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ORIGINAL ARTICLE

Phase I, Open-Label, Dose-Escalation Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of GSK2879552 in Relapsed/Refractory SCLC

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ABSTRACT

Introduction: This first-time-in-humans study assessed the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of GSK2879552 in patients with relapsed or refractory SCLC.

Methods: This phase I, multicenter, open-label study (NCT02034123) enrolled patients (≥18 years old) with relapsed or refractory SCLC (after ≥1 platinum-containing chemotherapy or refusal of standard therapy). Part 1 was a dose-escalation study; Part 2 was a dose-expansion study. Dose escalations were based on safety, PK, and PD. The primary end point (Part 1) was to determine the safety, tolerability, and recommended dose and regimen of GSK2879552. Secondary end points were to characterize PK and PD parameters and measure disease control rate at week 16. Part 2 was not conducted.

Results: Between February 4, 2014, and April 18, 2017, a total of 29 patients were allocated to one of nine dose cohorts (0.25 mg–3 mg once daily and 3-mg or 4-mg intermittent dosing). In all, 22 patients completed the study; 7 withdrew, primarily owing to adverse events (AEs). Most patients (24 of 29 [83%]) had at least one treatment-related AE, most commonly thrombocytopenia (12 of 29 [41%]). Twelve serious AEs (SAEs) were reported by nine patients; six were considered treatment related, the most common of which was encephalopathy (four SAEs). Three patients died; one death was related to SAEs. PK was characterized by rapid absorption, slow elimination, and a dose-proportional increase in exposure.

Conclusions: GSK2879552 is a potent, selective inhibitor of lysine demethylase 1A and has demonstrated favorable PK properties but provided poor disease control and a high AE rate in patients with SCLC. The study was terminated, as the risk-benefit profile did not favor continuation.

Keywords: GSK2879552; Small cell lung carcinoma; Pharmacokinetics; Pharmacodynamics; Safety

Introduction

Lung cancer is the leading cause of cancer death in the United States, accounting for an estimated 154,050 deaths in 2018, with 234,030 new cases predicted in the same year.[1] SCLC accounts for approximately 10% to 15% of all diagnosed lung cancers.[1,2] SCLC is a highly malignant form of lung cancer, and its prognosis is poor, with an estimated 5-year survival rate of only 6%.[2-4] Chemotherapy has been the standard of systemic treatment for SCLC for several decades; however, although SCLC is initially responsive to chemotherapy, relapse is common and the response to second-line therapy is poor, with survival of less than 6 months.[5,6] In addition, the overall median survival of patients with SCLC was found to be unchanged between 1983 and 2012, remaining at just 7 months throughout the period and thus highlighting the urgent need for novel treatments.[3,4] More recent studies of combination therapies, such as the addition of atezolizumab to carboplatin and etoposide chemotherapies, have demonstrated significantly longer overall survival and progression-free survival rates compared with placebo; however, the gains are modest (median 2 months' additional overall survival compared with placebo).[7]

Epigenetic dysregulation is an important pathogenic mechanism in many cancers, including SCLC,[8] and therapies that target epigenetic mediators have been shown to be successful in cancer.[9] Lysine-demethylase 1A (KDM1A [also known by the alias name lysine-specific histone demethylase 1A and the alias symbol LSD1]) is a histone demethylase, which catalyzes the removal of mono- and di-methyl groups on histone H3 lysine 4 (markers of active transcription) as part of a complex including the enzymes REST copressor 1 (RCOR1 [also known by the alias COREST]) and histone deacetylase, leading to suppression of gene expression.[10,11] KDM1A has been shown to be crucial for a range of cellular processes, including the regulation of pluripotency, self-renewal, and cellular differentiation.[12-14] KDM1A is overexpressed in primary SCLC,[15] and its inhibition in acute myeloid leukemia (AML) has been shown to relieve the differentiation block, thereby exerting an antileukemic effect and sensitizing AML cells to anticancer therapy.[16,17] Furthermore, inhibition of KDM1A provided an antileukemic effect in secondary engraftment models, indicating an effect on the leukemia-initiating cell population and further suggesting a role for KDM1A in the self-renewal of cancer stem cells.[18] Both SCLC and AML are poorly differentiated tumors[19,20]; thus, inhibition of KDM1A may invoke a similar differentiation mechanism in SCLC.

GSK2879552 is a potent, selective, mechanism-based, irreversible inhibitor of KDM1A/RCOR1 activity.[15] GSK2879552 has been shown to induce the expression of putative KDM1A target genes and demonstrate potent, predominantly cytostatic, antiproliferative activity in SCLC cell lines and tumor xenograft models, highlighting the potential of GSK2879552 for treatment of SCLC.[15,21] This first-time-in-humans, open-label, dose-escalation study aimed to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK2879552 in patients with relapsed or refractory SCLC.

