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

Maher Abdul-Hay[1]; Sameem Abedin[2]; Ibrahim Aldoss[3]; Ana Alfonso Piérola[4]; Juan M. Alonso-Domínguez[5]; Nikki Daskalakis[6]; Hartmut Döhner[7]; Amber D'Souza[8]; Neil Dunavin[3]; Jordi Esteve[9]; Matthew Exum[6]; Amir T. Fathi[8]; Pasquale L. Fedele[10]; Lucille Ferrante[6]; Sylvain Garciaz[11]; Ana Garrido Diaz[12]; Emmanuel Gyan[13]; Nahor Haddish-Berhane[6]; Elias J. Jabbour[14]; Madlen Jentzsch[15]; Marina Konopleva[16]; Jan Krönke[17]; Anita J. Kumar[6]; Dandan Luo[6]; Christina Loefgren[6]; Oliver Lomas[18]; Valentina Mancini[19]; Ioannis Mantzaris[18]; Anna Mitselos[20]; Daniel Morillo[5]; Teng F. Ng[21]; Marianna Norata[22]; Jenny O'Nions[23]; Kathryn Packman[24]; Cristina Papayannidis[25]; Ulrike Philippar[20]; Giorgos Psarros[20]; Christian Recher[26]; Christoph Röllig[27]; Naa Sackey[6]; Olga Salamero[28]; Tim Sauer[29]; Emma Searle[30]; Prathap N. Shastri[8]; Richard Stone[31]; Peter Tan[32]; Tao Sun[33]; Trevor Tucker[6]; Lachlin Vaughan[34]; Gala Vega[6]; Paresh Vyas[35]; Andrew H. Wei[36]; Marie Luise Hütter-Krönke[17]

[1]Laura and Isaac Perlmutter Cancer Center at New York University Langone Health, New York, NY, USA; [2]Medical College Of Wisconsin, Milwaukee, WI, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Clínica Universidad de Navarra, Navarra, Spain; [5]START Madrid-FJD Early Phase Unit, University Hospital Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain; [6]Johnson & Johnson Innovative Medicine, Spring House, PA, USA; [7]Universitätsklinikum Ulm, Ulm, Germany; [8]Hospital Clínic de Barcelona, Barcelona, Spain; [9]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [10]Monash Health and School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia; [11]Aix-Marseille Université, Inserm, CNRS, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille, Marseille, France; [12]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [13]Centre Hospitalier Universitaire de Tours, CIC INSERM U1415, Tours, France; [14]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [15]Universitätsklinikum Leipzig, Leipzig, Germany; [16]Montefiore Einstein Comprehensive Cancer Center, Bronx, NY, USA; [17]Charité – Universitätsmedizin Berlin, Berlin, Germany; [18]Janssen Research & Development, LLC, High Wycombe, UK; [19]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [20]Janssen Research & Development, LLC, Beerse, Belgium; [21]Griffith University and Gold Coast University Hospital, Australia; [22]IRCCS Istituto Romagnolo per lo Studio de Tuori (IRST) "Dino Amadori" Meldola, Italy; [23]University College London Hospitals NHS Foundation Trust and UCL/NIHR Clinical Research Facility, London, UK; [24]Johnson & Johnson Innovative Medicine, Cambridge, MA, USA; [25]Sant'Orsola-Malpighi Polyclinic, Bologna, Italy; [26]University Cancer Institute Toulouse Oncopole, Toulouse, France; [27]Universitätsklinikum TU Dresden, Dresden, Germany; [28]University Hospital Vall d'Hebron, and Experimental Hematology, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [29]Department of Internal Medicine V; Heidelberg University Hospital, Heidelberg, Germany; [30]The Christie NHS Foundation Trust and University of Manchester, Manchester, UK; [31]Dana-Farber Cancer Institute, Boston, MA, USA; [32]Royal Perth Hospital, Perth, Australia; [33]Johnson & Johnson Innovative Medicine, Raritan, NJ, USA; [34]Westmead Hospital and University of Sydney, Sydney, Australia; [35]Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine, Oxford University and Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, UK; [36]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Walter and Eliza Hall Institute of Medical Research and University of Melbourne, Melbourne, Australia.

