



A Phase II Trial of Prexasertib (LY2606368) in Patients With Extensive-Stage Small-Cell Lung Cancer

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Abstract

Patients with extensive-stage small-cell lung cancer (ED-SCLC) need improved outcomes in the relapsed/refractory setting. This phase II study evaluated the safety and efficacy of prexasertib, a checkpoint kinase 1 inhibitor, in platinum-sensitive and platinum-refractory ED-SCLC. Prexasertib demonstrated response rates of 5.2% in platinum-sensitive and 0% in platinum-refractory ED-SCLC. Prexasertib did not show prespecified efficacy as monotherapy in ED-SCLC.

Background: This study assessed the checkpoint kinase 1 inhibitor prexasertib in patients with extensive-stage small-cell lung cancer (ED-SCLC). **Patients and Methods:** This was a parallel-cohort phase II study of 105 mg/m² prexasertib once every 14 days for patients who progressed after no more than two prior therapies and had platinum-sensitive (Cohort 1) or platinum-resistant/platinum-refractory (Cohort 2) disease. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and pharmacokinetics. Exploratory endpoints included biomarker identification and assessment of an alternative regimen (Cohort 3: 40 mg/m² days 1-3, 14-day cycle). **Results:** In Cohort 1 ($n = 58$), ORR was 5.2%; DCR, 31%; median PFS, 1.41 months (95% confidence interval [CI], 1.31-1.64); and median OS, 5.42 months (95% CI, 3.75-8.51). In Cohort 2 ($n = 60$), ORR was 0%; DCR, 20%; median PFS, 1.36 months (95% CI, 1.25-1.45); and median OS, 3.15 months (95% CI, 2.27-5.52). The most frequent all-grade, related, treatment-emergent adverse events were decreased neutrophil count (Cohort 1, 69.6%; Cohort 2, 73.3%), decreased platelet count (Cohort 1, 51.8%; Cohort 2, 50.0%), decreased white blood cell count (Cohort 1, 28.6%; Cohort 2, 40.0%), and anemia (Cohort 1, 39.3%; Cohort 2, 28.3%). Eleven patients (19.6%) in Cohort 1 and one patient (1.7%) in Cohort 2 experienced grade ≥ 3 febrile neutropenia. Prexasertib pharmacokinetics were consistent with prior studies. Cohort 3 outcomes were similar to those of Cohorts 1 and 2. No actionable biomarkers were identified. **Conclusion:** Prexasertib did not demonstrate activity to warrant future development as monotherapy in ED-SCLC.

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Introduction

Patients with small-cell lung cancer (SCLC) have a dismal prognosis with a 5-year survival rate of less than 7%.^{1,2} A total of 60% to 70% of patients with SCLC present with extensive-stage disease (ED-SCLC).² Recently, the US Food and Drug Administration (FDA) approved either durvalumab or atezolizumab in

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Phase II Trial of Prexasertib for ED-SCLC

combination with platinum–etoposide as first-line therapy for patients with ED-SCLC.³⁻⁶ Although most patients respond to first-line treatment with response rates of approximately 60% to 68% with or without immune checkpoint inhibitors,^{3,4} the majority of patients with ED-SCLC relapse within a few months, and nearly all will eventually succumb to their disease.⁷

In the second-line setting, treatment options are limited for patients with ED-SCLC. Platinum-sensitive patients receiving topotecan have a response rate of 23%, and platinum-refractory patients have a response rate of 9%,⁸ but the responses are not durable.^{9,10} Encouragingly, lurbinectedin, a selective oncogenic transcription inhibitor, was recently granted accelerated approval by the FDA for patients with SCLC who progressed on or after platinum chemotherapy based on a response rate of 35.2% (95% confidence interval [CI], 26.2-45.2) and median response duration of 5.3 months (95% CI, 4.1-6.4) by independent assessment in a single-arm study.¹¹

There is still a critical need for novel treatment options that will improve outcomes in platinum-resistant or platinum-refractory patients. SCLC is characterized by factors that may predict sensitivity to prexasertib such as increased replication stress, a high rate of somatic mutations, genomic instability, and the near ubiquitous inactivation of tumor protein 53 (*TP53*) and retinoblastoma 1 (*RBI*), which leads to the increased expression of DNA damage response mediators poly (ADP-ribose) polymerase 1 (PARP1) and checkpoint kinase 1 (CHK1).^{2,12,13} Approximately 20% of SCLC tumors have *MYC* alterations, and the amplification or overexpression of *MYC* in SCLC cell lines was associated with increased sensitivity to CHK1 inhibitors.¹³ Additionally, CHK1 was identified as a candidate drug target in SCLC in an unbiased high-throughput drug screen.¹⁴ Prexasertib (LY2606368) is an adenosine-5'-triphosphate-competitive inhibitor of CHK1 that regulates DNA replication and the DNA damage response.^{13,15} In vitro and in vivo data from SCLC models demonstrated that prexasertib had single-agent anti-tumor activity, enhanced the effects of cisplatin or olaparib, and improved the response of platinum-resistant models.¹³ Prexasertib was evaluated as monotherapy in a multi-center, non-randomized, open-label, dose-escalation study followed by a cohort expansion study in patients with advanced cancer (I4D-MC-JTJA [JTJA]; NCT01115790).¹⁵ Patients received prexasertib on days 1, 2, and 3 of a 14-day cycle (schedule 1) or on day 1 of a 14-day cycle (schedule 2). Maximum tolerated doses of 40 mg/m² (schedule 1) and 105 mg/m² (schedule 2) were established. Both schedules had similar predicted efficacy/exposure relationships and safety profiles, but as a result of the increased patient convenience, schedule 2 (105 mg/m² prexasertib on day 1 of a 14-day schedule) was selected as the recommended phase II dose.¹⁵ Thus, we conducted a multi-center, non-randomized, parallel-cohort phase II study of prexasertib at 105 mg/m² every 14 days in patients with ED-SCLC who had either platinum-sensitive or platinum-resistant/-refractory disease.

