Phase 1b Study of Menin-KMT2A Inhibitor Bleximenib in Combination with Intensive Chemotherapy in Newly Diagnosed Acute Myeloid Leukemia with *KMT2Ar* or *NPM1* Alterations

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Bleximenib Combined With Intensive Chemotherapy in ND-AML

Background

- Newly diagnosed (ND) AML is a genetically heterogeneous disease with a median 5-year overall survival of ~30%[1,2]
- High intensity chemotherapy (IC), comprising '7+3' with cytarabine consolidation remains a cornerstone of therapy, in those 'fit' enough to undergo such therapy
- Bleximenib (JNJ-75276617) is a potent, selective inhibitor of the menin-KMT2A complex[3]
- Activity has been observed in *KMT2Ar or NPM1m* AML when given either as monotherapy or in combination[4,5]

Focus of this study: explore safety & preliminary efficacy of bleximenib in combination with IC ('7+3') for ND 'fit' AML

'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; IC, intensive chemotherapy; *KMT2Ar, KMT2A*-rearranged; ND, newly diagnosed; *NPM1m*, *NPM1*-mutated.

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4. Jabbour E at al. Presented at ASH; December 9–12, 2022; San Diego, California, USA. Oral presentation 616. 5. Wei AH, et al. Presented at EHA; June 13–16, 2024; Madrid, Spain. Abstract S133.

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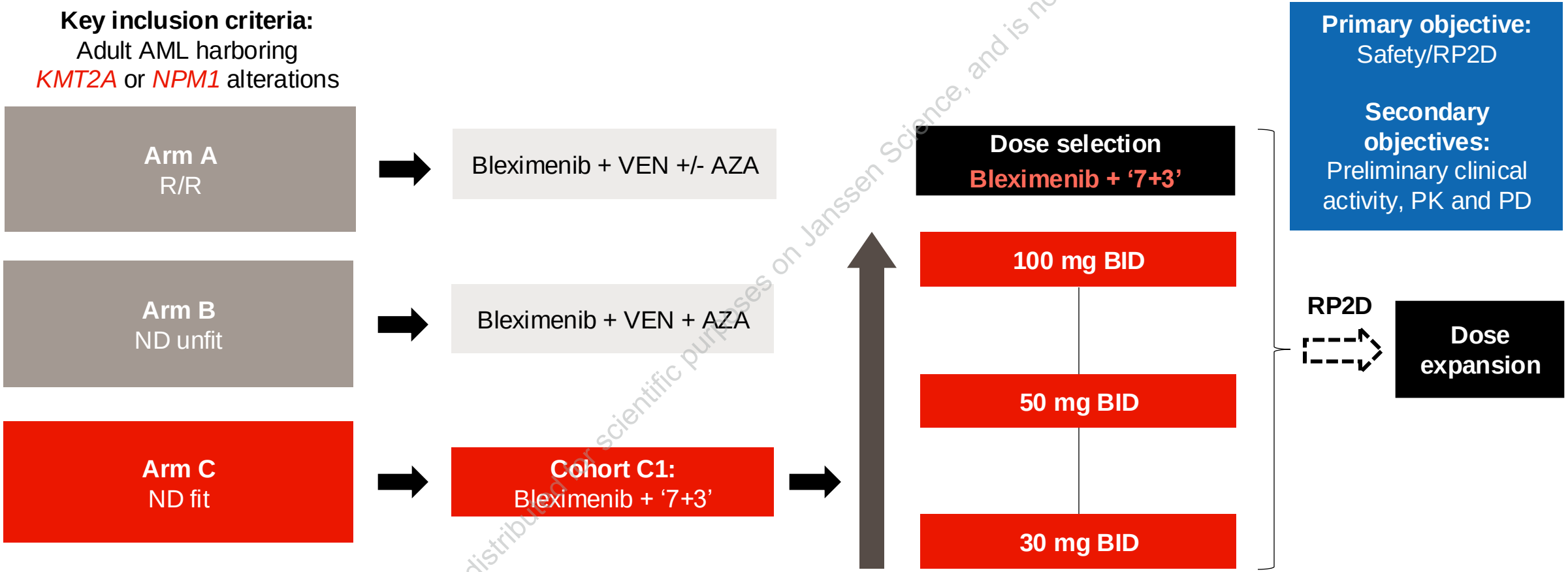
Study Design

Key inclusion criteria:
Adult AML harboring
KMT2A or *NPM1* alterations



NCT05453903
'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; ND, newly-diagnosed; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; VEN, venetoclax.

