Frontline treatment options for higher-risk MDS: can we move past azacitidine?

David A. Sallman and Zhuoer Xie
Malignant Hematology Department, Moffitt Cancer Center, Tampa, FL

Although remarkable international efforts have been ongoing for over 17 years to improve upon azacitidine, representing the standard of care therapy for higher-risk myelodysplastic neoplasms (MDS), there still has not been a positive randomized trial in comparison to azacitidine. Real-world data from numerous trials have shown similar results with a median overall survival of 14–18 months, a 40%-50% overall response rate, and a complete remission rate close to 20%. Despite these outcomes, 6 randomized controlled trials have failed to improve outcomes in this patient population, although relevant issues in some of these studies included improper dose adjustments of the hypomethylating agent, lack of placebo-controlled studies, and lack of overall survival (OS) as a primary endpoint, among others. Critical updates in MDS management include the development of molecular prognostication models (eg, the molecular international prognostic scoring system), updates in classification systems highlighting significant overlap in patients with MDS-increased blasts and acute myeloid leukemia (most relevant to *TP53* mutations), and refinement of response criteria. Although these paradigm-shifting studies have had great impact in MDS management, the current ongoing randomized phase 3 trials were initiated prior, and prognostic stratification remains via the revised international prognostic scoring system) and with bone marrow blast counts of <20%. Notably, azacitidine + venetoclax, azacitidine + sabatolimab, and azacitidine + magrolimab have shown exciting results in large, single-arm studies and have completed accrual in placebo-controlled, double-blind studies with OS as a primary endpoint. We all eagerly await the results of these studies.

LEARNING OBJECTIVES

- To understand major updates in HR-MDS diagnosis, prognosis, and response evaluation
- To understand potential reasons for past failures to improve upon azacitidine monotherapy
- To review the cutting-edge landscape of novel therapies that ideally will change the standard of care for HR-MDS

CLINICAL CASE

A 59-year-old male presents with severe pancytopenia with absolute neutrophil count (ANC) of 0.4 k/μL, hemoglobin of 7.5 g/dL, and platelets of 35 k/μL. Bone marrow aspirate shows 7% myeloblasts with trilineage dysplasia. Cytogenetics showed complex karyotype with monosomy and deletion 17p. Next-generation sequencing (NGS) shows a *TP53* mutation (mt) with a variant allele frequency (VAF) of 56%. The patient has symptomatic anemia but has excellent performance status and no comorbidities. The patient presents to an academic medical center for discussion of potential treatment options and wishes to focus on curative intent.

Introduction

The treatment paradigm for patients with higher-risk myelodysplastic neoplasms (HR-MDS) has remained largely unchanged for nearly 2 decades, with hypomethylating agent (HMA) therapy and allogeneic hematopoetic stem cell transplantation (HSCT) representing the standard-of-care (SOC) therapies to improve overall survival (OS). Tremendous advancements have been made in the prognostic discrimination of patients with HR-MDS with the inclusion of molecular data, although key clinical questions remain in the clinical implementation of these prognostic systems. Similarly, revised diagnostic classifications have further blurred the lines between HR-MDS and acute myeloid leukemia (AML). Although in the long-term these initiatives will ideally increase therapeutic options for our patients, the dichotomies in these systems have brought forth clinical challenges. In addition, although monumental efforts have been undertaken to improve upon azacitidine, we still currently have not had a positive randomized trial in HR-MDS. We believe the horizon remains bright. This review focuses on the key updates in defining the HR-MDS population,

understanding response assessment, and comprehensive discussion on past failed trials with lessons learned to ideally lead to future new SOC therapies.

