What's on the horizon for higher-risk MDS? An update on emerging novel agents

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Novel treatments for HR-MDS: What's on the horizon?

Definition of MDS and differentiation from AML

Myelodysplastic neoplasms (MDS): A spectrum of disorders characterised by cytopenia and morphological dysplasia[1]

(MDS was previously known as myelodysplastic syndrome)[2]

Bone marrow malignancy

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasm.

1. Fenaux P, et al. *Ann Oncol*. 2021;32:142–56; 2. Khoury J, et al. *Leukemia*. 2022;36:1703–19; 3. Garcia-Manero G, et al. *Am J Hematol*. 2020;95:1399–420.

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Diagnosis is suspected on presence of cytopenia:[3]

Bone marrow aspiration:
- Cellular morphology
- Blast percentage

Bone marrow biopsy:
- Marrow cellularity
- Marrow architecture

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasm.
1. Fenaux P, et al. *Ann Oncol*. 2021;32:142–56; 2. Khoury J, et al. *Leukemia*. 2022;36:1703–19; 3. Garcia-Manero G, et al. *Am J Hematol*. 2020;95:1399–420.

Definition of MDS and differentiation from AML

Prognosis uses risk scoring and cytogenetic markers

Prognostic risk scores:

- **IPSS-R:** Bone marrow blast percentage, extent of cytopenia,cytogenetic abnormalities[1]
- Updated **IPSS-M** also considers mutation burden[2]

Cytogenetic risk markers:[3]

- Cytogenetic markers are heterogenous in MDS
- Specific mutations can guide cytogenetic risk stratification
- Patients may acquire additional mutations (associated with increased risk of AML transformation)

Next generation sequencing:[3,4]

- Somatic or germline mutations can guide prognosis

AML, acute myeloid leukaemia; IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; MDS, myelodysplastic neoplasm.

1. Fenaux P, et al. *Ann Oncol*. 2021;32:142–56; 2. Bernard E, et al. *NEJM Evid*. 2022;DOI:10.1056/EVIDoa2200008;
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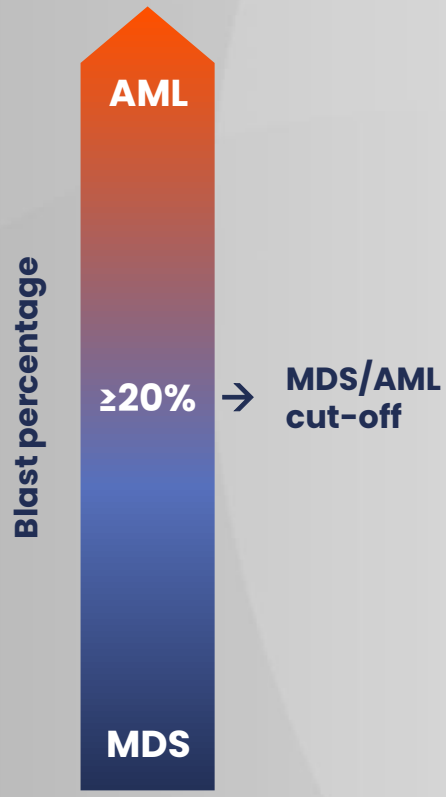
Blast percentage for MDS/AML differentiation

MDS and AML are differentiated by a blast percentage cut-off of 20%[1]



Limitations of 20% blast cut-off:[2]

- Patients with AML typically receive more intensive therapy than those with MDS

- Therapy for patients with 10% to 19% blasts may be suboptimal
- Patients are precluded from AML treatment or clinical trials for AML
- No consideration of mutations

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasm.
1. Khoury J, et al. *Leukemia*. 2022;36:1703–19; 2. Estey E, et al. *Blood*. 2022;139:323–32.

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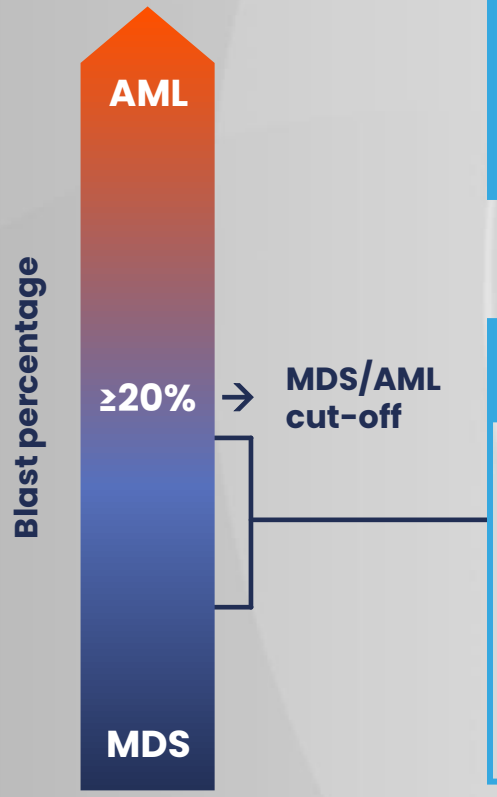

Recommendations have softened the boundary between MDS and AML[1]

Therapeutic decisions must still be based on the clinical situation[2]

MDS/AML (previously MDS-EB2):

- Cytopenic myeloid neoplasm and 10–19% blasts[3]
- High-grade MDS and secondary AML are biologically similar neoplasms[2]
- Patients should be eligible for both MDS and AML trials[3]
- Patients may be better classified by genetic features[2]

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasm; MDS-EB2, MDS with excess blasts.

1. Khoury J, et al. *Leukemia*. 2022;36:1703–19; 2. Estey E, et al. *Blood*. 2022;139:323–32; 3. Arber D, et al. *Blood*. 2022;140:1200–28.

IPSS-R and the updated IPSS-M

The updated IPSS-M score considers genetic mutations in addition to the cytogenetic risk[1]

IPSS-R[2]

Blood counts:

- Haemoglobin
- Platelet count
- Absolute neutrophil count

- **Cytogenetic risk**

- Blasts in bone marrow

IPSS-M[1]

- **Blood counts**
- **Cytogenetic risk**
- Patient age

- **16 prognostic genes**
- Number of mutated genes from group of 15 residual genes
- *TP53* allelic status

IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS.

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IPSS-M

- Blood counts
- Cytogenetic risk
- Patient age
- 16 prognostic genes
- Number of mutated genes from group of 15 residual genes
- *TP53* allelic status

→

- Personalized continuous score
- Improved endpoint prognostic accuracy
- Applicable in secondary MDS

IPSS-M available as free online calculator: https://mds-risk-model.com/

IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; MDS, myelodysplastic neoplasm.
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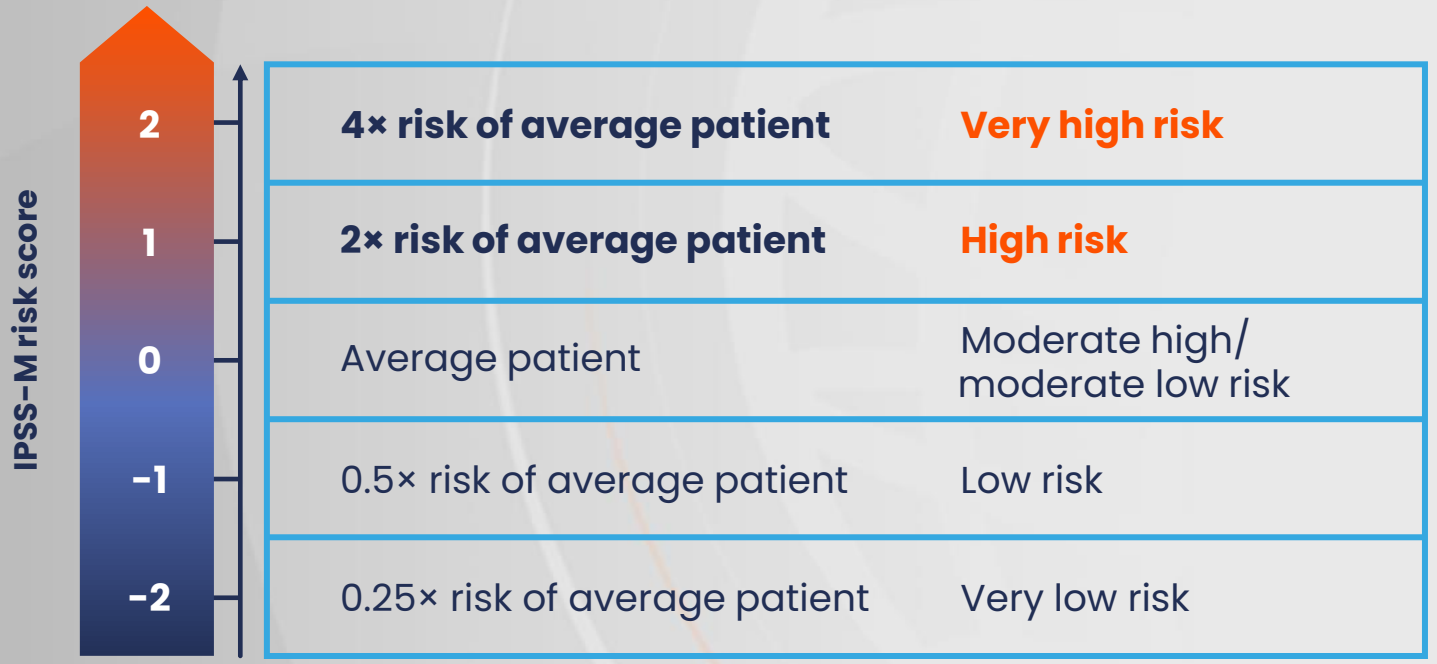
IPSS-R and the updated IPSS-M

The updated IPSS-M score considers genetic mutations in addition to the cytogenetic risk

The IPSS-M returns a score corresponding to the relative risk compared to an "average" patient



4× risk of average patient	**Very high risk**
2× risk of average patient	**High risk**
Average patient	Moderate high/ moderate low risk
0.5× risk of average patient	Low risk
0.25× risk of average patient	Very low risk

IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS.

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Treatment priorities vary by disease severity

Treatment goals in HR-MDS[1]

- Modify disease course
- Limit disease progression
- Improve survival rates

HR-MDS treatment priorities[1]

1
- Delay progression
- Improve survival
- Cure

2
- Reduce disease burden
- Improve cytopenia
- Reduce transfusions

3
- Treatment tolerability

4
- QoL

Survival outcomes remain poor[2]

Median OS
- IPSS-M HR-MDS: 1.7 years
- IPSS-M vHR-MDS: 1.0 years

HR-MDS, high-risk myelodysplastic neoplasm; IPSS-M, molecular International Prognostic Scoring System; QoL, quality of life; vHR-MDS, very high-risk myelodysplastic neoplasm.

1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. Bernard E, et al. *NEJM Evid*. 2022;DOI:10.1056/EVIDoa2200008.

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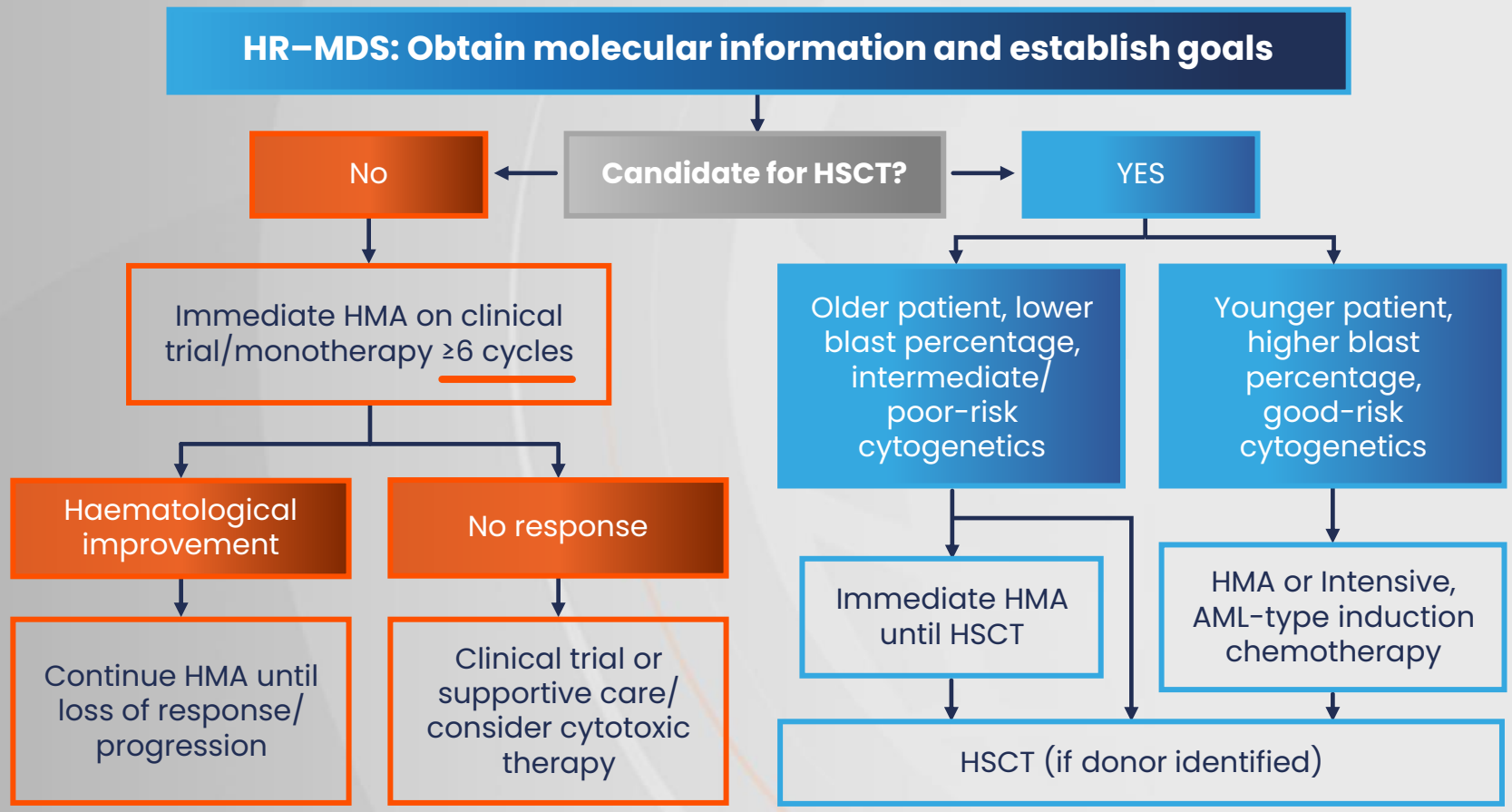
Treatment algorithm for HR-MDS

HMAs such as azacitidine are the current standard therapy for patients ineligible for HSCT



HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; HSCT, haematopoietic stem cell transplantation.
Sekeres M, Cutler C. *Blood*. 2014;123:829–36.

