OPEN-LABEL, PHASE 1 STUDY OF LOR-253 HCl IN PATIENTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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Abstract

Background: LOR-253 HCl (LOR-253) is a novel small molecule inducer of tumor suppressor Krüppel-like factor 4 (KLF4) that has shown potent antitumor activity in NSCLC and colon tumor xenograft models. Objectives are to determine the maximum tolerable dose (MTD) or target-appropriate dose (TAD), and to characterize safety.
Materials and Methods: Patients with advanced solid tumors who progressed on standard therapies received LOR-253 by i.v. infusion on Days 1, 2, 15, and 16 of each 28 day cycle. The study design consisted of a brief run-in (Stage I) with 100% dose escalation until 2 patients with Grade 2 toxicity or 1 patient with Grade 3 toxicity, followed by a standard 3+3 design with escalating doses (Stage II). Dose limiting toxicity (DLT) was defined as ≥ Grade 3 other than reversible electrolyte abnormalities. RECIST 1.1 assessments were performed every 2 cycles (8 weeks). Serum samples for pharmacokinetic (PK) were collected in Cycle 1 pre-treatment, at the end of infusion (EOI), and 0.5, 1, 2, 4 and 7 hours (hr) after EOI on Days 1 and 2 omitting the 7 hr sample and adding 24, 48 and 144 hr samples. Pre-treatment and EOI samples were also collected on Days 15 and 16.
Results: Twenty seven patients have been enrolled, with a mean age of 59 (range, 39-75), 67% male, and a mean of 4 (range, 1 – 7) prior regimens. Primary tumors included 16 colorectal, 3 appendiceal, 2 non-small cell lung, 2 esophageal, and 4 others. Of 24 patients dosed only 1 patient experienced a ≥ Grade 3 toxicity at least possibly related to drug (Grade 3 hypophosphatemia). The most frequent Grade 2 toxicity was hypersensitivity (2 patients). Dosing was at 20, 40, and 80 mg/m^2 in Stage I until a DLT of Grade 3 hypophosphatemia, and at 80, 104, 135, 176, and 229 mg/m^2 in Stage II. Of 17 patients evaluable for RECIST assessment, 7 (41%) had stable disease as best response. Stable disease of ≥ 4 cycles (4 patients; mean 154 days) was seen exclusively at the higher dose levels from 176 to 229 mg/m^2 which corresponds to a preclinically efficacious KLF4 inducing dose. PK elimination appeared biphasic with mean T½ at doses ≥ 80 mg/m^2 ranging from 44-61 hr with 144 hr profile. AUC(0-t) was dose proportional with a median accumulation ratio of 4 on Day 2 vs. Day 1.
Conclusions: LOR-253, a first-in-class molecule, is well tolerated to a TAD of 229 mg/m^2 without significant toxicity. A biomarker investigation has therefore been initiated with continued evaluation of PK and expansion for pre- and post-dose biopsies and correlative tissue analyses.

Background and Rationale

LOR-253 is a novel small molecule that is being developed by Lorus Therapeutics Inc. as an anticancer agent for treatment of solid tumors. In preclinical studies, LOR-253 has shown significant anticancer activity in a range of tumor types, including NSCLC and colon cancer, with minimal toxicity at efficacious doses.

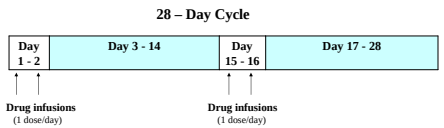
Efficacy and mechanism of action studies have revealed that the anticancer activity of LOR-253 is associated with induction of expression of KLF4, a tumor suppressor that is downregulated in several cancers including colon and NSCLC. Constitutive expression of KLF4 in cancer cell lines results in cell cycle arrest at G1/S due to increased expression of p27 and cyclin-dependent kinase inhibitor p21, both of which are induced by KLF4. In addition to cell cycle arrest, KLF4 also significantly inhibits cancer progression through induction of apoptosis and decreased metastasis.

Eligibility and Exclusion Criteria

Inclusion Criteria:
- Histologically confirmed diagnosis of solid tumor for which no effective therapy is available or that is unresponsive to conventional therapy.
- Meet laboratory parameter requirements at study entry.

Exclusion Criteria:
- Chemotherapy, radiotherapy, biologic therapy, immunotherapy or any other investigational drugs within 21 days of beginning study treatment with LOR-253.
- A hematologic malignancy.
- A history of brain or other central nervous system metastases.
- Uncontrolled intercurrent illness.
- With iron or copper overload syndromes.

Dose Schedule and Escalation Plan



Escalation Stage I: 100% dose increments until two patients within any accelerated dose level exhibit ≥ Grade 2 toxicity, or one patient exhibits a DLT.

Escalation Stage II: 30% dose increments until reaching target dose or either DLT defined MTD or MAD.

