A Phase I Dose-Escalation Study of Linsitinib (OSI-906), a Small-Molecule Dual Insulin-Like Growth Factor-1 Receptor/Insulin Receptor Kinase Inhibitor, in Combination with Irinotecan in Patients with Advanced Cancer

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Trial Information

- ClinicalTrials.gov Identifier: NCT01016860
- Sponsor(s): Stephen Leong
- Principal Investigator: Stephen Leong
- IRB Approved: Yes

Lessons Learned

- The maximum tolerated dose of the combination of linsitinib and irinotecan is linsitinib 450 mg daily on days 1–3 every 7 days and irinotecan 125 mg/m² days 1 and 8 of a 21-day cycle.
- The adverse effects associated with the combination are not significantly increased beyond what is expected of each drug as a single agent.
- Multiple negative trials of insulin-like growth factor-1 receptor inhibitors performed in unselected patient populations led to the early discontinuation of linsitinib development and this trial.
- Earlier integration of assessment of potential predictive biomarkers into clinical trials, as was planned in this study, is vital to the development of targeted therapies in oncology.

Abstract

Background. This phase I dose-escalation study was designed to evaluate the safety and tolerability of the combination of irinotecan and insulin-like growth factor-1 receptor (IGF-1R) inhibitor linsitinib in patients with advanced cancer refractory to standard therapy.

Methods. Dose escalation in three specified dose levels was performed according to a standard 3 + 3 design. Dose levels were as follows: (a) linsitinib 400 mg and irinotecan 100 mg/m², (b) linsitinib 450 mg and irinotecan 100 mg/m², and (c) linsitinib 450 mg and irinotecan 125 mg/m². Linsitinib was administered once daily on days 1–3, 8–10, and 15–17, and irinotecan on days 1 and 8. Assessment of a candidate predictive biomarker was planned in all patients, with further evaluation in an expansion cohort of advanced colorectal cancer.

Results. A total of 17 patients were treated, with 1 patient in both cohort 2 and 3 experiencing dose-limiting toxicity. Linsitinib 450 mg and irinotecan 125 mg/m² was the maximum tolerated dose. Sixteen (94%) patients experienced at least one treatment-related adverse event. Neutropenia was the only grade >3 toxicity (4%). No significant hyperglycemia or QT interval prolongation was noted. No objective responses were observed; 47% (n = 8) had stable disease with median duration of 5.25 months.

Conclusion. Although the combination was determined safe, the study was halted due to termination of linsitinib development, and biomarker testing was not performed.

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Discussion

Linsitinib is a potent small-molecule tyrosine kinase inhibitor of the human IGF-1R, with a half maximal inhibitory concentration (IC₅₀) of 35 nmol/L, and the homologous insulin receptor, with an IC₅₀ of 75 nmol/L. The drug is selective for these targets [1].

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Irinotecan is a topoisomerase I inhibitor that is U.S. Food and Drug Administration approved for the treatment of colorectal cancer with compendia for reimbursement including non-small cell lung, gastroesophageal, cervical, and ovarian cancers.

The combination of linsitinib and irinotecan was selected for further evaluation based on preclinical data suggesting a synergistic interaction between the drugs [2]. Eligible patients with refractory advanced cancer, and for which irinotecan is in the compendia for reimbursement, were treated with linsitinib, administered by mouth, and irinotecan, by intravenous (IV) infusion, in 21-day cycles at three dose levels. Once the maximum tolerated dose (MTD) was defined, expansion of this dose level was planned in patients with advanced colorectal cancer. A potential predictive biomarker, the linsitinib integrated classifier score [3], was to be evaluated in this cohort.

A total of 18 patients were enrolled in the trial at a single site. One of seven evaluable patients in the second cohort experienced a dose-limiting toxicity (DLT) of grade 3 nausea/vomiting requiring hospitalization. A DLT of grade 3 febrile neutropenia/grade 4 neutropenia was documented in one of seven patients treated in cohort 3. Linsitinib 450 mg and irinotecan 125 mg/m² was determined to be the MTD.

The most common toxicities at least possibly related to treatment and occurring in at least 10% of cycles were nausea, vomiting, fatigue, and anorexia. Hyperglycemia and QTc prolongation were considered adverse events of special interest, although no events above grade 1 severity were documented.

Eight patients (47%) had stable disease. No responses were documented, although one patient with metastatic rectal cancer had a 23% decrease in tumor burden and was treated for 18 cycles. Seven patients (41%) had progressive disease.

Although the combination of linsitinib and irinotecan was determined to be safe at the MTD, the study was halted at this point due to termination of linsitinib development. Thus, the expansion cohort and analysis of the linsitinib integrated classifier and other pharmacodynamic and pharmacokinetic data were not completed.

