

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 dysplasia¹

(MDS was previously known as myelodysplastic syndrome)²

Bone marrow malignancy

Definition of MDS and differentiation from AML

Myelodysplastic neoplasms (MDS): A spectrum of disorders characterised by cytopenia and morphological dysplasia¹

(MDS was previously known as myelodysplastic syndrome)²

Diagnosis is suspected on presence of cytopenia:³

Bone marrow aspiration:

- Cellular morphology
- Blast percentage

Bone marrow biopsy:

- Marrow cellularity
- Marrow architecture

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 abnormalities¹
- Updated **IPSS-M** also considers mutation burden²



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)

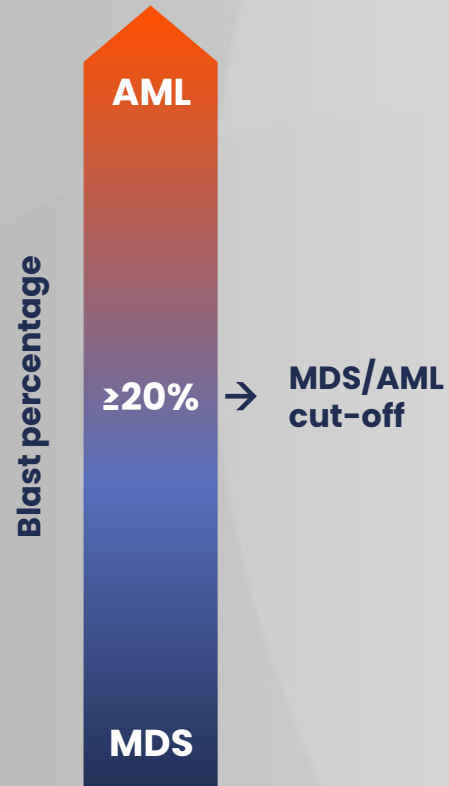


Next generation sequencing:^{3,4}

- Somatic or germline mutations can guide prognosis

Blast percentage for MDS/AML differentiation

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



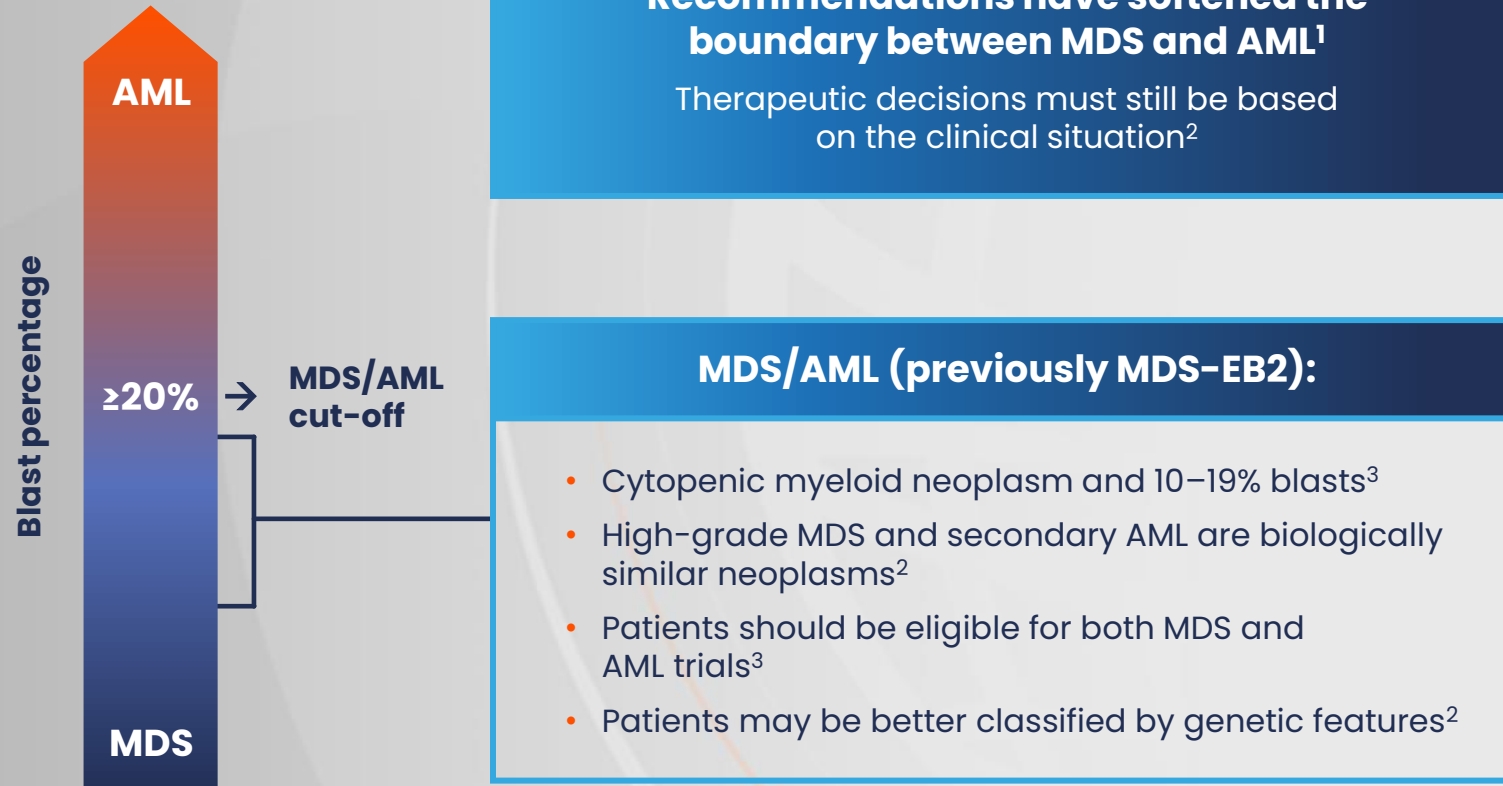
Limitations of 20% blast cut-off:²

- 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

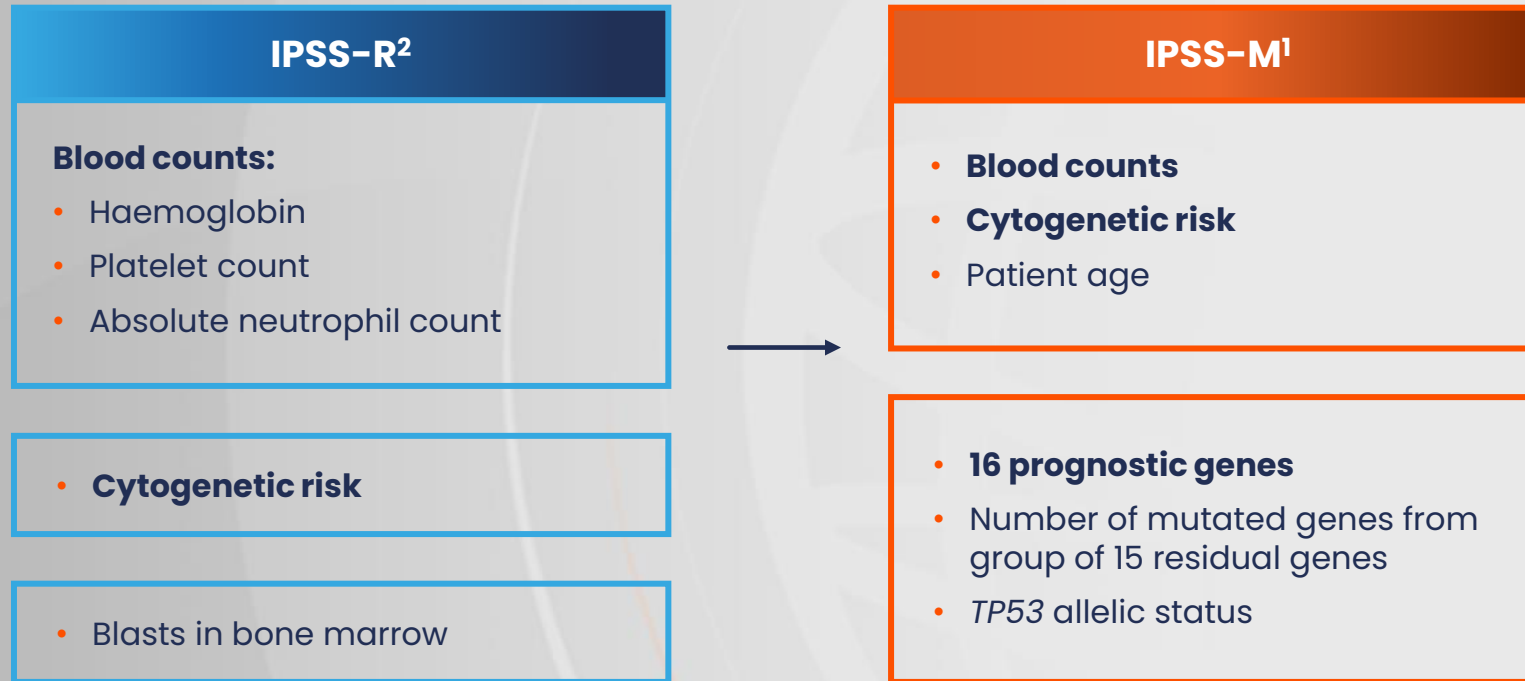
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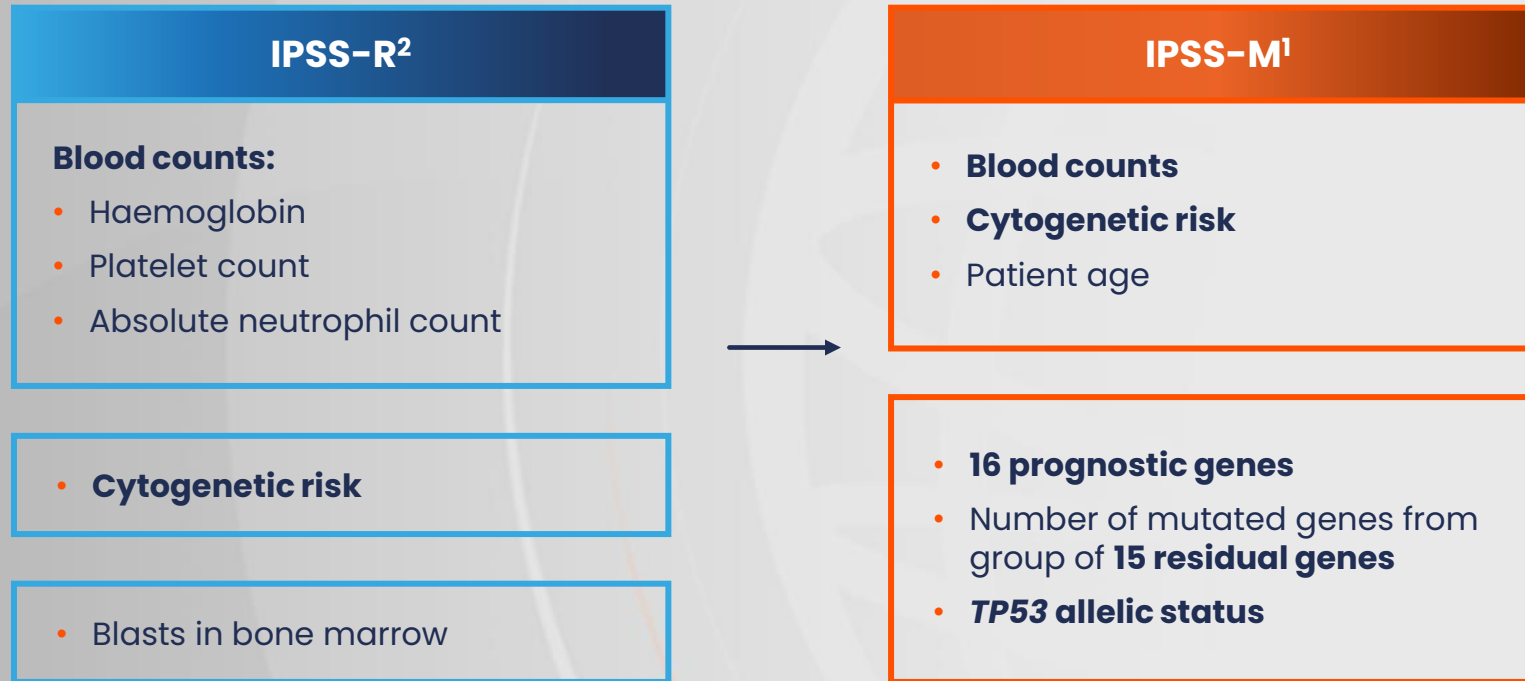
IPSS-R and the updated IPSS-M

The updated IPSS-M score considers genetic mutations in addition to the cytogenetic risk¹



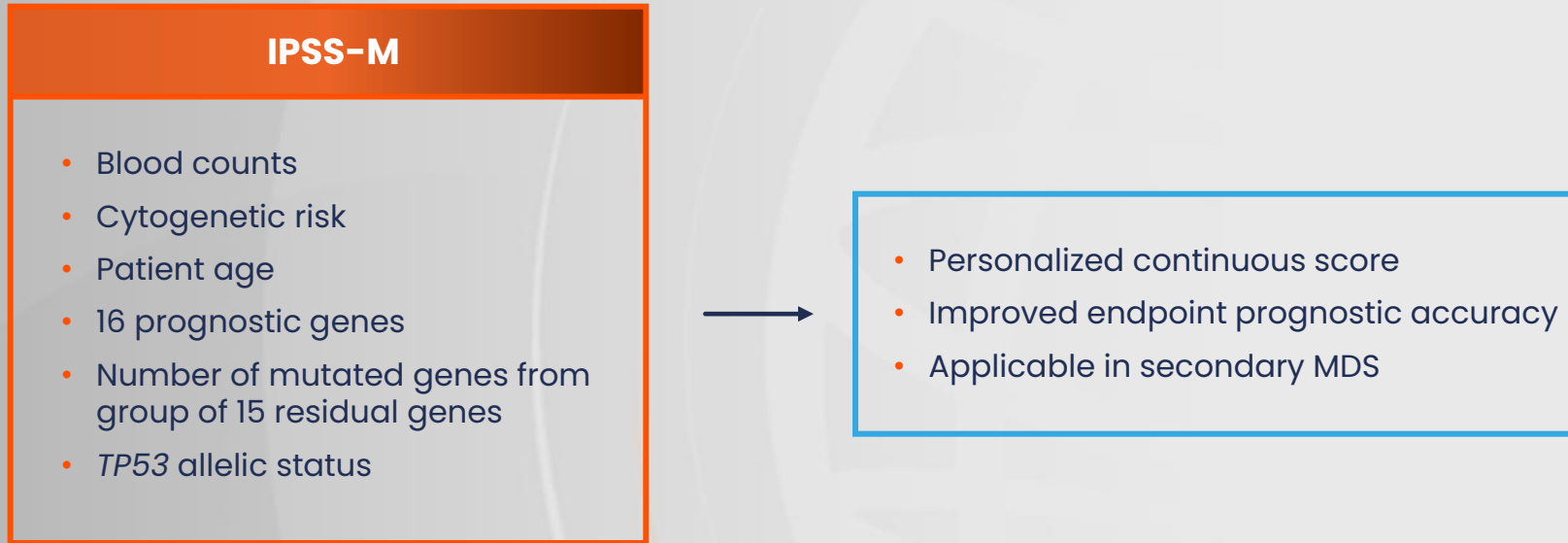
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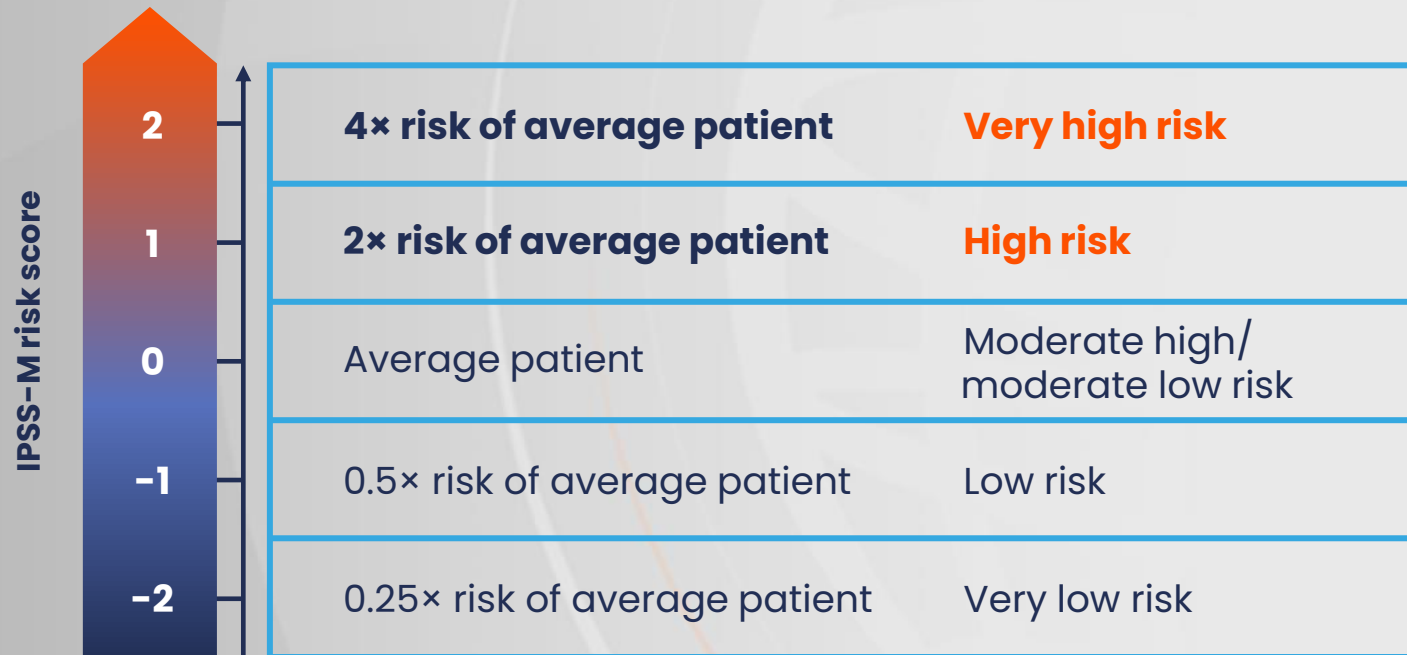