Updated classifications and risk stratification for MDS

A revised classification was published in 2022 as part of the 5th edition of the World Health Organization (WHO) classification.[1] In the same year, the International Consensus Classification (ICC) of Myeloid Neoplasms 2022 was published.[2] The similarity and differences between WHO 2022 and ICC 2022 are shown in Figure 1. The details on these 2 classification systems have been expertly reviewed elsewhere.[3] Herein, we briefly discuss how these new classifications and their differences might affect the SOC, clinical trial design/enrollment, efficacy evaluation, and response interpretation, as well as regulatory aspects of novel agent approval in patients with MDS. First, both WHO 2022 and ICC 2022 have incorporated the genetic aspects into MDS classification, including the mutations in *SF3B1*, biallelic *TP53* mutations, and deletion of 5q. Biallelic status, as defined by the WHO, includes *TP53* VAF ≥50%, 2 or more *TP53*mt, and/or *TP53*mt with deletion 17/17p abnormalities. Additionally, >90% of patients with biallelic *TP53*mt have complex karyotypes. Although comprehensive allelic status determination requires an assay to evaluate copy number status (eg, genomic hybridization or single nucleotide polymorphism arrays), a majority of patients can have determination with just standard cytogenetic and NGS evaluation. Separately, the WHO 2022 added 2 novel disease entities by morphology, including hypoplastic MDS and MDS with fibrosis, which are absent in the ICC 2022. These 2 unique entities have important clinical implications: hypoplastic MDS is associated with increased responsiveness to immunosuppressive therapy, and MDS with fibrosis is associated with a worse clinical prognosis.

On the other hand, ICC 2022 introduced a novel entity, MDS/AML, defined by 10%-19% blasts in the peripheral blood and/or bone marrow in the absence of AML-defining genetic abnormalities. The advantage of this new MDS/AML subtype is that it may facilitate the enrollment of patients with MDS 10%-19% blasts to either MDS or AML trials and thereby might speed up drug approval for patients with MDS. From a regula-

