Recommended Phase 2 Dose Determination of Bleximenib in Combination With Venetoclax + Azacitidine: Phase 1b Study in Relapsed/Refractory and Newly Diagnosed Acute Myeloid Leukemia With *KMT2A/NPM1* Alterations

Andrew H. Wei,[1] Jordi Esteve Reyner,[2] Sylvain Garciaz,[3] Ibrahim Aldoss,[4] Ana Alfonso Piérola,[5] Alicia Allred,[6] Juan Manuel-Alonso Dominguez,[7] Laura Barreyro,[6] Pierre Bories,[8] Nikki Daskalakis,[6] Matteo Giovanni Della Porta,[9] Hartmut Döhner,[10] Amber D'Souza,[6] James Dugan,[11] Amir Fathi,[12] Pasquale Fedele,[13] Lucille Ferrante,[6] Rachel Kobos,[14] Stan Gaj,[15] Ana Garrido Diaz,[16] Sara Garrido Paniagua,[17] Christina Guttke,[6] Emmanuel Gyan,[18] Brett Hiebert,[19] Elias Jabbour,[20] Danielle Trancucci,[14] Tosin Bamidele,[14] Madlen Jentzsch,[21] Hagop Kantarjian,[20] Marina Konopleva,[22] Jan Krönke,[23] Marie Luise Hütter-Krönke,[23] Christina Loefgren,[14] Oliver Lomas,[24] Valentina Mancini,[25] Ioannis Mantzaris,[22] Daniel Morillo,[7] Jenny O'Nions,[26] Kathryn Packman,[27] Cristina Papayannidis,[28] Christian Recher,[8] Christoph Röllig,[29] Olga Salamero,[17] Prathap Nagaraja Shastri,[6] Tim Sauer,[30] Emma Searle,[31] Natalia Tovar,[2] Nicolas Vallet,[32] Lachlin Vaughan,[33] Gala Vega,[7] Paresh Vyas,[34] Uwe Platzbecker[35]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Hospital Clínico de Barcelona, Barcelona, Spain; [3]Aix-Marseille Université, Marseille, France; [4]City of Hope, Duarte, CA, USA; [5]University of Navarra, Pamplona, Spain; [6]Johnson & Johnson, Spring House, PA, USA; [7]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [8]The Cancer University Institute of Toulouse Oncopole, Toulouse, France; [9]Humanitas Research Hospital, Milan, Italy; [10]Ulm University, Ulm, Germany; [11]Novant Health Cancer Institute, Mooresville, NC, USA; [12]Harvard Medical School, Boston, MA, USA; [13]School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia; [14]Johnson & Johnson, Raritan, NJ, USA; [15]Johnson & Johnson R&D, Beerse, Belgium; [16]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [17]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [18]University of Tours, Tours, France; [19]Johnson & Johnson R&D, Winnipeg, MB, Canada; [20]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [21]Leipzig University, Leipzig, Germany; [22]Jack D. Weiler Hospital of the Albert Einstein College of Medicine, New York, NY, USA; [23]Charité - Universitätsmedizin Berlin, Berlin, Germany; [24]Johnson & Johnson R&D, High Wycombe, United Kingdom; [25]ASST Niguarda Great Metropolitan Hospital, Milan, Italy; [26]University College London Hospital NHS Foundation, London, United Kingdom; [27]Johnson & Johnson, Newton, MA, USA; [28]University of Bologna, Bologna, Italy; [29]University of Dresden, Dresden, Germany; [30]University of Heidelberg, Heidelberg, Germany; [31]The Christie NHS Foundation Trust, Manchester, United Kingdom; [32]University Hospital of Tours, Tours, France; [33]Westmead Hospital, Sydney, NSW, Australia; [34]MRC Weatherall Institute of Molecular Medicine, Oxford, United Kingdom; [35]Klinik und Poliklinik für Hämatologie, Zelltherapie, Hämostaseologie und Infektiologie, Leipzig, Germany

KEY TAKEAWAY

Bleximenib 100 mg BID was selected as the RP2D based on its favorable efficacy and safety profile when combined with VEN + AZA in both R/R and ND *KMT2Ar* or *NPM1m* AML. The regimen demonstrated high response rates, including in participants with prior VEN exposure, with a safety profile consistent with the standard VEN + AZA backbone