IPSS-M available as free online calculator: <https://mds-risk-model.com/>

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

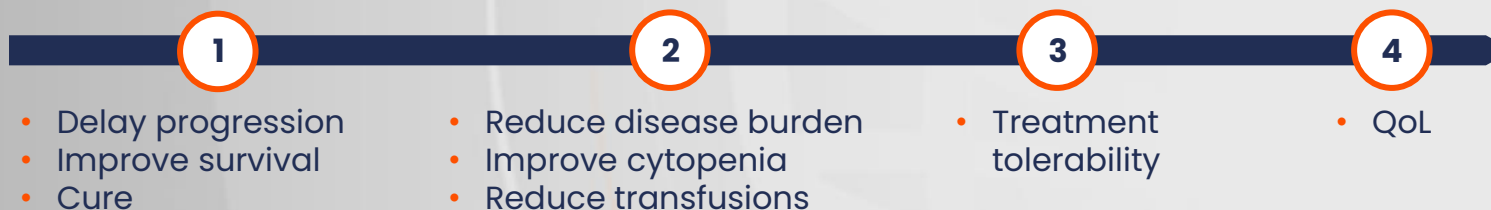


Treatment priorities vary by disease severity

Treatment goals in HR-MDS¹

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

HR-MDS treatment priorities¹



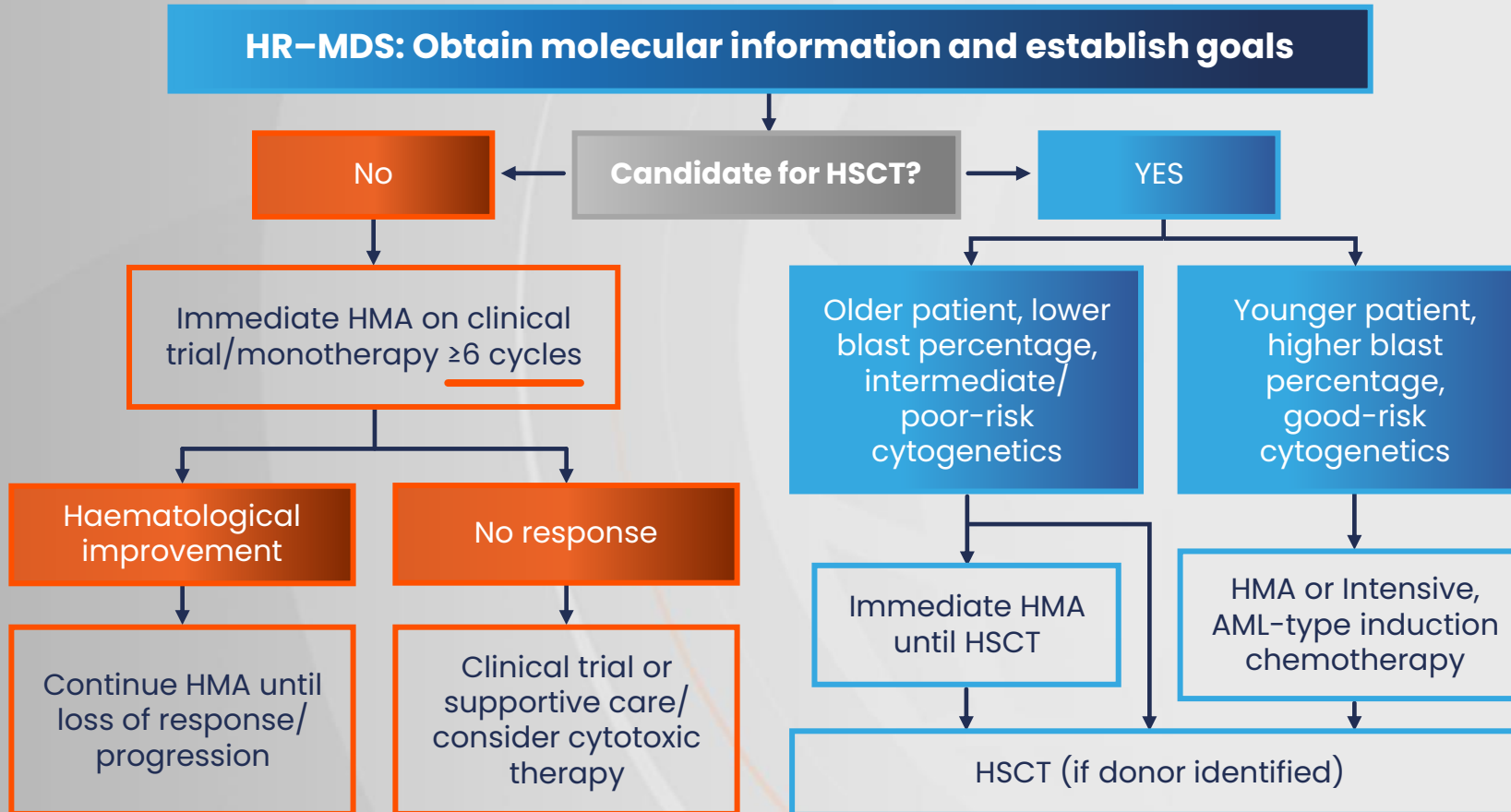
Survival outcomes remain poor²

Median OS

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

Treatment algorithm for HR-MDS

HMA's such as azacitidine are the current standard therapy for patients ineligible for HSCT



Limitations of current treatments

HSCT remains the only potentially curative treatment¹

Most patients are unable to tolerate HSCT¹

50–75 years

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

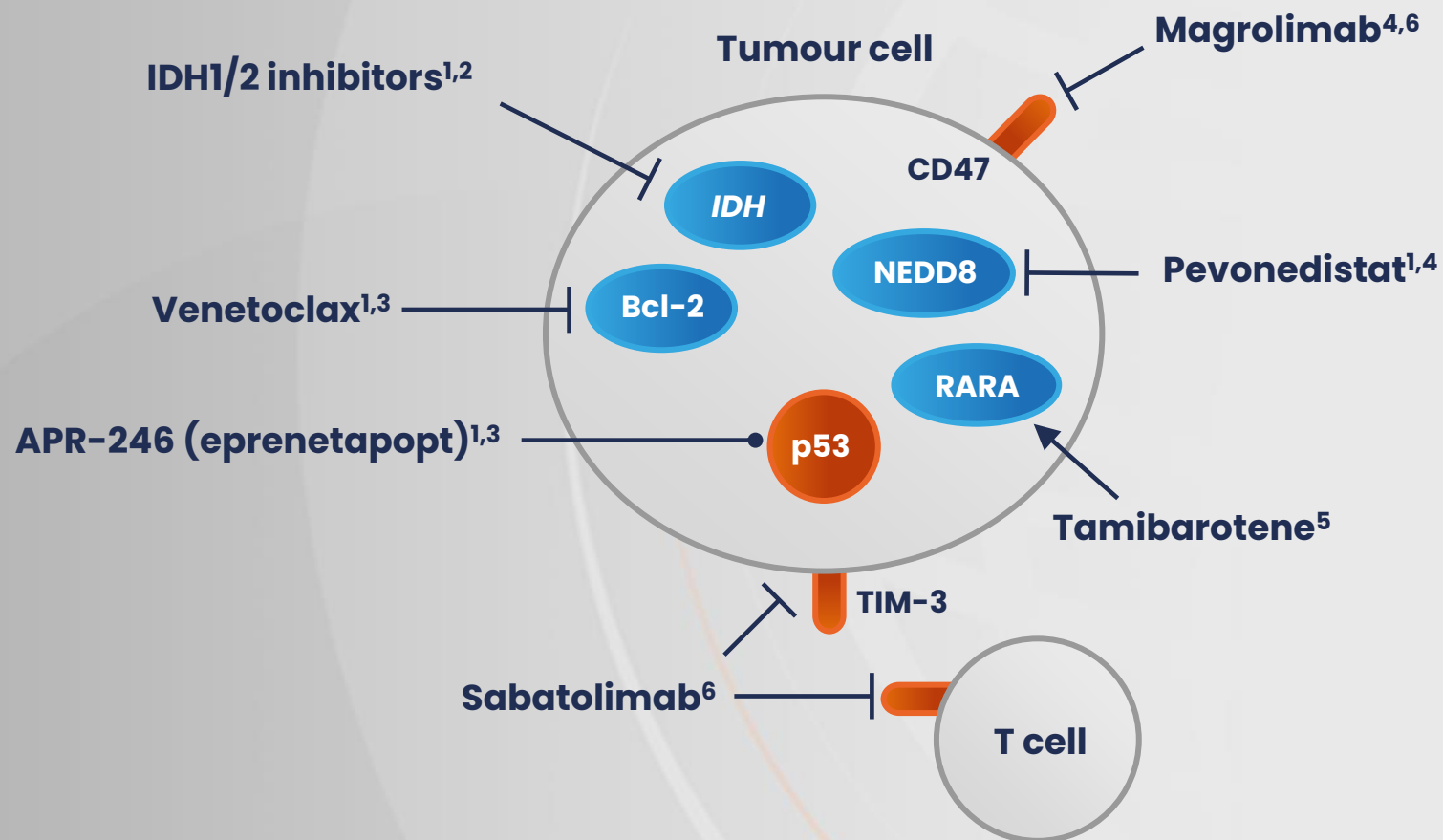
HSCT significantly prolonged survival over supporting therapy²

HMA remain the standard of care for patients ineligible for HSCT, but have limited efficacy³



There are limited treatment options after HMA failure, but several emerging treatments are under investigation³

Mechanism of action of current and emerging treatment options



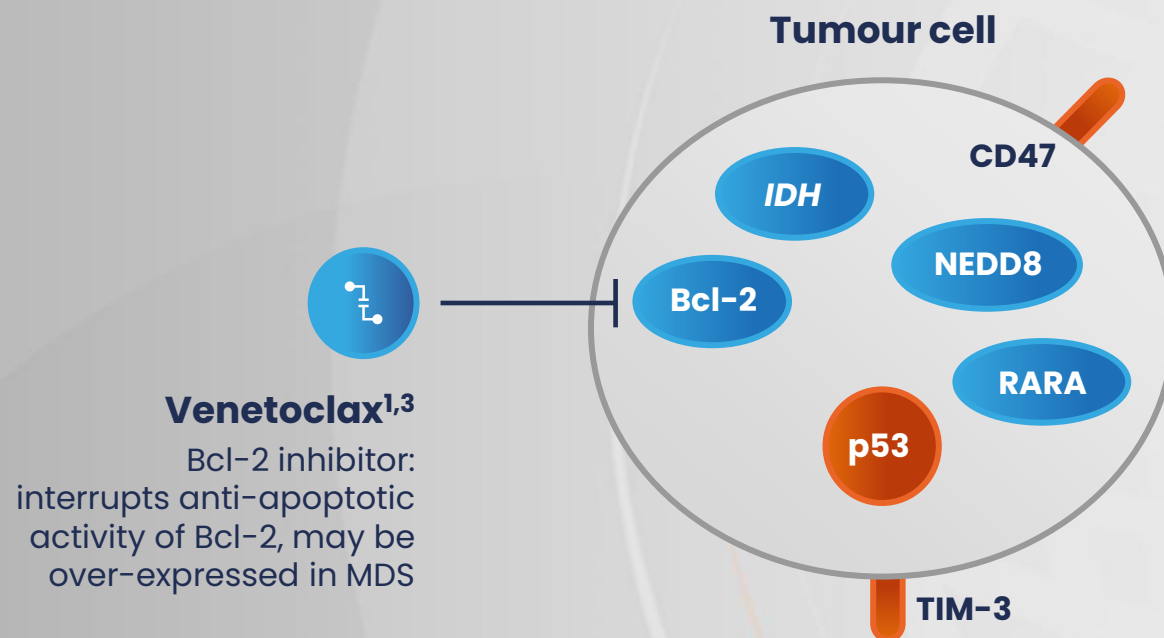
Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8;

RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3.

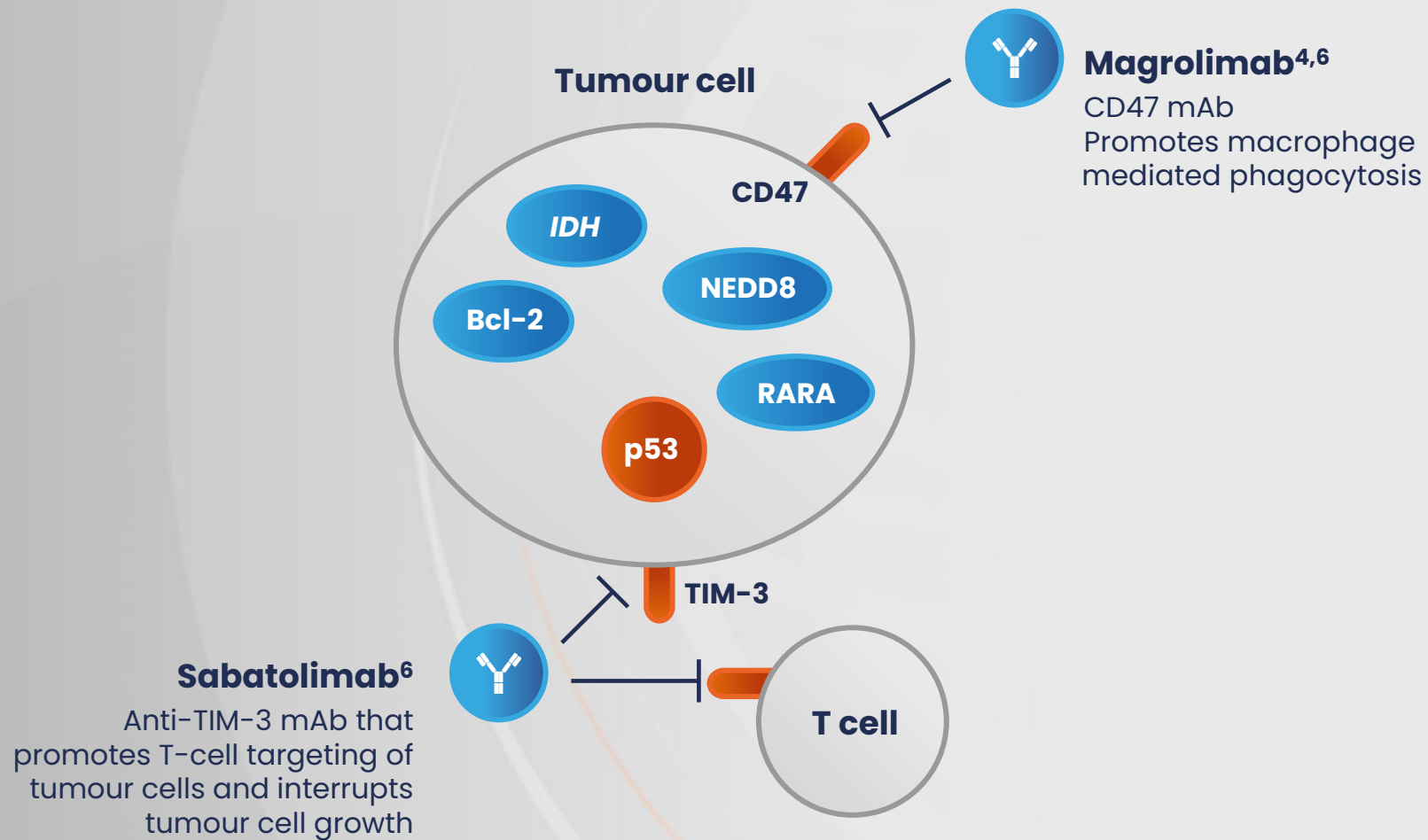
1. Platzbecker U. *Blood*. 2019;133:1096–107; 2. DiNardo C, et al. *Leukemia*. 2016; 30:980–4; 3. Hellström-Lindberg E, et al. *Haematologica*. 2020;105:1765–79;

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.