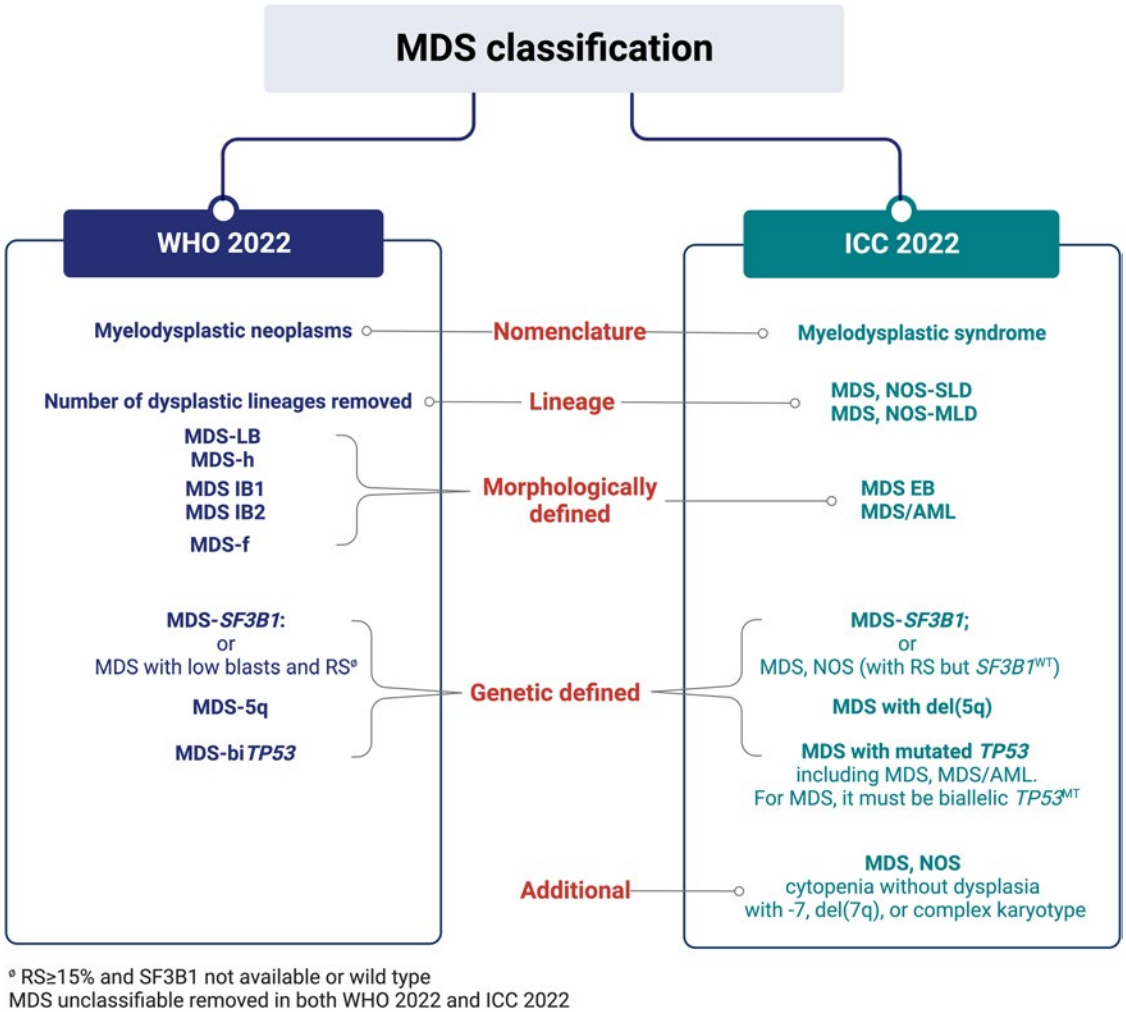

Figure 1. MDS classification comparison between WHO 2022 and ICC 2022. Bi, biallelic; f, fibrosis; h, hypocellular; IB, increased blasts; LB, low blasts; NOS-MLD, not otherwise specified with multi-lineage dysplasia; NOS-SLD, not otherwise specified with single-lineage dysplasia; NOS-MLD RS, ringed sideroblasts.

tory perspective, patients with MDS/AML defined by ICC 2022 may benefit from novel therapies approved in AML. However, we need to keep in mind that patients with MDS are relatively older than patients with AML and have decreased reserves for functional hematopoiesis, which may lead to an increased risk for cytopenia complications, including infection. As such, patients with MDS treated with AML-like therapy may therefore suffer from the risk of overtreatment and toxicities as was evidenced by the requirement of a reduced schedule of venetoclax in patients with MDS (see below). In addition, differences exist in the response criteria between the HR-MDS International Working Group (IWG) 2023 (see below) and AML European LeukemiaNet (ELN) 2022 guidelines. Whether the response to therapy should be assessed based on HR-MDS IWG 2023 or AML ELN 2022 needs further investigation.[4,5]

Recently, the molecular international prognostic scoring system (IPSS-M) was developed and incorporated molecular data, including the allelic state of *TP53*. The IPSS-M now has 6 categories from very low to very high, and the performance of IPSS-M has been recently validated.[6-8] Although clearly this model improves the risk prognostic performance in OS and AML transformation, many questions remain regarding how the IPSS-M should be incorporated into clinical practice, including clinical trial design. Notably, there has not been an HR-MDS study that has incorporated the IPSS-M, although this will likely occur in the near future.

Response criteria in MDS

Ultimate approval of therapeutic agents is partially dependent upon response criteria. In particular, the definition of complete remission (CR) is a critical criterion as it has been shown to be a robust predictor of outcomes in patients with MDS.[9] The IWG originally instituted consensus response criteria for MDS in 2000, with a major update in 2006, which has served as the response system in all pivotal trials on MDS to date.[10] However, these criteria have been subject to critique in HR-MDS, particularly around the stringency of CR calling (ie, blasts <5%, ANC >1.0 × 10^9/L, platelets ≥100 × 10^9/L, hemoglobin >11 g/dL), as well as the impact of marrow CR with or without hematologic improvement (HI).