Key Takeaway

No cardiac safety signal was identified across 334 pts enrolled in two Phase 1 trials exploring bleximenib as monotherapy or in combination with AML-directed therapies

Conclusions

Administration of bleximenib as monotherapy or in combination with AML-directed therapies did not prolong QTc, and no cardiac safety signal was identified, highlighting that this is not a class effect of menin inhibitors

Lack of QTc prolongation with bleximenib allows for combination with anti-leukemic therapies and the use of critical supportive care medications

Bleximenib is being further explored in late-stage clinical studies in R/R and ND *KMT2Ar* and *NPM1m* AML

Please scan QR code
Poster

https://www.congresshub.com/EHA2026/Oncology/Bleximenib/Abdul-Hay

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Acknowledgments

We thank the participants who are taking part in these global studies and their caregivers, the physicians and nurses who care for them, the staff at the study sites, and the staff involved in data collection and analyses. This study was funded by Johnson & Johnson. Medical writing support was provided by Ashfield MedComms, an Inizio Company and funded by Johnson & Johnson.

Abbreviations

'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; C, cycle; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; D, Day; DLT, dose limiting toxicity; DS, differentiation syndrome; ΔQTcF, change from baseline in the Fridericia-corrected QT interval; ΔQTcP, change from baseline in the population-based corrected QT interval; ECG, electrocardiogram; EOT, end of treatment; G, Grade; h, hours; *KMT2Ar*, *KMT2A*-rearraged; msec, milisecond; ND, newly diagnosed; *NPM1m*, *NPM1*-mutated; *NUP*, Nucleoporin; PK, pharmacokinetic; pt(s), participant(s); QD, once daily; QTc, corrected QT interval; QTcF, Fridericia-corrected QT interval; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; SE, standard error; TEAE, treatment-emergent adverse event; US, United States; VEN, venetoclax.

Background

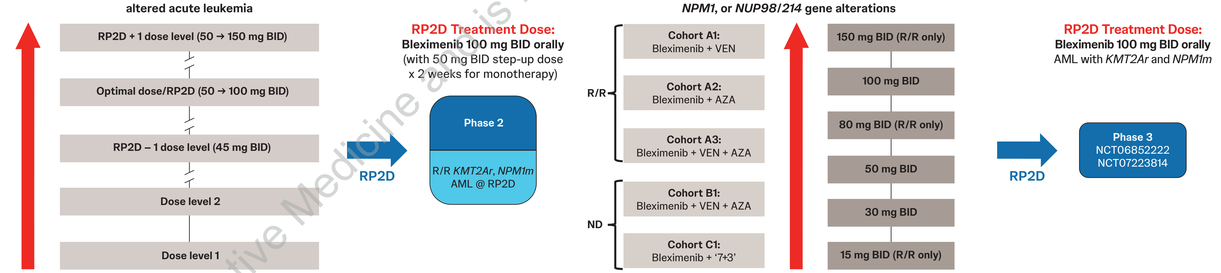
- QTc prolongation is a known risk for fatal cardiac arrythmias.[1] It has emerged as a safety signal with currently approved menin inhibitors (all-grade: 12%–36%; high-grade: 8–17%), and is included as a warning in US Prescribing Information[2,3]
- QTc prolongation may limit dose intensity of currently approved menin inhibitor therapy and complicate management of AML by preventing combination with AML-directed therapies and use of critical supportive care medicines
- Menin inhibitors may not all have the same cardiac safety profile. There remains a need for novel, tolerable, and combinable menin inhibitors
- Bleximenib is being explored in late-stage Phase 2 and Phase 3 clinical studies in pts with R/R or ND *KMT2Ar* or *NPM1m* AML eligible or ineligible for intensive chemotherapy

