Exploring the latest data on new and emerging treatments for the improvement of outcomes in higher-risk MDS and newly diagnosed AML

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Overview

New and emerging treatments for the improvement of outcomes in higher-risk MDS and newly diagnosed AML:

Part 1. MoA and key clinical data for emerging treatments for higher-risk MDS

Part 2. Current treatments and novel approaches for newly diagnosed AML, including management options when intensive induction therapy is not suitable

Part 3. Current and future potential of immunotherapy and the use of MRD monitoring in MDS and AML

AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; MoA, mechanism of action; MRD, measurable residual disease.

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MoA and key clinical data for emerging treatments for higher-risk MDS

EHA, European Association of Hematology; MDS, myelodysplastic syndromes; MoA, mechanism of action.

Management of higher-risk MDS

- Patients with MDS are classified into ‘lower-risk’ and ‘higher-risk’ based on prognostic scoring systems[1]
- For higher-risk disease the treatment goal is to **prolong survival**[2]
- For patients with higher-risk MDS, ASCT is considered the only **potentially curative** treatment. However, this option is **unsuitable** for the majority of patients[1,3]
- Intensive CT + HMA is used prior to transplant in patients with an excess of marrow blasts[1]
- HMA alone (e.g. azacitidine) may **improve survival** in certain patients[1,3]
- Novel agents, including venetoclax, pevonedistat and IDH1/2 inhibitors, are currently under investigation for the management of patients with higher-risk MDS[1,3]

ASCT, allogeneic stem cell transplantation; CT, chemotherapy; HMA, hypomethylating agents; IDH1/2, isocitrate dehydrogenase 1/2; MDS, myelodysplastic syndromes.

1. Fenaux P, et al. *Br J Haematol.* 2020;189:1016–27; 2. Garcia-Manero G, et al. *Am J Hematol.* 2020;95:1399–420; 3. Scalzulli E, et al. *Blood Rev.* 2021;45:100689.

Pevonedistat + azacitidine in higher-risk MDS

Sekeres M, et al.[1]

Efficacy and safety of PEVO (a NEDD8-activating enzyme inhibitor) + AZA vs AZA alone in patients with higher-risk MDS or CMML, or low-blast AML, already established in phase II PoC study[2]

- **OS, EFS and ORR benefits** particularly promising among patients with higher-risk MDS
- Safety profile of PEV + AZA comparable to AZA alone

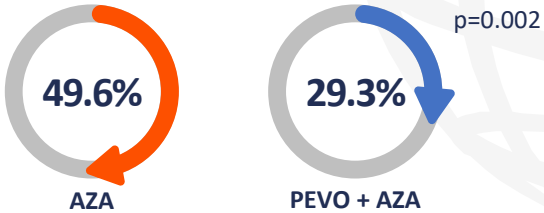
Prespecified comparative analysis of mutant allele burden in each study arm over time via ultra-sensitive duplex sequencing

58 samples underwent duplex sequencing
(33 higher-risk MDS; 7 higher-risk CMML; 18 LB-AML)

Samples were representative of the general study population

N=58

Results demonstrated significantly **less expansion of treatment-emergent mutations** with PEVO + AZA arm vs AZA alone*



*Expansion of treatment-emergent mutations was defined as either newly detected or numerically increased VAF after treatment. AML, acute myeloid leukaemia; AZA, azacitidine; CMML, chronic myelomonocytic leukaemia; CR, complete response; EFS, event-free survival; LB, low-blast; MDS, myelodysplastic syndrome; NEDD8, neural precursor cell expressed, developmentally downregulated 8; ORR, overall response rate; OS, overall survival; PEVO, pevonedistat; PoC, proof of concept; VAF, variant allele frequency.

1. Friedlander S, et al. Abstr. S166. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT02610777.
2. Sekeres MA, et al. *Leukemia.* 2021. doi: 10.1038/s41375-021-01125-4. Epub ahead of print.