Patients and Methods

Study Design and Eligibility Criteria

The JTJH study (I4D-MC-JTJH; NCT02735980) enrolled patients with a histological or cytological diagnosis of ED-SCLC who had received a prior platinum-based regimen, had an Eastern

Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, had at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1¹⁶, and had adequate organ function. Patients were included only if they had received no more than two prior lines of therapy for ED-SCLC (including immunotherapy, targeted therapies, or chemotherapy) and did not have symptomatic or unstable central nervous system metastases or a second primary malignancy.

This phase II study used a parallel-cohort design. Cohort 1 included patients with an objective response to prior platinum-based therapy with subsequent progression ≥ 90 days after the last dose of platinum (platinum-sensitive). If a patient had previously had more than one line of platinum therapy, the platinum sensitivity was to be determined from the last exposure to platinum. Cohort 2 included patients who either did not have an objective response to prior platinum-based therapy or had progression < 90 days after the last dose of platinum (platinum-resistant or platinum-refractory, respectively). In addition, an exploratory Cohort 3 was added to explore antitumor activity of an alternate regimen of prexasertib in patients with platinum-sensitive ED-SCLC (described separately).

Treatment Administration

Patients in Cohorts 1 and 2 received 105 mg/m² prexasertib as a 60 (+10)-minute intravenous infusion on day 1 of a 14-day cycle. In the exploratory Cohort 3, prexasertib 40 mg/m² was administered on days 1, 2, and 3 of a 14-day cycle. An interval of at least 14 days was maintained between doses, with the cycle length extended to accommodate any delays. The actual doses of prexasertib administered were determined by calculating the patient's body surface area at the beginning of each cycle. Treatment continued until patient showed evidence of progressive disease or experienced unacceptable toxicity or met other discontinuation criteria.

Endpoints and Assessments

The primary endpoint was investigator-assessed objective response rate (ORR) of 105 mg/m² prexasertib every 14 days administered to enrolled patients with ED-SCLC who had platinum-sensitive disease (Cohort 1) or platinum-resistant/platinum-refractory disease (Cohort 2). Objective response rate was defined as the proportion of patients who achieved a best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1. Tumor assessments were performed every 6 weeks for the first 52 weeks and then every 12 weeks thereafter. Secondary endpoints were safety and toxicity, pharmacokinetics (PK), and other efficacy measures including disease control rate (DCR); patients who achieved a best overall response of CR, PR, or stable disease (SD); duration of response (DoR); overall survival (OS); and progression-free survival (PFS). DoR was defined as the time from the date of first objective response until the first radiographic documentation of progression or death from any cause. OS was defined as the time from enrollment until death from any cause. PFS was defined as the time from enrollment until the first radiographic documentation of progression or death from any cause.

Safety was assessed in all patients who received one dose of study therapy using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Exploratory

objectives included assessment (antitumor activity, PK, OS, PFS) of an alternate regimen of prexasertib in patients with ED-SCLC and platinum-sensitive disease (Cohort 3) and the evaluation of biomarkers in all cohorts.

Pharmacokinetic Analyses

Blood samples were collected from patients who received at least one dose of prexasertib for PK analysis. Samples were analyzed using a validated liquid chromatography–mass spectrometry/mass spectrometry method. Pharmacokinetics were summarized by descriptive statistics. The observed prexasertib PK data combined during cycles one to seven were compared with historical prexasertib monotherapy PK data from the JTJA study to confirm the expected systemic exposure of prexasertib.¹⁵

Biomarker Analyses

Potential predictive or prognostic biomarkers were also evaluated. The association between clinical response and log₂ relative gene expression for a select set of genes related to cell-cycle regulation and DNA damage response (see Supplemental Table A1 in the online version at doi:10.1016/j.clcc.2021.04.005), with a focus on *MYC*, was evaluated in RNA extracted from formalin-fixed paraffin-embedded tumor tissue specimens using a quantitative multiplex expression assay (QIAGEN Modaplex[®] system) at the Eli Lilly and Company Clinical Diagnostics Laboratory as described previously.^{17,18}

Statistical Considerations

For the platinum-sensitive cohort (Cohort 1), it was assumed that a true ORR of less than 20% indicated inadequate antitumor activity. A sample size of 58 patients provided approximately 90% power to detect a true ORR of at least 35%: 16 or more confirmed overall responses (CR or PR) observed in all 58 patients. For the platinum-refractory/-resistant cohort (Cohort 2), it was assumed that a true ORR of less than 5% indicated inadequate antitumor activity. A sample size of 58 patients provided approximately 90% power to detect a true ORR of at least 15%: six or more confirmed overall responses (CR or PR) observed in all 58 patients. For Cohort 3, a sample size of 15 patients was selected to allow adequate assessment of safety at the recommended dose and explore preliminary antitumor activity. ORRs and DCRs with 95% CIs were summarized for each cohort using the Clopper–Pearson method. OS and PFS curves were estimated for each cohort using the Kaplan–Meier method. For patients alive or lost to follow-up at the time of analysis, OS time was censored on the last date the patient was known to be alive. For patients known to be alive and without disease progression, PFS time was censored at the last adequate tumor assessment. Analyses similar to those described were done in exploratory Cohort 3.

