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Clinical Trial Results

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/m^2 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 linistinib 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/m^2, (b) linsitinib 450 mg and irinotecan 100 mg/m^2, and (c) linsitinib 450 mg and irinotecan 125 mg/m^2. Linisitinib 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/m^2 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. ***The Oncologist*** 2018;23:1409–e140

Discussion

Linsitinib is a potent small-molecule tyrosine kinase inhibitor of the human IGF-1R, with a half maximal inhibitory concentration (IC_{50}) of 35 nmol/L, and the homologus insulin receptor, with an IC_{50} 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/m^2 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 linisitinb 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/m^2
Route	IV
Schedule of Administration	Day 1 and 8 every 21 days for all treatment cycles.

Dose Escalation Table

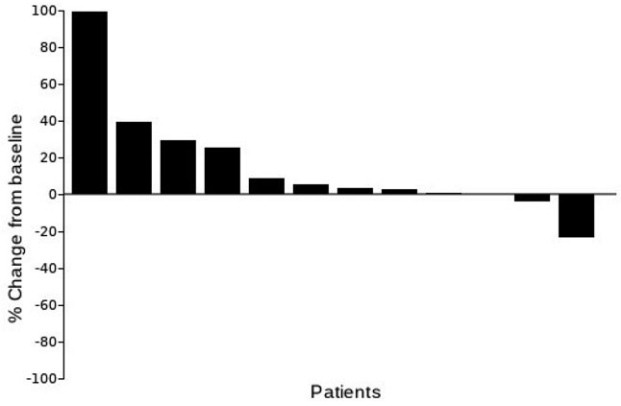
Dose Level	Dose of Drug: Linsitinib/ OSI-906	Dose of Drug: Irinotecan	Number Enrolled	Number Evaluable for Toxicity
1	400 mg	100 mg/m^2	3	3
2	450 mg	100 mg/m^2	8	7
3	450 mg	125 mg/m^2	7	7

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



Best percentage change from baseline in sum of longest diameters

Adverse Events

	All Dose Levels, All Cycles						
Name	**NC/NA**	**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%	0%	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/m^2	3	3	0	

2	450 mg	100 mg/m^2	7	7	1	Nausea/Vomiting
3	450 mg	125 mg/m^2	7	7	1	Febrile Neutropenia

Assessment, Analysis, and Discussion	
Completion	Study terminated before completion
Terminated Reason	Company stopped development
Investigator's Assessment	Drug tolerable, hints of efficacy

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/m^2 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 [5, 6], 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]. In this trial, no grade 3 or greater prolongation of QTc was observed. Unfortunately, due to early discontinuation of this clinical trial, we do not have pharmacokinetic data to further explore its relationship to this toxicity profile.

The early closure of this study and halting of linsitinib development is representative of the fate of IGF-1R inhibitors in oncology drug development in the last 10 years. Although initially a promising target based on data from various preclinical studies, nearly 40 clinical trials evaluating IGF-1R monoclonal antibodies, IGF-1/2-targeting antibodies, and IGF-1R/IR small molecule TKIs did not demonstrate a significant clinical benefit in any tumor type [8, 9].

This includes studies evaluating IGF-1R inhibitors in colorectal cancer, with both single-agent trials [10] and combination studies with FOLFIRI [11], panitumumab [12], cetuximab/irinotecan [13], and everolimus [6] negative for a significant clinical benefit to patients. However, there were outlier patients across these studies who did achieve partial response or prolonged progression-free survival on such therapy. It thus remains possible that a subset of colorectal cancer (CRC) patients may still benefit from IGF-1R inhibitor therapy, although clearly a predictive biomarker is required to select such patients.

An important goal of the expansion cohort of this study was to explore this possibility in patients with advanced CRC; in this case using an integrated classifier to predict response to linsitinib therapy based on *k*-Top Scoring Pair in combination with *KRAS* mutation status and IGF-1R fluorescence in situ hybridization. Unfortunately, this attempt to identify a predictive biomarker for IGF-1R targeted therapy came too late in the evaluation of this drug class, and the development of linsitinib was terminated before the classifier was explored in human patients.

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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