Summary of Patient Characteristics

Patient Characteristics	Category	No. (%) of Patients
Enrolled on Study	All Enrolled	27
Received Study Therapy	All Patients Dosed In Stage I Dose Escalation In Stage II Dose Escalation	24 (88.9) 7 (25.9) 17 (63.0)
Gender	Male Female	18 (66.7) 9 (33.3)
Race	White Black Other (Middle Eastern)	24 (88.9) 2 (7.4) 1 (3.7)
Age	Mean (range; yrs)	59.1 (range 39-75)
ECOG at Baseline	0 1	9 (33.3) 18 (66.7)
Primary Disease Site	Colon &/or Rectal Appendiceal Lung Esophageal Pancreatic Cholangiocarcinoma Urethral Uterus	16 (59.3) 3 (11.1) 2 (7.4) 2 (7.4) 1 (3.7) 1 (3.7) 1 (3.7) 1 (3.7)
Prior Chemo. Regimens	Median no. (range)	4 (1 – 7)
Reason for Off-Study	Objective disease progression Symptomatic deterioration Other* Serious or Intolerable Adverse Event Death**	10 (38.5) 4 (15.4) 8 (26.9) 4 (15.4) 1 (3.8)

*3 due to Investigator's clinical decision, 3 due to baseline failure/withdrawal, 1 due to CEA increase and 1 due to detection of brain metastases.
** Death 27-days post-last dose was due to hypercalcemia as a result of lung cancer.

Related Adverse Events by Severity–up to Target Dose

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥ Grade 3	Overall
Fatigue	3 (12.5%)	1 (4.2%)	0	0	0	0	4 (16.7%)
Infusion site inflammation	1 (4.2%)	0	0	0	0	0	1 (4.2%)
Hypersensitivity*	0	2 (8.3%)	0	0	0	0	2 (8.3%)
Arthralgia	1 (4.2%)	0	0	0	0	0	1 (4.2%)
Myalgia	1 (4.2%)	0	0	0	0	0	1 (4.2%)
Tinnitus	0	1 (4.2%)	0	0	0	0	1 (4.2%)
Constipation	0	1 (4.2%)	0	0	0	0	1 (4.2%)
Hypophosphatemia	0	0	1 (4.2%)	0	0	1 (4.2%)	1 (4.2%)
Neuropathy peripheral	1 (4.2%)	0	0	0	0	0	1 (4.2%)
Insomnia	0	1 (4.2%)	0	0	0	0	1 (4.2%)
Hiccups	1 (4.2%)	0	0	0	0	0	1 (4.2%)
Hyperhidrosis	0	1 (4.2%)	0	0	0	0	1 (4.2%)

* Hypersensitivity reaction in 2 patients resulted in implementation of routine pre-treatment prophylaxis for subsequent patients

Dose Limiting Toxicity by Dose Level Cohorts

Escalation Stage	LOR-253 (mg/m^2)	No. of DLT Assessable Patients.	No. of Cycles	DLT
I	20	1	2	0
I	40	1	2	0
I	80	3	5	Hypophosphatemia *
II	80	3	8	0
II	104	3	5	0
II	135	3	5	0
II	176	3	14	0
II	229	3	14	0

*DLT in escalation Stage I – hypophosphatemia was asymptomatic and reversible by supplementation, so by amendment not a DLT in Stage II

229 mg/m^2 was determined to be the target dose

Dose Escalation Extension – Preliminary Results

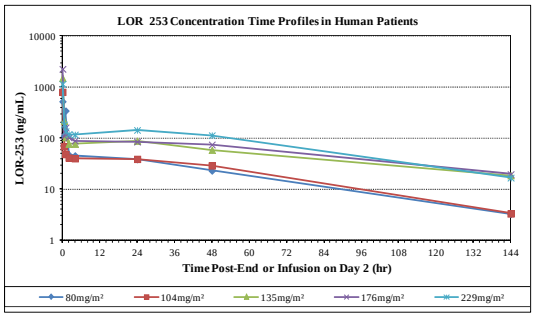
Dose Expanded*	No. of DLT Assessable Patients	DLT
298 mg/m^2	3	0
387 mg/m^2	3	2 (Hypersensitivity reaction**; Hypotension)