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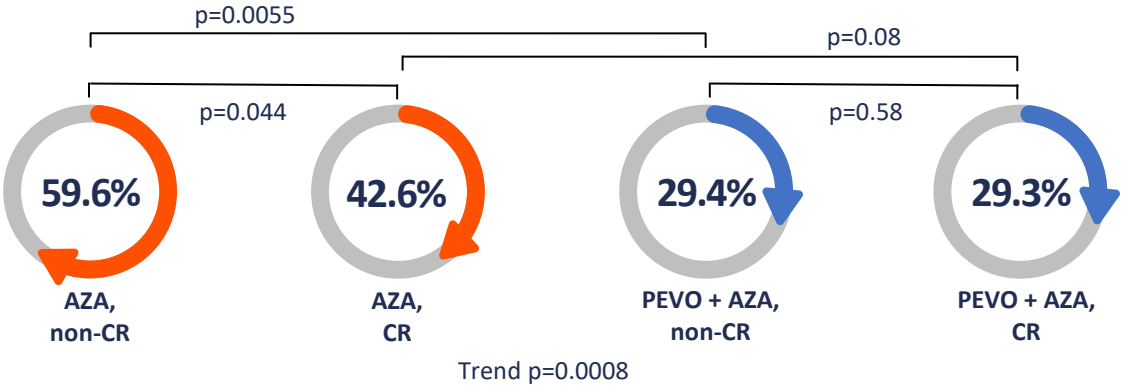
Pevonedistat + azacitidine in higher-risk MDS

Sekeres M, et al.

Clonal expansion for patients who did and did not achieve CR, mCR or CRi, %*



PANTHER (NCT03268954), PEVOLAM (NCT04090736) and PEVENAZA (NCT04266795) studies ongoing

PEVO + AZA reduces the mutational burden compared with AZA alone, therefore lowering the likelihood of treatment-emergent resistance and increasing durability of treatment response

*Expansion of treatment-emergent mutations was defined as either newly detected or numerically increased VAF after treatment.
AZA, azacitidine; CR, complete response; CRi, complete response with incomplete blood-count recovery; mCR, marrow complete response; MDS, myelodysplastic syndrome; PEVO, pevonedistat; VAF, variant allele frequency.
Friedlander S, et al. Abstr. S166. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT02610777.

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Sabatolimab + HMA in HR/vHR MDS and AML

Wei A, et al.

Promising **overall response rates, response durability and safety profile** of sabatolimab + HMA in patients with HR/vHR-MDS and newly diagnosed AML already established in phase Ib study[1]

To further explore safety/tolerability, efficacy in patient subgroups, and biomarkers with sabatolimab + HMA

- Eight countries, 11 trial centres
- Median age was 70 years for patients with vHR/HR-MDS

N=101

Patients with HR/vHR-MDS (n=53) or ND-AML (n=48) HMA-naive and non-eligible for intensive chemotherapy received sabatolimab (an immuno-myeloid therapy targeting TIM-3) + decitabine or AZA

Preliminary efficacy

Median DoR (CR/mCR/PR) 16.1 months

Estimated 12-month PFS 50.1%

AML, acute myeloid leukaemia; AZA, azacytidine; CR, complete response; DoR, duration of response; HMA, hypomethylating agents; HR, high-risk; mAb, monoclonal antibody; mCR, bone marrow CR; MDS, myelodysplastic syndrome; ND, newly diagnosed; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; TIM-3; T cell immunoglobulin and mucin domain-containing protein 3; vHR, very high-risk.

1. Wei A, et al. Abstr. S168. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT03066648. 2. Wei AH, et al. *Blood.* 2020;136(Suppl. 1):40–2.

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Sabatolimab + HMA in HR/vHR MDS and AML

Wei A, et al.