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Limitations of current treatments

HSCT remains the only potentially curative treatment[1]

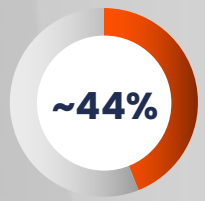
Most patients are unable to tolerate HSCT[1]

50–75 years

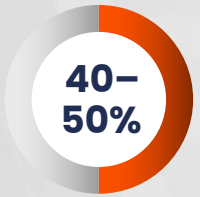
In patients 50–75 years old with IR/HR-MDS

HSCT significantly prolonged survival over supporting therapy[2]

HMA remain the standard of care for patients ineligible for HSCT, but have limited efficacy[3]



Patients eligible for treatment[3]



Patients who achieve CR[1]

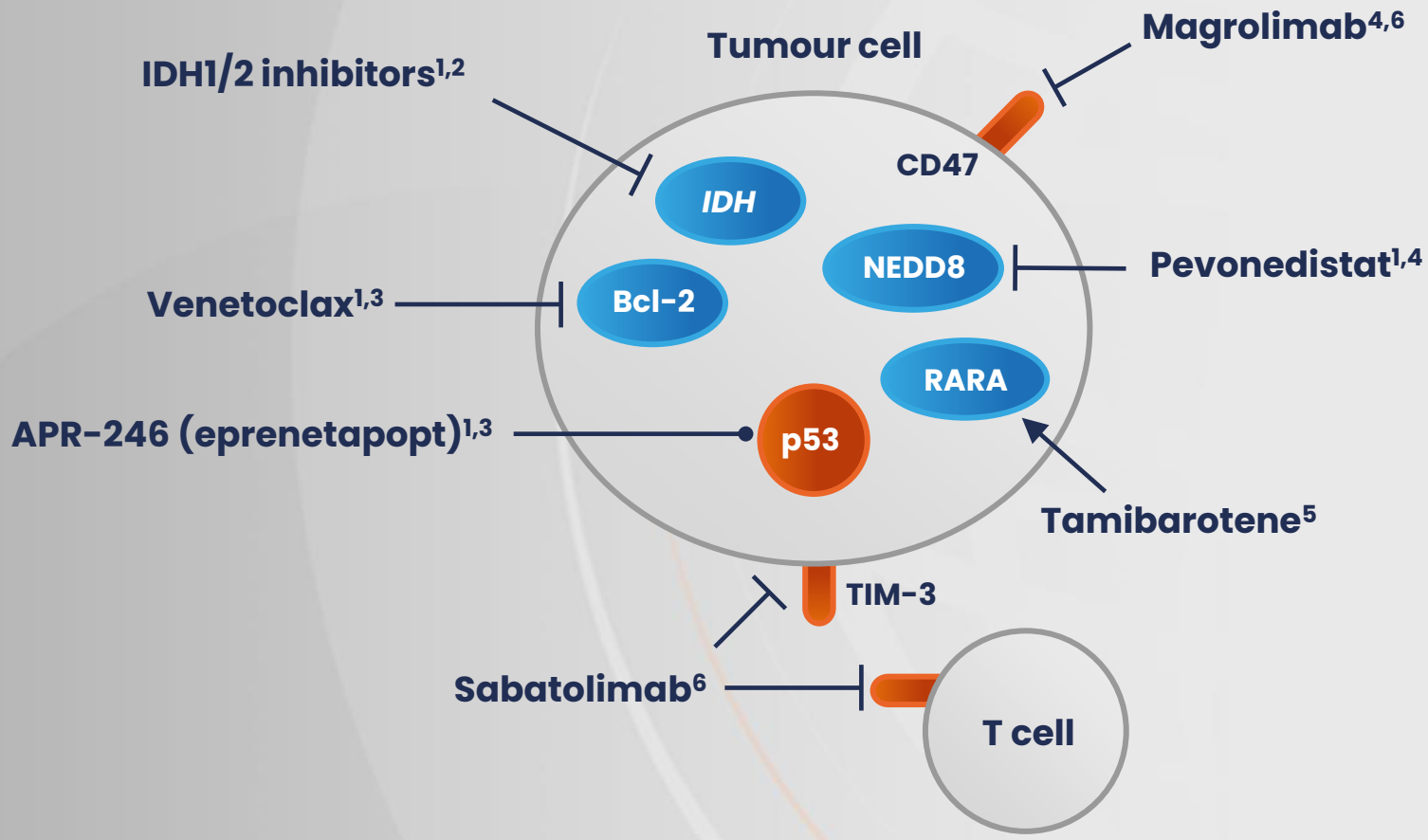
Median duration of response of **~1 year[1]**

There are limited treatment options after HMA failure, but several emerging treatments are under investigation[3]

CR, complete response; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; HSCT, haematopoietic stem cell transplantation; IR, intermediate risk.

1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. Nakamura R, et al. *J Clin Oncol*. 2021;39:3328–39; 3. Platzbecker U, et al. *Leukemia*. 2021;35:2182–98.

Mechanism of action of current and emerging treatment options



Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3.

1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. DiNardo C, et al. *Leukemia*. 2016; 30:980–4; 3. Hellström-Lindberg E, et al. *Haematologica*. 2020;105:1765–79; 4. Bewersdorf JP, et al. *Ther Adv Hematol*. 2020;11:2040620720955006; 5. DeZern A, et al. *Hemasphere*. 2022;6(Suppl.)1800–1; 6. Abaza Y, Zeidan A. *Cells*. 2022;11:2249.

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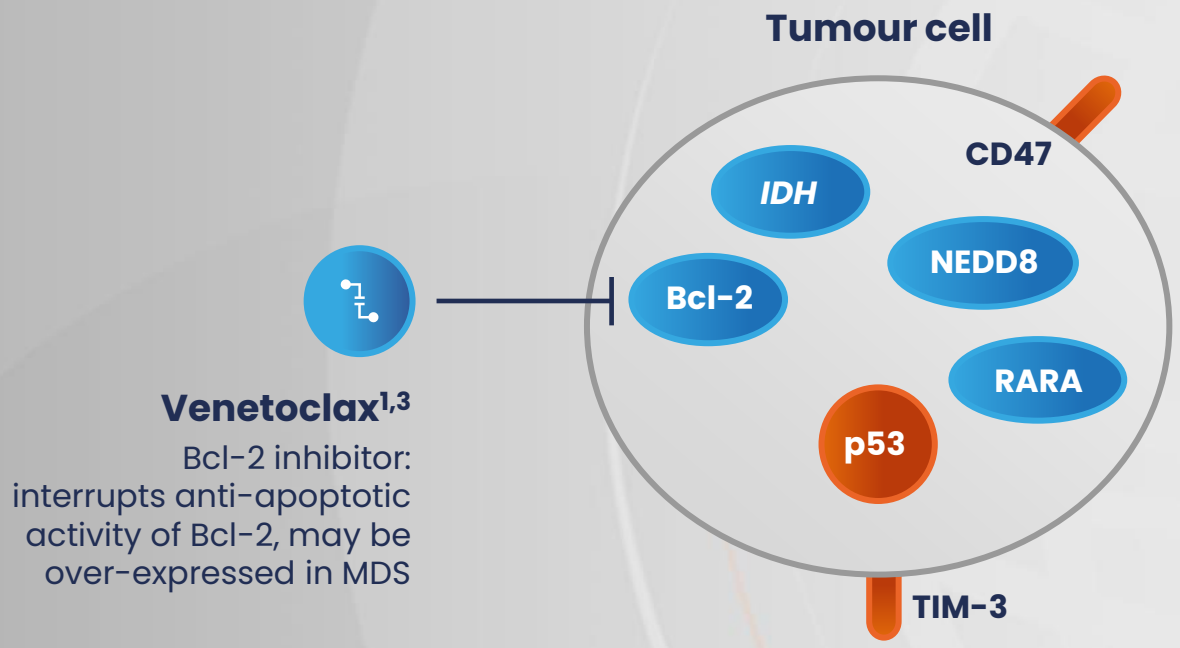

Venetoclax[1,3]

Bcl-2 inhibitor: interrupts anti-apoptotic activity of Bcl-2, may be over-expressed in MDS

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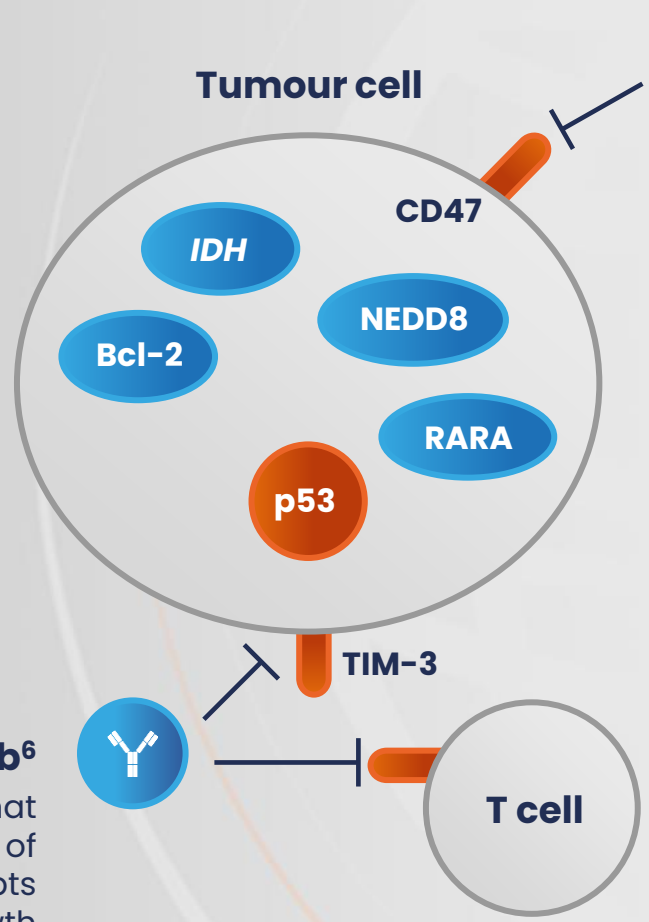

Magrolimab[4,6]

CD47 mAb
Promotes macrophage mediated phagocytosis

Sabatolimab[6]

Anti-TIM-3 mAb that promotes T-cell targeting of tumour cells and interrupts tumour cell growth

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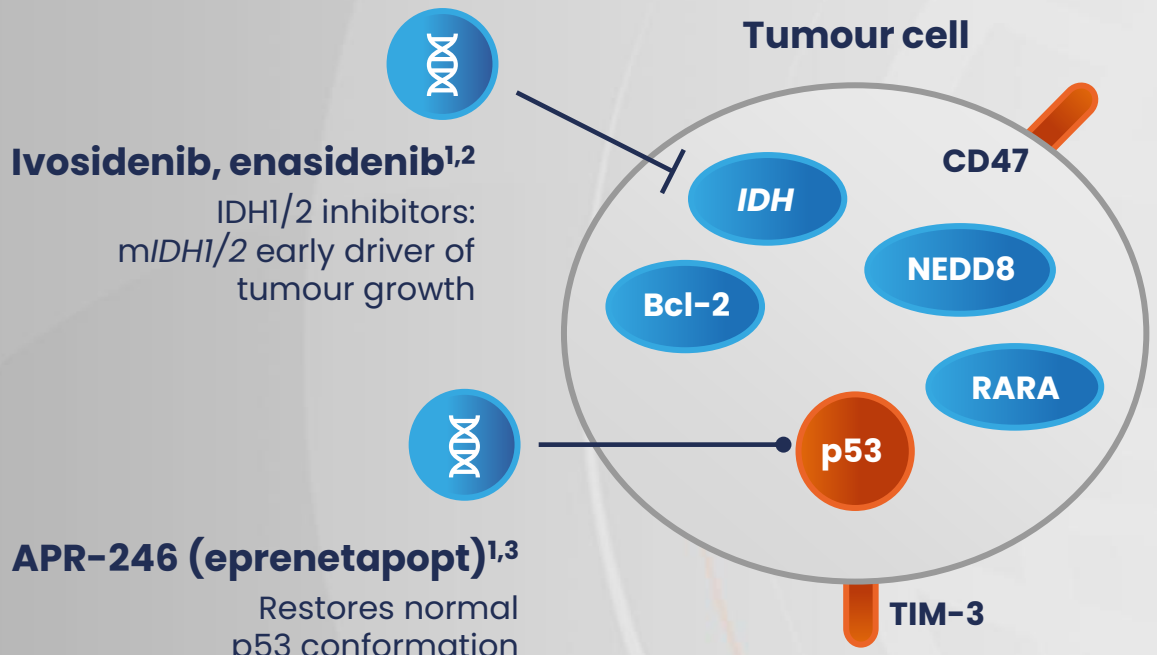