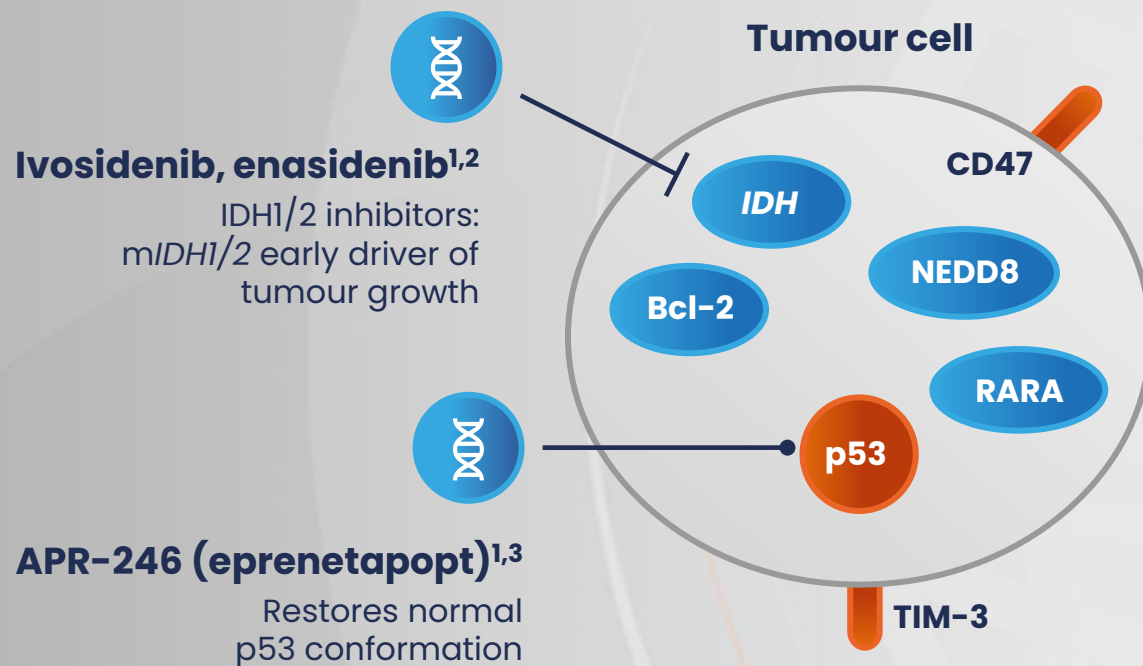
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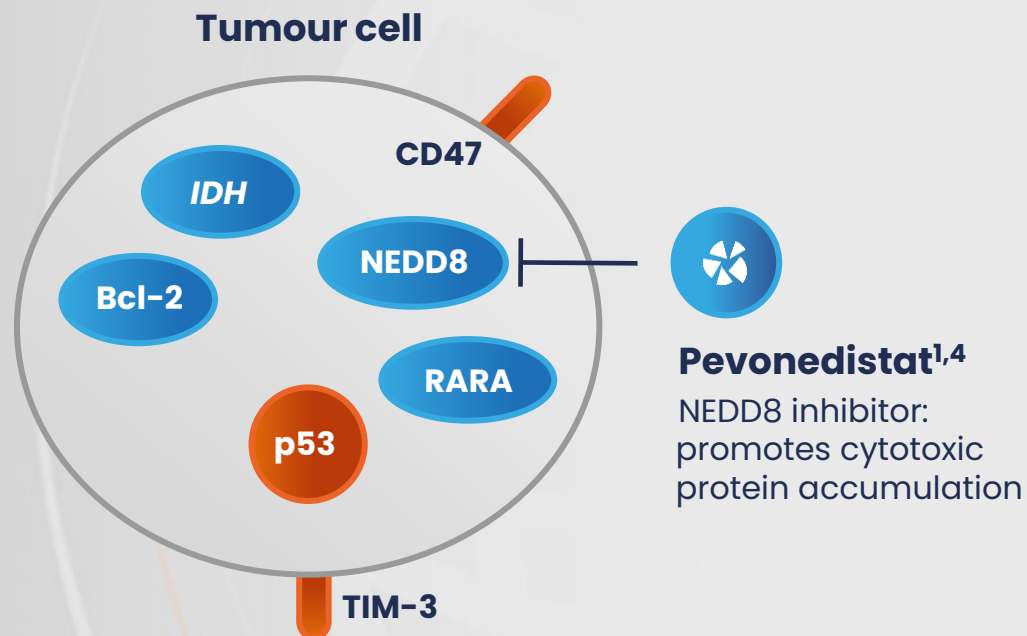


Bcl-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; mAb, monoclonal antibody; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; RARA, retinoic acid receptor alpha; TIM-3, T-cell immunoglobulin mucin-3.

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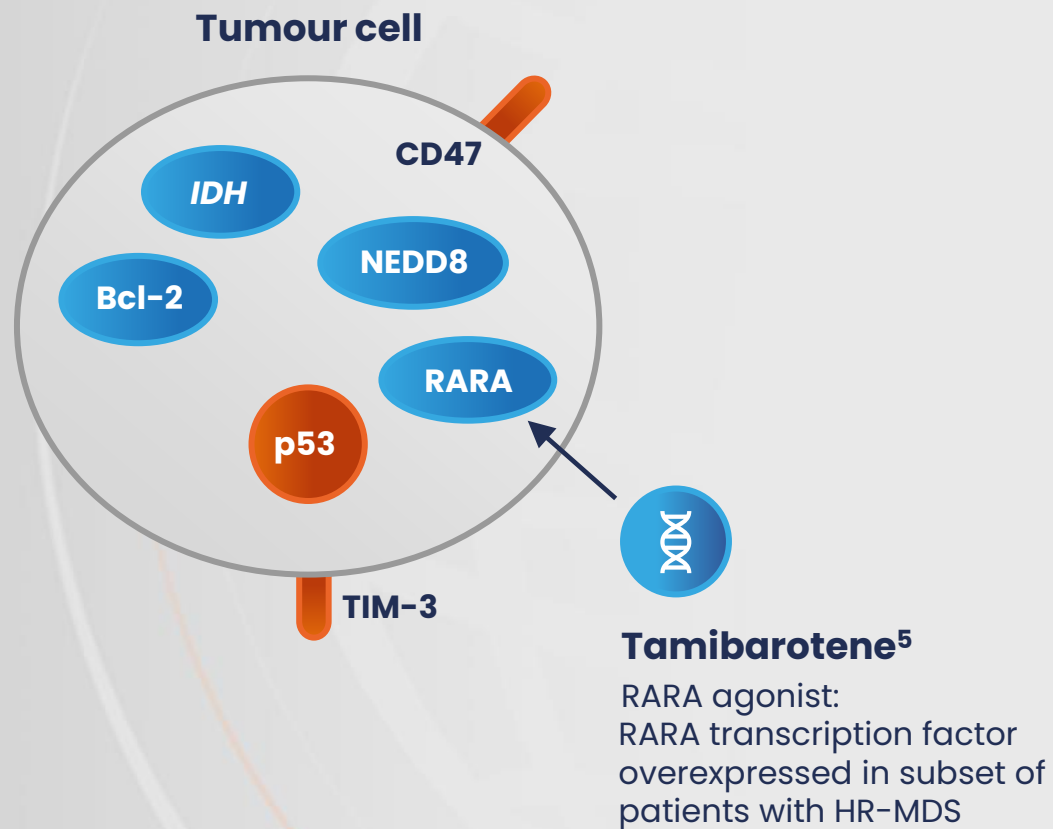


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Summary



The differentiation between MDS and AML remains a challenge^{1,2}



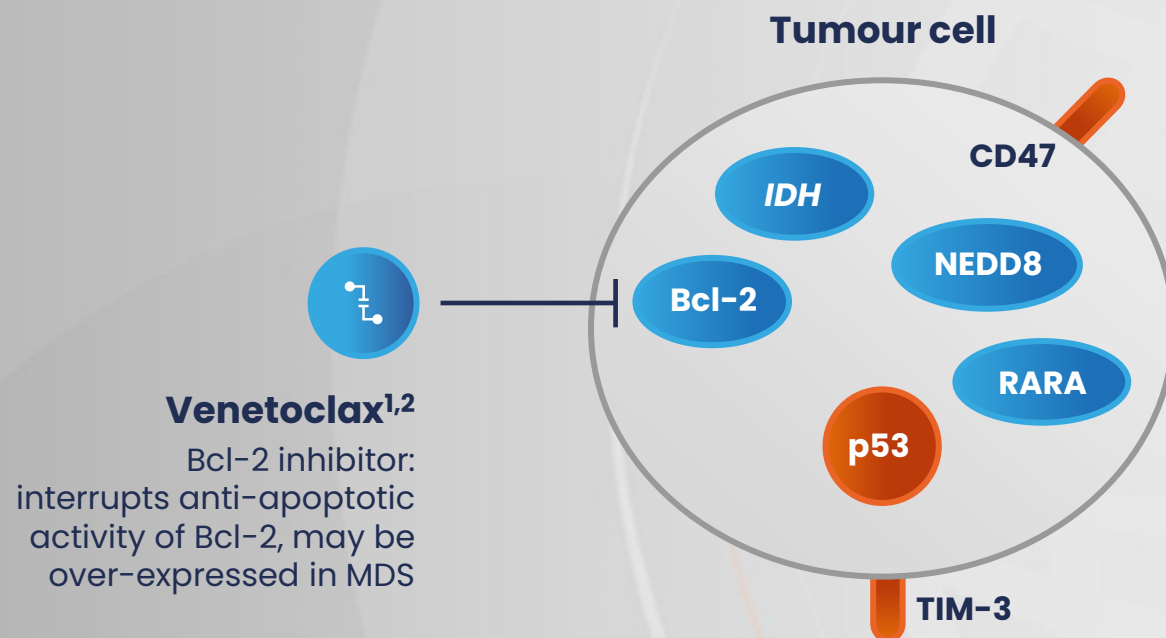
IPSS-M considers the mutation burden and offers an updated risk stratification tool compared with IPSS-R³



HMA is the standard treatment for HR-MDS, although response rates remain limited⁴

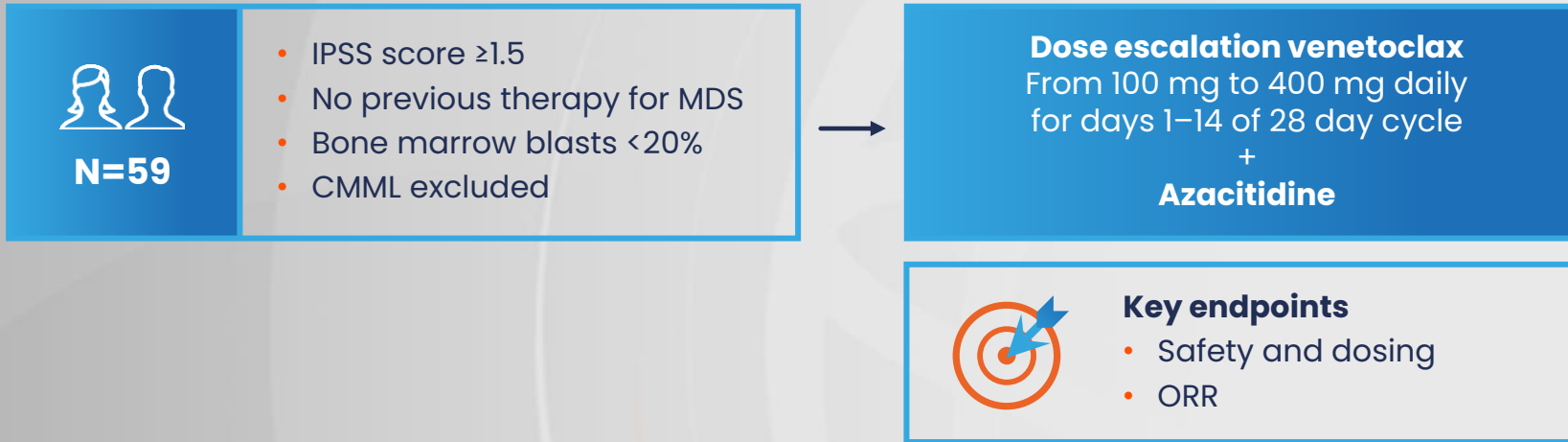
**Efficacy data for emerging treatments
for patients with HR-MDS**

Mechanism of action of current and emerging treatment options



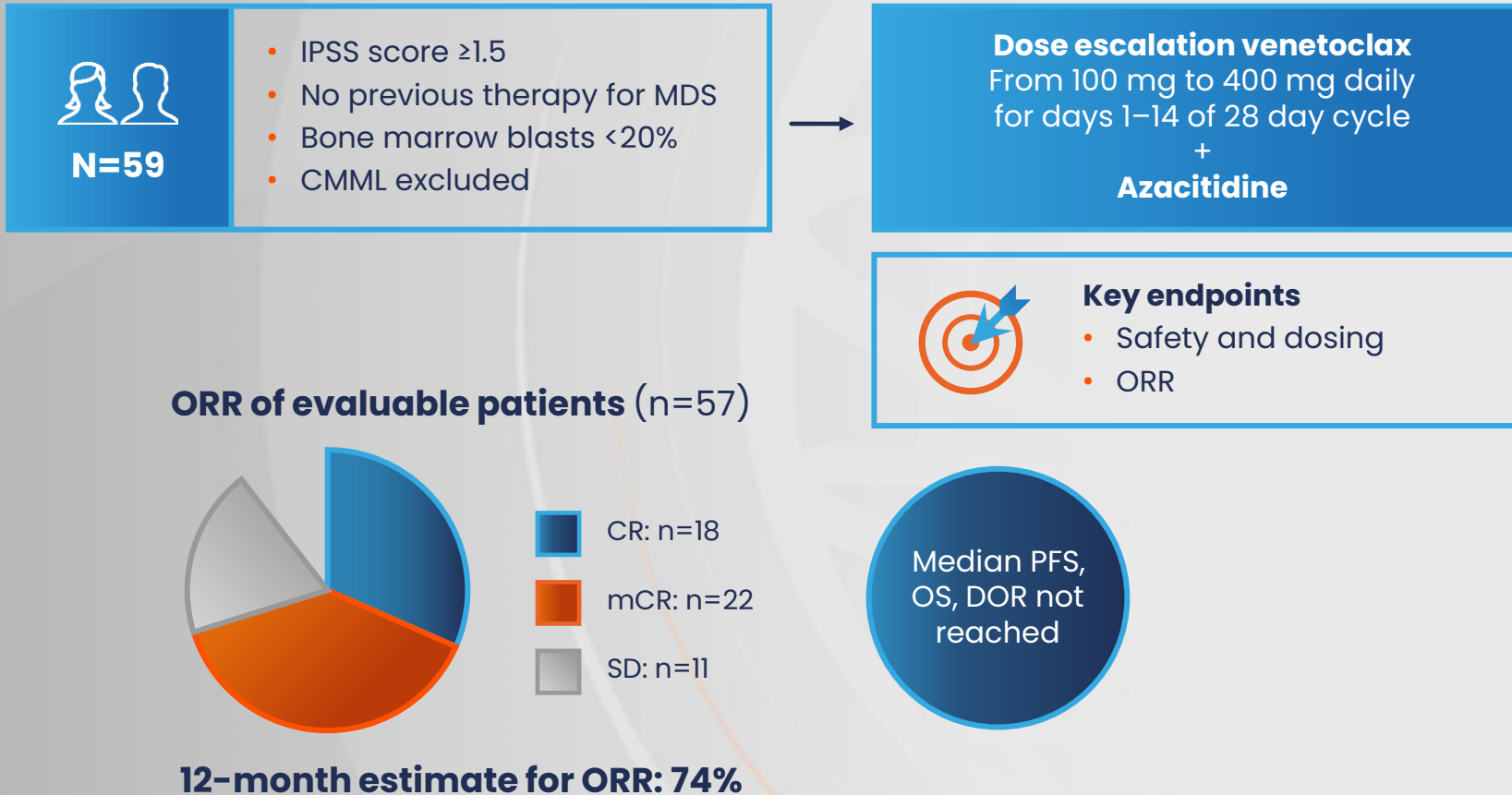
Venetoclax + HMA

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



Venetoclax + HMA

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



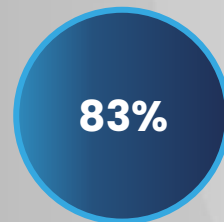
Venetoclax + HMA

Venetoclax + azacitidine in treatment-naïve HR-MDS: Phase Ib study (NCT02942290): Update¹