Preliminary efficacy

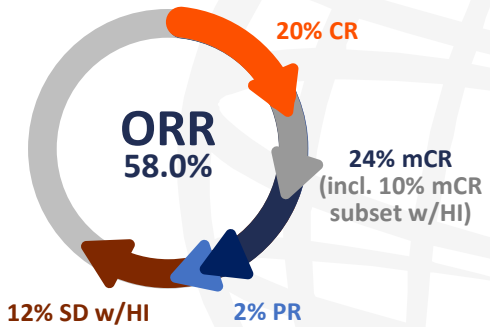
- Durable responses seen in patients with adverse risk mutations (*TP53/RUNXL1/ASXL1*) or poor cytogenetic risk
- Sabatolimab + HMA downregulates pro-inflammatory IL-1β in leukemic blasts and progenitors; upregulates IL-1β in immune myeloid cells

Preliminary safety and tolerability

- Most commonly occurring AEs: thrombocytopenia, neutropenia, constipation, nausea, anaemia, febrile neutropenia, diarrhoea and fatigue
- 35% required dose interruption due to an AE; 1% had a dose reduction
- 4% required a dose interruption/reduction or discontinued sabatolimab due to an immune-mediated AE

Sabatolimab + HMA demonstrated favourable tolerability and promising remission rates in patients with MDS and AML

Response rate in HR/vHR-MDS arm (n=50)



Phase II/III STIMULUS clinical trial program ongoing in MDS and AML (NCT04812548, NCT04878432, NCT03946670, NCT04266301 and NCT04150029)

AE, adverse event; AML, acute myeloid leukaemia; CR, complete remission; HMA, hypomethylating agents; HR, high-risk; IL, interleukin; mCR, bone marrow CR; MDS, myelodysplastic syndrome; ORR, overall response rate; PR, partial remission; SD, stable disease; vHR, very high-risk; w/HI, with haematologic improvement.

Wei A, et al. Abstr. S168. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT03066648.

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Venetoclax + AZA for treatment-naive higher-risk MDS

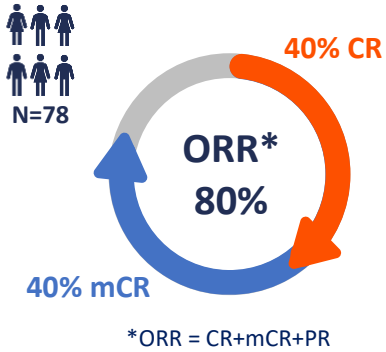
Wei A, et al.

Updated safety and efficacy findings from an ongoing phase Ib study evaluating VEN + AZA for treatment-naive HR-MDS

BCL-2 inhibitor

VEN is an oral B-cell lymphoma 2 inhibitor used for the treatment of myeloid malignancies

Efficacy outcomes



*ORR = CR+mCR+PR

	Median, months (95% CI)
OS	28.2 (17.7, NE)
OS for CR	28.6 (27.5, NE)
DoR for CR	13.8 (8.9, NE)
Time to CR [range]	2.6 [1.2–19.6]

Venetoclax + AZA provides a rapid and durable response for patients with HR-MDS

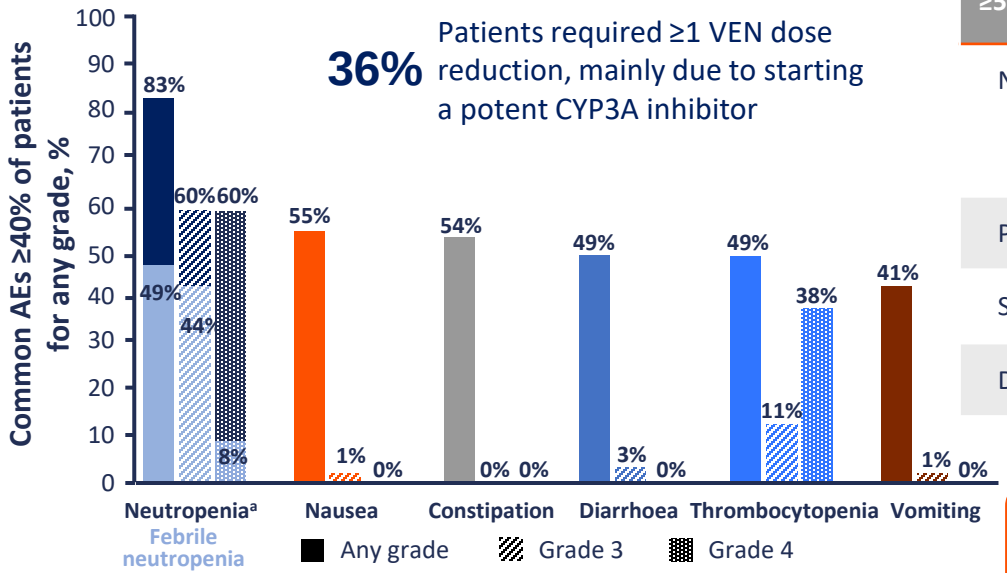
AZA, azacitidine; CI, confidence interval; CR, complete remission; DoR, duration of response; HR, high-risk; mCR, marrow complete remission; MDS, myelodysplastic syndrome; NE, not estimable; ORR, overall response rate; OS, overall survival; PR, partial remission; VEN, venetoclax.