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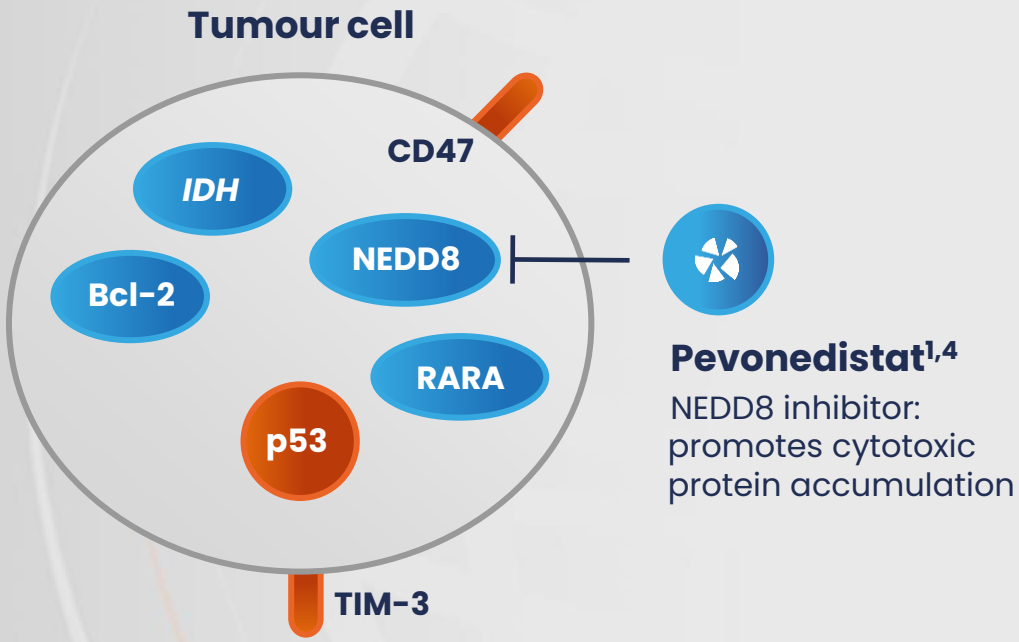

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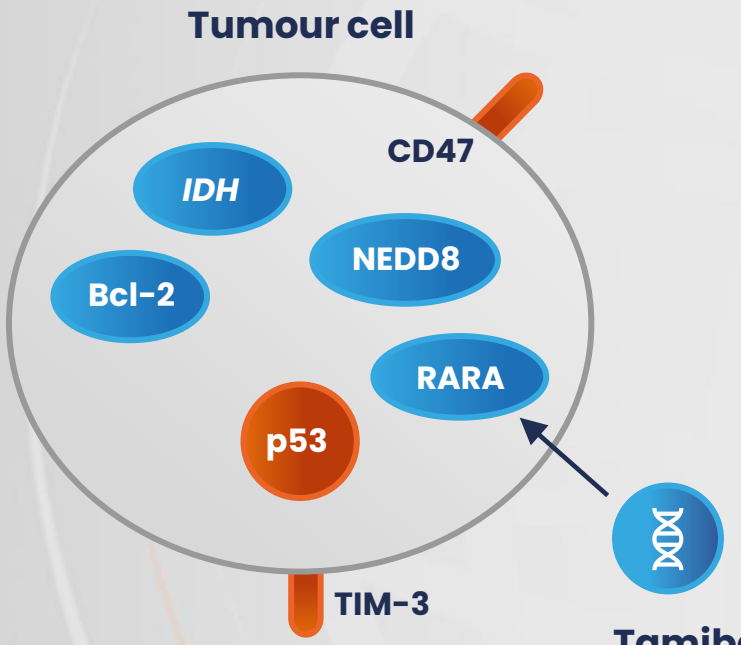

Tamibarotene[5]

RARA agonist:
RARA transcription factor overexpressed in subset of patients with HR-MDS

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Summary

The differentiation between MDS and AML remains a challenge[1,2]

IPSS-M considers the mutation burden and offers an updated risk stratification tool compared with IPSS-R[3]

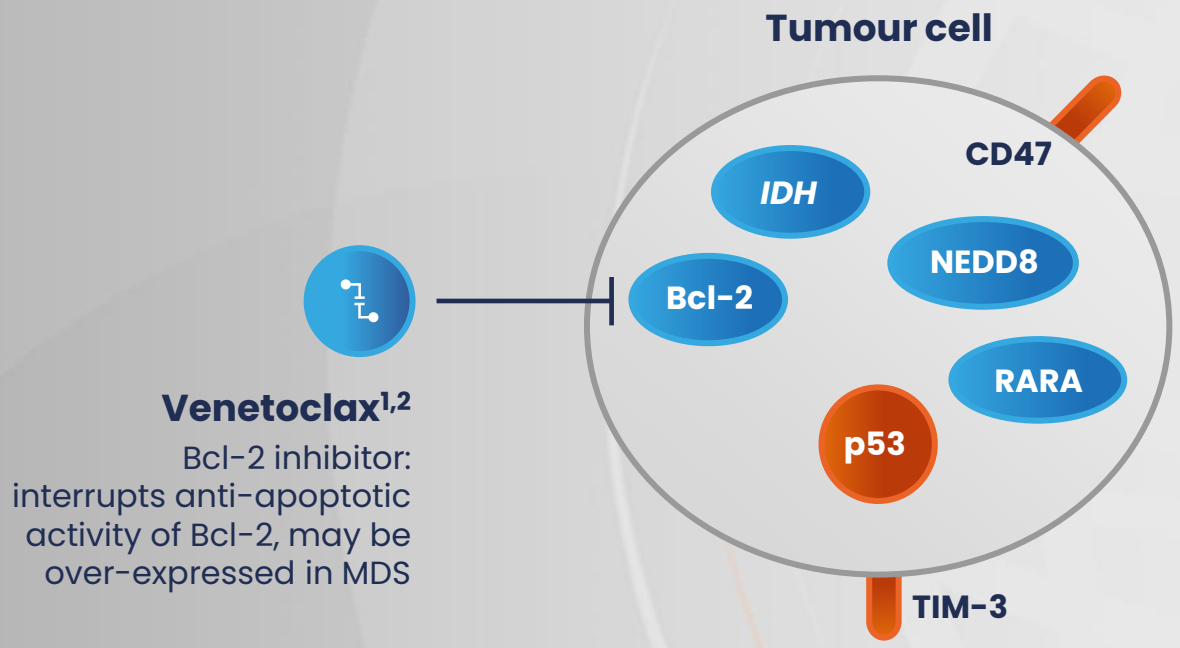
HMA is the standard treatment for HR-MDS, although response rates remain limited[4]

AML, acute myeloid leukaemia; HMA, hypomethylating agent; HR-MDS, high-risk MDS; IPSS-M, molecular International Prognostic Scoring System; IPSS-R; revised-International Prognostic Scoring System; MDS, myelodysplastic neoplasm.

1. Khoury J, et al. *Leukemia*. 2022;36:1703–19; 2. Estey E, et al. *Blood*. 2022;139:323–32; 3. Arber D, et al. *Blood*. 2022;140:1200–28; 3. Bernard E, et al. *NEJM Evid*. 2022;1:10.1056/EVIDoa2200008; 4. Platzbecker U. *Blood*. 2019;133:1096–107.

Efficacy data for emerging treatments for patients with HR-MDS

Mechanism of action of current and emerging treatment options



Venetoclax[1,2]

Bcl-2 inhibitor: interrupts anti-apoptotic activity of Bcl-2, may be over-expressed in MDS

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Venetoclax + HMA

Venetoclax + azacitidine in treatment-naive HR-MDS: Phase Ib study (NCT02942290)

N=59

- IPSS score ≥1.5
- No previous therapy for MDS
- Bone marrow blasts <20%
- CMML excluded

→

Dose escalation venetoclax
From 100 mg to 400 mg daily
for days 1–14 of 28 day cycle
+
Azacitidine

Key endpoints

- Safety and dosing
- ORR

CMML, chronic myelomonocytic leukaemia; CR, complete response; DOR, duration of response; HMA, hypomethylating agent; HR, high risk; IPSS, International Prognostic Scoring System; mCR, marrow complete remission; MDS, myelodysplastic neoplasm; ORR, overall response rate; OS, overall survival; PFS, progression free survival; SD, stable disease.

Wei AH, et al. *Blood*. 2019;134(Suppl. 1):568.

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Key endpoints
- Safety and dosing
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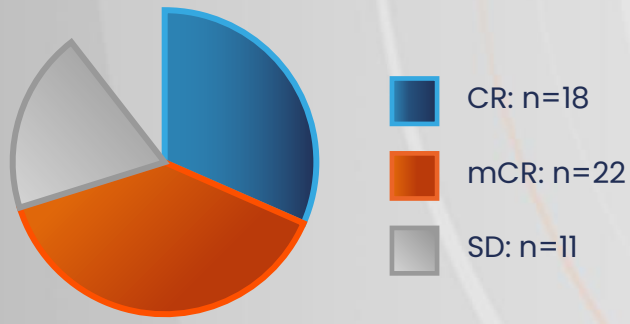
ORR of evaluable patients (n=57)



Median PFS, OS, DOR not reached

12-month estimate for ORR: 74%

CMML, chronic myelomonocytic leukaemia; CR, complete response; DOR, duration of response; HMA, hypomethylating agent; HR, high risk; IPSS, International Prognostic Scoring System; mCR, marrow complete remission; MDS, myelodysplastic neoplasm; ORR, overall response rate; OS, overall survival; PFS, progression free survival; SD, stable disease.

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Venetoclax + HMA

Venetoclax + azacitidine in treatment-naive HR-MDS: Phase Ib study (NCT02942290): Update[1]

N=78[1]

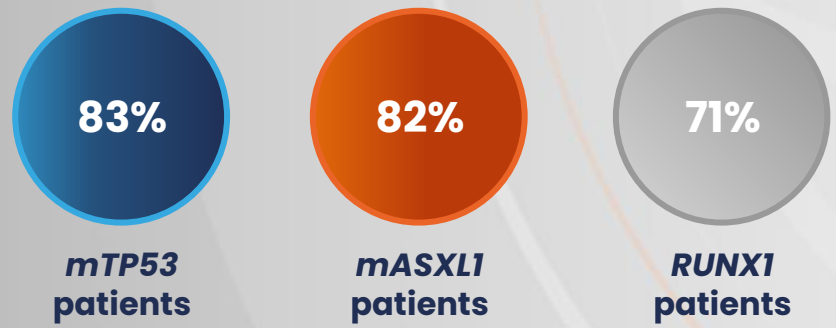
- IPSS score ≥1.5[2]
- No previous therapy for MDS[2]
- Bone marrow blasts <20%[2]
- CMML excluded

→

Venetoclax[1]
From 100 mg to 400 mg daily for days 1–14 of 28 day cycle (n=51 received 400 mg/day)
+
Azacitidine

A later update investigated clinical response by mutational status:[1]

Clinical response (CR + mCR) was consistent across mutational spectrum



mTP53 **patients**

mASXL1 **patients**

RUNX1 **patients**

Patients who achieved CR had greater reduction in variant allele frequencies[1]

CMML, chronic myelomonocytic leukaemia; CR, complete response; HMA, hypomethylating agent; HR, high risk; IPSS, International Prognostic Scoring System; mCR, marrow complete remission; MDS, myelodysplastic neoplasm; ORR, overall response rate.

1. Garcia J, et al. *Blood*. 2021;138(Suppl. 1):241; 2. Wei AH, et al. *Blood*. 2019;134(Suppl. 1):568.

Venetoclax + HMA

Venetoclax + azacitidine in HR-MDS or CMML: Phase I results of a phase I/II trial (NCT04160052)

N=23

- HR-MDS or CMML
- Naive to HMA, or following HMA failure
- >5% bone marrow blasts
- No previous Bcl-2 inhibitor treatment

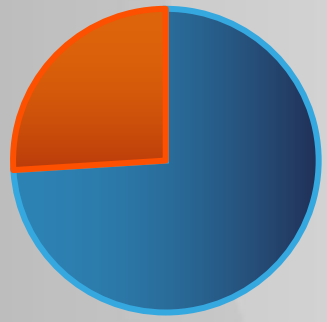
→

Venetoclax[1]
From 100 mg to 400 mg daily
for 7–14 days
+
Azacitidine

Phase I primary outcome
- Adverse event profile

Phase II primary outcome
- ORR

Patient demographic (N=23)



HMA naive:
74% (n=17)

HMA failure:
26% (n=6)

Bcl-2, B-cell lymphoma 2; CMML, chronic myelomonocytic leukaemia; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; ORR, overall response rate.
Bazinet A, et al. *Lancet Haematol*. 2022;9:e756–75.

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Venetoclax + HMA

Venetoclax + azacitidine in HR-MDS or CMML: Phase I results of a phase I/II trial (NCT04160052)

ORR by prior treatment

87% (n=20/23)
Total population
(95% CI 66–97)

82% (n=14/17)
HMA naive
(95% CI 57–86)

100% (n=6/6)
Post-HMA failure
(95% CI 54–100)

Median OS

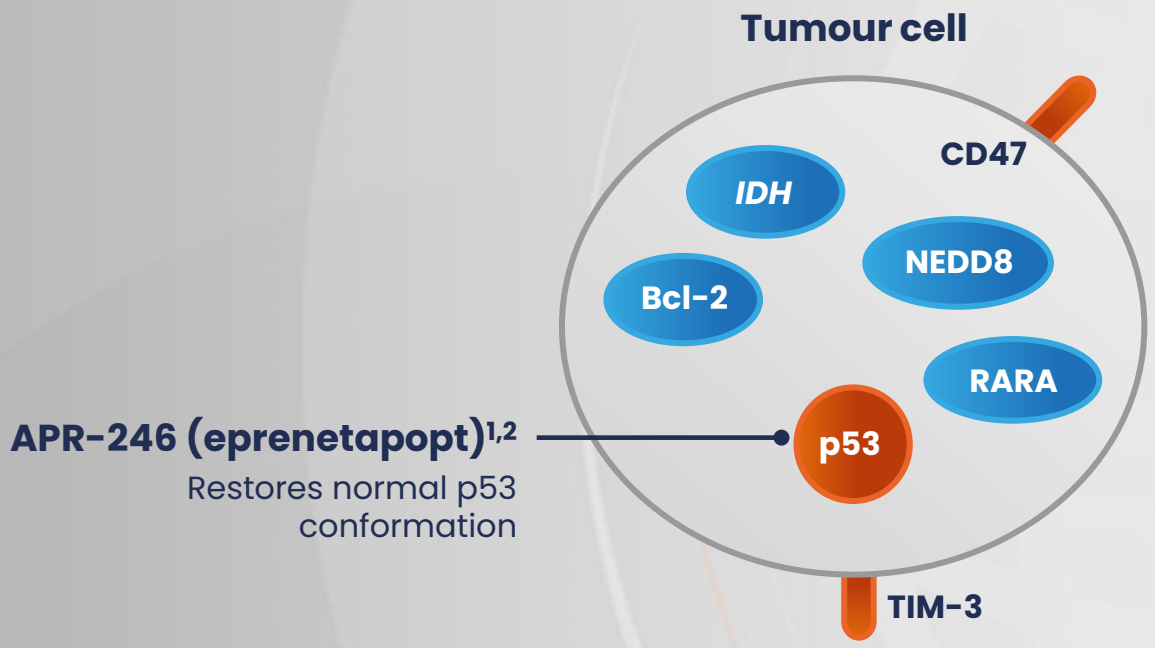
13.0 months
Total population
(95% CI 8.3–14.5)

Median PFS

7.4 months
Total population
(95% CI 5.1–13.1)

CI, confidence interval; CMML, chronic myelomonocytic leukaemia; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Bazinet A, et al. *Lancet Haematol*. 2022;9:e756–75.