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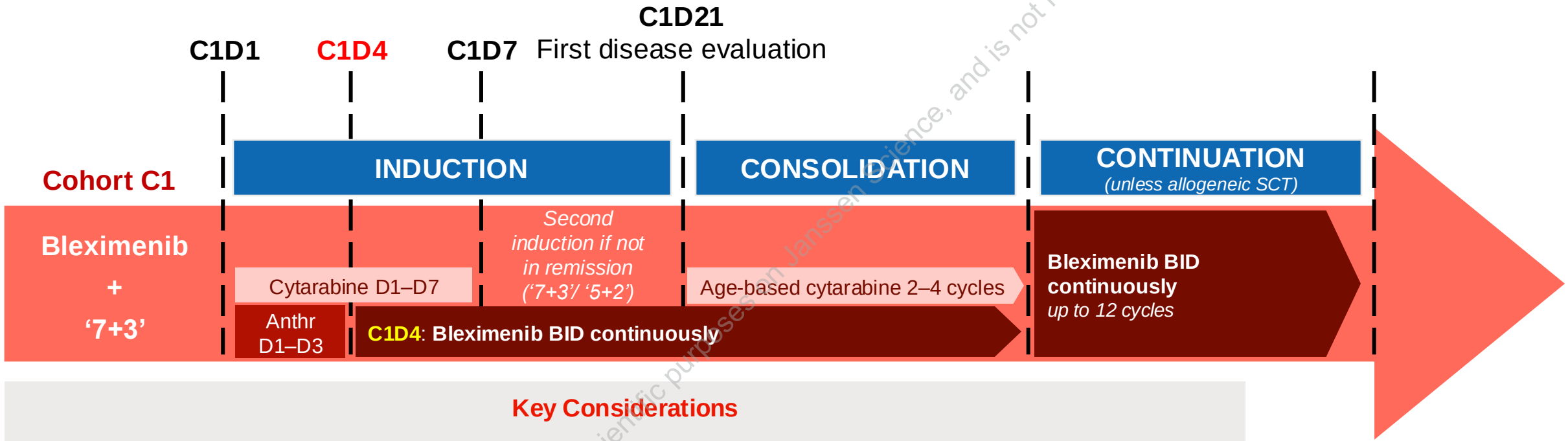
Dosing Schedule



Key Considerations

- Age ≥18 and fit for intensive chemotherapy
- Bleximenib BID commences on C1D4 without step-up dosing
- '7+3' dosing with anthracycline (daunorubicin or idarubicin) as per SOC / institutional guidelines with single cycle and reinduction if remission not achieved; consolidation begins for responders upon count recovery
- Continuation therapy available in absence of allograft
- Bleximenib PK exposures in combination studies similar to monotherapy study

NCT05453903

'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); BID, twice daily; C, cycle; D, day; ND, newly-diagnosed; PK, pharmacokinetic; SOC, standard of care.

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Bleximenib Combined With Intensive Chemotherapy in ND-AML

Baseline Demographics and Characteristics – Safety Group

Characteristic	Overall population (N=28)
Age, median (range), years	58 (24–70)
Female, n (%)	15 (54%)
ECOG PS, n (%)	
0	10 (35.7%)
1	17 (60.7%)
2	1 (3.6%)
Median leukocyte (range) x 10^9/L	3.22 (0.86–20.08)
Median bone marrow blast (range), %	51% (2–98)

Characteristic	Overall population (N=28)
Genetic alterations, n (%)	
KMT2A	13 (46%) [*KMT2Ar* n=9 (32%)]
NPM1	15 (54%)
Relevant co-mutations (in at least 4 pts)	
DNMT3a	6
FLT3 (ITD:TKD)	6 (3,3)
TET2	4

Data sources: TSIDEM01BBCOHORTC1, TSIDEM02BBCOHORTC1.
Data cut-off date: October 9, 2024.
AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ND, newly-diagnosed; *NPM1m*, *NPM1*-mutated.