* In biopsy suitable patients – biomarker data not available

** Despite pre-treatment of Dexamethasone, Diphenhydramine and Famotidine

DLTs at 387 mg/m^2 determined MAD

Concentration Time Profile



Summary of Pharmacokinetic Parameters

LOR-253 concentration (Standard Deviation)					
Dose mg/m^2 (N)	Cycle 1 Day 1		Cycle 1 Day 2		Cycle 1 Day 2
	Cmax (ng/mL)	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	AUC(0-t) (ng·hr/mL)	T½ (hr)
20 (1)	86 (ID*)	44.7 (ID)	ID	ID	ID
40 (2)	295 (ID)	607 (ID)	162 (ID)	2540 (ID)	13.1 (ID)
80 (8)	656 (148)	768 (380)	602 (396)	4300 (3970)	27.2 (27.8)
104 (3)	679 (499)	896 (512)	800 (182)	2820 (1950)	48.5 (ID)
135 (3)	1820 (1780)	1300 (937)	1500 (973)	8320 (2350)	47.2 (ID)
176 (3)	1190 (974)	3650 (2370)	2250 (1910)	9320 (1830)	54.8 (12.5)
229 (4)	1190 (693)	2220 (740)	1140 (699)	9240 (3510)	52.3 (ID)

* Insufficient Data
4 fold AUC accumulation from Day 1 to Day 2. T½ with full 144 hr profile ranged from 44 to 61 hr

Patients with Stable Disease (SD) by RECIST

Dose Level (mg/m^2)	Patient	Primary Cancer Site	Best Response	Cycles Started / Completed	Time to Termination (days)	Status on Termination
80	1-11	Colon (Cecum)	SD	4 / 4	112	Progressive Disease (PD): New lesion
104	1-13	Colon (Recto-sigmoid)	SD	1 / 1*	28	SD with radiological deterioration
135	1-18	Colon	SD	2 / 1*	42	SD with symptomatic deterioration
176	2-22	Uterus (Corpus)	SD	6 / 6	168	SD with symptomatic deterioration
176	1-23	Appendix	SD	7 / 6	182	SD with clinical deterioration
229	1-24	Liver	SD	4 / 4	112	SD with clinical deterioration
229	2-27	Lung (& Bronchus)	SD	8 / 8	224	SD with brain metastases

* Early tumor assessment

Dose Relationship of Disease Stabilization

Dose Range (mg/m^2)	Evaluable no.	All SD: N=7 Duration: mean days (range)	SD ≥ 4 cycles: N=5 % of evaluable patients
20-135	12	57 (23-108)	8% (1/12)
176-229	5	167 (112-205)	80% (4/5)

Note: 176 mg/m^2 was the first dose to show sustained tumor stabilization. In higher dose range all SD remained stable on termination or last assessment.

Case Study

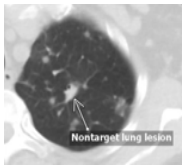
NSCLC Patient at 229 mg/m^2 Target Dose treated for 8 cycles

1. Female age 64 with poorly differentiated bronchogenic adenocarcinoma, heavily metastasized in lung, lymph and bone refractory to prior standard and investigational therapies
2. In 2½ months prior to study - most lung metastases increased in size
3. In 8 months on study treatment - Index tumors stable by RECIST and most non-index tumors decreased and some resolved
4. Withdrawn prior to Cycle 9 with detection of brain metastases

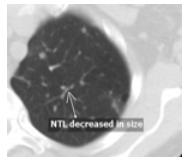
Target Lesions (Sum L.D. by RECIST 1.1)

Baseline	Cycle 2	Cycle 4	Cycle 6	Cycle 8
3.5 cm	3.0 cm	3.2 cm	3.4 cm	3.4 cm

Non-Target Lesions: Example of Regression



Non-target lung lesion at baseline



Non-target lung lesion at Cycle 2

Target Dose – 229 mg/m^2

1. Demonstrated sustained disease stabilizations not seen at doses below 176-229 mg/m^2 dose range
2. This dose corresponds approximately with the 40 mg/kg (human equivalent dose approximately 240 mg/m^2) for which significant efficacy and KLF4 induction was demonstrated with the same dose schedule preclinically
3. Higher doses are being explored in an extension study to explore a safety margin, but require longer infusions of ≥ 3 hours considered impractical for further development
4. Further optimization at the 229 mg/m^2 dose level is also being explored by dose schedule modification of the interval between dosing periods

Conclusions

1. LOR-253 was well tolerated in the dose range 20 mg/m^2 to 229 mg/m^2
2. Fatigue (16%) was the most frequent toxicity, and isolated reversible hypophosphatemia (Grade 3) was the only severe toxicity
3. Hypersensitivity was observed resulting in implementation of routine prophylaxis for all subsequent dosing
4. Pharmacokinetics was characterized by a rapid distribution phase < 2 hr and prolonged terminal phase >144 hr
5. Sustained disease stabilization activity maintained 4-8 cycles was observed at 176-229 mg/m^2 doses and not seen at lower doses. There was no CR or PR
6. 229 mg/m^2 was determined to be the target dose that was well tolerated without significant toxicities
7. An extension study is further exploring KLF4 determination in biopsy tissue and has determined safety margin above the target dose.
8. 387 mg/m^2 was the MAD in the extension study at which escalation was stopped due to toxicity