Mechanism of action of current and emerging treatment options



Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3.

1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. Hellström-Lindberg E, et al. *Haematologica*. 2020;105:1765–79.

Eprenetapopt (APR-246) + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Phase Ib/II dose-escalation study (NCT03072043)

N=55

Inclusion criteria:

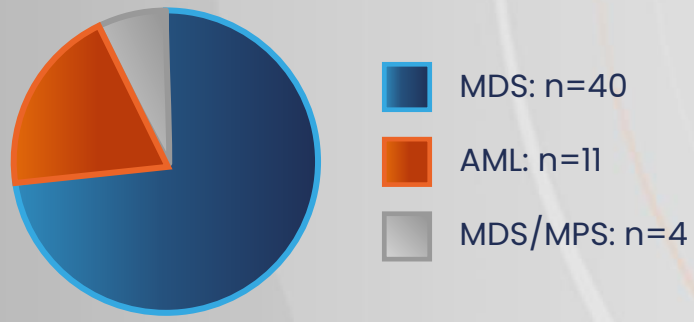
- HMA-naive MDS, MDS/MPN, CMML or oligoblastic AML
- IPSS-R high risk
- m*TP53* by NGS

Eprenetapopt + Azacitidine

Eprenetapopt dosing:

- Dose escalation phase: n=12 received APR-246 at 50, 75 and 100 mg/kg/day LBM
- Phase II phase: 4,500 mg/day

Patient demographic



Primary endpoint

- CR

Secondary endpoints

- DOR
- ORR
- OS

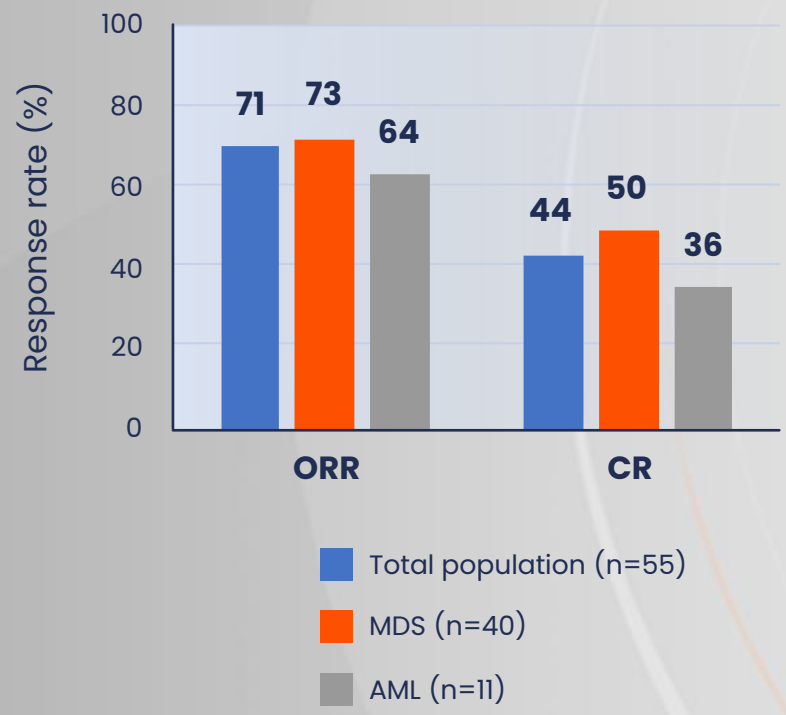
AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CR, complete response; DOR, duration of response; HMA, hypomethylating agent; IPSS-R, revised International Prognostic Scoring System; LBM, lean body mass; MDS, myelodysplastic neoplasm; MDS/MPN, MDS/myeloproliferative neoplasm; m*TP53*, *TP53* mutation; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival.

Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94.

Eprenetapopt (APR-246) + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Phase Ib/II dose-escalation study (NCT03072043)

Treatment response*



OS

10.8 months

Total population
(95% CI 8.1–13.4)

10.4 months

MDS
(95% CI 7.6–13.3)

10.8 months

AML
(95% CI 5.1–16.5)

*Data not shown for MDS/MPN cohort (n=4)
AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; ITT, intention to treat; MDS, myelodysplastic neoplasm; MDS/MPN, MDS/myeloproliferative neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate; OS, overall survival.
Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94.

Eprenetapopt + azacitidine

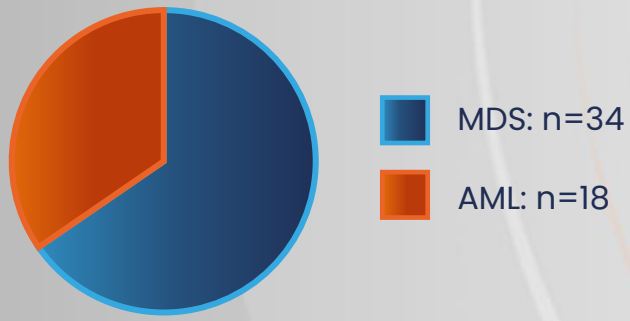
Eprenetapopt + azacitidine in m*TP53* MDS: Phase II, single-arm study (NCT03588078)

N=52

- ≥Intermediate risk MDS, CMML (by IPSS-R score), or AML
- HMA naive
- ≥1 *TP53* mutation by NGS

Eprenetapopt + Azacitidine

Patient demographic



Primary endpoint

- Treatment response

Secondary endpoints included:

- Adverse events
- OS
- DOR
- AML progression
- Response rate

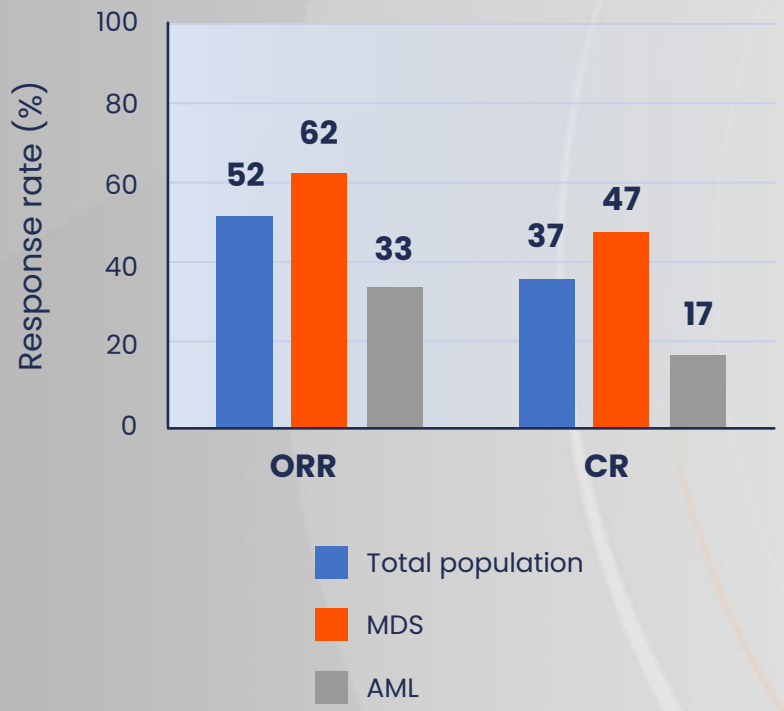
AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; DOR, duration of response; IPSS-R, revised International Prognostic Scoring System; HMA, hypomethylating agent; MDS, myeloproliferative neoplasm; m*TP53*, *TP53* mutation; NGS, next-generation sequencing; OS, overall survival.

Cluzeau T, et al. *J Clin Oncol*. 2021;39:1575–83.

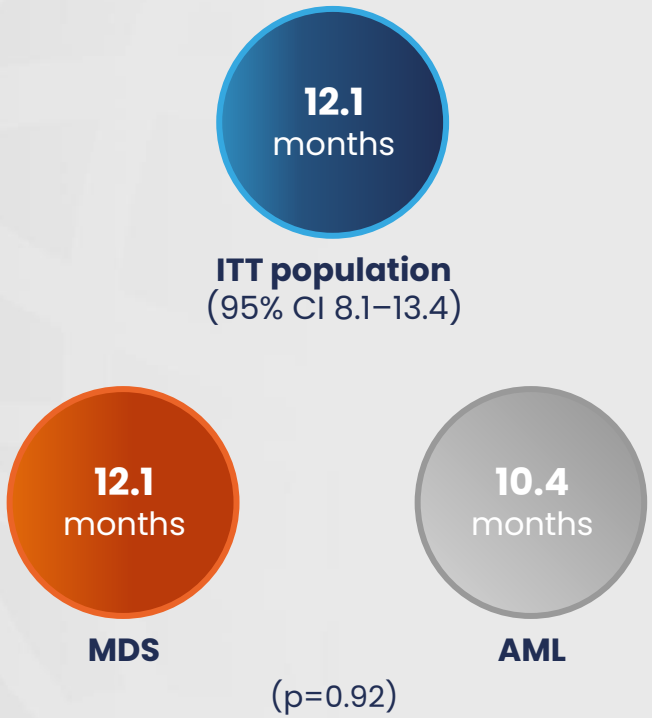
Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Phase II, single-arm study (NCT03588078)

Treatment response



OS



AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; ITT, intention to treat; MDS, myelodysplastic neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate; OS, overall survival.
Cluzeau T, et al. *J Clin Oncol*. 2021;39:1575–83.

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Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Long-term follow-up, combined phase II results (NCT03072043/NCT03588078)

N=100

Inclusion criteria:

- HMA-naive, MDS, MDS/MPN, oligoblastic AML
- IPSS-R high-risk
- m*TP53* by NGS

Eprenetapopt + Azacitidine

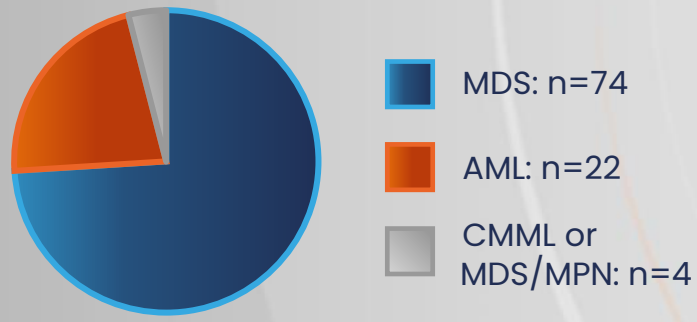
Primary endpoint

- CR

Secondary endpoints

- ORR
- OS
- Outcome after HSCT
- Measurable residual disease

Patient demographic

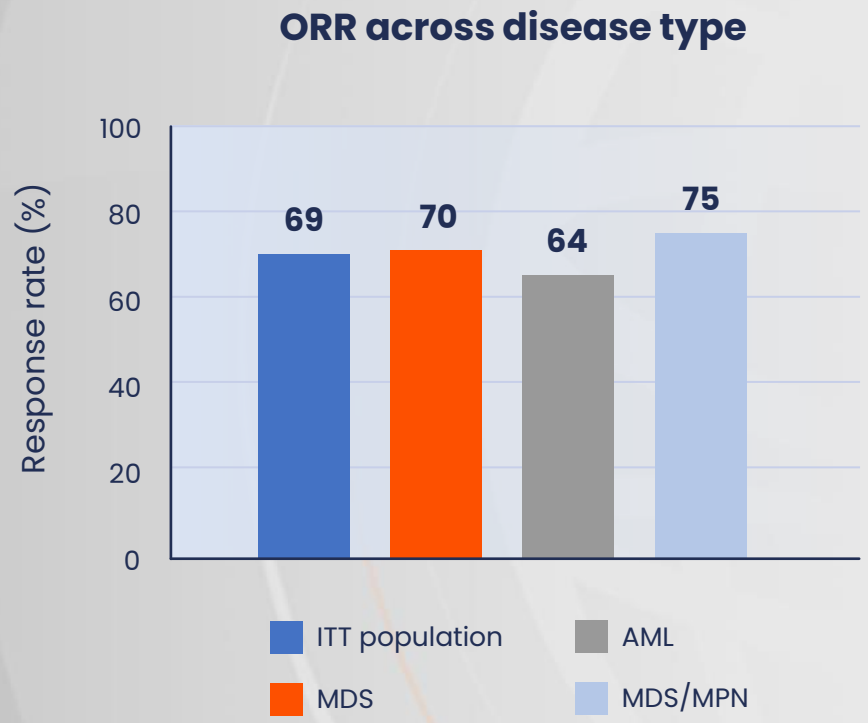


AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CR, complete response; HMA, hypomethylating agent; HSCT, haematopoietic stem cell transplant; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic neoplasm; MDS/MPN, MDS/myeloproliferative neoplasm; m*TP53*, *TP53* mutation; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival.

Sallman D, et al. *Blood*. 2021;138(Suppl. 1):246.

Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Long-term follow-up, combined phase II results (NCT03072043/NCT03588078)



AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasm; MDS/MPN, MDS/myeloproliferative neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate.
Sallman D, et al. *Blood*. 2021;138(Suppl. 1):246.

Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in m*TP53* MDS: Long-term follow-up, combined phase II results (NCT03072043/NCT03588078)

Median OS

ITT population

11.8 months

(95% CI 9.4–14.3)

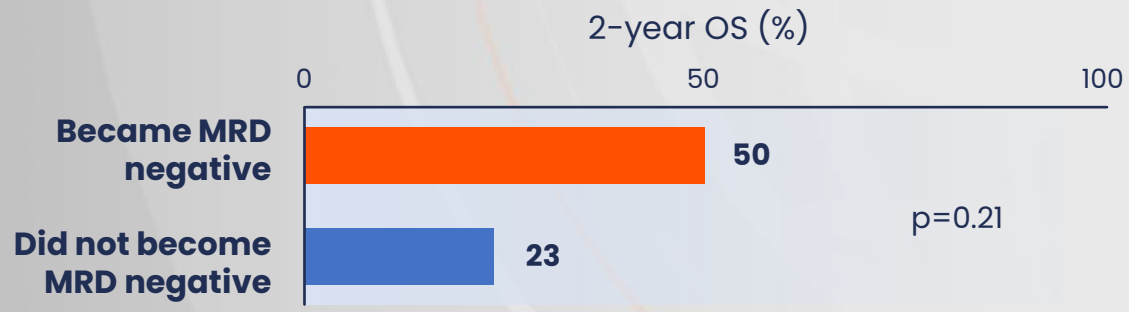
Patients achieving CR/PR or NGS negativity

15.8 months — **Yes**

p=0.002

10.1 months — **No**

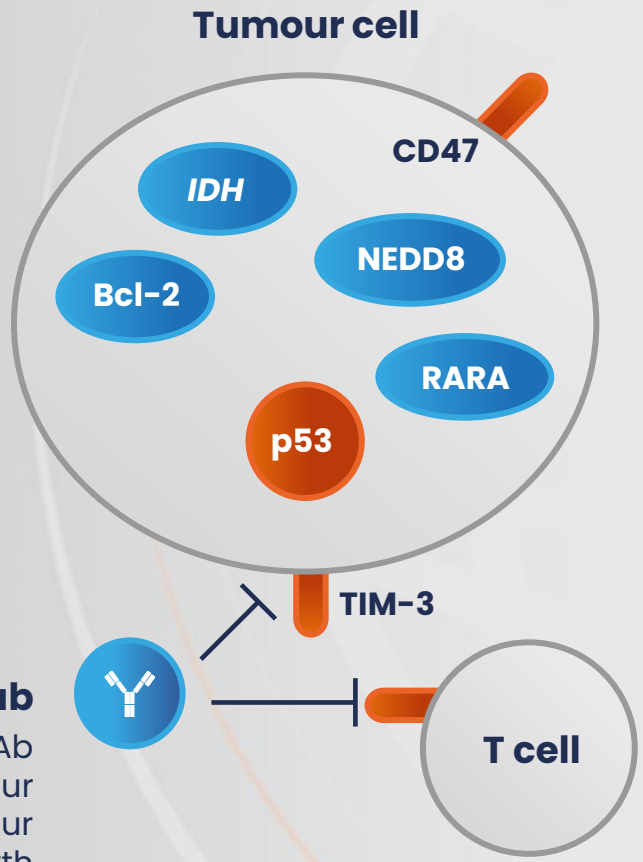
2-year OS in patients who became MRD negative



CI, confidence interval; CR, complete response; ITT, intention to treat; MRD, measurable residual disease; m*TP53*, *TP53* mutation; NGS, next-generation sequencing; OS, overall survival; PR, partial response.

Sallman D, et al. *Blood*. 2021;138(Suppl. 1):246.

Mechanism of action of current and emerging treatment options



Sabatolimab

TIM-3 mAb
T-cell targeting of tumour cells and interrupts tumour cell growth

Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3 .
Abaza Y, Zeidan AM. *Cells*. 2022;11:2249.

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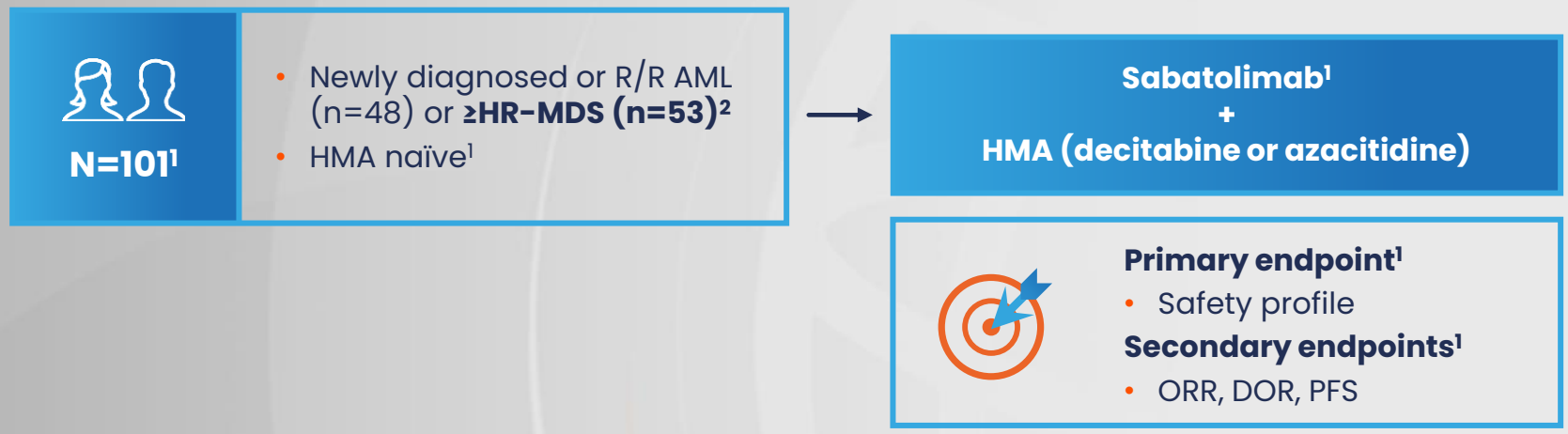
Sabatolimab + HMA

Sabatolimab + HMA in HR-MDS and AML: Phase Ib open-label, dose-escalation study results (NCT03066648)[1]



AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; DOR, duration of response; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; vHR, very high-risk.

1. Brunner A, et al. ASH 2020. Abstract 657; 2. Brunner A, et al. *Blood*. 2021;138(Suppl. 1):244.

Sabatolimab + HMA

Sabatolimab + HMA in HR-MDS and AML: Phase Ib open-label, dose-escalation study results (NCT03066648)[1]

N=101[1]

- Newly diagnosed or R/R AML (n=48) or **≥HR-MDS (n=53)[2]**
- HMA naïve[1]

Sabatolimab[1]
+
HMA (decitabine or azacitidine)

Primary endpoint[1]
- Safety profile

Secondary endpoints[1]
- ORR, DOR, PFS

vHR/HR-MDS (n=51)[2]

56.9% (n=29/53) → **CR = 19.6%**

ORR

Median DOR = 16.1 months

In patients with m*TP53* (n=14)[2]

71.4% (n=10/14)

ORR

Predicted 12-month PFS[2]

51.9%

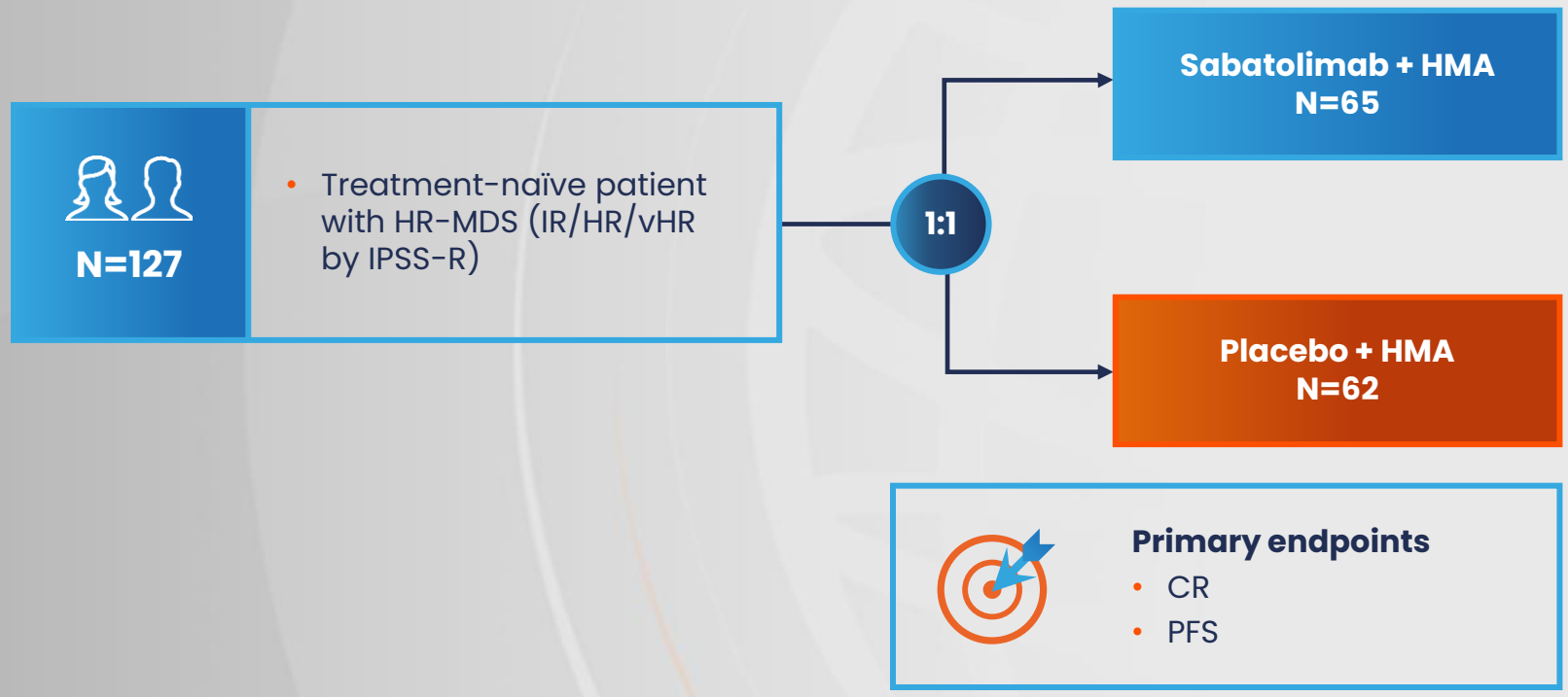
(95% CI 30.6–69.6)

AML, acute myeloid leukaemia; CI, confidence interval; CR, complete response; DOR, duration of response; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; vHR, very high-risk.

1. Brunner A, et al. ASH 2020. Abstract 657; 2. Brunner A, et al. *Blood*. 2021;138(Suppl. 1):244.

Sabatolimab + HMA

Sabatolimab + HMA in HR-MDS: Primary results from STIMULUS-MDS1, a phase II, double-blind, randomized trial (NCT03946670)



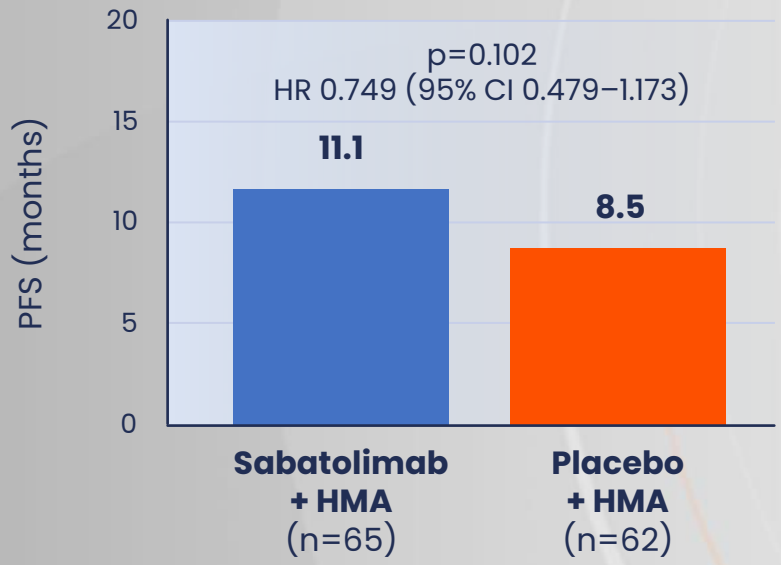
CR, complete response; HMA, hypomethylating agent; HR, high-risk; HR-MDS, high-risk myelodysplastic neoplasm; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; IR, intermediate risk; PFS, progression-free survival; vHR, very high-risk.

Zeidan AM, et al. *Blood*. 2022;140(Suppl. 1):2063–5.

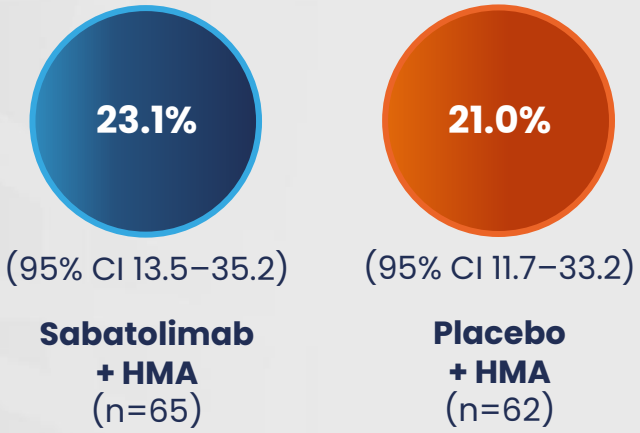
Sabatolimab + HMA

Sabatolimab + HMA in HR-MDS: Primary results from STIMULUS-MDS1, a phase II, double-blind, randomized trial (NCT03946670)

PFS was comparable between treatment arms



CR was not different between treatment arms



CI, confidence interval; CR, complete response; HMA, hypomethylating agent; HR, hazard ratio; HR-MDS, high-risk myelodysplastic neoplasm; PFS, progression free survival.

Zeidan AM, et al. *Blood*. 2022;140(Suppl. 1):2063–5.