Materials and Methods

Study Design

This was a phase I, open-label, multicenter, nonrandomized, two-part study designed to evaluate the safety, tolerability, PK, PD, and clinical activity of GSK2879552 given orally to patients with relapsed or refractory SCLC (200858, NCT02034123). The study was planned as two parts: Part 1 was a dose-escalation study to determine the recommended dose for Part 2 based on safety, tolerability, and PK and PD data; Part 2 was to be a dose-expansion study planned to further evaluate the safety and tolerability of GSK2879552 at the recommended dose and determine clinical activity (Supplementary Fig. 1).

This study was conducted at three centers in the United States, one center in France, and four centers in Spain. The first patient was enrolled on February 4, 2014, and the last patient visit was completed on April 18, 2017. On June 13, 2017, the study was terminated, as the risk-benefit profile in relapsed or refractory SCLC did not favor continuation of the study. There were no active subjects on study when the study was terminated. Part 2 of the study was not conducted.

The study protocol, amendments, and informed consent form was reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board. Written informed consent was obtained from each patient before the performance of any study-specific procedures. The study was conducted in accordance with the guidelines of the International Council for Harmonization and the ethical principles outlined in the Declaration of Helsinki 2008.

Study Population

Eligible patients ($\geq$18 years old) had recurrent or refractory SCLC (after receiving $\geq$1 prior standard platinum-containing chemotherapy regimen, or if standard therapy was refused) with an Eastern Cooperative Oncology Group performance status of 0 or 1. Full inclusion and exclusion criteria are included in the Supplementary Materials.

Interventions

GSK2879552 was provided as oral capsules, and the following dose and schedule combinations were assessed in nine dose cohorts: daily dosing of 0.25 mg, 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 3.0 mg and intermittent dosing of 3.0 mg for 4 days on and 3 days off, 3.0 mg for 4 days on and 10 days off, and 4.0 mg for 4 days on and 10 days off. The starting dose of 0.25 mg daily was selected on the basis of findings from preclinical studies and predicted minimum anticipated biologically effective dose with the goal of administering a pharmacologically active dose that is reasonably safe to use, according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use S9 guidelines.[22]

The dose-escalation phase followed a Bayesian adaptive design with one patient per cohort until a study treatment–related grade 2 or higher adverse event (AE) was observed; subsequently, at least 2 patients were allocated to each cohort. Sufficient numbers of patients were enrolled in each cohort to ensure that data for at least one patient who had completed the first 28 days of dosing were available before defining a new dose and/or schedule and initiating the subsequent cohort. The dose-limiting toxicity (DLT) period was 28 days. After the second cohort, the dosing recommendation for the next cohort was made by using the Neuenschwander Continual Reassessment Method based on the observed DLT data for all the patients treated under the same dosing schedule (further details are included in the Supplementary Materials). The dose increment was no more than 100% of the current dose in the absence of any safety signals and no more than 50% of the current dose if AEs were reported. A safety review was conducted to evaluate safety parameters, such as those in the primary end point (i.e., AEs and DLTs), tolerability, and available PK and PD data, to decide on the next dose or dosing schedule before recruitment to the next cohort. Any dose level(s) could have been expanded to include up to 12 patients to collect adequate data on safety, PK, or PD.

In response to patients experiencing DLTs of thrombocytopenia with daily dosing at the higher doses, an intermittent dosing schedule (3.0 mg for 4 days on and 3 days off) was initiated to investigate whether giving a predetermined break from dosing would allow recovery of platelets. Two patients were initially enrolled in the cohort, but as one patient experienced grade 4 thrombocytopenia, and considering the long half-life ($t_{1/2}$) of GSK2897552 and the irreversible binding to the target, it was deemed that a longer break period would be needed to decrease the risk of grade 3 and higher thrombocytopenia. Thus, the 4 days on and 10 days off dosing schedules were introduced and no further patients were enrolled in the 3.0 mg for 4 days on and 3 days off schedule.

Study End Points and Assessments

The primary end point of Part 1 was determination of the safety, tolerability and recommended phase II dose(s) and regimen of GSK2879552 by assessing AEs, DLTs, dose reductions or delays, withdrawals due to toxicities, and changes in safety parameters. The secondary end points were characterization of PK parameters after single-dose (day 1) and repeat-dose (day 15) administration of GSK2879552 (including area under the concentration-time curve [AUC], maximum observed

concentration [C_{max}], time of occurrence of C_{max} [T_{max}], terminal phase and/or effective $t_{1/2}$, accumulation ratio, and time invariance), evaluation of clinical response by measuring the disease control rate (DCR) at week 16, and evaluation of the relationship between GSK2879552 exposure markers (e.g., dose, C_{max}) and safety (e.g., platelet levels in blood) and efficacy parameters.