As an example in 2 prospective clinical trials utilizing CPX-351 as frontline treatment in patients with HR-MDS, the CR rate improved from the low 20s to >50% when ELN response criteria were used instead of IWG 2006 criteria.[11,12] In a large multicenter study evaluating the impact of complete remission with hematologic recovery (CRh) (ie, blasts <5%, ANC >0.5×10^9/L, platelets ≥50×10^9/L) in patients with MDS, there was no difference in OS in patients who achieved CR vs CRh (23 and 25 months, respectively), which were confirmed in multivariable analysis accounting for HSCT.[13] Ultimately, there was a recent consensus proposal in 2023 for revised IWG criteria with key updates shown in Figure 2.[4] Notably, for CR, the hemoglobin threshold has been decreased to ≥10 g/dL with the removal of marrow CR as a response (with caveat of consideration for patients bridged to HSCT). CR with limited count recovery (CR$_L$) and CRh are provisional entities focused on marrow responses in combination with hematopoietic recovery that require prospective validation. Additionally, the blood counts required for responses should occur temporarily around disease assessment (ideally within 2-4 weeks). For CR$_L$, there are additional delineations based on unilineage or bilineage response. Overall response rates (ORR) would include the composite CR response as defined previously in addition to partial remission and HI. Notably, the panel also recognized the importance of serial molecular annotation with the goal to ultimately defining measurable residual disease (MRD) negativity. Multiple studies have demonstrated that achieving NGS or flow negativity is associated with improved OS.[14-17] However, a majority of these studies have not utilized NGS with a sensitivity for robustly capturing MRD as can be done with error-corrected sequencing using molecular barcodes or duplex sequencing. Notably, in 1 key study using MRD NGS via error-corrected sequencing, the risk of progression after allogeneic HSCT was predicted based on analysis at day +30.[14] It is critical for multimodal assessment of MRD to occur in future clinical trials, which may help optimize selection of therapies for patients.

Similarly, clearance of *TP53* VAF to <5% has now been shown in multiple studies to predict improved OS.[16-18] Two recent prospective clinical trials highlighted that clearance of *TP53* VAF may be the best predictor of improved outcomes to HSCT.[19,20] These data are particularly relevant given controversies in the field about the utilization of HSCT in this molecular subset. However, long-term survivors are seen in patients with *TP53* mutant MDS/AML ranging between 20% and 30%; therefore, perhaps repeat NGS and cytogenetic evaluation after therapy and pre-HSCT could best decipher which patients should ultimately

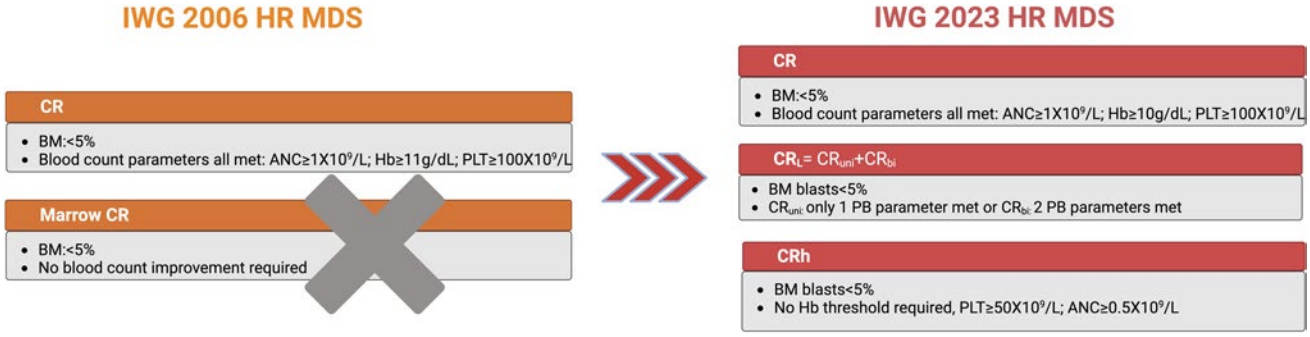

Figure 2. Comparison between IWG 2006 vs 2023 HR MDS response criteria. BM, bone marrow; CR$_L$, CR with limited count recovery; CRh, CR with partial hematologic recovery; CR$_{bi}$, CR with bilineage; CR$_{uni}$, CR with unilineage; Hb, hemoglobin; PB, peripheral blood; PLT, platelet.

move forward with HSCT.[21,22] This is particularly relevant given clear prospective data supporting allo-HSCT in patients that are fit, up to the age of 75 years.[23]

Azacitidine, the unbeaten standard of care for HR-MDS

There has been only 1 positive randomized control trial in patients with HR-MDS, which was azacitidine vs conventional care regimens. This trial showed an improved OS of 24.5 vs 15 months.[24] Unfortunately, real-world data, including current prospective clinical trials, have shown inferior outcomes, with median OS ranging from 14 to 19 months.[25] In addition, many randomized clinical trials (RCTs) comparing novel therapies vs azacitidine have failed (Table 1).[19,20,26-31] As it is critical to learn from past failures, we delve into some of the challenges in improving the SOC and flaws in clinical trial design to ideally help guide future studies in this patient population.