Wei A, et al. Abstr. EP917. Poster presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT02942290.

Venetoclax + AZA for treatment-naive higher-risk MDS

Wei A, et al.

Safety outcomes (N=78)



36% Patients required ≥1 VEN dose reduction, mainly due to starting a potent CYP3A inhibitor

Serious AE in ≥5% patients, %	73
Neutropenia[a]	49
Febrile neutropenia	45
Pneumonia	6
Sepsis	5
Diverticulitis	5

Phase III VERONA trial currently recruiting (NCT04401748)

! VEN + AZA has an acceptable safety profile for patients with HR-MDS

[a]Includes neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic sepsis, and neutropenic infection.
AE, adverse event; AZA, azacitidine; HR, high-risk; MDS, myelodysplastic syndrome; VEN, venetoclax.
Wei A, et al. Abstr. EP917. Poster presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT02942290.

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Enasidenib in high-risk *IDH2*-mutated MDS

Venugopal S, et al.

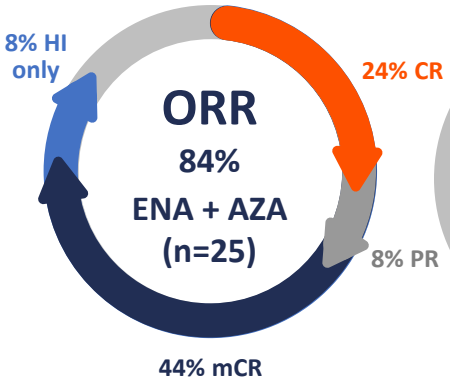
Determine the safety and tolerability of ENA ± AZA for patients with high-risk *IDH2*-mutated MDS

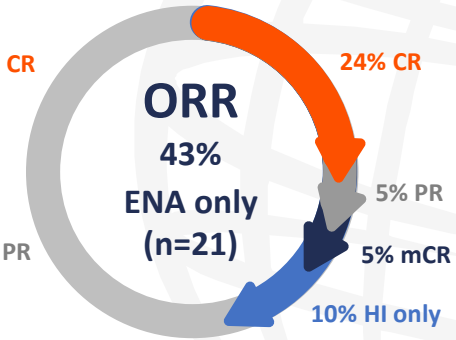
- *IDH2* mutations occur in 5–10% of patients with MDS
- Enasidenib is an oral selective inhibitor of the mutant *IDH2* enzyme

N=48

- Study enrolled patients with high-risk *IDH2*-mutated MDS/CMML or LB-AML
- Median age: 73 years
  - Arm A: HMA-naive (ENA + AZA; n=26)
  - Arm B: Refractory/progressive MDS to prior HMA therapy (ENA alone; n=22)

Efficacy outcomes





AML, acute myeloid leukaemia; AZA, azacitidine; CMML, chronic myelomonocytic leukaemia; CR, complete remission; ENA, enasidenib; HI, haematological improvement; HMA, hypomethylating agents; HR, high-risk; IDH, isocitrate dehydrogenase; LB, low blast; mCR, marrow CR; MDS, myelodysplastic syndrome; ORR, overall response rate; OS, overall survival; PR, partial remission.