Safety Assessments. Safety assessments included the monitoring of AEs, clinical laboratory test results, heart rate, blood pressure, temperature, 12-lead electrocardiogram findings, Eastern Cooperative Oncology Group performance status, and physical examination findings.

PK Assessments. Serial blood samples were collected for PK analysis on day 1 and day 15 before a dose to 24 hours after a dose. Most patients did not receive a dose on day 2 to allow for PK sampling at 48 hours after a dose to better characterize the terminal $t_{1/2}$ of GSK2879552. Further predose samples were collected regularly throughout the study.

The GSK2879552 concentration-time data were summarized by planned time point and dose cohort. PK analysis of GSK2879552 by using actual relative time was conducted by noncompartmental methods using WinNonlin. C_{max}, time of occurrence of C_{max}, $AUC_{(0-24)}$ and/or $AUC_{(0-\infty)}$ after single-dose administration and $AUC_{(0-24)}$ after repeated administration, apparent terminal phase elimination rate constant (λz), and $t_{1/2}$ were determined. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio was determined from the ratio of $AUC_{(0-24)}$ with a repeated dose (day 15 or later) to $AUC_{(0-24)}$ on day 1. The ratio of $AUC_{(0-24)}$ on day 15 to $AUC_{(0-\infty)}$ on day 1 was calculated to assess time invariance.

PD Assessments. As KDM1A inhibition results in a blockage of platelet maturation,[15,23] platelet count changes can be viewed as a PD effect and are expected to be reflective of the level of target engagement. Baseline platelet counts and nadir values were measured for the initial dose level and during the first 60 days of treatment. The platelet nadir was expressed as percent change from baseline platelet count.

Efficacy Assessment. Disease assessments, including imaging and physical examination, were performed every 8 weeks. Disease progression and response evaluations were determined according to the definitions in the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[24] Specifically, the DCR was defined as the sum of patients who had a complete response, partial response, or stable disease at week 16.

Statistical Methods

No formal hypotheses testing was conducted; all statistical analyses for safety and efficacy were descriptive.

PK and PD parameters were summarized using descriptive statistics by dose cohort. Dose proportionality for C_{max} and AUC after single and repeated administration was evaluated by using power models. Platelet nadir values expressed as percent change from baseline were plotted graphically against summary exposure measures (e.g., dose, C_{max}, AUC obtained on day 1). Only dose cohorts with repeat daily dosing were included in the analysis (i.e., 0.25-mg–3.0-mg daily dose cohorts). On the basis of the nature of the relationship, a sigmoidal maximum effect (E_{max}) model was fitted to the data to obtain the slope, with the exposure producing 50% of the E_{max} (ED50) and E_{max}. The baseline effect was set to zero and the upper bound of E_{max} was set to –100%.

Results

Study Population

In total, 29 patients were enrolled and allocated to one of the dose cohorts; 22 patients completed the study and seven prematurely withdrew, primarily because of treatment-related AEs (three of 29 [10%]) or withdrawal of consent (two of 29 [7%]) (Supplementary Fig. 2).

Most patients (18 of 29 [62%]) were in the 18- to 64-year-old group, with a mean age of 60.6 (±8.58) years; most of the patients (18 of 29 [62%]) were male. A summary of patient demographics is provided in Table 1.

Table 1. Patient Baseline Demographics (N = 29)

Characteristic	Patients, n (%)
Sex	
Female	11 (38)
Male	18 (62)
Age group, y	
<18	0
18-64	18 (62)
65-74	10 (34)
>74	1 (3)
Age, y	
Mean	60.6
SD	8.58
Median	62.0
Minimum	44
Maximum	78
Ethnicity	
Hispanic or Latino	2 (7)
Not Hispanic or Latino	26 (90)
Missing	1 (3)

Safety and Tolerability

Most patients (28 of 29 [97%]) reported at least one AE, most frequently thrombocytopenia (12 of 29 [41%]), fatigue (10 of 29 [34%]), and constipation (nine of 29 [31%]). Most patients (24 of 29 [83%]) had at least one AE that was considered by the investigator to be related to the study treatment (Table 2). The most frequently occurring treatment-related AE was thrombocytopenia (12 of 29 [41%]); eight of these patients had dose reductions or interruptions due to grade 3 or higher thrombocytopenia. Furthermore, two patients were withdrawn from the study because of drug-related AEs (one patient in the 2.0-mg daily group with grade 3 asthenia and one patient in the 3.0-mg daily group with grade 3 encephalopathy).

