(PF555) NO EVIDENCE OF QTC INTERVAL PROLONGATION WITH THE MENIN INHIBITOR BLEXIMENIB WHEN GIVEN AS MONOTHERAPY OR IN COMBINATION WITH AML-DIRECTED THERAPIES FOR KMT2A OR NPM1 ALTERED AML

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Corrected QT interval (QTc) prolongation is a known risk for fatal cardiac arrythmias and emerged as a safety signal with currently approved menin inhibitors (all-grade: 12%–36%; high-grade: 8–17%). QTc prolongation may limit dose intensity of available menin inhibitor therapy and complicate management of acute myeloid leukemia (AML) by preventing combination with anti-leukemic therapies and use of critical supportive care medicines. Bleximenib is being evaluated in late-stage clinical studies in relapsed/refractory or newly diagnosed *KMT2A*-rearranged or *NPM1*-mutated AML. We report cardiac safety analyses from two Phase 1 trials evaluating bleximenib as monotherapy (ALE1001 [NCT04811560]) or in combination with AML-directed therapies (ALE1002 [NCT05453903]).

Methods

As of Oct 2025, the safety population included 141 participants (pts) in ALE1001 and 193 pts in ALE1002. Pts were excluded from enrolment based on QTc to Fridericia's formula (QTcF) ≥450ms for males or ≥470ms for females, or with family history of long QT syndrome. Pts received oral bleximenib continuously on 28-day cycles at dose levels from 50–100mg daily (QD), or 15–150mg twice daily (BID), with various step-up doses, as a monotherapy, or from 15–150mg BID in combination with venetoclax (VEN)/azacitidine (AZA), and 30–100 mg BID in combination with intensive chemotherapy ('7+3'). Cardiac safety monitoring included collection of 12-lead triplicate ECGs at baseline and during treatment on Day 1 of each cycle (or as clinically indicated) with central cardiology review. Adverse events (AEs) were evaluated according to CTCAE v5.0. Coupled with intensive pharmacokinetic sampling and mean ΔQTcP, an exposure-response analysis using ΔQTcF as the dependent variable, and time-matched concentration of bleximenib as the explanatory variable, was performed in 139 pts enrolled in ALE1001 with central ECG data available.

Results

Of 334 pts receiving bleximenib across both studies, only one (0.3%) high grade (Grade [Gr] 3) event of QTc prolongation was observed in a pt receiving bleximenib 100mg QD as monotherapy with baseline comorbidities of ongoing cardiomyopathy and hypokalemia. At the recommended Phase 2 dose (RP2D) in ALE1001, a single (1.6%) Gr 1 QTcF prolongation treatment emergent AE (TEAE) occurred that resolved without dose reduction or interruption. In ALE1002, minimal QTcF prolongation TEAEs were reported in pts receiving bleximenib 15–150mg BID in combination with VEN, VEN+AZA, or '7+3'; 8 (4.1%) experienced a QTcF prolongation event. All were low-grade (7 Gr1, 1 Gr2), non-serious, and did not result in bleximenib dose modifications. No dose-dependent trend in QTcF interval increases were apparent across analyses in either study.
In ALE1001 central ECG data (n=139), time course of mean change in heart rate (HR) was comparable across different doses. No increase of >10 bpm was observed, with no QTc prolongation seen up to the highest dose explored (2-fold higher exposure vs RP2D). Observations from ALE1002 were similar, with no dose-dependent effects on QTc prolongation. ALE1001 exposure-response analysis based on time-matched central ECG data indicated no clinically relevant effect of bleximenib on cardiac repolarization following bleximenib monotherapy at all doses explored. Bleximenib had no clinically significant impact on HR.

Summary/Conclusion

Administration of bleximenib as monotherapy or in combination with AML-directed therapies did not prolong QTc interval and no cardiac safety signal was identified.