Venugopal S, et al. Abstr. S167. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT03383575.

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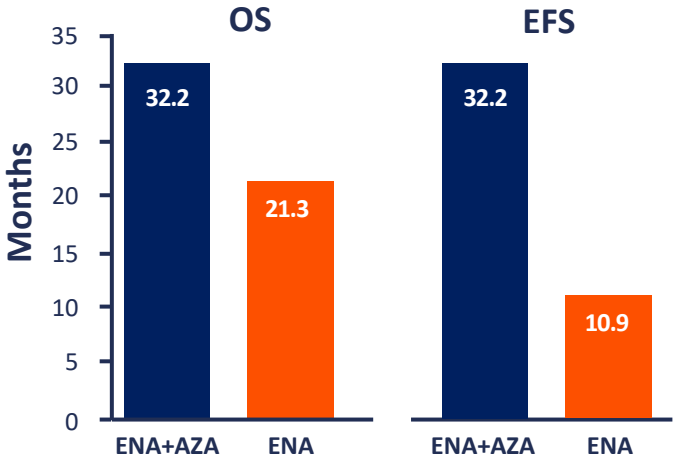
Enasidenib in high-risk *IDH2*-mutated MDS

Venugopal S, et al.

Efficacy outcomes



Safety outcomes

- Most common AEs (all grades) in both study arms were **nausea** (60%, 29%) and **constipation** (44%, 10%) in the ENA + AZA and ENA only arms, respectively
- Most AEs were mild (Grade 1/2) and transient
- Of all patients enrolled, eight developed differentiation syndrome – all with leukocytosis; all manageable
- Infections (all grades) occurred in 56% (ENA + AZA) and 5% (ENA); for patients receiving AZA + ENA, 14 days of ENA/cycle may be optimal to minimize cytopenia-related infections

ENA + AZA is well-tolerated with promising efficacy in patients with *IDH2*-mutated HR-MDS

AE, adverse event; AZA, azacitidine; EFS, event-free survival; ENA, enasidenib; HR, high-risk; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; OS, overall survival.

Venugopal S, et al. Abstr. S167. Oral presentation at EHA2021 Virtual, 9–17 June 2021. ClinicalTrials.gov identifier: NCT03383575.

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Summary

- Pevonedistat + AZA reduces the mutational burden compared with AZA alone in patients with higher-risk MDS, therefore lowering the likelihood of treatment-emergent resistance and increasing durability of treatment response
- Sabatolimab + HMA demonstrated favourable tolerability and promising remission rates in patients with HR/vHR MDS and AML
- Venetoclax + AZA provides a rapid and durable response for patients with higher-risk MDS, with a manageable safety profile
- Enasidenib + AZA is well-tolerated with promising efficacy in patients with *IDH2*-mutated higher-risk MDS

AML, acute myeloid leukaemia; AZA, azacitidine; HR, high-risk; HMA, hypomethylating agents; MDS, myelodysplastic syndrome; vHR, very high-risk.

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Current treatments and novel approaches for newly diagnosed AML, including management options when intensive induction therapy is not suitable

AML, acute myeloid leukaemia.

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Treatment options for newly diagnosed AML, including patients unfit for intensive therapy

- Traditional AML therapies include **intensive chemotherapy, HMAs and ASCT**[1]
- Identification of **specific mutations** in AML has resulted in novel targeted therapies[1]
- Novel **immunotherapies**, such as checkpoint inhibitors and CAR T-cell therapy, are currently under investigation[1]
- ***IDH1* and *IDH2* mutations** are present in up to 15% of patients with AML. IDH1/2 inhibitors, ivosidenib and enasidenib, are currently approved in the USA only for patients with ND-AML[2,3]
- Patients with ND-AML and an ***FLT3* mutation** who are suitable for intensive therapy can be treated with intensive chemotherapy + midostaurin; *FLT3* mutations occur in ~30% of patients with ND-AML[1]
- Several factors influence clinician decision-making when **determining patient fitness** for intensive therapy (age, performance status, comorbidities, assessment scores)[4]
- Novel therapies for older and/or unfit patients include HMAs, venetoclax, FLT3 inhibitors, IDH1/2 inhibitors and glasdegib[4]

AML, acute myeloid leukaemia; ASCT, allogeneic stem cell transplant; HMA, hypomethylating agents; ND, newly diagnosed.