### Trial Information

| Disease | Advanced colorectal, non-small cell lung, gastroesophageal, cervical, and ovarian cancer |
|---------|----------------------------------------------------------------------------------|
| Stage of Disease/Treatment | Metastatic/advanced |
| Prior Therapy | No designated number of regimens |
| Type of Study – 1 | Phase I |
| Type of Study – 2 | 3 + 3 |
| Primary Endpoint | Maximum tolerated dose |
| Primary Endpoint | Safety |
| Primary Endpoint | Tolerability |
| Secondary Endpoint | Preliminary antitumor activity |
| Secondary Endpoint | Correlative endpoint |

**Additional Details of Endpoints or Study Design:**

An expansion cohort of patients with advanced colorectal cancer who had failed a prior oxaliplatin-containing regimen was planned at the MTD. These patients were to be assigned to one of two cohorts according to a candidate predictive biomarker—the linsitinib integrated classifier score. The linsitinib integrated classifier is a k-Top Scoring Pair classifier, developed from gene array data from sensitive and resistant preclinical colorectal cancer (CRC) models, used in combination with IGF-1R fluorescence in situ hybridization and KRAS mutation status. This classifier was a successful predictor of sensitivity to linsitinib therapy in preclinical patient-derived CRC xenograft models [3]. Patients in the expansion cohort with a score of 4/5 or above were to be assigned to a single-agent linsitinib arm, whereas those with lower scores were to receive treatment with single-agent irinotecan, with linsitinib added to this regimen at the time of progression.

**Investigator’s Analysis:** Drug tolerable, hints of efficacy

### Drug Information

| Drug 1 | |
|--------|---|
| Generic/Working Name | Linsitinib/OSI-906 |
| Trade Name | |
| Company Name | OSI Pharmaceuticals |
| Drug Type | Small molecule |
| Drug Class | Insulin-like growth factors—IGF-1R and IGF-2 |
| Dose | mg per flat dose |
| Route | p.o. |
| Schedule of Administration | For cycle 1, patients were treated with a single dose of linsitinib on day −3, with further dosing days 2–4, 8–10, and 15–17. Patients received a single-dose of linsitinib on days 1–3, 8–10, and 15–17 for all additional cycles. |
Drug 2
Generic/Working Name  Irinotecan
Trade Name  Camptosar
Company Name  Pfizer
Drug Type  Other
Drug Class  Topoisomerase I
Dose  mg/m²
Route  IV
Schedule of Administration  Day 1 and 8 every 21 days for all treatment cycles.

**Dose Escalation Table**

| Dose Level | Dose of Drug: Linsitinib/OSI-906 | Dose of Drug: Irinotecan | Number Enrolled | Number Evaluable for Toxicity |
|------------|----------------------------------|--------------------------|----------------|-------------------------------|
| 1          | 400 mg                           | 100 mg/m²                | 3              | 3                             |
| 2          | 450 mg                           | 100 mg/m²                | 8              | 7                             |
| 3          | 450 mg                           | 125 mg/m²                | 7              | 7                             |

**Patient Characteristics**

| Number of Patients, Male | 10  |
| Number of Patients, Female | 8   |
| Stage                    | IV  |
| Age                      | Median (range): 51 (28–69) |
| Number of Prior Systemic Therapies | Median (range): 2 (1–6) |
| Performance Status: ECOG | 0 — 9 |
|                          | 1 — 9 |
|                          | 2 — 0 |
|                          | 3 — 0 |
|                          | Unknown — 0 |
| Cancer Types or Histologic Subtypes | Colon 10 |
|                                  | Rectal 4 |
|                                  | Esophageal 2 |
|                                  | Cervical 1 |
|                                  | Ovarian 1 |

**Primary Assessment Method**

| Title                                | Total patient population |
|--------------------------------------|--------------------------|
| Number of Patients Screened          | 21                       |
| Number of Patients Enrolled          | 18                       |
| Number of Patients Evaluable for Toxicity | 17                     |
| Number of Patients Evaluated for Efficacy | 12                     |
| Evaluation Method                    | RECIST 1.0               |
| Response Assessment CR               | n = 0 (0%)               |
| Response Assessment PR               | n = 0 (0%)               |
| Response Assessment SD               | n = 8 (53%)              |
| Response Assessment PD               | n = 7 (47%)              |
| (Median) Duration Assessments Response Duration | 12 weeks |
| (Median) Duration Assessments Duration of Treatment | 6 weeks |
**Adverse Events**

