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/m² intravenously or 2.3 mg/m² 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...
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, [18F]fluorodeoxyglucose-positron emission tomography [18FDG-PET] has been reported to predict response to linsitinib in mouse models of preclinical lung cancer [4], with “metabolic burden” similarly measured by 18FDG-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.
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/m² |
| 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 (C/A), 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 Nieve: 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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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<sup>a</sup>  | 7 (15.9)                   | 13 (29.5) | 20 (45.4) |
| Platinum resistant<sup>b</sup> | 8 (18.2)                   | 16 (36.4) | 24 (54.6) |

Data are given as n (%) unless otherwise indicated.

<sup>a</sup>Progression of disease < 90 days from previous treatment.

<sup>b</sup>Progression of disease > 90 days from previous treatment.
Table 2. Adverse events occurring in ≥2% of patients treated with linsitinib and topotecan

| Adverse eventa | Treatment | Grade 1/2 | Grade 3/4 | All grades |
|----------------|-----------|-----------|-----------|------------|
|                | 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 (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)   | 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.
aToxicity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
bTwo patients were excluded because they withdrew from study before starting therapy.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.