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Clinical Trial Results

A Randomized Phase II Study of Linsitinib (OSI-906) Versus Topotecan in Patients With Relapsed Small-Cell Lung Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01533181
- **Sponsor:** CTEP
- **Principal Investigator:** Alberto A. Chiappori
- **IRB Approved**: Yes

Lessons Learned

- Targeted therapy options for SCLC patients are limited; no agent, thus far, has resulted in a strategy promising enough to progress to phase III trials.
- Linsitinib, a potent insulin growth factor-1-receptor tyrosine kinase inhibitor, may be one agent with activity against SCLC.
- Despite lack of a reliable predictive biomarker in this disease, which may have partly contributed to the negative outcome reported here, linsitinib, although safe, showed no clinical activity in unselected, relapsed SCLC patients.

Abstract

Background. Treatment of relapsed small-cell lung cancer (SCLC) remains suboptimal. Insulin growth factor-1 receptor (IGF-1R) signaling plays a role in growth, survival, and chemoresistance in SCLC. Linsitinib is a potent IGF-1R tyrosine kinase inhibitor that potentially may be active against SCLC.

Methods. In this phase II study, 8 eligible patients were randomly assigned in a 1:2 ratio to topotecan (1.5 mg/m^2 intravenously or 2.3 mg/m^2 orally, daily for 5 days for 4 cycles) or linsitinib (150 mg orally twice daily until progression). The primary endpoint was progression-free survival. Patients with relapsed SCLC, platinum sensitive or resistant, performance status (PS) 0–2, and adequate hematologic, renal, and hepatic function were enrolled. Patients with diabetes, cirrhosis, and those taking insulinotropic agents were excluded. Crossover to linsitinib was allowed at progression.

Results. Fifteen patients received topotecan (8 resistant, 3 with PS 2) and 29 received linsitinib (16 resistant, 5 with PS 2). Two partial responses were observed with topotecan. Only 4 of 15 patients with topotecan and 1 of 29 with linsitinib achieved stable disease. Median progression-free survival was 3.0 (95% confidence interval [CI], 1.5–3.6) and 1.2 (95% CI, 1.1–1.4) months for topotecan and linsitinib, respectively ($p = .0001$). Median survival was 5.3 (95% CI, 2.2–7.6) and 3.4 (95% CI, 1.8–5.6) months for topotecan and linsitinib, respectively ($p = .71$). Grade 3/4 adverse events (>5% incidence) included anemia, thrombocytopenia, neutropenia/leukopenia, diarrhea, fatigue, dehydration, and hypokalemia for topotecan; and thrombocytopenia, fatigue, and alanine aminotransferase/aspartate aminotransferase elevations for linsitinib.

Conclusion. Linsitinib was safe but showed no clinical activity in unselected, relapsed SCLC patients. ***The Oncologist*** 2016; 21:1163–1164e

Discussion

Improved understanding of the molecular mechanisms and signaling pathways involved in tumor development and progression, leading to identification of potential targets (receptors and/or ligands) for anticancer therapy and development of pharmacological agents able to interfere with these targetable pathways, has resulted in therapeutic benefit in non-small cell lung cancer (NSCLC). However, SCLC has proven less amenable to a targeted approach. Few studies have