| Name                                  | NC/NA | All Dose Levels, All Cycles |
|---------------------------------------|-------|----------------------------|
|                                       |       | 1  | 2  | 3  | 4  | 5  | All grades |
| Hemoglobin                            | 11%   | 65%| 24%| 0% | 0%| 0% | 89% |
| Nausea                                | 12%   | 76%| 12%| 0% | 0%| 0% | 88% |
| Vomiting                              | 23%   | 65%| 12%| 0% | 0%| 0% | 77% |
| Fatigue (asthenia, lethargy, malaise) | 29%   | 53%| 18%| 0% | 0%| 0% | 71% |
| Neutrophils/granulocytes (ANC/AGC)    | 46%   | 12%| 24%| 12%| 6%| 0% | 54% |
| Diarrhea                              | 53%   | 35%| 12%| 0% | 0%| 0% | 47% |
| Anorexia                              | 53%   | 47%| 0% | 0% | 0%| 0% | 47% |
| Weight loss                           | 70%   | 24%| 6% | 0% | 0%| 0% | 30% |
| Constipation                          | 71%   | 29%| 6% | 0% | 0%| 0% | 29% |
| Platelets                             | 82%   | 0% | 12%| 6% | 0%| 0% | 18% |
| Lymphopenia                           | 82%   | 18%| 0% | 0% | 0%| 0% | 18% |
| Pain—Headache                         | 88%   | 6% | 6% | 0% | 0%| 0% | 12% |
| Dizziness                             | 88%   | 12%| 0% | 0% | 0%| 0% | 12% |
| Mucositis/stomatitis (clinical exam)  | 88%   | 12%| 0% | 0% | 0%| 0% | 12% |
| Bilirubin (hyperbilirubinemia)        | 88%   | 12%| 0% | 0% | 0%| 0% | 12% |
| Hair loss/alopecia (scalp or body)    | 88%   | 12%| 0% | 0% | 0%| 0% | 12% |

All AEs in all cycles occurring in at least 10% of patients.

Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count; NC/NA, no change from baseline/no adverse event.

**Serious Adverse Events**

| Name                              | Grade | Attribution |
|-----------------------------------|-------|-------------|
| Nausea/vomiting                   | 3     | Possible    |
| Gastrointestinal hemorrhage       | 3     | Unrelated   |
| Abdominal pain                    | 3     | Unrelated   |
| Small bowel obstruction           | 3     | Unrelated   |
| Febrile neutropenia               | 3     | Definite    |

The five documented Serious Adverse Events occurred in five unique patients.

**Dose-Limiting Toxicities**

| Dose Level | Dose of Drug: Linsitinib/OSI-906 | Dose of Drug: Irinotecan | Number Enrolled | Number Evaluable for Toxicity | Number with Dose-Limiting Toxicity | Dose-Limiting Toxicity Information |
|------------|----------------------------------|--------------------------|-----------------|-------------------------------|-----------------------------------|-----------------------------------|
| 1          | 400 mg                           | 100 mg/m²                | 3               | 3                             | 0                                 |                                   |
Although this study was discontinued early due to halting of linsitinib development, the dose-escalation data do provide important safety information regarding this insulin-like growth factor-1 receptor (IGF-1R) inhibitor in combination with irinotecan chemotherapy. In this study, the maximum tolerated dose of linsitinib was 450 mg daily on days 1–3 every 7 days in combination with irinotecan 125 mg/m² days 1 and 8 of a 21-day cycle. Overall, this combination was well tolerated across predefined dose levels, with most adverse events (AEs) grade 1–2 in severity.

Hyperglycemia is the primary class-effect toxicity of IGF-1R small-molecule tyrosine kinase inhibitors (TKIs) due to insulin receptor (IR) cross-targeting at clinically relevant doses [4, 5]. However, such AEs were overall mild in severity in this study, with no events meeting criteria for dose-limiting toxicity (DLT) in this patient population. It is possible that no significant hyperglycemia was documented in this study because lower doses of linsitinib were used for combination dosing with irinotecan, and patients with baseline glucose elevations were excluded from participation. Elevation in liver function tests has also been documented in phase I studies of linsitinib alone and in combination with everolimus [4, 5], and although grade 3 elevation was observed in one patient on this trial, it was attributed to underlying disease and improved to grade 1 following stenting of a malignant stricture. Although not considered a class effect, QTc prolongation has been a DLT in other studies of linsitinib [4, 5, 7]. However, such AEs were overall mild in severity.

Due to discontinuation of development of the majority of IGF-1R inhibitors, there have been few other efforts to identify a biomarker predictive of activity within or across tumor types. However, a small number of ongoing clinical trials continue to evaluate this target in select tumor types thought to be dependent on IGF-1R signaling, with the greatest interest in subtypes of sarcoma. Hopefully these and other ongoing studies specifically evaluating potential biomarkers of IGF-1R inhibitor activity (NCT0271185, NCT02719041, NCT02916394) will lead to the identification of a predictive biomarker that will provide better identification of patients likely to benefit from IGF-1R inhibition in the broader cancer patient population, as was an initial aim of this clinical trial.

**DISCLOSURES**

Jennifer R. Diamond: Merck, Bristol-Meyers Squibb, Bayer, Taiho, Immunomedics, Medimmune, Takeda. The other authors indicated no financial relationships.

(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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