During the dose-escalation phase, 12 SAEs were reported in patients who received a dose of 9 mg (Table 3). Six of the SAEs were deemed by investigators to be related to the study treatment, the most common of which was encephalopathy (reported in four patients [Supplementary Materials and Supplementary Tables 1 and 2]). There was no clear pattern in the timing of these cases in relation to the dose of study treatment, and no specific magnetic resonance imaging changes were seen (Supplementary Results). The study was put on hold three times because of cases of encephalopathy.

Three patients died during the study. One death was due to the treatment-related SAE of grade 5 encephalopathy in the 2.0-mg daily cohort. The patient in the 3.0-mg daily dosing cohort who had a treatment-related SAE of grade 3 encephalopathy subsequently died 40 days after the event because of disease progression. One death was due to an SAE of tumor lysis syndrome in the 4.0-mg for 4 days on and 10 days off cohort. The event occurred 14 days after the start of study treatment, and the patient died 4 days later; it was deemed by the investigator as unrelated to study treatment.

There were no DLTs in the 0.25-mg, 0.5-mg, 1.0-mg, or 1.5-mg GSK2879552 daily cohorts and one DLT in the 2.0-mg daily group (the fatal SAE was encephalopathy). Protocol amendments were made to exclude patients considered at risk of encephalopathy (those with prior therapy with temozolomide and/or poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors) and to withhold study treatment if the baseline Montreal Cognitive Assessment score fell to less than 22 or decreased by three or more points from baseline. Additional patients were subsequently recruited to the 2.0-mg and 3.0-mg daily cohorts according to the planned study design, and in parallel, intermittent dosing was initiated. Three patients in the 3.0-mg daily dosing group had DLTs (grade 4 thrombocytopenia). One patient in the 3.0-mg for 4 days on and 10 days off dose group had a DLT (grade 3 encephalopathy) that did not resolve after withdrawal of the investigational product; the relationship of the event to the study treatment was not established, as the patient also had carcinomatous meningitis, which potentially contributed to the encephalopathy.

Eight patients (28%) had at least one dose reduction; all were due to grade 3 or 4 thrombocytopenia, and seven of the eight patients were receiving doses of at least 2.0 mg of GSK2879552. A total of 18 patients (62%) had dose interruptions of GSK2879552; 44% of the dose interruptions were due to AEs. No patient had a grade 3 or higher increase from baseline in clinical laboratory

Table 2. Summary of Treatment-Related AEs by Frequency (≥7%) (N = 29)

		Maximum Grade, n (%)				
AE	Patients, n (%)	1	2	3	4	5
Any AE	24 (83)	5 (17)	6 (21)	5 (17)	7 (24)	1 (3)
Thrombocytopenia	12 (41)	2 (7)	0 (0)	4 (14)	6 (21)	0 (0)
Fatigue	8 (28)	4 (14)	4 (14)	0 (0)	0 (0)	0 (0)
Decreased appetite	7 (24)	3 (10)	4 (14)	0 (0)	0 (0)	0 (0)
Anemia	6 (21)	4 (14)	1 (3)	1 (3)	0 (0)	0 (0)
Nausea	5 (17)	4 (14)	1 (3)	0 (0)	0 (0)	0 (0)
Neutropenia	5 (17)	1 (3)	2 (7)	1 (3)	1 (3)	0 (0)
Encephalopathy	4 (14)	0 (0)	1 (3)	2 (7)	0 (0)	1 (3)
Asthenia	3 (10)	0 (0)	1 (3)	2 (7)	0 (0)	0 (0)
Abdominal pain	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Chills	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	2 (7)	0 (0)	2 (7)	0 (0)	0 (0)	0 (0)
Diarrhea	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Dysgeusia	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Platelet count decreased	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
White blood cell count decreased	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)

AE, adverse event.

Table 3. Summary of SAEs

Parameter	0.25 mg daily (n = 1)	0.5 mg daily (n = 1)	1.0 mg daily (n = 5)	1.5 mg daily (n = 3)	2.0 mg daily (n = 7)	3.0 mg daily (n = 3)	3.0 mg 4 d on/3 d off (n = 2)	3.0 mg 4 d on/10 d off (n = 5)	4.0 mg 4 d on/10 d off (n = 2)	Total (N = 29)
Patients with SAEs, n	0	0	0	2 (67%)	2 (29%)	1 (33%)	0	2 (40%)	2 (100%)	9 (31%)
SAEs, n	0	0	0	2	3	2	0	2	3	12
Drug-related SAEs, n	0	0	0	1	2	2	0	1	0	6
Fatal SAEs, n	0	0	0	0	1	0	0	0	1	2
Drug-related fatal SAEs, n	0	0	0	0	1	0	0	0	0	1

SAE, serious adverse event.

evaluations deemed to be related to the study treatment (other than thrombocytopenia).