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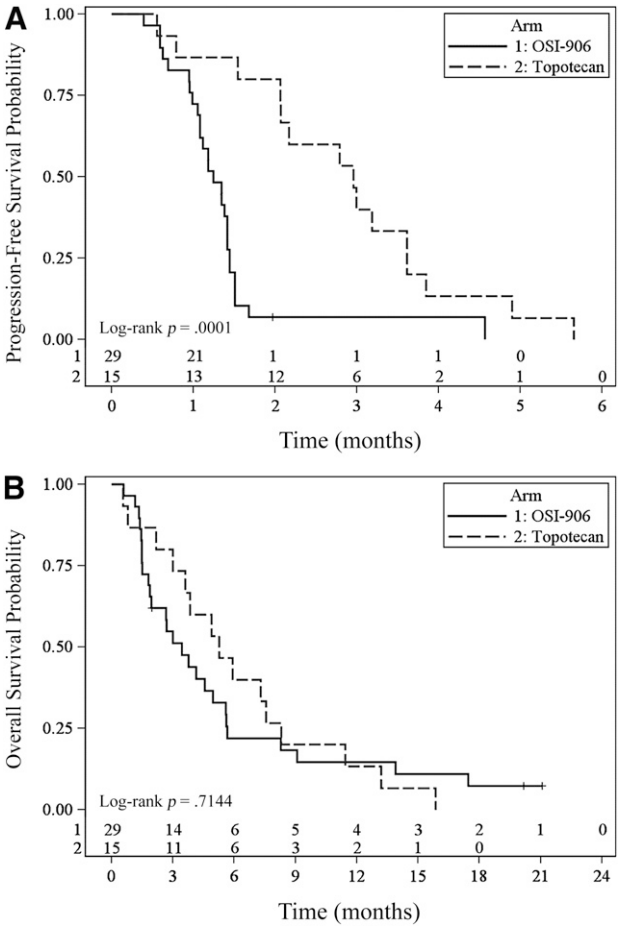

Kaplan-Meier curves for survival from the time of randomization by treatment arm. **(A)**: Progression-free survival. **(B)**: Overall survival.

attempted targeted therapy in this disease, and none has produced a strategy promising enough to progress to phase III trials [1].

The progress achieved in NSCLC is clearly related to the presence of powerful, predictive biomarkers (e.g., EGFR, ALK) and to access to tissue where these biomarkers are identified. The former (predictive biomarkers) and the latter (tissue obtained from biopsies) are routinely not available in SCLC.

Recently, ERK phosphorylation (pERK) has been proposed as a marker of resistance to insulin growth factor-1 receptor (IGF-1R) inhibition in SCLC [2]; additionally, circulating tumor cells (CTCs) have been described as a prognostic marker [3] and used as a source of tumor material in patients with SCLC. Furthermore, [^{18}F]fluorodeoxyglucose-positron emission tomography [^{18}FDG-PET] has been reported to predict response to linsitinib in mouse models of preclinical lung cancer [4], with "metabolic burden" similarly measured by ^{18}FDG-PET scan also described as a prognostic factor in patients with SCLC [5]. Therefore, a reasonable personalized trial would be one in which patients with relapsed SCLC, selected by pERK expression in CTCs, are treated with linsitinib and followed with PET scans as surrogates of response and/or clinical benefit.

Unfortunately, failure of benefit with agents targeting IGF-1R, including linsitinib, has not been limited to relapsed SCLC. Indeed, the addition of monoclonal antibodies against IGF-1R, like cixutumumab (IMCA12); to platinum-doublet chemotherapy in SCLC (E1508) [6]; or figitumumab to chemotherapy and targeted therapies in NSCLC [7] also failed to provide a significant clinical benefit.

Although it is tempting to speculate that the incorporation of a predictive biomarker could have produced a different outcome in our study, the repeated failure of various IGF-1R inhibitors is difficult to ignore or to attribute to lack of reliable predictive biomarkers for patient selection. Thus, in our view, linsitinib showed no activity against relapsed SCLC and further development of this agent is not justified.

Trial Information

Disease	Lung cancer – SCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase II
Type of study - 2	Randomized
Progression-Free Survival	P: 0.1, hazard ratio (HR): 0.6
Primary Endpoint	PFS
Secondary Endpoint	Overall Survival

Additional Details of Endpoints or Study Design

Study Design and Treatment

This Cancer Therapy Evaluation Program (CTEP) multi-institution, randomized phase II clinical trial (ClinicalTrials.gov: NCT01533181) was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable regulatory requirements. Approval from the institutional review board of each participating center was required, and patients provided written informed consent. Patients were randomly assigned to receive either linsitinib (150 mg orally, twice daily, every day until disease progression) or topotecan (1.5 mg/m^2 intravenously or 2.3 mg/m^2 orally, once daily on days 1–5 for 4 cycles). The treatment cycle was 21 days (Fig. 1). Linsitinib was provided by CTEP.