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Safety Profile – TEAEs (Regardless of Relatedness)

TEAE (N=28 participants)	Any grade	Grade ≥3
Total, n (%)	28 (100)	26 (93)
Hematologic AEs		
Thrombocytopenia	19 (68)	19 (68)
Febrile neutropenia	18 (64)	17 (61)
Neutropenia	15 (54)	15 (54)
Anemia	16 (57)	15 (54)
Leukopenia	9 (32)	9 (32)
Nonhematologic AEs		
Pneumonia	8 (29)	6 (21)
Sepsis	4 (14)	4 (14)
Nausea	15 (54)	3 (10)
Stomatitis	11 (39)	3 (10)
GGT Increased	5 (18)	4 (14)
Hypotension	6 (21)	3 (10)

	Bleximenib 30 to 100 mg BID + '7+3' N=28
Count Recovery in Induction	**Median days (range)**
Days to platelet count recovery ($50x10^9$/L)	32 (22–74)
Days to neutrophil count recovery ($0.5x10^9$/L)	33 (25–57)

Key Observations

- No DS or DLTs observed to date
- Safety profile consistent with intensive chemotherapy backbone therapy
- No clinically significant myelosuppression observed in induction

Data sources: TSFAE02BBCOHORTC1,TSFAE24BBCOHORTC1, TSFREC01
Data cut-off date: October 9, 2024.
AE, adverse event; AML, acute myeloid leukemia; BID, twice daily; DLT, dose-limiting toxicity; DS, differentiation syndrome; GGT, gamma-glutamyl transferase; ND, newly diagnosed; TEAE, treatment-emergent adverse event.

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Safety Profile: Key Adverse Events Related to Bleximenib

ND Fit AML (Cohort C1)

Adverse event, n (%)	All grade TRAEs All dosed (N=28)
Electrocardiogram QTcF prolongation	0
Differentiation syndrome	0

Key Observations

- No DS or DLTs observed to date
- DS rate with bleximenib in combination lower than bleximenib monotherapy
- No QTc prolongation signal identified with bleximenib
- Bleximenib dose reductions: 2 (7%)
- Bleximenib dose discontinuations: 2 (7%)

Data sources: TSFAE02BB, TSFAE02BBCOHORTC1 ; Data cut-off date: October 9, 2024.
'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; DLT, dose-limiting toxicity; DS, differentiation syndrome; ND, newly diagnosed; QTc(F), corrected QT interval (Friderica); TRAE, treatment-related adverse event.

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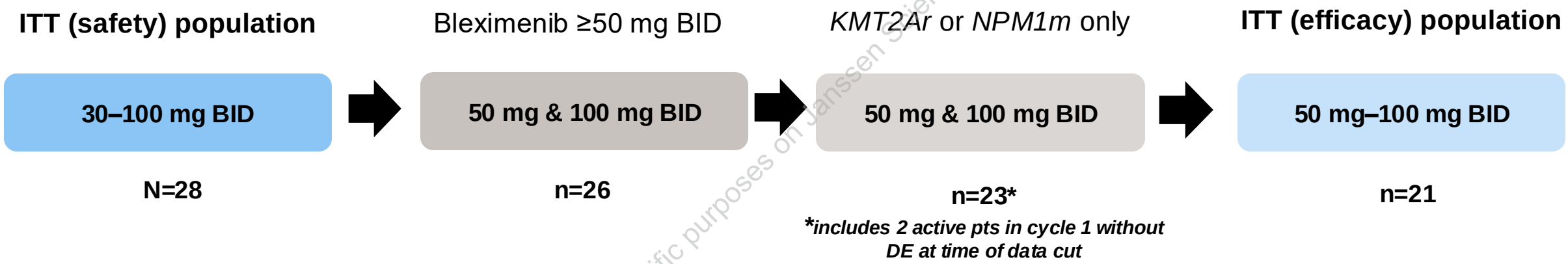
Safety and Efficacy Populations



Efficacy population includes the following participants:

- Received bleximenib ≥50 mg BID
- AML with *KMT2Ar* or *NPM1m* only
- Pts who discontinued - even if prior to first disease evaluation

Data cut-off: October 9, 2024.