INTRODUCTION

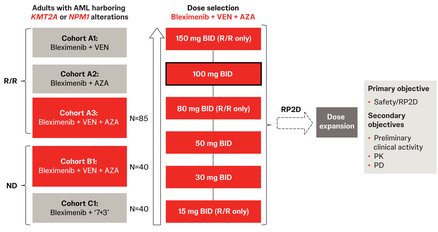
- Bleximenib is a potent, selective oral menin inhibitor with demonstrated preclinical and clinical activity in histone-lysine N-methyltransferase 2A (*KMT2*) rearranged (*KMT2Ar*) or nucleophosmin 1 (*NPM1*) mutated (*NPM1m*) acute myeloid leukemia (AML), both as a monotherapy and in combination with AML therapies, including venetoclax (VEN) + azacitidine (AZA)[1-5]
- VEN + AZA is approved for the treatment of patients with newly diagnosed (ND) AML who are older or unfit for intensive chemotherapy, and is also used in patients with relapsed/refractory (R/R) AML[6]
- Promising safety and efficacy of bleximenib in combination with VEN + AZA has been observed in patients with R/R AML harboring *KMT2Ar* or *NPM1m*[2]
- The primary objective of the ongoing ALE1002 study (NCT05453903) is to evaluate safety and preliminary efficacy of bleximenib in combination with AML-directed therapies in participants with R/R or ND AML harboring *KMT2A* or *NPM1* alterations[7]

OBJECTIVE

- To determine the recommended phase 2 dose (RP2D) of bleximenib in combination with VEN + AZA in participants with R/R or ND *KMT2Ar* or *NPM1m* AML

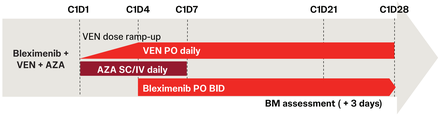
METHODS

FIGURE 1: Study design



7+3, cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; *KMT2A*, histone-lysine N-methyltransferase 2A; *NPM1*, nucleophosmin 1; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

FIGURE 2: Dosing schedules and exposures



Dosing schedules

- 28-day treatment cycles
- VEN and AZA administration guided by the approved label
  - VEN plateau dose 400 mg daily
  - No significant dose modifications to SOC VEN or AZA required in combination with bleximenib
- Bleximenib BID commenced on C1D4 (+3-day window)
  - 100% relative dose intensity seen in the first 3 cycles
- Hydroxyurea and steroids for DS prophylaxis and treatment permitted
- Isavuconazole primary antifungal of choice, when indicated, with no requirement for bleximenib dose modification

AZA, azacitidine; BID, twice daily; BM, bone marrow; C, cycle; D, day; DS, differentiation syndrome; IV, intravenous; PO, by mouth; SC, subcutaneous; SOC, standard of care; VEN, venetoclax.

FIGURE 3: Safety and efficacy populations



BID, twice daily; ITT, intent to treat; KMT2Ar, histone-lysine N-methyltransferase 2A rearranged; ND, newly diagnosed; *NPM1m*, nucleophosmin 1 mutated; R/R, relapsed/refractory.

- Efficacy population includes all participants who met the following criteria (**FIGURE 3**):
  - Participants who received bleximenib at doses of 50 mg, 100 mg, or 150 mg twice daily
  - Participants with *KMT2Ar* or *NPM1m* only
  - Participants who discontinued, even if before first disease evaluation, are included

RESULTS

- At the data cut-off date, 125 participants received bleximenib plus VEN + AZA (R/R, n=85; ND, n=40) (**TABLE 1**)
- Most participants (46/85) with R/R AML received ≥2 prior therapies: 40 participants received prior VEN and 32 participants received prior AZA (**SUPPLEMENTAL TABLE 1, QR Code**)

TABLE 1: Demographics and baseline characteristics, all treated

Characteristics	R/R AML (n=85)	ND AML (n=40)	Combined population (N=125)
Median age (range), years	60 (19–85)	75 (43–88)	67 (19–88)
Female, n (%)	51 (60)	21 (53)	72 (58)
ECOG PS, n (%)			
0	26 (31)	9 (23)	35 (28)
1	50 (59)	24 (60)	74 (59)
2	9 (11)	7 (18)	16 (13)
EMD at baseline, n (%)	9 (11)	3 (8)	12 (10)
Genetic alterations, n (%)			
KMT2A	44 (52)	8 (20)	52 (42)
NPM1	41 (48)	32 (80)	73 (58)
Relevant co-mutations occurring in ≥10% of participants, n (%)			
DNMT3A	24 (28)	9 (23)	33 (26)
FLT3	20 (24)	10 (25)	30 (24)
TET2	12 (14)	8 (20)	20 (16)
IDH2	9 (11)	5 (13)	14 (11)

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; *KMT2A*, histone-lysine N-methyltransferase 2A; ND, newly diagnosed; *NPM1*, nucleophosmin 1; R/R, relapsed/refractory.
Data cut-off date: May 7, 2025.