Safety evaluations for treatment-emergent adverse events (AEs) were performed using scheduled hematology, blood chemistry, urinalysis, vital signs, and physical examination assessments. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Two dose reductions were permitted per patient for grade 3 or 4 toxicities, with treatment resumed after AE resolution to grade 2 or below, and dose delays of up to 4 weeks were permitted to allow recovery from AEs.

Primary and/or secondary prophylactic growth factor support was allowed.

Tumor assessments were performed at screening and after every two cycles, using cross-sectional computed tomography and/or magnetic resonance imaging. Tumor response was evaluated by local investigator assessment and categorized according to RECIST version 1.1.

Statistical Analysis

Our primary endpoint was PFS. Secondary endpoints included overall response rate, overall survival, and safety. Patients were randomly assigned 2:1 in favor of linsitinib and stratified on the basis of sensitivity to first-line treatment (sensitive vs. refractory) and performance status (0/1 vs. 2) (Fig. 2).

An increase in median PFS from 10 weeks (2.5 months) in the topotecan arm (control) to 16.7 weeks (4.2 months) in the linsitinib arm (experimental) was hypothesized. Using a one-sided log-rank test, an overall sample size of 95 patients (31 in the topotecan arm and 64 in the linsitinib arm) would achieve 81.6% power at an α level of 0.1 to detect a hazard ratio (HR) of 0.60 (calculation performed using PASS; NCSS Statistical Software, Kaysville, UT, http://www.ncss.com).

Descriptive statistics were used to summarize patient characteristics and treatment administration, tumor response, and safety parameters. Overall survival (OS) and PFS were estimated using the Kaplan-Meier method; between-treatment comparisons for OS and PFS were conducted using the log-rank test.

Investigator's Analysis

Inactive because results did not meet primary endpoint.

Drug Information Arm A topotecan

Drug 1	
Generic/Working name	Topotecan
Trade name	Hycamtin
Company name	Novartis Pharmaceuticals
Drug type	Chemotherapy
Drug class	Topoisomerase I
Dose	1.5 mg/m^2
Route	IV
Schedule of Administration	Days 1–5

Drug Information Arm B linsitinib

Drug 1	
Generic/Working name	Linsitinib
Trade name	
Company name	Astellas Pharmaceuticals
Drug type	Small molecule
Drug class	Insulin-like growth factors IGF-1R and IGF-2
Dose	150 mg per flat dose
Route	Oral
Schedule of Administration	b.i.d.

Patient Characteristics

Number of patients, male	19
Number of patients, female	25
Stage	Extensive stage
Age	Median (range): 64 (34–86)
Number of prior systemic therapies	Median (range): 1
Performance Status: ECOG	0 — 36 (0–1) 1 — 2 — 8 3 — Unknown —
Cancer Types or Histologic Subtypes	Small cell 44

Primary Assessment Method

Arm A topotecan: Small Cell	
Number of patients enrolled	15
Number of patients evaluable for toxicity	14
Number of patients evaluated for efficacy	15
Response assessment CR	$n = 0$
Response assessment PR	$n = 2$
Response assessment SD	$n = 4$
Response assessment PD	$n = 9$
Response assessment OTHER	$n = 0$
(Median) duration assessments PFS	3 months, CI: 1.5–3.6
(Median) duration assessments OS	5.3 months, CI: 2.2–7.6

Arm B linsitinib: Small Cell	
Number of patients enrolled	29
Number of patients evaluable for toxicity	28
Number of patients evaluated for efficacy	29
Response assessment CR	$n = 0$
Response assessment PR	$n = 0$
Response assessment SD	$n = 1$
Response assessment PD	$n = 28$
(Median) duration assessments PFS	1.2 months, CI: 1.1–1.4
(Median) duration assessments OS	3.4 months, CI: 1.8–5.6

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Pharmacokinetics / Pharmacodynamics	Not collected
Investigator's Assessment	Inactive because results did not meet primary endpoint