AML, acute myeloid leukemia; BID, twice daily; ITT, intent-to-treat; *KMT2Ar, KMT2A*-rearranged; *NPM1m*, *NPM1*-mutated; pt, participant; R/R, relapsed/refractory.

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Preliminary ITT Efficacy

Efficacy Parameter	Bleximenib (≥ 50 mg BID) + '7+3' (N=21)	
ORR (≥PR), n (%)	95% (20/21)	
Composite BOR, n (%)		
cCR (CR/CRh/CRi)	86% (18/21)	
CR/CRh	*81% (17/21)*	
CR	*76% (16/21)*	
MLFS + PR	9.5% (2/21)	
Mutation-specific composite BOR, n (%)	*KMT2Ar* (N=8)	*NPM1m* (N=13)
ORR, n (%)	7 (88%)	13 (100%)
CR/CRh	7 (88%)	10 (77%)
MLFS + PR	0	2 (15%)

Responses were investigator-assessed per modified ELN 2017 criteria (AML)

Key Observations

- **Similar response rates** observed in both *KMT2Ar* and *NPM1m* AML
- **ELN 2022 Risk stratification* (efficacy cohort; n=21)**
  - Favourable 10 (48%)
  - Intermediate 8 (38%)
  - Adverse 3 (14%)
- **Local MRD status among tested responders (n=9)**
  - Bleximenib 50 mg BID + '7+3': 2/3 MRD-
  - Bleximenib 100 mg BID + '7+3': 6/6 MRD-

Data sources: TEFRS02BBB, TEFRS02EBB, TEFRS02FBB. Data cut-off date: October 9, 2024.
*As reported by investigators based on screening genetic data
'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; BID, twice daily; BOR, best overall response; C, cycle; CR, complete response; CRh, CR with partial haematological recovery; CRi , complete remission with incomplete recovery; ELN, European LeukemiaNet; ITT, intent-to-treat; *KMT2Ar, KMT2A* rearranged; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; ND, newly diagnosed; *NPM1m*, *NPM1*-mutated; ORR, overall response rate; PR, partial response.