PK Analyses

The PK concentration-time data showed a rapid increase in GSK2879552 concentration, with the maximum concentration achieved within 2 hours (Fig. 1).

Single- and repeat-dose PK parameters are summarized in Table 4. GSK2879552 was eliminated slowly, with an average terminal phase effective $t_{1/2}$ of 18 hours at the 2-mg daily dose. C_{max} and AUC values generally increased in a dose-proportional manner over the 0.25-mg to 3.0-mg daily dose range at both day 1 and day 15 (Supplementary Table 3).

Accumulation ratio based on AUC was assessed for the GSK2879552 1.0-mg, 2.0-mg, and 3.0-mg daily groups, as these cohorts each had at least three patients. The results showed a moderate accumulation of GSK2879552 with daily administration from day 1 to day 15, which is in line with the terminal phase effective $t_{1/2}$ (Supplementary Table 4).

PD Analyses

All dose cohorts had a negative mean percent change from baseline platelet count to nadir value (Supplementary Table 5). The percent decrease in platelet count generally increased across the daily dosing range; patients in the GSK2879552 3.0-mg daily group had the greatest drop (−94.7%). Doubling the dose of GSK2879552 from 1.0 mg to 2.0 mg daily led to a dramatic decrease in platelet count (mean percent change from the baseline platelet count to a nadir value of −25.4% to −78.2%). Individual platelet counts over time in the 2.0-mg and 3.0-mg daily groups are shown in

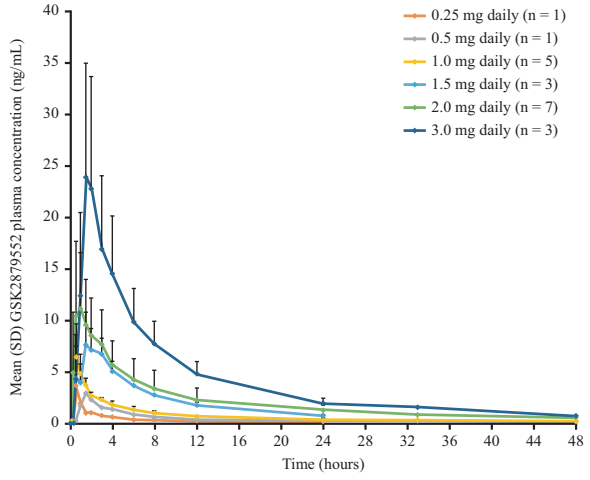

Figure 1. Mean (SD) GSK2879552 plasma concentration versus time after a single dose.

Table 4. Summary of Derived Plasma Pharmacokinetic Parameters on Day 1 and Day 15

Parameter	0.25 mg daily (n = 1)	0.5 mg daily (n = 1)	1.0 mg daily (n = 5)	1.5 mg daily (n = 3)	2.0 mg daily (n = 7)	3.0 mg daily (n = 3)	3.0 mg 4 d on/3 d off (n = 2)	3.0 mg 4 d on/10 d off (n = 5)	4.0 mg 4 d on/10 d off (n = 2)
Day 1									
C_{max}, ng/mL									
n	1	1	5	3	7	3	2	5	2
Geometric mean	3.8	2.9	6.4	9.3	12.9	22.0	31.2	23.9	23.4
%CVb	—	—	17.3	12.2	36.6	42.9	26.8	20.8	68.8
T_{max}, h									
n	1	1	5	3	7	3	2	5	2
Median	0.5	1.5	0.5	1.5	0.5	2.0	1.0	1.5	0.8
Min, max	—	—	0.5, 0.5	0.5, 2.9	0.3, 3.0	1.0, 2.1	0.5, 1.4	0.6, 2.0	0.5, 1.0
$AUC_{(0\text{-}24)}$, h*ng/mL									
n	1	1	5	3	6	3	2	5	1
Geometric mean	10.4	16.2	27.8	60.8	77.0	159.0	138.0	155.8	154.9
%CVb	—	—	12.7	14.1	52.2	30.5	19.1	29.1	—
$AUC_{(0\text{-}\infty)}$, h*ng/mL									
n	1	1	5	3	6	3	2	5	1
Geometric mean	14.5	27.2	40.0	70.7	108.6	206.3	163.6	182.9	180.9
%CVb	—	—	18.7	15.0	56.1	27.7	25.3	27.1	—
$T_{1/2z}$, h									
n	1	1	5	3	6	3	2	5	1
Geometric mean	16.9	24.0	17.3	8.8	18.1	15.4	11.5	8.9	8.4
%CVb	—	—	62.6	8.7	8.7	19.1	47.9	23.2	—
Day 15 (or later)									
C_{max}, ng/mL									
n	1	1	5	1	5	3	2	5	0
Geometric mean	3.4	4.3	6.9	13.8	15.7	15.2	24.4	28.1	
%CVb	—	—	29.2	—	39.4	23.1	21.5	7.7	
T_{max}, h									
n	1	1	5	1	5	3	2	5	0
Median	1.0	1.5	1.0	0.5	1.0	1.5	1.5	1.1	
Min, max	—	—	0.5, 2.1	—	0.5, 4.0	0.7, 3.0	1.0, 2.0	0.5, 1.5	
$AUC_{(0\text{-}24)}$, h*ng/mL									
n	1	1	5	1	5	3	2	4	0
Geometric mean	27.3	40.3	53.3	91.1	143.8	141.9	164.7	203.4	
%CVb	—	—	31.2	—	64.2	32.4	8.2	37.2	