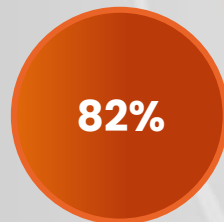


A later update investigated clinical response by mutational status:¹

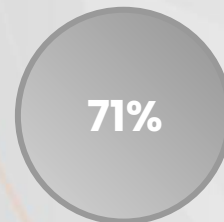
Clinical response (CR + mCR) was consistent across mutational spectrum



mTP53
patients



mASXL1
patients



RUNX1
patients

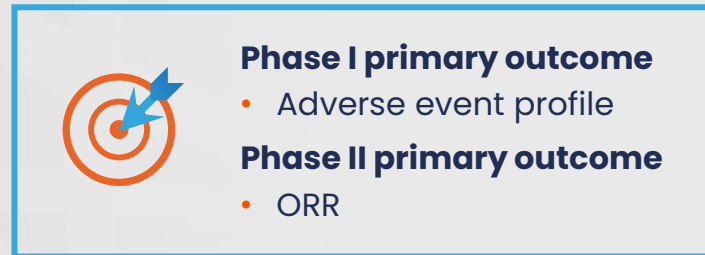
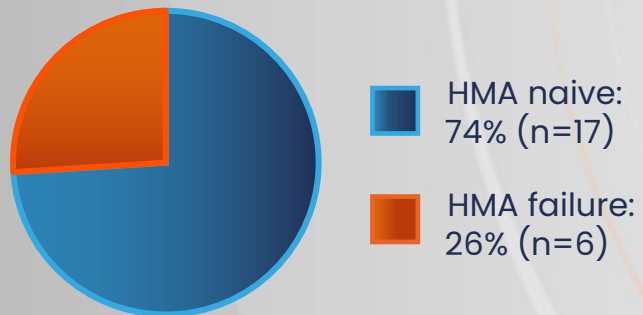
Patients who achieved
CR had greater
reduction in variant
allele frequencies¹

Venetoclax + HMA

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



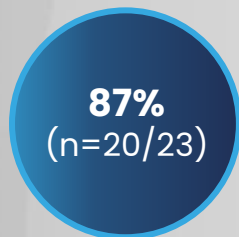
Patient demographic (N=23)



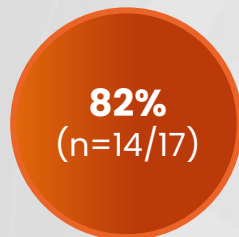
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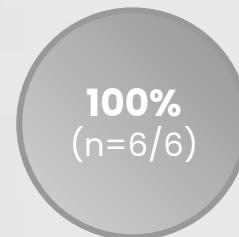
ORR by prior treatment



Total population
(95% CI 66–97)



HMA naive
(95% CI 57–86)



Post-HMA failure
(95% CI 54–100)

Median OS



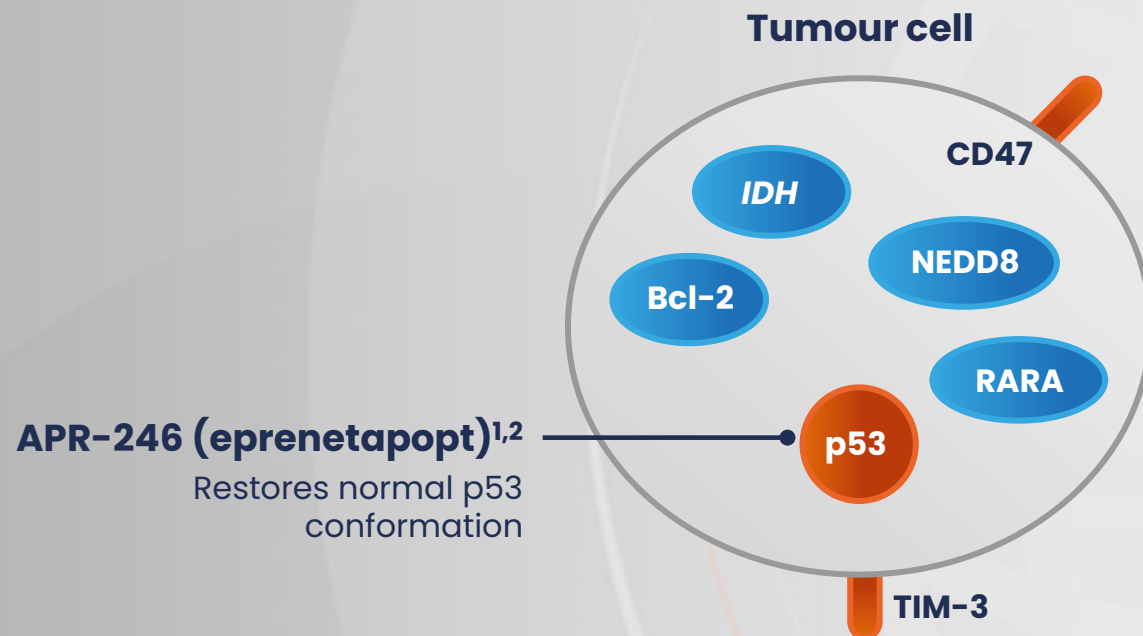
Total population
(95% CI 8.3–14.5)

Median PFS



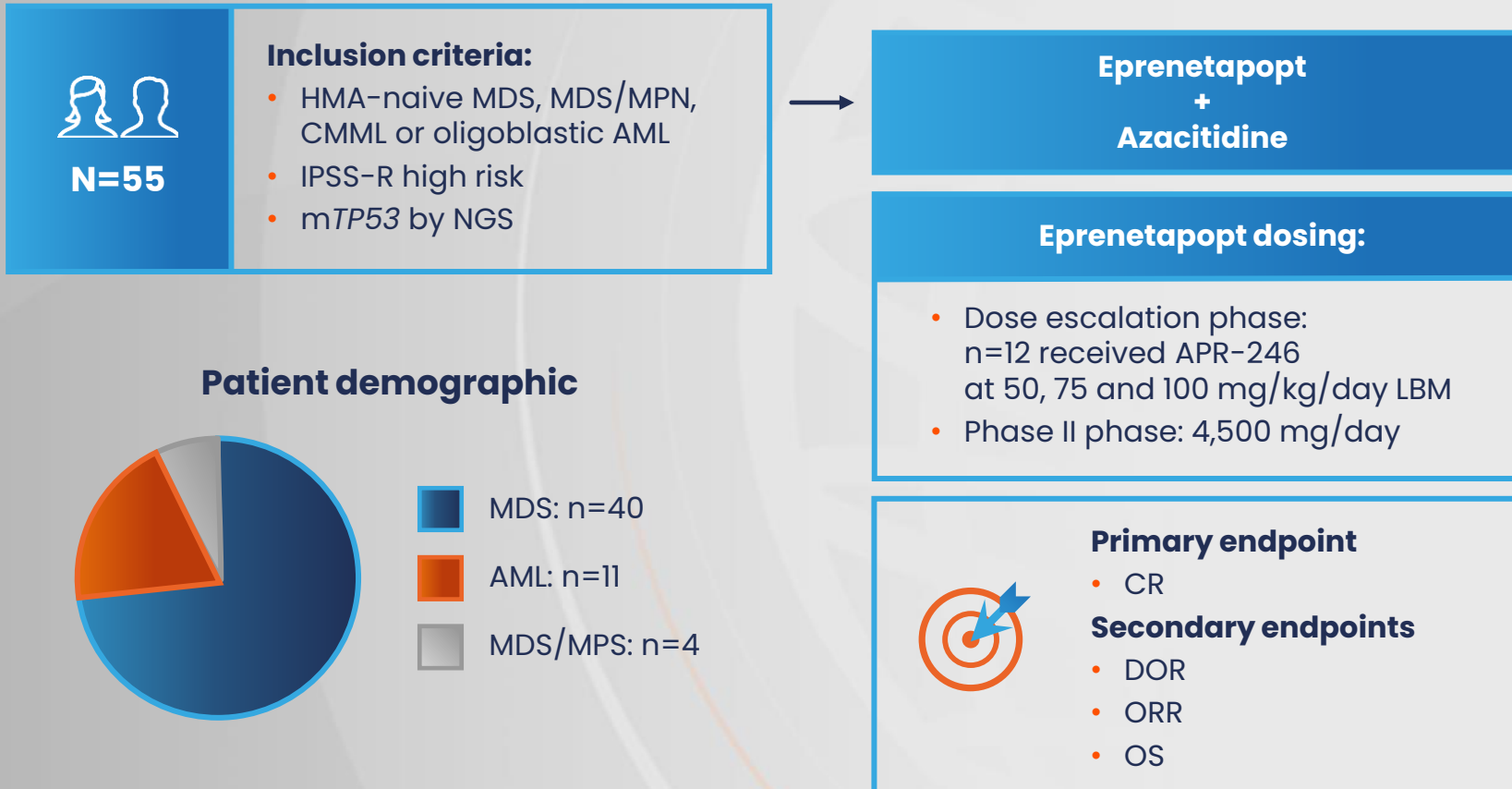
Total population
(95% CI 5.1–13.1)

Mechanism of action of current and emerging treatment options



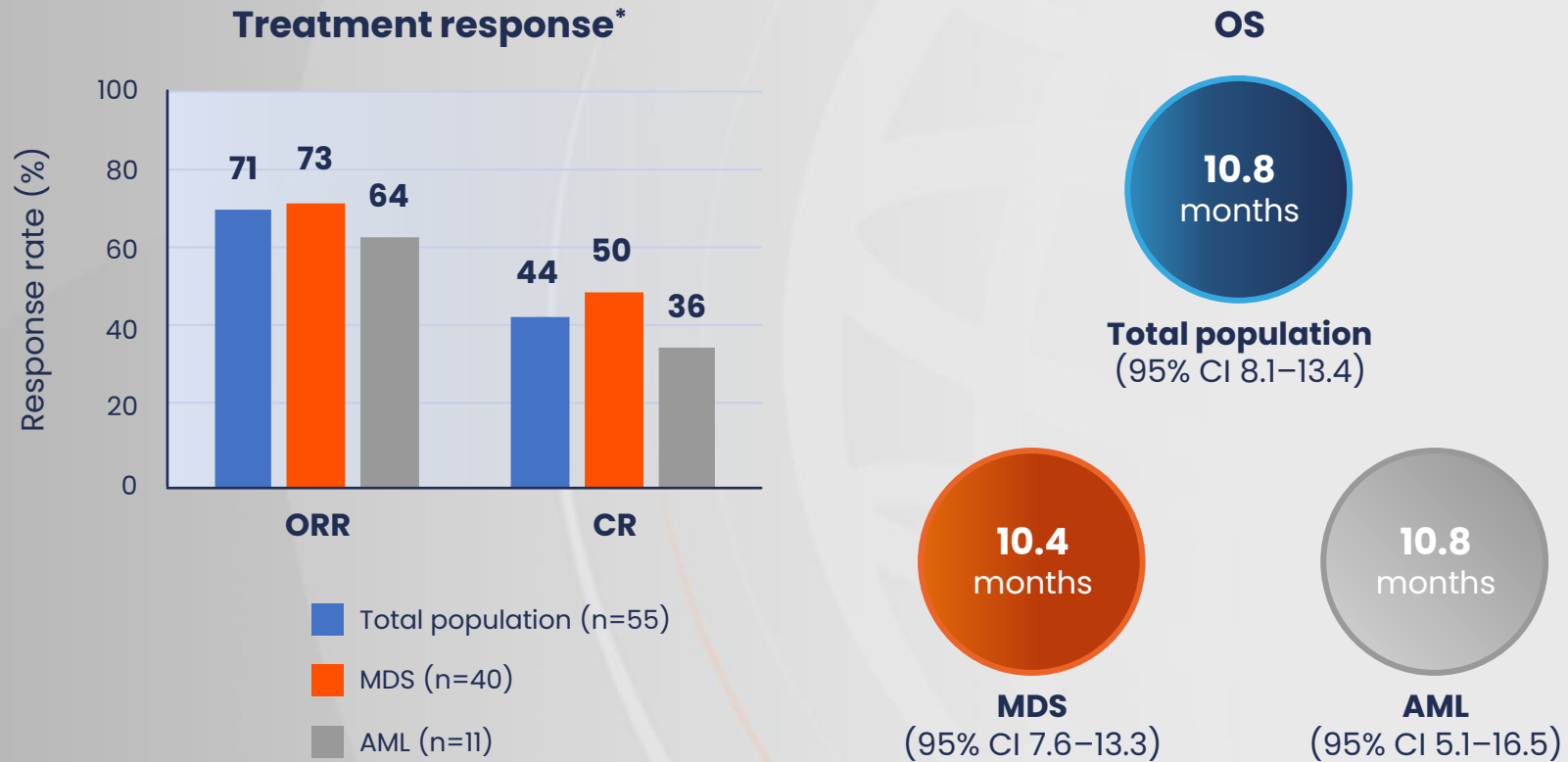
Eprenetapopt (APR-246) + azacitidine

Eprenetapopt + azacitidine in mTP53 MDS: Phase Ib/II dose-escalation study (NCT03072043)



Eprenetapopt (APR-246) + azacitidine

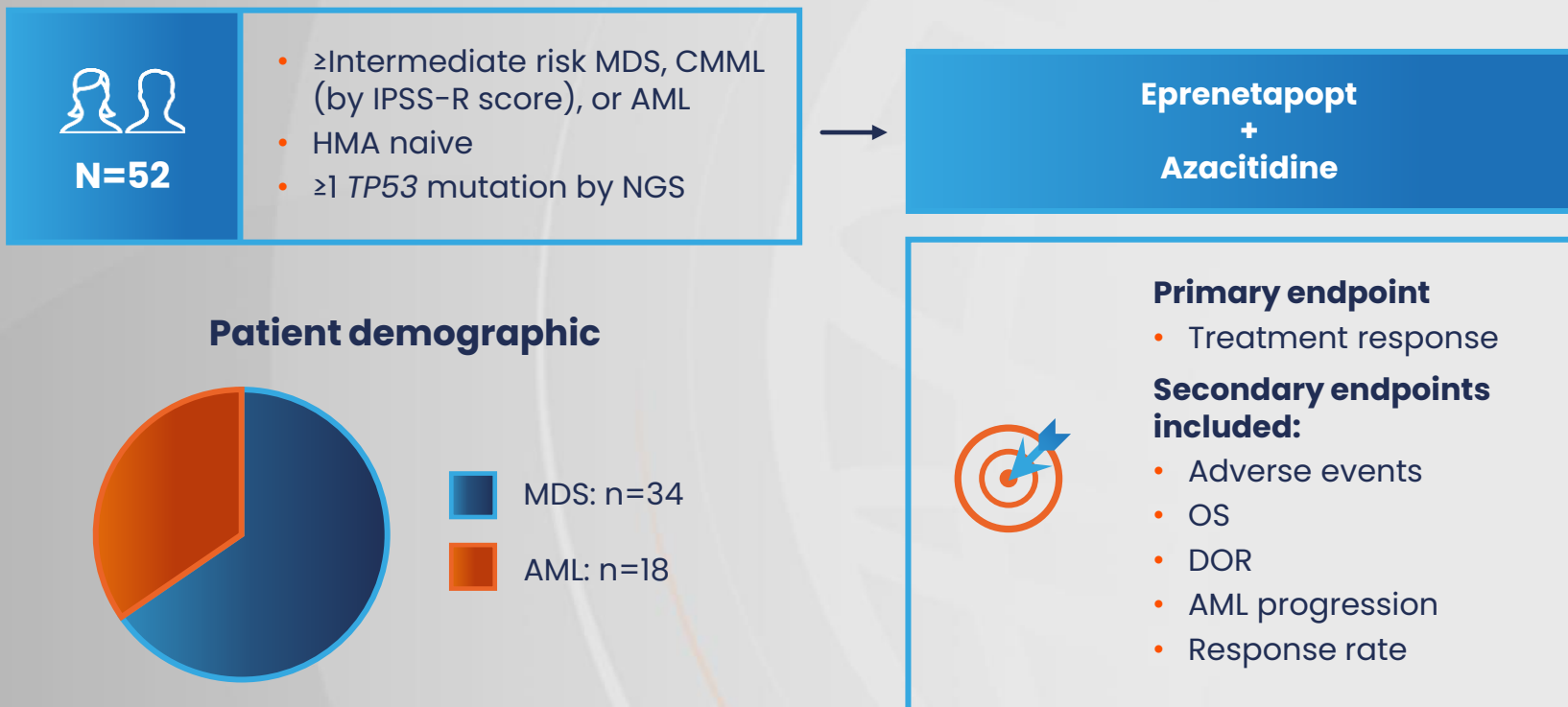
Eprenetapopt + azacitidine in mTP53 MDS: Phase Ib/II dose-escalation study (NCT03072043)



*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; mTP53, TP53 mutation; ORR, overall response rate; OS, overall survival.
Sallman D, et al. *J Clin Oncol*. 2021;39:1584–94.