Disclosures

Alberto A. Chiappori: Pfizer, Genentech, Boehringer Ingelheim, Merck (C/A); **Gregory A. Otterson:** Genentech, Boehringer (C/A), Bristol-Myers Squibb, Genentech, Boehringer, Xcovery, Pfizer, GlaxoSmithKline/Novartis, NewLink Genetics, Clovis (RF); **Leora Horn:** Bristol-Myers Squibb, Boehringer Ingelheim, Xcovery, Abbvie, Merck, Genentech (C/A), Merck, Genentech, Xcovery, Boehringer Ingelheim, Bristol-Myers Squibb, Astellas, Clovis (RF); **Taofeek K. Owonikoko:** Medivation (C/A); **Jorge Nieva:** Genentech (C/A), Merck (RF), Epic Sciences (OI).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

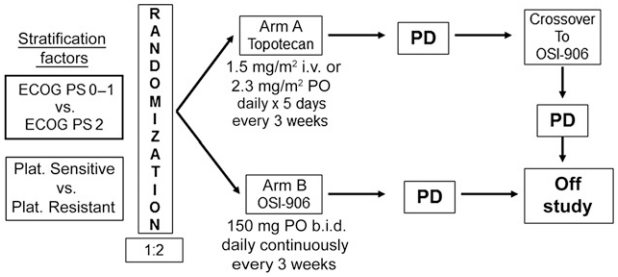

Figure 1. Trial design.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; Plat., platinum; PO, by mouth; PS, performance status.

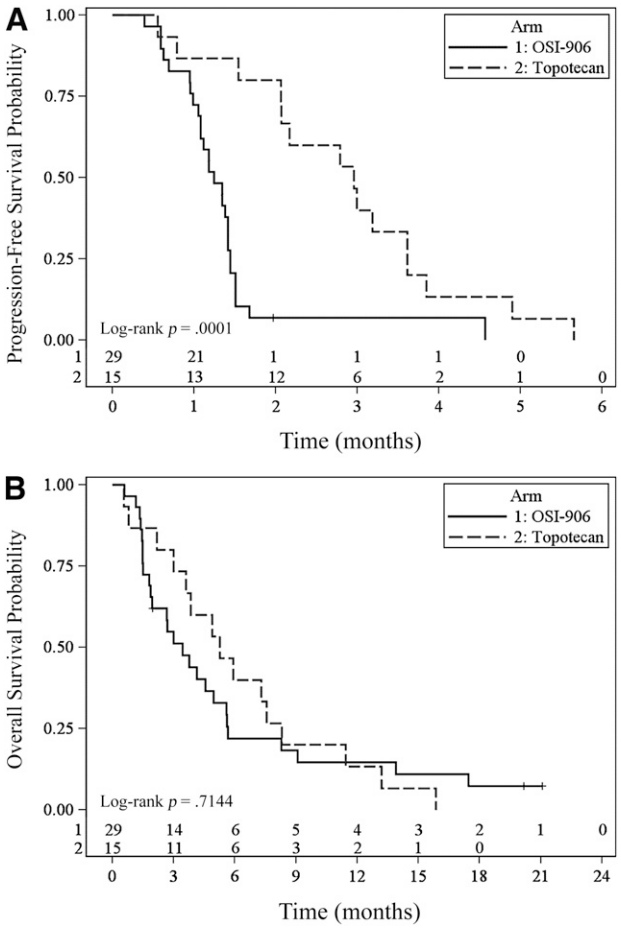

Figure 2. Kaplan-Meier curves for survival from the time of randomization by treatment arm. **(A)**: Progression-free survival. **(B)**: Overall survival.