C_{max}, maximum concentration; %CVb, percent coefficient of variation; Min, minimum; Max, maximum; $AUC_{(0\text{-}24)}$, area under the concentration-time curve from time zero (before dose) to 24 hours after dose; $AUC_{(0\text{-}\infty)}$, area under the concentration-time curve from time zero (before dose) extrapolated to infinite time; $T_{1/2z}$, half-life lambda z; T_{max}, time of C_{max}.

Figure 2. In the 3.0-mg group, platelets started to decrease shortly after initiation of treatment, with a similar rate of decrease observed in all three patients and the nadir observed around day 14. A similar recovery time after dose interruptions and/or reduction was also observed in all three patients.

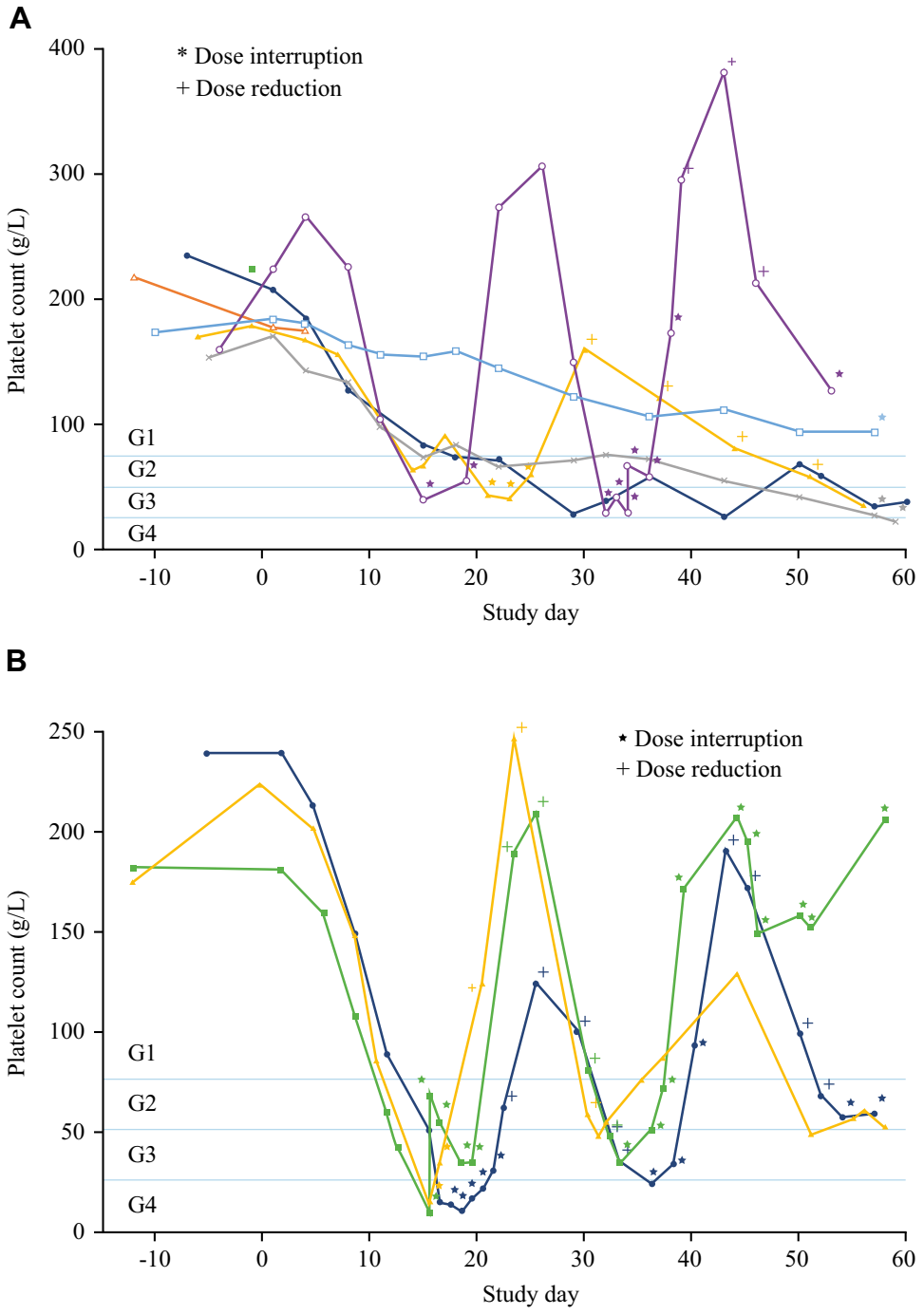

Figure 2. Time course of platelet count in individual patients who received 2 mg (*A*) or 3 mg (*B*) of GSK2879552 daily. Marks for dose interruptions (*asterisk*) and reductions (*plus sign*) show the dose administered on the day of the platelet counts but may not coincide with the exact day on which the dose interruption/reduction was started. The absence of a mark after a dose interruption means that treatment was restarted at the same dose. Grade (G) of toxicity is denoted as G1 to G4. No change in dose was required for G1. With G2 thrombocytopenia, the dose was either continued with no change or held for up to 2 weeks for toxicity to resolve to baseline or grade 1 or lower and then continued at the same dose, or reduced by no more than 25% if considered a dose-limiting toxicity. In the case of G3 and G4 events, the dose was held for up to 2 weeks for toxicity to resolve to baseline or grade 1 or lower and then reduced by no more than 25%; if recovery was achieved after 14 days, the patient was withdrawn.

