2 (50)	5 (83)	5 (100)	17 (53)
Vomiting	0	0	0	0	3 (75)	1 (25)	5 (83)	3 (60)	12 (38)
Decreased appetite	0	0	0	1 (33)	2 (50)	2 (50)	2 (33)	2 (40)	9 (28)
Diarrhea	1 (33)	0	0	1 (33)	2 (50)	1 (25)	2 (33)	1 (20)	8 (25)
Pyrexia	0	1 (33)	1 (25)	1 (33)	0	1 (25)	2 (33)	0	6 (19)
Edema peripheral	0	0	1 (25)	1 (33)	2 (50)	0	0	1 (20)	5 (16)
Cough	1 (33)	0	0	1 (33)	1 (25)	1 (25)	1 (17)	0	5 (16)

AE, adverse event.

Table 4
Pharmacokinetic parameters of ESK-440.

Parameter	Number of participants							
	25 mg/day (N = 3)	50 mg/day (N = 3)	100 mg/day (N = 3)	150 mg/day (N = 3)	250 mg/day (N = 4)	350 mg/day (N = 4)	500 mg/day (N = 5)	700 mg/day (N = 5)
Day 1								
C_{max} (ng/mL)	20.7 (11.41)	38.1 (12.26)	97.3 (51.39)	128.3 (117.15)	434.9 (165.63)	334.0 (192.89)	1159.6 (389.85)	838.8 (224.37)
t_{max} (h)	3.0 (2.0-3.1)	3.0 (2.0-24.5)	2.0 (2.0-24.9)	3.1 (3.0-4.4)	3.5 (2.0-4.0)	5.0 (3.0-24.2)	4.1 (3.0-6.2)	4.0 (3.0-6.2)
AUC_{0-t} (h•ng/mL)	222.9 (121.89)	517.0 (293.74)	1538.4 (477.73)	1555.6 (1147.29)	4854.9 (1505.50)	5324.2 (3133.30)	17810.9 (7352.42)	11489.6 (2951.60)
AUC_{0-24} (h•ng/mL)	221.6 (122.29)	508.5 (283.87)	1477.2 (449.79)	1582.3 (1200.54)	4739.0 (1533.53)	5178.7 (2928.64)	17667.3 (7237.38)	11267.8 (2903.97)
Parameter	25 mg/day (N = 3)	50 mg/day (N = 3)	100 mg/day (N = 3)	150 mg/day (N = 3)	250 mg/day (N = 4)	350 mg/day (N = 4)	500 mg/day (N = 4)	700 mg/day (N = 5)
Day 15[a]								
C_{max} (ng/mL)	36.7 (6.80)	55.6 (30.59)	273.1 (163.88)	320.9 (291.66)	731.7 (226.85)	869.0 (438.36)	1911.8 (725.12)	1310.7 (541.38)
t_{max} (h)	3.0 (1.1-6.0)	3.9 (3.1-4.0)	4.0 (3.0-6.1)	2.1 (2.1-23.1)	3.5 (2.1-6.1)	4.0 (2.1-6.0)	6.8 (4.6-8.0)	6.1 (6.0-22.4)
AUC_{0-t} (h•ng/mL)	665.9 (197.19)	1017.6 (575.98)	5659.6 (3095.39)	4948.3 (3865.64)	14212.9 (4024.13)	17949.7 (10370.43)	37638.2 (13463.21)	25870.4 (11988.66)
AUC_{τ} (h•ng/mL)	665.9 (1979.19)	995.3 (586.73)	5421.7 (3171.75)	4983.1 (3960.15)	13286.2 (3691.00)	16810.5 (8855.37)	36523.1 (131622.88)	25734.1 (12043.84)
R_{obs}	3.3 (0.76)	2.2 (1.11)	4.2 (3.47)	3.1 (0.17)	2.9 (0.81)	3.3 (0.63)	2.4 (0.43)	2.2 (0.74)

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; AUCτ, area under the plasma. concentration-time curve for the 24-hour dosing interval; C_{max}, maximum observed plasma drug concentration; R_{obs}, observed accumulation ratio = AUCτ on. day 15/AUC_{0-24} on day 1; SD, standard deviation; t_{max}, time to maximum observed drug concentration.

