A Phase I Study of Molibresib (GSK25762), a Selective Bromodomain (BRD) and Extra Terminal Protein (BET) Inhibitor: Patients with relapsed or refractory non-Hodgkin’s lymphoma (NHL) have poor overall prognosis, especially those with aggressive lymphomas. The BRD and extra terminal domain (ETD) family of proteins contribute to both carcinogenesis and treatment resistance in multiple solid and hematologic malignancies by promoting transcriptional complex assembly and the subsequent expression of oncogenic drivers.

Molibresib (GSK25762) is an orally bioavailable, small molecule BET inhibitor that has shown inhibition of growth in NAL cells, both in vitro and in vivo (GSK data on file). This study was designed to evaluate the safety, tolerability, and preliminary efficacy of molibresib in relapsed and refractory hematologic malignancies.

We report here the results from the NHL dose-escalation cohort.

Primary: safety, tolerability and maximum tolerated dose (MTD) of once-daily (QD) molibresib in patients with relapsed or refractory hematologic malignancies, and identification of the recommended Phase 2 dose (RP2D).

Secondary: preliminary pharmacokinetics (PK) and pharmacodynamics (PD).

Methods
This was a Phase I open-label, dose-escalation and expansion study (BET110633; NCT02493826) of molibresib in patients with mature B- and T-cell lymphoma malignancies, acute myeloid leukemia/myelodysplastic syndrome and multiple myeloma. We report results from the May 14, 2014 to June 24, 2016 data cut of patients with NHL, neoplastic myeloid.

An accelerated dose titration was employed with one patient per dose level until the occurrence of a Grade 2 drug-related toxicity; thereafter, patients were enrolled in a specific dose level or a +1 design.

A Neumayer-Chernoff continual reassessment method (NCRM) model was used to guide the next dose level. Dose escalation continued until the MTD was identified.

Overall Study Population
- Inclusion criteria: adults with relapsed or refractory acute myeloid leukemia (AML), who were 18 years of age and who had either relapsed or were not candidates for standard chemotherapy with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1. For NHL, patients must have had relapsed or refractory lymphoma.
- Exclusion criteria: hematologic malignancies associated with human immunodeficiency virus; history of HLA-B/C or a history of solid malignancy tumors within the previous 5 years.
- Patients currently undergoing other cancer therapies were also excluded.

Endpoints and Assessments
- Dose titration, safety evaluations included the monitoring of adverse events (AEs) and serious AEs (SAEs); routine physical examinations, vital sign measurements, laboratory assessments, electrocardiograms, and pregnancy testing.
- Blood samples were collected for PK analysis after daily administration of GSK25762 on Days 1, 2, 3, and 5 of Week 1; Days 4, 6, 7 and Week 2; and Day 1 of Weeks 3 and 7.
- Response rate assessments were carried out as per consensus recommendations.

- Inclusion: safety, tolerability, PK, PD, and efficacy. Safety assessments identified the RP2D.

Results
Patient Demographics
- Of 27 patients enrolled, 21 relapsed or refractory NHL, 19 (72%) had B-cell lymphomas and 8 (28%) had T-cell lymphoma malignancies. Results included at least one dose level of study drug (Table 1) and are included in this analysis.

- The median age was 64 years (range: 24–79); 74% of patients were male and 26% of patients were female. The median number of prior treatments was 3 (range: 1–11).
- Overall, 93% (33 patients) discontinued prematurely: 4 (15%) due to AEs, 4 (15%) at investigator discretion, and 4 (15%) due to voluntary withdrawal.

Dose Titration
- The oral molibresib dose was escalated from 10 mg QD (n=1) to 80 mg QD (n=7), and 60 mg QD (n=16) (Table 1).
- Two patients experienced dose-limiting toxicities (DLT) at the 60 mg QD dose level.

- All patients (100%) experienced an AE.

- Among all patients with treatment-related AEs, 11% (4 patients) did not require dose reduction for toxicity. A patient at the 60 mg dose level (20% of patients who were treated at that dose) and 5 at the 60 mg level (71% of patients who were treated at that dose) tolerated molibresib. Thrombocytopenia was the most common Grade 3+ treatment-related AE occurring in 32% (18 of 57) of patients. Other common Grade 3+ AEs were febrile neutropenia (n=5 [11%], neutropenia, and increased blood bilirubin (n=3 [7%] each); no Grade 5 treatment-related AEs were reported.

- DLT was identified in 2 patients treated with molibresib 60 mg QD; one patient with Grade 4 thrombocytopenia, which did not recover or resolve. This patient withdrew consent for participation in the study and no further information is available. One patient discontinued due to disease progression (6 of 14 increased alanine aminotransferase [ALT], elevated AST and lactate dehydrogenase). Molibresib 60 mg QD was recommended as the RP2D.

- Of 45 SAEs were reported in 17 (63%) patients. There were no drug-related SAEs; however, 1 (4%) patient, a 75-year-old Caucasian male with marginal zone B-cell lymphoma, experienced a fatal SAE (respiratory tract infection) not considered related to the study drug. This patient received 4 doses of study medication before treatment was discontinued and died 1 week later.

- Eight patients (30%) experienced an AE.

- PK analyses showed dose proportionality after single and repeat dosing, with large variability between patients. These data have previously been presented.

Clinical Response to Molibresib
- The magneto on study treatment was 1.41 months (range: 0.22–26.77); 67% of patients were on study for >2 months (Figure 1).

- Prior (29%) responses observed with molibresib: 3 PRs (60 mg QD and 1 patient at 60 mg QD and 1 patient at 40 mg QD) (Table 3).

- One patient with DLBCL achieved a complete remission that was durable through Week 55 (see Figure 2). Figure 2 shows an arc from this patient over the course of the study.

- Three additional patients (all with CTCL) achieved partial remission (one unconfirmed, two confirmed), for an overall response rate (ORR) of 42% (15%). Six patients (21%) had stable disease as best response.

- Of six patients with CTCL/ATL, three patients (one unconfirmed, two confirmed) had partial response with ORR of 50% in this subpopulation.

- The results of this study support the recommendation of the updated Ann Arbor classification to support the evaluation of molibresib as a potential therapeutic option in patients with relapsed or refractory hematologic malignancies.