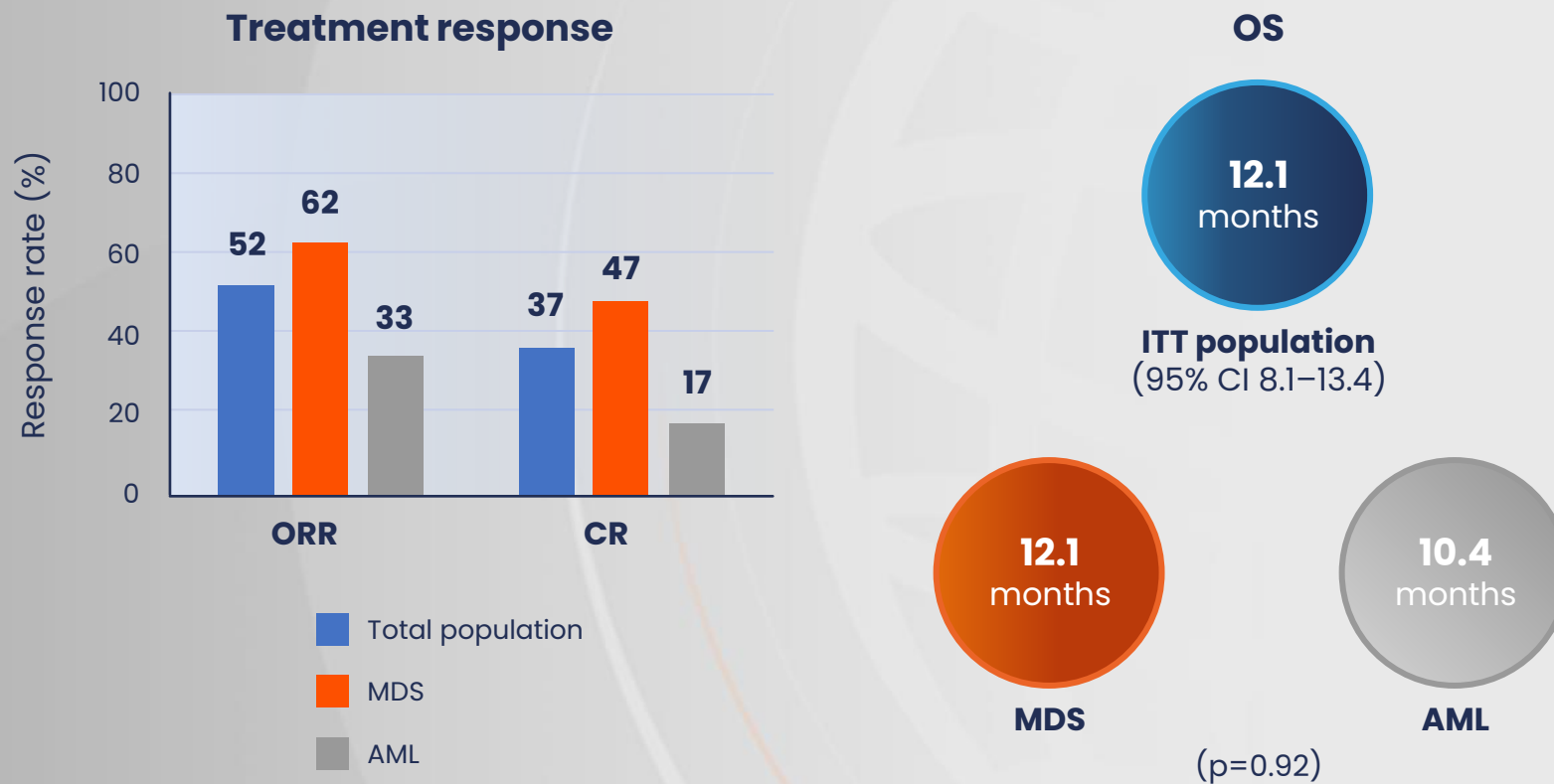
Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in mTP53 MDS: Phase II, single-arm study (NCT03588078)



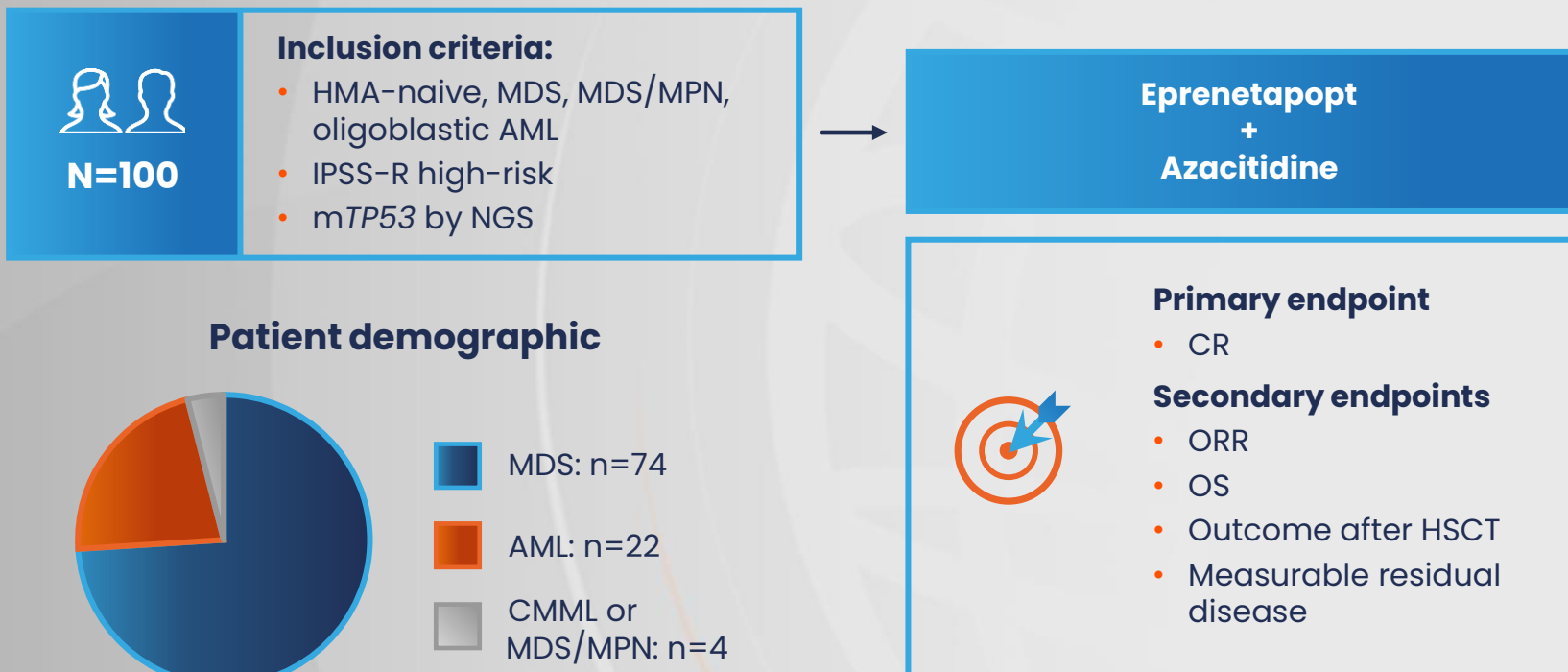
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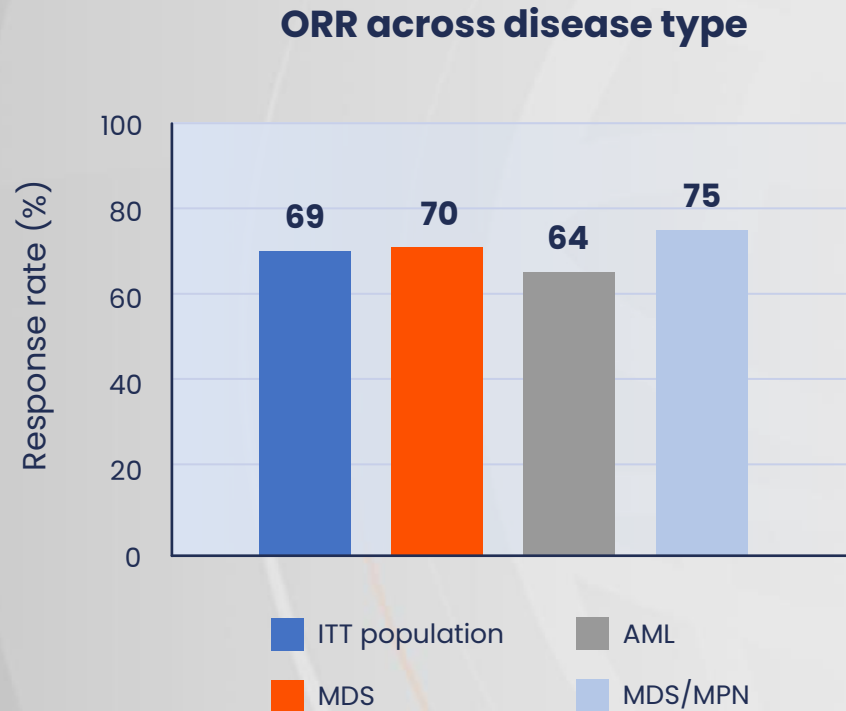
Eprenetapopt + azacitidine

Eprenetapopt + azacitidine in mTP53 MDS: Long-term follow-up, combined phase II results (NCT03072043/NCT03588078)



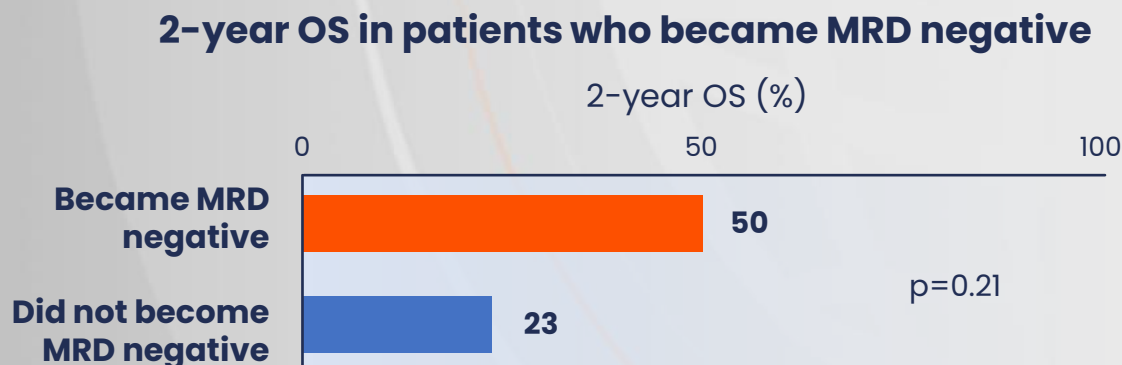
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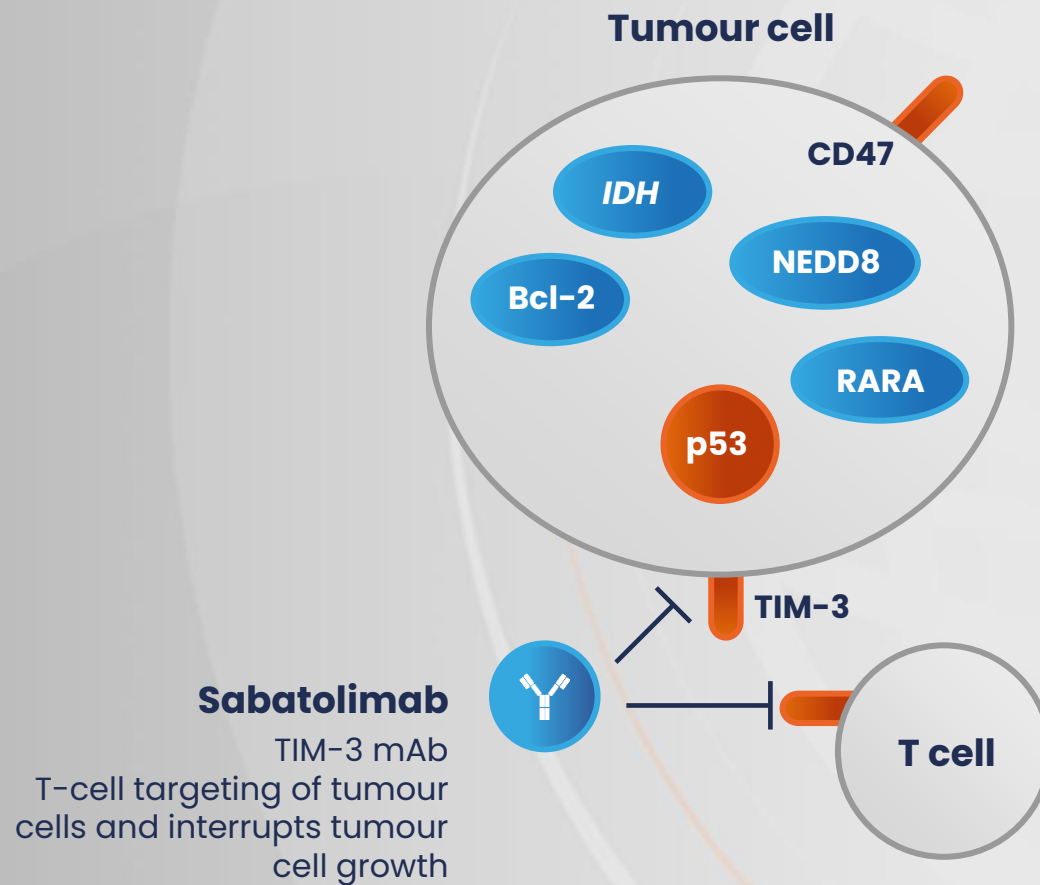


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Mechanism of action of current and emerging treatment options