Safety

- Safety profile was similar across 50 mg twice daily (BID) and 100 mg BID dose levels (**TABLE 2**)
- Safety was consistent with the VEN + AZA backbone
- No dose-limiting toxicities (n=0/49) were observed at 100 mg BID
- In participants who achieved complete response (CR) or CR with partial hematologic recovery (CRh) at 100 mg BID (R/R, n=9; ND, n=13)
  - Median (range) time to platelet recovery ≥50x10^9/L from cycle 1 day 1 was 38 days (21–50) in R/R AML and 29 days (18–57) in ND AML
  - Median (range) time to neutrophil recovery ≥0.5x10^9/L from cycle 1 day 1 was 32 days (21–67) in R/R AML and 31 days (22–66) in ND AML
- Median (range) duration of follow-up at 100 mg BID was 6.9 months (0.2–16.2)

TABLE 2: Safety profile: TEAEs regardless of relatedness

TEAEs	Any grade			Grade ≥3		
	50 mg BID (n=45)	100 mg BID (n=49)	All dosed (N=125)	50 mg BID (n=45)	100 mg BID (n=49)	All dosed (N=125)
Participants with ≥1 TEAE, n (%)	45 (100)	49 (100)	125 (100)	43 (96)	47 (96)	121 (97)
Hematologic TEAEs occurring in ≥20% of participants						
Thrombocytopenia	26 (58)	30 (61)	72 (58)	25 (56)	29 (59)	69 (55)
Anemia	26 (58)	24 (49)	69 (55)	25 (56)	24 (49)	67 (54)
Neutropenia	23 (51)	29 (59)	62 (50)	23 (51)	29 (59)	62 (50)
Febrile neutropenia	20 (44)	18 (37)	49 (39)	20 (44)	18 (37)	49 (39)
Leukopenia	15 (33)	5 (10)	31 (25)	14 (31)	5 (10)	29 (23)
Nonhematologic TEAEs occurring in ≥20% of participants						
Nausea	24 (53)	32 (65)	77 (62)	1 (2)	1 (2)	4 (3)
Vomiting	18 (40)	20 (41)	51 (41)	0	1 (2)	1 (1)
Constipation	20 (44)	17 (35)	44 (35)	2 (4)	1 (2)	3 (2)
Diarrhea	10 (22)	17 (35)	41 (33)	0	1 (2)	1 (1)
Pyrexia	10 (22)	17 (35)	39 (31)	1 (2)	1 (2)	3 (2)
Fatigue	10 (22)	11 (22)	30 (24)	3 (7)	3 (6)	7 (6)
Asthenia	11 (24)	8 (16)	27 (22)	3 (7)	1 (2)	6 (5)

BID, twice daily; TEAE, treatment-emergent adverse event. Data cut-off date: May 7, 2025.

- Low rates of differentiation syndrome (DS) were observed with implementation of safety mitigation measures (protocol-specified guidance, including study drug interruption, use of prophylactic steroids and hydroxyurea in select participants considered at high risk for the development of severe DS, and staggered initiation of bleximenib dosing on cycle 1 day 4 have been implemented as safety measures to mitigate and manage the risk of DS); 1 grade 5 event occurred in the R/R 50 mg BID combination cohort (**TABLE 3**)
- No corrected QT interval (QTc) prolongation signal was identified (**TABLE 3**)
  - All reported QTc prolongation events were grade 1 and required no bleximenib dose interruption or reduction

TABLE 3: Adverse events of clinical interest with menin inhibition

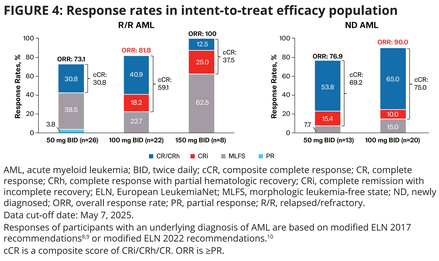
AE, regardless of relatedness	Any grade			Grade ≥3		
	50 mg BID (n=45)	100 mg BID (n=49)	All dosed (N=125)	50 mg BID (n=45)	100 mg BID (n=49)	All dosed (N=125)
Differentiation syndrome, n (%)	5 (11)	2 (4)	7 (6)	3 (7)	2 (4)	5 (4)
QTc prolongation, n (%)	2 (4)	3 (6)	5 (4)	0	0	0

AE, adverse event; BID, twice daily; QTc, corrected QT interval. Data cut-off date: May 7, 2025.