Table 1. Patient characteristics

Characteristic	Treatment		
	Arm A (topotecan)	Arm B (linsitinib)	Total
No. of patients	15 (34.1)	29 (65.9)	44 (100.0)
Age, years			
Median	64	62	64
Range	34–86	37–79	34–86
Sex			
Female	8 (18.2)	17 (38.6)	25 (56.8)
Male	7 (15.9)	12 (27.3)	19 (43.2)
Race			
Black	0 (0.0)	2 (4.5)	2 (4.5)
White	15 (34.1)	27 (61.4)	42 (95.5)
Ethnicity			
Non-Hispanic	15 (34.1)	29 (65.9)	44 (100.0)
Eastern Cooperative Oncology Group Performance Status			
0–1	12 (27.3)	24 (54.5)	36 (81.8)
2	3 (6.8)	5 (11.4)	8 (18.2)
Disease			
Platinum sensitive[a]	7 (15.9)	13 (29.5)	20 (45.4)
Platinum resistant[b]	8 (18.2)	16 (36.4)	24 (54.6)

Data are given as *n* (%) unless otherwise indicated.
[a]Progression of disease <90 days from previous treatment.
[b]Progression of disease >90 days from previous treatment.

Table 2. Adverse events occurring in ≥2% of patients treated with linsitinib and topotecan

	Treatment								
	Grade 1/2			Grade 3/4			All grades		
Adverse event[a]	Topotecan ($n = 14$)	Linsitinib ($n = 28$)	Overall ($N = 42$)	Topotecan ($n = 14$)	Linsitinib ($n = 28$)	Overall ($N = 42$)	Topotecan ($n = 14$)	Linsitinib ($n = 28$)	Overall[b] ($N = 42$)
Hematologic									
Anemia	8 (57.1)	3 (10.7)	11 (26.2)	1 (7.1)	1 (3.6)	2 (4.8)	9 (64.3)	4 (14.3)	13 (31)
Leukopenia	2 (14.3)	1 (3.6)	3 (7.1)	4 (28.6)		4 (9.5)	6 (42.9)	1 (3.6)	7 (16.7)
Thrombocytopenia		1 (3.6)	1 (2.4)	4 (28.6)	2 (7.1)	6 (14.3)	4 (28.6)	3 (10.7)	7 (16.7)
Neutropenia				4 (28.6)		4 (9.5)	4 (28.6)		4 (9.5)
Other, specify		1 (3.6)	1 (2.4)	2 (14.3)		2 (4.8)	2 (14.3)	1 (3.6)	3 (7.1)
Gastrointestinal									
Nausea	5 (35.7)	12 (42.9)	17 (40.5)				5 (35.7)	12 (42.9)	17 (40.5)
Vomiting	6 (42.9)	6 (21.4)	12 (28.6)				6 (42.9)	6 (21.4)	12 (28.6)
Diarrhea	2 (14.3)	5 (17.9)	7 (16.7)	1 (7.1)		1 (2.4)	3 (21.4)	5 (17.9)	8 (19)
General									
Fatigue	5 (35.7)	7 (25)	12 (28.6)	1 (7.1)	3 (10.7)	4 (9.5)	6 (42.9)	10 (35.7)	16 (38.1)
Laboratory									
ALT/AST elevation		10 (35.7)	10 (23.8)		2 (7.1)	2 (4.8)		12 (42.9)	12 (28.6)
Hyperbilirubinemia		3 (10.7)	3 (7.1)					3 (10.7)	3 (7.1)
Azotemia		3 (10.7)	3 (7.1)					3 (10.7)	3 (7.1)
Metabolism and nutrition									
Anorexia	3 (21.4)	6 (21.4)	9 (21.4)		1 (3.6)	1 (2.4)	3 (21.4)	7 (25)	10 (23.8)
Hyperglycemia		6 (21.4)	6 (14.3)		1 (3.6)	1 (2.4)	—	7 (25)	7 (16.7)
Dehydration	1 (7.1)	2 (7.1)	3 (7.1)	2 (14.3)		2 (4.8)	3 (21.4)	2 (7.1)	5 (11.9)
Hypokalemia		2 (7.1)	2 (4.8)	1 (7.1)		1 (2.4)	1 (7.1)	2 (7.1)	3 (7.1)
Neurologic									
Headache	2 (14.3)		2 (4.8)		1 (3.6)	1 (2.4)	2 (14.3)	1 (3.6)	3 (7.1)

Data given as *n* (%) unless otherwise indicated.
[a]Toxicity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
[b]Two patients were excluded because they withdrew from study before starting therapy.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.