The SWOG S1117 study was a 3-arm randomized study of either azacitidine + lenalidomide, azacitidine + vorinostat, or azacitidine monotherapy. The azacitidine + lenalidomide arm was supported strongly by a prior phase 2 study.[32] Although there was a trend for improved ORR, the trial failed to reach its primary endpoint and also had no improvement in key secondary endpoints. The decreased RR and worse outcomes than the earlier phase 2 study were possibly related to non–protocol-defined dose modifications.[28] Notably, lenalidomide dose reduction was associated with worse OS. Overall, the vorinostat arm did worse than single-agent azacitidine, which is consistent with another RCT with a histone deacetylase inhibitor (ie, entinostat).[29]

The azacitidine + durvalumab study represents the first RCT in HR-MDS to evaluate the combination of immune checkpoint blockade with durvalumab, a PD-L1 inhibitor, to build upon the paradigm shift in management of solid malignancies and some prior data suggesting improved response rates with HMA immune checkpoint combination.[30,33] The ORR (primary endpoint) was 61.9% in the combination arm vs 47.6% with no difference in OS.[30] Notably in patient samples, PD-L1 was increased on granulocytes/monocytes but was not increased on bone marrow blasts, with conflicting prior reports about expression levels in the setting of HMA therapy.[34,35]

Until this time, no RCT had an event-driven endpoint as the primary endpoint of the study. The PANTHER trial was a phase 3 RCT of azacitidine and pevonedistat, a selective inhibitor of NEDD8-activating enzyme, vs azacitidine alone. The trial was supported by a previous phase 2 RCT with a near doubling of the CR rate and improved event-free survival (EFS) in the HR-MDS cohort.[27,36] Notably, the EFS was not positive in the total intention-to-treat (ITT) population, which included patients with oligoblastic AML and CMML. Despite these data, the PANTHER trial enrolled the identical population as the phase 2 trial and had a primary endpoint of EFS. In the ITT analysis, there were no significant differences between the 2 arms regarding EFS and OS (Table 1).[27]

Two parallel phase 2 studies evaluated the combination of the p53 reactivator APR-246 (eprenetapopt) + azacitidine with high CR rates between 44% and 47%.[19,20] This led to the first phase 3 study for patients with mutant *TP53,* although unfortunately the study was negative, with the only reported data by press release and by update on clinical trials.gov (CR rate of 34.6% vs 22.4% by ITT; *P*=0.13).

Last, the phase 2 RCT of sabatolimab+HMA vs HMA alone was recently presented.[31] Sabatolimab is a novel immunotherapy targeting TIM-3. The study had co-primary endpoints of CR and PFS. The CR rate was no different between arms, 21.5% vs 17.7%, *P*=0.769. Although the PFS was not statistically different (11.1 vs 8.5 months; *P*=0.102), the PFS curves separated after 9 months, supporting a potential immune mechanism, and there were subsets of patients that had improved outcomes (ie, <10% blasts or patients without very-high-risk disease). Importantly, the OS curves were essentially superimposable, although notably the median follow-up was only 17 months and thus unclear if there would be late separation similar to the PFS results.

Together, there have been many challenges in prospective randomized trials for HR-MDS encompassing heterogeneous patient populations, response metrics/timing of response, dose adjustments/reductions, and, at times, lack of strong preclinical/translational rationale for the combination. Additionally, the impact of salvage off-label therapies (eg, venetoclax) and increasing utilization of allo-HSCT with clear improved OS in patients up to the age of 75 have added additional complicating factors.[23,37]

A bright horizon for patients with HR-MDS?

As described, there has not been a phase 3 RCT with a primary endpoint of OS, but now there are 3 ongoing studies that have completed accrual, all of which have either a sole primary endpoint or a co-primary endpoint of OS (Figure 3). Notably the STIMULUS-MDS2 phase 3 MDS study is a double-blind RCT study in intermediate to very-high-risk MDS or CMML-2 evaluating the combination of sabatolimab + azacitidine vs azacitidine alone with a sole primary endpoint of OS. Secondary to the negative readout of the phase 2 RCT as described,[31] the current ongoing studies are focused on the evaluation of lower-risk MDS. However, based on sabatolimab's safety profile, additional novel combinations are allowed with this agent.