Efficacy

- Evaluation of the data shows optimized responses with bleximenib 100 mg BID in combination with VEN/AZA (**FIGURE 4**)
- Response data are maturing; 6 participants with ND AML are currently receiving treatment with the potential to deepen response
- In participants receiving 100 mg BID, the median (range) time to first response was 23 days (18–50) in R/R settings and 22 days (18–57) in ND settings

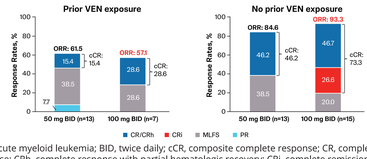
FIGURE 4: Response rates in intent-to-treat efficacy population



AML, acute myeloid leukemia; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete remission with incomplete recovery; ELN, European LeukemiaNet; MLFS, morphologic leukemia-free state; ND, newly diagnosed; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory.
Data cut-off date: May 7, 2025.
Responses of participants with an underlying diagnosis of AML are based on modified ELN 2017 recommendations[8,9] or modified ELN 2022 recommendations.[10]
cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

- Participants with prior VEN exposure demonstrated responses to bleximenib combination therapy (**FIGURE 5**)

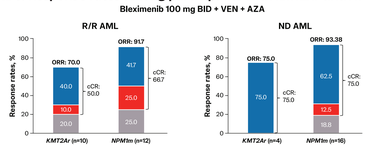
FIGURE 5: Response rates in participants with R/R AML and with/without prior VEN exposure



AML, acute myeloid leukemia; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete remission with incomplete recovery; ELN, European LeukemiaNet; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; VEN, venetoclax.
Data cut-off date: May 7, 2025.
Responses of participants with an underlying diagnosis of AML are based on modified ELN 2017 recommendations[8,9] or modified ELN 2022 recommendations.[10]
cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

- High rates of response were observed in participants with *KMT2Ar* and *NPM1m* (**FIGURE 6**)
- No acquired *MEN1* resistance mutations were found in 19 participants with R/R AML who had on-treatment samples available; the mean duration on treatment was 275 days

FIGURE 6: Response rates among participants with *KMT2Ar* and *NPM1m*



AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; cCR, composite complete response; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete remission with incomplete recovery; ELN, European LeukemiaNet; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearranged; MLFS, morphologic leukemia-free state; ND, newly diagnosed; *NPM1m*, nucleophosmin 1 mutated; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; VEN, venetoclax. Data cut-off date: May 7, 2025.
Responses of participants with an underlying diagnosis of AML are based on modified ELN 2017 recommendations[8,9] or modified ELN 2022 recommendations.[10]
cCR is a composite score of CRi/CRh/CR. ORR is ≥PR.

- 4 participants with R/R (18.2%) and 13 with ND (65%) AML were ongoing treatment at data cut-off (**SUPPLEMENTAL FIGURE 1, QR Code**)
- Median (range) number of cycles at 100 mg BID was 3 (1–13) in R/R AML and 3 (1–6) in ND AML
- 5 participants with R/R (22.7%) and 2 with ND (10%) AML at 100 mg BID proceeded to transplant

CONCLUSIONS

Combination of efficacy, safety, and resistance data informed bleximenib 100 mg BID as the RP2D when used in combination with VEN + AZA for both R/R and ND *KMT2Ar* or *NPM1m* AML

- Compared with lower doses, bleximenib 100 mg BID in combination resulted in higher efficacy and similar safety, consistent with that observed with the established monotherapy RP2D
- High response rates were observed in participants with *KMT2Ar* and *NPM1m*
  - Responses were also observed in participants with prior VEN exposure
  - 5 participants with R/R (22.7%) and 2 participants with ND (10%) AML at 100 mg BID proceeded to transplant
- Safety profile was consistent with the VEN + AZA backbone
- Low rates of DS were observed (4%); no QTc prolongation signal was identified
- No emergent *MEN1* resistance mutations have been identified to date

The placebo-controlled phase 3 cAMeLot-2 trial investigating VEN + AZA with or without bleximenib in participants with ND AML who are ineligible for intensive chemotherapy is now open and enrolling (NCT06852222)

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Myeloid Malignancies

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