Sabatolimab + HMA

Sabatolimab + HMA in HR-MDS: Primary results from STIMULUS-MDS1, a phase II, double-blind, randomized trial (NCT03946670)

Results were comparable in patients with <10% bone marrow blasts

	Sabatolimab + HMA (n=32)	Placebo + HMA (n=29)
CR	28.1% (95% CI 12.5–43.7)	17.2% (95% CI 3.5–31.0)
Median PFS	11.3 months (95% CI 6.0–19.0)	8.3 months (95% CI 4.4–9.2)

CI, confidence interval; CR, complete response; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; PFS, progression free survival.

Zeidan AM, et al. *Blood*. 2022;140(Suppl. 1):2063–5.

Sabatolimab ongoing trials

STIMULUS-MDS-US (NCT04878432): Single-arm, open-label, phase II trial[1]

N=90

- Treatment-naive HR-MDS unsuitable for intensive chemotherapy or HSCT

→ **Sabatolimab + Investigator's choice HMA**

Estimated primary completion:
January 2024[2]

Primary endpoint
- Safety and efficacy

STIMULUS-MDS3 (NCT04812548): Single-arm, open-label, phase II trial[1]

N=76

- vHR/HR-MDS
- Unsuitable for HSCT

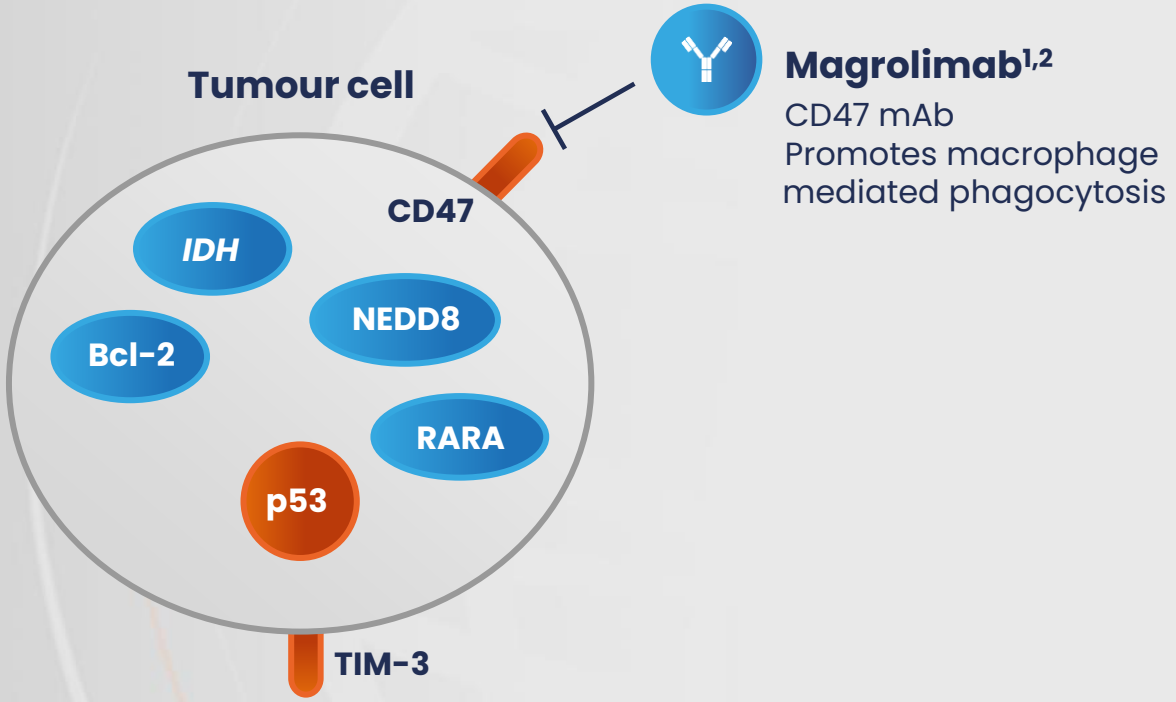
→ **Sabatolimab + azacitidine + venetoclax**

Estimated primary completion:
May 2026[2]

Primary endpoint
- Safety and efficacy

HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; HSCT, haematopoietic stem cell transplant; vHR, very high-risk.
1. Zeidan AM, et al. *Blood*. 2021;138(Suppl. 1)4669; 2. ClinicalTrials.gov. Available at: clinicaltrials.gov/ct2/show/NCT04878432 (accessed 7 December 2022);
3. ClinicalTrials.gov. Available at: clinicaltrials.gov/ct2/show/NCT04812548 (accessed 7 December 2022)

Mechanism of action of magrolimab

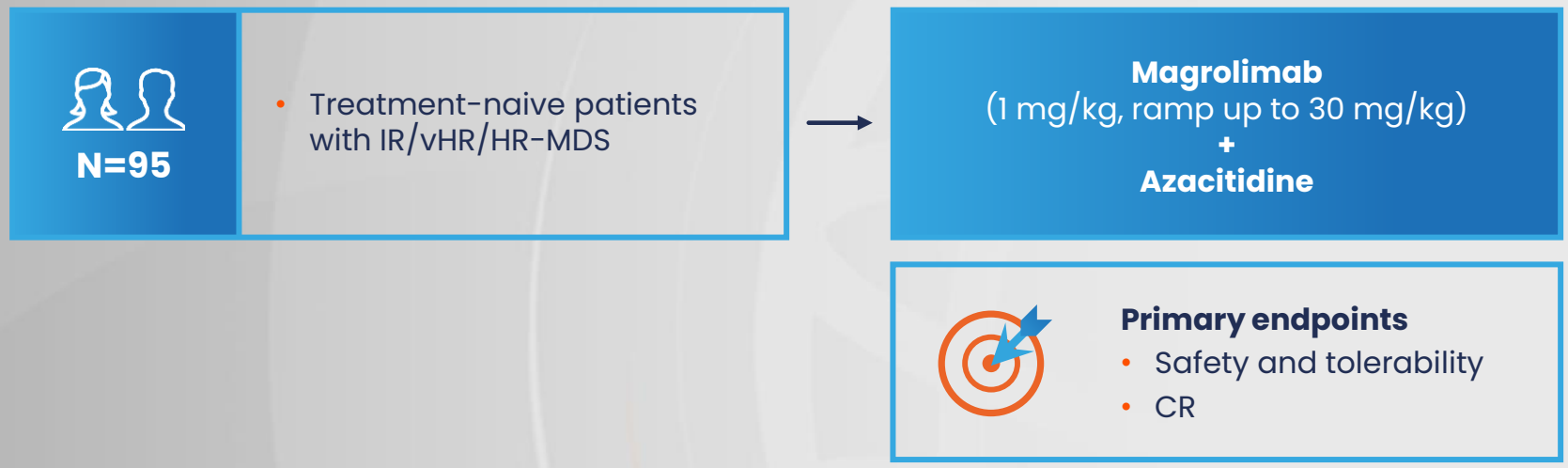


Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3 .

1. Bewersdorf JP, et al. *Ther Adv Hematol*. 2020;11:2040620720955006; 2. Abaza Y, Zeidan AM. *Cells*. 2022;11:2249.

Magrolimab + azacitidine

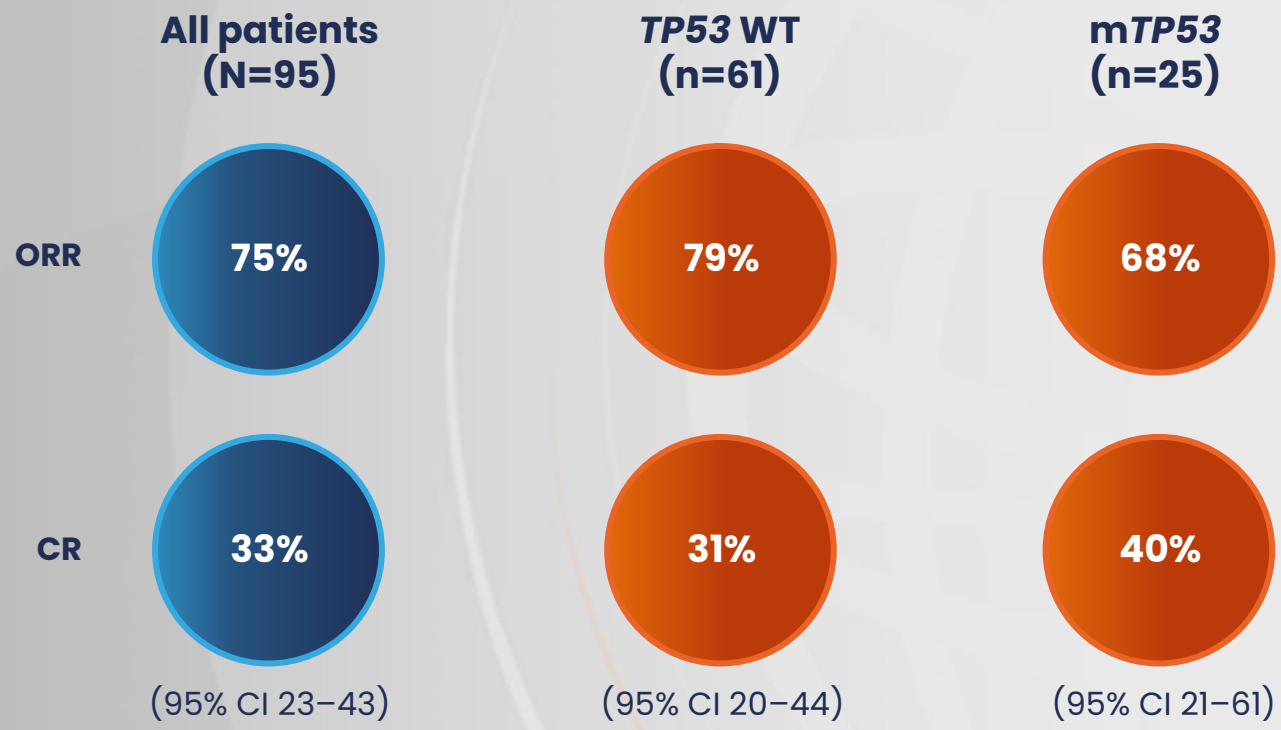
Results from phase Ib study in treatment naive HR-MDS (NCT03248479)



CR, complete response; HR-MDS, high-risk myelodysplastic neoplasm; IR, intermediate risk; vHR, very high-risk.
Sallman D, et al. *J Clin Oncol*. 2022;40(Suppl. 16):7017.

Magrolimab + azacitidine

Results from phase Ib study in treatment naïve HR-MDS (NCT03248479)



**TP53* status unavailable for 9/95 patients.
CI, confidence interval; CR, complete response; HR-MDS, high-risk myelodysplastic neoplasm; m*TP53*, *TP53* mutation; ORR, overall response rate; *TP53* WT, *TP53* wild type.
Sallman D, et al. *J Clin Oncol*. 2022;40(Suppl. 16):7017.

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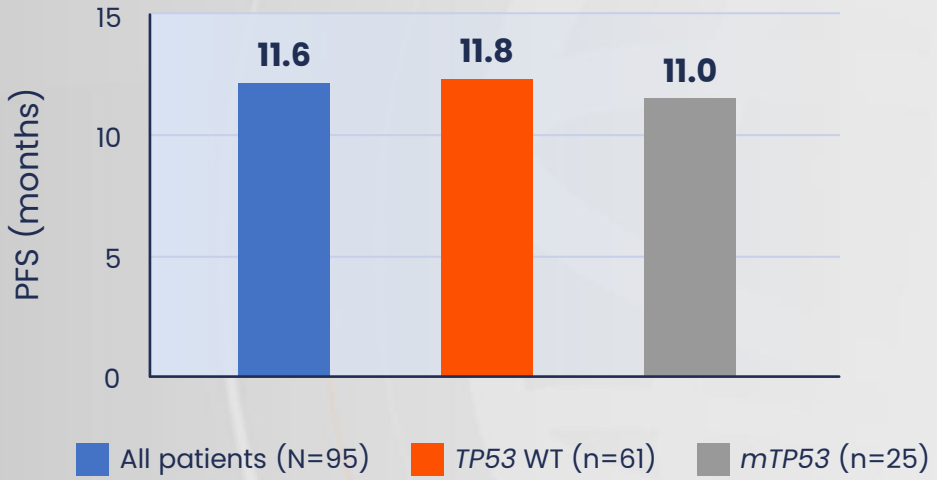
Magrolimab + azacitidine

Results from phase Ib study in treatment naïve HR-MDS (NCT03248479)

Median PFS



Median OS

All patients	*TP53* WT	m*TP53*
NR (95% CI 16.3–NR)	NR (95% CI 21.3–NR)	16.3 (95% CI 10.8–NR)

**TP53* status unavailable for 9/95 patients.
CI, confidence interval; m*TP53*, *TP53* mutation; HR-MDS, high-risk myelodysplastic neoplasm; NR, not reached; OS, overall survival; PFS, progression-free survival; *TP53* WT, *TP53* wild type.
Sallman D, et al. *J Clin Oncol*. 2022;40(Suppl. 16):7017.