The *t*-test was used with multiplicity adjustment using a Bonferroni correction to evaluate differences in gene expression between disease control categories (CR/PR/SD vs. progressive disease [PD]); logistic regression was used to assess the relationship between disease control categories and gene expression using quantile cutpoints (25, 50, and 75) with multiplicity adjustment using Holm stepdown adjusted *P* values for control of the family-wise error rate.¹⁹

Results

Patients

Between May 11, 2016, and February 12, 2019, a total of 118 patients were enrolled in Cohorts 1 and 2, and 116 patients (safety population) received at least one dose of the study drug. Fifty-six of 58 patients (96.6%) in Cohort 1 and 60 patients (100%) in Cohort 2 received prexasertib. Two patients (3.4%) in Cohort 1 were not treated as a result of physician decision. Characteristics of the 118 enrolled patients are in Table 1. A majority of patients were male. The median age was 62 years (38–85 years). Most patients (Cohort 1, 69.0%; Cohort 2, 68.3%) had an ECOG PS of 1 (Table 1). A total of five patients—three (5.2%) in Cohort 1 and two (3.3%) in Cohort 2—had received prior nivolumab treatment, four of whom received nivolumab as their immediate prior therapy (two in Cohort 1 and two in Cohort 2).

Treatment Received

An overview of treatment exposure is summarized in Table 2. Dose adjustments were required in 65 of 116 treated patients (56.0%) in Cohorts 1 and 2. In Cohort 1, adverse events (AEs) leading to dose reductions included decreased platelet count (five of 56 patients; 8.9%), decreased neutrophil count (four patients; 7.1%), febrile neutropenia (three patients; 5.4%), fatigue (two patients; 3.6%), anemia (one patient; 1.8%), and prolonged QT (one patient; 1.8%). In Cohort 2, AEs leading to dose reductions included decreased neutrophil count (four of 60; 6.7%), febrile neutropenia, decreased platelet count, laryngeal hemorrhage, and vomiting (one patient each; 1.7% each).

All 116 treated patients in Cohorts 1 and 2 discontinued study treatment. The reasons for discontinuation in Cohort 1 were progressive disease for 40 of 58 enrolled patients (69.0%), death due to a treatment-related AE or study disease for eight patients (13.8%), AEs for three patients (5.2%), physician decision for four patients (6.9%), and withdrawal by one patient (1.7%). In Cohort 1, one patient (1.7%) was discontinued due to an AE of acute encephalopathy, secondary to grade 3 pneumonia and grade 3 respiratory failure, which was deemed to be possibly treatment related. The patient was not neutropenic at the time of pneumonia/respiratory failure. Additionally, AEs deemed not related to prexasertib that caused discontinuation were bronchitis and pericardial effusion (one patient each; 1.7% each).

The reasons for discontinuation in Cohort 2 were progressive disease for 45 of 60 patients (75.0%), death due to study disease for seven patients (11.7%), AEs for four patients (6.7%), physician decision for two patients (3.3%), and withdrawal by two patients (3.3%). One of the AEs that led to study discontinuation and was considered treatment related was grade 2 decreased white blood cell count in one patient (1.7%). Adverse events leading to discontinuation that were considered not related to prexasertib included grade 1 abdominal pain, grade 4 acute kidney injury, and grade 2 dyspnea (one patient each; 1.7% each).

Efficacy

The confirmed ORR for patients in Cohort 1 was 5.2% (three patients with PR) and 0% in Cohort 2 (Table 3). Most patients in the study had PD (51.7% in Cohort 1 and 61.7% in Cohort 2) as

Phase II Trial of Prexasertib for ED-SCLC

Table 1 Baseline Demographics and Disease Characteristics (Enrolled Population)

Demographic	n (%)		
	Cohort 1 Platinum-Sensitive ED-SCLC (n = 58)	Cohort 2 Platinum-Refractory ED-SCLC (n = 60)	Total (N = 118)
Age (y), median (range)	63.5 (47-85)	62 (38-76)	62 (38-85)
Sex, male	35 (60.3)	50 (83.3)	85 (72.0)
Race			
White	50 (86.2)	47 (78.3)	97 (82.2)
African American	2 (3.4)	1 (1.7)	3 (2.5)
Asian	2 (3.4)	8 (13.3)	10 (8.5)
Missing	4 (6.9)	4 (6.7)	8 (6.8)
ECOG PS			
0	15 (25.9)	19 (31.7)	34 (28.8)
1	40 (69.0)	41 (68.3)	81 (68.6)
2	1 (1.7)	0	1 (0.8)
Missing	2 (3.4)	0	2 (1.7)
Prior anticancer therapy			
Surgical procedure	3 (5.2)	4 (6.7)	7 (5.9)
Radiotherapy	51 (87.9)	41 (68.3)	92 (78.0)
Systemic therapy	57 (98.3) ^a	60 (100.0)	117 (99.2)
Surgical procedure: intent			
Curative intent	0	1 (1.7)	1 (0.8)
Palliative intent	3 (5.2)	3 (5.0)	6 (5.1)
Radiotherapy: reason			
Curative	12 (20.7)	11 (18.3)	23 (19.5)
Other	1 (1.7)	2 (3.3)	3 (2.5)
Palliative	28 (48.3)	26 (43.3)	54 (45.8)
Prophylactic	24 (41.4)	13 (21.7)	37 (31.4)
Radiosensitizing	1 (1.7)	2 (3.3)	3 (2.5)
Systemic therapy: reason and type			
Adjuvant	2 (3.4)	3 (5.0)	5 (4.2)
Locally advanced	10 (17.2)	13 (21.7)	23 (19.5)
Metastatic	43 (74.1)	48 (80.0)	91 (77.1)
Neoadjuvant	7 (12.1)	0 (0.0)	7 (5.9)
Systemic therapy for locally advanced/metastatic disease			
1 regimen	35 (60.3)	31 (51.7)	66 (55.9)
2 regimens	13 (22.4)	26 (43.3)	39 (33.1)
3 regimens ^b	1 (1.7)	1 (1.7)	2 (1.7)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ED-SCLC = extensive-stage small-cell lung cancer.