1. Liu H. *J Hematol Oncol*. 2021;14:49; 2. US FDA. Ivosidenib prescribing information, revised May 2019 (accessed June 2021);
3. US FDA. Enasidenib prescribing information, revised Sept 2017 (accessed June 2021); 4. Cortes JE, Mehta P. *Am J Hematol.* 2021;96:493–507.

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Real-world data for venetoclax + HMA in AML

Jimenez-Vicente C, et al.[1]

Share real-life preliminary experience of treating ND- and R/R-AML with VEN + HMA

Clinical benefit (ORR, CR, OS) of combination therapy with VEN + HMA in ND-AML has already been established in the phase III VIALE-A trial (NCT02993523)[2]

N=51*

Patients with ND-AML unfit for standard chemotherapy or R/R AML without alternative salvage options who received VEN + AZA or decitabine were analyzed

Efficacy and safety outcomes

	ND-AML (N=13)	R/R AML (N=38)
ORR	54% (23% CR)	26% (12% CR)
Median OS (95% CI)	10.0 months (4.5, NR)	6.7 months (3.5, 9.4)
30-day mortality rate	8%	3%

Common AEs included neutropenia (94%), thrombocytopenia (88%), anaemia (88%), fever (53%) and febrile neutropenia (27%)

VEN + HMA is associated with a relatively low toxicity profile, with meaningful efficacy observed in patients with AML ineligible for higher intensity regimens

*Two patients had mixed-phenotype acute leukaemia. AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; HMA, hypomethylating agents; ND, newly diagnosed; NR, not reached; OS, overall survival; R/R, refractory/relapsed; VEN, venetoclax.

1. Jimenez-Vicente C, et al. Abstr. EP472. Poster presentation at EHA2021 Virtual, 9–17 June 2021. 2. DiNardo CD, et al. *N Engl J Med.* 2020;383:617–29.

ALICE: Iadademstat + azacitidine in AML

Salamero O, et al.

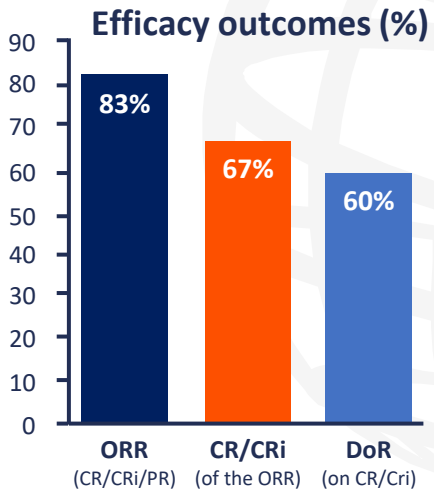
Report preliminary results of the first 30 months of the ongoing ALICE trial

- IADA: a first-in-class LSD1 inhibitor, potential treatment option for elderly unfit patients with AML
- Phase IIa study assessing safety and efficacy of IADA + AZA for elderly (>60 years) or unfit patients with treatment-naive AML (target N=36)

N=27

- Rapid clinical responses (mean time to first response was one cycle)
- Frequent AEs were platelet count decrease (48%) and neutrophil count decrease (44%). Other AEs in ≥10% of patients were dysgeusia, anaemia, asthenia, constipation, nausea and decreased appetite

IADA + AZA in patients with AML unfit for standard chemotherapy has a manageable safety profile with promising efficacy data



AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; CR, complete response; CRi, complete response with incomplete recovery; DoR, duration of response; IADA, iadademstat; LSD1, lysine-specific histone demethylase 1A; ORR, overall response rate; PR, partial remission.

Salamero O, et al. Abstr. EP450. Poster presentation at EHA2021 Virtual, 9–17 June 2021. EudraCT identifier: 2018-000482-36.