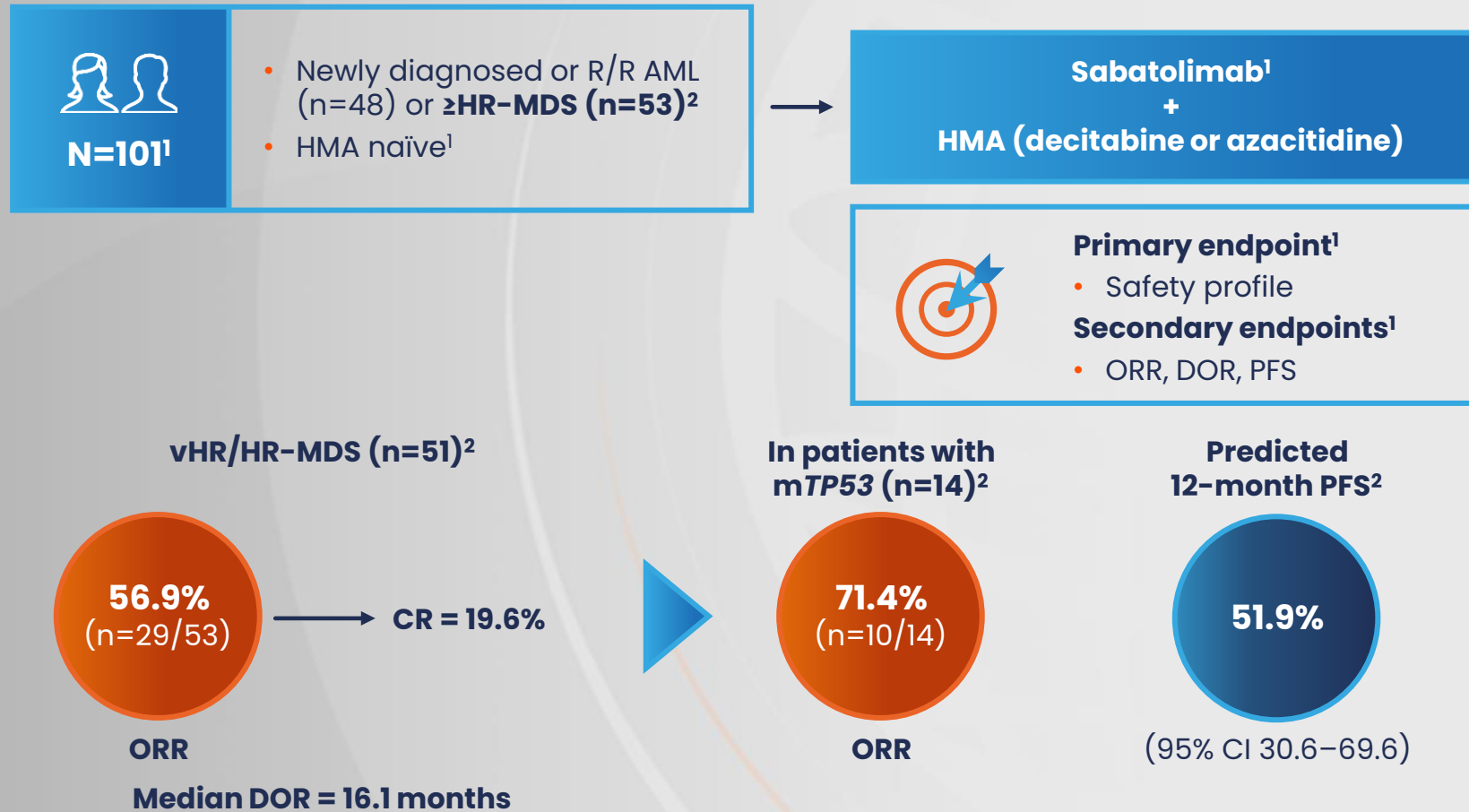
Sabatolimab + HMA

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



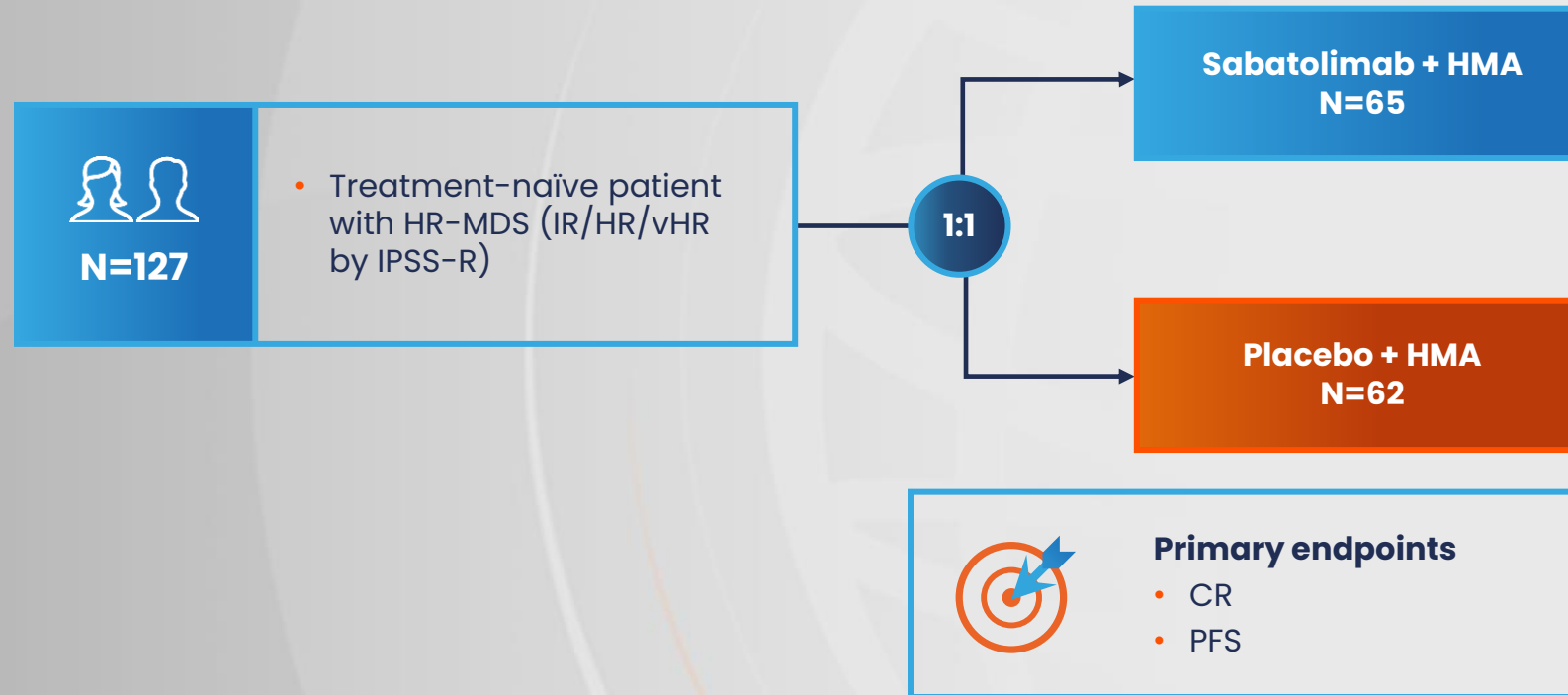
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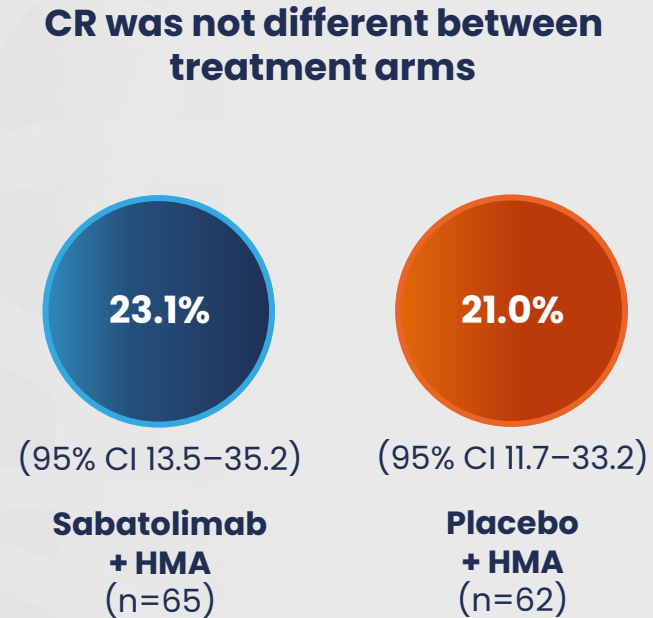
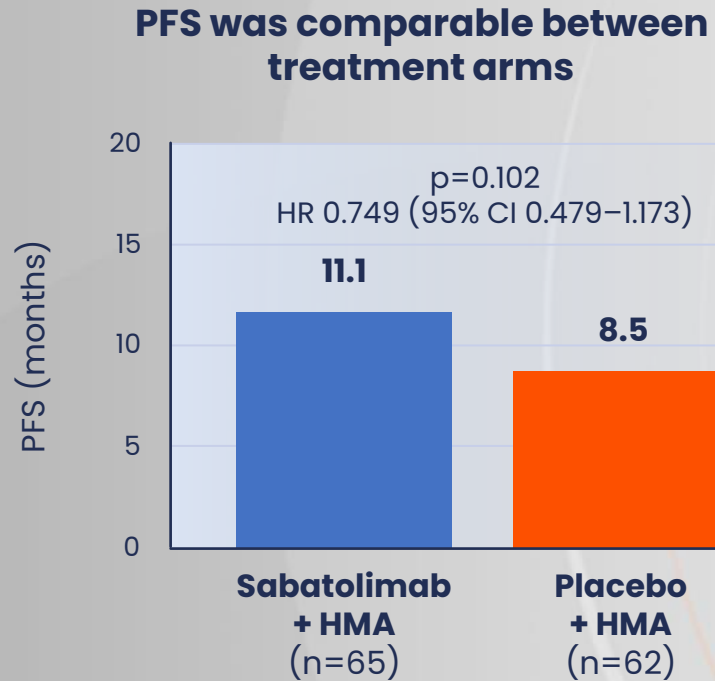
Sabatolimab + HMA

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



Sabatolimab + HMA

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



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

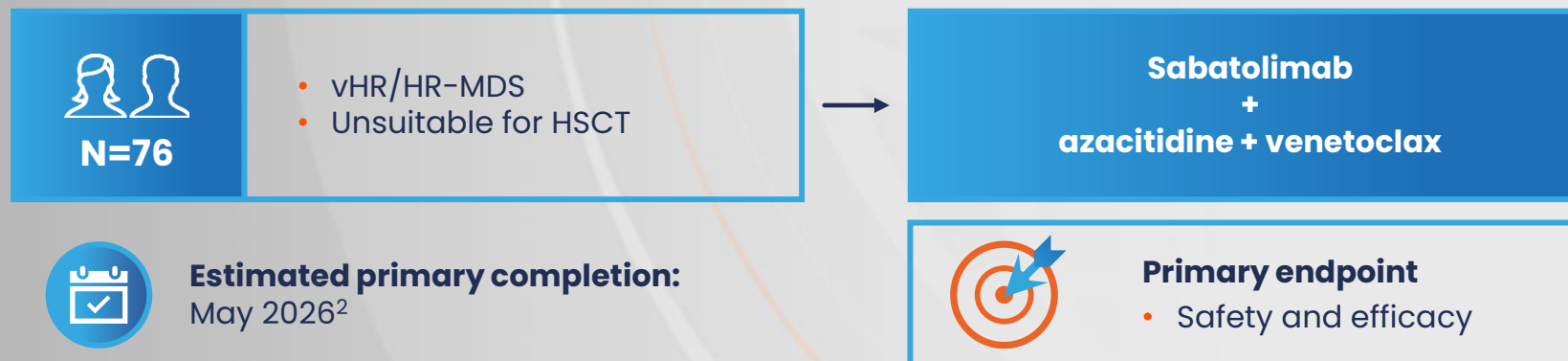
	Sabatolimab + HMA (n=32)	Placebo + HMA (n=29)
CR	28.1% (95% CI 12.5–43.7)	17.2% (95% CI 3.5–31.0)
Median PFS	11.3 months (95% CI 6.0–19.0)	8.3 months (95% CI 4.4–9.2)

Sabatolimab ongoing trials

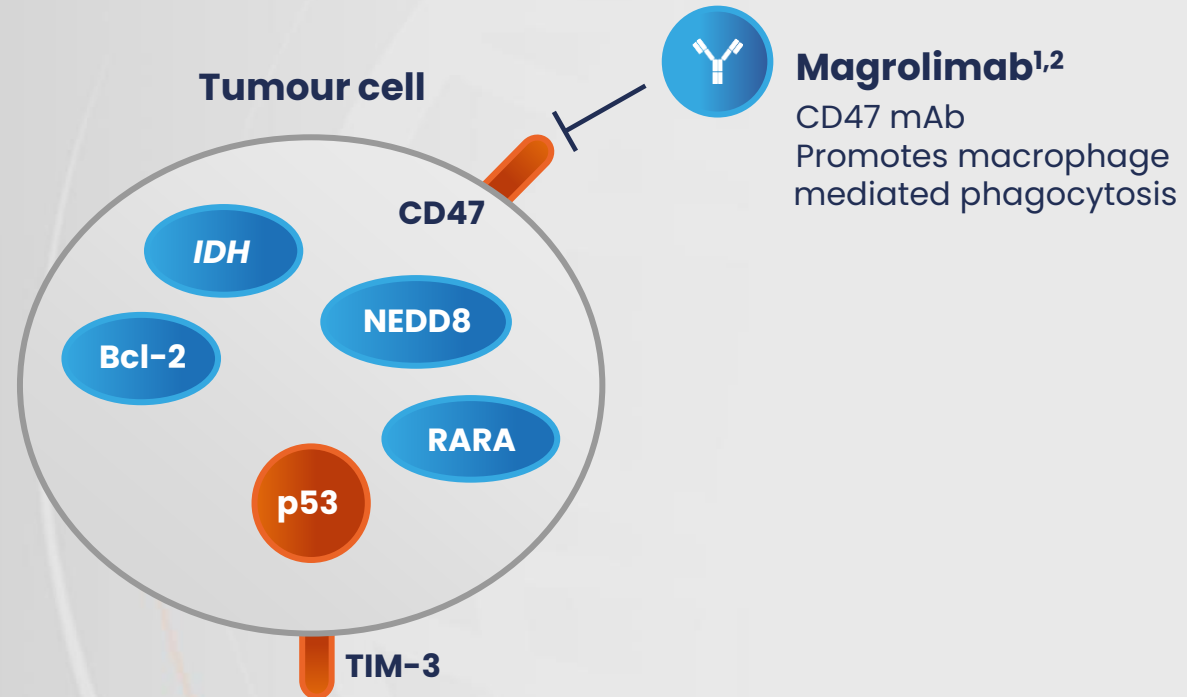
STIMULUS-MDS-US (NCT04878432): Single-arm, open-label, phase II trial¹