The model parameters for a sigmoidal E_{max} model describing the relationship between platelet nadir and dose, day 1 C_{max}, or $AUC_{(0-\infty)}$ are shown in Supplementary Figure 3 and Supplementary Table 6. The relationships are very steep, as is shown by the hill coefficients ranging from 2.2 to 3.5. The dose estimated to provide 50% of the E_{max} on platelets was between 1.3 and 1.7 mg, indicating significant target engagement in the dose range tested.

Efficacy Results

The DCR was 14% (four of 29 patients) at 16 weeks (Supplementary Table 7). A best response of stable disease was reported for two of 29 patients (7%); two patients did not meet the criteria of best overall response of stable disease. A patient narrative for one of the patients with stable disease is provided in Supplementary Materials.

Discussion

This study aimed to evaluate the safety, tolerability, PK, PD, and clinical activity of the KDM1A inhibitor GSK2879552 for the treatment of patients with relapsed or refractory SCLC. Specifically, Part 1 was designed to assess the safety of GSK2879552 and determine the recommended dose and Part 2 was planned to further evaluate the safety and tolerability of GSK2879552 at the recommended dose and determine clinical activity. However, AEs were common with GSK2879552 and included six drug-related SAEs, one of which was fatal. Although there were no complete or partial responses across all dose levels, the impact of the two observed responses of stable disease should not be underestimated, given the patient histories. The remaining patients either progressed or withdrew as a result of AEs. The investigators concluded that the risk-benefit profile of GSK2879552 in relapsed or refractory SCLC did not favor continuation of the study.

The GSK2879552 PK were characterized by very rapid absorption, with maximum concentrations achieved within 2 hours of dosing and by slow elimination, with a terminal $t_{1/2}$ of 18 hours with the 2.0-mg daily dose. Exposure tended to increase in a dose-proportional manner after single and repeated administration and to be higher with repeated administration in line with the long $t_{1/2}$.