We report cardiac safety analyses from two Phase 1 trials exploring bleximenib as monotherapy (ALE1001; cAMeLot-1 [NCT04811560]) or in combination with AML-directed therapies (ALE1002 [NCT05453903])

Methods

- Pts received oral bleximenib continuously on 28-day cycles, either as monotherapy or in combination with AML-directed therapies (**Figure 1**)
- As of May 2026, the safety population included 334 pts (141 pts in cAMeLot-1 and 193 pts in ALE1002)
- Cardiac safety monitoring included collection of 12-lead triplicate ECGs with central cardiology review at baseline and during treatment, including serial ECGs on C1D1 and C2D1 (pre-dose to 8 hrs post-dose) and weekly ECGs during the first cycle of therapy
- AEs were evaluated according to CTCAE v5.0. QTc prolongation was defined as Grade 1 if QTc 450–480 ms, Grade 2 if 480–500 ms, and Grade 3 if >500 ms or >60 ms increase from baseline
- Coupled with intensive PK sampling and central ECGs, an exposure-response analysis using ΔQTcP as the dependent variable, and time-matched concentration of bleximenib as the explanatory variable, was performed in pts with central ECG data available
- In both studies, pts were excluded from enrollment based on QTcF ≥450 ms for males or ≥470 ms for females, or with family history of long QT syndrome

Figure 1: Study designs of ALE1001 (cAMeLot-1) and ALE1002



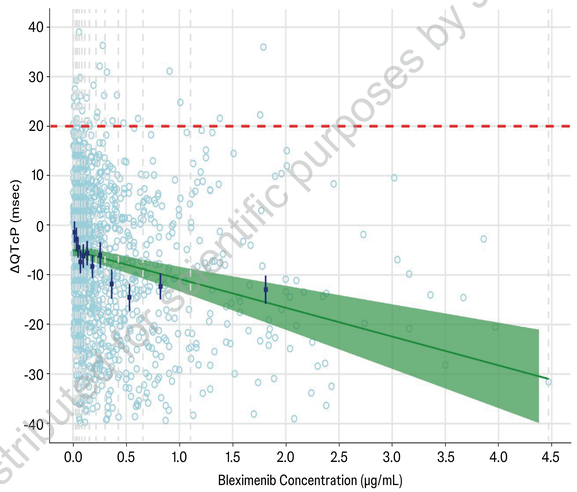
Bleximenib was received at dose levels 50–100 mg QD, or 15–150 mg BID, with various step-up dosing, as a monotherapy and at 15–150 mg BID in combination with VEN/AZA, and 30–100 mg BID in combination with '7+3'

Results

Exposure-response analysis

- 139 pts enrolled in cAMeLot-1 had central ECG data analyzed
- cAMeLot-1 exposure-response analysis indicated no clinically relevant effect of bleximenib on cardiac repolarization following bleximenib monotherapy at all doses explored (**Figure 2**)
  - Bleximenib had no clinically significant impact on heart rate
  - No time delay between bleximenib plasma concentrations and ΔQTcP was observed
- Similar findings were identified in ALE1002, with no concentration-dependent effects on QTc prolongation

Figure 2: Exposure-response analysis



The solid green line and shaded area represent the model-predicted mean ΔQTc and corresponding 90% CI, based on the intercept and the concentration-effect slope from the model fit. Red dashed lines indicate the ΔQTc threshold of a 20-msec change. Blue boxes and vertical bars represent the observed arithmetic means and corresponding 90% CI for the model adjusted ΔQTc within each bleximenib concentration range. Observations were adjusted by removing the effect of centralized baseline for each participant.