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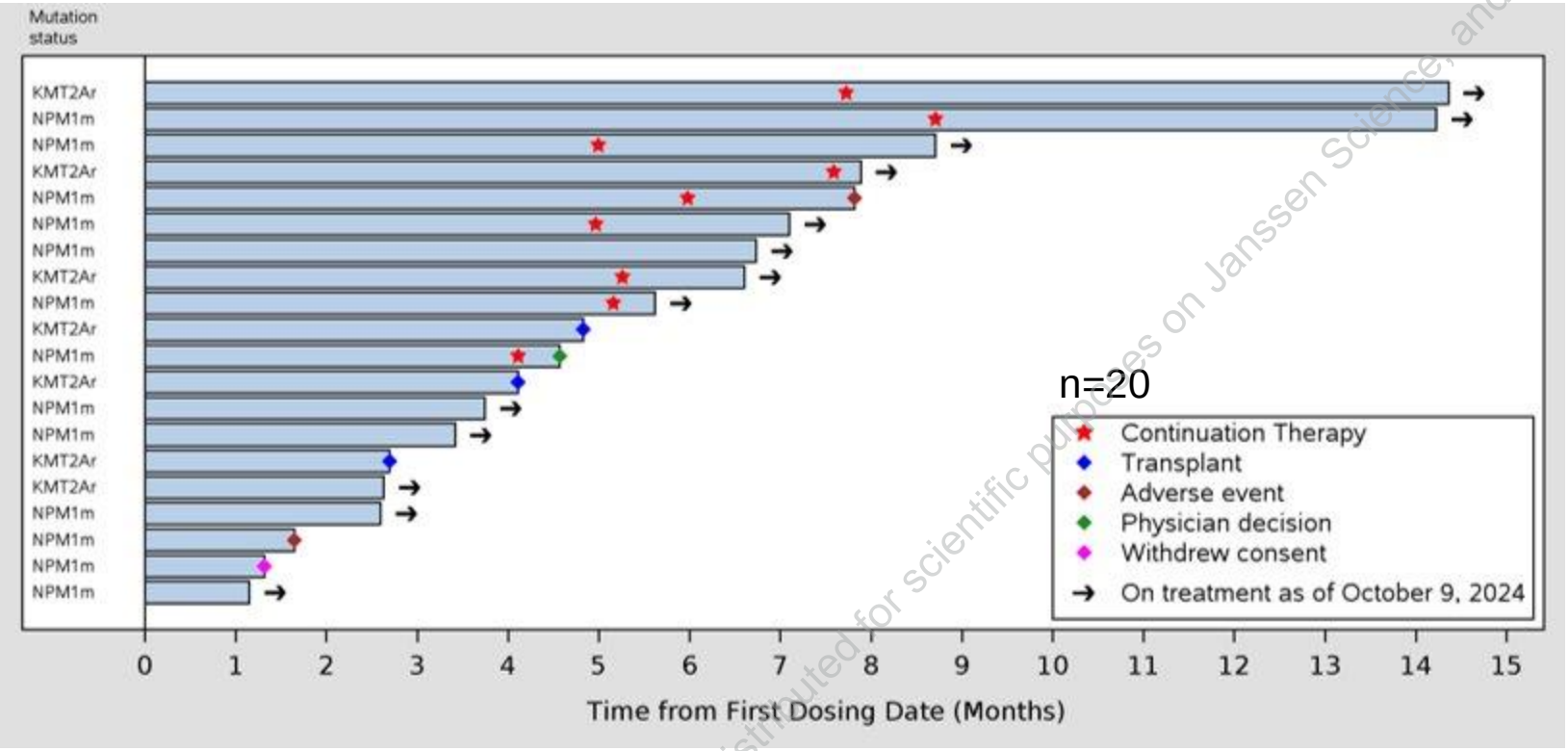
Duration of Treatment in Responders

≥ 50 mg BID Bleximenib + High Intensity Chemotherapy



Key Observations

- **3 pts proceeded to allograft** (all *KMT2Ar*)
- **13 pts active**; 9 in continuation therapy with **bleximenib monotherapy**
- **4 pts discontinued**
- No **relapse** or **mortality** observed

Data cut-off date: October 9, 2024. N=20: responders only.
AML, acute myeloid leukemia; BID, twice daily; *KMT2Ar*, *KMT2A* rearranged; ND, newly diagnosed; pt, participant.

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Bleximenib Combined With Intensive Chemotherapy in ND-AML

Conclusions

- Safety data demonstrate that bleximenib is combinable with SOC IC for ND fit AML
  - No DS or DLTs observed to date - DS rate with bleximenib in combination with '7+3' lower than bleximenib monotherapy
  - No clinically significant myelosuppression observed
  - No QTc prolongation signal identified
- Preliminary efficacy in ND AML - high response rates comparable across *KMT2Ar* or *NPM1m* with bleximenib and IC
  - 13 pts ongoing and 9 in continuation therapy
- Exploration ongoing of bleximenib in combination with AML-directed therapies (ALE1002: NCT05453903), supportive of future Phase 3 studies
- Phase 2 bleximenib monotherapy **cAMeLot-1** study ongoing (NCT04811560)

'7+3', cytarabine + anthracycline (daunorubicin or idarubicin); AML, acute myeloid leukemia; DLT, dose-limiting toxicity; DS, differentiation syndrome; IC, intensive chemotherapy; *KMT2Ar, KMT2A* rearranged; ND, newly-diagnosed; *NPM1m*, *NPM1*-mutated; pt, participant; QTc, corrected QT interval.

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