STIMULUS-MDS3 (NCT04812548): Single-arm, open-label, phase II trial¹

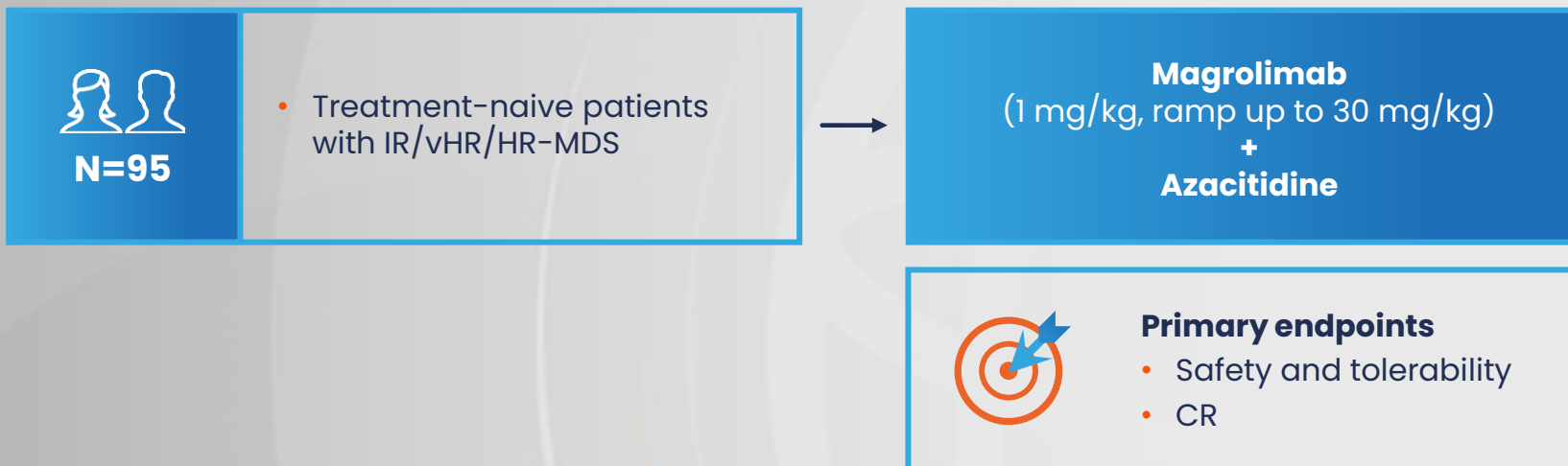


Mechanism of action of magrolimab



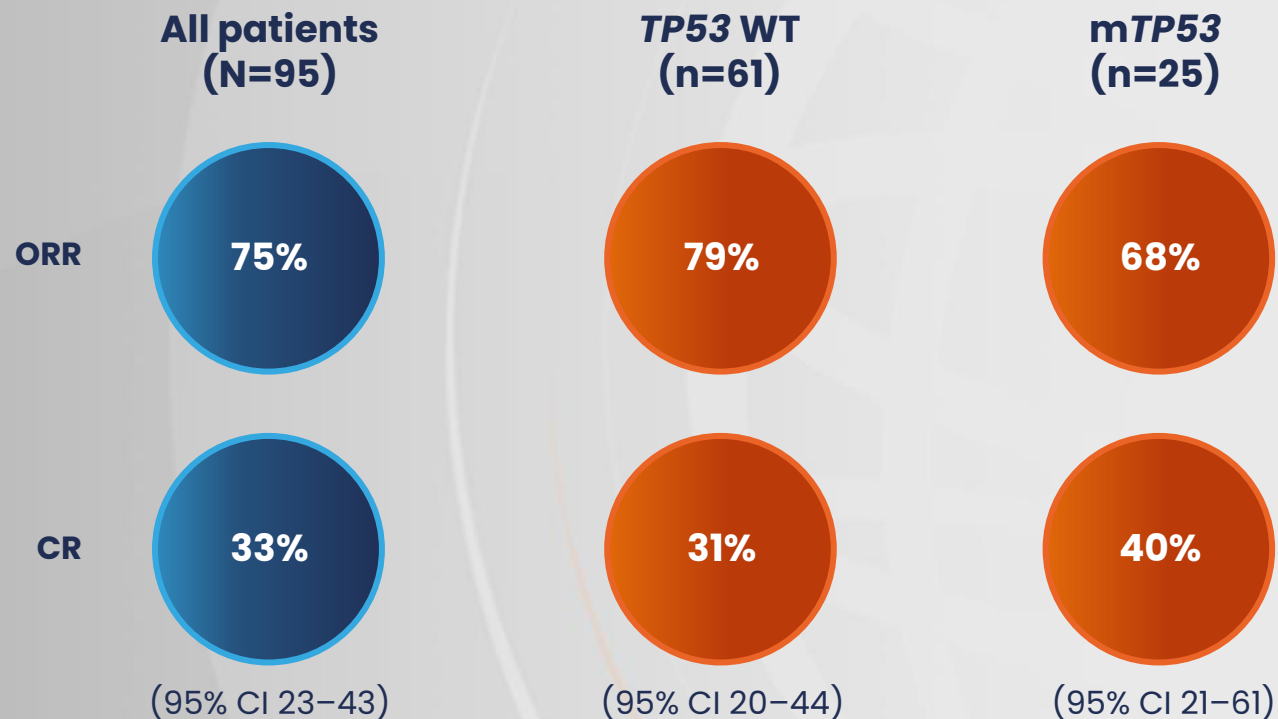
Magrolimab + azacitidine

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



Magrolimab + azacitidine

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



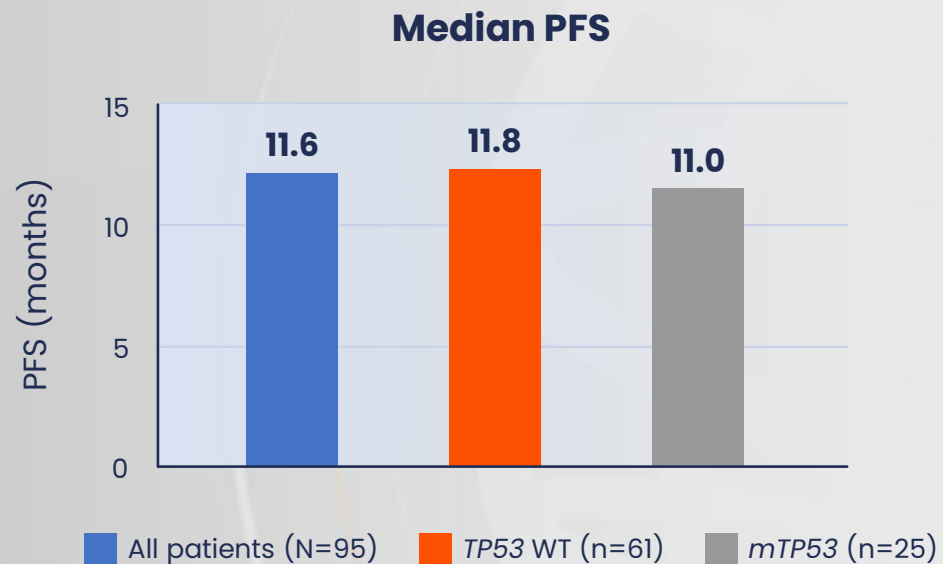
*TP53 status unavailable for 9/95 patients.

CI, confidence interval; CR, complete response; HR-MDS, high-risk myelodysplastic neoplasm; mTP53, TP53 mutation; ORR, overall response rate; TP53 WT, TP53 wild type.

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)



Median OS

All patients	TP53 WT	mTP53
NR (95% CI 16.3–NR)	NR (95% CI 21.3–NR)	16.3 (95% CI 10.8–NR)

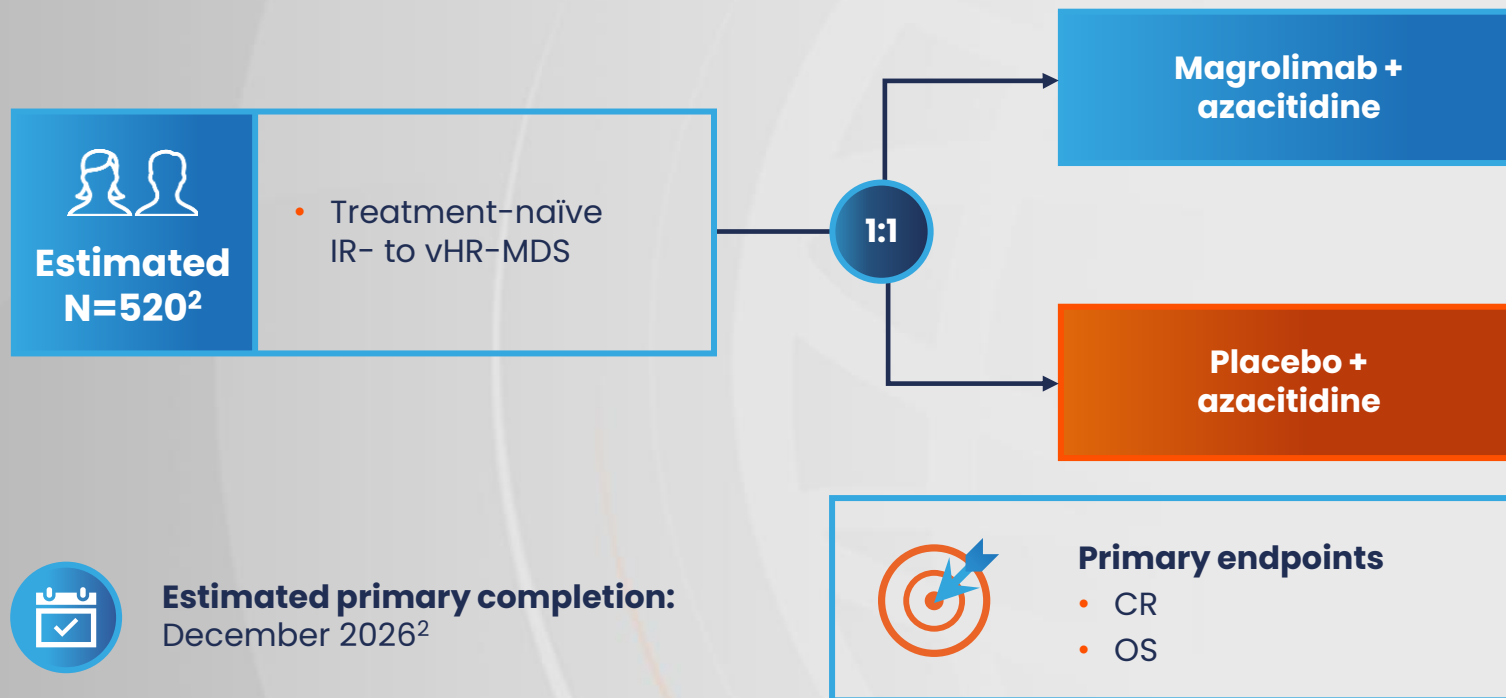
*TP53 status unavailable for 9/95 patients.

CI, confidence interval; mTP53, TP53 mutation; HR-MDS, high-risk myelodysplastic neoplasm; NR, not reached; OS, overall survival; PFS, progression-free survival; TP53 WT, TP53 wild type.

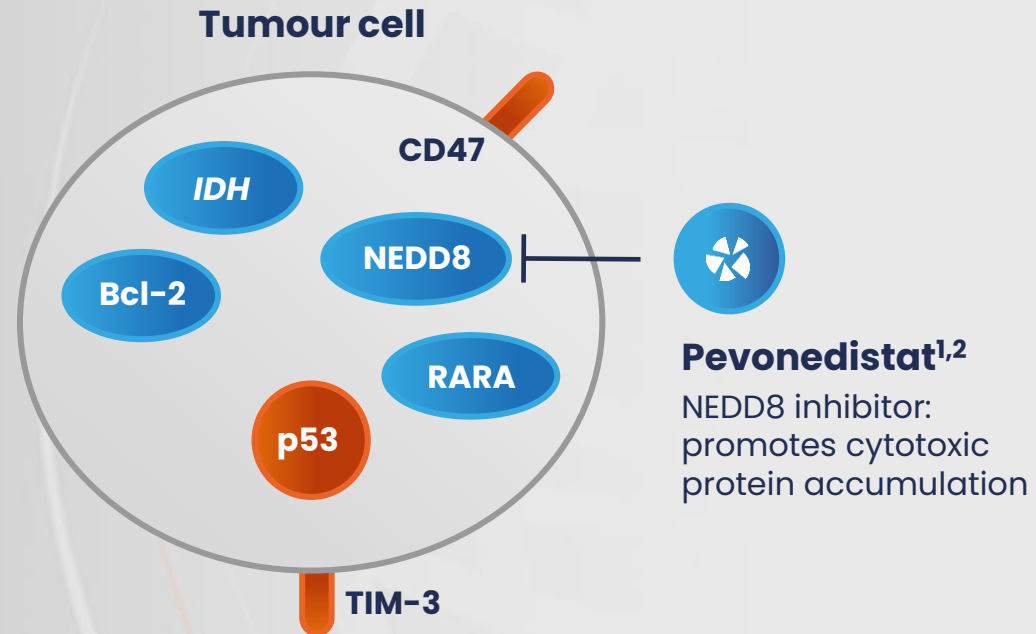
Sallman D, et al. *J Clin Oncol*. 2022;40(Suppl. 16):7017.

Magrolimab + azacitidine

ENHANCE (NCT04313881): Placebo controlled, phase III trial¹

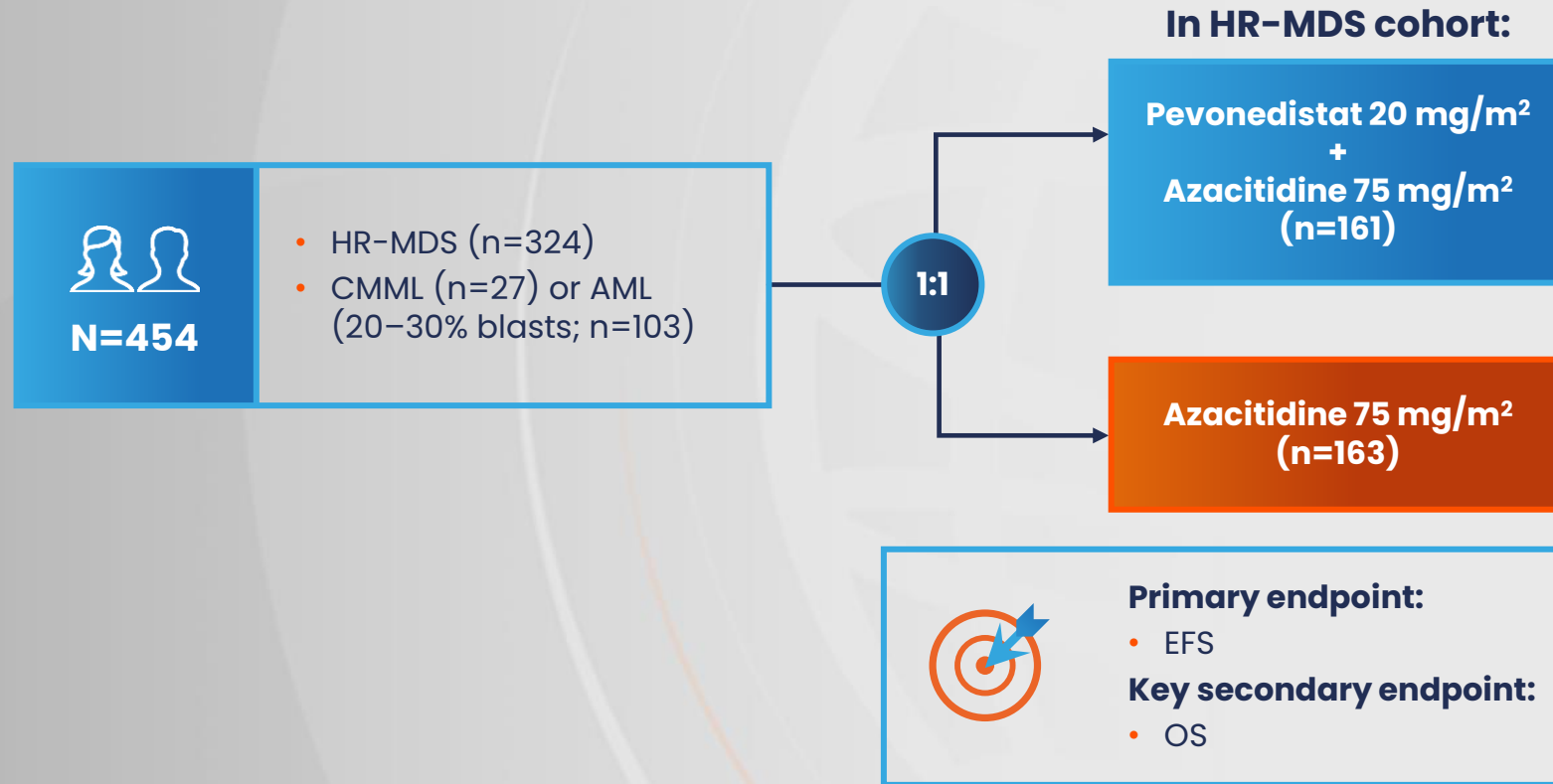


Mechanism of action of pevonedistat



Pevonedistat in HR-MDS

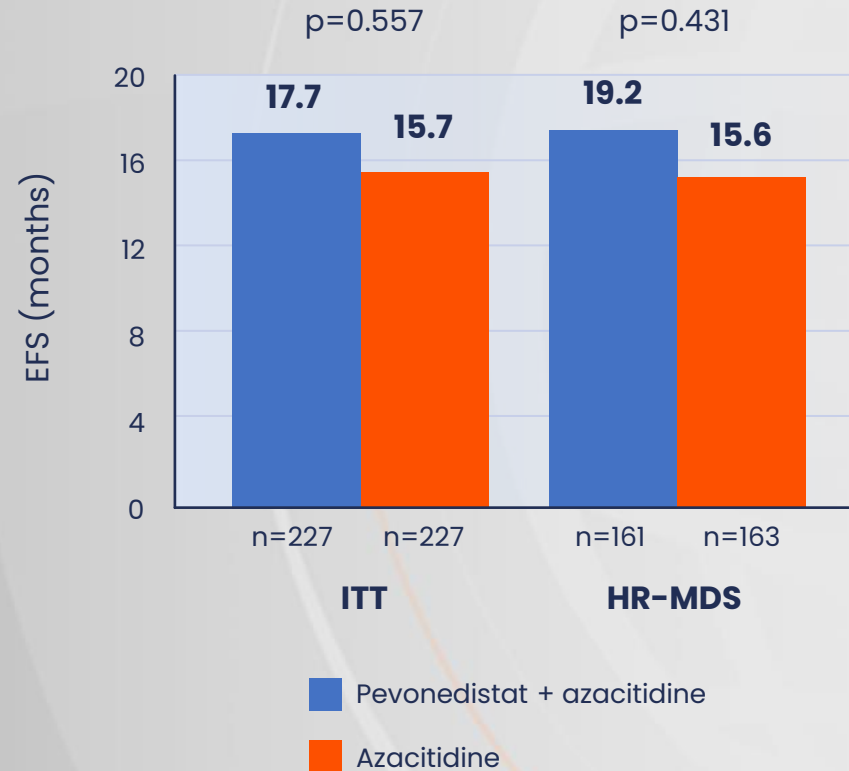
PANTHER (NCT03268954): Global, randomized, phase III trial