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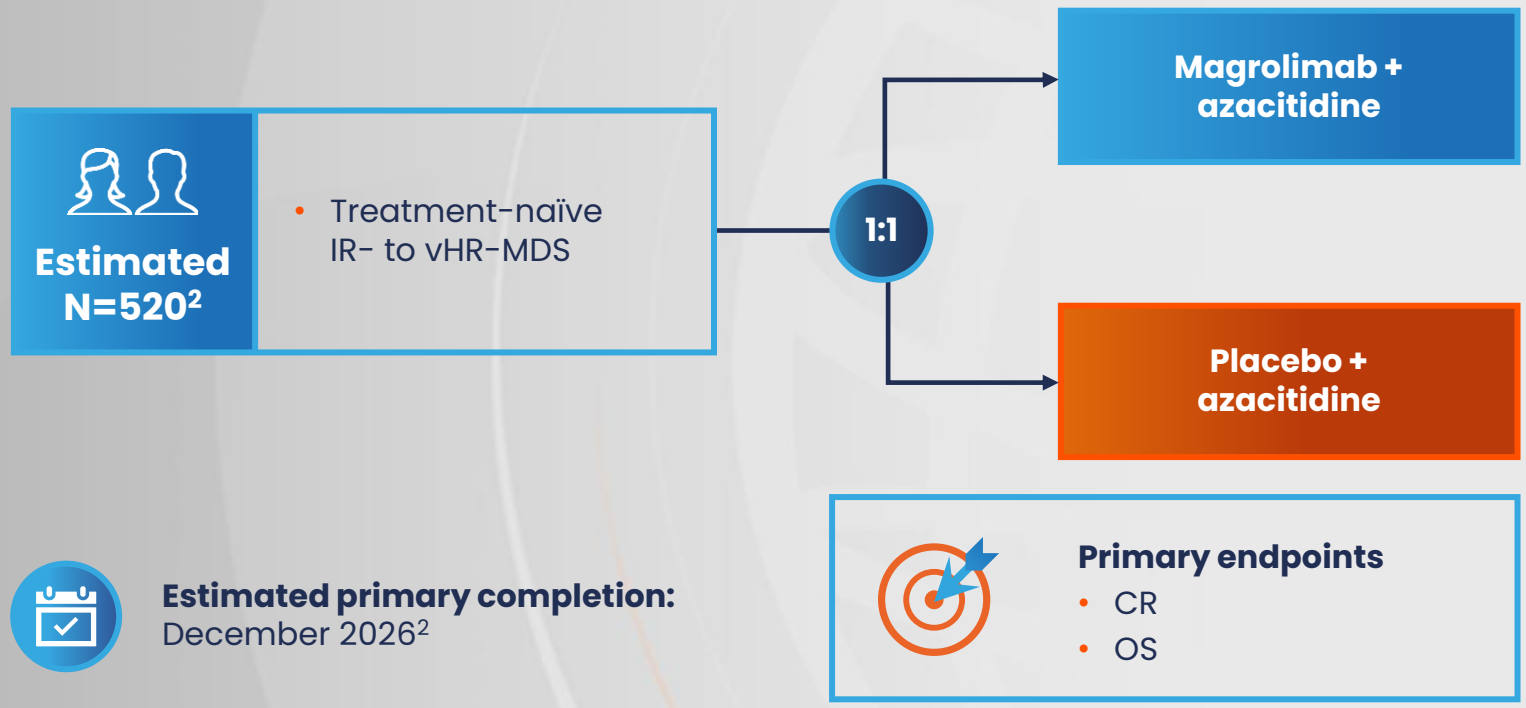
Magrolimab + azacitidine

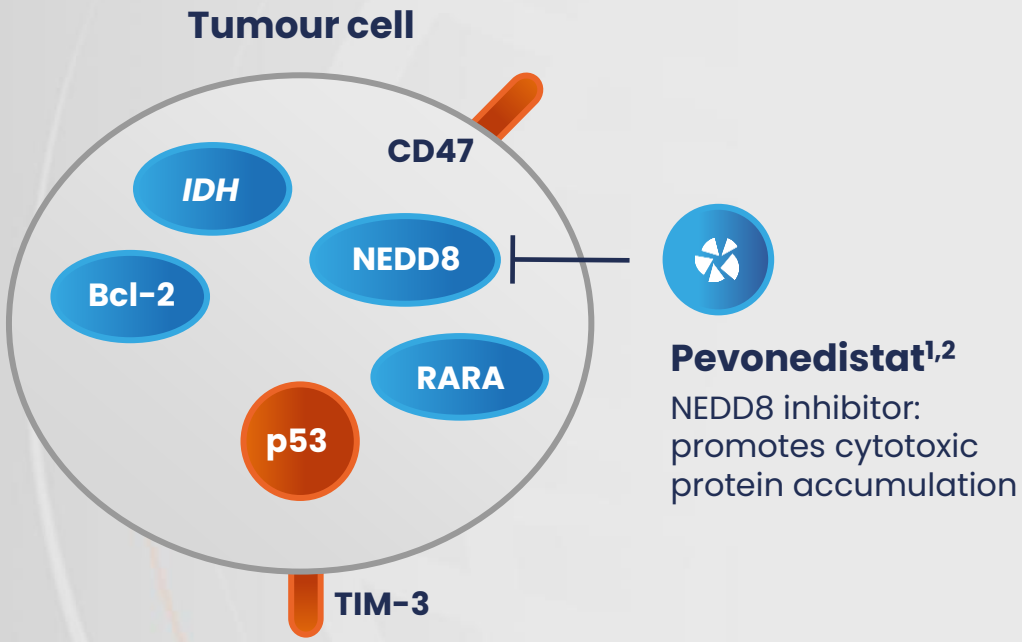
ENHANCE (NCT04313881): Placebo controlled, phase III trial[1]



CR, complete response; IR, intermediate risk; OS, overall survival; vHR-MDS, very high-risk myelodysplastic neoplasm.

1. Garcia-Manero G, et al. *J Clin Oncol*. 2021;39(Suppl. 16):7017; 2. ClinicalTrials.gov. Available at: clinicaltrials.gov/ct2/show/NCT04313881 (accessed 7 December 2022)

Mechanism of action of pevonedistat

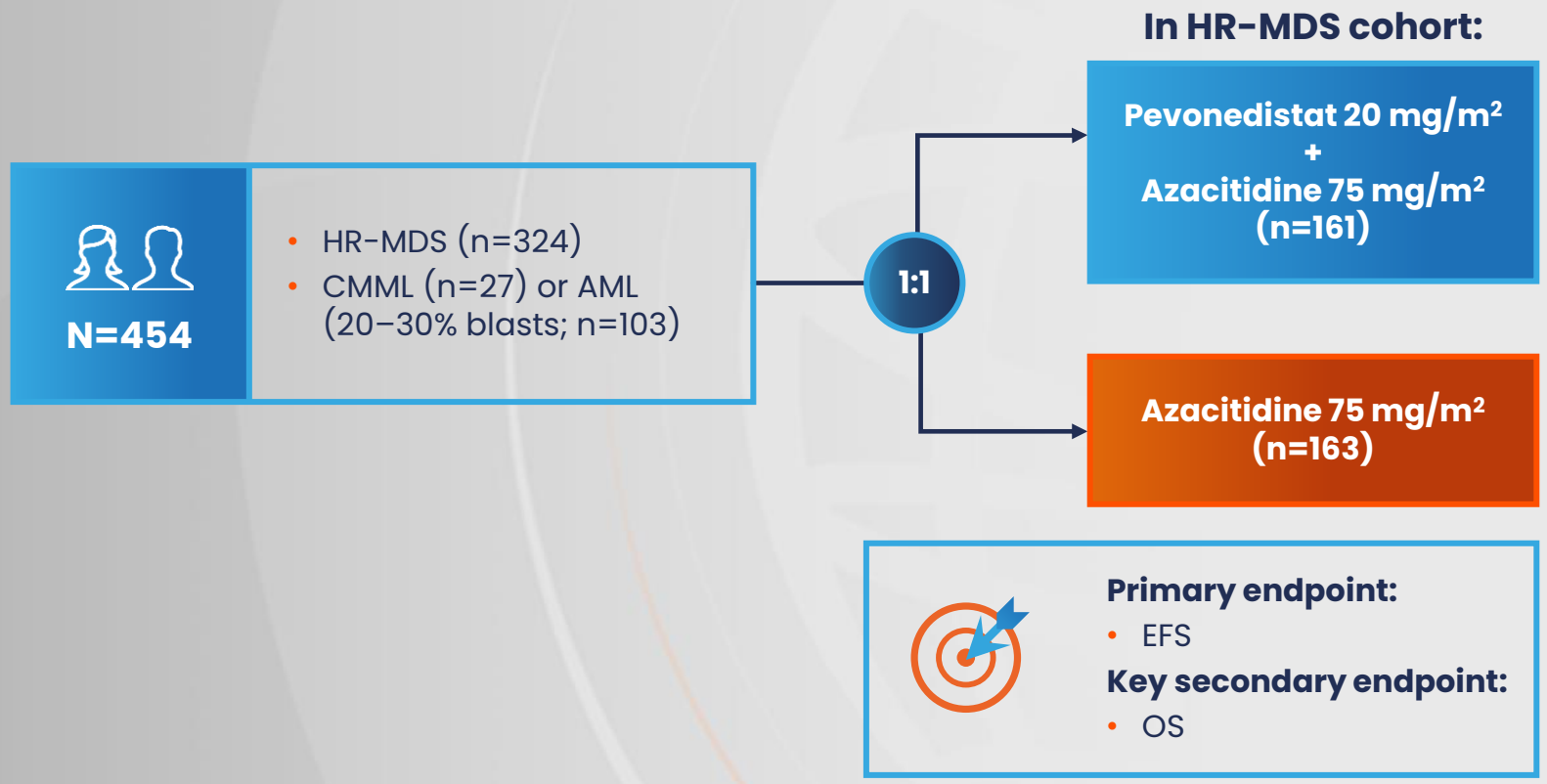


Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3 .

1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. Bewersdorf JP, et al. *Ther Adv Hematol*. 2020;11:2040620720955006.

Pevonedistat in HR-MDS

PANTHER (NCT03268954): Global, randomized, phase III trial

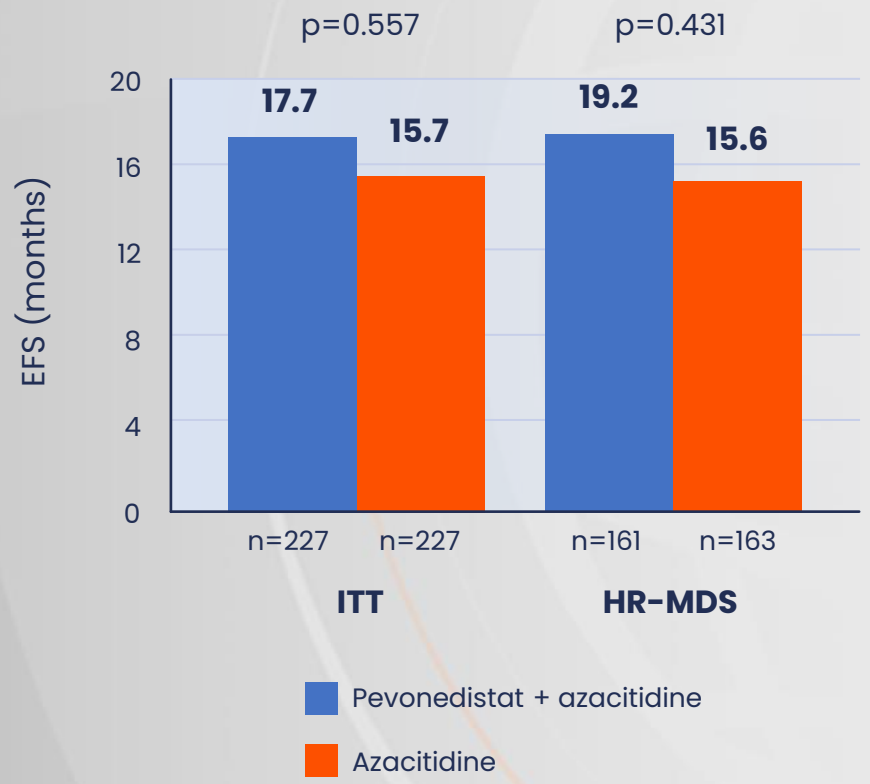


AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; EFS, event-free survival; HR-MDS, high-risk myelodysplastic neoplasm; IR, intermediate risk; OS, overall survival.
Adés L, et al. *Blood Adv*. 2022;6:5132–45.

Pevonedistat in HR-MDS

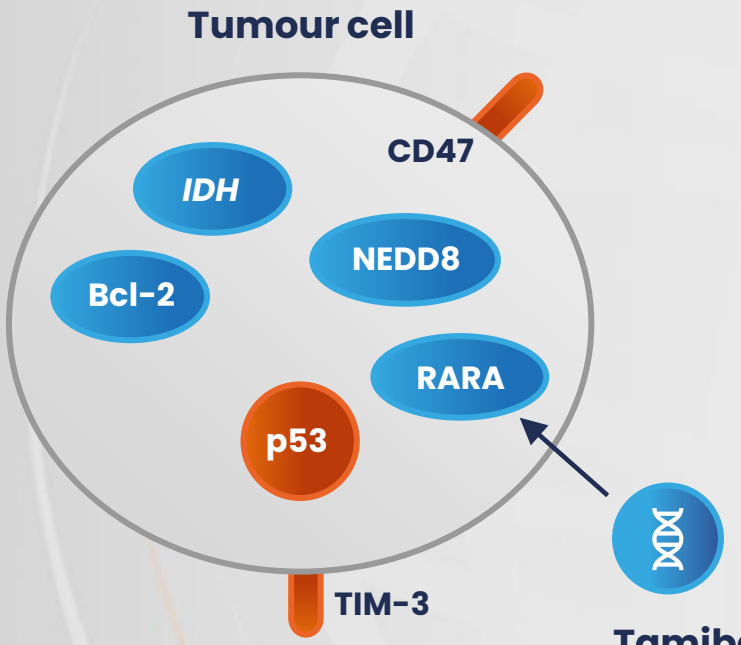
PANTHER (NCT03268954): Global, randomized, phase III trial

EFS was comparable between treatment arms



EFS, event-free survival; HR-MDS, high-risk myelodysplastic neoplasm; ITT, intention to treat.
Adés L, et al. *Blood Adv*. 2022;6:5132–45.

Mechanism of action of current and emerging treatment options



Tamibarotene

RARA agonist:
RARA transcription factor overexpressed in subset of patients with HR-MDS

Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3 .
DeZern A, et al. *Hemasphere*. 2022;6(Suppl.)1800–1.

Tamibarotene + azacitidine

Phase III SELECT-MDS-1 trial (NCT04797780)[1]

Ongoing: double-blind, placebo-controlled trial[1]

Estimated N=190

- RARA positive
- IR/vHR/HR-MDS
- Bone marrow blasts >5%
- No prior HMA treatment

2:1

- **Azacitidine + tamibarotene**
- **Azacitidine + placebo**

Primary endpoint:
- CR

Key secondary endpoints:
- ORR
- EFS
- OS
- Transfusion independence
- DOR
- Safety

Estimated primary completion:
December 2023[2]

CR, complete response; DOR, duration of response; EFF, event-free survival; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; IR, intermediate risk; ORR, overall response rate; OS, overall survival; RARA, retinoic acid receptor alpha; vHR, very high risk.
1. DeZern A, et al. *Hemasphere*. 2022;6(Suppl.)1800–1; 2. ClinicalTrials.gov. Available at: clinicaltrials.gov/ct2/show/NCT04797780 (accessed 7 December 2022).