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Summary

- Real-world data support the use of venetoclax + HMA in patients with AML ineligible for high-intensity chemotherapy regimens
- Iadademstat + AZA in patients with AML unfit for standard chemotherapy has a manageable safety profile with promising efficacy data

AML, acute myeloid leukaemia; AZA, azacitidine; HMA, hypomethylating agents.

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Current and future potential of immunotherapy and the use of MRD monitoring in MDS and AML

AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes; MRD, measurable residual disease.

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Role of MRD in the management of MDS and AML

- There have been **major advances** in molecular diagnostics and monitoring techniques for AML, in addition to the number of novel therapeutic agents available[1]
- This has led to **significant improvements** in treatment algorithms[1]
- MRD monitoring is a **useful outcome measure** and plays a key role in the MDS and AML setting, particularly pre- and post-ASCT[2]
    - *NPM1* mutations, present in ~30% of patients with AML, are an example of a target for MRD monitoring, which are associated with favourable outcomes[1]
- Currently, flow cytometry and quantitative PCR are the preferred methods of monitoring MRD. However, clinical trials are ongoing to assess the utility of **next-generation sequencing** in patients undergoing ASCT[2]

AML, acute myeloid leukaemia; ASCT, allogeneic stem cell transplant; MDS, myelodysplastic syndromes; MRD, measurable residual disease.

1. Dillon R, et al. *Br J Haematol.* 2021;193:231–44; 2. Shapiro RM and Kim DDH. *Curr Opin Hematol.* 2018;25:425–32.

VIALE-A: MRD response with venetoclax + AZA in AML

Pratz KW, et al.[1]

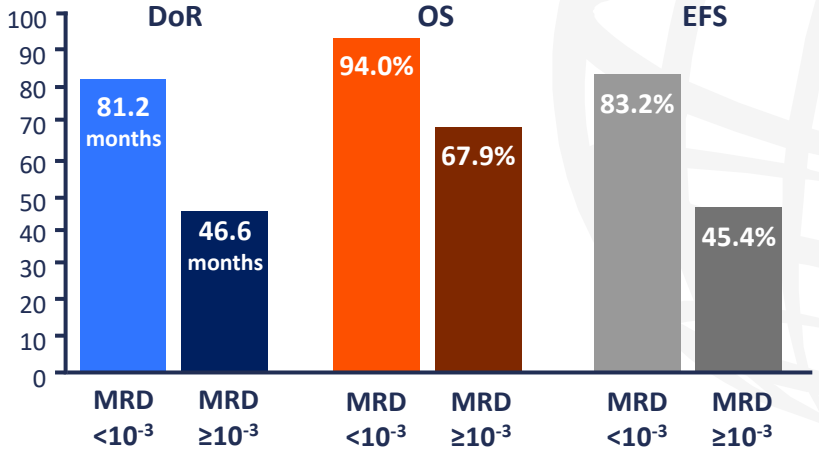
Evaluate the prognostic impact of MRD <10^{-3} on outcomes among patients with AML treated with lower-intensity chemotherapy

Clinical benefit (ORR, CR, OS) of combination therapy with VEN + HMA in ND-AML has already been established in the phase III VIALE-A trial (NCT02993523)[2]

N=164

This VIALE-A sub-study investigated the outcomes of patients with AML unfit for standard induction chemotherapy* treated with VEN + AZA with CR or CRi and evaluable MRD (n=67 and 97 for MRD <10^{-3} and ≥10^{-3}, respectively)

12-month efficacy outcomes



*Due to age ≥75 years or comorbidities.

AML, acute myeloid leukaemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete haematologic recovery; DoR, duration of remission; EFS, event-free survival; MRD, measurable residual disease; OS, overall survival; VEN, venetoclax.

1. Pratz KW, et al. Abstr. S137. Oral presentation at EHA2021 Virtual, 9–17 June 2021. 2. DiNardo CD, et al. *N Engl J Med.* 2020;383:617–29.