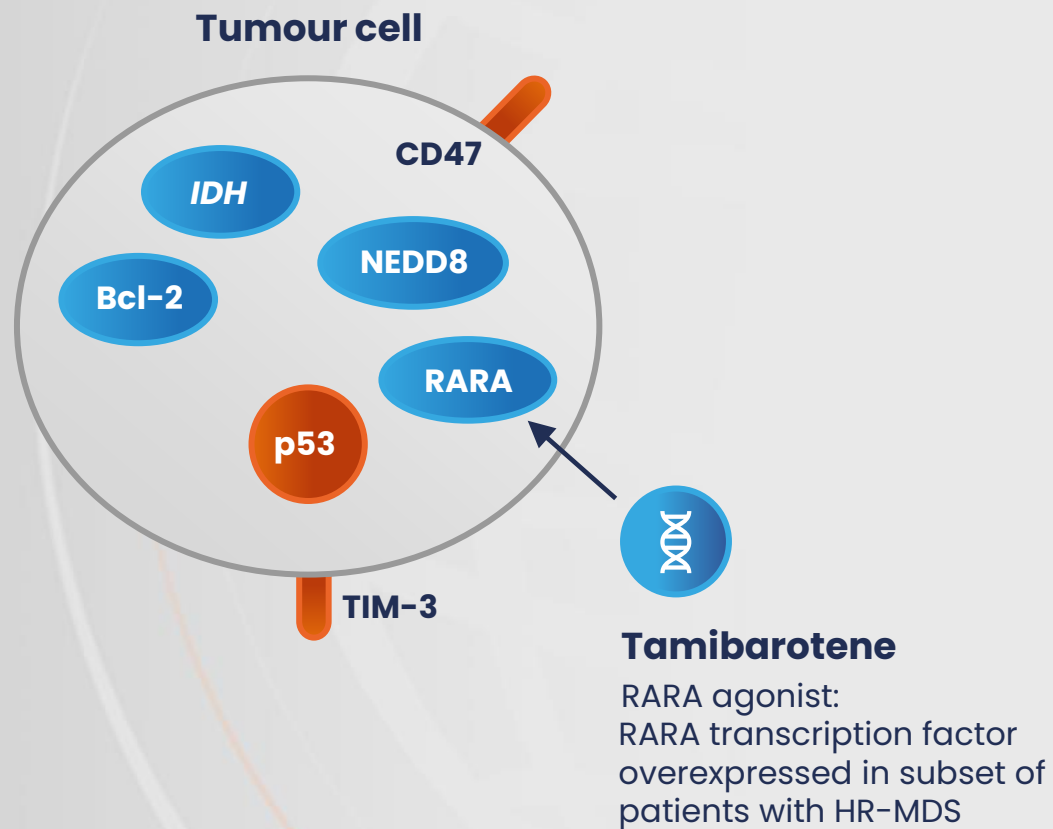
Pevonedistat in HR-MDS

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

EFS was comparable between treatment arms



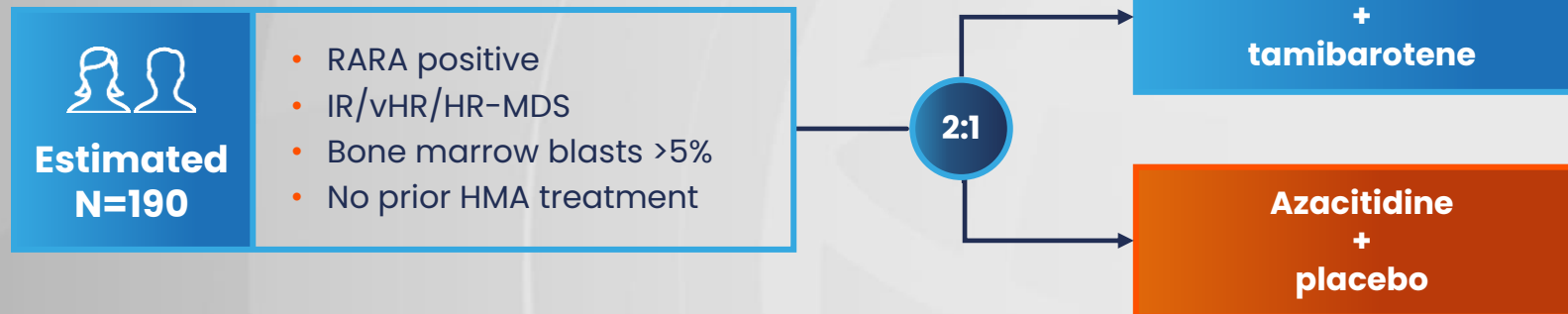
Mechanism of action of current and emerging treatment options



Tamibarotene + azacitidine

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

Ongoing: double-blind, placebo-controlled trial¹



Estimated primary completion:
December 2023²



Primary endpoint:

- CR

Key secondary endpoints:

- ORR
- EFS
- OS
- Transfusion independence
- DOR
- Safety

IDH1/2 inhibitors in HR-MDS

Ivosidenib and enasidenib have shown promising response rates in phase I/II trials^{1,2}

	Trial details	Results
Ivosidenib¹ (Phase I) (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 mIDH2 HR-MDS received enasidenib + azacitidine (n=27) HMA-refractory mIDH2 HR-MDS received enasidenib alone (n=23)	Enasidenib + azacitidine: ORR: 74%; OS: 26 months Enasidenib alone ORR: 35%; OS: 20 months
Olutasidenib³ (phase I/II) (NCT02719574)	Open-label trial Patients with mIDH1 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; mIDH1/2, 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.

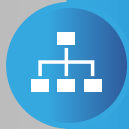
Immunotherapy in HR-MDS

	Trial details	Results
Pembrolizumab¹ (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
Durvalumab² (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)

Summary



Several treatment options are in development that show promising response rates in HR-MDS¹⁻³



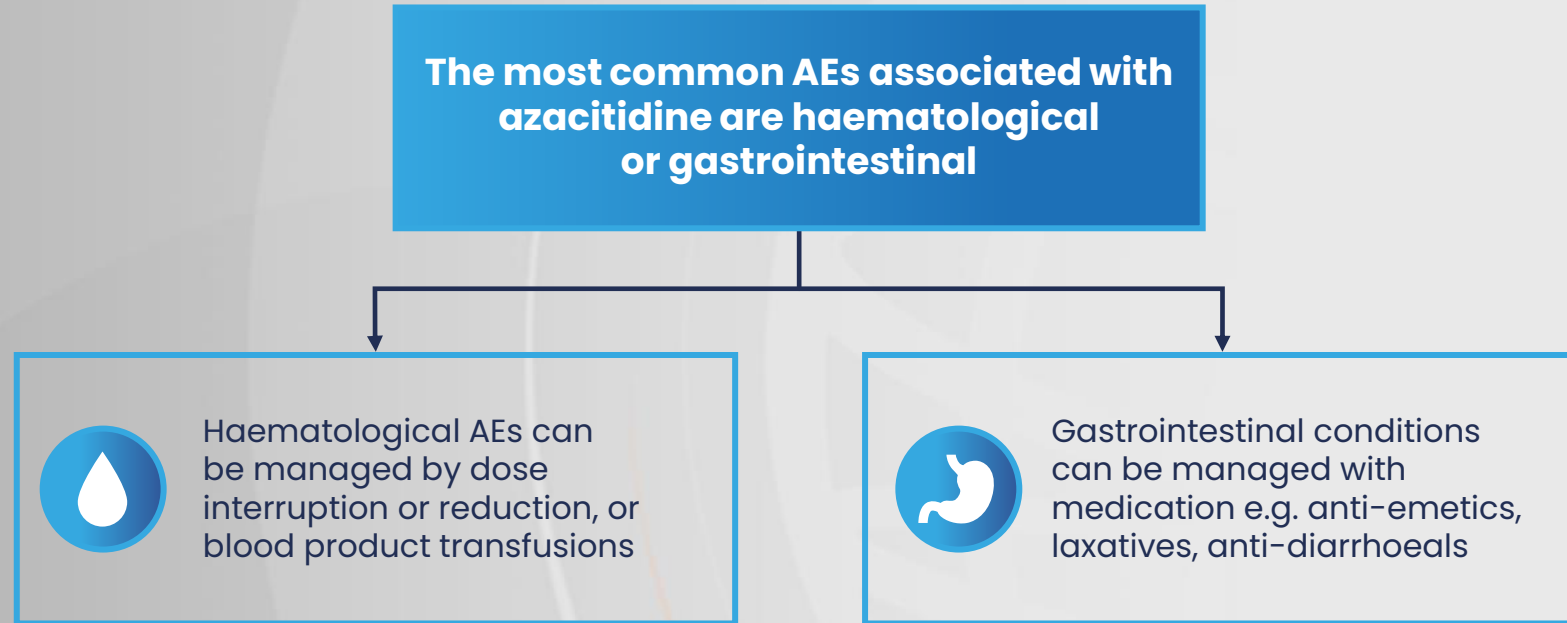
Novel drugs have been investigated in combination with HMAs, such as azacitidine¹⁻⁴







There is still a need for further data from placebo-controlled trials to confirm the efficacy of emerging treatment options

Safety data for emerging treatments for patients with HR-MDS






HMA treatment is associated with haematological AEs



Adverse events in venetoclax + azacitidine combination arms

	Reported AEs	
Venetoclax + azacitidine Phase Ib study ¹ (NCT02942290)	 Common GI symptoms: <ul style="list-style-type: none"> • Constipation, nausea, diarrhoea, vomiting 	 Most common grade 3/4 AEs: <ul style="list-style-type: none"> • Neutropenia (61%) • Thrombocytopenia (39%) • Leukopenia (31%) • Anaemia (20%)
Venetoclax + azacitidine Phase I results ² (NCT04160052)	 Most common grade 3/4 TEAEs <ul style="list-style-type: none"> • Neutropenia (39%) • Thrombocytopenia (39%) • Lung infection (30%) • Febrile neutropenia (17%) 	
	 <ul style="list-style-type: none"> • Myelosuppression was frequently reported with venetoclax + azacitidine² • This was usually managed with delay in cycle administration rather than dose reduction² 	

Adverse events in eprenetapopt + azacitidine combination arms

Reported AEs		
<p>Eprenetapopt + azacitidine¹ Phase Ib/II study (NCT03072043)</p>	<p> Most common any grade TEAEs</p> <ul style="list-style-type: none"> Nausea (64%) Vomiting (45%) Fatigue (44%) Constipation (42%) Edema (38%) <p> Most common any grade neurological AEs</p> <ul style="list-style-type: none"> Dizziness (36%) Peripheral sensory neuropathy (31%) Ataxia (24%) Tremor (20%) 	<p> Most common grade ≥ 3 AEs</p> <ul style="list-style-type: none"> Febrile neutropenia (33%) Leukopenia (29%) Neutropenia (29%) Thrombocytopenia (25%) Lung infection (25%)
<p>Eprenetapopt + azacitidine² Phase II study (NCT03588078)</p>	<p> Most common AEs ($\geq 20\%$)</p> <ul style="list-style-type: none"> Neurological (40%) including ataxia (25%) Febrile neutropenia (37%) <p></p>	<p>Most common grade 3/4 AEs</p> <ul style="list-style-type: none"> Febrile neutropenia (37%) Neurological (6%) including ataxia (4%)



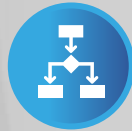
- Neurological AEs were transient and reversible after dose reduction of eprenetapopt and could be managed using supportive measures^{1,2}

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




Adverse events of sabatolimab + HMA combination arms

	Most common AEs	
Sabatolimab + HMA¹ Phase Ib study (NCT03066648)	 Most common grade ≥3 AEs <ul style="list-style-type: none"> • Neutropenia (47.2%) • Thrombocytopenia (43.4%) • Febrile neutropenia (35.8%) • Anaemia (28.3%) 	
Sabatolimab + HMA² STIMULUS-MDS1: Phase II trial (NCT03946670)	 Most common non-haematological AEs (all grade) <ul style="list-style-type: none"> • Constipation (46.8%) • Diarrhoea (43.5%) 	 Most common grade ≥3 AEs <ul style="list-style-type: none"> • 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

Adverse events of magrolimab + azacitidine combination

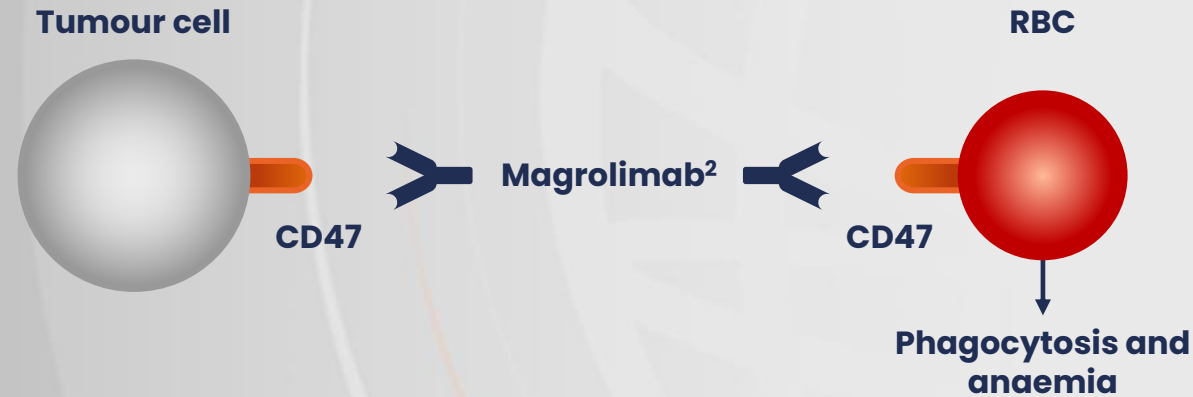
Most common TEAEs		
Magrolimab + azacitidine Phase Ib study (NCT03248479)	  Most common TEAEs <ul style="list-style-type: none">• Constipation (68%)• Thrombocytopenia (55%)• Anaemia (52%)• Neutropenia (47%)• Nausea (46%)• Diarrhoea (44%)	 Most common grade 3/4 AEs <ul style="list-style-type: none">• Anaemia (47%)• Neutropenia (46%)• Thrombocytopenia (46%)• Decreased WBC count (30%)

Magrolimab may also target RBCs, leading to anaemia








Clinical data has reported tolerable anaemia in patients receiving magrolimab for HR-MDS¹

Magrolimab targets CD47, which is a component of RBCs²








Patients receiving magrolimab should be closely monitored to anticipate the requirement for transfusion²

Adverse events reported with other compounds

	Most common AEs	
<p>Pevonedistat + azacitidine PANTHER: Phase III trial¹ (NCT03268954)</p>	<p> Most common any-grade TEAEs</p> <ul style="list-style-type: none"> • Constipation (37%) • Anaemia (37%) • Neutropenia (33%) • Thrombocytopenia (33%) • Nausea (35%) 	<p> Most common grade ≥3 TEAEs</p> <ul style="list-style-type: none"> • Anaemia (33%) • Neutropenia (31%) • Thrombocytopenia (30%) • Febrile neutropenia (23%) • Pneumonia (15%)
<p>Enasidenib (Phase II)² (NCT03383575)</p>	<p> Most common AEs (all patients)</p> <ul style="list-style-type: none"> • Neutropenia (40%) • Nausea (36%) • Constipation (32%) • Fatigue (26%) • Thrombocytopenia (22%) <p></p>	<p> Most common grade 3/4 AEs</p> <ul style="list-style-type: none"> • Neutropenia (19%) • Thrombocytopenia (11%) • Differentiation syndrome (5%) • Hyperbilirubinaemia (4%) • Leukopenia (4%)

Adverse events reported with other compounds

	Most common AEs	
<p>Pevonedistat + azacitidine PANTHER: Phase III trial¹ (NCT03268954)</p>	 <p>Most common any-grade TEAEs</p> <ul style="list-style-type: none"> • Constipation (37%) • Anaemia (37%) • Neutropenia (33%) • Thrombocytopenia (33%) • Nausea (35%) 	 <p>Most common grade ≥3 TEAEs</p> <ul style="list-style-type: none"> • Anaemia (33%) • Neutropenia (31%) • Thrombocytopenia (30%) • Febrile neutropenia (23%) • Pneumonia (15%)
<p>Enasidenib (Phase II)² (NCT03383575)</p>	 <p>Most common AEs (all patients)</p> <ul style="list-style-type: none"> • Neutropenia (40%) • Nausea (36%)  <ul style="list-style-type: none"> • Constipation (32%) • Fatigue (26%) • Thrombocytopenia (22%) 	 <p>Most common grade 3/4 AEs</p> <ul style="list-style-type: none"> • Neutropenia (19%) • Thrombocytopenia (11%) • Differentiation syndrome (5%) • Hyperbilirubinaemia (4%) • Leukopenia (4%)

Summary



Haematological adverse events are frequent with HMA therapy, but can be managed with dose interruption or reduction¹



Haematological adverse events are some of the most commonly reported safety concerns for novel treatments²⁻⁴



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.