^a One patient who was assigned to Cohort 1 was a screen failure and did not receive treatment. As a result, the prior therapy was not entered.

^b The patients who received three regimens received one of the regimens for locally advanced disease.

the best response to treatment. The DCR was 31.0% for Cohort 1 and 20.0% for Cohort 2. One patient in Cohort 1 and two patients in Cohort 2 had duration of stable disease of >5 months (5.8 months, 6.0 months, and 8.8 months, respectively). None of the four patients who had immunotherapy as their immediate prior therapy had an objective response. Waterfall plots of change in tumor size for patients in Cohorts 1 and 2 are presented in Figure 1. The individual DoR for the three partial responders in Cohort 1 were 4.2 months, 5.7 months, and 5.0 months. Median PFS was 1.41 months (95% CI, 1.31-1.64) for Cohort 1 (58 patients with 54 events) and 1.36 months (95% CI, 1.25-1.45) for Cohort 2 (60 patients with 60 events). Median OS was 5.42 months (95% CI,

3.75-8.51) for Cohort 1 and 3.15 months (95% CI, 2.27-5.52) for Cohort 2.

Safety

Treatment-emergent AEs (TEAEs) related to study treatment that occurred in ≥10% of the total safety population are shown in Table 4, and all-cause TEAEs that occurred in ≥10% of the total safety population are shown in Supplemental Table A2 (see the online version at doi:10.1016/j.clcc.2021.04.005). The most frequent grade ≥3 TEAEs related to study treatment were decreased neutrophil count (57.1% in Cohort 1 and 71.7% in Cohort 2), and decreased platelet count (26.8% and 25.0%, respectively) (Table 4).

Table 2 Prexasertib Exposure (Safety Population)

	Cohort 1 Platinum-Sensitive ED-SCLC (n = 56)	Cohort 2 Platinum-Refractory ED-SCLC (n = 60)
Median dose intensity (mg/m ² /wk)	47.37	51.58
Median relative dose intensity (%)	90.24	98.26
Dose adjustments ^a , n (%)	37 (66.1)	28 (46.7)
Reductions	18 (32.1)	8 (13.3)
Due to AEs	16 (28.6)	8 (13.3)
Decreased neutrophil count ^b	4 (7.1)	4 (6.7)
Febrile neutropenia	3 (5.4)	1 (1.7)
Decreased platelet count ^b	5 (8.9)	1 (1.7)
Fatigue	2 (3.6)	0
Other	2 (3.6)	0
Delays ^b	32 (57.1)	23 (38.3)
Due to AEs	25 (44.6)	19 (31.7)
Decreased platelet count ^b	12 (21.4)	10 (16.7)
Decreased neutrophil count ^b	8 (14.3)	3 (5.0)
Febrile neutropenia	3 (5.4)	1 (1.7)
Due to scheduling conflict	11 (19.6)	7 (11.7)
Omissions	5 (8.9)	2 (3.3)
Due to AEs	4 (7.1)	1 (1.7)
Thrombocytopenia	2 (3.6)	0

Abbreviations: AEs = adverse events; ED-SCLC = extensive-stage small-cell lung cancer.

^a Only events occurring in more than one patient in either cohort are listed.

^b Combined terms, such that decreased neutrophil count includes neutropenia, and decreased platelet count includes thrombocytopenia.

Table 3 Response (Enrolled Population).

Response	n (%) [95% CI]	
	Cohort 1 Platinum-Sensitive ED-SCLC (n = 58)	Cohort 2 Platinum-Refractory ED-SCLC (n = 60)
CR	0 [0.0-4.1]	0 [0.0-3.7]
PR	3 (5.2) [0.7-9.6]	0 [0.0-3.7]
SD	15 (25.9) [9.9-26.6]	12 (20.0) [6.6-20.6]
PD	30 (51.7) [24.3-45.0]	37 (61.7) [28.5-48.6]
Objective	30 (51.7) [24.3-45.0]	35 (58.3) [26.6-46.5]
Clinical	0 [0.0-4.1]	2 (3.3) [0.3-7.3]
Non-evaluable	10 (17.2) [5.6-19.9]	11 (18.3) [5.8-19.4]
Overall response rate (CR/PR)	3 (5.2) [0.7-9.6]	0 [0-3.7]
Disease control rate (CR/PR/SD)	18 (31.0) [12.6-30.4]	12 (20.0) [6.6-20.6]