Overall, 28 of the 29 patients (97%) reported at least one AE during the study, the most common of which were thrombocytopenia or fatigue. Thrombocytopenia was an on-target effect and was anticipated on the basis of preclinical findings in rats and dogs, in which a steep dose-exposure platelet decrease was observed (data on file). At their starting dose level, no patients experienced thrombocytopenia with 0.25 mg or 0.5 mg, and grade 1 thrombocytopenia was observed with 1.0 mg and 1.5 mg daily; however, grade 3 thrombocytopenia was observed in most patients receiving 2.0 mg who completed the study, and grade 4 was observed in all three patients receiving 3.0 mg daily. It should be noted that the patient who started treatment at 0.25 mg was dose-escalated to 0.5 mg (grade 1 thrombocytopenia) and then to 1.0 mg, the dose at which grade 4 thrombocytopenia was observed. Correspondingly, a steep sigmoidal E_{max} relationship was observed between the extent of thrombocytopenia and dose, C_{max}, or AUC of GSK2879552. Although a median –13.5% decrease in platelet count was observed with a 1.0-mg daily dose ($n = 5$), the median was –87.1% with a 2.0-mg dose ($n = 5$), showing that a doubling in dose translated to a dramatic increase in the thrombocytopenic effect of GSK2879552. The median maximum change from baseline was 95% with the 3.0-mg daily dose. These observations led to evaluation of the intermittent dosing schedule to allow for similar doses or higher doses to be administered and tolerated. The 3.0-mg for 4 days on and 3 days off schedule provided a limited reduction of the effect on the platelet count (26% and 86% reductions), which is in line with the long $t_{1/2}$ of GSK2879552. The 3.0-mg 4 days on and 10 days off intermittent dosing schedule, with a longer break between dosing cycles, allowed for a reduced impact on the platelets, with a lower median reduction of 59% (range 52%–75%). The 4 days on and 10 days off cohort did not provide exposure high enough to confirm any benefit of this schedule. Tumor-specific gene expression changes were also used to monitor target engagement in preclinical models.[15] Although dose-limiting thrombocytopenia did not allow for prolonged daily administration beyond 1.5 mg/kg of GSK2879552, doses up to 135 mg/kg were tolerated for up to 5 days of daily administration. Moreover, dose-response studies in mice indicated that changes in tumor gene expression continued to increase in magnitude well beyond the maximally tolerated dose. The dose at which the platelet maximal tolerated dose was reached resulted in approximately 50% of the maximal gene expression change; therefore, although the current study revealed target engagement and grade 3 or 4 thrombocytopenia, this likely reflects only 50% of maximal PD, suggesting that complete biological response may have been dose-limited.[15] Together, these results are consistent with the important role that KDM1A plays in hematopoiesis and with previous findings that KDM1A knockdown in mice inhibits platelet production.[23]

Four patients experienced events of encephalopathy, one of which was fatal and eventually led to termination of the study. The first two patients had been previously exposed to temozolomide with or without a PARP

inhibitor (as part of a randomized controlled clinical trial) and had received prophylactic cranial irradiation (PCI). These were initially considered to be predisposing factors; however, the third patient to experience encephalopathy had not received PCI, and the fourth had not been exposed to temozolomide or PARP inhibitors. Overall, 75% of patients in this study had received PCI previously, and most did not experience encephalopathy. Furthermore, the exposure and platelet decreases in patients who experienced encephalopathy were within the range of values observed in the other patients.

Although encephalopathy was not anticipated on the basis of preclinical studies, KDM1A is known to be important in brain development and function. Loss of KDM1A in adult mice induced transcriptional changes in neurodegeneration pathways, with increased stem cell gene expression in the hippocampus, and resulted in paralysis, hippocampus and cortex neurodegeneration, and memory impairment.[25] KDM1A has also been shown to be important for neuronal differentiation and the regulation of neuron-specific gene expression programs.[26]

Furthermore, a preclinical study in a rat model revealed that [^{14}C]GSK2879552-related material was distributed into central nervous system tissues (data on file), suggesting that GSK2879552 is able to cross the blood-brain barrier. Thus, GSK2879552 may lead to gene deregulation in the brain, potentially leading to encephalopathy.

Several other KDM1A inhibitors are in development for potential cancer therapies. Treatment of AML cell lines and a xenograft model with the cyclopropylamine-based irreversible KDM1A inhibitor RN-1 led to inhibition of tumor cell growth and increased cellular differentiation.[27] Another study found the combination treatment of an irreversible KDM1A inhibitor T-3775440 with the neural precursor cell expressed, developmentally down-regulated 8–activating enzyme inhibitor pevonedistat resulted in synergistic growth inhibition of AML cells and improved survival in a tumor xenograft model of AML.[28] The KDM1A inhibitor ORY-1001 was investigated in a multicenter phase I study in relapsed or refractory acute leukemia.[29] Select biomarkers indicated a dose-dependent response with ORY-1001; however, AEs were common, and consistent with our study, thrombocytopenia occurred in some patients (seven events in five of 27 patients). In an extension cohort ($n = 14$), objective responses were observed in five patients and ORY-1001 promoted blast cell differentiation in nine patients. Encephalopathy was not observed in these studies of leukemia. Together, these findings highlight the therapeutic potential of KDM1A inhibitors in cancer, but there is also a risk of side effects, such as encephalopathy, although thrombocytopenic effects may prevent the desired exposure from being achieved.

In conclusion, KDM1A is an epigenetic regulator that is highly expressed in primary SCLC. GSK2879552 is a potent, selective inhibitor of KDM1A and has favorable PK properties in patients with SCLC. Although the thrombocytopenic effects of GSK2879552 indicate that it successfully inhibited KDM1A in patients, it resulted in poor DCRs and high rates of AEs, including four events of encephalopathy, leading to the termination of the study.

Data Sharing Statement

Within 6 months of this publication, anonymized individual participant data, the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw data set, analysis-ready data set, and clinical study report will be available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access agreement will be required.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.06.021.

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