IDH1/2 inhibitors in HR-MDS

Ivosidenib and enasidenib have shown promising response rates in phase I/II trials[1,2]

	Trial details	Results
Ivosidenib[1] (Phase 1) (NCT02074839)	Single-arm, phase I results, R/R HR-MDS (N=16)	CR: 44% (n=7/16) PR: 6% (n=1/16) mCR: 31% (n=5/16) ORR: 81% (95% CI 54–96)
Enasidenib (Phase II)[2] (NCT03383575)	Treatment-naive m*IDH2* HR-MDS received enasidenib + azacitidine (n=27) HMA-refractory m*IDH2* HR-MDS received enasidenib alone (n=23)	**Enasidenib + azacitidine:** ORR: 74%; OS: 26 months **Enasidenib alone** ORR: 35%; OS: 20 months
Olutasidenib[3] (phase I/II) (NCT02719574)	Open-label trial Patients with m*IDH1* IR/vHR/HR-MDS or AML received olutasidenib + azacitidine (n=46) or olutasidenib alone (n=32)	**In HR-MDS cohort (evaluable patients):** **Olutasidenib + azacitidine (n=7):** CR: 57% (n=4/7) **Olutasidenib alone (n=6):** CR: 17% (n=1/6)

CI, confidence interval; CR, complete response; HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm; IR, intermediate risk; mCR, marrow CR; m*IDH1/2*, isocitrate dehydrogenase enzyme 1/2 mutation; ORR, overall response rate; PR, partial response; R/R, relapsed or refractory; vHR, very high risk.

1. DiNardo D, et al. *Hemasphere*. 2022;6:660–1; 2. DiNardo C, et al. *Blood* Adv. 2022;doi: 10.1182/bloodadvances.2022008378;
3. Watts J, et al. *Lancet Haematol*. 2022;doi: 10.1016/S2352-3026(22)00292-7.

Immunotherapy in HR-MDS

	Trial details	Results
Pembrolizumab[1] (Phase II) (NCT03094637)	Patients with IR/HR-MDS received pembrolizumab + azacitidine (N=37)	**First-line treated cohort (n=17):** ORR: 76%; CR: 18% mOS: not reached **HMA-failure cohort (n=20):** ORR: 25%; CR: 5% mOS: 5.8 months
Durvalumab[2] (FUSION-AML-001; phase II; NCT02775903)	Patients with IR/vHR/HR-MDS received durvalumab + azacytidine or azacitidine alone as first-line treatment (n=84)	**Durvalumab + azacitidine (n=42):** ORR: 61.9% **Azacitidine alone (n=42):** ORR: 47.6% (p=0.1838)

CR, complete response; HR-MDS, high-risk MDS; IR, intermediate risk; MDS, myelodysplastic neoplasm; mOS, median overall survival; ORR, overall response rate; vHR, very high-risk.
1. Chien K, et al. *Br J Haematol*. 2021;195:378–87; 2. Zeidan A, et al. *Blood Adv*. 2022;6:2207–18.

Summary

- Several treatment options are in development that show promising response rates in HR-MDS[1–3]
- Novel drugs have been investigated in combination with HMAs, such as azacitidine[1–4]
- There is still a need for further data from placebo-controlled trials to confirm the efficacy of emerging treatment options

HMA, hypomethylating agent; HR-MDS, high-risk myelodysplastic neoplasm.

1. Wei AH, et al. *Blood*. 2019;134(Suppl. 1):568; 2. Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94; 3. Zeidan AM, et al. *Blood*. 2022;140(Suppl. 1):2063–5; 4. Adés L, et al. *Blood Adv*. 2022;6:5132–45.

Safety data for emerging treatments for patients with HR-MDS

HMA treatment is associated with haematological AEs

The most common AEs associated with azacitidine are haematological or gastrointestinal

- Haematological AEs can be managed by dose interruption or reduction, or blood product transfusions
- Gastrointestinal conditions can be managed with medication e.g. anti-emetics, laxatives, anti-diarrhoeals

AEs, adverse events; HMA, hypomethylating agent.
Santini V, et al. *Eur J Haematol*. 2010;85:130–8.

Adverse events in venetoclax + azacitidine combination arms

	Reported AEs	
Venetoclax + azacitidine Phase Ib study[1] (NCT02942290)	**Common GI symptoms:** • Constipation, nausea, diarrhoea, vomiting	**Most common grade 3/4 AES:** • Neutropenia (61%) • Thrombocytopenia (39%) • Leukopenia (31%) • Anaemia (20%)
Venetoclax + azacitidine Phase I results[2] (NCT04160052)	**Most common grade 3/4 TEAEs** • Neutropenia (39%) • Thrombocytopenia (39%) • Lung infection (30%) • Febrile neutropenia (17%)	
	• Myelosuppression was frequently reported with venetoclax + azacitidine[2] • This was usually managed with delay in cycle administration rather than dose reduction[2]	

AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent AE.
1. Wei AH, et al. *Blood*. 2019;134 (Suppl. 1):568; 2. Bazinet A, et al. *Lancet Haematol*. 2022;9:e756–75.

Adverse events in eprenetapopt + azacitidine combination arms

	Reported AEs	
Eprenetapopt + azacitidine[1] Phase Ib/II study (NCT03072043)	**Most common any grade TEAEs** • Nausea (64%) • Vomiting (45%) • Fatigue (44%) • Constipation (42%) • Edema (38%) **Most common any grade neurological AEs** • Dizziness (36%) • Peripheral sensory neuropathy (31%) • Ataxia (24%) • Tremor (20%)	≥3 **Most common grade ≥3 AEs** • Febrile neutropenia (33%) • Leukopenia (29%) • Neutropenia (29%) • Thrombocytopenia (25%) • Lung infection (25%)
Eprenetapopt + azacitidine[2] Phase II study (NCT03588078)	**Most common AEs (≥20%)** • Neurological (40%) including ataxia (25%) • Febrile neutropenia (37%)	**Most common grade 3/4 AEs** • Febrile neutropenia (37%) • Neurological (6%) including ataxia (4%)

- Neurological AEs were transient and reversible after dose reduction of eprenetapopt and could be managed using supportive measures[1,2]

AE, adverse event; TEAE, treatment-emergent AE.

1. Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94; 2. Cluzeau T, et al. *J Clin Oncol*. 2021;39:1575–83.

Immunotherapies require specific safety considerations

Immunotherapies such as sabatolimab may lead to AEs affecting numerous organ systems

AEs may affect numerous organ systems and clinicians should consider if AEs are treatment related

Management remains a challenge, although can be treated with medications including corticosteroids

irAEs can be managed by dose interruption or supportive care

Early identification and management is needed to ensure treatment continuation

AE, adverse event; irAE, immune-related AE.

Schneider B, et al. *J Clin Oncol*. 2021;39:4073–126.

Adverse events of sabatolimab + HMA combination arms

	Most common AEs	
Sabatolimab + HMA[1] Phase Ib study (NCT03066648)	**Most common grade ≥3 AEs** • Neutropenia (47.2%) • Thrombocytopenia (43.4%) • Febrile neutropenia (35.8%) • Anaemia (28.3%)	
Sabatolimab + HMA[2] STIMULUS-MDS1: Phase II trial (NCT03946670)	**Most common non-haematological AEs (all grade)** • Constipation (46.8%) • Diarrhoea (43.5%)	**Most common grade ≥3 AEs** • Neutropenia (53.2%) • Thrombocytopenia (37.1%) • Febrile neutropenia (35.5%) • Anaemia (22.6%) • Leukopenia (22.6%)

In STIMULUS-MDS1, one patient developed a fatal immune-related adverse event (pneumonitis)[2]

AE, adverse event; HMA, hypomethylating agent.

1. Brunner A, et al. Presented at: 63rd ASH Annual Meeting, Atlanta, GA, USA. 10–14 December 2022. Abstr 637; 2. Zeidan A, et al. *Blood*. 2022;140(Suppl. 1):2063–5.

Adverse events of magrolimab + azacitidine combination

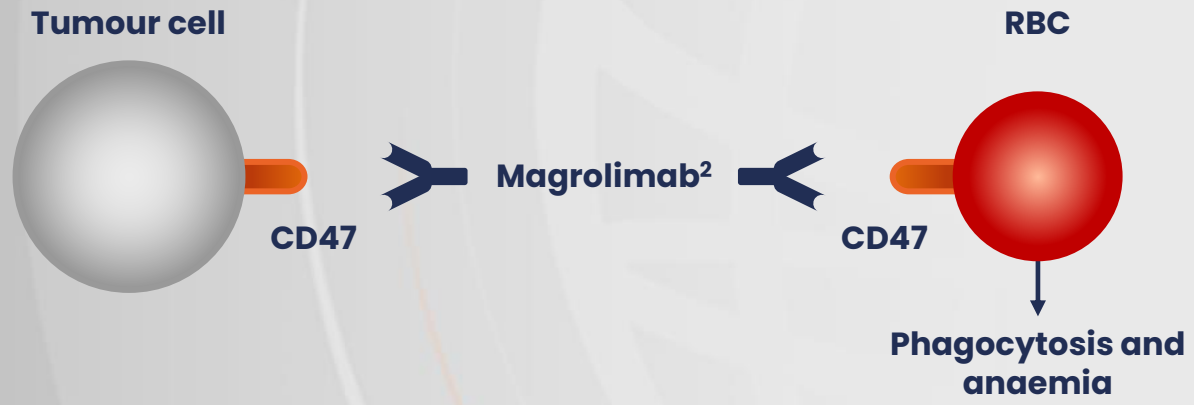
	Most common TEAEs	
Magrolimab + azacitidine Phase Ib study (NCT03248479)	**Most common TEAEs** • Constipation (68%) • Thrombocytopenia (55%) • Anaemia (52%) • Neutropenia (47%) • Nausea (46%) • Diarrhoea (44%)	**Most common grade 3/4 AEs** • Anaemia (47%) • Neutropenia (46%) • Thrombocytopenia(46%) • Decreased WBC count (30%)

AE, adverse event; TEAE, treatment-emergent AE; WBC, white blood cell.
Sallman D, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 3–7 June 2022. Abstr 7017.

Magrolimab may also target RBCs, leading to anaemia

Clinical data has reported tolerable anaemia in patients receiving magrolimab for HR-MDS[1]

Magrolimab targets CD47, which is a component of RBCs[2]



Patients receiving magrolimab should be closely monitored to anticipate the requirement for transfusion[2]

CD47, cluster of differentiation 47; HR-MDS, high-risk myelodysplastic neoplasm; RBC, red blood cell.
1. Chen J, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 3–7 June 2022. Abstr 7054; 2. Tan M, et al. *Intern Med J.* 2022;DOI:10.1111/imj.15934.

Adverse events reported with other compounds

	Most common AEs	
Pevonedistat + azacitidine PANTHER: Phase III trial[1] (NCT03268954)	**Most common any-grade TEAEs** • Constipation (37%) • Anaemia (37%) • Neutropenia (33%) • Thrombocytopenia (33%) • Nausea (35%)	**Most common grade ≥3 TEAEs** • Anaemia (33%) • Neutropenia (31%) • Thrombocytopenia (30%) • Febrile neutropenia (23%) • Pneumonia (15%)
Enasidenib (Phase II)[2] (NCT03383575)	**Most common AEs (all patients)** • Neutropenia (40%) • Nausea (36%) • Constipation (32%) • Fatigue (26%) • Thrombocytopenia (22%)	**Most common grade 3/4 AEs** • Neutropenia (19%) • Thrombocytopenia (11%) • Differentiation syndrome (5%) • Hyperbilirubinaemia (4%) • Leukopenia (4%)

AE, adverse event; TEAE, treatment-emergent AE.

1. Adès L, et al. *Blood Adv*. 2022;6:5132–45; 2. DiNardo C, et al. *Blood Adv*. 2022;bloodadvances.2022008378.

Adverse events reported with other compounds

	Most common AEs	
Pevonedistat + azacitidine PANTHER: Phase III trial[1] (NCT03268954)	**Most common any-grade TEAEs** • Constipation (37%) • Anaemia (37%) • Neutropenia (33%) • Thrombocytopenia (33%) • Nausea (35%)	**Most common grade ≥3 TEAEs** • Anaemia (33%) • Neutropenia (31%) • Thrombocytopenia (30%) • Febrile neutropenia (23%) • Pneumonia (15%)
Enasidenib (Phase II)[2] (NCT03383575)	**Most common AEs (all patients)** • Neutropenia (40%) • Nausea (36%) • Constipation (32%) • Fatigue (26%) • Thrombocytopenia (22%)	**Most common grade 3/4 AEs** • Neutropenia (19%) • Thrombocytopenia (11%) • **Differentiation syndrome (5%)** • Hyperbilirubinaemia (4%) • Leukopenia (4%)

AE, adverse event; TEAE, treatment-emergent AE.

1. Adès L, et al. *Blood Adv*. 2022;6:5132–45; 2. DiNardo C, et al. *Blood Adv*. 2022;bloodadvances.2022008378.

Summary

- Haematological adverse events are frequent with HMA therapy, but can be managed with dose interruption or reduction[1]
- Haematological adverse events are some of the most commonly reported safety concerns for novel treatments[2–4]
- Neurological adverse events were reported with some treatments but were transient and reversible[5,6]

HMA, hypomethylating agent.

1. Santini V, et al. *Eur J Haematol*. 2010;85:130–38; 2. Bazinet A, et al. *Lancet Haematol*. 2022;9:e756–75; 3. Zeidan A, et al. *Blood*. 2022;140 (Supplement 1):20635; 4. Sallman D, et al. Presented at: ASCO Annual Meeting, Chicago, IL, USA. 3–7 June 2022. Abstr 7017; 5. Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94; 6. Cluzeau T, et al. *J Clin Oncol*. 2021;39:1575–83.