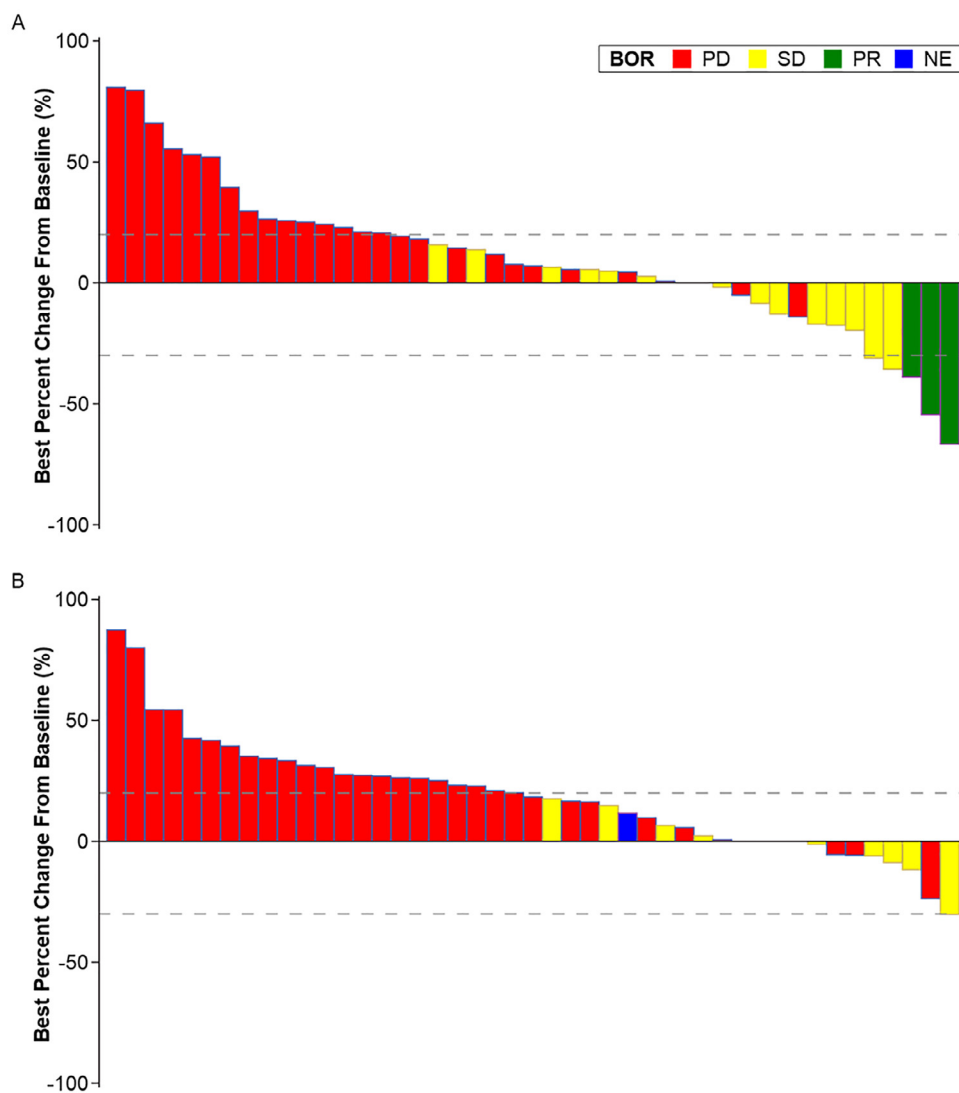
Abbreviations: CI = confidence interval; CR = complete response; ED-SCLC = extensive-stage small-cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease.

The most common treatment-related any-grade non-hematologic toxicities for both cohorts (116 total) included fatigue (25.9%; grade ≥2, 15.5%; grade ≥3, 4.3%) and nausea (12.1%; grade ≥2, 4.3%; grade, ≥3: 0) (Table 4). A total of 14 patients (25.0%) in Cohort 1 and nine patients (15.0%) in Cohort 2 experienced serious adverse events (SAEs) related to study treatment, including febrile neutropenia (7.8%; combined cohorts), decreased platelet count (6.0%), and decreased neutrophil count (3.4%). Anemia, decreased appetite, and fatigue each occurred in one patient (1.7% each; combined cohorts), and 2.9% of patients had sepsis. Supplemental

Table A3 (see the online version at doi:10.1016/j.clcc.2021.04.005) outlines the SAEs by cohort.

A total of 17 of 116 patients (14.7%) died while on therapy. Five patients (8.9%) in Cohort 1 and all seven patients (11.7%) in Cohort 2 died due to study disease. Five deaths (8.9%) in Cohort 1 were due to AEs, of which ischemic colitis, fatigue, and sepsis (one patient each; 1.8% each) were deemed related to study treatment. The AEs unrelated to study treatment were bronchitis and pericardial effusion (one patient each; 1.8% each). An additional patient experienced a rapid deterioration 22 days after the start of

Figure 1 Waterfall Plot of Percentage of Change in Tumor Size (RECIST 1.1 Criteria) from Baseline. The best percent change in tumor size from baseline for evaluable patients in Cohort 1 (A) and in Cohort 2 (B). Hashed lines represent 20% and -30% change in tumor size from baseline. Abbreviations: BOR = best overall response; PD = progressive disease; SD = stable disease; PR = partial response; NE = not evaluable.



treatment and died 24 days after receiving the first and only dose of prexasertib. This patient experienced SAEs of fatigue and anorexia, with a fatal outcome. The events in this patient were confirmed by the investigator to be due to disease progression. Five patients (8.9%) in Cohort 1 and 16 patients (26.7%) in Cohort 2 died within 30 days of discontinuation of study therapy; the reason for all deaths was study disease.

Prexasertib Plasma Concentrations

A total of 767 plasma samples were collected from 115 patients enrolled in Cohorts 1 and 2 and analyzed to determine the prexasertib plasma concentration. Plasma concentrations of prexasertib

following administration of 105 mg/m² on day 1 of cycles one to seven are summarized in Supplemental Table A4 (see the online version at doi:10.1016/j.clcc.2021.04.005), and plasma concentrations following administration of 80 mg/m² prexasertib on day 1 of cycles three to seven in 23 patients are summarized in Supplemental Table A5 (see the online version at doi:10.1016/j.clcc.2021.04.005). The prexasertib PK data displayed a high degree of concordance with the prexasertib monotherapy population PK model-predicted PK profile across days and cycles of treatment (see Supplemental Figure A1 in the online version at doi:10.1016/j.clcc.2021.04.005), indicating that the expected systemic exposure of prexasertib following administration of the recommended phase II dose (105 mg/m²)