[a] N=4 for the day 15 500 mg/day cohort.

portion of this trial reported here, no tissue biopsies were centrally collected or analyzed for ALK or FAK expression. Investigator-reported ALK status was positive for 2 participants (6 %), negative for 6 participants (19 %), and was not reported for 24 participants (75 %). Focal adhesion kinase status was positive for 1 participant (3 %), negative for 5 participants (16 %), and was not reported for 26 participants (81 %).

All participants in the study received prior anticancer therapy. Among antineoplastic agents, the most frequently used were carboplatin (13 participants, 41 %), paclitaxel (12 participants, 38 %), doxorubicin (11 participants, 34 %), and gemcitabine (11 participants, 34 %). Nineteen participants (59 %) had received prior radiotherapy.

ESK-440 exposure

The overall mean duration of drug treatment for study participants was 62.8 days, with a range of 4 to 287 days. The mean total of cycles (SD) of treatment received was 2.5 (1.95). Only 1 participant in the 150 mg/day treatment group received >6 cycles of treatment. There was no relationship between treatment duration and the dose of ESK-440.

Dose limiting toxicities

Three participants reported a DLT: 1 in the 500 mg/day treatment group and 2 in the 700 mg/day treatment group. In all 3 cases, the DLT was grade 3 nausea that was considered related to ESK-440 and ESK-440 was withdrawn. Two participants recovered after ESK-440 withdrawal. The MTD for the study was defined as the dose level immediately below the dose level at which 2 or more participants in a cohort experience a DLT. Therefore, the MTD was determined to be 500 mg/day.

Safety and adverse events

During treatment, 31 participants (97 %) reported at least 1 AE (Table 3). The most frequently reported AEs were nausea and fatigue (17 participants each, 53 %). Other AEs that occurred frequently were vomiting (38 %), decreased appetite (28 %), diarrhea (25 %), pyrexia (19 %), peripheral edema (16 %), and cough (16 %). Twenty-four participants (75 %) reported an AE that was considered related to ESK-440. Nausea (in 16 participants, 50 %), fatigue and vomiting (each in 11 participants, 34 %), and diarrhea (in 8 participants, 25 %) were the most frequent treatment-related AEs.

Fifteen participants (47 %) reported grade 3+ AEs. The most common grade 3+ AE was nausea reported in 3 participants (9 %). No other grade 3+ AE was reported by >2 participants. Nine participants reported SAEs, and only 1 (nausea) was considered related to ESK-440. Seven participants (22 %) withdrew from treatment due to AEs and 4 deaths were reported during the study. Two of the deaths were due to AEs during the study (pulmonary embolism and cholangitis), and 2 were due to disease progression after withdrawal from the study. None of the deaths were considered by investigators to be related to ESK-440.

During the study, there were no clinically significant changes in vital signs, ECG findings, physical exam findings, or pulmonary function tests. Nineteen participants had no change from baseline in ECOG performance status; 13 participants had a decline in ECOG performance status. There were abnormal hematology and serum chemistry parameter values reported with no apparent relationship to the dose of ESK-440. No patient had a QTcF value that met the protocol-defined criterion for a DLT.

Efficacy

No participant in the study had a complete or partial response to treatment with ESK-440. The best overall response reported was stable disease in 7 participants. This response was recorded in participants with the following tumor types: thymic carcinoma, pancreatic adenocarcinoma, cervical carcinoma, squamous cell carcinoma of unknown primary, renal cell carcinoma, invasive ductal carcinoma of the breast, and adenoid cystic carcinoma.

Pharmacokinetics of ESK-440

Of the 32 participants enrolled, 30 had evaluable PK parameters for day 1, and 29 had evaluable PK parameters for day 15. On day 1 and day 15, C_{max} and AUC_{0-24} generally increased in a dose-proportional manner