As the innate immune system plays a significant role in cancer immune surveillance, unleashing key effectors cells of innate immunity, specifically macrophages, represents an attractive therapeutic modality. The antitumor activity of macrophages is tightly regulated by a balance of prophagocytic ("eat-me"; eg, calreticulin) and antiphagocytic signals ("don't eat-me," ie, CD47). CD47 is widely overexpressed on cancer cells, including HR-MDS subsets with overexpression on myeloblasts and leukemia stem cell populations.[38] Importantly, azacitidine leads to robust upregulation of the pro-"eat me" signal calreticulin in myeloid cell lines and animal models.[39] The most mature anti-CD47 agent is magrolimab, which has completed a large phase 1b expansion the study was published.[15] The trial showed a CR rate of 32.6% (40% in *TP53* mutant cohort) with a median duration of CR of 11.1 months and a median OS not reached at a median follow-up of 17.1 months. Importantly, around 60% of *TP53* wild-type patients were alive at data cutoff vs a median OS of 16.3 months in the *TP53* mutant group. Additionally, 36% of patients were bridged to HSCT with a 1-year survival of 91%. Last, MRD negativity, as previously discussed, was achieved in 23% and predicted for improved outcomes. Responses were seen across molecular cohorts, although questions remain if there is enhanced efficacy in patients with *TP53* mutations. The phase 3 ENHANCE study is a 520-patient, double-blind, placebo-controlled study with co-primary endpoints of CR and OS.

Table 1. Randomized trials in higher-risk MDS

Trial name	Phase	Investigational arm	Control arm*	Patient population	Eligibility	Primary endpoint	Results of primary endpoint	Secondary endpoint	Reference #
SWOG S1117	2	azacitidine + lenalidomide (10 mg/day days 1–21)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	49% vs 38% ($P = 0.16$)	No improvement in OS	[27]
SWOG S1117	2	azacitidine + vorinostat (300 mg twice daily on days 3–9)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	27% vs 38%; ($P = 0.16$)	11.6 versus 16.7 months ($p = 0.74$)	[27]
E1905 Study	2	azacitidine + entinostat (4 mg/m^2/day on days 3 and 10)	azacitidine	Therapy-related MDS/AML	Any IPSS	CR, PR, or trilineage HI	17% vs 46%	OS versus 13 months	[28]
FUSION-AML-001 (MDS Cohort)	2	azacitidine + durvalumab (1500 mg IV q 4 weeks)	azacitidine	Int to very high MDS	IPSS-R int to very high	ORR (CR, mCR, HI)	61.9% vs 47.6% ($P = 0.18$)	No Increase PDL1 on BM Blasts	[29]
SUPPORT	3	azacitidine + eltrombopag (200 mg/day, up to 300 mg/day)	azacitidine	Int to HR-MDS	int-1, int-2, high IPSS	Platelet transfusion-free interval	16% vs 31% ($P = 0.001$)	ORR 20% vs 35%	[25]
NCT02610777	2	azacitidine + pevonedistat (20 mg/m^2 IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	OS	21.8 vs 19.0 months ($P = 0.334$)	EFS 20.2 vs 14.8 months ($p = 0.045$) for HR-MDS	[34]
NCT03745716	3	azacitidine + eprenetapopt (4.5 g IV days 1–4)	azacitidine	*TP53* mutant HR-MDS	IPSS-R int to very high	CR	34.6% vs 22.4%; $P = 0.13$	NA	NA
PANTHER	3	azacitidine + pevonedistat (20 mg/m^2 IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	EFS	17.7 months vs 15.7 months ($P = 0.447$)	OS 21.6 vs17.5 (0.293) in HR-MDS	[26]
STIMULUS-MDS1	2	azacitidine/decitabine + sabatolimab (400 mg day 8 and 22)	azacitidine/ decitabine	Int to very high MDS	IPSS-R int to very high	CR and PFS	PFS 11.1 vs 8.5 months ($P = 0.102$); CR 21.5% vs 17.7% ($P = 0.769$)	Lower risk and <10% blasts with improved PFS	[30]
STIMULUS-MDS2	3	azacitidine + sabatolimab (800 mg day 8)	azacitidine	Int to very high MDS/CMML-2	IPSS-R int to very high	OS			
ENHANCE	3	azacitidine + magrolimab (priming/loading over C1–2; C3+30 mg/kg days 1 and 15)	azacitidine	Int to very high MDS	IPSS-R int to very high	CR and OS			
VERONA	3	azacitidine + venetoclax (400 mg days 1–14)	azacitidine	Int to very high MDS; excludes t-MDS	IPSS-R int to very high	OS			

*Azacitidine 75 mg/m^2 in all studies with exception of E19905 study, which used 50 mg/m^2×10 days).