Table 4 TEAEs (Any Grade in ≥10% of Total Population) Related to Study Treatment (Safety Population)

Preferred Term	n (%)					
	Cohort 1 Platinum-Sensitive ED-SCLC (n = 56)		Cohort 2 Platinum-Refractory ED-SCLC (n = 60)		Total (N = 116)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	51 (91.1)	39 (69.6)	55 (91.7)	50 (83.3)	106 (91.4)	89 (76.7)
Decreased neutrophil count	39 (69.6)	32 (57.1)	44 (73.3)	43 (71.7)	83 (71.6)	75 (64.7)
Decreased platelet count	29 (51.8)	15 (26.8)	30 (50.0)	15 (25.0)	59 (50.9)	30 (25.9)
Decreased white blood cell count	16 (28.6)	13 (23.2)	24 (40.0)	17 (28.3)	40 (34.5)	30 (25.9)
Anemia	22 (39.3)	7 (12.5)	17 (28.3)	7 (11.7)	39 (33.6)	14 (12.1)
Fatigue	17 (30.4)	3 (5.4)	13 (21.7)	2 (3.3)	30 (25.9)	5 (4.3)
Nausea	7 (12.5)	0	7 (11.7)	0	14 (12.1)	0
Decreased appetite	6 (10.7)	2 (3.6)	7 (11.7)	0	13 (11.2)	2 (1.7)
Febrile neutropenia	11 (19.6)	11 (19.6)	1 (1.7)	1 (1.7)	12 (10.3)	12 (10.3)

Abbreviations: ED-SCLC = extensive-stage small-cell lung cancer; TEAE = treatment-emergent adverse event.

was achieved and was in a predicted efficacious exposure range. Patients that were dose reduced to 80 mg/m² also demonstrated concordance with the population PK model-predicted PK profile for an 80-mg/m² dose. Across cohorts, there was no unexpected accumulation of prexasertib when administered at 105 mg/m² across cycles one to seven or when the dose was reduced to 80 mg/m² across cycles three to seven (see Supplemental Figure A1 in the online version at doi:10.1016/j.clcc.2021.04.005).

Exploratory Cohort 3

Patients and Treatment. Fifteen patients with platinum-sensitive ED-SCLC were enrolled in the exploratory Cohort 3 and received at least one dose of prexasertib at 40 mg/m² administered on days 1, 2, and 3 of a 14-day cycle. Eleven patients were males, and four patients were females. A total of nine patients (60.0%) had an ECOG PS of 1, whereas the remaining six patients (40.0%) had an ECOG PS of 0. Eleven patients (73.3%) in Cohort 3 needed at least one dose adjustment: eight patients (53.3%) had a dose reduction, and eight patients (53.3%) had a dose delay. All of these adjustments were due to AEs, most frequently due to decreased neutrophil count and decreased platelet count. All patients in Cohort 3 discontinued study treatment. The main reason for discontinuation was PD (11 patients; 73.3%). Other reasons were physician decision (two patients; 13.3%), adverse event related to study treatment (one patient; 6.7%), or death (one patient; 6.7%).

Efficacy. No objective responses were observed in Cohort 3; however, six patients (40.0%) had a best response of SD (see Supplemental Figure A2 in the online version at doi:10.1016/j.clcc.2021.04.005), with relatively long duration for two of these patients (5.7 and 6.4 months, respectively). Median PFS was 1.58 months (95% CI, 1.38-3.12). Median OS was 7.26 months (95% CI, 2.00-9.49).

Safety. Treatment-emergent AEs related to study treatment in Cohort 3 are shown in Table 5, and all TEAEs regardless of causality are presented in Supplemental Table A6 (see the online version at doi:10.1016/j.clcc.2021.04.005). The most frequent grade ≥3

Table 5 TEAEs (Any Grade in ≥10%) Related to Study Treatment by Decreasing Frequency (Safety Population) in Cohort 3

Preferred Term	Cohort 3 (n = 15), n (%)	
	Any Grade	Grade ≥3
Patients with ≥1 TEAE	15 (100.0)	13 (86.7)
Decreased platelet count	13 (86.7)	6 (40.0)
Decreased neutrophil count	12 (80.0)	12 (80.0)
Anemia	9 (60.0)	2 (13.3)
Fatigue	7 (46.7)	1 (6.7)
Decreased white blood cell count	5 (33.3)	3 (20.0)
Febrile neutropenia	3 (20.0)	3 (20.0)
Decreased lymphocyte count	3 (20.0)	1 (6.7)
Decreased appetite	3 (20.0)	0
Vomiting	2 (13.3)	0
Nausea	2 (13.3)	0
Diarrhea	2 (13.3)	0
Stomatitis	2 (13.3)	1 (6.7)
Pyrexia	2 (13.3)	0
Lung infection	2 (13.3)	2 (13.3)

Abbreviation: TEAE = treatment-emergent adverse event.

TEAEs related to study treatment were decreased neutrophil count in 12 patients (80.0%), decreased platelet count in six patients (40.0%), decreased white blood cell count in three patients (20.0%), and febrile neutropenia in three patients (20.0%). The most common any-grade non-hematologic toxicities included fatigue (46.7%) and decreased appetite (20.0%). Four patients experienced SAEs related to study treatment: febrile neutropenia and lung infection, each experienced by two patients (13.3%). A total of 11 patients (73.3%) in Cohort 3 died. Two patients (13.3%) died on therapy due to AEs of treatment-related pneumonia or treatment-unrelated subdural hematoma (one patient each; 6.7% each). Two patients (13.3%) died within 30 days of

Phase II Trial of Prexasertib for ED-SCLC

discontinuation of study therapy; both deaths were due to study disease.