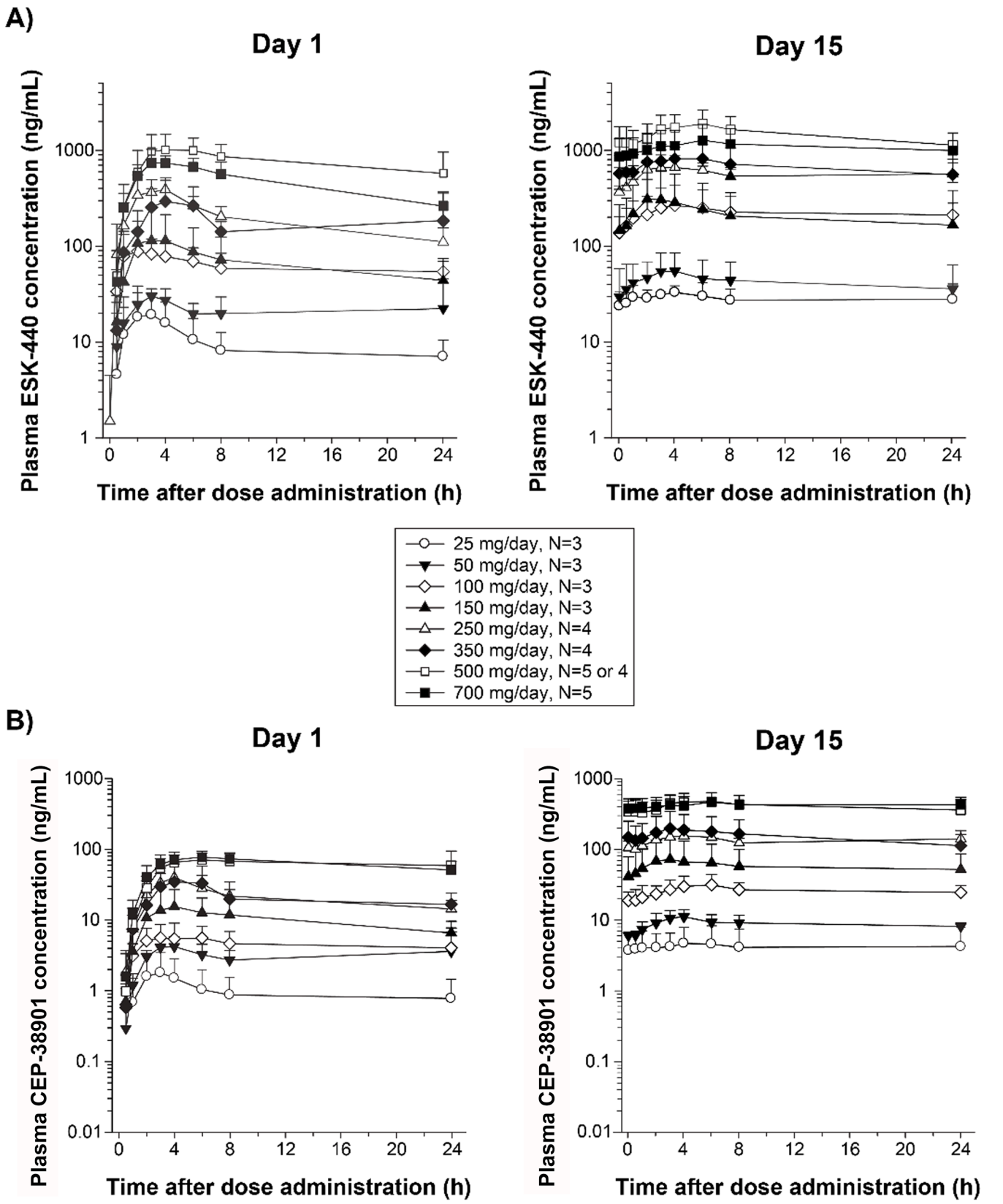

Fig. 2. Mean (+SD) Plasma Concentration-versus-Time Profiles of A) ESK-440 and B) Its Active Metabolite (CEP-38901) in Cancer Patients (N = 3-5/Dose Level) on Days 1 and 15 of Daily Oral Administration of ESK-440.
SD, standard deviation.
Note: N = 4 for 500 mg/day on day 15.
Source: Pharmacokinetic report (DP-2015-180).

between the 20 and 500 mg/day dose levels; the 700 mg/day values were slightly lower than the 500 mg/day values (Table 4). The median t_{max} did not change consistently with dose and ranged from 2.0 to 5.0 h on day 1 and 2.1 to 6.8 h on day 15, indicating a moderately rapid absorption following oral administration. After reaching peak plasma concentrations, ESK-440 levels declined in a generally biphasic manner characterized by an initial rapid phase of drug distribution followed by a much slower terminal elimination phase (Fig. 2). At higher dose levels, only the later phase was evident due to what appeared to be a more prolonged period of drug absorption. The $t_{1/2}$ of the terminal phase ranged from 9.4 to 20.8 h in a small sample of the patient population for whom the values could be estimated. The $t_{1/2}$ could not be reliably estimated for most participants due to the apparent slow elimination of ESK-440 and the relatively short duration of sampling. The $t_{1/2}$ values should be viewed with caution due to the apparent slow elimination of the compound and the relatively short duration of sampling.