BM, bone marrow; CMML, chronic myelomonocytic leukemia; HI, hematologic improvement; Int, intermediate; IPSS-R, revised International Prognostic Scoring System; mCR, marrow CR; PR, partial remission.

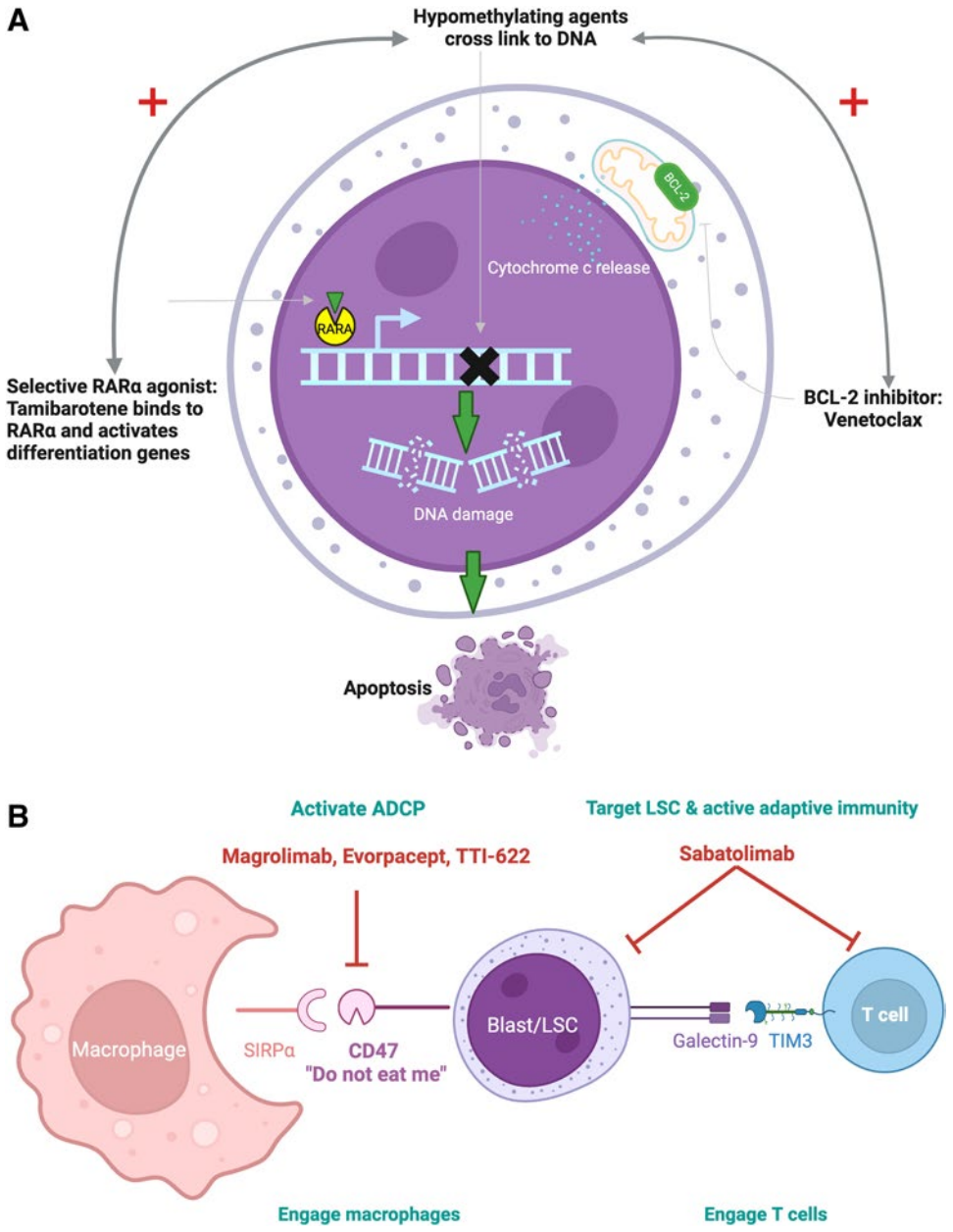

Figure 3. Novel therapy in higher-risk myelodysplastic neoplasms (HR-MDS). (A) Targeted therapy in patients with RARα overexpressing cells with tamibarotene (SY-1425), a selective RARa agonist and blockade of the anti-apoptotic protein BCL-2 via the BH3 mimetic venetoclax; ultimately leading to apoptosis induction with the combination of hypomethylating agents. (B) Novel immune myeloid therapy targeting both the underlying leukemic stem cell (LSC)/blast as well as activating both innate and adaptive immunity. Magrolimab, and other inhibitors of the CD47/SIRPα axis, allowing for activation of antibody dependent cellular phagocytosis (ADCP) and likely subsequent adaptive immune activation via increased antigen presentation. Sabatolimab blocks the galectin-9/TIM-3 pathway leading to direct targeting of the LSC as well as T-cell activation and potentially augmentation of ADCP.

Unfortunately, as of July 2023, there was a press release that magrolimab will be discontinued for patients with MDS, based on futility. Critical questions remain from this study, including the molecular demographics and outcomes in *TP53* mutant vs wild-type populations, among others. Notably, there are 2 additional phase 3 studies in AML evaluating the doublet for *TP53* mutant AML (ENHANCE-2; NCT04778397) and a triplet with venetoclax in all-comer elderly AML (ENHANCE-3; NCT05079230).

Last, the selective BCL-2 inhibitor venetoclax, which has led to a paradigm change in the management of elderly patients with AML,[40] has undergone evaluation in patients with HR-MDS. Specifically, a large phase 1b expansion study with the combination of azacitidine with venetoclax, at a reduced 14-day schedule secondary to cytopenia toxicity, had a CR rate of 40% (16% for patients with *TP53* mutations) and particularly favorable OS for patients who achieved CR/mCR. These data are supported