Pharmacokinetics. A total of 249 plasma samples were collected from 16 patients enrolled in Cohort 3 and analyzed to determine the prexasertib plasma concentration. The eight patients that required a dose reduction to 30 mg/m² had PK samples collected after receiving the protocol-defined starting dose of 40 mg/m². Plasma concentrations of prexasertib following administration of 40 mg/m² on days 1, 2, and 3 of cycles one to three are summarized in Supplemental Table A7 (see the online version at doi:10.1016/j.clcc.2021.04.005), and plasma concentrations following administration of 30 mg/m² prexasertib on days 1, 2, and 3 of cycles two to five are summarized in Supplemental Table A8 (see the online version at doi:10.1016/j.clcc.2021.04.005).

The prexasertib PK data displayed a high degree of concordance with the prexasertib monotherapy population PK-predicted PK profile across days and cycles of treatment (see Supplemental Figure A3 in the online version at doi:10.1016/j.clcc.2021.04.005), demonstrating that the expected systemic exposure of prexasertib following the daily administration of prexasertib at 40 mg/m² or 30 mg/m² (when dose reduction was needed) on the first 3 days of each cycle was achieved. There was also no unexpected accumulation of prexasertib following five cycles of treatment on this schedule of administration (see Supplemental Figure A3 in the online version at doi:10.1016/j.clcc.2021.04.005).

Exploratory Biomarkers

Fifty-five patients had both biomarker and clinical response data available. The expression of MYC did not differ between disease control categories (see Supplemental Figure A4 in the online version at doi:10.1016/j.clcc.2021.04.005), and there was no significant association with disease control at any quantile evaluated. After multiplicity adjustment, no other genes had a significant association with disease control, although a modest trend was observed for improved disease control in patients with high cyclin E1 expression using the 75% cutpoint (odds ratio = 5.6; 95% CI, 1.7-18.3; unadjusted *P* = .0039; adjusted *P* = .195).

Discussion

Despite the convincing preclinical and mechanistic rationale,¹³ treating platinum-sensitive and platinum-refractory ED-SCLC patients with prexasertib resulted in minimal efficacy. Hematotoxicity was the most common and severe toxicity, resulting in more than half of patients developing drug-related grade ≥ 3 decreased neutrophil count and 10% of patients experiencing any grade of febrile neutropenia. Although the nonclinical rationale was compelling, it is common for the results from nonclinical models not to translate to the clinical setting. Patient tumors are complex and heterogeneous, often containing numerous subclonal populations with different molecular characteristics.²⁰⁻²² There are multiple interactions among tumor cells, extracellular matrix, stromal cells, and tumor-associated vasculature that are difficult to recapitulate in even the best nonclinical models. Additionally, changes in immune system signaling following treatment with prexasertib have been observed.²³ These interactions are difficult to

model in traditional nonclinical models due to the lack of immune cells in immunocompromised models and differences between the stromal microenvironments of animal models and humans. Finally, metastasis, which is an important predictor of outcomes in patients with SCLC, is difficult to mimic in nonclinical models.²⁴ Together, these considerations may have contributed to the discrepancy between what was observed in nonclinical models and the outcome of this clinical study.

Clinical factors that may have influenced the unexpected lack of efficacy were explored. Baseline demographic data and prognostic factors such as age, performance status, and presence of brain metastases at baseline were generally consistent with what would be expected for this population of patients. It may be notable that the median age was 62 years. In the IMpower133 study evaluating atezolizumab with chemotherapy in first-line ED-SCLC patients, patients younger than 65 years of age had a decreased survival benefit.³ The biological drivers for this discrepancy, and whether they would also apply to prexasertib-treated patients, are not known. Prexasertib pharmacokinetic data from this study exhibited concordance with the prexasertib monotherapy population PK profile derived from a previous monotherapy clinical study (see Supplemental Figures A1 and A3 in the online version at doi:10.1016/j.clcc.2021.04.005; data on file). These data confirm that patients attained the expected systemic exposure for each dose and schedule of administration investigated, indicating that altered PK behavior was not a factor for the lack of activity.¹⁵ In all three cohorts, dose reductions were required in 26% of patients, and two patients (1.7%) discontinued due to a treatment-related AE. However, these were not deemed to have affected the efficacy outcome.

Previously, prexasertib was associated with clinical benefit in phase I expansion cohorts (I4D-MC-JTJA; NCT01115790).²⁵ This supported the hypothesis that the subset of SCLC patients with *MYC* amplification would be particularly susceptible to prexasertib. Although *MYC* amplification status was not assessed in the present study, *MYC* gene expression did not have a significant association with disease control. The low response rate in this study makes the retrospective identification of other potential markers of efficacy challenging and complicates the monotherapy development of prexasertib in a biomarker-unselected population.

Because there were no clear reasons why the expected efficacy was not observed, it was hypothesized that, for SCLC, a more sustained duration of CHK1 inhibition may be required to effectively disrupt DNA replication and result in monotherapy activity. In the first-in-human study, the maximum tolerated dose of an alternative regimen (40 mg/m² on days 1, 2, and 3) was identified, which has a higher total dose intensity/cycle (120 vs. 105 mg/m²/cycle).¹⁵ Additionally, the alternative schedule was predicted to provide a more sustained level of percent phosphorylated CHK1 inhibition over days 1 to 3. It was hypothesized that the difference in the temporal PD profiles may result in differences in efficacy and that, in the setting of SCLC, a tumor with a rapid doubling time, the greater sustained level of inhibition achieved with the alternative schedule may be required to more effectively disrupt DNA replication. However, none of the patients treated in the small exploratory cohort with the alternate regimen had an objective response. The overall safety profile was similar to that when prexasertib was administered once

every 14 days, but the incidence of hematologic toxicity, including the febrile neutropenia rate, was generally higher. Although the cohort was small, it does not appear as though the alternative dose or schedule resulted in an improvement in the efficacy profile of prexasertib.