Pharmacokinetics of CEP-38901

After oral administration of ESK-440, the major active metabolite, CEP-38901, was observed within 0.5 to 1.0 h after dosing. The AUC of CEP-38901 ranged between approximately 7 % (for 100 mg/day) to 18 % (for 150 mg/day) of the AUC of ESK-440 on day 1, and approximately 13 % (for 100 mg/day) to 40 % (for 700 mg/day) on day 15 **(Table S3)**. The systemic exposure of the metabolite increased in a dose-proportional manner between 25 mg/day and 500 mg/day. Systemic exposure at the 700 mg/day dose was comparable to the 500 mg/day dose. Similarly to the parent ESK-440, the median t_{max} of the metabolite did not change consistently with oral doses of ESK-440 and ranged between 3.0 to 8.0 h on day 1 and 3.6 to 8.1 h on day 15. The $t_{1/2}$ values of the metabolite also did not differ substantially from the parent compound, ranging from 10.2 to 22.9 h on day 1. The $t_{1/2}$ values should again be viewed cautiously due to the apparent slow elimination of the compound and the relatively short duration of sampling.

Discussion

Anaplastic lymphoma kinase inhibitors that can overcome resistance mechanisms represent an unmet medical need for patients with solid tumors with ALK mutations. To this end, this study set out as the first-in-human assessment of the safety, tolerability, and PK properties of ESK-440 in adults with recurrent, locally advanced, or metastatic solid tumors.

All 32 participants who were enrolled in the study received at least 1 dose of ESK-440 and were evaluated for safety and tolerability. A total of 24 participants (75 %) completed cycle 1 of treatment, and the results indicate that ESK-440 was generally safe and well tolerated with a MTD of 500 mg/day. Three DLTs, all grade 3 nausea, were reported in the study, despite patients receiving optimum antiemetic therapy as determined by the treating physician. Nausea and vomiting are common AEs in patients treated with TKIs, and have been reported to occur in 17 % to 31 % and 13 % to 26 % of patients, respectively, in clinical trials for different TKIs [12–16]. Although evidence-based management for TKI-related nausea and vomiting are lacking, antiemetic treatment, and avoidance of chocolate, caffeine, alcohol, and nicotine before dose administration, may help manage symptoms [16].

The AEs most frequently reported included nausea and fatigue (53 % each), vomiting (38 %), decreased appetite (28 %), and diarrhea (25 %), which are consistent with known class effects of ALK inhibitors and other TKIs in patients with advanced disease [16].

Regarding pharmacokinetics, ESK-440 is rapidly absorbed when administered orally, with peak plasma concentrations and systemic exposure increasing in a dose-proportional manner between 25 and 500 mg/day. In animal models, the 700 mg/day dose was predicted to be an efficacious dose (data on file). The mean observed accumulation ratio for ESK-440 after 15 days of daily dosing ranged from 2.2 to 4.2. The primary active metabolite, CEP-38901, was formed rapidly following oral administration of ESK-440 and had exposures ranging from 7 % to 40 % of ESK-440.

ESK-440 showed limited evidence of efficacy, with a best overall response of stable disease in 7 patients; there were no partial or complete responses.

Limitations of the current study include the small sample size leading to large variability in the measured parameters; limited plasma sample collection timepoints for PK analysis; missing data regarding ALK and FAK alterations; lack of pharmacodynamic endpoints, and the limited efficacy results because phase 1b was never conducted.

Conclusions

The phase 1a study of ESK-440 met its primary objective of dose determination with an MTD of 500 mg/day. ESK-440 was otherwise well tolerated, with expected AEs for this drug class in advanced cancer patients. Limited efficacy was observed in this unselected patient population, with no objective responses. The planned phase 1b study that would have expanded on the 500-mg dose level in patients with ALK or FAK abnormalities did not commence due to a sponsor decision to not conduct the study.

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CRediT authorship contribution statement

Russell J. Schilder: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Drew Rasco:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Manish R. Sharma:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

I have no conflicts.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neo.2025.101133.

Data availability

Clinical trial datasets are confidential information of Cephalon, Inc and Esanik Therapeutics, Inc.

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