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Phase 1b/2 Trial of Taladegib (LY2940680), a Hh/Smo Inhibitor, in Combination with Carboplatin and Etoposide Followed by Taladegib Maintenance in Extensive-stage Small-cell Lung Cancer

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BACKGROUND

- Small-cell lung cancer (SCLC) is the most aggressive form of lung cancer;[1] although carboplatin and etoposide (C/E), a standard treatment for extensive-stage disease (ED-SCLC), can improve quality of life and prolong survival, the disease remains incurable[2]
- Activation of Type II and III Hedgehog (Hh) pathways (ligand dependent) and the Smoothened protein (Smo) has been implicated in ED-SCLC pathogenesis,[3] with *GLI1* overexpression reported in ≥50% of SCLC tumors[4]
- Preclinical studies found that SCLC cell lines increased expression of both Hh ligand and *GLI2* following exposure to C/E, and that C/E followed by Hh inhibitor (LDE-225) prevented tumor recurrence in mice bearing SCLC human xenografts, suggesting that C/E treatment precedes an emergence of cells upregulating the Hh pathway to survive and proliferate[5]
- Taladegib is a potent inhibitor of Hh signaling that binds to the Smo receptor and competitively inhibits binding of a known Smo agonist
- Based on these preclinical findings, the phase 1b part of a phase 1b/2 study in ED-SCLC was conducted

Study Objectives

- The primary objective of the phase 1b portion of this study was to determine a safe and tolerable dose of taladegib in combination with C/E for use during phase 2
- Secondary objectives included:
  - Pharmacokinetic (PK) assessment of taladegib and its major circulating and equipotent metabolite, LSN3185556
  - Documentation of any antitumor activity of the combined treatment
  - Pharmacodynamic (PD) assessment of the combined treatment by measuring changes in Hh pathway-related markers in skin samples

METHODS

Key Eligibility Criteria

- Histological or cytological diagnosis of SCLC with malignant pleural effusion graded as extensive stage per International Staging System
- Eastern Cooperative Oncology Group performance status of 0 to 1
- No prior systemic chemotherapy, immunotherapy, or biological therapy for SCLC
- At least 1 unidimensionally measurable lesion (RECIST v. 1.1)
- ≥18 years of age with ≥12 weeks life expectancy

Treatment

- Eligible patients received 100 mg, 200 mg, or 400 mg oral taladegib daily on a 21-day cycle in combination with C/E (carboplatin: AUC 5, IV, day 1; etoposide: 100 mg/m^2, IV, days 1-3) for at least 6 cycles, followed by taladegib monotherapy
- Taladegib dose escalation began at 100 mg and proceeded in cohorts of at least 6 evaluable patients until at least 2 patients experienced a dose-limiting toxicity or up to the 400 mg/day dosage

Figure 1. Study Design

ClinicalTrials.gov identifier: NCT01722292

RESULTS

Table 1. Patient Characteristics

	Total (N = 26)
Males, n (%)	13 (50.0)
Age, years	
Median	63.5
Range	43-84
Race, n (%)	
African-American	3 (11.5)
Caucasian	22 (84.6)
Not reported	1 (3.8)
Tobacco use, n (%)	
Previous	25 (96.2)
Current	14 (53.8)
Prior therapy, n (%)	
Surgery	14* (53.8)
ECOG PS, n (%)	
0	8 (30.8)
1	18 (69.2)

*Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status. *One patient also received radiotherapy*

Table 2. Patient Disposition

	100 mg (N = 6)	200 mg (N = 6)	400 mg (N = 14)	Total (N = 26)
Maximum number of treatment cycles started				
Median	6.0	6.0	4.5	6.0
Range	1-13	1-8	1-10	1-13
Primary reason for discontinuation, n (%)				
Adverse event	0	0	3 (21.4)	3 (11.5)
Acute myocardial infarction	0	0	1 (7.1)	1 (3.8)
Acute respiratory failure	0	0	1 (7.1)	1 (3.8)
Febrile neutropenia	0	0	1 (7.1)	1 (3.8)
Death	1 (16.7)	1 (16.7)	1 (7.1)	3 (11.5)
Study disease	0	1 (16.7)	0	1 (3.8)
Adverse event	0	0	1 (7.1)	1 (3.8)
Study drug toxicity	1 (16.7)	0	0	1 (3.8)
Subject decision	0	2 (33.3)	2 (14.3)	4 (15.4)
Progressive disease	5 (83.3)	3 (50.0)	8 (57.1)	16 (61.5)

Dose-limiting Toxicities and Deaths

- There were 4 dose-limiting toxicities
  - 100 mg: Grade 5 enterocolitis
  - 200 mg: Grade 1 dysgeusia*
  - 400 mg: Grade 4 neutropenia, grade 3 febrile neutropenia
- There were 15 deaths
  - 4 on study
    - Disease progression: 2
    - Study drug toxicity: 1 (neutropenia leading to enterocolitis)
    - AE not deemed to be related to study drug: 1 (intracranial hemorrhage)
  - 3 ≤30 days post-treatment discontinuation
    - Disease progression: 2
    - AE not deemed to be related to study drug: 1 (cause uncertain but judged by investigator to be respiratory failure related to disease progression)
  - 8 >30 days post-treatment discontinuation
    - Disease progression: 7
    - AE not deemed to be related to study drug: 1 (intestinal ischemia)