QT interval measurements over time

- There was no trend in QTcF prolongation observed across cAMeLot-1 in central ECG data from the all-treated population (**Figure 3; top panel** [n=139])
- No QTc prolongation was seen with bleximenib up to the highest dose explored, which resulted in 2-fold higher exposure vs RP2D
- Time-matched observed ΔQTcP values show no apparent concentration-dependent QTc prolongation across the range of bleximenib plasma concentrations (**Figure 2**)
- Observations from the combination therapy study ALE1002 were similar and indicated no dose-dependent effects on QTc prolongation (**Figure 3; bottom panel**)

Treatment-emergent adverse events

Table 1: Maximum Grade of QTc prolongation TEAEs in the safety population

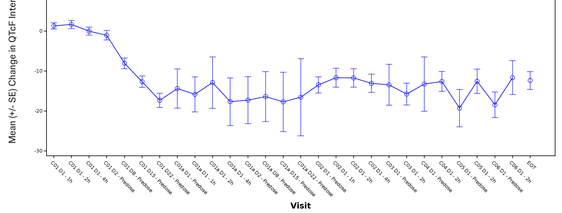
TEAE, n (%)	cAMeLot-1 Phase 1 Monotherapy study (N=141)	ALE1002 Combination study (N=193)
Grade 1/2 TEAEs of QTc prolongation	0 (0)	8 (4.1)
Grade 3 TEAEs of QTc prolongation	1 (0.7)	1 (0.5)

Data cut off: May 2026

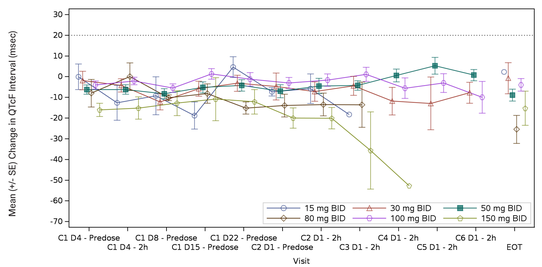
- Across both studies, Grade 3 QTc prolongation was reported in one pt (0.7%) in cAMeLot-1 and one pt (0.5%) in ALE1002 (**Table 1**)
  - In cAMeLot-1, the only G3 QT prolongation event was observed at a non-RP2D dose level (100 mg QD without step-up dosing) as a DLT. This event occurred in a pt with clinically relevant baseline ongoing cardiovascular comorbidities and in the setting of rapid clinical progression. Bleximenib was discontinued; the event resolved in 7 days
  - In ALE1002, one G3 QT prolongation event occurred at bleximenib 50 mg BID in combination with VEN + AZA on study D15, resolving within 2 days; confounded by QT-prolonging medications. The patient developed G3 DS on D17, discontinued bleximenib, and died on D18. Two additional QTc prolongation events were identified by central ECG review, meeting G3 CTCAE criteria based on >60 ms from baseline without an absolute QTcF >500 ms. Both events occurred in the context of electrolyte imbalances (including hypokalemia) with concomitant QTc-prolongation medications . All events resolved following electrolyte correction
- No dose modifications due to QTc prolongation occurred in either study in the BID dosing cohorts, including at the RP2D dose level
- No deaths or treatment discontinuations due to QTc prolongation occurred in either study

Figure 3: ΔQTcF interval across bleximenib dose groups and time-points

cAMeLot-1 monotherapy study: Combined dose data across time points*



ALE1002 combination study: Data across doses and time points



*Cycle 1a was limited to a subset of pts in a single dose escalation cohort exploring an alternative step-up dosing regimen.
Data cut off: May 2026

References

1. Farzam K, Tivakaran VS. QT Prolonging Drugs. In: StatPearls [Internet]. StatPearls Publishing; 2026.
2. REVUFORJ [Prescribing Information]®. New York, NY: Syndax Pharmaceuticals, Inc. 2025.
3. KOMZIFTI [Prescribing Information]™. San Diego, CA: Kura Oncology, Inc. 2025.

Myeloid Malignancies

Presented by M Hütter-Krönke at EHA; June 11–14, 2026; Stockholm, Sweden.