Prexasertib has been assessed in phase I studies with the PARP inhibitor olaparib and with an anti-programmed cell death ligand 1 antibody (LY3300054).²⁶ Although there is mechanistic support for considering these combinations in SCLC,^{12,27} the lack of monotherapy efficacy observed in this study in a biomarker-unselected population suggests that prospective biomarkers may have to be identified before evaluating prexasertib combinations in SCLC patients.^{13,23} The CHK1 inhibitor SRA737 is currently being investigated in a phase I/II study that includes an expansion cohort of SCLC patients (ClinicalTrials.gov identifier NCT02797977). However, like the JTH study, the SCLC expansion cohort treated with SRA737 does not require prospective genetic profiling based on the rationale that SCLC tumors have a high prevalence of cancer-related alterations in tumor suppressor genes (eg, *TP53* and *RBI*).^{2,12,13} Results from the study with SRA737 may provide further insights into the role of CHK1 inhibition in SCLC.

Conclusion

A dose of 105 mg/m² prexasertib administered once every 14 days did not demonstrate activity in SCLC. The side-effect profile of prexasertib was consistent with what has been previously reported, with hematologic toxicity being the most common toxicity.

Clinical Practice Points

As a result of previously reported non-clinical data that identified CHK1 as a candidate drug target in SCLC, the CHK1 inhibitor prexasertib was evaluated in patients with platinum-sensitive and in patients with platinum-resistant SCLC who had received no more than two prior lines of treatment.

Although there was strong mechanistic rationale, a dose of 105 mg/m² prexasertib monotherapy administered once every 14 days did not demonstrate activity in this study.

The adverse events associated with prexasertib were consistent with what has been previously reported, with hematologic toxicity being the most common toxicity. Exploratory analysis of *MYC* gene expression did not have an association with disease control.

Other CHK1 inhibitors are being evaluated in SCLC patients, and these data may provide further insights into the role of CHK1 in SCLC.

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Phase II Trial of Prexasertib for ED-SCLC

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2021.04.005.

References

1. Wakuda K, Kenmotsu H, Naito T, et al. Efficacy of rechallenge chemotherapy in patients with sensitive relapsed small cell lung cancer. *Am J Clin Oncol*. 2015;38:28–32.
2. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer*. 2015;121:664–672.
3. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
4. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
5. US Food and Drug Administration. FDA approves atezolizumab for extensive-stage small cell lung cancer. Available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer>. Accessed: September 9, 2020.
6. US Food and Drug Administration. FDA approves durvalumab for extensive-stage small cell lung cancer. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-extensive-stage-small-cell-lung-cancer>. Accessed: September 9, 2020.
7. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20:4665–4672.
8. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol*. 2014;32:4012–4019.
9. O'Brien ME, Ciuleanu TE, Tsekou H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24:5441–5447.
10. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17:658–667.
11. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21:645–654.
12. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov*. 2012;2:798–811.
13. Sen T, Tong P, Stewart CA, et al. CHK1 inhibition in small-cell lung cancer produces single-agent activity in biomarker-defined disease subsets and combination activity with cisplatin or olaparib. *Cancer Res*. 2017;77:3870–3884.
14. Christensen CL, Kwiatkowski N, Abraham BJ, et al. Targeting transcriptional additions in small cell lung cancer with a covalent CDK7 inhibitor. *Cancer Cell*. 2014;26:909–922.
15. Hong D, Infante J, Janku F, et al. Phase I study of LY2606368, a checkpoint kinase 1 inhibitor, in patients with advanced cancer. *J Clin Oncol*. 2016;34:1764–1771.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
17. Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR(+)/HER2(-) breast cancer. *Clin Cancer Res*. 2020;26:566–580.
18. Gong X, Litchfield LM, Webster Y, et al. Genomic aberrations that activate D-type cyclins are associated with enhanced sensitivity to the CDK4 and CDK6 inhibitor abemaciclib. *Cancer Cell*. 2017;32:761–76.e6.
19. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist*. 1979;6:65–70.
20. Stewart CA, Gay CM, Xi Y, et al. Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer. *Nat Cancer*. 2020;1:423–436.
21. Simpson KL, Stoney R, Frese KK, et al. A biobank of small cell lung cancer CDX models elucidates inter- and intratumoral phenotypic heterogeneity. *Nat Cancer*. 2020;1:437–451.
22. Berns A. The therapy escapes of small-cell lung cancer. *Nat Cancer*. 2020;1:374–375.
23. Sen T, Rodriguez BL, Chen L, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. *Cancer Discov*. 2019;9:646–661.
24. Gómez-Cuadrado L, Tracey N, Ma R, Qian B, Brunton VG. Mouse models of metastasis: progress and prospects. *Dis Model Mech*. 2017;10:1061–1074.
25. Hong DS, Moore K, Patel M, et al. Evaluation of prexasertib, a checkpoint kinase 1 inhibitor, in a phase Ib study of patients with squamous cell carcinoma. *Clin Cancer Res*. 2018;24:3263–3272.
26. Do KT, Hill SJ, Kochupurakkal B, et al. Abstract CT232: Phase I combination study of the CHK1 inhibitor prexasertib (LY2606368) and olaparib in patients with high-grade serous ovarian cancer and other advanced solid tumors. *Cancer Res*. 2019;79:CT232.
27. Lok BH, Gardner EE, Schneeberger VE, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. *Clin Cancer Res*. 2017;23:523–535.