by additional studies, including recent real-world data in both HMA-naïve and HMA-failure settings, particularly for patients that can be bridged to HSCT.[41-43] These data support the ongoing placebo-controlled VERONA study with a primary endpoint of OS. Although this trial is for all molecular subsets, growing data support lack of improved efficacy in the patient population with *TP53* mutations.[44] Importantly, there are growing data supporting synergy of venetoclax with multiple agents, including with magrolimab.

Ideally, the previously mentioned phase 3 trials will lead to new approvals in HR-MDS, although clearly we are all awaiting the first breakthrough in this patient population; we have now suffered again a major setback with the negative phase 3 magrolimab study. Major questions will arise as far as best sequencing and questions of triplet combinations or sequenced doublets will be of high value. In addition, the only actively accruing phase 3 trial is with SY-1425 (tamibarotene) for RARA-overexpressing HR-MDS (~30%-50% of patients) with a primary endpoint of CR (Figure 3). Additionally, there are multiple trials incorporating oral HMA therapy (particularly oral decitabine/cedazuridine) with the novel agents described previously in efforts to decrease the burden of clinic visits required by parenteral HMA therapy.

CLINICAL CASE (follow-up)

As the patient was identified to have multi-hit *TP53*-mutant MDS, the patient was presented a clinical trial option with a novel HMA combination regimen. In addition, the patient was referred for HSCT consultation with the plan to bridge to transplant when *TP53* VAF was <5%.

Conflict-of-interest disclosure

David A. Sallman: research funding, Aprea; advisory board and steering committee member, Gilead.
Zhuoer Xie: no competing financial interests to declare.

Off-label drug use

David A. Sallman: Venetoclax in MDS.
Zhuoer Xie: Venetoclax in MDS.

Correspondence

David A. Sallman, Moffitt Cancer Center, 12902 Magnolia Dr, CSB 7th Floor, Tampa, FL, 33612; e-mail: david.sallman@moffitt.org.

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