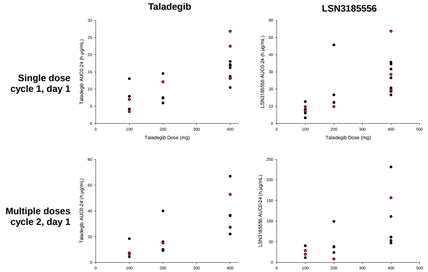
** Patient's dysgeusia was complicated by dehydration and subsequent hospitalization*

Table 3. Maximum Grade TEAEs Possibly Related to Study Drug in ≥25% of Patients

	Treated Patients (%) (N = 26)		
Event	Grade 1-2	Grade ≥3	Total
Dysgeusia	14 (53.8)	0	14 (53.8)
Fatigue	11 (42.3)	2 (7.7)	13 (50.0)
Neutropenia	1 (3.8)	11 (42.3)	12 (46.2)
Nausea	11 (42.3)	0	11 (42.3)
Muscle spasms	9 (34.6)	0	9 (34.6)
Alopecia	8 (30.8)	0	8 (30.8)
Vomiting	7 (26.9)	1 (3.8)	8 (30.8)
Decreased appetite	8 (30.8)	0	8 (30.8)
Anemia	6 (23.1)	2 (7.7)	8 (30.8)
Thrombocytopenia	2 (7.7)	5 (19.2)	7 (26.9)

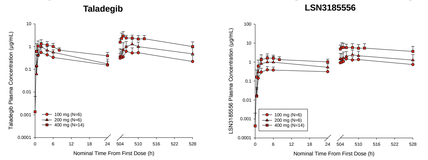
Abbreviation: TEAEs = Treatment-emergent adverse events. MedDRA 18.0 terminology

Figure 2. Individual Taladegib and LSN3185556 AUC_{0-24} after Taladegib in Combination with Carboplatin and Etoposide



- Patients experiencing taladegib-related grades 3-4 AEs during cycle 1 are represented in red
- PK analysis showed no clear relationship between exposure and toxicity

Figure 3. Arithmetic Mean (SD) of Taladegib and LSN3185556 after Taladegib in Combination with Carboplatin and Etoposide



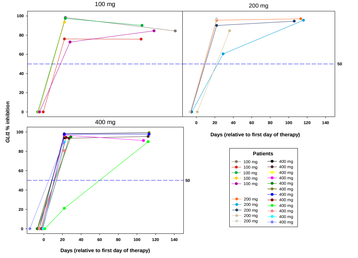
- The mean ± standard deviation profiles for taladegib and LSN3185556 are shown for both cycle 1, day 1 and cycle 2, day 1 following administration of taladegib in combination with carboplatin and etoposide
- PK variability was approximately 65% for both taladegib and LSN3185556
- LSN3185556 concentrations were on average higher than taladegib concentrations both on cycle 1, day 1 and cycle 2, day 1; accumulation after daily dosing was also higher for LSN3185556 compared to taladegib

Table 4. Response and Progression-free Survival

	100 mg (N = 6)	200 mg (N = 6)	400 mg (N = 14)	Total (N = 26)
Complete response (CR)	0	0	0	0
Partial response (PR), n (%)	3 (50.0)	3 (50.0)	8 (57.1)	14 (53.8)
90% CI	16.4, 83.6	16.4, 83.6	35.4, 78.9	37.8, 69.9
Stable disease (SD), n (%)	2 (33.3)	1 (16.7)	4 (28.6)	7 (26.9)
90% CI	1.7, 65.0	0.0, 41.7	8.7, 48.4	12.6, 41.2
Progressive disease	0	0	0	0
Not assessed*	1 (16.7)	2 (33.3)	2 (14.3)	5 (19.2)
Objective response (CR + PR), n (%)	3 (50.0)	3 (50.0)	8 (57.1)	14 (53.8)
90% CI	16.4, 83.6	16.4, 83.6	35.4, 78.9	37.8, 69.9
Clinical benefit (CR + PR + SD), n (%)	5 (83.3)	4 (66.7)	12 (85.7)	21 (80.8)
90% CI	58.3, 100.0	35.0, 98.3	70.3, 100.0	68.1, 93.5
Median progression-free survival, months				4.5
90% CI				3.0, 6.0
Median duration of response, months				4.6
90% CI				3.0, 6.1

*Abbreviation: CI = confidence interval. *Patients discontinued prior to efficacy assessment*

Figure 4. *GLI1* Inhibition in Skin by Patient



- Although the plasma exposures increased with dose, the levels of *GLI1* inhibition in normal skin are consistently high (>70%) across all doses tested, indicating a robust PD effect

CONCLUSIONS

- The recommended phase 2 dose for taladegib in combination with C/E is 400 mg/day
- The type and frequency of TEAEs observed in this combination are comparable to those seen with another Hh/Smo antagonist given in combination with C/E[6]
- The PK profiles of taladegib and LSN3185556 in this combination study are consistent with those obtained in a taladegib monotherapy study
- *GLI1* inhibition was high across all doses, suggesting robust target engagement in the dose range tested
- Due to limited enrollment and the emergence of clinical data from another agent in the same class, the study was discontinued prior to phase 2

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References:

1. Jackman DM, Johnson BE. *Lancet* 2005;366:1385-96.
2. Kalemkerian GP. *Expert Opin Pharmacother* 2014;15:2385-96.
3. Watkins DN, et al. *Nature* 2003;422:313-7.
4. Vestergaard J, et al. *Lung Cancer* 2006;52:281-90.
5. Park KS, et al. *Nat Med* 2011;17:1504-8.
6. Belani CP, et al. *Cancer* 2016;122:2371-8.