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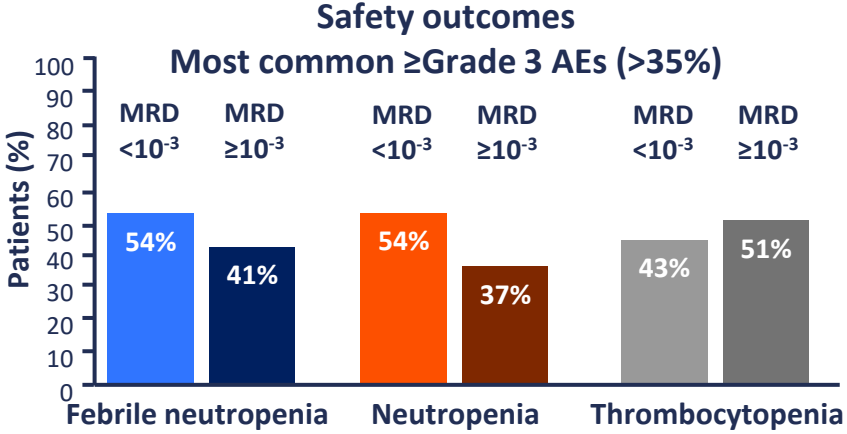
VIALE-A: MRD response with venetoclax + AZA in AML

Pratz KW, et al.



Key sub-study takeaways

- MRD $<10^{-3}$ response was associated with longer DoR, EFS and OS compared with patients who were MRD $\geq 10^{-3}$
- MRD response was a significant predictor of OS
- MRD responses were observed later than clinical responses
- Higher rates of neutropenia were observed in patients with an MRD response

MRD response in patients with AML treated with VEN + AZA is valuable and further investigation is warranted to establish its role in clinical management

AML, acute myeloid leukaemia; AZA, azacitidine; DoR, duration of response; EFS, event-free survival; MRD, measurable residual disease; OS, overall survival; VEN, venetoclax.
Pratz KW, et al. Abstr. S137. Oral presentation at EHA2021 Virtual, 9–17 June 2021.

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NGS-based MRD monitoring in *FLT3*-ITD+ AML treated with midostaurin

Herzig JK, et al.[1]

Validate an NGS-based *FLT3*-IDT MRD assay and evaluate its prognostic impact in *FLT3*-IDT+ AML treated with intensive CT + midostaurin in the phase II AMLSG 16-10 trial (NCT01477606)

- *FLT3*-ITD occurs in ~25% of patients with AML and is associated with a poor prognosis
- Midostaurin, a multi-targeted protein kinase inhibitor, combined with intensive CT and continued as maintenance therapy, has demonstrated significant improvements in EFS for patients with *FLT3*-ITD+ AML[2]

N=110

- Samples analyzed at diagnosis, after two treatment cycles and/or at EOT
- Median follow-up of the patients was 3.8 years
- Total ITD VAF significantly decreased ($p<0.0001$) and MRD negativity was achieved in 87% at EOT

NGS-based MRD monitoring is a promising tool for assessing response to therapy and for identifying patients with AML at high risk of relapse

AML, acute myeloid leukaemia; CT, chemotherapy; EFS, event-free survival; EOT, end of treatment; ITD, internal tandem duplication; MRD, measurable residual disease; NGS, next-generation sequencing; VAF, variant allele frequency.

1. Herzig JK, et al. Abstr. EP376. Poster presentation at EHA2021 Virtual, 9–17 June 2021. 2. Schlenk RF, et al; German-Austrian AML Study Group. *Blood.* 2019;133:840–51.

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Summary

- MRD response in patients with AML treated with VEN + AZA is valuable and further investigation is warranted to establish its role in clinical management
- NGS-based MRD monitoring is a promising tool for assessing response to therapy and for identifying patients with AML at high risk of relapse

AML, acute myeloid leukaemia; AZA, azacitidine; CR, complete response; HMA, hypomethylating agents; MDS, myelodysplastic syndrome; MRD, measurable residual disease; NGS, next-generation sequencing.